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Michel Sadelain, MD, PhD


Nicole Paulk, PhD


Federico Mingozzi, PhD

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- Progress and lessons 12 months after the historic approval of Casgevy, the first CRISPR-based medicine
- Gene therapy for rare and ultra-rare diseases: a fireside chat with **Terence Flotte**
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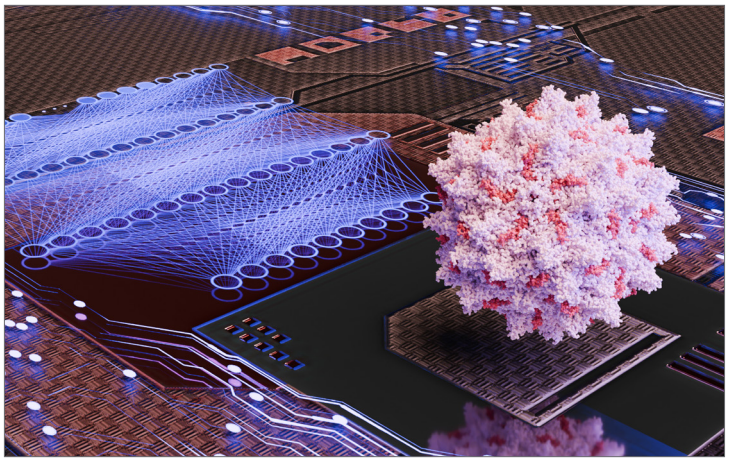

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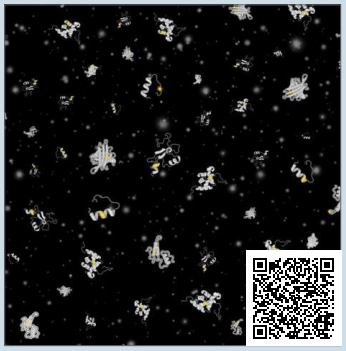
Johnson & Johnson to Acquire Intra-Cellular for $14.6B

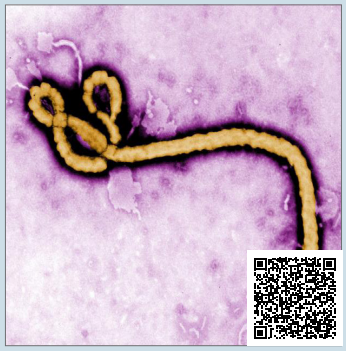


Queralt Tolosa/Centro de Regulación Genómica]

"Human Domainome" Reveals Cause of Many Diseases

Yuichiro Chino / Getty Images

Seven Biopharma Trends to Watch in 2025



CDC/ Frederick A. Murphy

Ebola Virus Translocation Model May Clarify Human Skin Transmission

Cover Image: Elo Life Sciences is using its proprietary gene editing platform to engineer resistant banana plant varieties that retain the signature taste.

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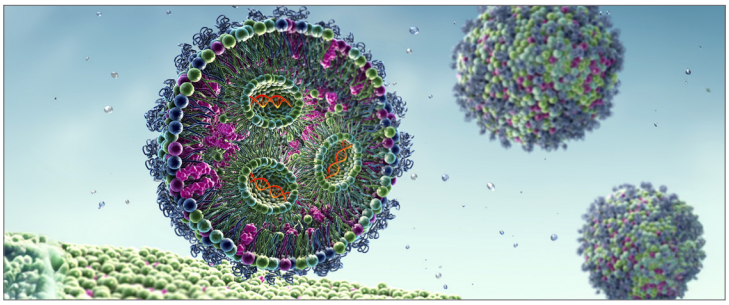

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From the **Editor in Chief**

The famous Asilomar Conference in 1975 set up the first guidelines on the physical and biological containment of recombinant DNA organisms that still serve as the model for the NIH. Asilomar concluded that there was no basis for any real fear. Yet, when *GEN* was born in 1981, there was still concern over the safety of recombinant products. Indeed, even today, it is not uncommon to see a sizable number of foods labeled "non-GMO."

Later this month, "The Spirit of Asilomar and the Future of Biotechnology" summit (https://www.spiritofasilomar.org) will take place on the historic Asilomar Conference Grounds in Pacific Grove, CA, to mark the 50th anniversary of the iconic meeting. Topics will include AI, pathogens research & biological weapons, deployment of biotechnologies beyond conventional containment, and new frontiers in synthetic cells.

On the conference web page, the questions are asked ***"Why Now? Why Asilomar?"*** The responses are listed below in light of past and recent biotech concerns and how the conference will address these and other issues impacting the current world of biotech research. It looks like the spirit of Asilomar does indeed live on.

"If we had any guts at all, we'd tell people not to do these experiments until we can see where we are going."
—Norton Zinder (1974)

"The issue was not an issue that scientists could decide ultimately for themselves in splendid isolation from the rest of the world." — David Baltimore (1975)

"Once you get to synthetic genetics the scope is just unbelievable."
— John Tooze (1976)

"We believed, somewhat naively, that there was a treaty that everyone held to prohibiting use of technology to make biological weapons…We clearly have an unfinished agenda from Asilomar on biowarfare." — David Baltimore (2006)

"Do I want to go ahead with experiments that could have catastrophic consequences?"
— Paul Berg (2015)

Some key talking points for the conference:

- Today, software analyzes and emits strings of life—DNA, RNA, proteins. Increasingly accessible AI tools are accelerating. Who or what is steering the ship? To what ends?
- Researchers are organizing to construct life entirely from scratch. What seemed fantastical just a few years ago is now reducible to clear questions, programs of work, and budget proposals. Life beyond lineage, long contemplated, raises entirely new concerns and questions.
- Nations now publicly accuse one another of having offensive biological weapons programs. The foundational argument that those advancing biological weapons are enemies of all mankind is eroding. How do we make sure the peace holds?
- Half a century of recombinant DNA is yielding burgeoning bioeconomies operating at scales attracting national and geopolitical attention. Are we citizens, consumers, subjects, or objects of the resulting bioeconomies? Are we the people building the bioeconomies the people wish for?
- Consumers can source and grow bioluminescent petunias, blueberry tomatoes, and other GMOs. Policies based only on physical containment may no longer best match a moment in which biotechnologies are increasingly deployed on, in, and around us all.

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Illumina, Nvidia Launch AI-Based Genomics Partnership

By Alex Philippidis

Announced early during the 43rd J.P. Morgan Healthcare Conference held last month, Nvidia and Illumina announced that they will partner to apply genomics and AI technologies to analyze and interpret multi-omic data in drug discovery, clinical research, and human health.

Illumina will offer its DRAGEN analysis software on Nvidia's accelerated computing platforms through the NGS giant's Illumina Connected Analytics (ICA) platform. By integrating their technologies, the companies aim to expand the reach of DRAGEN and Illumina multi-omics analysis globally to wherever users access Nvidia's computing platform.

"Nvidia has had great success in building GPUs as an acceleration platform, and they have a wide distribution of that asset. They have GPUs everywhere driven by the AI demand that has risen. We'll work together to make sure that we can also run DRAGEN on GPUs," Rami Mehio, Illumina's head of global software and informatics, told *GEN*.

That work, Mehio said, has been in progress for a year and is very far along, but will take some additional time to complete.

"Our code is quite big, and to basically port it all in an efficient way on GPU takes time," Mehio explained. "Both teams, Nvidia and us, have been working together on it. We do have prototypes running today, but they're not production quality yet. We're still adding functionality and removing bugs."

"I would expect that we will have something certainly before the end of this year that's available," Mehio added.

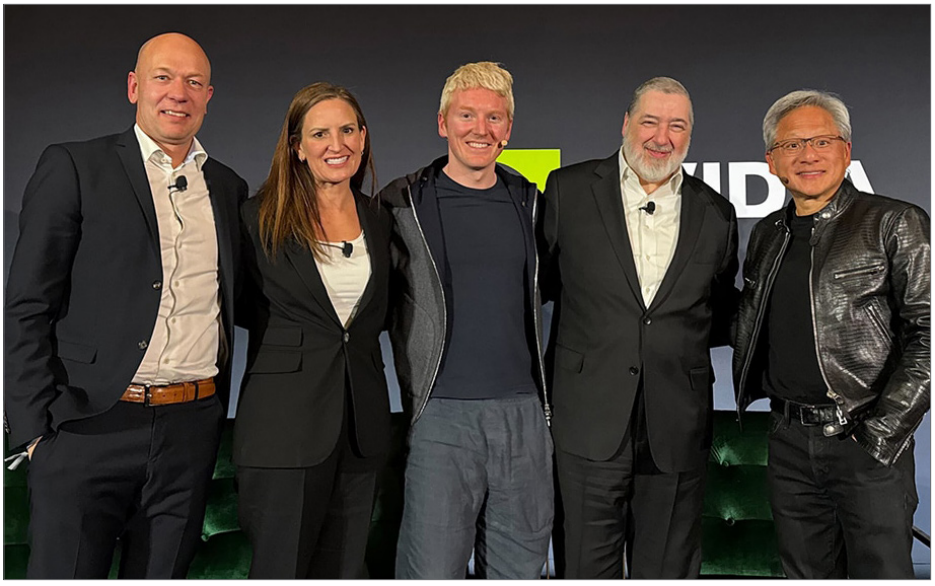
Nvidia and Illumina have also agreed to collaborate on advancing multi-omic data analysis using Illumina Connected Analytics, in addition to developing new biology foundation models, with plans to incorporate Nvidia's image processing and single-cell tertiary analysis tools onto the Illumina Connected Software multiomics module.

The multimodal AI models expected to result from the companies' efforts can uncover insights and streamline processes to boost the capabilities of human experts, Illumina CEO Jacob Thaysen, PhD, told Jensen Huang during an informal "Fireside Chat" hosted by the Nvidia CEO Monday evening at the Fairmont San Francisco hotel, about a hilly half mile north of where the J.P. Morgan conference was taking place.

"Combining other information, other modalities, other 'omics,'" Thaysen observed, "is going to give us much deeper insight into biology. But while DNA was very difficult itself, when you then combine all the omics, it becomes exponentially more challenging. It's getting so complicated that we do need huge computing power and AI to really understand and process it."

Bringing DRAGEN into Illumina Connected Analytics helps Nvidia at a time when it is working with several undisclosed countries as they establish national sovereign AI strategies.

"They want to protect their population data, but they also want to create the conditions that will enable them to have a world-class health system, all at the same time. So, we have a really unique opportunity by bringing DRAGEN in the Illumina platform on our GPUs," Kimberly Powell, Nvidia's vice president of healthcare and life sciences, told *GEN*. "We're going to have the ability to really bring all of this amazing genomics capability into these sovereign AI efforts and allow them to have state-of-the-art genomics capabilities in these nations." GEN



[*L.-R.*] Illumina CEO Jacob Thaysen, PhD; Christina Zorn, chief administrative officer at Mayo Clinic; Patrick Collison, cofounder of Stripe and the Arc Institute; Ari Bousbib, chairman and CEO of IQVIA; and Jensen Huang, founder and CEO of Nvidia. Illumina will partner with Nvidia to apply genomic technologies toward drug discovery and human health. Nvidia

New Prime Editing System, mvGPT, Combines Editing and Regulation

Sherry Gao, PhD, Tyler Daniel (pictured), and their coauthors developed a new tool that can simultaneously and independently edit multiple genes and regulate their expression. Bella Ciervo

A new genome editing tool—minimal versatile genetic perturbation technology (mvGPT)—can achieve simultaneous and orthogonal gene editing and gene regulation in human cells. The coming together of these two goals into a single tool—that can independently address different genetic diseases in the same cell—opens new doors to treating genetic diseases and investigating the fundamental mechanisms of how our DNA functions.

This work is published in *Nature Communications* in the paper, "Orthogonal and multiplexable genetic perturbations with an engineered prime editor and a diverse RNA array."

"Not all genetic diseases are solely caused by errors in the genetic code itself," said Sherry Gao, PhD, associate professor in chemical and biomolecular engineering (CBE) and in bioengineering (BE) at the University of Pennsylvania. "In some cases, diseases with genetic components—like type I diabetes—are due to how much or little certain genes are expressed."

The platform works by combining an improved prime editor, capable of modifying DNA sequences, with previously invented technologies for increasing and decreasing the expression of genes.

More specifically, the mvGPT combines "an engineered compact prime editor, a fusion activator MS2–p65–HSF1 (MPH), and a drive-and-process multiplex array that produces RNAs tailored to different types of genetic perturbation."

"All these functions are orthogonal," said Tyler Daniel, a doctoral student in the Gao Lab. "They can happen independently of each other at the same time."

The authors note that mvGPT can "precisely edit human genome via a prime editor coupled with a prime editing guide RNA and a nicking guide RNA, activate endogenous gene expression using the prime editor with a truncated single guide RNA containing MPH-recruiting MS2 aptamers, and silence endogenous gene expression via RNA interference with a short-hairpin RNA."

The team tested mvGPT on human liver cells by simultaneously correcting a c.3207C>A mutation in the ATP7B gene linked to Wilson's disease, upregulating the PDX1 gene expression to potentially treat type I diabetes, and suppressing the TTR gene to manage transthyretin amyloidosis.

In multiple tests, mvGPT achieved all three tasks with high precision, demonstrating its ability to target multiple genetic conditions simultaneously.

Because mvGPT takes up less space than three separate tools, the system is also easier to transport into cells. The researchers showed that mvGPT can be delivered by multiple means, including strands of mRNA and viruses used to deliver genetic editing tools.

"When you have a single tool that can accomplish all of these things at the same time," said Gao, "you make the process so much simpler because there's less machinery you have to deliver to the cell."

Now that the technology has shown promise in human cells, the researchers plan to test mvGPT in animal models, and against other diseases with genetic components, including cardiovascular diseases. "The more advanced our tools become," continued Gao, "the more we can do to treat genetic diseases." GEN

Sticky ends

Salmonella from Your Dog? It's PAW-Sible

Anna Reshetnikova / iStock / Getty Images Plus

Many of us live closely with canine companions. But new research suggests that we may want to consider keeping a little distance. Researchers found that household dogs are an overlooked transmission point for zoonotic pathogens such as nontyphoidal *Salmonella*. "Especially with *Salmonella*, we think about the role of agriculture and transmission—we think about eggs, we think about beef. But the thing is, we don't let cows sleep in our beds or lick our faces, but we do dogs," said Sophia Kenney, a student in the doctoral program at Penn State. The researchers leveraged the U.S. FDA's Veterinary Laboratory Investigation and Response Network to identify all nontyphoidal *Salmonella* strains isolated from domestic dogs between May 2017 and March 2023. They then matched the timing and location of 87 cases to strains isolated from humans. The results, published in *Zoonoses and Public Health*, found 77 suspected zoonotic cases.

Making Vegan Cheese More Cheesy

jirkaejc/iStock / Getty Images Plus

Plant-based diets are gaining in popularity. But even some of the most loyal vegans admit that the food offerings are just not the same. Specifically with alternative dairy products, manufacturers have a hard time replicating the creamy qualities that make cheese, well, "cheesy." "Now, consumers expect essentially the same animal product but with plant-based ingredients, which is very difficult," said Alejandro Marangoni, PhD, professor at the University of Guelph. Marangoni and colleagues are trying to produce plant-based cheese that more closely resembles real cheese. The team studied isolates from three proteins—a pea protein isolate, a faba protein isolate (FP1), and a lentil protein isolate, at a concentration of 7.5% (w/w)—to evaluate their effect on the cheese's physical characteristics. Results published in *Physics of Fluids* suggest that tuning protein-fat interactions can tweak cheese's properties like hardness while potentially improving the sustainability and health benefits of the final product.

Cheryl Ramalho / iStock / Getty Images Plus

When Chimps Have to Go, They Go Together

One (somewhat peculiar) human social phenomenon is urinating together. Now, new research in *Current Biology* suggests that this practice, known as "contagious urinations," may have deep evolutionary roots. The study of 20 chimpanzees living at the Kumamoto Sanctuary in Japan found that chimpanzees tend to urinate in response to the urination of nearby individuals. Peeing behaviors were analyzed for more than 600 hours, including 1,328 urination events. The evidence showed that urination was significantly more synchronized during observations than would be expected if the chimpanzees were simply peeing at random with respect to one another. The likelihood of contagious urination increased with physical proximity to the initial urinator and individuals with lower dominance ranks were more likely to pee when others were peeing. Taken together, the findings suggest that urination patterns are influenced by social hierarchy.

Digitized Chemistry

Leads Developers Deeper into Chemical Space

By Gail Dutton

Chemify combines robotics, AI, and a purpose-built programming language to streamline the design and production of chemical molecules

Since its inception, the chemical industry has fixated on what molecule to make and then on how to make it. Chemify is shaking up that process, enabling scientists to advance more quickly using a novel digital approach.

"If you design a molecule (the traditional way), you don't know if that molecule can really be made…or made quickly," says Lee Cronin, PhD, founder and CEO of Chemify. His company's three-pronged approach, dubbed "chemputation," aims to be a more dependable, reproducible, and efficient means to transition molecules from design to a physical entity and to scale easily from laboratory to clinical trial or commercial quantities.

The idea blends digitization and robotics with molecule discovery. Chemify combines a new, purpose-made programming language with robotics and artificial intelligence to create what Cronin expects will become "the world's largest repository of molecules that can be made."

Chemify converts molecules and the chemical procedures into digital code. Robots can then use that code to manufacture existing and yet-to-be-designed molecules on demand. Quantities can be scaled up by adding bioreactors rather than enlarging reactors.

This technology should result in the rapid creation and production of superior small molecules. As Cronin explains, "We do all the chemistry first, so we only choose molecules we know we can make." By training the robots to perform the chemistry, this approach can make two orders of magnitude more reactions than traditional automation (1,000 to 5,000 reactions, Cronin says, compared to the 10-15 reactions that are feasible with existing robots).

In contrast, "Typically, everybody doing in silico drug discovery invents the molecule before they know if they can make it." The challenge with such an approach, Cronin says, is that drug designers can only go so deep. "Small molecule drug discovery is slowing…some might say failing…because we're at the bottom (using a diving analogy) and we're all searching the same space." By creating a large library of digital molecules, similar to the computational libraries created for biologics, chemists may be able create entirely new, purpose-built chemical entities.

One of the first challenges, Cronin says, "is to convince chemists we're not taking their jobs. Instead, we're just giving them a (metaphorical) exoskeleton to let them go deeper into a chemical space." The difference, he says, is like free diving versus scuba diving. "With scuba, you can go deeper. Likewise, with chemputation, scientists can make more complex molecules."

There's also a misperception that Chemify is a manufacturer. Actually, the company is more of a boutique designer, he says. "We're making complicated molecules for people quickly, that they couldn't get anywhere else." The goal complements their customers' existing capabilities.

Manufacturing facility

Chemify's first manufacturing facility is scheduled to go online in 2025 in Glasgow. Once that pilot plant is operating smoothly and optimized, Cronin says he may look to build a similar facility in the U.S.

Walking through the planned facility, Cronin says "It won't look that different from a normal laboratory because we're using a few hoods, like in a chemistry lab, for air management. In the future, a chemputation facility will look like a server farm with racks of serv-

Vital SIGNS

Chemify

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Website
www.chemify.io

Principal
Lee Cronin, PhD, Founder & CEO

Number of Employees
120

Focus
Uses advanced robotics and programming of chemical molecules, and designs of chemputation systems needed to manufacture them.

ers and computers." Here, however, rather than racks of servers, there will be racks of reactors with ducting and fire suppression. "Solvents and solids will move in, and molecules will move out."

The sweet spot in terms of production is the milligram to gram scale, "but we automate the gram scale. No one else does that," Cronin maintains.

Using a chemputation approach, scaling up production will be a matter of adding more reactors rather than adding larger reactors. That makes it most cost-effective and easier to scale from lab and preclinical quantities to clinical and commercial quantities, he says.

There also may be a regulatory advantage because standardized robotic units are used. Product output will be comparable from each robot, which avoids the uncertainties associated with up- or down-sizing reactors. "The robot history, code, and chemicals will all be known," he says, and the log and audit trail are accessible.

The standardized programming language that Cronin developed is an important element in the chemputation approach, he points out. "That programming language works to standardize robots." Coupled with traceability capabilities, "it enhances performance and reliability, which makes regulatory oversight easier," he adds.

In-house, for now

While Chemify mines chemical space, the entire chemputation process, including its robotics, will remain in-house. "At the rate at which we're iterating the technology, it makes no sense (to do otherwise)," Cronin says. Instead, "We want to give partners the ability to co-design with us, making molecules and new drugs at scale."

Once the chemputation concept is fully mature and outside entities are contributing to the digital molecule knowledge base, the company could become more of a digital developer, Cronin speculates. However, "right now, it's important for us to make sure the robots work correctly, safely, and traceably."

This positions Chemify as "an enabler of the design. I view us as the architect and the structural engineer" designing and building actual molecules, he adds.

Disruptive innovation

Cronin formed Chemify in 2022 after developing a chemical description language, χDL (pronounced ChiDL). "Everyone said the language was boring," he recalls. But, "boring" doesn't mean "bad." This purpose-built language, he believed, was an important tool "to make chemistry accessible and reusable," and thus power the discovery of new drugs.

This vision of digital chemistry resonated with others, prompting Cronin to spin-out the company from the Digital Chemistry Laboratory at the University of Glasgow. "The first employee came on board the first of March, 2022. Now we're at 120 people, two-and-a-half years on.

"We have a hybrid set of chemical informaticians, chemists, operations engineering, and software developers, all working under one roof," he says. They're united around the goal of digitizing chemistry–"this thing that's never been done before," he continues.

The potential discoveries in the coming decades, he predicts, "are mind-blowing, and I think that's got a lot of people excited because they want to contribute to something that has a bigger meaning than just making money."

In the not-too-distant future, Cronin envisions pharmaceutical companies buying or accessing discovery computer engines to mine chemical space. They could then run their results through Chemify's chemputation platform to produce physical molecules. "It's a bit like using a Nvidia chip for openAI," he explains, in that "Nvidia enables the compute system as well as the model building tools.

"One of the things we're doing is making sure our customers understand that their intellectual property remains their intellectual property. The only thing Chemify learns (from its clients) is how to do the chemistry. The descriptions of their targets, proteins, and specifications remain completely owned by the customer." GEN

Chemify says its new robotic system reduces the amount of labor in the lab. Chris James

A-List

Top 10 Takeover Targets of 2025

Patent cliff, second Trump administration fuel expectation of rising M&A activity in 2025

Yuichiro Chino/Getty Images

By Alex Philippidis

Merger and acquisition (M&A) deals have declined from their most recent boom year of 2021, when the scramble to develop COVID-19 vaccines and drugs stoked interest by biopharma giants in buying out usually smaller companies with a pipeline or single promising drug based on clinical success, strong commercial sales, or both.

EY—the professional services firm originally known as Ernst & Young— reported an uptick in the volume of biopharma deals during 2024, with the number of such transactions rising 17% year-over-year, to 95 deals last year from 81 in 2023.

However, the average dollar value of biopharma M&A deals nosedived 51% last year to $92 billion from $186 billion the previous year, as buyers increasingly sought "bolt-on" acquisitions of under $5 billion in therapeutic areas that matched or complemented their own. The best reflection of that trend is the fact that the largest M&A deal of 2024 was Vertex Pharmaceuticals' acquisition of Alpine Immune Sciences for a mere $4.9 billion—89% less than the $43 billion shelled out by **Pfizer** for Seagen in 2023's priciest buyout.

Subin Baral, EY global life sciences deals leader, told *GEN* M&A deals are expected to increase in 2025, driven by biopharmas that are eager to recoup revenues they expect to lose as their aging blockbuster drugs lose patent exclusivity. EY projects that patent expirations will erase $300 billion in biopharma revenue by 2028.

Deloitte also forecasts a $300 billion loss of biopharma revenue, albeit by 2030. Pete Lyons, a vice chair with Deloitte and the firm's U.S. Life Sciences Sector Leader, said some of the biggest-name blockbuster drugs of recent years stand to lose patent protection over the next five years—such as **Johnson & Johnson/Bayer's** blood thinner Xarelto® (rivaroxaban), **Boehringer Ingelheim/Eli Lilly's** Jardiance® (empagliflozin), and **AstraZeneca's** top-selling drug Farxiga® (dapagliflozin). Jardiance and Farxiga are both sodium-glucose cotransporter 2 (SGLT2) inhibitors indicated for type 2 diabetes, chronic kidney disease, and heart failure.

In addition to the patent cliff, Lyons said, the expectation of more M&A activity in 2025 is also being driven by a stabilizing economy as interest rates have begun declining, and by the second administration of Donald Trump, which is expected to offer less resistance to M&A deals through a Federal Trade Commission (FTC) that Trump has vowed will be business-friendlier.

So which biopharma companies are most likely in the sights of would-be buyers?

As in past years, *GEN* lists 10 biopharma companies that analysts and other market watchers have seen as buyout targets in recent months. This list is based on notes to investors and comments in news outlets. For each company mentioned, the list explains where talk of acquisition has surfaced, and why.

GEN began publishing A-Lists of takeover targets in 2013. None of the 2024 list of Top 10 Takeover Targets has found buyers yet, though just as savvy investors think long-term, so too should market watchers of biotech M&A. Three of the nine companies on *GEN's* initial list 12 years ago have been acquired: Ariad Pharmaceuticals (by **Takeda Pharmaceutical** in 2017), Medivation (by Pfizer in 2016), and Seattle Genetics (which renamed itself Seagen before Pfizer bought the company in 2023).

That gives *GEN* a batting average of .333; good enough for Major League Baseball.

ARCELLX (NASDAQ: ACLX)

Arcellx's preliminary data presented in December from its pivotal Phase II iMMagine-1 trial (NCT05396885) assessing anitocabtagene autoleucel (anito-cel) in relapsed or refractory multiple myeloma was so positive that it revived talk about the company being an acquisition target—and not just for Gilead Sciences, whose Kite subsidiary partners with Arcellx in developing anito-cel. "While a takeout by Gilead would be nice, we think a takeout by someone else would be even better," Matthew Biegler (Oppenheimer) opined, adding that many analysts consider anito-cel a best-in-class chimeric antigen receptor T-cell (CAR-T) therapy for multiple myeloma. At the 66th American Society of Hematology (ASH) Annual Meeting and Exposition, Arcellx reported an overall response rate of 97% (83/86 patients) with a complete response/stringent complete response rate of 62% (53/86) and a very good partial response or higher rate of 81% (70/86).

BIOMARIN PHARMACEUTICAL

(NASDAQ: BMRN)

In the year-plus since becoming BioMarin's President and CEO, Alexander Hardy has restructured the company by supporting additional uptake of marketed drugs Roctavian® and Voxzogo®, and accelerating development of three pipeline candidates deemed to have the highest commercial potential (BMN 333, BMN 349, and BMN 351) while ending development of four others in April (BMN 331, BMN 255, BMN 355 and BMN 365) and a fifth in August (BMN 293). The additional halt increased BioMarin's job cuts from 170 to 225 positions. By October, Hardy credited BioMarin's "Innovation, Growth, and Value" commitment with a 19% rise in revenue and near-doubling of net income during Q1-Q3 2024. BioMarin's robust results plus low valuation ($12.737 billion market cap as of January 3) "provides an attractive M&A opportunity especially for companies facing LOEs," Kostas Biliouris, PhD, of BMO Capital Markets wrote July 8. BioMarin appeared on last year's *GEN* A-List of takeover targets, and on every earlier one published between 2013 and 2019.

BLUEPRINT MEDICINES

(NASDAQ: BPMC)

Three times in 2024, Blueprint Medicines raised its sales guidance for its sole commercial drug Ayvakit® (avapritinib), whose indications include gastrointestinal stromal tumor as well as advanced and indolent systemic mastocytosis (SM). From an initial $360 million-$390 million, Blueprint raised its guidance range to $390 million-$410 million in May, then to $435 million-$450 million in August, and finally $475 million to $480 million in October. The company has also raised its Ayvakit peak year sales forecast, to $2 billion from $1.5 billion. "If SM market is worth $2B, we're not sure why a large pharma hasn't pounced," Matthew Biegler (Oppenheimer) wrote. Biegler included Blueprint among five potential biotech buyout candidates in a January 3 note. Blueprint was also among Wells Fargo's 31 potential small- to mid-cap biopharma M&A targets for 2024.

EVOTEC (FRANKFURT: EVT; NASDAQ: EVO)

Evotec sought to boost its earnings before EBITDA through a "priority reset" in April that including eliminating some 400 jobs, withdrawing from gene therapy, and selling a chemical active pharmaceutical ingredient manufacturing site in Halle/Westphalia, Germany. Instead, its EBITDA swung to a loss and its stock price plunged 60% by November 8, when Evotec disclosed in a regulatory filing that private equity firm Triton Partners took a 9.99% stake in the company. Three days later, Bloomberg reported that Triton was among several investment firms looking to acquire the contract research organization. On November 14, Halozyme Therapeutics confirmed making an unsolicited offer to acquire Evotec for €2 billion ($2.1 billion), only to withdraw that offer two weeks later after an Evotec spokesperson said the company wished to remain independent.

IMMUTEP (ASX: IMM)

Andrew Hamilton (Antares Equities) declared Immutep could be an acquisition target based on its cancer-fighting lead candidate, the soluble LAG-3 protein and first-in-class antigen presenting cell activator eftilagimod alpha (Efti). In September, the combo of Efti and Merck & Co.'s Keytruda® (pembrolizumab) showed a 31% overall response rate in first-line head and neck cancer vs. 18% for Keytruda alone. Hamilton noted Efti's patents extend to the mid-2030s while Merck is set to lose key U.S. patent protection for Keytruda in 2028. "It's not just Merck. Many of the largest global drug companies are facing significant patent cliffs before 2030 which, we think, makes a drug with Efti's enormous potential revenue and quality data very appealing."

INSMED (NASDAQ: INSM)

With Insmed's shares more than doubling in 2024, zooming 144% from $28.68 to $69.86, Christina Cheddar Berk (CNBC Pro) predicted the company's stock has "a good chance of breaking out in 2025"—a forecast based in part on Andrea Newkirk, PhD (Goldman Sachs)'s conclusion that the company could make an attractive buyout target for larger biopharmas focused on treating respiratory diseases. Insmed ended 2024 close to submitting a New Drug Application (NDA) for its lead pipeline candidate brensocatib in the chronic pulmonary disorder non-cystic fibrosis bronchiectasis (NCFBE)—a drug the company says could generate peak year sales of $5.9 billion, but which Newkirk concluded "likely significantly" underestimated the drug's true potential. Insmed shares rocketed 150% in May when the company announced its NDA plans for brensocatib following positive Phase III data.

LEGEND BIOTECH (NASDAQ: LEGN)

Legend lived up to its name in 2017 by attracting $350 million upfront from Johnson & Johnson's Janssen Biotech to partner on developing, manufacturing, and commercializing the CAR T-cell therapy Carvykti® (ciltacabtagene autoleucel), which treats adults with relapsed or refractory multiple myeloma by targeting the B-cell maturation antigen (BCMA). J&J has projected $5 billion-plus in peak-year sales for Carvykti—a key reason why, despite its net losses, Legend reportedly hired Centerview Partners in July to evaluate a takeover offer, according to StreetInsider.com, which cited an unnamed source. Legend has declined to comment. Following reported rumors that they differed on an acquisition price, Legend's parent GenScript said in October it had deconsolidated from onetime subsidiary Legend. Carvykti sales helped Legend shrink its nine-month net loss year-over-year, to $203.310 million from $373.436 million in Q1-Q3 2023.

NUVALENT (NASDAQ: NUVL)

Nuvalent says it is on track to bring its first targeted cancer treatment to market in 2026. Nuvalent achieved all anticipated 2024 milestones, including positive Phase I data for its Phase I/II candidates for ROS1-positive and ALK-positive non-small cell lung cancer (NSCLC)—the former (Zidesamtinib) expected to report pivotal data this year, the latter (NVL-655) set to launch a Phase III trial vs. Roche/Genentech's Alecensa® (alactinib) in H1 2025. Those drugs plus a HER-2 positive NSCLC candidate could generate $205 million in 2026 revenue, growing to $4.5 billion in 2032, predicted Swayampakula Ramakanth

See A-List on page 23

History May Not Be Repeating
but It Is Certainly Rhyming

By Fintan Steele, PhD

Science and scientists are under renewed attack: Will we rise to the challenge?

Fintan Steele, PhD

Trofim Lysenko, the mid-20th century anti-Mendel scientist and Stalin favorite, is poised for a comeback. Millions of Soviet citizens died as a result of his government-backed pseudoscientific biological ideas. Even though he was eventually dismissed in shame, Russian science tanked for several generations, struggling to catch up with the rest of the world to the present day.

How did so many people, including so many scientists, become so willing to abandon the scientific method and support Lysenko, helping pave the way for catastrophe after catastrophe? Clearly many were scared into accepting his ideas, aligned as they were with Soviet philosophy and policies (and the government's ruthless enforcement of them). But that still doesn't fully account for his rapid rise and—coming way too late for many—his dramatic fall.

My recent interest is more than just historical curiosity. When one looks at the incoming administration's nominees for Health and Human Services, NIH, FDA, NASA, CDC, etc., one could be forgiven for fearing that ideology is again ascendant over scientific reality: The very dynamic that led to Lysenkoism less than a century ago. These possible "science" leaders are indeed a threat, particularly if they get a high level of popular support for "theories" they have publicly announced that defy years of scientific discovery. What is going on in the American public?

What is wrong with us?

It is too easy to place the blame on a poor education system for the deep suspicion of science and scientists in many parts of our country. But asking "what is wrong with them?" should be secondary to the far more important question of "what is wrong with us?" Scientists and their supporters may be about to reap a whirlwind that we have at least partially sown.

It is a tragedy that so many people I talk with have experienced science in their school education as only a set of facts to be memorized and spit back out at test time. I think we can all agree that is not good science, or even science at all. No, the best science is built on the twin pillars of scientific method and scientific language, both of which have tremendous power to enlighten reality and unite or—sadly—to obscure and fragment.

What we say and do matters

Scientific method at its best is an intellectual openness to considering, debating, and testing new findings that enhance or even contradict current understandings. That philosophy is obviously inimical to more dogmatic belief systems, whose proponents simply dismiss scientists and scientific discoveries (e.g., vaccines) as incompatible with deeply held "truths." The growing out-of-hand dismissal of science at least partially reflects a failure by us scientists to impart in both our communications and our actions just how

freeing and even existentially satisfying the scientific method is.

The other pillar, scientific language, evolved out of necessity for scientists to communicate new concepts and discoveries accurately with each other as succinctly as possible. But for the non-scientist (or even the scientist in a different field of expertise), scientific language might as well be Sumerian when used outside the relevant laboratory. Modern day scientists tend to be particularly guilty of relying on professional language even in settings in which they may be the only one fluent, basically rendering concepts and ideas inaccessible to others, and thus more easily dismissed as "just another belief system."

As a result of our unintentional obscuring of science, all manner of crazy ideas and charlatans can gain political and social ascendancy thanks to the relative accessibility of their mendacious language that offers "insider" knowledge and comfort. Lysenko's twisting of method and language gave him (initially) great power over the Soviet population and even over many scientists. Those few scientists and science-supporters who opposed him did so initially only from inside the scientific ivory tower, and they were quickly and easily silenced. Others simply fled or hid, hoping he wouldn't last long, which ended up only prolonging his tenure.

All of us must step up

Are we on the verge of a new American version of Lysenkoism? Maybe not, but there is no question we are facing at the very least a rough few years ahead for science. The temptation is strong to lay low until this madness is over. But that is what most scientists did in the face of Lysenkoism, to their own detriment. If we truly believe science is a critical element of a healthy and just society, scientists and their supporters cannot hide now.

The December 9th letter to the U.S. Senate from 75+ Nobel Laureates requesting that the senators turn down the nomination Robert F. Kennedy, Jr., to head the Department of Health and Human Services was a first step in the right direction. But all of us must push back, individually and collectively, on the emerging anti-scientific forces. Each of us needs to engage a much wider audience—using more accessible language—than our usual comfortable setting. In short, we must model a fearless commitment to good science and undertake a clear unmasking of bad science, no matter the political winds. GEN

An alternate version of this article first appeared on December 11, 2024, in the Boulder *Daily Camera* under the title "This is no time for scientists and science-supporters to hide."

Fintan Steele, PhD, has worked in science communications for over thirty years, with a focus on making emerging science accessible and accurate for multiple audiences via multiple media.

Jozef Polc / Getty Images

Optimizing AAV Gene Delivery

Hitting the Target Safely and Effectively

Researchers are enhancing the best features of AAV capsids and overcoming their limitations to accelerate gene-based therapies

By Kathy Liszewski

The great hope for gene therapy is that one day it will be out of the clinic and into mainstream therapeutics. Bearing enormous potential to treat or cure disease, such technology can replace a defective gene with a healthy one, modulate a disease-causing one, and even introduce a gene as a form of therapy. Successes are building including recent FDA approvals for gene therapy products that treat cancer, hemophilia, and sickle cell diseases. Yet many more applications await.

One of the most actively investigated gene transfer vehicles and emerging platforms is that of adeno-associated virus (AAV). Simply put, AAV consists of a protein shell (capsid) encasing a small single-stranded DNA genome. For recombinant versions (rAAV), scientists replace the viral genome with the desired therapeutic genetic cargo. Key attributes of rAAV include its established safety profile, broad tissue tropism, and versatile manufacturing capabilities.[1]

Indeed, last November the FDA approved **PTC Therapeutics'** Kebilidi, the first U.S. gene therapy to be administered

Above. Dyno Therapeutics uses generative AI to design improved AAV capsids for gene therapy delivery.

directly into the brain.[2] The AAV-based therapeutic treats a rare fatal genetic disorder characterized by a deficiency of aromatic L-amino aciydecarboxylase (AADC).

Other advances coming from clinical trials include remarkable vision improvement for rare blinding eye disorders such as Leber congenital amaurosis 1 (LCA1).[3]

Despite these steady successes, numerous challenges remain such as AAV's limited cargo capacity (~ 4.7 kb), tissue specificity, and complex manufacturing. *GEN* spoke with experts in this field for their input as to how they are working to overcome issues to optimize AAV gene delivery.

For example, to address targeting challenges, companies are refining and optimizing capsid design via sophisticated screening platforms or via artificial intelligence (AI). Some modular platforms utilize similar capsids and manufacturing platforms yet primarily alter genetic cargo in order to treat more than one disease target. Others modify capsids to penetrate specific tissues such as the blood-brain barrier (BBB) for treating central nervous system (CNS) diseases. One piece of advice offered by a veteran scientist is to optimize early on every process involved in AAV-development technologies.

Targeting bottlenecks

In business, "location, location, location" can determine success or failure. The same could be said for AAV gene therapy. "The old adage goes that gene therapy is all about delivery, and if you are able to get your therapy to the right tissue or cell type, they will likely show a therapeutic benefit," says Brian Kevany, PhD, CSO and CTO of **Abeona Therapeutics**.

According to Kevany, "Many therapies today lack a high degree of specificity to home in on a specific location or, alternatively, are attracted to off target tissues leading to unintended consequences. Further, traditional approaches of AAV capsid shuffling and rational design have not resulted in the predicted advances despite the recent involvement of AI/machine learning (ML). Thus, effective targeting remains a bottleneck to the development of AAV-based therapies."

To overcome this targeting bottleneck companies are increasingly using higher AAV doses to reach a therapeutic benefit. These higher doses can result in potentially harmful immune responses. Kevany dismays, "Recent examples of therapies in the clinic using these high doses have resulted in vision loss, or even death."

The company is addressing delivery problems using a multifaceted approach involving a novel capsid and a unique route of administration that only requires a lower dose. As Kevany explains, "Our proprietary AAV204 capsid has been shown to efficiently transduce cells of the retina upon injection directly into the vitreous cavity of the eye. For our lead preclinical program, for X-linked retinoschisis (XLRS), we are taking advantage of this capability and administering it using a para-retinal injection. This method is less invasive than a traditional subretinal injection and also positions the therapy closer to its intended target and at a lower dose than what is used in a standard intravitreal injection."

The XLRS therapy is intended to treat patients with mutations in the RS1 protein that result in deleterious splitting of the layers of the retina, ultimately leading to vision loss. The therapeutic payload of this drug is a corrected version of the RS1 protein driven by a photoreceptor-specific promoter.

Abeona's development pipeline also includes AAV-based therapies targeting Stargardt Disease and Autosomal Dominant Optic Atrophy.

Crossing the BBB

"The BBB prevents the uptake of many investigational therapies, including in gene therapy," remarks Todd Carter, PhD, CSO, **Voyager Therapeutics**. According to Carter, the company is seeking to overcome these challenges through their TRACER™ (Tropism Redirection of AAV by Cell-type-specific Expression of RNA) capsid discovery platform. He reports, "This is an RNA-based screening platform that has allowed us to create multiple families of novel, IV-delivered AAV capsids demonstrating robust penetration of the BBB. Our capsids have been shown to transduce a broad range of CNS regions and cell types, with decreased transduction of the liver. Further, we've seen cross-species CNS tropism (including rodents and multiple non-human primate species) resulting in widespread payload expression across the CNS at relatively low doses."

Following the robust performance of the TRACER platform, the company has selected five gene therapy development candidates. Carter discloses, "We feel that 2025 is therefore going to be a very important year for us. By mid-2025, we plan to submit an IND for our TRACER-derived capsid with vectorized anti-SOD1 siRNA for the treatment of amyotrophic lateral sclerosis (ALS). Also in 2025, we expect IND filings by our partner **Neurocrine** in one program ad-

Todd Carter, PhD
Chief Scientific Officer
Voyager Therapeutics

Eric Kelsic, PhD
CEO and Co-founder
Dyno Therapeutics

Walid Abi-Saab, MD
Chief Medical Officer
uniQure

Alexandria "Zandy" Forbes, PhD
President and CEO
MeiraGTx

dressing Friedreich's ataxia and a second program for Parkinson's disease and other *GBA1*-mediated disease." Mutations in *GBA1*, the gene encoding glucocerebrosidase, are among the most common genetic risk factors for development of Parkinson's and other related diseases.

Looking to the future, Carter says the company is aiming for an even bigger impact. "We're excited about the potential of leveraging the receptors we've identified through our AAV capsids to shuttle other macromolecules across the BBB in a manner that is non-viral. We expect that each receptor could have its own profile in pharmacokinetics and safety to provide opportunities in different diseases and indications. We're still in the preclinical stages, but ultimately, we aim to use these different approaches to solve the fundamental problem of CNS delivery that the field has struggled with, and to expand into other modalities of neurogenetic medicine broadening our impact."

AI-assisted AAV design

Recent advances in generative AI are beginning to revolutionize AAV capsid design. Eric Kelsic, PhD, CEO and cofounder, **Dyno Therapeutics** weighs in, "Optimizing AAV capsids for efficiency, specificity, and reduced immunogenicity is an immensely complex task in itself. Dyno was the first company to recognize that ML, when supported by the right data, is uniquely suited to address this problem."

According to Kelsic, new AI-assisted models can be trained to generate AAV capsids with more highly optimized properties compared to other capsid design methods. "The key advantage is that they leverage vast datasets with diverse input sources ranging from experimental studies to protein databases, to access and navigate areas of the sequence space that cannot be explored by traditional approaches."

Kelsic explains that the company's ML models produce and test billions of candidate sequences in silico, filtering out nonviable sequences and advancing the most promising candidates. "Our LEAP℠ (Low-shot Efficient Accelerated Performance) technology allows engineers to bypass entire rounds of experimental de-risking, replacing years of experiments with a few hours of computation. This year we reported that 9 out of 19 novel capsids designed using LEAP outperformed any of our previously measured capsid sequences with respect to brain transduction and liver detargeting, and that a small number of capsids designed in silico using LEAP could match the performance of an experimental capsid design round testing millions of capsids using traditional directed evolution methods."

The pioneering technology is "validated and already demonstrating value for partners," Kelsic reports. He continues, "We recently showcased the Dyno eCap™ 1 capsid, which achieved an 80-fold improvement in gene delivery efficiency to the eye, and the Dyno bCap™ 1 capsid, which demonstrated a 100-fold improvement in delivery to the brain. Both capsids are available for licensing to partners who have payloads ready to go."

Dyno's partnership-centric model aims to maximize the reach and overall patient impact of their technology. Kelsic summarizes, "By working collaboratively with industry leaders, we ensure that our innovations benefit the entire gene therapy ecosystem, rather than being confined to a select few therapeutic pipelines."

Modular platform

Following approval of their groundbreaking AAV-based gene therapy for hemophilia B (HEMGENIX®), **uniQure** continues to optimize their technologies and address challenges such as how to provide a more focused delivery, increase cellular transduction, and overcome pre-existing neutralizing antibodies.

The company is targeting liver and CNS disorders employing a array of tools. Their "Smart AAV" technology provides novel capsids for CNS delivery that utilize antibodies and peptides for specific targeting and for crossing the BBB. Cargo-specific technologies include miQURE, a single gene silencing platform, LinQURE that provides multiple gene-silencing microRNAs in a single AAV, and GoQURE that simultaneously knocks down a diseased gene and replaces it with a healthy version.

The company has several candidates in clinical trials. Their Huntington's disease-targeting AMT-130 (an AAV-encoding miRNA that non-selectively lowers huntingtin protein) is undergoing PhaseI/II trials. According to Walid Abi-Saab, MD, chief medical officer, the company has reached agreement with the FDA on core components of an Accelerated Approval pathway for AMT-130 and has initiated Biologics License Application (BLA) activities. A gene therapy candidate for treating temporal lobe epilepsy, AMT-260, is undergoing Phase I/IIa testing. AMT-260 provides local delivery of miRNA silencing technology against the GRIK2 gene that encodes epilepsy-triggering receptors. Another therapy, AMT-162, in PhaseI/IIa trials, targets amyotrophic lateral sclerosis (ALS) resulting from *SOD1* mutations. The miRNA-containing AAV vector serves to knock-down mutant *SOD1* as a one-time administration.

Prioritizing process optimization

"Every gene therapy company should optimize and develop every technology in their arsenal of viral vectors," advises Alexandria "Zandy" Forbes, PhD, president and CEO **MeiraGTx**. She continues, "We started out about nine years ago focusing on diseases which we could address using local delivery of small doses of optimized vectors to achieve a clinical impact, rather than focusing only on inherited genetic diseases."

Since manufacturing AAV's can be challenging, Forbes says they decided early on to tackle each facet of the process. She reports, "We started one of the first GMP facilities in the U.K. and wanted it to be a premier manufacturing company that is both flexible and scalable. We created a single GMP-ready platform process based on greater than 20 vectors with datasets from hundreds to thousands of conditions. This allows us to provide the highest yield in the industry and bring down the cost of goods."

Another strategy the company used to enhance efficiency was to develop and validate their own internal quality control (QC) assays. Forbes notes, "We found during the clinical development of our early programs that using outside vendors for QC is very rate-limiting, causing delays of weeks to months. Therefore, we built our own QC facility which now has a commercial license, as well as aligning with the regulatory agencies globally on a path to commercial manufacturing approval. Overall, this strategy provides a robust manufacturing platform for clinical material and shaves years off the clinical development timeline for these products. We currently have four late-stage clinical programs with potential BLA filings expected in 2025, 2026, and 2027."

According to Forbes, one of the most exciting recent developments is the company's Riboswitch technology that allows the precise control of gene expression using an oral medication. She concludes, "Thus, taking a simple pill could allow us to precisely control the amount of any gene product produced in the body, be it antibody or peptide. This technology allows the delivery of naturally occurring fast-acting agonists such as those involved in the control of metabolism, which opens an entirely new approach to the selection of therapeutic biologic targets compared to the industry-wide history of focusing on inhibitors." GEN

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MeiraGTx can customize vector elements like promoters, capsids, and riboswitch gene regulation, in order to design a product candidate specific to the disease being targeted.

Julianna LeMieux

AGBT
Celebrates Its Silver Anniversary

By Julianna LeMieux, PhD

Eric Green describes the past 25 years of the premier genomics meeting known for its mix of sequencing, sun, and sand

The Advances in Genome Biology and Technology (AGBT) meeting is celebrating its 25th anniversary this February. Its reputation is twofold: first, the five days in Florida are considered *THE* place to go to stay on top of advances in new genomics technologies. Second, the meeting is famous for its research talks, networking (including a very active social scene that lasts into the early morning), and an amazing setting on the beach in Florida. (If you include this year's meeting, 19 of the meetings have been on Marco Island, four have been in Orlando, two have been in Hollywood, FL, and one was virtual.)

Many of us have been fortunate enough to be able to attend AGBT at one point or another. But Eric Green, MD, PhD, NHGRI director since 2009, has attended every single AGBT meeting to date. And he has been co-chair since 2002. As we approach the 25th anniversary, we couldn't think of a better person to share thoughts on the significance of the meeting, how it has changed over time, and what to expect this year.

This interview has been edited for length and clarity.

LeMieux:

I know it is a long story, with a lot of nuanced history of what was happening in the field of genomics in the late nineties. But can you tell us a brief history of AGBT's origin story?

Green:

If we go back in time, to the year 2000, we were at the height of the final stages of the Human Genome Project (HGP). It was also the height of the tension and drama between Celera Genomics and the public HGP. At that time, the most popular annual gathering in the genomics field, for many years, was the Cold Spring Harbor Genome Mapping and Sequencing Meeting (now known as the Biology of Genomes Meeting.)

Cold Spring Harbor meetings are wonderful and incredible. But they're limited in size, largely because of the nature of Grace Auditorium. And they are not a good venue for commercial integration with meetings. As the HGP started to march along, technology was a very important part of that. It became very clear that the infusion of the technology side of the science required the involvement of a lot of private companies and a mixing of the academic scientists, the genome centers, and the companies.

In fact, another meeting that had been started in 1994, called Automation and Mapping and Sequencing (AMS), was starting to involve robotics and other technologies that were important to be discussing in genomics.

And then there was drama around the formation of a genomics meeting at Hilton Head (Genome Sequencing and Analysis Conference, GSAC). The general perception was that Craig Venter, PhD, and Celera Genomics had a significant influence on the Hilton Head meeting. Many perceived it as Craig and his friends getting together to the exclusion of a fair way of portraying the rest of the science going on—especially in the HGP.

This was during the last years of the Genome Project when there was a lot of tension and drama between the public effort of the HGP and GSAC.

There was a lot of frustration about this at the time, including from companies who were not happy about how Hilton Head was going. That led to companies stepping in to create a not-for-profit meeting, which was quickly branded AGBT. I even think that there was a subtitle to it at that time, "Back to the Science," because there was a feeling of making sure we just got back to the science and away from the drama. It became enfranchised under the Genome Partnership, and the first meeting was in 2000. That year was a critical juncture because it was right

It isn't an AGBT meeting if Eric Green, MD, PhD, is not at the podium. As part of the organizing committee since almost the first meeting, he is committed to maintaining a balance between the technology and the science. This year, Green told GEN that he will be giving a talk on a somewhat unconventional topic at the meeting: a retrospective of 25 years of AGBT.

before the draft sequence came out and the truce between Celera Genomics and the HGP.

This moment in time had just the right mix of things that were needed for the meeting. There was a thirst, there was a need, and there was also the importance of having a neutral, scientist-driven agenda. A program committee was formed, which I quickly joined. Also, the venue on Marco Island was big and allowed companies to come in. It was an expensive venue, but companies were willing to donate the money and have sponsorship because they got quality time with the scientists. In addition, the AMS meeting was brought in from the beginning and co-branded with AGBT. Over time, the AMS branding went away. And all of a sudden, there was a mixture of academic scientists and the private sector, including a lot of companies. Soon, AGBT became *THE* meeting to go to learn about the latest in technology around genomics.

The meeting became an incubator in many ways. And to this day, 25 years later, it's still an incubator. There is just as much going on outside the meeting rooms and the poster halls as there is inside. There have been, I am sure, *thousands* of collaborations that have been formed. Because this was the place everybody came to get this done. And it was needed in a way that hadn't been needed in genomics as much before.

LeMieux:

What for you has been the biggest moment so far, if you had to pick one?

Green:

I'm not sure I can say that there has been one biggest moment. What has been fairly reliable—and I'm not sure it would be every year out of the 25—is that AGBT was the place people went, including science writers {chuckling}, to find out what is the coolest and the latest and the neatest. A lot of the companies would synchronize the release of a brand-new instrument, or a new generation of an instrument, or a new technology, with the meeting. You knew you were going to learn about something that you didn't know about before, that was going to be part of the future. It was a preview of the future!

AGBT attendees can expect much more than research talks and instrument demos. The expression "work hard, play hard" is alive and well at the meeting. Social opportunities include parties in the companies' suites and entertainment events (for example, a B-52s concert on the beach). Eric Green

There was an expectation of shock and awe. And, as always, some of it ultimately proved to be hype. But some of it was an accurate preview of the future. It was the place to geek out on technology. And the rigor of the discussion was unprecedented.

Obviously the setting is nice, but it's always been a very good mix of networking time, poster time, talks, parallel sessions, etc. People say that it's an incredibly exhausting meeting because you can just go nonstop.

LeMieux:

How has the meeting changed over the past 25 years?

Green:

There are a lot of ways of answering that. I'm not sure everybody remembers this, but it hasn't been puppies and kittens and sunshine throughout. Early on, for the first four or five years, as the HGP came to an end, there was so much excitement and also a lot of investment in that space. At first, the meeting was incredibly oversubscribed. But then there was a lull—which followed the curve of a lull in new technologies—just before the next-gen platforms really took off. It was not entirely clear that enough money could be raised from sponsorship to be able to keep the meeting going.

In the late 2000s, there were a lot of nitty gritty discussions about whether the meeting was sustainable. And then it just took off. About 12 years ago, the meeting started to be incredibly successful; it got to be too big. There is a massive waiting list. But there were some nail-biting years.

Also, as the years went on and genomics disseminated broadly, we always wanted to keep the focus on the technology. But of course, we wanted to showcase the science and the applications. There was just so much going on.

No matter what we would do, we would get criticized for not having enough of this or not having enough of that. And that is why AGBT, as an organization, has now spun out two other meetings: the agriculture meeting and the precision health meeting. This gave the main meeting the ability to breathe a little, keep its emphasis on technology, and showcase all areas. But now, the AGBT general meeting doesn't feel like it has to overly showcase medicine and health, nor does it have to overly showcase agriculture. Each of those spin-off meetings are now grand experiments.

LeMieux:

What is something that has happened at the meeting that most people don't know about?

Green:

Some of the bigwigs from the big companies will show up at the meeting and get really nice suites but they won't ever show their face at the meeting. They'll have all sorts of private things going on, including nice social gatherings, but also intense meetings. There is a lot that goes on quietly up in the nice suites, including high-level deals. There is a lot of behind-the-scenes, company-to-company brokering, and academic-to-company collaborations that go on.

It is the place where everyone gathers. And a lot goes on behind the scenes that people are completely unaware of.

LeMieux:

What do you think we can expect this year?

Green:

Marco Island has gotten so expensive; we just can't go there very often. So, I think first of all, people will just be happy because Marco Island is such an ideal physical venue for a variety of reasons. From the natural beauty to the way the hotel is laid out.

There will certainly be a celebratory and retrospective kind of flavor of some of the speakers we've invited. It's a quarter century of this meeting, from its somewhat humble roots. I mean, the meeting started because of a bit of a rebellion within the field! Some could have imagined it wouldn't have lasted long. So, it's pretty impressive that this has a lot of legs and the Genome Partnership (the non-profit organizer) is a financially healthy organization. So, I think it's a success story.

There are a lot of professional meetings where companies are sponsors. And sometimes there is a lot of tension between that arrangement. But this is one where there has been a very good relationship between the academic scientists that run the program, the folks that worry about how the not-for-profit runs, and the companies that come in and sponsor and reliably appreciate the value of the meeting. So, it's turned out to be a very healthy partnership involving multiple stakeholders.

LeMieux:

Are you personally looking forward to anything this year?

Green:

We have some people that don't often come to this meeting. Busy luminaries that we were able to get, in part, because this is an important anniversary meeting. I think the quality of the speakers will speak for themselves. And, of course, I'm certainly glad to be back on Marco Island! GEN

A-List, Top 10 Takeover Targets

Continued from page 13

(H.C. Wainwright). Another attraction to potential buyers: Nuvalent's $1.2 billion cash runway into 2028. Nuvalent bolstered its M&A expertise in December by appointing to its board Grant Bogle, a nearly four-decade biotech industry veteran who was most recently CEO of Epizyme, acquired in 2022 by Ipsen.

SILENCE THERAPEUTICS (NASDAQ: SLN)

Initiating coverage of Silence's stock on September 2, Kelly Shi, PhD (Jefferies) highlighted the short interfering RNA (siRNA) drug developer's collaborations with several larger biopharmas, including AstraZeneca, Mallinckrodt, and Hansoh Pharmaceutical. Silence's "collaboration agreements highlight the potential of Silence's technology platform, which could attract acquisition interest as well," Shi wrote. Silence has applied its mRNAi GOLD™ platform to develop a pipeline led by Lp(a)-targeting cardiovascular candidate zerlasiran and TMPRSS6-targeting polycythemia vera (PV) candidate divesiran. Shi also noted that another siRNA drug developer, Dicerna Pharmaceuticals, was acquired by Novo Nordisk in 2021 for $3.3 billion, an 80% premium above its stock price: "We believe additional clinical data from Lp(a) and PV programs will validate Silence's platform to attract similar acquisition interest."

VIKING THERAPEUTICS (NASDAQ: VKTX)

The success of Novo Nordisk's and Eli Lilly's glucagon-like peptide receptor 1 (GLP-1) blockbuster obesity/diabetes drugs has fueled talk about other metabolic drug developers finding buyers—notably Viking, whose VK2735 targets both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. VK2735's Phase III-ready status and plans to file an investigational New Drug (IND) application for its first amylin agonist candidate for obesity in 2025 "offers a unique set of attractive characteristics in the lens of big pharma," much as "it is risky to base our investment thesis on an eventual takeout," Andy T. Hsieh (William Blair) wrote in November. A month later, takeover talk cooled after Merck & Co. gained exclusive rights to Hansoh's oral small molecule GLP-1 receptor agonist HS-10535 through an up-to-$2 billion licensing agreement. ■

Sergey Nivens / AdobeStock

AI-Enabled Gene Editing

Produces Fewer Off-Target Outcomes

By creating gene editors not found in nature, or optimizing existing editors, AI can improve the accuracy, effectiveness, and accessibility of gene editing

By Gail Dutton

Artificial intelligence (AI) is known for enabling deeper insights into drug development, identifying patterns and molecules that may otherwise go unnoticed. Now it is poised to make similar contributions to gene editing. A few companies are using AI to develop gene editing tools that are more specific and more efficacious.

CRISPR systems such as CRISPR-Cas9 revolutionized gene editing, but genomic rearrangements are becoming a real concern for in vivo therapies, and nonspecific editing has been a long-standing issue that affects subsequent generations of cells. Zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) also have challenges, thus underscoring the need for improvements.

Using rational design to find new gene editors, however, hasn't yielded anything notably different from CRISPR-Cas9, says Chelsea Trengrove, PhD, CEO of **Neoclease**, and a platform approach to their development tends to limit efficacy and specificity.

AI technology is emerging as a possible solution to enhance the precision of multiple types of gene editors. And the addition of generative AI lets scientists look beyond what exists in nature.

GenAI-created editors

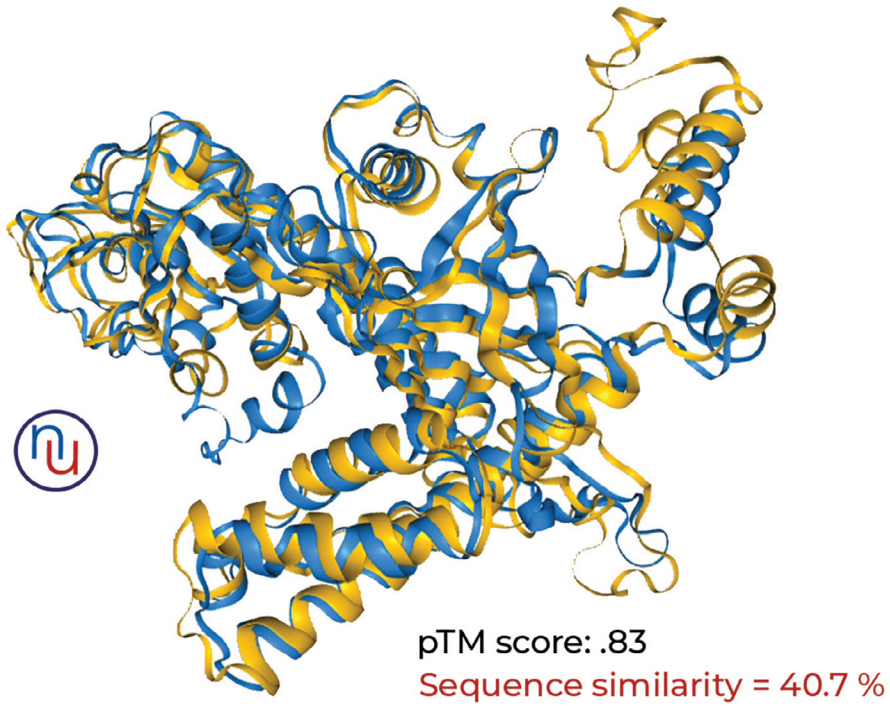
Neoclease's custom AI model develops gene-specific editors in silico. Eventually, top candidates may direct gene editing for humans in vivo, using the CRISPR nucleases, ZFNs, TALENs, and other gene editing nucleases.

"We're using a generative AI model," Trengrove says. "This is a large language model that's trained on millions of known proteins that cut DNA." The idea, she adds, isn't to create a workhorse enzyme that can do everything, but to optimize every editor for a specific gene of interest.

Trengrove explains that generative AI enables Neoclease to create a knowledge network of variables to understand how editors can be optimized, and to make a virtue of hallucination such that truly novel sequences can be generated. The goal, she stresses, is to generate additional editors that are "optimized and weighted in the direction we want to push them toward."

"It's almost like ChatGPT for proteins," Trengrove remarks. "While some associate hallucinations with errors, we leverage them… as an innovation tool to generate novel and effective protein designs."

Generating potential gene editors is just the first step. After tens of thousands of novel sequences have been generated that can be optimized toward specific features—certain binding energies, degrees of polarity, or domains, for example—the features are fed through a series of computational checkpoints. Those checkpoints identify which editors are best suited to



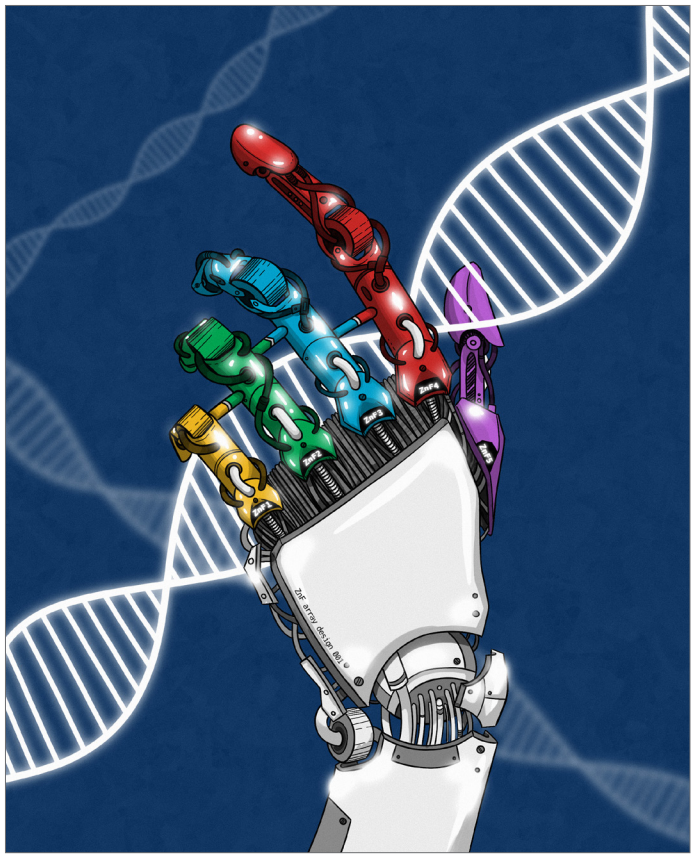
Neoclease's AI-generated Cas12, overlaid with a known Cas12, shows only 40.7 percent sequence similarity, enabling new intellectual property to be generated by engineering-in new functional domains. Neoclease

advance into in vitro validation based upon their features and functionality. Of the tens of thousands of nucleases the company has created in silico, it has, to date, advanced about 7,000.

Some of these editors are about half the size of the CRISPR-Cas9 system, Trengrove notes. They include the miniaturized nucleases developed by Jin Liu, PhD, chief technology officer and co-founder of Neoclease and tenured professor of pharmaceutical sciences in Texas. According to Trengrove, Liu "has shown that some of her miniaturized editors have comparable cleavage, energy, and efficacy in vitro, and have reduced off-target effects by sixfold."

These small editors can be packaged into adeno-associated vectors or similar vehicles to deliver them to tissues throughout the body. "We're actually looking at targeting the brain for Parkinson's disease," Trengrove says.

Currently, most of the testing has been done in silico, with only limited in vitro validation. Neoclease plans to take these editors into mouse and zebrafish models in mid-2025, and that the company anticipates Investigational New Drug–enabling studies will begin in 2026. Trengove adds that the company is also "working on a small deal with a pharma company to evaluate thousands of nucleases in vitro."



AI is making it possible to design gene editors that are more precise than ever before, based not just on nature, but on entirely new relationships. Wayne Danter, 123Genetix

AI CRISPR-like technology

In 2017, Wayne Danter, MD, CEO of **123Genetix**, pioneered the development of artificial human stem cells and organoids for medical research. This work led to the development of aiHumanoid simulations for virtual drug trials. "To produce a specific type of cell, I had to… alter the cell's genetic makeup," Danter says. "I did that by creating a symbolic representation of a gene and then adding to it or deleting it." The AI system he developed to do that, DeepNEU, simulates the CRISPR-Cas9 enzyme.

DeepNEU is built around an intelligent database. It functions like a text editor for genes to enable rapid prototyping and quality checks. It is fully developed and is already in use as a complement to CRISPR-Cas9 gene editing.

The advantage of AI-enabled gene editing is specificity. Off-target effects are avoided so that when the virtual results are compared to those of CRISPR-Cas9 experiments, any differences can be identified and, perhaps, minimized or eliminated.

Rather than train algorithms on data and outcomes, DeepNEU makes use of a healthcare-oriented Wise Learning process. As Danter indicated in a recent *bioRxiv* preprint (DOI: 10.1101/2022.06.18.496679), Wise Learning "combines fuzzy cognitive map simulations, with data from multiple experts and a generic decision-making system." He added that the Wise Learning process "should also explore available learning algorithms including deep learning methods when available." Essentially, Wise Learning uses an unsupervised (untrained) approach based on experiences. According to Danter, AI technology that incorporates Wise Learning can emulate human thought more closely.

DeepNEU applications yield "a very large matrix of relationships and weights," Danter says. "The basic information includes gene–gene and gene–protein relationships." 123Genetix's gene relationship network has approximately 65 million neurons.

Danter's passion is to find effective treatments for rare diseases, and he is proud that DeepNEU has been used for multiple studies of rare diseases. He indicates that access to DeepNEU has been free for rare disease organizations, and that he is currently "bringing on board a number of pharma partners interested in using the technology."

This fall, 123Genetix plans to release a version of the aiHumanoid that includes Serious Second Look. This addition enables the AI system to pause to consider whether it accurately answered the question before presenting results. If the results fall short, the AI reoptimizes on subsequent attempts.

Danter is also validating an AI system that is designed to use simulated sentience to make ethical decisions, specifically, decisions in line with the "first do no harm" principle of the Hippocratic Oath. Danter notes that the system is not self-aware.

Zinc finger improvements

Marcus Noyes, PhD, co-founder of newly formed **TBG Tx** and assistant professor of biochemistry and molecular pharmacology at New York University Langone Health, is developing an AI-enabled gene editor for ZFNs with his collaborator and co-founder, Philip Kim, PhD, professor of molecular genetics and professor of computer science at the University of Toronto. This gene editor, ZFDesign, is ready for commercial use.

Since publishing ZFDesign in 2023, Noyes and his team have increased the editor's precision. "The first version of the model was trained to understand how to design an array of ZFs, but it didn't really know which of the thousands of designs returned for each target would be the most specific," Noyes says. "We needed to teach the model which target sequences and which proteins will provide the most precise activity genome wide."

The latest iteration of ZFDesign incorporates several improvements. "We added more interface data to increase our understanding of compatibility," Noyes details. "We also screened the specificity of hundreds of ZFNs to train the model." As a result of this work, ZFDesign can identify the most precise options and thus reduce off-targeting. "We've also modified the model to express all the ZFNs in the array continuously, rather than skipping bases between pairs," Noyes adds. "This reduces the modularity in the design." He says he expects to publish the updated model in 2025.

The most notable aspect of ZFDesign, Noyes says, is the gene editor's ability to understand whether trends regarding modifications to a ZFN could be generalized to subsequent designs: "In the past, you could ask questions about how modifications of a designed ZFN array might change its on- or off-target activity, but it was never really clear if the trends were generalizable or were specific to just that protein, because you would need to design, validate, and test several arrays. By contrast, ZFDesign allows the simple design of any number of proteins for any number of target sequences, making the confirmation of generalizability a trivial process."

How well this model works depends on function and precision requirements. Regarding activation and repression—the areas for which he has the most data." Noyes says, "In general, about 80% of the designs will produce a change in target gene expression."

> **"We needed to teach the model which target sequences and which protein will provide the most precise activity."**
>
> —Marcus Noyes, PhD
> Co-founder, TBG Tx

About 30% of the designs have more than fivefold activation and more than 70% repression when assayed by transient transfection. Precision for highly functional designs appears high. However, Noyes cautions, "We have only tested off-target activity for around 20 constructs designed with the new model." About half have shown minimal to no off-target activity without optimization. And according to Noyes, even better results are obtained with optimization: "Typically, we can develop a candidate for any target gene with single-target resolution. … If we design 10, we expect about 8 will do something, 3 will be really good, and those 3 should have limited off-target activity."

ZFDesign is being used in the research community now. "One scientist tried three activators in cardiomyocytes, and two worked very well," Noyes reports. "Another group created a nearly complete set of precise probes that bind each of the human centromeres, allowing them to be labeled in live cells. Yet another group found four potent repressors in neurons from a screen of 12 candidates.

"We are finding that the amount of off-target activity is often tied to the mechanism. For example, activation, repression, labeling, and cutting all seem to have different optimal affinity regimes. Moving forward, we hope our model will be precise enough that users will only need to test a few designs, and that any optimization will be a straightforward affinity adjustment to match the mechanism."

Additional tools

Several other companies are creating tools that support the use of AI for gene editing. In October, **Shape Therapeutics** published two preprints. One detailed how it engineered guide RNA to fit into adeno-associated viruses. The other discussed how the Sharpes's system, which is based on the company's DeepREAD technology, allows therapeutic guide RNA to be expressed within cells.

Last spring, **Profluent** announced that its open source, AI-based gene editor, OpenCRISPR-1, successfully edited the human genome. The company reported the gene editor generates "millions of diverse CRISPR-like proteins that do not occur in nature."

AI tools for gene editing are helping scientists enact more precise edits, which lowers off-target effects for multiple gene editing technologies. Ultimately, this may help make gene editing more accessible. ■

AgBio Companies Embrace Gene Editing for Stronger Food Future

By Uduak Thomas

Cutting-edge editing techniques are accelerating efforts to create high-yield, resilient varieties of major agricultural products

Gene editing technologies have been used to improve agricultural products for more than two decades. One of the earliest editing technologies was Transfer DNA, T-DNA, which is extracted from *Agrobacterium tumefaciens*, a tumor-causing bacteria that infects plants and injects its DNA into their cells to reproduce.

Julien Curaba, PhD, chief scientific officer at **Eremid Genomic Services**, tells *GEN* that the technology, which is still used to generate transgenic plants, is not without challenges, primarily the inability to control where the new genes are inserted once they enter the cell. It helps explain why newer technologies like CRISPR have begun to gain ground both for plant and animal genomes.

Last year, British company **Genus** developed CRISPR-edited pigs that are resistant to porcine reproductive and respiratory syndrome, which has decimated pig populations. Companies like **Elo Life Sciences** and **Inari** are using gene editing techniques to sustainably improve food crops. While Eremid does not provide gene editing services directly, the company works with various agbio partners that do. It provides sequencing services to help its partners assess the outcomes of the editing efforts and ensure that their changes yield the desired phenotypes without damaging the integrity of the plant.

From Curaba's perspective, one of the primary benefits of editing technologies is the ability to get improved varieties of agricultural products to market much faster than with traditional breeding. The largest bottleneck for agricultural producers is the turnaround time for developing improved varieties with traditional breeding. Gene editing gives scientists "a fast way of creating new varieties of plants," he says.

CRISPR-based editing fulfills another important purpose. Academic scientists, in particular, are using the technology to better understand gene function and the effects of modifying genes on plant development and specific phenotypes, Curaba notes. That information can then feed into commercial efforts to improve global food systems.

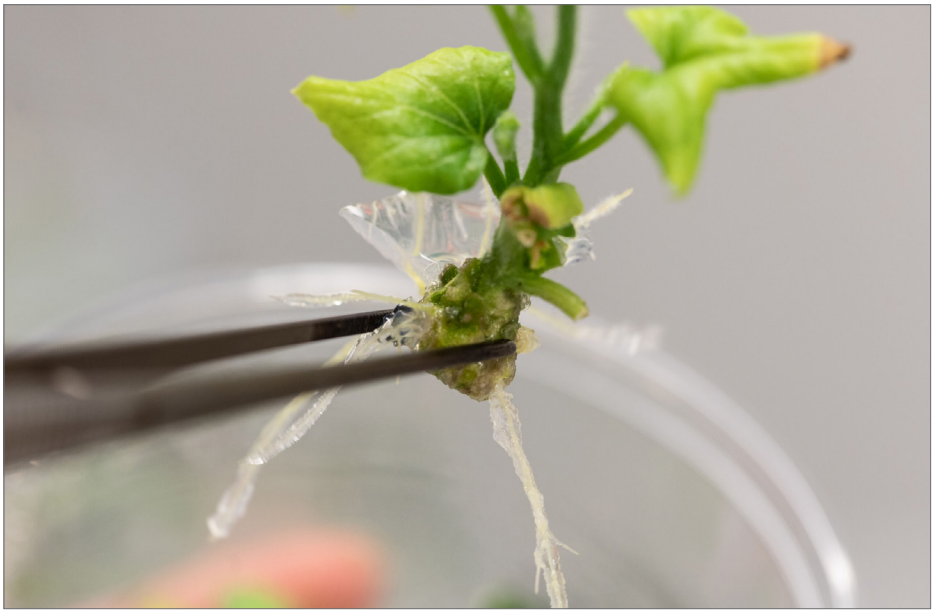
Smart gene editing with AI

When she first came across CRISPR-based editing, Catherine Feuillet, PhD, immediately saw its potential to transform plant breeding. As an expert in the space, she was familiar with the challenges of older editing technologies like TALENs.

"You had to produce a TALEN for every edit you wanted to do so it was not amenable to multiplexing," she ex-

Julien Curaba, PhD
Chief Scientific Officer
Eremid Genomic Services

Catherine Feuillet, PhD
Chief Scientific Officer, Inari



Left. The Cavendish banana is one of the most popular fruits around and is found in grocery stores and homes around the world. Its survival is threatened by Fusarium Tropical Race 4, an aggressive and destructive fungus that infects the circulatory system of plants. In collaboration with the multinational agricultural company Dole, Elo Life Sciences is using its proprietary gene editing platform to engineer resistant varieties that retain the signature taste.

Besides gene editing capabilities, Elo also has a molecular farming platform that uses transgenic plants like the watermelon seedling, pictured above, to produce ingredients that are difficult to grow or synthesize artificially. Its first product is a monk fruit-derived sweetener slated for launch in 2026.

plains to *GEN*. "You also need to have a specific knowledge and a partner company to help to produce your TALEN." In contrast, CRISPR editing is cheaper and easier to make and use.

Feuillet is now the chief scientific officer of Inari, a company using gene editing to develop improved seed varieties. Armed with predictive design tools powered by artificial intelligence (AI) and a toolbox of multiplex gene editing capabilities, Inari scientists are working on generating improved varieties of soybean, corn, and wheat for commercial use.

Current breeding practices have been crucial for boosting food production, but it takes years and multiple crosses to identify and cultivate plants with desirable characteristics. Modern sequencing instruments and other advanced technologies have markedly "changed our ability to produce data," Feuillet says. "We have the capacity to extract a lot of information from this data" and to "really change the way we do breeding."

Urgent efforts

There is an urgency to these efforts. With threats to agriculture systems from climate change and emerging infections on the rise, food producers can't wait 10–15 years to get improved crops, Feuillet says. "We need to do these edits, and we need to predict how this improves the characteristic that we are trying to improve. That timeline should be five years maximum."

Inari's proprietary platform pairs computational modeling with gene editing to find the best versions of its target crops. On the computational side, Inari has developed AI-based technology to identify gene sequences that are causal to plant performance and to identify ways to edit them to boost preferred traits. The company's multiplex editing platform lets it edit several genes simultaneously. That's important because "the big problems in agriculture cannot be addressed by single gene solutions." Feuillet says, "It's not enough to knock out the function of a gene or even 10 genes. Multiplexing is about editing several genes at the same time and doing different types of edits."

Inari chose to work with soybean, corn, and wheat because these have the biggest impact on global agricultural production. The company has made the most progress on developing improved soybean plants with corn as a close second, Feuillet says. The first wave of edits has been focused on increasing plant yield without requiring more input from producers. The next wave of edits will focus on efficient resource use. That means obtaining the same yield from plants using less water and less nitrogen.

Matt DiLeo, PhD
Head of R&D
Elo Life Sciences

Over the last three years, Inari has also invested resources in generating the data needed to train its AI models to filter and rank genes of interest. Plants have significantly larger genomes than humans and there are a lot less data available from plant genomes than there are from human genomes. Inari has hired several scientists who previously worked in drug discovery and Feuillet says they are often surprised at the dearth of data on plant genomes. "Compared to pharma we [don't] have the same amount of data at all because there is less investment and much less access to it."

Furthermore, plants have a lot of duplication in their genomes that is not seen in animal genomes. In soybean for instance, which is a palaeopolyploid species, 75 percent of its 50,000 genes have multiple copies.

Besides helping scientists select which genes and combinations of genes to edit, the company is also using its models "to build hypotheses on what the next set of data we need to have to continue to train and fine tune them" as well as what assays they could use to validate their hypotheses.

As with traditional breeding, edited plans also need to undergo field testing to ensure that they have the traits of interest.

"I see CRISPR as an acceleration of breeding and that's why it's so important," Feuillet says. "It's fantastic that this is applicable both for human therapeutics and for agriculture. It has also opened an opportunity for new players like us to come into an industry that has not seen a lot of new players. I believe that this is here for the long term and it's starting to change things."

Rescuing endangered foods crops

Matt DiLeo, PhD, head of R&D at Elo Life Sciences, describes the company's goal as reimagining the future of food. "The way that we're approaching this is to unlock nature's abilities to make consumers' favorite foods more delicious, healthy, and friendly," he explained.

Gene editing is one of the tools helping Elo accomplish its mission. Here the company is focused on editing fruits and vegetables with an eye towards preventing the extinction of different fruits and vegetables due to factors like climate change. "There's many cases where we know exactly what's holding the plant back, we know the gene that we have to

change but when you do this with traditional breeding it takes a very long time," DiLeo noted.

The power of gene editing is that it is possible to make small changes to the genome and get results quickly.

While some companies in the agbio space have embraced CRISPR-based editing, Elo opted to develop its own proprietary gene. It's a protein-based technology that uses a gene editing capability. "It's actually the oldest of all the editing technologies" older than even TALENs and zinc fingers, DiLeo said. "Because it's protein, you have to have a team that can build [them] it's not something you can just order online. But it's sensitive and you can tune it in a way that gives you additional advantages over CRISPR."

For example, they are able to make edits to address a broader set of traits than may be possible for other technology providers. Additionally, because Elo owns the intellectual property, the company can commercialize its nucleases with whatever terms make the most sense for its partners, something that would be challenging to navigate with CRISPR, especially considering the current patent disputes.

Both of these factors are important to partners like Dole, who tapped Elo to work on a project aimed at creating resistant banana cultivars. The goal was to develop varieties of banana that are resistant to a Tropical race 4 (TR4) deadly fungus that has wiped out banana farms around the world. Banana producers have been scrambling to find varieties capable of resisting the fungus. As it turns out, cultivars of Cavendish bananas have been able to resist the fungus. Cavendish bananas, which are widely sold in North America and Europe, are grown in a small number of Central and South American countries due to the invasive infection. However, producers know that it's only a matter of time before even those farms are under threat.

That's why "the big banana companies have partnered up with universities and tech companies to try and find some solution to this problem," says DiLeo, who is a plant pathologist by training. Working with Dole, Elo used its gene editing approach to make only the small changes to the Cavendish banana's genome to strengthen its resistance to the fungus. When they started the project in June 2020, Elo's scientists had not worked with bananas before. To understand just what they were up against, bananas have about 36,000 genes, and unlike humans, scientists have access to much less data on banana genes and their functions.

In the roughly four years since the project began, Elo has designed editing methods for the bananas and "done a deep analysis of all the molecular changes that we could make to bananas to make them resistant," DiLeo says.

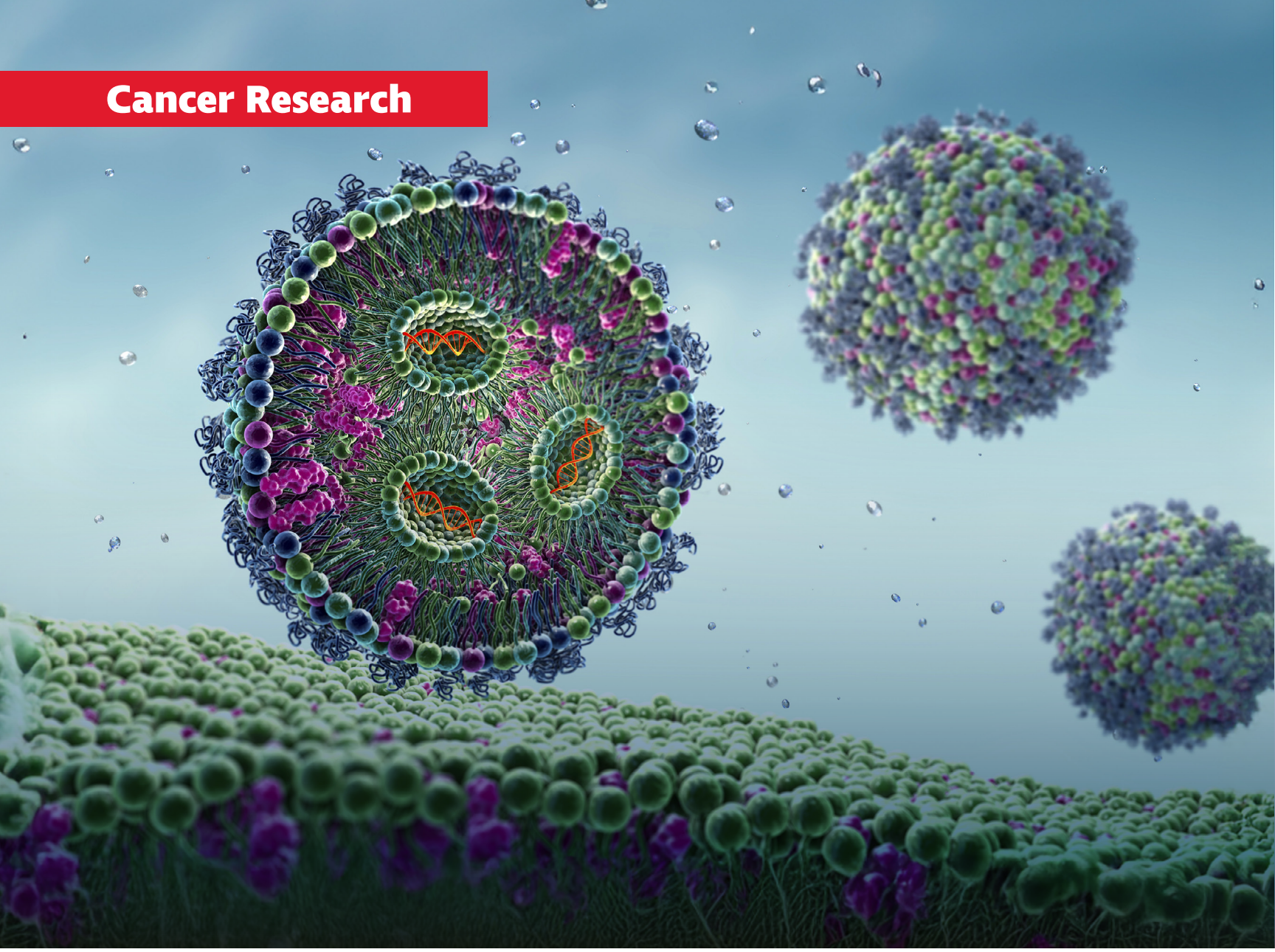
The company has grown its edited bananas in greenhouses and tested them with large inoculations of TR4 to ensure that the edits worked. Now the company is running field trials of the edited bananas in farms in Latin America that test their ability to resist infection.

Besides the banana project, Elo is also applying its gene editing capabilities to other partnerships including a project with a large NGO focused on improving crops like cassava for subsistence farming.

"We really want to have an impact on people's health and well-being sustainability," DiLeo said. "Having a clear path where you can do it in a way that is economically viable is really important and there's a lot of exciting technologies out there. The ones that are going to change the world are going to find a way to make people's lives better while saving their money." GEN

As a key part of the global agricultural system, soybeans are an important source of food for many populations and used in a wide range of commercial products. Millions of metric tons of the crop are produced each year in countries like Brazil and the United States. Agbio firm Inari is using AI-based predictive design and multiplex gene editing to help growers improve the yield of their soybean plants without increasing their input.

GoodLifeStudio / Getty Images



Cancer Immunotherapy

From Nineteenth-Century Beginnings to Modern Breakthroughs

By Tiffany Yesavage

Scientists have progressed from merely provoking an anti-cancer immune response to designing it

Immuno-oncology seeks to harness the body's immune system to identify and destroy cancer cells. Although often considered a modern medical breakthrough, its roots trace back to the late 19th century. During this time, William Bradley Coley, MD at the New York Hospital (now the Weill Cornell Medical Center) made the fascinating observation that several cancer patients had experienced spontaneous remission after contracting streptococcal infections. Coley believed the immune response drove the remissions, and he undertook the injection of bacteria into tumors as a potential treatment for bone cancer. Over a century after this early foray into immuno-oncology, the field is rapidly advancing with checkpoint inhibitor drugs, CAR T-cell therapies, and innovative cancer vaccines. *GEN* spoke with four leading companies to highlight how the latest breakthroughs are shaping the present and future of this longstanding field.

Employing pairs of cytokines

Deka Biosciences is developing new therapeutic modalities called Diakines™ that consist of paired cytokines, natural proteins that can stimulate or suppress the immune system. John B. Mumm, PhD, Deka's president and CEO, explains that cytokines are natural proteins that variously affect the immune system.

"There are stimulatory cytokines that activate the immune system and inhibitory cytokines that shut down things like inflammation," Mumm says. "If you really want to push biology in a therapeutically relevant direction with cytokines, you need more than one."

Deka Biosciences' leading immuno-oncology platform combines interleukin 2 (IL-2) with interleukin 10 (IL-10). Mumm explains that the IL-2 stimulates the immune system to fight cancer, while the IL-10 minimizes toxicity. "IL-2 is like jet fuel. It massively activates the immune system, but it is super toxic. Meanwhile, IL-10 is one of nature's anti-inflammatories. The presence of IL-10 compresses that fuel into a useful direction, like the nozzle of a jet engine."

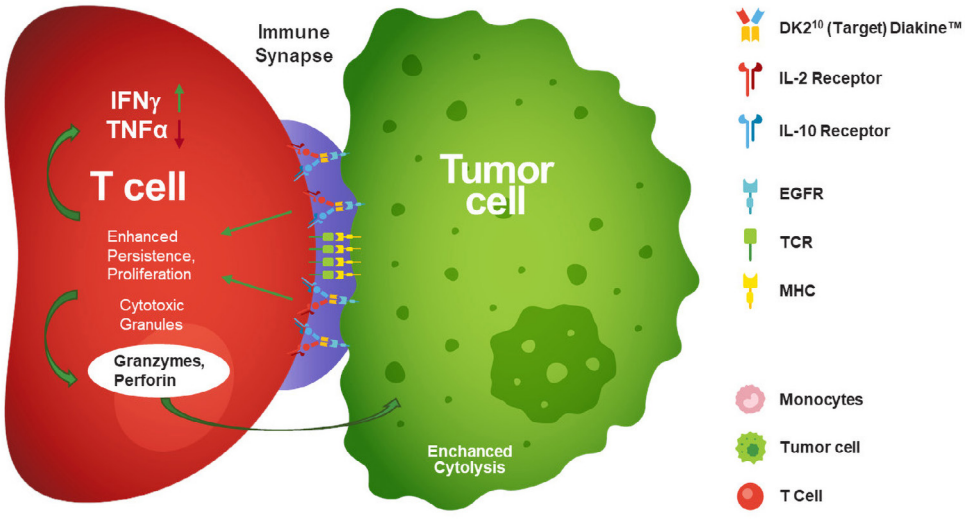
Mumm explains that these paired cytokines accumulate in tumors by binding to the EGF receptor on the surfaces of the tumor cells. "This keeps the T cells stuck to the tumor cells and further enhances the potency," he says.

In its Phase I study, the company has treated 35 patients with EGF receptor-positive tumors who have experienced relapses on checkpoint inhibitors. "Our studies indicate that our Diakines are super-safe," says Mumm. "Because of the IL-10, we block cytokine release syndrome and avoid common IL-2 side effects like vascular leaks."

Mumm also notes that around 50% of patients have exhibited radiologically stable

John B. Mumm, PhD
President and CEO
Deka Biosciences

Howard L. Kaufman, MD
President and CEO
Ankyra Therapeutics



Deka Biosciences' DK210 (EGFR) Diakine™ accumulates in the immune synapse after it binds the EGF receptor on the tumor cell surface and the cytokine receptors on the T cell. This localization enables enhanced cytolysis of tumor cells and promotes T-cell activation, proliferation, and survival within the tumor microenvironment.

Left. Hopewell delivers mRNA via lipid nanoparticles that enter the cell through endocytosis. The nanoparticle is then engulfed by the cell membrane, releasing therapeutic mRNA into the cytoplasm.
KATERYNA KON/ Science Photo Library/ Getty Images

Steve Harr, MD
President and CEO
Sana Biotechnology

Kate Zhang, PhD
Chief Scientific Officer
Hopewell Therapeutics

disease at the first scan. Furthermore, he says that he expects to see partial responses once patients are on treatment longer.

Diakines are available as a convenient off-the-shelf therapy that can be dosed at home. Furthermore, the platform has a personalized component. "Our tagline mission is that we can build a Diakine for every patient," says Mumm. "We are building assay systems and understanding the genetics behind who is likely to respond to a given cytokine pair."

Finally, Mumm is optimistic about combining Diakines with other treatments. He notes that IL-2 is often administered along with CAR T-cell therapy and cancer vaccines. "Now that we have solved the problem of IL-2 toxicity, Diakines can be combined with these therapies to reduce toxicity and dramatically enhance function," he says.

Anchoring drugs to the tumor site

Howard L. Kaufman, MD, president and chief executive officer of **Ankyra Therapeutics**, explains that ankyra is the Greek word for anchor. "Our company is all about anchoring. We are trying to anchor or retain drugs in the tumor microenvironment."

Kaufman explains that Ankyra has developed aluminum hydroxide as a scaffold to which toxic cytokines like interleukin 12 can be attached. "Aluminum hydroxide is a really interesting compound," Kaufman says. "It is an inert metal that tends to stay where you put it. We directly inject it into the tumor, and our modeling predicts that it may be retained for up to 12 weeks."

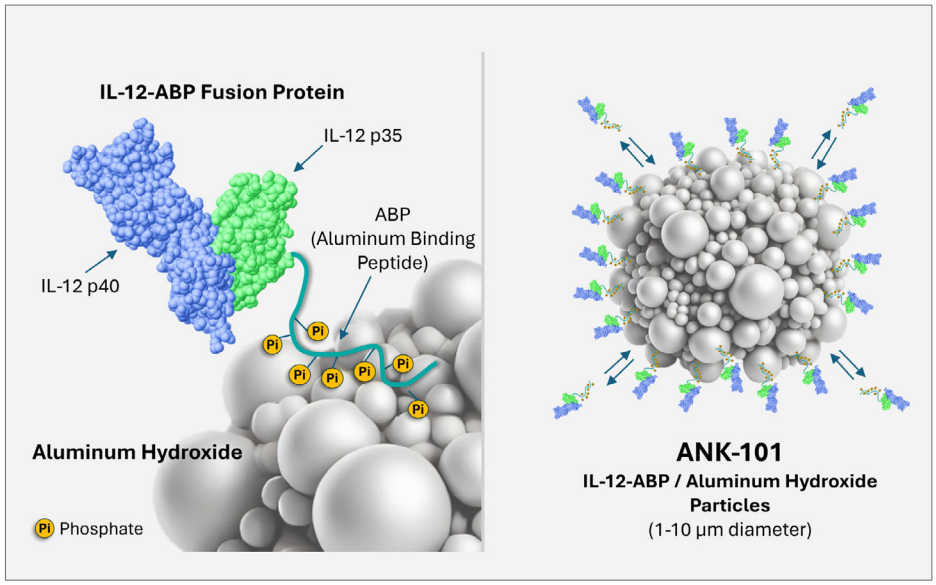
Kaufman compares Ankyra's technology to antibody-drug conjugates, which use antibodies to bind to specific tumor-site antigens to deliver toxic drug payloads. However, he notes that cancer cells often down-regulate these antigens over time, diminishing the effects of treatment. "The advantage of our drug is that it will sit there much longer because it is anchored to the aluminum hydroxide," he says.

Kaufman highlights the company's Phase I study in dogs with melanoma. "We treated 18 dogs with a canine version of our drug," he says. "There were no major safety signals, and some of these dogs are still alive two years after treatment without evidence of disease."

Ankyra has also begun a Phase I study in people with accessible lesions like skin cancer. "We have tested the drug at six different doses, and, to date, we see no dose-limiting toxicities in any of the patients."

The Phase I study is also showing signs of biological activity. "Many patients with one dose of our drug experience a ten-fold increase in T cells coming to the tumor site," according to Kaufman. "In gene expression profiles, we also see significant upregulation of several pro-inflammatory genes involved in activating the immune system."

In the future, Ankyra hopes to add monoclonal antibodies to its scaffolds. It has also started a Phase I study to inject its treatment directly into solid tumors in the lungs, liver, and other visceral locations.



Ankyra's aluminum hydroxide particles, which concentrate in the tumor microenvironment, use aluminum-binding peptides to in turn bind interleukin 12 to enhance immune response to the tumor.

Making CAR T cells more accessible

Steve Harr, MD, president and chief executive officer of **Sana Biotechnology**, is optimistic about CAR T-cell therapy, noting that "In many settings, it produces durable and complete responses that may be curative in one-third to one-half the blood cancer patients who receive them."

However, Harr also notes that most people who would benefit from CAR T-cell therapy—including those in the United States—will die without receiving it. "Most patients cannot access those drugs globally because they take time to manufacture, manufacturing capacity is limited, they are expensive, and hospital capacity is limited," he says.

Although multiple CAR T-cell therapies have been approved, Harr notes that all of them are autologous, meaning that the patient's own cells are genetically reprogrammed in a time-consuming and expensive process. In contrast, Sana is taking a different approach—referred to as allogeneic CAR T-cell therapy—in which donor T cells are reprogrammed in a manufacturing process that creates enough medicine to treat hundreds of patients.

"Unlike autologous CAR T-cell therapy, our technology is scalable and cheaper to make. The technology offers the potential for patients to have off-the-shelf therapy to treat their cancer immediately when it is needed," says Harr, who also stresses that the company's key challenge has been to overcome allogeneic recognition and rejection. "If somebody put my cells into you, your immune system will recognize them as foreign and kill them," Harr notes. He explains that Sana's hypoimmmune technology resolves this problem by genetically reprogramming the cells so that a recipient's body will not recognize them as foreign.

But how do we know that allogeneic CAR T-cell therapy is safe? "We have to approach biology with a lot of humility," stresses Harr. "It is incumbent on us to take our time through dose escalation to ensure we do the right thing for patients."

Nevertheless, Harr emphasizes that data from the company's dose escalation study in leukemia and lymphoma showed "a good safety profile and early evidence that the patient's immune system does not recognize these allogeneic cells." Furthermore, two out of four patients experienced complete responses, meaning they had no detectable cancer. "I think we have reasons to be encouraged," concludes Harr.

> **"We have to approach biology with a lot of humility."**
>
> —Steve Harr, MD
> President and CEO, Sana Biotechnology

Lipid nanoparticles deliver mRNA to fight cancer

Lipid nanoparticles—called LNPs—are tiny, spherical lipid particles used to deliver various cargoes, such as mRNA, for vaccines or genomic medicines. Kate Zhang, PhD, chief scientific officer of **Hopewell Therapeutics**, notes that LNPs provided the mode of delivery for the **Pfizer-BioNTech** and **Moderna** COVID-19 vaccines. "However, even though LNP technology has demonstrated its overall safety through the broad use of COVID vaccines," Zhang says, "we still need to demonstrate its safety for other therapeutic applications."

Zhang further explains how Hopewell is using tissue-targeting LNPs encapsulating mRNA-encoded therapeutic proteins to treat various diseases. "We can optimize the lipid structure and formulation of these LNPs to target specific organs with specific cargo types," she notes.

In the realm of immuno-oncology, the company is currently developing LNPs to deliver mRNA-encoding bispecific T-cell engagers (BiTEs) to treat both hematologic malignancies and solid tumors. Zhang explains that BiTEs are single-chain proteins with two different antigen-binding sites that can recruit cytotoxic T cells to cancer cells, destroying the tumor cell.

Hopewell's strategy has many advantages over conventional recombinant BiTEs, which are typically administered intravenously and often result in serious adverse events like cytokine release syndrome and neurotoxicity. In contrast, Hopewell's LNP-based approach allows for the direct delivery of the therapeutic agent to the organs of interest, minimizing side effects from whole-body exposure.

Hopewell's lead development program encodes a specific type of BiTE (a CD19-CD3 T-cell engager) to treat B-cell malignancies. "This LNP targets the liver, lymph nodes, and bone marrow so that B cells can be targeted," she explains.

Zhang highlights that the company's multiple BiTE assets have achieved preclinical proof of concept. Meanwhile, its lead BiTE asset has demonstrated favorable properties in nonhuman primates. "Our goal is to initiate IND-enabling studies and hopefully bring the drug candidate to clinical development soon," she says.

The future of immuno-oncology

What does the future of immuno-oncology hold? Will it be dominated by cytokine-based therapies, gene therapies, CAR T-cell treatments, or some other emerging approach? "I think all of the above," says Harr. "Cancer is a complicated adversary. We would be crazy to ignore any of these tools in our toolbox." ■

Bioprocessing

Microbioreactors

Small and Smart, Power More with Less

By Mary Ann Labant

Shrinking in size but growing in might, microbioreactors are transforming biologics manufacturing

As new targeted biologic modalities ramp up for commercialization, manufacturing methods must keep pace. If new efficacious therapeutics cannot be produced at reasonable costs they remain in restricted use or are shelved for economic reasons in lieu of other options.

For example, autologous CAR T-cell therapies have demonstrated remarkable success, but manufacturing costs remain extremely high due to the large footprint and substantial clean room costs. Miniaturizing manufacturing and bringing it to the point-of-care setting could, potentially, benefit more patients at a lower cost to the healthcare system.

CAR T cells are just one example. Many processes that produce recombinant proteins use either mammalian or microbial cells and could reap cost savings if development and optimization at small scale better reflected that at scale-up or scale-out volumes. A promising resource, microbioreactors are just beginning to show their might as they become more sophisticated with integrated sensors and automation instrumentation.

A microbioreactor is a way of "doing more with less" succinctly stated Wei-Xiang Sin, PhD, research scientist at **SMART CAMP**. As these tiny growth machines become even more sophisticated with machine learning and AI algorithms they can only positively impact the future of biologics production.

Point-of-care manufacturing

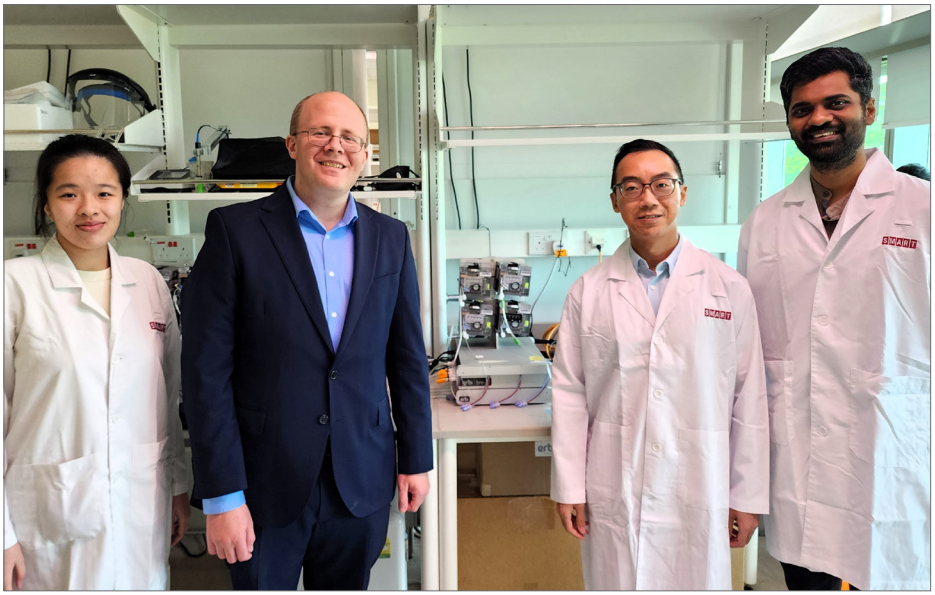
Over a decade ago, Kevin Lee, PhD, and Harry Lee, PhD, and their colleagues in the MIT laboratory of Professor Rajeev Ram, PhD, developed the 2 mL "Breez" microbioreactor platform technology, which was subsequently spun out as Erbi Biosystems. In 2020 **Millipore-Sigma**, the U.S. and Canada Life Science business of Merck KGaA, acquired Erbi Biosystems and expanded their Mobius bioreactor portfolio.

"We have been working with the Breez since its development," said Sin. Various designs of the microfluidic chip, ranging from 100 µL to 1 and 2 mL working volumes, have been used for microbial and mammalian cell culture applications.

"We thought that automated, closed-system microfluidic bioreactors might also be a novel production approach for the personalized nature of autologous cell therapies," said Sin. Autologous cell therapy manufacturing has lengthy processes, with large equipment footprints, low production throughputs, the need for centralized cleanroom facilities, and a high cost of goods. "In particular, the perfusion-capable, modular Breez can support extremely high viable cell densities in a small volume and footprint," continued Sin. The parallelized format, with four "pods" per system, allows up to four simultaneous runs per system to raise production throughputs and enable efficient scale out.

The 2 mL design was used to test human CAR T-cell production. Various timelines of activation and transduction as well as two different perfusion schemes, were evaluated to determine optimal conditions.[1] Minimal system modifications were made in this proof-of-concept study. Engineering improvements should help move the Breez closer to GMP compatibility on the way to potentially enabling decentralized, point-of-care manufacturing.

The small working volume could reduce the amount of GMP-grade viral vectors and reagents and thus the costs associated with CAR T-cell manufacturing. Importantly, the Breez has the smallest



SMART CAMP researchers have been working with the microfluidic-based Breez since its development. A new application for the 2 mL volume device is a novel production approach for the personalized nature of autologous cell therapies. *Left to right*: SMART researchers Denise Teo, research engineer, Michael Birnbaum, PhD, associate professor of biological engineering, MIT, Wei-Xiang Sin, PhD, research scientist, and Narendra Suhas Jagannathan, PhD, senior postdoctoral associate, pose with the microbioreactor system at the Singapore center.

Left. The automated, high-throughput BioLector XT Microbioreactor from Beckman Coulter Life Sciences, is a microbial screening platform that allows users to design and execute sophisticated experiments. Online measurements increase data reliability and robustness for a wide variety of applications.

footprint (0.044 m2 per dose) compared to existing manufacturing methods, noted Sin. This attribute substantially decreases cleanroom fixed costs.

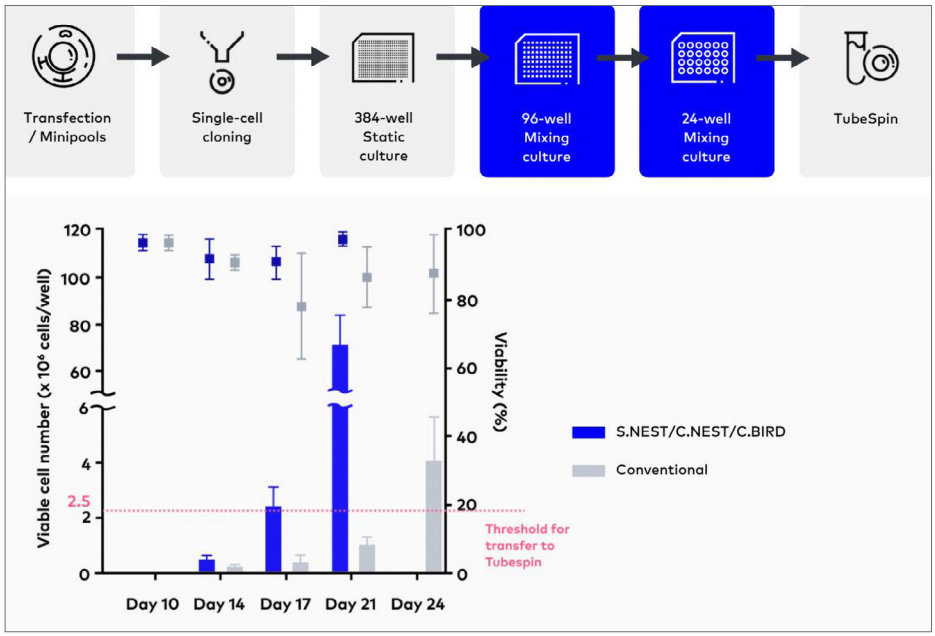
"The ability to make clinical-scale CAR T-cell doses in an extremely small form factor essentially means doing more with less—more production runs in parallel with less reagents, space, and manpower," said Sin.

Better prediction and optimization

Many biological drugs are produced using mammalian cells. The process begins with cell line development (CLD) to determine which cell lines will produce the highest levels of recombinant proteins while maintaining stability during large-scale manufacturing.

According to Cheng-Han (Charles) Tsai, PhD, CEO at **Cytena BPS**, in the CLD workflow cell lines undergo incremental scaling of culture from static formats to shaker flask expansion and, eventually, to bioreactors. However, static formats lacking agitation technology face significant limitations. The size of multiwell plates and the cell numbers often restrict the ability to effectively agitate the culture, which in turn limits oxygen transfer and the overall culture environment. Microbioreactors offer small-scale, controlled culture environments that allow for better oxygen transfer and optimized cell growth conditions that can replicate the conditions needed for larger-scale bioreactors.

Currently focused on CLD applications, Cytena BPS's microbioreactors provide precise control over culture conditions, enabling faster and more efficient cell line screening and optimization, according to Tsai, who adds that "additional applications include spheroid culture, stem cell/iPSC culture, long-term proliferation, metabolism and dynamic cellular behavior monitoring."



Currently focused on cell line development applications, Cytena BPS's microbioreactors are backed by field-tested data. The systems' single-cell up-scaling workflows drive faster and more efficient cell line screening and optimization by providing precise control over culture conditions.

The company's C.NEST® microplate agitation culture system is designed for high-throughput screening in 96- and 24-well plate formats. Customizable mixing intensities allow adjustment of the agitation levels according to the specific cell type and concentration improving oxygen transfer and environmental conditions. In addition, the S.NEST™ system incorporates sensors that provide real-time measurement of dissolved oxygen (DO) and pH to provide more accurate assessments of cell growth conditions to accelerate cell line development, improve process optimization, and efficiently evaluate cell culture health.

"Customers report that introducing mixing early has accelerated their scale-up processes, increased cell concentrations at each stage, and reduced the number of passaging steps," said Tsai. Notably, the Cytena BPS workflow not only reduced a client's CLD process time but also significantly increased cell viability in later-stage selection. "Facilitating tests at smaller scales while allowing for precise control of production parameters can permit better prediction and optimization of results before scaling up to larger production volumes," he added.

Expediting screening

When contemplating the addition of microbioreactors to a workflow, Cristina Martija-Harris, product manager, **Beckman Coulter Life Sciences**, recommends evaluating usability, scalability, reproducibility, and reliability, as well as compatibility with existing data management and analysis tools. Suppliers can assist with a cost-benefit analysis to determine the economic viability of adoption.

The automated high-throughput BioLector XT Microbioreactor expedites the screening process for different microbial strains/clones, explained Martija-Harris. Applications are diverse including food and beverage, microbiome studies, agriculture, and many aspects of academic, pharmaceutical, and biotech R&D.

The microbial screening platform allows users to design and execute sophisticated experiments that align with biological signals, enhancing scalability and reproducibility, Martija-Harris continued. Online measurements increase data reliability and robustness. In combination with the Biomek i5 Liquid Handler workstation the system permits individually triggered actions such as sampling, dosing of inducers or feed solutions, and inoculation of culture wells in a microtiter plate. "These actions are executed in response to real-time signals from the microbioreactor, including biomass, pH value, DO concentration, and experiment time without interruption to the shaking of the microtiter plate," said Martija-Harris.

She pointed out that the BioLector XT Microbioreactor allows efficient clone selection along with problem solving during process development and optimization when there are many mutually influencing parameters.[2] The system utilizes a standard 48-well microtiter plate format that operates with online, pre-calibrated optical sensors for real-time measurement of cultivation parameters. Patented microfluidic technology facilitates concurrent pH control and feeding processes per cultivation well.

An optional Light Array Module (LAM) provides customizable light settings of 400-700 nm within the photosynthetic spectrum. Sixteen different LED-types can be controlled individually to deliver maximum irradiances and photon flux densities up to 3500 µmol/m2/s to support work with light-dependent organisms that require photosynthesis to grow, said Martija-Harris. "One of the standout features of the BioLector XT system is its strict anaerobic module, which is specifically designed to cultivate microorganisms that require an oxygen-free environment," she explained. GEN

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Measuring Intact (Full-length, Capped, Tailed) mRNA in a Single Assay: 5′CapQ

InDevR partners with Aldevron to describe how the VaxArray 5′Cap*Q* assay can be used to measure intact mRNA in a single assay to streamline bioprocess development

By Erica Dawson, PhD, and Rebecca Young, PhD

In the years after the 2020 COVID-19 pandemic, it is clear that mRNA as a modality for vaccines and therapeutics is here to stay based on the number of mRNA programs currently in clinical development. The speed at which safe, effective COVID-19 vaccines were developed and licensed required Herculean efforts—and, out of necessity, required a reliance on existing analytical methodologies quickly adapted to the task at hand for assessing these life-saving vaccines.

InDevR's early conversations with mRNA vaccine manufacturers made it apparent that bioprocess optimization of mRNA vaccine constructs was often slowed by analytical methods reliant on expensive, complex instrumentation. These methods are often performed at a centralized analytical lab or CDMO by a scientist with specialized training, and with sample analysis occurring only after a substantial time in a queue.

When more sophisticated methods are not accessible for reasons of cost or complexity, reliance on sub-optimal techniques such as semi-quantitative dot blot employing an anti-m7G antibody may also be utilized. Recently highlighted methods to assess analytics such as mRNA integrity, 5′ capping efficiency, and polyA tailing detailed in recent guidance documents[1] certainly have their place and can provide rich mRNA characterization needed at certain phases of a program's development. However, it seemed there was room in the toolbox for rapid, easy to use, at-line methods that can be utilized as screening tools to inform the bioprocess more immediately.

VaxArray: a foundation for vaccine analytics

InDevR has offered the VaxArray platform of microarray-based, multiplexed analytical solutions to the vaccine industry since 2014. The VaxArray platform consists of a benchtop fluorescence-based imaging system, 21 CFR part 11-compatible software, and a suite of off-the-shelf and custom reagent kits, as shown in *Figure 1*. Applications currently utilizing VaxArray analytics include bioprocess development and optimization, QC release testing, and clinical studies.

While historically focused on traditional protein-based vaccine analytics, InDevR, in response to market needs for mRNA analytical tools in recent years, has been expanding a suite of VaxArray microarray-based analytics offerings to include detection and characterization assays for mRNA and other nucleic acids that offer high ease of use and rapid times to result for high impact at the bioprocess bench and beyond.

Measuring intact mRNA: 5′Cap*Q* assay approach

As shown in the highlighted schematic at left in *Figure 1*, the 5′Cap*Q* assay utilizes an anti-5′ cap antibody printed in replicate spots on the microarray substrate to capture the 5′ cap of an mRNA construct of interest (confirmed reactivity to Cap 0 and Cap 1 structures, including caps added with popular commercial 5′ capping kits). The mRNA is subsequently labeled with a fluorescent polyT oligonucleotide that binds to the 3′ polyA tail. This detection scheme ensures that mRNA that is cap-less, tail-less, or fragmented will not be detected, enabling a measurement of only the fully intact mRNA in a single assay. The kit is

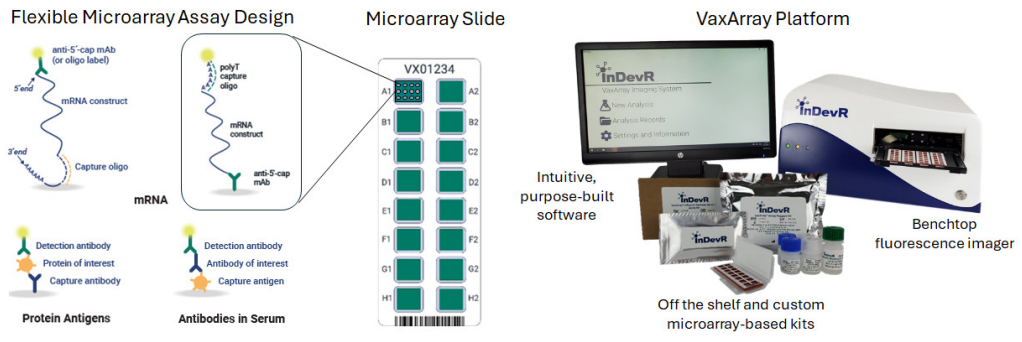

Figure 1. (*Left*) examples of flexible VaxArray microarray-based assay designs, with 5′Cap*Q* assay schematic highlighted, (*Center*) a schematic of a single VaxArray microarray slide with 16 replicate arrays, (*Right*) components of the VaxArray Platform.

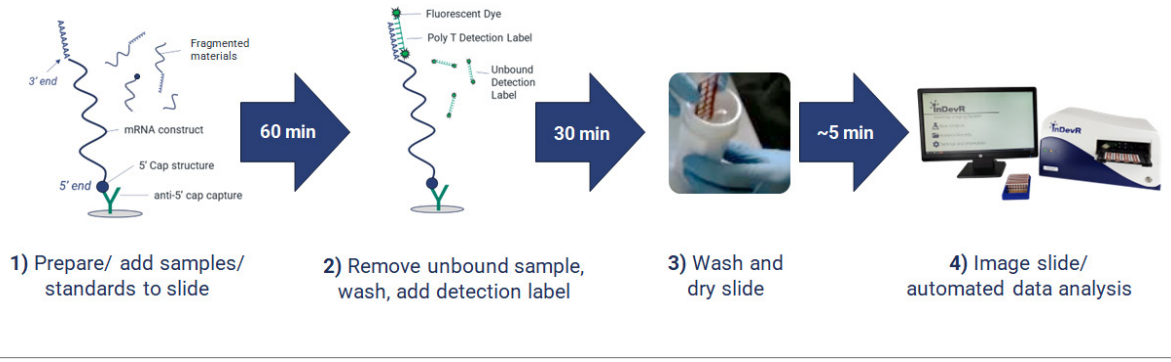

Figure 2. 5′Cap*Q* assay procedure, with a time to result of < 2 hours including sample preparation.

provided with all associated ancillary reagents needed for mRNA incubation and labeling steps. The 5′Cap***Q*** assay procedure is outlined in *Figure 2*.

A unique measurement of intact mRNA

Currently, manufacturers make up to three separate measurements for mRNA integrity, 5′ capping efficiency, and 3′ poly(A) tailing to estimate how much mRNA is intact from cap to tail. mRNA integrity is typically measured via an electrophoretic method, and 5′ capping efficiency and 3′ poly(A) tailing are increasingly measured via LC and LC-MS based methods and typically require an upfront enzymatic digestion or cleavage step prior to analysis, which eliminates the tie between the full-length mRNA sequence and the cap or tail.

In contrast, the 5′Cap***Q*** assay provides a single measurement of the total amount of intact mRNA in a sample that is both capped and tailed. This can be a relative measurement if comparing different samples of the same construct (say as a function of differing IVT conditions, enzymatic capping conditions, or purification steps), or when compared to a standard of known intactness.

Alternatively, a *quantitative* assessment of intact and capped mRNA can be determined if a user-provided, sequence matched standard is analyzed as a calibration curve alongside the unknown samples of interest. If the standard has been measured for integrity and 5′ capping efficiency via alternative methods, these values can be utilized to assign a known "capped, intact" value to the standard.

To generate the data in *Figure 3* and *Table 1*, we mixed intact (full-length, capped) and uncapped versions of the same mRNA construct (commercially available construct coding for GFP) in different ratios to create a series of samples that should differ by 5% intactness. When assessed using the 5′Cap***Q*** assay, the expected step function is observed as the amount of intact, capped mRNA decreases. The standard used for quantification was the intact, capped material (which had known integrity/capping efficiency). As shown in *Table 1*, the accuracy of the measurement was quite high, with all values producing intactness values close to expected.

To highlight the utility of the assay, Aldevron provided InDevR with four samples of the same underlying mRNA construct and same polyA tail length generated under different enzymatic 5′ capping conditions. Aldevron assessed the samples via semi-quantitative m7G dot blot assay for comparison, and intactness/integrity measurements were made via capillary electrophoresis. As shown in *Table 2*, all four samples had similar intactness, but differed in 5′ capping efficiencies by dot blot analysis.

A standard for quantification was also provided (same mRNA construct sequence and polyA tail length) with known integrity and high 5′ capping efficiency (> 90%). The 5′Cap***Q*** assay was conducted by analyzing a dilution series of the standard (assuming 90% capping efficiency and 73.7% integrity based on Aldevron's measurements) alongside the unknown samples.

The % of intact, capped mRNA of the unknown samples was then back calculated from the standard curve. Given that the 5′Cap***Q*** assay only measures mRNA that is intact and has both a cap and a tail, we would expect the 5′Cap***Q*** assay result to be an approximate convolution of the

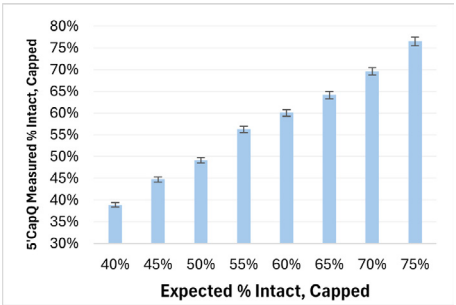

Table 1.

Expected Value	Measured % Intact, Capped (95% CI)	Difference from Expected
40%	38.9 (38.4 – 39.4)	-1.1%
45%	44.8 (44.1 – 45.3)	-0.2%
50%	49.2 (48.5 – 49.8)	-0.8%
55%	56.3 (55.5 – 57.0)	+1.3%
60%	60.1 (59.3 – 60.8)	+0.1%
65%	64.2 (63.3 – 65.0)	-0.8%
70%	69.6 (68.7 - 70.5)	-0.4%
75%	76.5 (75.5 - 77.5)	+1.5%

Figure 3 and Table 1. 5′Cap*Q* measured % intact, capped mRNA in samples prepared by mixing intact and uncapped, sequence-matched mRNAs and measuring against the intact material (% intact known). Error bars in figure at left are upper and lower 95% confidence intervals (95%CI), with accuracy of the measurement also shown in the table at right.

Table 2. 5′Cap***Q*** assay analysis of Aldevron materials along with associated % intact mRNA and capping metrics

Sample	% Intact mRNA (provided by Aldevron)	Relative 5' capping efficiency by m7G dot blot (provided by Aldevron)	% Intact, Capped mRNA (5' Cap*Q* Assay)
Sample 1	77.0%	High	78.0%
Sample 2	82.9%	Moderate	54.9%
Sample 4	84.1%	Moderate	40.8%
Sample 3	83.9%	Low	Unreactive
Standard	73.7%	90%	N/A

intactness and 5′ capping measurements (assuming similar tailing efficiencies). Given this, the four samples showed the expected 5′Cap***Q*** assay trend in that the sample with the highest capping showed the highest 5′Cap***Q*** result, and the two samples only moderately capped produced an intermediate 5′Cap***Q*** assay result. Sample 3 was expected to have low capping efficiency by dot blot and was below the detection limit of the 5′Cap***Q*** assay.

The VaxArray approach provides a high-throughput assessment of a variety of bioprocess conditions, simultaneously assessing capping efficiency and intactness. This allows for fast turnaround times and increased throughput for development of new bioprocess conditions and for assessment of RNA CQAs. Minimizing the time and complexity of these analyses is a great support to programs which often rely on quick results and require reliable data.

InDevR's 5′Cap***Q*** assay for the VaxArray Platform is a rapid, 2-hour solution for measuring intact mRNA molecules from cap to tail at the bioprocess bench and can be successfully executed with no specialized training other than basic laboratory and pipetting skills. 5′Cap***Q*** can offer relative quantification without a standard as a function of in vitro transcription (IVT) or enzymatic capping optimization to maximize yield of intact mRNA or can offer absolute quantification if assessed alongside a user-provided, matched standard of known intactness and capping efficiency. We hope the availability of new tools for mRNA analytics will help expand the toolbox to enable more rapid development and optimization of mRNA vaccines and therapeutics. GEN

Erica Dawson, PhD, is chief R&D officer at InDevR and Rebecca Young, PhD, is a senior scientist at Aldevron.

Reference

1. Analytical Procedures for mRNA Vaccine Quality (Draft Guidelines)—3rd Edition. USP-NF, (accessed 2025 Jan 13).

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- Foundational models to read and write the language of biology with **Ali Madani, PhD** (Profluent), **Brian Hie, PhD** (Arc Institute), **Alex Rives, PhD** (EvolutionaryScale), and **Elizabeth Wood, PhD** (JURA Bio)
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- AI in drug discovery's evolving business landscape with **Simon Barnett** (Dimension), **Sabrina Yang, PhD** (Empress Therapeutics/Flagship Pioneering) and **Colin Hill** (Aitia Bio)
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People In This Issue

Andy Orth

CITY THERAPEUTICS

Orth has been added as CEO and director. Orth brings more than 25 years of experience in biopharmaceutical research and development and commercialization. He most recently served as chief commercial officer of Krystal Biotech and earlier at Alnylam Pharmaceuticals.

Caroline Hensley

XILIO THERAPEUTICS

Hensley has been appointed as the new chief legal officer. She most recently served as SVP, assistant general counsel and chief compliance officer at Seres Therapeutics. Previously, she was a corporate associate at Latham & Watkins, where she represented public and private companies in biotechnology.

THEOLYTICS welcomed **David Apelian, MD, PhD**, as chief executive officer.

FAIRJOURNEY BIOLOGICS has established its new scientific advisory board with the appointments of **Janine Schuurman, PhD, Elaine Sullivan, PhD, Tariq Ghayur, PhD**, and **Victor Greiff, PhD**.

CRISPR THERAPEUTICS added **Briggs Morrison, MD**, to its board of directors.

ABZENA strengthened the board with the appointment of **Moncef Slaoui, PhD**.

PROQR added **Peter A. Beal, PhD**, as chief ADAR scientist.

BIOLIZARD welcomed **Arjan van Manen** as commercial director.

Gabe Longoria was added as chief commercial officer at **4BASEBIO**.

PRECISIONLIFE appointed **Bill Keating** as chief commercial officer of diagnostics and healthcare.

SILEXION THERAPEUTICS welcomed **Amnon Peled** as an independent director to its board of directors.

Drew Trivisonno joined the board of directors at **NOVADIP**.

CELLEVATE welcomed **Jennifer Valdes** as VP of sales and marketing.

Cayce Denton has joined as chief financial officer at **ACTIO BIOSCIENCES**.

OSE IMMUNOTHERAPIES strengthened their leadership team with the appointments of **Fiona Olivier** as chief corporate affairs and investor relations officer and **Aurore Morello** as head of research and director of R&D programs.

COMPANY INDEX

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Products To Watch

High-Throughput Genomic Sample Preparation

The Biomek Echo One System provides integrated acoustic liquid handling options for applications in genomic workflows, including high-throughput isothermal DNA assemblies and NGS library sample preparations. The system combines two Beckman Coulter Life Sciences core liquid handling instruments, the Echo 525 Acoustic Liquid Handler and the Biomek i7 Hybrid Workstation, which can be integrated with existing laboratory automation instrumentation. The company claims users can easily scale up walk-away time and throughput to adapt to changes in workflow demands and needs, creating a future-proof solution that can grow with laboratory needs and complexities.

Beckman Coulter Life Sciences
www.beckman.com

Super-Resolution Microscope

The Aplo Scope is a new single-molecule super-resolution microscope designed for molecular imaging. The microscope combines imaging, laser control, and what the company describes as intuitive software to deliver results from research on the foundations of life to drug discovery, biomarkers research, and disease studies. The microscope transitions live-cell to super-resolution imaging at 15nm resolution and contains 110 by 110 micrometers of field-of-view in both diffraction-limited and single-molecule localization microscopy.

Oxford Nanoimaging
www.oni.bio

High-Throughput Single Cell Kit

Parse Biosciences has announced an expansion of its Evercode™ WT Mega Kit functionality. The company says researchers can now analyze up to 384 samples and one million cells in a single run, unlocking new possibilities for high-throughput studies and notes that the new functionality is enhanced when paired with Evercode™ Low Input Fixation, which they say will benefit researchers working with limited cell numbers per sample.

Parse Biosciences
www.parsebiosciences.com

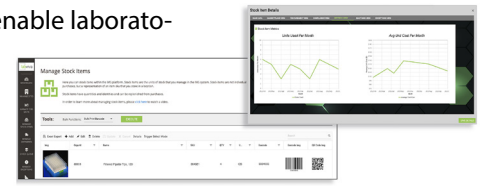
Single-Cell Analysis Platform

Sphere Fluidics has launched the Cyto-Mine® Chroma to accelerate and streamline workflows. Cyto-Mine Chroma builds on the original Cyto-Mine platform's ability to leverage picodroplet technology to encapsulate single cells, assess cellular function, and isolate target cells for downstream expansion or analysis. The company says the new platform will enable researchers to conduct multiplexing in a single droplet, improving the throughput and precision of clone selection, by analyzing single cells for viability, productivity, and target specificity in one step.

Sphere Fluidics
www.spherefluidics.com

AI Inventory Management System

Labviva has launched its automated inventory management system (IMS) to enable laboratory scientists, researchers, and procurement professionals to work in real time by streamlining inventory management of external suppliers and internal supplies of a shared organizational inventory or stock room. The company says lab managers can track shipments, access AI-driven operational recommendations across 15 million SKUs and 8,000 manufacturers, and increase efficiencies using AI-driven replenishment.



Labviva
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Acid Digestion Fume Hood

HEMCO has launched their new UniFlow HDPE Acid Digestion Fume Hood. According to the company, the fume hood has been engineered specifically for corrosive operations involving procedures for element analysis; UniFlow Acid Digestion Hoods feature a chemical-resistant hood construction with a welded one-piece HDPE interior fume chamber including hood walls, ceiling, worksurface, and rear drain trough. The exterior is also chemical resistant, being constructed of composite resin. Available in 48", 60", 72", and 96" models, this series of fume hoods can be supplied with or without a built-in wash-down system and rear drain trough.

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- A keynote presentation by **Sonia Vallabh**, PhD, co-leader of the Broad Institute's initiative to develop preventive drugs for prion disease
- An opening keynote with **David Altshuler,** MD, PhD, Executive VP and Chief Scientific Officer of Vertex Pharmaceuticals
- A keynote presentation with **John Crowley**, President and CEO of the Biotechnology Innovation Organization (BIO)
- Back by popular demand, the co-hosts of the popular Biotech Hangout podcast—**Daphne Zohar**, **Brad Loncar**, and **Chris Garabedian**—review the highs and lows of the biotech space
- A conversation with **Tim Harris**, PhD, author of the new book *In Pursuit of Unicorns: A Journey through 50 Years of Biotechnology*—a crackling memoir chronicling the history of biotech
- Building a path for CRISPR therapies with **Brad Ringeisen**, PhD (IGI) and **Sadik Kassim**, PhD (Danaher)
- Parallel breakout sessions hosted by Cytiva

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