Benchling

A Two-Pronged Approach to Automation for Gene Therapy Research

How Beam Therapeutics Developed a Modern Lab with Benchling

Introduction

The field of cell and gene therapy is exploding, thanks in large part to the Nobel Prize-winning gene-editing technology, the CRISPR-Cas9 system. Beam Therapeutics, a biotech company developing a new class of genetic medicines, uses similar technology, but with one key difference: unlike the so-called "molecular scissors" of CRISPR-Cas9, Beam is using a more precise, higher efficiency approach, one that scientists analogize as "molecular pencils and erasers." With this approach – termed "base editing" – Beam is able to edit a precise set of base pairs without introducing a double-stranded break in the DNA, leading to fewer unwanted errors due to stochastic DNA repair machinery. Beam's ultimate goal is to treat genetic diseases caused by point mutations.

The research necessary to meet that goal, however, is complex and demanding — especially once Beam scientists attempt the process at scale, evaluating hundreds or even thousands of biological samples each week. Yet they know that this kind of scale is mandatory in order to dramatically speed up the process of gene therapy discovery, which relies on trial and error and the continual modification of many different variables.

The Answer: Automation

Beam's work now thrives thanks to the successful integration of two forms of automation: robotic automation, which employs automated lab instruments for repetitive tasks, and data automation, which utilizes informatics software to capture, organize, and analyze the tremendous amount of data being generated each day. The combination of the two creates a fully automated data pipeline, allowing scientists to move quickly and focus on high-level design and analysis instead of rote tasks.

Beam uses Benchling, the industry's leading cloud-based informatics platform for life sciences R&D, to build this fully integrated, automated pipeline, and to solve the many challenges associated with high-throughput gene therapy discovery. As a result, the process of discovery is much faster and more reliable, leading to greater potential transformations in human health.

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THE CHALLENGES

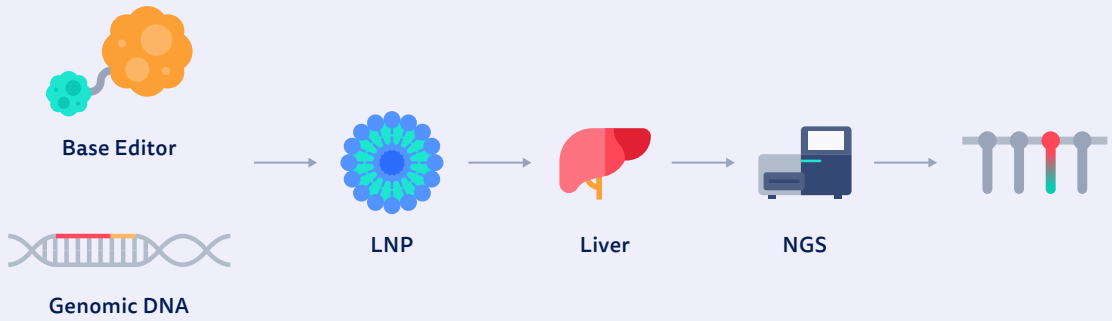
Research Complexity

Sample Volume and Turnaround Time

Cell and gene therapy is one of the fastest growing segments of the regenerative medicine market. Revenue, for instance, is expected to jump nearly a third by 2025, according to Research and Markets. Beam scientists have realized that the only way to stay competitive is to substantially increase sample volume while shortening the turnaround time for each experimental process.

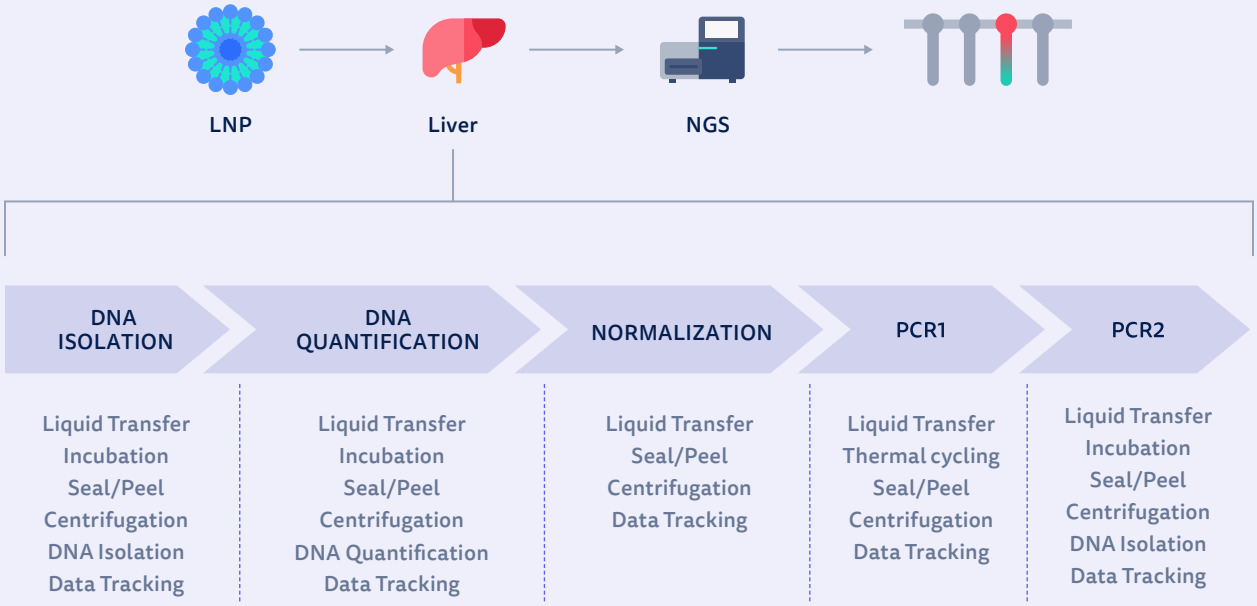
Yet achieving both speed and scale can be very complex. For example, one of the core research processes at Beam — like many other companies conducting gene therapy research — is their In Vivo Lipid Nanoparticles (LNP) workflow.

STANDARD IN VIVO LNP EXPERIMENTAL WORKFLOW



In broad strokes, scientists insert a base editor and guide RNA into a fat molecule, before injecting that molecule into a mouse. There, the insertion acts like a Trojan horse, allowing the editor to be taken in and processed by the liver. Scientists harvest the liver from the mouse and analyze the results. Did they achieve that specific G to A conversion in the DNA sequence they were aiming for, for example?

HIGHLY MANUAL PROCESS

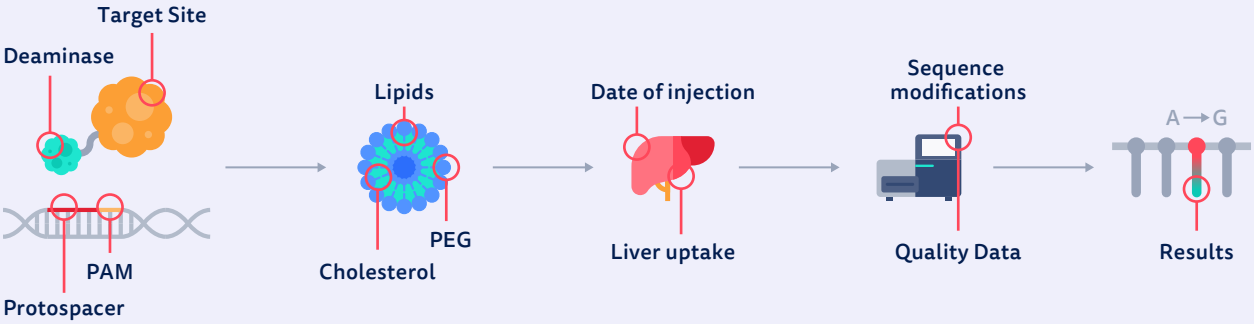


If they conducted this level of experimentation manually, one sample at a time, it could take decades to produce actionable results. Every single aspect of this workflow has multiple steps, and those steps have steps. Each time scientists process a harvested liver, for instance, their work includes DNA isolation, DNA quantification, normalization, and multiple rounds of PCR processing. Scaling these processes quickly becomes complicated.

Complex Data Tracking

The beauty of CRISPR-Cas9 and associated gene editing technologies is their modularity. The key to building base editing machinery with high efficiency and low error-rates is varying the different components of the molecules. Scientists can make molecular tweaks to any of the involved compounds, such as the lipid composition or the nuclease in the base editor. They can also target different areas of the genome. But modularity like this comes with a major data tracking problem.

EXAMPLES OF EXPERIMENTAL VARIABLES



As soon as any change is made to any component or aspect of experimental design, it needs to be recorded and tracked through all downstream experiments and results. Otherwise, experimental results will lose the critical linkages between cause and effects. Naturally, an enormous amount of data gets generated, and each piece of data has a relationship to other data.

Manual solutions to track this amount of interrelated data are time-consuming and resource-intensive at best. They are likely to lead to errors in data capture or to significantly slow down research efforts.

THE SOLUTIONS

Robotics Automation and Data Automation

The Fully Automated Lab

Beam knew that all of these complexities couldn't be addressed by throwing more people at the problem. Not only would it be prohibitively expensive, it simply wouldn't work; no matter the number of scientists involved, discovery would remain slow, painstaking, and error-prone. The answer was automation.

That means lab robotics, such as liquid handlers and other lab instruments, but it also means data automation. Today, scientists and leaders at Beam don't stop with an automated lab machine. They spend as much time, if not more, thinking about automated data management.

That's because high-throughput lab machines that capture hundreds or thousands of samples can collect some data, but they can't make it well-organized and accessible from anywhere, and they can't analyze it on their own. If data can't be understood in context — if it's not seen and evaluated by scientists — can it truly be useful?

Through implementing several pilots, Beam Therapeutics came to understand over time that the benefits of automation go far beyond hardware. Automation has to be a strong, integrated partnership between hardware and software. At Beam, robotics and data automation work hand in hand.

The Robotics Automation Journey

Like many companies, Beam struggled at first with the tedious workload of manual research processes. Automating some tasks through the purchase of a robotics liquid handler helped somewhat, but offered little return on investment. Scientists still had to wait for the machine to finish, then take the plates off themselves, seal them, and move them along to the next step. What's more, as soon as those plates were off the liquid handler, they'd lose the most crucial aspects of the machine: its data tracking integration and chain of custody capabilities.

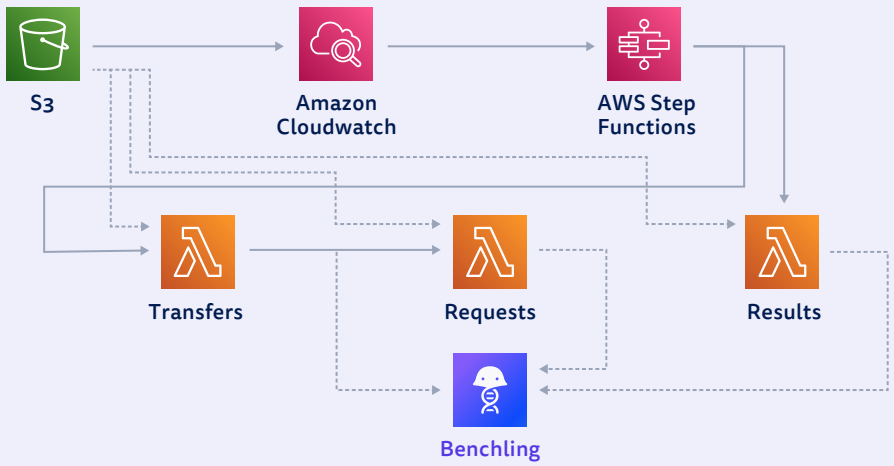
As a result, it was clear that moving only part way toward automation didn't solve a lot of the challenges associated with huge sample sizes and complex data tracking. So the team pushed for full automation of as many of their lab processes as possible, as soon as possible. Now, Beam scientists essentially load their samples onto their automated lab machines and walk away. They can use the time they save on the big-picture tasks, such as data analysis and experimental design. But this is not simply because they have more, better robotics; it's because they've connected and automated their data informatics systems, too.

The Data Automation Journey

As with lab automation, data management was once also conducted manually at Beam. The team relied on Excel spreadsheets for lab entries and other tasks, and stored company data on personal computers and thumb drives. Data lived in many places and data capture was not yet standardized.

Knowing they needed an informatics system that was far more integrated and accessible, they brought in Benchling, initially for a few of the cloud-based platform's key functionalities, including the Notebook, Registry, and Inventory application. They were able to record experiment details in a digital platform that any scientist could access from anywhere, and support the kind of complex, end-to-end sample lineage tracing the team needed. For each in vivo LNP experimental workflow, for example, they were able to track each batch of cholesterol, all of its metadata, where it was located in their inventory, and so on, enabling a readily accessible understanding of each experiment, as each piece of data was immediately connected to all of its associated data.

AUTOMATED TRANFER, REQUEST, AND RESULT UPLOAD



These features were a huge improvement, but Beam wanted to move things along even faster. They adopted all seven of Benchling's applications, including Workflows and Insights, and added a few additional best-in-class kinds of software, pushing automation to the next level: where all data capture, tracking, organization, and initial analysis is fully automated, using Benchling as a hub to integrate with other technologies and create a data pipeline. Benchling's Rest API and Beam's custom integration software help tie it all together.

Now, Beam scientists do all their work in Benchling, but seamless connections allow them to submit data directly to automated robotics platforms, with those platforms streaming the collected data directly back to Benchling. Inventory is automatically updated, and data points are automatically rendered within Benchling Insights, generating a real-time picture of everything that is happening. Beam scientists can do their experimental work without having to worry about all the data tracking and organization going on behind the scenes. They simply create experiments and get results.

THE RESULTS

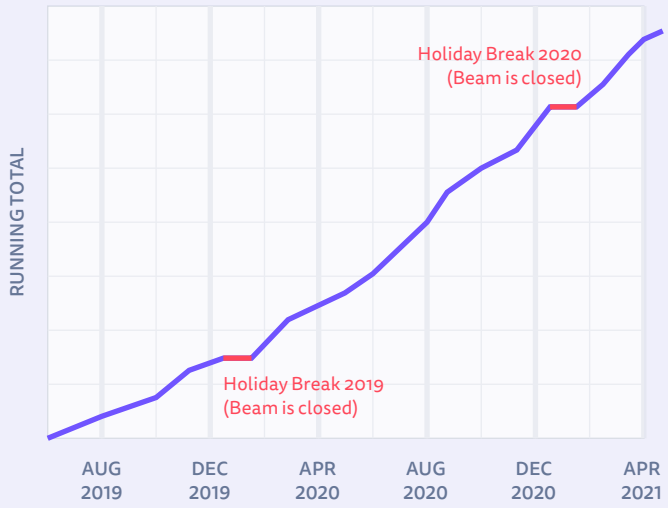
Faster Discovery

Beam considers speed to be the biggest impact from Benchling's automated data management system, and all of the other automated tools and processes they use alongside it. They have been able to create a thriving partnership between lab robotics and the data management side of experimentation.

But the success of all of these connected systems ultimately lies in their ability to accelerate the process of discovery. The faster Beam Therapeutics can discover safe, effective formulations for genetic medicines, the faster they can produce life-changing treatments for genetic diseases.

NGS SAMPLE PROCESSING DURING THE PANDEMIC

Automated sample processing and data tracking enabled Beam to continue research through the Covid pandemic



So far, so good. Beam has maintained an impressive research velocity — even during a global pandemic. In 2020, while many organizations struggled to maintain the pace of research, Beam scientists were able to continue their work at full speed. Social distancing protocols were easily built into the existing systems, as anyone could access the data they needed from anywhere,

thanks to Benchling's centralized, cloud-based platform. Plus, thanks to automated lab machines and other automated tasks, there weren't many scientists who needed to be physically present in the lab at a given time.

At the 2021 ASGCT Annual Meeting, Beam scientists reported that they were on track to submit their first Investigational New Drug (IND) application for one of their proprietary LNP formulations during the second half of 2021. They also plan to initiate IND-enabling studies for several other formulations and nominate a first development candidate from their liver portfolio. All of this is thanks to the high-throughput gene therapy research that automation makes possible.

About Benchling

Benchling's unified cloud-based informatics platform supports Beam Therapeutics and 500+ other companies to automate and accelerate their research. Through a suite of interconnected applications, Benchling supports everything from flexible early research to rigorous development, as well as full, comprehensive tracking of the experiment lifecycle. In short, the system provides a 360-degree view of both R&D processes and operations.

Beam Therapeutics takes advantage of all seven of Benchling's capabilities, which, like a fully automated lab, has synergistic benefits: because all of Benchling's applications are natively integrated, there is never any need to enter data more than once, switch between different applications, or hunt for data in various locations. All data and its context are instantly accessible via a single platform in the cloud.

Benchling delivers value to Beam and other clients in a number of other ways, too, including high-quality data capture, a complete view of sample lineage all the way back to the sequence level, and process intelligence, given the platform's ability to fully trace every experimental process, from experimental conditions, samples, and inputs to assay results and more. A comprehensive API and out-of-the-box connectors allow for straightforward integration with lab instruments and other unique systems. Benchling can augment any client's custom software and infrastructure, enabling functions such as data transfer, requests, and alerts between systems. All of this results in better productivity, collaboration, and operational efficiency, allowing scientists to focus on what they do best.

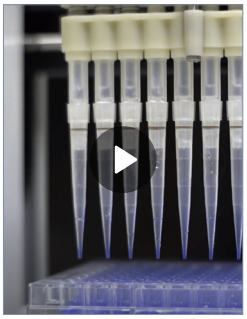
Overall, Benchling enables Beam to:

- **Track relationships:** Model lineage from samples to results
- **Create intuitive documentation:** A single source of truth for Beam scientists
- **Rely on rich API extensibility:** Connect external data and systems
- **Adapt and scale:** No-code flexibility meets growing team and process needs

Conclusion

There is little question that both gene editing technology and the technology that supports it are becoming more and more sophisticated. As R&D teams race for the next cure, maintaining accuracy at scale is exactly what they need to reach their goals. Over the next few years, as biotech and biopharma have an increasing impact on human life, leaders at Beam Therapeutics know one thing for sure: scientists will need to rely on automation to keep paceget there.

Resources



VIDEO

Benchling Powers Automation and NGS at Beam Therapeutics

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APPLICATION NOTE

Benchling for Gene Therapy and Gene Editing R&D

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