



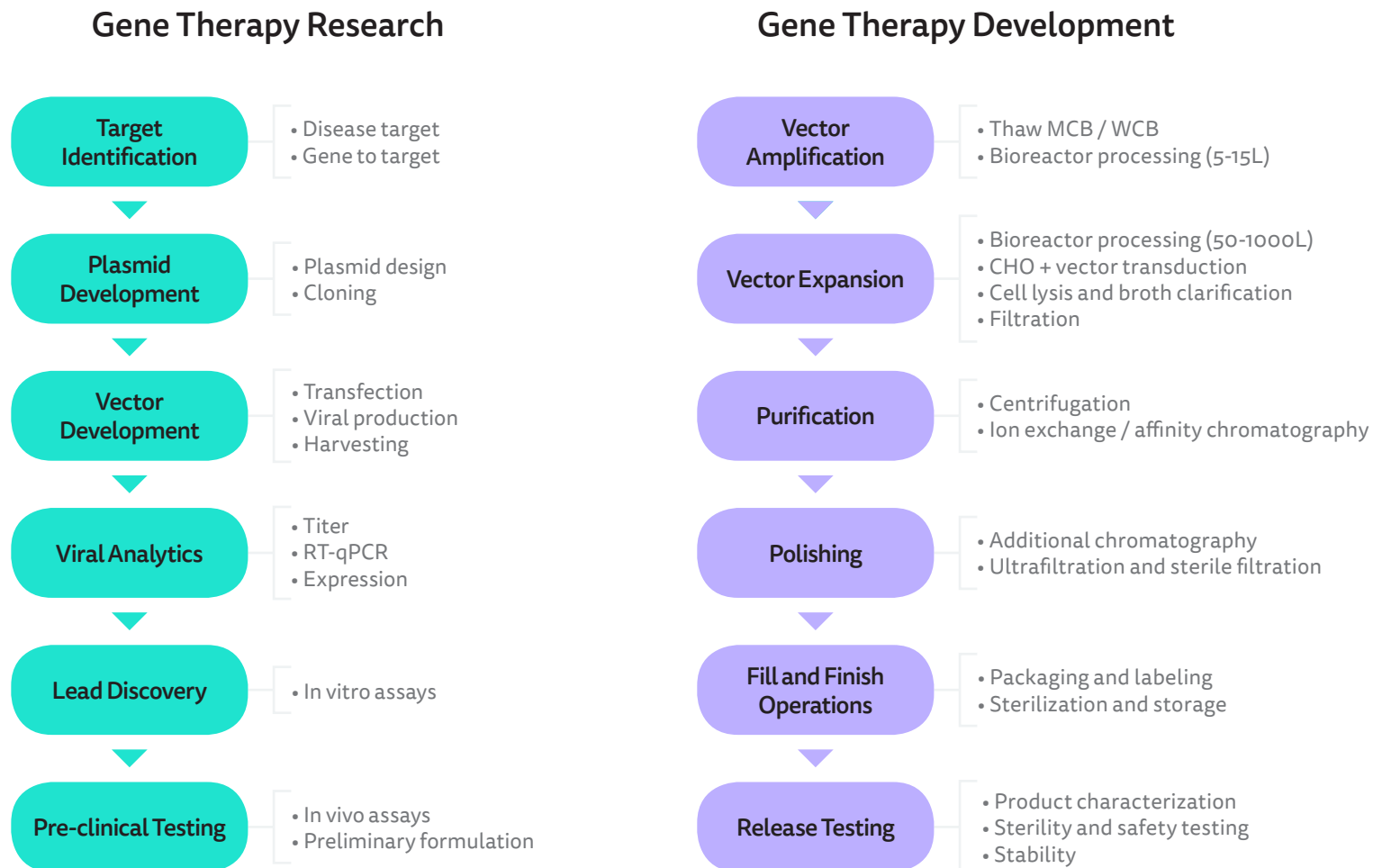
Benchling

for Gene Therapy and Gene Editing R&D



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— Gene therapy, nucleotide therapy, and gene editing technologies encompass a wide range of products, including plasmid DNA, viral vectors, bacterial vectors, oligonucleotides (short-strand DNA and RNA), siRNA, CRISPR, ZFNs, and TALENs. These products have been of significant research interest, especially with the recent approval of breakthrough therapies like Luxturna. However, several hurdles persist for companies seeking to develop these novel therapies.





Complexities in Gene Therapy Research

- Expanding therapeutic applications of gene therapy means research teams need to **manage a wide range of genetic material and delivery vectors** across their organizations
- Increasing diversity in scientific platforms and enabling technologies requires a system that can **support a variety of genetic engineering and vector design processes** as the organizational needs evolve
- Designing novel agents that are not only effective but also safe means that organizations need to monitor and **prevent genotoxicity from integrating vectors or off-target gene editing** throughout research

Complexities in Gene Therapy Development

- Developing a complex product such as gene therapy reproducibly requires extensive **DOE and scale-up studies** during process development
- Establishing a close partnership between product characterization and process development to **support complex product characterization needs** is essential to successful gene therapy development
- Improving efficiencies by **centralizing and automating upstream and downstream production processes** to manufacture the highest quality product possible with minimal impact on COGS

— This paper outlines the critical needs and complexities of gene therapy R&D, and how Benchling has helped address these challenges for leading gene therapy and gene editing companies.

Gene Therapy & Gene Editing Research

Gene therapy research involves innovative science and cutting-edge techniques with the goal of identifying novel gene therapy candidates that have promising efficacy and safety signals. Here are some of the key research complexities and needs that define gene therapy research.

1

Managing a wide range of genetic material and delivery vectors

Why is it a critical need?

Gene therapy R&D organizations are investigating a wide variety of genetic material and gene editing technologies for antigens, cytokines, receptors, deficiency, growth factors, tumor suppressors, and other targets. As a result, organizations need to manage a wide range of genetic material (e.g., DNA and RNA), proteins and enzymes (e.g. Cas9 and other nucleases), viral vectors (e.g., AAVs, adenoviruses, lentiviruses, and retroviruses), non-viral vectors (e.g., phospholipids and ribonucleoprotein complexes), and other related entities (e.g., plasmids and cell lines).

Why do current solutions fail?

Most current registry systems were not designed for managing gene therapies. Thus, the underlying data models cannot effectively model the complexity and variety of genetic material and vectors. As a result, these systems struggle to capture the diverse set of properties and attributes associated with each entity type and its batches. Another shortcoming of these systems is the inability to map the interrelationships between the entities used to create a gene therapy. On top of this, design tools are separate from entity registration systems. The disconnect between these two steps leads to poor compliance among users.

Gene Therapy & Gene Editing Research

How Benchling helps

Benchling provides a comprehensive suite of molecular biology tools with sequence-level intelligence to perform CRISPR experiments and design DNA sequences. A flexible registry system is integrated directly with these tools to manage the various entities and sub-entities used in gene therapy and gene editing. Benchling's unified Molecular Biology, Registry, and Inventory applications work together to help you design, register, and manage the physical locations of your entities.

Perform CRISPR guide design with built-in on-target and off-target scoring

- Use the CRISPR guide design tool to walk through gRNA design step-by-step
- Sort sequences by both on-target and off-target scores to select optimal guides

Create a library of genetic material that links to the physical inventory

- Build a library for all your samples such as DNA sequences, proteins, vectors, plasmids, and cell lines, and capture detailed properties in customizable schema fields
- Link physical locations of batches stored in different container types to the parent entities in the Registry

Design, create, and map relationships between components of a gene therapy

- Link genetic material to plasmids and viral vectors using fully configurable data models
- Create a vector diagram or gene map with relevant annotations such as gene insert, promoter, enhancer, and restriction sites

2

Supporting a variety of genetic engineering and vector design processes

Why is it a critical need?

The process of making a gene therapy varies widely, depending on the technology used to generate the genetic material and the methods used to engineer viral or non-viral vectors. For example, how an AAV capsid is engineered for optimal DNA packaging and ejection varies depending on the AAV serotype and target tissue. Similarly, gene editing workflows vary depending on the type of editing technology used (e.g., CRISPR, TALEN, or ZFN). Process management systems need to be able to map and manage these various research workflows effectively. Such systems also need to flexibly adapt to evolving research methods.

Why do current solutions fail?

Currently, workflows are managed through LIMS systems, which are typically custom-built and highly specialized. As a result, they are difficult to configure and are unable to evolve as genetic engineering workflows change. Gene therapy research needs a standardized solution that not only effectively manages the variety of workflows but also has inherent flexibility to evolve with scientific needs.

Gene Therapy & Gene Editing Research

How Benchling helps

Benchling's fully configurable Workflows application balances the need for process standardization with the need for flexibility to create new processes and modify existing methodologies.

Build custom workflows to manage a variety of gene editing processes

- Create a complete gene editing workflow, mapping each step from in silico design to sample output and storage
- Manage workflows custom-designed to capture the needs of different therapeutic programs and methodologies

Tailor your viral and non-viral vector production processes to fit the needs of your programs

- Create a Registry of custom viral and non-viral vectors to support unique research needs
- Keep processes up-to-date as needs change and maintain real-time visibility into the status of the process steps

Track editing efficiency, transfection efficiency, yield, and other metrics

- Link results from experiments and workflows to specific vectors and lead candidates in the Registry
- Create custom schema fields to track key metrics and properties, such as editing efficiency and transfection efficiency

3

Preventing genotoxicity from vector integration or off-target gene editing

Why is it a critical need?

Development of viral vectors requires the study of genotoxicity signals such as inflammation, disruptive insertion into normal genes, activation of proto-oncogenes, and insertional mutagenesis. Gene editing technologies have additional safety concerns, such as off-target editing. The genotoxicity of gene therapies needs to be studied comprehensively and linked to all available experimental results, helping to improve vector design and genetic engineering.

Why do current solutions fail?

Currently, disparate tools are used to manage this process. For example, molecular biology tools are used to design vectors; registries are used to store sequence information on the DNA, gRNAs, or viral vectors; while physical notebooks and other unstructured tools, such as spreadsheets and text documents, might be used to record protocols and results from genotoxicity studies. This fragmentation of software tools leads to the loss of critical insights and an incomplete understanding of genotoxicity.

Gene Therapy & Gene Editing Research

How Benchling helps

With Benchling, research organizations can study and track the genotoxicity profiles of lead candidates at the sequence level and centralize all related experimental results. This leads to higher quality, unified insights that can be used to generate vectors with superior safety profiles.

Track genotoxic sequences including specific enhancers and promoters

- Create and edit custom annotations to mark genotoxic sequences
- Auto-annotate sequences and plasmids in bulk to tag enhancers and promoters of interest

Study different vectors and their distinct integration profiles

- Create custom schema fields to capture information related to vector integration, such as integration site, integration preference, and integration profile
- Compare genotoxicity attributes across vectors in the Registry to identify optimal vectors

Design vectors with a lower risk of insertional mutagenesis

- Centralize results from disparate data sources, such as in silico, in vitro, and in vivo studies to optimize insertional mutagenesis profile
- Use alignments to identify regions of high risk in experimental sequences

Gene Therapy & Gene Editing Development

Gene therapy development involves developing reproducible and well-controlled processes that ensure a quality, safe, and efficacious final product. Here are some of the key development complexities and needs that define gene therapy development.

1

Facilitating DOE and scale-up studies

Why is it a critical need?

During scale-up studies, it is critical to identify the process steps with potential for significant variability or failure. Organizations need to develop an optimization plan that specifies the process steps, the preferred reagents, and the measurable outcomes (e.g., viable cell yield and target population number). Finally, multivariate DOE studies need to be performed to identify relationships between critical quality attributes and process parameters. These studies help define the process design space with boundary conditions for optimal process conditions. Development organizations will benefit from a single system that can comprehensively support all of the critical needs of DOE and scale-up studies.

Why do current solutions fail?

Unstructured software tools, such as spreadsheets, text files, and paper documentation, are highly prevalent. Gene therapy development teams need a central software ecosystem that can not only help with DOE and optimization planning, but can also manage scale-up studies and generate actionable insights.

Gene Therapy & Gene Editing Development

How Benchling helps

Benchling facilitates gene therapy scale-up studies by providing a single platform on which organizations can identify critical quality attributes, evaluate key process parameters, perform DOE studies, and map the entire production process.

Establish relationships between critical quality, material, and process attributes

- Identify and define key quality attributes and process parameters that need to be tracked across experiments or workflows
- Use structured data tables to map relationships between critical quality attributes and process parameters

Perform DOE scale-up and process development studies

- Design multivariate DOE experiments to study key process parameters (e.g., temperature, stirring speeds, and nutrient concentration)
- Define process design space that describes the most important process parameters and their ranges

Design and map the entire production process for a gene therapy product

- Map all the steps of the production process, including processing stages and in-process input and output
- Create and adjust workflows to accommodate variability in starting materials and gene therapy products

2

Supporting product characterization needs during process development

Why is it a critical need?

Characterization of gene therapy products and intermediates is integral to developing a scalable production process. This process requires close partnership between product characterization and process optimization teams. From a scientific perspective, organizations need to comprehensively study the source material, in-process samples (vectors, gene inserts, host cells, and other reagents), and final gene therapy products. These results need to be conveyed back to key stakeholders so that process optimization activities can continue in a timely manner. From an organizational perspective, there is a need to better coordinate various activities such as sample submission, analytical testing, communication of results, and scientific decision-making.

Why do current solutions fail?

The software tools used for managing gene therapy characterization are comprised of point solutions, custom software, and unstructured tools. Analytical results are fragmented across systems, and software is only used to manage specialized analytical workflows. Managing analytical testing requests is challenging because it requires complex testing panels and numerous hand-offs within analytical groups and across cross-functional teams. Gene therapy development needs a central platform that can facilitate the coordination of analytical requests and centralize all available characterization results.

Gene Therapy & Gene Editing Development

How Benchling helps

Benchling closely integrates analytical characterization with process development and scale-up efforts by facilitating communication and sample hand-offs, unifying online and off-line analytical tools, and centralizing all available analytical results.

Better coordinate sample chain of custody and communicate across analytical and process development teams

- Streamline every step of request management for comprehensive characterization of source materials or isolates, in-process samples, and final gene therapy products
- Create and assign specific tasks with detailed sample information for tests that need to be performed

Integrate process monitoring technologies for better in-process control

- Directly connect PAT tools to the Benchling platform to automate data capture
- Collect real-time data from PAT tools to inform your experimental design and study optimization

Centralize in-process, product release, and investigational assay results

- Centralize results from all analytical testing to gain a comprehensive understanding of the gene therapy product
- Link assay results to specific batches of in-process materials and final product for complete traceability

3

Centralizing and automating upstream and downstream processes for maximizing vector product yield

Why is it a critical need?

Production of vector products, such as AAVs, involves multiple upstream and downstream processes. The yield achieved through each of these steps is significantly reduced with each successive step, especially in downstream vector purification. Gene therapy R&D organizations need to carefully monitor and optimize process conditions such as pH, salt content, and media conditions throughout to maximize vector product yield. Additionally, the production process processes need to be automated to improve production efficiency and minimize manual errors.

Why do current solutions fail?

Current solutions depend on specialized software associated with specific pieces of equipment. Spreadsheets might be then used to analyze results and production output across batches. This fragmentation of software tools leads to a lack of complete process visibility and unnecessary manual steps in transferring and processing data. Gene therapy development needs a workflow management software that can integrate the upstream and downstream processes for vector production and automate as many of the steps as possible.

Gene Therapy & Gene Editing Development

How Benchling helps

Benchling integrates upstream and downstream steps onto a single platform that can be leveraged to track key process and output metrics, ultimately maximizing vector production. Additionally, Benchling integrates with process automation to increase throughput and improve efficiencies.



Seamlessly integrate upstream and downstream vector production operations with Benchling's built-in flexibility

- Collect results from both upstream and downstream production equipment to a single data warehouse
- Configure workflows to create and manage vector production end-to-end



Integrate with semi-automated and automated bioreactors for vector production

- Integrate with production automation to reduce the number of manual steps and boost production efficiency
- Set-up automatic data collection and data parsing to monitor process performance



Track process output such as transfection efficiency, viability, purity, potency, and yield

- Capture results and process outputs from multiple runs in a central location
- Build custom dashboards to track key process outputs and time series trends

Conclusions

Gene therapies are a promising new therapeutic modality that are expected to have a major impact on several serious disease conditions. The technologies and processes that support the discovery and development of novel gene therapies are evolving rapidly and are likely to transform in the next several years, ultimately helping to bring these breakthrough therapies to patients.

Benchling provides a modern, fully configurable, and user-friendly platform that adapts to the rapidly evolving needs of gene therapy and gene editing R&D. This enables biopharmaceutical organizations to accelerate gene therapy R&D and bring more breakthrough therapies to market faster.

Here are some companies that use Benchling for gene therapy and gene editing R&D:



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