Benchling

for Cell Therapy R&D

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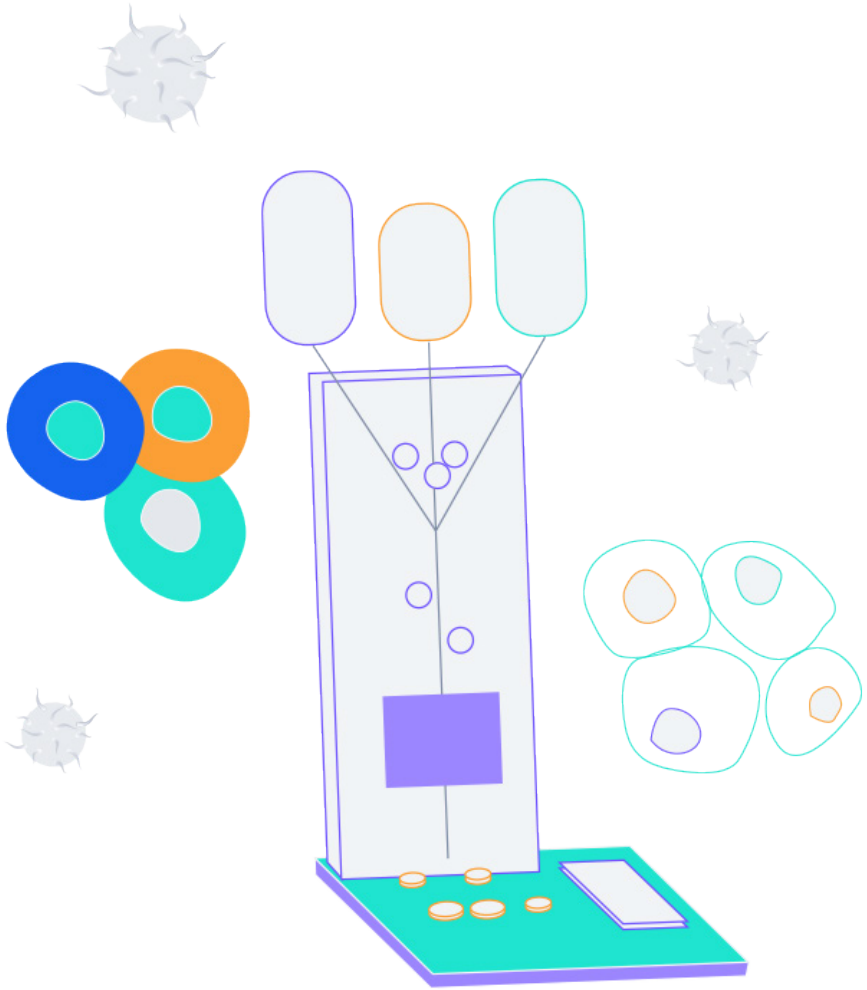
Cell therapies such as stem cells, CAR T cells, and TCR have been of significant interest in research over the past few decades. The recent FDA approvals of CAR T therapies have led to renewed interest in the field. As companies rush to bring more novel cell therapies to the market, they face several R&D complexities.

CAR T / TCR Research

- **Candidate Discovery**
  - NGS discovery of scFv / TCR chains
  - Target identification
  - Library screening
  - In vivo screening
- **Lead Candidate Primary Screens**
  - Protein production
  - Protein purification
  - ELISA
  - Flow cytometry
- **Viral Production**
  - CAR / TCR construction
  - Viral generation
  - Viral expression assays
- **Secondary Screen**
  - Cytokine production
  - Cell killing assays
- **In vivo Screen**
  - Cancer / tumor cell models
  - CAR production or TCR expression
  - Monitoring survival
  - Tumor growth

CAR T / TCR Development

- **Isolation**
  - Collect samples from patients
  - Extract CD4 and CD8 T cells
- **Activation**
  - Activate T cells
  - Prime to proliferate
- **Viral Production**
  - Generate vectors
  - Express CARs or TCRs on virus
- **Transduction**
  - Infect T cells with virus
  - Test stable expression of CARs or TCRs
- **Expansion**
  - Increase T cell numbers
  - Monitor and optimize conditions
- **Harvest**
  - Harvest T cells from culture
  - Purify product
- **Formulation**
  - Make final product for dosing
  - Fill and finish
- **Product QC**
  - QC testing
  - QA review and release



Complexities in Cell Therapy Research

- As new therapeutic targets are identified, organizations need to **manage an ever expanding array of cell-based entities and DNA constructs** for CAR Ts, TCRs, and stem cells
- Discovery of new tools such as CRISPR, that can **edit the genetic code of novel targets, cell lines, and stem cells** in highly specific locations with low incidence of off-target activity, needs to be incorporated into research
- As the science behind cell therapies evolves, R&D organizations need to **integrate new cell engineering methods** into existing R&D workflows and quickly update methods as needed

Complexities in Cell Therapy Development

- Need to **support product characterization** throughout production as cells are isolated, processed, modified, and delivered to patients
- To ensure the highest level of product quality and performance while minimizing cost, teams need to **optimize scale-up processes that are constantly evolving**
- Need to efficiently **facilitate tech transfer from research to development** to ensure that complete scientific context and historical knowledge is fully incorporated into process development activities

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

Cell Therapy Research

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

1

Managing a variety of cell-based entities and DNA constructs

Why is it a critical need?

Cell therapy is a diverse class of cells that vary by patient source, cell type, and the engineering technology used to modulate cellular function. In addition to the variety of cell therapy products, there is a whole host of biological entities used to modulate the activity of cells and produce cell therapies. For example, with somatic cell technologies, organizations need to manage stem cells (haematopoietic or mesenchymal), progenitor cells, and differentiated sub-populations. With gene modification technologies, labs need to manage DNA sequences, plasmids, and viral vectors, in addition to the PBMCs and CAR T or TCR cells. Thus, cell therapy R&D organizations need a flexible registry system that can manage this broad array of entities.

Why do current solutions fail?

Most current registry systems were originally designed to handle small molecules and are being repurposed to manage cell therapies. As a result, the underlying data models are often too simple; they cannot effectively model the complexity of cell therapies or the relationships between the final cell products and the cell-based entities used to produce them. Additionally, these systems lack the flexibility to manage different sets of entities and samples to meet the needs of specific cell therapy research programs.

Cell Therapy Research

How Benchling helps

Benchling provides a comprehensive Molecular Biology application to design DNA and AA sequences and a flexible Registry to manage the various cell-based entities and sub-entities used in cell therapy research. Benchling's Molecular Biology, Registry, and Inventory applications work together to help organizations optimally design, register, and manage the physical locations of entities and samples on a single platform.

Design and analyze cell-based entities with sequence-level intelligence

- Use Benchling Molecular Biology to design DNA sequences, scFv, TCR chains, and CAR / TCR plasmids
- Perform bulk cloning, bulk annotation, and bulk translation of CAR or TCR plasmids

Map relationships between donor cells, vectors, genetic material, and final products

- Link DNA sequences, chains, plasmids, and viral vectors using intuitive data models customized for your organization's research
- Track lineage across entities, studies, and programs

View complete experimental context of cell therapy product lots

- Automatically link Notebook entries and results to specific batches of cell therapy product
- Find and filter results across experiments, workflows, and programs with advanced search and filter options

2

Editing the genetic code of novel targets, cell lines, and stem cells

Why is it a critical need?

Gene-editing technologies such Zinc finger nucleases (ZFNs), TALENs, meganucleases, and CRISPR have emerged as powerful tools to precisely manipulate the function of biological targets and cells. These technologies are essential to research applications, such as ex vivo modification of T cells and in vivo gene correction of induced pluripotent stem cells (iPSCs). In order to realize the true potential of these technologies, these cutting-edge techniques need to be closely integrated into cell therapy research.

Why do current solutions fail?

The primary software tools that support gene editing are specialized molecular biology applications, built only for sequence design and analysis. Separate software tools are used to actually perform experiments and manage the biological entities linked to experiments. As a result of this fragmentation, results are handled efficiently and the experimental context is lost.

Cell Therapy Research

How Benchling helps

Benchling helps edit cells with precision and provides all the tools needed to design and execute gene-editing experiments, track edits, and study the cellular response to edits.

Create and edit gRNA sequences with on- and off-target scoring

- Design gRNA and ssODNs for CRISPR experiments by using the step-by-step design guide
- Within seconds, score and sort sequences based on on-target and off-target effects

Manage a library of targeted nucleases

- Create a central library of all pre-programmed nucleases including ZFNs, TALENs, and RGENs
- Link experiments, workflows, and results directly to the specific nuclease in the Registry

Perform gene-editing experiments

- Create, execute, and track gene-editing protocols or methods with Benchling's Notebook
- Capture and track results across gene-editing experiments and Benchling applications

3

Integrating new cell engineering methods and workflows

Why is it a critical need?

There is a broad range of cell engineering methods in use, such as somatic cell engineering, cell immortalization, ex vivo gene modification, gene editing, cell plasticity, 3-D technologies, and synthetic biology. Depending on the needs of the scientific platform and program, one or more of these methods could be employed. Additionally, these methods are continuously evolving alongside advances in science. Cell therapy R&D organizations need a software system that can map these complex cell engineering workflows and can still retain the flexibility to evolve as organizational or program needs change.

Why do current solutions fail?

Because of the diversity in cell engineering methods, the workflows to support these methods are highly specialized. A specialized or custom software might be adept at managing a limited set of scientific workflows, but it will likely fail to map the complexities of different technologies. Additionally, cell engineering processes are evolving quickly, while existing LIMS systems are rigid and difficult to configure. This leads to clunky and outdated software that cannot keep pace with the needs of research.

Cell Therapy Research

How Benchling helps

Benchling provides a fully configurable workflow and process management application that expertly balances the need to standardize a process across batches and candidates with the need to create new processes and modify existing ones as research evolves.

Create custom workflows for specific cell engineering methods

- Create a structured workflow template that maps the steps of ex vivo cell modification and leverage it across programs
- Automatically register entities, create batches, and assign physical containers from one central entry that propagates across the entire Benchling platform

Modify workflows without vendor involvement as program needs change

- Use fully configurable templates to easily edit cell engineering workflows and create new processes with a few clicks
- Manage the visibility of and changes to cell engineering workflows with access controls and version histories

Get real-time visibility into research processes

- View process stages, branches, and connections in one simple, intuitive process map
- Track the status of cell therapy research workflows including creation date, current status, and last status change

Cell Therapy Development

Cell 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 cell therapy development.

1

Supporting cell therapy product characterization

Why is it a critical need?

Cell therapy characterization and testing are extremely challenging. Many factors contribute to the complexity of cell therapy characterization, including the inherent variability of starting materials and in-process samples, incomplete scientific understanding of functional characteristics, limited quantities of samples, and the need to integrate novel characterization tools. Additionally, cell product and in-process samples need to be studied thoroughly across acceptance testing, in-process testing, and release testing.

Why do current solutions fail?

Currently scientists use spreadsheets, emails, or specialized software to manage sample handoffs and characterization requests. Experimental results are relayed back through emails or data storage solutions, such as GDrive, Box, and SharePoint. As a result, coordination of analytical activities is inconsistent and inefficient. Cell therapy R&D organizations need a central platform that can track results, facilitate requests across groups, and interface with analytical instruments and software.

Cell Therapy Development

How Benchling helps

Benchling simplifies the challenges of cell product characterization by providing applications that integrate directly with instruments, link characterization results with cell-based entities, and enable advanced analysis and visualization. As a result, organizations can create a more comprehensive characterization profile of cell therapy candidates.

Integrate with cutting-edge instruments and analytical tools

- Connect analytical instruments directly to Benchling to create a central hub for all characterization results
- Interface with process analytical tools (PAT) to collect real-time characterization data

Track batch history and link with functional characteristics

- Link characterization results to specific batches and their metadata, which is critical for patient-specific autologous cell therapies
- View complete batch history of allogeneic therapies and optimize processes based on real-time results

Manage results from complex, quickly evolving assays and execute large-scale queries

- Easily manage results from multiple assays and data sources, and use automatic cell validation to flag out-of-spec results
- Use Benchling's SQL data warehouse to run complex custom queries and gain a clearer understanding of cell characterization results

2

Optimizing processes that are constantly evolving to scale up allogeneic and autologous cell therapies

Why is it a critical need?

Scaling up involves optimizing key processing steps, such as cell selection, expansion, manipulation, purification, and formulation. These steps are technically challenging because of the number of genetic modifications cells must undergo. Depending on whether a cell therapy is autologous or allogeneic, there are additional considerations. For example, autologous therapies require tracking chain of custody and end-to-end closed manufacturing. Allogeneic therapies, on the other hand, need larger-scale and more extensive testing to ensure processes are consistent with minimum batch-to-batch variations.

Why do current solutions fail?

Because process development for cell therapies is a new and evolving area, the software systems to support these workflows are relatively nascent. Custom LIMS software or specialized software designed for specific pieces of equipment are most prevalent today. As processes quickly evolve, development teams need to capture both unstructured (but queryable) results along with structured results. Cell therapy development organizations need a central platform to manage end-to-end processes, integrate with automation, and generate timely insights for process optimization.

Cell Therapy Development

How Benchling helps

Benchling addresses scale-up challenges by providing software applications to design production processes for both allogeneic and autologous therapies, track process output and steps in real-time, and integrate with production automation to improve efficiencies.

Design a standardized cell therapy production process with built-in flexibility

- Map all the steps of the production process, including processing stages and inputs and outputs for each stage
- Modify and optimize the production process to accommodate variability inherent in the starting material of autologous therapies

Track production process parameters and batch-to-batch variations

- Gain better visibility into a process and track process parameters and bioreactor data in real time
- Analyze and view historical trend data and batch-to-batch variations

Integrate with automated solutions to monitor yield and output

- Fully integrate with production automation to ensure a fully closed, safe, and efficient process that is critical for autologous cell therapies
- Build custom dashboards to monitor process metrics, yield, and output

3

Facilitating tech transfer from research to development

Why is it a critical need?

As a cell therapy progresses through development, several information hand-offs occur between research and development organizations. Successful tech transfers are essential to the timely execution of manufacturing campaigns and achievement of organizational milestones. These tech transfers require significant collaboration across multi-disciplinary teams and access to information that will help identify and mitigate potential risks. Additionally, the experience and knowledge of the Scientist or team that developed the process is a critical component of these tech transfers and needs to be leveraged during the transition.

Why do current solutions fail?

Currently tech transfer is managed through unstructured software tools like emails, documents, spreadsheets, data storage tools, and communication platforms. Cell therapy R&D organizations need a central source of truth that can not only help with complete context transfer, but that also enables real-time collaboration between key stakeholders.

Cell Therapy Development

How Benchling helps

Benchling enables seamless tech transfer by creating a central repository of information that can be easily shared with key stakeholders, and by providing a platform for real-time collaboration and troubleshooting among team members.

Create a central repository of all experimental data

- Support the flexibility of research and the rigidity of process development in a single system, and access all available tech transfer-related results and documents from a central platform
- Access sample lineage easily across research and development

Define preliminary critical product and process attributes

- Identify critical quality attributes of cell products - such as cell number, titer, and mass - that need to be tracked throughout tech transfer
- Systematically evaluate the impact of key production process parameters based on historical knowledge and data

Enable real-time collaboration across research, development, and production to identify and mitigate risks

- Highlight risks and flag data that is out of range with cell-level validation
- Use the @-mentioning feature to notify key stakeholders of the tech transfer team as soon as new data becomes available

Conclusions

Cell therapies represent a promising new therapeutic modality that is expected to have a major impact on several serious disease conditions. However, the technologies and processes supporting the discovery and development of novel cell therapies are just taking shape and are likely to transform in the future.

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

Here are some companies that use Benchling for cell therapy R&D:

AgenTus THERAPEUTICS

Dragonfly

OBSIDIAN™

RubiusTherapeutics

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