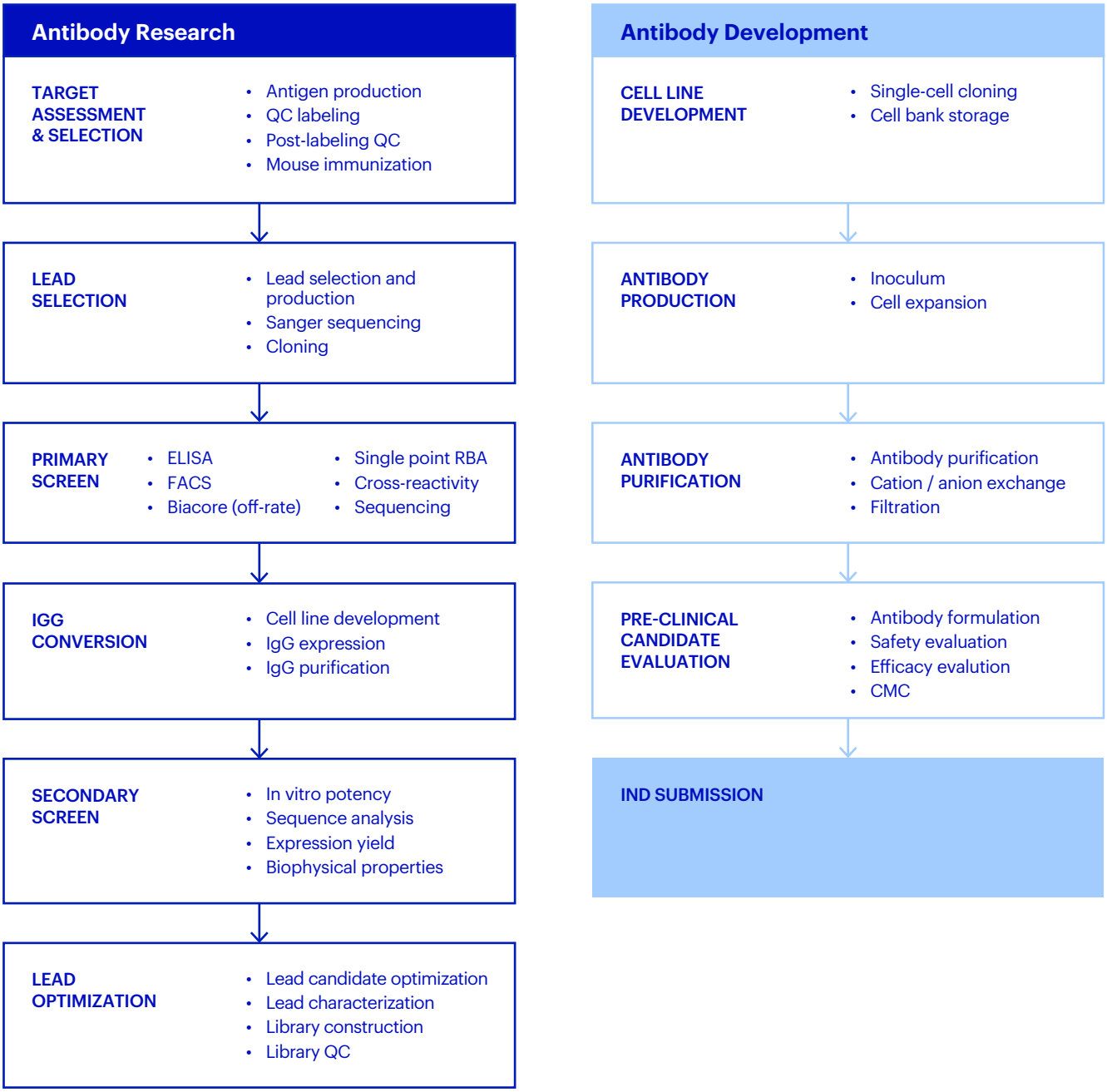
Application Note

Benchling for Antibody Therapeutics R&D

Introduction

Antibodies are an important class of therapeutic agents which have evolved significantly over the past 30 years. Antibody R&D is now more streamlined than ever, but several factors continue to contribute to its complexity.



Complexities in Antibody Research

Persistent concern around the **safety and immunogenicity of antibodies** means more rigorous testing is required before the drug candidates are ready for human testing

Increasing program and workflow diversity due to the discovery of novel **antibody formats such as bi-specifics and antibody drug conjugates**

Growing need to incorporate the latest b**reakthrough technologies, such as NGS and CRISPR gene-editing**, into traditional workflows as quickly as possible

Complexities in Antibody Development

Need for **early developability risk assessment** that helps proactively inform risk mitigation strategies

Need for **advanced analytics over large-scale data** to help inform process optimization and production campaigns

Need for **tight integration of QbD and DOE principles** into every aspect of antibody process development to gain a thorough understanding of antibody product quality

This paper outlines the critical needs and complexities faced during both research and development phases, and how Benchling has helped address these challenges for leading antibody companies.

Antibody Research

Improving immunogenicity profile of antibody lead candidates

Why is it a critical need?

Immunogenicity is the key reason antibodies have failed in clinical trials. Chimerization and humanization have helped reduce the risk of immune response significantly. However, immunogenicity against the variable regions of mAbs is still a concern. Thus, scientists want to identify immunogenicity risks as early as possible in order to iterate and optimize lead candidates. This has led to the development of in silico screening techniques to identify and predict potential T-cell epitopes, MHC class-II restricted epitopes, and aggregation-prone regions. Traditional in vitro (binding antibodies assays and neutralization antibodies assays) and in vivo screening are supposed to build on this knowledge to provide a comprehensive picture of a candidate's immunogenicity profile.

Why do current solutions fail?

In reality, the immunogenicity data reside in silos across computational biology, analytical characterization, and animal testing groups, with each group using different software to analyze and store the data they generate. The lack of cross-talk between software tools leads to less robust sequence and structure-level understanding of immunogenicity.

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

How Benchling helps

Seamlessly integrate in silico, in vitro, and in vivo screening

Centrally document all in silico, in vitro, and in vivo immunogenicity, toxicity, and tolerability data on a single platform allowing you to record, query, and cross-reference the safety data

Link in vitro and in vivo immunogenicity data to specific batches of antibodies; establish two-way hyperlinks between the batches and all supporting studies using the batches

Establish a feedback loop for candidate optimization

Track lineage across scFV to full-length antibody and corresponding safety data to inform optimization of novel antibody candidates

Enable selection of chains across antibody programs by preserving the full context of historical safety data

Continuously improve in silico predictive methods

Capture data from a variety of in silico approaches, such as T-cell epitope prediction, into a central data warehouse to access higher level insights

Enable comparison, refinement, and optimization of screening methodologies by building custom dashboards and metrics to track output from in silico predictions

Benchling helps centralize data generated across in silico, in vitro, and in vivo screening groups, resulting in a single source for all immunogenicity-related information. This leads to higher quality insights that can be used to improve predictive methods across R&D programs.

Antibody Research

Handling multiple types of novel antibodies

Why is it a critical need?

With monoclonal antibodies maturing as a platform, bispecific formats and antibody-drug conjugates are the next wave of novel antibodies. The processes for screening and producing these novel antibodies are different and are evolving rapidly. Antibody engineering techniques such as hybridoma, phage display, and B-cell cloning that are used to make mAbs are well established. However, newer antibody engineering technologies such as knobs-into-holes, CrossMab, Dock-and-Lock, and strand-exchange engineered domain (SEED) introduce complexities and variations to the traditional discovery workflow.

Why do current solutions fail?

Software tools have not kept pace with this explosion of novel antibody formats. For example, current registration systems can't handle the variety of novel formats, while current molecular biology tools don't support the design of these entities. This has led to the development of more specialized tools with limited flexibility, resulting in the fragmentation of software systems used for novel antibody research.

How Benchling helps

Design and analyze antibody types

Visualize and design sequences for a variety of antibody formats — such as BiTE, tandAbs, DART, and triomab — by using molecular biology tools with sequence-level intelligence

Automate bulk antibody creation, cloning, annotation, and translation for any antibody type

Create custom registries and antibody workflows

Manage a diverse range of custom entities such as ScFV, BiTE, b-Nanobody, and DART with a highly customizable and powerful registration management system

Create flexible workflows for each antibody engineering technique or platform, such as knobs-into-holes, CrossMab, and SEED

Share data and insights across antibody formats

Retain rich contextual data as chains are reused across antibody formats such as monoclonal, bispecifics, BITE, and heteromAbs

Optimize selection of follow-on next gen antibody candidates based on characterization results generated and recorded against lead candidates sharing genealogy

Benchling provides a unified suite of applications with the flexibility to design and analyze novel antibody formats in bulk, register a range of custom entities in the Registry, and create specialized production workflows on the fly as needs of R&D programs change.

Antibody Research

Integrating next-gen approaches to antibody screening and discovery workflows

Why is it a critical need?

Antibody research organizations seek cutting-edge technologies that can be used to diversify antibody libraries, increase depth of sequence-level and structure-level understanding, and support the development of highly efficacious and specific antibody candidates with optimal biophysical characteristics. Enabling technologies — such as deep sequencing, humanization of IgG, and CRISPR to engineer libraries and cell lines - are fundamentally changing research paradigms. These breakthrough technologies need to be incorporated into routine screening and discovery workflows in a structured manner. Additionally, the systems and processes need to be flexible enough to adapt and evolve in the future as newer techniques are discovered.

Why do current solutions fail?

Most novel technologies, such as NGS and CRISPR, use specialized software. Existing workflow software is unable to integrate with this new, specialized software, which often has more complex data needs. Additionally, these new technologies are rapidly evolving, but current LIMS systems aren't flexible enough to handle this rapid change. This leads to fragmented workflows and inefficient hand-offs between systems.

How Benchling helps

Leverage the full power of cutting edge molecular biology tools

Access over 10 molecular biology tools, including CRISPR, Golden Gate, Gibson assembly, and sequence alignment

Automatically calculate properties of novel antibodies such as MW, pI and extinction coefficient using computed fields

Embed latest technologies into existing workflows

Map sample preparation for technologies like NGS from start to finish, and integrate with existing research workflows

Create NGS core and manage the flow of samples, data, and communication across your R&D organization

Flexibly scale and adapt to changing data needs

Full flexibility to configure and capture both structured and unstructured data as processes change

Drag and drop data from various sources irrespective of file type, and analyze most common file formats by using native desktop applications

Benchling gives you access to the latest molecular biology tools, such as CRISPR gene-editing, and integrates with existing software for seamless data capture and results analysis. Benchling can also be used to create flexible workflows that keep pace with the evolution of technology.

Antibody Development

Performing developability risk assessment early

Why is it a critical need?

Full development activities such as production of a cell line, formulation, and optimization of manufacturing processes are resource intensive. Developability assessments employ a set of smaller scale, fast, and predictive studies to address biochemical and biophysical features of the antibody drug candidate and antibody products. Thus, these are critical to efficient development. The earlier in development these studies are performed and potential development liabilities identified, the more cost effective it is for a R&D organization. Antibody developability liabilities that need to be flagged as early as possible include aggregation propensity, poor solubility, chemical instability (disulfide bond shuffling, deamidation, oxidation, cyclization, etc.), and charge variants.

Why do current solutions fail?

Because of the lack of a cohesive solution, current software is used in a piecemeal manner. The design and execution of developability studies are handled through disparate tools, such as lab notebooks and spreadsheets, while slide presentations and emails are used to report these studies.

Antibody development involves creating 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 antibody development.

The Benchling Difference

Identify developability liabilities

Predict developability risks of antibody candidates with hook ups to backend APIs, and perform sequence based predictions (e.g. which sites are glycosylated vs. not)

Flag development risks by tracking discrete lot-to-lot relationships between the most critical antibody intermediates and the reagents used to make them

Thoroughly study antibody liabilities throughout R&D

Track antibody entities from discovery through development with rich contextual characterization data linked to specific batches

Assess developability properties of lead candidates against performance metrics and stage gate criteria set-up in a custom dashboard

Generate actionable insights to mitigate potential risks

Streamline the feedback loop between assay requests and results to rapidly optimize scale-up and mitigate development risks

With lineage tracking, access results and insights to better design and execute key development activities such as cell-line development

Benchling enables you to identify and thoroughly study developability risks early on, as well as track both promising and high-risk antibody properties throughout development.

Antibody Development

Leveraging advanced analytics to manage large-scale equipment

Why is it a critical need?

Large-scale equipment used in upstream processing operations, such as cultivation and fermentation, and downstream processing operations, such as purification, have traditionally been distinct unit operations with unique needs for data generation and analysis needs. Additionally, because of the complicated nature of biological processes and sensitivity of cell lines, equipment — such as bioreactors — has to be continuously monitored. This monitoring generates real-time data related to process parameters, including temperature, pH, dissolved oxygen, and nutrient concentration. Finally, there are sophisticated in situ process analytical technologies (PAT), such as imaging and raman spectroscopy, that give real-time insights on the antibody batch being prepared. Advanced analytics are required to analyze data from disparate upstream and downstream equipment and accompanying PAT tools to inform optimization of the bioprocess.

Why do current solutions fail?

Large-scale instruments generate vast amounts of real-time monitoring data. Furthermore, the PAT tools generate a separate stream of characterization results. Data from these different sources are typically handled by their respective dedicated software or through heavily customized LIMS systems. The lack of integration among these different sources makes data analysis slow and cumbersome.

The Benchling Difference

Unify upstream and downstream operations

Consolidate traditionally distinct upstream and downstream process equipment on a single unified software platform

Create custom dashboards to track antibody manufacturing processes through direct connection to a SQL warehouse

Integrate large-scale equipments with PAT tools

Collect real-time data from both equipment and PAT tools to enable live monitoring and insight generation

Set up automatic triggers when data recorded is off from predetermined ranges

Optimize bioreaction with real-time insights

Build custom apps and analytics to gain deeper, insights not possible otherwise by leveraging both instrument and PAT data

With end-to-end integration, use data insights from any single unit operation to optimize upstream and downstream process parameters as necessary

Benchling not only integrates upstream and downstream operations, but also enables the integration of PAT data in the same platform. This ease of access and centralization of data allows for advanced real-time data analysis and insight generation.

Antibody Development

Seamlessly embedding DOE into antibody process development

Why is it a critical need?

A typical mAb manufacturing process involves >20 unit operations with >200 process parameters and more than 50 different raw materials, making the process significantly complex. Quality by Design (QbD) is a scientific, systematic, and risk-based approach to understand how variability in these processes and materials affects a final antibody product. Achieving QbD in process development requires establishing functional relationships between process parameters, such as seeding cell density, nutrient feed rate, and temperature, and critical quality attributes such as glycosylation pattern, charge variants, and low MW species. Multivariate experimental strategies like DOE are used to study these relationships and potential interactions between the process parameters. Companies need to establish an integrated approach to DOE; this can help define the design space of process input variables and their ranges to ensure consistent quality for antibody manufacturing.

Why do current solutions fail?

Currently, software is primarily used for statistical design of experiments and analysis of results. Meanwhile, process development studies occur independently and rely on disparate data management systems to manage raw data acquisition and store processed data. This lack of end-to-end integration leads to inconsistent use of QbD and DOE in process development.

The Benchling Difference

Identify critical quality attributes

Identify and track potential critical quality attributes of antibodies, such as glycosylation pattern, charge variants, and low MW species across experiments and workflows

Use cell-level validation to flag critical quality attributes that are out of range

Model and execute DOE studies

Design multivariate DOE experiments to study key process parameters and identify potential interactions between these process parameters

Study functional relationships between process parameters and critical quality attributes by integrating with advanced statistical tools

Define process design space

Generate process design space with the most important process parameters and their ranges

Set up automatic triggers when process parameters are out of range from defined design space

Benchling can help identify and track critical quality attributes through Notebook entries and Registry entities and link them with process parameter data that is generated from DOE studies and performed with pre-configured workflows. Additionally, Benchling stores all the process related data in a central data warehouse, which can be queried to generate the design space.

Breakthroughs are built on Benchling

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