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TECHday 2024

Co-hosted with InterSystems

November 15, 2024 – Boston – InterSystems Global Headquarters

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Welcome

Today, we'll uncover how AI is not just transforming but revolutionizing competitive strategies in this fast-paced landscape.

Powering the ability to decode complex datasets, seamlessly integrate diverse data sources, and gain insights at a depth never before possible..

TECHday
2024
Co-hosted with InterSystems

Agenda

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Intro

AI

Streamlining Antibody Discovery: Integrating Data for Smarter Candidate Selection

Wet lab

In Vivo Discovery Meets *In Silico* Scalability

Disruptive Dialogue Session

Fireside chat

Partners

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Thank you

InterSystems®
Creative data technology

powered by aws

Clear Street®

Quantum
PUBLIC RELATIONS
INVESTOR RELATIONS
EQUITY RESEARCH

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LENSai™

Streamlining Antibody Discovery: Integrating Data for Smarter Candidate Selection

Universal Foundation AI model for life sciences

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Core challenges in drug discovery: The first principles perspective

LENS^{ai}™ was developed to address three key industry issues

1. Fragmented data and slow discovery processes

Siloed data handling causing delays and increased costs

2. The Information Integration Dilemma (IID)

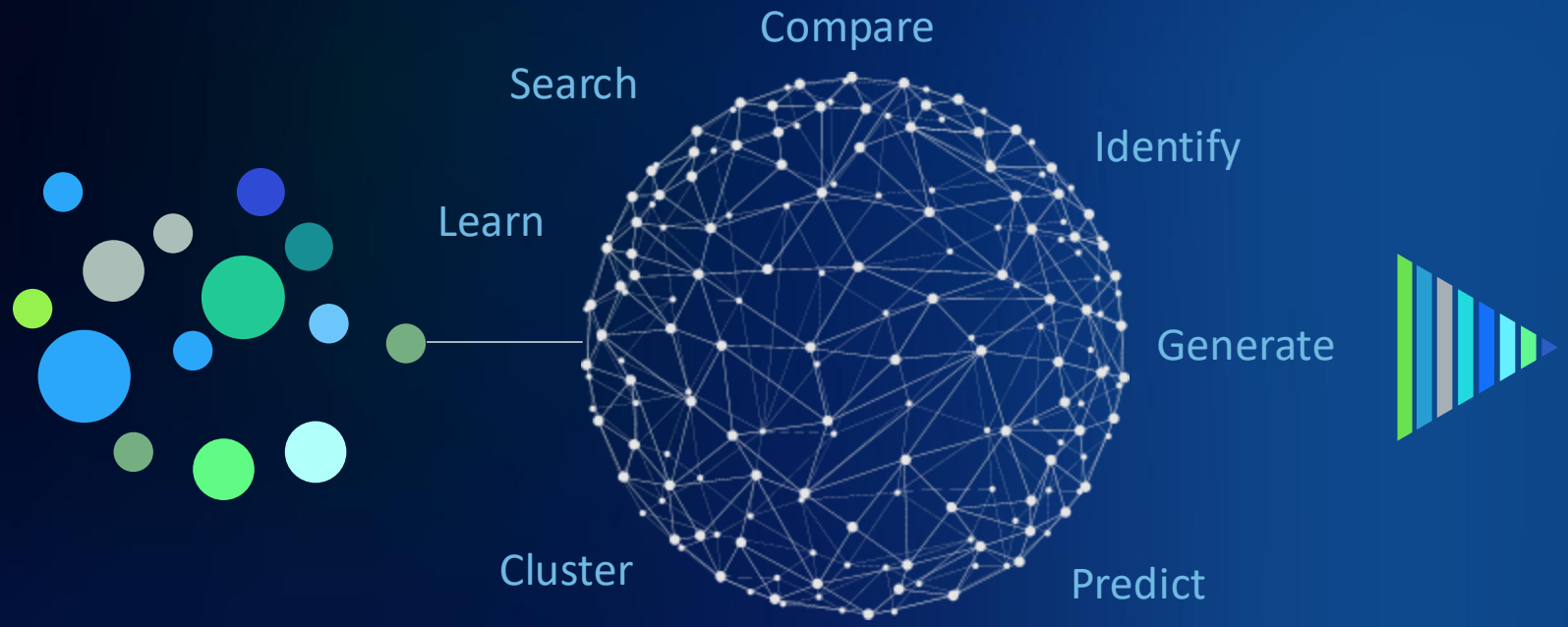
Expanding omics data creates isolated datasets, limiting integration and insight extraction

3. Lack of transparency in AI-driven predictions

Many AI platforms operate as black boxes, limiting interpretability and reliability

Data granularity meets data integration

LENS^{ai} powered by patented Hyft® Technology



Insight example

LENS^{ai} screens the human proteome, delivering 5 months of data in 2 minutes

Technology engineered for speed, precision, and limitless scalability.

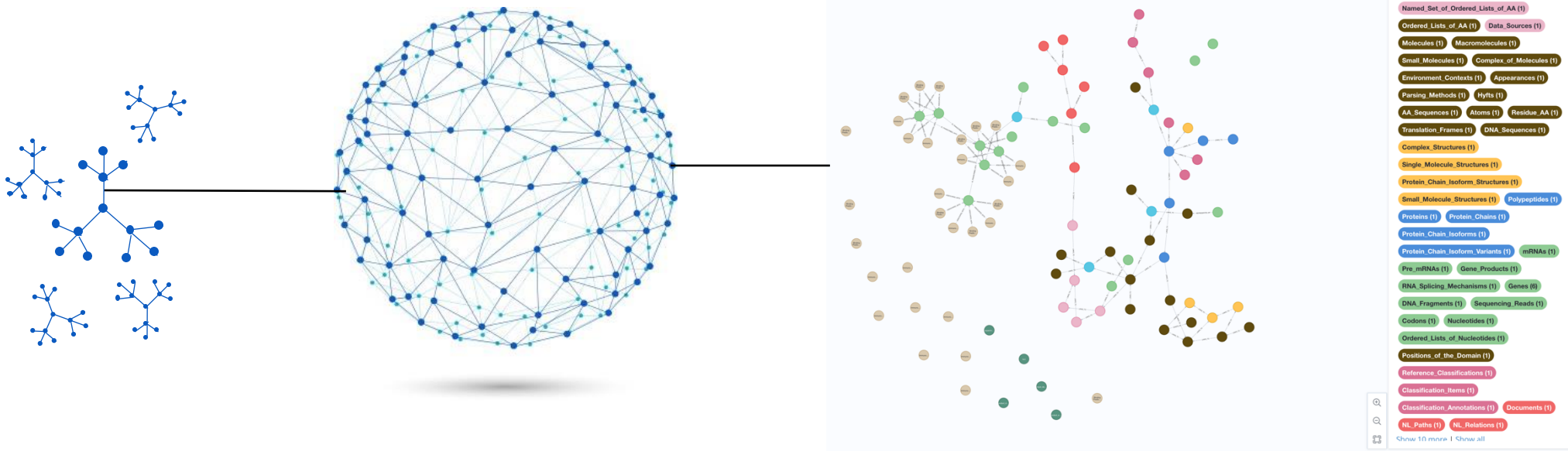
Welcome to LENS^{ai}: a Foundation AI Model for multiscale biological data integration

A transformative foundation model designed for the integration of complex, multiscale biological data

Vast number of novel data points

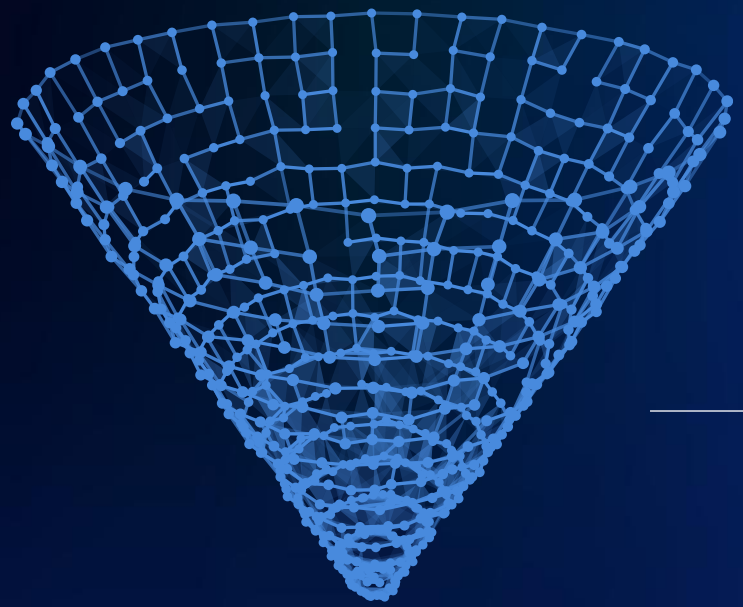
Pre-Integrated Data

Application ready connections



Antibody Discovery and Development

Data-driven down selection



End-to-End Analysis

Target

Target Analysis
- Antigen Modeling & Design
- Epitope Prediction
- Epitope Specificity

Discovery

Hit Selection
- NGS Data Processing
- Hit Expansion
- Epitope Binning

Leads

Candidate Characterization
- Epitope Mapping
- Developability
- Off-target Screening

Lead Optimization
- Immunogenicity Screening
- Affinity Maturation
- De-risk Engineering
- pH Optimization
- Humanization

+ Many microservice tools and technologies

Target Analysis:

Optimize clinical success at project onset

Target

LENS^{ai} Target Analysis
Antigen Modeling & Design
Epitope Prediction
Epitope Specificity

Input

Omic Sequence Data

Structural Models

Text Data

LENS^{ai}

Output

Target Selection Criteria

Disease causality

Druggability

Toxicity

Novelty

Target Insights

Benefits

- **Commoditize all data types (sequence, structure, function) at inception of discovery workflow**
- **Gain insights from historical data and utilize external data sources effectively**
- **Create the first entry point for system-based-screening through data feedback loop**

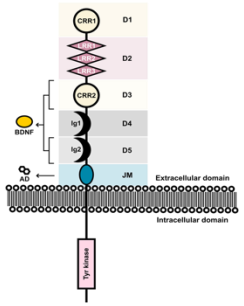
LENS^{ai} Protein Structure Prediction

Modeling complex targets: from high-throughput to detailed refinements

Structural Modeling

Target | Discovery | Leads

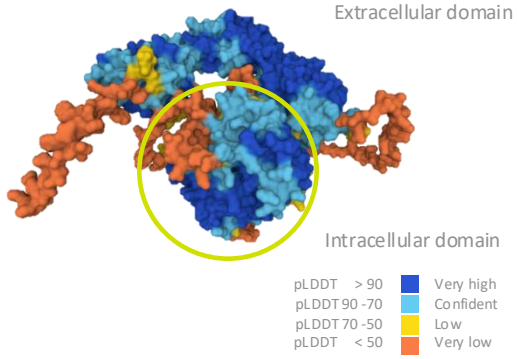
Target is a multi-domain, heavily glycosylated protein



Alpha Fold

Modeling of the EC domain of target

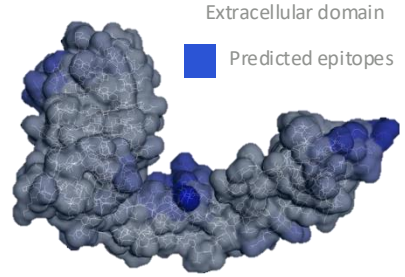
In various regions of the protein, AlphaFold structure prediction shows low to very low model confidence.



Epitope prediction

Using our target model as an input

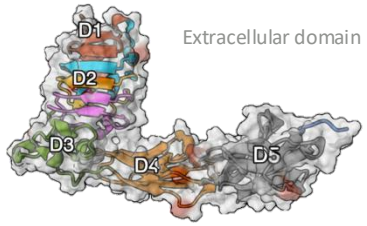
Using AI based epitope prediction tools, we define potential binding areas on the antigen. We combine predicted epitopes with known epitopes in our final model.



Template-based

Modeling of the EC domain of target based on family member model

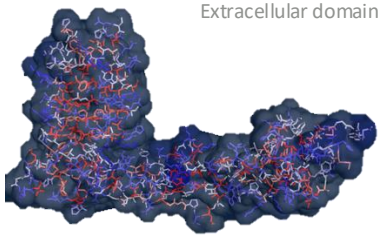
family member model (resolution X-ray diff 1.84 Å) has the largest coverage and and a seq. identity of 37.8% with respect to target EC.



Multimer & Complex Proteins

Molecular dynamics-based workflows

Utilizing physics-based engines to model atomic interactions and to estimate stability of multimeric protein complexes.



LENS^{ai} Hit Expansion Analysis

Selection and prioritization of diverse antibody sequences

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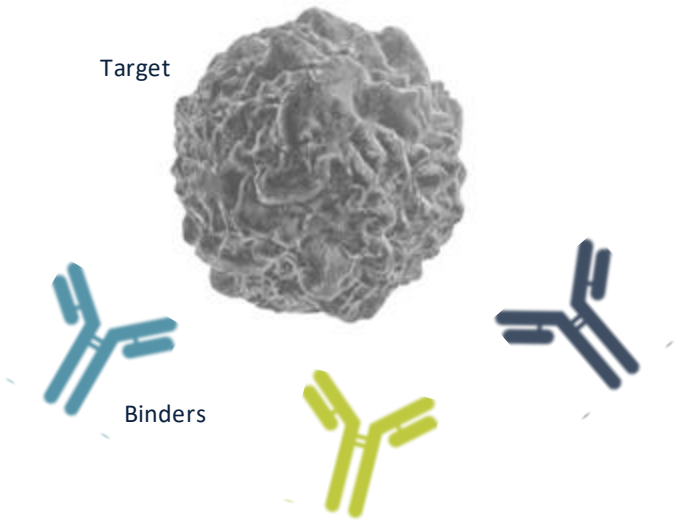
Discovery

LENS^{ai} Hit Selection

Hit Expansion: Optimizing diversity through multi-modal strategy

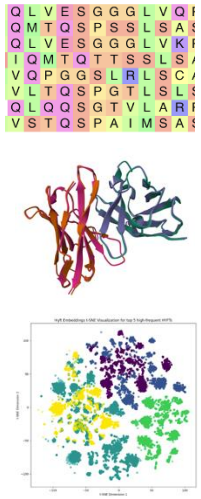
Input

NGS antibody repertoire & functional seed antibodies



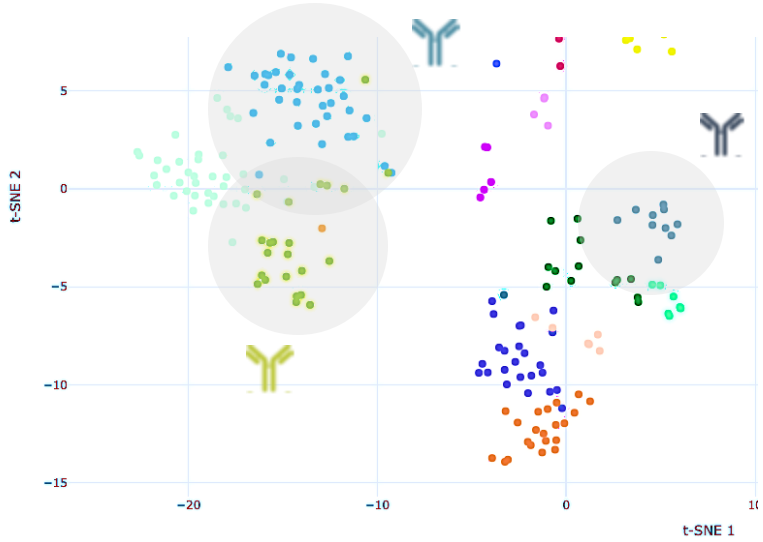
LENS^{ai}

Multi-dimensional analysis



Output

Additional clusters of functional clones



LENS^{ai} Hit Expansion pipeline is an end-to-end workflow built to extract all relevant hits for downstream analysis.

Epitope Binning:

More-informed early triaging of lead candidate panel

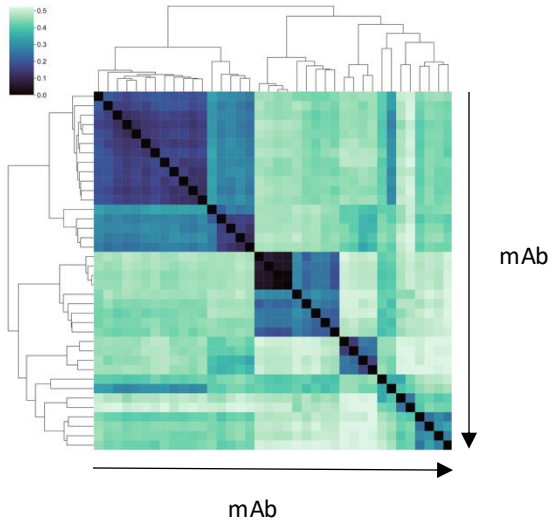
Discovery

LENS^{ai} Hit Expansion
Epitope Binning

Input

Combination of sequence and structural features to identify main bins

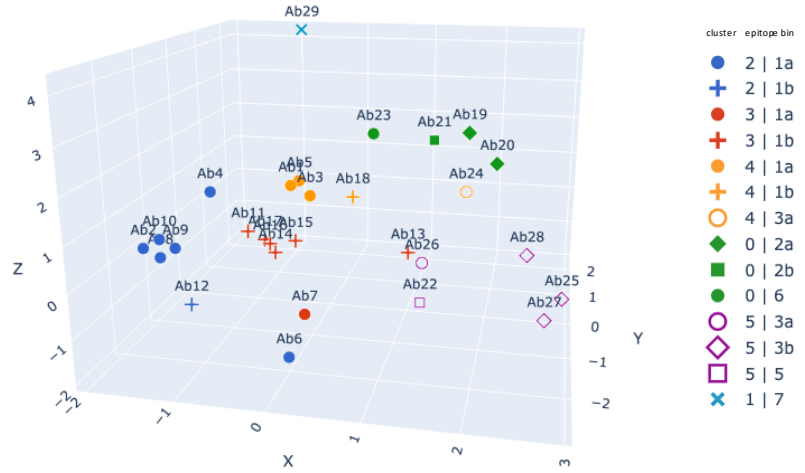
Antibody sequence input:
- from single cell sequences up to full immune repertoires
- target-agnostic



Output

Integration of physics-based engines and advanced target modeling for high granularity

Resolving larger bins and sub-bins: Cohen's Kappa score
cluster -> bin **0.93***
bin -> cluster **0,84**
** [-1 to 1]; [>0.8 = perfect agreement]*



LENS^{ai} Epitope Binning relies on a hybrid prediction engine for optimal results without the need for physical material

Epitope Mapping:
Informed lead selection

Leads

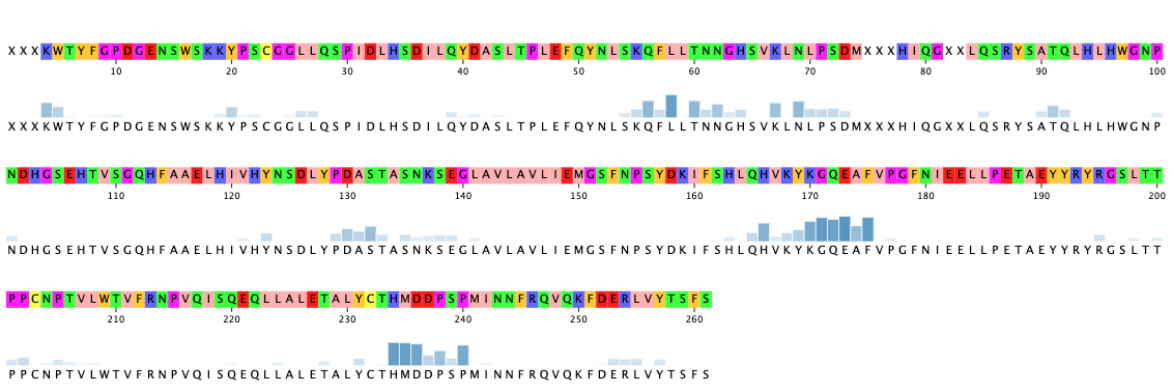
LENS^{ai} Candidate Characterization
Epitope Mapping

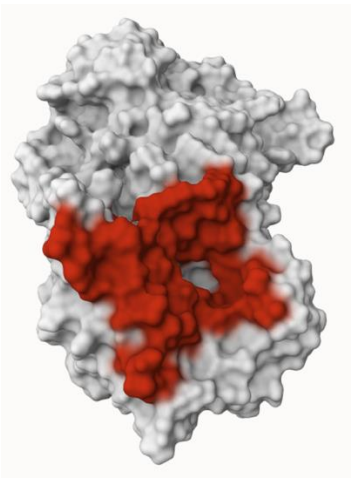
Input

Amino acid sequences of hits or candidates

Output

Multi-feature-based Epitope Mapping:
Based on syntactical-, structural profiling and, atomic interactions to enable affinity propagation clustering. Function driven information package to select potential lead candidates.





Immunogenicity & Developability profiling:

Compare your antibodies against a database of all therapeutic antibodies

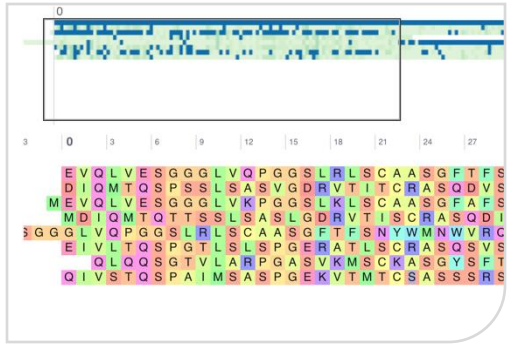
Leads

LENS[ai] Lead Optimization
Immunogenicity Screening
Affinity Maturation

De-risk Engineering
pH Optimization
Humanization

Input

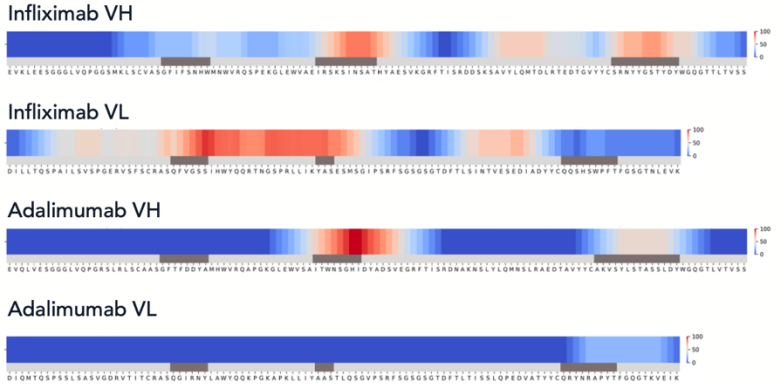
Amino acid sequences of lead candidates



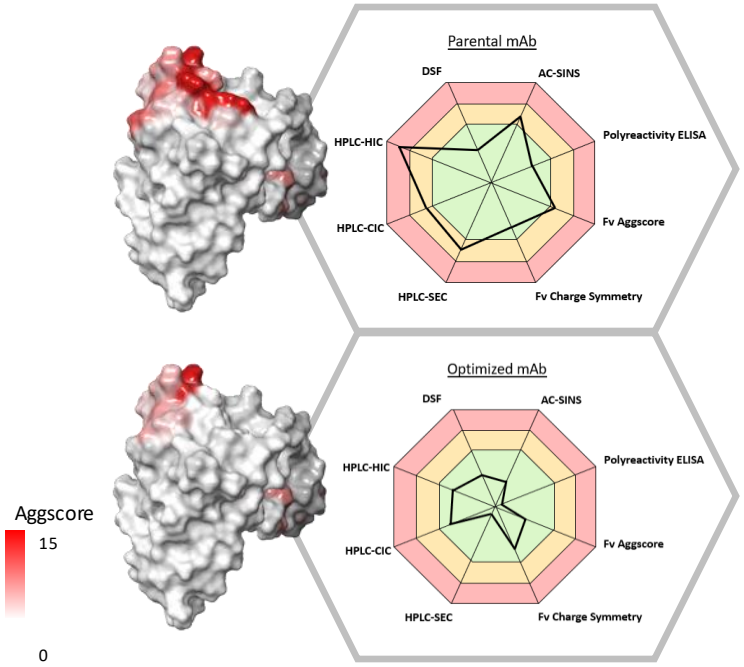
Output

Multi-parameter optimization to create therapeutic leads
Analyse candidates to gain 360-degree insight in developability and immunogenicity profiles to guide engineering. Easily humanize and optimize candidates to become leads.

Immunogenic heat maps illustrating hotspots



Developability profile radar chart of a parental mAb and an optimized humanized variant. Data is relatively ranked towards the red/orange/green flag areas of the clinical benchmark mAb library.



LENS^{ai} Universal foundation AI

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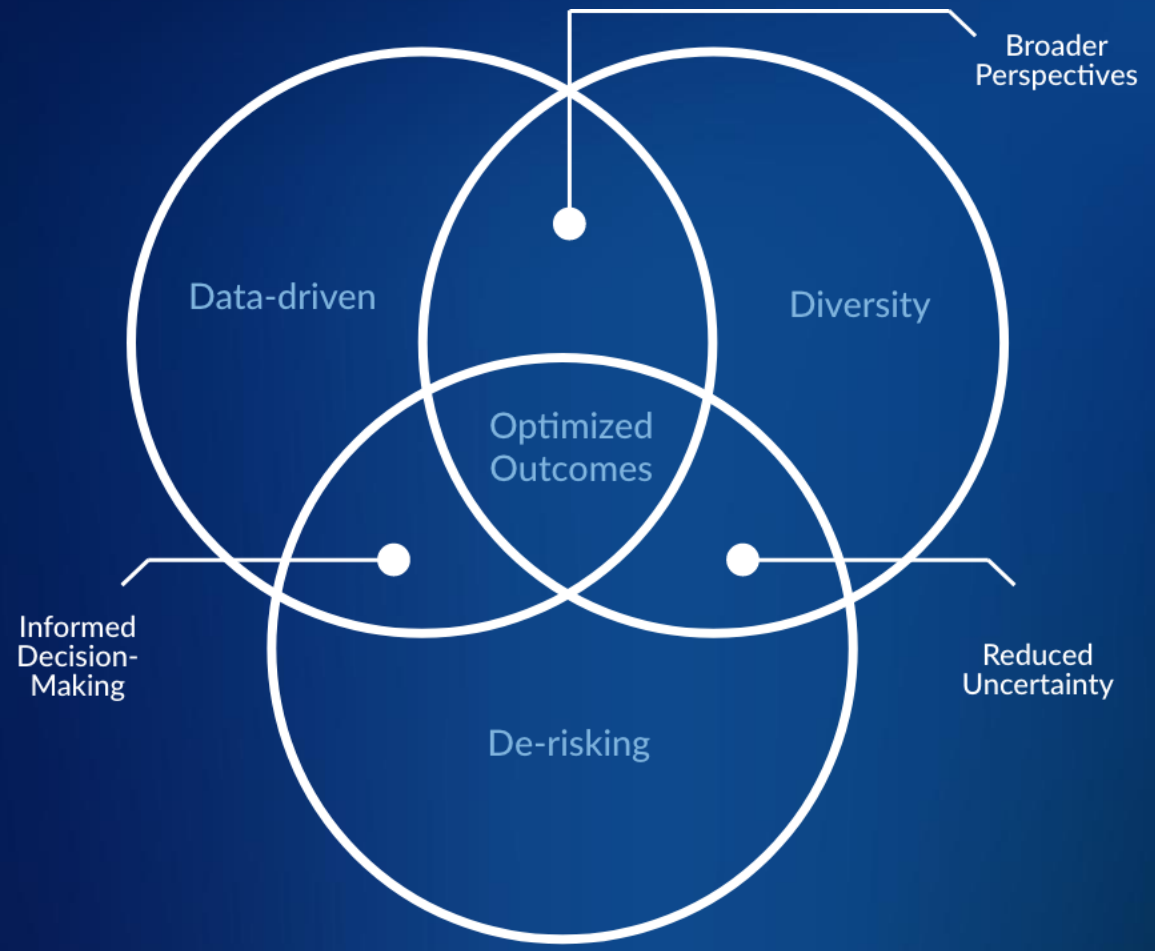
Data granularity meets data integration

Powering rational, data-driven drug design, enabling critical decisions early in the process and driving faster, more precise paths to clinical success.



"You pioneered discovery insights that previously could not be solved"

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LENS^{ai} Integrated Intelligence Platform

In action:

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DEMO

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Shaping the Future of Rational Drug Discovery with First Principles Thinking

Thank you for joining us on this journey through LENS^{ai}'s.

- Built for transparency and ultra scalability
- Reshaping drug discovery with a comprehensive suite of tools
- Accelerating research and optimizing costs for a streamlined process
- Driving breakthroughs that set new standards in therapeutic advancement

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In Vivo Discovery Meets *In Silico* Scalability

Intersection of phenotypically rich B cell Select® discovery and multidimensional, high-throughput LENS^{ai}™ applications

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Integration of infinitely scalable and accurate multi-modal *in silico* methods to exhaustively mine functional B cell repertoires

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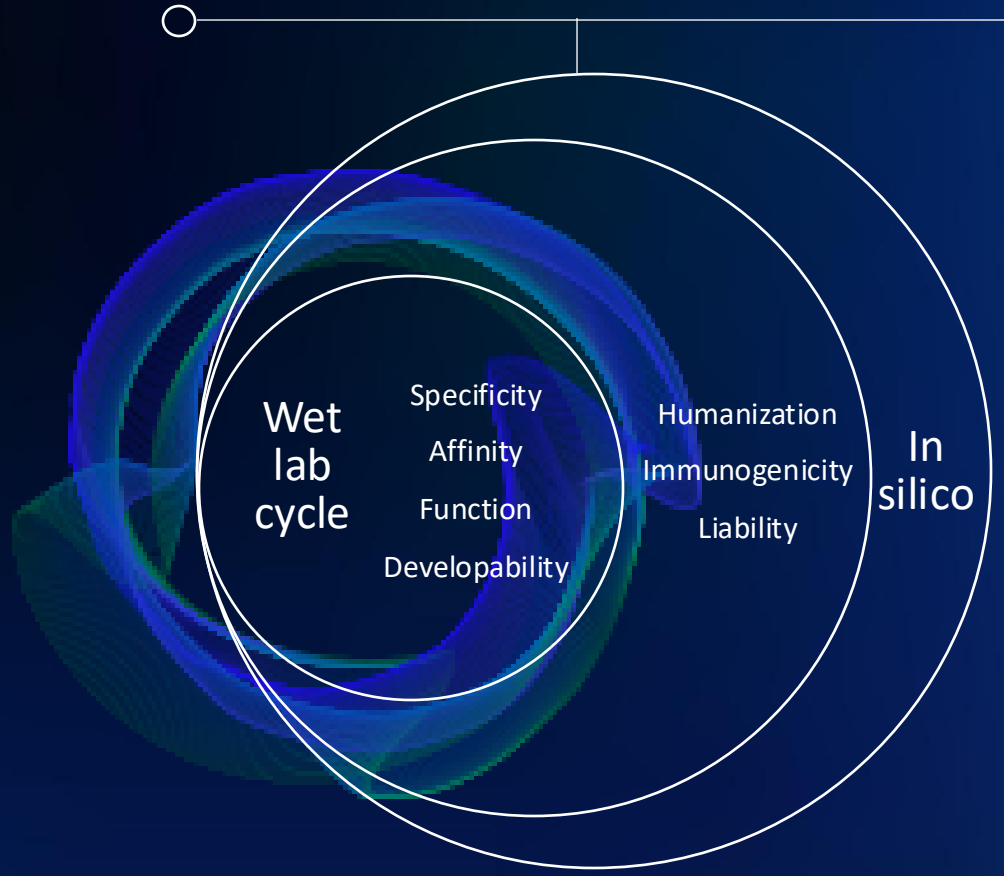
Fully-integrated therapeutic end-to-end lead generation workflow

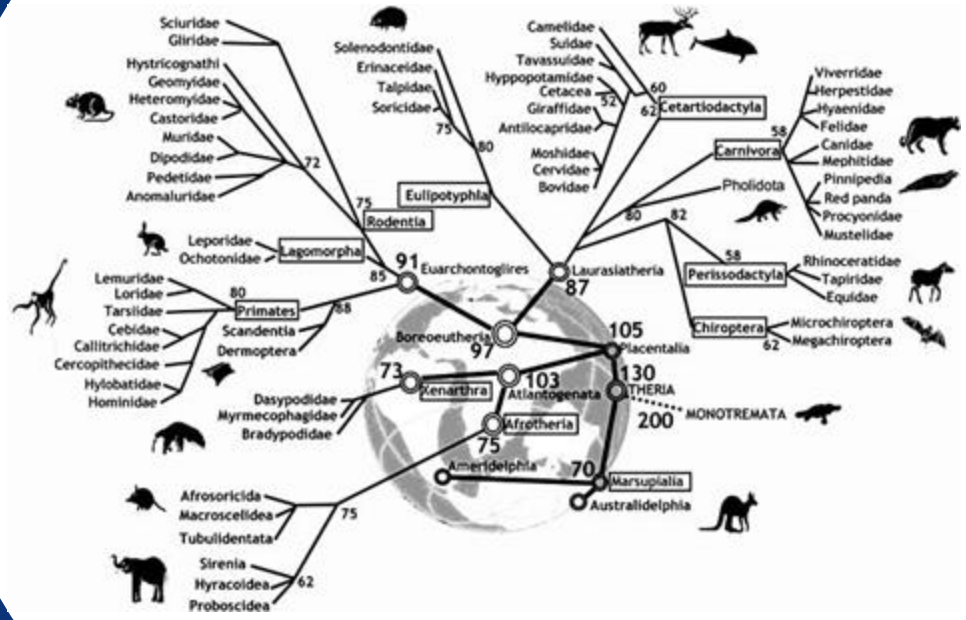


Key Benefits:

- **Diversity-driven** discovery design
- **Early-stage** identification of (functional) lead candidates
- Integration of **high-throughput** *in silico* methods to fully harness the **functional** B cell repertoire
- Decision support for **de-risking/optimization** to increase clinical suitability

What about rabbit antibodies?

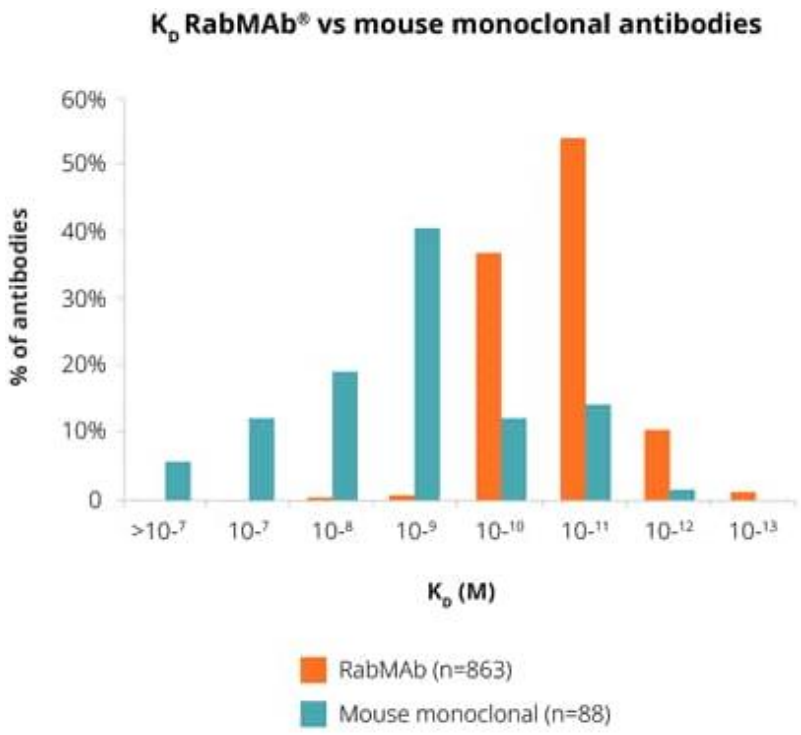
- Phylogenetically distinct from rodents
- Higher B cell diversity:
  - outbred
  - gene conversion



https://commons.wikimedia.org/wiki/File:An_evolutionary_tree_of_mammals.jpeg

What about rabbit antibodies?

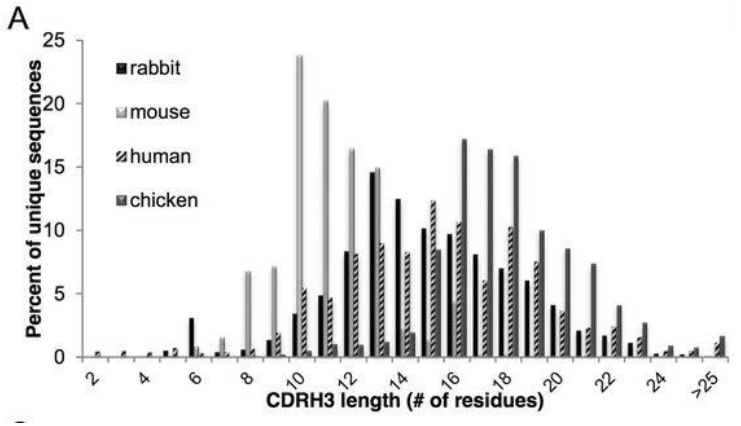
- High affinity (sub-nM) with exquisite specificity



https://www.abcam.co.jp/primary-antibodies/kd-value-a-quantitive-measurement-of-antibody-affinity

What about rabbit antibodies?

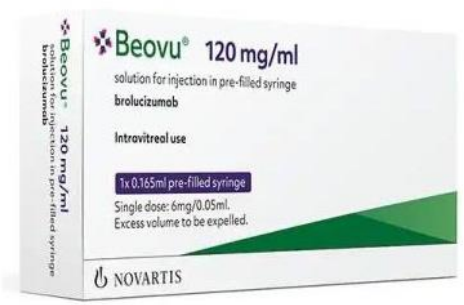
- CDRH3 length is closer to human than is mouse
- Greater diversity in light chain sequence compared with human/mouse



Lavinder *et al*. PLOS One (2014).

What about rabbit antibodies?

- 2 approved humanized rabbit mAbs as therapeutics (8 more in clinical trials)
- At least 11 approved for diagnostics



Rabbit Antibody Discovery at IPA

Superiority of Rabbit B Cell Select®

IPA's proprietary Rabbit B cell Select® workflow success

- a versatile solution that is unmatched in the industry, with a >98% program success rate in therapeutics, anti-drug/anti-id and diagnostics.

IPA discovers rabbit anti-LILRB2 antibody for OncoResponse

- This molecule has entered Ph1/2 as a best-in-class anti-LILRB2 to reverse macrophage-mediated immunosuppression in cancer patients.

OncoResponse progresses dual-blockade antibody to IND studies

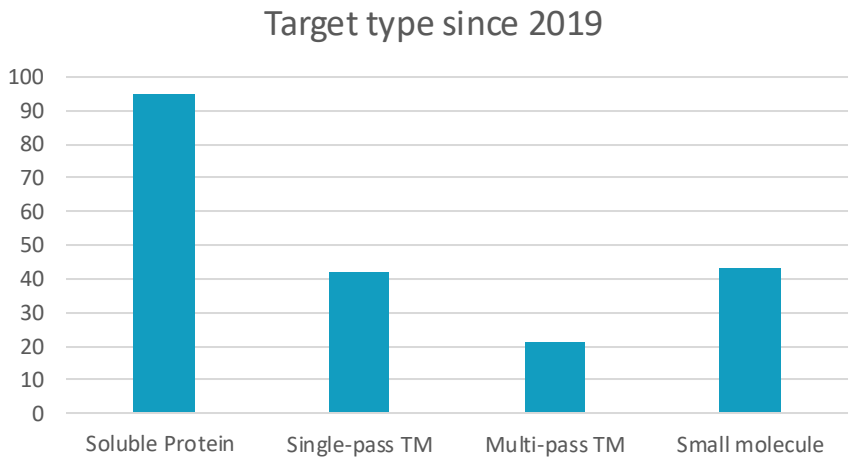
- Second molecule from IPA collaboration campaign cross-reacts with LILRB1 and 2 as a dual-blockade antibody, potentially enhancing efficacy.

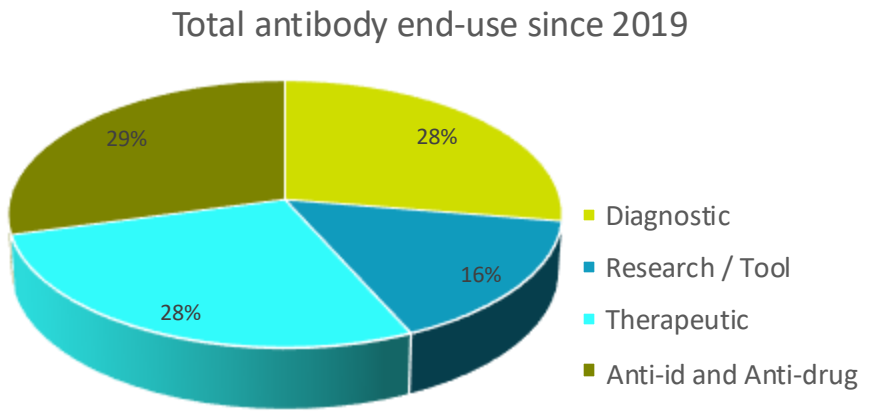
Rabbit B cell Select®

Industry leading success rate with high quality, diverse output

Rabbit B Cell Select program overview

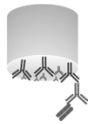
207 Number of projects since 2019





Rabbit B cell Select® workflow

Versatility and efficiency (~500-fold higher efficiency than hybridoma)



Pre-Phase

Target Validation:
QC of immunogen prior to immunization

Target Validation

QC by ELISA, Octet®

Phase I

Immunization:
28-day immunization

Immunization:

Short timeline

Phase II

PBMC isolation:
30 mL whole blood (no sacrifice required)

B cell enrichment:
Proprietary antigen specific enrichment

B cell culture and primary screen:
40x 96-well plates

Test Bleed:

- ELISA: Immunogen
- ELISA: Off-target
- Flow cytometry (multiplexed)

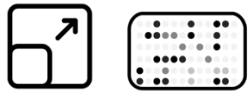
Phase III

Molecular cloning and sequencing: in sets of 48 lead candidates based on primary screening data

Secondary screening:
Sequence confirmation and further testing of sets of 48 recombinant lead candidates

1° Screening (B cell supernatant):

- ELISA: Human Target
- ELISA: Off-target
- ELISA: Cyno Target
- Flow cytometry (multiplexed)
- Octet®:
  - In-solution binding
  - Competition
  - Off-rate ranking



Phase IV

Recombinant expression and purification:
in sets of 48 clones

Tertiary testing:
Testing of purified material

2° / 3° Screening (Recombinant)

- ELISA: Target
- ELISA: Off-target scaffold
- Flow cytometry (multiplexed)
- Octet®:
  - In-solution binding
  - Competition/epitope bin
  - kinetics

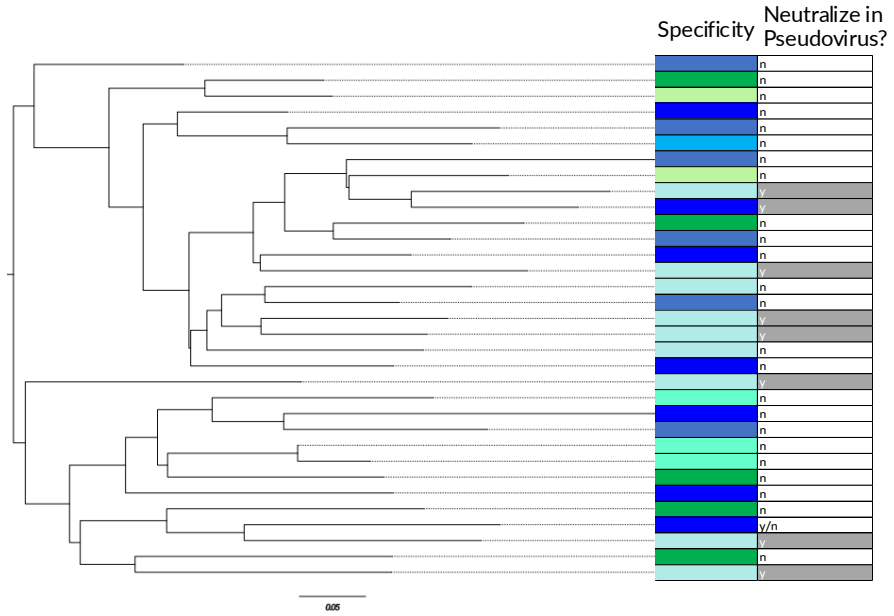
The B cell Select® advantage

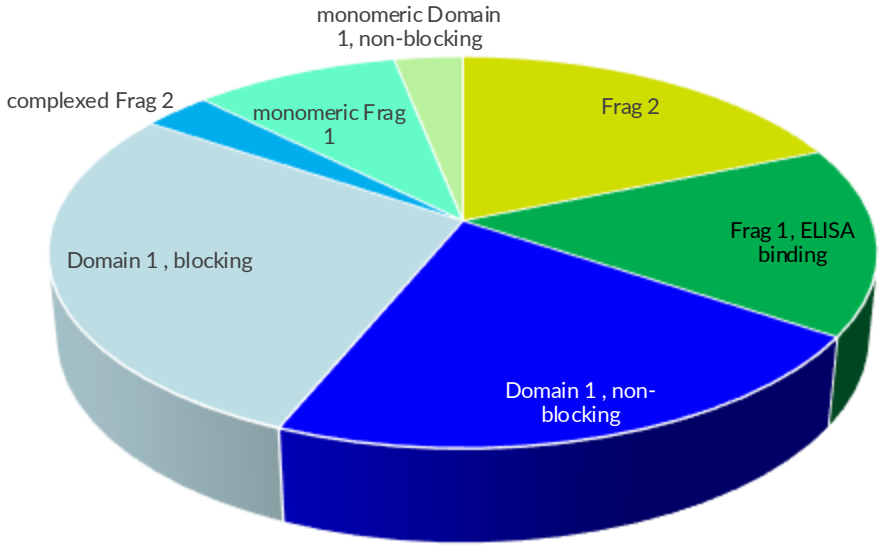
Phenotypically rich, multilayer screening uncovers functional clones at an early stage

Case study: Infectious Disease program

Generating diverse output while screening for potent function

Immunogens	Screening Methods	Cloning Efficiency	Bins
Frag 1, Full protein complex	ELISA, Octet HTX	38/48 (79%)	7





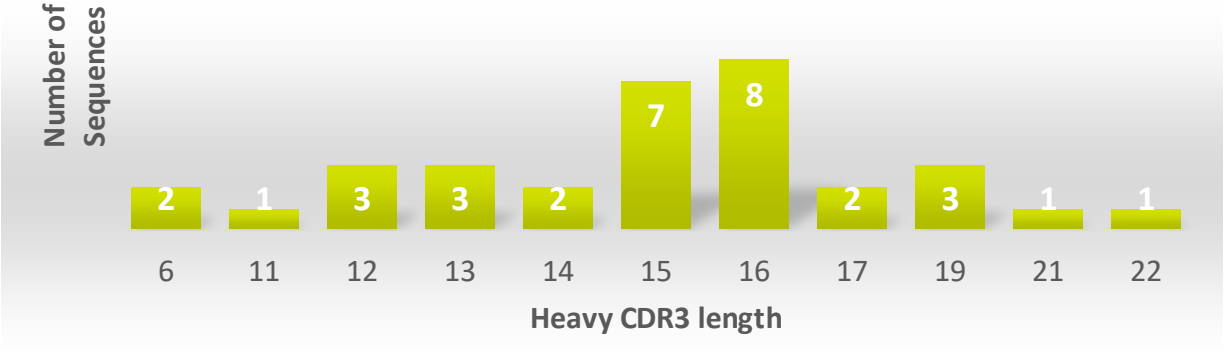
The B cell Select® advantage

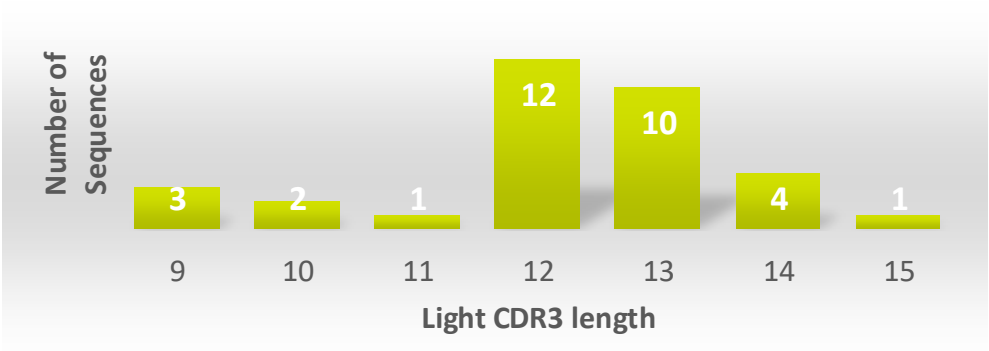
Clonal diversity of functional leads identified due to high efficiency workflow

Case study: Infectious Disease program

Germline Usage

4 IGHV, 9 IGHD and 5 IGHJ,
14 IGKV and 1 IGKJ



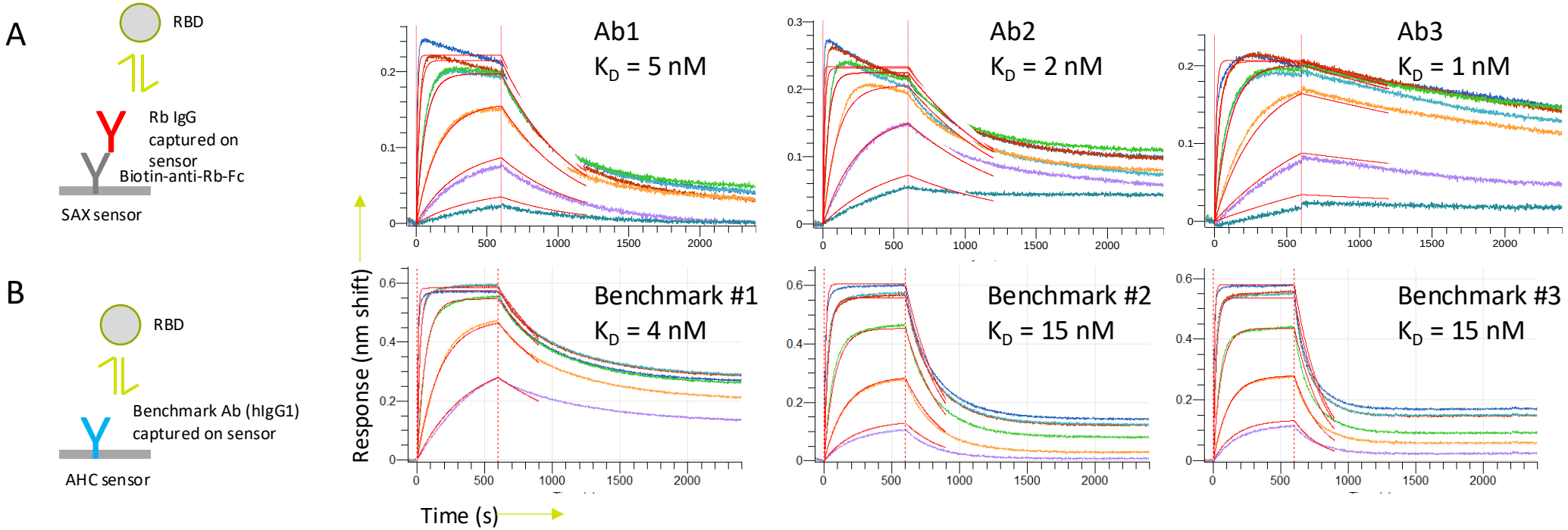


The B cell Select® advantage

Superior affinity of identified leads negates the need for costly downstream engineering

Case study: Infectious Disease program

Functional characterization – benchmarked against clinically relevant / commercially available antibodies



LENS^{ai} Hit Expansion Analysis

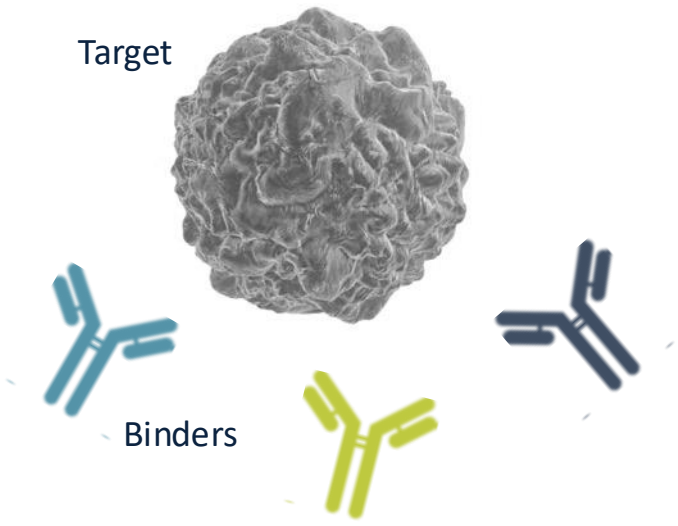
Mining complete repertoires to extract ALL relevant clones

Discovery

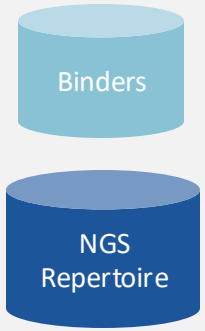
LENS^{ai} Hit Selection
Hit Expansion: Phage display, B-cell, and Hybridoma output as *seed* sequences

Input

Wet lab lead candidates



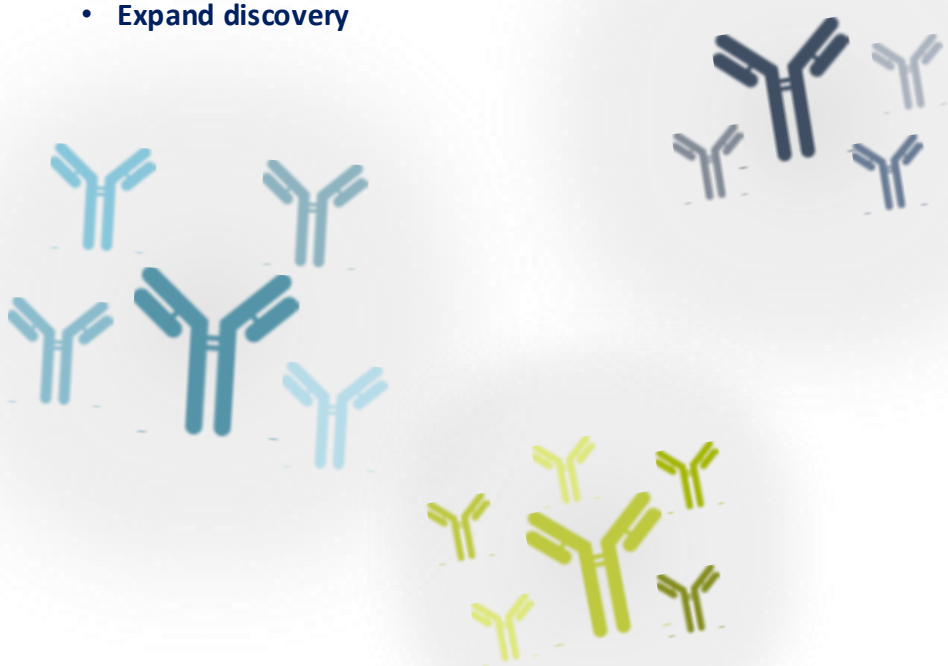
LENS^{ai}



Output

Hit expansion

- **Multi-modal analyses to retrieve additional hits**
- **Expand discovery**



LENS^{ai} Hit expansion pipeline is an end-to-end workflow built to extract all relevant hits for downstream analysis.

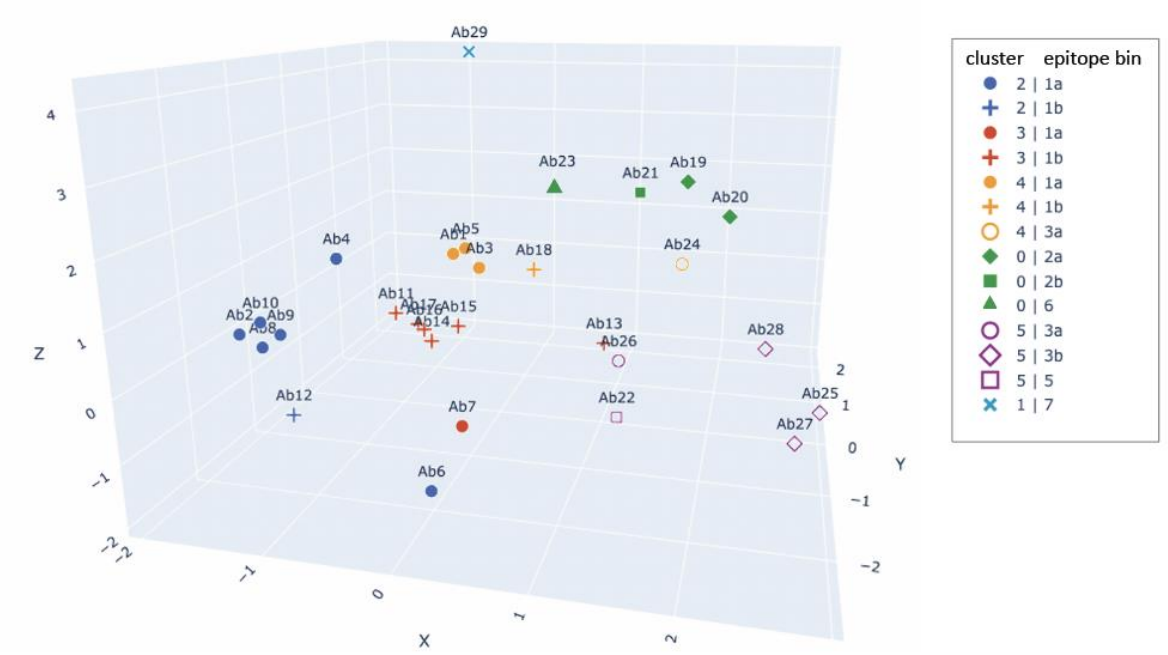
LENS^{ai} Epitope Binning

An infinitely scalable clustering tool without the need for physical material

Integration of physics-based engines and advanced target modeling enables clustering of clones from sequences alone

LENS^{ai} sequence and structure-based epitope binning

- Highly scalable clustering of antibody sequences based on predicted target binding region
- Rapid and early-stage epitope landscape profiling of large panels of hits
- No need for physical material



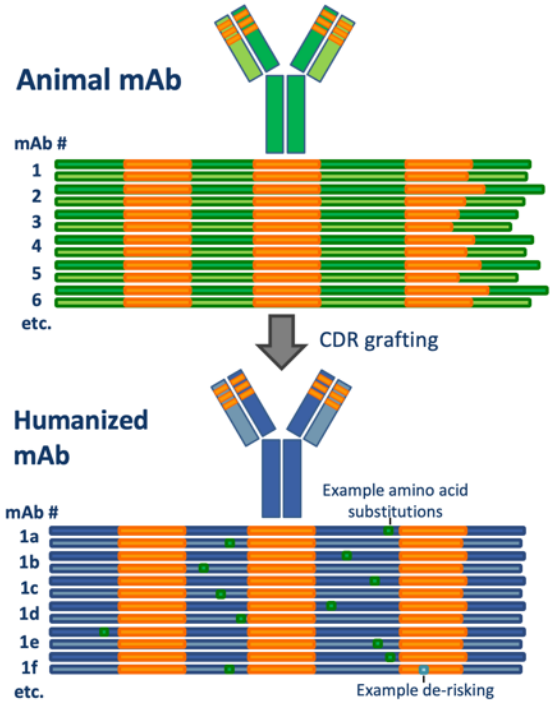
Rapid high-throughput over >5,000 candidates

Immunogenicity Screening: De-risking lead candidates

Highly scalable *in silico* risk assessment during humanization of top leads

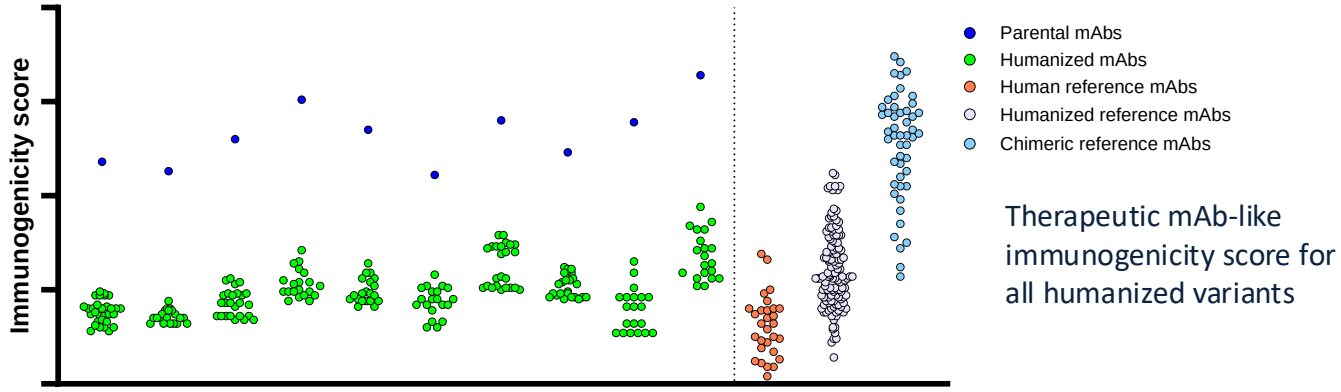
Input

Non-human lead sequences



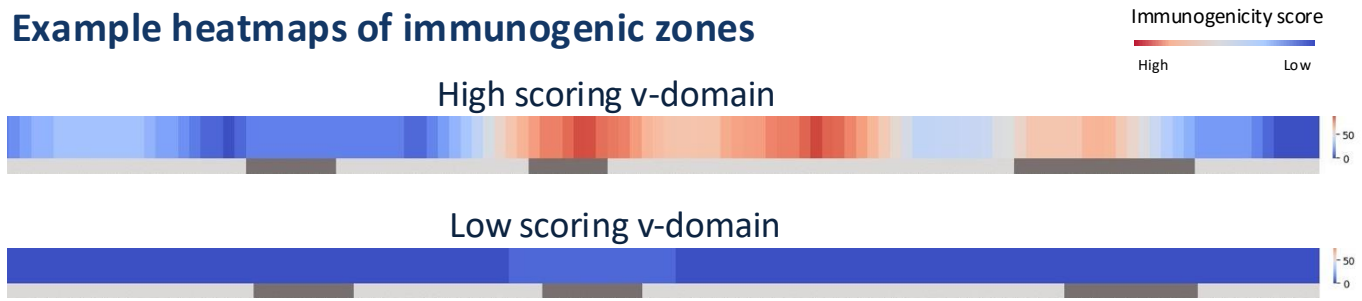
Output

Multiparametric humanization design to derisk therapeutic candidates



Therapeutic mAb-like immunogenicity score for all humanized variants

Example heatmaps of immunogenic zones



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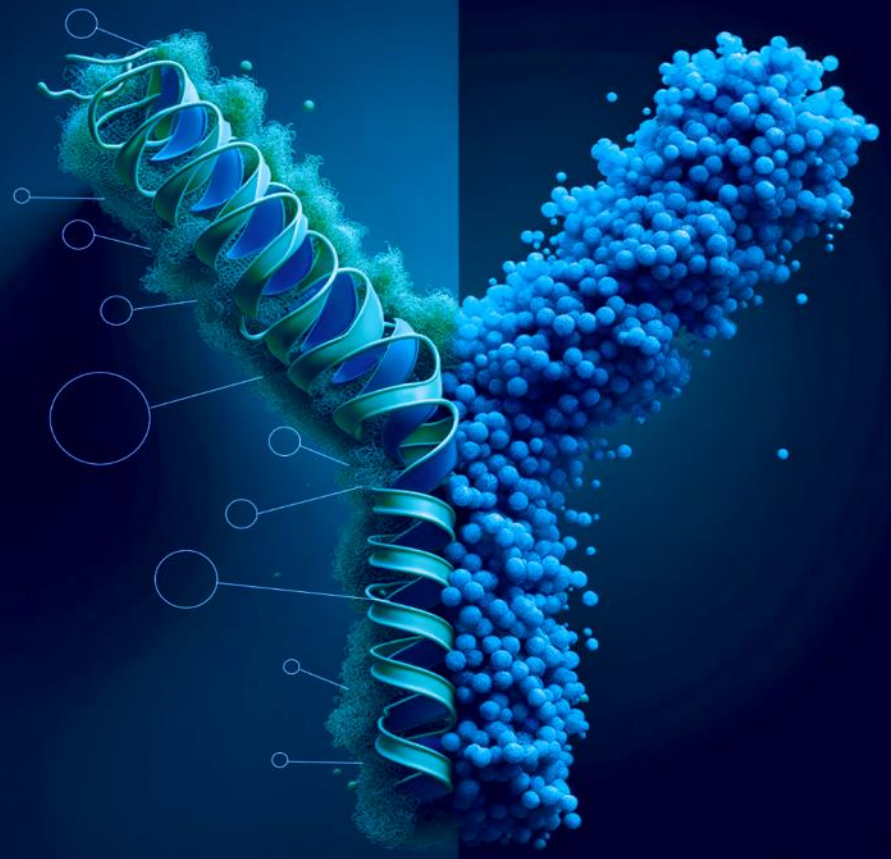
Advanced antibody technologies: speed + quality

In today's ever-evolving clinical landscape, uniting the industry-leading *in vivo* mAb discovery platform that harnesses the unmatched power of nature with the scalability of *in silico* methods amplifies therapeutic lead generation.



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Disruptive Dialogue Session

Dirk Van Hyfte + Jeff Fried

TECHday
2024
Co-hosted with InterSystems

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Data granularity meets data integration

Bridging the gap between disparate data and discovery, transforming complexity into clarity for a future where innovation and precision drives every breakthrough

Disclosures

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