



Wrangling Diverse OmniAb Antibody Repertoires with OmniDeep™

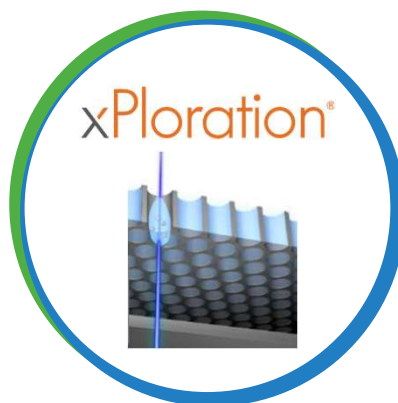
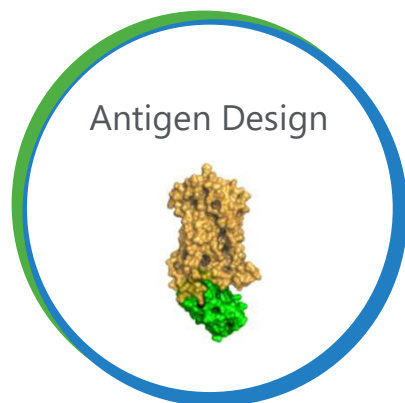
Bob Chen, PhD

PEGS 2023



The OmniAb Technology Suite

OmniAb®



The only platform
leveraging **four species**

Robust solutions for
bispecific antibodies

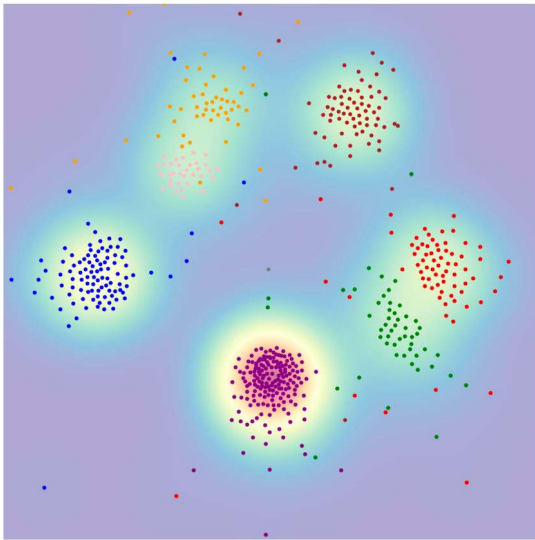
Human frameworks with
ultralong CDR-H3s

**Most diverse host
systems** in the industry

Proven success

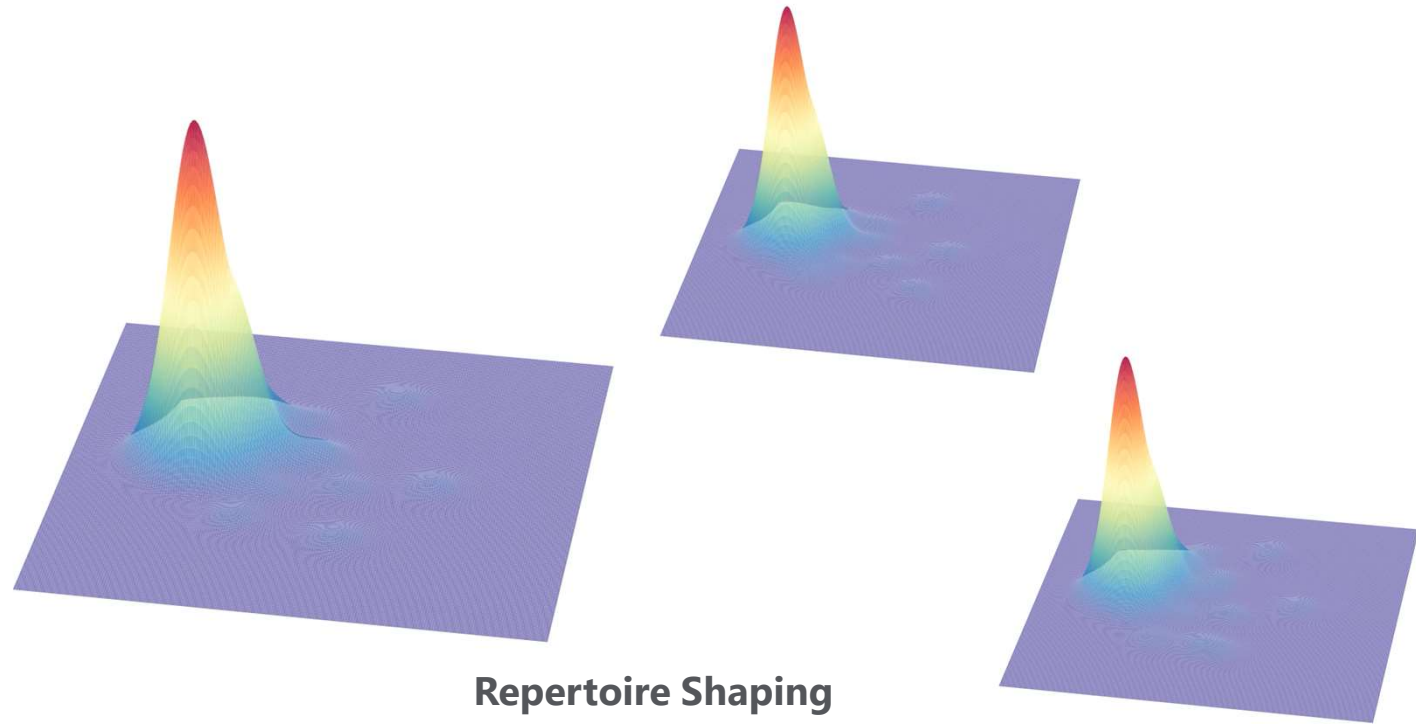
Custom Antibody Repertoires for Every Target

BIOLOGICAL INTELLIGENCE™: INTERPLAY BETWEEN RATIONAL GENETIC DESIGN AND POWERFUL IN VIVO PROCESSES



Building Animal Systems

- Immunological robustness
- V gene building blocks
- Diversification architecture
- Structural attributes







Repertoire Shaping

- Campaign strategy
- Antigen design
- Host immune recognition
- Immunization protocols

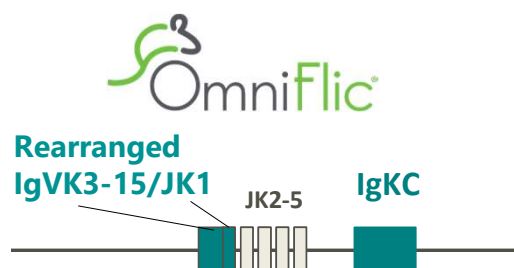
OmniAb Antibody Repertoires

BROAD PLATFORM AVAILABLE TO ADDRESS DIVERSE PARTNER OBJECTIVES

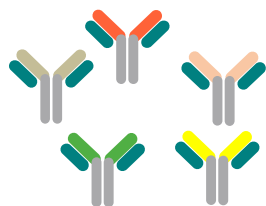
Host	V genes	Structural and immunological features	Benefits for therapeutics discovery and development
 OmniMouse	<ul style="list-style-type: none"> • Full human V gene diversity • Choice of light chain isotype 	<ul style="list-style-type: none"> • Diverse V gene usage and mixed genetic backgrounds 	<ul style="list-style-type: none"> • Widely accessible and flexible workflows
 OmniRat	<ul style="list-style-type: none"> • Full human V gene diversity • Choice of light chain isotype 	<ul style="list-style-type: none"> • Diverse V gene usage and mixed genetic backgrounds • Distinctive target recognition 	<ul style="list-style-type: none"> • Industry standard • Widely accessible and flexible workflows • Extensive track record
OmniChicken	<ul style="list-style-type: none"> • Single framework • VH3/VK3 or VH3/VL1 	<ul style="list-style-type: none"> • Evolutionarily divergent host system for robust immune responses 	<ul style="list-style-type: none"> • Diverse and new epitope coverage • High homology targets • Excellent physical properties
 OmniFlic	<ul style="list-style-type: none"> • Full human VH gene diversity with non-diversifying VK3 	<ul style="list-style-type: none"> • Fixed light chain for bispecific applications 	<ul style="list-style-type: none"> • Bispecific applications leveraging standard IgG format
OmniClic	<ul style="list-style-type: none"> • Single framework • VH3/non-diversifying VK3 	<ul style="list-style-type: none"> • Fixed light chain for bispecific applications 	<ul style="list-style-type: none"> • Diverse epitope coverage • Excellent physical properties • Ease of manufacturing
Omni <i>d</i> Ab™	<ul style="list-style-type: none"> • Single camelized human VH framework with truncated LC 	<ul style="list-style-type: none"> • Domain antibody of the “VHH” type 	<ul style="list-style-type: none"> • Diverse and new epitope coverage from human single-domain format, 12-15kD • Building blocks for multispecific molecules
 OmniTaur™	<ul style="list-style-type: none"> • Single framework • VH4/VL1 	<ul style="list-style-type: none"> • Ultralong CDR-H3's for enormous structural diversity 	<ul style="list-style-type: none"> • Access cryptic epitopes • Unique modalities (picobodies™) • Building blocks for multispecific molecules

Common Light Chain Platforms

STANDARD IGG FORMAT TO DE-RISK DOWNSTREAM DEVELOPMENT[†] OF BISPECIFIC MABS



Rearranged human VK3-15 light chain combined with diversifying heavy chain



Simple reformatting from monospecific into bispecific for efficient production



"Germlining" human VK3-15 light chain combined with diversifying heavy chain

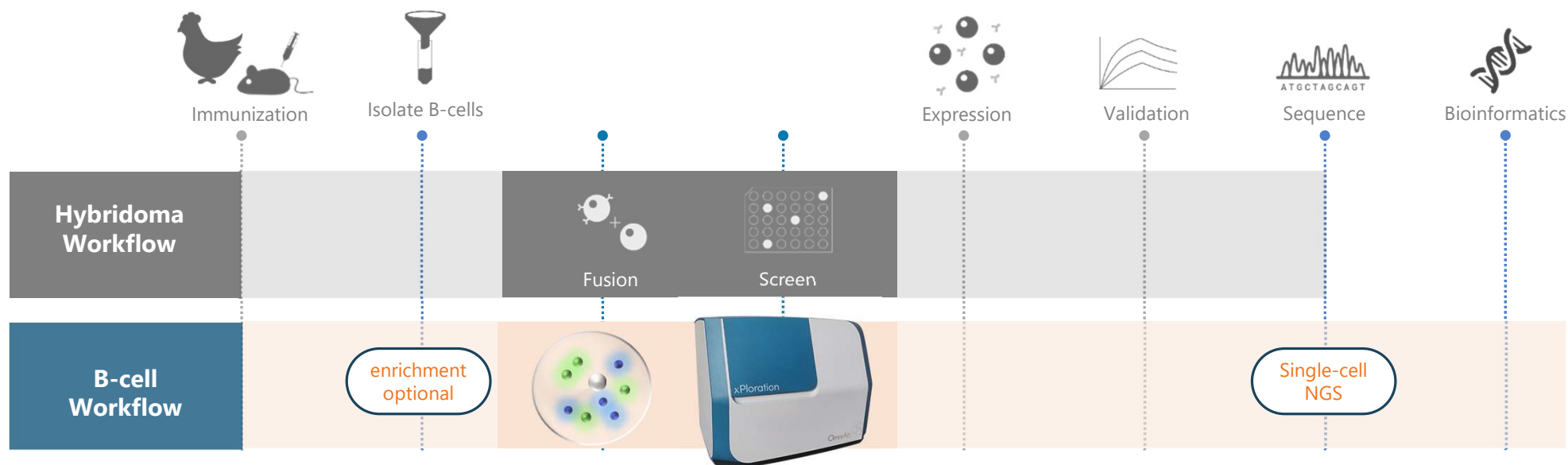


Monospecific IgG

Common light chain for OmniFlic[®] and OmniClic[®] allows interchangeability between the platforms

[†]The Evolution of Bispecific Antibodies, Nimish Gera
<https://doi.org/10.1080/14712598.2022.2040987>

Discovery Platforms

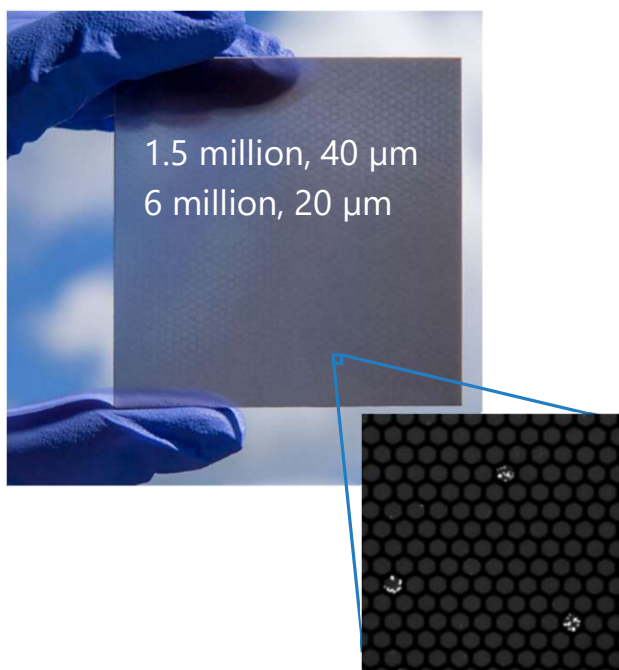


Our powerful single B-cell screening technologies, **xPloration®** and **GEM assay**,
bypass bottlenecks of hybridoma workflows

AI-driven multi-parameter screening of **tens of millions** of cells in **hours instead of weeks**

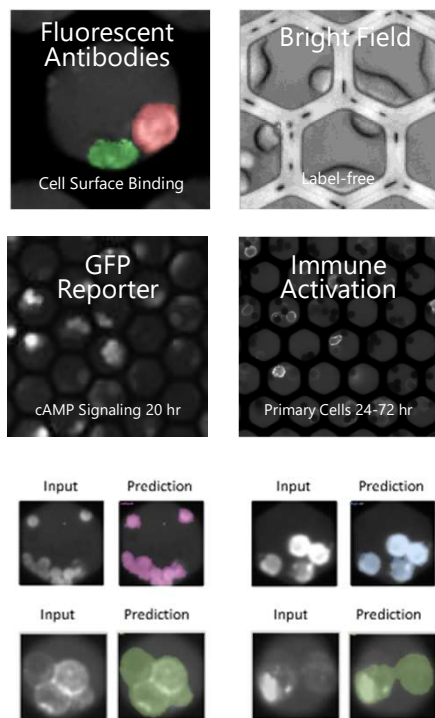
Technologies enable **screening against difficult targets**:
GPCRs, ion channels and surface antigens

1 | Loading



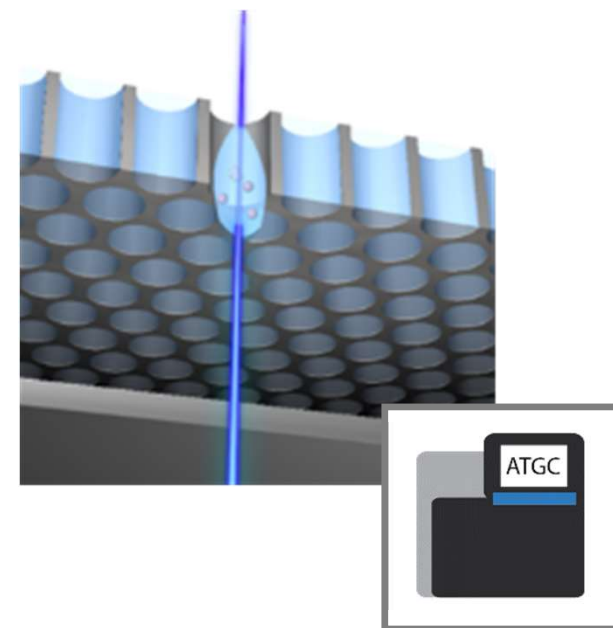
Unique through-hole format
Workflows for OmniAb B-cells

2 | Assay + Machine Vision



AI-driven hit detection

3 | Recovery & Single-Cell NGS

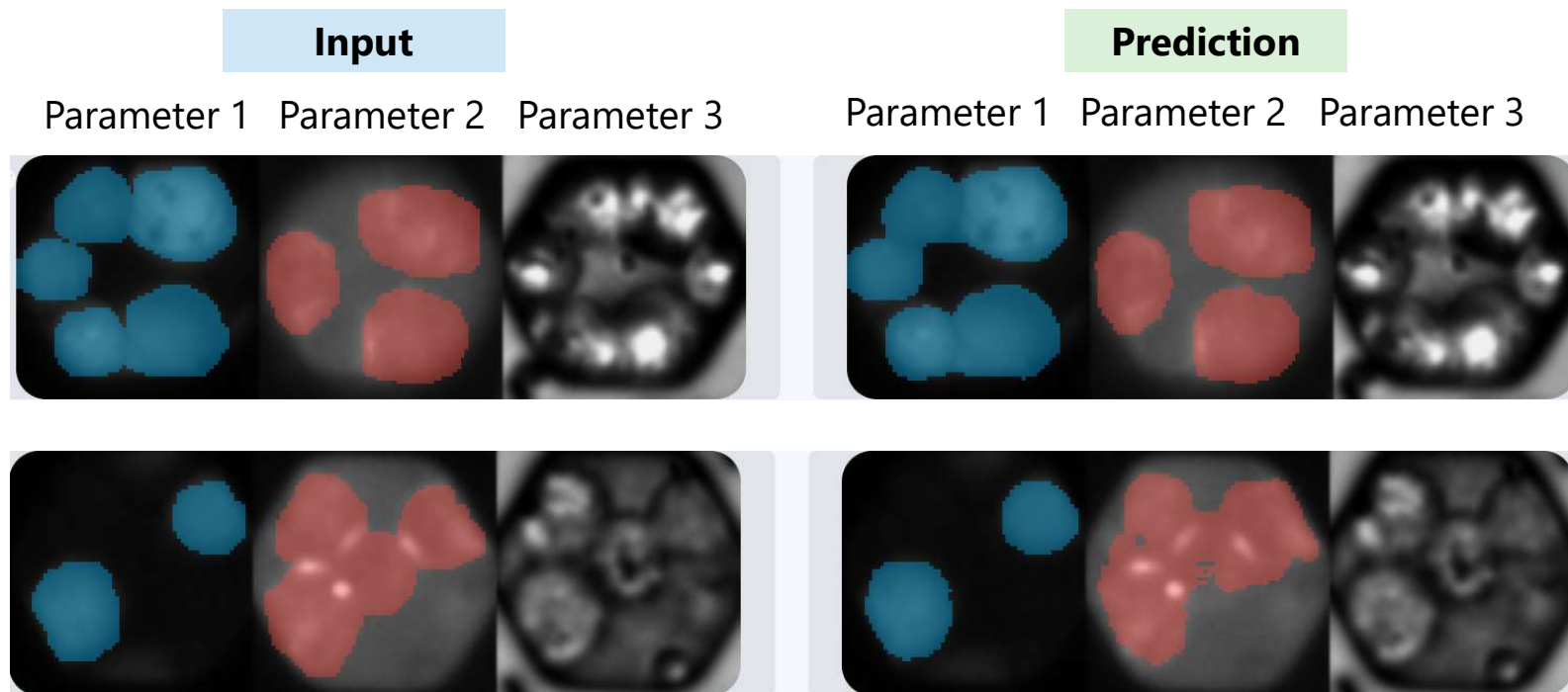


Precise laser-based recovery
1 cell/sec
Single-cell barcoding or pooled

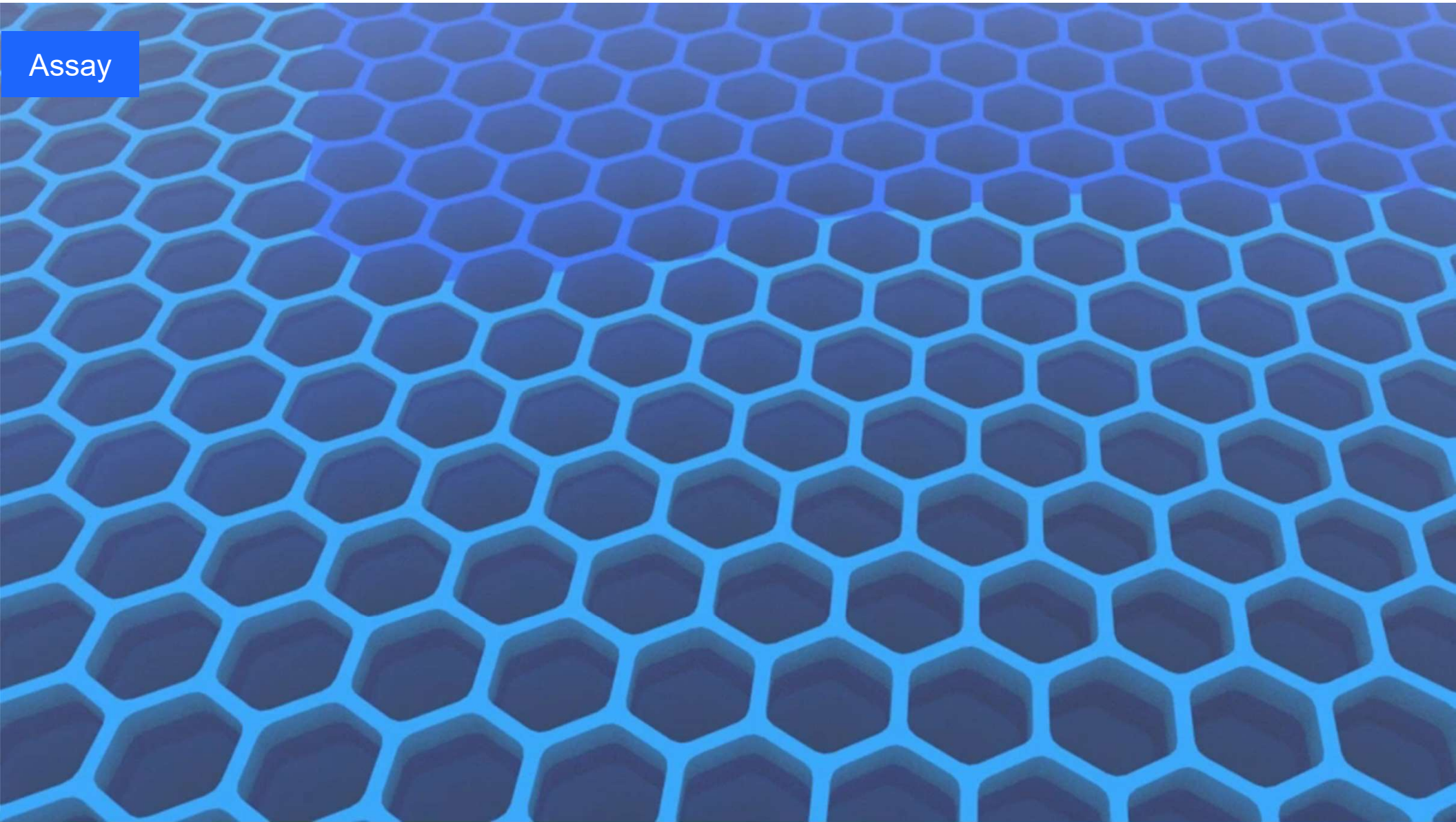
AI-Driven Multiplex Assays



- LandingLens AI platform enables selection of hits from xPloration based on multiple phenotypical assays



Assay



Assay

Antibody
secreting cell



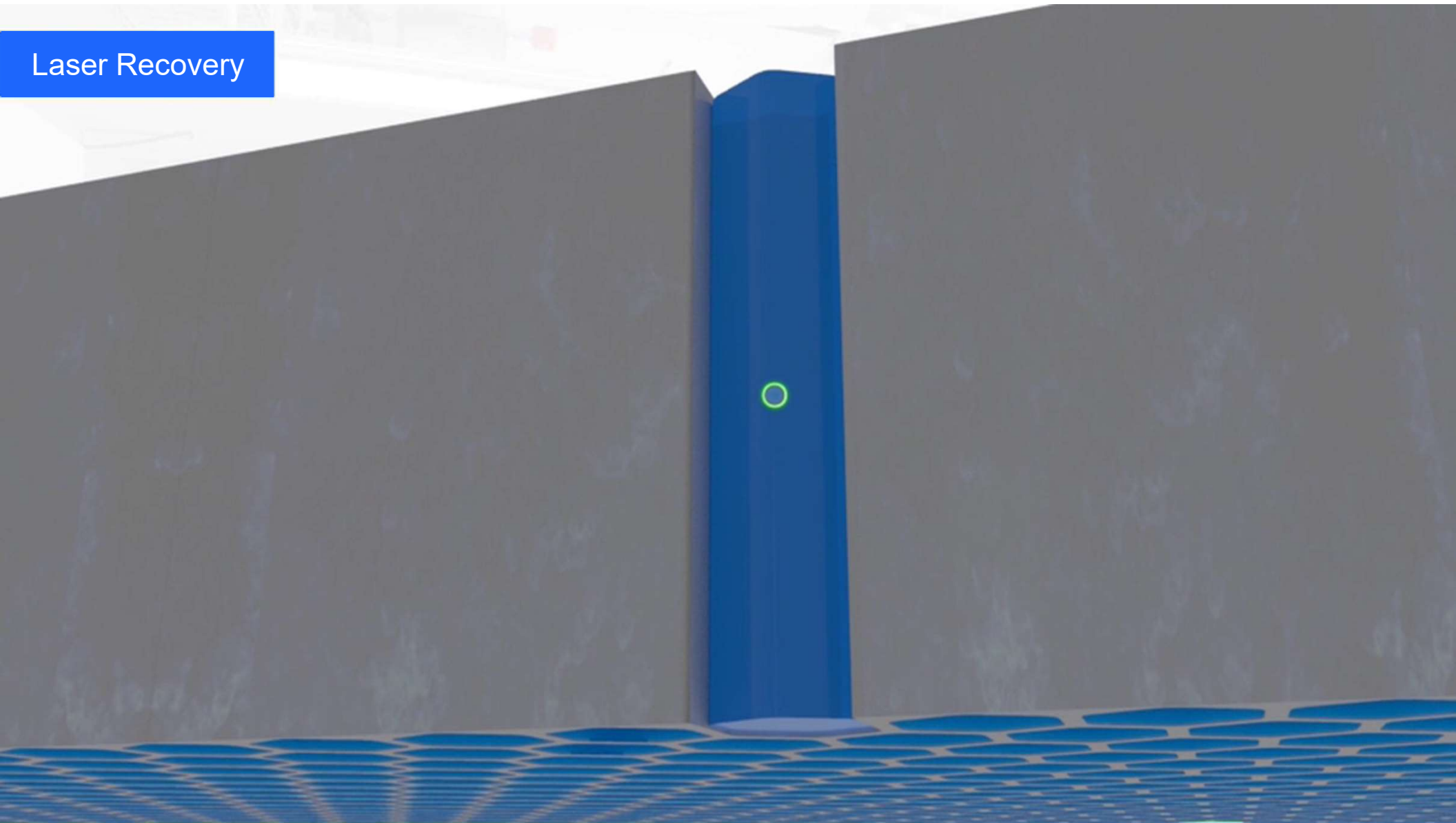
Target cell



Assay



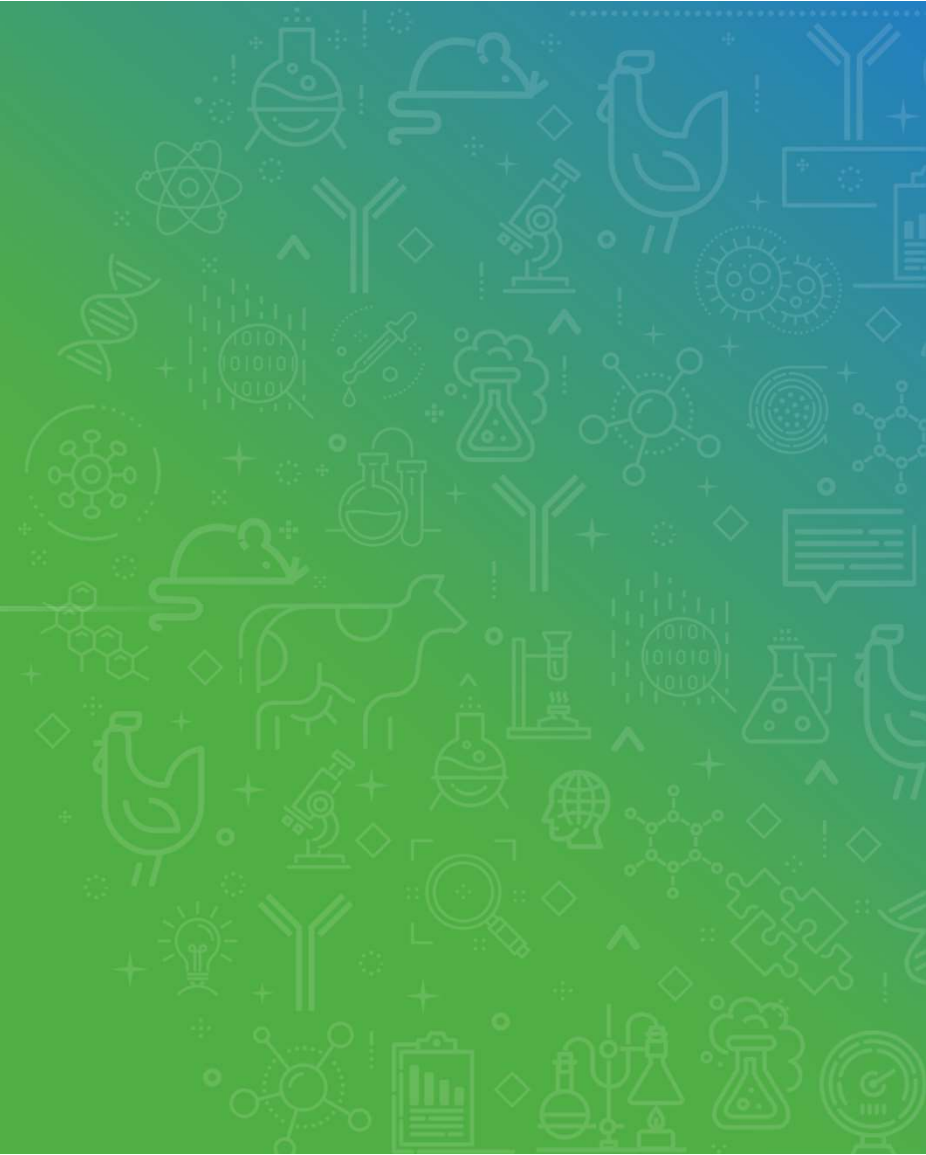
Laser Recovery





NKp46 Case Study:

Discovering NK cell engager arm for
bispecific antibody

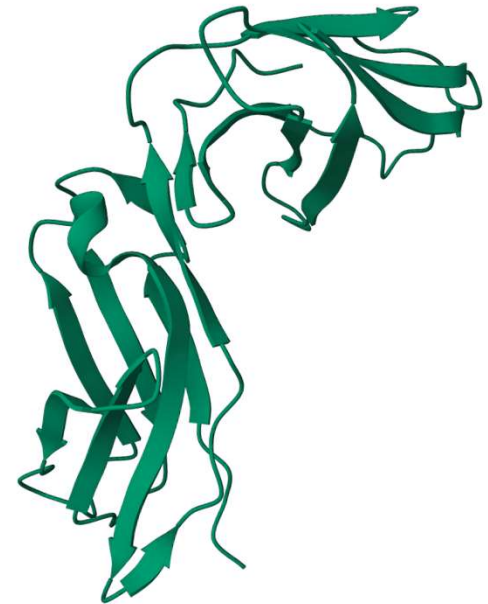


Biological Background

- **Target**

- NKp46 (NCR1, CD335) is a 46-kDa glycoprotein
- No statistically significant downregulation of NKp46 on both NK and T cells has been observed in many cancers

- **Goal:** Discover anti-NKp46 antibodies from OmniClic and OmniFlic as one arm of a bispecific antibody (NKCE)



From PDB 6IAP

Large-Scale Antibody Discovery

 OmniFlic®

+ xPloration®

OmniClic®

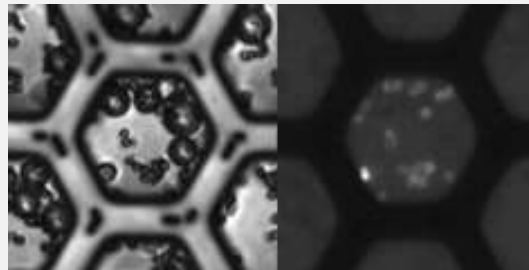
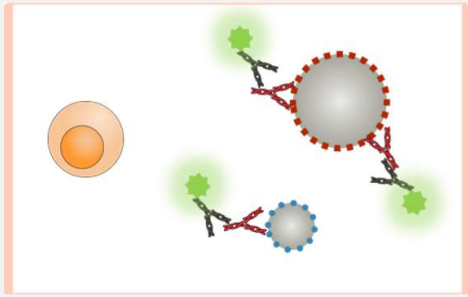
OmniDeep™

Multi-Parameter Screening: Multiplex Phenotypic Data

Selective binding of target on beads

BF

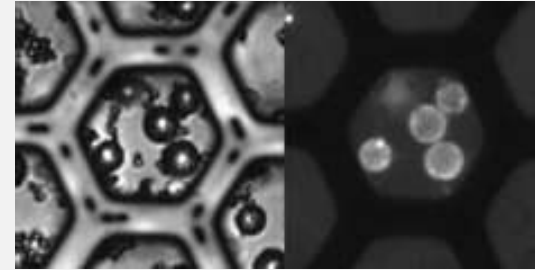
Binding



Binding to NKp46

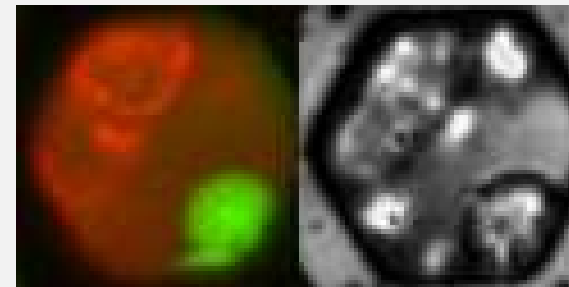
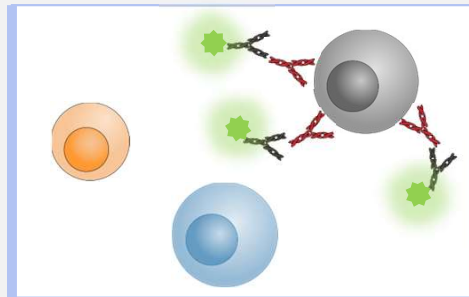
BF

Binding



Binding to Tags

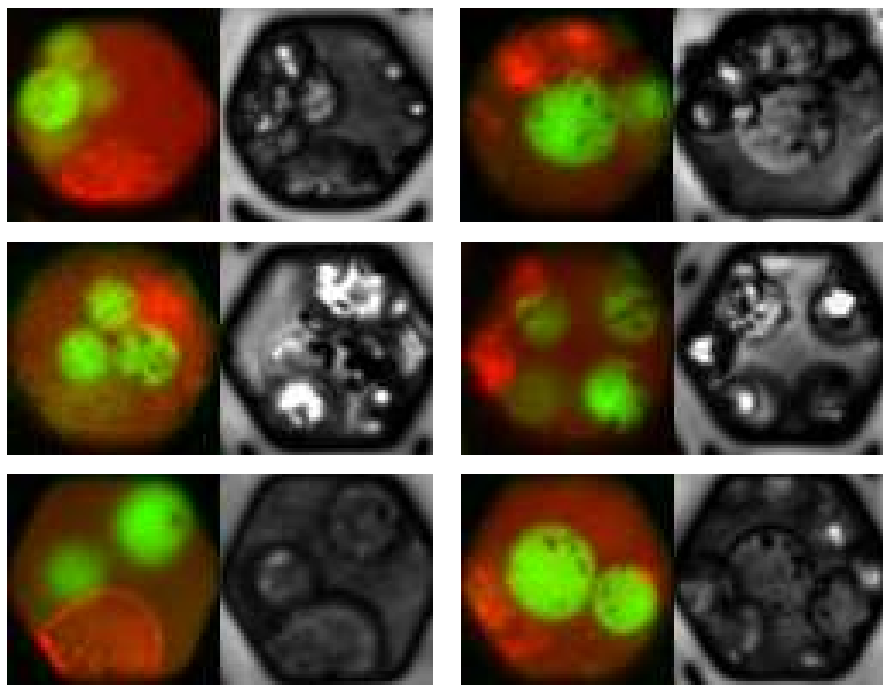
Selective binding of target cell



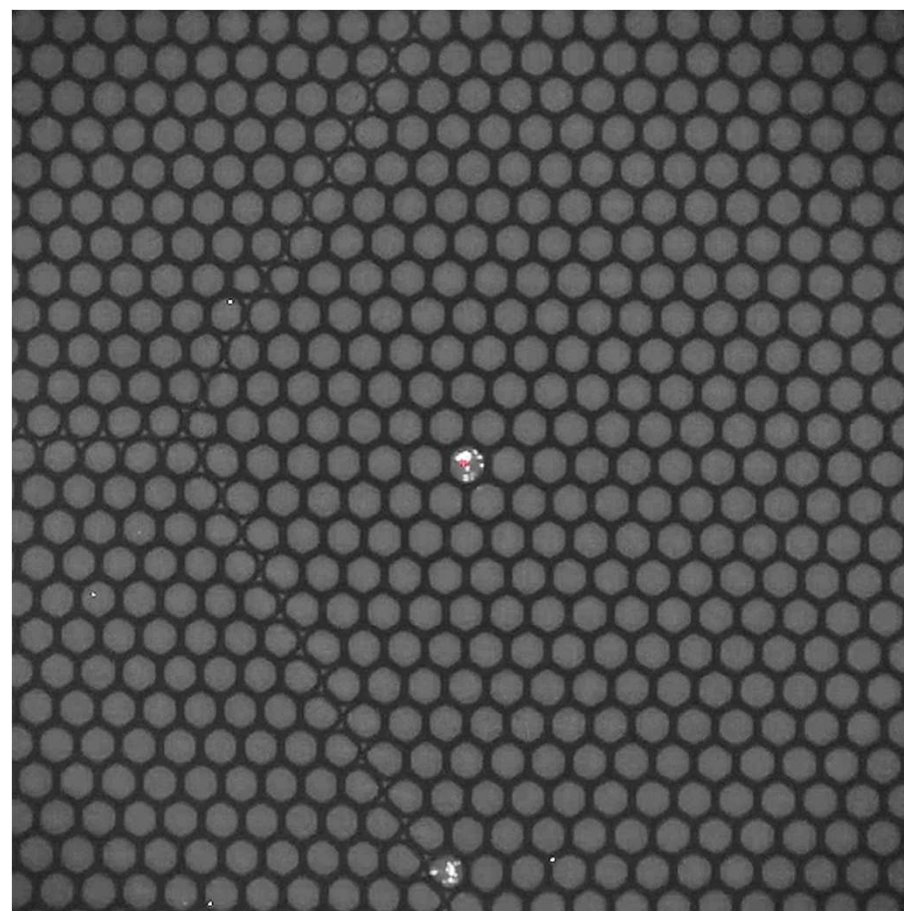
Negative Cell
Binding Signal
BF

Hit to Laser Recovery

Target	Negative
CHO K1 NKp46	Parental CHO K1 stained with CellTracker Blue



Red = Target
Green = Negative



1x speed video

OmniFlic Screening Summary



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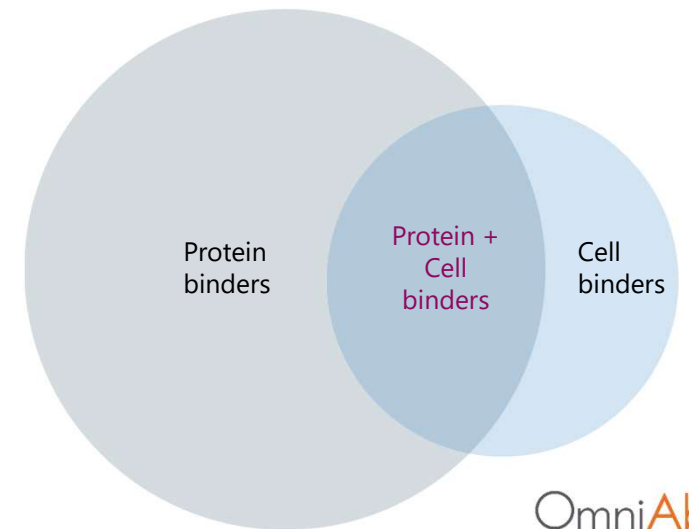
	Screen type	# cells screened	# hits
OABI01-1	Antigen on beads	5.0 M	1429
	Cells	7.7 M	345
OABI01-2	Antigen on beads	3.7 M	751
	Cells	3.7 M	158
OABI01-3	Antigen on beads	3.7 M	308
	Cells	3.7 M	33

- Recovered over 3000 positive events in 6 screens
- Cells were extracted with pooled recovery
 - Single NGS library for each sort

OmniFlic Repertoire Space

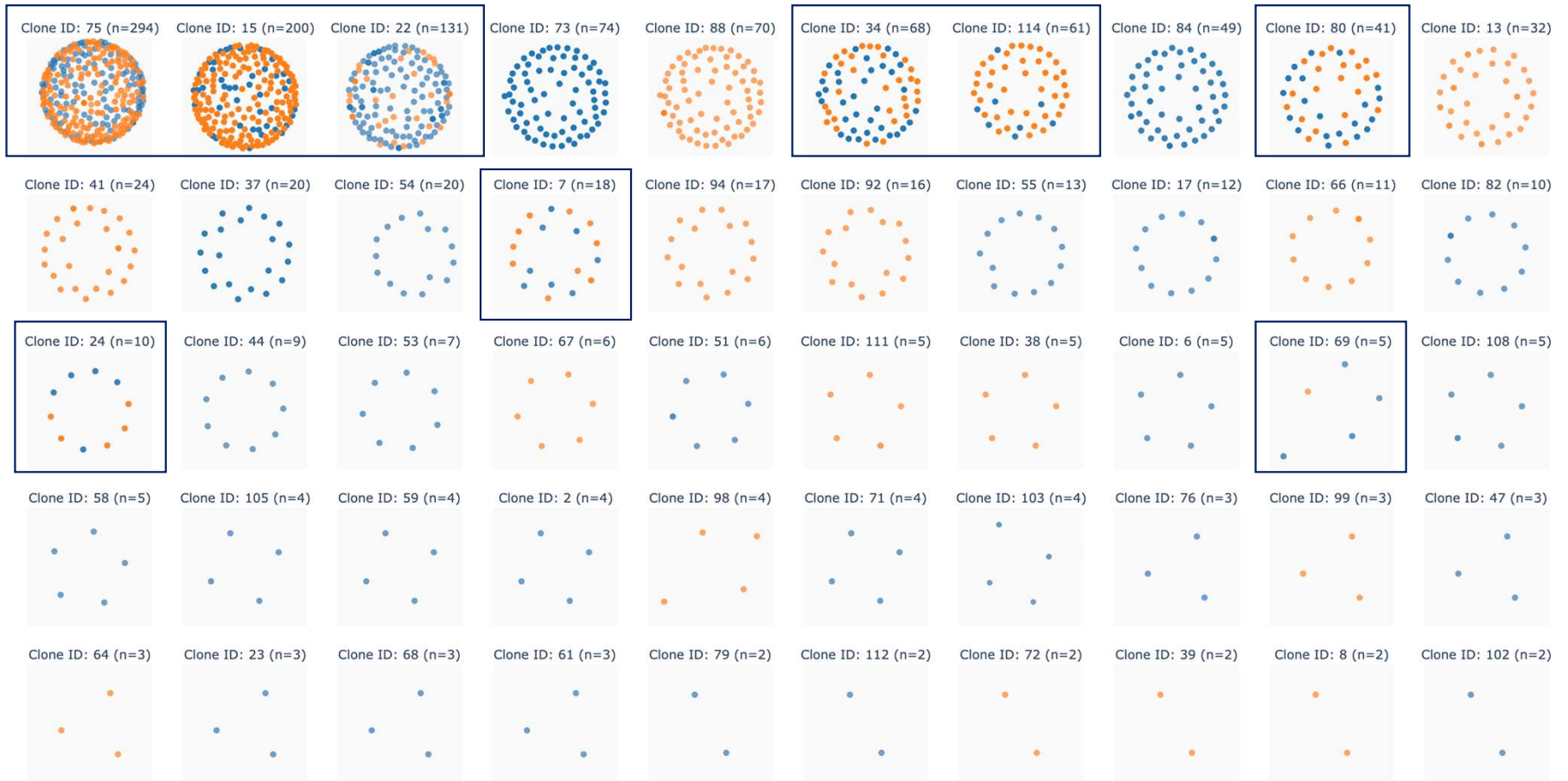
	# Unique Sequences	# Lineages	Overlapping Lineages	Overlapping Unique Sequences
OABI01-1	356	51	3	185
OABI01-2	621	42	4	445
OABI01-3	398	31	2	68

- **1375 Unique Clones** in 124 lineages
- Focus on 9 overlapping lineages between cell and protein screens



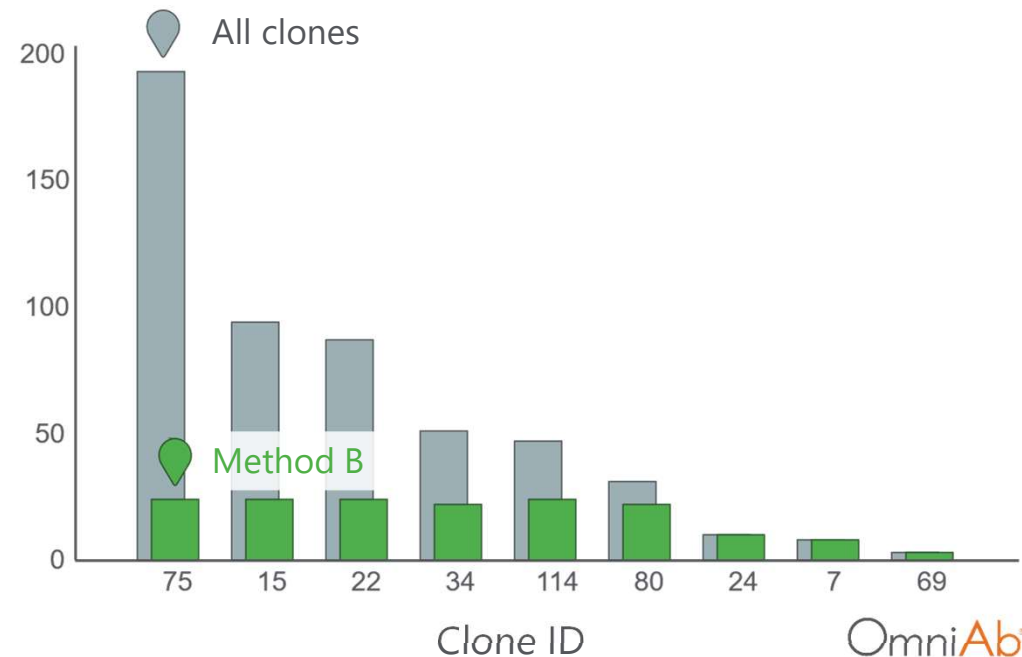
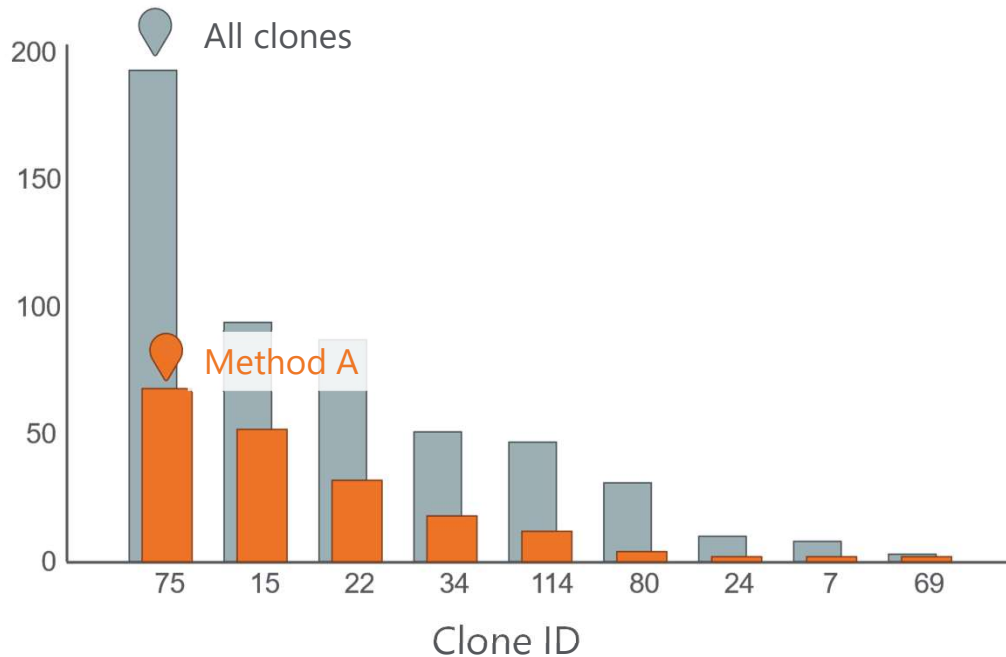
OmniFlic Repertoire Space

- Bead screen
- Cell screen

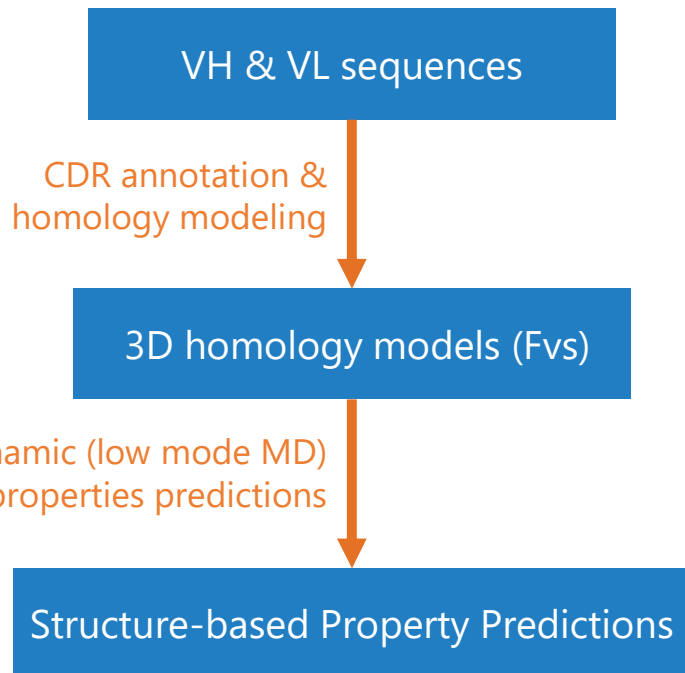


Bioinformatics-Aided Antibody Selection

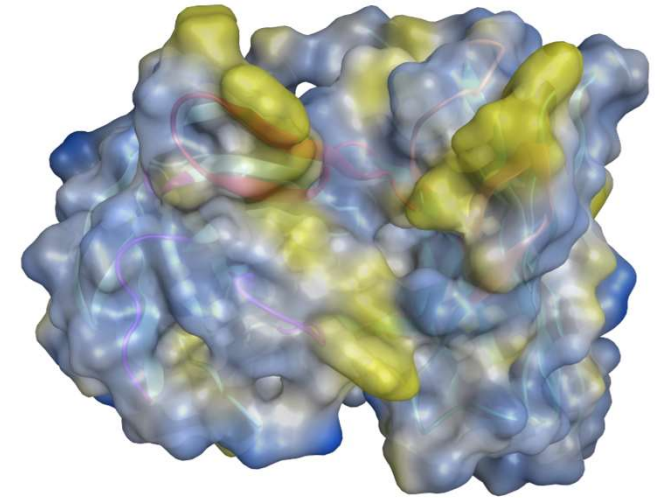
- Clone selection considerations
 - Sequence differences: maximize coverage of sequence space
 - Sequence read counts: bias towards most represented via read count
 - Bias towards or away lineage distribution



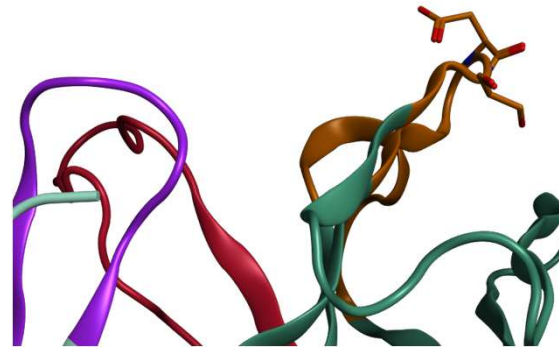
Structure-Based In Silico Developability Filter



Example 1: Fv_128 surface.
Large lipophilic (yellow) surface near the CDRs (Hydrophilic areas shown in blue.)



Example 2: Fv_55 Asp-62.
Asp-62 within CDR_H2 followed by small AA (Ser-63) and highly flexible (RMSD derived from low mode MD conformational search) : potential isomerization site.

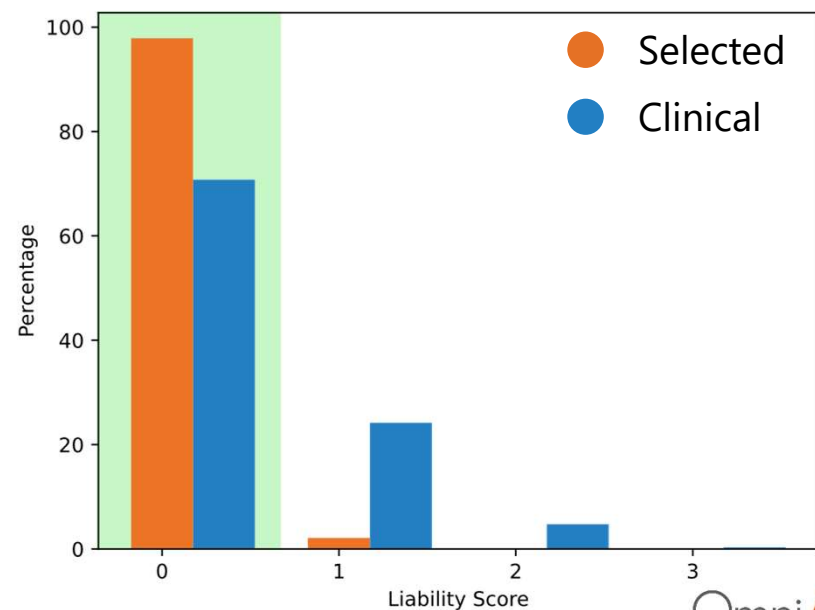
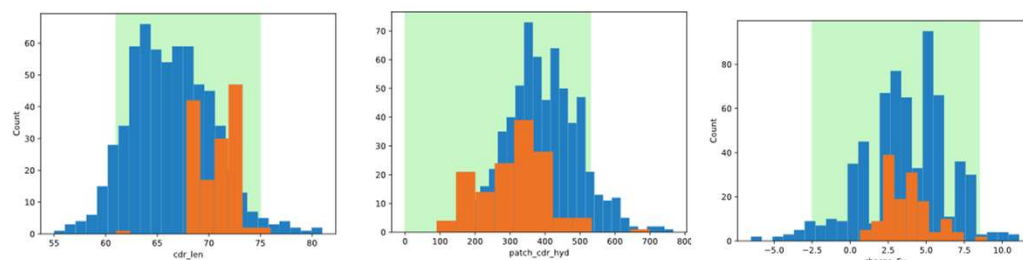


Cost and time efficient filtering for the most promising Fvs based on predicted properties

Most Selected Clones Pass In Silico Developability Filter

Liability score (Goal = 0)

- Total CDR Length
- Area of Hydrophobicity near CDRs
- VH-VL Charge balance
- Fv Charge

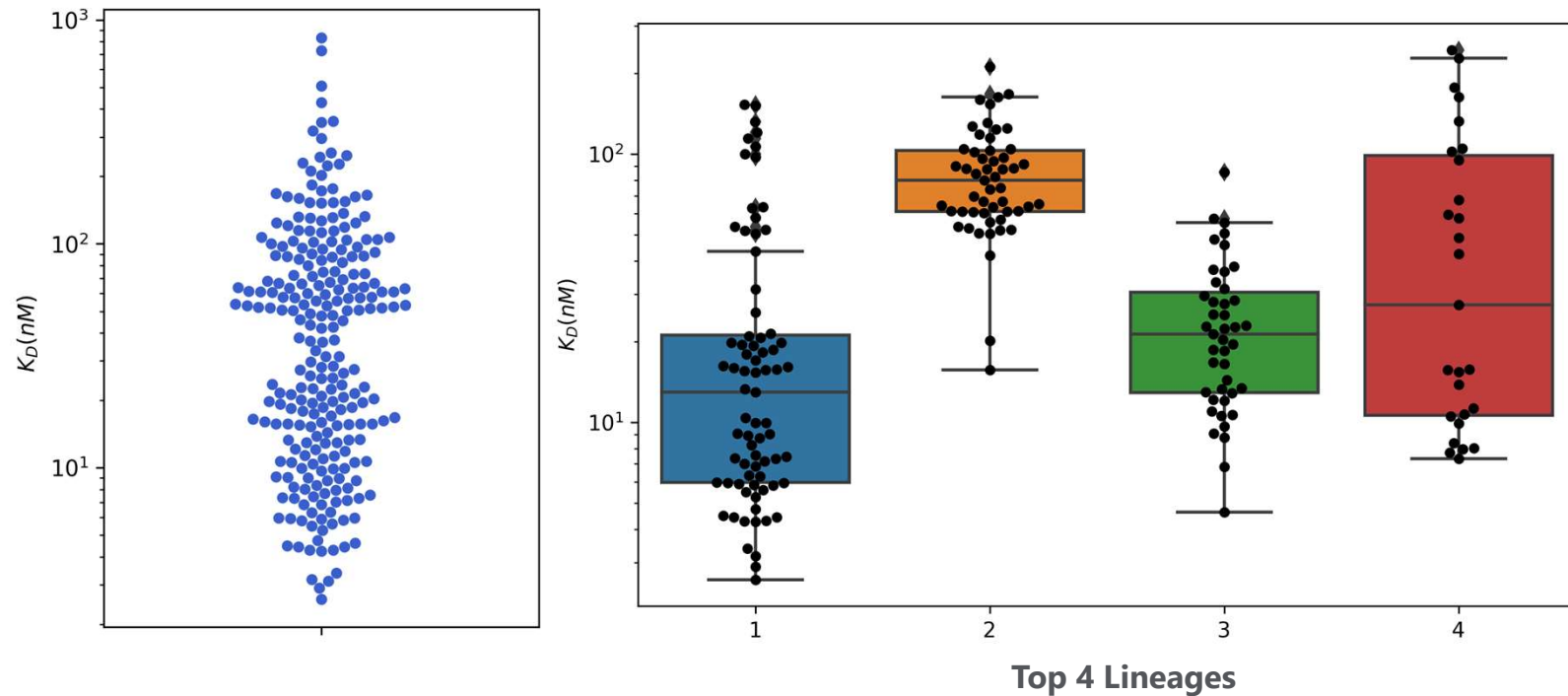


Most selected OmniFlic antibodies pass

- Filtered 2% of sequences

Discovery of High Affinity NKp46 Binders

# Selected Clones	Expression (%)	Binding (%)	<10 nM (%)
301	95.7	84.7	20.1



OmniClic Screening Summary

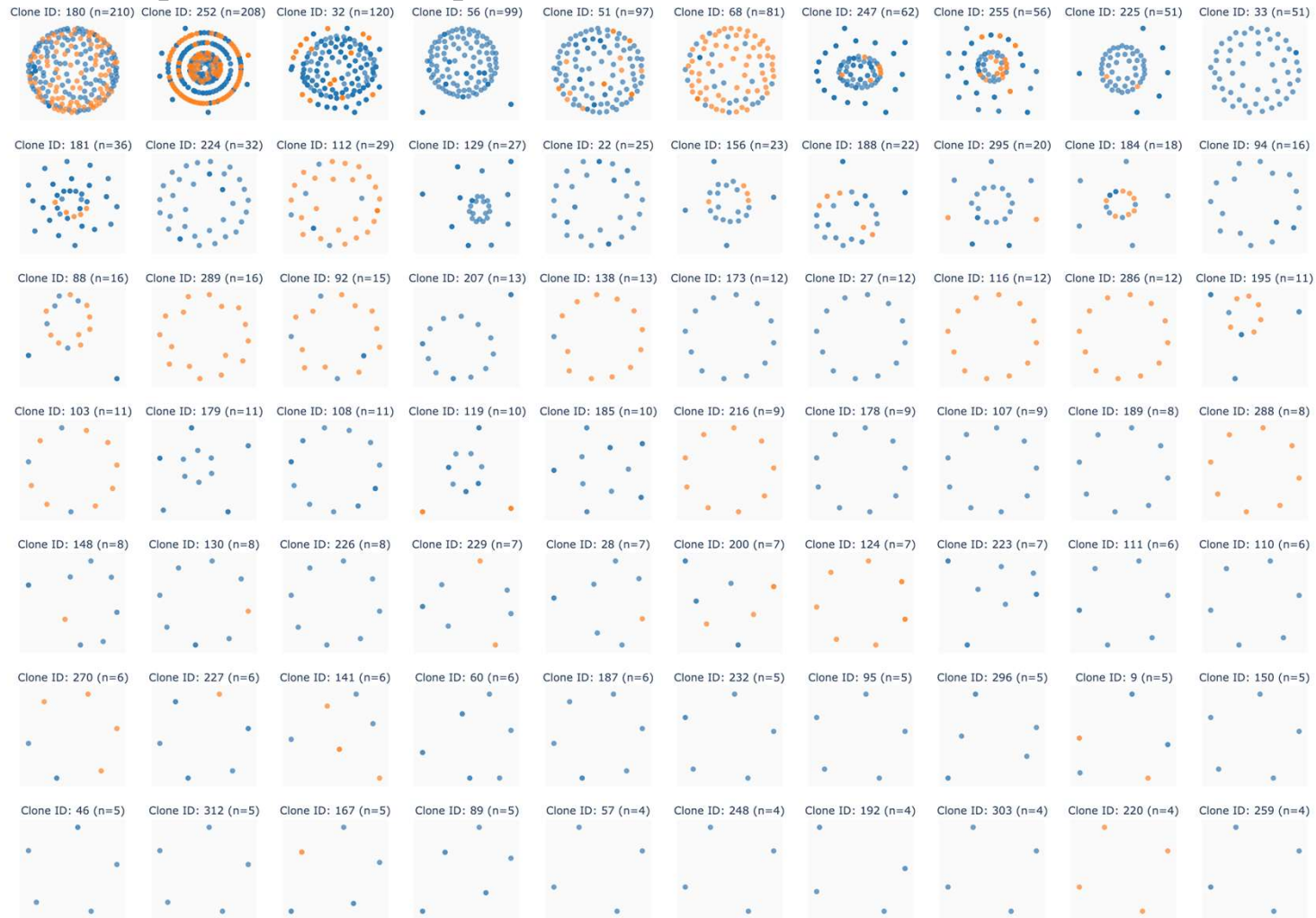


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	Screen Type	# Cells Screened	# Hits
69786	Antigen on beads	1.4 M	1200
	Cells	3.2 M	203
69789	Antigen on beads	1.4 M	1199
	Cells	3.1 M	602
69797	Antigen on beads	2.6 M	1326
	Cells	1.3 M	699

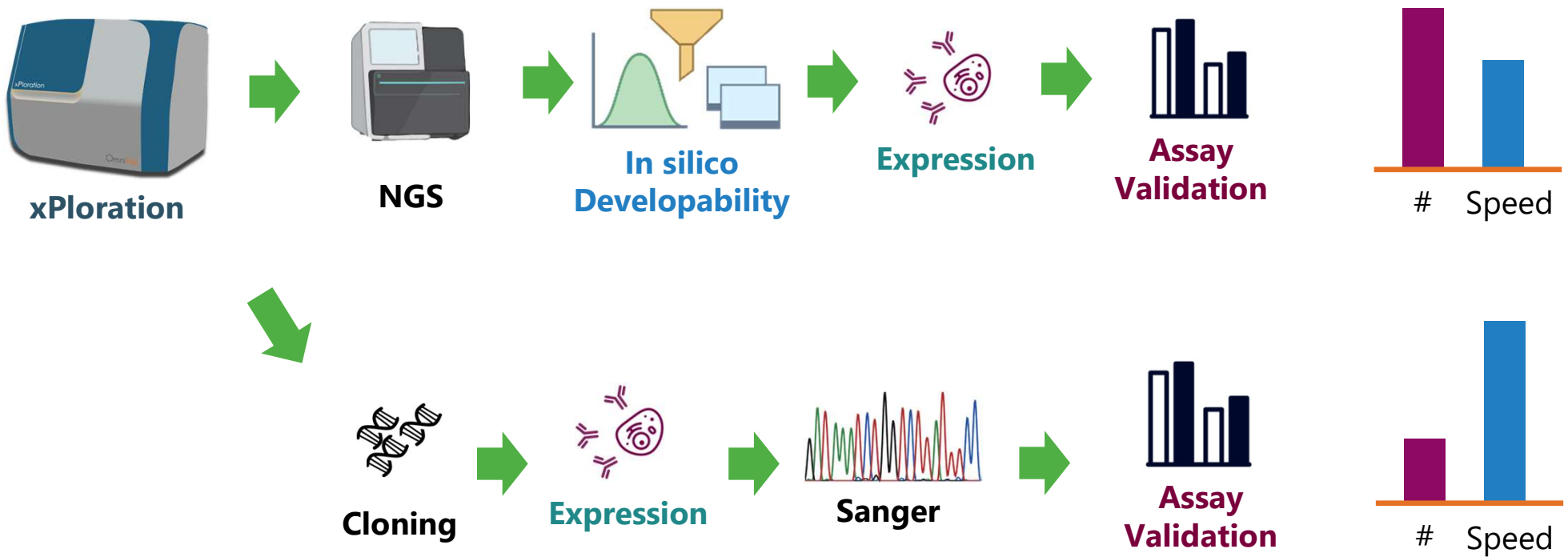
- Overall extraction count: **5229**
- Overall unique sequences count: **2231**

OmniClic Repertoire Space



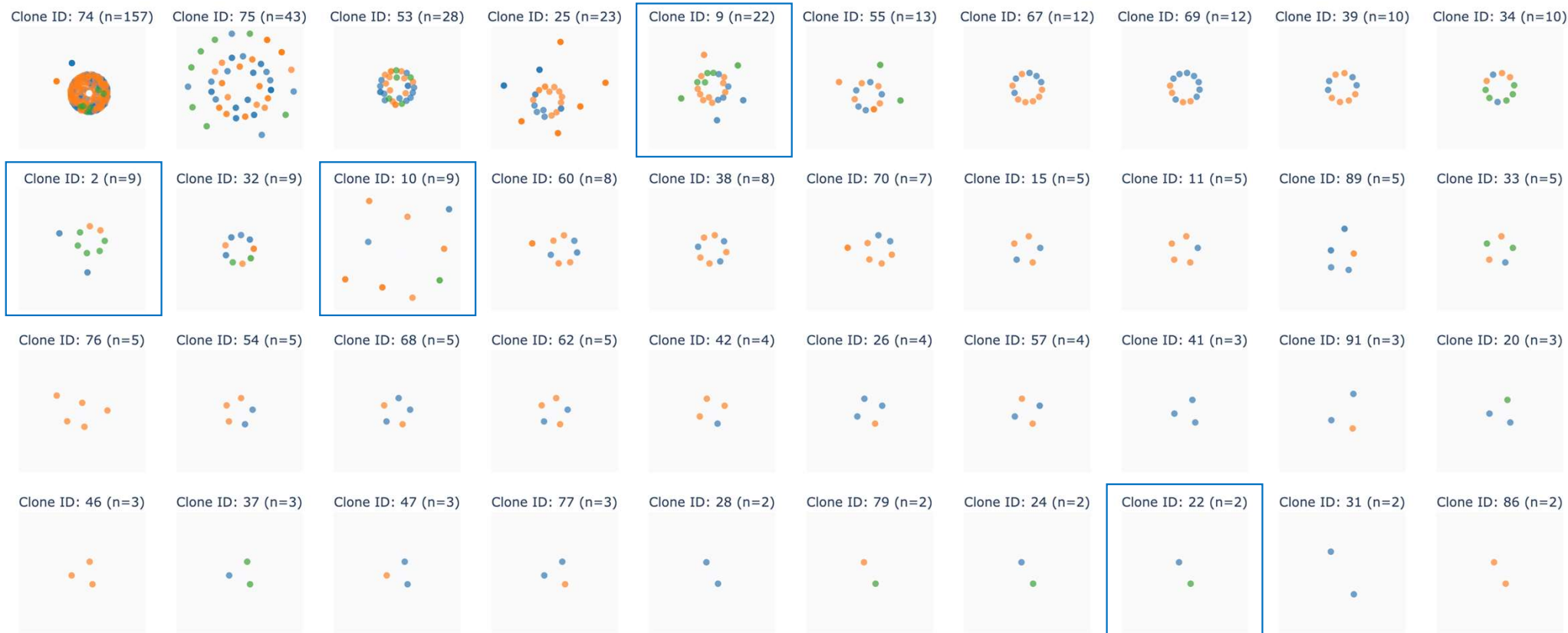
- Bead screen
- Cell screen

Parallel Processing of NGS and Cloning Workflows



Confirmed High Affinity Binders Overlay

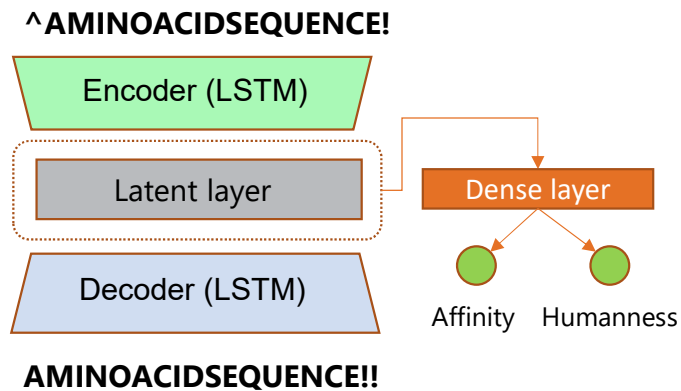
- Bead
- Cell
- Confirmed



OmniDeep: Deep Learning on Antibody Sequences

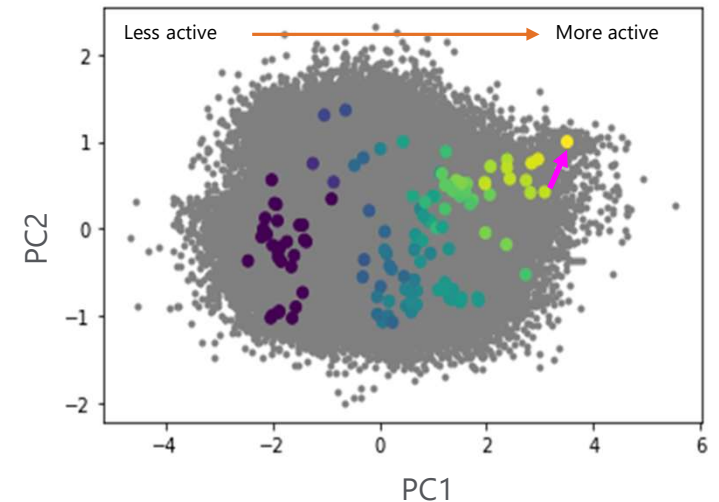
- Deep learning allows fuzziness and non-obviousness in antibody discovery and design
 - Adaptable and scalable
 - Help design and prioritization of novel antibodies with the desired therapeutic profile
 - Data-driven: built on input data and/or associated databases
- Tools:
 - Autoencoders/Variational Autoencoders (VAEs)
 - Masked Language Models (MLMs)

Encoding Antibody Repertoires into Latent Space



The Decoder portion of the model also allows exploration of sequences from the latent space

Latent space trained with activity prediction is organized by activity

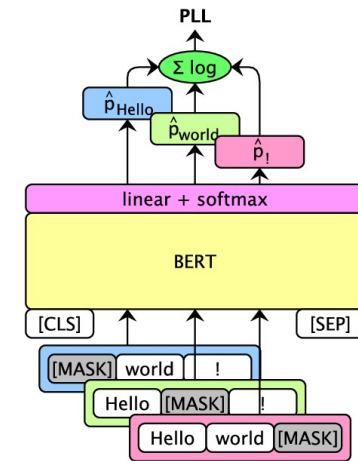


Colored by $-\log(\text{Binding Affinity})$ gray points are unmeasured. Purple \rightarrow low affinity; Yellow \rightarrow high affinity

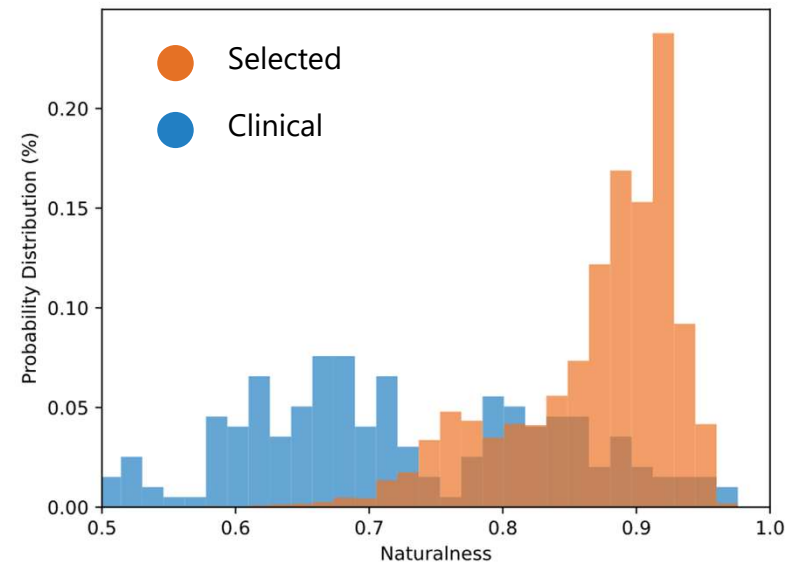
- The model is trained on:
 - Bulk NGS VH sequences
 - xPloration sorted sequences
 - Affinity measured IgG's
 - Computed humanness scores
- AI learns repertoire space from Biological Intelligence™

Scoring Model for Humanness

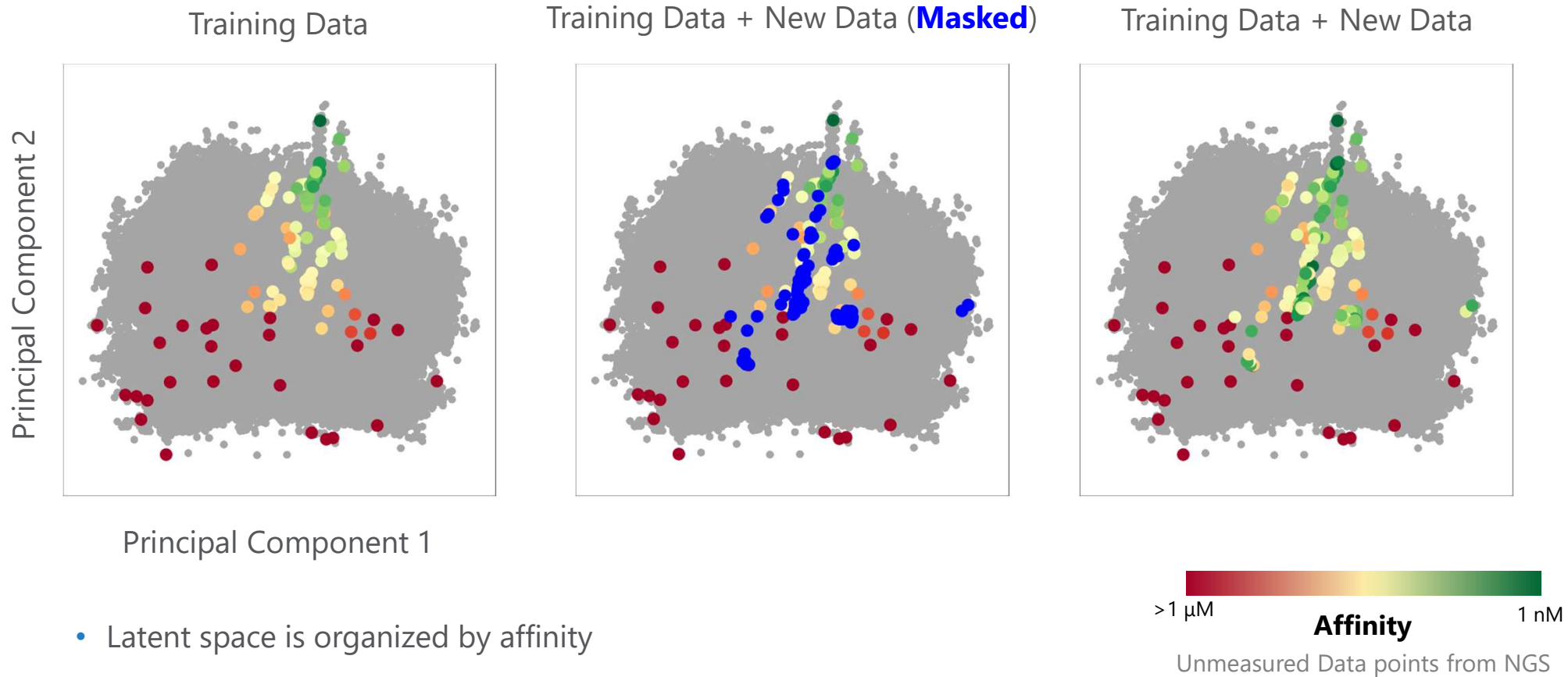
- **Humanness score** – trained on human sequences from OAS database
- Employs RoBERTa masked language model
 - robustly optimized bidirectional encoder representations from transformers (BERT)
- Most OmniFlic sequences have scored highly



Pseudo-LogLikelihoods (PLLs) from RoBERTa masked language model



Validating VAE Latent Space

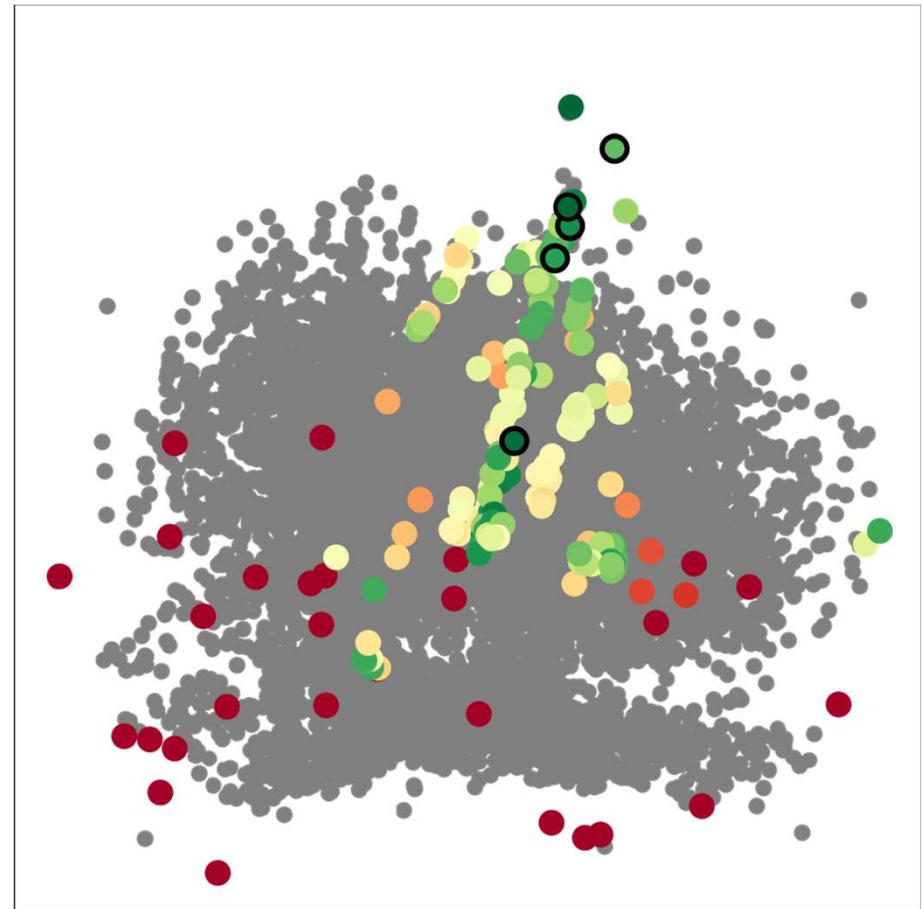


- Latent space is organized by affinity
- 2nd round of affinity data seems to follow latent space

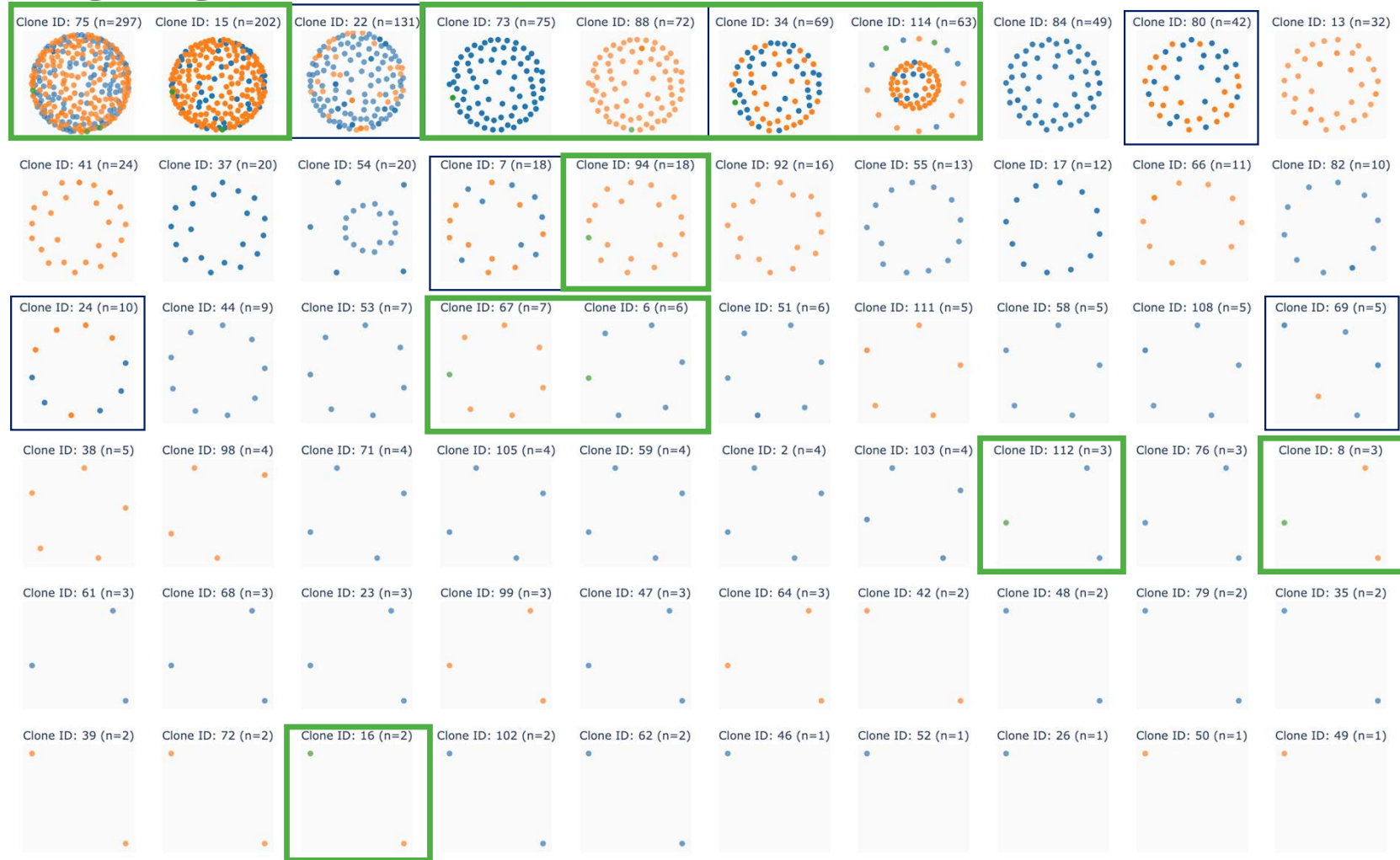
Leveraging VAE Latent Space to Select Clones

Use cases:

1. Guide to navigate antibody repertoire
 - Focused on 5 high affinity clones
 - Selected clones close in latent space but not in sequence
 - Non-obvious insights
2. Extend beyond observed sequences



VAE Highlight New Clusters to Prioritize



Deep Repertoires

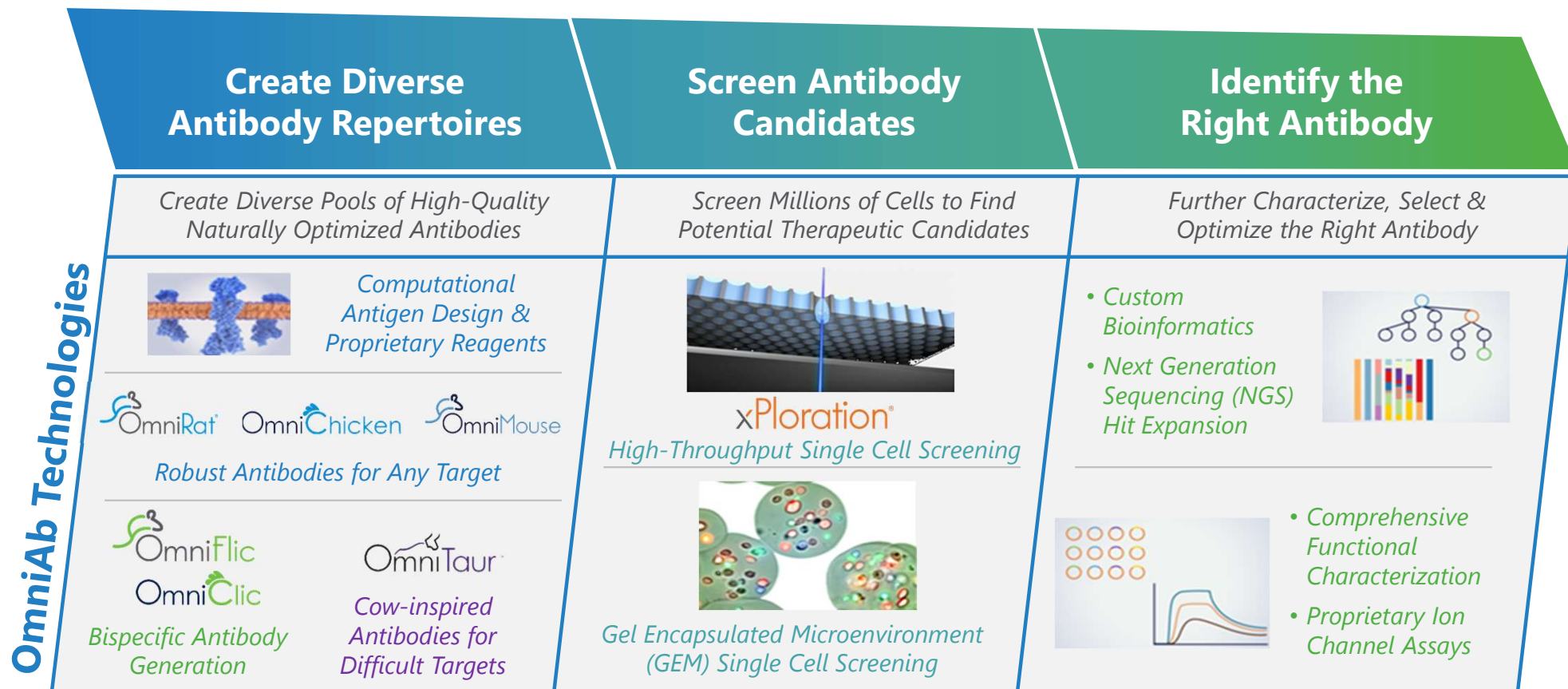
Deep Screening

OmniDeep™

Deep Sequencing

Deep Learning

OmniAb Technology Stack



Technology offering addresses the most critical challenges of antibody discovery

OmniAb[®]

THANK YOU!

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www.OmniAb.com

