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Membrane Protein Solutions

1 in 3 mAbs Binds Off-Targets

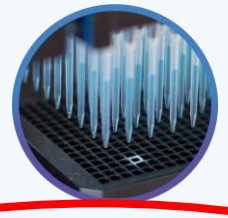
How To Predict and Avoid Adverse Events Caused by Polyspecificity

PEGS Europe
Tuesday, November 17th, 2026

Rachel Fong
Sr. Director, MPA Commercial Operations
Integral Molecular

Integral Molecular: How We Can Expedite Your Programs

Solutions for Antibody R&D



Membrane Proteome Array™

Antibody specificity screening for lead selection and IND safety profiling

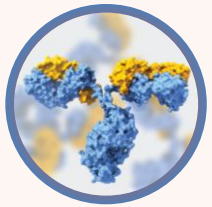
Lipoparticles (VLPs)

Virus-like particles with high concentrations of native membrane proteins for the highest quality immunization and screening

Epitope Mapping & CDR-scanning

Detailed binding analyses for intellectual property and mechanism of action studies

Therapeutic and Reagent Antibodies



Preclinical MAb Discovery

Application of the MPS antibody discovery platform to deliver lead candidates to IND

Therapeutic Pipeline

Therapeutic antibody assets available for licensing

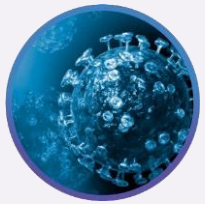
Reagent MAbs

Extensively validated, recombinant MAbs with unparalleled specificity

Available through Cell Surface Bio

CELL SURFACE BIO

Virology Reagents and Services



Reporter Viruses

Non-replicative viral particles with easy detection for safe neutralization assays

Influenza TiterSafe™ Particles

Ready-to-use influenza virus-like particles for easier hemagglutination inhibition assays using non-replicative particles

Neutralization Assay Services

For antibody developers who need neutralization data

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Specificity Testing is Critical for the Safety of Biotherapeutics

1 in 3

MAbs tested are polyspecific



- Off-target binding is a major source of side effects and clinical failures
- FDA requires specificity testing prior to clinical studies in humans

The emergence of cell-based protein arrays to test for polyspecific off-target binding of antibody therapeutics. Norden et al. 2024 mAbs, 16(1).

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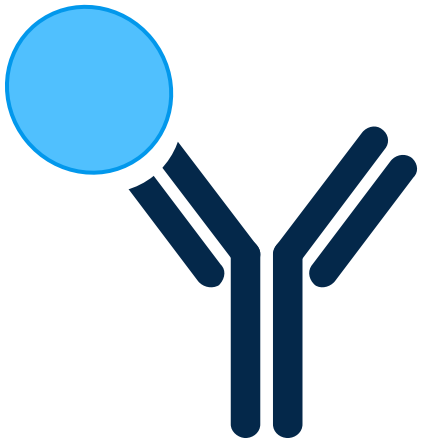
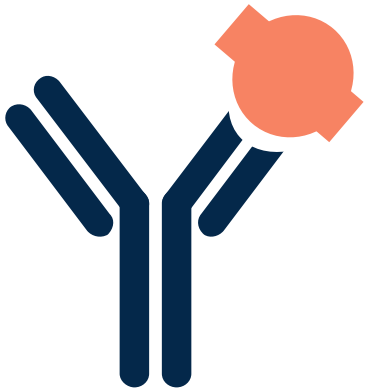
Mechanisms of Antibody Off-target Binding

On-target

target protein



Off-target



Polyspecific

- CDR-mediated binding
- Similar epitope to target protein
- Methods for detection: TCR, protein arrays



Polyreactive

- CDR- and non-CDR mediated binding
- Different epitope than target protein

- Interactions due to hydrophobic or charged residues
- Non-specific binding (proteins, carbohydrates, surfaces)
- Methods for detection: PSR and BVP binding, CIC

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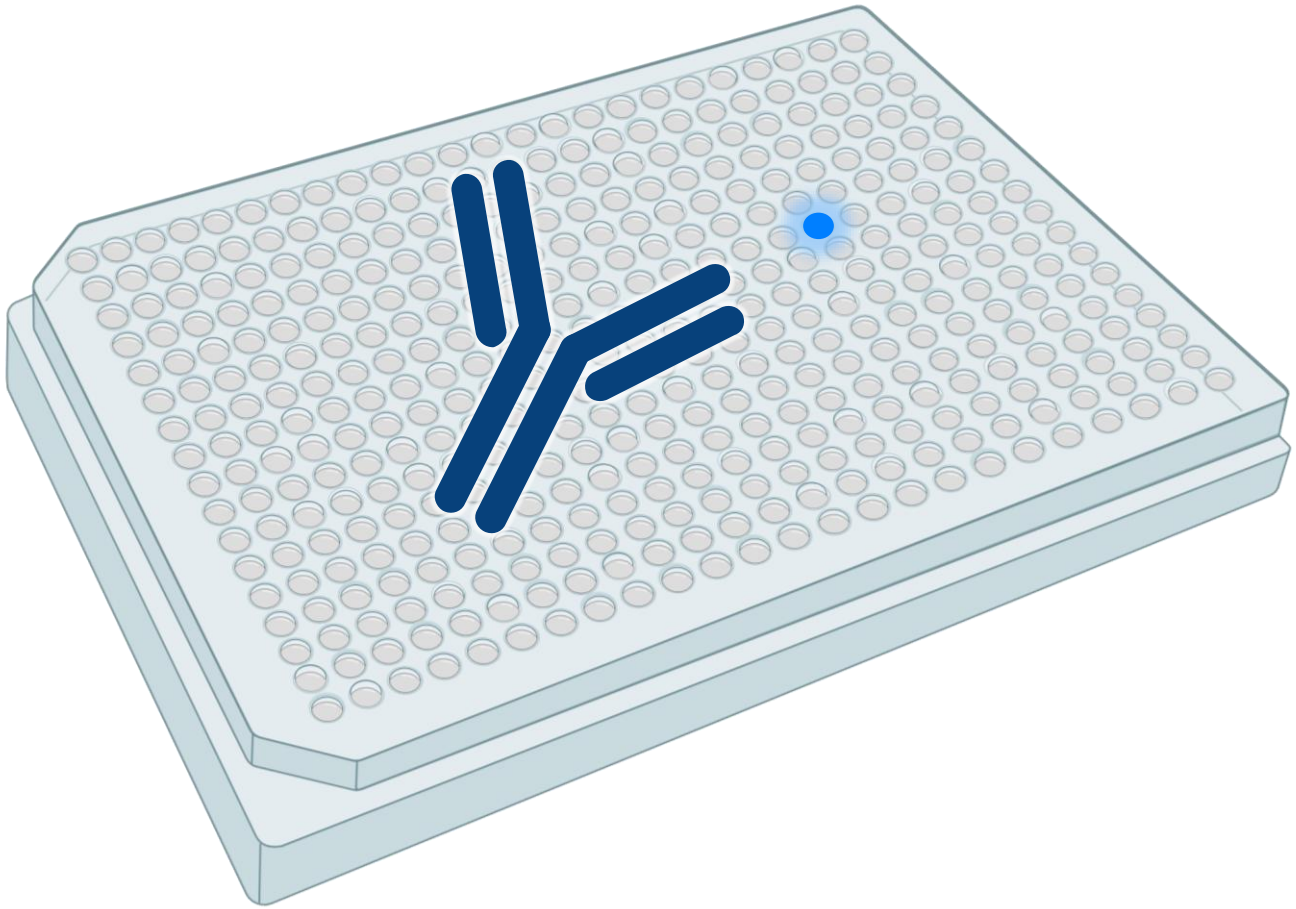
Norden and Doranz, 2021, *Translational Medicine*

Off-target binding: Clinical Relevance Beyond Developability



High Prevalence of Polyspecificity in Clinical Stage MAbs

Clinical mAbs Screened on the MPA				
	All	**Withdrawn**	**Phase 2/3**	**Approved**
# MAbs	83	18	25	40
Off-target	15	4	5	6
Rate	**18%**	**22%**	**20%**	**15%**

- Polyspecificity at all stages of clinical development, including drugs on the market today
- Off-target rates indicate polyspecificity is a major factor in drug attrition
- **Off-targets in the approved drugs were undiscovered and not in the BLAs**

Norden et al., 2024, *mAbs*

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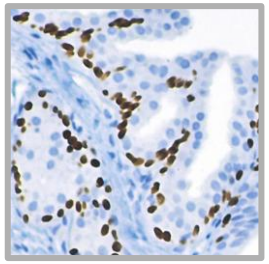
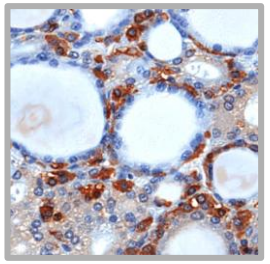
Conventional Methods

Tissue Cross-Reactivity (TCR) Studies

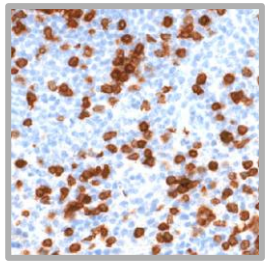
Prostate



Thyroid



Spleen

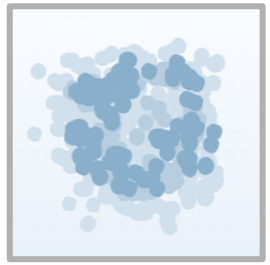


Protein Array Alternatives

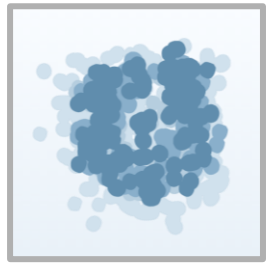
Medium



Medium/Strong



Strong



Conventional Method Limitations

- **Non-native (IHC/fixed)**
- **Non-quantitative**
- **Not FDA qualified**
- **Not validated**

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- ✓ Biologically Relevant
- ✓ Quantitative
- ✓ High Quality
- ✓ Predictive of Safety

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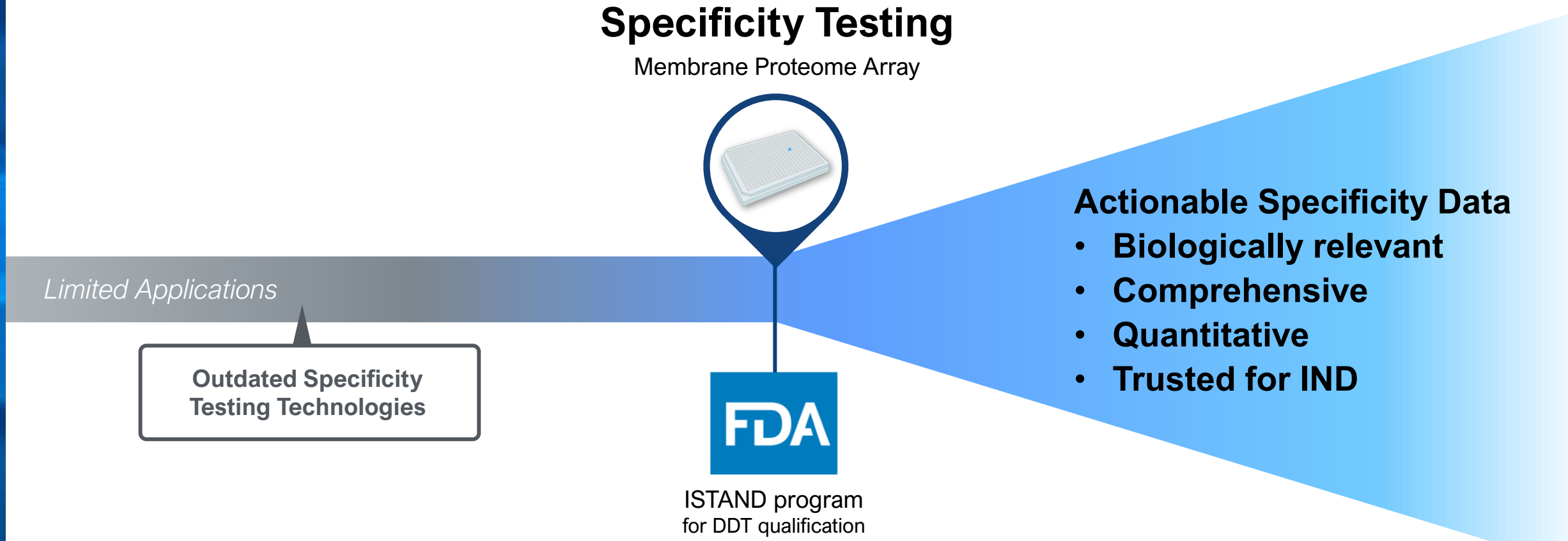
The FDA is Helping us Define the Next Generation of Specificity Testing



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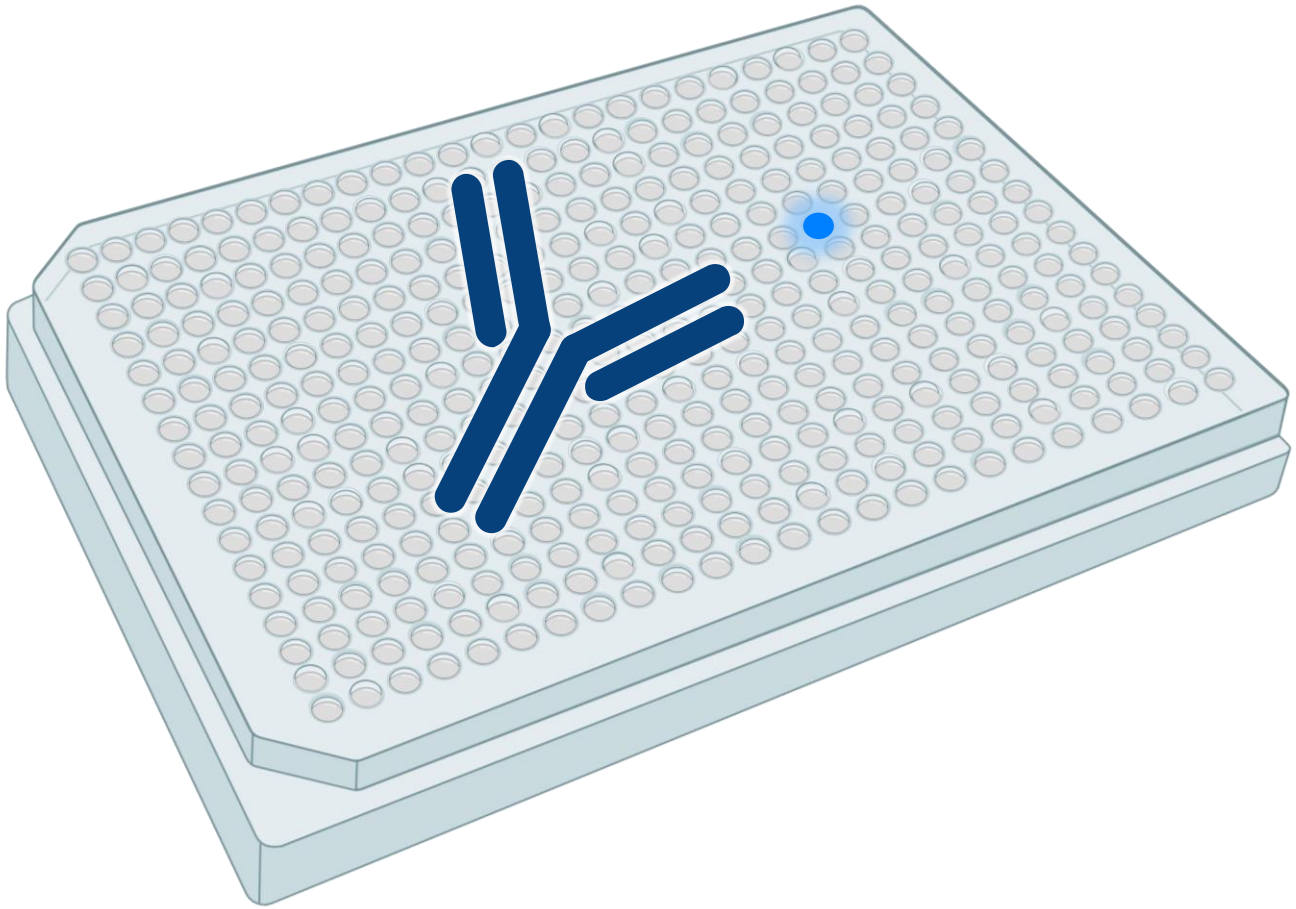
v0121

Membrane Proteome Array:

Platform Validation Overview



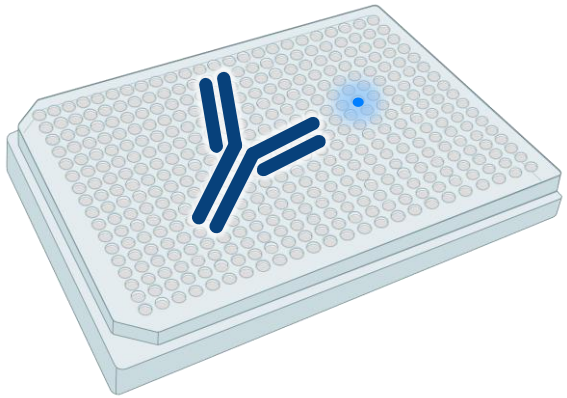
Membrane Proteome Array™ (MPA)

ISO 9001

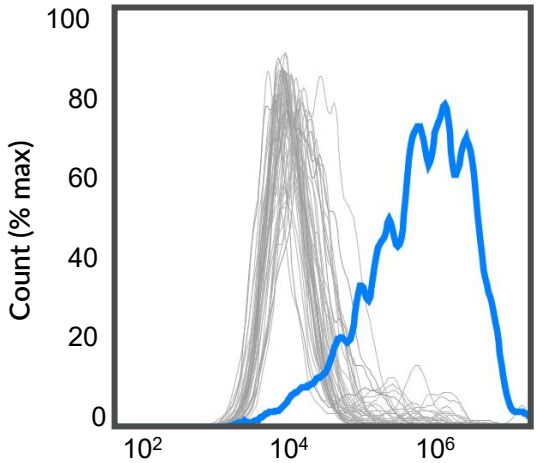
~6,000
native human membrane proteins

Quantify Binding
using flow cytometry

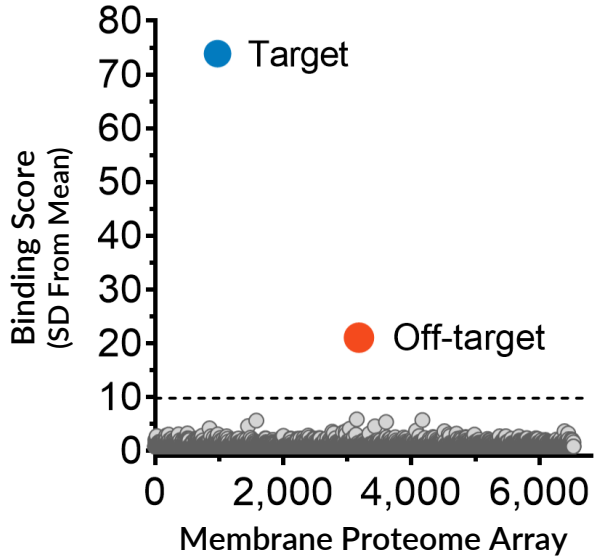
Test Specificity
across the library



384-well plate



Fluorescence



Membrane Proteome Array

- *Only* platform to use **native proteins** (unfixed cells) at each step
- *Only* platform to use **quantitative** screening (flow cytometry) for highest sensitivity
- Compatible with all modalities: mAbs, bi/multi-specifics, ADCs, CAR-Ts, peptides, etc.

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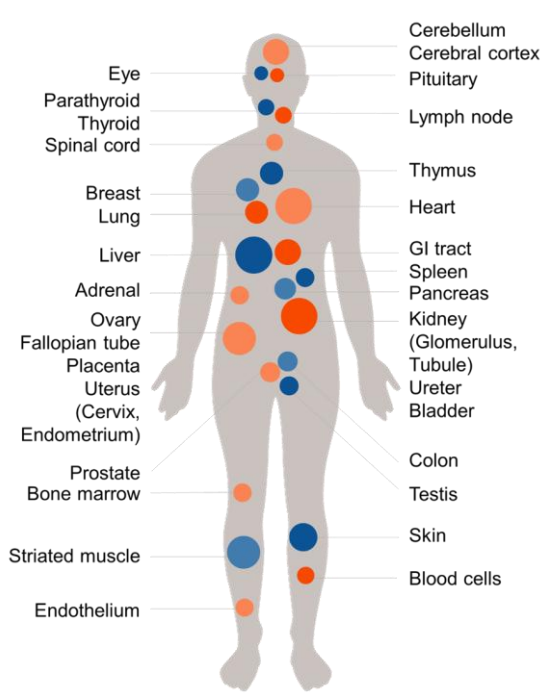
v0121

MPA Library Design Based on FDA Guidance



from

34

human tissues

94% coverage
of membrane proteome

Membrane Proteins

- GPCRs, ion channels, 1TMs etc
- Protein heterocomplexes
- Fetal, neonatal, placental
- Intracellular and extracellular membrane proteins

Membrane Proteome Array
~6,000 proteins

MPA library includes all 34 tissues identified in FDA guidance (1997 PTC)
Also includes 1,758 fetal, neonatal, and placental proteins

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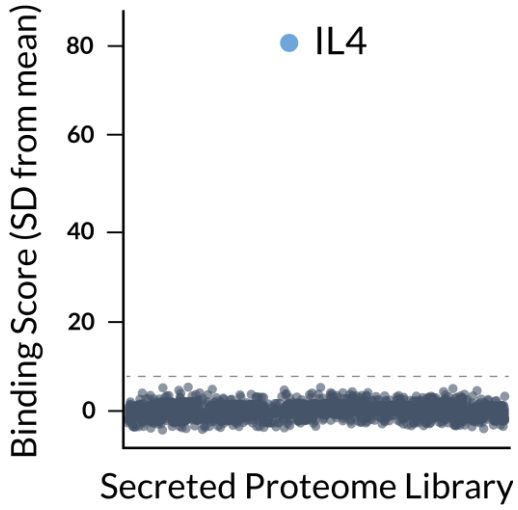
[1] FDA, 1997. Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use

The Most Comprehensive Coverage for Specificity Testing

Additional libraries for comprehensive specificity testing

⊕ SPL

Secreted Protein Library



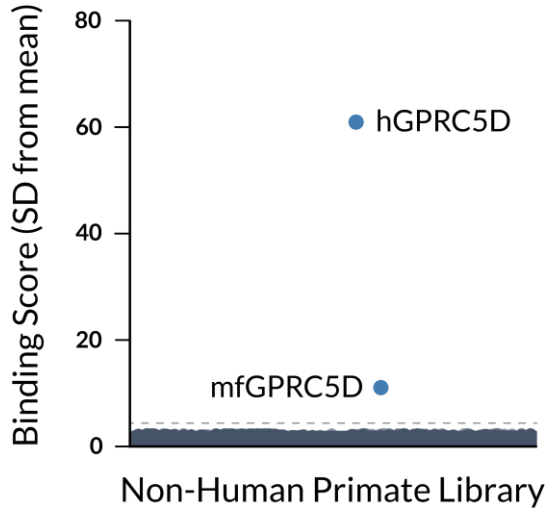
~1,200 Secreted Protein Library

Growth factors, interleukins, chemokines, interferons, complement factors, proteases & more.

- Additional insight into a molecule's safety and pharmacokinetics
- Non-tethered, native protein sequences analyzed by ELISA

⊕ NHP

Non-Human Primate Library



~250 NHP Protein Library

Cynomolgus macaque membrane proteins with <90% homology to human proteins. Continual library additions.

- Supports pre-clinical toxicity models
- Membrane proteins analyzed by flow cytometry

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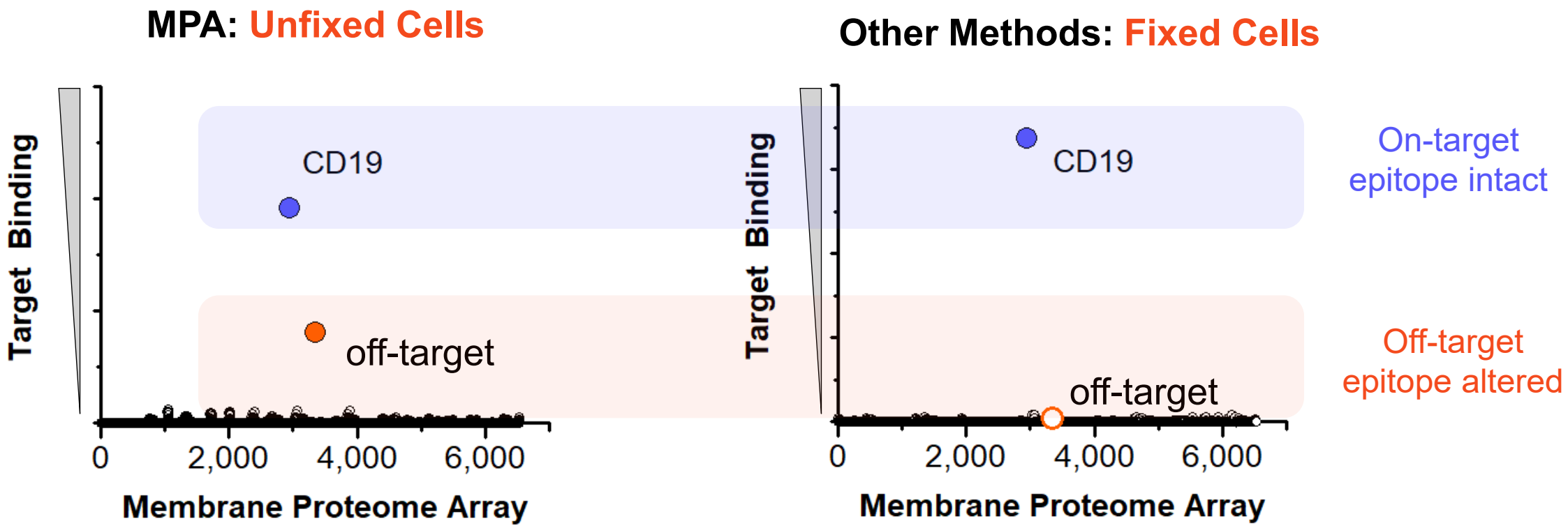
Screening on **Biologically Relevant** *Unfixed* Proteins



Screening native unfixed cells reduces false-negatives

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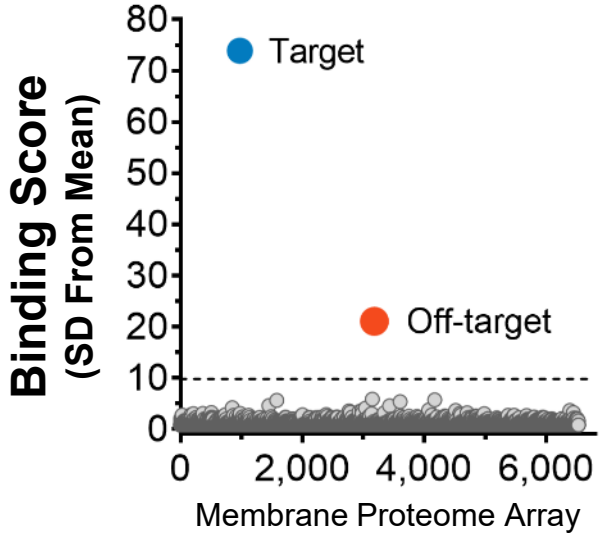
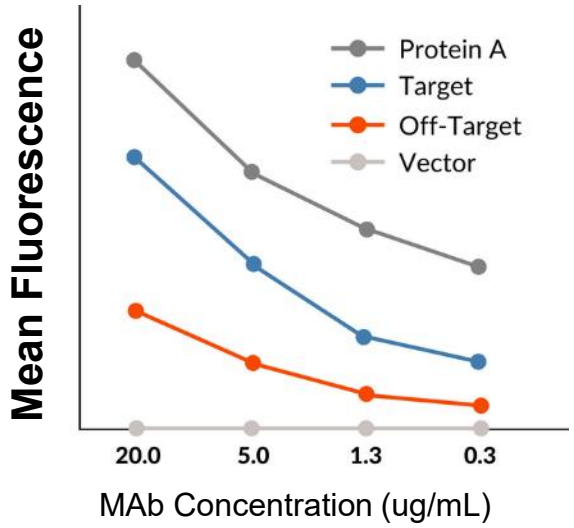
Quantitative Analysis of On/Off-Target Binding

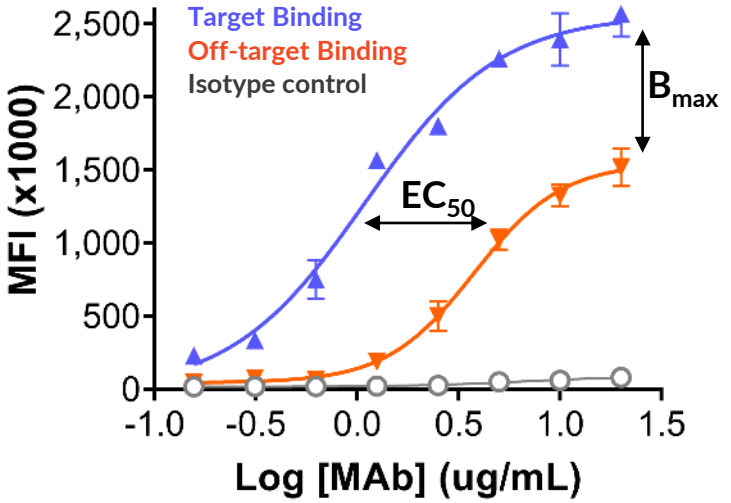
Primary Screen
Binding score (confidence in interaction)



Validation Assay
Quantitative binding titration



Enhanced Binding Analysis
EC_{50} and Bmax



8 point titration in quadruplicate
EC_{50}, Bmax, ANOVA

Quantitative binding at all 3 stages, including primary screen

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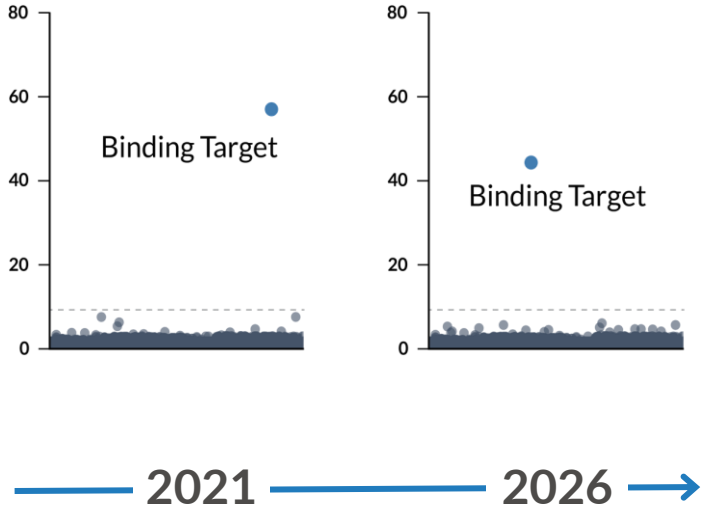
Quality Controlled: **Reproducible and Reliable**

1. Intermediate Precision Analysis

Across days, concentrations, lots, operators



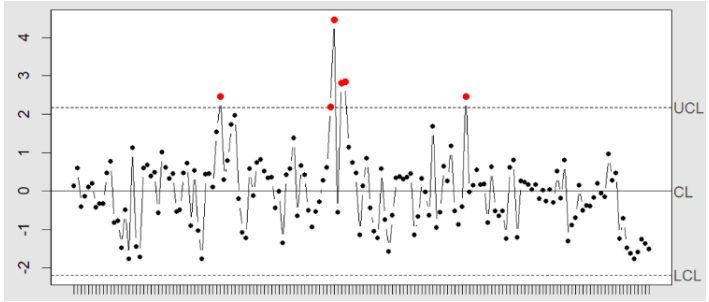
2. Controls

Assay and experimental Controls in every project

- ProA control for 1°
- MAb controls for 2°
- Isotype control
- V5 expression
- GFP transfection
- 2 cell types
- Negative controls
- Replicates
- Sensitivity controls

3. Quality Management

ISO 9001 Certified,
Control Charting and Library Maintenance



ISO 9001

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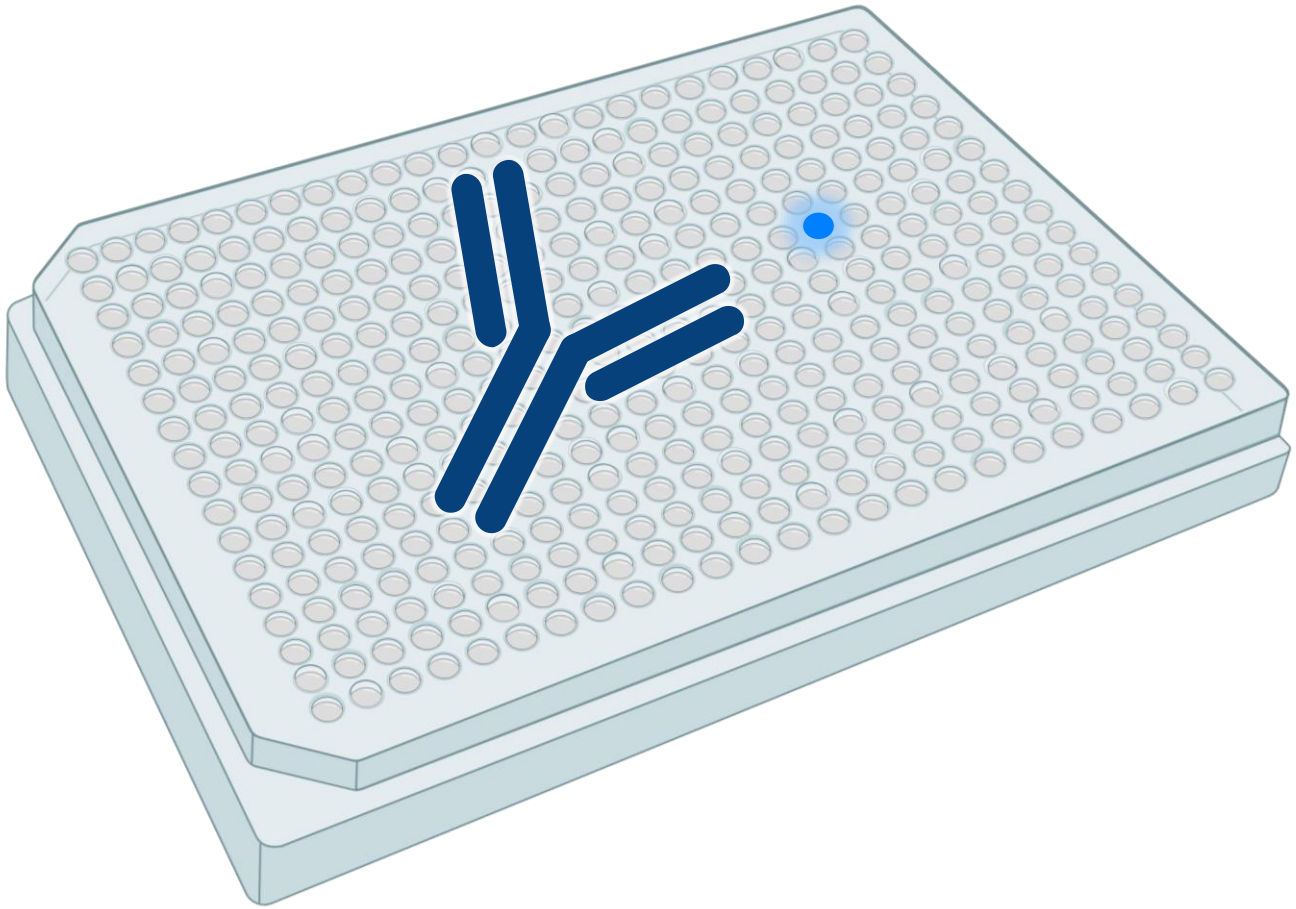
Membrane Proteome Array:

Better Prediction of Clinical Safety



Do MPA Results Predict Human Safety Compared to TCR?

35 FDA Approved MAbs with Tissue Cross-reactivity (TCR) Data

# MAbs	MPA result	TCR result
7	Off-target binding	Clean
	4 have FDA black box warnings 2 have FDA warnings of severe side-effects 1 shows no toxicity, but MPA off-target is in brain	
3	Clean	Unexpected cross-reactivity
	In all 3 cases, no off-target toxicity was identified in NHP or human studies	
17	Clean	Clean
8	Clean	Additional cytoplasmic staining

Results suggest that TCR results do not correlate with off-target safety, while MPA results are predictive of safety in humans

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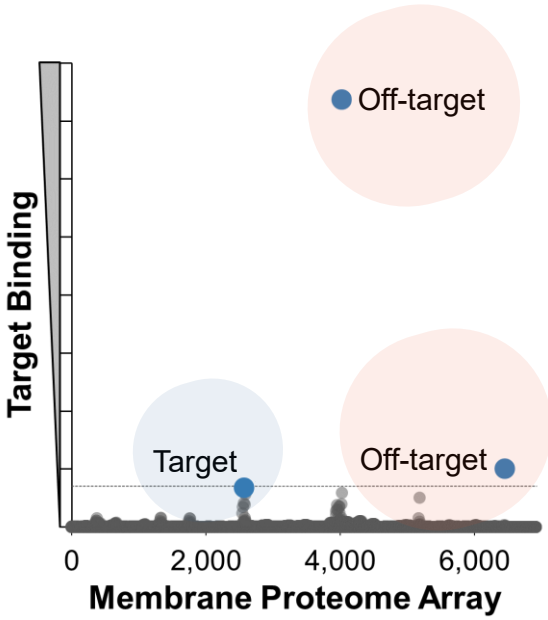
Examples of TCR Studies Missing Off-Targets

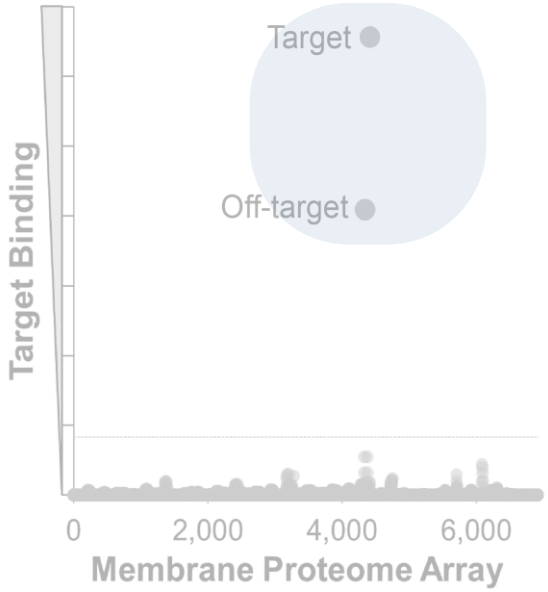
BLA Molecule #1

TCR did not identify off-target proteins.



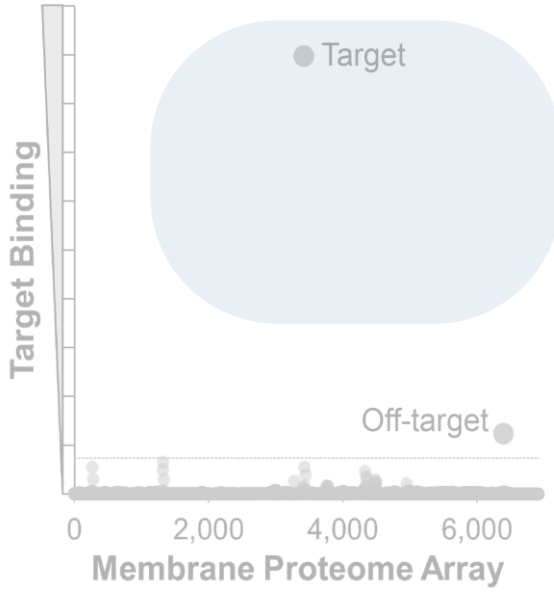
BLA Molecule #2

On- and off-targets on same cell type.



BLA Molecule #3

Target has widespread tissue expression.



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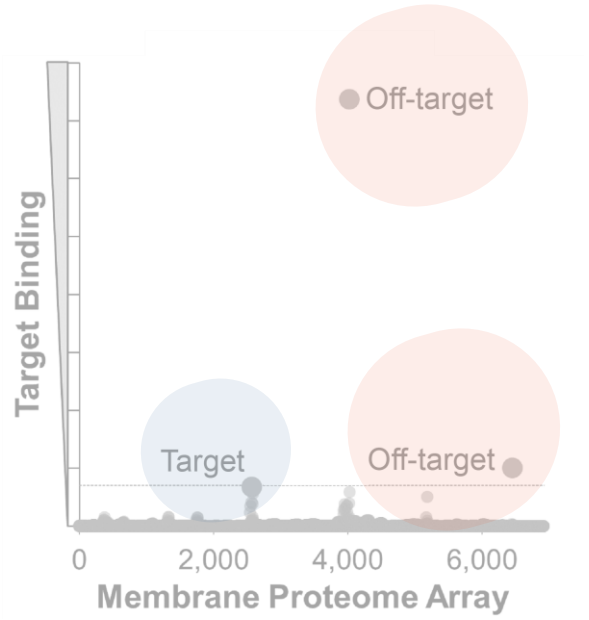

BLA Molecule #2

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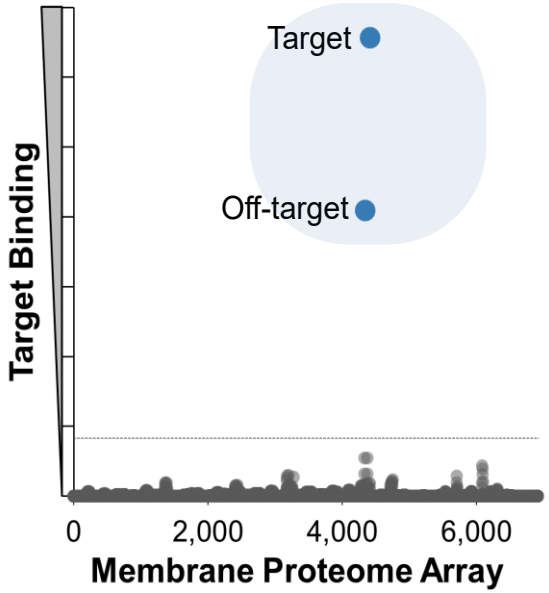

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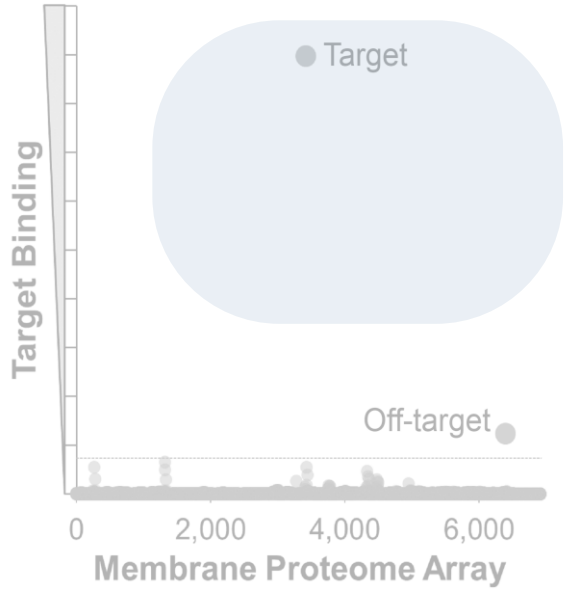

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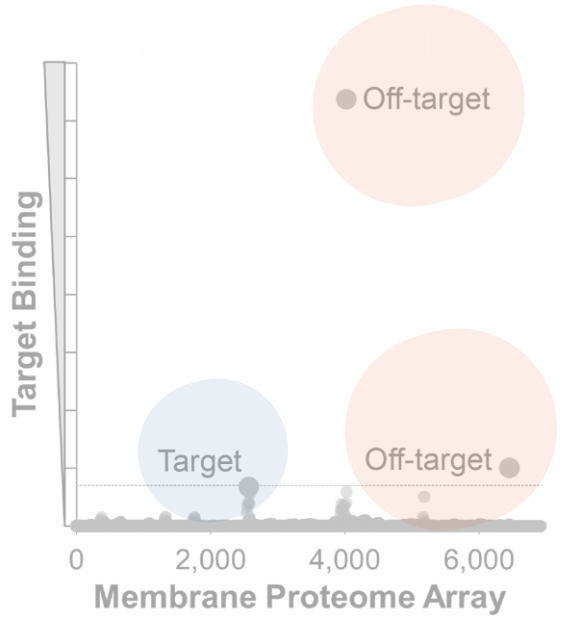

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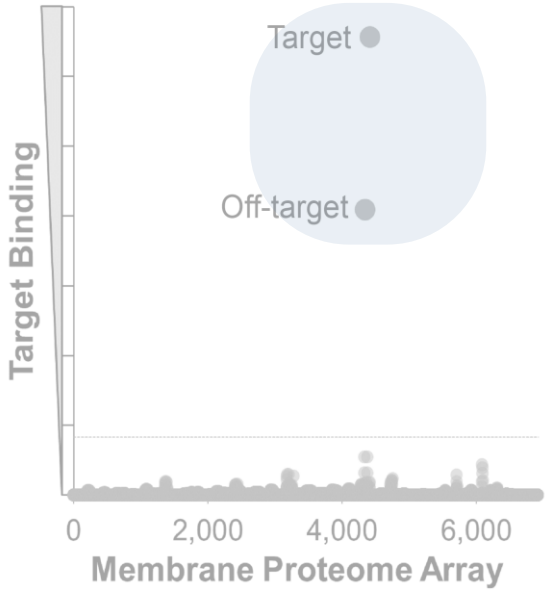

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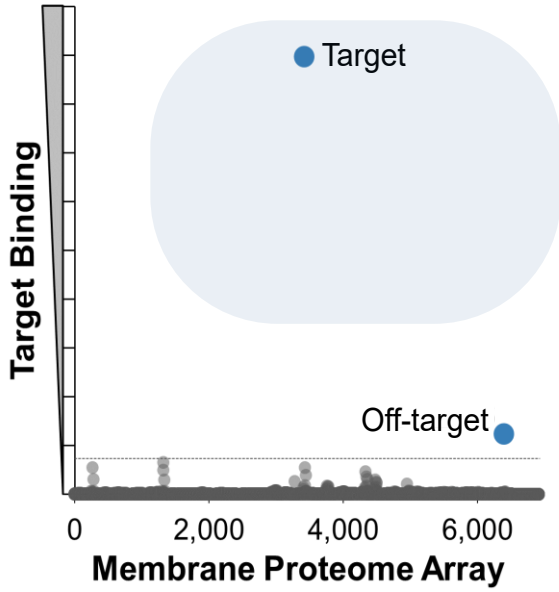
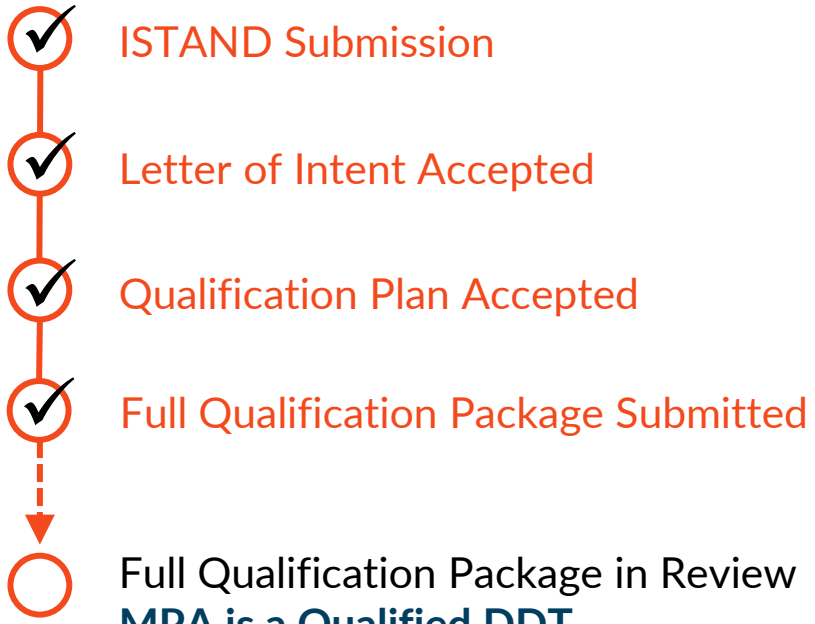


MPA Nears FDA-Qualification as a Drug Development Tool (DDT)

Qualification Through New FDA Program, ISTAND



MPA Drug Development Tool Application DDTIST00006

***Once qualified**, any sponsor could use that New Approach Methodology (NAM) in an application with **confidence** that the **FDA will accept the data.**[1]*

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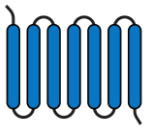
[1] Roadmap to Reducing Animal Testing in Preclinical Safety Studies

What Does Qualification Entail?



Library Composition & Validation

- Plasmid design
- Tissue representation
- Full-length sequence analysis
- Protein expression
- Library QC and storage



Assay Performance & QC

- Data analysis methodology
- Subjectivity in flow cytometry
- Analytical sensitivity
- Reproducibility analysis
- Accurate measurements w/ variable protein expression



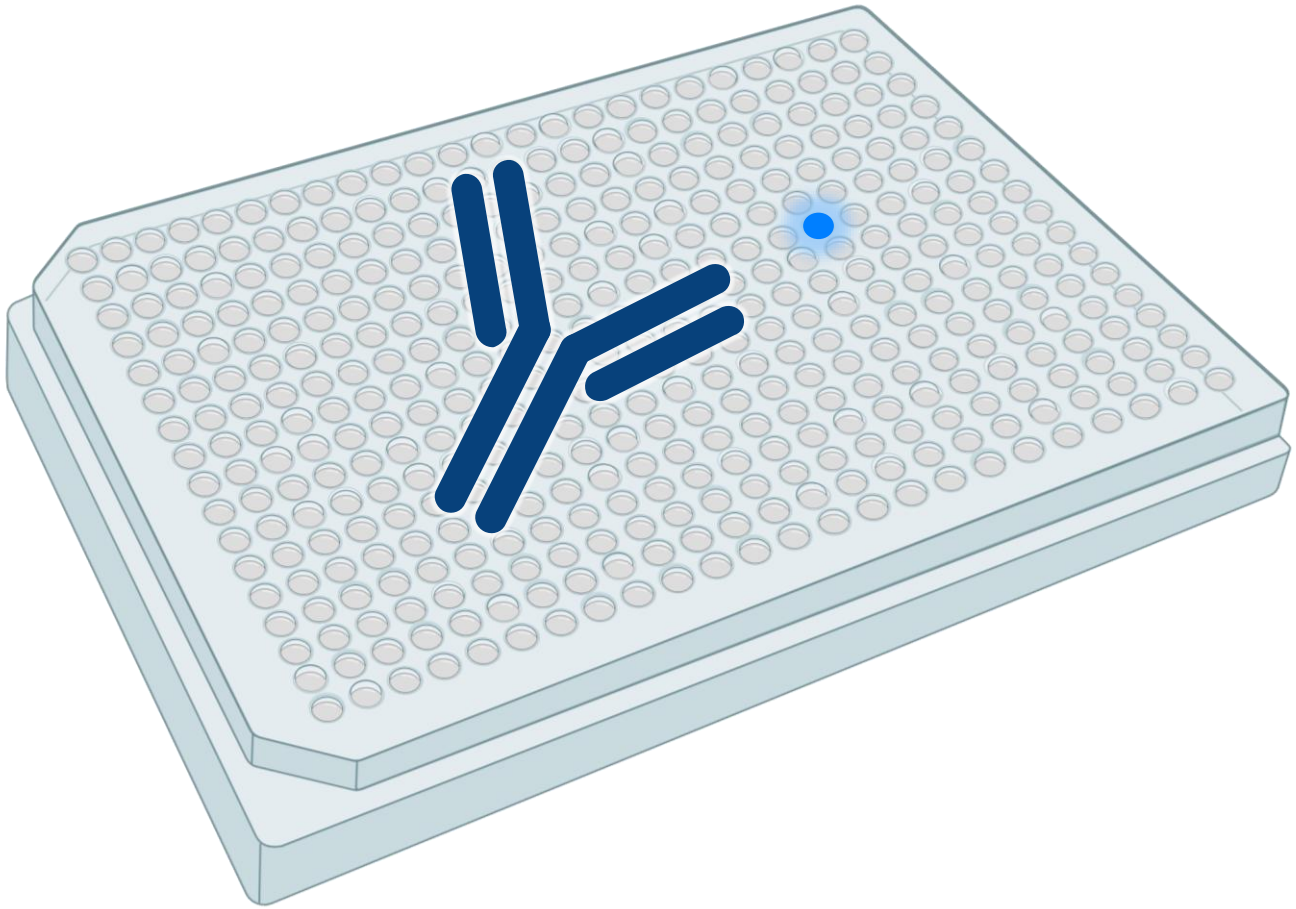
Comparative Analyses

- Comparison of results to Tissue Cross Reactivity results
- Specificity testing clinical MAbs

Comprehensive 100+ page document detailing MPA validation & usage

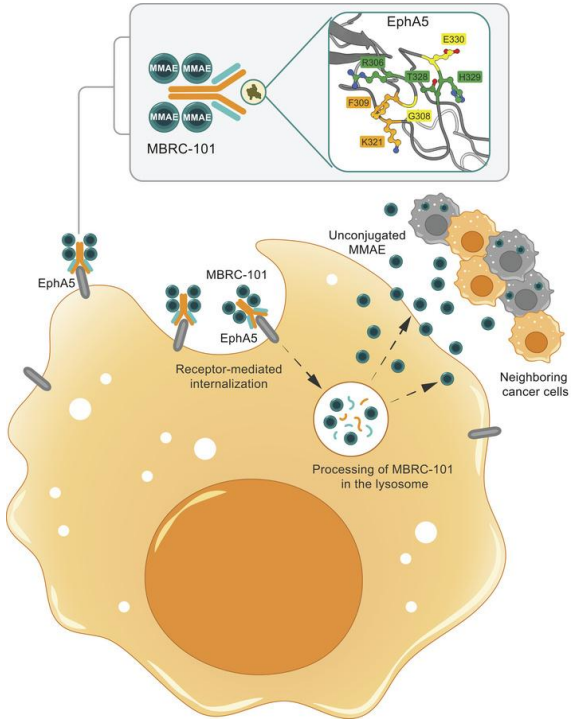
Membrane Proteome Array:

Case Studies



Antibody-drug Conjugate MPA Case Study

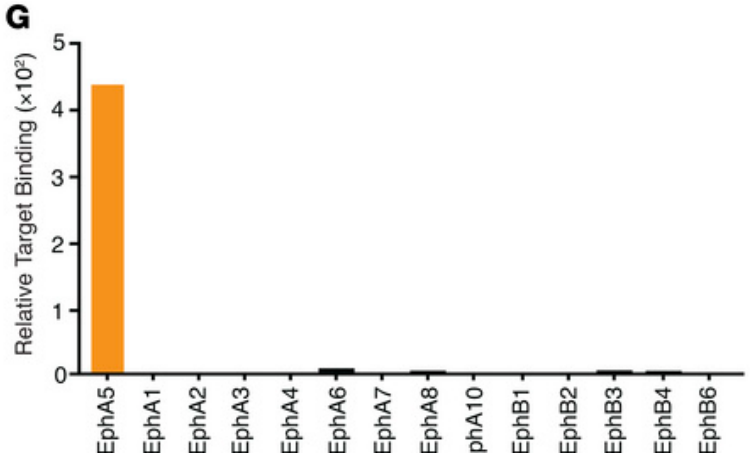
EphA5 – A novel solid tumor target:



- EphA5 is a novel solid tumor target
- High expression in solid tumors, no or limited expression in normal human tissue
- MBRC-101 is a humanized anti-EphA5 antibody conjugated to MMAE through a ThioBridge

ADC Regulatory Filing

☑ *MPA + IND*



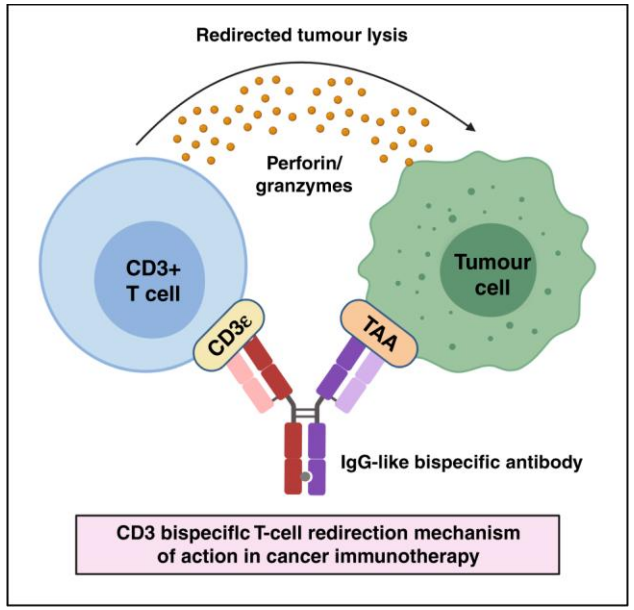
- MPA showed specificity to EphA5 only, no binding to any other family members
- FDA granted IND, no tissue cross-reactivity study required
- Currently in Phase 1/2 (NCT06014658)

MBRACE THERAPEUTICS

Staquincini, F. et al, *J Clin Invest.* 2025;135(14):e188492

Case Study – T-cell Engager Binds Secreted Off-Target

Partner Screen: T-Cell Engager Therapeutic

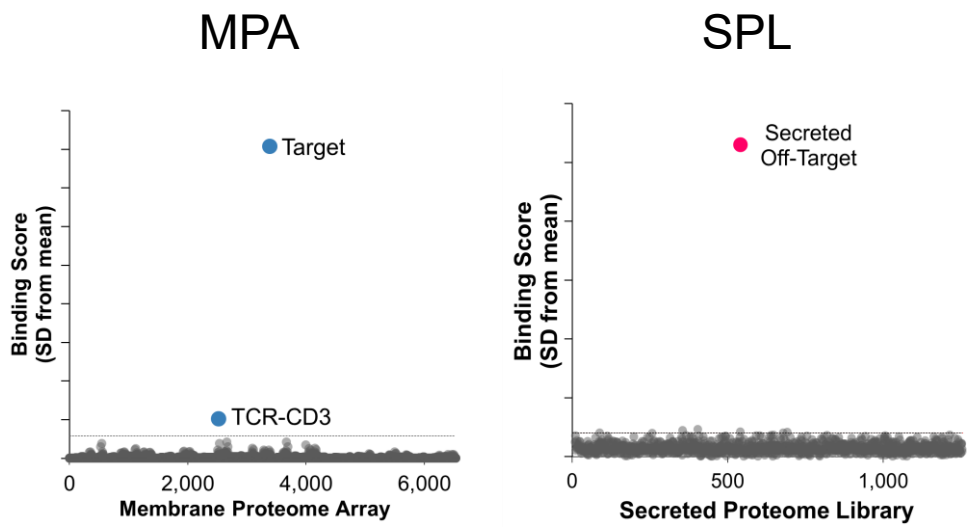


Adapted from Singh, A., et al, 2021

- Bi-specific TCE screened on MPA and SPL libraries
- Unexpected binding to secreted protein, expected binding to membrane targets
- Partner orthogonally confirmed binding to secreted off-target protein

Comprehensive Screening

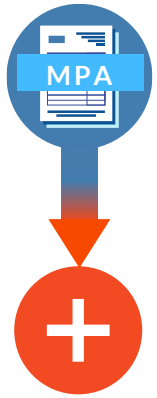
☑ *MPA + SPL*



- Off-target protein plays significant role in skin tissue, potential for dermatitis/skins AEs
- Interaction independently confirmed, no adverse reactions in follow-up animal studies
- MPA data incorporated into WoE, candidate advancing toward clinical trials

Unpublished, project completed April 2026

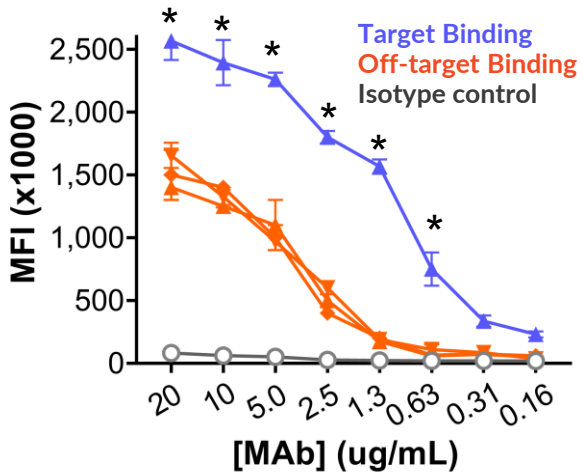
What if the MPA Reports an Off-target... What's Next?



Enhanced Binding Analysis

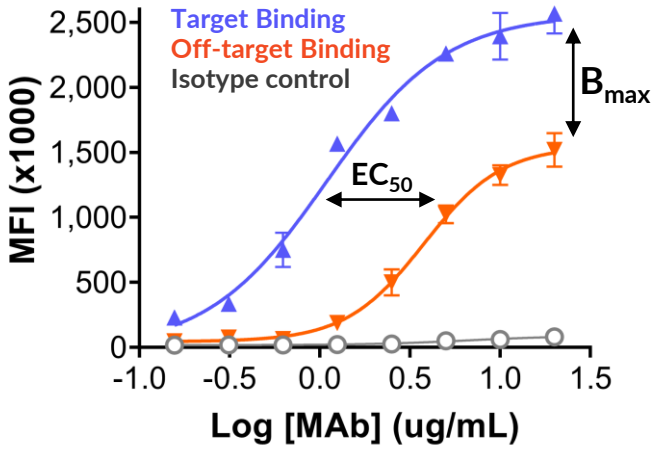
Distinguish binding risk from biological risk with weight of evidence

Statistical Confidence



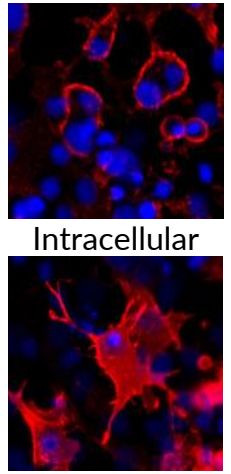
- ✓ More replicates and controls
- ✓ Statistically (ANOVA) differentiate weak binding and low expression

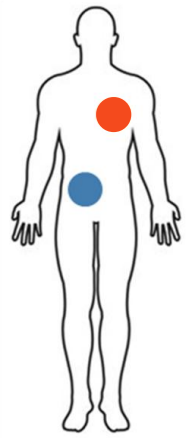
Relative Binding Strength



- ✓ B_{max} (relative expression)
- ✓ EC_{50} (interaction strength)

Epitope Accessibility





- ✓ Extra- or intra-cellular
- ✓ Tissue expression profile

What if You Need to Remove an Off-target Liability?

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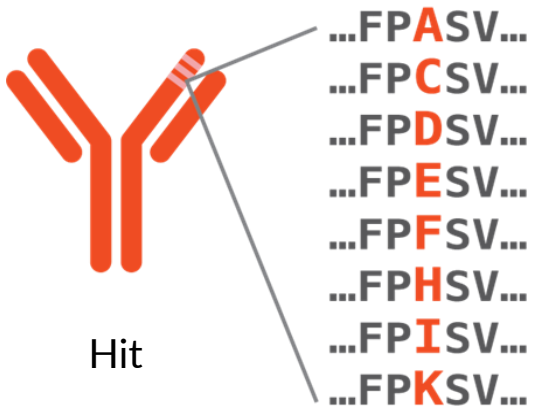
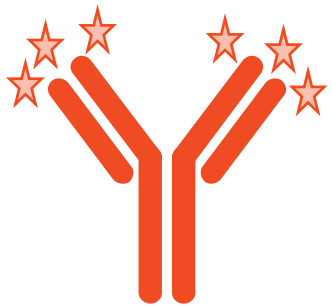
Comprehensive CDR-Scanning



ML/AI Combinations



Optimized Lead Candidate



Parallel optimization of:

- ✓ Specificity
- ✓ Affinity
- ✓ Developability
- ✓ NHP cross-reactivity
- ✓ Humanization
- ✓ IP (genus claims)

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Luncheon Presentation

100+ Undruggable Targets Unlocked through Parallel MAb Engineering

Ross Chambers, VP Antibody Discovery
Wed, Nov 18, 12:15 PM, Auditorium VII



Posters

A040: How Specific Are Antibody Therapeutics?: A Systematic Evaluation of Drugs Throughout Preclinical and Clinical Development

A041: Antibodies Against 100+ Impossible Protein Targets: High-Quality mAbs for Previously Intractable GPCRs, Ion Channels, and Transporters

B041: Engineering GPRC5D Multispecific Antibodies: Parallel Engineering to Optimize Affinity, Developability, Species Reactivity, and IP

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Thank you!

Questions?

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