A New Approach Methodology (NAM) for Specificity Testing

FDA qualification of the Membrane Proteome Array to evaluate off-target binding of MAb-based therapeutics

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Off-Target Binding Poses Safety Risks

1 in 3

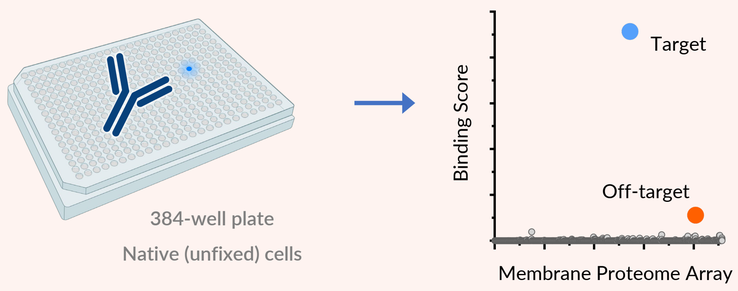
MAbs tested are polyspecific

Off-target binding can cause:

- Unintended cellular toxicity
- Adverse events
- Clinical trial failures

Membrane Proteome Array™ (MPA)

A Better Specificity Test To De-Risk Antibody Development

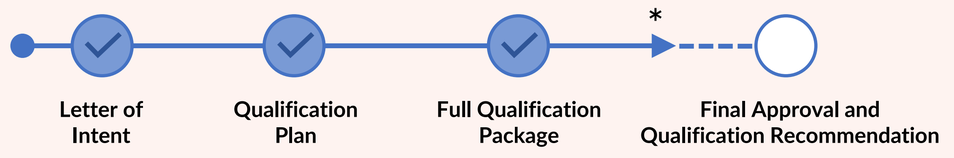


- Cell-based, native-conformation protein array
- Comprehensive human membrane proteome
- High-throughput assessment of antibody specificity using quantitative flow cytometry

MPA in Final Review to Become an FDA-Qualified NAM

Validation process for qualification through FDA's ISTAND program

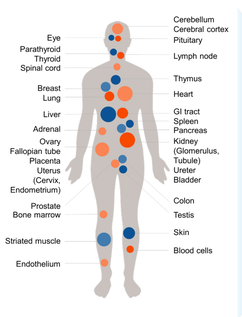
Analytical Validation	Clinical Validation
Validation of platform, protocols, procedures and justification of data analysis	Evaluate overall utility for clinical relevance and drug development
• Performance characteristics (target identification rate, false-negative rate) • Precision, sensitivity, reproducibility	• Prospective and retrospective studies on pre-clinical and clinical samples • Comparison to current standard



*MPA's Full Qualification Package (FQP) currently under review

A Quantitative, Human-Relevant NAM to Test Specificity

1. Cell-Based Protein Array of ~6,000 Native Human Membrane Proteins



from **34** human tissues

Tissues identified in FDA's "Points to Consider in the Manufacturing and Testing of Monoclonal Antibody Products for Human Use"

Membrane Proteome Array: 5,220 unique proteins

Membrane Proteins
- GPCRs, ion channels, 1TMs etc
- Protein heterocomplexes
- Intracellular and extracellular membrane proteins

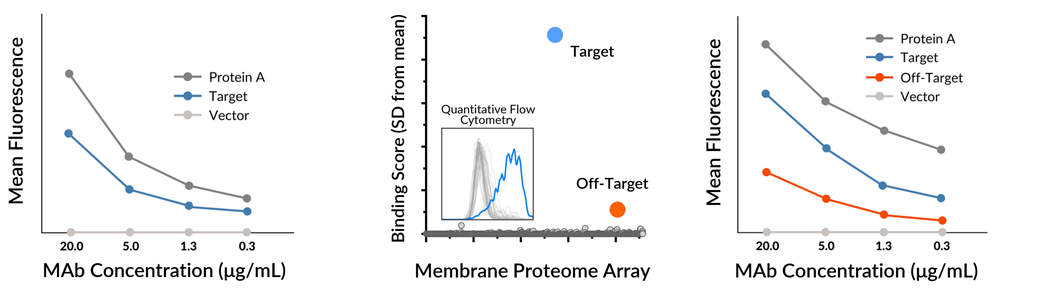
94% coverage of membrane proteome

Key features:
- ✓ *V5 tag to confirm expression*
- ✓ *Heterocomplexes*
- ✓ *GPI-linked proteins*
- ✓ *Sex-specific proteins included*
- ✓ *Developmental stages represented*
  - *Fetal proteins*
  - *Placental proteins*

- All targets are tested for binding while expressed within human cells
- Additional 1,200 native secreted proteins screened by ELISA

2. Quantitative Binding Data

Assay Setup *in unfixed cells by flow cytometry* → **Test Specificity** *across the membrane proteome* → **Validate Interactions** *using antibody titration analysis*



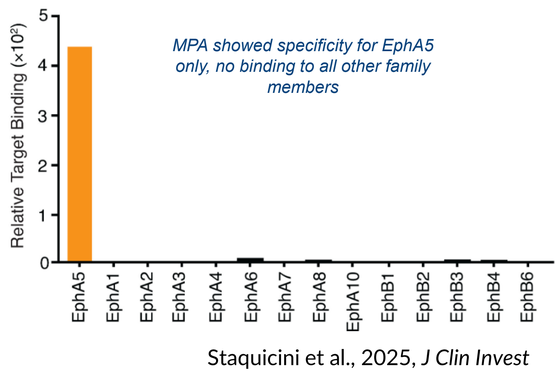
- Compatible with all biotherapeutic modalities

3. Specificity Data Routinely Accepted by FDA for IND Submissions

- MBRC-101 is a first-in-class antibody-drug conjugate (ADC) targeting EphA5, a receptor tyrosine kinase expressed in multiple solid tumors
- Anti-EphA5 antibody tested on MPA
- FDA granted IND, no tissue cross-reactivity study required

MBRC-101 currently in Phase 1/2 (NCT06014658)

MBRACE THERAPEUTICS

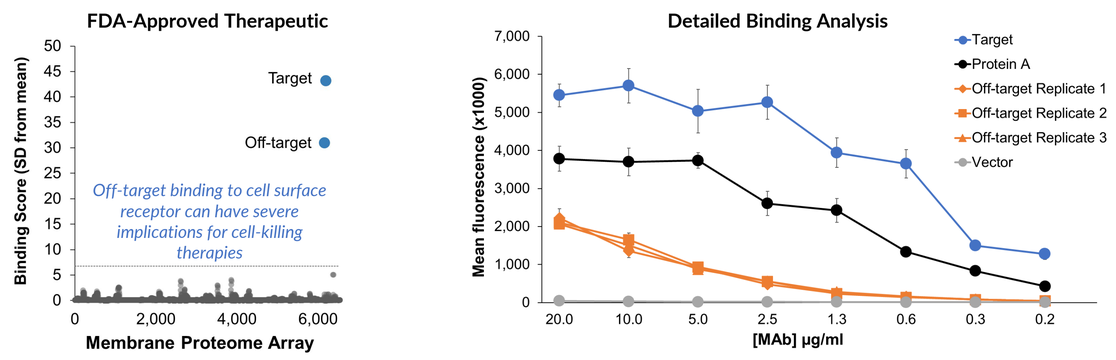


Staquicini et al., 2025, *J Clin Invest*

MPA provides confidence for lead selection and specificity data for IND

Comparison to Tissue Cross-Reactivity (TCR) Studies

1. MPA Identified Off-Target Binding in Clinical Antibodies



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

Norden et al., 2024, *mAbs*

- Clinical-stage and FDA-approved MAbs were tested on the MPA
- The MPA identified polyspecificity at all stages of clinical development, underscoring the critical need for improved specificity testing

2. MPA Superior Over TCR in Identifying Off-Target Safety Risks

# 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	Inconclusive (additional cytoplasmic staining, technical limitations, variability, false-positive staining)

- An unbiased selection of 35 FDA-approved antibody therapeutics were screened on the MPA and results were compared to TCR results obtained from public BLA reviews
- Ambiguous TCR results highlight technical limitations and the lack of actionable data associated with many TCR studies

MPA identified off-targets missed in TCR studies; preliminary data suggests MPA results are better correlated with clinical toxicity

Why Choose the MPA

TRUSTED – Successfully screened 2,500+ MAbs using **ISO 9001** certified quality processes; trusted by **hundreds of customers**

BIOLOGICALLY RELEVANT – The *only* screening platform that assesses its entire library under **native conditions**

ACCEPTED – Data accepted by FDA, EMA, NMPA; **100+ IND submissions** filed with MPA data

QUANTITATIVE – Flow cytometry provides sensitive and quantitative measurements

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