Up to One-Third of Antibody Drugs Are Nonspecific

A Systematic Evaluation of Drugs Throughout Preclinical and Clinical Development

Diana M. Norden, J. Tabb Sullivan, Carmen T. Navia, Rachel H. Fong, and Benjamin J. Doranz

Integral Molecular, Philadelphia, PA

Off-Target Binding Poses Safety Risks

1 in 3
MAbs tested are polyspecific

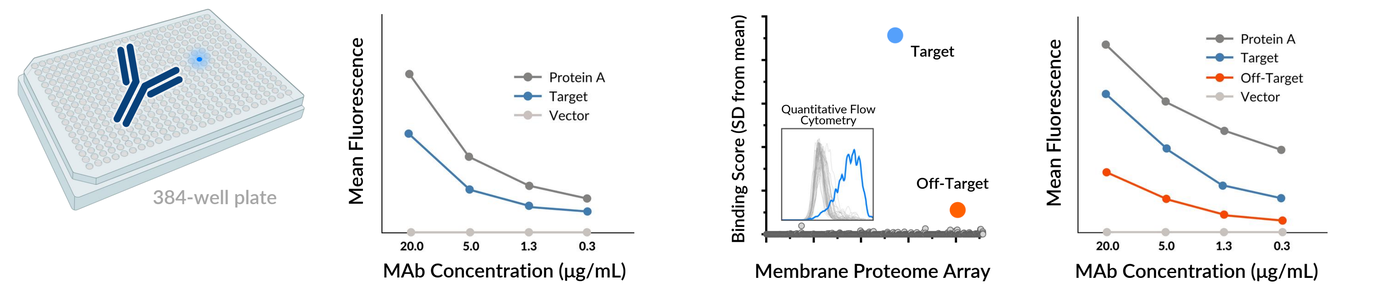


- Off-target binding can cause unintended cellular toxicity, adverse events, and clinical trial failures
- Conventional specificity tools such as tissue cross-reactivity (TCR) studies, cannot identify proteins responsible for off-target binding

Membrane Proteome Array™ (MPA)

Better Specificity Screening Can De-Risk Antibody Development

Cell-Based Protein Array *~6,000 native human membrane proteins* → **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
- Proteins screened under unfixed conditions and maintain native conformations
- MPA screening enables confident lead selection and better specificity data for IND
- Optional libraries include: NHP membrane proteins, as well as secreted proteins screened by ELISA

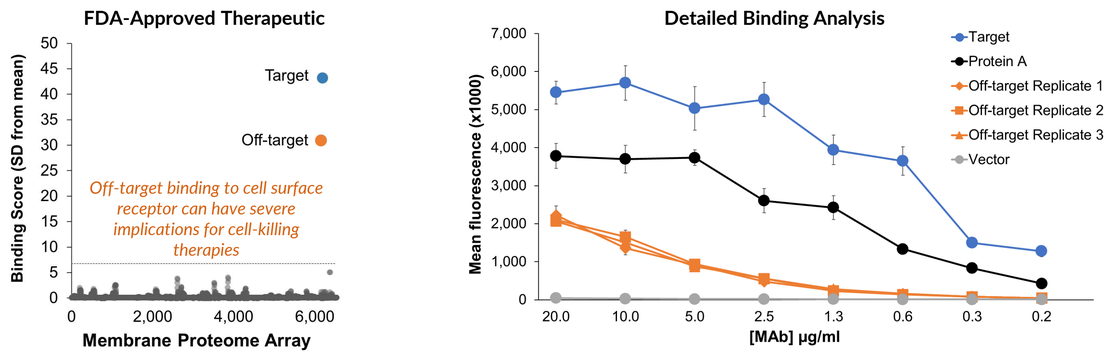
Up to One-Third of Antibody Drugs are Nonspecific

Clinical MAbs Screened on the MPA			
	Approved	Phase 2/3	Withdrawn
# MAbs screened	40	25	18
Off-target (rate)	6 (15%)	5 (20%)	4 (22%)

Preclinical MAbs	
	Leads
# MAbs screened	254
Off-target (rate)	83 (33%)

Norden et al., 2024, *mAbs*

Detailed analysis of off-target binding



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

MPA vs TCR in predicting drug safety in humans

# 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 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)

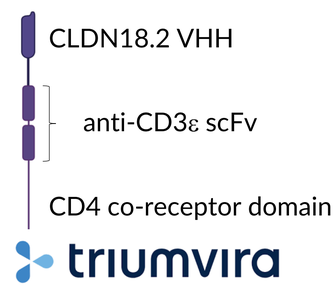
- An unbiased selection of 35 FDA-approved antibody therapeutics was screened on the MPA and results were compared to TCR results obtained from public BLA reviews
- Ambiguous TCR results highlight technical limitations and the lack of actionable data associated with many studies

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

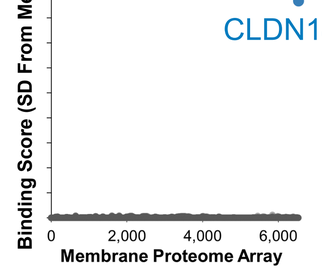
MPA Data Routinely Used for IND Submissions

Case Study: MPA specificity testing of a new therapeutic modality (TAC)

Therapeutic: CLDN18.2-TAC T cell



Screened on MPA: VHH-GFP fusion



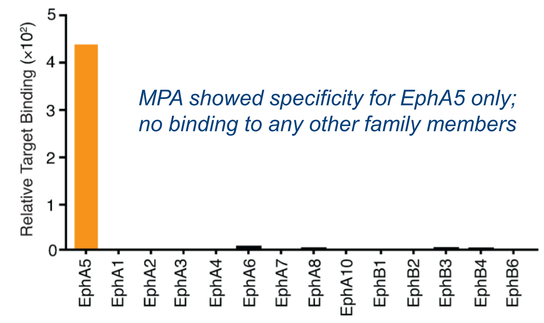
Xu et al., 2025, *Cancer Immunol Res*

- Novel chimeric receptor, T cell antigen coupler (TAC), T cell therapy for solid tumors
- Specificity testing on 'antigen recognition domain' consistent with FDA's CAR-T guidance
- CLDN18.2 VHH bound known target with no off-target binding identified (including against all CLDN family members)
- FDA granted IND, no tissue cross-reactivity study reported (NCT05862324)

Case Study: MPA contributed to successful IND submission of an ADC

MBRACE THERAPEUTICS

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



MPA showed specificity for EphA5 only; no binding to any other family members

- 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
- Currently in Phase 1/2 (NCT06014658)

MPA provides confidence for lead selection and specificity data for IND

In final review to become an FDA-qualified Drug Development Tool (DDT)



Why Choose the MPA

TRUSTED – Successfully screened 3,000+ 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; **200+ IND submissions** filed with MPA data

QUANTITATIVE – **Flow cytometry** for sensitive and quantitative measurements, compatible with all modalities

v1026

Rachel Fong
215-966-6061
rfong@integralmolecular.com
www.integralmolecular.com

Integral Molecular is the industry leader in working with membrane proteins, backed by 25 years of experience, 600+ customers, and 500+ manuscripts using our technologies.

MPA services are available directly through Integral Molecular or via our partners and international distributors.

Download this poster