Up to One-Third of Antibody Drugs Are Nonspecific

A systematic evaluation of drugs throughout clinical and preclinical development

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How Specific Are Antibodies, *Really?*

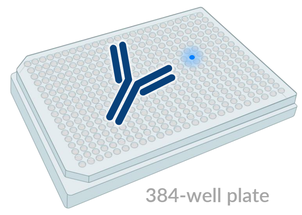
- Off-target binding can cause unintended cellular toxicity, adverse events, and clinical trial failures
- Conventional specificity tools such as tissue cross-reactivity (TCR) studies have been unreliable, leading to off-target binding going undetected

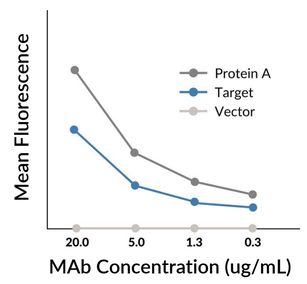
Goal: to determine the true prevalence of polyspecificity in antibody-based drugs

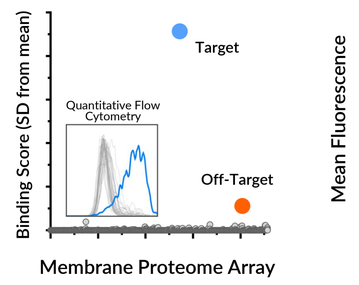
Membrane Proteome Array™ (MPA)

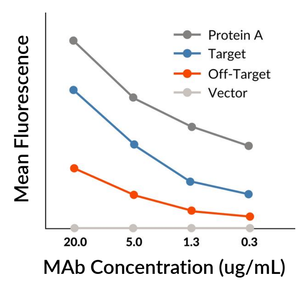
Better Specificity Screening Can De-risk Antibody Development

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*







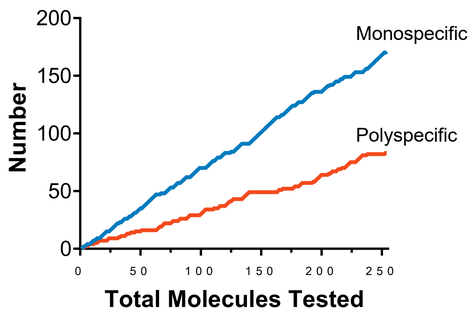


- Compatible with all biotherapeutic modalities
- Proteins screened under unfixed conditions to maintain native conformations
- MPA screening enables confident lead selection and better specificity data for IND
- Optional additional 1,200 native secreted proteins screened by ELISA

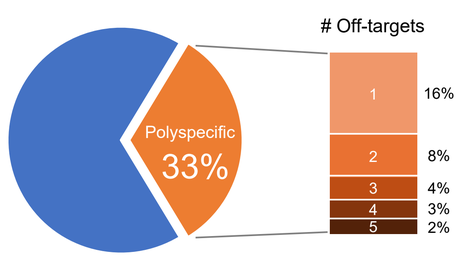
Up to One-Third of Antibody Drugs are Nonspecific

1. Systematic analysis of preclinical lead candidate antibodies

33% of Molecules Tested are Polyspecific



Polyspecificity Profile



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- Retrospective analysis of 254 lead candidate antibodies found 83 polyspecific MAbs (32.7%) with validated off-target binding
- About half of the polyspecific antibodies had a single off-target
- Off-target binding was usually against completely unpredictable membrane proteins with no significant sequence homology (common non-CDR-mediated interactions such as binding to Fc receptors or lectins were not counted)

2. Off-target binding contributes to drug attrition

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

- Biosimilars of clinical or FDA-approved MAbs were produced and tested on the MPA
- The MPA identified polyspecificity among MAbs at all stages of clinical development
- These findings challenge the assumption that antibodies are inherently specific and underscore the critical need for improved testing

Off-target binding is likely a major cause of drug attrition

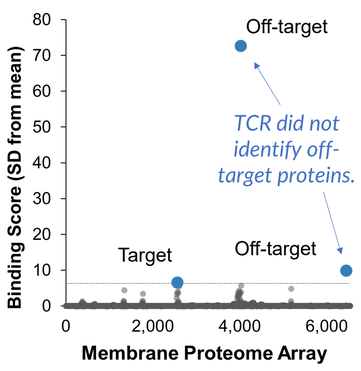
mAbs

Norden et al., 2024

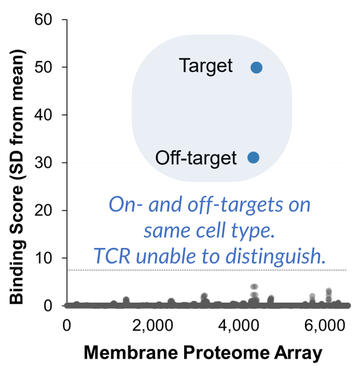
Advantages of the Membrane Proteome Array Over TCR

1. MPA superior over tissue cross-reactivity (TCR) in identifying off-targets

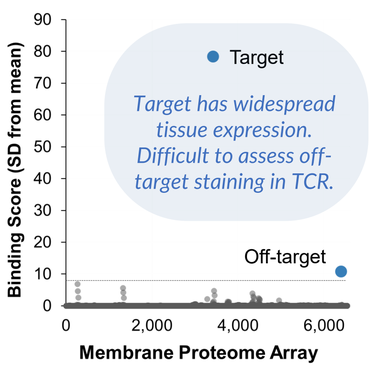
Drug #1
TCR missed off-targets



Drug #2
Off-target masked in TCR



Drug #3
Off-target buried in TCR



- Biosimilars of FDA-approved MAbs were tested for off-target binding on the MPA, and results were compared to TCR summary data obtained from BLA applications
- MPA identified several off-targets that were missed in immunohistochemistry based TCR studies

Norden et al., 2024, *mAbs*

2. Comparison of tissue cross-reactivity (TCR) studies vs MPA

TCR	MPA
Identifies target **tissue, not protein**	Precisely identifies off-target **proteins**
Fixed/frozen tissues can **alter epitopes**	**Native conformation** in unfixed cells
Qualitative assessment (IHC), low sensitivity prone to false positives & negatives	**Quantitative analysis**, high sensitivity, low false positives & negatives
Incompatible with newer biotherapeutics including CAR-T	**Compatible with all biotherapeutics** including MAbs, scFv, VHH, ADC, CAR-T
14 weeks, $$$$	*4 weeks, $*

Recent FDA guidance recommends the use of advanced, human-relevant, in vitro assays to assess antibody specificity and drug safety

v1025

MPA in Final Review as an FDA-Qualified Drug Development Tool

- FDA guidance recommends the use of advanced, human-relevant, *in vitro* assays to assess antibody specificity and drug safety
- MPA's ongoing process enhancements incorporate direct feedback from the FDA through its **ISTAND program**

Why Choose the MPA

TRUSTED - Successfully screened 2,000+ 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; **100+ IND submissions** filed with MPA data

QUANTITATIVE – **Flow cytometry** provides sensitive and quantitative measurements

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