Reshaping undruggable membrane-obligate targets: AI antigen design to drive antibody discovery and optimization

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ADIMAB

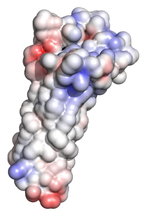
MEMBRANE PROTEIN CHALLENGES

Membrane proteins such as GPCRs and ion channels remain challenging therapeutic discovery targets, primarily due to the absence of soluble, native-like reagents for immunization and screening with display-based discovery technologies. Here we present an ML-guided membrane protein solubilization pipeline and its successful application to antibody discovery and optimization.

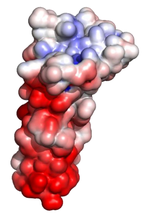
Can solubilized membrane-obligate target antigens be used for discovery and optimization?

MEMBRANE-OBLIGATE TARGET (MOT) ANTIGEN SOLUBILIZATION & PRODUCTION

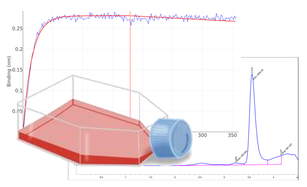
Wild-type MOT



MOT soluble antigen



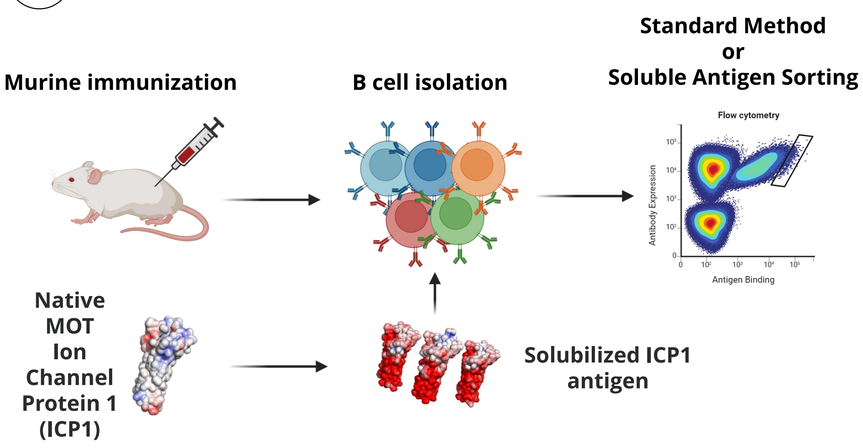




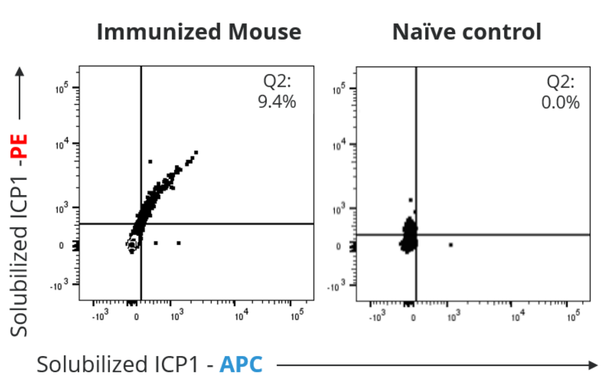
Experimental or predicted 3D structure of WT protein → ML-guided sequence optimization for solubilization → Yeast screening to identify leads → Mammalian expression and antigen QC

CASE STUDY 1: ML-GUIDED ANTIGEN SOLUBILIZATION FOR ION CHANNEL ANTIBODY DISCOVERY

1 Antibody discovery methodology

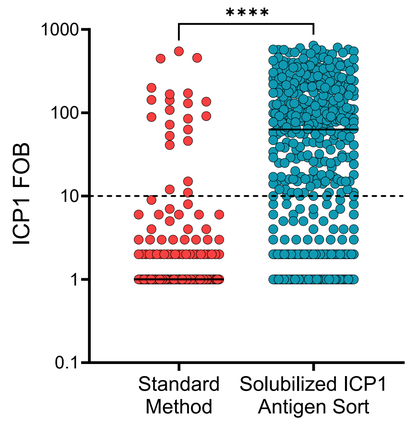


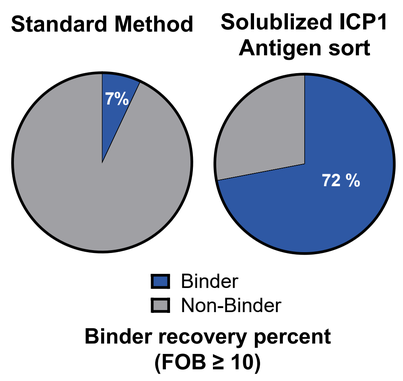
2 Solubilized ICP1 antigen-specific B cell sorting



Plots depict live, class-switched B-cells stained with solubilized ICP1 antigens

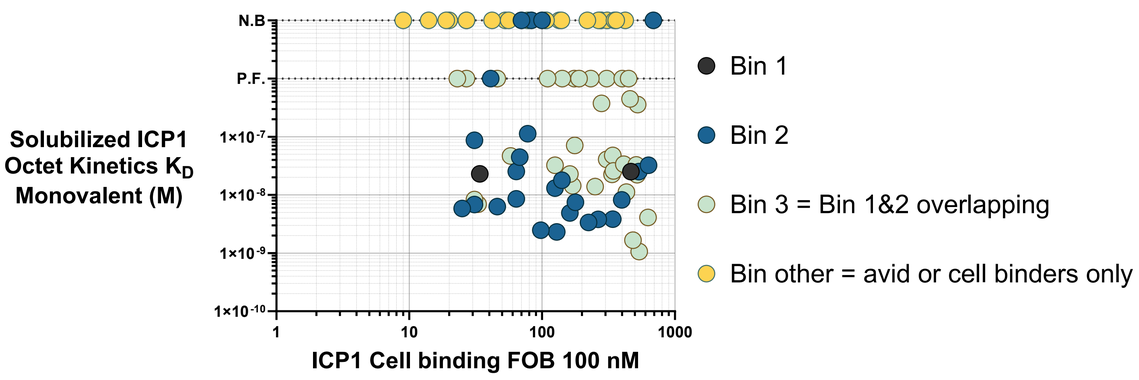
3 Solubilized ICP1 antigen sorting improves target-specific recovery



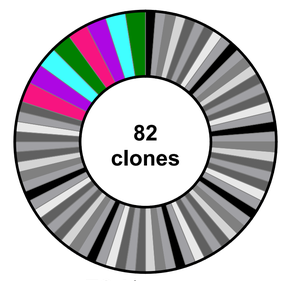


FOB = Fold Over Background

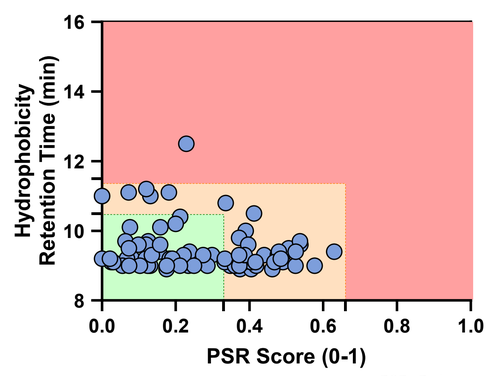
4 Clones cover distinct epitope bins



5 ICP1-specific clones span diverse lineages and show favorable developability profiles



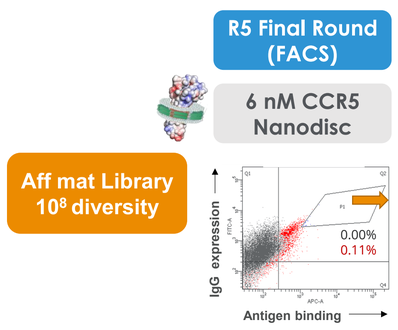
72 Lineages
- Singlet Lineages: 63
- Expanded Lineages: 9

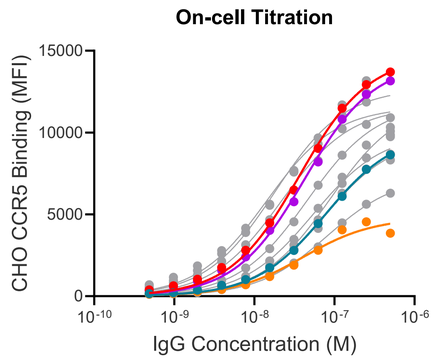


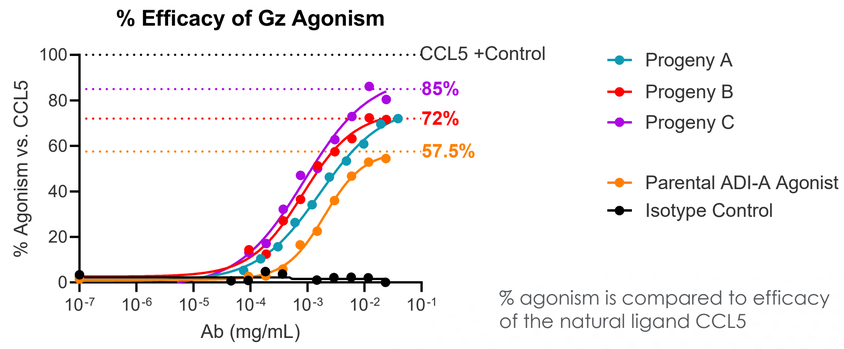
PSR: Polyspecificity Reagent

CASE STUDY 2: ML-GUIDED ANTIGEN SOLUBILIZATION FOR CLASS-A GPCR ANTIBODY OPTIMIZATION

1 Selection against CCR5 nanodisc improves agonist efficacy





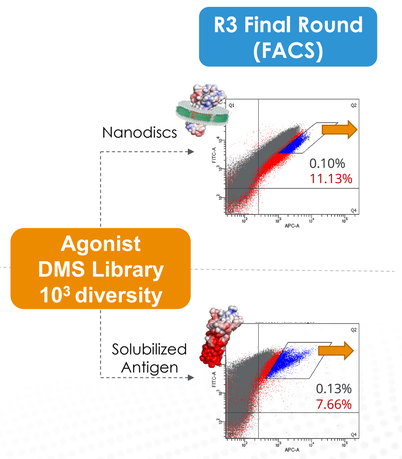


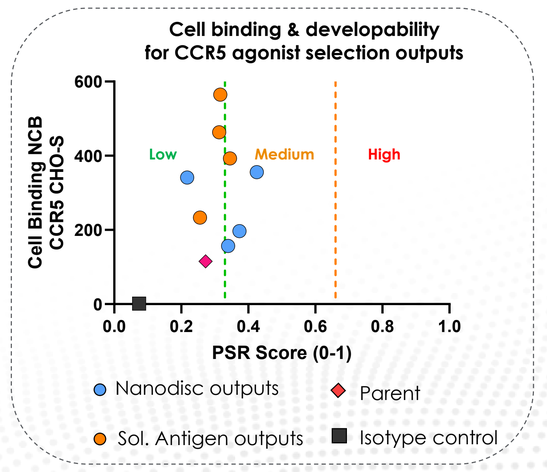
% agonism is compared to efficacy of the natural ligand CCL5

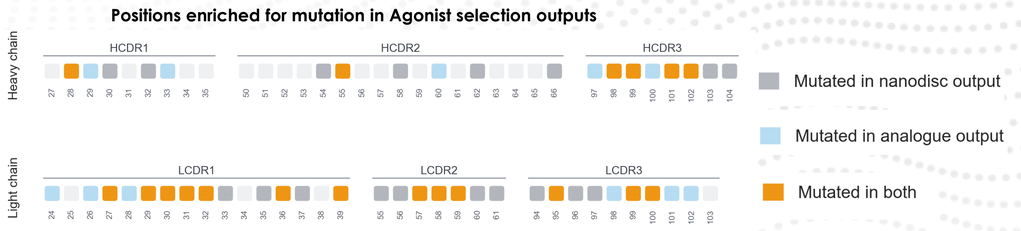
2 MOT antigen comparison

Properties	MOT Nanodisc antigen	Solubilized MOT antigen
Conformational Fidelity	High	Moderate
Batch-to-batch homogeneity	Variable (empty discs)	Defined single species
Valency control for display sorting	Poorly defined	Defined monomer/ multimer
Preparation Complexity	High	Low
Production scale	Low to Moderate	High
Production Cost	Expensive	Economical
Suitability for lead optimization	Yes	TBD

3 Both antigen formats select for affinity improvements and display consensus amino acid positions







SUMMARY

- **Adimab's ML-guided solubilization** turns membrane-obligate targets into native-like soluble antigens
- **Discovery:** solubilized ion channel protein increases antibody recovery in mice
- **Optimization:** solubilized CCR5 matures existing IgG agonist lead

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