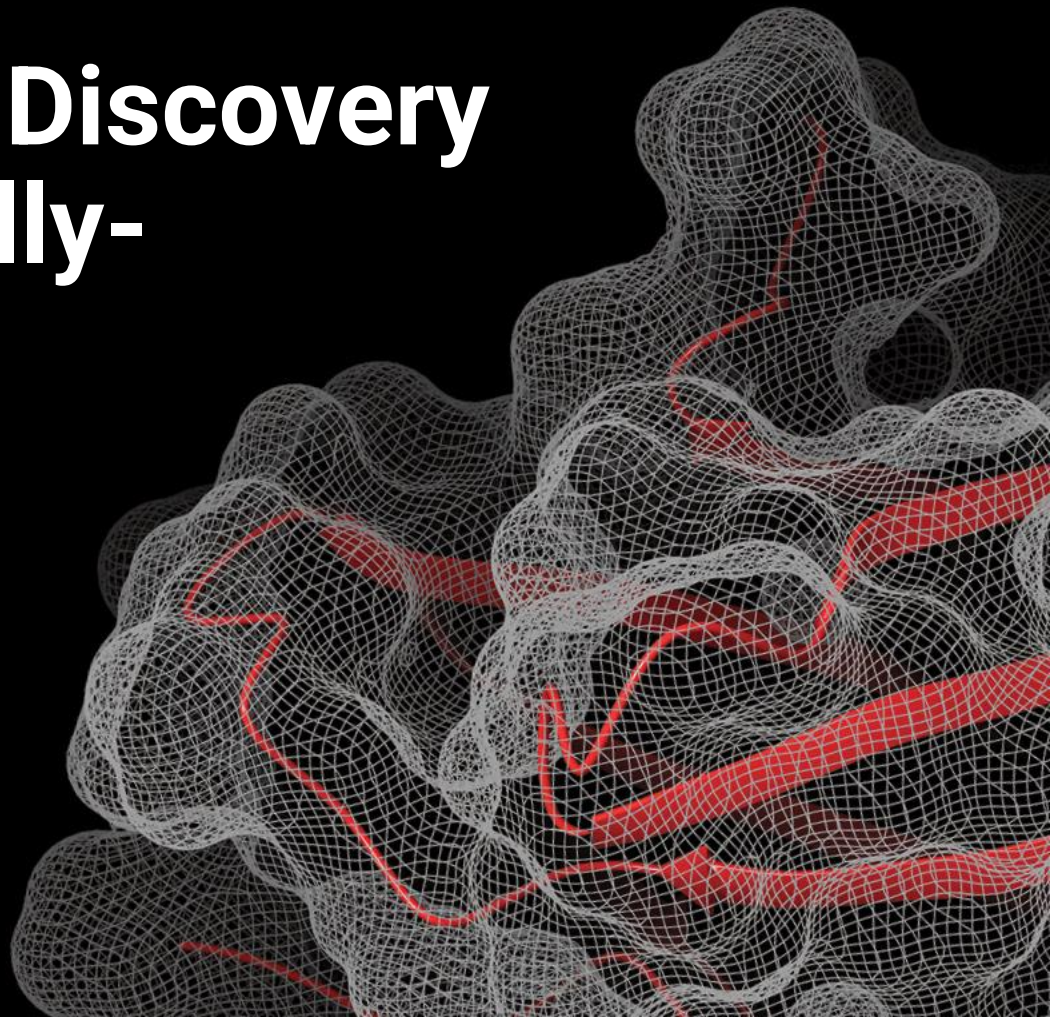
Immuto Scientific

Bridging the Data Gap for Discovery Via Multimodal, Biologically-Relevant Data Generation

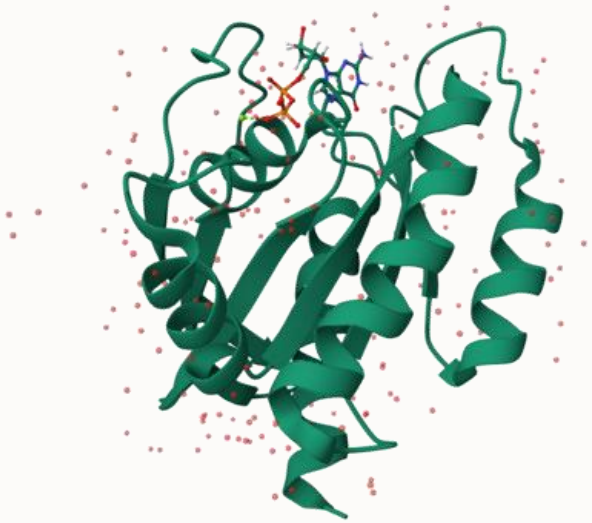


Hetal Marble, PhD

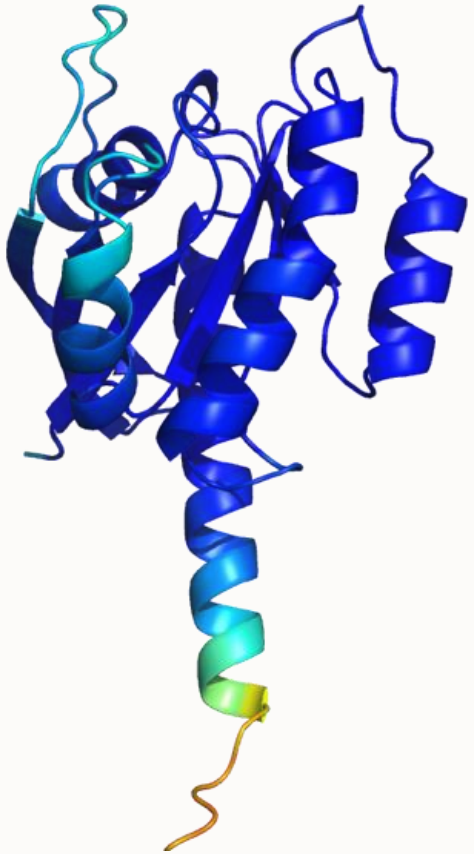
Carterra Symposium – Boston 2026

AI Has Transformed Structural Biology

PDB: 4OBE



AlphaFold



KRAS

200M+

Structures Predicted

AlphaFold2 covered the human proteome and beyond - structures that took decades now take seconds

2018→Now

From Research Tool to Core Workflow

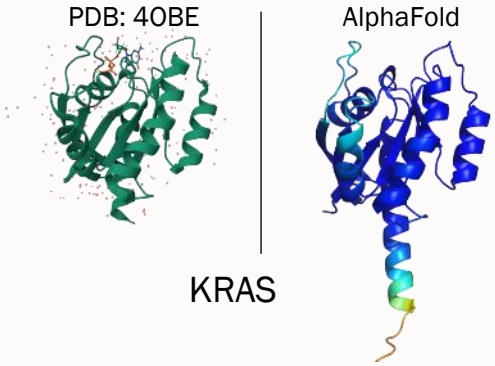
Structure prediction is now integrated into drug discovery, target ID, and lead optimization

Major Accuracy Gains

Across Well-Characterized Protein Families

For established protein families, prediction accuracy has improved dramatically - replacing months of experimental work

Limitations of Protein Folding



AlphaFold has shown remarkable success in predicting structure from sequence

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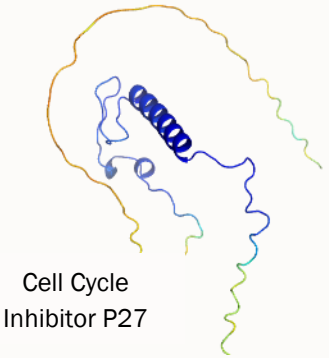
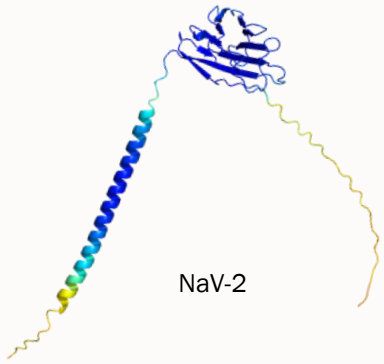
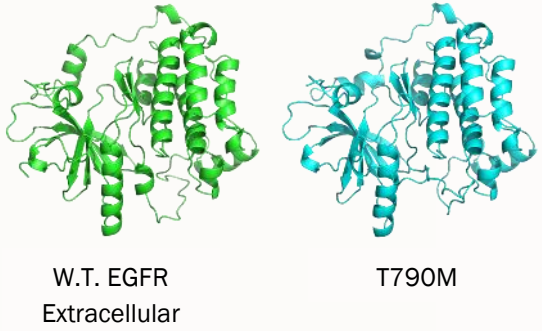
Flexible regions



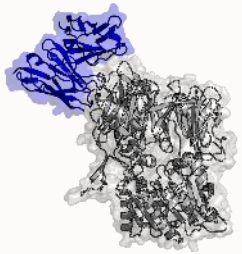
Transmembrane domains



Point mutations:



Novel P/P Interaction



Protein Folding Failure Modes

The Structural Data Gap Is Most Severe in Antibody–Antigen Systems

1,800

Public,
Nonredundant
Ab–Ag structures

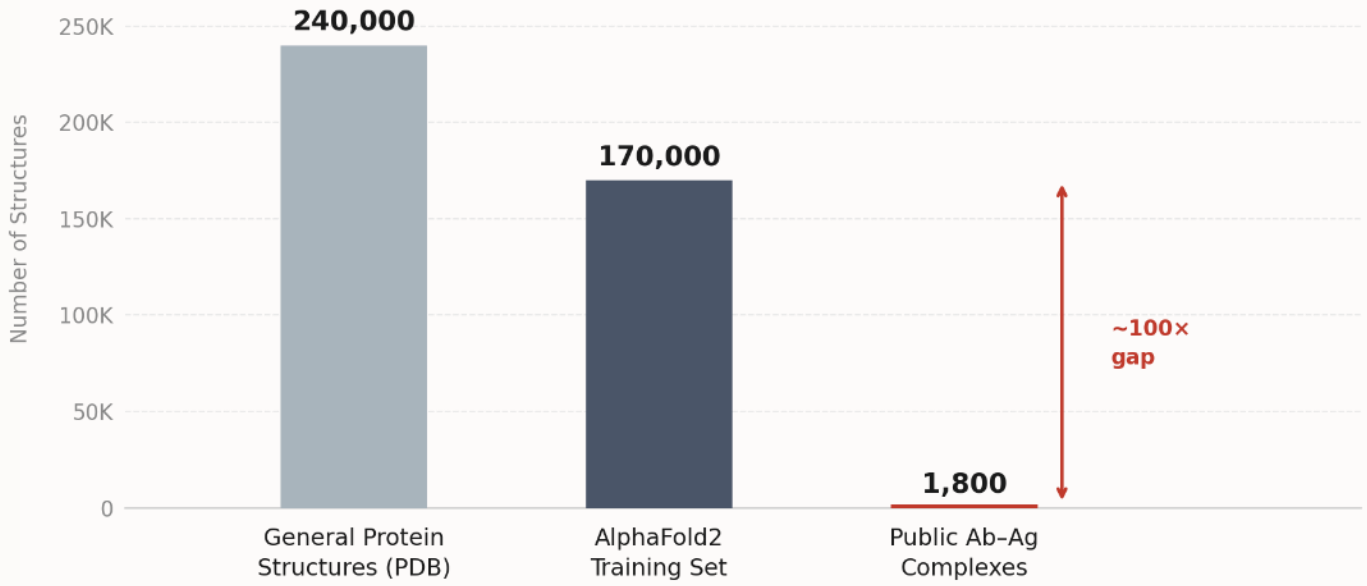
170,000

structures in
AlphaFold2 training set

~100x

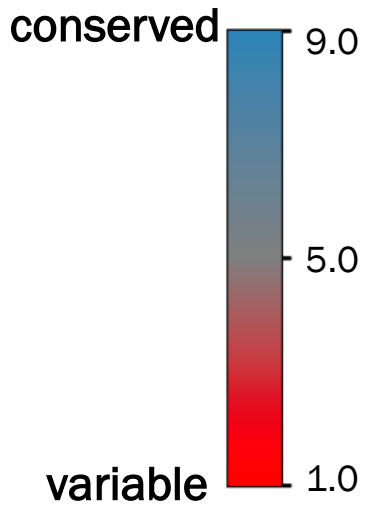
coverage gap:
antibodies vs. general proteins

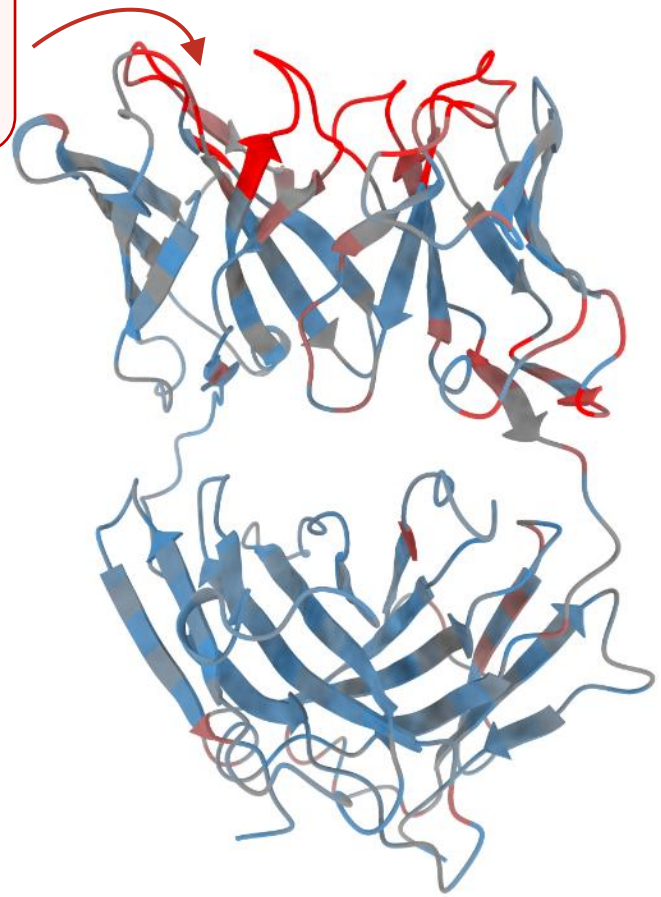
- Private datasets remain orders of magnitude below what is needed for generalizable structural AI
- The limiting factor is no longer model architecture — it is structural data availability



Antibody CDRs lack the evolutionary conservation that drives co-folding models.

CDR loops
Weak co-evolutionary signal



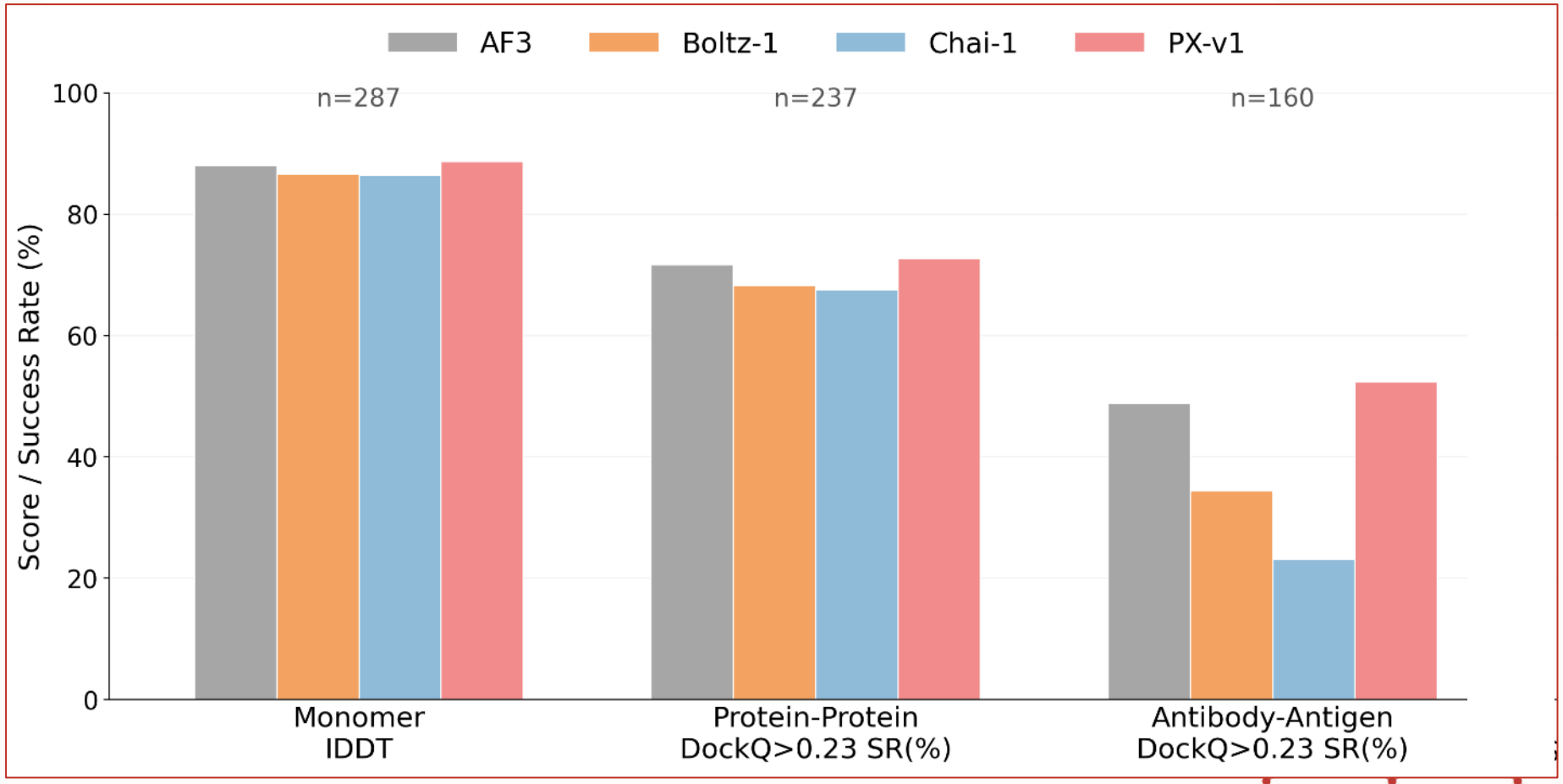


Cetuximab Fab

Cetuximab – Heavy Chain

```
  1  QVQLKQSGPG LVQPSQSLSI TCTVSGFSLT
 31  NYGVHWVRQS PGKGLEWLGV IWSGGNTDYN
 61  TPFTSRLSIN KDNSKQSVFF KMNSLQSNDT
 91  AIYYCCARAL TYYDYEFAYW GQGTLVTVSS
121  ASTKGPSVFP LAPSSKSTSG GTAALGCLVK
151  DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
181  GLYSLSSSUV TVPSSLGTQT YICNVNHKPS
211  NTKUDKRVEP K
```

Co-folding models still struggle with antibody-antigen complexes



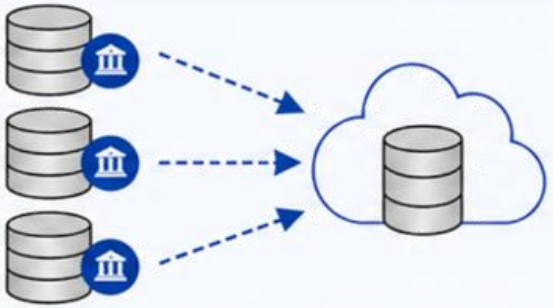
Source: Protenix Team et al., ByteDance, bioRxiv, Feb. 2026.

How The Field Is Trying To Solve This

1 Data Sharing / Federated Learning

Pools datasets across organizations

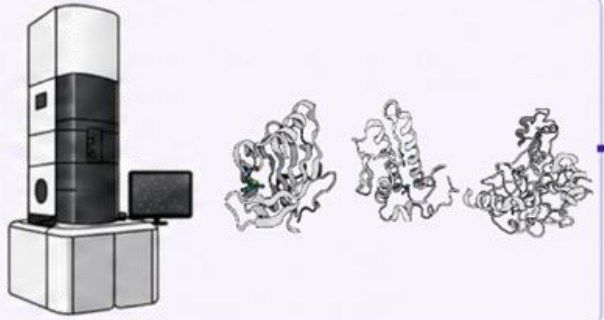
Limited to previously explored targetspace



2 Scaling Existing Structural Methods

High-throughput Cryo-EM, microED

Still low throughput vs. discovery needs



3 Model-Centric Approaches

Better architectures

Fundamentally the same structural dataset

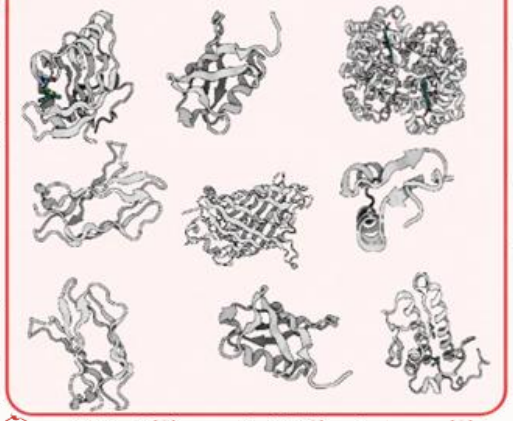
STRUCTURAL DATA BOTTLENECK

All three approaches converge on the same limitation.

Still constrained

All three approaches remain limited by the same underlying structural dataset.

None generates net-new experimental data at discovery scale.



What is required to overcome this bottleneck?

	Cryo-EM / X-ray	HDX-MS	Immuto Scientific
Throughput	●○○ Very low (weeks–months)	●●○ Moderate (days/target)	●●● High (100s/week)
Resolution	●●● Atomic (Å-level)	●○○ Region-level (low)	●●● Atomic
Target Compatibility	●●○ Moderate (tractable only)	●●● Broad	●●● Broad (membrane, flexible)
Output Format	●●○ PDB (sparse)	●○○ Exchange profiles	●●● PDB
Discovery Scale	●○○ No	●●○ Partial	●●● Yes

●●● High / Broad / Yes ●●○ Moderate / Partial ●○○ Low / Limited / No

From MS-Derived Signal to PDB-Compatible Structures

1

HT-MS Experiment

Ab–Ag complexes characterized at scale

2

Constraint Extraction

Residue-level contact information

3

Structural Modeling

MS-constrained Ab–Ag prediction

4

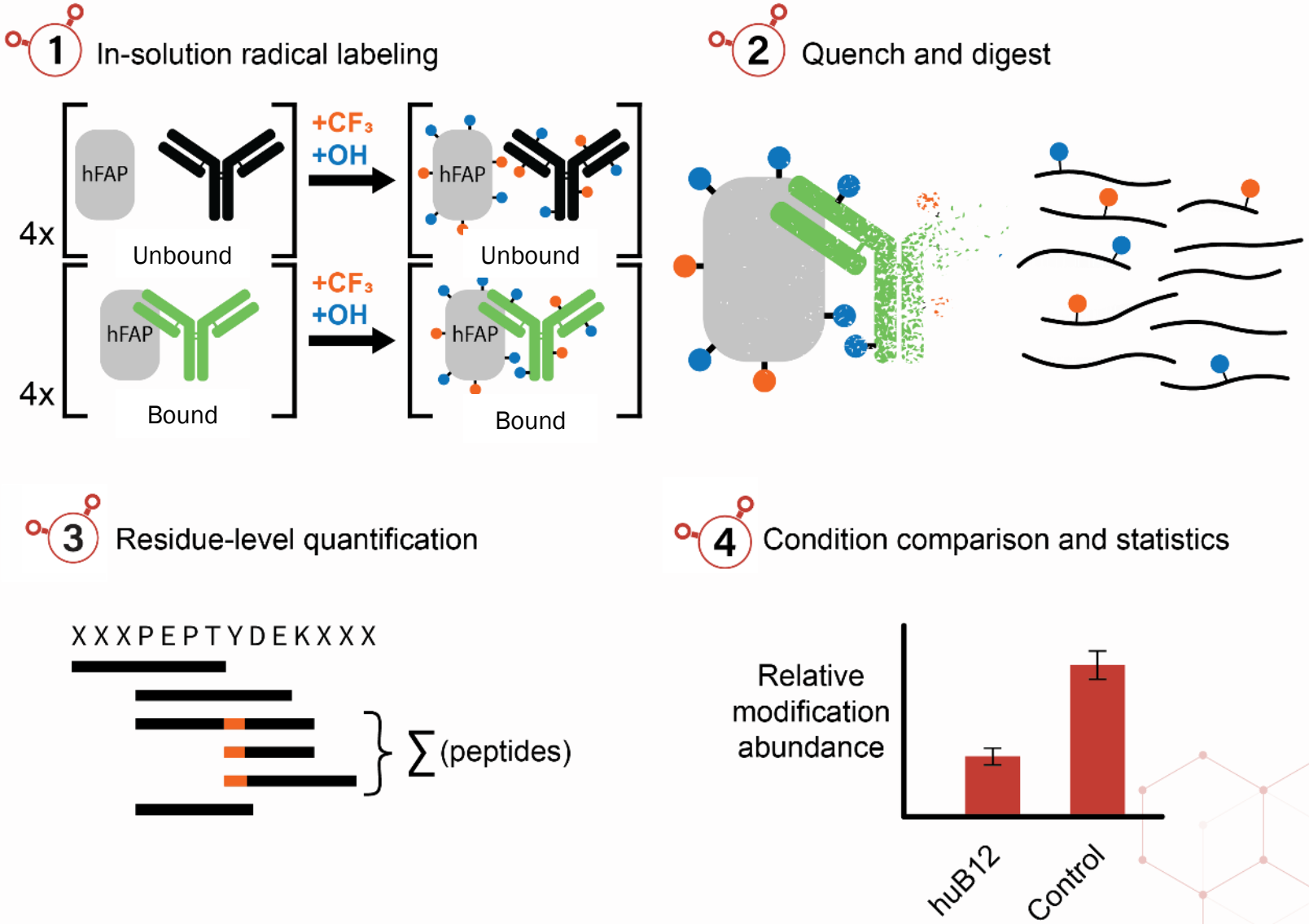
PDB-Form Output

Compatible with existing structural workflows

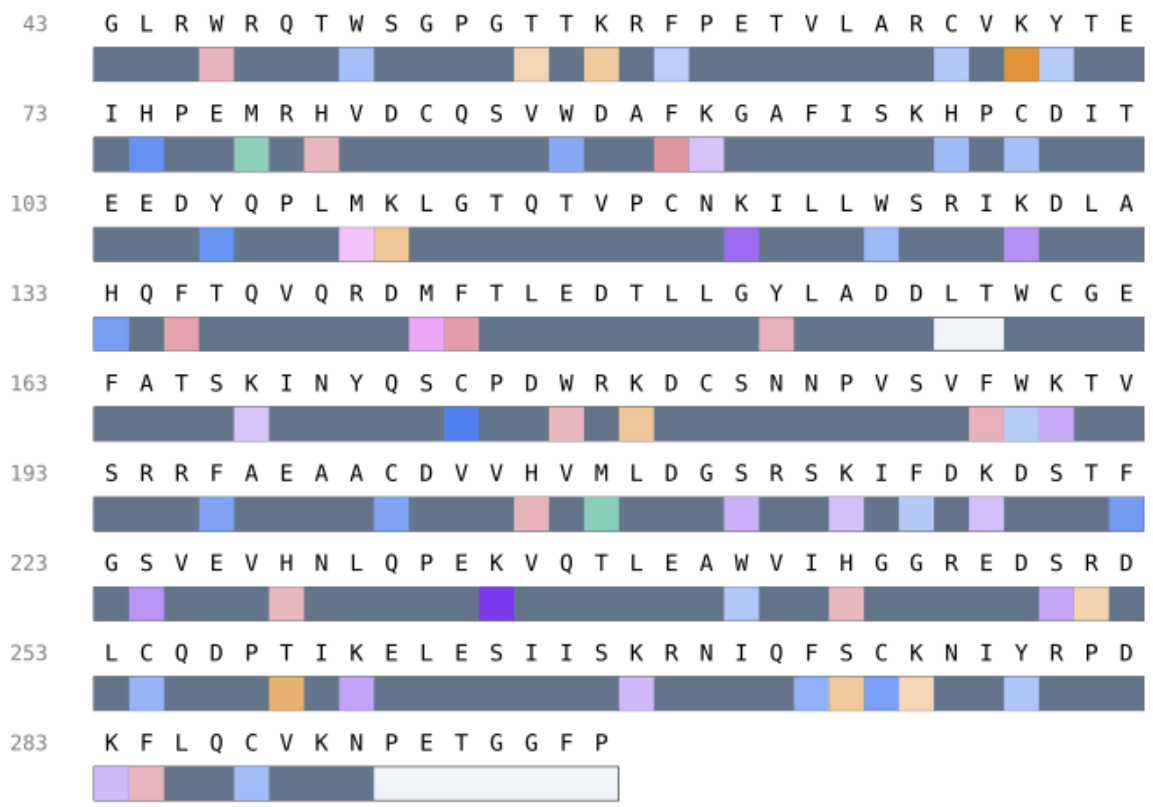
PDB outputs integrate directly with:

- Docking workflows
- Epitope mapping
- Affinity maturation
- AI / ML training datasets

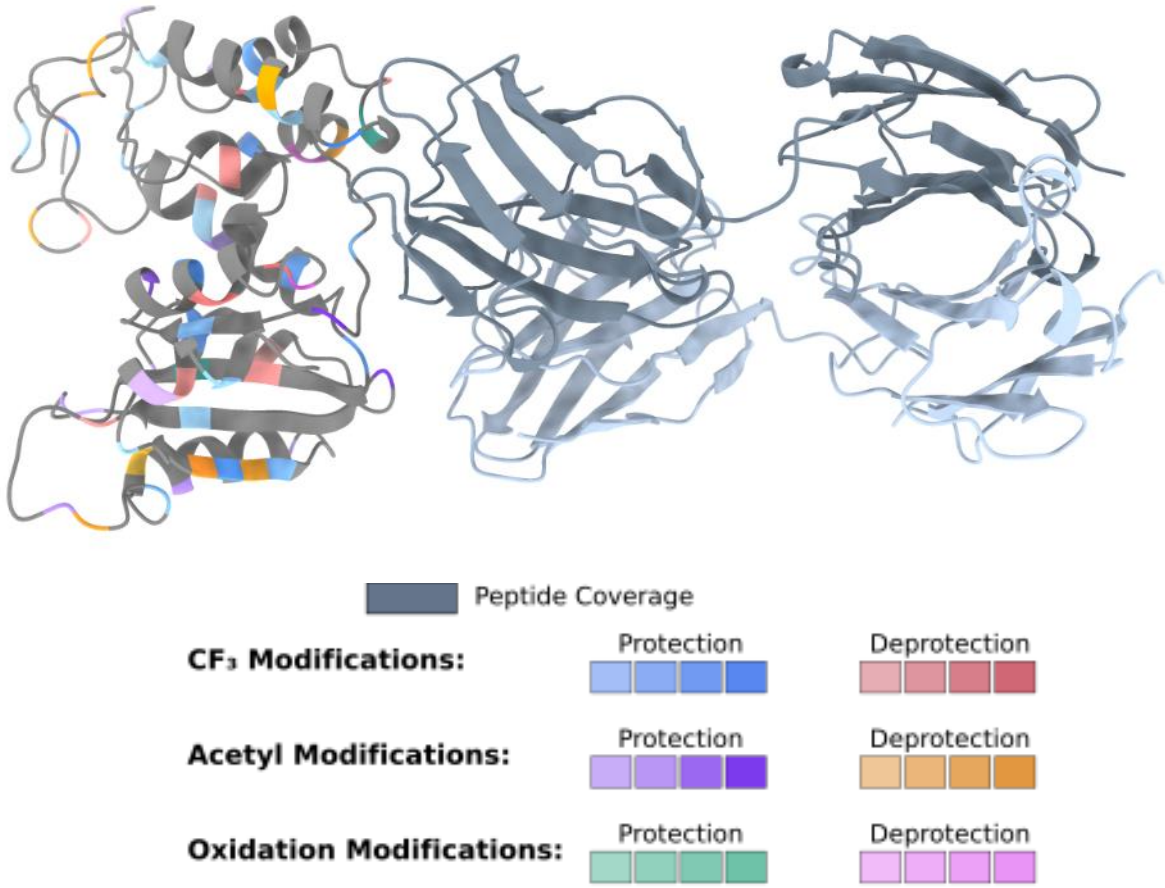
Epitope Mapping Experimental Workflow



Our proprietary radical labeling technology generates high-coverage, residue-level constraints



CD38:Erzotabart

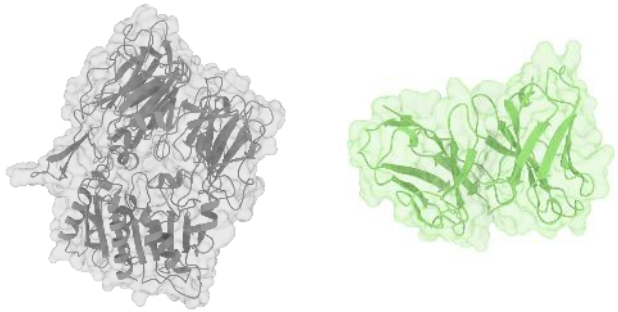


Peptide coverage: 95.3%

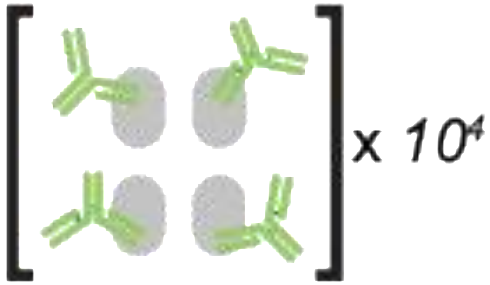
Modification coverage: 24%

RadicalRank: A deep learning model for ranking antibody-antigen structures using radical labeling data

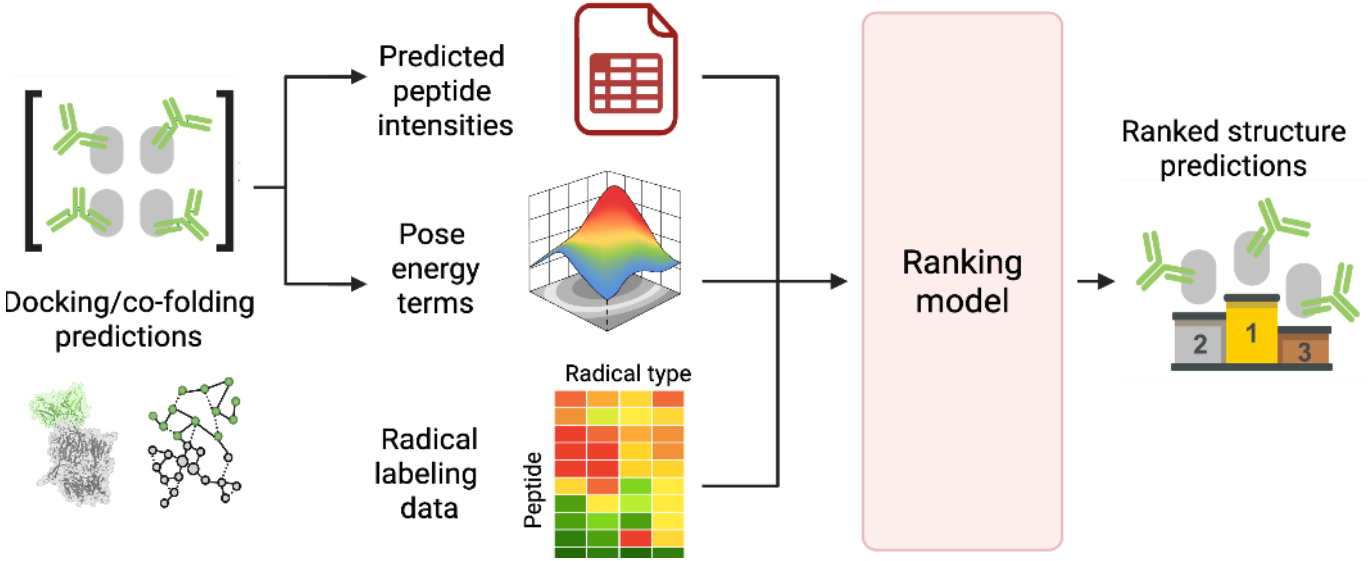
1 Generate conformational ensembles of antibody and antigen structures



2 Rigid + flexible high-throughput docking simulations



3 Rank docked structures using a deep learning model incorporating radical labeling data



Training data combines high-resolution structures, radical labeling, and docked decoys

Each antibody–antigen complex contributes a high-resolution PDB structure, paired peptide-level radical labeling, and a pool of docked poses used as ranking targets.

STRUCTURES

25

Antibody–antigen complexes

High-resolution PDB structures

LABELING

11,862

Peptides

Radical labels across 25 structures

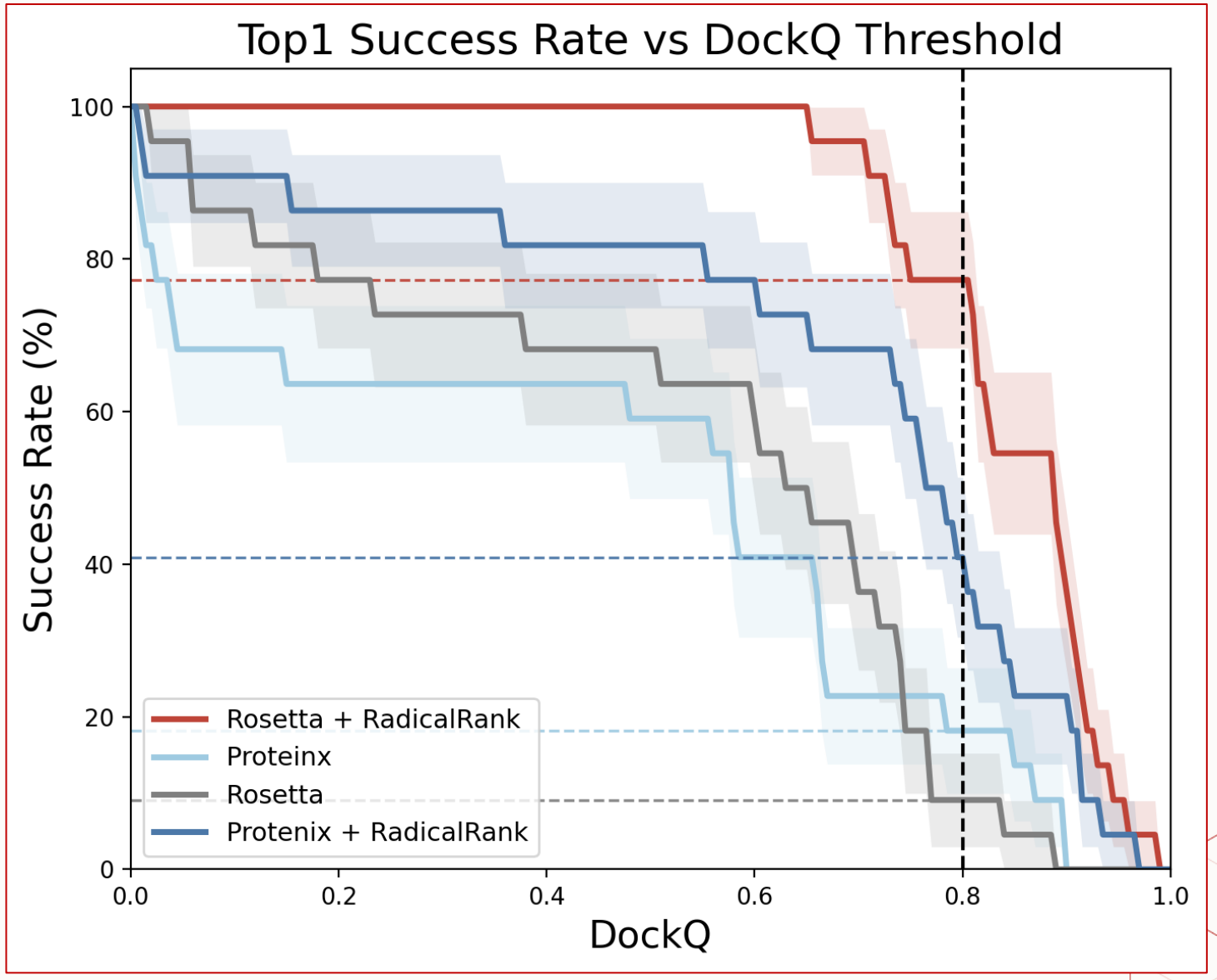
DECOYS

250K

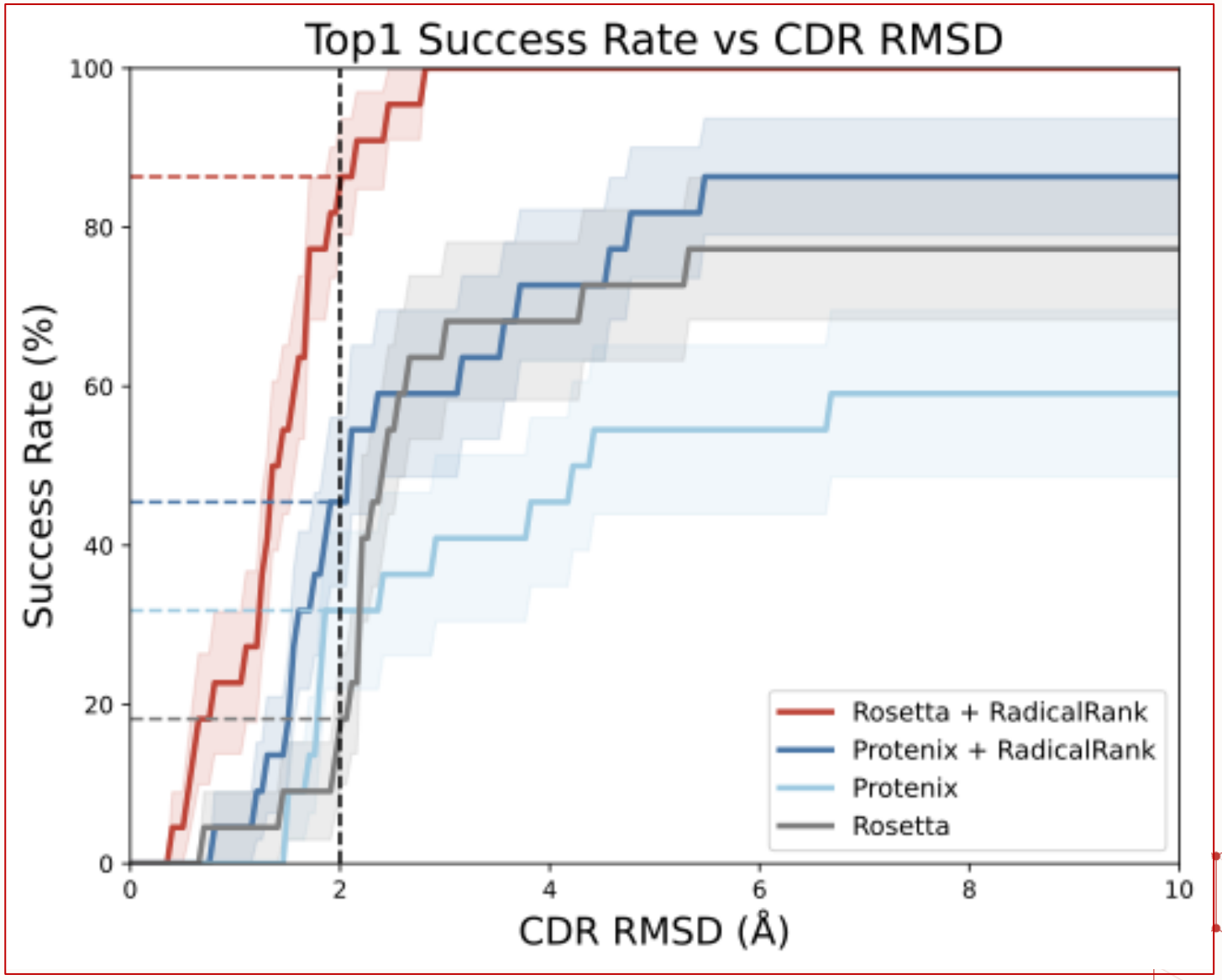
Docked models

10,000 poses per complex

RadicalRank generates high quality antibody-antigen structures



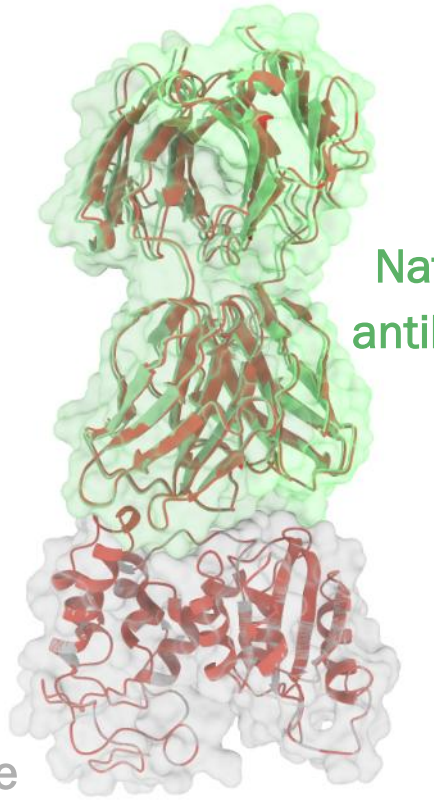
RadicalRank generates high quality antibody-antigen structures



RadicalRank performs well as a sole predictor

CD38:Erzotabart

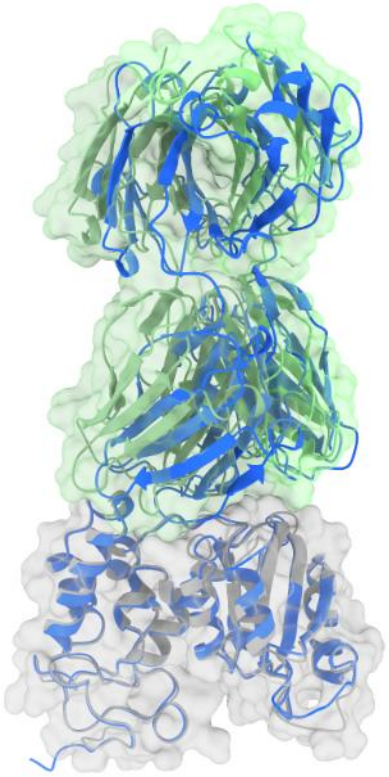
RadicalRank
(DockQ = 0.956)



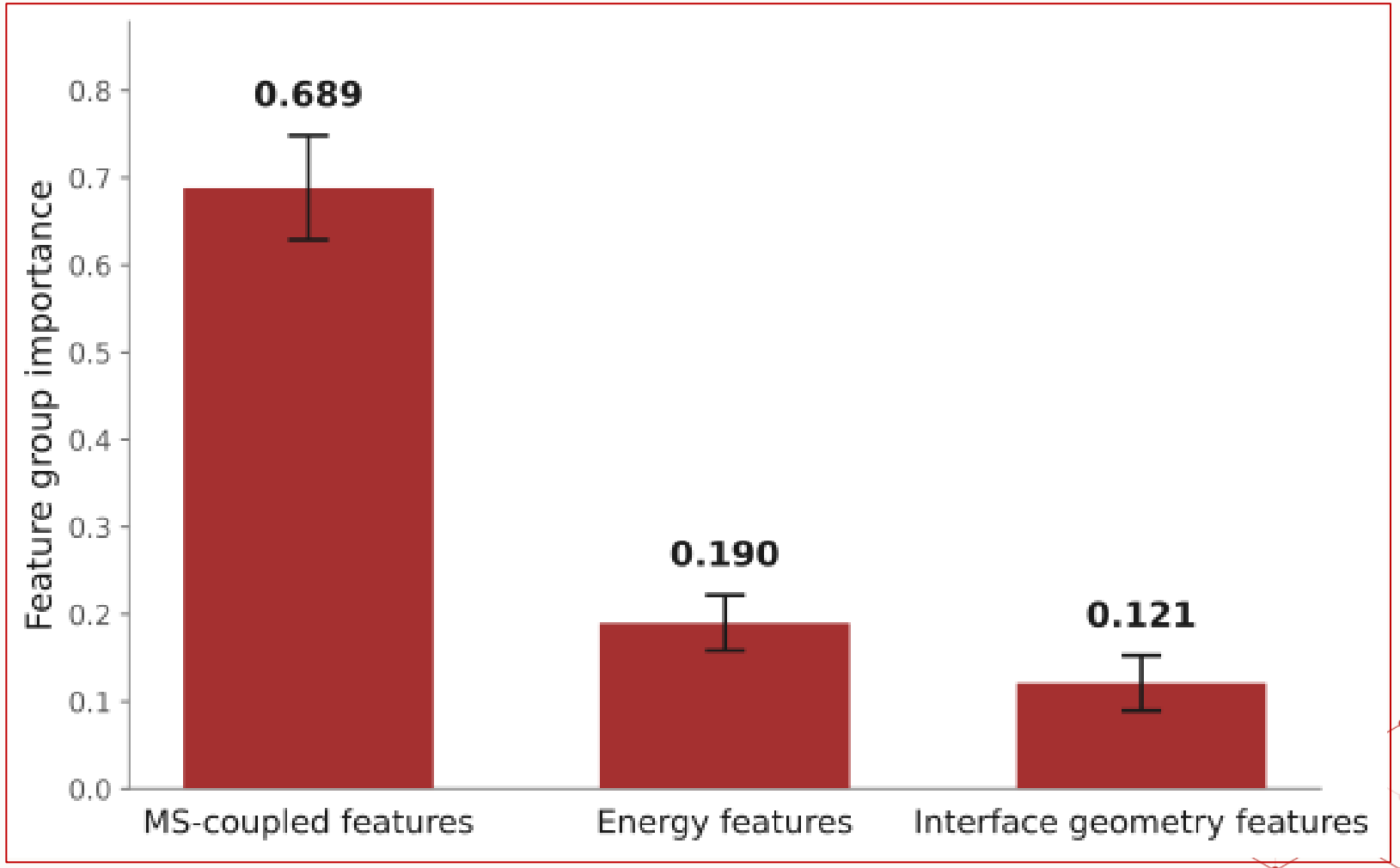
Native antibody

Native antigen

Protenix + RadicalRank
(DockQ = 0.359)



Experimental data agreement is the most important ranking model feature

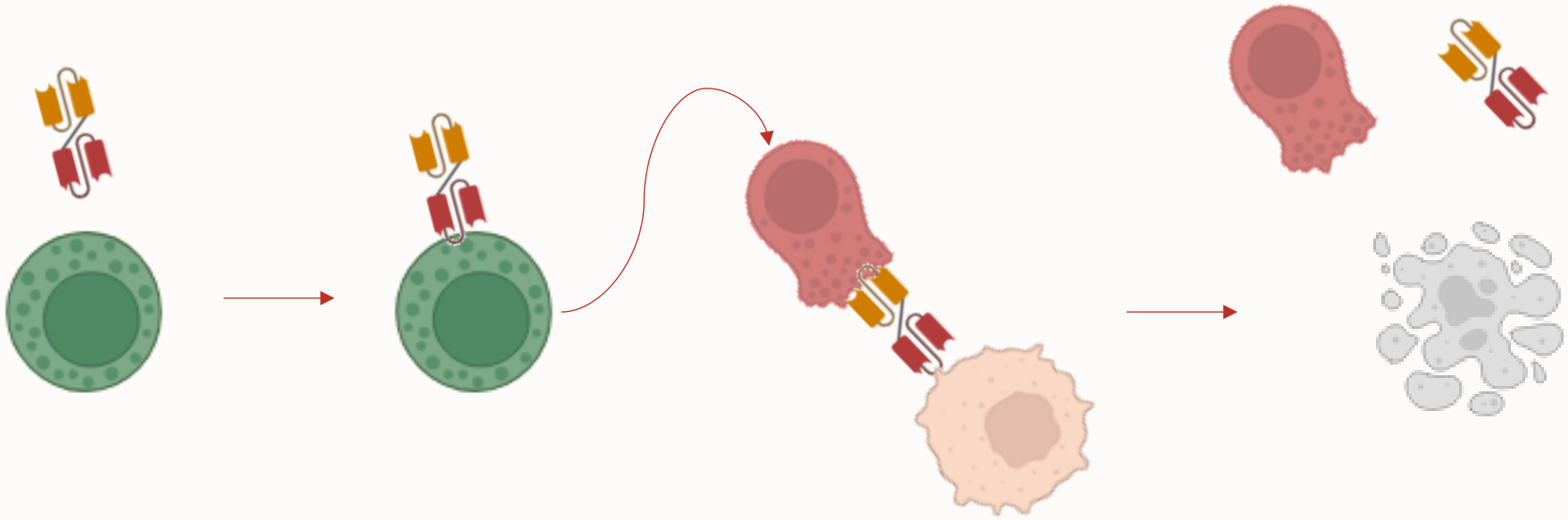


A novel workflow in partnership with:

avsbio

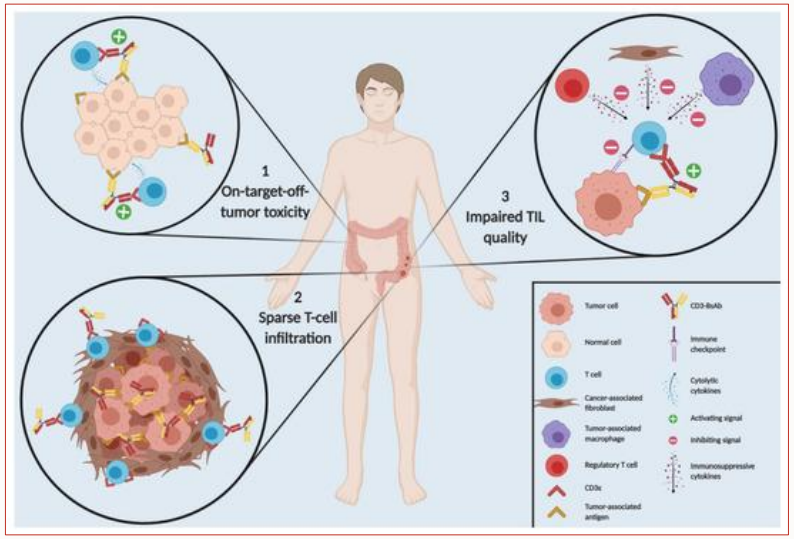
carterra®

Advanced Biophysical Characterization Supercharges anti-CD3 Antibody Discovery for Oncology



Targeting CD3 is Challenging

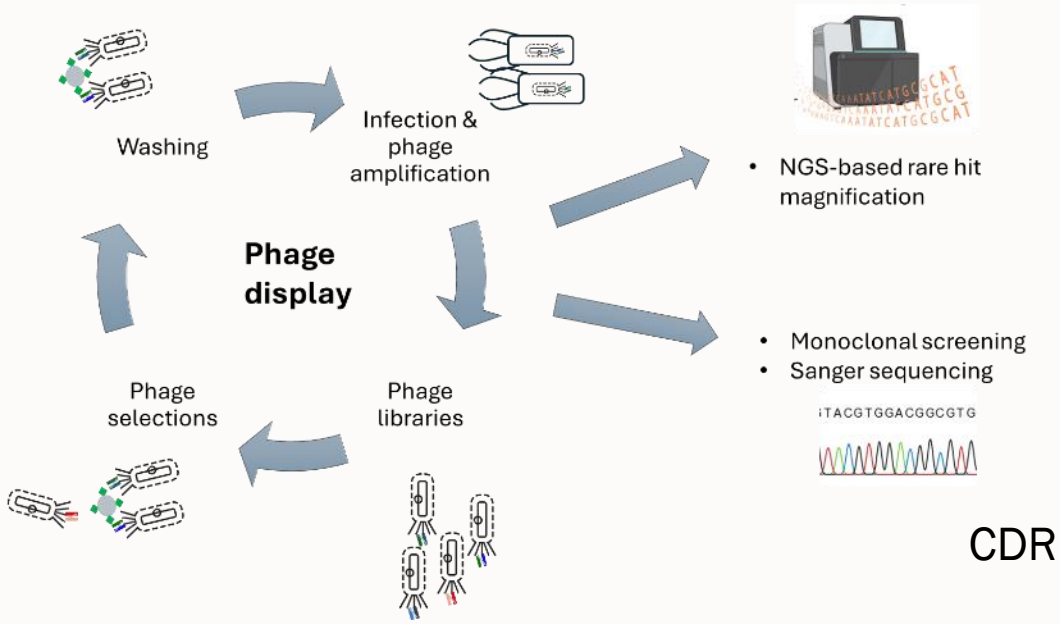
- **Binding CD3 isn't sufficient** – different binding kinetics, epitopes, and modalities all have different effects on therapeutic antibody function
- To select candidate antibodies, consider:
  - Are you targeting a **functional/activating epitope**?
  - Is the epitope engagement allowing for **optimal distance** between the T-cell and the tumor/tumor antigen?
  - Is your binding affinity so high that you are causing **cytokine release syndrome** (cytokine storm)?



1. https://www.nature.com/articles/s41416-020-01225-5
2. https://www.mdpi.com/2072-6694/13/2/287

Starting Strong: Diversity-Driven Antibody Discovery to Find Rare Hits

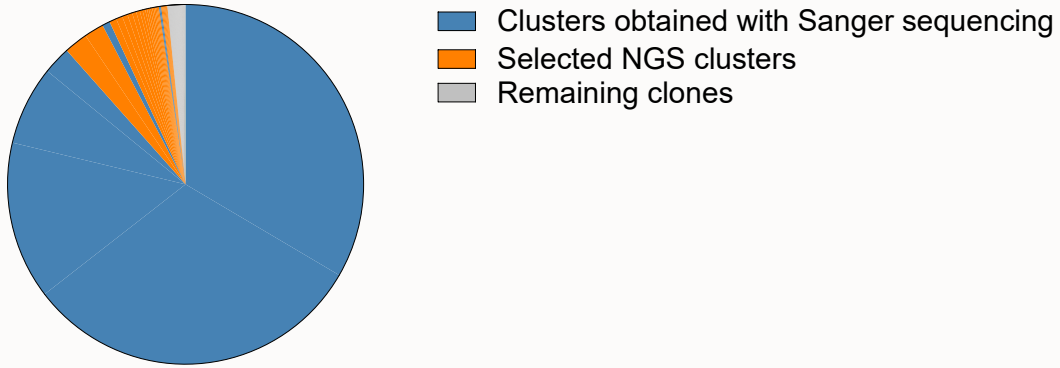
Accelerate identification of fully human, epitope-diverse antibodies that bind to endogenously expressed target



Ready-to-screen natural human repertoires

- Phage display-based selection of binders
- High throughput reactivity screening for cell binding
- Sequence recovery hits and target-enriched polyclonal phage outputs
- In silico-guided rare NGS cluster identification

CDRH3-based clustering of recovered sequences



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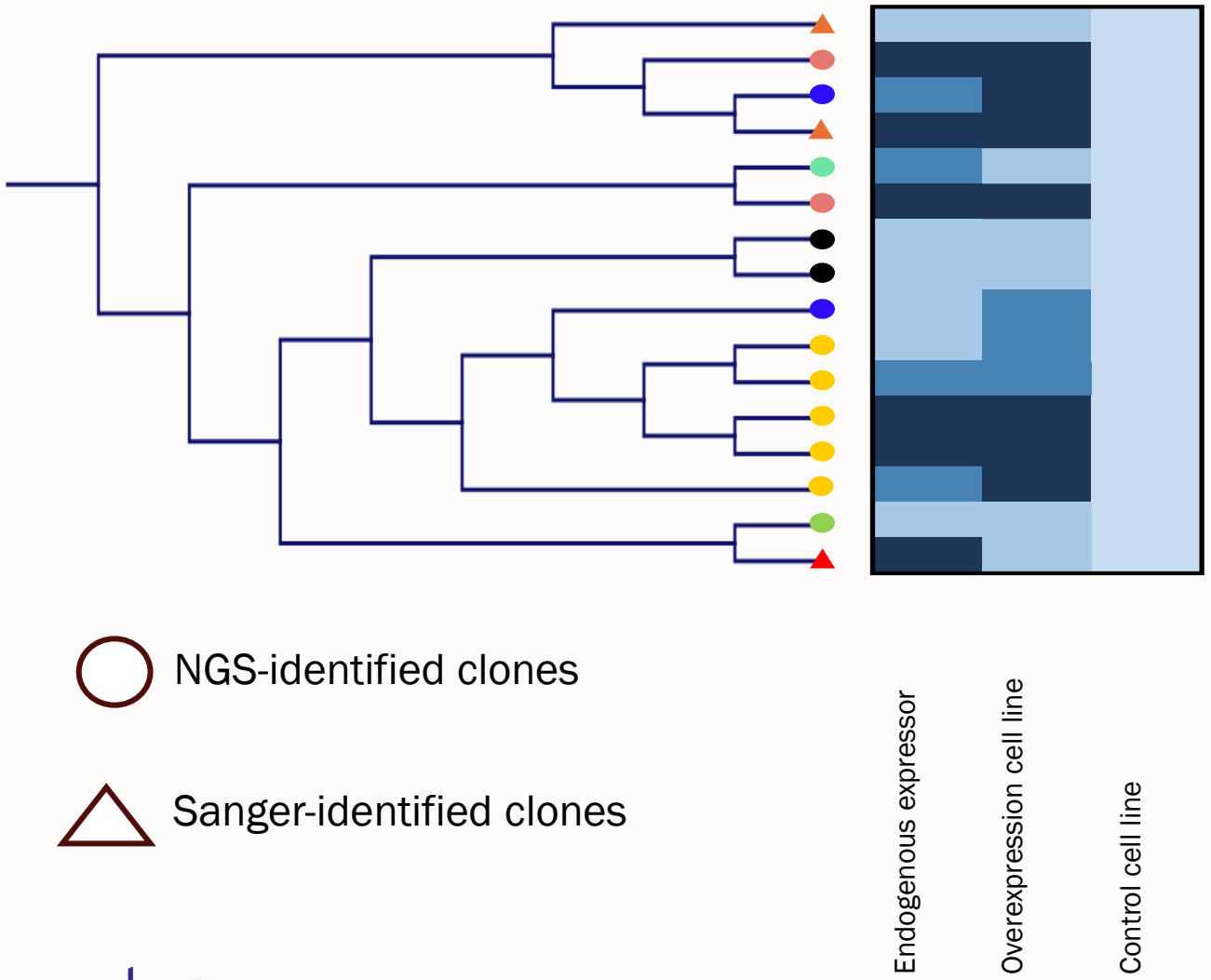
Starting Strong: Diversity-Driven Antibody Discovery to Find Rare Hits



Rapid identification of rare hits from target-enriched repertoires

- Isolation of clusters of interest by using unique identifiers
- Initial on/off screening of scFvs
- Deep mining for rare hits yielded additional cell binders

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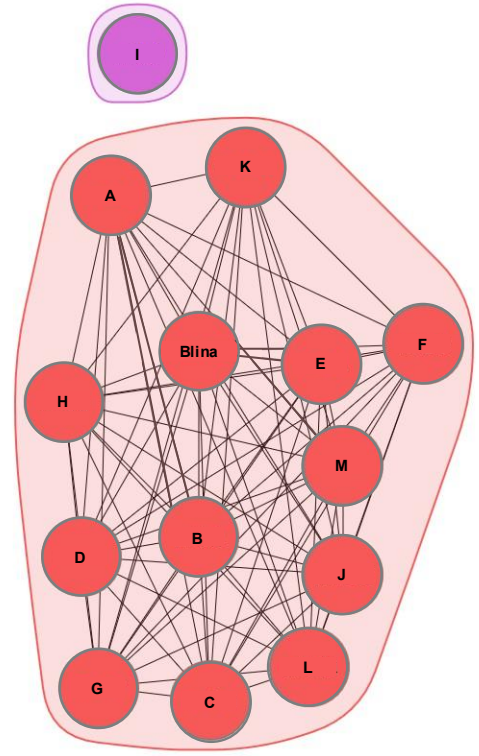
Key Kinetics: Bioanalytical Profiling to Triage Hits

- Kinetics revealed that most of the binders are lower affinity
- Upfront kinetics were used to inform epitope mapping studies
- Competition-driven epitope binning demonstrated that all the antibodies compete for binding

Bins	ID	CD3_Blina	M	G	D	C	B	L	J	F	E	H	A	K	I
	CD3_Blina	-0.01	-0.02	-0.03	-0.02	-0.01	0.00	-0.02	0.00	-0.01	0.00	-0.01	-0.01	0.00	4.63
	M	-0.10	-0.29	-0.23	-0.11	-0.04	-0.02	-0.26	-0.04	-0.04	-0.03	-0.07	-0.03	-0.02	2.34
	G	-0.07	-0.21	-0.17	-0.08	-0.03	-0.02	-0.18	-0.04	-0.03	-0.03	-0.06	-0.03	-0.02	2.92
	D	-0.01	-0.02	-0.02	-0.01	0.00	0.00	-0.02	0.00	0.00	0.00	-0.01	-0.01	0.00	4.59
	C	-0.01	0.00	-0.03	0.00	-0.02	0.01	0.01	0.01	0.00	-0.01	-0.01	0.00	0.00	6.66
	B	0.08	0.15	0.02	0.03	0.03	0.02	0.19	0.17	0.02	-0.01	0.07	0.02	0.11	1.04
	L	0.09	-0.16	-0.20	-0.15	-0.11	-0.14	-0.06	0.09	-0.04	-0.07	-0.03	-0.19	0.09	2.25
	J	-0.02	0.03	-0.04	-0.02	-0.02	-0.01	-0.01	0.00	0.00	-0.01	-0.01	-0.03	-0.01	6.20
	F	-0.02	-0.02	-0.03	-0.03	-0.02	-0.01	-0.02	-0.01	-0.01	-0.01	-0.02	-0.03	0.00	4.29
	E	-0.02	-0.02	-0.03	-0.03	-0.01	-0.01	-0.02	-0.01	-0.01	-0.01	-0.01	-0.01	0.00	4.24
	H	-0.01	0.01	-0.02	-0.01	-0.01	-0.01	-0.02	-0.01	-0.01	0.00	-0.01	-0.01	0.00	4.43
	A	-0.02	-0.02	-0.02	-0.01	-0.01	0.00	-0.01	0.01	0.00	0.00	0.00	0.00	0.01	4.10
	K	0.00	-0.03	-0.01	0.03	0.00	0.01	-0.02	0.03	0.08	0.04	0.04	-0.01	0.01	1.34
	I	0.56	1.05	1.34	1.39	0.27	0.27	1.85	0.86	0.11	0.11	0.15	0.03	0.05	-0.14



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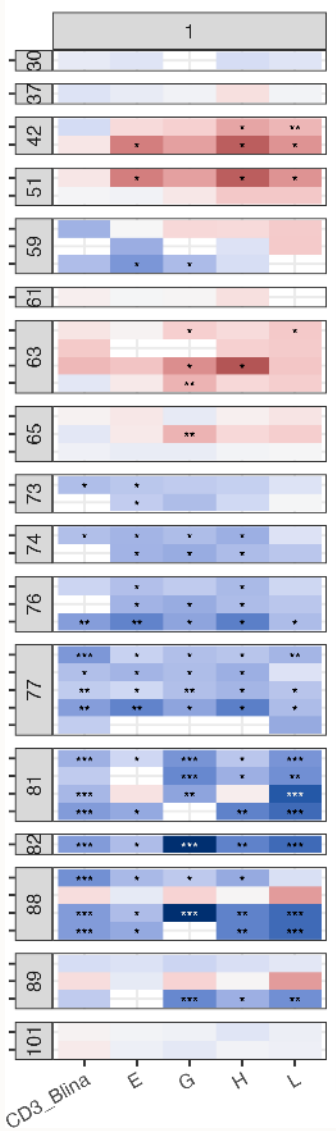
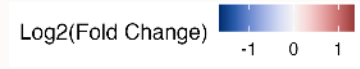
Structural Epitope Mapping Sharpens Kinetic Analyses and Accelerates Lead Optimization

- Peptide-level analysis of antibody binding sites determined 3 main structural clusters of changes - Clusters are influenced both by regions and degrees of changes
  - Majority of binding induced changes were mapped to CD3 epsilon and largely overlap with CD3 arm of Blinatumomab (CD3-Blina)
- Clusters 1 and 2 show similar patterns of solvent exposure
- Cluster 3 shows a distinct pattern of solvent exposure – which indicates a different binding mode or epitope when compared to clusters 1/2
- Cluster 4 did not show significant changes in solvent accessibility



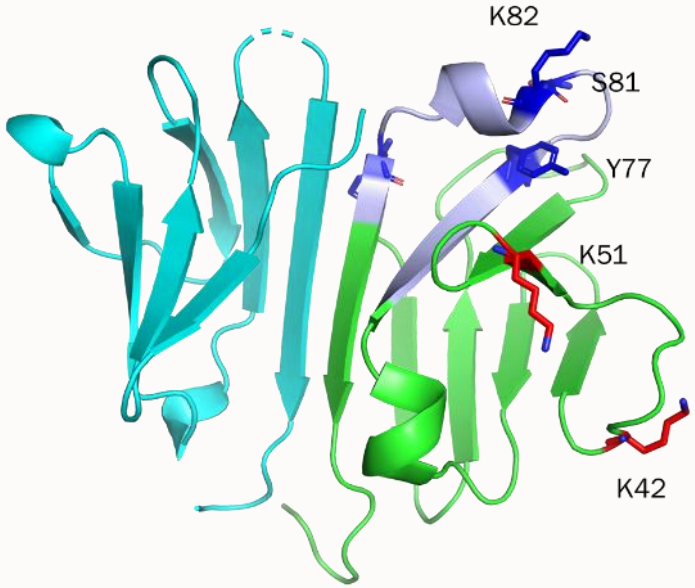


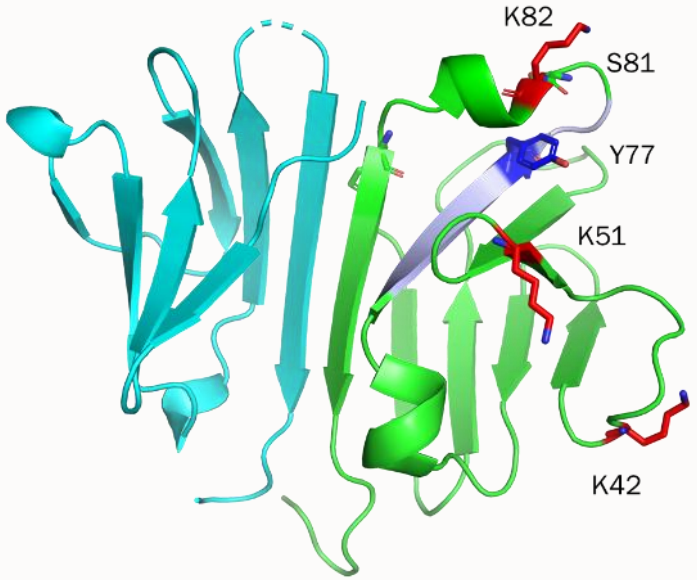
Increased Solvent Exposure

Decreased Solvent Exposure

Structural Epitope Mapping Sharpens Kinetic Analyses and Accelerates Lead Optimization

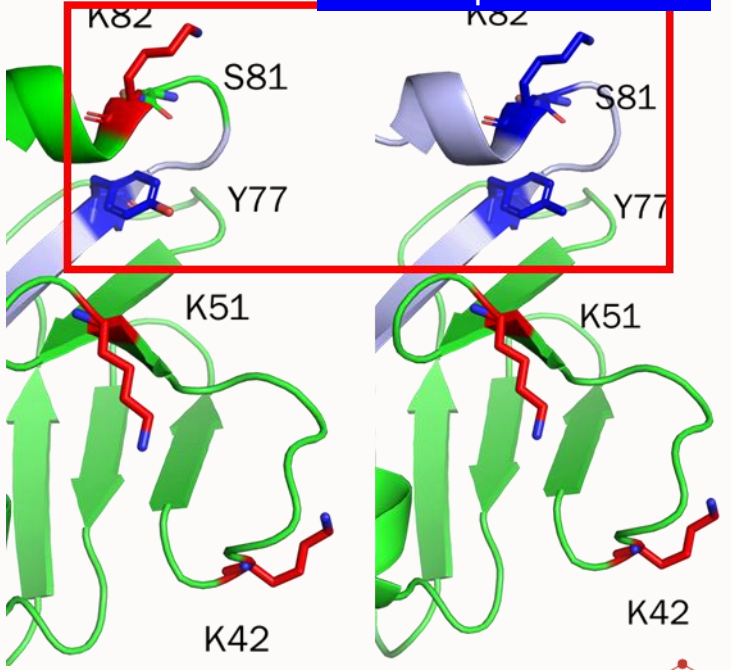
- When comparing the epitopes of CD3-Blina (left) from cluster 1 and mAbs I and K (right) from cluster 3, we see the differences in solvent accessibility reveal distinct modes of engagement





Increased Solvent Exposure

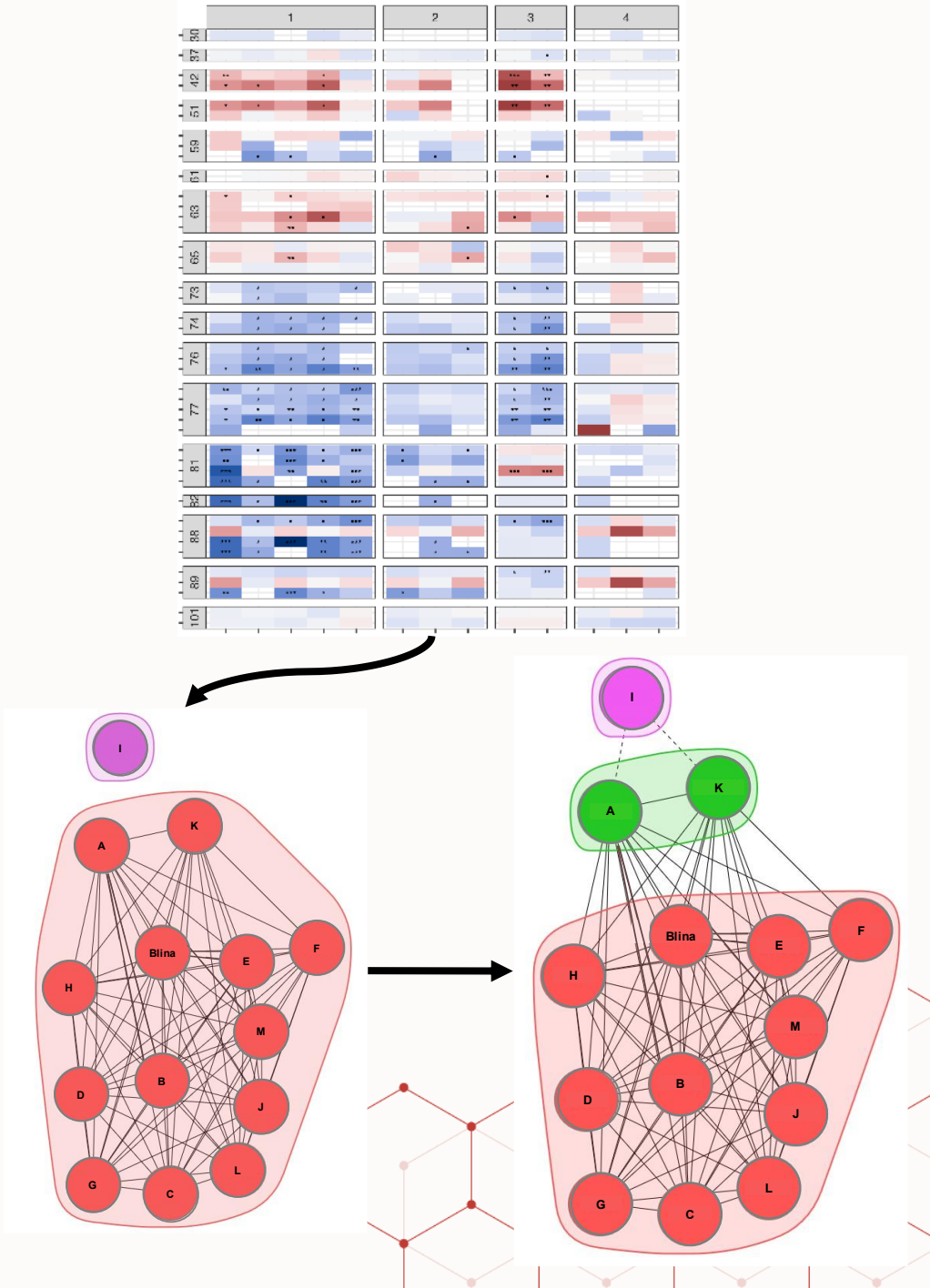
Decreased Solvent Exposure



- CD3-Blina engages the CD3E antigen along the loops extending from lysine-82 - lysine-42; whereas mAbs I and K appear to engage the antigen at a slightly downshifted position, beginning to engage at tyrosine-77 down through lysine-42.

Mode of Engagement Governs Function

- Clusters 1 and 2 largely represent functional, **activating** antibodies, such as blinatumomab, while cluster 3 represents functionally **inactive** antibodies
- Function-focused antibody discovery campaigns might be less epitopically diverse – but **subepitopic** changes are indicative of function and suitability as a therapeutic
- Interestingly, the **structural epitope data was used to inform the network groupings by SPR**. This facilitates deep mining of remaining sublibraries to identify additional antibodies that fit the binding modes



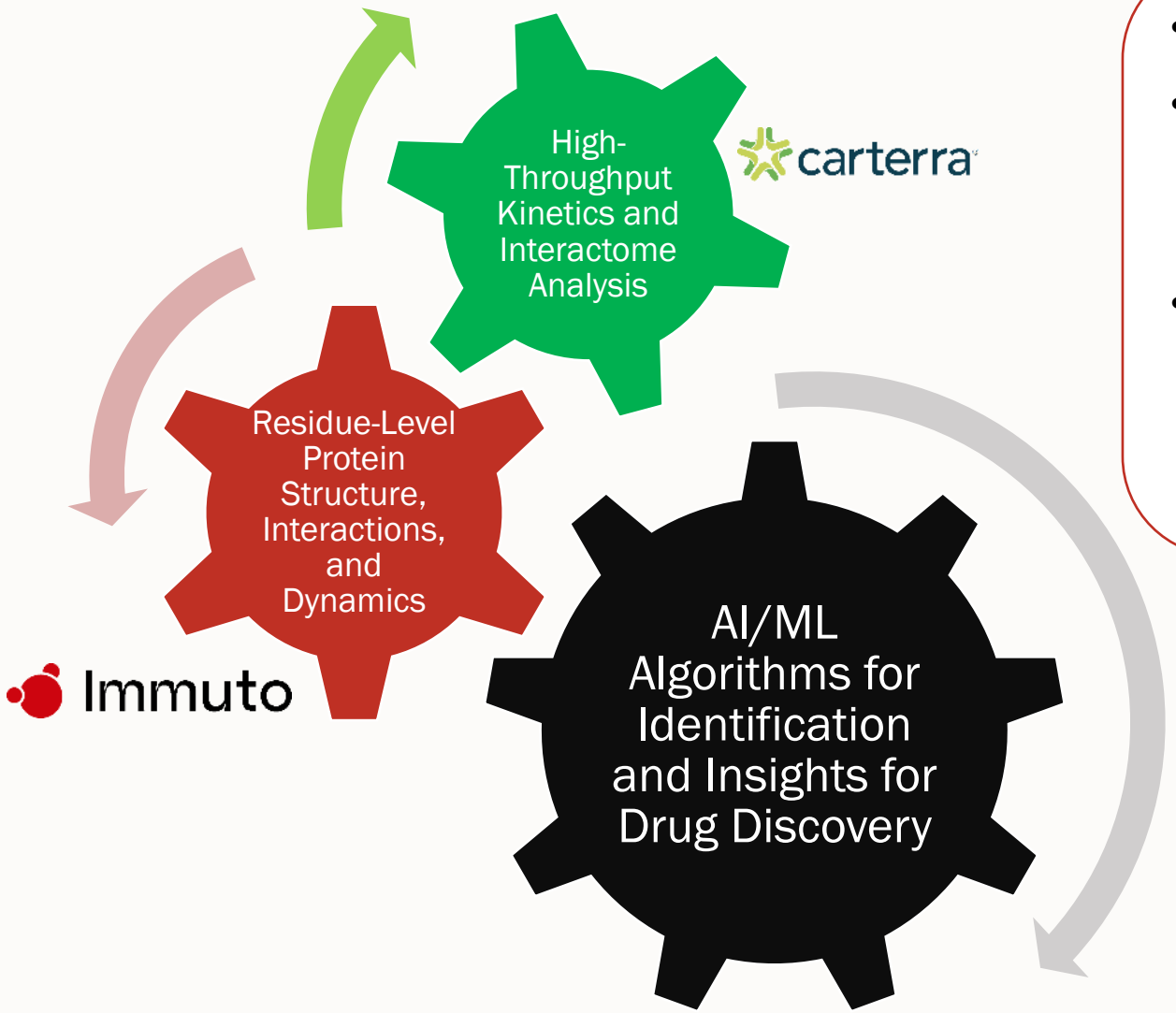
Key Findings

- In parallel deep repertoire mining for rare hit identification delivered a diverse set of antibodies directed against natively folded CD3E
- **Comprehensive epitope assessment is necessary**, even when functional assays provide clear data
  - The mode of engagement of an antibody, including **orientation, engaged residues, positioning**, etc., all govern the function of the molecule
  - These variables are **not addressable** systematically with just functional screening
- Even where epitopic diversity is limited, **subepitopic groupings reveal key functional behaviors**
  - **Binning and mapping are both necessary** to achieve subepitopic resolution in these settings – they inform each other and reciprocally augment the insights gleaned from both approaches

Next steps:

- We plan to use **empirical epitope data to constrain *in silico* modeling** as we refine binders to CD3E for potential use as therapeutics
  - Non-functional epitopes from cluster 3 will inform the engineering and affinity fine-tuning of functional clones to prevent a switch in mode of engagement

High-Throughput Multimodal Data is the Next-Gen Path for Biologics Discovery



- Carterra Ultra/LSA creates an **interactome atlas**
- Immuto generates high-resolution **structural PPIs at scale**, based on binding confirmation from Carterra
- Feed **proprietary, purpose-built** interaction data, kinetic information, and structural data to AI/ML algorithms to identify novel Ab/Ag pairs, targeting mechanisms, and endogenous ligands

Scalable Structure in Practice

Drug Discovery Workflows

- ✓ Structural visibility across the full lead panel
- ✓ Earlier epitope and mode-of-engagement insight
- ✓ Higher-confidence triage and optimization
- ✓ Structural feedback while campaigns are still moving
- ✓ Rescue low affinity binders

AI and Model Development

- ✓ Generate target-class and cross-target structural datasets
- ✓ Train more accurate Ab–Ag complex prediction models
- ✓ Enable program- and dataset-specific model refinement
- ✓ Support future de novo design and engineering workflows

Thank you!

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Appendix

- Setting a cutoff for network diagrams is difficult when there is heavy cross-competition of binders
- Epitope mapping data demonstrated that there is validity in setting the cutoff at the red bar versus yellow

Mapping-informed cutoff

Original cutoff