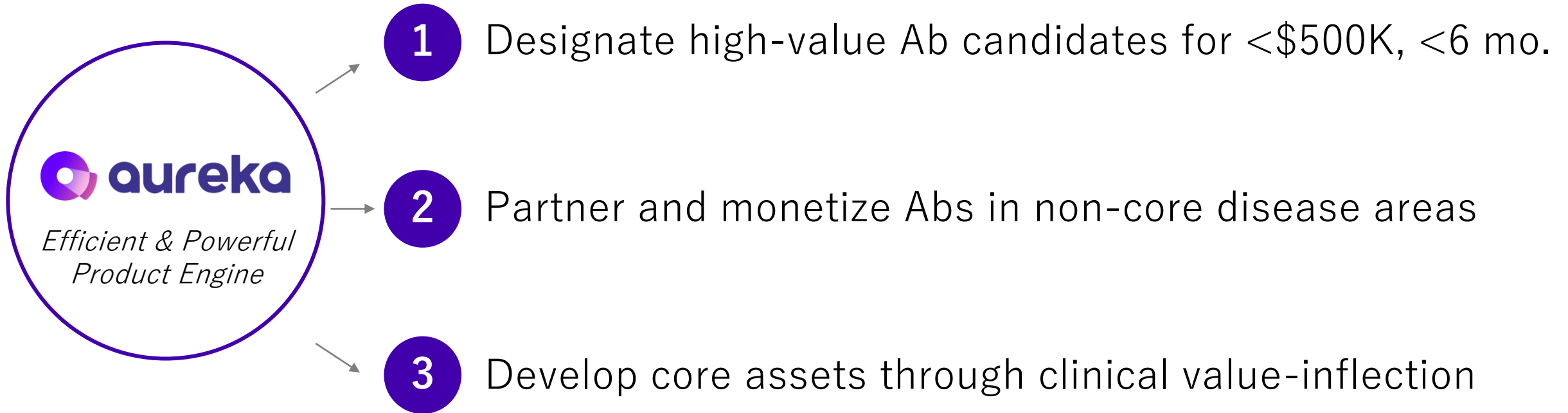# Rapid Design of Dual-Specific Antibody Therapeutics Using AI and High-Throughput Biology

Jack Hu

Jun 2025

Company Vision

1 Designate high-value Ab candidates for <$500K, <6 mo.

2 Partner and monetize Abs in non-core disease areas

3 Develop core assets through clinical value-inflection

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Efficient & Powerful Product Engine

Transformative Discovery Platform

- Solves challenge of finding unique antibodies – the "high-hanging fruit"

  Dual-specificity   **Agonism**   **Internalization**   **Degradation**   **pH sensitivity**

- Orders of magnitude more efficient to DC vs. traditional Ab discovery

  <$500K $2 – 20M

            vs.

  <6 months   1 – 3 years

- Proven by repeatedly delivering for partners in high-value areas

Top 15 Biopharma	Tier 1 Venture Firm	Mid-Cap Biotech	Biotech Start-up

DC: Designated Candidate.

3

Antibody Discovery Problem

🔍 Current methods are not set up to find the "needle-in-the-haystack"

Inefficiency		**Inefficiency**	
Discover Binders ▶	**Generate Library** ▶	**Screen Function** ▶	**Select Candidate**

Discover Binders
- Generate IgG, VHH, and/or scFv
- Use diverse range of affinities/epitopes

Generate Library

x 100

x 100

- Combine into library of single format or multiple formats
- Generate 10 – 1,000 members to screen

Screen Function

22Rv1
- PSMA-1 x CD3
- PSMA-2 x CD3
- NEG x CD3

% specific lysis vs. Concentration (nM)

- Assay in disease-relevant context
- Screen 10 – 1,000 Abs in 96-well plates

Select Candidate
- Select candidate with desired function
- Optimize Ab for developability

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Aureka's Platform and Differentiation

10x Our technologies drive a >10x improvement in Ab discovery throughput

Solves challenge of finding unique antibodies – the "high-hanging fruit"

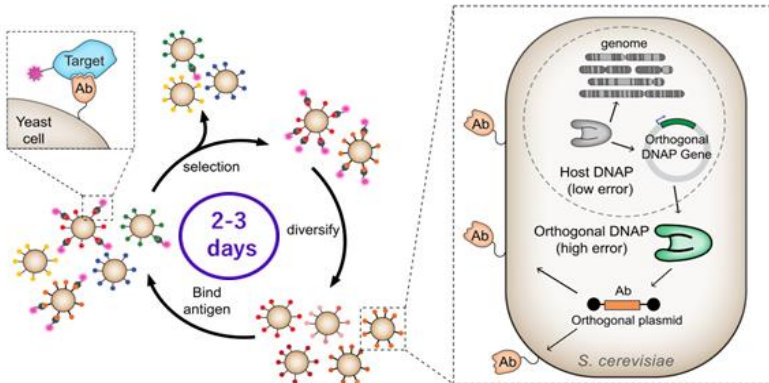**3 weeks vs. 3 months per campaign**   **1 Million compounds in days vs. years**
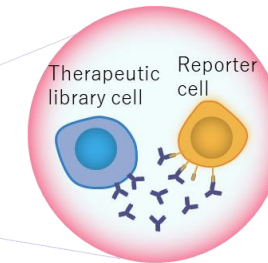
Discover Binders ▸ **Generate Library** ▸ **Screen Function** ▸ **Select Candidate**

AuraQuest: Hypermutating Yeast Display

Each campaign generates panel of diverse affinities

Multi-objective optimization (e.g., pH-sensitivity, polyspecificity)

AuraGlow: Microdroplet-based Cell Screening

1 tube

- Picoliter droplets contain 1 library cell, 1 reporter cell
- High-content readouts (e.g., internalization, activation)

AuraPicasso: Generative AI

Structural Modeling	Library Design	Fitness Prediction

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Dual-Specific Antibodies

- **Regular IgG (not BsAB) that can bind to two different targets**

- Superior developability and manufacturability over BsABs

- Enabling novel MOA (exert different logic gate AND, OR functions)

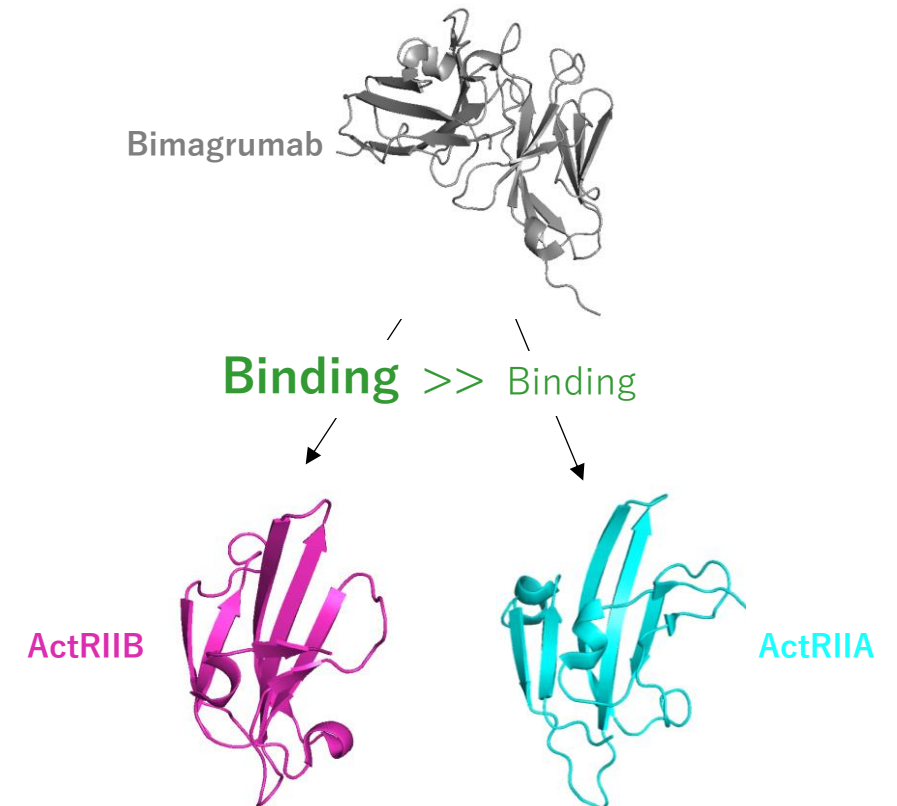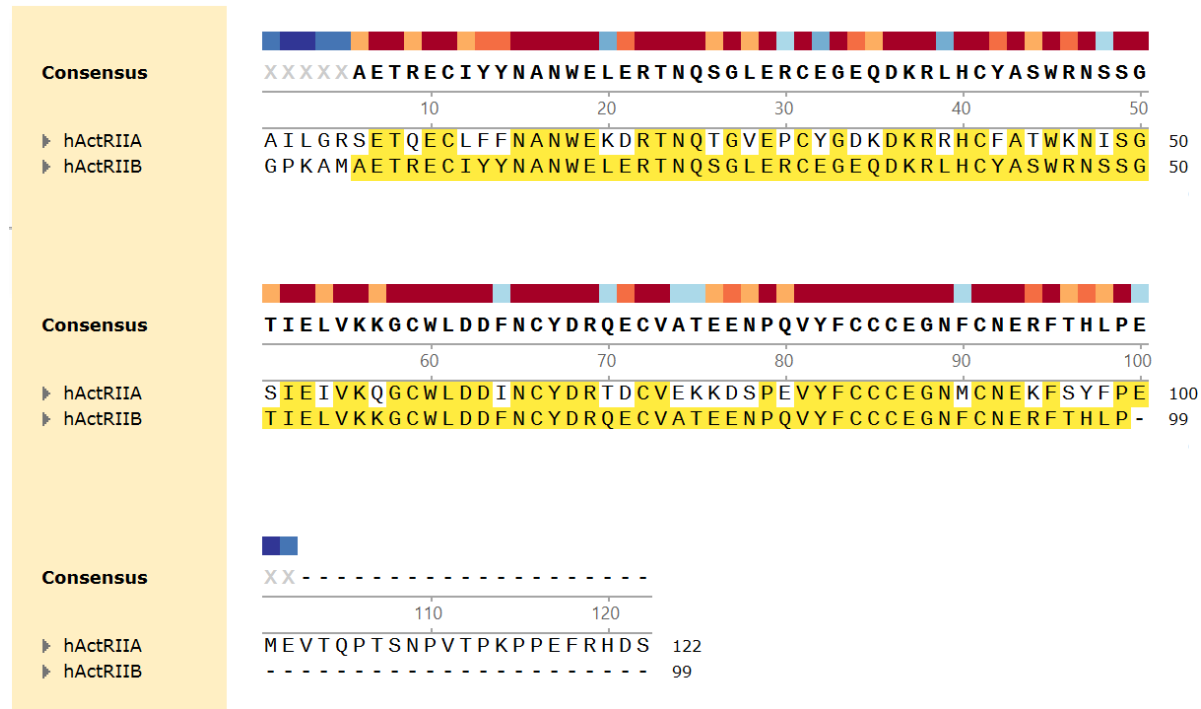# Case Study #1: Dual-specific Binding *(Single Paratope Ab)*

Technologies Deployed: | **Hypermutating Yeast** | Microdroplet Screen | **Generative Models**

- About 50% conservation between **ActRIIA** (Activin receptor 2A) and **ActRIIB** (Activin receptor 2B)

Bimagrumab

Binding >> Binding

ActRIIB   ActRIIA

Case Study #1: Dual-specific Binding *(Single Paratope Ab)*

Technologies Deployed: **Hypermutating Yeast** Microdroplet Screen **Generative Models**

● Designed combinatorial library against targets in silico
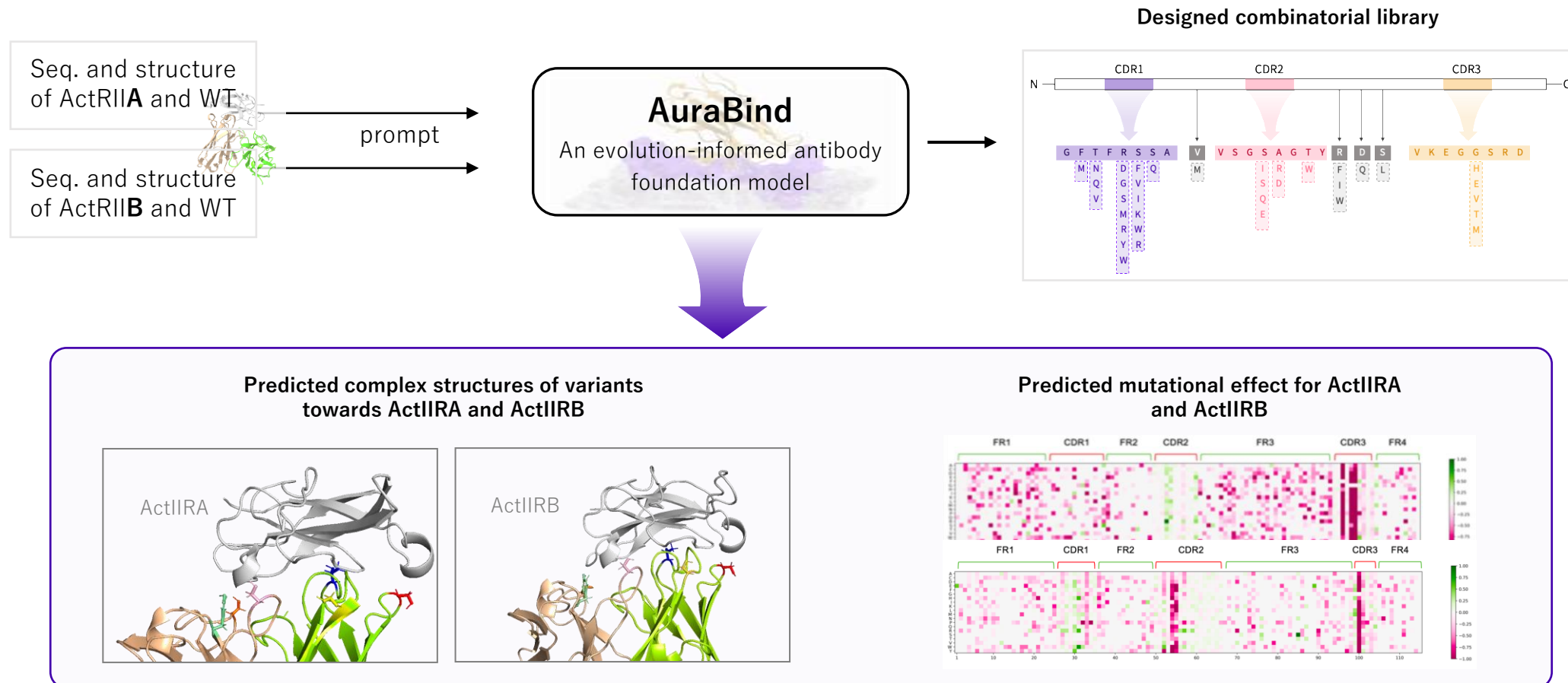
Designed combinatorial library

Seq. and structure of ActRII**A** and WT

Seq. and structure of ActRII**B** and WT

prompt

AuraBind
An evolution-informed antibody foundation model

Predicted complex structures of variants towards ActIIRA and ActIIRB

ActIIRA

ActIIRB

Predicted mutational effect for ActIIRA and ActIIRB

Case Study #1: Dual-specific Binding *(Single Paratope Ab)*

Technologies Deployed: | **Hypermutating Yeast** | Microdroplet Screen | **Generative Models**

● Express library in hypermutating yeast and evolve solution

Seq. and structure of ActRIIA and WT

Seq. and structure of ActRIIB and WT

prompt →

AuraBind
An evolution-informed antibody foundation model

finetune

Designed combinatorial library

Yeast campaign + two rounds of FACS + NGS

High-throughput affinity measurement data
(> 10⁶ labelled dataset)

Fitness data for ActIIR A/B

Seq1 0.87 | Seq1 0.62
Seq2 0.86 | Seq2 0.64
Seq3 0.45 | Seq3 0.25
Seq4 0.34 | Seq4 0.41
Seq5 0.11 | Seq5 0.08
Seq6 0.12 | Seq6 0.82
Seq7 0.78 | Seq7 0.14
... . | ... .

Display / Binding

Affinity to Target B / Affinity to Target A

50 designs (A > B by > 100x)

50 designs (A ~= B)

Experimental measurements

We closed the loop of integration between AI and high-throughput screening

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Case Study #1: Dual-specific Binding *(Single Paratope Ab)*

Technologies Deployed: | **Hypermutating Yeast** | Microdroplet Screen | **Generative Models**

● Workflow for evaluating the affinity of AI-predicted antibodies
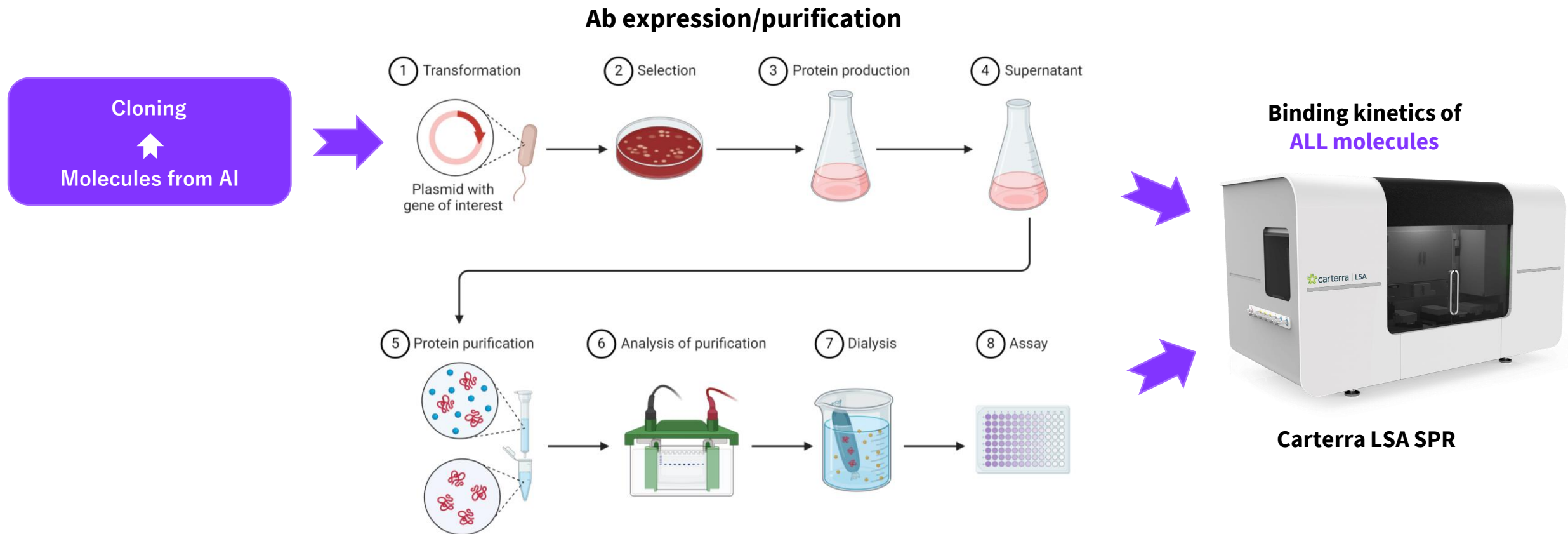
Ab expression/purification

Cloning
↑
Molecules from AI

Binding kinetics of ALL molecules

Carterra LSA SPR

Case Study #1: Dual-specific Binding *(Single Paratope Ab)*

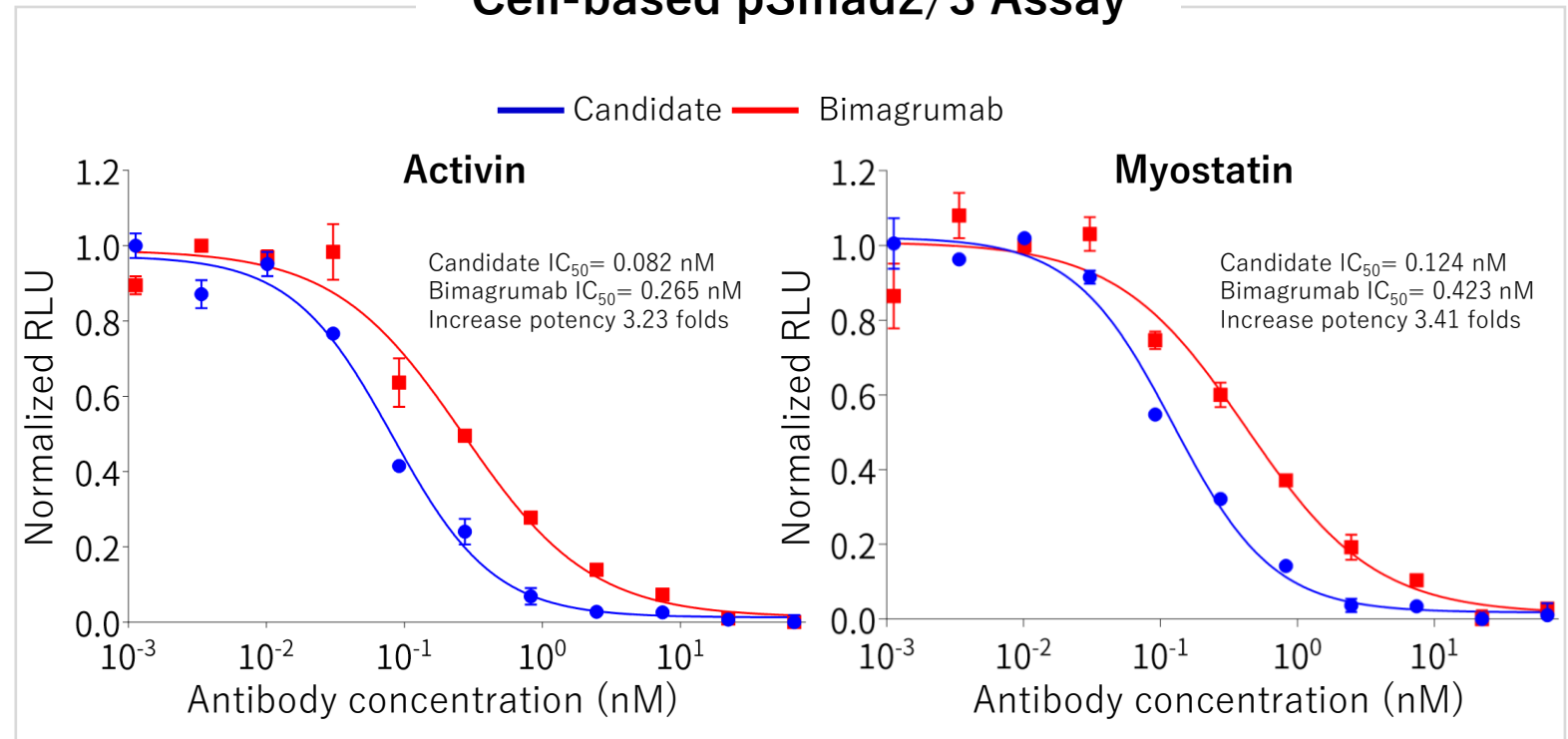| Technologies Deployed: | Hypermutating Yeast | Microdroplet Screen | Generative Models |

Evaluate system robustness of Carterra HT SPR

A
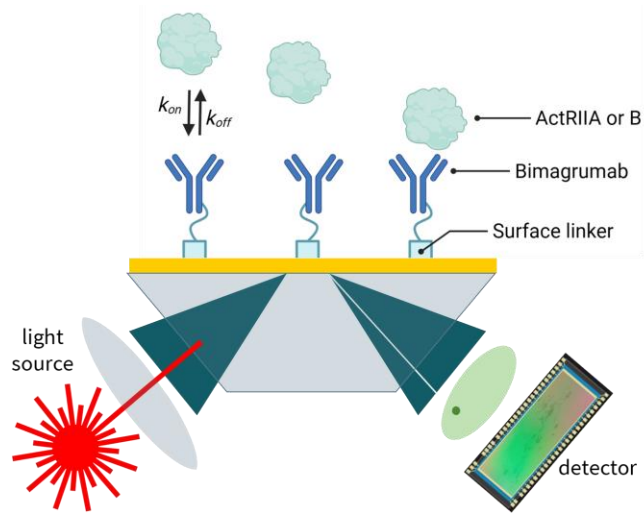
B
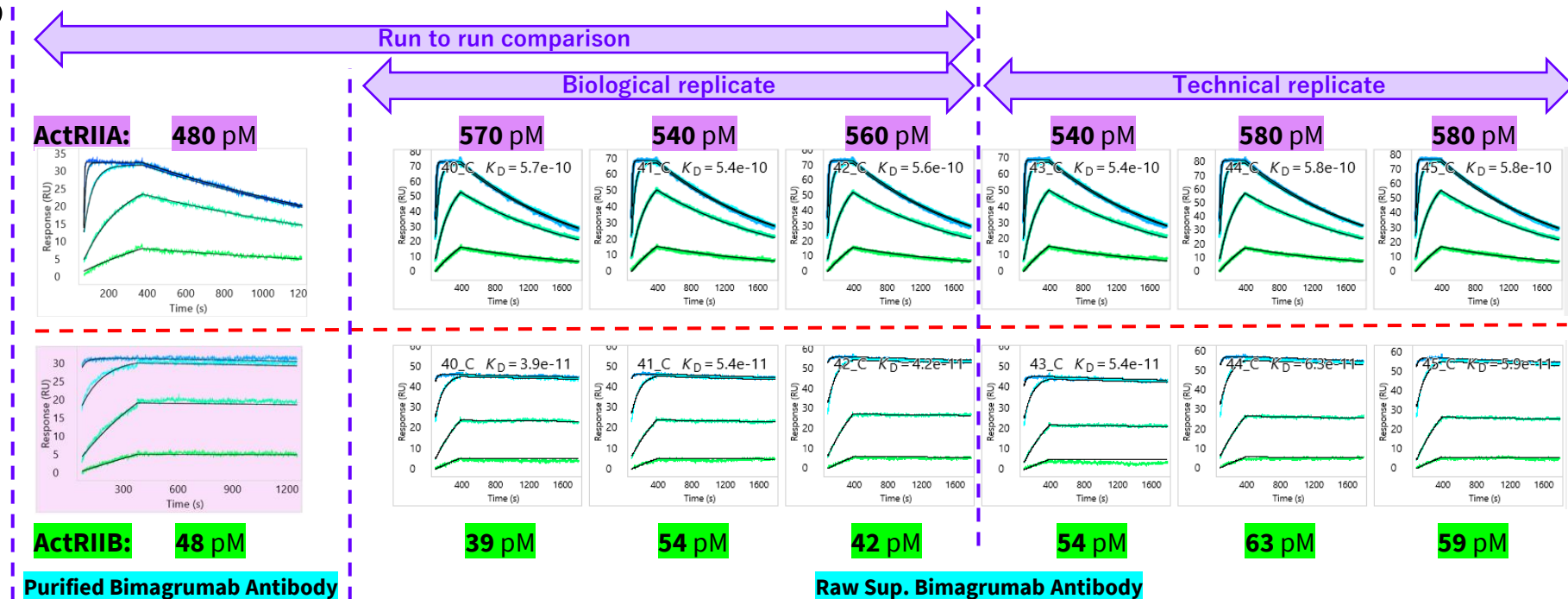
- The affinities between Bimagrumab and ActRIIA/B from different replications are very consistent.
- The Bimagrumab in the raw supernatant works similarly as the purified one.

Case Study #1: Dual-specific Binding *(Single Paratope Ab)*

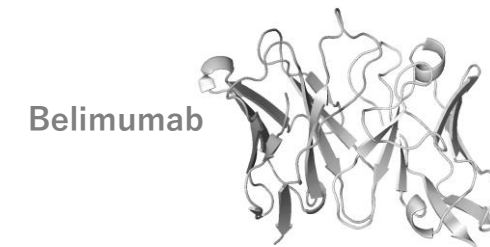**Technologies Deployed:** | **Hypermutating Yeast** | Microdroplet Screen | **Generative Models**

● Evaluate affinity by Carterra HT SPR

Prompt #1: A~=B, bind at pM

23 out of 50 (46%) designs have comparable affinities for both Target A and B at pM level.
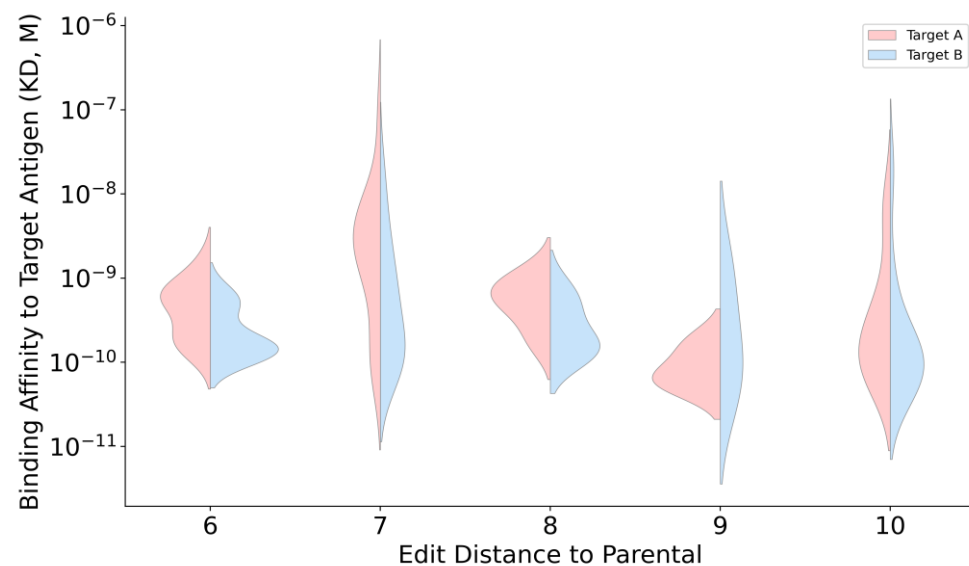
Prompt #2: A>B, 100x selective

11 out of 50 (22%) designs have a >100-fold higher affinity for Target A relative to Target B.
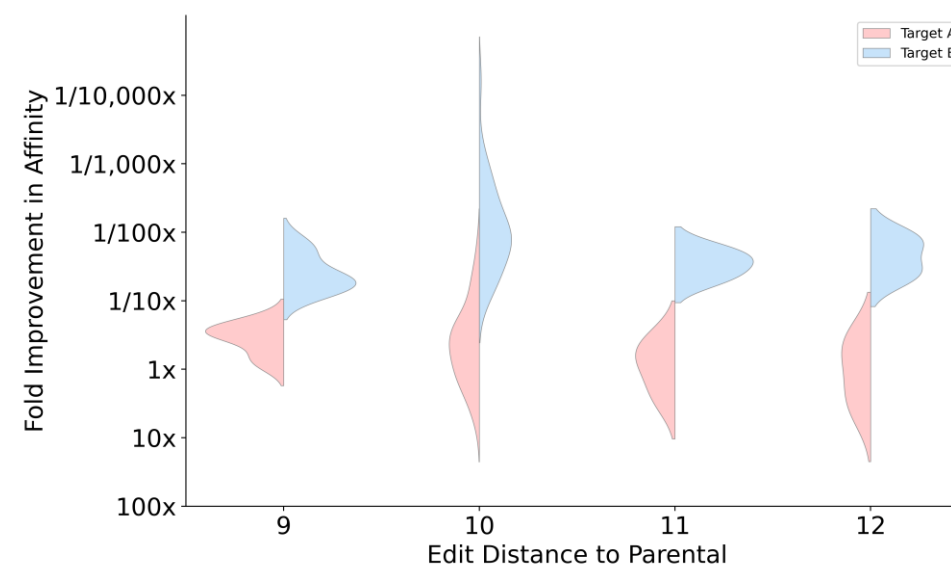
We can design antibodies with controllable selectivity targeting ActRIIA/B

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Case Study #1: Dual-specific Binding *(Single Paratope Ab)*

Technologies Deployed: **Hypermutating Yeast** | Microdroplet Screen | **Generative Models**

● The candidate exhibits stronger ligand Inhibition *in vitro*

Affinity (SPR)

■ Bimagrumab ■ Candidate

K_D (pM)

- ActRIIA: Bimagrumab 693, Candidate 35
- ActRIIB: Bimagrumab 9, Candidate 3
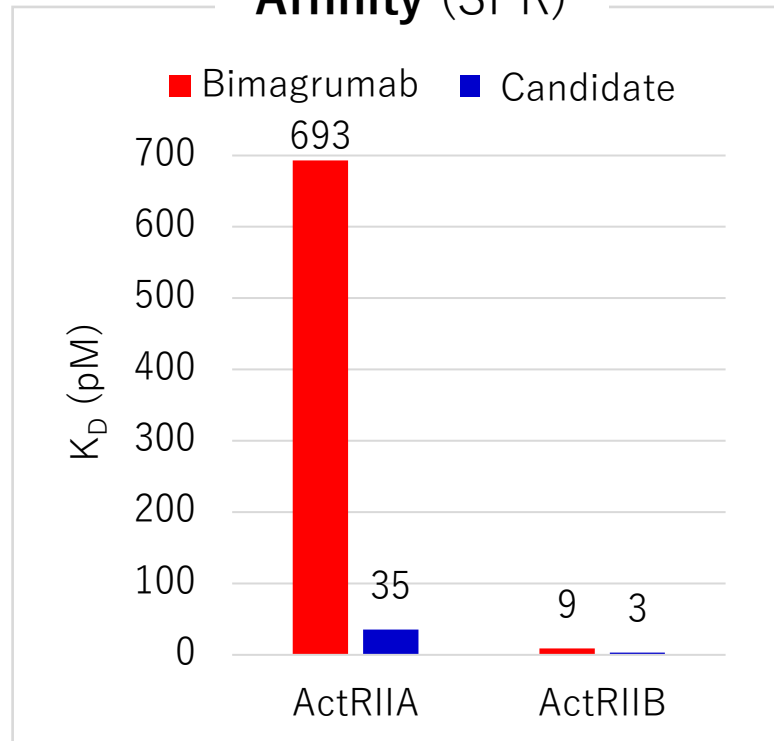
Cell-based pSmad2/3 Assay

— Candidate — Bimagrumab

Activin

Normalized RLU vs Antibody concentration (nM)

Candidate IC_{50}= 0.082 nM
Bimagrumab IC_{50}= 0.265 nM
Increase potency 3.23 folds

Myostatin

Normalized RLU vs Antibody concentration (nM)

Candidate IC_{50}= 0.124 nM
Bimagrumab IC_{50}= 0.423 nM
Increase potency 3.41 folds

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Case Study #2: Dual-specific Binding *(Single Paratope Ab)*

Technologies Deployed:	Hypermutating Yeast	Microdroplet Screen	Generative Models

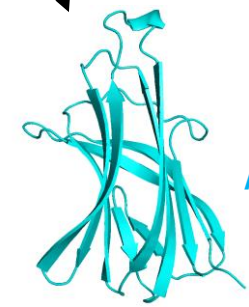- The challenge is low sequence identity between **BAFF** (B cell activating factor) **and APRIL** (A proliferation inducing ligand) (< 30%)

Belimumab has no detectable binding to APRIL even at 100uM.

Belimumab

Binding — No binding

BAFF — **APRIL**
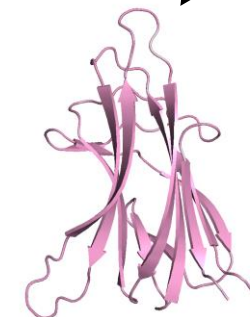
BAFF: B cell activating factor, APRIL: A proliferation inducing ligand

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Case Study #2: Dual-specific Binding *(Single Paratope Ab)*

Technologies Deployed: **Hypermutating Yeast** **Microdroplet Screen** **Generative Models**

> **Our goal is to discover a best-in-class BAFF/APRIL dual-targeted antibody through the Aureka platform.**

● Enhance potency and extend half-life by leveraging the IgG format alongside a diversified spectrum of affinity and specificity.

Limitations of current drugs

1 Single receptor binding
(Belimumab binds only BAFF)

2 Skewed receptor binding profile
(Povetacicept favors APRIL, ~60× over BAFF)

3 Relative short half-life
(Povetacicept: Q4W; Telitacicept: QW)

Aureka solutions

1 Design BAFF/APRIL dual-targeting mAb

2 Offer a broader affinity/specificity range

3 Use IgG format, prolonging half-life ≥3x

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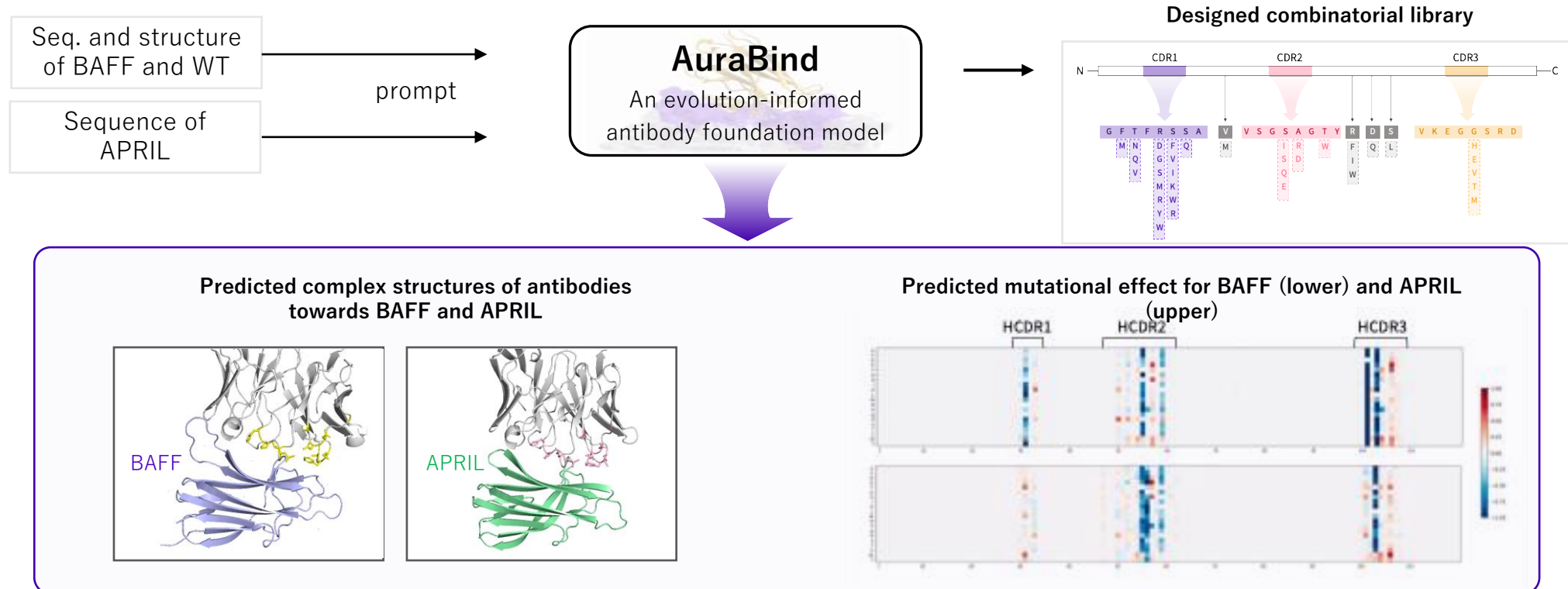# Case Study #2: Dual-specific Binding *(Single Paratope Ab)*

- Iterative in silico design and yeast screening of a combinatorial library targeting both BAFF and APRIL, based on Belimumab, a clinically approved antibody specific to BAFF.

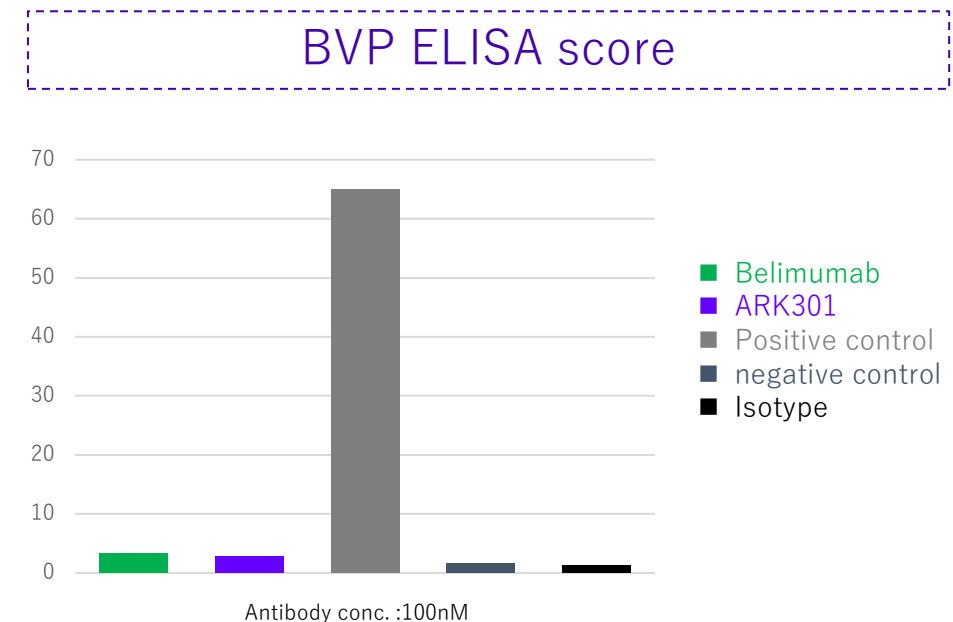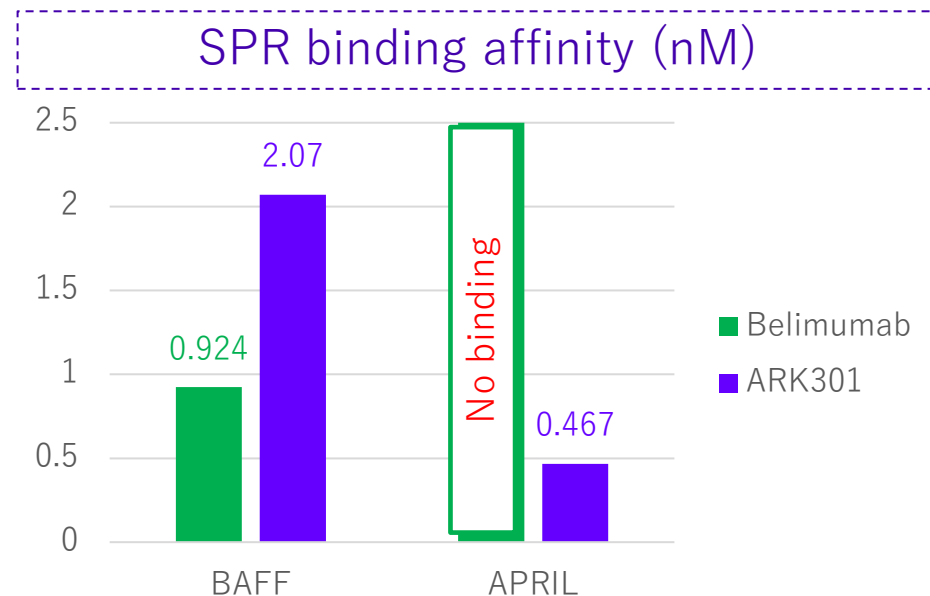# Case Study #2: Dual-specific Binding *(Single Paratope Ab)*

Technologies Deployed: | **Hypermutating Yeast** | Microdroplet Screen | **Generative Models**

● Representative candidate (ARK301): Characterize binding affinity and screen for non-specific interactions.

SPR binding affinity (nM)

- Belimumab
- ARK301

BAFF: Belimumab 0.924, ARK301 2.07
APRIL: Belimumab No binding, ARK301 0.467

BVP ELISA score

- Belimumab
- ARK301
- Positive control
- negative control
- Isotype

Antibody conc. :100nM

ARK301 demonstrates dual-specific binding to both BAFF and APRIL, while exhibiting very low polyreactivity.

A Broad Array of High-hanging Fruit Applications

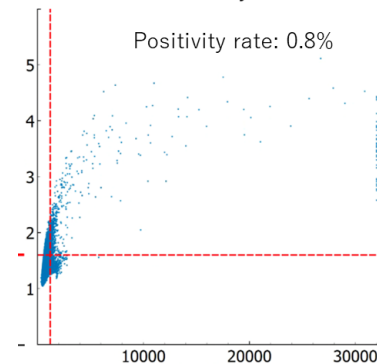● Orders of magnitude more efficient to DC vs. traditional antibody discovery

<$500K   **$2 – 20M**
          vs.
<6 months   **1 – 3 years**

Today's Case Studies

Dual-specific Binding
(Single Paratope Ab)

Other Capabilities

Agonism	pH Sensitivity	De Novo Design	GPCRs

Positivity rate: 0.8%

pH 6.7
pH 7.4
% Tumor Cell Killing
Antibody Concentration (nM)

GPCR-biotin (NanoDisc)
Strep-APC
VHH
Aga2
HA
αHA-AF488
Aga1
Yeast cell
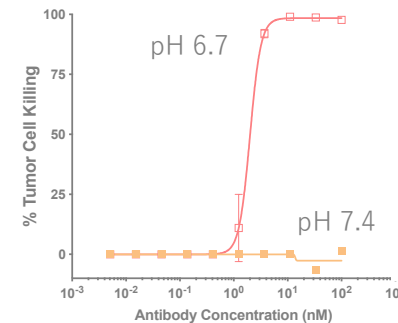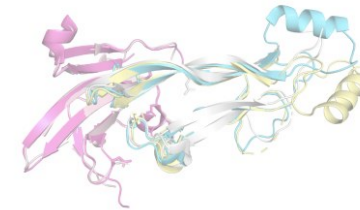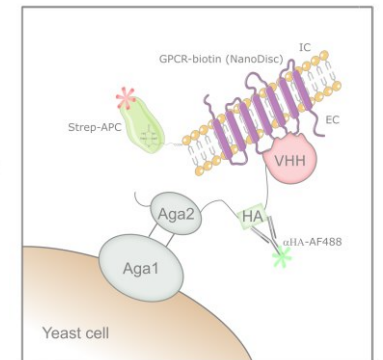
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