Abveris
Diversimab

The Mouse Model that Makes Antibodies of Maximum Diversity and Epitopic Coverage

abveris
A Division of Twist Bioscience

One Discovery Platform. Many Powerful Applications.

HIGH HOMOLOGY TARGETS

CELL SURFACE RECEPTORS

SPECIFIC, CONSTRAINED EPITOPE TARGETING

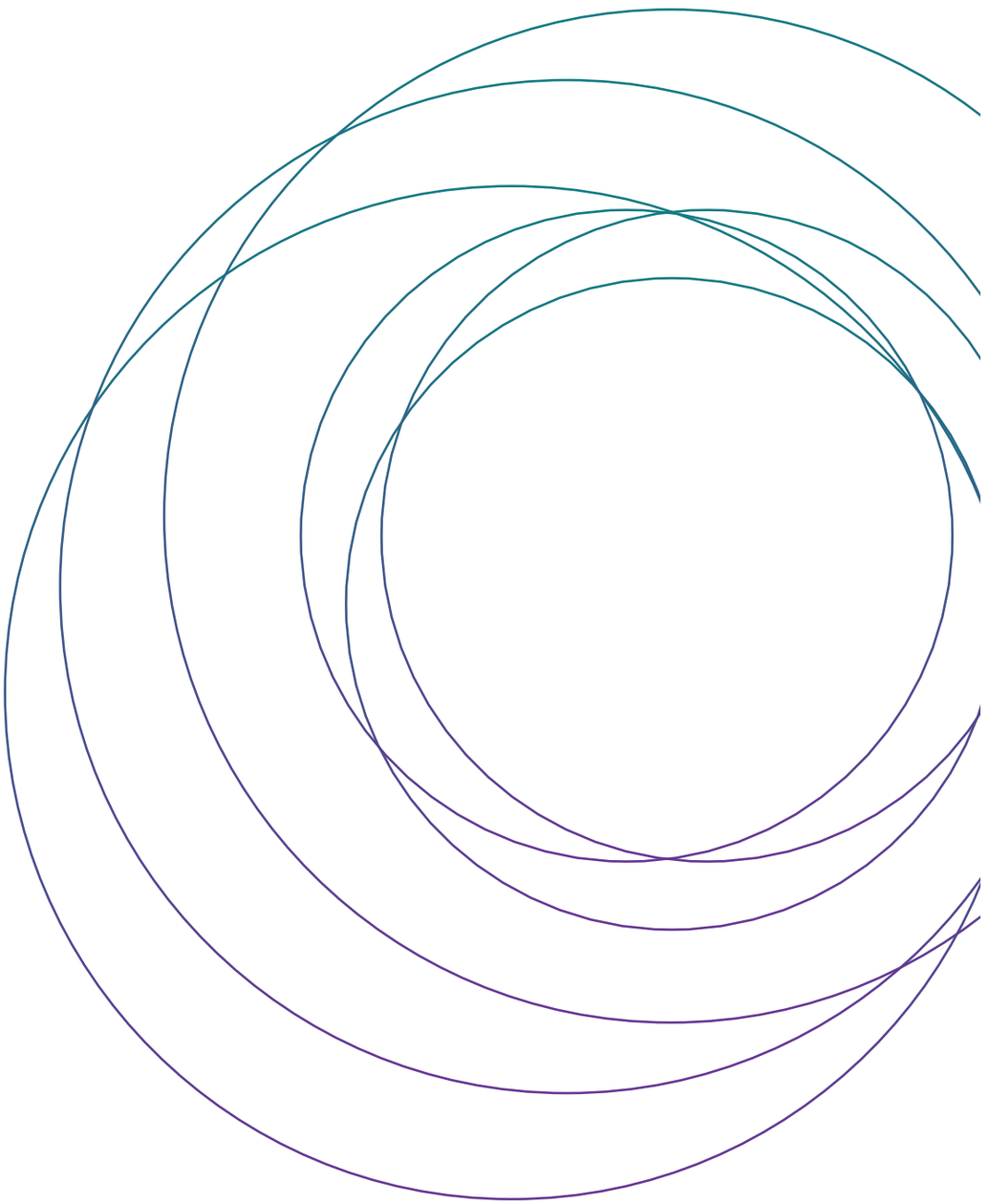
SPECIES CROSS-REACTIVITY

GLYCANS, POLYSACCHARIDES & SMALL MOLECULES

MULTI-PASS TRANSMEMBRANE TARGETS

FUNCTION-FORWARD ANTIBODIES

RAPID PROJECT TIMELINES



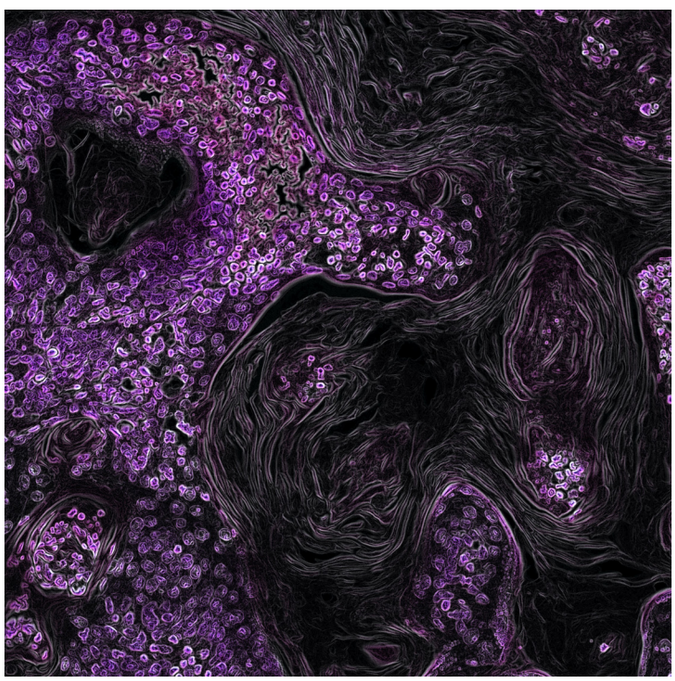
Contents

Introduction to DiversimAb™

MAB DISCOVERY WITH DIVERSITY

The Abveris DiversimAb discovery technology is propelled by proprietary genetically-engineered mice that elicit robust, rapid immune responses against traditionally challenging and poorly immunogenic targets. The DiversimAb™ technology delivers antibodies that traditional systems cannot, enabling deep, efficient screening of key antibody attributes including affinity, diversity, specificity, cross-reactivity, and functionality.

The DiversimAb™ family is comprised of two best-in-class hyperimmune mouse strains (**DiversimAb™** & **DivergimAb™**) designed to maximize starting repertoire diversity for antibody discovery.



DIVERSIMAB TECHNOLOGY

1 Broaden Diversity & Overcome Immunodominance

2 Shorten the Timeline to High Affinity Antibodiess

3 Discover Antibodies against Challenging Targets

WIDE VALIDATED APPLICATIONS

- Cell surface targets
- Anti-idiotype mAbs for PK & ADA
- Therapeutics discovery
- Mouse anti-mouse surrogate mAbs
- Glycan-targeting antibodies
- Single amino acid mutations
- Large, diverse panels of antibodies
- Rapid turnaround time

Designed for Diversity & Performance

BROKEN TOLERANCE FOR A RAPID, ROBUST IMMUNE RESPONSE

DiversimAb mice produce a more robust immune response than wild-type mice (WT) against the same antigen, offering key advantages in the generation of antibodies against highly conserved targets compared to traditional models (Figure 1).

To fully leverage the DiversimAb platform, Abveris has developed a variety of tools and techniques to generate antibodies against a broad range of antigen classes via multiple immunization strategies. The platform can effectively drive robust antigen-specific immune responses against many different types of cell surface receptors including GPCR and ion channels (Figure 2).

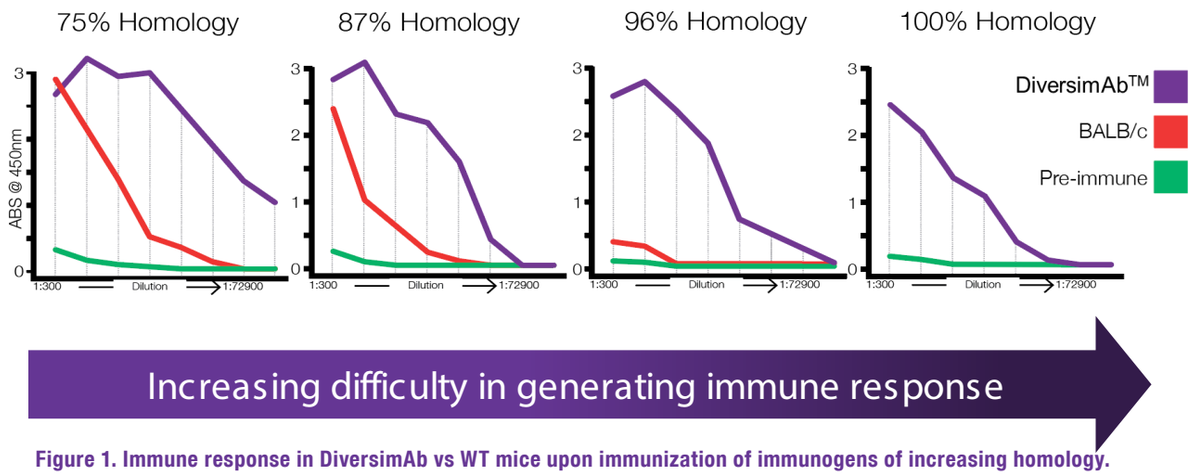


Figure 1. Immune response in DiversimAb vs WT mice upon immunization of immunogens of increasing homology.

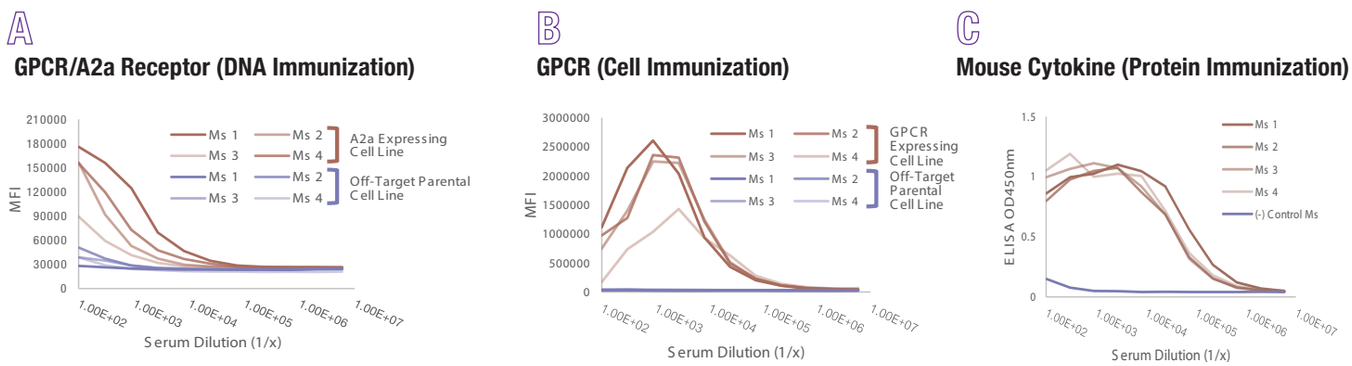


Figure 2. Examples of titer of DiversimAb mice immunized with different immunogens: (A) DNA, (B) whole cell, and (C) recombinant protein.

Designed for Diversity & Performance

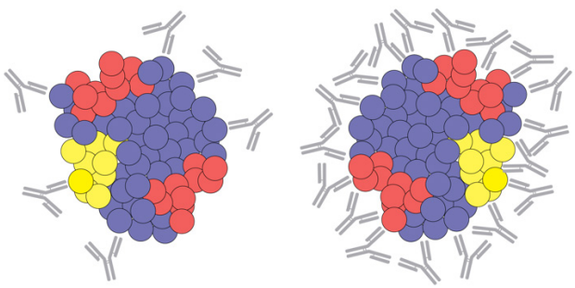
EXPANDED OPPORTUNITIES FOR UNIQUE IP FILING

Small changes in binding epitopes can drastically impact the effectiveness of an antibody as a therapeutic. The engineered DiversimAb™ mouse has a proven track record in generating antibodies of superior epitope coverage over WT mice (example in figure 3).

The DiversimAb platform provides a competitive advantage in the discovery of antibodies with diverse epitope specificities, providing unique IP opportunities for the development of therapeutic antibodies and critical antibody-based reagents.

WT Mice

DiversimAb™



BROADENED EPITOPE DIVERSITY PROVIDES MORE SHOTS ON GOAL WHEN SEARCHING FOR FUNCTIONAL ANTIBODY BINDERS.

Broadened Epitopic Coverage

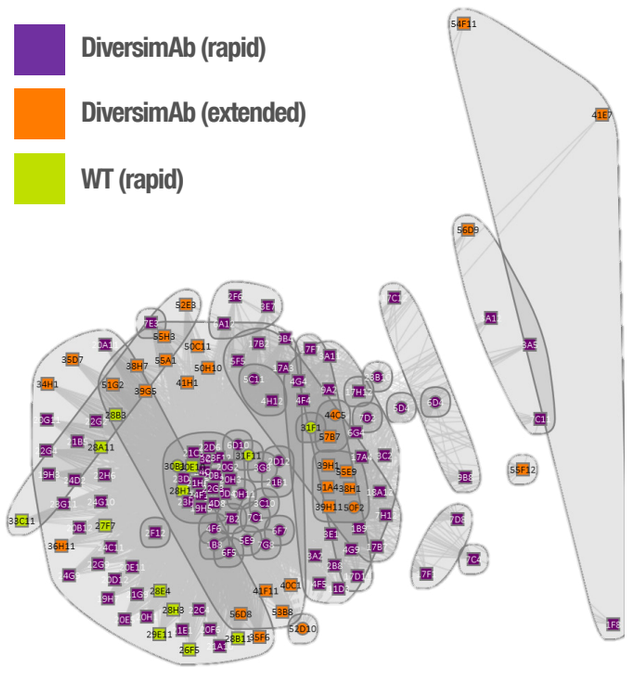


Figure 3. Community plot showing epitopic coverage of anti-CD22 anti-bodies from DiversimAb mice vs WT mice with a comparable immunization schedule. Additionally, duration of immunization (rapid vs. extended) does not dramatically alter the antigen-specific epitopic diversity in DiversimAb mice.

Desirable affinity range for therapeutic antibodies under accelerated timelines

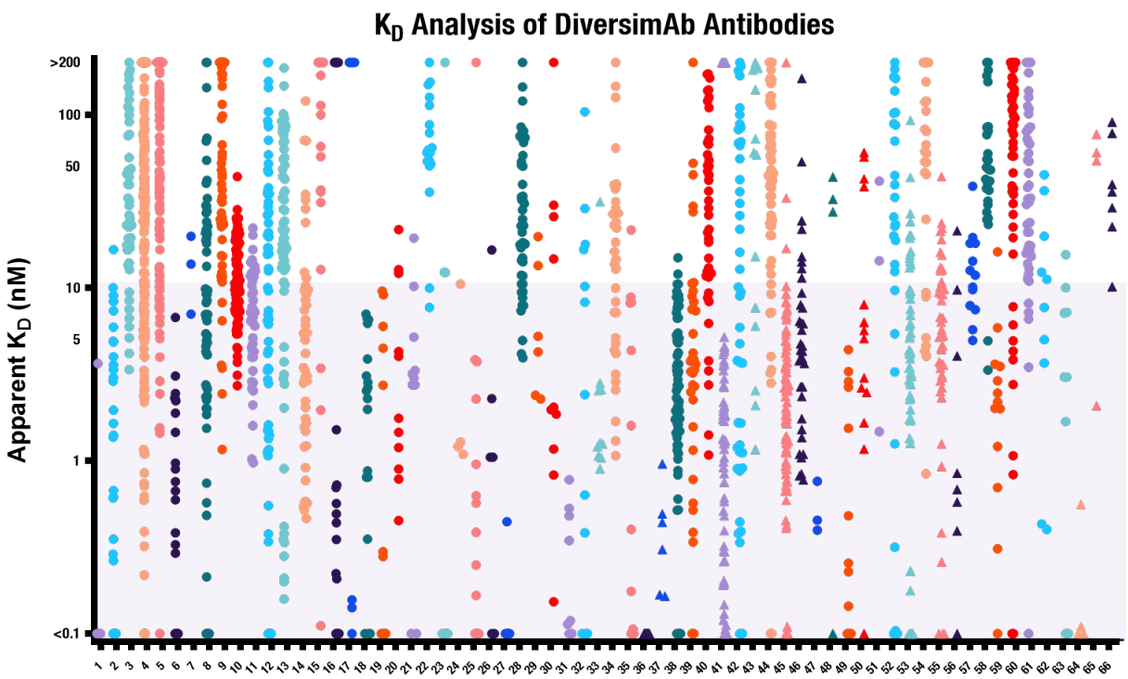


Figure 4. Affinity plot of recent Abveris discovery campaigns using the DiversimAb technology.

DiversimAb Advantages

SPECIES CROSS-REACTIVE ANTIBODIES

Cross-reactivity is an important attribute of therapeutic candidates required for *in vivo* efficacy testing in animal models. In many cases, it is challenging or impossible to discover cross-reactive antibodies using WT mice.

Driven by the enhanced antibody diversity of the DiversimAb mice, the platform has shown an exceptional ability to generate species cross-reactive antibodies against a wide range of conserved therapeutic targets. DiversimAb has enabled consistent identification of rare species cross-reactive (including human/cyno/mouse) antibodies that may not be easily obtained by other platforms (Figure 5 & 6).

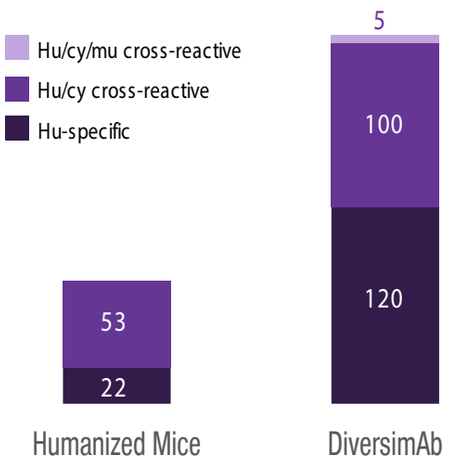


Figure 5. Cross-reactive antibodies generated from different mouse models against a cell surface receptor.

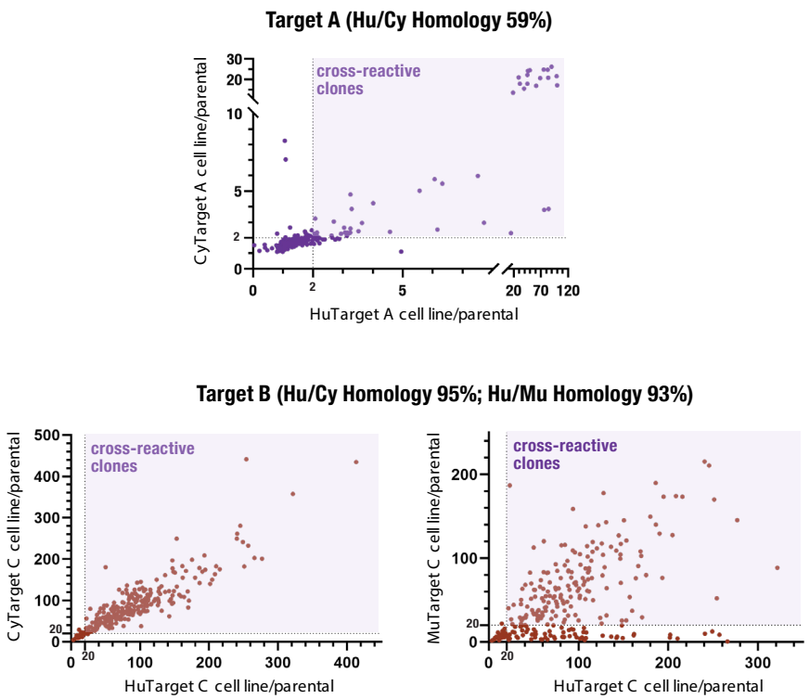
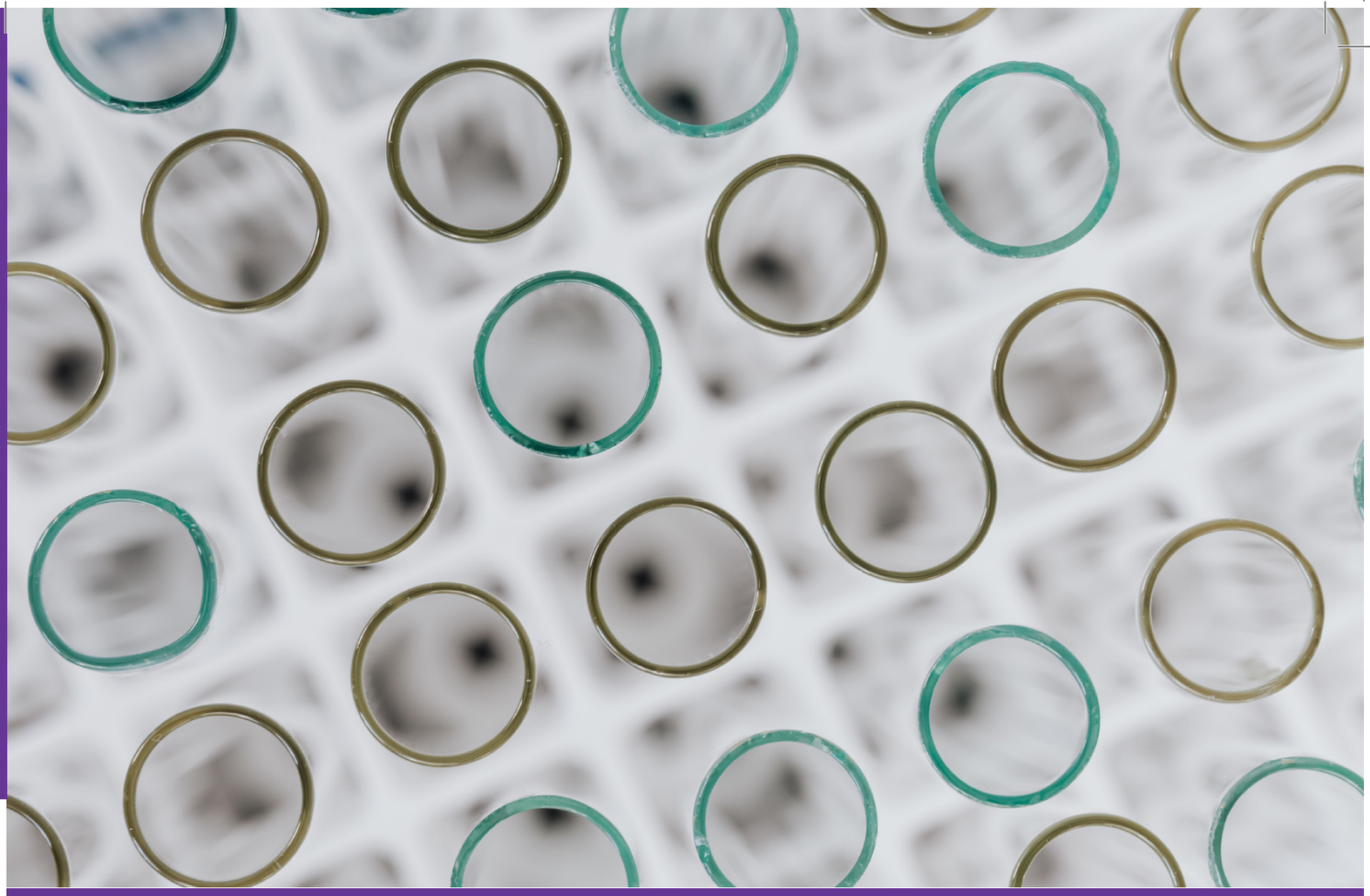


Figure 6. Screening for species cross-reactive antibodies from DiversimAb mice for targets of different homologies.



Case Studies

Case Study #1

ANTI-HMWK ANTIBODY DISCOVERY

Target Background:

High-molecular weight kininogen (HMWK) is a circulating plasma protein involved in contact pathway activation and coagulation. It is a non-enzymatic cofactor responsible for generating bradykinin, an inflammatory mediator. Due to the fact that HMWK is cleaved during contact pathway activation, its cleaved form is a promising biomarker target for antibody discovery.

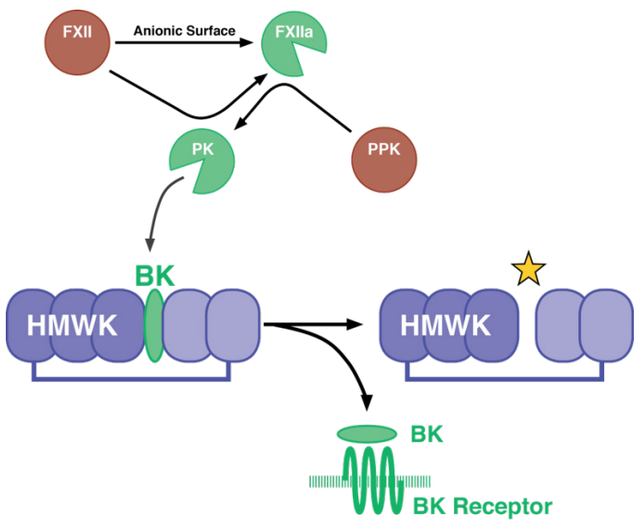


Figure 7. Molecular pathway of bradykinin generation.

Project Goals and Approach:

Investigate the epitopic diversity and affinity of antibodies generated from two strains of proprietary hyperimmune mice, DiversimAb and DivergimAb.

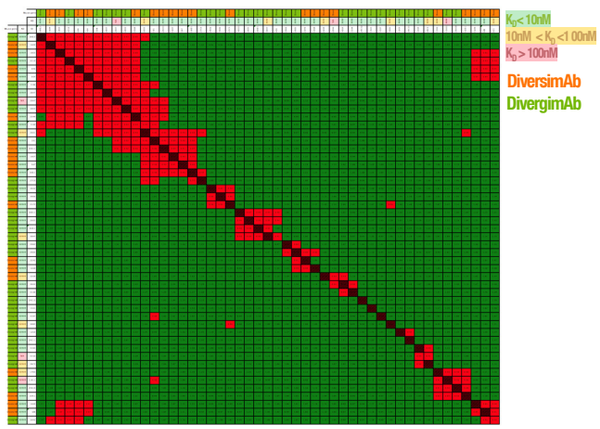
In this campaign, two cohorts of mice were immunized (DiversimAb and DivergimAb) using recombinant HMWK protein. Two hybridoma fusions were performed, followed by ELISA screening and validation by Carterra for binning and kinetics studies.

PROJECT OUTCOMES:

Wide and complimentary epitopic diversity:

In an array-based epitope binning experiment of the selected clones, multiple bins were successfully identified using Carterra SPR, demonstrating the diverse epitopic coverage of the combined panel of antibodies from DiversimAb and DivergimAb as visualized in both the binning map and community plot (Figure 8). Importantly, one bin specific to the cleaved form of HMWK was identified, and antibodies falling in that bin were carried forward for additional biomarker assay development.

A



B

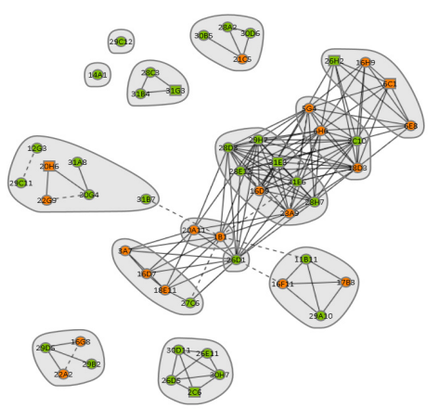


Figure 8. Epitopic coverage of anti-HMWK antibodies as illustrated by (A) binning map and (B) community plot. Data points are depicted by colors: DiversimAb (orange) and DivergimAb (green).

Broad Affinity and Sequence Diversity

1. Broadened Range of Affinities
Lead antibody candidates also demonstrated diversity in affinity. Single-digit nanomolar and subnanomolar mAbs were identified from both DiversimAb and DivergimAb strains (Figure 9).

2. Highly Diverse Antibody Sequences Identified
The combined antibody panel obtained from both DiversimAb & DivergimAb demonstrated broad sequence diversity in critical binding domains, as exemplified by the diverse CDR H3 sequences (Figure 10) and broad V-gene usage (Figure 11).

CONCLUSION

DiversimAb technology is capable of rapidly producing anti-HMWK antibodies with a broad range of affinities and exceptional epitopic coverage. The use of complementary strain backgrounds (DiversimAb & DivergimAb) provides further epitopic and sequence diversity.

1 Broad range of affinities down to subnanomolar range

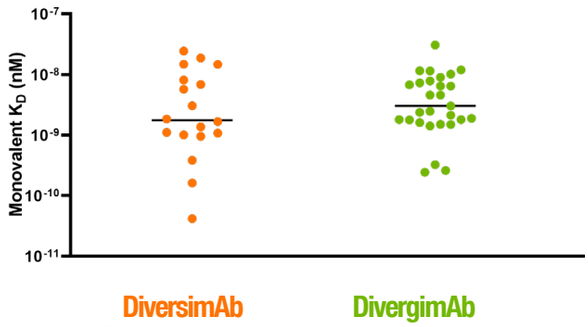


Figure 9. Affinity plot of anti-HMWK antibodies from DiversimAb & DivergimAb mice.

2 Sequence diversity in CDR H3

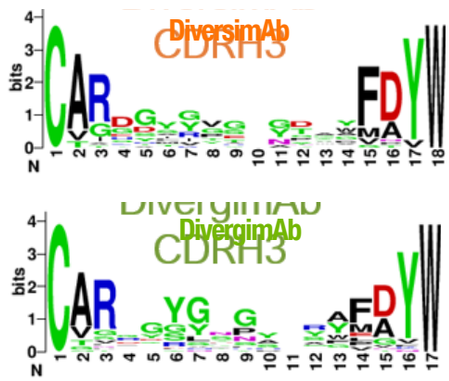


Figure 10. Sequence analysis of CDR H3 in anti-HMWK antibodies from DiversimAb & DivergimAb mice.

3 Broad V-Gene Usage Achieved Using Complementary Hyperimmune Mouse Strains

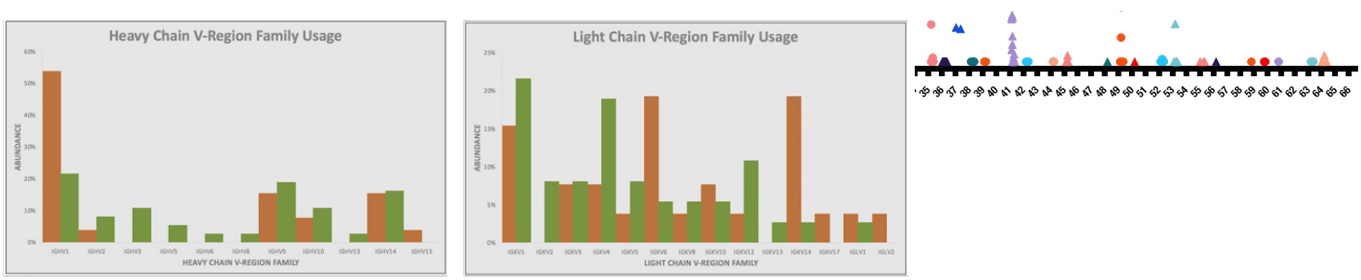


Figure 11.V-gene usage and CDR length distribution of heavy and light chains of antibodies from DiversimAb (orange) and DivergimAb (green) mice.

Case Study #2

DIVERSITY WITH CROSS-REACTIVITY & FUNCTIONALITY

Target:

A cell surface receptor with a human/cyno sequence homology of 95% and a human/mouse sequence homology of 93%, respectively.

Project Goals and Approach:

The goal of this campaign was to develop therapeutic antibody candidates for the partner's desired disease indication. Previous attempts failed to generate a sufficient number of species cross-reactive clones. Specific requirements of the project included:

- Human/cyno and human/murine cross-reactivity
- Functional ligand blocking activity
- Broad range of affinities

In this discovery campaign, Abveris deployed a rapid (3-week) immunization strategy using two cohorts of DiversimAb mice. Two fusions were performed, followed by a hybridoma screening workflow using both ELISA and HTP flow cytometry to select specific binders. Hits were then analyzed by Octet BLI for blocking/non-blocking activity. All screening was completed within 10 days (Figure 12).

PROJECT OUTCOMES

1. 174 hu/cyno/mu and 70 hu/cy cross-reactive cell-binders identified, respectively (Figure 13)
2. Broad range of affinities achieved (Figure 14)
3. Potent blockers identified (Figure 15)

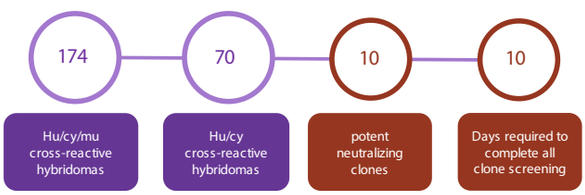


Fig 12. Summary of cross-reactive and functional clones identified.

1 Cross-reactivity validated by ELISA & flow cytometry

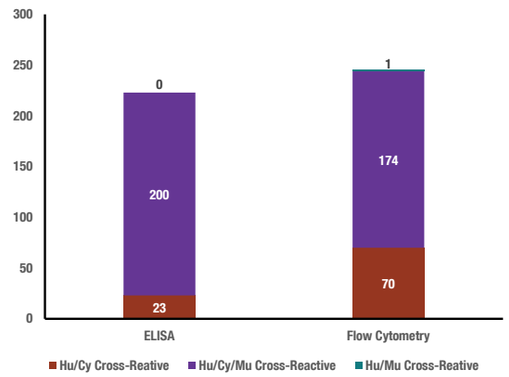


Figure 13. Screening of species cross-reactivity against Target B.

2 Broad range of affinities down to subnanomolar range

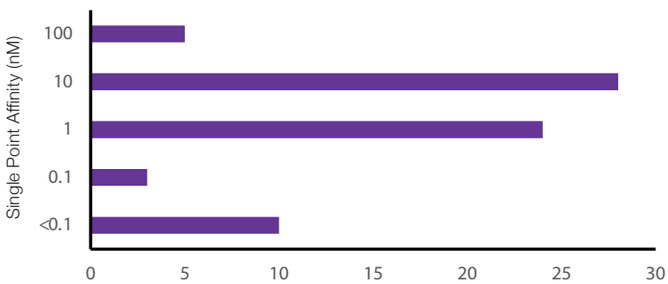


Figure 14. Affinity range of antibodies in nanomolar ranked by K_D.

3 Range of potencies among blockers from a pre-mixed Oct BLI blocking assay

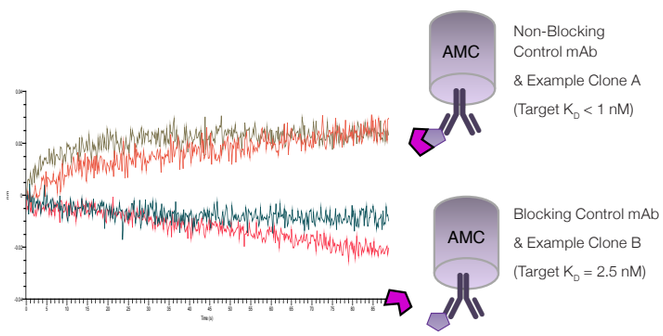


Figure 15. Selected examples of blockers/non-blockers by Octet blocking assay in a pre-mixed format.

Case Study #3

GLYCAN & POLYSACCHARIDE (PS) TARGETS

The DiversimAb platform boasts a 100% success rate for the discovery of antibodies against glycan and PS targets.

Challenges of Glycan Targets:

- Weakly immunogenic to wild-type mice
- Difficult to obtain robust and antigen-specific titers for hybridoma fusion
- Lack of diversity in hybridoma clones obtained from WT mice (if any)
- Very few or no specific antibodies typically obtained using WT mice

Abveris Approach and Success:

- Immunization of both DiversimAb & DivergimAb mice using a proprietary immunization protocol and adjuvant cocktail
- Representative antigen-specific immune responses achieved across multiple glycan and PS campaigns (Figure 16)
- Representative number of specific binders identified across multiple glycan-targeting campaigns (Figure 17)

1 Consistent, robust glycan and polysaccharide target-specific immune responses

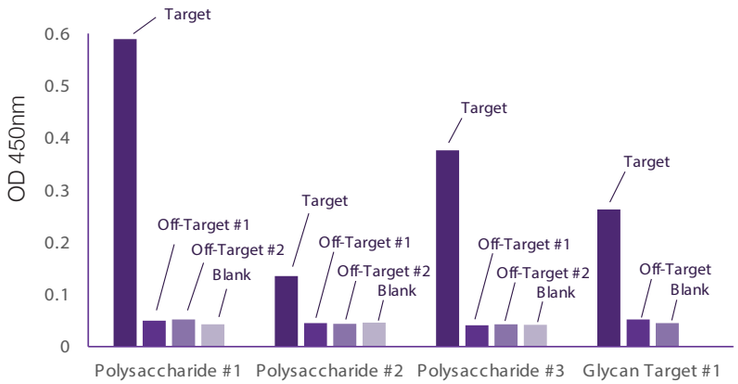
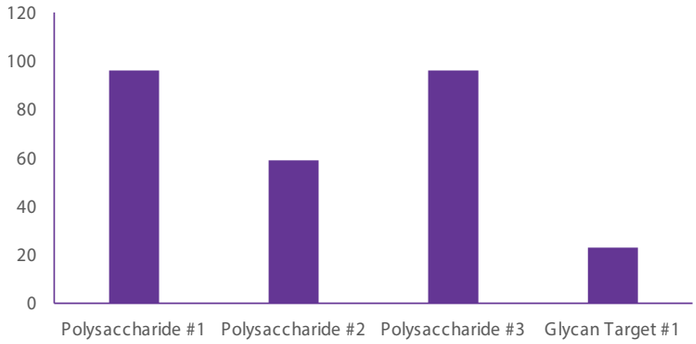


Figure 16. Fusion-ready ELISA titer results for hybridoma workflow (1:72900*).

*** 1:72900 is the dilution point indicating fusion readiness in Abveris' immunization protocols**

2 Number of specific hits identified using the DiversimAb platform



Figire 17. Number of hits from hybridoma workflow across different targets.

ANTIBODY SPECIALISTS

Abveris is Boston's premier antibody discovery partner providing contract research services to the biopharma industry. Abveris applies industry-leading technologies to provide comprehensive gene-to-antibody discovery services. Abveris is developing the next generation of biologics, cell therapies, vaccines, and diagnostics in partnership with global leaders in biopharma.

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