carterra®

WHITE PAPER

Discovering an Antibody's Therapeutic Fingerprint

Utilizing Multi-parameter Epitope Binning to Understand a Therapeutic Antibody's Mechanism of Action

Abstract

Understanding an antibody's mechanism of action (MOA) is critical to its clinical success. Not only does MOA have a large impact on safety and efficacy, but it also influences the intellectual property (IP) and commercial potential of a therapeutic. Those antibodies with novel MOAs represent significant opportunities in the competitive world of pharmaceuticals, and so identifying them is key.

High throughput Surface Plasmon Resonance (SPR) offers a unique advantage in the quest for successful next-generation therapeutic antibodies. Its expanded capabilities compared with traditional SPR and other label-free methods enable comprehensive screening of antibody libraries at the earliest stage of drug discovery, with the additional advantage of high resolution binding characterization through kinetics and epitope binning assays. Combining these results with those from orthogonal studies produces a fingerprint of each antibody's therapeutic potential.

Understanding the significance of multi-parameter data within the context of an antibody library's epitope landscape enables an informed selection of high-value clones based on MOA, and subsequent prioritization of resources to converge upon high-quality therapeutic candidates.

This white paper outlines the process of multi-parameter epitope binning, including the methods used to generate and analyze the data and how to interpret an antibody's therapeutic fingerprint, while keeping an epitope-centric view of the entire data set. A case study will illustrate the application of this method for identifying antibodies of interest and in elucidating MOA.

Introduction

Antibodies represent the fastest growing class of drugs in the market today, with over 60 antibody drugs currently approved for use and more than 550 in clinical development[1]. In 2017, the number of antibodies granted a first approval in either the European Union (EU) or United States (US) reached double digits for the first time, a trend that continued into 2018[2].

The discovery and development of therapeutic antibodies therefore represents an especially lucrative opportunity for biopharmaceutical companies worldwide, as demonstrated by Adalimumab (marketed by AbbVie Pharmaceuticals as Humira), the first fully human antibody to be granted approval by the US Food and Drug Administration (FDA). It serves as a benchmark for the commercial potential of therapeutic antibodies, with considerable success in the treatment of several autoimmune diseases and conditions including rheumatoid arthritis, Crohn's disease, and ulcerative colitis. Humira's reported sales of almost $18.5 billion USD annually in 2017[3] establishes it as the top blockbuster drug in terms of sales.

While it can be incredibly valuable both in terms of advancing human health and increasing profits, the search for the next blockbuster therapeutic antibody is expensive, time-consuming, and has a high failure rate. New technologies that help minimize risk to pharmaceutical companies and increase the chance of finding "the next Humira" are highly sought-after.

High throughput Surface Plasmon Resonance (SPR) technology has recently facilitated a paradigm shift in the discovery of therapeutic antibodies, enabling the rapid and detailed characterization of large antibody libraries at the earliest stage of the process—so-called high-information-content screening. This allows researchers to expand their screening efforts to much larger libraries, learn about antibody:antigen binding interactions in greater depth, and combine orthogonal data to create a highly informative fingerprint of the antibodies of interest. Composing a detailed picture from multiple sources of information enables informed lead selection and helps to determine an antibody's mechanism of action (MOA).

With many of the best understood antibody drug targets already extensively exploited in drug development, identifying antibodies with novel MOAs is the key to discovering and marketing new biotherapeutics and extending applications[1]. This is critical in the competitive world of pharmaceuticals and intellectual property (IP) rights.

In this white paper, we first look at antibody libraries and the importance of understanding their binding properties in detail. High throughput SPR provides a method for characterizing the binding kinetics, affinities and epitope specificities of large antibody panels, and when these data are merged with the results from other assays, they can aid in determining MOA. We will outline the process of antibody fingerprinting and describe a case study where combining epitope binning with orthogonal data enabled the identification of human antibodies responsible for neutralizing the pathogenic activity of *Staphylococcus aureus (S. aureus)* via two distinct MOAs.

Understanding your antibody library

The importance of the epitope

The primary evolutionary purpose of an antibody is to recognize and bind its antigen—historically an invading pathogen—with appropriate affinity and specificity to neutralize it. A specific site on an antigen, termed an epitope, is recognized and bound by so-called antigen-binding sites located at the tips of the Y-shaped antibody molecules, termed the paratope. The complex and hypervariable architecture of these antigen-binding sites enables a vast range of epitopes to be recognized by an organism's antibody repertoire.

It is this virtually limitless target range, combined with the trademark high affinity and exquisite target specificity of antibodies that is of great interest for biotherapeutics.

The ability to develop an antibody *de novo* that can bind to a specific target of interest would be a model solution to drug discovery. However, while all other characteristics of an antibody drug can be optimized by engineering - such as the binding kinetics, affinity, and thermostability - it is currently impossible to apply rational design and engineering to epitope recognition and binding, as epitope specificity is an innate property that cannot be predicted. The epitope is highly complex and unknown *a priori*, and the *in silico* design of an equally complex complementary paratope on the antibody presents a significant challenge to computational biologists. The discovery of an antibody with appropriate characteristics therefore relies on informed, empirical selection from large antibody libraries.

Epitope specificity is also critical for dictating an antibody's biological function and MOA, providing the means to recognize, interact, and affect a biological mechanism. The discovery of antibodies with unique epitope binding characteristics and MOA is therefore *the* critical step in successful biotherapeutics research to differentiate an IP portfolio from the competition.

Antibody screening: Then and now

A therapeutic antibody discovery program involves functionally screening large antibody libraries that could potentially contain billions of unique clones. Through an empirical triage process, promising candidates are selected and progressed through the development pipeline. However, as a result of modern antibody generation techniques, extremely large and diverse libraries are created. While this is beneficial for increasing the possibility of finding a desirable and optimal antibody in the original library, it also creates major practical challenges in terms of their screening. Before the advent of high throughput SPR, drug discovery scientists would commonly use high throughput but low-information-content assays (e.g. ELISA and FACS); or low throughput but high-information-content SPR to triage only a subset of clones from a library. Specifically, these techniques do not provide any information on the epitope coverage of the library, with detailed characterization only used as a secondary step. This approach underappreciates the full epitope and kinetic diversity of the original library, resulting in under-sampled pools and the possible selection of suboptimal clones that require extensive engineering. It is also likely to miss potentially high-value antibody drugs completely, or eliminate them from the sample pool prematurely.

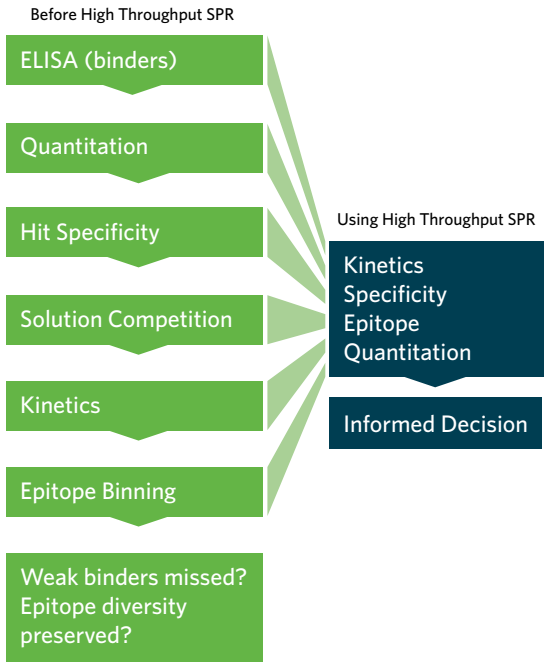

Figure 1: High throughput SPR revolutionizes antibody screening for drug discovery by allowing screening and characterization to be accomplished in the same step at the very start of drug discovery.

High throughput SPR revolutionizes antibody screening for drug discovery by allowing screening and characterization to be accomplished in the same step. By expanding the throughput of SPR, a *de facto* technique for delivering exceptional resolution and high data quality, it can now be positioned upstream in the drug discovery process, which means it can be used to triage a much larger antibody panel. Researchers become better informed, earlier, and can carry out detailed studies of the binding interactions between the target antigen and large antibody libraries. Information on antibody:antigen binding interactions, such as their kinetics, affinity, and epitope specificity, provide researchers with comprehensive information that guides decisions on which antibodies to follow up on with other assays.

Why do we need to know a specific antibody's MOA?

In pharmacology, MOA describes the specific biochemical interactions that occur for a drug to produce an effect. MOA is driven by the molecular binding properties of a candidate drug and how it interacts with its specific (intended) and unspecific (unwanted) binding partners in terms of its kinetics, affinity, selectivity and epitope specificity.

Elucidating the MOA of any novel drug, including therapeutic antibodies, is important for several reasons. Knowledge of the MOA drives better-informed decisions that impact both the safety and efficacy of a drug. Greater understanding of MOA helps in predicting a patient's likeliness to respond to a particular treatment. The knowledge gained can also be used to decide how best to combine drugs for the treatment of diseases such as cancer, in order to reduce risks of resistance and treatment failure. In addition, understanding MOA is advantageous in the development of new drugs, either highlighting an important molecular interaction and/or target for further drug development; or identifying novel MOAs that offer IP and commercial potential.

With high throughput SPR, it is possible to survey the epitope landscape of an antibody screening program during early-stage research, where large numbers of clones are available in low quantities. This provides a functionally-relevant way of navigating an antibody panel to guide the triaging of hits and prioritize resources to determine MOA.

Multi-parameter epitope binning

Epitope binning using high throughput SPR

Epitope binning using high throughput SPR is an incredibly powerful tool in guiding the discovery of therapeutic antibodies because it can be used to organize antibodies into families based upon their epitope specificities. Using high throughput SPR, epitope binning experiments can be performed at the earliest stage of drug discovery to assess an antibody libraries epitope coverage.

This competitive assay tests antibodies in a pairwise and combinatorial manner for their ability to bind simultaneously to a specific antigen:

- If both antibodies bind their specific antigen at the same time then it is presumed that they are targeting distinct, non-overlapping epitopes. These antibodies would therefore belong to different epitope families or bins.

- If one antibody blocks another's binding to their specific antigen then it is presumed that they compete for overlapping or similar epitopes and would belong to similar, if not the same, epitope bin. Further, if two antibodies show the same blocking profile towards all other antibodies in the test set, they would be assigned to the same epitope bin.

- Antibodies sharing an epitope bin are likely to exhibit similar binding interactions, while those in different bins are expected to have distinct epitopes and binding mechanisms.

Through epitope binning experiments, those antibodies with unique epitope specificities can be rapidly identified to provide diversification of selected candidates. Pinpointing and progressing those antibodies that target unique epitopes is highly desirable for the selection of therapeutic leads as they are likely to offer differentiated MOAs and associated IP opportunities.

In addition, identifying antibodies in the same bin that likely share similar functional properties and binding modes gives researchers further options for lead selection. For example, certain antibodies in a bin may display superior properties than others in the same bin in terms of their affinity, sequence liabilities, developability, and cross-reactivity to the target's orthologs or homologs, which may be relevant to toxicology studies and MOA. It is therefore possible to select and advance those antibodies with properties that make them better suited as a therapeutic lead, and which still provide the same or similar function and binding modes.

On its own, epitope binning serves to cluster antibodies in a relative sense to one another, but when combined with orthogonal data, the relevance of the epitope clusters to biological function is revealed. In a multi-parameter epitope binning experiment, additional data from orthogonal studies can be layered onto the epitope bins to better understand the relevance of the epitope landscape.

Gaining early insight into an antibody library's epitope coverage and layering it with the results from other, functional tests, builds up a detailed overview of the therapeutic potential of each antibody. This enables more informed choices to be made when selecting leads that merit further study, making it possible to converge upon those clones with potential therapeutic applications sooner. Investigations into MOA can also occur earlier, increasing the efficiency of the pipeline and shortening the time from library to lead.

High throughput SPR is the only technique that can deliver the throughput and multiplex capabilities that provide comprehensive data to enable epitope binning studies and resultant MOA fingerprints. The Carterra® LSA™ high throughput SPR platform can perform these experiments in unprecedented high throughput, with the added benefit of minimal sample consumption, making these assays amenable to early-stage research and discovery. Furthermore, Carterra's proprietary Epitope Data Analysis Software enables the results from several orthogonal studies, such as structural or mutagenesis data, to be merged with the epitope binning results, producing a detailed fingerprint (Fig. 3). This provides a highly informative visualization tool that aids researchers in decision-making throughout the drug development process.

Using the Carterra LSA for multi-parameter epitope binning

The unique, high throughput capabilities of the Carterra LSA are realized through proprietary technology that enables a panel of up to 384 antibodies to be arrayed and reloaded onto a single chip. Antibodies are immobilized as ligands to produce a 384-ligand array per chip. Antibodies are then injected in series as analytes to test for sandwich pairing. Using this one-on-many analyte-on-ligand assay format, the LSA delivers real-time data on up to 384 ligands in parallel. In this format, all antibody analytes are tested for sandwich pairing with all antibody ligands, providing a comprehensive 384x384 interaction matrix and a detailed picture of the antibody panel's epitope landscape.

Each time an antibody is injected as an analyte, the antibody spot is measured for any change in mass. Sensorgrams are produced that show the binding interaction of the antibody of interest with the antigen, and then with every other antibody in the panel in turn (Fig. 3). Since each binding cycle includes the entire 384-ligand array, in 384 binding cycles it is possible to rapidly perform a full 384x384 interaction analysis matrix and gain a comprehensive data set for all antibodies in the test set. Using the LSA, a typical 384x384 experiment can be completed in an unattended run within three days using very little sample (typically only 10 µg per antibody).

Carterra's proprietary Epitope Data Analysis Software collates the data for all of the antibodies in an epitope binning experiment and combines this with data from orthogonal experiments (e.g. cell-based neutralization data, kinetics, affinity, mutagenesis) in a network plot (Fig. 3). In this way, an antibody fingerprint is constructed to help researchers improve efficiency and productivity for optimum outcomes.

Incorporating binding kinetics and affinity data

As well as epitope binning experiments, the Carterra LSA can perform high throughput and detailed kinetic and affinity determinations of up to 384 antibodies in parallel. Using the full capacity of the instrument's autosampler it is also possible to load three 384 microtiter plates and determine full kinetic and affinity on up to 1152 unique clones in a single unattended run. These are important parameters in drug discovery for understanding an antibody's MOA, pharmacodynamics, and pharmacokinetics; while the ability to screen large numbers has become crucial in the evaluation of the expansive libraries now available.

The strength of a binding interaction between an antibody and its specific antigen is characterized by the association and dissociation kinetic rate constants (k_a and k_d). These constants describe the formation and decay of the bimolecular complex respectively, and the ratio of these values gives the equilibrium dissociation constant ($K_D = k_d/k_a$). This describes the binding affinity of the molecules for one another and influences the recommended dose of a medicine (Fig. 2).

Early-stage screening often does not include the generation of kinetic data because of the limited throughput of traditional SPR or other label-free platforms. However, with the Carterra LSA, it is possible to perform kinetic studies at the first stage of drug discovery, combining affinity and binding data with results from epitope binning. As a result, researchers can start to determine an antibody fingerprint and build up a more complete picture of the antibody library as a whole, from the very start of the drug discovery process.

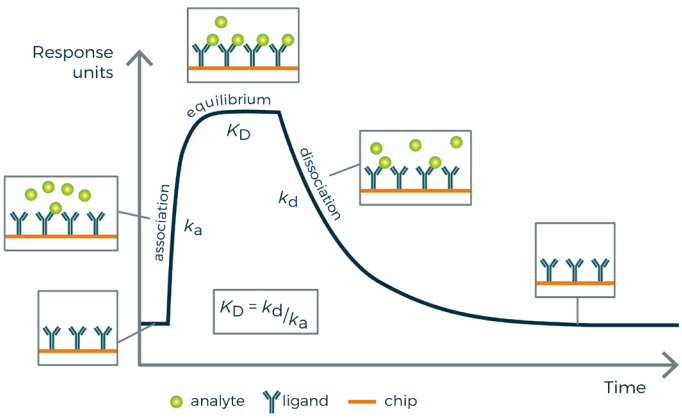

Figure 2: High throughput and detailed kinetic determinations are possible with the Carterra LSA. Kinetic rate constants (k_a and k_d) and the equilibrium dissociation constant (K_D) describe the association and dissociation of an analyte: ligand complex and the binding affinity respectively.

High sensitivity, high throughput SPR kinetics

Using the Carterra LSA instrument, it is possible to perform high throughput antibody screening and characterization in the same step and generate high quality, reliable kinetic data at the earliest stage of drug discovery.

The binding kinetics of up to 1152 antibody interactions can be determined in a single run due to Carterra's patented flow printing technology, which also makes it possible to obtain data from low titer crude antibody preparations. These types of samples are common in early stage screening where *in vitro* antibody libraries are often supplied as crude periplasmic extracts (PPEs).

Despite the low expression levels of recombinant antibody fragments within these extracts (e.g. single-chain variable-fragments (scFv)), the highly sensitive Carterra LSA can be used to measure the binding kinetics in high throughput. The LSA's bi-directional or multi-pass flow for sample delivery extends the contact time during immobilization, generating multiple passes between sample and chip. This effectively concentrates material onto the chip surface, enriching capture levels of crude antibodies and therefore greatly enhancing assay sensitivity.

The Carterra LSA delivers kinetic data of comparable quality to other called gold-standard SPR platform, but with the added benefits of significantly higher throughput and the ability to detect lower PPE concentrations, while using less sample.

Combining orthogonal data to produce an antibody fingerprint

The key to multi-parameter epitope binning is the incorporation of data from additional orthogonal studies to identify functionality within bins, which aids in the development of the MOA fingerprint and the selection of clones with high therapeutic potential. The type of orthogonal data needed to determine functional activity depends somewhat on the system being investigated, however, mutagenesis, functional cell-based assays, cross-reactivity studies, and structural studies are all highly informative. While the specifics of a functional test are target dependent, epitope binning is agnostic of the type of therapeutic target or indication and is a universal test that can be performed on any antibody panel to understand its epitope coverage.

In some cases, orthogonal studies can be incredibly expensive and time-consuming. This is especially true for structural studies, such as the generation of crystal structures of antibody complexed with target antigen. These experiments are critical in confirming MOA but can be very complex, involving significant resources and large amounts of researchers' time. By combining functional and epitope binning studies, it is possible to navigate the decision making of drug discovery scientists to those epitope bins of most interest prior to this step, thereby both speeding up the process and reducing costs.

Carterra's proprietary Epitope Tool data analysis software can be used to collate all data from a multi-parameter epitope binning experiment in a network plot, highlighting the bins of interest in terms of epitope and MOA. It contains a node for each antibody in the investigation, identifiable by its number. Nodes are connected to one another via chords to denote the blocking relationships. An envelope then inscribes antibodies that belong to the same bin–defined by sharing the same pattern of reactivity (blocking or sandwiching) against all other antibodies tested (Fig. 3).

Once the bins are assigned, orthogonal data is applied by coloring the plot in different ways. In this way, a comprehensive fingerprint is produced that helps to identify those bins with similar functional effects for progression through to MOA elucidation studies.

Case Study: Neutralization of a Staphylococcus aureus virulence factor by the human antibody repertoire

Yeung *et al.* clearly demonstrate the power of multi-parameter epitope binning using High throughput SPR for elucidating MOA in a recent paper published in Nature Communications[4]. In this section, we show how the process described above was applied to not only identify antibodies that neutralized a *Staphylococcus aureus* virulence factor but to differentiate two distinct mechanisms for neutralization.

Understanding the pathology

S. aureus is a major human pathogen that is also a commensal, with most individuals not experiencing a serious infection. However, it can cause significant morbidity and mortality through conditions such as bacteremia, pneumonia, and infective endocarditis among others[5]. The paper investigates the mechanism that *S. aureus* uses to steal iron from hemoglobin in a process necessary for its colonization and pathogenesis.

A protein called IsdB (iron-regulated surface determinant B) is central to this process. It is a surface-exposed protein anchored to the cell wall that removes heme from hemoglobin and transfers it to other Isd proteins. These, in turn, import and degrade it to release the necessary iron into the bacterial cytoplasm[6].

Anti-IsdB antibodies can confer protection against *S. aureus* infections in animal models, which makes this system and

mechanism interesting to study not only to better understand the human immune repertoire since *S. aureus* is a commensal pathogen, but also in selecting therapeutic antibodies.

Molecular characterization of the antibodies of interest - combining epitope binning and orthogonal data

The researchers investigated recombinant anti-IsdB antibodies sourced by B-cell cloning from four healthy donors. The antibody repertoire was screened through epitope binning and studied in detail using a number of molecular characterization techniques. This enabled the antibodies to be organized into epitope clusters onto which the additional data was layered to create an antibody fingerprint that helps better understand the relevance of the epitope landscape.

Epitope binning using high throughput SPR organized the antibodies quickly into epitope clusters. This study investigated 70 unique antibodies, which were screened in a pairwise and combinatorial manner yielding the network plot shown in Figure 4.

Once sorted into bin clusters, the researchers performed cell-based functional studies to determine whether the antibodies blocked IsdB's interaction with its natural binding partner, hemoglobin, to neutralize *S. aureus.* Figure 4A shows that hemoglobin blockade was restricted to two distinct bin clusters, namely bin C and bin P (red nodes). Biosensor-based hemoglobin blocking assays also corroborated this result. This observation suggested that two distinct MOA's may be responsible for neutralization, which motivated further study.

Examining the source of the antibodies contained in bin C and bin P showed that they were populated by antibodies from multiple donors (Fig. 4B), which suggests that nature has found universal solutions to neutralization that are available in the human antibody repertoire. Remarkably, examining the genetic sequences of the antibodies contained in bin C and bin P revealed a strongly biased use of two immunoglobulin heavy chain germlines that neutralized IsdB (Fig. 4C), namely IGHV4-39 (bin C) and IGHV1-69 (bin P).

Antigen mutagenesis studies showed that bin C and bin P specifically targeted different IsdB NEAT (NEAr iron Transporter) domains, which are responsible for the binding of hemoglobin and heme respectively. Antibodies in bin C were shown to target NEAT1 and antibodies in bin P were shown to target NEAT2 (Fig. 4D). These observations are consistent with bin C and bin P providing neutralization via different MOA's.

These results were confirmed by crystallography data, which showed at atomic resolution that antibodies in bin C, targeting NEAT1 primarily using IGHV4-39, used a near-identical binding motif to do so. Similarly, antibodies in bin P, targeting NEAT2 primarily using IGHV1-69, shared a near-identical binding mode.

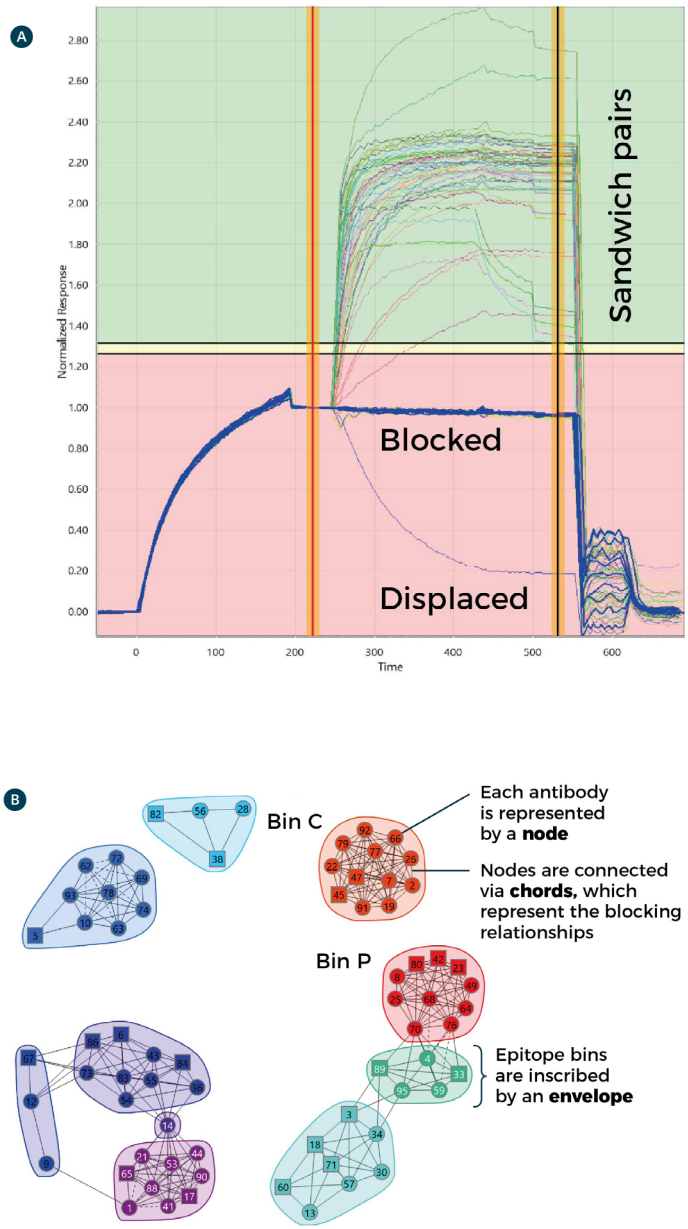

Figure 3: (A) A sensorgram is produced for each coupled antibody (ligand). It depicts the ability of the ligand to sandwich pair, block or be displaced by a panel of analytes (antibodies in solution). An analyte/ligand pair that sandwich pairs indicates that the ligand and analyte bind non-overlapping epitopes. An analyte that gives no signal presumably targets a similar or non-overlapping epitope to the ligand. An analyte that shows an inverted sandwich response displaces the ligand as a result of the analyte and ligand targeting closely adjacent or minimally overlapping epitopes. Taken from Abdiche et al. (B) A network plot summarizes the blocking relationships determined from the binning experiment by clustering the antibodies (represented by nodes) into bins. This provides a visual framework for understanding the biological relevance of results from other assays to produce a detailed fingerprint for each antibody (see Fig. 4). Here, we show that two distinct, non-overlapping bins (bin C and bin P) were both able to neutralize IsdB, implying different MOAs, which was confirmed by further investigation, and ultimately, by structural studies.

Structural Studies for MOA While atomic-level structural data determined via crystallographic studies is the gold standard for defining an epitope, it is low-throughput, slow and resource-intensive. It is therefore used to confirm the MOA of high-value candidates rather than to predict or screen for them. In contrast, the results from high throughput SPR-based epitope binning studies enable a quick surveyance of an antibody panel's epitope landscape, effectively clustering antibodies into epitope families. When merged with orthogonal data, such as functional cell-based neutralization data, antibody sequence data, antibody source, and antigen mutagenesis studies (as shown in Fig. 4), the relevance of these epitope families is revealed, guiding the selection of high-value clones meriting further study.

Indeed, the study by Yeung et al. elegantly shows how multi-parameter epitope binning enabled the identification of function-blocking clones with two distinct MOA's, which were then confirmed with structural studies.

The fact that the same phenotype of cell-based *S. aureus* neutralization could be achieved through two different MOAs is an important consideration in drug discovery, where pharmaceutical companies seek mechanistically-differentiated ways to solve a biological problem. This is important to both gain IP advantages over their competition and offer a safer or more efficacious medicine to patients.

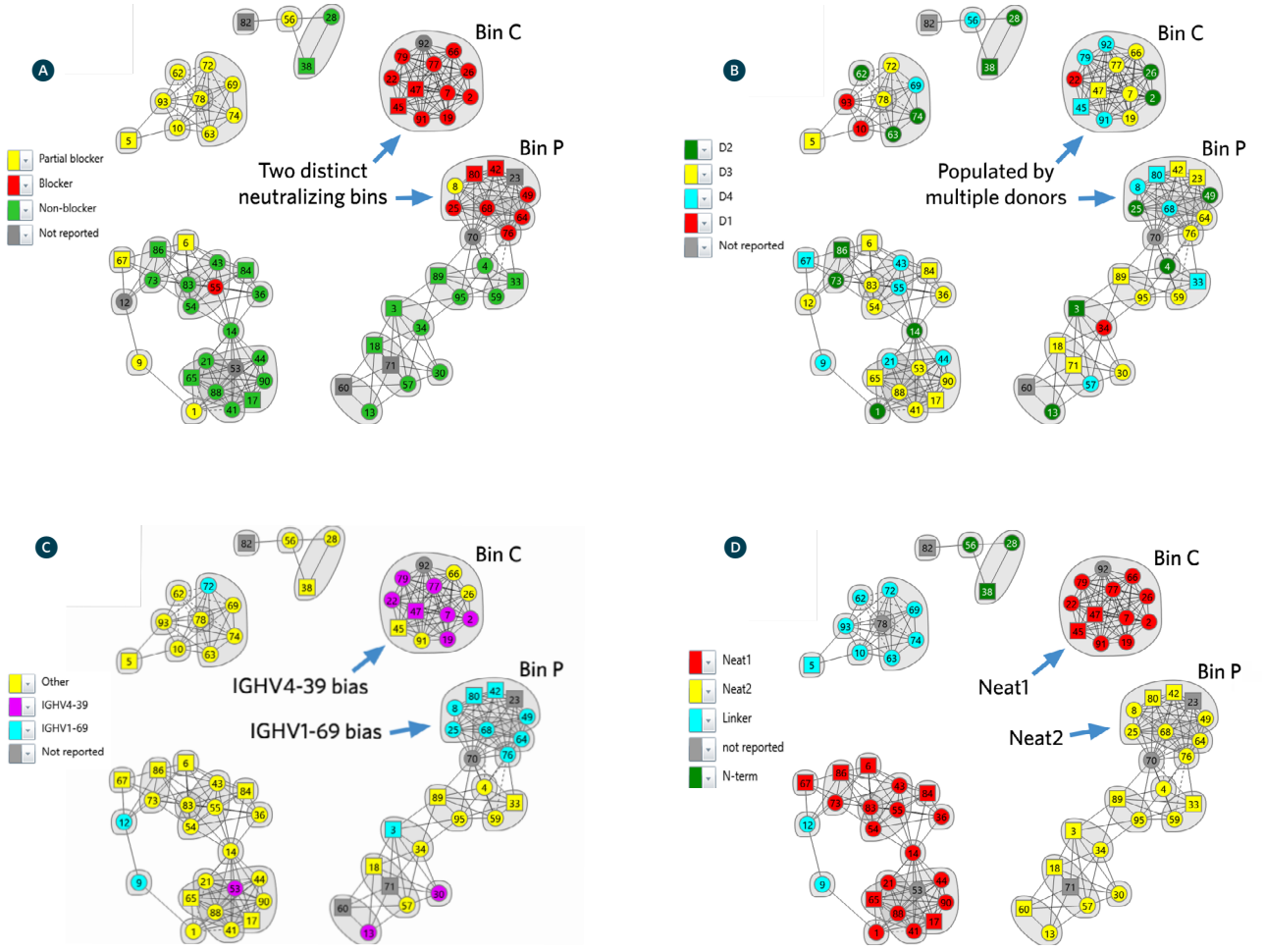

Figure 4: Network plots from multi-parameter epitope binning experiment colored by orthogonal data to reveal two distinct MOAs for S, aureus neutralization by the human antibody repertoire. (A) Hemoglobin blockade/neutralization was demonstrated by antibodies in bin C and bin P. (B) Bin C and bin P were shown to be populated by antibodies from multiple donors. (C) Antibodies in bin C and bin P revealed a strong bias for IGHV4-39 and IGHV1-69 respectively. (D) Antibodies in bin C were shown to target NEAT 1 and antibodies in bin P were shown to target NEAT2.

Summary

With high throughput SPR, drug discovery scientists have the potential to perform powerful epitope binning experiments and detailed characterization of antibodies of interest at the earliest stage of the discovery process. This technology facilitates a paradigm shift in antibody discovery, identifying blocking relationships for a whole antibody panel from the beginning for a streamlined and highly-informed lead selection process.

The results from epitope binning provide the first layer of information in constructing a detailed fingerprint of an antibody library, where groups of antibodies are clustered together based upon their epitope specificity, which correlates to their functional activity. In other words, antibodies targeting the same or similar epitope are likely to share the same or similar MOA. Combining orthogonal data from functional and other studies builds on this layer-by-layer, helping researchers to navigate through the epitope landscape, prioritizing resources and characterizing binding interactions to aid in elucidating MOA.

Using the Carterra LSA platform for high throughput SPR, it is possible to perform multi-parameter epitope binning to understand a therapeutic antibody's mechanism of action—a critical feature in drug discovery and development campaigns.

References

1. *Carter, PJ. and Lazar, GA. Next generation antibody drugs: pursuit of the 'high-hanging fruit'. Nature Reviews Drug Discovery 17, 197-223 (2018)*
2. Kaplon, H. and Reichert, JM. Antibodies to watch in 2018. MAbs 10(2), 183-203 (2018)
3. AbbVie Inc. AbbVie Reports Full-Year and Fourth-Quarter 2017 Financial Results. 2018 [Press Release] Available from: https://news.abbvie.com/news/abbvie-reports-full-year-and-fourth-quarter-2017-financial-results.htm
4. Yeung, YA et al. Germline-encoded neutralization of a Staphylococcus aureus virulence factor by the human antibody repetoire. Nature Communications 7:13376 (2016)
5. Tong, SY et al. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations and management. Clin. Microbiol. Rev. 28, 603-661 (2015)
6. Cassat, JE et al, Iron in infection and immunity. Cell Host Microbe 13, 509-519 (2013)
7. Abdiche, YN et al, Antibodies Targeting Closely Adjacent or Minimally Overlapping Epitopes Can Displace One Another. PLOS ONE (2017)

 WP102.2-060619

carterra®
info@carterra-bio.com
825 N 300 W Suite C309
Salt Lake City, UT 84103
www.carterra-bio.com