

# Accelerating Biotherapeutic Discovery

# Using High Throughput SPR to Explore the Full Kinetic and Epitope Diversity of Large Antibody Libraries

# Abstract

A new way of thinking and working has evolved for the discovery of therapeutic antibodies. Until recently, large numbers of antibodies were generated, only for a relatively small fraction to be sampled and engineered for further lead generation. Now, high throughput SPR (Surface Plasmon Resonance) facilitates a paradigm shift in antibody screening, enabling higher information content assays to be conducted earlier in the research pipeline to streamline lead selection. This essentially combines screening and detailed characterization in the same step.

Generating antibody libraries in an intelligent manner, so that they contain sequences more likely to produce marketable medicines, forms part of this new methodology. High throughput SPR provides a high-resolution method for characterizing the binding interactions of hundreds of antibodies in parallel, enabling deeper exploration of a library's kinetic and epitope diversity from the start of the drug discovery process. The traditional role of SPR as a de facto standard for performing high quality kinetics, but in limited throughput, positioned it as a secondary tool. Performing SPR in a high-throughput array format shifts its role upstream in drug discovery where it facilitates the identification of near-optimal leads within large libraries, requiring minimal engineering and thus expediting library-to-lead timelines.

This white paper outlines the challenges associated with the discovery and development of therapeutic antibodies – an especially promising and lucrative field for the biopharmaceutical industry. It discusses the benefits of using large antibody panels for screening and interrogating the epitope diversity of the whole panel in early-stage using high throughput SPR to accelerate discovery.

# Introduction

Making medicines is an expensive, time-consuming, and high-risk challenge, while also being a lucrative business. Though the cost of failure is significant in terms of both time and money, the reward can be incredibly valuable. Therefore, any method or technique that can minimize time and costs, while increasing the chance of finding and developing a successful therapeutic agent, is highly sought-after.

The search for biotherapeutics in the form of monoclonal antibodies (subsequently referred to as antibodies) is especially laborintensive. However, the naturally high affinities and exquisite target specificities found in this class of molecule provide unique therapeutic benefits to patients, making antibodies a worthwhile investment even when considering the various challenges that complicate their development.

Many successful pharmaceuticals are small molecules, developed through a process of rational design and engineering to optimize desirable characteristics, including binding affinity and specificity. In the case of antibodies, however, epitope specificity is an innate property that cannot be designed rationally, requiring empirical investigation.

Discovering an antibody with appropriate characteristics relies upon an informed selection from the large antibody libraries produced using modern methods. Characterization of the binding interaction between the target antigen and therapeutic antibody candidates is an important step in this process, aiding in the selection of candidates to progress and helping to determine the crucial mechanism of action (MOA).

High throughput SPR systems make possible the evaluation of large sets of antigen:antibody interactions quickly and cost-effectively by adding throughput to the proven SPR technique. This technology can be used to run parallel investigations into kinetics, affinities, and epitope specificities from the very start of the drug discovery process. This ability to perform higher throughput and comprehensive characterization early in the drug discovery workflow changes the paradigm of therapeutic antibody screening. Researchers become better informed, earlier, to fully appreciate the epitope landscape of a campaign and so identify the superior candidates from the original library.

Before the advent of high throughput SPR screening, researchers commonly used high throughput but low information content assays to triage a subset of clones for subsequent detailed characterization. This approach meant underappreciating the full epitope and kinetic diversity of the original library. As a result, under-sampled pools led to picking suboptimal clones, which then required extensive engineering in the hope of improving their properties; or completely missing highly valuable potential therapeutics altogether.

High throughput SPR screening avoids a great deal of redundant work, saves time and cost, and ultimately results in superior leads. Importantly, it also avoids researchers repeating or abandoning screening campaigns unnecessarily when they failed to identify desired clones; not because they weren't in the library but because it was not possible to look deep enough, early enough.

In this white paper, we look at the specific challenges surrounding the discovery of therapeutic antibodies and present high throughput solutions for antibody characterization. High throughput SPR provides more information sooner, improving decision making and changing the paradigm of antibody screening. The result is faster and highly informed candidate selection/progression with a reduced risk of failure, increased intellectual property (IP) understanding, and minimized sample consumption. These properties make it particularly attractive to early-stage research where large numbers of samples are available for testing, but in limited quantities.

# What makes a successful medicine?

One of the main factors necessary for a successful therapeutic agent is a well-defined MOA in the human body. This is an important consideration for safety and efficacy, and therefore for regulatory approval and clinical success. In addition, knowing and understanding a unique MOA is an essential part of securing IP rights and supporting successful commercialization.

A medicine can take many forms, from small molecules to vaccines and antibodies. In an ideal world, whether small or large molecule, all medicines should be straightforward to manufacture and produce consistent and predictable results, both in production and the clinic. For the patient, medicines should be safe, effective, and as convenient as possible to dose, in terms of size, frequency, route of administration, and cost.

# Why antibodies?

The field of therapeutic antibodies is producing massive and growing sales for the pharmaceutical industry, with the number granted first approval in either the European Union or the United States reaching double figures for the first time in 2017<sup>1</sup>. This accelerated pace is projected to continue through 2018 and beyond, cementing antibody therapeutics as an increasingly important part of the pharmaceuticals business, representing over 40% of all newly approved drugs.

Antibodies are highly attractive as therapeutic agents as they have a naturally high affinity and specificity for their target antigen. These are desirable characteristics that enable an antibody to bind well to a single target, maximizing the desired biological effect, while minimizing off-target issues. In turn, this means that antibodies can be dosed at relatively low levels compared with small molecules. Furthermore, because of their large size, they are cleared from the body much more slowly than small molecules, so they can be administered less often (typically once a month), providing substantial patient convenience.

Adalimumab (marketed by AbbVie Pharmaceuticals as Humira) was the first fully human antibody granted US FDA approval and serves as an example of a highly successful therapeutic antibody. It is now used to treat several diseases and conditions including rheumatoid arthritis, Crohn's disease, and ulcerative colitis. In 2017 AbbVie reported \$18.427 billion USD of sales from Humira alone<sup>2</sup>.

# The nature of antibodies

In mammals, an antibody is a specialized, Y-shaped glycoprotein produced and secreted by B lymphocytes in the immune system of an organism. Its primary function is to recognize and bind a unique pathogen (via an antigen) and neutralize it. The recognition and precise binding by the antibody to an antigen occurs via the antigen-binding sites located at the tips of the Y-shaped molecule's Fab fragments. These regions provide a complex interface that recognizes and binds to a specific site on an antigen - termed an epitope.



Graphic representation of a Y-shaped antibody binding an antigen epitope.

"It is not likely that in silico tools/algorithms will ever be predictive enough to replace empirical selections in my career - the math is too daunting. No technology can exhaustively sample all the theoretical sequence space of an antibody molecule, let alone screen that diversity. Combine that with the huge diversity of possible antibody:antigen binding conformations and it seems like there will always be a need for actually generating variant libraries and screening them."

Bill Harriman - VP, Antibody Discovery Services at Ligand Pharmaceuticals

The architecture of an antibody's antigen-binding site is composed of stretches of conserved framework amino acid residues alternated with hypervariable portions, termed complementarity-determining regions (CDRs). As a result, an organism's antibody repertoire is vast, with enormous sequence and structural diversity, enabling it to recognize an equally enormous range of antigen epitopes.

It is this virtually limitless target range and unique process of target recognition and binding that is of great interest when making medicines. The ability to develop an antibody capable of binding to a specific target of interest with its trademark high affinity and specificity is a model solution to drug discovery.

## Discovering an antibody

Making a medicine, whether a small molecule or biologic such as an antibody, is not a prescriptive process where the end, target molecule is known. Rational design and empirical science represent two polarized, yet complementary approaches to drug discovery.

In the case of therapeutic antibodies, some characteristics, such as affinity, can be optimized via engineering, but it is not possible currently to predict or design the epitope specificity in a rational way. Rather, this is an innate property, which dictates binding to the target of interest (antigen). It cannot be engineered by design in silico and/ or de novo synthesis.

Empirical science is therefore critical for the discovery of antibody therapeutics, and can be aided, but not replaced by computational methods.

A collection of antibodies can be functionally screened to determine which potential drug candidates to move through the pipeline. This method of using empirical evidence to 'triage' the antibodies available and select promising candidates is labor- and timeintensive, as well as expensive. However, this experimental selection step is also crucial to the discovery process. Some of the routine methods for triaging, such as ELISA, FACS, and kinetic studies, result in information being missed. However, the combination of modern antibody generation methods to create large diverse libraries and high throughput analytical tools for screening make it possible to carry out more comprehensive screens.

# Library-to-leads triaging

Current techniques for generating antibodies include the use of hybridoma technology in normal and transgenic animals, phage display, and synthetic libraries. All these can produce prolific numbers of clones to feed drug discovery pipelines with increasingly large panels of potential therapeutic antibodies. A library produced by phage display, for example, typically includes over ten billion clones, while the current SuperHuman 2.0 library from Distributed Bio contains almost 100 billion unique members.

This colossal number of clones far exceeds the practical capacity of current expression and analytical methods, but rather, provides a diverse library from which binder clones towards a target of interest can be extracted, via panning strategies. This typically yields 100's to 1000's of hits, depending on the screening strategies used, which are routinely whittled down to a subset for detailed characterization.

Greater numbers of candidates increase the possibility of finding both an optimal antibody to treat a disease, and one which presents a good starting point in IP free space. This is crucial for selecting the most successful and commercially attractive medicine.

The process of deciding which antibodies to progress through the pipeline is termed library-to-leads triaging. Ideally, this triage step should take place in the early stage and examine the largest number of antibodies possible, generating information on as many binding interactions as practically possible to fully appreciate the epitope landscape of the campaign and minimize the need for further engineering.

High throughput analytical tools allow a broader and deeper diversity of the library to be discovered from the beginning of the process, enabling the identification of suitable candidates for progression, and reducing the need for extensive and costly engineering. Commercially, the generation of antibody libraries is a substantial investment. For example, a new line of transgenic animals can involve costs of greater than \$1 million USD. Add to this the hugely competitive nature of drug discovery, where multiple large pharmaceutical and numerous biotechnology companies are often working on the same drug target, and the importance of rapidly realizing the full value of a purchased or generated antibody library to maximize output, return on investment, and identify/ defend IP space is business critical. "With small libraries, you struggle to identify weak hits with the characteristics you are interested in, and then spend a lot of time attempting to optimize them. Large libraries change this paradigm by ensuring that you have swarms of hits with any characteristic you are interested in, and don't have to optimize them. Our new libraries have 1000x more molecules than old libraries and being able to find what you want up front is the core advantage."

Jacob Glanville - Founding Partner, Chief Science Officer, and Chairman of the Board at Distributed Bio

#### A closer look at the epitope

The library-to-leads triage process involves characterizing the binding interactions between candidate antibodies and target antigen. The physical contacts occurring within the antigen:antibody binding interaction form the epitope:paratope interface, where epitope refers to the contact residues contributed by the antigen and paratope refers to those contributed by the antibody. It is this interaction, and therefore the epitope itself, that defines an antibody's MOA, making it important and relevant to the success of a therapeutic antibody program.

A therapeutic antibody's epitope specificity is a critical characteristic, and defining it is crucial in terms of IP rights in the fiercely competitive world of pharmaceuticals, where multiple companies are often working on the same targets to become first-inclass and/or best-in-class.

For example, although there are five antibodies targeting the PD-1 (programmed cell death-1) pathway already on the market to treat cancer, it remains a popular target for development. A further nine antibodies targeting PD-L1 (programmed death-ligand 1) are currently in clinical development1. Multiple companies also have antibodies targeting CGRP (calcitonin gene-related peptide) either on the market or in late-stage clinical trials for the prevention of migraines<sup>3</sup>.

The ability to claim a novel epitope offers both a competitive edge and IP opportunities. Surveying the epitope landscape of a large antibody library at the earliest possibility, through functional library-to-leads triaging, is advantageous to this end, providing the opportunity to expand and defend IP space. Importantly this technology ensures that only those antibody clones exhibiting the most appropriate epitope specificity for commercial and clinical success are progressed.

# Characterizing binding interactions: kinetics, affinity, and epitope specificity

The combination of three key characteristics – kinetics, affinity, and epitope specificity – provides a full understanding of antibody binding interactions. Each is important in isolation, offering specific and useful information for the antibody's characterization. In combination, the three properties help to enable highly informed selection decisions.

# Antibody Libraries IN FOCUS

#### Why does antibody discovery require the generation of large libraries?

Antibodies are incredibly diverse molecules. While small molecules often bind weakly and with limited specificity to an intended target, it is possible to generate antibodies with high affinity and specificity. These highly desirable properties are rare and therefore require much larger libraries as starting points for their discovery. In antibody discovery, there is always a need to generate many hits through sampling a large amount of sequence space and then sort through them quickly to generate optimal leads.

#### How large is large enough?

The bigger the library, the better. Antibody generation techniques have made it possible to create libraries with up to 100 billion unique members that feed the panning strategies against the target of interest to yield binder clones, typically 100's or 1000's of on-target hits.

#### What are the key benefits of using large libraries?

The availability of such large libraries has resulted in a change of paradigm – instead of finding 10-50 hits that require significant engineering, thousands of hits are possible, from which those with the desired features need to be selected.

# Binding kinetics and affinity data

The strength of a binding interaction between two molecules, such as an antibody and its specific target, is characterized by the association and dissociation kinetic rate constants ( $k_a$  and  $k_d$ ), which describe respectively the formation and decay of the bimolecular complex. 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.

Binding kinetics and affinities are important parameters in drug discovery for understanding an antibody's MOA and can influence its pharmacodynamics and pharmacokinetics. Additionally, the binding kinetics provide useful information for guiding the evaluation of an antibody's performance throughout the entire drug discovery and development pathway – from screening to manufacture.

Early-stage screening often does not include the generation of kinetic data because of the limited throughput of commonly used methods such as SPR, meaning that they are used as a secondary step after large antibody libraries have already been screened and triaged into smaller subsets. This is due to the large numbers of antibodies that require empirical investigation and the resultant need to reduce the processing burden wherever possible, often necessitating compromise on throughput or accuracy<sup>4</sup>.

A typical example of this approach might involve preliminary screening with a high throughput but low information (end-point) content assay, such as ELISA. Potentially important data is missed at this stage, increasing the likelihood that otherwise lucrative candidates are rejected through less than fully-informed decisions on pipeline progression.



Simultaneous kinetic analysis of 384 antigen/antibody binding interactions using high throughput SPR. (A) The results from a single capture kinetics assay where a monovalent target (analyte) was titrated over 384 antibodies, each captured onto individual spots of a 384-array. Each panel represents the global kinetic analysis on a single spot; all 384 spots were analyzed in parallel (some spots are excluded). (B) Enlarged view of the data from 3 spots showing antibodies that bound their target with diverse kinetics (low, medium, and high affinities, from left to right), where the measured data are shown as a green-blue gradient and the global fit is shown in red.

# **Epitope binning**

Epitope binning – the empirical investigation of an antibody's epitope specificity – involves clustering antibodies that bind to the same or similar epitopes into families, or "bins." It is a competitive assay that tests antibodies in a pairwise and combinatorial manner for the ability to bind simultaneously to their specific antigen.

Should both antibodies bind at the same time, it is presumed that they are targeting distinct, non-overlapping epitopes. If one antibody blocks another, the inference is that they compete for overlapping or similar epitopes.

In this way, all antibodies in the library are tested against each other, grouped according to their epitope specificity, and a "blocking footprint" generated for each. Antibodies sharing a bin are likely to also share similar binding interactions. Antibodies that exhibit unique epitopes can be rapidly and easily identified to provide diversification of selected candidates. Performing epitope binning early in the discovery pathway using a large library of antibodies, rather than a subset, ensures that you see the full picture of all interactions. As a result, it is possible to identify binding pairs that would likely be missed if only a limited, smaller pool of antibodies were investigated.

Epitope binning can also reveal sandwiching antibody pairs that target different epitopes to the functional one and are therefore useful as companion reagents and/or diagnostics. This helps to support the therapeutic antibody discovery program, which involves numerous antibody-based assays throughout preclinical and clinical development. These further applications for antibodies - as diagnostic tools, companion diagnostics and reagents - can also provide large additional financial opportunities.



Carterra's proprietary network plotting software provides an intuitive way of navigating the epitope binning results. In a network plot, the nodes represent the antibodies (identified by number), the chords indicate the pairwise blocking relationships, and the envelopes inscribe the bins.<sup>5</sup>

"Exploring the depth and breadth of an antibody library's epitope coverage requires information on as many antibodies as possible to simultaneously probe all targeted epitopes and their relationships to one another. Performing these studies on large antibody arrays enables exquisite discrimination of near-identical clones and provides an efficient way of surveying the entire epitope landscape.

Increasing the number of antibodies interrogated increases the resolution of the binning results, which in turn increases the chances of finding antibodies with unique or nuanced binding modes to strengthen IP.

High throughput SPR is an ideal tool for high throughput early-stage epitope characterization, revealing the full epitope repertoire of an antibody library, where clones are numerous but available only in limited quantities."

Yasmina Noubia Abdiche - CSO, Carterra Inc.

#### Label-free biosensors

As discussed, the large number of antibodies present in a starting panel necessitates the use of an analytical tool to screen outputs and help triage library-to-lead candidates. Many available methods are slow, resource-intensive, and/or complicated. Researchers are therefore turning to label-free biosensors, such as SPR and BLI (biolayer interferometry) instruments. These are ideally suited to measure binding in real-time and without the need to conjugate or modify either partner.

SPR and BLI instruments can screen numerous clones from crude samples and are routinely used in the pharmaceutical industry to characterize antibody:antigen interactions. However, these techniques have limited throughput and require complex assays and relatively large sample volumes, meaning that they are often only used as a secondary screen.

# High throughput mAb characterization using High throughput SPR for kinetics and epitope studies

Increasing the potential throughput of label-free biosensor technology would be a major development for those involved in antibody discovery. Additionally, performing both kinetic and epitope binning studies on a complete antibody library would allow the full interrogation of epitope diversity. High throughput SPR systems, such as Carterra®'s LSA<sup>™</sup> instrument, meet both demands. This technology rapidly and easily delivers throughput orders of magnitude higher than other label-free methods, making it possible to analyze many hundreds of interactions in parallel. This enables both kinetic screening and epitope binning studies of large antibody panels, ideally positioning them for early-stage screening. This ability to identify a few highquality leads with relevant epitopes so early in the discovery process is invaluable to antibody discovery teams<sup>5</sup>.

In terms of kinetic analyses, the capability to perform high throughput experiments with antibodies is important due to their uniquely tight binding with antigens. Compared to small molecules, which have generally transient binding interactions, antibody:antigen interactions often exhibit affinities that are a million-fold tighter. Accurately measuring kinetic rate constants of such high-affinity reactions, therefore, requires long binding cycles<sup>6</sup>. As a result, the ability to increase throughput is especially beneficial to achieve overall gains in efficiency and cost savings.

With Carterra's LSA instrument, it is now possible to measure the binding kinetics of up to 1,152 antibody interactions in a single unattended run (3 x 384-well plates). High throughput SPR technology is thus gaining popularity for accelerating the kinetic screening of large antibody libraries, demonstrated by recently published studies<sup>7, 8</sup>.

Epitope binning experiments ideally involve the pairwise comparison of each antibody to every other antibody in the panel, as well as itself, and not just a preselected subset. Consequently, the number of interactions required scales geometrically with the number of antibodies in the test panel. For example, analyzing ten antibodies requires 100 interactions, while analyzing 100 antibodies requires 10,000 interactions.

When exploring the epitope coverage of large antibody panels, the required number of interactions to perform a comprehensive binning analysis can escalate quickly and become prohibitively high, making throughput and sample consumption vital considerations for epitope binning investigations. This makes such experiments unfeasible on standard biosensor platforms. However, Carterra's LSA instrument makes it possible to perform up to a 384x384 epitope binning experiment, equating to over 147,000 interactions, in a single run and using minimal sample volume.

The "one-on-many" array format employed by high throughput SPR means that the sample consumption per antibody does not scale with the size of the antibody panel. The same amount of antibody and ligand (coupled) or analyte (in solution) is used whether the array contains one or 384 antibodies, a significant practical advantage over other technologies.

# Comparison to other label-free biosensors

It is the throughput capabilities and corresponding low sample consumption that set the Carterra LSA platform apart from other systems on the market. This is demonstrated in several recent studies comparing different label-free biosensor systems in terms of accuracy, throughput, and other key parameters.

The Biacore® 4000 from GE Healthcare (an 8-channel SPR instrument) and the MASS-1 system from Sierra Sensors (8-channel SPR instrument with hydrodynamic isolation (HI)) produce comparable kinetic rate constants for antigen/antibody interactions<sup>9</sup>. However, these systems have limited throughput, being restricted to only eight, or sixteen interactions at a time respectively. Even the more recent versions of these systems, the Biacore 8K and MASS-2, can only provide eight and thirty-two interactions at a time respectively. The Carterra LSA platform generates equivalent kinetic rate constants and data quality, but facilitates the rapid generation of kinetic screening data from up to 384 samples in parallel and 1,152 samples per unattended run, representing the highest throughput available on the market.

Another recent study compared the Octet-HTX from Forte Bio/ Pall to a high throughput SPR platform for epitope binning of 96-antibody arrays<sup>5</sup>. The Octet-HTX uses BLI technology, which is highly flexible and provides the ability to simultaneously analyze interactions of 96 independent analyte/ligand pairs. However, since sample consumption scales with the size of the antibody panel, it is often only possible to perform investigations with relatively small panels<sup>10</sup> due to the high demand for material, complicated layout, and the additional robotic integration needed to automate multi-plate feeding. This limits the potential for large-scale earlystage antibody screening with BLI technology. By comparison, high throughput SPR provides a method that enables the simultaneous analysis of 384 binding interactions and requires an exceptionally low sample consumption, making high throughput epitope binning assays possible<sup>11</sup>. The Carterra LSA can perform a comprehensive 384x384 binning assay in a single unattended run.

	Carterra LSA	Carterra LSA	BLI <sup>5*</sup>
	384x384	96x96	96x96
Plates required to accommodate analytes	One 384-well plate	One 96-well plate	24 x 384-well plates
Volume per ligand	200 µl	200 μl	100 μl
Volume per analyte	250 µl	250 μl	10 ml
Unattended throughput	147,456 interactions (384 analytes x 384 ligands)	9,216 interactions (96 analytes x 96 ligands)	384 interactions (4 analytes x 96 ligands)
Run time	4 days	30 hours	Several days involving
Number of manual setups	1 unattended run	1 unattended run	24

\* Robotic integration with the BLI platform results in a higher unattended throughput, longer unattended runtime, and significantly shorter total runtime by automating multi-plate analyses.

Comparison of the key capabilities between the Carterra LSA for 384x384 and 96X96 epitope binning experiments and BLI systems for a 96x96 epitope binning experiment.

#### Summary

Despite challenges in their discovery, antibody therapeutics have proven to be highly effective and commercially valuable medicines. Standard characterization technologies require compromises in workflow that ultimately reduce the effectiveness of antibody discovery. Streamlining the library-to-lead process through advanced technology helps deliver medicines faster, cutting costs and increasing commercial value.

The advent of high throughput SPR instruments, such as the Carterra LSA platform, now allow researchers to realize the full kinetic and epitope potential of their large antibody libraries earlier in the drug discovery process. Positioned upstream relative to traditional lower throughput SPR platforms, high throughput SPR combines both high-throughput and high-resolution analysis to enhance screening methods and permit the rapid identification of unique, highly sought-after antibody clones for clinical and commercial benefit.

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Carterra technology is protected by the following patents and other patents pending: 8,210,119, 8,211,382, 8,383,059, 8,999,726, 9,682,372, 9,682,396

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