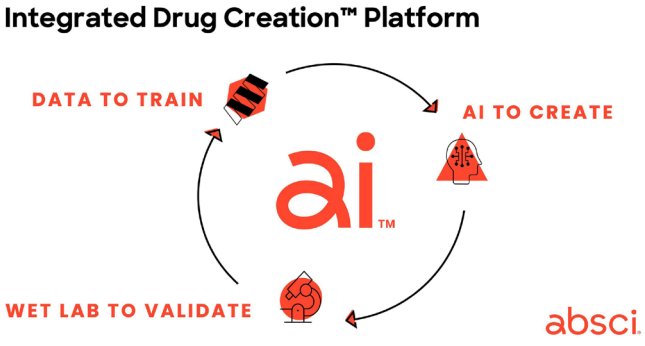
AI in Drug Discovery: High-throughput SPR Boosts Breakthroughs

Artificial intelligence (AI) is revolutionising drug discovery, enabling scientists to identify novel therapeutic candidates in a fraction of the time it once required. Until now, the main obstacle for researchers has been the ability to quickly screen and characterise large libraries of candidates for an efficacious therapeutic, as well as the inability to spot failed candidates earlier in the process. Consequently, pharmaceutical companies have spent significant development dollars on molecules that will not prove to be suitable therapeutics – prolonging the time-to-market and increasing the cost of life-saving medicines. With the introduction of generative AI and machine learning (ML), it is now possible to select more promising candidates using fewer resources, saving time and money. But how are AI/ML algorithms created and fine-tuned to become reliable methods for candidate selection?

Therapeutic antibodies traditionally undergo five sequential stages leading up to preclinical development. First, the drug's target is investigated for its relevance in the disease based on primary research. Then the antibody is generated by immunising an animal and growing its immune cells that produce the antibodies. These antibodies are initially tested in the lab, and those that look most promising pass on to the next step as lead candidates. These lead candidates undergo optimisation, a critical stage in which they are honed for biological activity and properties that will impact a future drug's efficacy, safety, and developability.

To design a promising lead drug candidate for further development, you need to find antibodies with several different properties, all falling within a small range. It's like searching for the proverbial needle in a haystack, except the haystack is larger than the known universe, and the needle is smaller than a speck of sand. Using traditional drug discovery methods, this can be a long, expensive process with little probability of success. AI-guided design of drug candidates can dramatically speed up both the discovery and the lead optimisation process as well as produce unique, generative variants that could never be found using standard methods.



In recent years, numerous antibody-related databases have emerged, offering valuable resources for training machine-learning models. However, many of these databases can often lack critical information, such as affinity, aggregation parameters, or epitope data.[1] The Carterra® high-throughput surface plasmon resonance (HT-SPR) platforms are playing an essential role, both upstream and downstream in the discovery process. Josh Eckman, CEO of Carterra, when asked about the role of Carterra's HT-SPR technology in AI-driven drug discovery has said, "We believe we can help in this [process] by providing high-resolution binding information on epitope, affinity, and kinetics at the earliest stages of screening."

The platforms provide reliable data on affinity maturation using its kinetic and epitope software to feed the AI model, as well as verifying the model's predictions. This validation is then fed back into the model, continually strengthening its intelligence.

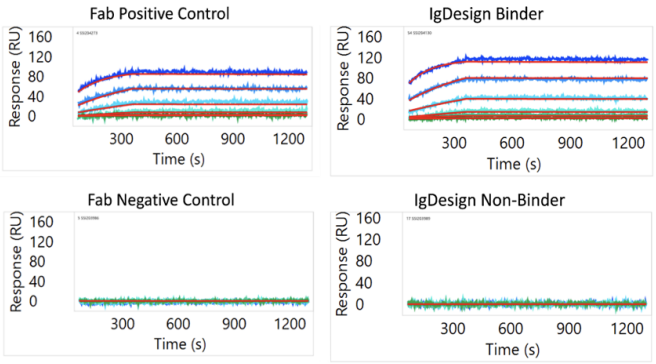
AI Drug Discovery in Action

AI promises to revolutionise drug discovery, but advances in drug creation also continue to depend on scalable wet lab technologies to produce and validate biological data at scale. One company leading the way in this combined approach is Absci Corporation. Established in 2011 and headquartered in Vancouver, Washington (United States) the team is using a zero-shot AI approach, which designs antibodies without prior learning on the specific target and are, therefore, generating candidates unlike those found in existing databases. It created a proprietary Integrated Drug Creation™ platform, which combines the data to train, the AI to create, and the wet lab capabilities to validate millions of AI-generated designs. Jens Plassmeier, PhD and Senior Vice President for Biologics Discovery Technologies at Absci, noted that this platform enables their team to develop new therapeutics using the same AI technology celebrated for generating text and images from natural language prompts.

Working from massive biology datasets, generative AI is applied to design optimal drug candidates based on target affinity, safety, manufacturability, and other traits. Absci supports its generative AI designs with its wet lab's extensive validation capabilities, which includes the Carterra LSA®. David Eavarone, PhD and Director of High-Throughput Screening at Absci, said, *"This workflow can take us from AI-designed antibodies to wet lab-validated candidates in as little as six weeks. The quality and scale of wet lab data give us incredible training data, propelling our iterative design-build-test-learn cycle."*

High-Throughput SPR: What it is and How it Benefits AI-led Drug Discovery

High-throughput SPR systems make possible the evaluation of large sets of antigen:antibody interactions quickly and



Carterra LSA HT-SPR enables rapid assessment of AI-designed binders with high quality data

cost-effectively by adding throughput to the proven surface plasmon resonance 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 characterisation early in the drug discovery workflow changes the paradigm of therapeutic antibody screening. Researchers become better informed earlier in the process, fully appreciating the epitope landscape of a campaign and thus, can identify the superior candidates from the original library. Importantly, it also avoids researchers repeating or abandoning screening campaigns unnecessarily when they have 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.

The Carterra LSA HT-SPR antibody discovery and characterisation platform was launched in 2018, which was then followed by the even more sensitive LSA^{XT} platform in 2023. Newest to the market, introduced this month, is the Carterra Ultra™ platform, which allows for small molecule and fragment drug development research to benefit from the speed, low sample usage, and breadth of data provided by the previous Carterra HT-SPR platforms. The instruments combine high-throughput microfluidics for array printing with label-free SPR detection. This enables all antibodies to be rapidly and comprehensively screened early in the discovery process so that unique epitopes and potential novel therapeutic candidates can be identified while expanding and enhancing IP coverage.

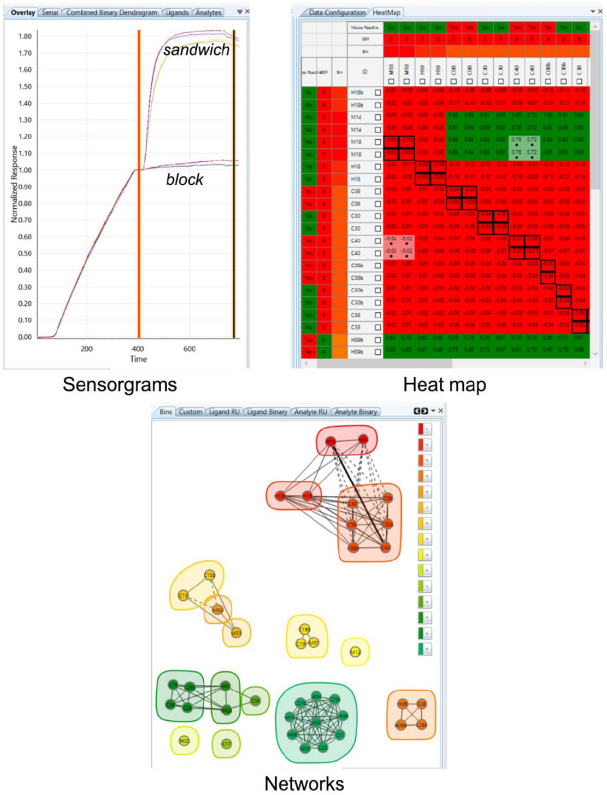
Characterising binding kinetics and epitope coverage of large numbers of molecules early in the drug discovery process has been transformative. Through high-resolution and high-throughput binding analysis, detailed interrogation of protein and epitope binding has become a reality at a pace that was previously unimaginable. In short, months of work can be compressed to just a couple of weeks, enabling improved clinical candidates.

HT-SPR stands as one of the primary methodologies for Absci's wet lab validation. To this end, the Carterra LSA platforms have been invaluable to the team and their success. Dr. Eavarone underlines the critical role that having these instruments has provided their team, stating, "LSA data is indispensable in testing and training our generative AI models. The Carterra LSA enables precise quantification of single target affinity for our AI models used in de novo drug discovery. The Carterra SPR technology is also extremely versatile and enables the testing and advancement of AI models for high throughput lead optimisation. We have reported success using these systems for multi-parametric lead optimisation including for epitope specificity, pH sensitivity, and co-optimised binding against multiple antigens. Put simply, to have the best AI drug creation platform, you need the best data. Carterra's HT-SPR is at the heart of our wet-lab data generation and has been instrumental in the success of our drug discovery platform."

Conclusion

Despite billions of dollars of investment every year, only an estimated 4% of drug leads succeed in their journey from discovery to launch. Even more unfortunate, only 18% of drug leads that pass preclinical trials eventually pass phase I and II trials, suggesting that most drug candidates are unsafe or ineffective. While much of this failure rate is attributable to incomplete understanding of the underlying biology and pathology, insufficient drug lead optimisation also contributes to many failures. The ability to create and optimise new therapeutic antibodies *in silico* using AI could reduce the time it takes to get new drug candidates into the clinic by more than half, while also increasing their probability of success.

Artificial intelligence and machine learning are sure to continue to be key tools in improving the speed and accuracy of therapeutic development in the future. With that said, the accuracy and learning capabilities of these models will also need to continually grow and improve. While AI-assisted antibody design and lead optimisation of biological sequences can reduce therapeutic development time, it does not by itself currently offer an *in silico* replacement for all drug discovery efforts. Fully generative and broadly applicable modeling approaches are needed. However, the training and validation of such models face an immense data challenge due to the vast combinatorial design space where strong selective binders represent an incredibly small piece of that space. Dr. Eavarone predicts that as high-throughput structural data generation becomes more advanced and training data sets become larger, Absci's AI models will improve to be able to create de novo antibodies against any target, including those without any known existing binders and even those for emerging pathogens previously unseen as targets in the therapeutic space.



Carterra's Epitope Analysis Software showcases data linked across three visualization panels: sensorgrams, heat map, and networks.

In summary, although AI can help expedite the design and optimisation of antibodies, it currently falls short of replacing all aspects of drug discovery. Developing fully generative models that can be broadly applied remains a significant challenge due to the immense complexity of the design space and the rarity of highly effective binders. Nevertheless, as the ability to generate structural data at scale improves and training datasets expand, it is expected that AI will eventually evolve to meet this challenge. In combination with technologies such as HT-SPR, the rate and dependability of AI/ML in drug discovery will advance at an accelerated rate. AI is unlocking new opportunities, allowing researchers to create better biologics for patients faster, and the hope is that it will go a long way to improved quality of life and better therapeutic outcomes for patients.

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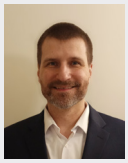
Josh Eckman

Josh is the founder and Chief Executive Officer of Carterra. Mr. Eckman graduated summa cum laude in Business Administration and Asian Studies from the University of Utah. At graduation, he was awarded the Outstanding Scholar in Business Administration and the Honors Baccalaureate Award. Mr. Eckman then received a M.S. in Mechanical Engineering (microfluidics focus) from the University of Utah. Mr. Eckman was also selected by Ernst & Young LLP as a 2022 Entrepreneur of the Year® Mountain West Award winner – a preeminent competitive business award for entrepreneurs and leaders of high-growth companies.



David Eavarone

David Eavarone is currently the Director of High-Throughput Screening at Absci. His scientific background spans over a decade in industry-leading wet lab development efforts for antibody-based therapeutics for immuno-oncology and infectious disease targets. He obtained his PhD in Biomedical Engineering at MIT through the Health Sciences and Technology program joint with Harvard Medical School.

Jens Plassmeier

Jens Plassmeier is the SVP for Biologics Discovery Technologies at Absci. During his time in industry, he has led projects relating to the development and production of therapeutical antibodies, development and scale up of microbial produces large and small molecules. Jens obtained his PhD in Biology from the University of Bielefeld in Germany and did postdoctoral research at MIT.

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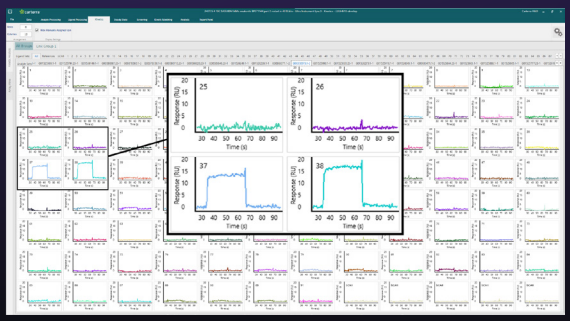
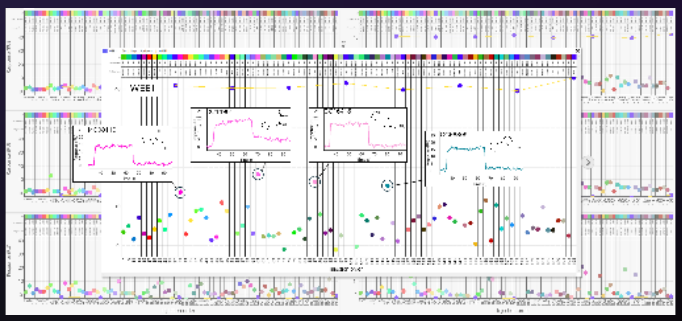


Fragment hit identification against 96 proteins using the Carterra Ultra platform.



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