



Better AI Begins at the Bench

Twist Bioscience's synthetic DNA enables A-Alpha Bio to deliver more precise, AI-driven antibody engineering

A-Alpha Bio has created an AI and synthetic biology-enabled workflow to enable rapid discovery and optimization of therapeutic antibodies. For each project, their AI model is tailored to provide focused predictions that match the unique therapeutic requirements. To do that, they first need a wet-lab-validated training dataset that captures the vast sequence space of specific antibody-target interactions. Generating this data requires precise, unbiased DNA libraries of hundreds of thousands of sequences, supplied by Twist Bioscience.



Introduction

Therapeutic antibodies have transformed modern medicine. Their high specificity has made them exceptional therapeutic molecules, capable of binding to novel, disease-relevant targets.

Yet, optimizing antibodies for therapeutic use is inherently complex. Multiple interconnected properties, such as binding affinity, specificity, and developability (which includes expression, stability, aggregation, immunogenicity, and more), must be finely tuned to achieve the desired performance.

Target affinity is typically optimized first, followed by specificity and developability. Improving one property often compromises another, creating a recursive cycle of designing, testing, and re-engineering.

At the same time, antibody design criteria have grown more sophisticated. Beyond simple monospecific IgGs, today's pipeline includes multispecific antibodies with biparatopic binding domains, AND and NOR logic with finely tuned affinities to improve targeting specificity, and environmental responsiveness to pH or other factors. These advanced characteristics expand the number of variables for optimization and exponentially increase engineering complexity.

A-Alpha Bio makes antibody optimization faster and more reliable by eliminating these iterative cycles. By combining synthetic biology and AI, the company condenses months of sequential optimization rounds into a single, data-driven step.

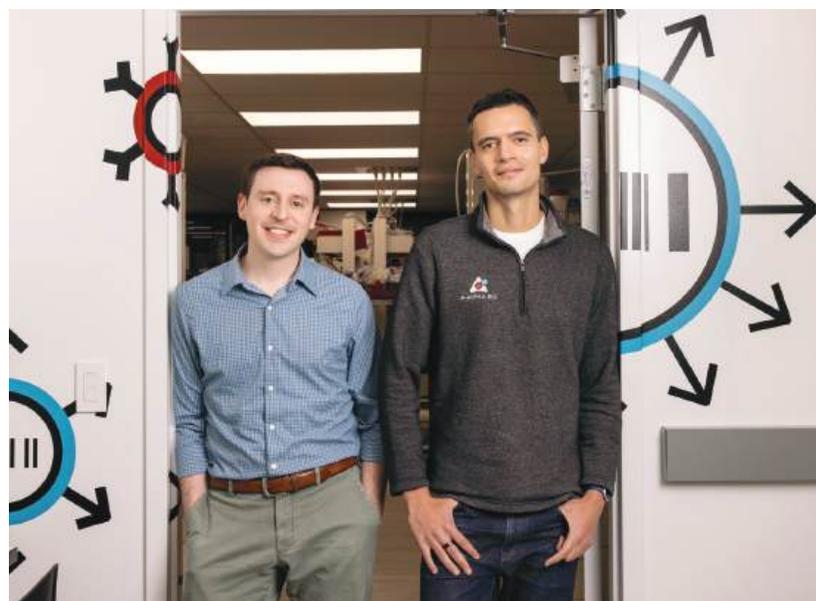
“In traditional antibody optimization, you start by identifying a binder, then improving its affinity. Once that’s done, you optimize developability. However, in doing so, you may lose some affinity and have to revisit and re-optimize. Adding another property, such as pH-dependent binding, risks losing both affinity and developability. The optimization of each property pulls on another thread, creating a knot of interdependencies that make timelines long and outcomes uncertain.”

DAVID YOUNGER, PHD,
CO-FOUNDER & CEO OF A-ALPHA BIO

Their accelerated workflow requires massive, high-quality datasets that measure interactions between tens of thousands of antibody variants and their targets, which are then used to train and validate an AI model to predict antibody binding from protein sequences. For each new antibody-target pair, A-Alpha Bio fine-tunes its AI models using a new dataset, ensuring accurate predictions across the entire sequence space of the parental antibody.

Building and testing these expansive antibody libraries requires large amounts of synthetic DNA with explicitly defined, diverse sequences. Traditional suppliers often fall short in terms of scale and precision. Twist Bioscience's massively parallel DNA synthesis platform provides A-Alpha Bio with the foundational reagents to perform these high-throughput experiments, enabling the continued training of the company's AI-driven workflows.

A-Alpha Bio's Beginnings



A-Alpha Bio was born out of the University of Washington's Institute for Protein Design, where co-founder David Younger, PhD, was studying protein design and synthetic biology with pioneers David Baker and Eric Klavins. Younger developed a powerful wet-lab technique, AlphaSeq, to systematically measure millions of protein-protein interactions in parallel.

What began as a tool to understand the basic principles of binding soon evolved into a platform with enormous potential to transform how therapeutic antibodies are developed. Recognizing that the same technology could bridge wet-lab biology and AI, Younger and his co-founder, Randolph Lopez, PhD, spun out A-Alpha Bio to bring data-rich, predictive protein engineering to the biopharmaceutical industry.

Since its founding, A-Alpha Bio has successfully deployed its AlphaSeq and AlphaBind platforms for diverse applications across internal programs and numerous pharmaceutical partnerships. These applications include the rapid discovery and optimization of dual-specific, biparatopic binders, engineering pH-sensitive antibodies with precisely tuned affinities, and optimizing cross-reactivity across animal homologs or hundreds of diverse pathogen antigens - all notoriously difficult antibody engineering challenges.

“We can generate as much high-quality binding data in a single day as exists in the world’s largest public repositories. This scale of wet-lab data generation is what’s required to make AI truly transformative for antibody engineering – from optimization to *de novo* design.”

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Precise DNA = Precise Data = Precise AI

A critical part of A-Alpha Bio’s workflow requires the synthesis of DNA oligonucleotides that encode an antibody or target protein variants for screening. Producing synthetic DNA sequences at the scale that A-Alpha Bio requires is a challenging task, one in which errors can cause cascading damage to a project. Mistakes in oligonucleotide synthesis waste valuable space in a protein library, thereby reducing the efficiency of the measurements. The risk of such errors is compounded when researchers assemble multiple fragments to form a single antibody or target coding sequence.

Many DNA synthesis platforms struggle to keep error rates low, particularly when assembling longer sequences needed for antibody or target screening. Furthermore, DNA synthesis can be biased, over-representing some sequences and under-representing others. In turn, this biases the library, and underrepresented variants require deeper sequencing and additional replicates to generate reliable data. Paired with the challenges of precisely coding combinatorial mutations, these challenges have limited the field’s ability to produce high-quality training datasets.

DEVELOPING BIOLOGY-BACKED AI

AlphaSeq is powered by a modified yeast surface-display system, allowing A-Alpha Bio’s researchers to experimentally test entire libraries of antibodies against corresponding libraries of targets, simultaneously capturing affinity data for every combination, rather than one at a time.

“Our high-throughput approach gives us a data advantage that no database can match: The largest public repository of binding data, [BioGRID](#), contains roughly 2 million recorded protein-protein interaction affinities aggregated from decades of academic literature. In contrast, A-Alpha Bio can generate that amount of data per day, and all within a standardized system where every measurement is directly comparable.”

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By producing these massive, high-quality, and consistent datasets, AlphaSeq provides the foundational data for A-Alpha Bio’s AI model—AlphaBind—to accurately map and predict antibody-target binding landscapes. This task was previously impossible using fragmented public data alone.



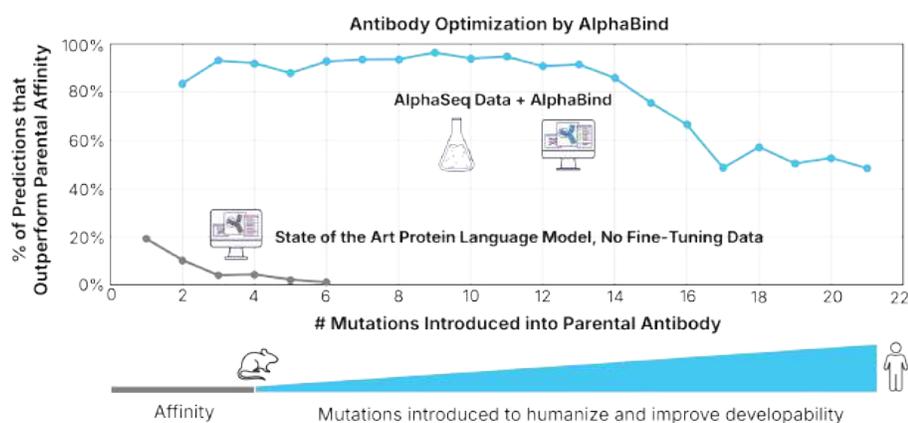


Figure 1. Antibody Optimization with AlphaBind. Powered by high-throughput AlphaSeq data, A-Alpha Bio's AlphaBind model predicts and experimentally validates variants that retain or improve binding affinity up to 20 mutations away from the parental. This enables rapid, simultaneous optimization of multiple antibody properties, all within an eight-week cycle (blue line).

Twist Bioscience offers solutions to these challenges by producing single stranded Oligo Pools (up to 300 nts), double stranded Multiplexed Gene Fragments (301- 500bp) and Gene Pools (300bp - 1.8kb). The high precision and scale has played a critical role in A-Alpha Bio's success. Twist's Oligo Pools, Multiplexed Gene Fragments and Gene Pools are synthesized bias-free and with high uniformity, so every variant defined within the pool of intended sequences is accurately represented. With the ability to synthesize 1 million unique oligonucleotides in a single run, the scale of antibody-target pairs that can be synthesized and screened is a perfect fit for A-Alpha Bio's workflow using AlphaSeq.

The length of Twist's products also reduces the number of DNA assembly steps and combinatorial uncertainty, ensuring that every sequence of the antibody and target library generates an accurate and interpretable data point. Taken together, access to Twist's high-quality Oligo Pools and Multiplexed Gene Fragments keeps costs manageable for the large number of antibody and target variants being analyzed.

Once A-Alpha Bio uses Twist's DNA to construct their antibody and target libraries, protein binding data is generated with AlphaSeq and fed directly into AlphaBind. The AI platform learns the "affinity landscape" of each parental antibody, predicting how millions of sequence variants will bind their targets, even up to 20 amino acid mutations away (**Figure 1**).

With this improved understanding of binding across sequence space, A-Alpha Bio can pick variants that maintain affinity while optimizing all other properties in parallel. The result is a closed feedback loop: Twist's synthetic DNA enables large-scale, high-quality experimentation; AlphaSeq converts those experiments into quantitative data; and AlphaBind transforms that data into predictive models that drive faster, more accurate antibody design. Through additional rounds of DNA synthesis, experimentation, training, and wet-lab validation, A-Alpha Bio continues to improve the predictive accuracy of AlphaBind.

Pushing Fast-Forward on Antibody Engineering

This integrated approach may accelerate antibody discovery and optimization timelines for increasingly complex, multi-specific antibodies, pH-dependent binders, and other biologics. By combining Twist's DNA synthesis technology with its own wet-lab and computational platforms, A-Alpha Bio is not only advancing individual therapeutic programs, but also building foundational datasets that the entire field can use.

As antibody engineering continues to evolve, A-Alpha Bio is expanding its efforts to generate structural datasets and refine predictive models for even greater accuracy in antibody optimization. The company also contributes to the broader scientific community through open-source initiatives, including the public release of early versions of the [AlphaBind model](#).

For A-Alpha Bio, synthetic DNA is a central component of their workflow, and each advancement, whether small or large, starts with high-quality sequences and the partnership with Twist Bioscience.

"We're entering a phase where antibody engineering is becoming a true data science. The more data we generate, the better our models get. As the models improve, so will the success rates. But just as importantly, it will push the field to tackle more challenging and sophisticated design challenges."

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