Alamar Biosciences, Inc.
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ALAMAR BIOSCIENCES

To high affinity and beyond for biotherapeutics

California-based Alamar Biosciences is beating antibodies at their own game, boosting affinity by targeting multiple epitopes on the same antigen using its Attobody platform.

The monoclonal antibody revolution has produced a wave of important new therapeutics, but developing effective antibodies remains elusive for many targets and indications. The discovery and development of lead molecules with the required affinity, selectivity and developability characteristics is time-consuming and inefficient, with the output often being only a few candidates that may not be optimal for the required parameters. This challenge is often insurmountable with the assumption and limitation of antibodies targeting only a single epitope.

Alamar Biosciences goes beyond the single-epitope assumption with its Attobody platform, which efficiently discovers optimized bi-paratopic nanobodies consisting of two variable domains of single heavy chain (VHH) antibodies. Central to Alamar's Attobody platform is a proprietary strategy for screening VHH pairs with a linker library. This unique approach generates an exceptionally diverse set of candidates with higher affinity, selectivity, and epitope coverage than traditional screening methods.

Screening VHH pairs creates an unbiased pool of antibodies with broader functionality, and through selection of optimal linkers even low-affinity, single-epitope binders function synergistically to become ultra-high affinity bi-paratopic binders (Fig. 1). The versatility of the platform also allows affinity to be dialed up or down to achieve exquisite specificity. This proprietary approach dramatically increases the number of leads, increases epitope coverage, and creates the potential for agonistic and antagonistic activities. This is all achieved in half the time of traditional antibody approaches and without the developability risks of affinity maturation mutagenesis.

Enter Alamar Biosciences

The company was founded in 2018 by chairman and CEO Yuling Luo, VP of Technology Yiyuan Yin, and COO Steve Chen. The company is focused on proteomics technologies for early detection of cancer and other diseases, developing immunoassays with high sensitivity and low background noise. The Attobody concept is rooted in the founders' insights that by pairing binders, affinity and specificity can be greatly enhanced. These attributes were anticipated to enable superior therapeutics, diagnostics, and proteomic tools. This hypothesis has been borne out by external clinical data demonstrating that ciltacabtagene autoleucel (cilta-cel), an approved chimeric antigen receptor (CAR)-T cell therapy using bi-paratopic nanobody as its binder, is superior to its competitors in multiple myeloma.

"Even though we were not involved with the development of cilta-cel, its approval effectively validated this therapeutics approach," said Luo.

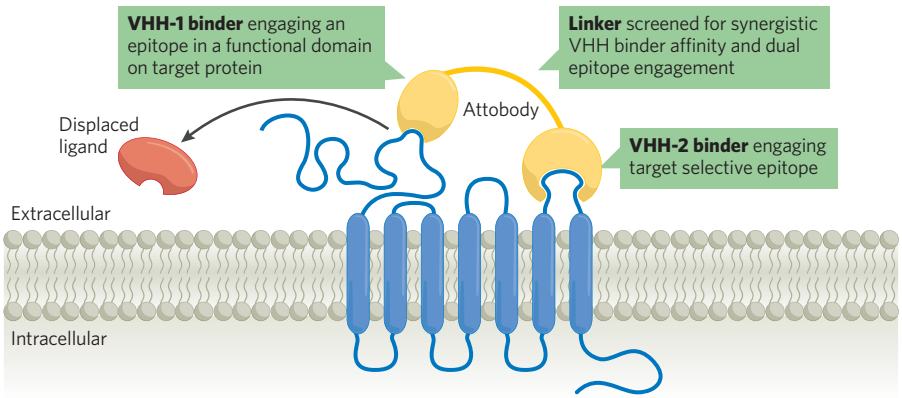

Fig. 1 | A schematic of bi-paratopic single heavy chain (VHH) binders linked to create an ultra-high affinity antibody.

"Cilta-cel's CAR used bi-paratopic nanobodies, like an Attobody, with two different VHH antibodies attached by a linker. It led to fantastic overall and complete response rates, compared with conventional scFv [single-chain variable fragment] cell therapies against the same target, BCMA [B cell maturation antigen]."

> **"Biotechs tend to have specialized expertise in their therapeutic areas. When it comes to discovery of high affinity antibodies, we want to be their partner of choice**
>
> Yuling Luo, Chairman & CEO, Alamar Biosciences

That may be just the tip of the iceberg for CAR-Ts. "We know if you use a conventional linker, as Legend Biotech did with cilta-cel, the nanobody will more likely function like a bivalent IgG antibody with minimal increase in affinity. But we use an unbiased screen of bi-paratopics and a linker library to find the optimal linker. The output is a large and diverse set of leads with affinities over a one thousand-fold range and as high as single-digit picomolar," Luo added. "As we demonstrate this to our partners, many potential use cases will become apparent."

An approach with advantages

The affinity advantage of bi-paratopics is clear. What may be less appreciated is how this approach generates many more leads and significantly expands target epitope coverage. Unlike conventional antibody screening approaches that require months sifting through low affinity binders—and yield only a few viable candidates, which still require affinity maturation—an Attobody screen generates a large and diverse set of leads that are more likely to include strong therapeutic molecules. "The greater number of high-affinity lead molecules is what makes our platform promising for otherwise intractable targets, like GPCRs, ion channels, and targets with limited epitopes and low expression levels," said Luo.

Antibodies are of increasing importance in cancer therapy and immunotherapies. Bi-paratopic nanobodies with higher affinity may improve targeting specificity and localization in tumors, ultimately driving better efficacy. Moreover, their much smaller size than IgGs enables greater tumor penetration, which will also enhance efficacy.

Alamar announced its first therapeutics partnership with SciNeuro Pharmaceuticals in February. Together, they have already generated 30–50 unique high-affinity Attobody leads for each neurology target—a strong demonstration of the company's impact on discovery programs, said Luo. "Biotechs tend to have specialized expertise in their therapeutic areas. When it comes to discovery of high affinity antibodies, we want to be their partner of choice."

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