NEWS maker

Anaphore

This protein engineering firm claims its therapies, modeled on the naturally secreted human serum protein tetranectin, could compete with antibodies.

Katherine Bowdish, Anaphore CEO and founder.

With the global economy still in the throes of the credit crunch, Anaphore, a company developing a new class of protein pharmaceuticals that it calls 'atrimers' sailed through. In May 2009, the La Jolla, California–based firm raised $38 million in a series A round from London-based Apposite Capital; GlaxoSmithKline's venture arm SR One of Conshohocken, Pennsylvania; Merck Serono Ventures, headquartered in Geneva; and Aravis Venture Associates of Zurich.

The ready flow of funds from biotech investors points at the appetite for new therapeutic formats that potentially overcome some of the limitations of antibodies. The atrimer technology was developed by Borean Pharma, a spin-off from Aarhus University in Denmark. The Danish scientists created these second-generation, adjustable scaffolds that share the exquisite specificity of antibodies without the drawbacks of size, glycosylation and structure complications that makes manufacture in mammalian tissue culture cumbersome and expensive.

Richard Ulevitch, a professor in the department of immunology of the Scripps Research Institute, initially sniffed out the potential in Borean's technology, in 2007, in collusion with Andrew Schwab, founder and managing partner at 5AM Ventures in Menlo Park, California, for whom Ulevitch served as an advisor. The company was seeded initially by 5AM Ventures, and subsequently by Versant Ventures, both of Menlo Park, California, for a total seed round of $8 million.

In preparation for acquiring all of Borean's assets, Ulevitch and Schwab asked Kathy Bowdish, now the biotech's CEO, to help with the due diligence. Bowdish, then president of Alexion Pharmaceuticals, in Cheshire, Connecticut, was well placed to see how Borean's work might compete in the second-generation scaffold market. She found herself captivated by the technology. When she expressed interest in coming on board as CEO, Borean's assets were moved to La Jolla in 2008 and Anaphore was born. Founders Ulevitch, Schwab and Bowdish were joined by Phyllis Whiteley, then entrepreneur-in-residence at 5AM. More recently, Russell Greig, formerly president of GSK's SR One corporate venture group, joined the company as executive chairman.

Anaphore's atrimers are modeled on a human protein of trivalent structure—tetranectin—which is naturally secreted in plasma although its precise function remains unclear. Each of tetranectin's three binding domains contains five amino-acid loops that can be tweaked to bind virtually any target of interest, and Anaphore has systematically changed them, to produce a library of more than 10^{11} versions of atrimers.

Atrimers' three sites engage and 'lock on' to their target with increased avidity, and in theory they could bind any target protein. But atrimers are particularly suited to interact with trimeric targets, a class that includes several proteins of therapeutic interest in the human immune system: tumor necrosis factor (TNF), the receptor for nuclear factor κB ligand (RANKL) and the TNF-related apoptosis-inducing ligand (TRAIL). But Anaphore's first lead compound, ATX3105, targets the heterodimeric interleukin-23 receptor complex (IL-23R). IL-23R activation normally leads to inflammation, but Bowdish says ATX3105, by blocking soluble IL-23 from docking with its receptor and inducing its subsequent dimerization, can dampen this harmful response in mice.

With molecular weights of 60–70 kDa, atrimers are much smaller than antibodies and achieve greater target tissue penetration. Because they are encoded by one gene and are not glycosylated, they can also be mass produced in *Escherichia coli*. Bowdish says the company doesn't expect any adverse immunological reactions because tetranectin should not be recognized by the human immune system, and tests in mice suggest that the animals don't mount a response against injected tetranectin.

Over 50 companies are currently exploring alternative protein scaffolds, including anticalins (derived from the lipcalin family, featuring an eight-stranded β-barrel structure), adnectins (based on an extracellular domain of fibronectin III) and affibodies (adapted from a three-helix bundle domain of protein A from *Staphylococcus aureus*).

Bowdish notes that since acquiring the atrimer platform from Borean, the company's team of 12 scientists has substantially re-engineered and fine-tuned the process, creating a number of new in-house libraries. They use directed evolution to refine initial lead atrimers, using an iterative process of mutation and binding assays. Bowdish says that the five loops offer a large footprint for tinkering and refinement. She adds that the atrimers have naturally occurring lysine-rich unstructured regions at each tip that can be used to conjugate payloads, an option which the company is also exploring.

Arne Skerra, professor and chair of the department of biological chemistry at Technische Universität, Munich, and an expert on emerging protein scaffold technologies, including the anticalins, thinks that the trimeric quaternary structure of the atrimers is an interesting approach that will probably be advantageous when applied to trimeric receptors. He also notes that the avidity of the trimer should be a plus. He is cautious, however, about whether they will be as good as antibodies against nontrimeric target proteins, citing symmetry-related restrictions to the shape space that are imposed by trimers. Anaphore needs to publish some data, Skerra says, before the field can judge its technology.

In the meantime, Anaphore is focusing on autoimmune diseases and secondarily on cancer. Bowdish says that the company aims to bring one or two products to clinical trials unaided, then will collaborate with others outside of the area of immunology and oncology. She predicts that investigational new drug applications from the FDA for a clinical trial could be submitted as early as mid-2012 for an immunological therapy, and late 2012 for an oncological one.

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