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Ambagon: creating molecular glues for disordered proteins

BY DANIELLE GOLOVIN, STAFF WRITER

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Ambagon has a new approach to a challenging target class: intrinsically disordered proteins. The San Carlos, Calif.-based start-up is forcing disordered proteins to acquire a druggable interface using molecular glues to stabilize their interaction with a signaling hub.

Fresh off his CEO experience at Tizona Therapeutics Inc., Scott Clarke joined Ambagon Therapeutics Inc. as CEO in February 2021.

At Tizona, Clarke had closed a deal with Gilead Sciences Inc. (NASDAQ:GILD) in July 2020 that made the big biotech owner of nearly half of Tizona for $300 million up front. The deal came with an exclusive option to buy the rest of the company after a clinical readout.

Then, in August 2020, Clarke spun out a company from Tizona called Trishula Therapeutics to develop anti-CD39 mAb TTX-030, which is partnered with AbbVie Inc. (NYSE:ABBV), for advanced cancers.

With a liquidity event behind him, Clarke told BioCentury he was on the hunt for an early-stage platform company to lead with "a uniquely differentiated platform with strong science, great people and great investors." That landed him Ambagon.

Ambagon's roots originate in the labs of co-founders Christian Ottmann and Luc Brunsveld at Eindhoven University of Technology and Michelle Arkin at University of California San Francisco. The scientists collaborate on small molecule modulation of protein-protein interactions, with a focus on 14-3-3 adaptor proteins, signaling hubs that govern critical cell processes. Ottmann is CTO of Ambagon.

The seven mammalian 14-3-3 proteins form complexes with specific phosphorylated serine- or threonine-containing motifs in disordered domains of their partner proteins, which Ambagon calls "clients." The interaction of 14-3-3 proteins with their estimated 3,000 endogenous clients affects the functions of the clients to regulate cell processes such as gene expression, signal transduction and protein trafficking.

"With the traditional molecular glue approach, you have protein A and protein B and you're trying to figure out how to stick them together when there's not necessarily a reason for

them to go together. We're starting with a native interaction between 14-3-3 and a client that does go together," said Clarke.

Once a 14-3-3 protein is in a complex with a client, it confers order to the disordered protein, creating a structure that a small molecule can bind. The small molecule then stabilizes the interaction and amplifies the outcome of client binding — for example, degradation of a client protein that drives disease.

Clarke said the company is focused on validating reported 14-3-3 clients rather than identifying new ones. "Three thousand clients is 15% of the genome, and that's plenty of substrate to work with. We validate the literature reports and the second step is to validate the consequences of binding."

Ambagon's three-part platform includes an encyclopedia of 14-3-3:client structures using x-ray crystallography; a 14-3-3 chemotype library to find compounds that stabilize 14-3-3:client complexes; and a toolbox of structure, potency, selectivity and cell activity assays to inform small molecule drug design based on the various chemotypes from natural products to molecular fragments.

The founders showed in a 2013 PNAS study that the fungal compound fusicoccin stabilized the interaction between 14-3-3 and ER, which reduced downstream gene expression and inhibited breast cancer cell proliferation. In 2020, they reported in Journal of Medicinal Chemistry identification of fragments to stabilize the interaction between 14-3-3 and partner proteins p53 and WWTR1.

The company has five programs in discovery that aim to attenuate a signal to treat cancer. The targets are undisclosed, but include an adaptor/scaffold protein, two transcription factors, a phosphatase and a regulatory protein. Clarke said three of the targets currently have no competition, since they are generally considered undruggable due to their disordered nature.

For some clients, binding 14-3-3 results in enhanced signaling rather than degradation. For example, binding of 14-3-3 proteins to the disordered regulatory domain of CFTR enhances the chloride channel's trafficking to the plasma membrane. Clarke said Ambagon's next round of targets may include an activator.

COMPANY PROFILE
AMBAGON THERAPEUTICS INC.
San Carlos, California

Technology: Molecular glue stabilizers of 14-3-3:target complexes

Origin of technology: Michelle Arkin's lab at University of California San Francisco; Christian Ottmann and Luc Brunsveld's labs at Eindhoven University of Technology

Disease focus: Cancer and other undisclosed indications

Clinical status: Discovery

Founded: 2020 by Christian Ottmann, Luc Brunsveld and Michelle Arkin

Academic collaborators: University of California San Francisco, Eindhoven University of Technology, Netherlands Cancer Institute

Corporate partners: N/A

Number of employees: 18

Funds raised: $103 million

Investors: Nextech Invest, RA Capital Management, MRL Ventures Fund, Mission BioCapital, INKEF Capital, Droia Ventures, AbbVie Biotech Ventures, Surveyor Capital

CEO: Scott Clarke

Patents: None issued

The company raised $18 million in seed funding in July 2020 and launched with $85 million in series A funds Jan. 6. Clarke said the company will use the series A to continue to invest in the platform, advance the five projects and add new projects outside of cancer.

Neurology is "a natural place to explore," Clarke said, because molecular glues are small molecules, which means they can get into the brain more easily than classic protein degraders, which are larger molecules that join separate ligands for each protein with a linker.

Ambagon expects to announce at least one development candidate next year, and enter the clinic in 2024.

Nextech Invest led the series A financing, with participation from seed investors RA Capital Management, Droia Ventures, INKEF Capital, AbbVie Ventures, MRL Ventures Fund and Mission BioCapital, and new investor Surveyor Capital.

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