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A-Alpha advances its rational molecular glue discovery strategy with BMS

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A deal between A-Alpha and BMS is part of the growing push to take molecular glue discovery from serendipitous to rational, and to take protein degradation beyond the usual E3 ligases.

On Tuesday, A-Alpha Bio Inc. announced a collaboration with Bristol Myers Squibb Co. (NYSE:BMY) to discover molecular glue degraders for an undisclosed number of cancer targets. The deal — the biotech's second for targeted degradation — includes undisclosed upfront and near-term success payments, development milestones and royalties on product sales, according to A-Alpha co-founder and CEO David Younger.

The first molecular glue therapy, thalidomide, was identified based on its phenotypic effects, and only later shown to act by bringing an E3 ubiquitin ligase and target together to trigger the latter's proteasomal degradation. Companies aiming to find new compounds that "glue" a target and an E3 ligase together, without a heterobifunctional "TAC" design, often use high-throughput phenotypic screening as a starting point.

The protein degradation space has also been dominated by a few well-trodden E3 ligases — primarily the thalidomide target cereblon — though several degradation companies have indicated they are searching for new options among the over 600 E3 ligases in the human genome, particularly ones overexpressed in target cells.

A-Alpha will use its yeast mating-based system to screen interactions between a wide array of E3 ligases and targets, and BMS will use the most attractive ligase/target pairs as a starting point for rationally designed molecular glue therapies.

A-Alpha's protein-protein interaction platform, dubbed AlphaSeq, works by knocking out the cell surface proteins that mediate mating between MATa and MATα yeast strains, and replacing them with constructs displaying proteins of interest. If a target displayed on a MATa cell interacts with a separate target displayed on a MATα cell, the cells will recover the ability to fuse.

In the context of the partnership, one cell type will express a library of about 40 human E3 ubiquitin ligases, and the other will express target candidates nominated by BMS. Labeling the cells with DNA barcodes enables the company to screen

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thousands of interactions in a single step, with the aim of finding weak ones that could be pharmacologically stabilized.

"What we're detecting is a key that doesn't quite fit into a lock," Younger told BioCentury. "Those are the interactions that could be 'gluable' by small molecules."

To help guide small molecule development, A-Alpha then generates a detailed picture of what residues are important for the E3 ligase/target interaction by making many mutant versions of each protein, then re-testing the interactions to see if any mutational pairs have higher affinity for each other.

"Once we find pairs that fit better, those give a partner a huge amount of information about how they would design a small molecule to essentially replicate the mutations," said Younger.

He said identifying the E3 ligase/target pairs takes about six months, and the mutational approach, which A-Alpha accelerates via working with Twist Bioscience Corp. (NASDAQ:TWST), can take six months or more depending on how many pairs were identified.

Founded in 2017 as a spinout from the University of Washington's Institute for Protein Design, A-Alpha raised a $20 million series A round in September. Its platform is amenable to applications beyond E3 ligase-target interactions, such as discovering antibody-antigen pairs, and the company is developing an internal pipeline of antibody therapies.

In December, the biotech partnered with Kymera Therapeutics Inc. (NASDAQ:KYMR)

to discover and characterize druggable interactions between undisclosed targets and E3 ubiquitin ligases. Kymera has the option to license up to two targets for development of molecular glues; A-Alpha Bio received undisclosed upfront and research payments, and is eligible for downstream milestones.

Tuesday's deal is also the latest in a series of targeted degradation partnerships for BMS; in May, the pharma extended its 2018 molecular glue partnership with Evotec AG (Xetra:EVT), and announced a new partnership with Amphista Therapeutics Ltd., which is developing protein degraders using an approach that does not depend on E3 ubiquitin ligases.

BMS is building out its targeted degrader pipeline, gained via its 2019 acquisition of thalidomide owner Celgene Corp., along two axes: next-generation cereblon modulators and engineered targeted degraders.

Other companies focused on rational molecular glue discovery include Triana Biomedicines Inc., which launched in April with $110 million in total funding, including a series A round co-led by Lightspeed Venture Partners and seed investors RA Capital Management and Atlas Venture.

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