DRUG DISCOVERY

Molecular glue firms get investment, strike partnerships

Degron is the latest to attract funding for new method of degrading proteins

by ***Gina Vitale***

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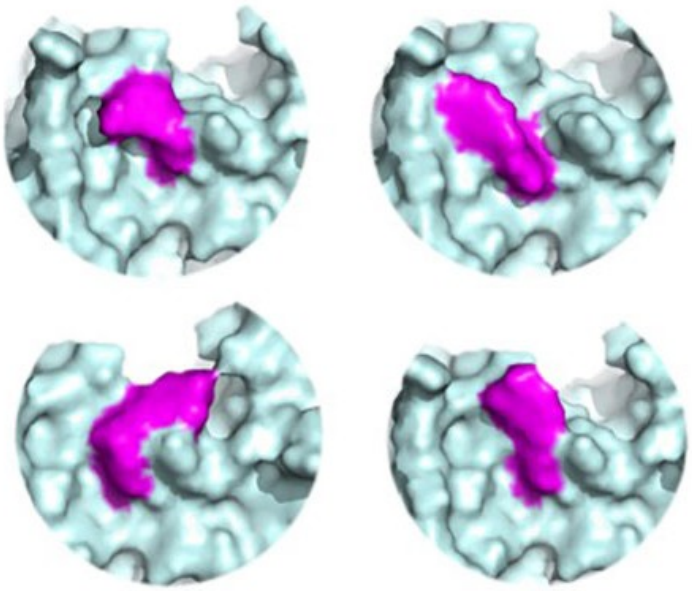

Credit: Degron Therapeutics

The altered surfaces of the E3 ligase component Cereblon (aqua) after binding to different molecular glues (purple). These altered surfaces could recruit different protein targets.

Degron Therapeutics has garnered $22 million in series A financing to develop a class of targeted protein degraders known as molecular glues. The biotech startup joins a growing group of firms to receive investment as the molecular glue field heats up.

Founded in April 2021 and based at JLABS @ Shanghai, an incubator of Johnson & Johnson, Degron spun out of the lab of cofounder Yong Cang, a professor at ShanghaiTech University.

Many drugs work by inhibiting bad-behaving proteins implicated in a disease. Targeted protein degradation takes advantage of the body's own protein-disposal machinery to mark proteins for termination. An early class of protein degraders are proteolysis targeting chimeras (PROTACs), which are small molecules with two ends; one binds to the protein of interest, and the other binds to an E3 ligase, an enzyme that tags the protein for cellular disposal.

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Molecular glues simplify the process. The small molecule binds to either an E3 ligase or the target protein, altering the surface of one so that the other can bind to it. They serve as direct molecular adhesives between the ligase and the protein, and they're often smaller than PROTACs.

"Because they are smaller and typically more drug-like, they're typically easier to formulate," says Nico Thomä, a structural biologist at the Friedrich Miescher Institute for Biomedical Research who is also on the advisory board of the molecular glue company Monte Rosa Therapeutics. "The disadvantage is a big one—they're typically also largely found serendipitously."

Credit: Lily Zou

Lily Zou

Indeed, the main classes of molecular glue degraders were discovered more or less by accident, including thalidomide and related immunomodulatory drugs (iMiDs). The scaffolds that most companies use for their molecular glues are based on iMiDs, says Degron cofounder and CEO Lily Zou. That's not the case for Degron's scaffolds, which Zou says are structurally distinct from the iMiDs.

Degron employs three types of screening to find protein targets and molecular glue candidates, another approach that sets the company apart, Zou says. Several firms are also touting their screening programs as investment flows into the industry. Proxygen recently teamed up with Merck KGaA in a deal worth up to $554 million to identify and develop molecular glue degraders. Triana Biomedicines launched with $110 million in April to develop molecular glues, and Bristol Myers Squibb extended a glue degrader partnership with Evotec in a deal worth up to $5 billion.

Degron's platform has yielded a library of more than 6,000 compounds, almost all of which are able to bind to cereblon, a component of an E3 ligase. The company has identified a target it calls Protein A, which Zou says plays a role in many types of cancers as well as inflammatory diseases

and is susceptible to degradation from one of its degraders. Protein A was previously considered undruggable because it does not have a pocket that can be activated or inhibited by another entity; the molecular glue is effective because it does not need a pocket to bind to.

So far, Degron has been focused on cancer, although Zou says it is also interested in tackling neurological or immunological diseases. She says the company will use the series A financing to advance its lead programs, grow its compound library, and strengthen its artificial intelligence tools.

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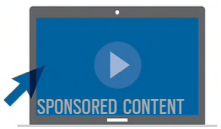

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