DRUG DISCOVERY

Molecular glues are beginning to stick

Researchers have already hijacked the body's protein-disposal system with bifunctional protein degraders, or PROTACs. Small-molecule glues can do more with less—but can we find them?

by ***Gina Vitale***

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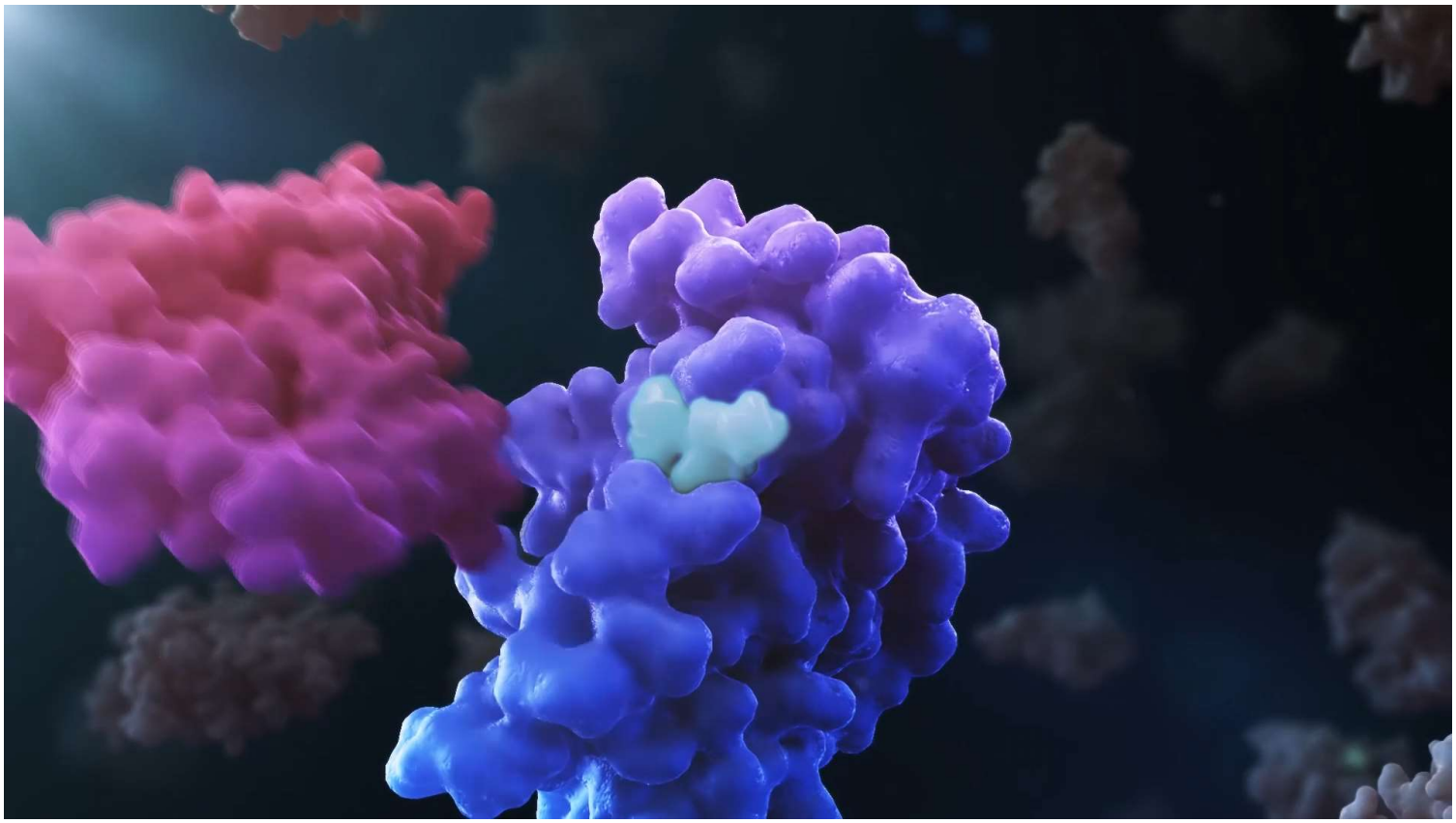

Credit: Novartis/Mark Mazaitis

In the late 1950s and very early '60s, doctors prescribed a drug as a sedative to treat morning sickness in pregnant people. Marketed as safe, it was sold under numerous names in 46 countries; it's now known most commonly as thalidomide. In 1961, it became clear that a sudden increase in infants born with severe physical abnormalities was linked to thalidomide exposure in utero. Thousands of children were born with malformed limbs and other impairments as a result of the drug.

IN BRIEF

One way to treat disease is to tether proteins responsible for harm to an enzyme that causes them to be destroyed by the cell's own machinery. Researchers have designed large, two-ended molecules for this purpose but their size can pose challenges, and the proteins they target need to have a binding

MOST POPULAR IN PHARMACEUTICALS

Most countries withdrew thalidomide from their markets in 1961. Still, it remained available in some places. In 1964, a doctor prescribed it as a sedative to a person with leprosy who had an inflammatory complication involving skin eruptions. Thalidomide cleared the eruptions within days.

The ability of thalidomide to treat the leprosy complication led researchers to test it on several other inflammatory and skin conditions. In 1994, researchers **reported** that it could interfere with the growth of new blood vessels, a finding that sparked new interest in how it might be used against tumors. Thalidomide was found to be effective in treating multiple myeloma, a cancer of the plasma cells, in the late '90s.

Researchers didn't know it yet, but the mechanism responsible for the congenital conditions, at least in part, was likely the same one that fights cancer. In fact, it would be years before scientists discovered that thalidomide was a molecular glue.

spot. One solution could be molecular glues: small molecules that bring a target protein and enzyme together by sticking to the enzyme and changing the shape of its surface. Glues don't require a druggable pocket in the proteins, meaning more proteins can potentially be targeted. Several of these elusive molecules have been found, but often by chance. Now scientists are racing to find and design more. Ultimately, companies hope to develop ways to find molecular glues for any protein of interest.

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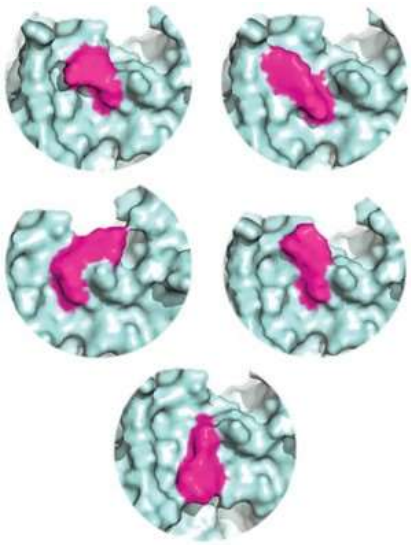
The term *molecular glue* refers to a small molecule that sticks two proteins together. The most common type links a target protein—typically one that causes disease—to an enzyme that causes the target to be broken down by the cell's protein-degradation machinery.

In the body, the glue molecule first binds to a type of enzyme called an E3 ubiquitin ligase, altering the shape of the ligase's surface so it can then bind to the target protein. Once all three are bound together, the E3 ligase adds a chain of ubiquitin molecules to the protein; the chain acts as a signal to the cell's protein-degradation machinery to chop up the target protein. The novelty of molecular glues is that they co-opt a natural cellular process and force an interaction between E3 ligases and proteins that might not normally bind to them. The result is the degradation of disease-causing proteins on demand.



Credit: Degron Therapeutics

Molecular glues (pink) are bound to the E3 ligase component cereblon (turquoise), altering its surface in distinct ways to recruit different protein targets.

In people given thalidomide for morning sickness, the drug may have acted in several ways, including causing the destruction of proteins needed for normal fetal development. It also seems able to mark for destruction proteins that play a key role in multiple myeloma, hence its success in treating that disease.

Researchers first identified molecular glues in the early 1990s, says Stuart Schreiber, a chemical biologist at Harvard University and a trailblazer in protein degradation. Schreiber also cofounded the Broad Institute of MIT and Harvard and several start-ups, including molecular-glue firm Magnet Biomedicine.

Schreiber wanted to determine how several natural product drugs or drug candidates were acting as immunosuppressants, which can be used to prevent organ transplant rejection, among other things. Jun Liu, then a postdoc in Schreiber's lab, discovered that the natural products were causing two proteins to bind to each other, thereby interrupting an immune-signaling pathway.

“These three natural products, very complicated structures, had these amazing mechanisms of action,” says Schreiber, who coined the term *molecular glue*, first in a group meeting and then in a 1992 *Cell* paper (DOI: **10.1016/0092-8674(92)90158-9**), to describe this phenomenon. “I thought, Well, we chemists probably won’t be able to do that”—make molecular glues—“it’s too complicated . . . maybe it’s really a billion years of natural selection that’s required to achieve this.”

This, Schreiber now says, is where he “didn’t see the future.” Because while it isn’t easy to discover molecular glues, it can be done—and researchers and companies have since risen to the challenge. In the past year, a wave of firms has launched or raised significant investment to develop new molecular glues. All are striving to design or discover glues that target disease-causing proteins previously considered undruggable, meaning they aren’t susceptible to existing approaches for stopping them. The ultimate goal—being able to find a molecular glue for any protein target—may still be far off, but systematic approaches for finding glues are yielding new clinical candidates.

THE RISE OF GLUES

Schreiber says that once he appreciated the huge challenge of designing molecular glues, he and his colleague Gerald Crabtree devised a work-around.

“We said, ‘Why don’t we find a binder to one protein and a binder to another protein, and just chemically stitch them together?’ ” he says.

Essentially, they took the concept of a molecular glue—a single molecule that can join two proteins—and separated its functions into opposite ends of a larger molecule. Each end, connected by a linker, could be customized to recruit its own protein. When one of the proteins being recruited is an E3 ligase that destroys the other protein—akin to what molecular glue degraders do—the bifunctional compound is known as a proteolysis-targeting chimera, or **PROTAC**.

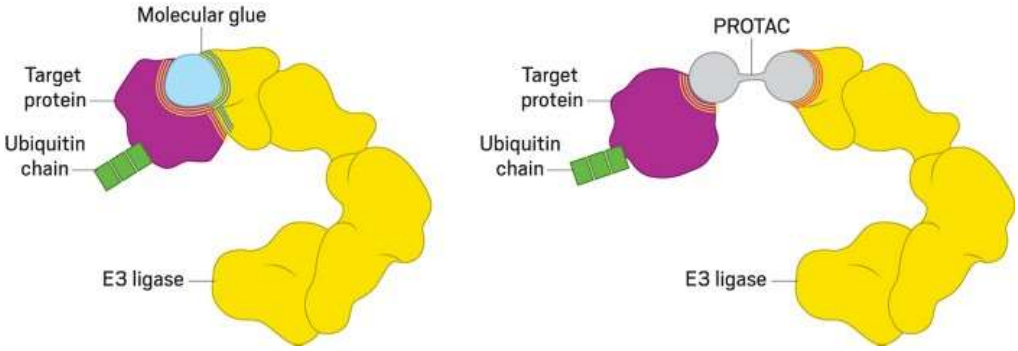
Such targeted protein destruction offered a significant advantage over inhibition, which was the more common protein-targeting strategy. An inhibitor molecule binds to a protein, preventing the protein from doing its intended action. But the inhibitor has to stay bound to that individual protein to stop its action, which requires higher doses than PROTACs and could lead to higher toxicities. A PROTAC, on the other hand, can be used again and again. Once its target protein is destroyed, it can bind to another and repeat the process.

In recent years, the development of PROTACs as pharmaceuticals has boomed. **Arvinas**, a company founded by Yale University biochemist Craig Crews, has two candidates in Phase 2 trials, one to treat prostate cancer and one in partnership with Pfizer to treat breast cancer. Several others, including **Nurix Therapeutics**, **Kymera** Therapeutics, and **Foghorn Therapeutics**, have candidates in Phase 1, mostly for cancers.

GLUES VERSUS PROTACS

Molecular glues bind to and alter the surface of an E3 ligase, changing the shape enough so that the target protein can attach. They are smaller than proteolysis-targeting chimeras (PROTACs), which have one distinct end that binds to the ligase and another that binds to the target protein. Once the E3 ligase and

protein are bound together, the E3 ligase causes the target to be tagged with a chain of ubiquitin proteins. The ubiquitin chain indicates to the body that the protein is ready for disposal.



Credit: Adapted from C4 Therapeutics

Although PROTACs are promising, their multipart nature means they are relatively big molecules, which can make bioavailability a challenge. PROTACs also require the target protein to have a structural pocket for one end to bind to, and not all proteins have one. Molecular glues have the potential to overcome these obstacles.

“Molecular-glue degraders have a major advantage in that they can exploit the collective binding pocket that’s formed from bringing two protein interfaces together,” says Daniel Nomura, a chemical biology professor at the University of California, Berkeley, who cofounded **Frontier Medicines** and founded **Vicinitas Therapeutics**, which target typically undruggable proteins through degradation and stabilization, respectively.

“You may not have enough surface to bind to on either protein alone,” Nomura says. “But when you now bring those two proteins together via a small molecule, you create enough of a pocket there to engage in enough interactions to glue those proteins together.” This strategy likely allows a broader swath of previously undruggable proteins to be targeted, he notes.

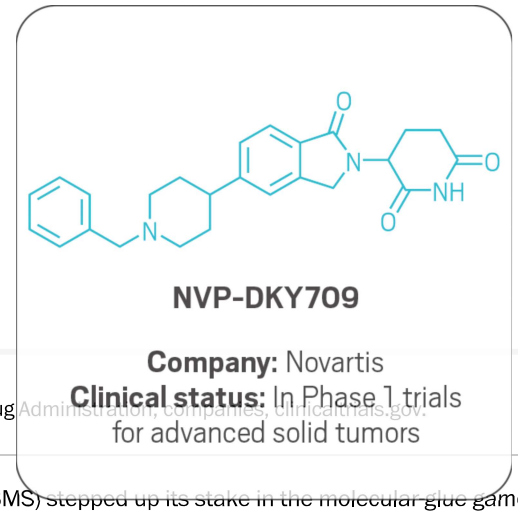
No one particular moment set off this year’s “explosive phase” of interest in molecular glues, Schreiber says. Yes, new tools have moved the field forward, but this is a renaissance 30 years in the making. “It was not a story of anyone forgetting about the potential, or not trying hard,” he says. “It was a continuous activity that was like brick by brick.”

GETTING UNSTUCK

Finding an all-in-one protein connector is a huge challenge, and until recently, many compounds’ molecular-glue properties—such as those of thalidomide—were found by chance. But tweaking known molecular glues to find new and more effective versions has been a fruitful strategy.

GLUES IN THE CLINIC

A selection of molecular glues approved by the US Food and Drug Administration or undergoing clinical trials.



Source: US Food and Drug Administration, companies, clinicaltrials.gov

Bristol Myers Squibb (BMS) stepped up its stake in the molecular-glue game in 2019 when it acquired Celgene, which had marketed thalidomide since the late '90s. The US Food and Drug Administration approved it in 1998 for a complication of leprosy and in 2006 for multiple myeloma.

Celgene also developed more potent analogs of the drug. In 2006, the FDA approved one of these, lenalidomide, to treat multiple myeloma. The agency approved a third, even more potent analog, pomalidomide, as yet another multiple myeloma treatment, in 2013. Building on this expertise, BMS has several new glues in Phase 1 and 2 trials for conditions including multiple myeloma, lymphoma, and acute myeloid leukemia.

BMS's collection of new glue candidates provides something of a proof of concept for intentional glue discovery. It shows it is possible to systematically find glue candidates for clinical development.

Most companies working on glue discovery are trying to find the molecules by mixing and matching traditional drug discovery approaches. **Degron Therapeutics**, for instance, uses three distinct screening methods, CEO Lily Zou says. The first, called a phenotypic screen, pits drug candidates against a target—in Degron's case, cancer cell lines. If a candidate is effective at killing the cancer in an E3-ligase-dependent manner, the researchers identify what protein was degraded and confirm that the drug acted as a molecular glue.

This type of screen "is similar to finding a needle in a haystack," Cristina Mayor-Ruiz, an expert on targeted protein degradation at the Institute for Research in Biomedicine Barcelona, says in an email. "You just need to set up a cellular assay that allows you to find it."

In its second method, Degron uses mass spectrometry to identify how protein levels change when the proteins are treated with candidate glues. In this type of screen, a glue is introduced to proteins in cells containing an E3 ligase component called cereblon (the same one that thalidomide targets) and in cells without it. If protein levels decrease only in the cells containing the ligase, that confirms the proteins are degraded through a molecular-glue mechanism. Of the proteins that are degraded with a glue, Degron focuses on targeting ones that play a key role in disease.

The third method relies on artificial intelligence to predict what protein targets may be susceptible to degradation by a glue. Degron researchers then look for a compound to serve as a glue for that target.

> "The truth is, you can only design when there's already something known.
>
> — ***Markus Warmuth**, CEO of Monte Rosa*

Other glue firms cite AI as being a key part of their discovery process. **Triana Biomedicines** uses a deep-learning algorithm to choose E3 ligases that will complement the proteins the firm aims to target, on the basis of protein surface features. **Monte Rosa Therapeutics** uses an AI-powered deep neural net to identify surface features that serve as recognition signals for an E3 ligase on potential target proteins.

Although companies have a host of methods for discovering molecular glues, unlike PROTACs, glues so far can't be designed and built from scratch. Researchers design PROTACs by taking two disparate ligands that each serve a purpose and chemically connecting them via a linker. A molecular glue, in contrast, is one tiny molecule that binds to both proteins, and determining an atomic configuration that will do this is much more difficult. Some companies say they are designing, rather than finding, glues. But it's often a matter of how those terms are defined.

For example, Monte Rosa's CEO, Markus Warmuth, considers the company's work to fall under design. But he notes that no molecular glue can be made entirely from scratch.

"The truth is, you can only design when there's already something known," he says. "For me, it's sort of taking a core that you know, and with the input of structural information, expand the chemical space in a meaningful way." He considers this to be different from classic drug discovery, which is "making millions of molecules and see what sticks."

Shanique Borteley Alabi, a molecular-glue expert who was formerly at Monte Rosa, agrees there isn't a hard line that delineates discovery from design of molecular glues. "If you have some type of hypothesis, or you're able to not just go fishing but use some type of structural insights to give yourself a sense of what can bind—in the world of glues, I will allow for that to be called rational design," she says.

Whether or not companies can truly design molecular glues, they are being given a lot of money to try. With $22 million in series A funding raised in June, Degron is the latest in a surge of glue companies to launch or win investment. Triana emerged in April with $110 million; funders included Pfizer's venture capital arm. Monte Rosa went public in June 2021, claiming the ticker symbol "GLUE," with a $222 million initial public offering.

Big Pharma companies are in the game as well. BMS **paid** the contract research firm Evotec $200 million up front in May to extend a 2018 glue collaboration for 8 more years, and in June Merck KGaA struck a partnership with the Vienna-based glue company Proxygen worth up to $554 million. Some early-stage glue companies say they have cancer and inflammation in their sights as disease targets, but most won't get more specific than that.

Several molecular glues have reached clinical trials. Novartis has a candidate, NVP-DKY709, in Phase 1 for advanced solid tumors. Bayer has a molecular-glue candidate (BAY 2666605), codeveloped with the Broad Institute, in Phase 1 for metastatic melanoma and other advanced solid tumors. **C4 Therapeutics**, spun out of Jay Bradner's research at Dana-Farber Cancer Institute, has two candidates in Phase 1 trials—one molecular glue and one PROTAC. The glue, CFT7455, is in trials for treating multiple myeloma and lymphoma, and the PROTAC, CFT8634, is being tested for synovial sarcoma and certain solid tumors.

"We didn't really set out to be a bifunctional degrader company or a monofunctional," says Stew Fisher, C4's chief scientific officer, referring to PROTACs and glues. Rather, the firm made the strategic decision to focus on cereblon, the well-studied E3 ligase component, and develop degraders, regardless of type, that are best suited to target proteins of interest.

> **"We're not there, where I can say, 'This is the protein; I'm going to glue it.'**
>
> — ***Shanique Borteley Alabi**, molecular-glue expert*

Despite the growing buzz, molecular glues haven't surpassed PROTACs in clinical interest. Over a dozen PROTACs are in clinical development—some as far as Phase 2 trials—and there are no signs that their development is slowing.

"PROTACs are certainly modular in their design. And I think they'll stick around for a long time," says Nomura, the Berkeley scientist and entrepreneur. "But because of the more drug-like properties of these monovalent molecular-glue degraders, if we are able to more systematically discover these things, I think that will take a strong foothold in the drug discovery space."

WHAT'S NEXT FOR GLUES?

Most molecular glues are designed to stick a target protein to a ligase that triggers degradation, but glues could in principle stick any two proteins together. Some companies don't want to only destroy targets, so they are exploring proteins other than E3 ligases.

Generian Pharmaceuticals, for instance, **recently teamed up** with a subsidiary of Astellas Pharma to look beyond degradation. The companies are pursuing small molecules not only to degrade protein targets but also to activate and stabilize them. Generian CEO Hank Safferstein says the company has done work on stabilizing proteins that decline with age, for instance.

"There are a lot of protein complexes that you want to ideally glue together where the end result is not degradation," Nomura says. "Selectively gluing together specific protein complexes over others that manipulate transcription, for example . . . that's a much more challenging problem. And I think that's where the field is going."

As scientists and companies continue to hone their discovery and design methods, many contenders in the glue arena have their eye on the same lofty goal: an on-demand method for finding molecular glues for any protein target.

With that capability, researchers could develop small-molecule drugs for any disease-causing proteins that can be glued. But it's no simple task. Even with advances in technology and discovery approaches, glues are challenging to find, and they can't be designed de novo like PROTACs. Finding a method to readily produce a glue for any disease target will be no small feat.

"We're not there, where I can say, 'This is the protein; I'm going to glue it,' " Alabi says. "I think that it's not a 5-year thing and maybe not a 10-year thing. I think we have a lot more to understand . . . but I think we're working well in that direction as a field."

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