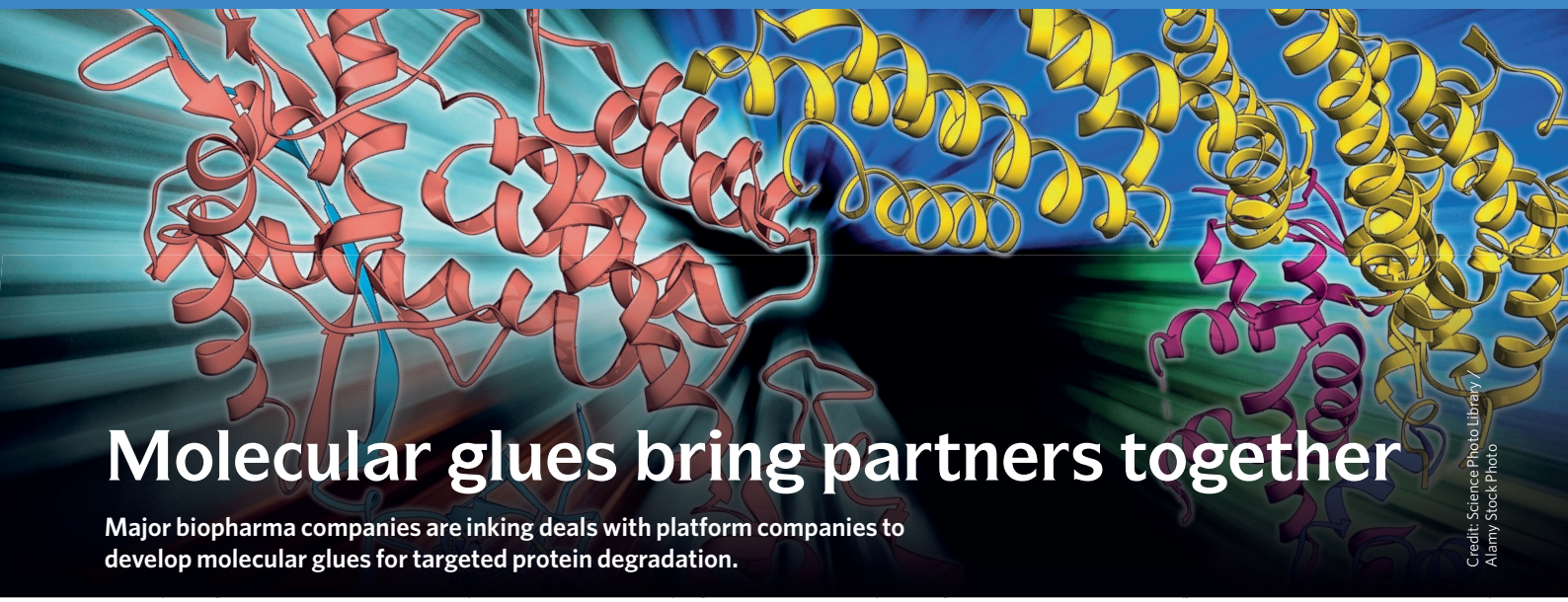

Molecular glues bring partners together

Major biopharma companies are inking deals with platform companies to develop molecular glues for targeted protein degradation.

Biopharma Dealmakers

Since the first bifunctional protein degrader entered clinical development in 2019, there has been an explosion of interest in the potential of this drug class to tackle historically challenging targets by promoting their degradation via the ubiquitin–proteasome system. Around 20 targeted protein degraders (TPDs) are now in clinical trials, and companies working on TPDs have raised more than $2 billion in venture financing as well as signing multiple high-value deals (*Biopharma Dealmakers* B38–B41; 2022).

Many of the first generation of TPDs are of a type known as proteolysis-targeting chimeras (PROTACs), which are rationally designed bifunctional molecules, in which one component that binds to the desired target protein is linked to a second component that binds to a ubiquitin E3 ligase. The TPD acts by bringing the target into proximity with the E3 ligase, leading to ubiquitination of the target and its degradation by the proteasome. The modular nature of PROTACs means they can be designed by joining a ligand for the desired target and a ligand for an E3 ligase with a suitable linker. However, they are larger than typical small-molecule drugs as a result, which can make it challenging to develop PROTAC drug candidates that are orally bioavailable.

Another class of TPDs known as molecular glues are based on the elucidation of the mode of action of anticancer drugs such as lenalidomide, which modulate the surface of the E3 ligase cereblon such that it binds to particular target proteins known as neosubstrates, resulting in their degradation. These monovalent compounds are smaller than PROTACs and are orally bioavailable. However, the complex molecular basis of their activity makes it difficult to identify molecular glues for a novel combination of a target protein and an E3 ligase.

Nevertheless, several small companies, including Proxygen, Biotheryx and SyntheX, have developed platforms that aim to address the challenge of identifying molecular glues with desired novel activities. Details of exactly how these platforms enable molecular glue discovery are sparse, but they have attracted companies including Merck and Co., Bristol Myers Squibb and Incyte to sign deals potentially worth hundreds of millions of dollars in recent months, as summarized in the deal snapshots below.

Proxygen signs licensing deal with Merck & Co. to develop molecular glue degraders

Deal announced: 5 April 2023

Potential deal value: $2,550 million

Deal overview

- Proxygen, a spin-out company from the Research Center for Molecular Medicine of the Austrian Academy of Sciences in Vienna, founded in 2020, has entered a research collaboration and license agreement with Merck & Co. to identify and develop molecular glue degraders against multiple therapeutic targets.
- Proxygen has developed E3-ligase-agnostic screening strategies to identify molecular glues that trigger therapeutic protein degradation, involving comparison of the effects of compounds in disease-relevant cells with cells that are genetically modified to lack expression of particular E3 ligases.
- Under the terms of the agreement, Proxygen will receive an undisclosed upfront payment from Merck & Co. and is eligible to receive up to $2,550 million in potential research, development and commercial milestone payments, as well as royalties on sales of any resultant products.

Biotheryx partners with Incyte on molecular glue degraders for oncology targets

Deal announced: 5 April 2023

Potential deal value: $360 million

Deal overview

- Biotheryx, a company founded in San Diego in 2007, has signed a deal with Incyte to identify and develop molecular glue degraders for multiple targets in oncology that have historically been considered 'undruggable'.
- Biotheryx has developed a proprietary platform known as PRODEGY (PROtein DEgrader technoloGY) for identifying molecular glue and bifunctional degraders that harness the E3 ligase cereblon.
- Biotheryx will receive a technology access fee of $7 million and up to $6 million in funding for work on the initial target, and is eligible to receive milestone payments of up to $347 million, as well as royalties on product sales. Incyte will be responsible for further development and commercialization of any degraders identified for the initial target. The collaboration may also be expanded to additional targets with the same financial terms.

SyntheX enters research collaboration with Bristol Myers Squibb on molecular glue degraders

Deal announced: 4 October 2022

Potential deal value: $550 million

Deal overview

- SyntheX, a company founded in San Francisco in 2016 that is building a preclinical portfolio of anticancer drugs for challenging targets such as RAS family proteins, has established a collaboration with Bristol Myers Squibb focused on discovering and developing molecular glue degraders.
- SyntheX has developed a proprietary platform known as ToRNeDo that enables the discovery of molecular glues for a range of pre-specified E3 ligases and targets of interest, as well as a platform known as ToRPPIDO for discovering functional disruptors of protein–protein interactions.
- Under the terms of the agreement, SyntheX will receive an undisclosed upfront cash payment and investment from Bristol Myers Squibb, and is eligible to receive up to $550 million in milestone payments, as well as royalties on sales of resultant products.