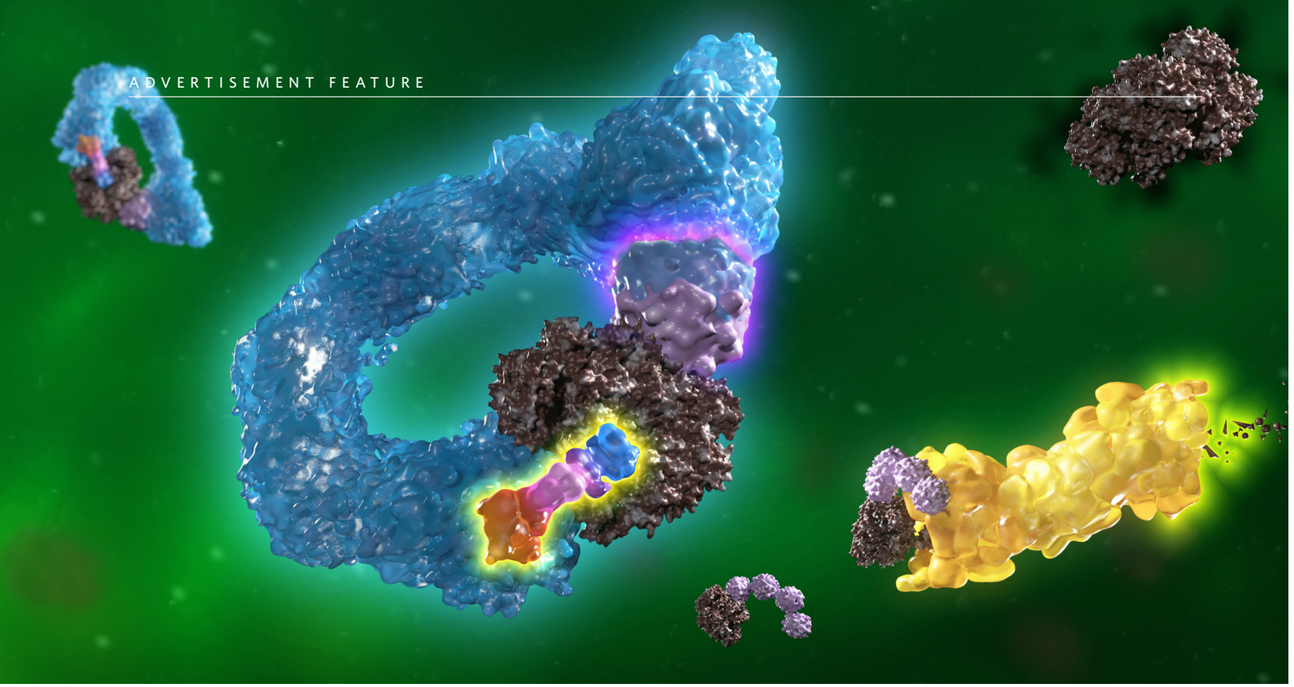


NOVEL CANCER-DRUG STRATEGY COULD HIT NOTORIOUS PROTEINS

Undruggable targets are proving no match for EMERGING PROTEIN-DEGRADER TECHNOLOGIES.

Many drugs work by attaching themselves to disease-related proteins and temporarily shutting them down. But a novel strategy used by Astellas Pharma Inc., a pharmaceutical company based in Japan, exploits the body's own molecular trash-disposal system to address problematic proteins.

Around 80% of human proteins have traditionally been deemed 'undruggable' because they lack suitable binding pockets that conventional drugs need to be effective. Known as targeted protein degradation because drugs degrade proteins, the new approach is now empowering pharmaceutical companies to disable such proteins in a selective, effective and potentially long-lasting way.

▲ **Unlike most conventional drugs, ASP3082 (with yellow halo) can bind to the protein KRAS, an important target for many cancers.**

TACKLING A TRICKY PROTEIN

One notoriously difficult-to-drug target is the protein KRAS, whose encoding gene is mutated in about one-quarter of all cancers. KRAS plays critical roles in cell growth and division — processes that become dysregulated in tumours, leading to uncontrolled cell proliferation.

Unfortunately, KRAS is largely devoid of pockets and crevices in which a therapeutic molecule can nestle, so most of its mutated forms — including the most prevalent, a variant called G12D (in which the 12th amino acid, normally a glycine (G), is replaced with an aspartate (D)) — have proved resistant to classical drug-discovery paradigms, despite the best efforts of the world's leading pharmaceutical companies over the past several decades.

Now, thanks to the unique properties of protein degraders, which require only weak binding to their target, scientists from Astellas Pharma have created a potent drug candidate that selectively destroys the G12D-mutant form of this cancer driver. Named ASP3082, the investigational drug is the first degrader directed against G12D-mutant KRAS to enter human trials anywhere in the world.

On a molecular level, ASP3082 has a dumbbell-like structure, with a pair of binding ends connected by a thin tether. One end latches onto the G12D-mutated site of KRAS, while the other grabs a special type of 'tagging' enzyme, E3 ligase. Once everything is bundled together, the enzyme adds protein tags, ubiquitin, to the target protein that signal to the cell's rubbish-removal machinery to get rid of this pesky protein.

Since protein degraders work without binding to the target protein to inhibit their function, the absence of a clear binding pocket in a protein or poor binding affinity will be no longer be a limitation when identifying suitable drug candidates. Thus, protein degraders have potential to bring about a paradigm shift in chemically synthesised drugs.

TESTING THE STRATEGY

A first-in-human study of ASP3082 was launched in June 2022 at cancer hospitals across the United States.

In lab experiments, researchers from the company's cutting-edge laboratory in Tsukuba found that ASP3082 powerfully induced protein degradation and subsequently inhibited downstream signaling pathways, with minimal effects on non-mutated KRAS proteins. The drug also blunted tumour growth in mice bearing G12D-mutated pancreatic cancer cells, with evidence of sustained reductions in target protein levels. "It significantly depletes the target protein," says Masahiko Hayakawa, head of Targeted Protein Degradation at Astellas.

In clinical trials, after determining an appropriate dose level, Astellas plans to begin administering ASP3082 both alone and in combination with other drugs including an anti-EGFR antibody called cetuximab. The hope is that concurrent treatment with both ASP3082 and other drugs, depending on the type of cancer, could maximize the benefit, to help combat tumours of the pancreas, colon and other organs.

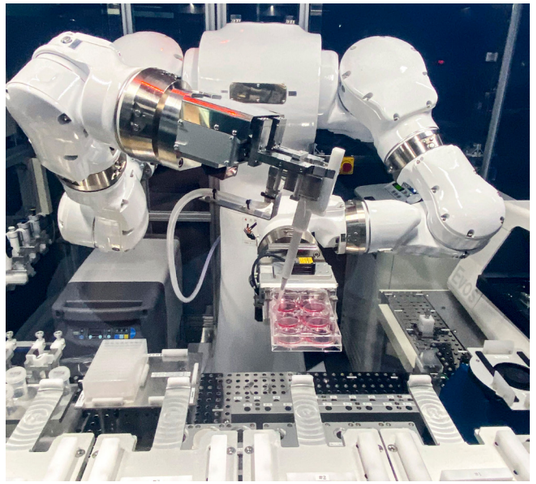
A UNIQUE APPROACH

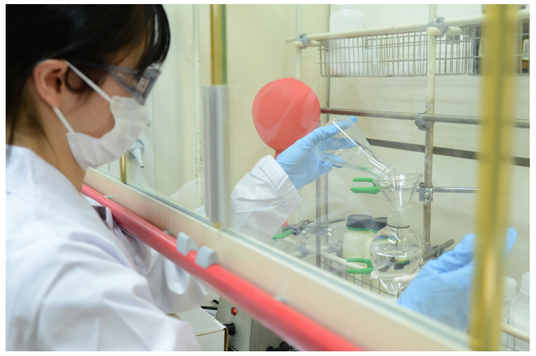
Around a dozen other experimental degraders from rival drug makers are currently in clinical testing, almost all targeting various proteins tied to cancer growth. What sets the Astellas drug candidate apart is its unique target, as well as the proprietary molecular pieces that constitute its makeup. "We have differentiating technologies and assets that put us in a leading position in the field," says Hayakawa.

Hayakawa points to the library of molecules the company has developed for targeting different proteins of interest. Astellas and its partners are also working to develop binders capable of recruiting various types of E3 ligases with disease- or tissue-specific characteristics. Some, for example, preferentially work inside tumours, while others work only in disease-impacted organs.

Because of the unusual chemistry of protein degraders, with their bifunctional design features, Astellas scientists can mix and match the various tools in their arsenal to design optimal compounds — as they did with ASP3082. That degrader required just five months of optimization, followed by a year of preclinical studies before the company was ready to start clinical trials with patients.

Hayakawa and his colleagues have followed a similar strategy with several next-generation approaches that degrade other mutants of KRAS besides the G12D-mutant form as well as other proteins implicated in cancer and autoimmune diseases.





▲ **In Astellas's laboratories, robots (top) assist humans (bottom) in conducting research into targeted-protein-degradation drugs that bind to proteins that are difficult to target using conventional drugs.**

JUST THE BEGINNING

Add in the company's capacities and expertise in medicinal chemistry, artificial intelligence, molecular synthesis, computational modeling and state-of-the-art robotic manufacturing, and it's conceivable the degrader platform could help eliminate a wide range of harmful proteins.

"We see huge potential in this technology to tackle numerous undruggable target molecules," says Chief Scientific Officer Yoshitsugu Shitaka, who oversees Astellas's drug-discovery research organization. Other advantages of protein degraders over standard small-molecule drugs include greater targeting precision, with treatment effects that should be longer lasting, he explains.

WE SEE HUGE POTENTIAL IN THIS TECHNOLOGY TO TACKLE NUMEROUS UNDRUGGABLE TARGET MOLECULES

The company's first programmes, like ASP3082, involve a modular approach that offers plug-and-play design flexibility. But Astellas is also working on degraders that use other mechanisms. These include molecular glues that are more compact and could penetrate deeper into tissue and give other pharmacological benefits. "We're a very active player in all these new modalities," says Shitaka, noting that Astellas has also been a trailblazer in cell therapies and other cutting-edge drug designs.

"In the near future, targeted protein degradation will become a more standard part of drug discovery," Shitaka says. "And thanks to our team working on industry-leading targeted protein degradation, we stand poised to potentially transform patients' lives with this innovative science." ■

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