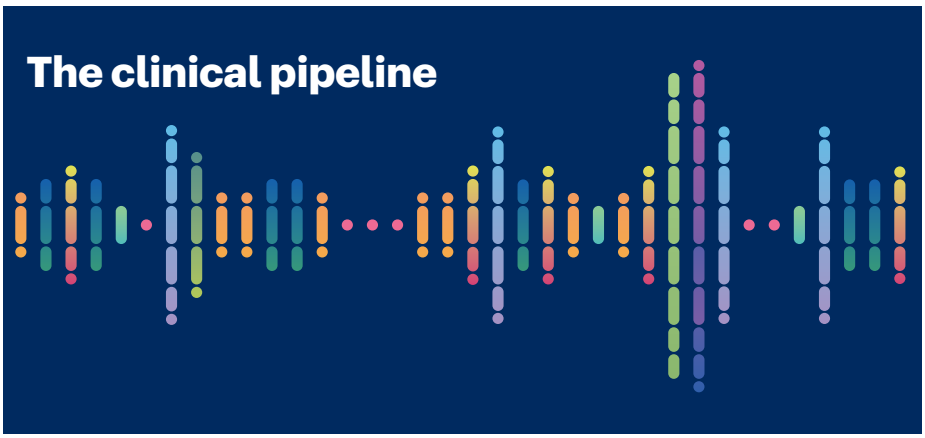
PROTAC protein degraders to drug the undruggable enter phase 3 trials

Pharmaceutical companies are investing in therapies that target proteins for degradation, with trials ongoing for cancer, autoimmune diseases and neurological disorders.



By Carrie Arnold

Despite billions of dollars in research and development, some proteins remain stubbornly undruggable. Some lack an active site to inhibit or agonize, whereas others are inaccessible in the dense chemical 'soup' of the nucleus and cytoplasm. In the past, if drug developers could not find a druggable target, they were simply out of luck. But now, previously undruggable proteins can be targeted for degradation via proteolysis. Sometimes known as PROTAC protein degraders (PROTAC is an acronym of 'proteolysis targeting chimera' and has been trademarked by Arvinas), these new drugs are now entering late-stage clinical trials.

A PROTAC is not a standard enzyme inhibitor. Instead, it promotes degradation of the targeted protein via the proteasome. For Angela Cacace, chief scientific officer at New Haven, Connecticut–based Arvinas, PROTACs have opened new avenues of possibility in drug discovery.

"This has been game-changing technology. We've started a mini biotech industry around this idea of proximity biology," Cacace says.

Degrading receptors

Although these drugs are generating excitement, only a few clinical trials of protein degraders are underway, including a phase 3 trial by Arvinas (in partnership with Pfizer) of vepdegestrant (ARV-471), which aims to degrade the estrogen receptor in breast tumors, destroying a key signaling pathway for tumor growth (Table 1). The drug is being tested both as a first-line therapy and as a second-line therapy for metastatic breast cancer and saw positive results in phase 1 and 2 trials. Cacace expects the first-line trial will be completed by November 2024, with topline readouts available in early 2025. In April 2024, Arvinas teamed up with Novartis to develop and commercialize the androgen receptor degrader ARV-776 as a treatment for prostate cancer (this is Arvinas' second PROTAC in this space, after ARV-110).

Beyond their anti-cancer drugs, Arvinas is also developing a neuroscience pipeline, with their most advanced candidate targeting LRRK2, hyperactivation of which has been identified as a key driver of Parkinson's disease, and is currently completing studies aimed at enabling Investigational New Drug status.

"PROTACs open up all sorts of possibilities, because now all of these proteins that are very difficult to inhibit have new potential binding sites that you can create a drug against," says Andrew Tsourkas, a biomedical engineer at the University of Pennsylvania. This new class of drugs "don't have to have an effect on protein functionality, they just have to bind, and they can drag the protein towards degradation."

Other drug companies are close on Arvinas' heels with trials of protein degraders in other cancers, as well as autoimmune conditions and neurological disorders. Although no company has made it over the finish line and netted regulatory approval yet, industry insiders say that it is only a matter of time before one of these trials leads to success.

Tricking the proteosome

For cells, recycling misfolded and defunct proteins is as important as their synthesis. This is why two major degradation pathways have evolved: ubiquitin-based proteolysis, and autophagy. As a chemist at Yale University, Craig Crews was focused on the ubiquitin–proteasome pathway. A family of proteins called ubiquitin ligases add ubiquitin tags to lysine residues of proteins ready for recycling, which directs them to the proteasome. The proteasome acts as an enzymatic 'garbage disposal', breaking down proteins into their component amino acids, which can then be reused.

Crews wanted to know if he could hijack this system and trick the E3 ubiquitin ligase into ubiquitinating a protein it would normally ignore. The type of molecule Crews and Raymond Deshaies, a biochemist at Amgen (who was then at the California Institute of Technology), designed was a heterobifunctional protein degrader. This contained two protein-binding peptides – one that bound to an E3 ligase and one that bound to the target protein – connected by a linker. Their proof-of-principle paper published in 2001 used this protein complex as the first targeted protein degrader. Later work would develop small molecules that were just as effective.

"The beauty of a heterobifunctional approach is that one is liberated in terms of what proteins you can target," says Crews, "because all you need is a small molecule binding to one protein and a small molecule to bind to another – and you just have to bring them together."

The fact that the chemical 'matchmaking' properties of protein degraders would be useful to the pharmaceutical industry was immediately obvious. The development of small-molecule PROTACs meant that the drugs could be administered orally rather than by

Table 1 | Selected protein degraders being tested in clinical trials

Treatment	Organization(s)	Target	Phase	Lead indication
Vepdegestrant (ARV-471)	Arvinas and Pfizer	Estrogen receptor	3	Metastatic breast cancer
ARV-766	Arvinas and Novartis	Androgen receptor	3	Metastatic castration-sensitive and castration-resistant prostate cancer
Bavdegalutamide (ARV-110)	Arvinas	Androgen receptor	1/2	Metastatic castration-resistant prostate cancer
ARV-102	Arvinas	LRRK2	1	Parkinson's disease
KT-474	Kymera Therapeutics	IRAK4	2	Hidradenitis suppurativa and atopic dermatitis
KT-333	Kymera Therapeutics	STAT3	1a/b	Refractory leukemias and lymphomas
NX-5948	Nurix Therapeutics	BTK	1a/b	B cell cancers
NX-2127	Nurix Therapeutics	BTK and IKZF	1b	B cell cancers

injection or infusion, as most biologics are. Moreover, drug developers were no longer limited to targeting a protein's active site. As long as the PROTAC bound somewhere on the protein, the lysines would be ubiquitinated and the protein would be shuttled to the proteasome.

"We're not inhibiting anything. We're just co-opting the cell's natural machinery to do what it does best for targets that are meant to be destroyed and eliminated," Cacace says.

In 2009, Yale University licensed PROTAC technology to the startup Arvinas to begin work on drug development. The company turned to cancer biology both for high unmet need and because PROTACs are effective at sub-stoichiometric concentrations, which means that a single drug molecule is effective against multiple copies of the target protein. This activity is key for proteins that are rapidly synthesized and present in large numbers, Cacace says.

"Inhibitors can't overcome that, and that's why they failed," for many diseases, she says.

The ability of a protein degrader to function as a drug had already been shown, albeit inadvertently and with severe side effects. Thalidomide, which was developed in the 1950s to treat morning sickness (and was later banned because it caused birth defects), was later shown to exert its effects through targeted protein degradation.

Disease-modifying targets

Arvinas is not alone in developing protein degraders. Massachusetts-based Kymera Therapeutics completed a phase 1 trial for their IRAK4 degrader KT-474 in hidradenitis suppurativa in late 2023. A study published in *Nature Medicine* showed that the drug was safe and tolerable in a cohort of 105 healthy control study participants and 21 people with moderate to severe disease. IRAK4 is a multifunctional scaffolding kinase that sits at the intersection of the innate and adaptive immune responses.

"By actually removing IRAK4, we can block all of the functions and have a real, profound impact," says Kymera founder, president and chief executive officer Nello Mainolfi.

This makes their IRAK4 degrader ideally suited not just for the autoimmune skin condition hidradenitis suppurativa but also for similar conditions, such as atopic dermatitis; they are now testing the drug in people with each condition in a phase 2 trial. In July 2024, Kymera and partner Sanofi announced they were expanding the number of phase 2 trial sites of KT-474 in hidradenitis suppurativa and atopic dermatitis to move more quickly to phase 3 trials, although they did not disclose the final number of sites.

Another Kymera drug, KT-333, targets STAT3, which regulates cell growth and division. An open-label, dose-escalation, phase 1a/b safety and tolerability trial is currently underway in people with several types of refractory leukemias and lymphomas.

Nurix Therapeutics, headquartered in San Francisco, is advancing three drug candidates. NX-5948 is an oral degrader of BTK, a non-receptor kinase that is involved in the proliferation of B cell cancers. Initial findings of the phase 1a/b trial evaluating this drug were presented in December 2023 at the American Society for Hematology and showed that it was safe and well tolerated. In January 2024, the drug was granted fast-track status by the US Food and Drug Administration.

"We get better removal of a disease-causing protein and better control of the pathway via degraders and that is a fundamental value that can be applied anywhere," says Gwenn Hansen, chief scientific officer at Nurix Therapeutics.

Another drug from Nurix, NX-2127, targets both BTK and the DNA-binding protein IKZF, giving it both anti-cancer and immunomodulatory capabilities. Also intended for use in B cell malignancies, this drug is in first-in-human phase 1b trials. Nurix also has partnerships to develop other protein degraders with Gilead, Sanofi and Pfizer. Hansen says that the evolution of drug resistance may also be tempered in protein degraders, which would give them an additional advantage.

"The degraders don't have to occupy an active-site pocket for extended periods of time, and that gives them more flexibility to maintain that interaction," says Hansen, "even subject to slight changes like point mutations, deletions or small variations of the protein surface,"

To Eric Fischer, a biochemist at the Dana–Farber Cancer Institute in Boston, these trials are at the forefront of a potential drug revolution that he compares to the development of antibody therapies several decades ago.

"Being able to remove a protein using an orally available small molecule allows you to address biology that you can't with other modalities," Fischer says. "We're essentially saying, let's try not to be constrained by what you think is druggable. Let's really try to think about what would be the most disease-modifying target. And this is happening as we speak."

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