Stapled peptide to enter human testing, but affinity questions remain

As potential therapeutics, peptides offer many advantages over existing technologies, such as greater specificity than small-molecule drugs. And their small size, typically fewer than 50 amino acids, allows these protein fragments to be made cheaply and taken as pills—something that can't be done with large antibodies and most other biologics. Yet, peptides, in their native state, have an Achilles' heel: they remain prone to unraveling, which leads to their degradation by the cell's clean-up enzymes.

In a clever workaround, a Cambridge, Massachusetts-based startup has come up with a way to lock peptides into certain shapes by introducing chemical 'staples' into their amino acid backbones. And last month, the company, Aileron Therapeutics, announced that it had secured the \$12 million it needs to advance its lead stapled-peptide drug into phase 1 testing.

"The clinical trial announcement is great news for the field," says David Lane, chief scientist at A*STAR in Singapore who also works on stapled-peptide technologies. "This is a new class of potential medicine, and the trial will hopefully establish that they are safe and effective in man."

The Aileron drug, known as ALRN-5281, is designed to boost the release of human

growth hormone in people with rare endocrine disorders. Preclinical data for ALRN-5281, which could replace frequent injections of synthetic hormones, will be presented publicly for the first time later this month at a conference in Japan. Meanwhile, Aileron is also looking at other stapled-peptide candidates for treating cancer, inflammation and various metabolic disorders. Last year, for example, Aileron cofounder Loren Walensky, of the Dana-Farber Cancer Institute in Boston, published a report describing how treatment with a stapled peptide designed to modulate the B-cell lymphoma 2 (BCL-2) pathway led to remission in a mouse model of leukemia (*J. Clin. Invest.* **122**, 2018–2031, 2012).

Pepped up peptides?

Not all the results from stapled peptides are as promising. In November, researchers at the Walter and Eliza Hall Institute of Medical Research (WEHI) in Parkville, Australia, in collaboration with scientists from Genentech in South San Francisco, California, tested a chemically reinforced peptide that, like Walensky's drug, targeted BCL-2 proteins. Unexpectedly, the stapling actually destabilized the peptide in its normal protein state, so it couldn't target and kill cells as well as hoped (*ACS*

Chem. Biol. doi:10.1021/cb3005403, 2012).

Joseph Yanchik, Aileron's president and chief executive, remains unfazed by the findings. "To use the WEHI work as the basis for general conclusions about stapled peptides is a bit of a stretch," he says, noting that the study used a particular stapled peptide that Walensky's group had previously intentionally weakened for structural experiments.

Genentech's parent company, Roche, doesn't seem too concerned by the data coming from its subsidiary, either. In 2010, the Swiss pharmaceutical giant inked a deal with Aileron worth up to \$1.1 billion, and last year the two partners started to present work stemming from the collaboration at scientific meetings. Most recently, in December, Lane and his colleagues showed that stapled peptides can successfully reach and reactivate a tumor-suppressor protein called p53 to block cancer cell growth (*ACS Chem. Biol.* doi:10.1021/cb3005148, 2012).

The true test, of course, will come later this year when ALRN-5281 enters the clinic. "Promising results from the first series of clinical trials would serve to validate an entirely new therapeutic approach for treating human disease," Walensky says.

Yevgeniy Grigoryev

Amgen deal triggers watchful waiting in targeted nanomedicine

When it comes to getting drugs to reach cells in the body, precision arguably matters just as much as size. That is the idea behind a recent deal between Amgen and BIND Biosciences that may drive the field of anticancer nanomedicine into molecularly targeted therapy.

On 8 January, the companies announced a new agreement designed to jointly develop and commercialize an anticancer therapy that combines BIND's nanomedical delivery technology with one of Amgen's targeted kinase inhibitors. "The field has exploded scientifically, but it hasn't yet translated to the clinic," says Baran Sumer, a cancer researcher at the University of Texas Southwestern Medical Center in Dallas. "This deal could be the first step."

BIND Biosciences has been working on a class of therapeutics called Accurins, polymer-based nanoparticles that diffuse through the large pores of tumor vasculature to deliver drugs against cancerous cells. At last year's American Association for Cancer Research Annual Meeting in Chicago, the Cambridge, Massachusetts-based company presented phase 1 trial data showing that treatment with

an Accurin combined with the chemotherapy drug docetaxel led to anticancer activity in 6 of 17 patients with advanced or metastatic solid tumors. But until now, BIND hadn't combined its proprietary nanotechnology with a molecularly targeted cancer therapy—in this case, a kinase inhibitor that Amgen declined to disclose for competitive reasons.

Under the terms of the agreement, both companies will work on preclinical development, but Amgen will have the exclusive right to commercialize the drug for solid tumors. BIND could receive payments totaling almost \$47 million with an additional \$134 million in regulatory and sales payments. It will also receive royalties on any future sales.

Currently, marketed anticancer nanomedicines that combine generalized chemotherapy drugs with nano-based delivery mechanisms include DepoCyt, a long-lasting formulation of cytarabine, and Abraxane, an albumin-bound formulation of paclitaxel. Several other comparable products are at earlier stages in clinical development.

Because of all the activity in the space,

Paul Evers, an analyst with BCC Research near Boston, says it would be a "mistake to view the BIND-Amgen deal as uniquely groundbreaking." Although, with many big pharma players with targeted cancer drugs in their pipelines, "it may interest other companies developing kinase inhibitors," he says.

Evers adds that nanomedical technology has advanced enough that it is no longer the limiting factor. "The BIND-Amgen project will stand or fall mainly on the clinical performance of the kinase inhibitor," he predicts.

The overall anticancer nanomedicine market is predicted to grow from \$5.5 billion in 2011 to \$12.7 billion by 2016, according to a report by BCC Research, although how much of that could involve combining targeted therapies with nanodelivery systems is unknown.

Scott Minick, BIND's chief executive, says that for nano-based targeted cancer therapy to really take off, large pharmaceutical companies will need to invest, because many of the targeted agents are proprietary, so smaller nanotech developers would need to collaborate with them.

Monica Heger

Correction

In the February 2013 issue, the article entitled "Amgen deal triggers watchful waiting in targeted nanomedicine" (*Nat. Med.* **19**, 120, 2013) incorrectly referred to the drug docetaxel as decoxtel. The error has been corrected in the HTML and PDF versions of the article.