Next-generation proteasome blockers promise safer cancer therapy

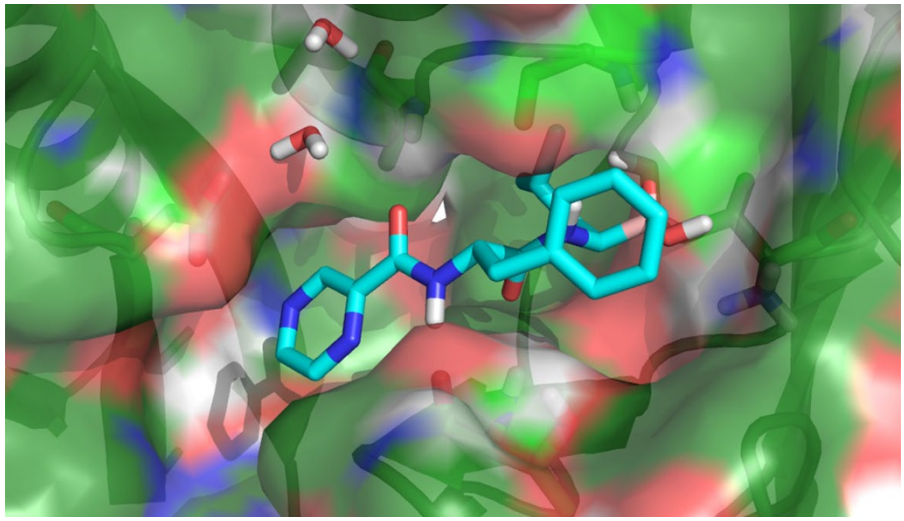
As recently as a decade ago, the life expectancy for individuals with multiple myeloma, using the best available treatment options, was just three to four years. But, nowadays, some people with the debilitating blood cancer can expect to live ten years or longer thanks in large part to bortezomib, a proteasome inhibitor that hit the US market in 2003. Despite radically changing the landscape for myeloma therapy, however, bortezomib—which is sold as Velcade by Cambridge, Massachusetts–based Millennium Pharmaceuticals—still has some serious limitations. The drug's side effects can be severe, ranging from nerve damage and low blood counts to nausea and constipation. And, as with other myeloma therapies, the cancer almost always develops resistance to bortezomib. But doctors could soon have less toxic proteasome-blocking agents in their arsenal.

"We have a class of agents that work, and there is now a race to manufacture drugs that are better and safer," says Vincent Rajkumar, a hematologist at Mayo Clinic in Rochester, Minnesota. "Each one will fight for its own place."

The first such agent could be carfilzomib, a so-called 'next-generation' proteasome inhibitor developed by South San Francisco's Onyx Pharmaceuticals. Off the back of positive results from a 266-person phase 2 trial reported at several conferences last year, on 29 November the US Food and Drug Administration agreed to review carfilzomib for approval in people with multiple myeloma. A regulatory decision is expected before the end of July.

The proteasome is a large protein complex that acts as the cell's trash collector, getting rid of unneeded or damaged proteins that have been tagged for destruction. Like bortezomib, carfilzomib blocks one of the three main enzymes responsible for the proteasome's cellular degradation. But carfilzomib is more selective and seems to have fewer off-target effects, which could help explain the lower rates of toxicity seen thus far in clinical trials.

Biren Amin, an analyst with the New York investment bank Jeffries, estimates that, if approved, carfilzomib will earn just under $1 billion in annual sales in the US and EU by 2020. That's slightly less than what bortezomib—the early leader—made last year in global sales. But according to Rajkumar, who is currently co-leading a 700-person, phase 3 trial involving carfilzomib, the improved safety profile observed with Onyx's drug could cause many physicians to eventually adopt the newer agent as the proteasome inhibitor of choice.



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Cancer a-bort-ed: New proteasome inhibitors are expected to supplant bortezomib (shown here).

Despite positive phase 2 trial data for carfilzomib, however, experts say it's not a sure bet that the Onyx agent will necessarily prove safer in the long term. Ping Dou, a pharmacologist at Wayne State University in Detroit, points out that whereas bortezomib is a reversible agent that can separate from its target, carfilzomib binds its target irreversibly such that the proteasome is always blocked. Theoretically, more sustained inhibition by carfilzomib may provide better efficacy, Dou notes. But it could likewise lead to more toxicity, he adds.

Special delivery

One thing bortezomib and carfilzomib have in common is that they both must be administered in doctors' offices, twice a week by intravenous injection. "It basically ruins your life," says Rajkumar, about current dosing. Millennium is currently seeking approval to give bortezomib by subcutaneous injection. But, ultimately, the companies behind bortezomib and carfilzomib hope to have pill versions to offer people with multiple myeloma.

At the American Society of Hematology meeting in San Diego last month, Millennium reported data from three early-stage trials of its experimental proteasome inhibitor pill, called MLN-9708, which the company says support further development. "We are very excited that MLN-9708 will be the first oral proteasome inhibitor to enter phase 3 trials," says Millennium spokesperson David Albaugh, noting that the pivotal trial will begin recruiting this year. Onyx is close behind, however, with plans to advance its own pill, dubbed ONX-0912, also in the works.

Physicians also hope that the next-generation proteasome blockers—and combinations of these agents with other classes of drugs—will be effective in a broad range of cancers beyond multiple myeloma and a rare type of lymphoma, both of which bortezomib is approved to treat. Drug developers are currently testing carfilzomib and similar experimental drugs in a variety of cancers, including those of the lungs, kidney and ovaries.

Meanwhile, some researchers are already thinking ahead to 'third-generation' strategies of proteasome inhibition. For instance, Stig Linder, a cancer biologist at the Karolinska Institute in Stockholm, recently identified an agent that blocks the proteasome's regulatory subunit instead of the complex's catalytic core (*Nat. Med.* **17**, 1636–1640, 2011). Because this agent acts slightly upstream of the known proteasome inhibitors, it seems to have more cancer-killing potential, at least in cellular experiments, notes Linder. "Small mechanistic differences, we believe, will translate into very different therapeutic effects," he says.

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Correction

In the November 2011 issue, the article entitled "Stanford program gives discoveries a shot at commercialization" stated that the SPARK program had 80 projects, 50% of which were licensed. In fact, the program has handled 40 projects, roughly half of which have been licensed. The error has been corrected in the HTML and PDF versions of the article.