IN brief

Drug user fees top $1 million

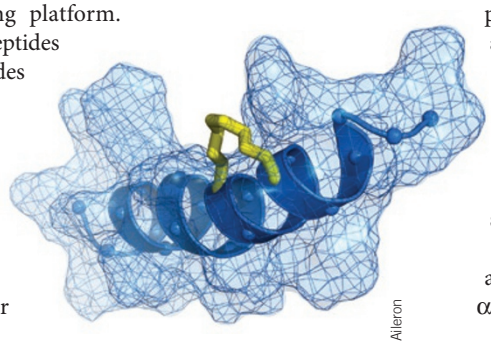
For the ninth straight year, the US Food and Drug Administration (FDA) is raising the fees companies must pay to have their drugs reviewed. As of October 1, new applications will cost over a million dollars. User fees were instituted in 1992 by the Prescription Drug User Fee Act (PDUFA) to provide funding so that the FDA can conduct timely reviews of drugs. The fees have risen from $100,000 in 1993 to $1,542,000 for a new drug application with clinical trial data. Whether PDUFA has been good for the biotech industry is debatable. Reducing the time to approval (50% reduction since the late 1990s) has meant millions of dollars in revenue, as drugs can be brought to market earlier in their patent lives, according to Mary Olson, at Tulane University in New Orleans. "This expected revenue for most drugs greatly exceeds the user fee even with the proposed increases," she says. However, Kurt Karst, a lawyer at Hyman, Phelps, and McNamara in Washington, DC, with clients in the biotech industry, says the fees are a concern for smaller companies deciding whether to seek approval for a drug. In a letter to the FDA, the Biotechnology Industry Organization of Washington, DC, pointed out that PDUFA fees now pay a greater share of the budget for drug reviews, almost two-thirds in 2008 up from 42.5% in 2006, and called for transparency on how the fees are used. *Laura DeFrancesco*

Sugar beets still in the game

Seed producers will be allowed to plant biotech sugar beets again following a September decision from the United States Department of Agriculture's crop approval arm to allow planting under interim guidelines. The Animal and Plant Health Inspection Service (APHIS) will issue limited permits to seed developers authorizing genetically modified (GM) beet planting this fall as long as the harvested beets are not allowed to flower. The permits are a legal way around a federal judge's 13 August decision to ban all commercial farming of Monsanto's Genuity Roundup Ready sugar beets beyond that date. GM sugar beets planted before the ruling may be harvested, processed and sold without restriction and the beets remain eligible for future commercial approval pending USDA/APHIS's full environmental review of the beets. A federal judge had revoked APHIS's beet deregulation and prohibited further planting and sale on the grounds that the agency had not adequately considered the potentially irreparable harm GM beets might cause related species through cross-fertilization (*Nat. Biotechnol.* **27**, 970, 2009). APHIS has announced it will expedite the sugar beets review, which will take about two years. Luther Markwart, of the American Sugarbeet Growers Association and Sugar Industry Biotech Council, Washington, DC, says GM beet farmers, who grow 95% of the US crop, already voluntarily maintain 4-mile isolation from related crops to prevent cross-fertilization. "Most of the interim measures that we're looking at…are things that we're already doing," he says. *Lucas Laursen*

Roche backs Aileron's stapled peptides

A company that staples peptides into drugs to target 'undruggable' proteins has landed a $1.1 billion deal with Swiss drug maker Roche. The deal signed in August will see Aileron pocket $25 million upfront in technology and access fees and R&D support. More than that, it provides validation from big pharma for Aileron's stapling platform. Chemically stapled peptides result in helical peptides that reputedly combine high stability with the ability to cross the cell membrane to hit cellular targets. This is the first major industry collaboration for Aileron, although the Cambridge, Massachusetts–based biotech has already received the industry's collective imprimatur. Last year, the corporate venture arms of no less than four pharmaceutical firms —Roche Venture Fund, Lilly Ventures, Novartis Venture Funds and GlaxoSmithKline-owned SR One—backed the company's vision of peptide modification with a $40 million investment round. "They've looked very hard at this question. In most cases—without naming names —they have tried [to do this themselves]. And I suspect they will continue to try," says Aileron CEO Joseph Yanchik. Notwithstanding such concerted industry support, converting the promise of stapled peptides into clinically validated drug molecules is going to be a complex and difficult challenge, the scale of which is not lost on its promoters—or its investors. "You can imagine we've had to run a pretty difficult scientific gauntlet," says Yanchik. "The length and nature of the due diligence was extraordinary."



Atomic structure of a single-turn stapled peptide bound to its target. Stapling locks peptides into stable, biologically active alpha-helices.

Peptides make more attractive medicines than proteins or nucleic acids. They have evolved in nature to take on highly specific functions, work with great potency and are far smaller than recombinant proteins and antibodies. But they are inherently unstable chains. As soon as a job is done, they are degraded quickly by proteases—a factor that has tended to limit their utility as pharmaceuticals. "The catch-22 is you want the peptide for its biological activity, but you don't want the peptide for its pharmacological vulnerability," says Loren Walensky, assistant professor of pediatrics at Harvard Medical School, in Boston, and a member of Aileron's scientific advisory board. Exposure of their amide bonds renders peptides susceptible to proteolytic breakdown, and their polarity makes cell penetration difficult. "The major problem in the discovery of peptide-based drugs has been the ability to get robust cell penetration," says Gregory Verdine, professor of chemistry at Cambridge-based Harvard University and chairman of Aileron's scientific advisory board. "We're not the first to stabilize helices."

Stapled peptides are locked into an α-helical—and, thus, a biologically active—conformation. To achieve this, hydrocarbon cross-links are added between two non-natural amino acid residues inserted at each end of the target peptide sequence. A ruthenium-catalyzed olefin metathesis reaction generates the hydrocarbon linkages that impart structural stability to the stapled peptide and render it resistant to proteolytic breakdown. The method is general in its scope. "You can apply this to any peptide that is naturally inclined to be helical," says Walensky.

Stapled peptides have a dual role, serving both as molecular probes for studying biological processes, such as protein-protein interactions, and as drug leads that target those same processes. "This really changes the paradigm, in that we can create bioactive secondary structures and use them *in vivo* to target a disease and study the biology," Walensky says. For example, his group has generated a stapled peptide, based on the BH3 domain found in the BCL2 protein family member BID, tha t can activate apoptosis in human leukemia xenografts (*Science* **305**, 1466–1470, 2004). More recently, they have identified a second function for the pro-apoptotic BCL2 protein BAD, in insulin secretion and beta cell survival. Stapled peptides, based on the BAD BH3 domain, act directly on glucokinase and thereby influence glucose-stimulated insulin secretion (*Nat. Med.* **14**, 144–153, 2008). Over the summer, the Walensky group also reported on a stapled peptide that was a highly selective inhibitor of MCL1, an anti-apoptotic protein implicated in tumor survival (*Nat. Chem. Biol.* **6**, 595–601, 2010). Similarly, Verdine's group has used stapled peptides to demonstrate inhibition of the Notch transcription factor complex,