Beyond protease inhibitors

Despite a growing collection of effective HIV reverse transcriptase (RT) and protease inhibitors (see "Two more HIV protease inhibitors approved"), the search for agents that interfere with other components of this virus is accelerating.

One still unexploited target is HIV's Gag protein, which plays a prominent role in assembling new viral particles and is essential for infectivity. Stephen Goff of Columbia University (New York) and his colleagues learned that Gag associates with the host-cell protein, cyclophilin, which plays an important role in folding and reshaping cellular proteins. Moreover, cyclophilin is at least an indirect target of the immunosuppressant drug, cyclosporin, which is believed to disrupt the refolding of yet another protein in T cells.

Meanwhile, Goff points out, the interaction between Gag and cyclophilin is "unique to the Gag from HIV-1—a curious fact." Together these findings suggest another, potentially exploitable point of HIV vulnerability. Indeed, chemically modified cyclosporin derivatives apparently disrupt cyclophilin–Gag interactions, according to Heinrich Gottlinger of the Dana Farber Cancer Institute (Boston, MA). Some derivatives show high anti-HIV activity in vitro, but are relatively free of immunosuppressive activity, he says.

The HIV integrase protein is another candidate target. This protein binds to RT-produced DNA copies of the HIV genome and helps to integrate them into host-cell DNA. Other research groups report progress toward identifying HIV integrase inhibitors. For example, l-chicoric acid appears to block the removal or excision of the HIV genome from host DNA, thereby inhibiting HIV replication in vitro, according to Sam Chow of the University of California School of Medicine, Los Angeles. And, according to researchers at Merck Research Laboratories (West Point, PA), a group of low molecular weight sulfonate compounds they identified contains some of "the most potent inhibitors of integrase identified to date."

Jeffrey L. Fox

Diabetes treatments near and far

Several new technologies approaching US Food and Drug Administration (FDA, Rockville, MD) approval may significantly impact the lives of diabetes patients.

Nearly half of all diabetes patients rely on daily insulin injections to regulate blood glucose levels. However, the inconvenience of current insulin products—the most rapidly absorbed insulin formulations require 30 to 45 minutes to reach effective blood levels—is a serious problem. On February 29, a faster-acting insulin product developed by the pharmaceutical company Eli Lilly & Co. (Indianapolis, IN) was unanimously recommended for marketing clearance by the Endocrine and Metabolic Drug Advisory Committee of the FDA. The product, to be marketed under the name of Lispro, reduces the lag time to approximately 15 minutes. Like other insulin formulations, Lispro is injected as a hexamer. In Lispro, however, the order of two amino acids is reversed (from proline-lysine to lysine-proline), causing a structural change in the tail of the insulin B chain that increases its flexibility and results in dissociation to the free, biologically active protein significantly faster than other forms of insulin in current use.

Lilly launched the product in Switzerland in mid-February under the brand name Humalog, and the company says the product has also received a favorable opinion from the Committee for Proprietary Medicinal Products (Brussels). The new development continues Lilly's heavy involvement in the insulin field: in 1982 the company launched its human insulin, Humulin, the first recombinant polypeptide to reach any pharmaceutical market. "[Lispro] is the first truly new insulin recommended for approval in 50 years. We are delighted with the unanimous recommendation for approval," said Richard DiMarchi, vice president of endocrine research at Lilly Research Laboratories.

Two other earlier-stage developments in the diabetes field were reported in February at the annual meeting of the American Association for the Advancement of Science (AAAS) in Baltimore. Robert Lanza, director of the transplantation facility at Biohybrid Technologies (Shrewsbury, MA) presented animal model data demonstrating a different way of providing insulin to diabetes patients. Work at Biohybrid has focused on implanting bovine or porcine islet cells surrounded by protective membrane into the peritoneum. These "microreactors" are composed of a proprietary porous hydrogel-based polymer that permits only molecules of molecular weight 150 kD or below to penetrate to the interior. This limit means that nutrients from the bloodstream can reach the encapsulated pancreatic cell while denying immune system cells and antibodies access, thereby preventing an immune reaction to the foreign cells.

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Previous encapsulated islet cell technology has been limited to transplantation of islet cells of closely related species, but Lanza presented convincing evidence that bovine islets can survive—and thrive—in dogs. After three to six weeks of implantation in the dogs, the microreactors were removed. The encapsulated cells produced insulin levels four to six times higher than basal insulin secretion when placed in glucose-containing media. "This is the first kind of technology that allows you to [perform] a discordant xenograft through a syringe needle," says Lanza. He anticipates that phase I clinical trials using encapsulated pig islet cells could begin by the end of this year, if Lanza can identify a clinical collaborator among the several pharmaceutical concerns to which the company is talking.

Also at the AAAS meeting, Gail Naughton, president and CEO of Advanced Tissue Sciences (ATS, La Jolla, CA), reported initial clinical data on the use of their skin product Dermagraft to treat diabetic ulcers. Dermagraft is grown from the subdermal fibroblasts of donated infant foreskins, and the skin product avoids immune rejection because, like the parent fibroblasts, they surround themselves with a non-immunogenic protein matrix. In clinical trials, patients with chronic diabetic skin ulcers—which can eventually lead to amputation of the affected limb—were treated with Dermagraft. After eight weeks, wound closure in treated patients showed marked improvement over controls. Patients treated with Dermagraft showed no recurrence of ulcers after 14 months; the expected recurrence rate in untreated patients is 20–50%. FDA has notified ATS that its premarket approval application for Dermagraft will receive expedited review.

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