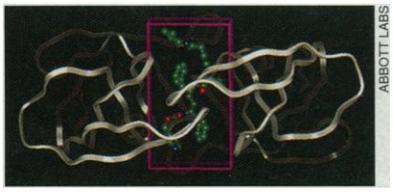
DRUG DEVELOPMENT

# Protease Inhibitors: A Tale of Two Companies

Last January, as Merck & Co. prepared to reveal data from a human trial of its new anti-HIV drug indinavir, Edward Scolnick, the head of the company's research labs, was beside himself with glee. The data on this inhibitor of the HIV enzyme protease, which the virus depends on to assemble itself properly, would cause "a complete paradigm shift," predicted Scolnick. The trials showed that indinavir, when used with two other anti-HIV drugs that attack a different target, could reduce the amount of HIV in people so dramatically that the most sensitive tests could not detect any virus in more than 85% of the patients. "It's dynamite," said Scolnick, predicting that this treatment would be "analogous to the first triple drug therapy for tuberculosis."



ABBOTT LABS

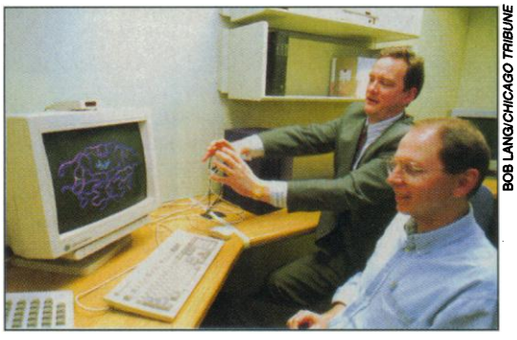
**Space invader.** Ritonavir *(green)* jams the active site of HIV's protease.

It will take years to tell if Scolnick was right. But the data on indinavir and another protease inhibitor made by Abbott Laboratories called ritonavir have already caused a paradigm shift both for people living with the virus and for those studying it. The new results are dispelling a funk that has pervaded the AIDS field because of the mediocre success of drugs like AZT that target HIV's reverse transcriptase (RT). But these protease inhibitors, both of which were licensed by the U.S. Food and Drug Administration (FDA) in March, are a different story. Their early successes suggest that the hundreds of millions of dollars invested in AIDS drug studies may at last be paying off, and they have given a shot in the arm to a field that was desperate for some good news.

Merck and Abbott are but two of a dozen companies making protease inhibitors. Hoffmann-La Roche actually won the race to market, licensing a rapidly metabolized—and thus less effective—drug called saquinavir in December 1995. Agouron's nelfinavir may be licensed by early 1997, and Vertex/Glaxo, Nikko Kyoto, and Pharmacia & Upjohn all have products in human trials. At least half a dozen other companies have compounds in the preclinical phase. But it was the data from the clinical trials of the Merck and Abbott drugs that started researchers giddily talking about the new era of "guarded optimism." And it was data from these trials that spurred the FDA to approve these drugs in record time.

The story of how Merck and Abbott sped their protease inhibitors from the lab bench to the pharmacy shelf is a study in contrasts, revealing how two front-runners ran the race with significantly different corporate, scientific, and political strategies. Now both face the same question: How long will their drugs' effects last?

**Blood pressure, sweat, and tears.** The work on protease inhibitors at Merck and Abbott owes much to pre-existing efforts to develop inhibitors of renin, another protease that regulates blood pressure. In 1987, the year both companies began searching for drugs that could find a chink in HIV's armor, AIDS researchers were just beginning to understand the critical role that protease played in making viable copies of the virus. HIV replicates by weaving its genetic material into that of a host cell's, which produces the proteins that can form new infectious virions. But protease must cut the freshly minted proteins into the proper size to make them work. So researchers tried to find a compound that could jam itself between the blades of the protease scissors and block the replication process. Chemists at both companies knew their mission was formidable.



BOB LANG/CHICAGO TRIBUNE

**Testing 1, 2, 3.** Abbott's Dale Kempf *(right)* and John Leonard saw several drugs crash on road to ritonavir.

Developers of renin inhibitors had wrestled with an identical, vexing problem: The part of the scissors that had to be jammed was hydrophobic, requiring a molecule that did not like water. But any drug that is not water-soluble would be difficult to take by mouth. Says Abbott chemist Dale Kempf: "We recognized very early on that oral bioavailability would be the key issue with HIV protease inhibitors as a whole." But their work with renin gave Merck and Abbott scientists a head start on HIV protease inhibitors. "Intellectually, the approach wasn't out of the blue," says Merck virologist Emilio Emini.

Although similar scientific challenges face the companies, upper management pursued them differently. Merck, a pharmaceutical Goliath that last year grossed $16.7 billion, went all out in January 1987. To Merck's Scolnick, developing an AIDS drug was critical for the U.S. biomedical community. "There was an enormous amount of pressure to do something about AIDS," says Scolnick. "The community at large, academic and industrial, was on the line. ... The backlash would be enormous if nothing was delivered."

Abbott, which made less than 15% of its $8.2 billion in revenues last year from pharmaceuticals, did not get into the AIDS drug development business at all until May 1987. It launched a protease program in 1988, when it won a grant from the National Institute of Allergy and Infectious Diseases to do so. Abbott put just three chemists on the protease team. Kempf, who says he had heard that Merck had a few dozen chemists on its team, says "I remember walking down the hallway one day and someone giving me their condolences."

Both companies soon met big obstacles. "It turned out to be a lot harder than we expected," says Scolnick. Calamity struck at Merck in December 1988, when biochemist Irving Sigal, a leader in the protease program, died on the infamous Pan American Flight 103, which was blown up by a terrorist bomb. Other setbacks were more routine, as experiments built up hopes, then dashed them.

One of Merck's first big successes came when researchers discovered and published in the 16 February 1989 issue of *Nature* the three-dimensional structure of HIV's protease, a key advance. The molecule resembles a set of butterfly wings joined at an active site—the part responsible for snipping HIV proteins. With this computer image in hand, scientists could fine-tune the design of protease inhibitors, attempting to make a compound that would clog the active site.

Getting the design to work in a living system—rather than just in a computer model—is another thing, however. More often than not, the protease developers resorted to the standard way of finding a drug that works: trial and error.

**Two giant leaps.** For many months, all the scientists could manage were small steps. But in the 1990s, their protease research suddenly took two giant leaps.

After testing a few dozen renin inhibitors off the shelf, the Merck team found one that

was potent against HIV and began tinkering with it, adding a chemical here and taking one off there. "Some of these compounds were as soluble as sand," says Merck chemist Joseph Vacca. Once they had the protease structure, they saw places to add soluble molecules that they hoped would not hurt potency. They finally created an inhibitor that had good activity in the test tube, L-689,502, and, in March 1990, tested it on eight dogs. The animals suffered serious liver damage. L-689,502 was history, but Merck had at least learned some new manufacturing tricks.

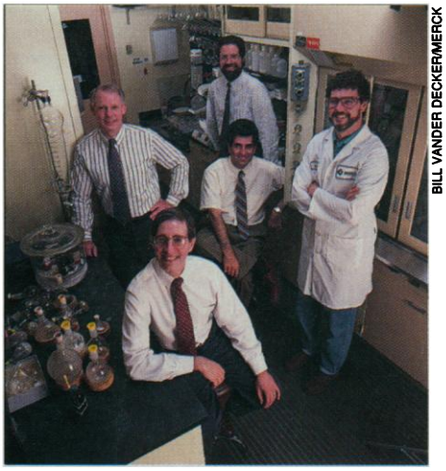
At about the same time, an Abbott team was making progress on a parallel track. Led by John Erickson, chemists Daniel Norbeck and Kempf published in the 3 August 1990 issue of *Science* details of their first-generation protease inhibitors. By January 1991, they were in the clinic with what seemed a promising candidate. But the molecule was so large that the drug's oral bioavailability was pathetic.

The trial-and-error process continued over at Merck, which by then had attracted the attention of AIDS activists. In March 1991, the company made the then-unusual move of forming a community advisory board with these often strident agitators, who wanted to play a role in the company's drug-development effort. "The price of cooperation is tremendous criticism," says organic chemist Paul Reider, who oversees the scale-up production of drugs. Nine months later, Merck chemists Vacca, Joel Huff, and Bruce Dorsey synthesized L-735,524. Now known as indinavir, or by the trade name Crixivan, the drug had high potency in the test tube and moved into animal studies that summer. No red lights flared. "It was remarkably clean in toxicity tests," says Emini.

Early in 1992, Abbott synthesized ABT-538, and in August, Kempf presented data from rat studies at an in-house meeting. Not only was the drug, now known as ritonavir (trade name Norvir), incredibly potent, it stayed in the rats' systems for 6 hours—as compared to 90 minutes with the next-best candidate. "It was unbelievable," says Norbeck.

In 1993, both indinavir and ritonavir began the climb from small safety tests to larger trials. Abbott, which the year before had been pilloried by AIDS activists for not allowing its preparation of HIV antibodies known as HIVIG to be tested (*Science*, 17 July 1992, p. 316), began trials in France in an "out-of-the-way site," says John Leonard, head of AIDS clinical development at Abbott. "We were trying to be off the beaten path. Abbott was very sensitive to activists at that time." Their drug often caused bouts of nausea. It also interfered with a critical liver enzyme, cytochrome P450, which was a double-edged sword: It slowed down the metabolism of ritonavir, causing it to remain active longer, but it interfered with the actions of many other drugs. Still, the data looked so positive that Abbott launched trials all over the world in sicker patients to see whether the drug could help them lead healthier, longer lives.

Despite the promising start, by January 1994, Merck was getting worried about indinavir. Within 6 months of starting treatment, patients were developing resistant strains of HIV. "We were pretty depressed at that point," says Scolnick. "Had the next set of studies had similar results, I would have pulled the plug." There was reason to hope, however. Virus levels had been knocked down so low in one patient, number 142, that researchers could no longer cultivate virus from his blood. And his count of white blood cells known as CD4s, used as an index of immune function, was rebounding steadily. The researchers asked themselves: If we can do it with one patient, why not others? Maybe the dose was too low. Merck's researchers increased it by 50%, and viral levels in the other patients started to drop and stay down. Merck quickly decided, like Abbott, to launch full-scale trials.



BILL VANDER DECKER/MERCK

**Testing 4, 5, 6.** The Merck team saw its share of problems en route to indinavir.

Ailing activists, seeking "compassionate use" of indinavir outside the trials network, began clamoring for the difficult-to-make drug. It was a demand the company could only partially meet. "We thought we had enough drug all the time, but the ante kept getting raised," says Reider of his scale-up team

After 7 months, Abbott had data from a placebo-controlled study with 1090 patients showing that the drug, in combination with RT inhibitors, could cut the number of cases of AIDS-related disease and death in half. On 29 February 1996, the company asked an FDA advisory committee for permission to market ritonavir. After deliberating into the evening, the committee gave a thumbs up.

The next day, Merck presented the committee with results from three of its indinavir studies involving more than 550 people. The most impressive data came from the trial that had excited Scolnick, reporting that 24 weeks after starting indinavir plus the RT inhibitors AZT and 3TC, 20 of 22 people (90%) had no detectable HIV. CD4 counts had also seen significant rises.

Later that day, on 1 March, the FDA approved ritonavir and the advisory committee gave indinavir its blessing. Only 72 days had passed since Abbott had filed its request, setting a new FDA speed record for drug approval. And on 14 March, the FDA approved Merck's indinavir, a mere 42 days after the company's filing.

**Coming up next.** At the international AIDS conference in Vancouver, Canada, next week, ritonavir and indinavir are destined to be the stars. Researchers, health care providers, and media from around the world will celebrate the new era of therapy that these drugs have ushered in. But expressions of optimism are likely to be guarded, for sobering limitations still exist.

Ritonavir causes nausea in one-fourth of the people who take it (although it may be reduced by a new dosing schedule), and it interferes with the action of 23 drugs—a staggering list for physicians and patients to remember. Indinavir, which Merck has had trouble producing in adequate supply (a new plant comes on line this fall), causes kidney stones 4% of the time, and it must be taken three times a day either 1 hour before or 2 hours after a meal. Both drugs are expensive, now retailing for more than $6000 a year. And both must be taken every day, in combination with other anti-HIV drugs, forever. "Triple therapy is tough for people to take for 20 or 30 years," acknowledges Scolnick.

Long-term use raises another problem, the most profound of all: viral resistance. When people forget—or refuse—to take their pills, they give drug-resistant HIV mutants a chance to multiply. Even at full dosage, resistance becomes more likely to occur the longer people stay on the drugs. And, as with AZT, people infected with protease-resistant strains will one day transmit them to others.

Inarguably, the protease inhibitors have pushed the resistance horizon out into the distance, as studies to be unveiled in Vancouver will show. One study will also show that the less bioavailable protease inhibitor saquinavir packs a surprising wallop when combined with ritonavir, suggesting that new, powerful combinations may soon be found.

Whether protease inhibitors will sustain today's excitement with enduring antiviral protection is something that will be revealed only with the passage of time. But for the moment—and it is one of the brightest moments in many years—the glass is at least half full.

–Jon Cohen