Birth of a Notion

Anne-christine d'Adesky slips inside the drug pipeline to shine light on a dazzling new promise for "salvage" therapy. So hold onto your hope, beware the hype -- here comes The Next Bi*g Thing.*

June 1, 2001 By Anne-christine d'Adesky

People with HIV face a Sophie's Choice about treatment: on the one hand, there is HAART and its side effects, which may disable, disfigure or worse, and, on the other, no treatment, with the prospect of sickness and death. But from the gloom are emerging glimmers of light that may herald a new dawn: fusion inhibitors (FIs).

FIs are the first in a novel class of weapons called entry inhibitors, which block HIV outside the cell -- not, like the current arsenal, inside it. Trailing behind FIs are attachment and coreceptor inhibitors; in the back of the pack, integrase inhibitors block another step called integration (see "Enter, Blocking" below, and "LIF(E) After Birth").

Entry inhibitors are especially tantalizing because they may avoid the nastiness of existing anti-HIV drugs. HAART regimens attack HIV after it enters the cell, blocking the enzymes -- reverse transcriptase and protease -- that let the virus do its work. Imagine a smooth-running mini-Xerox machine into which a paper clip suddenly gets dropped and you'll get the idea. The problem is, the drugs block not only the "bad" HIV enzymes but also the cell's "good" enzymes, mucking up its functioning. That leads to a metabolic mess -- and side effects.

But FIs use peptides, a protein's core ingredients, to keep HIV from binding to the cell's surface and then merging. It's a neat one-two punch to HIV: First block the virus, then protect the cell. And as these are peptides unique to HIV, the drugs shouldn't block anything else.

Still, there are some big IFs about FIs. HIVers remember well how, in the demand and haste to get nukes and protease to market, activists, researchers and government agencies failed to anticipate and study drug-related toxicity. Why should entry inhibitors be any different? Though peptides may appear safe at first, what awaits us down the line?

"After protease, no one is going to be cavalier about the safety of fusion inhibitors," says John Moore, MD, a leading AIDS researcher from Cornell University, "but everything we've seen so far shows they are safe." As well known for his bullshit detector as for his pioneering work on how HIV infects cells, Moore is never happier than when finding problems. But so far the FIs' peptides have proved safe because they target a unique HIV sequence. "I would be surprised if toxicity ever happened," he says. "It would be bad luck." Instead, the foreseeable problems of the new entry-

inhibitor class are their method of delivery -- an injection -- and their potency down the line.

Others are more suspicious. Joseph Sonnabend, MD, a community doctor famous for accusing the emperor (from Pharma to ACT UP) of having no clothes, worries. “The issue is, we don’t know much about peptide drugs,” the veteran naysayer says. “The cell’s natural processes -- for example, its binding receptor, or ”doorway,“ on the cell surface -- may react with fusion inhibitors, and cause problems. The receptors are not there for HIV alone -- we need them.” Softening a bit, he adds, “My overall sense is they’re mostly safe. The worst that may happen is that people will develop antibodies to [FIs] and the drug will stop working.”

Sonnabend’s measuring stick is the patient in his office who has a buffalo hump or med-related hepatitis. “My big caution is that almost nothing has worked out the way it’s been presented,” he adds. “One could write a nice story about promises made and broken. Entry inhibitors may be yet another.” Looking ahead, he advises, “Let’s ratchet down the expectation raised every two years. We need drugs that really work and more people on them.”

So what’s hype and what’s hope? Is the emperor nude or decently clothed? T-20, produced by Trimeris, a small biotech, is the first good FI to emerge from the pipeline. Close behind is Trimeris’ second-generation FI, the more potent T-1249, or, as insiders joke, “son of T-20.” Both peptides are made up of a long chain of amino acids too big to be taken orally; as a pill, stomach acid dissolves them, so they must be injected. T-20 is a peptide that binds to a unique viral sequence of the gp41 protein of HIV. “Son of” blocks a part of the gp41 molecule that’s different from T-20’s target, and early studies show the two drugs are also synergistic -- they are more potent when used together.

Trimeris recently signed a deal with Hoffman-LaRoche to develop and market the two T’s worldwide. For now, there’s no official word on how long it will take to get FDA approval of T-20. The drug was initially developed as a potency-booster of “salvage therapy” for patients who failed first- and second-line regimens. A first study of the drug in 1998 showed that T-20 could reduce HIV levels over a 14-day period as powerfully as some protease inhibitors. In a Phase II study of HIVers (none treatment-naive) with CD4 cells below 200 and viral-load levels above 100,000 copies, T-20 seemed to give an extra kick to HAART. Encouraged, Trimeris/Roche has enrolled patients into a multicenter Phase III efficacy trial that will provide more info about T-20’s pluses and minuses.

“I’m very enthusiastic about T-20,” says Joseph Eron, MD, a lead investigator for the T-20 Phase III at the University of North Carolina. “It has a 30-fold effect on HIV, so we know it’s potent -- maybe not as potent as some, but one that works on a new target. It will have its niche because a lot of people have burned through their options.” Even better, T-20 restores immune defenses. “I can tell you that we’ve seen very good rises in CD4 counts in some patients,” Eron says. “Even if the viral load starts to come back up, the CD4 levels stay high.” Although the trial isn’t looking at how functional these regenerated CD4 cells are, Eron says they’re a good sign.

Joseph Church, a pediatric researcher at Children’s Hospital in Los Angeles, has found equally

promising results. Working with T-20 in infants, Church says, “Overall, the results are quite encouraging. Pharmacologically, T-20 is unlikely to interfere with normal enzyme functions, and as a peptide with a sequence unique to HIV, it is also unlikely to interfere with normal protein functions.” At February’s Retrovirus Conference in Chicago, Church reported on a 24-week study of HAART plus T-20 in 13 positive children that showed the drug was well tolerated and caused rapid suppression of HIV. Again, the added benefit was CD4-cell increases -- up by an average of 82 at day 10, and continuing through week 16. He attributes the initial boost to T-20 alone.

Great, *but*,“ critics say. Are these increases sustainable? Will they protect the kids from OIs? T-20’s main downside is that peptides are reportedly expensive to manufacture, so if and when T-20 reaches the pharmacy, it may carry a high price tag. Another hitch is its inconvenient method of delivery -- via pump infusion or, more likely, a twice-daily injection. Ouch! It’s also messy to prepare; the drug comes in a powder that’s mixed with sterile water before injection. How commercially viable does that make T-20? ”It is certainly going to be very marketable,“ says Eron, ”but it may not be an agent that will be used outside of salvage settings at this point.“ He’s keen on T-20 as a booster to first-line regimens: ”It may be very useful for a few months when starting therapy, to get a more potent effect up front and avoid failure later on."

Again, there are unexpected ironies. This downside of FIs makes them attractive for pediatric use. For babies, shots are easier to take than pills or formula. In the baby T-20 trials, Church’s biggest worry is less about side effects or resistance than potential needlesticks by family members.

Next problem? Rapid resistance. Studies show that you can take the peptide drug just once and HIV develops resistance. But Eron warns about overstating the problem. “I think the rapid resistance issue is overplayed. Some of our most successful drugs select for quick resistance,” he adds, ticking off 3TC, nevirapine and efavirenz. Moore agrees, adding that a simple solution is using FI in multidrug cocktails.

As for the dreaded potential side effects, it’s hard to say. In clinical studies to date, Trimeris reports mild to moderate problems, including small, hard nodules under the skin at the injection site. There’s also headache, nausea, fever, weakness, diarrhea and dizziness. But with HAART known to cause all of these and more, which can be attributed to T-20 alone? Better future clinical trials might pinpoint the answer.

And the serious metabolic problems and damage to organs seen with other anti-HIV drugs? Nope, say researchers, no sign of anything like that. Early on, scientists worried that people might develop antibodies against T-20 -- Sonnabend’s concern -- because the immune system is primed to create antibodies to foreign molecules. But HIV-positive folks already have natural antibodies directed against gp41, so Eron thinks it’s unlikely that T-20 will produce a new reaction. In fact, the opposite may be occurring. Moore says that rather than stimulating antibody reactions, T-20 studies suggest the drug lowers them.

Now, the $64,000 question: What possible toxicity could be caused by having peptides acting outside of CD4 cells? As PWAs fret, researchers say no sweat. “It will either bind tightly to the

virus, or extracellular peptides will be cleared quickly through the blood or kidney," Eron says.

What about son of T-20? The buzz is building. Now entering Phase III trials, T-1249 is anywhere from two to 100 times more powerful than T-20, according to Cornell's Trip Gulick, MD, with double T-20's half life, so it can be taken only once a day. It also works against HIV-2 -- a bonus for people in Africa and the Caribbean with HIV-2 co-infection -- and SIV, the simian surrogate for HIV used in AIDS research. Best of all, T-1249 works against T-20-resistant viruses. Eron is testing T-1249 and, at the doses used so far, hasn't seen any T-20-like skin nodules.

Where do we go from here? Some envision an entry-inhibitors-only fix that can block HIV's entry at multiple points like a well-primed alarm system. Dreaming bigger, others hope the new drugs will prove their mettle as potent first-line combos, allowing HIVers to avoid costly protease drugs and nightmare side effects. But with such issues as FI resistance and drug delivery already plain to see, no one's shouting from any rooftops.

For now, the industry's goal is more good data, low toxicity and the holy grail: FDA approval of T-20. Leading treatment activists have a more urgent agenda. A very limited expanded-access program is starting for those in need of "deep salvage" therapy -- people with OIs or under 50 T cells and no other drug options. At press time, there were only 400 slots, with 147 promised to U.S. patients. Trimeris/Roche claims the peptide drug is hard to manufacture, slowing rollout. Allowing that this may be true, Linda Grinberg, who heads the Foundation for AIDS and Immune Research in Los Angeles, says, "When money is available to pay for a drug, companies manage to boost their production." With so few slots, she's worried. "A lot of people, including myself, will fall through the cracks." One reason: the protocol requires HIVers to have failed at least three new agents. "That leaves a lot of people out in the cold," Grinberg says.

She's eyeing the approaching wrenching ethical debates over who qualifies, how to add slots and beef up drug production. All that begs the critical question of how much T-20 will eventually cost, its commercial prospects and whether insurance will cover it -- but these are political, not clinical, hurdles. So start making some noise. We'll keep ya posted.

Enter, Blocking

Entry Inhibitors, the hot new class of anti-HIV drugs, target the virus as it attempts to unlock each door leading through the cell's surface: **attachment, coreceptor binding, fusion** and **integration**. HIV uses its first "key," a gp120 protein on its skin, to slip into a cell's CD4 receptor, giving access to coreceptor "locks" such as CXCR4 and CCR5. This messes with the gp41 molecule and lets the virus -- in a "coiled-coil" action -- harpoon and anchor itself inside the cell membrane.

With the help of Cornell University researcher Trip Gulick, MD, here's a brief bio of the pipelines' leading dark horses:

Attachment Inhibitors
PRO 542 (Progenics) is a potent anti-HIV agent, based on early human trials. It binds to gp120 on

HIV’s surface and blocks attachment. Its several days’ half-life may allow for once-daily dosing. In a Phase I trial, 15 patients who got a one-dose injection had significant reductions in viral load. Pediatric trials also show viral cuts. The drug is now in Phase I/II.

CXCR4 Blockers

Given the cell’s **CXCR4** coreceptor’s negative charge, small positively charged molecules are being tested to see if they bind strongly to CXCR4. **AMD 3100** (AnorMed) is a synthetic molecule with a powerful anti-HIV punch in lab studies. In mice, the drug worked against HIV viruses that use both the CXCR4 and the CCR5 coreceptors, but not against viruses that selectively use the CCR5 coreceptor. AMD 3100 is in Phase I/II.

CCR5 Blockers

The cell’s CCR5 coreceptor has a neutral charge, but small molecules may lock tight to it. **Schering C** (Schering Plough) is a CCR5 blocker that works against both viruses that use the CCR5 coreceptor and those using both CCR5 and CXCR4 coreceptors, but not viruses that use just the CXCR4. Got that? The drug is taken orally once daily. Development of Schering C is on hold; instead, the company is pushing a cousin, Schering D.

Integrase Inhibitors

Protease, reverse transcriptase and integrase are the three HIV-specific enzymes. Development of drugs that keep the viral genes from fusing with cell genes are underway. **AR-177** (Aronex), well-tolerated in the lab, is now in Phase I. **S1360** (Shinogi) is set to enter early human trials.
