Seattle Rattle

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By the close of the wonkish wonderland in Seattle known as the 9th-annual Conference on Retroviruses and Opportunistic Infections, 2002 had been hailed as The Year of the Entry Inhibitors (EIs). Imagine an entirely new strategy to attack HIV. Are happy days here again?

Nearing the finish line first is Trimeris/Roche's EI, T-20. In a one-year study of T-20 in combo with HAART, half of 50 pre-treated and 70 untreated HIVers saw their viral load disappear below 400. Both Schering-Plough and Bristol-Myers Squibb (BMS) showcased their EIs, too. Along with T-20, these three compounds represent three unique approaches to blocking HIV from entering (duh!) a cell: docking, attachment and fusion. First, HIV sinks its gp120 protein spike into your cell's CD4 receptor. Second, HIV hooks onto one of the "co-receptors," such as CCR5. Third, HIV "fuses" with the cell to insert its RNA.

BMS' aptly named BMS-806 targets the first step of the entry process, altering the structure of the gp120 spike to prevent it from latching onto a CD4 cell. While BMS is gushing over its test-tube data, human tests -- set for this year -- will be the acid test.

Schering's EI, SCH-C, has made it that far. SCH-C is a molecule that inhibits the second stage of entry: It glomms onto a cell's CCR5 co-receptors and mucks up viral attachment. In a preliminary eight-week study, SCH-C used alone in 12 pre-treated patients reduced viral load by two-thirds in 10 of them.

T-20 blocks the final step of HIV entry: fusion with the cell and insertion of viral genes. T-20 (and its sister T-1249) have previously shown a potent punch against drug-resistant HIV, with relatively little toxicity. Trimeris hopes for the FDA stamp of approval later this year.

In addition to the EIs with their docking, attachment and fusion targets, the Retrovirus pageant debuted the first human data on a fourth new strategy: integrase inhibitors (IIs), which gum up the machinery of the HIV integrase gene. This important gene, so named because it incorporates, or "integrates," HIV into your cell's genes, remains a fast-moving target. An earlier II gave a stellar performance in the test tube but bombed in humans. Still, hopes are high for two new IIs -- Shionogi's S-1360, which recently moved into human studies, and Merck's L-708,906, set to enter Phase I human trials in March.