Receptor decoy shows promise against AIDS

The first two clinical trials of a novel AIDS drug suggest the experimental treatment is safe, researchers report, and one study provides subtle evidence that the treatment may help slow progression of the disease.

Scientists emphasize that both studies – the first to investigate the value of a genetically engineered compound called soluble CD4 – are preliminary and that detailed efficacy trials remain far from complete. But they express enthusiasm that the drug caused no significant toxicity even at the highest doses given. If the still-experimental treatment helps slow viral replication in AIDS patients, as hinted by one of the studies, then it may prove especially useful in conjunction with AZT or other antiviral drugs currently under investigation, researchers say.

"There are some real scientific hurdles before we can say this treatment works," warns Robert T. Schooley, an infectious-disease specialist at Massachusetts General Hospital in Boston, who led one of the studies. "This is a progress report along a long road that may go nowhere."

However, with promising results starting to emerge in the patients who received the largest doses, Schooley says his team plans to test even higher doses. "There's no particular reason to stop when you don't see toxicity," he told SCIENCE NEWS.

Schooley and 21 colleagues tracked the effects of soluble CD4 injected into 25 patients with AIDS or advanced AIDS-related complex (ARC). The drug mimics the lymphocyte receptor CD4, through which the AIDS virus (HIV) infects these white blood cells. On the basis of previous work *in vitro,* researchers had hypothesized that by flooding the body with excess quantities of free-floating CD4 receptors, they might "mop up" circulating HIV before the viruses had a chance to invade white blood cells.

In the Schooley study, patients gave themselves intramuscular injections of the soluble CD4 – much as diabetics self-administer insulin – three times a day for up to 28 days. The most serious side effect was a rash that disappeared when the patient who developed it stopped taking the drug. On average, patients receiving the highest dose of soluble CD4 experienced a 23 percent drop in blood levels of HIV p24 antigen – an indication of modestly reduced HIV activity.

In the other study, James O. Kahn of San Francisco General Hospital and his colleagues provided soluble CD4 to 42 AIDS and ARC patients by intravenous, intramuscular or subcutaneous injection for 11 weeks. Using doses about one-third those of Schooley's group, the researchers noted no serious side effects, but they also saw no immediate benefits.

The two studies, described in the Feb. 15 ANNALS OF INTERNAL MEDICINE, allay some of the fears previously expressed by researchers, who until now could only guess about soluble CD4's safety. For instance, scientists had wondered whether the protein might trigger an immune response that could destroy useful white blood cells bearing CD4 receptors. So far, that does not appear to be a problem. The studies also provide valuable data on the schedules and dosages required to maintain significant quantities of the drug in the bloodstream.

But other questions remain, such as whether soluble CD4 blocks HIV infection of other white cells such as macrophages and monocytes, which can also serve as HIV reservoirs. Scientists also wonder whether CD4 may prove even more valuable as a "carrier molecule" to deliver toxins to HIV or infected cells.

Ultimately, cost may emerge as a serious problem. A British company, SmithKline Beecham PLC, announced this week it had abandoned its efforts to make a commercial CD4-based AIDS drug, citing high costs and production hurdles. Only two other companies make soluble CD4 – Genentech Inc. of South San Francisco and Biogen Inc. of Cambridge, Mass.

"It's going to be expensive," Schooley warns. Although Biogen has developed a new process that cuts production costs to one-tenth, he says, the drug will probably remain more expensive than AZT, the only AIDS drug to gain FDA approval.

Despite such concerns, the new results suggest "cautious optimism is warranted," write virologists Edmund C. Tramont and Robert R. Redfield of the Walter Reed Army Medical Center in Washington, D.C., in an editorial accompanying the research report. – *R. Weiss*

Hominid skull has human-like drainage plan

An expanding network of veins controlling the flow of blood from the brain characterized the more than 2-million-year-old hominid species *Australopithecus africanus,* a pivotal but poorly understood member of the evolutionary family that includes modern humans. This finding, confirming work with other *A. africanus* skulls, suggests that the sprouting of these veins and the reorganization of other venous channels may have set the groundwork for the dramatic increases in brain size observed in the *Homo* lineage that led to modern humans, Glenn C. Conroy of Washington University Medical School in St. Louis and his colleagues assert in the Feb. 16 SCIENCE.

The researchers literally looked right through the rocky filling clogging an *A. africanus* skull by using computerized tomography (CT) scans whose special computer software produced two- and three-dimensional images (SN: 12/19& 26/87, p.408). The computer imaging technique also reconstructed a missing portion of the cranium based on a statistical analysis of the endocranium, or inner surface of the braincase.

The endocranial capacity of the specimen, which provides an estimate of brain size, is fairly small, Conroy says, and confirms a previous calculation based on indirect comparisons with another *A. africanus* skull.

CT analysis of the endocranium reveals a venous drainage system similar to that observed on four of the five additional *A. africanus* skulls that have been discovered, the researchers note. The other skulls do not have a hardened filling to obstruct endocranial measurements. The drainage pattern, which occurs in more pronounced form among modern humans, consists of enlarged sinus grooves running laterally down the temporal bone, as well as marks made by a network of veins around the foramen magnum, the large opening in the skull through which the spinal cord passes.

Prior studies of *A. afarensis,* the 3.5-million-year-old hominid species to which the famous Lucy belongs, and the robust australopithecines – a hominid lineage that emerged around 2 million years ago and died out 1 million years later – show a contrasting venous drainage pattern. Enlarged sinus grooves run down the occipital bone, from the back of the head to the foramen magnum; branching veins around the foramen magnum are not apparent.

The new CT study adds to a growing body of evidence that *A. africanus* shared an evolving mechanism for clearing blood from the brain with later members of the *Homo* lineage, Conroy maintains.

The finding also fuels a theory developed by Conroy and two others – Phillip V. Tobias of the University of the Witwatersrand in Johannesburg, South Africa, and Dean Falk of the State University of New York in Albany. They propose that early hominids developed an altered blood flow from the brain when they began walking upright. In some species, such as *A. africanus,* a network of veins was established to cool the brain and allow it to increase greatly in size. Other species, such as the robust australopithecines, had no extensive cooling system and thus remained small-brained.

However, the evolutionary role of *A. africanus* – which dates to between 3 million and nearly 2 million years ago – remains unclear, Conroy adds. Most researchers class it as a sister species or direct ancestor of the *Homo* lineage.

– *B. Bower*