AIDS-related complex (ARC) and AIDS patients is that bone marrow progenitor cells are HIV-1 infected, requiring that the virus could be tropic for CD34+ progenitor cells. Brian Davis and Jeffrey Marx of the Medical Research Institute, San Francisco and colleagues at Pacific Presbyterian Medical Center and Stanford University Medical School (Palo Alto, CA) purified CD34+ cells from the bone marrow of HIV-infected individuals and analyzed the cells for the presence of viral nucleic acid using the polymerase chain reaction (PCR) immediately or following growth in colony assays. Despite the extreme sensitivity of the PCR assay for HIV, no virus could be detected in either freshly isolated CD34+ cells or cells allowed to form colonies in culture. Interestingly, efficiency of colony formation by CD34+ cells from HIV-positive asymptomatic individuals did not differ from that of cells isolated from seronegative control individuals, but these same cells isolated from symptomatic HIV-positive patients generated colonies very poorly.

The investigators concluded that infection of bone marrow progenitor cells cannot explain hemopoietic suppression in ARC/AIDS patients. Marx points out that, based on previously published reports, they fully anticipated finding HIV present in the CD34+ cells and will continue to "look elsewhere" for the suppression mechanism.

These findings parallel those reported by Von Laer et al. from the Bernhard-Nocht Institute of Tropical Medicine (Hamburg, F.R.G.); this group was unable to demonstrate that progenitor CD34+ cells were infected when the cells were purified from 12 AIDS patients, ARC patients, and 10 HIV-infected individuals with cytopenia.

Davis noted that, with respect to the poor colony formation results with CD34+ cells from symptomatic individuals, "What you'd like to have is a clear-cut case of bone marrow suppression paralleling reduced colony formation. But there's not enough data at this time to make a clear-cut connection. Some people with perfectly good cell counts show colony suppression. We're going to see if this finding holds up in a greater number of individuals."

Such studies defining the molecular mechanisms evolved by HIV to survive and infect its host with maximum efficiency provide sobering evidence of the challenges facing the research and clinical communities confronted with the current pandemic. **—Patricia F. Dimond**

CLINICAL TRIALS UPDATE

ADVANCES IN GAUCHER'S, AIDS

CHICAGO—Highlights of recently published literature on clinical trials of biotechnology-derived products include:

- *Ceredase—On Top of Its Game.* Although Phase III clinical trials have been completed on the use of Ceredase (glucocerebrosidase) in the treatment of Gaucher's disease, few examples of the safety and efficacy of the product appeared in the literature until a recent study published in the *Proceedings of the National Academy of Sciences* (**87:**1913, March 1990).

Gaucher's disease is a genetically inherited disorder characterized by the absence of the enzyme glucocerebrosidase (GCR), which is critical for metabolizing lipids. The absence of GCR results in the life-threatening accumulation of lipids in certain body tissues.

Gaucher's disease has three distinct forms that correlate with the severity of the disease. The most benign form is Type I, resulting in an enlarged spleen and recurrent bone pain. These symptoms, however, are not without consequence: Type I patients have been shown to have 30-pound spleens, compared with the normal half-pound organ. Type II is characterized by enlargement of the spleen and liver, and neurological complications that begin at infancy. Afflicted children have significantly impaired motor skills and, as the disease progresses, death can often result by the age of two or three. The disease is prevalent among Jews of European descent. The National Institute of Mental Health estimates that as many as 20,000 individuals in the U.S. suffer from the illness. There is no current therapy and Genzyme's (Boston, MA) Ceredase represents a striking new advance against the disease.

Ceredase was administered on a weekly basis by IV infusion at a dose of 10 million units over a five-minute period. In this case, infusions were begun at age four and 14 infusions were administered during the first 26 weeks of the protocol. A gradual and progressive increase in hemoglobin from severely depressed levels to near-normal was seen. Significantly, upon withdrawal of the infusions, hemoglobin declined. A rise in platelet counts from severely depressed levels to near-normal also occurred. The patient also appeared to be more vigorous, the abdomen was less extended, and the spleen size dramatically decreased. There were no toxic side effects.

- *Recombinant Soluble CD4 in AIDS—Keep Holding Your Breath.* Considerable attention is being placed on the development of recombinant soluble CD4 (rsCD4) as a potential therapy for AIDS. A recent edition of the *Annals of Internal Medicine* (**112:**247, February 1990) described a Phase I/II escalating-dose trial using rsCD4.

Although AZT has been shown to reduce the mortality and morbidity associated with AIDS, dose-limiting side effects of bone-marrow toxicity and tolerance levels have created an opportunity for the development of alternate therapies.

It appears that the HIV virus affects immune cells through the binding of the HIV envelope glycoprotein (gp120) to the CD4 molecule on T cells. This observation has led to the development of anti-viral agents that interfere with this binding. Two biotechnology companies—Biogen (Cambridge, MA) and Genentech (So. San Francisco, CA)—are using rsCD4 to inhibit gp120 binding to T cells. The current study describes the safety, pharmacokinetics, and preliminary efficacy of Biogen's product.

Twenty-five AIDS patients with fewer than 300 T4 cells per cubic millimeter were included in the trial. The dosing regimen involved intramuscular injection of rsCD4 to cohorts of three patients at each dose level. Patients received 27 courses of therapy; 17 received 0.9, 3, or 9 milligrams per day and 10 received 30 milligrams per day. The serum half-life after intravenous administration is approximately 45 minutes. Following intramuscular injection, peak levels were not reached in the bloodstream until 4–6 hours. Repeated intramuscular administration showed that a stable concentration of the drug could be measured in the bloodstream. No severe or life-threatening toxicities were observed, although some developed a mild reaction at the injection site. HIV-related p24 antigen levels were determined in each patient. No changes were seen at the three low-dose regimens, but patients receiving 30 milligrams daily had decreased levels by an average of 23 percent from baseline (statistically significant with $p=0.021$).

This study provides the first evidence of potential anti-viral activity of rsCD4 in humans. However, these decreases in p24 antigen levels were not as significant as those previously seen with nucleoside analogs such as AZT, ddI, or ddC; thus, the potential use of rsCD4 will likely involve a cocktail approach. **—Peter F. Drake**