Gene injections stem clotting disorder

For most people, a bump on the arm means dull pain and a purple bruise. For an estimated 5,000 men in the United States, the same bump can cause uncontrollable internal bleeding and a frantic trip to the emergency room. Relief from this inherited clotting disorder, hemophilia B, has now come a step closer, thanks to gene therapy performed on a unique group of hemophiliac dogs.

According to two reports in the January NATURE MEDICINE, a single infusion of a clotting-control gene slowed bleeding in these animals. The dogs, from a colony bred for more than 30 years from a hemophiliac ancestor, are good models of human hemophilia because their disease occurs naturally and mimics that in people.

Normal blood quickly gels when it spills from blood vessels, but that of people and dogs with hemophilia B lacks a clotting protein called factor IX. Using the gutted shell of a common virus, each research team delivered copies of the gene for factor IX to the dogs' liver or muscle cells.

"What's important is that we get sustained expression of clotting factor at a level that would be therapeutic to humans," says Katherine A. High of the Children's Hospital of Philadelphia.

High and her team injected the adeno-associated virus loaded with the factor IX gene into the leg muscles of five hemophiliac dogs. The increase in the clotting protein, a result sustained for the 18 months since the dogs were treated, was equivalent to 1.4 percent of its concentration in normal human blood. Clotting improved enough in the treated dogs to prevent most of their spontaneous internal bleeding. What's more, the dogs' immune systems did not attack the carrier virus.

Even such a tiny increase in factor IX could save the lives of people with hemophilia B, who can suffer dangerous spontaneous bleeding in the joints or the brain, High says. High is now seeking approval from the Food and Drug Administration to try out similar muscle injections in people.

Doctors have been looking for ways to replace faulty or missing genes for 20 years, but no therapy is yet used in general practice, says geneticist and gene therapist Savio L.C. Woo of the Mount Sinai School of Medicine in New York City. "I'm rather optimistic that the new technology will show significant clinical benefit for people," he says.

One reason for Woo's optimism is the success of a second group, led by his former colleague Mark A. Kay, now at the Stanford University School of Medicine. Kay's team injected virus carrying the clotting-factor gene directly into blood vessels entering the dogs' livers, the natural source of clotting proteins in healthy animals. Kay says injections into the liver are more potent than into muscle.

In a study 6 years ago, Kay, Woo, and their colleagues used a different type of virus to carry the clotting gene into dogs' cells (SN: 10/2/93, p. 215). Concentrations of clotting proteins that resulted, however, were only one-tenth those in Kay's current study. In addition, the earlier experiment required lopping off two-thirds of a dog's liver to stimulate cell division and gene uptake. At that time, Kay says, he never imagined the technique could be translated to humans.

In the past decade, biotechnology companies have developed viruses that are better at inserting a needed gene into cells' chromosomes. Genes integrated into chromosomes are passed on when a cell divides. "There's a very high probability that [the therapy] should last lifelong with one infusion," says Kay.

High, however, suspects that patients would have to have new gene infusions every year or two. With or without such booster treatments, gene therapy offers better care than current techniques, she says.

Intravenous infusions of factor IX protein prepared synthetically or from human blood can stop bleeding episodes, but the factor lasts only about 24 hours in the bloodstream. Annual costs for preventive infusions can run more than $300,000 per patient, pushing such care out of the reach of most patients.

As longtime competitors, Kay and High may not always agree on the therapy's details, but they plan to work together on the human trial proposed by High. The pair expects to hear from the FDA later this year. —*S. Simpson*

Diagnosing the Internet's ills

Doctors fire X rays into a patient, collect them as they emerge, and then use computers to piece together information on the health of internal organs. Researchers are now developing an analogous scheme to visualize what is going on within the vast, international network of computer networks and telecommunications links known as the Internet.

Daniel McRobb, Tracie E. Monk, and Kimberly C. Claffy of the Cooperative Association for Internet Data Analysis (CAIDA), based at the University of California's San Diego Supercomputer Center, describe their Internet tomography project in a paper available at the NATURE Web site (http://helix.nature.com/webmatters/tomog.html).

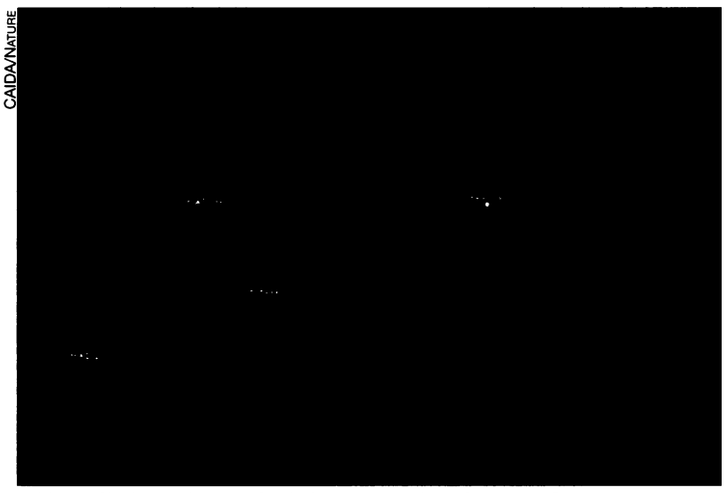
Made up of researchers from academia, government, and industry, CAIDA represents a significant effort to track data traffic (SN: 10/17/98, p. 255), map usage patterns, and depict the Internet's structure.

The Internet can be thought of as a rapidly growing organism, the researchers say. With new connections among the backbone networks made hourly, "it is critical for the evolution of the Internet that insights into its overall health . . . are obtained," the team asserts.

Claffy's team has developed a computer program called skitter to send small, standard packets of data from six sources in the United States to more than 29,000 destinations around the world. The scientists collect data on the round-trip time and path followed as each packet hops from computer to computer to get to its destination.

Computer mapping of that information allows the researchers to visualize how the parts of the Internet are connected at a given time. "One of the useful features is the identification of critical Internet components," says Dave Plonka of the University of Wisconsin-Madison.

Preliminary images of the Internet's structure reveal that a surprisingly small number of backbone networks carry the bulk of the data, Claffy and her colleagues report. Future plans include increasing the number of sources and destinations and refining visualization techniques. —*I. Peterson*



CAIDA/NATURE

This preliminary image depicting connections between Internet computers reflects traffic data between a U.S. source and thousands of destinations worldwide. The colors represent different backbone networks: purple for AT&T, red for MCI, and so on. MAE denotes a major network interconnection point.