AIDS Vaccine: Research on Target

Since the AIDS virus, now known as HIV, was first identified in 1983, more than a half-dozen related viruses have come under scrutiny by scientists trying to understand HIV's mechanism of infection. Two previously unknown relatives of HIV have also been discovered (HIV-2 and STLV-III), leaving researchers awash in an alphabet soup of distinct but related viruses — including some that infect humans, some that are restricted to monkeys, some that cause disease and some that apparently do not. The genetic diversity displayed by the HIV family, and the fact that HIV itself fails to cause AIDS in other animals, has hampered the study of the disease and the search for a vaccine (SN: 5/9/87, p.297).

But two new studies published in the Aug. 6 NATURE go a long way toward sorting out the relationship among these viral varieties. Moreover, they offer hope that AIDS vaccine development may proceed more rapidly than was anticipated.

Researchers at the National Cancer Institute (NCI) report that they have determined the entire 9,264-nucleotide sequence that makes up the genome of an AIDS-like virus found in African green monkeys. The researchers, Genoveffa Franchini, Robert C. Gallo and their colleagues, then compared that sequence to the genetic codes of previously cloned AIDS-related viruses. They found that the newly sequenced STLV-III_{AGM} virus, although apparently nonpathogenic in green monkeys, is genetically very similar to HIV-2 (the cause of AIDS in West Africa) and is to a lesser extent related to HIV-1 (the cause of AIDS in the United States).

The new analysis resulted in two important findings. First, the scientists identified genetic variations that may explain why certain strains of AIDS-like viruses do not cause disease. Second, and more important from the standpoint of vaccine development, they found striking similarities within certain genomic regions that code for the production of viral envelopes, or outer skins, of the strains they compared. In almost all cases, for example, the nucleotides that code for the amino acid cysteine are located in exactly the same positions on the genome. This is true even in strains whose genomes otherwise vary by as much as 25 percent.

Researchers theorize that such highly conserved regions are critical to the process of infection — perhaps enabling the virus to bind to the T4 antigen on human lymphocytes. Because so many strains of AIDS-related viruses share these nucleotide sequences, the proteins they code for may be ideal targets for antibody tests and vaccines.

In related research, Pierre Tiollais and others at the Institut Pasteur in Paris say they have cloned and sequenced the entire genome of a virus that causes an AIDS-like disease in macaque monkeys. The virus, STLV-III_{MAC}, is the only virus that is known to share most of the properties of human AIDS-causing viruses and that actually causes an AIDS-like disease in animals. The accomplishment opens the door to preliminary tests of recombinant vaccines on animals.

Animal models are considered essential for testing potential vaccines, but until now scientists have been frustrated by the lack of an appropriate animal to work with. Chimpanzees, although they can harbor HIV, are in short supply, and in any case fail to develop AIDS when infected. Although the STLV-III_{MAC} virus differs somewhat from human AIDS-causing viruses, it has several genetically conserved regions identical to some regions in HIV-1 and HIV-2. Scientists hope to test a variety of STLV-III_{MAC} antigens as potential vaccines in macaques, and then — by referring to the newly created nucleotide map — test analogous HIV antigens in humans. *— R.Weiss*

Manipulating milk in mammals

All mammals produce milk, but not all mammal milk is identical. In ruminants such as cows and sheep, for example, the major milk protein is beta-lactoglobulin (BLG). Rodents, on the other hand, don't produce any BLG at all. At least they never used to.

J. Paul Simons and fellow researchers at the Edinburgh (Scotland) Research Station report in the Aug. 6 NATURE that they have successfully bred mice carrying the sheep BLG gene, and that these mice now produce milk that is chock full of BLG. The researchers suggest that similar experiments with dairy animals may not be far behind, and that "the manipulation of milk composition by gene transfer has considerable potential."

The experiments were done by microinjecting genetic material coding for BLG into fertilized mouse eggs that were then reimplanted into "surrogate" female mice. Of the 46 offspring successfully weaned, 16 carried the BLG sequence, and the females among them later produced BLG-rich milk. In the case of one such female, BLG was produced at more than five times the concentration usually found in sheep milk. Moreover, some of the mice passed on the BLG gene to their offspring.

The authors note that milk provides 20 to 30 percent of the total protein intake of people in the industrialized world, and claim that "gene transfer into dairy animals should be viewed as a realistic approach for the production of milk with enhanced nutritional value."

In addition, they say, it may be possible to engineer dairy animals to produce nonnutritional but otherwise valuable proteins in milk. They have already taken the gene that codes for the production of human Factor IX (a blood protein lacking in certain forms of hemophilia) and fused it to the BLG gene in sheep — with an eye, it seems, toward extracting Factor IX along the whey. *— R. Weiss*

No resistance to superconductivity

If it's true that sound travels faster than the speed of light in the nation's capital, then the phrase "high-temperature superconductivity" might have set new records last week, prompting a pack of political proposals designed to speed commercialization of an as-yet-unproven technology.

Led by President Reagan, officials announced the creation of councils, committees and consortia to aid the push to move superconductivity out of the lab and into the marketplace before foreign competitors do so. The proposals came at a Washington, D.C., gathering of more than 1,000 government officials, industry experts and academics brought together by invitation only for the Federal Conference on Commercial Applications of Superconductivity.

The major thrust of government involvement came under the President's Superconductivity Initiative, an 11-point plan designed to speed research on the technology that enables certain materials to lose their electrical resistivity at temperatures high enough to replace today's expensive liquid-helium cooling with more affordable liquid-nitrogen cooling techniques (SN: 3/28/87, p.196). If scientists can overcome the obstacles needed to perfect the technology, high-temperature superconductivity could eventually cut costs and increase per-

formance of many existing electrical and electronics systems.

The initiative includes:

- three legislative proposals that would relax antitrust laws to allow manufacturers to enter into some types of joint ventures, amend patent laws so that U.S. companies may seek damages when imported products infringe on patents, and change the Freedom of Information Act so that federal labs may withhold from the private sector information deemed commercially valuable.
- creation of a three- to five-person group from industry and academia that would advise the administration on superconductivity research and commercialization policies.
- initiating measures that would speed the commercialization of superconductivity, including "quick start" grants for research into processing superconducting materials and allocating $150 million for the Department of Defense to apply the technology to military systems over the next three years.

The initiative also calls for several federal departments and agencies to set up a number of Superconductivity Research Centers across the United States to conduct research and disseminate information. The Department of Energy will set up three: the Center for Superconductivity Applications at the Argonne (Ill.) National Laboratory, the Center for Thin Film Applications at the Lawrence Berkeley (Calif.) Laboratory and the Center for Basic Scientific Information at the Ames (Iowa) Laboratory. The Department of Commerce will establish a center at the National Bureau of Standards laboratory in Boulder, Colo., which will focus on electronic applications.

Reagan also announced the formation of a Council on Superconductivity for American Competitiveness that will be headed by former White House Science Adviser George A. Keyworth. Based in Washington, D.C., the council will serve as a clearinghouse of information on superconductivity for those who want to commercialize the technology.

In addition, the Energy Department's Office of Scientific and Technology Information has started a computer data base for superconductivity.

And on Capitol Hill, Rep. Dave McCurdy (D-Okla.) and Rep. Don Ritter (R-Pa.) introduced separate bills last week to facilitate the manufacturing of superconducting materials through additional funding and the formation of more cooperatives among government, industry and academia. — *K. Hartley*

Frogs get the jump on microbes

While staring at a frog recovering from a surgical procedure last summer, microbiologist Michael Zasloff took a leap of thought that led to the discovery of a fast-acting family of microbe-killing peptides. The frogs used in Zasloff's genetics studies at the National Institute of Child Health and Human Development swim in water teeming with bacteria, fungi and parasites. Yet in spite of the incisions and sutures giving the microbes a perfect entrée into the frogs' bodies, the invaders appear to be thwarted because the frogs heal normally, without a trace of infection.

As described in the August PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol. 84, No. 15), Zasloff first posited and then showed that something in the frogs' skin staves off microbial attack. The something turned out to be two 23-amino-acid peptides that Zasloff says are functionally distinct from any substance so far described in animals. Moreover, their discovery in frogs represents the first time a chemical defense system outside of the immune system has been identified in vertebrates. Zasloff suspects that similar peptides — which he has dubbed "magainins" after the Hebrew word *magain*, or shield — will be found in humans. If so, they may help scientists understand and treat a variety of diseases and conditions.

In low concentrations, the frog magainins kill various (though not all) types of invading bacteria, fungi and protozoans, but they leave human red blood cells intact. Zasloff says he doesn't know how the magainins are able to distinguish between the invaders and the "good" cells indigenous to the body. But he does have some clues to how they attack the infecting microbes.

The peptides are amphiphilic: Half the molecule is oily and half is water-loving. This enables them to coil into structures that are ideal for interacting with membranes. When Zasloff exposed a paramecium to magainins, it swelled and burst within seconds.

"What exactly [the magainins] are doing to membranes we don't know," he says. "But in [the paramecium] they are dramatically affecting water flux." His laboratory is now testing magainin potency against viruses and cancer cells.

Zasloff suspects that magainins may be the vertebrate counterpart of cecropins, 37-amino-acid-long antibacterial peptides found circulating in insects such as the *Cecropia* moth, which lacks both lymphocytes and antibodies. "This is almost certainly part of the invertebrate defense system generally," says Zasloff. "It was thought that things like this would not be found in vertebrates. But [magainins] are a major component of the frog's skin and [probably] circulate throughout its body."

Zasloff believes that magainins in the frog represent a first-line defense system developed very early in evolution. How, he asks, did simple metazoan creatures, devoid of white cells or other immune system elements, survive the microbial soup in which they lived? "Why weren't they seen as pieces of meat [by the microbes]?" Like these creatures, frogs, which survived millions of years in water and which now have immune systems similar to ours, must also have had some primitive way of protecting themselves or they wouldn't have survived, he adds.

If frogs possess magainins, why not humans? Zasloff notes that the frog magainins are made throughout the animal's skin by the granular gland, which also produces neurotransmitters and hormones. Many proteins isolated from this gland, he says, have been found to have analogs in the gut and nervous systems of mammals. There's a good chance, he says, that "we're going to find the same antimicrobial peptides in those sites in mammals, including humans."

Zasloff has cloned the genetic message of the frog magainins and is using these clones as probes to search for similar peptides in humans. If they are found, they might explain how corneas and other body parts are able to heal without the inflammation associated with white blood cells.

The discovery of magainins in frogs may explain the frog's popularity in folk medicine. Zasloff says he's been told, for example, that people living in Argentine villages commonly strap a frog onto wounds to help them heal. Perhaps this practice induces the frog to release magainins in the same way Zasloff has found that a shot of adrenaline will cause frogs in his laboratory to release the contents of their granular glands. The finding also suggests that synthesized magainins may have medicinal uses such as the treatment of burns.

But what excites Zasloff most about his discovery is that it might offer a long-sought explanation of cystic fibrosis. From about the time of birth, the lungs of children with this inherited disease become colonized by bacteria, but for some reason the bacteria do not infect the rest of the body. Moreover, mucus-secreting cells in the children's airways (and other secreting cells elsewhere) have difficulty transporting water and ions across their membranes. If magainins, with their antibacterial and membrane-damaging abilities, are found in humans and especially in the respiratory tract, he says, "my gut sense is that a defect or interference in [the magainin system] could underlie some of the symptomatology of cystic fibrosis."

As a pediatrician as well as a microbiologist, Zasloff says he has been plagued by the cystic fibrosis question for a decade. With the frog magainins, he thinks he has at last found an experimental entry into the study of the disease.

— *S. Weisburd*