als have rested on optically active organic molecules known as chromophores. Chemists can easily tailor these molecules and incorporate them into transparent host polymers. In 1989, Garito and his colleagues proposed a strategy for developing chromophores that have strong third-order NLO properties: create molecules that can sustain large separations of electric charge.

These researchers knew that many chromophores can essentially shuttle negative charges to one end of the molecule, leaving the other end positively charged, and that this separation increases in response to light. They calculated that the greater this light-driven charge separation, the greater the material's light-changing NLO properties would be. As Marder's collaborator George Stegeman, a physicist at the University of Central Florida in Orlando, explains, the charge separation alters the electronic structure of the molecule, making it easier for trios of photons to interact in the material.

In 1993, Marder and his colleagues improved a class of small chromophores to more than double their NLO properties. In the current experiment, the team turned to longer molecules whose charges could separate even farther. The researchers started with a batch of β-carotene, a well-known third-order NLO chromophore consisting of a long, narrow chain of carbon atoms capped on either end by ring-shaped groups. One of the rings is an electron-hungry "acceptor" group that snags an electron from the other end of the molecule, giving β-carotene its NLO properties, among the strongest yet observed.

To enhance these properties, Marder and his colleagues replaced the β-carotene's acceptor with successively stronger electron grabbers. When Stegeman and his colleagues at Central Florida added these chromophores to a polymer known as poly (methyl methacrylate) and spun it into films, they found that the films made with chromophores that had the strongest electron grabbers produced an NLO effect 35 times stronger than the starting molecule. For many applications, says Garito, that is "very close" to what's needed for commercial success.

The chromophores break down when they are exposed to light and heat, ruling out their use in light-based communication devices, says Nasser Peyghambarian, an NLO expert at the University of Arizona, Tucson. But he and others believe that the same charge-separation strategy could improve the NLO properties of other types of molecules, among them more robust chromophores made from chains of linked rings or compounds containing stable metal complexes. "It's fairly wide open," says Garito. If so, more and more communications visionaries are likely to see the light.

–Robert F. Service

AIDS VACCINE

Looking for Leads in HIV's Battle With Immune System

BETHESDA, MARYLAND—When officials at the National Institutes of Health (NIH) tapped Nobel laureate David Baltimore last December to head its newly formed AIDS Vaccine Research Committee, they hoped he would give a much-needed boost to a floundering field. It is too early to tell whether Baltimore's committee will live up to those expectations. But a 4-day meeting* on AIDS vaccine development held here at the NIH last week suggests that it will have plenty of new leads to follow.

AIDS vaccine development has been limping along since 1994, when NIH decided not to push ahead with large-scale tests of the leading vaccine candidates because they didn't look promising enough (see sidebar). The organizers of last week's meeting—the ninth in a series of these annual gatherings—tried to give the field a booster shot by adding reports of cutting-edge basic research on how HIV causes disease to the standard AIDS vaccine fare. This strategy seemed to pay off. Several reports—including one by Baltimore—on the protective role played by the immune system's killer cells, called cytotoxic T lymphocytes (CTLs), sparked much discussion. A presentation on the possible capture of a long-sought factor that provides some protection against HIV sent a ripple through the meeting, as did a suggestion that a goat virus might provide the basis for an HIV vaccine.

> **"I'm convinced that we will have a vaccine ... in a reasonable period of time."**
>
> **—Anthony Fauci**

Although the 550 attendees heard no headline-grabbing talks, veterans in the field came away moderately encouraged. "Pessimism is destructive," said Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID). "I'm convinced that we will have a vaccine and that we'll have it in a reasonable period of time."

For many AIDS vaccine researchers, the most troubling roadblock has been teasing out which immune responses a vaccine should trigger to protect a person from HIV. Most viral vaccines work by stimulating the immune system to produce antibodies that bind to a virus, preventing it from infecting cells. But it's not clear that antibodies offer much protection against HIV. "As I try to understand the role of antibodies, ... I keep coming up with a blank," said Baltimore, hence the focus on CTLs.

Like smart bombs, CTLs search out and destroy cells that a virus has infected. They play a key role in the body's natural defenses, and many traditional vaccines stimulate their production along with antibodies. "Cytotoxic T lymphocytes are at least very important, if not the most important, thing [for protection from HIV]," said Baltimore.

However, an AIDS vaccine that stimulates CTLs would face hurdles too, as Baltimore's own work shows. When a cell is infected by HIV, it typically puts a piece of the virus on its surface. CTLs are trained to pulverize any cells that display these viral peptides. Baltimore and his Massachusetts Institute of Technology colleague Kathleen Collins, collaborating with HIV CTL guru Bruce Walker of the Massachusetts General Hospital, have new evidence that HIV escapes the deathblows of CTLs by preventing cells from displaying viral peptides.

Building on work first published in the March 1996 *Nature Medicine* by the Pasteur Institute's Olivier Schwartz and co-workers, the Baltimore group focused on the HIV protein Nef. As the Schwartz group showed, Nef can prompt cells to yank down from their surfaces a molecule known as the major histocompatibility complex (MHC), which displays viral peptides to the immune system. The group predicted that this "down-regulation" of MHC would make HIV-infected cells resistant to CTL killing—just what the Baltimore group's new data now show. Baltimore says these findings imply that if researchers hope to base a vaccine on stimulating CTLs, the timing is critical: Unless CTLs flood the bloodstream shortly after an infection occurs, HIV may undermine their utility by dispatching Nef.

That may be a tall order, but one heartening talk at the meeting, by Duke University's Kent Weinhold, suggests that the down-regulation of MHC by Nef does not completely shut down CTL activity. "I don't think it's an all-or-none phenomenon," says

* Conference on Advances in AIDS Vaccine Development, 4–7 May, sponsored by NIAID, Bethesda, Maryland.

Planned Tests in Thailand Spark Debate

While researchers in the United States are looking for new approaches to developing AIDS vaccines (see main text), two first-generation vaccines are inching toward full-blown efficacy trials in Thailand. However, as plans for the trials advance, a debate is heating up. Critics within Thailand, using data supplied by U.S. researchers, contend that the vaccines are likely to prove worthless, while others worry that the furor could frustrate the best chance to determine once and for all whether these preparations can slow the epidemic.

To date, more than two dozen AIDS vaccines have been tested in small-scale human studies to assess their safety and ability to trigger immune responses. None of these tests has as yet moved into an efficacy trial, which would involve several thousand people at a cost of $20 million or more. In June 1994, two vaccines, both made from genetically engineered versions of HIV's surface protein gp120, were set to take the plunge. But a panel convened by the National Institutes of Health (NIH) decided that the probability of the preparations' efficacy was too low for the government to fund these trials. The panel's decision, however, applied only to the United States; countries facing more intense epidemics might deem it worth the risk.

DARROW MONTGOMERY

Front lines. AIDS patient and family in a Thai hospital. Thailand is facing a growing epidemic.

Indeed, researchers in Thailand, facing a serious AIDS epidemic, pressed ahead with small-scale trials of these vaccines, originally made by Genentech of South San Francisco and Chiron Corp. of Emeryville, California. Thai researchers hope to begin these efficacy tests as early as next year. David Baltimore, the Nobel laureate who heads a committee that advises NIH on AIDS vaccines, says he recently discussed Thailand's interest in testing these vaccines with Natth Bhamarapravati, who chairs a similar group in Thailand. Baltimore says he thought their thinking "was all very reasonable."

Last month, however, Praphan Phanuphak, who directs the Thai Red Cross Society's Programme on AIDS, wrote to the deputy governor of Bangkok that the gp120 vaccines are "not useful in preventing HIV infection" and that it was "not appropriate for Thailand to allow (approve) an efficacy trial of the mentioned vaccine." Praphan based his doubts on data that he requested from Steven Wolinsky of Northwestern University and David Ho of the Aaron Diamond AIDS Research Center in New York City. However, these data, on "breakthroughs"—people who became infected despite receiving the gp120 vaccine in the small-scale U.S. trials—should not be overinterpreted, according to Wolinsky: "We'd be remiss if we didn't provide the Thais with that information. But it never was intended to stop or start a trial. Our colleagues in Thailand are very intelligent, and they don't need David Ho or Steven Wolinksy to tell them what to do."

Praphan's criticisms are troubling Thai officials. William Heyward, an epidemiologist who heads the AIDS vaccine program of the Centers for Disease Control and Prevention in Atlanta—which has been helping Thailand stage AIDS vaccine trials—says the issue came up last week when a delegation visited from the Thai Ministry of Health. They were "very concerned" that Thai politicians "would not fully understand the debate and would back off [from efficacy trials]," says Heyward.

That worries the U.S. companies supplying the vaccines, as well as their academic and government collaborators. Chiron hopes to begin a 300-person study this summer that includes a new gp120 vaccine made with HIV subtype E, a strain found in Thailand. If all goes well, the company hopes to start efficacy trials around 2000. Donald Francis, who a few months ago started the company VaxGen to develop Genentech's gp120 vaccine, calls the attacks on the trials "myopic." VaxGen has raised more than $24 million during the past few months to stage efficacy trials of the Genentech vaccine, which Francis says could begin next year. **–J.C.**

Weinhold. In contrast to the Baltimore group's finding, Weinhold and co-workers showed that CTLs could kill 10% to 40% of HIV-infected cells in a test-tube assay.

And Weinhold had more good news about CTLs. Researchers have long worried that an HIV vaccine might only work against the particular viral strain from which it is made. But Weinhold's study of blood taken from people given experimental vaccines made from pieces of HIV showed that their CTLs could kill cells infected with a wide range of HIVs. "The extent to which he found cross-reactivity [to different HIV strains] with CTLs is surprising people," said Patricia Fast, NIAID's associate director for vaccines and prevention. Still, many questions remain about how long these CTL responses will last, and whether they pack enough wallop to fend off a real infection.

Mary Klotman of New York's Mount Sinai School of Medicine presented intriguing findings pointing to another possible criterion for a promising vaccine. Klotman's work addresses a finding by Jay Levy of the University of California, San Francisco, that some white blood cells carrying a CD8 receptor on their surface produce some kind of soluble factor that can suppress HIV. Levy called this mysterious substance the CD8+ Antiviral Factor (CAF). But despite years of trying to identify CAF, Levy has been stumped. Recently, Klotman and Arevik Mosoian of her lab isolated and characterized an "extremely small protein" that she thinks might be the elusive CAF. If so, vaccine developers may have yet another lead to analyze in their hunt for immune responses that correlate with protection.

Perhaps the meeting's most unusual talk suggested that infection with a goat virus might protect humans from HIV. Angeline Douvas of the University of Southern California in Los Angeles reported that people infected with caprine arthritis-encephalitis virus—a distant HIV relative, common in Mexico, that appears harmless to humans—make antibodies that react with HIV. Bruce Weniger, an epidemiologist at the Centers for Disease Control and Prevention in Atlanta, went to the microphone and connected the dots. "This is really a remarkable finding that raises the wild speculation that you discovered the natural accidental vaccine for HIV ... [in] the way cowpox was the natural accidental vaccine that works for smallpox," said Weniger. Douvas replied that they hope to test this hypothesis by doing an epidemiologic study of people infected with the goat virus to see if they have a lower incidence of HIV infection.

Will any of these exotic findings pan out? Who knows. But this meeting proved that AIDS vaccine research is at least bubbling with ideas.

–Jon Cohen