AIDS Vaccine Conference: Is "More" Better?

The search for an AIDS vaccine seems to be turning to approaches that include more and more HIV proteins

Clearwater Beach, Florida—RONALD Kennedy didn't do the expected at the third annual International Conference on Advances in AIDS Vaccine Development held here last week. The conference program called for Kennedy to give a presentation on the latest results from his anti-idiotype vaccine research at the Southwest Foundation for Biomedical Research in San Antonio. Instead the gregarious, 35-year-old microbiologist gave the international audience of 300 AIDS researchers a tongue-lashing. Too many investigators, he said, are chasing too few leads. In particular, he was critical of the large number of papers that focus on the V3 loop, a specific 36–amino acid portion of the HIV envelope protein.

"I'm a little tired of hearing about the V3 loop," fumed Kennedy. "If V3 is so great, where's the vaccine? I, for one, believe that if you put all your eggs in one basket, you tend to break a bunch of them. Perhaps there are other regions. . .that are going to be important relative to developing an HIV vaccine."

Kennedy's impromptu exhortation to follow more leads created a good deal of hallway talk at the meeting, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). But a variety of presentations here suggested that, in fact, at least part of the field may already be turning away from narrowly focused approaches. Although the first HIV proteins to be exploited in vaccines were from the viral envelope—and most prototype vaccines still rely on envelope proteins—other HIV proteins and combinations of proteins approximating the whole virus are becoming increasingly common.

"The V3 loop is an extreme example of the reductionist approach, and there's a sense that it's carrying [that approach] too far," says Alan Schultz, chief of preclinical development at the AIDS Vaccine R&D branch of NIAID. "I'm encouraged by a more broad-based approach. Concentrating on the V3 loop might be too focused and too limited. We may be throwing out the baby with the bath water."

But Scott Putney of Repligen in Cambridge, Massachusetts, retorts: "The people who are skeptical of V3 have their own things they're working on." And Putney, who is working with Merck & Co. on a vaccine that may rely on as few as eight amino acids of the V3 loop, adds that "V3 appears to be the only sure thing so far.... The experiments strongly show that you can neutralize virus with V3 antibodies."

The roots of this skirmish go back to the origins of AIDS vaccine research. At that time recombinant DNA technology was already available to formulate a vaccine based on subunits of the virus. A traditional vaccine, relying on whole killed virus, was considered much too risky—since it might still include some infectious particles. Of the proteins available for making a subunit vaccine, the proteins making up the viral core were thought to be of little use. Envelope proteins, on the other hand, were known to be capable of evoking sought-after neutralizing antibodies with other viruses. As a result, almost every early prototype vaccine was based on the HIV envelope precursor protein (gp160), the finished protein that sits outside the viral membrane (gp120), or some fragment thereof—such as V3, which has an unusual potency to stimulate the immune response.

But envelope-based approaches have not yet produced a workable vaccine. Much of the pessimism about them stems from their repeated failure to protect immunized chimpanzees challenged with live AIDS virus. By contrast, work on more broadly based approaches has been encouraged by repeated successes in protecting monkeys against simian immunodeficiency virus (SIV), a close relative of HIV, using whole killed virus vaccines. "We don't know which epitopes—maybe all of them—need to be included in a vaccine," says Reinhard Kurth, director of Germany's Paul Ehrlich Institute.

The non-envelope-based prototype vaccines range from those relying only on core proteins to those that include whole killed virus or artificial, virus-like particles. Three candidate vaccines described at the meeting are based specifically on proteins that make up the viral core. These come from MicroGeneSys of West Haven, Connecticut, British Bio-technology, Ltd., in the United

AIDS-VACCINE RESEARCH OVERVIEW: CONCENTRATING ON THE ENVELOPE

COMPANY	CORE ANTIGEN	ENVELOPE ANTIGEN	R&D STATUS
APPLIED BIOTECHNOLOGY, INC.	pseudovirion contains both core proteins and envelope proteins, deletes infectious RNA, vaccinia carrier		Animal trials
ONCOGEN (BRISTOL-MYERS SQUIBB CO.)		gp 160 in vaccinia, with gp 160 subunit (MicroGeneSys)	In clinical trials since 1988
BRITISH BIO-TECHNOLOGY GROUP	p 24 in virus-like particle		Phase I clinicals to start, 9/90
BIOCINE (CHIRON/CIBA-GEIGY)		gp 120; p 120 (protein portion of gp 120)	Pre-clinical on gp 120; In clinicals since 1989 with p 120
GENENTECH, INC.		gp 120	Animal trials; clinicals by end of 1990
IMMUNE RESPONSE CORP.	all core proteins, inactivated by radiation and chemicals	some envelope proteins	Entering phase III for immunotherapy
CAMBRIDGE BIOSCIENCE CORP.		gp 160	Primate studies nearing completion
CONNAUGHT LABORATORIES, LTD.	pseudovirion contains both core proteins and envelope proteins, deletes infectious RNA		Animal trials
MICROGENESYS INC.	p 24	gp 160	In clinicals with gp 160 since 1987; p 24 trials started 9/90
MOLECULAR VACCINES		gp 160	In laboratory
REPLIGEN CORP.		gp 120 "loop"	Chimp trials ongoing; clinicals next
VIRAL TECHNOLOGIES, INC.	p 17		Phase I clinicals ongoing since 1989

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Kingdom, and Allan Goldstein of George Washington University School of Medicine. All three might ultimately be used either for prophylaxis or for immunotherapy in people already infected with the AIDS virus.

Three other workers described "pseudovirion" vaccines, which include constructs that resemble whole HIV particles, but are modified to exclude the viral genome (which mediates infection) or render the genome harmless. Larry Arthur, who works for NCI contractor Program Resources, Inc., in Frederick, Maryland., is manipulating HIV core proteins to develop an RNA-deficient pseudovirion. Joel Haynes of the Connaught Centre for Biotechnology Research in Canada has chosen the route of removing part of the viral genome in constructing his pseudovirions. And a group led by Dennis Panicali of Applied bioTechnology in Cambridge, Massachusetts, is making HIV-like particles by stitching HIV genes into a vector that has also been used for other vaccines: the vaccinia virus.

Perhaps the ultimate extension of the "more is better" approach is the use of whole, killed virus vaccines. Jonas Salk has long advocated using whole HIV in a killed preparation, both for prophylaxis and for therapy. Salk's work, presented at the last two international AIDS conferences, has aroused controversy. Here Salk outlined the next step in his vaccine research program, presenting plans for a 1-year trial of his gp120-depleted (but otherwise whole) HIV preparation. That trial will rely on PCR data, among other tests, to find out how much Salk's experimental preparation can reduce the viral load seen in asymptomatic, infected patients.

Although the whole-virus technique is still viewed with skepticism by much of the field, new results seem to give it more credence. Jim Stott of the U.K. Medical Research Council reported here that, using a whole, killed SIV vaccine, his group protected monkeys against a challenge with a strain different from the one used to formulate the vaccine. Protecting against such a "heterologous" challenge, which is obviously a likelihood in real-life situations, has been of prime concern to researchers who feared that some AIDS vaccines might protect only against the single strain they were made from.

Such results suggest that what seemed utterly farfetched just a couple of years ago may in the not-too-distant future enter the mainstream of research leading to an AIDS vaccine.

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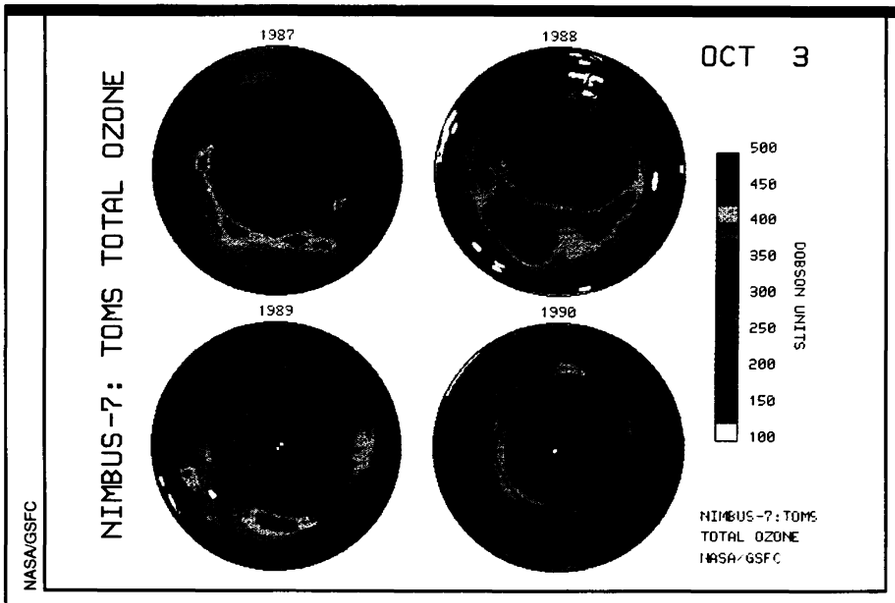

Another Deep Antarctic Ozone Hole

For the second year in a row, the annual destruction of stratospheric ozone over the South Pole has equaled its historic maximum. "Pretty much all the ozone at the base of the stratosphere is destroyed," says Arlin Krueger, who has been monitoring this year's Antarctic ozone hole via satellite. This is the third time in the past 4 years that such extreme ozone depletion has occurred. It may now be the norm.

The 1990 hole got off to a roaring start. Ozone destruction, which is brought about by sunshine acting in combination with the chlorine released from chlorofluorocarbons (CFCs) by icy stratospheric clouds, usually begins over Antarctica in mid-August and reaches a maximum in early October. This August, the amount of ozone, as monitored by the satellite-borne Total Ozone Mapping Spectrometer, rapidly plummeted to about 140 Dobson units, far below the 220 Dobson units typically seen over Antarctica before the hole forms. By mid-September, however, the rate of decline had slowed so that the hole reached a minimum of 125 Dobson units on 4 October, according to Krueger, who works at NASA's Goddard Space Flight Center in Greenbelt, Maryland.

Such extensive ozone depletion made this year's hole comparable to 1987's record-setter (121 Dobson units) and the 1989 hole (124 Dobson units). In all three years, almost all of the ozone was wiped out in the stratospheric cloud region between the altitudes of 15 and 23 kilometers.

The hole is defying the empirical rules meteorologists had developed to predict its depth. Last year's depletion was severe even though the stratospheric winds over the equator blew from the east, a circumstance supposedly linked to shallow holes (*Science*, 20 October 1989, p. 324). And the 1990 hole breaks the pattern in which years of severe, persistent ozone destruction alternated with years of more moderate, shorter-lived depletion.

It may be, says Mark Schoeberl of Goddard, that CFC concentrations have now increased enough to ensure the near total destruction of ozone in the lower stratosphere in most years. If so, the longevity of CFCs in the atmosphere would guarantee that such extreme holes would be around for much of the next century. And things could get even worse before international controls on CFCs take hold. Further increases in CFC concentrations might cause the ozone hole to extend upward or outward, Schoeberl says.

If the hole grew, it would bulge over more of the Antarctic Ocean, push toward the southernmost population centers of the Southern Hemisphere, and greatly increase the volume of ozone-depleted air dispersed over the hemisphere each year. That would increase the exposure of the hemisphere's human populations and marine ecosystems to the possibly damaging effects of ultraviolet radiation. Schoeberl does not expect such hole expansion in the next few years, but he is not so sanguine about the mid to late 1990s.

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