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THE SEARCH FOR PROTECTION AGAINST HIV INFECTION

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Barre-Sinoussi and Montagnier isolated and identified the human immunodeficiency virus (HIV) in 1983. Twenty-five years later, however, no effective vaccine has been developed, and the latest trial in 2007 resulted in more HIV infections in the vaccinated group than in the placebo group (Editorial, *Nature*, 2007).

I felt from the start that using classical approaches for vaccine development wasn't going to work. The biggest barriers are that a protective immune response and natural immunity have never been demonstrated in HIV/AIDS disease.

Perhaps the most important observation of my career was the realization in 1986/7 that some men who are repeatedly exposed to HIV fail to become infected. This observation was made on a cohort of 200 homosexual students who we first recruited in 1981. The cohort was expanded in 1984/5 to 1645 men when we were successful in achieving funding from the U.S. National Institutes of Health. Four of the five investigators funded for these cohort studies of homosexual men decided to join together to form the Multicenter AIDS Cohort Study (the MACS), which continues to generate important information about the natural history of HIV/AIDS, the immunologic response to the virus, the impact of treatment, and the long-term consequences of treatment. In this short article, I will present the evolution of the concept of "resistance" to HIV infection. In view of the failure of classical vaccine strategies to stop the epidemic, understanding this phenomenon is vitally important if we are to develop an effective strategy/tool to prevent successful HIV infection in vulnerable populations.

Shortly after we realized that HIV was the etiologic agent of HIV, the MACS made the decision to implement isolation studies of HIV. All four centers agreed to attempt to isolate virus from men who were HIV antibody-positive. At UCLA, however, we felt that trying to determine the relationship between initial infection with HIV and the subsequent immune response was of greater interest. We realized that in order to observe this relationship, we would need to attempt viral isolations from individuals who had only recently been infected and had not yet developed an antibody response. We therefore decided to attempt isolating virus from the subset of homosexual men in the UCLA cohort who had the highest number of different partners with whom they were the receptive partner. This would maximize the probability that we would catch some of them very early in the infection process. Our virologist, Professor David Imagawa, also decided to vary the isolation procedure by "activating" both the uninfected cells in culture (the usual procedure) and the cells collected from the subject (HIV can only infect cells that are "activated" to replicate).

As anticipated, we were able to isolate HIV from a number of the most sexually active men; some of these men from whom we isolated HIV did NOT subsequently seroconvert to being HIV antibody-positive (i.e., become infected), which we did not anticipate! This observation

raised both alarming and hopeful possibilities. Were there some individuals who were infected with HIV but who did not develop antibodies, and could therefore not be detected by HIV/AIDS testing? If that was true, how could we protect the blood supply? Alternatively, were these men able to clear HIV from their bodies? If so, this observation had significant implications for artificially inducing protection in susceptible individuals.

Should we report these observations, realizing the fear that might result if the test did not identify everyone who was infected? We made the decision not to publish until a means to independently confirm these viral isolations was established. That means became available with development of the polymerase chain reaction (PCR) assay, which recognizes the presence of viral proteins in the blood. As soon as the assay became available, we sent blinded specimens from those individuals from whom we had and had not isolated virus to the PCR laboratory for confirmation. To reduce the possibility that the specimens from which isolated virus had been contaminated, we sent specimens for PCR testing from our viral repository, which contained specimens that had never been in Professor Imagawa's laboratory. Many of the specimens from which we had isolated virus were confirmed to be PCR-positive as well.

We were presented with an ethical dilemma — should we publish knowing that there was a possibility that the publication would create panic, or should we not publish to prevent the panic? We realized that if we did not publish, there was a possibility that many individuals might become infected by persons harboring HIV who were not HIV antibody test-positive. We decided to publish.

As expected, the publication in the *New England Journal of Medicine* in 1989 (Imagawa et al., 1989) aroused panic. Appropriately, many researchers wrote to the journal questioning all aspects of the study. We responded to each of these letters with additional details and evidence supporting our findings. Inappropriately, the *New York Times* published a scathing article in 1991 (Altman, 1991) calling Professor Imagawa and myself unethical, and implying that Professor Imagawa's laboratory had actually contaminated the specimens. The author of the article, Lawrence Altman, had interviewed me for an hour before the article was published. However, nothing that I said in response to Mr. Altman's questions was included in the article, nor did we have the opportunity to respond to the allegations in the *New York Times*. Professor Imagawa was extremely disturbed and offended by the article and the lack of an opportunity to respond.

He died of a heart attack several days after the article appeared.

Subsequent to the appearance of the article, we realized that persisting latent infection was not likely to explain the observation as clearance of the virus. In 1986, the men of the MACS realized that anal intercourse was risky and was the probable route of HIV infection. Thus, most of them reduced their number of partners dramatically, started using condoms for anal intercourse, or ceased having anal sex. We were not able to make additional isolations of HIV from those formerly high-risk men who sharply reduced their risky behavior. On the other hand, we continued to isolate HIV from those few men who continued to be the receptive partners in anal intercourse with many men. If the men were latently infected, we should have been able to continue to isolate HIV from all of them even though they had reduced their HIV exposure. The fact that we isolated HIV ONLY from those men who continued their high-risk exposure suggested that transient infection and clearance of HIV was the more likely explanation.

Identifying the reasons these men were able to clear HIV was essential. We therefore continued our studies of the 27 persistently HIV antibody-negative men from whom we had isolated HIV. In 1994, we documented that these men had increased levels of CD8+ T cells

and neutrophils. CD8+ T cells are those that respond to HIV infection by replicating and attacking cells that are infected with HIV. The increased levels of CD8+ T cells were particularly interesting because these are the cells that are responsible for clearing virally infected cells from the body.

Meanwhile, several other investigators reported results of studies that supported our observations. Ranki and colleagues reported in 1989 that five antibody/virus-negative regular sex partners of HIV-positive persons responded immunologically to artificial (recombinant) HIV gp120 proteins (the gp120 protein is present on the surface of HIV), suggesting that these five had been previously exposed to HIV (Ranki et al., 1989). In 1991, Shearer and colleagues reported that four high-risk, persistently HIV antibody-negative men produced an interleukin 2 (IL-2) cytokine (a chemical produced by cells when exposed to HIV) in response to manufactured envelope peptides, again suggesting that these individuals had previously been exposed to HIV (Berzofsky et al, 1991).

In 1995, in collaboration with Dean Mann and Mary Carrington, we observed that the men from whom we had isolated HIV differed genetically, in that they had significantly higher levels of the TAP 1.4 and 2.3 gene variants (alleles) than uninfected matched controls. The transported-associated protein (TAP) genes control breakdown and transport of viral proteins that enter particular cells of the human immune system. These viral subproteins are then presented by these cells to the CD8+ cells and activate them to attack HIV-infected cells. This process is known as “antigen (protein) presentation”. Our further immunologic studies with Janis Giorgi revealed that the HIV-negative resistant men also had higher levels of activated CD25+/CD8+ cells than low-risk HIVseronegative matched controls. CD25+/CD8+ cells are those cells that are activated to destroy HIV-infected cells.

On the basis of these observations, we hypothesized that the resistant men had genetically mediated, more efficient transport and presentation of HIV epitopes (subunits of proteins) that stimulate higher levels of activated CD8+ cells, which were then capable of clearing cells infected with HIV.

In 1996, in collaboration with Jon Braun, we observed higher levels of a very strong antibody (“superantigen-binding antibody”) to a protein on HIV, gp120 (a protein component of HIV), in the HIV-resistant men, further indicating that our “resistant” men had previously been exposed to HIV (Townsend-Fuchs et al., 1996).

In 1997, Murphy et al observed that some resistant men in the MACS lacked the receptor for the CCR5 protein, which is required for HIV-1 to attach to their target, CD4+ cells (Zimmerman et al., 1997). Thus, these cells could not be infected by HIV-1, and these men were resistant to the typical HIV-1 virus.

In 1998, Plummer and colleagues and Rowland-Jones and colleagues observed that female sex workers in two different world regions who remained uninfected with HIV despite many different partners with very high HIV rates among men had cytotoxic CD8+ cells that were broadly reactive against a wide range of HIV-1 subtypes (Rowland-Jones et al, 1998). Individual CD8+ cells respond to specific subtypes of HIV. Thus, the presence of many CD8+ cells responding to a range of different HIV subtypes would provide broad protection. These observations supported our hypothesis of the role of antigen presentation in conferring resistance to HIV infection. Further support of that hypothesis came from a report in 2007 by Goldstein and colleagues that the frequency of the HLA-B*5701 gene variant (associated with antigen processing and presentation) was associated with a lower viral set point (level of HIV infection) and long-term non-progression to disease in HIV-infected men (Fellay et al, 2007).

It is our belief that these innovative uses of epidemiologic strategies incorporating immunologic and genetic measures were essential in allowing us and others to identify key factors that can confer natural protection against HIV in some individuals. Further study of the mechanisms that allow some individuals to resist or clear HIV should lead to development of a non-traditional “vaccine” that will protect individuals lacking the resistance mechanism.

Our conclusion from these studies is that antigen-presenting cells play a key role in protecting against HIV infection through more effective presentation of HIV-1 epitopes (subproteins) to CD8⁺ cells. Thus, we recommend that researchers focus their attention on the process of antigen presentation as a potential strategy to develop an effective, nontraditional “vaccine” to prevent HIV infection.

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