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Intelligent discussion on HIV vaccine serves as a small consolation for slow progress

Bicentennial Symposium

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Despite great public interest and desperate need, progress toward a viable human immunodeficiency virus (HIV†) vaccine remains incredibly slow. Since Merck began its HIV vaccine research in 1985, the pharmaceutical company has yet to produce a vaccine capable of passing Phase II testing. Merck Laboratories President Peter S. Kim recently delivered a speech at Yale University that detailed his company's previous attempts to create an HIV vaccine and outlined a possible strategy for the future. By Kim's own admission, Merck will not produce a viable vaccine in the near future. However, the speech served as an important endorsement for HIV vaccine development from a highly respected leader in the pharmaceutical industry, which, historically, has produced drugs aimed at management rather than prevention.

Audience members may have been scratching their heads. Not because the technical jargon and cutting-edge scientific developments recounted at the Yale School of Medicine Bicentennial Symposium were too complex, but because one of the event's most intriguing presenters seemed to focus mainly on his company's series of failures.

When Dr. Peter S. Kim, President of Merck Laboratories, chose to address the topic of HIV vaccine development, he must have known more than half of his time would be spent rehashing the pharmaceutical giant's unsuccessful ventures. But despite the lack of an HIV vaccine, the talk still represented a small victory for proponents of HIV vaccine development who may be frustrated by the focus of current pharmaceuticals on disease management rather than infection prevention. The subject matter carries additional weight considering the source. Pharmaceutical companies profit most easily from long-term treatments directed toward economically stable markets. In spite of this, Merck's president chose to champion a vaccine that represents the most cost-effective, and least profitable, treatment of a disease that mainly affects the world's poorest countries.

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†Abbreviations: HIV, human immunodeficiency virus.

"I believe this is the largest public health issue that science needs to address," Kim said.

Why then, after such a strong endorsement and more than 25 years of research, has Merck failed to produce a viable HIV vaccine? "It's not for lack of trying," Kim said. "Coming up with a vaccine for HIV has proven to be very difficult."

Merck began research on an HIV vaccine in 1985 and has discovered a variety of dead ends. Researchers quickly found that using killed versions of HIV did not work. Merck also tried a humoral approach, attempting to persuade human antibodies to disable the virus. This tactic also initially failed.

A more promising solution seemed to present itself in the cell-mediated strategy. If one cannot prevent HIV from entering the body, Merck researchers thought, why not prime the body's cytotoxic T cells to recognize and destroy any cell that has been infected with HIV? It seemed like a massive breakthrough when Merck scientists elicited this very response in monkeys using the new MRKAd5 vaccine. The vaccine appeared to reduce the peak and baseline viral loads in HIV-infected monkeys. Better yet, the vaccine even produced a durable cytotoxic response in infected humans.

Problems arose when the vaccine moved into Phase II human testing. A larger study, called the STEP study, began in 2004 to measure the protective quality of the vaccine [1]. The goal of this study was not just to lower viral counts but to prevent initial infection in healthy subjects. The result was an utter failure. Not only did the vaccine fail to provide protection against HIV, but more vaccinated subjects became infected than the unvaccinated controls [1]. The study was halted in 2007, and the scientific community was stunned. "I think it sets a solid framework for what *doesn't* work," Kim said.

The failure represented a major setback for HIV vaccine development and the overall campaign against HIV and AIDS.

Since the disappointing results of the STEP study, Merck has shifted its attention back to a humoral-based vaccine. The goal of this strategy is to prevent the entry of HIV into cells by blocking the fusion of viral and host cell membranes [2]. Merck researchers hope to accomplish this by forcing antibodies to target the transient structure the virus uses to enter cells. This structure, known as the hairpin intermediate, has been targeted by peptide inhibitors in previous studies [2]. This plan, however, presents its own challenge: Since the target structure exists transiently, scientists must engineer a stable proxy to act as an immunogen and elicit an antibody response. That goal remains elusive.

While he is optimistic about the renewed emphasis on a humoral approach to the vaccine, Kim said, the medical community will have to combat HIV without the relief of a vaccine in the near future.

"My gut feeling is we still have a long way to go," Kim said. "And I don't mean 'we' as in Merck. I mean 'we' as a scientific community."

In the meantime, Kim's presentation on HIV vaccine development offers important insight for the discussion of an HIV vaccine and its role in combating the HIV epidemic. It is vital that high-profile corporations and industry leaders continue to place an emphasis on important health issues that do not necessarily represent the greatest opportunity for profit, but reflect the most desperate needs of the global population.

By including Kim's presentation in its Bicentennial Symposium, Yale School of Medicine has demonstrated a commitment to issues that exist not only in test tubes and sterile laboratories, but in homes and communities around the world. While we are far from vaccine-based eradication of HIV, symposium participants, as well as the larger medical community, should appreciate the continued discussion of this topic by industrial and academic leaders.

REFERENCES

1. Iaccino E, Schiavone M, Fiume G, et al. The aftermath of Merck's HIV vaccine trial. Retrovirology. 2008;5:56.
2. Bianchi E, Joyce J, Miller M, et al. Vaccination with peptidemimetics of the gp41 prehairpin fusion intermediate yields neutralizing antisera against HIV-1 isolates. Proc Natl Acad Sci USA. 2010;107(23):10655-60.