Responses to Conventional Objections about a Killed-Virus Vaccine for HIV/AIDS

The development of a killed-virus HIV vaccine makes good sense from numerous practical perspectives, including public health, financial, scientific, as well as on philosophical grounds. However this approach strongly challenges the conventional wisdom in the AIDS research sector that a "novel" and better vaccine method will be required. So you won't have to look far to find respected and accomplished scientific experts who will dismiss the idea out of hand for various reasons. A conversation with the experienced vaccine development experts behind this project usually serves to assuage those concerns. However in case such a conversation is not readily available, listed below are some of the most common concerns/objections, and their related responses.

"IF THIS WAS SUCH A GREAT IDEA, IT WOULD HAVE BEEN TRIED ALREADY"

You would think so! Indeed, it doesn't make sense that one of the best-established vaccine methods has been entirely omitted from the entire research agenda. The shortest explanation is that killed-virus has simply slipped through the cracks. The various entities engaged in HIV vaccine research have had greater incentives to pursue other concepts. Biotech and pharmaceutical companies see greater incentive to pursue novel, proprietary approaches with potential to produce patents and profits. Meanwhile academic scientists find it easier to get grants aimed at novel ideas and new scientific understanding. It never has been anyone's explicit policy to entirely omit one of the most historically-successful vaccine methods from the mix for HIV/AIDS, but that effectively has been the outcome.

"THAT WILL NEVER WORK"

Speculative. Many theoretical objections have been raised, but at this point those objections are indeed entirely theoretical. Any experienced vaccinologist (or product development expert more generally) knows that hypothetical predictions are only predictions; you cannot know the answer until you do the experiments. If any expert knew which vaccine approaches would and wouldn't work, the world would already have an AIDS vaccine.

Dr. Marcus Conant says it best in a video on killhivnow.org: "In science you never really know if something is going to work or not until you get in the laboratory. A few experts say that's not going to work, based not on research but based on their feelings, their intuition. Well that's not science, that's religion. To be scientific, you have to actually test it."

"WOULD USING KILLED VIRUS VACCINES BE SAFE?"

Yes. Contemporary industrial technology and laboratory methods are able to ensure that every last infectious virus particle is eliminated during the manufacture of killed-HIV vaccines. Killed-virus vaccines have been used safely for decades for viral diseases including polio, hepatitis, and rabies— a pathogen just as lethal as HIV but one that claims its victims far more quickly. Again from Dr. Conant: "When the science is done correctly you can be absolutely certain that you have killed that virus. A dead virus is a dead virus, and you can prove that it is dead."

"THE HIV VIRUS MUTATES TOO RAPIDLY FOR A KILLED-VIRUS VACCINE TO BE EFFECTIVE"

Maybe yes, maybe no. The HIV variability/mutability issue is in no sense special to killed-virus vaccines; every vaccine paradigm must confront this issue with HIV. However killed-virus vaccines do offer useful strategies to address viral variability. In principle, chemical or biomedical modifications can also be employed to blunt immunogenicity of variable viral epitopes. "Multivalent" killed-virus vaccines such as the flu vaccine and poliovirus vaccine have proven effective against multiple virus strains. Both of these strategies arguably can be investigated much more efficiently and more promptly using killed virus than using any high-tech approach based on genetically-engineered constructs. Finally, even if we never get a globally-effective vaccine, effective vaccines targeting circulating strains in specific locales could alleviate suffering and save countless lives.

"YOU'LL NEVER GET A VACCINE THAT WORKS FOR THE MULTIPLE STRAINS OF THE AIDS VIRUS"

Speculative. This concern arises because the vaccines tested to date typically produce quite "narrow" responses, i.e., antibodies that do not neutralize many strains different than the immunizing strain. At this point, we simply do not know enough about the underlying biology to make meaningful predictions about how well any approach might work; we can only speculate about why it might, or why it might not. But if we could make a vaccine that produced clinically useful endpoints, even if the protection was "narrow" in the sense described above, arguably this would help us to define correlates of narrow protection, and it might be a useful step on the way to a more broadly-protective vaccine. Bottom line, were we to exclude study of vaccines that might not work, or that might not yield broad protection, we would have nothing at all to investigate.

"YOU'LL NEVER GET STERILIZING IMMUNITY"

Probably true, but not a prerequisite. Sterilizing immunity (complete prevention of infection) would be a wonderful goal for a vaccine, but is an unprecedented and quite possibly unnecessary requirement for an effective AIDS vaccine. Had we insisted on approaches that offered sterilizing immunity, we would have few if any successful vaccines today. Countless lives have been saved from deadly diseases using vaccines that, rather than preventing infection, instead prevented or merely reduced the severity of disease.

"SOMEONE ELSE IS ALREADY DEVELOPING A KILLED VIRUS HIV VACCINE (e.g. SAV001)"

Yes and (mostly) no. It is true that other vaccines have been formulated using virus that has been killed, as in the SAV001 study. But the mere fact that the virus has been killed does not tell us the vaccine will work. There are dozens — perhaps hundreds — of ways to formulate a killed virus vaccine. Experienced vaccinologists will be aware that vaccination outcomes can be influenced by a sizable list of vaccine input variables. We typically have needed a large number of guesses, considerable empirical screening, multiple iterative trials, and numerous small incremental improvements before we hit upon vaccine formulations that worked. It would be wonderful if a vaccine formulated from a single guess, as in the SAV001 study, were to prove safe and effective when it reaches human efficacy trials. But a successful classical vaccine is more likely to emerge from

a comprehensive, systematic product development effort. Barring a stroke of massive good luck, considerable empirical trial and error experimentation is apt to remain an essential element of any successful AIDS vaccine development effort.

"FIRST YOU NEED TO ESTABLISH PROOF-OF-PRINCIPLE IN ANIMAL MODELS"

Doubtful. In the context of HIV/AIDS, this idea sounds better than it actually is. A vaccine concept that works in one species may or may not work in another. So far, we do not have any animal model that reliably predicts outcomes in humans. Furthermore, to develop a retrovirus vaccine that works in animals might take just as much time, money and effort as to develop a vaccine that works in humans. Bottom-line, other than information on acute toxicity, there is little to be gained from animal testing of killed-virus or any other retrovirus vaccine. It likely would be much more informative to compare and contrast head to head a variety of candidate killed-HIV vaccine formulations in small human microtrials.

"ISN'T THERE ALREADY ANOTHER SUCCESSFUL AIDS VACCINE CURRENTLY IN CLINICAL TRIALS?"

Yes and no. So far, only a single candidate vaccine has demonstrated any efficacy at preventing AIDS. The so-called "Thai" trial, RV 144, demonstrated 31% efficacy in trial results reported in 2009-2010. A followup trial, HVTN 702, was launched in South Africa in December, 2016. Results are expected to be available in 2020.

The truth is, scientists do not yet understand enough about HIV biology and human immunology to make reliable predictions about just how well this or any HIV vaccine approach will work. Many scientists think it may be decades more, if ever, before novel methods will produce an effective vaccine. By contrast, it is likely that a classical killed-virus vaccine could be formulated, tested, and deployed globally within 5 to 10 years—perhaps *decades* sooner than other options under investigation.

"IT DOESN'T TAKE INTO ACCOUNT THE MANY SCIENTIFIC ISSUES THAT WE NOW KNOW MAY IMPACT VACCINE EFFICACY, OR THE NUMEROUS BIOLOGICAL MYSTERIES THAT REMAIN TO BE UNRAVELED."

Exactly so! There are already hundreds of dedicated scientists trying to take into account the scientific issues and biological mysteries. Theirs is a heroic and highly commendable undertaking. But we hear no one predicting their effort will produce a vaccine any time soon. Basic research is not famous for near-term solutions to practical problems. So we propose to frame our effort quite differently, as a problem in classical vaccinology — try it, test it, tweak it, and keep at it until you get something useful!!

"I HAVE ANOTHER REASON THIS ISN'T WORTH TESTING"

Let's talk. We would love to discuss it further. So far, we have not encountered objections based on proven product development experience that have not been resolved through conversation.

Said more strongly, in the words of one Nobel laureate biologist who supports this approach:

"I can see no earthly reason why the [killed-virus vaccine] strategy should not be tried. After all, it has produced many effective vaccines in the past, including one against a retrovirus (FIV, now in commercial use). And given the woeful state of understanding of the immune response against HIV, I would distrust any criticisms based on theoretical grounds."

Let's do the experiments.

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