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25 years after discovering HIV as the cause of aids: prospects for a vaccine

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Live attenuated HIV vaccines cannot be tested in humans because of their danger. Inactivated virions are still dangerous and also poorly immunogenic. For that reason subunit vaccines in one form or another have been the approach of almost all investigators since 1984 when adequate HIV culture systems became available.

With the exception of using small animals for testing immune responses all in vivo experimental vaccine testing research utilize subhuman primates, especially macaques, challenged with SIV or the chimeric SHIV (using an HIV envelope with SIV). Thus, we begin with two handicaps – a limitation to subunit vaccines and a limitation in our animal model. However, the limits of the animal model in my view are not due to any inadequacy of the model but rather the limitation of monkeys. This has been a problem from the beginning, but is one that could have been overcome long ago with adequate investments from funders. Instead, we witness most quality investigators limited in their experiments to 4 to 6 animals per group, so as to require multiple repeated experiments and years of delay, while a few groups can afford 20 to 30 animals per group. Obviously, this needs to change. A third handicap is HIV variation. Generally, investigators have challenged macaques with homologous SIV (or SHIV), but this is inadequate. However, in recent years the need for heterologous viral challenges has finally been recognized. It would be ideal to challenge with several different heterologous challenges, but there are serious limitations in available primate viral stocks, particularly SHIV. The best protocol for testing a candidate vaccine in macaques is controversial. Many have favored a single relatively high dose challenge, while recently several groups argue for multiple low dose challenges. The fact is arguments can be made for either, and no one knows which one will be more predictable for a HIV vaccine in man.

By far the greatest hurdle to an effective vaccine is the retrovirus characteristics of HIV, namely its capacity to rapidly integrate its genes into our DNA. This establishes life-long infection, rapid diminished function of immune responses, and the emergence of variants. This feature has major implications all too often forgotten in the 1984 to 2008 period of HIV vaccine research, namely an effective HIV vaccine: (1) must protect against infection not just reduce HIV after infection; (2) must be long lasting; and (3) must be broad.

Early in HIV vaccine history (roughly 1984-1990) the candidate immunogen was focused on the gp120 envelope delivered as protein, DNA, or vector with an HIV env gene insert. Mostly these led to type specific immune responses so vaccines of this type failed in the monkey model when challenges were made with heterologous strains of SIV or SHIV, especially with protein alone. Nonetheless, a company (VaxGen) still went forward with a gp120 protein clinical trial, and all too predictably, completely failed, and caused much negativity for HIV vaccine research.

Many investigators then turned to CMI based vaccines. Though CMI is important and likely helpful to any vaccine candidate, CMI alone is a predictable failure, and indeed such vaccines have failed (e.g., recent NIAID – Merck trials in Africa).

We and some other groups think the answers will be in finding, "fixing," and properly presenting *conserved* sequences of gp120 which are *functionally* required for HIV infection. Finding conserved sequences is an obvious need and a readily achievable one. "Fixing" means making a *constrained* envelope because the mobile envelope is a difficult and ever changing target. We have chosen the CCR5 binding domains of gp120 as the conserved *and functionally necessary* region. This

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region of gp120 contains novel epitopes called CD4i epitodes and Abs to them are known as CD4i Abs. We approach this by linking gp120 to domains of CD4 that bind gp120. We have developed a candidate vaccine based on inducing CD4i Abs. These Abs are often broadly reactive, and although we have not as yet reached sterilizing immunity, the vaccine ultimately protects against a high dose heterologous challenge and often has ADCC activity [1].

From our primate experiments and our studies in human elite viral suppressors [2] *we predict that a successful HIV vaccine* may consist of an immunogen that induces CD4i Abs and ADCC type responses.

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