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Reverse HIV vaccinology failed because it has no sound theoretical basis in the case of this virus

Van Regenmortel Marc Hubert Victor
University of Strasbourg, France

It has been repeatedly argued that the failure to develop a successful HIV vaccine after 30 years of intensive research efforts is mainly due to the fact that investigators remained committed to a number of misleading paradigms that made them pursue unfruitful lines of investigation. Paradigms are based on various presuppositions and assumptions that determine how investigators approach a scientific problem and choose the experimental strategies they will use for trying to solve the problem. Unfortunately scientists are not always aware of the many implicit presuppositions that underlie a fashionable but nevertheless invalid paradigm. It is therefore essential to examine whether the underlying presuppositions that are made are in fact compatible with current immunological theory. The immune system is degenerate which means that antibodies (Abs) are never monospecific for a single epitope but are polyspecific or even heterospecific for numerous epitopes. There is therefore no reason why the one HIV epitope that binds to a neutralizing (n) Mab in a RV experiment will also be a suitable vaccine immunogen able to induce the same nAbs. Effective HIV vaccine immunogens cannot be discovered by studying the antigenic structure of HIV epitopes that bind to nMabs. The so-called rational design of an effective HIV vaccine immunogen consists only in improving empirically the antigenicity of a single epitope-paratope pair. Neutralizing anti-HIV Abs are only obtained after a lengthy process of Ab affinity maturation that is not required in the case of other viruses. RV is therefore not applicable to HIV and current attempts to develop HIV immunogens able to bind germline B cell receptors or maturation intermediates depart from RV which does not require the unraveling of Ab maturation pathways. All known Abs that neutralize HIV undergo induced fit and mutual adaptation of the epitope-paratope partners and recognize transient 3D structures dependent on the tertiary and quaternary structure of HIV Env. The reactivity of such discontinuous epitopes cannot be studied outside the native Env protein in which they are embedded and it is extremely difficult to reconstitute them by chemical synthesis. Reproducing the immunogenic activity of discontinuous epitopes by synthesizing short linear peptides has never been entirely successful and is unlikely to lead to a practical HIV vaccine.

Biography

Van Regenmortel Marc Hubert Victor is an Emeritus CNRS Research Director at the University of Strasbourg, France. He has previously held Professorship appointments at various Universities in South Africa, France and Italy. He is currently an Editor-in-Chief of *Archives of Virology, J Molec Recognition, J AIDS Clin Res*, Executive Editor of *Analytical Biochem*, Associate Editor of *Frontiers in Immunology, J Immunol Methods, Bionomina, Exp Rev Proreomics*. He has published 17 books in Virology and Immunochemistry, 400 research and review papers and co-edited with Brian Mahy the 3rd edition of the *Encyclopedia of Virology* published by Elsevier.

vanregen@unistra.fr

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