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Impediments to the rational design of a structure-based HIV-1 vaccine

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The term reverse vaccinology (RV) refers to the strategy of generating a viral vaccine by studying the interaction of human Mabs with viral antigens. Instead of the usual approach of trying to generate protective antibodies by vaccination, RV uses the reverse approach of generating a vaccine from the known structure of neutralizing antibodies (Burton DR, Nat Rev Immunol 2, 706; 2002). It is assumed that by analyzing the crystallographic structure of broadly neutralizing Mabs (bnMabs) bound to epitopes of different HIV-1 strains, it should be possible to design an HIV-1 immunogen that will re-elicit bnAbs by using a reverse engineering approach. This is based on the expectation that if a viral antigen can be engineered to bind better to a bnMAb, it will have acquired the immunogenic capacity of eliciting neutralizing polyclonal antibodies similar to the bnMab. It will be argued here that the claims of RV are based on several misconceptions regarding the nature of immunological specificity and on the unwarranted hypothesis that it is possible to extrapolate from an antigenic structure observed in a crystallographic complex to the immunogenic structure needed in a vaccine. The finding that sterilizing protection can be obtained in non-human primates by administering bnMabs prior to viral challenge has been used to justify extensive research programs aimed at isolating additional neutralizing antibodies from human subjects. However, successful passive immunotherapy with bnMabs does not tell us how such antibodies can be induced by vaccination. As a result of the extensive polyspecificity of antibody molecules as well as the degeneracy of the immune system, it is futile to search for the single fictional intrinsic epitope of a bnMab or for a putative unique immunogen capable of inducing protective polyclonal antibodies. It is only possible to rationally design and optimize one epitope to fit a particular Mab, or to improve the binding efficacy of a Mab intended for passive immunotherapy. It is not possible to rationally design an HIV vaccine immunogen capable of eliciting protective antibodies because vaccine immunogenicity also depends on numerous extrinsic factors present in the immunized host. An effective vaccine immunogen can only be discovered by investigating experimentally the immunogenicity of a candidate molecule and demonstrating that it is able to protect against virus infection. It cannot be discovered by determining which epitope structures in an engineered antigen molecule are recognized by a bnMab. There is no reason to expect that the antigen activity of an epitope is always accompanied by a related immunogenic activity capable of eliciting neutralizing antibodies. The failure to distinguish antigenicity from immunogenicity is related to the reductionist fallacy that it is possible to reduce biology to chemistry.

Biography

Marc HV Van Regenmortel is currently an Emeritus Research Director at the CNRS (French National Research Center) in the School of Biotechnology of the University of Strasbourg, France. He was for 22 years Director of the Immunochemistry Laboratory at the CNRS Molecular Biology Institute in Strasbourg and previously held professorship appointments at various Universities in South Africa, France and Italy. He is currently Editor-in-Chief of ARCHIVES OF VIROLOGY, JOURNAL OF MOLECULAR RECOGNITION and THE OPEN VACCINE JOURNAL, an Executive Editor of ANALYTICAL BIOCHEMISTRY, an Associate Editor of ADVANCES IN VIRUS RESEARCH, FRONTIERS IN IMMUNOTHERAPIES AND VACCINES, JOURNAL OF IMMUNOLOGICAL METHODS, ISRN IMMUNOLOGY and BIONOMINA. He has published 17 books in the fields of Virology and Immunochemistry and 390 research and review papers. In 2009 he co-edited with Brian Mahy of the CDC in Atlanta, the third edition of the Encyclopedia of Virology in 5 volumes published by Elsevier.