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Autore	Marc H. V. Van Regenmortel
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Sommario/riassunto

In his 1962 book "The Structure of Scientific Revolutions", Thomas Kuhn famously argued that researchers in every field of scientific enquiry always operate under a set of presuppositions known as paradigms that are rarely explicitly stated. In the field of HIV vaccine research, several prevailing paradigms led scientists for many years to pursue unfruitful lines of investigations that impeded significant progress. The uncritical acceptance of reigning paradigms makes scientists reluctant to abandon their mistaken assumptions even when they obtain results that are not consistent with the paradigms. The following five paradigms which disregard the degeneracy of the immune system were particularly harmful. 1) There is a primary and intrinsic epitope specific for each B cell receptor and for the corresponding monoclonal antibody. In reality, there is no single, intrinsic or "real" epitope for any antibody but only a diverse group of potential ligands. 2) Reactions with monoclonal antibodies are more specific than the combined reactivity of polyclonal antibodies. In reality, a polyclonal antiserum has greater specificity for a multiepitopic protein because different antibodies in the antiserum recognize separate epitopes on the same protein, giving rise to an additive specificity effect. By focusing vaccine design on single epitope-Mab pairs, the beneficial neutralizing synergy that occurs with polyclonal antibody responses is overlooked. 3) The HIV epitope identified by solving the crystallographic structure of a broadly neutralizing Mab –

HIV Env complex should be able, when used as immunogen, to elicit antibodies endowed with the same neutralizing capacity as the Mab. Since every anti HIV bnMab is polyspecific, the single epitope identified in the complex is not necessarily the one that elicited the bnMab. Since hypermutated Mabs used in crystallographic studies differ from their germline-like receptor version present before somatic hypermutation, the identified epitope will not be an effective vaccine immunogen. 4) Effective vaccine immunogenicity can be predicted from the antigenic binding capacity of viral epitopes. Most fragments of a viral antigen can induce antibodies that react with the immunogen, but this is irrelevant for vaccination since these antibodies rarely recognize the cognate, intact antigen and even more rarely neutralize the infectivity of the viral pathogen that harbors the antigen. 5) The rational design of vaccine immunogens using reverse vaccinology is superior to the trial-and-error screening of vaccine candidates able to induce protective immunity. One epitope can be designed to increase its structural complementarity to one particular bnMab, but such antigen design is only masquerading as immunogen design because it is assumed that antigenic reactivity necessarily entails the immunogenic capacity to elicit neutralizing antibodies. When HIV Env epitopes, engineered to react with a bnMab are used to select from human donors rare memory B cells secreting bnAbs, this represents antigen design and not immunogen design. The aim of this Research Topic is to replace previous misleading paradigms by novel ones that better fit our current understanding of immunological specificity and will help HIV vaccine development.