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REVIEW

What does it mean to develop an HIV vaccine by rational design?

Marc H. V. van Regenmortel[1]

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Abstract
This review argues that the three popular concepts of design, rationality and reductionism, which guided vaccine research for many years, actually contributed to the inability of vaccinologists to develop an effective HIV vaccine. The strong goal-directed intentionality inherent in the concept of design together with excessive confidence in the power of rational thinking convinced investigators that the accumulated structural knowledge on HIV epitopes, derived from crystallographic studies of complexes of neutralizing antibodies bound to HIV Env epitopes, would allow them to rationally design complementary immunogens capable of inducing anti-HIV protective antibodies. This strategy failed because it was not appreciated that the structures observed in epitope-paratope crystallographic complexes result from mutually induced fit between the two partners and do not represent structures present in the free disordered molecules before they had interacted. In addition, reductionist thinking led investigators to accept that biology could be reduced to chemistry, and this made them neglect the fundamental difference between chemical antigenicity and biological immunogenicity. As a result, they did not investigate which inherent constituents of immune systems controlled the induction of protective antibodies and focused instead only on the steric complementarity that exists between bound epitopes and paratopes.

Design

A scientist's ability to design something extremely complex finds its conceptual origin in the intention of the designer to achieve a certain goal, although the design procedure itself is highly tentative and mostly devoid of any logical or methodological rules that will necessarily lead to success.

Metaphoric language is extremely widespread in molecular biology, and the "Book of Life" metaphor was described by Kay [1, p. 296] as producing information without meaning, codes with no language, messages with no sender, and writing devoid of authorship. The metaphors of molecular recognition, attraction and repulsion are widely used in biology for describing the stereocomplementarity between molecules that selectively bind to each other, and the term "design" is itself a useful metaphor for analyzing the many useful biological functions that seem to arise from the activity of a designer [2, p. 271]. Design is thus a metaphor for referring to attempts made to achieve a particular intentional goal by the use of certain procedures but without necessarily achieving it.

Although it used to be commonly accepted that, in biology, structure causes function, it seems more relevant to say that it is actually binding that causes function. The belief that the structure of a protein causes a biological function arises from a misunderstanding of the notion of causality, which is a relation between successive events and not between a structure and an event. A biological event such as a binding reaction cannot be the inevitable consequence of something that is not an event, such as the structure of a molecule. The complex nature of organisms with their apparent end-directed activities has made the use of the design metaphor very attractive for describing the success of the many underlying mechanisms that constitute a biological system, although attributing a purpose to each constituent is entirely subjective, since a purpose has no real existence outside the mind thinking of it [3, p. 143-155]. The design metaphor is actually inappropriate for explaining the appearance and the development of living organisms on earth as well as for describing the process of inventing a new vaccine [4].

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✉ Marc H. V. van Regenmortel
vanregen@unistra.fr

[1] Medical University of Vienna, Vienna, Austria

Rational design and bounded rationality

Rationality is the ability of cognitive agents to adopt certain explanatory beliefs on the basis of observations and appropriate reasoning, and the term "rational" is used to describe both the agents and their specific beliefs. Rational beliefs are obtained by accumulating sufficient amounts of evidence derived from observation and empirical information obtained by our senses, and they are said to represent the "truth" when they seem to correspond to the reality of what is perceived by a human mind [5].

Science nowadays tends to be considered the best method for reaching reliable rational beliefs because scientists follow the so-called "scientific method", which is commonly believed to use successful rules for obtaining explanatory hypotheses and theories derived from valid experimental evidence. In recent years, the validity of the rules of the scientific method has, however, become increasingly challenged because it became obvious that the same "method" could lead to valid results and interpretations as well as to incorrect ones, since scientific theories are always tentative and never deductively proven beyond any doubt [6–8]. There is, indeed, no scientific recipe book that can be used for making discoveries (revealing something that always existed but was unknown to anybody) or inventions (achieving something new that was previously not possible such as a new vaccine). Since the scientific method never leads to absolute certainty, scientific theories always remain only approximately true, and this leads to the somewhat unexpected beneficial consequence that it is subsequent future evidence obtained by induction that makes scientific progress actually possible [5]. The concept of intentional design in fact remains as mysterious as the indispensable contributions of human imagination, intuition and talent needed for realizing artistic creations or for producing scientific discoveries and useful inventions.

In modern biological research, the term "rational" is often used in the sense of "reasonable", and it describes procedures that focus on elements of the system under study for which molecular information is available. For instance, in rational vaccine design, the term "rational" is borrowed from the concept of rational drug design, which uses the 3D structure of a biological target for designing molecules that will selectively bind to it and inhibit its biological activity. Such a computer-assisted approach based on molecular docking can, for instance, be used for designing either antigens or antibodies (Abs) that bind better to each other, although it has never succeeded in producing an effective HIV vaccine immunogen capable of inducing protective antibodies in heterogeneous populations of vaccinees [5]. The reason for this is that cross-protective immunogenicity is a biological phenomenon involving the contribution of numerous constituents present in highly complex immune systems (ISs) and which does not arise simply from the presence of a chemical complementarity between an epitope and a paratope [9]. When an antigen or epitope is introduced in a host IS, it becomes known as an immunogen although it is of course the IS that produces the Abs, since the antigen is only a triggering agent that initiates a chain of reactions in the IS. This is only successful if the particular host IS possesses B cells able to recognize the immunogen as well as various types of T cells and other regulatory mechanisms. Vaccinologists often tend to assume erroneously that all these features are always present in the individual IS they work with.

Although B-cell epitopes are usually defined as surface regions of an antigen that can bind both free Abs and membrane-bound Abs present in B-cell receptors (BCRs), it must be stressed that the chemical environment of a free Ab (binding the antigen) and the lipid environment of the same Ab in a B-cell receptor (binding the immunogen) are very different [10]. Since lipids present in B-cell membranes may contribute to the binding observed when an antigen interacts with a B-cell receptor, the same antigen may bind more weakly to the corresponding free Ab molecule. Furthermore, when an Ab binds to a free viral peptide, the binding may also be weaker than when that Ab binds to the same peptide embedded in a viral membrane because of additional hydrophobic interactions with membrane lipids [10].

Many scientific laws are used in physics and chemistry for accurately predicting the behaviour of physicochemical systems, but since there are no universal laws in biology [11], it is not possible to infer that a single biological event is the cause of a subsequent event, because the effect always has a multiplicity of causes. Since all biological systems are inherently always complex, an observed effect is always due to a network of causal interactions and internal regulations, which require the analysis of a multitude of contributory causes [12].

It is often claimed that a major goal of biotechnology is to transform the process of developing a drug from a trial-and-error empirical operation into a rational, structure-based process. Such a statement accredits the view that empiricism and rationality are two separate approaches to problem solving and that the rational approach is to be preferred. A rational approach is usually based on accepted scientific theory and implies that the outcome of experiments is sometimes predictable, whereas an empirical approach admits that the outcome cannot be predicted from pre-existing knowledge and must be derived from the experimental observations themselves. Although rationality and scientific knowledge are both necessary for setting up a research program, many novel findings and discoveries are not obtained

by rational deduction but are derived from the unpredictable outcome of controlled experiments.

In recent years, a method of explanatory reasoning called "inference to the best explanation", also known as abductive reasoning, has become popular for generating which testable scientific hypotheses are best able to explain the scientific evidence that is available. These attempts were unsuccessful and led to the conclusion that classical rules of logic were unable to lead to a rational model of discovery and of hypothesis formulation that could reliably decide between competing scientific theories [13, 14]. The inability to develop logical rules for guiding the creative, cognitive processes of scientific discovery agrees with the conclusion that the design of vaccines by rational reasoning is not feasible and that trial-and-error experimentation is the most effective strategy for developing scientific inventions.

The economist and Nobel laureate Herbert Simon introduced the concept of bounded rationality [15] to describe the intrinsic limitations of human cognition that result from the many unavoidable constraints that always limit our ability to make rational decisions. To arrive at a truly rational decision, it would be necessary to possess a complete knowledge of all the relevant parameters that may influence the behaviour of a complex system. However, humans never have unlimited time and resources for collecting precise information on all the initial states of the innumerable constituents of a dynamic biological system, and this prevents them from predicting the subsequent states of the system [16, p. 36-73]. As a result, rationality on its own cannot guarantee that humans will reach correct solutions, since their bounded rationality forces them to make tentative decisions that always remain uncertain because they are based on incomplete or incorrect information. In fact, the same applies to our limited understanding of all complex systems [17], and it explains, for instance, our inability to predict the occurrence of major economic events such as a world financial crisis as well as our very poor ability to predict long-term weather changes [18].

It is unfortunate that many researchers in the life sciences do not appreciate the considerable benefits that accrue from philosophical insights because they are not aware that science and philosophy of science utilize the same human tools of logic, mathematics, conceptual and empirical analysis, imagination and creativity that are required for increasing our scientific and philosophical understanding of the world [19].

Reductionism

The reductionist mindset in biology is exemplified by the assertion of Francis Crick [20]: "The ultimate aim of the modern movement in biology is to explain all biology in terms of physics and chemistry". Since most biologists accept that organisms are composed solely of atoms and molecules without the participation of extraneous forces, they tend to accept that biological systems can be fully described and understood in terms of the physico-chemical properties of their constituent parts. Methodological reductionism, which dissects a biological system into its constituent parts, has been an extremely successful research strategy in molecular biology, and this seemed to confirm that biology could indeed be reduced to physics and chemistry. It was initially believed that the discovery of the double-helical structure of DNA solved the mystery of life because it elucidated the molecular mechanisms involved in gene replication and expression, although it later became evident that this knowledge did not provide much insight on how genes actually lead to phenotypes [1]. As a result, the claims of genetic reductionism that link human traits to genes became totally discredited.

The validity of reductionist explanations in biology was also questioned when it became evident that biological systems possess so-called emergent or relational properties that arise from the multiple interconnections and relations that exist between the individual components of the system. These emergent properties, which are absent when the parts are studied separately, also cannot be predicted from the properties of the parts. Furthermore, interactions between the parts as well as inputs from the environment give rise to novel features such as network behaviour as well as to the characteristic self-organizing dynamic stability of biological systems [21].

Reductionist thinking also blurred the distinction between the chemical nature of antigenicity, which describes the ability of antigens to bind Abs, and the biological nature of immunogenicity, which refers to the ability of antigens to trigger immune systems to elicit Abs. The resulting confusion between antigenicity and immunogenicity made investigators accept that if a structurally defined HIV Env epitope was able to bind strongly to a broadly neutralizing monoclonal antibody (bnMab), the same epitope was likely to also induce similar neutralizing Abs in an immunized human host [22]. This common reductionist confusion between chemical antigenicity and biological immunogenicity is difficult to understand because Berzofsky more than 30 years ago had already clearly established that antigenicity refers to intrinsic binding properties of the antigen that arise from its chemical structure, whereas immunogenicity arises from properties of the host IS that are extrinsic to the antigen molecule, for instance, the Ab gene repertoire of the host, antigen processing, the specificity of helper and suppressor cells, and a variety of other immunoregulatory mechanisms [23]. Although this confusion in the case of HIV partly contributed to the failure of structure-based reverse vaccinology, since investigators only paid attention to the binding

specificity of single epitope-paratope pairs, there are numerous other reasons why it has not been possible to develop an HIV vaccine. HIV has a very high mutation rate and an extremely long Ab maturation process that is required for obtaining neutralizing Abs; in addition, the virus integrates in the host genome and establishes a latent pool of infected cells that conceals the virus from immune recognition and allows it to destroy the IS [24-26].

Although the advent of monoclonal antibodies (Mabs) obtained by hybridoma technology completely transformed our understanding of immunological recognition by individual Abs, it also introduced a reductionist bias in the analysis of protein antigens and immunogens because investigators tended to focus on a limited number of viral epitopes and ignored the fact that the HIV Env surface is a continuum of overlapping epitopes [27]. Natural protective immune responses against pathogens are always polyclonal, and their efficacy is usually caused by a considerable neutralization synergy between Abs directed against the numerous epitopes that are always present on the surfaces of proteins. Any residue present at the protein surface can be part of neighbouring epitopes recognized by different Abs, and no sharp boundaries exist between different epitopes, which together always form an antigenic continuum. It is only because epitopes are today mainly defined with Mabs that antigenicity appears to be located in discrete regions of the protein.

An Ab is always polyspecific because the two fairly large Ab-binding pockets of an IgG molecule always contain a significant number of smaller paratope subsites of 10-20 residues, some of which may be overlapping [28, 29]. These paratopes can bind different epitopes found in various proteins, with the result that a single Mab may sometimes appear to be less specific than a polyclonal antiserum that contains Abs that all recognize the same antigen [9].

Many Abs are also heterospecific, which means that they may react more strongly with another antigen than the one that was used in the immunization process that elicited the Ab. Heterospecificity occurs because B cells can be selected and triggered by immunogens that possess only minimal affinity for the Ab present in a BCR. Such Abs may have such a low affinity for the immunogen that it may seem that they have been elicited by an antigen with which they are unable to react. Ab heterospecificity is responsible for the common observation that early antisera obtained soon after immunization with any antigen often contain levels of total Igs that far exceed the level of Abs that are able to react with the immunizing antigen [30]. The heterospecificity of Abs also helps to clarify the difference between protein antigenicity and immunogenicity, which can be located in different regions of a protein and explains why immunogenicity is not necessarily accompanied by an antigenic reactivity that enables the epitope to bind to the induced Ab [9]. The reductionist belief that confounds antigens with immunogens is largely responsible for the failure of structure-based reverse vaccinology to develop an HIV vaccine.

The elusive rational design of an HIV vaccine

The rational design of an HIV vaccine is an approach that has been advocated for more than 15 years although it never succeeded in developing an effective HIV vaccine [31–35]. The persistent inability to develop an HIV vaccine by rational design raises the interesting question of why investigators pursued this approach at great expense for so many years. Before it was recognized that the vast majority of epitopes in proteins were discontinuous, i.e., composed of surface residues from distant parts of the protein sequence brought together by the folding of the peptide chain, many attempts had been made to use short linear peptides from viral proteins or other pathogens as potential synthetic peptide immunogens. Although many such peptides did induce Abs that bound to the peptide used for immunization, very few of these Abs recognized the virus protein itself, and they were therefore unable to neutralize the infectivity of the virus [36]. Since discontinuous epitopes in their intact 3D conformation cannot be isolated in their active form from the viral protein in which they are embedded, it is impossible to study their intrinsic ability to act as vaccine immunogens on their own. When the intact protein is used as an immunogen, it elicits a heterogeneous response induced by the different epitopes of the protein, and the contribution of the discontinuous epitope to any observed neutralization effect is difficult to ascertain [9].

In order to study the structure of discontinuous epitopes implicated in neutralization, Burton [37] introduced a reverse vaccinology approach in virology, which attempts to generate a vaccine from the observed crystallographic structure of neutralizing Mabs bound to their complementary epitopes. The term “reverse” is used because the investigator tries to generate a vaccine starting from the structure of a bound neutralizing Ab instead of trying to generate it by immunization. Which process is actually reversed is not evident, since the Mab is simply used as a template to reconstruct its complementary binding epitope, by reverse engineering. The investigator usually assumes that this reconstructed antigen designed to fit the Mab will also possess the immunogenic capacity of inducing a polyclonal Ab response with the same neutralizing property as the Mab, although there is no reason why this should be the case. Since every Ab is polyspecific, it is not intrinsically specific for a single epitope and it could have been elicited by any one of the antigens with which it is able to react.

The concept of reverse vaccinology introduced by Rappuoli [38] in the field of bacterial vaccines referred to a

completely different strategy based on predicting potential vaccine immunogens using *in silico* analyses of entire bacterial genomes and identifying all the antigens that a bacterial pathogen is able to express. Investigators worked in a reverse manner, starting from the genome rather than from the organism and were able to evaluate hundreds of expressed bacterial proteins for their capacity to induce a protective immune response [39]. Since the strategies used in virology and in bacteriology are completely different, calling them structure-based (SBRV) and genome-based reverse vaccinology (GBRV) would have made it easier to distinguish them. The GBRV approach was more successful because it included testing the cross-protective immunogenicity of expressed bacterial proteins, whereas the SBRV strategy simply assumed that reconstructed viral antigens that strongly bind to a neutralizing monoclonal antibody (nMab) must automatically also be effective immunogenic inducers of protective Abs. SBRV is often assimilated to and called "vaccine design" although the approach in fact only achieves antigen design. GBRV and SBRV are sometimes called reverse vaccinology 1.0 and 2.0, which can be confusing, since it led, for instance, to the exaggerated claim that reverse vaccinology 2.0 shows great promise as a powerful vaccine design strategy [40] although it is GBRV that deserves that accolade.

Another difficulty in the case of viruses is that their surface proteins often contain multimeric assemblies of identical subunits with a quaternary structure that gives rise to novel transient epitopes, called neotopes [41, 42], that are not present in the viral protein monomers or on bacterial surfaces. Neotopes arise either from juxtaposed residues in neighbouring subunits that are recognized by Abs as a single epitope or from conformational changes induced in the protein by intersubunit interactions. Although they exist in all viruses, neotopes were not detected in HIV for many years, which delayed their utilization as superior immunogens.

When it was discovered that HIV epitopes recognized by affinity-matured nMabs derived from chronically infected individuals did not bind the germline predecessors of these Abs [43, 44], it became clear that SBRV was doomed, since a lengthy process of Ab affinity maturation would be required for obtaining neutralizing anti-HIV Abs by vaccination. Mascola and Haynes [45] concluded that “our best efforts to construct vaccine immunogens that present these key epitopes to the IS have failed to generate Abs that neutralize most strains of HIV-1”, and they also stated that “a structure-based approach was unlikely to solve the HIV-1 vaccine problem”. The SBRV approach, which was not based on sound immunological theory [9], was then increasingly replaced by a new research strategy that attempted to unravel individual Ab maturation pathways that lead from non-neutralizing to neutralizing Abs by using sequential immunization with various Env immunogens [46, 47]. In view of the huge number of possible alternative maturation pathways, such an approach faces considerable difficulties for developing a widely applicable HIV vaccine [48].

Vaccine design not only requires deciding which are the structural elements of virions that should be used for immunization but also involves choosing appropriate vaccine formulations and schedules as well as selecting suitable adjuvants and routes of administration. The need to incorporate helper T cells or cytotoxic T cell epitopes in the vaccine construct must also be considered, and all these parameters need to be optimized by testing empirically whether they contribute to the effectiveness of the vaccine [49, 50].

Most protective immune responses against viruses and other pathogens are polyclonal and involve the participation of neutralizing Abs specific for different epitopes present in one or more vulnerable antigenic sites that may exceed the surface that is in contact with one Mab paratope. Since SBRV usually concentrates on the immune response elicited by a single epitope, it may miss the neutralizing synergy that occurs when several antibodies directed to neighbouring epitopes are induced. Furthermore, the binding of one Ab to an Env epitope can lead to conformational changes in the protein that may expose additional neighbouring epitopes recognized by Abs that could also give rise to neutralization synergy.

Another explanation for the inability to discover a potent vaccine immunogen from the analysis of bound HIV epitopes and paratopes is that the HIV-1 p17 matrix protein that lines the inner surface of the viral membrane is the most disordered viral protein ever observed on our planet [51, 52]. The p17 matrix protein possesses a percentage of intrinsic protein of 70%, which reverberates across the viral membrane, leading to shell disorder and to an increased flexibility of polysaccharide moieties, which prevents Abs from binding to the highly glycosylated HIV gp120. It may seem odd that a high degree of disorder is able to completely abolish the immune reactivity of HIV antigens, since structural flexibility in Abs does increase the size of the Ab repertoire of ISs while segmental mobility in epitopes and paratopes facilitates immunochemical recognition. Clearly, 70% disorder prevented HIV immunogenic structures from being recognized by the IS and allowed the virus to escape the onslaught of mature Abs designed using the most sophisticated tools of modern biotechnology.

Most vaccinologists are not aware that most problems they need to solve are so-called inverse problems rather than the usual direct scientific problems they solve by determining experimentally what effects follow from certain causes. Solving inverse problems consists in guessing what are the multiple past causes that produced an observed beneficial effect, for instance the absence of deleterious HIV infection in elite controllers. An inverse problem thus starts with a result and requires that the investigator must try to imagine

what the multiple causes are that could have produced it [18]. Obviously, it is not possible by scientific experimentation to investigate past events, and the only possible approach is to conceptualize a theoretical model of HIV immunity that could account for what has been observed and then to demonstrate that what the model predicts actually does occur. For instance, HIV vaccinologists must hypothesize what the multiple causes are that sometimes allow the IS in a small number of individuals to elicit weak protective immune responses, and they must then try to make these rare events occur regularly in large populations of genetically heterogeneous human vaccinees. Sometimes, system vaccinology based on high-throughput microarray technologies [53] allows the identification of certain gene signatures that are correlated with the immunogenicity of different vaccines, although these signatures do not provide a mechanistic insight on how a particular vaccine stimulates protective immunity [54]. The IS consists of numerous subsystems that are poorly understood and do not make it possible to solve the inverse problems posed by each subsystem. Solving an inverse problem amounts to predicting something that happened in the past, a feat that scientists find much more difficult to do compared to what they excel at, namely to analyze direct problems by investigating experimentally what are the effects that follow from certain causes. Inverse problems appear to create unsurmountable problems for developing a preventive HIV vaccine, since our ignorance of which features and constituents of the IS are responsible for the production of protective Abs does not allow us to propose testable models and hypotheses for reaching that goal.

The failure of rational HIV vaccine design is in line with the fact that vaccinology is an empirical science that only sometimes succeeds, partly because we also lack a full understanding of the complex mechanisms responsible for the effectiveness of some of our currently used vaccines. Several reviews in this current special issue on HIV vaccines discuss novel empirical approaches that have not yet been used successfully with HIV, and it cannot be excluded that some of these empirical explorations may succeed, as have many earlier vaccines in the past. Empiricism could still succeed in achieving protective immunity against HIV by vaccination even if we remain ignorant of all the multiple mechanisms and interactions involved in the appearance of protective responses in human ISs.

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