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Review Article

Is the Rational Design of Viral Vaccines a Realistic Enterprise?

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Abstract

The development of molecular biology in the 20th century fostered the expectation that biology could be reduced to chemistry and this blurred the distinction between the chemical nature of antigen-antibody binding and the biological nature and capacity of the immune system to elicit the formation of neutralizing antibodies able to protect against viral pathogens. Belief in the rational design of viral vaccines is problematic because the complex notions of human rationality and of design are rarely described or defined accurately, which leads investigators to overestimate their capacity to solve inverse problems. Vaccinologists are often confronted with such problems which consist for instance in identifying what were the multiple biological causes in the past that give rise to a wanted beneficial result in the future, such as the absence of deleterious HIV infection in human elite controllers. In addition to the impossibility of investigating past immunological events by doing scientific experiments in the future, the common failure of rational vaccine design is also due to the fact that vaccinology is essentially an empirical science that needs to rely on the results of immunogenicity trials that must necessarily be based on trial-and-error experimentation rather than on bounded rationality.

Review

A scientific procedure is said to be rational if it is based on reason and accepted scientific theory and successful rational vaccine design in virology usually implies that researchers are expected to be able to predict the outcome of an immunization process aimed at inducing the production of neutralizing antibodies (Abs) that abolish the infectivity of a viral pathogen. The concept of structure-based vaccine design is derived from rational drug design which relies on knowledge of the 3D structure of a biologically active target molecule in order to discover candidate molecules that will bind with high activity and selectivity to the target and abolish its biological activity [1]. Such computer-assisted strategies based on structural bioinformatics and molecular docking are usually considered to be superior to the empirical screening and trial-and error approaches commonly used in the past [2,3] although they mostly failed when they were applied to the rational design of viral vaccines. The reason for this is that vaccinologists mostly tried to improve the antigenic binding capacity of their candidate viral immunogens instead of investigating whether superior immunogens could be designed that would be able to generate protective Abs in vaccinees [4-7]. Improving immunogenicity would have required an investigation of the numerous factors, extrinsic to chemical epitope-paratope recognition, that control the biological capacity of human immune systems for eliciting the induction of protective antibodies which depend on the Ab gene repertoire and antigen processing ability of the host, the specificity of helper and suppressive immune cells and various other immunoregulatory mechanisms. Even when a vaccine has been "designed" on the basis of computer-based predictions, there is in fact no guarantee that it will necessarily be able to induce protective Abs if it has not been tested empirically in the human biological context in which it is expected to be effective. The remarkable development of molecular biology in the 20th century did foster the expectation that all biological phenomena may eventually be understood by reducing biology to chemistry and such reductionist thinking did blur the distinction between the chemical nature of antigen-antibody binding and the biological nature of the capacity of immune systems to elicit the production of neutralizing Abs. The structure-based reverse vaccinology (SBRV) approach introduced by Burton [8] was based on a confusion between antigenicity and immunogenicity which led many vaccinologists to expect that if a structurally defined HIV epitope was able to bind strongly to a broadly neutralizing monoclonal Ab, this epitope would also be able to induce similar neutralizing Abs in a vaccinated human host [9]. However, all Abs are both polyspecific (i.e. they always contain a variety of different paratopes) as well as heterospecific (i.e. they are able to react more strongly with other antigens than with the one that was used in the immunization process that elicited the Ab); these properties explain why the antigenic and immunogenic properties of proteins are often located in different regions of the molecule which is the reason why immunogenicity is not necessarily accompanied by an antigenic reactivity of the immunogenic epitope that would allow it to bind to the induced Ab [10]. Many vaccinologists are not aware that most problems they need to solve are so-called inverse problems. Solving inverse problems consists in proposing a theory that is able to explain the multiple past causes that produced an observed beneficial effect, for instance the absence of deleterious HIV infection in elite controllers [11]. An inverse problem thus starts with a result and requires that the investigator must try to imagine what are the multiple causes that could have produced it. Since scientific experimentation cannot

investigate past events, it is necessary to develop 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. Since the human immune system is extremely complex and consists of numerous subsystems that are currently only poorly understood, it has been impossible to solve the numerous inverse problems posed by each subsystem and to develop plausible models that could be tested experimentally. In the absence of testable hypotheses, the only alternative was to rely on trial-and-error investigations which are the classical tools that have been used by vaccine developers in the past. These consist in selecting plausible vaccine candidates as well as appropriate vaccine formulations, schedules, adjuvants and routes of administration and testing these empirically since there was no knowledge of how the immune system induces the formation of neutralizing rather than non-neutralizing Abs.

Burton and Topol [12] have argued that since HIV infection elicits in patients broadly neutralizing Abs that recognize many HIV strains, it should in principle be possible to design an HIV vaccine, although they acknowledged that investigators would have to know how the immune system is able to induce neutralizing antibodies! This self-evident truth regarding the consequences of our ignorance of the mechanism of neutralizing Ab induction is of course one of the main reasons why the rational design of an HIV vaccine did not succeed although many other reasons for this failure have been well documented [7,13]. Burton and Topol [12] nevertheless stated that a rationally designed HIV vaccine may perhaps only be a decade away. They also suggested that rational vaccine design could be successfully applied to a virus like SARS-CoV-2 and that a pan-virus vaccine able to protect against more severe and antigenically distinct coronavirus variants that could appear during any epidemic, may in future be obtained by rational design, even before such variants had emerged or had caused considerable damage. They envisaged that this could be achieved by investing hundreds of millions of $ for stockpiling enormous quantities of vaccines for future use although they did not clarify which rational design strategies would make it possible to produce effective vaccines against new viruses of unknown pathogenicity.

In fact, rational vaccine design is actually problematic for two reasons that are linked to the concepts of both rationality and of design. The economist and Nobel laureate Herbert Simon introduced the notion of "bounded rationality" to explain the intrinsic limitations of human cognition and rationality that are due to the many unavoidable constraints that always limit the ability of humans to achieve a complete analysis of complex systems [14]. Such limitations exist because our information is always insufficient or inaccurate, we have limited time and resources for investigating the countless numbers of interacting components in any complex biological or immunological system and we cannot reach entirely rational decisions that would require a complete knowledge of all the relevant parameters. Instead of guaranteeing that a correct solution to complex problems can be reached, bounded rationality inevitably forces us to make tentative decisions that always remain uncertain.

Physicists and chemists used to believe that the universe was ruled by mathematical laws that would make it possible to predict the future behavior of a system if one had an intimate knowledge of all its initial conditions. However, in spite of our enormous modern computational power, we were actually unable the predict the 2008 world financial crisis and we also fail to be able to make long-term weather predictions. Chaos theory has reconciled us with the reality that extremely small differences in the initial conditions of a dynamic biological complex system prevents us from making accurate predictions about its future state [15,16].

The concept of design which implies the deliberate and intentional conceiving of an artificial, novel object or process by an intelligent being is equally ambiguous.

Adepts of so-called "intelligent design" for instance argue that a mythical, intelligent deity is responsible for having designed all living forms on our planet according to a preconceived plan and they do not accept that evolution took place through the filter and pressure of Darwinian natural selection. The design metaphor is also equally inappropriate for explaining the evolution of living organisms on earth as it is for describing the activity of scientists when they try to achieve a particular intentional goal in the form of a discovery or invention since their intentional design activities in most cases are not successful [6]. Intentional successful design remains as mysterious as the indispensable contributions of human imagination, intuition and talent that are needed for producing artistic as well as scientific creations and success is not obtained by simply following the numerous steps of a design procedure as if they were the obvious rules of a conceptual recipe book.

The popular paradigms of rational design and reductionism led many HIV vaccinologists to assume that the detailed structural knowledge of HIV spikes would allow them to design complementary binding antigens capable of inducing neutralizing Abs by vaccination [7]. This strategy failed because it was not appreciated that the structures observed in HIV complexes of spikes bound to Abs resulted from a process of mutually induced fit between the two partners and did not correspond to the structures present in the free, mobile and frequently disordered partners before they had interacted. For instance, the HIV-1 p17 matrix protein possesses an intrinsic protein disorder of 70% that reverberates across the viral membrane and produces a shell disorder that prevents the HIV immunogens used as vaccine from inducing a protective immune response [13,17]. It is well-known that although segmental mobility in proteins does enhance the binding capacity of epitopes and paratopes, extreme disorder in a protein antigen on the other hand can prevent antigen recognition and vaccine effectiveness [18].

The common failure of rational vaccine design is in line with the well- known fact that vaccinology is essentially an empirical science that relies more on trial-and-error experimentation than on available fundamental scientific knowledge of immunological phenomena. As emphasized by Hacking [19] in his book *Representing and Intervening,* we need to interfere with the material world (for instance immune systems) in order to obtain knowledge about it and our understanding increases when we are able to intervene successfully in it, for instance by achieving protective immunity by immunization. An understanding of the immune system is thus achieved because of a prior successful

intervention and effective vaccines have often been obtained empirically in the past even before their mode of action had been elucidated. During the last ten years innumerable unsuccessful attempts have tried to identify which series of successive HIV immunogens should be used in a vaccine in order to mimic the Ab maturation pathway that is required for eliciting neutralizing protective Abs [20,21].

Since we know very little about which features of human immune systems regulate the production of protective antibodies, it seems evident that empirical vaccination trials will remain a prerequisite for developing effective vaccines against HIV and many other viral pathogens.

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