



Paradigms in HIV vaccine research

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Abstract

Although a large number of preventative human immunodeficiency virus (HIV) vaccine trials have been carried out during the last 30 years, it is remarkable that an effective HIV vaccine has not yet been developed. Research paradigms correspond to theoretical assumptions and particular strategies that scientists use when they try to solve a particular problem. Many paradigms used successfully in vaccinology were ineffective with HIV. For instance: 1) The structure-based reverse vaccinology approach failed because investigators tried to generate a vaccine starting with the antigenic structure of HIV-envelope (Env) epitopes bound to neutralizing monoclonal antibodies (mAbs) derived from HIV-infected individuals. They assumed that this antigenic structure would also possess the immunogenic capacity of inducing in vaccinees a polyclonal antibody (Ab) response with the same neutralizing capacity as the mAb. 2) The structures observed in epitope-paratope crystallographic complexes result from mutually induced fit between the two partners and do not correspond to the structures present in the free molecules before they had interacted. 3) The affinity-matured neutralizing mAbs obtained from chronically infected individuals did not recognize the germline predecessors of these Abs present in vaccinees. 4) The HIV p17 matrix protein that lines the inner surface of the viral membrane is one of the most disordered proteins identified on our planet and this prevents the induced Abs from binding to the glycosylated HIV gp120 protein. 5) Vaccinologists need to solve so-called inverse problems, for instance, guessing what are the multiple causes that produced an earlier wanted beneficial effect such as the absence of deleterious HIV infection in elite controllers. Since the immune system consists of numerous subsystems that have not yet been elucidated, it is impossible to solve the inverse problems posed by each subsystem. 6) Vaccinology is an empirical science that only sometimes succeeds because we do not understand the complex mechanisms that lead to protective immune responses.

Keywords

Causality, direct problem, inverse problem, explanation, paradoxes, immunogenicity

Introduction

Paradigms refer to the hypotheses and theories that researchers must consider when they try to solve a scientific problem such as developing a new vaccine. However, the validity of paradigms can never be

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established beforehand, which explains why an effective human immunodeficiency virus (HIV) vaccine has not yet been developed.

Causality and inverse problems in biology

Humans tend to agree that causality exists in the world as well as in their minds and Cohen et al. [1] suggested that the entire universe can be seen as an intricate web of step-by-step causality but with so many steps that on a large scale we seem to see only contingency. The importance of any cause then has little meaning, since momentous events are always initiated in some sense by trivial, indeed immeasurably small, causes. This is reminiscent of chaos theory that gives importance to the flapping of a butterfly's wings for explaining weather change on the basis that everything is caused by everything that preceded it. However, such an interpretation is not compatible with the view that Darwinian evolution is always a valid explanation for the appearance of certain biological features. For instance, the wings of insects, bats, and birds have evolved separately at different times from different ancestors rather than from a unique DNA sequence because these wings resulted from the usefulness for different types of organisms to be able to get off the ground, which is a case of convergent evolution.

Humans have a natural desire to understand which is best achieved by seeking explanations for various phenomena. Explanations can take the form of

- 1) narratives that describe how some event came about;
- 2) deductions that are feasible in a quantitative science such as physics;

3) mechanisms that describe how events causally result from regular changes in systems of connected and interacting parts [2]. Identifying causal links is useful because it allows humans to manipulate the world.

In their review entitled "Inverse problems and uncertainties in science and medicine", Anger et al. [3] argued that inverse problems are the opposite of direct problems and that engineering, for instance, solves direct problems, whereas many problems in biology and medicine, for instance, diagnosis, are inverse problems. The logical deduction that if it rains, the street will be wet is reasoning from cause to effect which is answering a direct problem, whereas the inverse reasoning that the street is wet because it has rained is a case of induction since it could have been caused by a broken waterpipe. Induction is the inverse problem of deduction and is more difficult to solve because one is arguing from an effect to numerous possible causes.

Whereas deduction proceeds from the general to the particular using, for instance, a general law, induction proceeds from a particular case for deriving a general theory which is much more problematic. Popper [4] argued that no number of causal factors can ensure the validity of a theory whereas a single refutation may be sufficient to overthrow it. However, the refutation itself may only be apparent if it was based on a measuring error since in this case the theory could in fact still be true. Every measurement must always be accompanied by a measurement of its accuracy, using for instance the so-called standard error, since an erroneous measurement obviously cannot falsify a theory. In medicine, the so-called placebo effect arises when a patient is treated with a novel revolutionary drug, which may then lead to the patient's conviction that the drug is relieving his symptoms although the drug may in fact be ineffective.

Uncertainties in logic may also lead to logical paradoxes such as the famous set of all sets which does not contain itself as a member. This paradox was exemplified by Bertrand Russell in the case of a small village that has only one barber which shaves all male persons in the village who do not shave themselves. In such a case, the barber shaves himself if and only if he does not shave himself. This paradox did actually shatter the very foundations of logic and of mathematics [3]. In an analogous manner, the paradox of the liar which refers to the statement that says "This statement is false", is correct if and only if it is false. This paradox was used by Goedel [5] to argue that in mathematics there are propositions that cannot be proved or disproved within the system itself since a logical system cannot prove its own consistency; this conclusion has been considered to be one of the most significant contributions to logic ever made. He was in fact throwing doubt on the provable exactness of mathematics and logic and arrived at the disconcerting conclusion that "This statement is false"

is provable if and only if it is not provable! Goedel chose to believe in God although he accepted that God's existence could not be proven.

Computers only work algorithmically which means that they cannot act intelligently as humans do when they reflect about themselves and recognize that a proposition may be true even if it cannot be derived from certain axioms. The reason is that humans also reason non-algorithmically for instance by intuition or self-referential thinking. Artificial intelligence, sometimes attributed to robots, does not involve self-consciousness since robots do not know what they are doing and therefore cannot be responsible for it. The imaginary wars of robots against humankind therefore only belong to science fiction [3]. Consciousness is self-referential because we know that we possess consciousness. What is more difficult to explain is not the self-referential nature of consciousness but our ability to derive cognitive conceptual knowledge from a huge quantity of partially structured sensory data acquired by neurons. The ability of brains to make conscious choices is actually a feature of large systems of neurons that arises from the manner in which they interact [1].

Since the laws of nature are never absolutely exact because of unavoidable uncertainties, they can only be approximately true. Biologists no longer accept that biology can be reduced to physics and chemistry, and they recognize that inverse problems in biology and medicine are difficult or impossible to solve by modern science because intrinsic instabilities do lead to small causes having large effects. Chaos theory was developed by Lorenz [6] and it reconciled mankind with the unreliability of long-range meteorological weather predictions as well as with the fact that nonlinear dynamics in biological phenomena produce a constant unpredictable interplay between complexity and simplicity [1]. The dynamic complexity of living systems is now seen as the result of the huge number of constituents that exist in all of them as well as by the existence of emergent properties that are not present in the individual constituents before they have interacted with each other. Emergent properties are possessed by the whole but not by the parts and are not just aggregates of the properties of the parts because they result from interactions of the parts [2]. Living organisms are also no longer considered to consist of stable material objects but are viewed as dynamic processes that are actively maintained over very different time scales that involve development, metabolism, and evolution. The diachronic identity of an organism refers to an identity through time that actually corresponds to the continuity of the organism's life [7].

Solving a direct problem in biology consists in identifying which causal interactions between the numerous parts of a complex system are responsible for the occurrence of a particular phenomenon; this is based on analyzing the effects of known causes and is the mainstream of scientific research. On the other hand, solving an inverse problem requires inferring from a set of observations what are the multiple causes that may produce a certain effect which is based on inductive reasoning that may be extremely difficult or even impossible to do correctly. This is the reason, for instance, why it has not been possible to develop an HIV-1 vaccine by rational design [8].

From old to new paradigms

The following unwarranted assumptions that underlie five paradigms used in HIV-1 vaccine research have contributed to the failure of developing an effective HIV-1 vaccine [9].

- 1) Vaccine immunogenicity can be predicted or derived from viral antigenicity.
- 2) There is a primary and intrinsic epitope specific for each B-cell receptor and for its corresponding antibody (Ab) since Abs are always polyspecific.
- 3) HIV-1 epitopes recognized by mature neutralizing monoclonal Abs (mAbs) isolated from HIV-1 infected individuals after a lengthy process of Ab affinity maturation must be able to induce an immunogenic protective immune response in naive individuals.
- 4) The so-called rational design of HIV-1 vaccine immunogens based on the presence of antigenicity in viral epitopes is more effective than the trial-and-error screening of immunogens used in the past for developing effective vaccines.

5) Reactions of viral antigens with mAbs are more specific and can better inform vaccine design than the combined reactivity of polyclonal Abs present in an antiserum.

These failures suggest that novel paradigms may be required that better fit the complexity of immune systems as well as the nature of HIV-1 immune responses.

It used to be believed in the past that successful paradigms used for developing effective vaccines against various viruses would also be applicable to HIV-1. It was believed, for instance, that immunization with HIV-1 envelope (Env) recombinant proteins should be able to confer protection against HIV-1 infection. Subsequently, a paradigm based on cell-mediated immunity was tried for several years but was also abandoned when vaccine trials showed no efficacy [10]. A third paradigm based on structure-based reverse vaccinology (SBRV) proposed by Burton [11] was pursued for many years without any success. SBRV assumed that it is possible to derive an effective HIV vaccine immunogen from the structure of an HIV epitope that is bound to a neutralizing mAb obtained from a patient infected with HIV. This assumption overlooks the fact that the binding reaction between an epitope and a paratope achieved by induced fit leads to novel conformations in both partners that are not present in them before they have interacted with each other. This means that the structure of the bound epitope does not correspond to the initial immunogenic structure that induced the formation of neutralizing Abs in infected humans. Molecular recognition based on stable complementary shapes is different from molecular recognition based on induced fit. By confusing antigenicity with immunogenicity, SBRV was unable to rationally design an effective HIV vaccine [12].

In recent years, a broader paradigm was advocated which argued that extensive basic research programs in immunology should be undertaken to improve our inadequate knowledge of immune systems and of HIV-1 immunopathology [13, 14]. After ten years, this paradigm was also shown to be unsuccessful which was in line with the warning of Hacking [15] that it is necessary to intervene in a complex system such as the immune system in order to obtain knowledge about it and to be able to control it for instance by achieving protective immunity. This means that the empirical development of an effective vaccine must take place before the mode of action of an ideal HIV-1 has been elucidated by basic research [16, 17]. An additional novel paradigm proposing the development of a tolerogenic HIV-1 vaccine that may be effective without inducing neutralizing Abs and cell-mediated immunity is discussed by Christine Jacomet in this special issue.

Abbreviations

Ab: antibody

mAbs: monoclonal antibodies

HIV: human immunodeficiency virus

SBRV: structure-based reverse vaccinology

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The author contributed solely to the work.

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The author declares that he has no conflicts of interest.

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