Nomenclature for Immune Correlates of Protection After Vaccination

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Identification of immune correlates of protection after vaccination is an important part of vaccinology for both theoretical and practical reasons. The terminology and definition of correlates have been confusing, because different authors have used variable terms and concepts. Here, we attempt to give precision to the field by defining 3 terms: correlate of protection (CoP), mechanistic correlate of protection (mCoP), and nonmechanistic correlate of protection (nCoP). A CoP is a marker of immune function that statistically correlates with protection after vaccination that may be either an mCoP, which is a mechanistic cause of protection, or an nCoP, which does not cause protection but nevertheless predicts protection through its (partial) correlation with another immune response(s) that mechanistically protects.

The identification of immune markers that correlate with protection against infection or disease after vaccination (or natural infection) is an important quest. In addition to their basic immunologic interest, those immune markers enable the correct choice of antigens to include in vaccines, determine individual and population immunity, bridge from previously collected protection data, and can sometimes be used to supersede efficacy trials that are not feasible or ethical. The importance of such markers is evident in the search for a vaccine against HIV, in which natural immunity is not present but in which the putative identification of an immune response that may correlate with protection has stimulated the field [B. F. Haynes, P. B. Gilbert, M. J. McElrath, et al, unpublished data].

Correlates of protection (CoPs) have generally been inferred from studies of passive antibody administration, analysis of immune responses in protected and unprotected subjects in nature, and in efficacy trials, observations of immunosuppressed humans or animals, human challenge studies, and extrapolation from the results of challenges in animals. However, the terminology used by scientists in discussing correlates has become confusing. Each of us has written about correlates and surrogates of protection, but the terms have been defined differently, and other authors have also used the words with varying meanings. For example, although both Qin [1] and Plotkin [2–4] define a surrogate as an immune marker that can substitute for the clinical end point and, thus, can be used to reliably predict vaccine efficacy, Qin's surrogate may or may not be a causal agent of protection, whereas Plotkin's surrogate definitively is not.

We have now collaborated and wish to propose a new terminology that is less ambiguous and unifies and supplants the old. The central concept is that a correlate reflects a statistical relation between an immune marker and protection but does not necessarily imply causal agency of the marker. However, data accumulated by the aforementioned means may show that a CoP is indeed a protective immune response or, conversely, that it is only an immune response that accompanies protection but is not causally responsible for it.

This idea is set out in Table 1 and Figure 1.

Following are remarks on the nomenclature.

Table 1. Terminology for Immune Correlates of Protection

Term	Synonyms	Definition
CoP (correlate of protection)	Predictor of protection	An immune marker statistically correlated with vaccine efficacy (equivalently predictive of vaccine efficacy) that may or may not be a mechanistic causal agent of protection[a]
mCoP (mechanistic correlate of protection)	Causal agent of protection; protective immune function	A CoP that is mechanistically and causally responsible for protection
nCoP (nonmechanistic correlate of protection)	Correlate of protection not causal; predictor of protection not causal	A CoP that is not a mechanistic causal agent of protection

[a] A correlate of protection can be used to accurately predict the level of vaccine efficacy conferred to vaccine recipients (individuals or subgroups defined by the immune marker level).

1. The terms are nested in that mechanistic correlates of protection (mCoPs) and nonmechanistic correlate of protection (nCoPs) are CoPs. Moreover, mCoPs and nCoPs are mutually exclusive and exhaustive, such that a CoP is either an mCoP or an nCoP.

2. Mapping of new nomenclature to previous nomenclature:

a. Specific CoP = specific surrogate of protection in the nomenclature of Qin et al [1]

b. Bridging CoP = general surrogate of protection in the nomenclature of Qin et al

c. mCoP = correlate of protection in the nomenclature of Plotkin [2–4]

d. nCoP = surrogate in the nomenclature of Plotkin [2–4]

3. Statistical assessment of CoPs in a vaccine efficacy trial is preceded by assessment of "correlates of risk (CoRs)" in the trial (Qin terminology), in which a CoR is an immune marker statistically associated with the rate of the clinical end point used for measuring efficacy in the vaccine or control group. A CoR in the vaccine group is hypothesized to be a CoP, but may not be if the CoR merely marks pathogen exposure or intrinsic biological susceptibility to the clinical end point in a way not manipulable by vaccination (the risk of these CoP

failures can be minimized by controlling for known exposure and natural resistance factors in the statistical assessment of CoRs). Moreover, CoRs may be directly statistically assessed as CoPs in efficacy trials in 2 main ways, each of which combines assumptions with CoR analysis. The first approach is based on CoR analyses in each of the vaccine and control groups and on the association of vaccination status on the clinical end point, and assesses the validity of the CoR as a replacement for the clinical end point [5]. The second approach is based on CoR analysis in the vaccine group and on a modified CoR analysis in the control group, which assesses the association between the immune marker that control subjects would have had if they had received vaccine with the rate of the clinical end point. This approach collects additional data in the efficacy trial to predict the vaccine-induced immune marker level in control subjects [6], and assesses how strongly vaccine efficacy varies with this marker level [7]. The first approach applies only for immune markers that vary over a similar range in the vaccine and control groups (thereby not applying in efficacy trials that only enroll pathogen-naive persons), whereas the latter approach applies generally.

Three examples may suffice to clarify this terminology. Responses to meningococcal vaccine can be measured by enzyme-linked immunosorbent assay (ELISA) or bactericidal antibodies. However, it has been clearly demonstrated that bactericidal antibodies are responsible for efficacy and that, conversely, ELISA antibodies may be induced without causing protection [8]. Thus, bactericidal antibodies are a CoP and an mCoP, whereas ELISA antibodies are a CoP and an nCoP.

Zoster vaccine has been developed to correct the waning of cellular immunity to varicella-zoster virus that occurs with increasing age. When antibody and cellular responses were measured after vaccination, both were correlated with efficacy, and therefore, both were CoPs [9]. However, the correlation was statistically stronger for the cellular response, and in view of the biology of the disease, the cellular response is an mCoP, whereas the antibody, although more conveniently
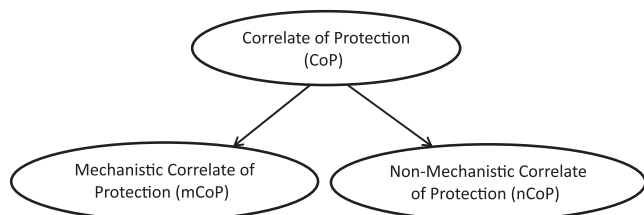

Figure 1. A correlate of protection (CoP) may be either a mechanism of protection, mCoP, or a nonmechanism of protection, termed nCoP, which predicts vaccine efficacy through its (partial) correlation with another immune response(s) that mechanistically protects.

measured, is an nCoP. Thus, in this case, the nCoP is more useful than the mCoP.

There has been great difficulty in identifying the protective mechanism of rotavirus vaccines, which is probably present in the intestine. Nevertheless, a serum immunoglobin A (IgA) response is elicited in most vaccine recipients and that response has been useful in gauging protection [10]. Because it is unlikely that serum IgA is the actual protective mechanism, it is a CoP and an nCoP, not an mCoP. It should also be understood that CoPs, mCoPs, and nCoPs may vary with type of vaccine, pathogenesis-pathogenetics of disease, or host population [1]. This variation is exemplified by the pneumococcal conjugate vaccine, in which mCoP depends on type of antibody, location of the infection, and country in which vaccination is practiced [4].

The definition of a CoP is often crucial in vaccine development, and for both theoretical and practical reasons, identification of the mCoP rather than an nCoP is preferable; however, an nCoP may be very useful. We hope that the use of this new terminology will be adopted by other scientists to give more precision to discussions of a crucial concept in vaccinology.

Notes

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