

A Disquisition on MHC Restriction and T Cell Recognition in Five Acts

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Abstract

The seminal discovery in the early 1970s, credited to Peter Doherty and Rolf Zinkernagel, of major histocompatibility complex (MHC) restriction exhibited by cytotoxic T cells represented a major conceptual advance in understanding antigen recognition by conventional T cells. This advance also led to other major new insights into the ontogeny and immunobiology of T cells and catalyzed a renaissance in viral immunology. In this commentary in honor of Peter Doherty, I offer five brief reflections on different aspects of the phenomenon of MHC restriction and the process by which it was discovered and explained. In the first of these sections, I offer a reinterpretation of MHC restriction that reframes the constraints on self-MHC recognition in terms of the probabilities of recognizing a given nominal antigen peptide in the context of an MHC molecule that is nonself on the basis of differing in amino acid sequence from the self-restriction element at one or more positions. Subsequent sections address: (i) the ways in which general ideas, developed subsequent to the discovery of MHC restriction, about the intricacies of antigen recognition by antibodies apply to T cell receptors binding to MHC/peptide complexes; (ii) how to reconcile the existence of MHC restriction with the impressive magnitude of T cell responses to nonself MHC antigens; (iii) the possible relevance to MHC restriction and immune system function of ideas from mathematical logic that relate to the consequences of self-reference; and (iv) the implications for the philosophy of science of MHC restriction and the processes of its discovery and acceptance within the immunology research community.

Keywords: T cells, specificity, MHC restriction, alloimmunity, philosophy of science

Act I: A Probabilistic Reinterpretation of MHC Restriction

IN APRIL OF 1974, Peter and his then-collaborator Rolf Zinkernagel published an enormously consequential two-page paper in *Nature* with three tables, no figures, and zero supplementary information (38). Rolf and Peter presented results suggesting that virus-specific cytotoxic T cells from immunized animals of the CBA/H inbred strain of mice, possessing H-2^k haplotypes, effectively killed target cells infected with lymphocytic choriomeningitis virus (LCMV) but not uninfected target cell lines that were H-2^k. However, these same T cells did not effectively kill LCMV-infected cell lines displaying the H-2 antigens of the b or d haplotypes on their plasma membranes. The interpretation offered was that CTL could only recognize viral antigen (in a form later shown to be a peptide) in association, in some sense, with self-MHC (2,4).

The following is a typical statement about the nature of MHC restriction in a reasonably current textbook of immunology (30):

“As a consequence of MHC restriction, a T cell that responds to a peptide presented by one MHC allotype will not respond to another peptide bound by that same MHC allotype or to the same peptide bound to another MHC allotype.”

The seeming implication of the quote just given is that MHC restriction is absolute.

This sort of dependence of viral or other nominal antigen recognition by cytotoxic T cells on the identities of the MHC antigens of target cells had not been previously observed nor had Peter and Rolf anticipated such an effect according to their own account of this momentous discovery (39). Somewhat similar effects had been previously noted (22,24,31) in the context of helper T cells delivering help to B cells, but the interpretation of the corresponding phenomena had remained thoroughly unsatisfying and unenlightening in any broader context.

Of course, recognition of viral antigens on cell surfaces by antibodies had not been observed to depend on or be influenced by the MHC molecules displayed on the plasma

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membranes of the cells displaying the viral antigens in question. So, for both cytotoxic and probably helper T cells, recognition of antigen seemed to be significantly more complex than was known to be the case for antibodies.

Initially, it was not clear whether the recognition of both the foreign (or nominal) antigen and the self-MHC molecule was performed by one receptor interacting with some sort of physical complex between a foreign (e.g., viral antigen) and an MHC antigen or by two receptors, one each for foreign antigen and self-MHC antigen. After another decade-plus of intensive investigation, as alluded to earlier, studies in both murine and human systems revealed that MHC restriction involved the noncovalent binding of peptides derived from immunogenic proteins to either class I or class II MHC molecules (2,4). By the late 1990s, investigators had resolved crystal structures of MHC/peptide/T cell receptor (TCR) complexes that depicted the precise atomic contacts between TCRs and their bi-molecular, MHC/peptide ligands (9,10). Thus, for T cells, recognition of nonself was necessarily tied to recognition of one aspect of self, a complication for the immunological dogma that the immune system recognizes and responds to nonself.

Beginning in the 1990s, Alessandro Sette and his associates and collaborators began to explore instances in which class I antigens differing in amino acid sequence could, nevertheless, bind some of the same nominal antigen peptides (33). Further, some of these nonself class I antigens presenting the same peptide as a self-class I molecule product could effectively present the peptide to CD8⁺ T cells derived from mice or humans expressing only the self-class I MHC molecule. For example, for some peptides, an A3-restricted CD8⁺ T cell clone might be able to kill not only A3-bearing target cells but also A11-bearing or A68-bearing target cells that do not display A3 (35). Sette and his colleagues used the term “super-type” to refer to a group of class I human leukocyte antigen (HLA) molecules with related peptide-binding patterns and potentially overlapping recognition by MHC-restricted TCRs. These same authors also defined class II supertypes (12).

The significance of the phenomena that define supertypes for understanding MHC restriction is that a given clone of peptide-specific self-HLA restricted T cells, whether CD4⁺ or CD8⁺, is not absolutely unable to effectively bind and respond to complexes composed of the “correct” nominal antigen peptide and a nonself HLA molecule. Such recognition of the cognate peptide presented by a nonself MHC molecule diverges from the original interpretation of MHC restriction in which T cells from a given host can only bind and respond to a complex composed of the “correct” nominal antigen peptide and the relevant self-HLA molecule.

Of course, a thought experiment can compel one to realize the high likelihood that some nonself MHC molecules will be sufficiently similar to any self-MHC molecules to permit both effective binding of a common peptide amino acid sequence and the ability to successfully present to T cells from a host expressing the pertinent self-MHC molecule. After all, the alpha3 domain contains about 90 amino acids. This domain is not believed to have a direct role in the ability of the MHC molecule to bind nominal antigen peptide or present to a T cell. Some of the numerous (maximum of >10⁹⁰) possible amino acid substitutions would likely constitute a nonself MHC amino acid sequence that could support both peptide binding and peptide presentation to any relevant T cell.

This, therefore, leads to the following re-interpretation of MHC restriction (Fig. 1). This phenomenon is best described not by stating that T cells recognize nominal antigen peptides only in the context of a single self-MHC molecule, as textbooks generally do. Instead, in this revised view, MHC restriction means that T cells from a given host will recognize certain nominal antigen peptides in the context of one or another self-MHC molecule or a finite number of nonself MHC molecules that share much greater than a random extent of amino acid sequence with the relevant self-molecule such that: (i) the nonself MHC molecule can bind the relevant peptide sufficiently well to present it to T cells and (ii) the nonself MHC molecule has sufficient structural/thermodynamic similarity in the peptide binding region to interact with the TCRs of the cognate-specific T cells.

Although recognition of nominal antigen peptide in complex with a subset of nonself MHC molecules is no longer ruled out, what can be claimed requires a probabilistic perspective. In this framework, a randomly selected nonself MHC molecule (with an average degree of relatedness in amino acid sequence to the relevant self-MHC molecule) is unlikely to both: (i) bind the relevant peptide well enough to present it to T cells and (ii) possess the thermodynamic and structural features in the peptide binding domains that are necessary for

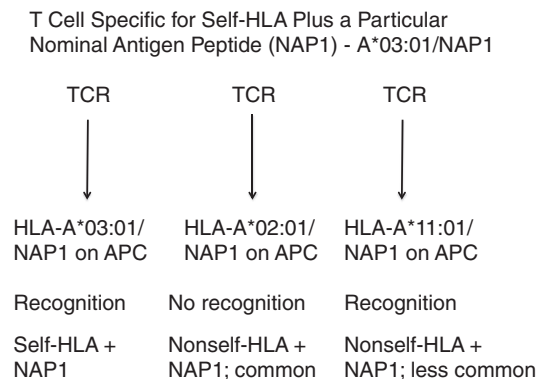


FIG. 1. Revised interpretation of MHC restriction in a human context. (*Left panel*) A CD8⁺ T cell can recognize (bind to), such that cell-activating signals can be transduced) a noncovalent complex of a peptide (nominal antigen peptide 1 or NAP1) derived from a foreign (e.g., viral) protein and a self-class I HLA molecule (in this instance, HLA-A*03:01). (*Middle panel*) The same CD8⁺ T cell cannot bind sufficiently well to the same peptide presented by most nonself (i.e., allogeneic) class I HLA molecules to transduce signals that result in cellular activation (or the nonself HLA molecules cannot bind the peptide well enough to present it). (*Right panel*) The same CD8⁺ T cell can bind sufficiently well to the same peptide presented by a subset of nonself (i.e., allogeneic but of the same supertype) class I HLA molecules to transduce signals that result in cellular activation. These class I molecules will, in most cases, share critical stretches of the amino acid sequence of the self-HLA molecule in the peptide-binding portions of the alpha 1 and alpha 2 domains. For CD4⁺ T cells and class II restriction elements, similar options would pertain. Under the conventional interpretation of MHC restriction, the possibilities illustrated in the *right-hand panel* are not considered. Of course, for a given T cell, the identity of the peptide would also affect the extent of recognition (not depicted in the figure). APC, antigen-presenting cell; TCR, T cell receptor.

interaction with the self T cell bearing specificity for that nominal antigen peptide plus a particular self-MHC molecule.

An example in the human context may help to clarify the difference between the two perspectives. Consider a CD8⁺ T cell that binds an influenza A virus-derived peptide that we can call hemagglutinin 1 (HA1). Suppose that HA1 interacts strongly with HLA-A*03:01, a specific allele encoded at the HLA-A locus. The standard interpretation would suggest that any class I HLA molecule that differs from HLA-A*03:01 by even one amino acid in any of the three domains of the class I polypeptide chain, that is, nonself or allogeneic MHC, could not both bind HA1 and present it to our HLA-A*03:01/HA1-specific effector T cell to initiate the cytotoxic process.

In the new probabilistic framework, the possibility that the A*03:01/HA1-specific effector T cell could recognize a small subset of nonself class I HLA molecules that are able to effectively bind HA1 is nonzero. For example, there might be CD8⁺ T cells (from a host for which A*03:01 is self) that can lyse target cells displaying either A*03:01/HA1 complexes or A*011:01/HA1 complexes on the plasma membrane. These two A-locus antigens are members of the same supertype as defined by Sette and colleagues (34).

On the other hand, taking a randomly selected class I HLA molecule the likelihood of such crossreactive recognition is extremely low because the selected class I molecule may not bind the HA1 peptide or because, even if it does possess adequate affinity for the peptide, it may not be effectively bound by the portions of the relevant TCR that interact with the walls of the peptide binding groove.

One can fairly ask whether such non-canonical recognition has any evolutionary or biomedical relevance. Peter has suggested that these crossreactivities are of minimal significance *in vivo* (15). In the context of human evolution, I am not aware of published evidence suggesting that superotypes have an influence on selection for human HLA alleles, but it is plausible that appropriately designed studies could reveal such effects. One speculation I would make is that selection influenced by relative allele frequencies or other inter-allelic effects might have different effects depending on whether a specific allele belongs to a highly represented supertype or not. In other words, the existence of superotypes and the less than absolute nature of MHC restriction could conceivably influence the evolution of the HLA genes and related aspects of human immune mechanisms.

In the clinical arena, there is one study addressing the relevance of superotypes in the setting of hematopoietic cell transplantation in which the donor was matched with the recipient for seven of eight alleles at the four prioritized class I and class II HLA loci: A, B, C, and DRB1 (26). In these types of transplants, the question is whether the influence of the single allele mismatch varies depending on whether the mismatched alleles are or are not members of the same supertype. Lazaryan *et al.* found that supertype mismatches at the B locus were associated with significantly increased risk of grade II–IV and III–IV acute graft-versus-host disease. In this study, the mechanisms underlying this effect were not addressed.

I believe that the clinical relevance of superotypes in either hematopoietic or organ transplantation is worthy of further investigation. An issue I would particularly like to see explored is whether supertype matching in the context of allele

mismatch between recipient and donor influences the risk of post-transplant infection.

Act II: MHC Restriction and Broader Concepts of Immunological Specificity

Investigators have clearly demonstrated that a given TCR can recognize the same self-MHC molecule presenting more than one nominal antigen peptide with varying affinities that are above some necessary threshold to permit signal transduction via TCR/CD3 and cellular activation (3,37). Therefore, TCR specificity for antigen, such as antibody specificity for antigen, is not absolute, as argued earlier in discussing HLA supertypes and as addressed later in discussing how to reconcile MHC restriction with the high potency of alloimmune responses by both CD4⁺ and CD8⁺ T cells.

Previously, I proposed (14) that immunological specificity is actually a family of concepts, including specificity defined with respect to: (i) monovalent recognition, (ii) multivalent recognition, (iii) cellular activation and effector function, and (iv) endpoints that are the result of the functioning of the whole immune system. In exploring this concept, I focused on antibodies and B lymphocytes. I would now suggest that a similar framework can be applied to TCR-based antigen recognition and T cells.

According to this concept, it is of interest to investigate both magnitudes of binding between TCR variable domains and different MHC/peptide complexes and see how well they predict measures of T cell activation and function. Reasons to expect some deviations from absolute correlation between TCR binding affinity and cellular phenotypes involve not only the complexities of signal transduction through the TCR/CD3 complex but also the contributions to cellular activation of signal transduction through other receptors on the T cell surface, such as CD4 or CD8, CD28, and numerous other cell surface glycoproteins that have ligands on antigen-presenting cells. Another way to state this point is that specificity as assessed solely by binding assays involving TCR and MHC/peptide ligands may differ from specificity as evaluated on the basis of measures of cellular behavior.

The preceding point is also consistent with results from experiments using what have been termed “altered peptide ligands,” which correspond to cognate nominal antigen peptides with one or a small number of amino acid substitutions. In 1991, Evavold and Allen demonstrated, using a mouse model, that some such peptides when presented by the appropriate class II MHC molecule to a clonal population of CD4⁺ T cells specific for the same MHC restriction element and the cognate peptide can elicit a range of responses by the T cells that differ in one or more respects from the responses induced by the recognition of the cognate MHC/peptide ligand (8). In their 1991 experiments, stimulation with the altered peptide/MHC antigen complex elicited cytokine production but not clonal proliferation whereas stimulation with the cognate ligand elicited both cytokine production and clonal proliferation.

Subsequent work over the years since 1991 has revealed that stimulation of clonal T cells by altered peptide ligands presented by the cognate MHC molecules can elicit diverse responses corresponding to various types of partial agonism to antagonism of T cell activation (5). Therefore, investigators of these phenomena have appropriately

inferred that signal transduction through the TCR-CD3 complex can vary in a variety of ways that yield distinctive constellations of functional outputs.

Another set of ideas related to molecular interactions that I have explicitly applied to how antibodies recognize antigens can equally be applied to the recognition of MHC/peptide complexes by TCRs. In a series of publications (13,16,17) beginning in the early 1990s, I suggested that the term “epitope” can be associated with at least three operational meanings. For the purposes of this discussion, I will assume that both receptor and ligand are proteins composed of amino acids.

These three senses of “epitope” in the context of MHC restriction are: (i) the set of HLA and nominal antigen peptide amino acid residues that make van der Waals contact with TCR residues, (ii) the set of MHC/peptide residues that contribute substantially to the free energy of complex formation (a useful but not always straightforward means), and (iii) the set of MHC/peptide residues that contribute substantially to the differential free energy of complex formation for a given TCR when comparing cognate and non-cognate MHC/peptide complexes. The necessity for the third definition arises in part from the fact that an amino acid residue of the cognate MHC/peptide complex might be weakly contributory or effectively neutral with respect to the energetics of the interaction with the relevant TCR, but a different amino acid at the same position in the non-cognate MHC/peptide complex may massively oppose an interaction. In that case, the residue in question in the cognate ligand is an unimportant component of the epitope in sense 2 but critical in sense 3.

A comprehensive analysis of these ideas applied to the full range of TCR-MHC/peptide interactions involving standard or nominal antigens as well as major and minor alloantigens is beyond the scope of this article. My purpose here has been to illustrate the connection between my ideas on the intricacies of immune recognition and those of Peter and Rolf on the basis of T cell specificity.

Act III: MHC Restriction and the Potency of T Cell-Mediated MHC Antigen-Directed Alloimmunity

In Peter and Rolf’s joint papers over a period of several years, allorecognition of target cells differing in plasma membrane class I molecules from the relevant effector T cells was not an issue because of the relatively short duration of the cytotoxicity assays. Consequently, Peter, Rolf, and other viral immunologists did not have much reason to confront the issue of how one can reconcile MHC restriction with the magnitude of allorecognition of nonself MHC molecules by T cells.

I have been forced to confront this issue in my capacities as a director of a clinical histocompatibility and immunogenetics laboratory and as a lecturer and small group facilitator in the pre-clinical curriculum for medical students at Case Western Reserve University School of Medicine. The effort to explain the existence of both MHC restriction and MHC antigen-focused allorecognition by T cells presents significant challenges. Next, I provide a brief summary of the perspective I have provided to medical students when prompted. Interestingly, no transplant surgeons or physicians

have ever asked for an explanation of how MHC-restricted T cells are consistent with the existence of strong T cell-mediated alloimmune responses to nonself HLA antigens.

In general, any T cell (CD4⁺ or CD8⁺) that survives positive selection will have specificity, respectively, for one particular self-class II (CD4⁺ T cells) or -class I (CD8⁺ T cells) MHC molecule plus some set of peptides that will usually share one, or one of a few, amino acid sequence motifs. Due to negative selection in the thymus, the affinity for the relevant self MHC antigen plus peptide will not be extremely high. In the context of reconciling MHC restriction and potent alloimmunity, I believe it is important to acknowledge that there is no selection specifically against T cells displaying TCRs recognizing allogeneic MHC antigens with whatever bound peptides.

Also of relevance, because TCR (or antibody) specificity is generally not absolute (arguably for structural and thermodynamic reasons; 1, 28), the fact that a given T cell recognizes a particular self-MHC molecule plus a particular foreign peptide does not imply that there is not at least one (possibly more) allo-MHC molecule (perhaps plus some peptide that may bear no predictable structural relationship to the peptide recognized in the context of the self-MHC molecule) that binds effectively to the TCR in question. It has been clear for two decades that the recognition of MHC/peptide complexes by conventional T cells is far from absolute with respect to the peptides (21,23) or MHC molecules (20 and above references pertaining to HLA supertypes).

If the TCRs on one T cell surface bind with sufficient affinity to self-MHC + foreign peptide 1 or to allo-MHC + foreign (or self) peptide 2, there is no reason to necessarily expect the latter to fail to activate the T cell bearing the TCRs (assuming that in both instances co-stimulation is adequate). Note that in the first case (the original immunological dogma about immune cells responding only to nonself notwithstanding), what is being recognized in many cases is both self (MHC) and nonself (nominal antigen peptide), and what is being recognized in the second case can be attributed potentially to similarities of the alloMHC-peptide complex to self-HLA as well as possibly to nonself peptide. Another consideration is that, according to some investigators, alloreactivity in a subset of cases may result from recognition of allogeneic MHC molecules without major contributions to the energy of binding (for the relevant TCR) from the MHC-bound (i.e., presented) peptides.

If a T cell responds to a particular influenza A virus hemagglutinin peptide bound to HLA-A*02:01 (self-MHC), it may also react to a completely unrelated peptide bound to, for example, HLA-A*25:01 (allogeneic MHC), but not to the same influenza virus peptide bound to HLA-A*25:01 (assuming that the same influenza virus peptide can bind effectively to HLA-A*25:01, which may not be the case). In other words, such a T cell is both alloreactive and MHC-restricted, examples of which have been described (11).

Act IV: Gödel, Escher, Bach, Zinkernagel, and Doherty: Self-Reference and MHC Restriction

In 1979, Douglas Hofstadter published *Gödel, Escher, Bach: An Eternal Golden Braid* (18), an unusual, long, and challenging book that was widely praised and that garnered a Pulitzer Prize in general nonfiction and a National Book

Award in science. In this work, Hofstadter explored abstract concepts from mathematical logic, such as undecidability, recursion, and self-reference, and revealed how these notions connect the fundamental advances in the mathematical logic of Kurt Gödel, the uniquely mind-bending art of Maurits Escher, and the extraordinary music of J.S. Bach (all three of which appeal to me).

Since Hofstadter, as a computer scientist, was not likely paying attention to advances in immunology, he did not take the opportunity to relate the ideas cited earlier to the advances in the understanding of antigen recognition by T cells wrought by Peter, Rolf, and many other investigators. My purpose here is to just briefly note that MHC restriction embodies a form of molecular self-recognition or self-reference, as highlighted earlier. The consequences of this form of antigen recognition are of both practical and conceptual significance.

As noted earlier, since immunologists accepted MHC restriction as an accurate description of how T cells sense foreign molecules in ways that lead to immune responses and in many instances immunity, it has become legitimate to state that the immune system does not distinguish self from nonself in an absolute sense even in the circumstances of normal physiology. For T cells, recognition of foreign molecules includes a degree of self-recognition.

Investigators further advanced our appreciation for the intricacies underlying immunological sensing by the finding that T cells need to weakly recognize self-MHC molecules presenting self-peptides to undergo homeostatic proliferation or remain viable, depending on which investigators you believe. Either way, such findings in conjunction with others imply that the signal transduction responsible for activating T cells and/or eliciting cell-mediated immune responses varies quantitatively and perhaps has more than one dimension as assessed by functional outcomes such as signal transduction, proliferation, cytokine production, and cytotoxicity.

The preceding comments only provide a minimal introduction to the ways in which Hofstadter's ideas might be relevant to understanding the immunological processes and phenomena. A fuller exploration of such connections could be interesting and enlightening.

Act V: MHC Restriction and the Philosophy of Science

In addressing the nature of science, Peter has emphasized the centrality of experimental results (6). Of course, in biomedical research, acquisition of data is an activity that is essential to the ability of investigators to generate new insights and enlarge or refine understanding of processes, phenomena, and mechanisms. However, I support the view that research progress, at least some of the time, also depends on new or improved conceptualizations or theoretical constructs.

No less a biologist than Darwin supported the view that the best interpretation of data may depend on the use of an appropriate conceptual framework or the asking of the right question, perhaps prompted by particular conceptual commitments. In an 1861 letter to Henry Fawcett, he remarked (19),

“About thirty years ago there was much talk that geologists ought only to observe and not theorise; and I well remember some one saying that at this rate a man might as well go into a

gravel-pit and count the pebbles and describe the colours. How odd it is that anyone should not see that all observation must be for or against some view if it is to be of any service!”

Similar views have been endorsed by biomedical scientists, such as Steven Wiley, who provided an example (36) of a difference in inferences about a mechanism of ligand-induced receptor internalization based not on inconsistencies in data but on differences in underlying assumptions. Similarly, the U.S. National Academies of Science convened a committee of accomplished investigators that published a report in 2007 (29) to emphasize that

“Biologists’ theoretical and conceptual frameworks inform every step of their research, affecting what experiments they do, what techniques and technologies they develop and use, and how they interpret their data.”

In his book *The Knowledge Wars* (6), Peter devotes considerable space to extolling the importance of Francis Bacon, the 16th- and 17th-century English statesman, essayist, thinker, and author of *Novum Organum*, who advocated for the collection of empirical data and the use of inductive reasoning in transforming such observations into scientific insights. I agree that collection of data and inductive reasoning are important components of the scientific process, but I also find that deductive and perhaps other forms of reasoning can be among the cognitive tools that are useful to experimental scientists.

In light of Peter's emphasis on the dominant role of data acquisition, it is interesting to point out, as noted earlier, that Peter's own greatest triumph involved experimental results that were similar in key respects to previously obtained data by other investigators studying the interactions between T cells and B cells in the context of promoting antibody production. So, what made Peter and Rolf's work more influential as well as consequential?

In their 1997 paper (39) on the history of how they came to do their seminal work together, Peter and Rolf delineated the advantages of the experimental system they employed. Nevertheless, what probably made their work particularly deserving of the recognition conferred by the Nobel Prize Committee, and not the studies of the investigators who found evidence for MHC restriction of helper T cells, was the insight that they brought to explaining the wider implications of their findings. Peter and Rolf related MHC restriction to human evolutionary biology as well as to medicine by suggesting that this phenomenon might explain the remarkable degree of polymorphism at the HLA class I and class II loci (7). Specifically, they suggested that HLA heterozygosity might, on average, cause increased survival rates in the face of infection by viral and other pathogens and, therefore, favor HLA allelic diversification (6). So, I am suggesting that what made the impact of Peter and Rolf's experimental results greater than the impact of the similar results of other groups was, at least in some degree, the conceptual framework within which they thought about them.

In what many commentators regard as an exceptionally influential book, *The Structure of Scientific Revolutions* (25), which explored the nature of science and scientific advance, Thomas Kuhn claimed that scientific research could be divided into two basic types: (i) normal science and (ii) revolutionary science. According to Kuhn, normal

science involved the working out of the details of one phenomenon or process or another within an agreed-on conceptual and experimental framework. On the other hand, in Kuhn's scheme, revolutionary science is focused on work that contributes to overturning an old research framework and further developing a new research framework or "paradigm."

A second connection between the discovery of MHC restriction and the philosophy of science is that the revolution in understanding how T cells recognize foreign molecules catalyzed by Peter and Rolf conforms poorly to Kuhn's rather rigid scheme, which was based on examples from the physical sciences. Kuhn's analysis was largely based on inductive inference, and as emphasized by Bertrand Russell (32), inductive inferences no matter how rigorously executed cannot guarantee the truthfulness of the conclusions.

In Kuhn's view, after a major unanticipated finding, the very character of scientific practice changes from normal mundane work of refining the details of a reigning framework or paradigm to the efforts to develop a new and competing paradigm. He claims that the very concepts used in such revolutionary science are incommensurable with those previously employed in the old "normal science" paradigm. I do not believe that these expectations are accurate in describing the transition in cellular immunology created by the discovery and relatively rapid acceptance of MHC restriction.

After the publication of the April 1974 paper (38) in *Nature* by Rolf and Peter and follow-up papers over the next 2 years, immunologists largely accepted the basic findings. The transition in understanding did not require the demise of the senior investigators of that time, as may have been true for some other major advances in science as proposed by Planck (27):

"A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it."

It took more than two decades to work out many of the molecular and cellular details underlying MHC restriction, but fundamental concepts of immunology, such as clonal selection, antigen specificity, cellular activation, effector function, memory, and tolerance may have been updated and refined but were not rendered incommensurable as Kuhn would presumably have anticipated.

A final aspect of the discovery of MHC restriction that has some relevance to how science is done in this far from comprehensive survey relates to my proposed re-interpretation of the phenomenon. My speculation is that had Peter and Rolf, in the mid-to-late 1970s, come to the probabilistic perspective I am now putting forward (and I do not take for granted that either Peter or Rolf will be persuaded by the view I propose), it might have made the acceptance of their ideas substantially slower and more challenging.

As everyone who has ever taught immunology or any other highly technical subject may know, to get across key but complex or subtle ideas to students or trainees encountering them for the first time typically requires a degree of simplification that may be in tension with, as close as we can approach them, complete accuracy and truth, that is, there is an inherent pedagogical trade-off. This same trade-off can be applicable to a degree in convincing fellow investigators of new findings and interpretations. Thus, since I believe that

Peter and Rolf actually deserved the recognition they were accorded, I do not begrudge them their 1970's interpretation of how virus-specific cytotoxic T cells recognize antigen.

Coda: P.C.D. and N.S.G.

I joined Peter's relatively newly organized lab at the Wistar Institute in 1977 as a graduate student in the Medical Scientist Training Program of the University of Pennsylvania School of Medicine. Peter had been recruited to Philadelphia from Australia by the then-Director of the Institute, Hilary Koprowski, a highly visible and colorful virologist.

My initial reason for checking out Peter's lab was his connection to the discovery of MHC restriction, which I believe I learned about in my early medical school lectures soon after arriving at Penn in 1975. As an undergraduate, I had already defined a strong interest in immunology in general, and I was focused in particular on the role of genetic variation in influencing immune responsiveness.

The additional reasons that I decided to train with Peter after my initial interactions with him were that he displayed a very unpretentious manner and a sense of humor. I had previously encountered some immunologists who did not share these personality traits in great measure and decided that I preferred those who did. Since he seemed amenable to accepting me into the group, I joined the lab.

Although Peter and I may have had differences regarding the best way to organize the workflow of a research laboratory, I appreciated then and subsequent to my leaving the lab (and up to the present day) that Peter actually cared about how the immune system operates or at least how we can best describe or think about how it operates. In other words, Peter really strived to arrive at the scientific "truth." For example, in his 2016 book *The Knowledge Wars* (6), Peter notes that "... getting the result we think we want is not what science is about..." I was not interested in working with a mentor who was more concerned with embellishing his or her own reputation and image than with arriving at the best possible understanding of biomedical processes and phenomena.

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