



## On Immunologists and Microbiologists: Ground Zero in the Battle for Interdisciplinary Knowledge

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# On Immunologists and Microbiologists: Ground Zero in the Battle for Interdisciplinary Knowledge

**ABSTRACT** The individual disciplines of microbiology and immunology are exploding with new information necessary for understanding host-pathogen relationships, infectious diseases, cancer, and autoimmunity. Because of overlapping scientific interests, immunologists and microbiologists often share common academic affiliations. The coexistence is uneasy. Significant problems arise because the groups have evolved different intellectual traditions. Pressures are intensified by sporadic changes in perceptions of their relative worth. As the mixing of microbiologists and immunologists can be likened to ground zero in the fight for interdisciplinary knowledge, it is useful, at this time of escalating data acquisition and growing appreciation for multidisciplinary research, to examine their histories, the challenges to amalgamation, and the advantages of their association for the advancement of knowledge and the delivery of protection against disease. The exploration supports a recommitment to integration of the disciplines and a proposal to facilitate this by inclusion of expertise bridging the areas.

## BACKGROUND

Through efforts at studying host-pathogen interactions, the disciplines of immunology and microbiology emerged tightly integrated in the late 1800. Characterization of the immune system was then dependent on probing it with large microbes and on vaccination for protection against infections. This early merger led to important discoveries concerning interactions between the immune system components and infectious organisms, perhaps best exemplified by the Mechnikov and Ehrlich studies, recognized with a Nobel Prize in 1906 (<http://nobelprize.org>). Since that time, the fields have had long periods of independent evolution. This resulted from the fact that new scientific knowledge has been predominantly advanced by the development of independent experimental questions for each discipline, barring requirements for attention to the other, and by linear discovery of finer details in a specific area. External pressures resulting from changing interests in each discipline, however, have also influenced the process of separation. By the 1950s, introduction of numerous antimicrobial agents combined with an increasing number of effective vaccines against childhood diseases suggested that the problem of infection was largely solved. In this environment, basic medical microbiology underwent a decline in relative importance. It came to be regarded as a quaint old discipline, and some schools, such as Yale University, closed their microbiology departments. Because of these changes, microbiologists shifted their focus to using microbes as tools for exploring sensitivity to drugs, genetics, and molecular biology. Immunologists increasingly turned their focus away from microbial infections and to immune system characterization, cancer therapy, and autoimmunity.

The extended period of separation led to important discoveries in each discipline. Examples of these discoveries in microbiology are demonstrated by the Fleming, Chain, and Florey Nobel Prize in 1945 for the discovery of penicillin and the inclusion of Lederberg in the 1958 Nobel Prize for characterization of “the genetic material of bacteria,” and examples of these in immunology are demonstrated by the Nobel Prizes in 1980 awarded to Benacerraf, Dausset, and Snell for genetically “regulating immunological reactions” and in 1987 awarded to Tonegawa for “the genetic principle for the generation of antibody diversity” (<http://nobelprize.org>). Beginning in the mid-1970s, however, with the shock of newly described infectious diseases, such as Legionnaires’ disease and Lyme disease, and continuing in the 1980s with the catastrophe of the human immunodeficiency virus (HIV) epidemic, it

became clear that microbial diseases remained a tremendous threat to human populations and that understanding the immune system, as it pertained to host-microbe interactions, was critical for the development of vaccines and immunotherapies.

Because of their overlapping histories and scientific interests, microbiologists, particularly medical microbiologists, and immunologists often inhabit shared academic homes in departments of microbiology and immunology at universities and medical schools. This structure should in theory provide an environment for integrating knowledge of the two fields. There are, however, many hindrances to collaborations between, and even the peaceful coexistence of, these groups. As the 2nd decade of the 21st century begins, it is worthwhile to survey the evolution of the microbiological and immunological landscape and the challenges to assimilation. Perhaps the best point for departure is consideration of the *American Heritage Dictionary* definitions of these two fields. Here, immunology is defined as “the branch of biomedicine concerned with the structure and function of the immune system, innate and acquired immunity, the bodily distinction of self from nonself, and laboratory techniques involving the interactions of antigens with specific antibodies.” Microbiology is defined as “the branch of biology that deals with microorganisms and their effects on other living organisms.” Thus, the immunology and microbiology disciplines are described for the general readership as focused primarily on hosts and microbes, respectively. The same definitions hint at the commonalities of microbiology and immunology, with the immunological focus on the distinction of self from nonself overlapping with the microbiological focus on the effects of microorganisms on other living organisms. Overall, however, the characterizations are based on specific and real distinctions between immunology and microbiology.

## INTELLECTUAL DIFFERENCES

The separate evolutions of the fields have now produced generations of microbiologists and immunologists focused on the indi-

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**FIG 1** Representation of the intellectual separation of microbiologists and immunologists (illustration by Samantha E. Canesi, reproduced with permission).

vidual disciplines. The explosion of scientific information is a major challenge to any single discipline, and integration of any two disciplines is a formidable task, but there are additional challenges unique to the integration of immunology and microbiology. First, the knowledge in the two disciplines is very different. The immune system is complex, with many interacting soluble and cellular constituents. Much of the detailed knowledge has been obtained using components of the immune system to probe itself. As a result, immunology has its own language, and much of it is obscure to the uninitiated (Fig. 1). Who would want to talk to an immunologist except another immunologist? On the other hand, microbiology has a dramatically expanding list of infectious organisms, and these can rapidly change their genetic information, resulting in many variants expanding under the pressure of selection during infection. These are detailed by investigators in the field at the level of nucleic and amino acid sequences. Who would want to know these details for each organism except an expert focusing on the organism?

More daunting challenges are presented by the fact that even when these two camps are considering host-pathogen interactions, they approach problems differently. At the interface, microbiologists tend to use the microbe as the variable while keeping the host constant. In contrast, immunologists immunize, delete cell subsets, and induce mutations that inactivate the function of host genes. Hence, when immunologists study microbial immunity, they tend to use the host as the variable while keeping the microbe constant. Finally, and perhaps presenting the greatest challenge to integration, these groups have been selected and/or trained to think differently. Given the complex series of cascade reactions that follow infection with a single agent, immunologists considering the process of infection think like biochemists and chemists considering catalytic or chain reactions. On the other hand, microbiologists confront great genetic variation at a fine point and consequently think in a more concentrated, linear manner, like molecular biologists or geneticists. These intellectual differences are barriers to the integration of knowledge. As exemplified at the University of Colorado School of Medicine and Duke University, they have resulted, at times, in the separation of the two disciplines into different academic units.

## IDENTITY PROBLEM

These experimental and intellectual differences have led to profound differences in personal identity, with microbiology seeming stalwart to immunologists and immunology appearing trendy to microbiologists. Microbiologists are inclined to define themselves by the organism that they study and see the department of microbiology and immunology needs for future recruitments based on the type of organism the candidates would be investigating (e.g., virology, bacteriology, etc.). By focusing on a particular organism(s), microbiologists often ignore developments outside phylogenetic boundaries and stick to their microbes through changing threats. In the past century, individuals studying *Mycobacterium tuberculosis* have seen appreciation of their work rise with the problem of tuberculosis, fall with the introduction of effective therapy, and then rise again when tuberculosis returned with drug-resistant organisms. In contrast, immunologists define themselves and consider future recruitment needs by immune processes (e.g., T or B cell development, innate immunity, etc.). They find, exploit, and then often ignore entire processes. In the past half century, immunology has assumed a riotous enthusiasm with such areas as antibody immunity, idiotype networks, T cells, innate immunity, Toll-like receptors (TLRs), and most recently, interleukin-17 (IL-17), such that these subjects often burn brightly for a while and then dim to a point at which they are ignored. The immunologists' tendency to favor generalizable processes can seem superficial to microbiologists because, despite global themes, the interaction of each microbe with the immune system is, by definition, unique. The attachment of microbiologists to particular organisms and their particular genes, in the face of their extreme variations over a single infection, is seen as narrow to the point of modest relevance by immunologists. Both groups have a preferred interest in developing expertise in specific new branches of knowledge within their respective fields rather than expertise in bridging areas within or across fields.

Adding to the diversity of scientists in these areas are "vaccinologists," who want to exploit immunology to make vaccines that protect against clinically important microbes. These individuals occupy a niche that is not in the mainstream of either microbiology or immunology and are viewed with suspicion by both sides. When vaccinologists approach their problem and succeed, they often seem to violate established immunological principles, thus annoying immunologists. For example, several successful vaccines against intracellular pathogens mediate protection by eliciting protective antibody responses, thus demolishing the neat separation of function for humoral and cellular immunity found in immunological textbooks. Moreover, successful vaccines prevent disease and consequently reduce the clinical importance of the targeted pathogenic microbes. By eliminating microbial disease, vaccinologists threaten the importance of microbiologists who study that organism. Historically, entire research fields focused on pathogenic microbes have either disappeared or been marginalized by the introduction of effective vaccines.

## THE FUTURE

Given that immunologists and microbiologists (i) come from different intellectual traditions, (ii) define themselves differently, and (iii) have different experimental approaches when working on related questions, why join them in the same de-

partment? Each field has something the other lacks, and their integration is important for advancing understanding of the immune system and microbes. In the same way that using either the microbe or the host as a single variable while holding the other one constant does not mirror the real-life situation in which genetically diverse hosts encounter genetically diverse microbes, work in either discipline in isolation fails to inform on the condition as a whole. Both microbiologists and immunologists have a stake in understanding microbial virulence, because it is a property that is expressed only in the context of a susceptible host. In fact, virulence is not an independent microbial property, and any expression of virulence must occur in a host setting with intimate involvement of the immune system. Moreover, for many microbes, the phenomenon of virulence is dependent directly on the immune response because disease is a consequence of immune-mediated damage. Thus, medical microbiology and immunology are codependent, and their cross-fertilization is ultimately required to advance understanding of the host-microbe relationship. Finally, knowledge at the interface of these disciplines has consequences for the understanding of cancer and autoimmune diseases because these conditions are largely influenced by host-microbe interactions.

In addition, however, there are many recent examples of significant advances in basic knowledge that have been made by combining the approaches. Here, it is fair to say that microbes have been exploring the immune system for much longer and at a more intimate level than immunologists and that the immune system has been studying microorganisms longer than microbiologists. The groundbreaking work by Doherty and Zinkernagel, distinguished by a 1996 Nobel Prize, established how T cells recognize differences by examining the specificity of interactions with virus-infected cells (<http://nobelprize.org>). The power of combining the use of microbial variants to probe the immune system has been underscored through studies of host genes incorporated into viruses to define new elements of the immune system and how they function. The approach has led to the characterization of many intermediaries in the type I interferon system, of cytokines, of chemokines (1–3), and of the innate microbial pattern recognition sensors and their signaling pathways (4–6) and is emerging as useful in the understanding of how activating and inhibiting receptors on NK cells function (7, 8). The role for microbiota in the “laying down” of the immune system network is a surprising and highly important discovery relevant to immune system development (9), and the consequences of the composite of host resident microflora on aging, metabolism, and carcinogenesis, as well as the role played by the immune responses to these microbes in the process, are now becoming apparent (10, 11). Finally, the identification of individuals with genetic predispositions to infections in combination with approaches for isolating genetic polymorphisms has allowed the characterization of novel molecules with important immune functions in the human first (12–14). Without the combination of the knowledge resulting from the two disciplines, these discoveries would have been delayed or even missed.

At a time when the benefits of multidisciplinary work are more generally appreciated, it is important to remember that microbiology and immunology have been struggling, with mixed success, at interdisciplinary work for several decades, perhaps even a century. The exploding rate of new information

accrual has put any one field in danger of imploding under the weight of facts. Multidisciplinary work is difficult because of the requirement for expertise and the command of knowledge in each discipline and for broad perspectives to synthesize information across disciplines. You cannot have multidisciplinary work without single disciplines, but a continuum is required. In exploring the current landscape and interactions, recruitment of scientists in areas bridging or across fields is resisted in the competition for resources within a common departmental structure and completely lacking when the disciplines of microbiology and immunology are separated. This is an impediment to integration. This can be rectified by an acknowledgment of the need and a commitment to the development of such expertise in a common academic unit and to the training of scientists able to cross these disciplines. It is clear that if mixes are not encouraged or forced, the new information gathered will look like the old information. Opportunities for dramatic leaps of knowledge resulting from putting together different kinds of thinking will be lost, and important questions will be overlooked.

In conclusion, history has taught us that microbial diseases are not going away and that host immune responses are central to the regulation of many acute diseases as well as long-term processes resulting from exposure to microbes. Evidence supports the value of getting immunologists and microbiologists to work together, particularly for developing knowledge important in the complex world of microbes we face. In an integrated academic unit, the groups can learn to speak each other's language, to respect their different ways of thinking, and to train the next generation of scientists with an appreciation for both disciplines. These efforts will result in novel contributions to basic knowledge as well as in the development of new therapeutic approaches for the treatment of disease.

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