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The human condition – an immunological perspective

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In medical school, physicians are taught the 4 classic signs of inflammation – rubor, dolor, calor, and tumor – redness, pain, heat, and swelling, a tetrad first recorded by Celsus in the 1st century AD¹. We have progressed a great deal since then and can explain these signs on the basis of the function of specific cells, molecular mediators, and tissue responses. Indeed, the wealth of information about even a simple inflammatory response can be overwhelming when brought together in one place, as in any of the attractive diagrams put out by various journals or drug companies for the edification of clinicians and researchers. But do we really have a deep understanding of human immunity? Do we know the details of what goes awry in the many diseases that are widely seen as immune in origin, including autoimmune states like multiple sclerosis, rheumatoid arthritis (RA), or type 1 diabetes, no less in the many other conditions that are now being revealed as driven by chronic inflammation such as cancer^{2,3}, metabolic syndrome or obesity^{4,5}, chronic obstructive pulmonary disease, atherosclerosis⁷, and many others?

The good news is that tremendous progress has been made in the past few decades in translating basic findings about the immune system from both animal models and human studies into new therapies that have had a dramatic effect on human health. In some cases, the tools are blunter than we would like, but nonetheless quite effective^{8,9}. These include a raft of immunosuppressive drugs such as cyclosporin or rapamycin that permit tissue transplantation and ameliorate several autoimmune diseases. In other cases, specific molecules involved in driving devastating symptoms, if not themselves responsible for the underlying inciting events, have been identified in several syndromes. Spectacular patient improvement is seen using specific biologic therapies, mainly monoclonal antibodies or soluble receptor analogs^{8,9}, that neutralize the offending substance, be it interleukin 1 (IL-1) β in the case of several auto-inflammatory syndromes¹⁰, tumor necrosis factor (TNF) in the case of RA¹¹ and psoriasis¹², or IL-6 in juvenile arthritis¹³. In some cases, these approaches represent some of the most dramatic examples of successful therapy for patients with defined monoallelic genetic disorders¹⁰. The use of IL-1R α for gout and pseudogout^{14–16} may represent one of the best cases of well-designed therapeutics and rational drug design based on the biology of the disease. An explosion in genome-wide association studies (GWAS) has led to the identification of key genetic loci at which allelic variation is linked to a variety of immune and autoimmune diseases¹⁷, although the mechanistic basis for their involvement remains unknown in many cases and new therapies based on these linkages often remain a distant prospect.

But we cannot rest on these laurels. A dispassionate view of the larger landscape of human disease and the functioning (or malfunctioning) of the immune system makes it all too clear

that our knowledge is limited and the ability to identify the right targets and produce therapeutics with higher efficiency and selectivity is still inadequate. We lack many critical vaccines because we do not know how to elicit the desired immune response against the relevant infectious agents or even if the immune system is capable of the required protective response – qualitatively or quantitatively^{18–23}. We are uncertain what initiates many of the chronic inflammatory conditions that contribute to malignant transformation and cancer progression, to aberrant metabolism, or to inflammatory bowel disease. Only an early glimpse exists of the connection between the microbiota on our skin and mucous membranes or in the gut and an individual's overall health, immune status, and response to environmental perturbations in the context of diverse genetic backgrounds^{24,25}. In some cases, we have reasonable knowledge about relevant players in a disease state, but not how these components are connected. And we certainly lack a quantitative understanding of how much one or another molecule or cell population needs to be neutralized or eliminated to have a desired therapeutic effect without posing an unacceptable risk of opportunistic infection or the recrudescence of one of the many 'endogenous' infectious agents that are typically kept in check by an intact immune system. The latter is a major problem with the use of anti-TNF drugs due to *M. tuberculosis* emergence from latency^{11,26} and it temporarily halted the use of natalizumab, an $\alpha 4$ integrin blocking antibody, because interference with effector function in the central nervous system allowed reactivation of latent virus and the development of progressive multifocal leukoencephalopathy²⁷.

One could come away from this summary despairing of making rapid progress in solving these many outstanding and complex issues. However, the emergence of new tools and technologies and concerted efforts to apply them give hope that the future can be very bright. It is increasingly apparent that the pace of not just information acquisition but also of developing a deep understanding of human immunophysiology and immunopathology is accelerating. Two interwoven threads are responsible for this positive outlook.

The first theme is the emergence of methods and instruments that permit global or near-global analysis of gene expression, genotype, epigenome, cell surface and functional phenotype, serum protein composition and so on – that is, that measure in much greater depth and breadth the composition and state of the immune system as compared to previous limited serologic or cell-mediated immune tests^{23,28,29}. We now have a cost-effective capacity to analyze an individual's genetic make-up³⁰ and also to probe genome-wide transcriptional states using commoditized microarrays, and soon, second and third-generation sequencing methods³¹. This enables investigators to conduct broad and deep analyses of gene expression by hematopoietic cells of the immune system, primarily but not exclusively from peripheral blood, and increasingly, from small tissue samples that can be ethically collected and then to relate these findings to both the person's history and genotype. The power of such a genomic approach is evident in some of the remarkable insights and drug leads arising from expression-quantitative trait loci (eQTL) studies and Bayesian inferential modeling of various diseases such as obesity and diabetes³², as well as in the effective use of expression profiling in facilitating diagnosis and prognosis of patients with various infectious^{33,34} and autoimmune diseases³⁵ or in the development of predictors of vaccine efficacy^{36,37}. The same nucleic acid-based technologies are now also permitting a definition of the microbiome³⁸, so that this important factor in setting the 'tone' of the immune system^{39,40} can be factored into analyses along with measurements of the host's condition. Such advances also suggest that we may be able to obtain insight into environmental influences long known to contribute to immunological disorders, such as in multiple sclerosis⁴¹.

There have also been major improvements in single cell analytic technologies, chief among them fluorescence-based flow cytometry. This methodology now allows nearly routine

analysis of 9–10 parameters, and as many as 15 with some difficulty, permitting detailed profiling of cellular subsets in blood and other samples⁴² (though more automated analytic tools are needed to handle these dense data sets). But even these numbers may soon be grossly exceeded by application of mass spectrometry to cellular phenotyping^{43,44} – indeed, Stanford scientists are now measuring as many as 37 parameters per cell, combining surface marker analysis with multiplexed staining for intracellular cytokines and phosphoproteins, to not only define the type of cell being examined, but learn about its state of functional activity⁴⁵. Mass spectrometric technology is also advancing rapidly, allowing a much deeper quantitative analysis of protein, lipid, and metabolic components in cells, serum, and other bodily fluids of interest^{46–48}.

The second thread is the development of new statistical and computational methods for analyzing enormous data sets, which enable investigators and clinicians to take advantage of these new technologies and extract relationships that are otherwise hidden and unsuspected^{32,44}. The result is a segue from small scale, descriptive science, to more global insights into how the complex machinery of the immune system is wired together and what happens to the behavior of these highly connected circuits when one or another part is missing, hypoactive, or excessive in its function. We can begin to simulate the effects of drug interventions using such network models, whether built at the molecular, cellular or tissue or organ level^{49,50}. New algorithms for diagnosis, patient stratification, and targeted therapeutic intervention can be derived from these analyses. The cancer literature now provides a wealth of examples of such personalized analyses used to guide therapeutics^{51,52}, and the application of such techniques to immune-mediated disease is clearly a high priority³⁵.

Just because new machines and methods are available, however, does not mean they are being or will be effectively utilized, that additional technologies are not urgently needed, that the social fabric of the research enterprise is optimally suited to taking advantage of these opportunities, or that the support for research will be adequate to make progress as rapidly as might otherwise be. Each of these issues poses a significant hurdle for acquiring the insight into human immune function we require, if we are to reduce the burden of disease and, hopefully, the associated costs.

In the first instance, many investigators trained in traditional methods of inquiry are hesitant to adopt very different ways of conducting science. ‘Omic’ scale technologies, bioinformatics, and computational systems biology together allow one to take an agnostic approach to a question in which the newly generated data guides future experimental work. This contrasts with the more classic approach of beginning with a clear hypothesis based on past knowledge that limits the scope of inquiry, which in turn may lead the investigator to miss consideration of relevant elements that had not been previously suspected in this context and thus fail to be examined. There is no question that research using biological knowledge and insight to guide focused, selective experimentation will not lose its great value and will continue to provide critical new ‘aha’ moments. Indeed, such focused work led to the discoveries needed for the ‘omic’ and network approaches that we now argue are so central to future progress. Furthermore, such guided research is critical for the evaluation and translation of findings from large-scale “omics” studies. But it would be a mistake to underestimate the potential of our recently acquired capacity to probe a system both broadly and deeply without preconceived ideas of how it operates and discover entirely new mechanisms underlying physiological or pathological behavior. One striking example involves recent studies of metabolic syndrome, using eQTL analysis with transcriptional profiling tools. Although confirming a major signature involving pathways of intermediary metabolism, what also emerged was an unexpected macrophage-centered signature⁵³. Such examples suggest that these approaches will be informative for understanding the underlying

pathology in other diseases in which immune contributions may not normally be considered as key elements. In turn, these findings will continue to fuel hypothesis-driven, focused experimental science that can take us to the next phase of translating these findings to achieve better understanding and treatment of human disease.

In the second instance, our present methods are reasonably well developed for analysis of cells in the blood, and to a more limited extent, from reasonably sized biopsy specimens. This limits what tissue and organs can be examined robustly, especially in normal individuals, yet we need normal data as a baseline for understanding the perturbations present in disease. There is an urgent need for miniaturization of the methods, so that fewer cells or smaller tissue samples can be used, and even for ways to probe tissues *in situ* in a non-invasive manner, to complement the *ex vivo* methods. In the near term, such a capacity could come from judicious application of advances in targeted contrast agent-based MRI. Probes that each give a distinct signature, allowing multiplexing like in flow cytometry, and that are self-amplifying and hence useful in detection of weak signals without inordinately long imaging times, are being developed⁵⁴. They could allow non-invasive probing of cells and perhaps even secreted factors located in tissue sites anywhere in the body where probe penetration is adequate, which is likely to be the case in inflammatory sites with vascular leak. Further work is needed to bring these early technical developments to a useful state. Creative developments of other techniques for *in situ* study would also be extremely valuable.

In the third instance, we are faced with learning how to be more interactive as scientists. Like particle physics, in which small laboratory science gave way to large scale team-based studies, or with the genome⁵⁵ and ENCODE⁵⁶ projects, which rely on large multidisciplinary teams in well-equipped and funded centers, multiplex, large-scale studies of human immune function will require a combination of expertise and facilities beyond those available in a typical PI-directed laboratory^{23,29,49}. In addition, to aggregate enough information on normal individuals and especially on patients with a specific disease, it will be necessary to combine data from multiple centers. The importance of such co-operative studies is evident in recent genome-wide association studies, for example, those examining diabetes or autoimmunity, in which a single well-powered study was published from a consortium of centers in each of these cases, rather than being submitted as many smaller, underpowered reports from individual laboratories^{17,57}. This lesson on pooling resources has not been lost on those studying human immunity – the CRI Cancer Immunotherapy Consortium has proposed an ImmunoAssay Proficiency Panel to allow data from diverse studies to be harmonized and included in meta-analyses⁵⁸; this is also a recommendation of the Global HIV Vaccine Enterprise with respect to future studies of immune function in HIV infected individuals and vaccines⁵⁹, and is a long-standing goal of the Immune Tolerance Network⁶⁰; the Human Immune Project Consortium recently funded by the NIAID, NIH is discussing how to ensure data compatibility and aggregation of the large scale, immune-directed screening efforts these groups will be undertaking in the coming years⁶¹; the NIH's intramural Center for Human Immunology, Autoimmunity, and Inflammation (CHI) has made the creation of a well-curated public database of information arising from its studies of human immunity a top priority⁶²; the ImmGen project, although initially focused on transcriptional profiling of mouse cells, is moving to human hematopoietic cell analysis and puts its data online in a very rapid and easily accessible manner (including an iPhone app)⁶³. Data storage, curation, and accessibility are all critical issues that are not yet resolved for the more clinical of these studies – will an early release strategy similar to that of the genome project⁵⁵ be a viable way forward, so that the entire community can examine the data at the earliest time? How will the contributions of investigators be recognized in such a case? How does one deal with anonymizing the data while keeping it connected to critical clinical and patient metadata? There is above all an urgent need to address the sociology of academic

translational research – we have to define viable career paths for individuals who are members of these necessarily large teams whose primary output will be publications with extensive co-authorship; in this regard intramural NIH has taken a first step by incorporating special tenure consideration for authors on such team-science publications⁶⁴.

Finally, there is the issue of money. One can argue cogently that success in the exploration of human immune function and dysfunction will lead to new methods for preventing and treating disease, with a concomitant reduction in overall health care costs in the long term. Nonetheless, there is clearly a short-term cost to be borne when applying these various (expensive) technologies and supporting the substantial professional staff necessary for their proper use and interpretation of the emerging data. Where will these funds come from? In many countries, especially in the West⁶⁵, the recent financial meltdown has raised questions about whether substantial new monies will be made available for research in the coming years. Will there be an intensification of the ‘us *versus* them’ debate about investigator-initiated grants *versus* large program support that has simmered for years⁶⁶? Or will the rapid deposition in public repositories of the data emerging from the large-scale studies, data that can then be mined by everyone, along with the recognition that R01 science is a critical complement to these large-scale studies, assuage some of these concerns? Will public servants (i.e., legislators) take the longer term view that rapid acquisition of the knowledge and insight promised by these new approaches will ameliorate rapidly rising health care costs, and that, even in times of budgetary limitations, it is a good investment to avoid cutting, and possibly even add to the allocation for biomedical research? Will the biotech and pharmaceutical industry consider these large efforts to be generating data that they consider ‘pre-competitive’ and form a consortium to help underwrite the cost of developing this globally valuable information? Will they contribute in another manner, through low or no-cost provision of drugs for studies of the impact of therapy on the immune system, not only when it represents the intended aim, but when it may be considered an ‘off-target’ effect (for example, for many drugs used in cancer therapy)?

Each year the US President goes before Congress to describe the state of the union. And nearly every year, the speech begins with “The State of the Union is good”. When considering the state of modern human immunology, we think it is accurate to conclude that the situation is also good, perhaps even excellent. The field has an exciting future if the recent nascent efforts to power-up global assessments of the human immune system don’t falter, if those involved in such studies keep their eye on the goal of real progress in disease prevention and therapy, if there is effective co-operation between those conducting more traditional hypothesis-driven research efforts and those involved in larger-scale studies, with their focus on team science, global data gathering and computational analysis, and if the larger public and its representatives see the long-term value in both types of work and don’t starve these efforts in their infancy.

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Figure 1.

The intertwined cycles involving hypothesis-driven research and systems-level analysis. Each of the three funnels represents a major collaborative group that conducts clinical and 'omic-scale' data collection and computational analysis; these groups also provide data for meta-analyses. The interpretation of the data from such hypothesis-generating activities is based on knowledge acquired by hypothesis-driven research; the data and findings from the systems analyses help drive further directed research at a fundamental level.