nature immunology

Assessing the status of human immunology

Although excellent animal model systems are available, more studies of human immunology are needed.

Despite the high costs of animal husbandry, much of today's immunological research uses mouse or other animal models. The relative ease of genetic malleability and intervention through adoptive transfer or pharmacological means, the ability to make in-depth physiologic analyses, and ethical concerns precluding the use of humans for similar experiments provide ample reason for the utility of such models. The main justification for animal research is that it lends insight into human immunology. Such studies are essential before any human trials of promising therapeutic interventions can begin. However, the cliché that 'mice are not men' is certainly true.

Many examples suggest that human physiology and immunity can differ from those of animal models. The clinical trial in the United Kingdom involving the anti-CD28 monoclonal antibody TGN1412 illustrates this well. It is unlikely that any one mouse model, such as the nonobese diabetic mouse strain, can fully recapitulate the multifarious aspects of human autoimmune diseases such as diabetes. Likewise, it remains to be seen how well animal infection models mimic human diseases such as malaria. Whether certain immune cell developmental pathways are shared, such as the cytokine requirements for the generation of interleukin 17–producing $CD4^+$ T helper cells, has been a source of recent controversy (as discussed in the News and Views by Anne O'Garra and colleagues in this issue). Obviously, the genetic diversity of inbred laboratory strains of mice differ from the genetic diversity of humans. Likewise, such mice raised in specific pathogen–free housing conditions experience a relatively defined 'immunological history', whereas exposure to various microbes, environmental allergens or toxins, underlying infection, diet and stress, in addition to genetics, probably contribute to the human immunological state of wellness or disease.

As noted in the perspective presented by Adrian Hayday and Mark Peakman in this issue, a good physiological definition of what defines a healthy immune system in humans is still lacking. The authors offer a provocative view of research into human immunology and what is needed to advance knowledge as well as to reward or credit those contributing to this endeavor. One of the more ambitious proposals put forth is the generation of a massive data set to profile the state of the human immune system. This would probably require thousands of subjects and involve in-depth genetic and proteomic 'fingerprints' of the subjects such that immune correlates of what constitutes a 'healthy' immune state can be inferred with rigorous statistical analyses. This project would also require long-term longitudinal studies of the participating subjects to delineate how age and 'health' status, as described above, influence or (as with cancer or various chronic inflammatory diseases) are influenced by immune responses.

Such a project, involving intensive long-term studies, is intriguing and worth undertaking. No doubt this massive data collection would provide many beneficial insights, including those unforeseen at present. Much as genetic microarrays or 'chip-on-ChIP' assays offer an abundance of data that provide the basis on which specific hypotheses can be formulated, human immune profiling should generate a rich data set that could be 'mined' by bioinformatics approaches. Notably, many insights garnered from such studies can be readily 'translated' into clinical practice. The issue, however, is how quickly the fruits can be realized from such profiling efforts. In the interim, other studies based on more 'hypothesis-driven' research focused on human subjects are needed.

One comment we sometimes hear is that *Nature Immunology* is 'mouse-centric'. Although we do publish many papers that use mouse models, it may come as a surprise to some that roughly 25% of the primary research articles published this year focused on human studies. So what does *Nature Immunology* look for in human immunology papers? We seek research that provides new mechanistic insights of high interest to the wider immunology community. A few examples might be illustrative here. Articles by the Beyaert and Thome labs demonstrated the protease activity of MALT1 in human lymphocytes and identified several targets, Bcl-10 and the NF-κB inhibitor A20, that have been linked to several human disease states. Similarly, papers by Ivashkiv and colleagues have provided new insights into 'tuning' type 1 interferon signaling in human monocytes and the regulation of interferon-regulated gene expression. More descriptive data that nevertheless address important topics are of interest. Articles by the Littman and Soumelis groups in this issue describing the generation of human interleukin 17–producing T helper cells from cord blood cells illustrate this well. Another example is the identification by Freeman and colleagues of HVEM as a new ligand for CD160. Studies with correlations to human diseases, such as the identification of a new receptor for human immunodeficiency virus by Fauci and colleagues, also provide important insights. Studies initiated in mouse models but verified with human samples continue to be of interest to the journal; a recent example is the identification by Prat and colleagues of ALCAM's involvement in leukocyte recruitment into the brain.

As with all *Nature Immunology* articles, findings should be novel and of broad interest to the immunology community and should provide a considerable advance over previous work. Although we recognize that tissue or sample availability is more limited with human subjects, as a guide, we find referees generally request data derived from primary cells or tissues, rather than cell lines. Many important questions about the human immune state remain unanswered, and findings exploring such questions are worthy of publication in high-profile journals. We welcome studies focused on human immunology and we encourage authors who might think *Nature Immunology* is not interested to consider submitting their manuscripts to us.