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EDITORIAL

Human immunology: a case for the ascent of non-furry immunology

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During the late 19th and early 20th century, tremendous progress was made in our understanding of human immune regulation with extensive studies on humoral and cellular immunity. Of particular interest was the development of the side-chain theory by Paul Ehrlich that led to the delineation of the mechanism of interaction between antigen and antibody. His contribution toward the understanding of humoral immune regulation was recognized by the award of a Nobel Prize in 1908, which he jointly shared with Elie Metchnikoff, founder of cellular immunology. In addition, some of the seminal studies carried out by Louis Pasteur, Robert Koch, Walter Reed and many others also provided an important platform for the understanding of human immunity. However, this direct focus on human immunology was diverted in the 20th century with the development of inbred murine models. It is important to recognize that these models have provided major conceptual advances in areas, such as major histocompatibility complex-restricted recognition of virus-infected cells,[1] identification of different subsets of dendritic cells,[2] T–B cooperation in antibody production,[3] characterization of FoxP3+ regulatory T cells (reviewed in ref. 4) and natural killer (NK) T cells (reviewed in ref. 5). Translation of many other important findings from murine models to humans has been rather disappointing. This is best exemplified by models of autoimmunity and cancer immunotherapy where numerous studies showing promising outcomes in murine models have achieved limited success in a human setting.

One can argue that, rather than blaming the murine model, we should carefully look at our experimental design and how we have used artificial model antigens, recombinant viruses and inappropriate cancer cell lines to skew the outcome of studies based on these animal models. Indeed, over the last two decades, well over a thousand papers have been published where model antigens such as ovalbumin have been used to study efficacy of cancer vaccines and novel therapies for autoimmune diseases. Similarly, use of murine models to study the immunobiology of infectious diseases, such as malaria and herpes simplex virus, has severely skewed our understanding of immune control of these pathogens in humans, and it could be argued that over reliance on these model systems may have slowed progress in the development of effective vaccines against many human pathogens. Confidence in these model systems has eroded, as we now know that there are significant differences in human physiology and the immune regulatory pathways from these animal models. Indeed, clinical testing of the anti-CD28 monoclonal antibody TGN1412 illustrates this very well.[6]

Poor translation of murine model studies into the human setting can be explained by a number of factors. First, most studies carried out in murine models are conducted in inbred strains of mice, which can dramatically skew the immune responses. Second, humans and mice display numerous discrepancies in both innate and adaptive immunity, including T-cell subsets, cytokine receptors, costimulatory molecule expression and function, Th1/Th2 differentiation, Toll-like receptors, the NK inhibitor receptor families Ly49 and KIR, and many more.[7] Third, as highlighted above, inappropriate use of inbred mice as disease/therapeutic models to delineate immune regulatory pathways or test novel vaccine formulations has also contributed. In spite of these significant limitations, we continue to invest huge resources in conducting immunology studies using transgenic murine models, and many of our colleagues often feel highly defensive when questioned on the validity of their model systems. One comment we often hear from our colleagues is that it is difficult to provide mechanistic insights with human immunology studies that are essential to publish their research in high-ranking journals. This is indeed a potential limitation of human immunology research but it can be addressed by looking for more appropriate systems where the human immune system can be more diligently investigated. Development of 'humanized' mice, which involves transplantation of human hematopoietic stem cells in immunodeficient animals, has provided a promising platform to study human immune responses *in vivo*.[8] Christian Munz and colleagues review this model system in this Special Feature.[9] Their group and others have successfully used these humanized mice to study immune regulation and pathogenesis of herpes viruses.[10,11] Although these models have shown some promising results, further improvement will be required to fully exploit these humanized mice for mechanistic studies. Another potential murine model system based on N-ethyl-N-nitrosourea mutagenesis has been successfully used to reveal new pathways of host defense, allergy and autoimmune diseases in humans.[12,13] More importantly, it is critical to acknowledge that these mice may not accurately reflect human immune responses, unless we can establish objective metrics of the human immune system for comparison.

This raises an important but neglected question in the field of immunology: What are the objective metrics that characterize a healthy human immune system? Although biochemical diagnosis of cardiovascular and gastrointestinal diseases is now routinely used by general practitioners, we are still limited to counting white blood cells and using these as 'biomarkers' to identify immune disorders. There is increasing awareness in the community that a healthy immune system

is crucial for not only resisting infectious diseases but also cancers, autoimmune diseases and other diseases related to the cardiovascular and digestive systems. While immunologists were busy discovering how the murine immune system handles ovalbumin protein, our colleagues working on human genetics have revolutionized their field by establishing large consortia to map the human genome that has led to the identification of novel genes and mechanisms by which the proteins encoded by these genes regulate our susceptibility to numerous diseases.[14–17] These studies have established an excellent network of collaborative links and a highly impressive infrastructure that will provide an important platform for mapping novel regulatory pathways for cell survival, DNA repair and most importantly relevant genes/proteins for human immune regulation. Can we replicate similar success for human immunology? Of course we can, and we hope our colleagues will join us in lobbying respective Governments and their funding agencies to invest in human immunology research, which will have important implications for human health. Early initiatives have already been established by the National Institutes of Health (US) and other institutions. These include the Trans-NIH research program, the Center for Human Immunology, Autoimmunity and Inflammation (CHI), NIH-funded Cooperative Centres for Translational Research and Biodefense and human immune profiling centers. In addition, individual institutions have also established large programs devoted to human immunology, such as the Institute for Immunity, Transplantation and Infection at Stanford University and the Emory Vaccine Center in Atlanta. More details about these research initiatives can be found in the articles published by Mark Davis and Ron Germain.[18,19] It is very likely that such collaborative studies involving large investment will be opposed by many of our colleagues who strongly believe that innovative research emerges from small labs, and a major investment in human immunology will deplete funding for basic immunology research. They are probably correct; but how long can we justify investing millions of dollars of taxpayers' funds on delineating the murine immune system, which in most cases has limited application for human diseases.

This Special Feature on Human Immunology is a small effort to highlight the current and emerging areas of research in basic and translational aspects. These reviews cover wide-ranging topics, including human regulatory T cells, T-cell responses to herpes viruses,[9, 20–29] T-cell receptor selection, immune evasion mechanisms, humanized murine models, challenges in vaccine design and application of a system biology approach to identify biomarkers of successful vaccines. We hope these reviews will provide greater impetus for human immunology research and thus provide opportunity to translate immunology research from bench to bedside.

Rajiv Khanna and Scott R Burrows
Australian Centre for Vaccine Development, Queensland Institute of Medical Research, Heston, Australia
E-mail: rajiv.khanna@qimr.edu.au

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