Human studies at *JEM*: Immunology and beyond

Jean-Laurent Casanova, Carl F. Nathan, and Michel C. Nussenzweig, on behalf of the Editors

Editors, *The Journal of Experimental Medicine*

Since its inception in 1896, *The Journal of Experimental Medicine* (*JEM*) has aimed to publish outstanding and enduring studies in medical biology, with an emphasis on pathogenesis (Welch, 1896). The founding editors and their successors have strived to provide a prestigious platform for the publication of studies integrating different disciplines within the field of human pathogenesis (McCarty, 1990). As the field of human pathogenesis has evolved, so has *JEM*. Building on a foundation of publishing groundbreaking research in microbiology, virology, and infectious diseases, from the 1960s onwards, *JEM* has been a leading journal in immunology and immunopathology. It now embraces studies from other disciplines that, like microbiology and immunology, "connect" different molecules, cells, tissues, and organs within the organism, such as genetics, hematology, metabolism, and neuroscience, as well as stem cell, cancer, and vascular biology. *JEM* publishes a wide range of studies, ranging from atomic-level structural analyses of medically relevant molecules to clinical interventions revealing new physiological mechanisms. A distinctive feature of *JEM* is its long-term impact; the half-life of citations of *JEM* papers is higher than that of papers in most other prestigious journals (http://wokinfo.com/).

Within the broad area of human pathogenesis, *JEM* has fostered studies that emphasize whole-organism physiology and disease mechanisms. Such studies have often required animal models of disease, which were developed during the 19th century and became prominent in the 20th century because it was rarely possible to study pathogenesis in a rigorous and controlled manner in patients. Claude Bernard's *Introduction to the Study of Experimental Medicine* was likely an inspiration behind the journal's name and focus on the deterministic study of physiology and pathology in animal models (Bernard, 1865). A quarter century after the launch of *JEM*, *The Journal of Clinical Investigation* was established at The Rockefeller Institute in 1924 to provide a suitable medium for the publication of patient-based studies, with mechanistic research continuing to be published in *JEM* (Brainard, 1959). The contents of *JEM* papers in the first half of the 20th century naturally reflected this tradition. However, Henry Kunkel and then Ralph Steinman recognized that late 20th century advances in molecular genetics, cell biology, and clinical medicine made it possible to bring a rigorous analytical approach to human studies (Bearn et al., 1985; Steinman, 2005). In keeping with this tradition, *JEM* has recently become the official journal of the Henry Kunkel Society (http://www.henrykunkelsociety.org). We are keen to reinforce the pioneering leadership of Kunkel and Steinman and to invite the scientific community to focus further on high-caliber human research for publication in the journal.

Why human immunology? Immunological studies in healthy and sick individuals have wide-ranging implications for pathogenesis, diagnosis, prognosis, treatment, and public health. Few fields have had a broader or stronger impact on the analysis of pathogenesis, across all areas of medicine, than immunology. Yet, the molecular and cellular basis of most of the clinical manifestations of immunological diseases has remained elusive. The time has arrived when studies of individual immunological conditions, and even of specific manifestations in single patients, can provide unique insights into basic physiological mechanisms. The diversity of immune-related clinical manifestations is enormous, much broader than anticipated when studies of pathogenesis were in their infancy, with an ever-increasing spectrum of infectious, malignant, allergic, autoinflammatory, and autoimmune conditions. This diversity makes it especially exciting to study immunity in humans.

By and large, in vitro studies and animal models have preceded and led the way for human studies. Needless to say, *JEM* will continue to welcome all of these approaches. Studies in model systems remain highly relevant to physiology and pathology and are constantly improving. However, models cannot replace studies of human physiology and disease in human subjects (Davis, 2012). Society at large—as reflected by the priorities of many funding agencies—is encouraging the scientific community to carry out human studies. Moreover, the unique basic biological implications of human studies, in which physiology and pathology can be studied in natural as opposed to experimental conditions, should not be overlooked. Evolutionarily selected functions of genes, cells, tissues, and organs are best re-

Correspondence to Jean-Laurent Casanova: casanova@rockefeller.edu; Carl F. Nathan: cnathan@med.cornell.edu; or Michel C. Nussenzweig: nussen@rockefeller.edu

The Rockefeller University Press $30.00
J. Exp. Med. 2016 Vol. 213 No. 4 467–468
www.jem.org/cgi/doi/10.1084/jem.20160211

vealed by analyses of experiments of nature. Molecular and cellular studies in humans reconcile the two branches of biology, experimental physiology and evolutionary biology.

Human studies are especially timely because it is now possible to carry out "experimental medicine" in humans. The recent explosion in the development of new technologies, including genetic methods (exome, genome, and transcriptome sequencing by next-generation sequencing and in vitro gene editing by CRISPR/Cas9), cell biological approaches (epigenomics, proteomics, metabolomics, and advanced microscopies), and cell developmental methods (to and from induced pluripotent stem cells), has greatly facilitated human studies. Largely thanks to stem cell technology, in-depth investigations of unprecedented breadth, using an enormous variety of hematopoietic and nonhematopoietic cells and even tissues (e.g., organoids), can now be undertaken from small and even unrelated biological samples (e.g., a skin biopsy or a blood sample). The genetic diversity of humans, which was an obstacle to rigorous research, has become an advantage in the era of genome sequencing and editing. A major expansion in immunological research is under way, and *JEM* welcomes it.

Why is *JEM* an ideal place for immunologists to publish their findings involving human studies? First, *JEM* has always been at the forefront of immunological research. Classic human immunology papers, including the study on human monocyte–derived dendritic cells (Sallusto and Lanzavecchia, 1994) and the phenotypic separation of human naive and memory CD8 T cells (Hamann et al., 1997) and B cells (Klein et al., 1998; Tangye et al., 1998), were published in *JEM*. Investigators of human immunology are well represented among the editors of *JEM*—a long tradition that the journal will continue to uphold. A third of the papers published in 2015 in *JEM* include human data, a substantial increase when compared with the 10% at the time of Ralph Steinman's call for human studies in 2005 (Steinman, 2005), and we hope to further increase their numbers. We encourage authors of papers reporting experiments in animal models to cross-reference relevant human studies and vice versa. We also encourage authors to cite the species in which the study was conducted in their titles, abstracts, or both. Human studies published in *JEM* will frequently be accompanied by highlights or commentaries. Reviews focusing on aspects of human physiology and pathology will help mark the progress of this major growth in human research under way in all biomedical fields, including immunology.

Finally, our editorial system makes *JEM* an ideal place to publish human immunology. Peer review at *JEM* engages two complementary groups of editors: PhD-trained editorial professionals at The Rockefeller University Press and 12 prominent working scientists, 8 of whom have been immersed in human biology through medical training. The shared goal of the editors is to work with authors to facilitate and expedite the publication of groundbreaking research. To this end, we have eliminated multiple rounds of review and unnecessary supplementary information, which often slow down publication. We will advise authors on which of the reviewers' requests are key for the present manuscript and which can be left for the next chapter in their research. It's our philosophy that the excitement of discovery should continue through with the joy, not the ordeal, of sharing important new findings about human biology with the scientific community.

ACKNOWLEDGMENTS

We thank Carol Moberg for helpful discussions.

REFERENCES

Bearn, A.G., F.J. Dixon, and B. Benacerraf. 1985. Henry G. Kunkel 1916-1983. An appreciation of the man and his scientific contributions & a bibliography of his research papers. *J. Exp. Med.* 161:869–895. http://dx.doi.org/10.1084/jem.161.5.869

Bernard, C. 1865. An Introduction to the Study of Experimental Medicine. Dover Publications, New York. 226 pp.

Brainard, E.R. 1959. History of the Journal of Clinical Investigation, 1924-1959. I. Personnel and policies. *J. Clin. Invest.* 38:1865–1872. http://dx.doi.org/10.1172/JCI103962

Davis, M.M. 2012. Immunology taught by humans. *Sci. Transl. Med.* 4:117fs2. http://dx.doi.org/10.1126/scitranslmed.3003385

Hamann, D., P.A. Baars, M.H. Rep, B. Hooibrink, S.R. Kerkhof-Garde, M.R. Klein, and R.A. van Lier. 1997. Phenotypic and functional separation of memory and effector human $CD8^+$ T cells. *J. Exp. Med.* 186:1407–1418. http://dx.doi.org/10.1084/jem.186.9.1407

Klein, U., K. Rajewsky, and R. Küppers. 1998. Human immunoglobulin $(Ig)M^+IgD^+$ peripheral blood B cells expressing the CD27 cell surface antigen carry somatically mutated variable region genes: CD27 as a general marker for somatically mutated (memory) B cells. *J. Exp. Med.* 188:1679–1689. http://dx.doi.org/10.1084/jem.188.9.1679

McCarty, M. 1990. The Journal prepares for its second century. *J. Exp. Med.* 172:1–6. http://dx.doi.org/10.1084/jem.172.1.1

Sallusto, F., and A. Lanzavecchia. 1994. Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha. *J. Exp. Med.* 179:1109–1118. http://dx.doi.org/10.1084/jem.179.4.1109

Steinman, R.M. 2005. Research on human subjects in the *JEM*. *J. Exp. Med.* 201:1349–1350. http://dx.doi.org/10.1084/jem.20050723

Tangye, S.G., Y.J. Liu, G. Aversa, J.H. Phillips, and J.E. de Vries. 1998. Identification of functional human splenic memory B cells by expression of CD148 and CD27. *J. Exp. Med.* 188:1691–1703. http://dx.doi.org/10.1084/jem.188.9.1691

Welch, W. 1896. The Journal of Experimental Medicine: Introduction. *J. Exp. Med.* 1:1–3.