

similar. Important details may differ, and our job is to define these similarities and differences. In the long run, we might learn just as much or more from the differences as we do from the similarities.

I fully agree that reference to an animal model needs to be stated in the title (as this author has always done). Finally, let me comment regarding the perceived discrimination against human studies in high-impact journals. It is true that human research poses particular difficulties in meeting the rigorous causal and mechanistic standards of many of these journals. But, it should not be forgotten that this American Thoracic Society journal (*AJRCCM*) is very friendly to human studies and has a greater impact factor than its sister basic research journal (*AJRCMB*). Let us also not forget that the *New England Journal*

of Medicine, the ultimate “human” journal, now has an impact factor of 44, dwarfing *Science*, the journal with the second highest impact factor of 30. Thus, although human investigation is difficult and publication potentially a struggle, the clinical arena rules—and appropriately so. It is hoped that we can bring the two worlds together and understand and translate findings in animal models to improve patient care. An open debate among the constituents of the different camps is an ideal way to continue to bring us to a common understanding and collaboration.

STEVEN D. SHAPIRO, M.D.
University of Pittsburgh
Pittsburgh, Pennsylvania

DOI: 10.1164/rccm.2609003

Rebuttal from Drs. Wenzel and Holgate

Dr. Shapiro raises excellent points in his argument for the use of mouse models in asthma research. We, like Dr. Shapiro, are not arguing for their complete abandonment, rather a measured approach to their use which fully appreciates “how far to take the analogy.” To paraphrase Clint Eastwood/Dirty Harry, “A mouse has got to know its limitations”!

That said, we would like to challenge a few of the points raised by Dr Shapiro:

1. *The specific molecular pathways are similar in both species.* Although this may be true in some cases, numerous examples exist for species differences in molecular pathways. Of specific relevance to asthma are the profound differences in responses to interleukin (IL)-4/IL-13 activation of airway cells. In murine models, it has been reported that Th2 cytokines markedly inhibit expression of inducible nitric oxide synthase (iNOS), the enzyme responsible for the majority of exhaled nitric oxide (F_{ENO}). Despite this inhibition, F_{ENO} is known to be markedly increased in human asthma. To explain this apparent paradox, several studies have reported using various combinations of stimuli in hopes of understanding why F_{ENO} is increased in human asthma. However, in studies presented at the 2006 American Thoracic Society meeting, IL-13 stimulation of primary human epithelial cells in air–liquid interface culture caused a dramatic up-regulation of iNOS, in contrast to the opposite effect in previously reported murine studies (1). Taking a further example of major difference between humans and mice, studies using human macrophages failed to reproduce the up-regulation of arginase with IL-13 noted in murine cells (2). Hence, when evaluating Th2 cytokine effects on pathways demonstrated to be important to human asthma, the mouse and the human would appear to behave in an opposite manner.

2. *Mouse models are representative of the known etiology or insult that causes human disease/asthma.* Although we would even argue that there are serious questions to be answered about the primary role of environmental allergens in human asthma development, we are convinced that ovalbumin, the most commonly used murine “allergen,” has almost never caused human asthma. In addition, we are surprised by Dr. Shapiro’s statement that human researchers claim the Th2 hypothesis as their own. Clearly, the early

studies of Th1 and Th2 used murine cells and cell lines (3). In fact, there is a long history of skepticism for the dichotomy of Th1 and Th2 as applied to human models.

3. *Strain differences are a great strength of mouse models.* We are in complete agreement on this point. However, few studies have exploited this obvious strength. Rather, the majority of studies still report largely positive results in a single strain, rather than attempting to understand why their positive response may occur profoundly in one strain and not in another. Indeed, one gains the impression that researchers deliberately select strains to reveal a specific response.

4. *Animal models can prove causality.* Animal studies only prove causality in the model system used, not in human disease. We would strongly argue against “going back to the animal model to confirm the mechanism.” This is especially unnecessary when the pathway is already known to be active in human disease, targeted approaches in mice are supportive, and the mechanistic pathways can be further identified in primary human cells or tissues.

As introduced, mouse models can and should be used to better understand diseases like asthma through their unique ability to dissect selective pathways in a complex animal system. However, we reiterate our view that journals that publish papers using mouse or any other animal in relation to asthma should always refer to the animal species in the publication’s title. Finally, we will continue to argue that the human should be at the center of research into unique human diseases such as asthma, with murine studies undertaken for preliminary and supporting purposes.

SALLY WENZEL, M.D.
University of Pittsburgh
Pittsburgh, Pennsylvania

STEPHEN T. HOLGATE, B.Sc., M.B.B.S., M.D., D.Sc.
School of Medicine
University of Southampton
Southampton, United Kingdom

References

1. Trudeau JB, Chu HW, Hu HZ, Bleecker ER, Meyers DA, Wenzel SE. 2006. Interleukin-13 increases iNOS expression in human air-liquid interface (ALI) epithelial cells [abstract]. *Proc Am Thorac Soc* 2006;2:A66.

2. Scotton CJ, Martinez FO, Smelt MJ, Sironi M, Locati M, Mantovani A, Sozzani S. Transcriptional profiling reveals complex regulation of the monocyte IL-1 beta system by IL-13. *J Immunol* 2005;174:834–845.
3. Cherwinski HM, Schumacher JH, Brown KD, Mosmann TR. Two types of mouse helper T cell clone. III. Further differences in lymphokine synthesis between Th1 and Th2 clones revealed by RNA hybridization, functionally monospecific bioassays, and monoclonal antibodies. *J Exp Med* 1987;166:1229–1244.

DOI: 10.1164/rccm.2609004