

### Mouse Models of Human Disease: Lessons Learned and Promises to Come

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As a human geneticist, I first discovered the mouse as a model organism for biomedical research while I was a postdoctoral fellow at Baylor College of Medicine, Houston, Texas. I had become interested in an unusual group of human inherited disorders—those that were X-linked dominant and lethal in hemizygous males. The male lethality suggested that the genes involved in these disorders would be necessary for normal development. None of the genes responsible for any of these disorders had been identified at the time, and prospects for their isolation seemed rather bleak. Most of the disorders were very rare (incidence of  $<1/100,000$ ), and large pedigrees of affected females were rarer still, making human linkage studies virtually impossible. However, due to X-inactivation and dosage compensation, there is almost absolute conservation of genes on mammalian X chromosomes, and I became aware of examples of spontaneous and induced mouse mutations with phenotypes similar to some of the human disorders. Among these examples was a mouse mutant called bare patches (*Bpa*), which became the major focus for my research. In 1999, we identified the genes involved in three X-linked, male lethal mouse mutations (bare patches, striated, and tattered) and a homologous human disorder called X-linked dominant chondrodysplasia punctata or Happle syndrome (reviewed in Herman 2000). During the intervening years, I entered the realm of mouse genetics. I took the “Short Course in Medical and Experimental Mammalian Genetics” at The Jackson Laboratory in Bar Harbor, Maine, in 1989, approximately 2 mo after a fire destroyed much of the laboratory’s production facilities. Since then, I have returned to Bar Harbor several times and have served as a member of the laboratory’s Genome Informatics Advisory Board (1994–1997). I became a regular participant in the annual International Mouse Genome Conferences and served as Chair of the Mouse X Chromosome Committee from 1993 to 1996.

When asked to serve as editor for an issue of *ILAR Journal* on mouse models of human disease, I found the

biggest challenge was deciding what to include. One could focus on novel technologies enabling scientists to manipulate the mouse genome or on the wealth of resources, inbred strains, and mutant stocks available to perform genetic studies in mice. Indeed, these features, as well as its relatively short generation time and reasonable housing costs, make the mouse the ideal mammalian model for many human diseases. For recent reviews on the applications of genetic technologies in the mouse, I refer the reader to the October 2001 issue of *Nature Reviews Genetics*, which is devoted to this topic.

Even I would admit that the mouse is not the perfect model for everything. For studies of early development and organogenesis, lower vertebrates (e.g., zebrafish or *Xenopus*) have the advantage that early embryogenesis and differentiation take place outside the mother, where the processes can be viewed easily in the laboratory. The ability to perform genetic mapping and manipulate the genomes of both of these model organisms is now being developed and will make these models even more valuable. For some complex human disorders, one could question whether it is preferable to “humanize the mouse” or choose another model system. For example, by virtue of its sophisticated genetics and the ability to manipulate its genome, the mouse has become a valuable model to study atherosclerosis even though mice are generally resistant to this disorder (Fazio and Linton 2001; Paigen et al. 1994). However, for many human infectious diseases (e.g., HIV) despite the use of immunodeficient severe combined immunodeficiency (SCID) mice, the mouse remains, at best, an imperfect model to study the disease pathogenesis.

I have chosen to select examples from the wealth of disease models that illustrate some lessons we have learned in the last 15 to 20 yr. Just as some of the first descriptions of inherited human disorders were enzyme deficiencies that produce metabolic diseases, some of the earliest and best studied mouse models are for the same metabolic disorders. One of the surprises or lessons learned from some of these models is the difference in or lack of phenotype for the same enzyme deficiency in the mouse compared with human. Although lack of a phenotype for a mouse mutation may initially cause some angst for the researcher, as discussed by Elsea and Lucas (2002), these differences may, in fact, be very useful because they teach us about the consequences of

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alternate biochemical and physiological pathways. An understanding of these alterations may provide future means to develop therapies for the human disease.

Although the causes for many human metabolic disorders were deciphered decades ago, for some disorders, we are still describing the full spectrum of disease. One such group of disorders are those involving fatty acid oxidation (FAO<sup>1</sup>). The first human disorders of FAO were described in the 1970s and 1980s. More than 22 disorders of FAO have now been documented, many within the last 10 yr (Rinaldo 2001). Their phenotypes and pathogenesis are still being worked out. Dr. Phil Wood detected and described the first mouse model of FAO—short-chain acyl CoA dehydrogenase deficiency in the BALB/cByJ strain of mice—while he and I were postdoctoral fellows working together in the laboratory of Dr. Arthur Beaudet, Baylor College of Medicine. In their article, Schuler and Wood (2002) describe this and other mouse models developed to examine the pathogenesis of FAO.

Although mouse models of mendelian single gene disorders have proved invaluable in biomedical research, their promise to help us understand the pathogenesis of more complex disorders appears even greater. Some would argue that human variation and complex diseases can be studied and modeled only in our own species. Certainly there are common human diseases that do not occur naturally in the mouse, such as mental illness, autism, and Alzheimer's. As described in this issue, using technologies to genetically alter their genomes, researchers have created mice that recapitulate many, but not all, of the features of human Alzheimer's (Richardson and Burns 2002). Using detailed behavioral phenotyping and standardized tests, investigators are defining traits in the mouse that may be equivalent to human mental illness and behavioral disorders (Tarantino and Bucan 2000). An advantage of many of these mouse models is the ability to dissect out parts of a complex human disorder and study the contributions of individual components to the complete phenotype. The influence of environmental factors on a genetic trait can be studied under controlled conditions in the mouse. This characteristic is extremely important in cancer, where effects of diet and chemical exposures on an underlying genetic predisposition may be difficult to discern. Hunter and Williams (2002) discuss how the genetic resources of inbred mouse strains with varying cancer susceptibilities, recombinant inbreds, consomics, and congenics can be applied to study human cancer or other complex traits.

The raw starting material for the human or mouse geneticist is variation. The initial discoveries in mouse genetics were related to variations among different strains (e.g., differences at the major histocompatibility complex) or spontaneous or induced mutations. The latter were often generated as parts of large X-irradiation programs after

World War II. Subsequently, the ability to alter the mouse genome specifically through transgenesis and homologous recombination in embryonic stem cells led to the generation of many additional specific mutant phenotypes. As we near the completion of the sequencing of the mouse and human genomes, our ability to discern the function of the ~30,000 to 40,000 genes contained within them may be hampered by a lack of sufficient mutant phenotypes. Although it is not addressed specifically in this issue, there has been a resurgence in chemical mutagenesis studies using ethylnitrosourea to generate additional mouse mutants and phenotypes. Large and smaller-scale mutagenesis projects have been initiated worldwide, and the fruits of these efforts are beginning to be reported (Balling 2001; Brown and Balling 2001). It is likely that the number of mice with interesting and varied phenotypes produced by ethylnitrosourea programs will outnumber those produced by other methods many fold. In this issue, Dennis (2002) discusses the welfare implications of housing and caring for increasing numbers of mice used in biomedical research—some with novel, and sometimes unexpected, phenotypes.

For a more comprehensive review of mouse models of human disease, I refer the reader to Craigen (2001). For an "easy read" on mouse genetics, including information on the history of the inbred strains of laboratory mice, mouse husbandry, and an introduction to genetic mapping in the mouse, I refer the reader to Lee Silver's (1995) book, *Mouse Genetics* ([www.informatics.jax.org/silver/](http://www.informatics.jax.org/silver/)), which is required reading for everyone entering my laboratory.

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<sup>1</sup>Abbreviation used in this Introduction: FAO, fatty acid oxidation.