Published in final edited form as:

Lab Anim (NY). 2017 April 19; 46(5): 204–206. doi:10.1038/labanim.1256.

Training Mouse Pathologists: 15 Years of Workshops on the Pathology of Mouse Models of Human Disease

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Keywords

mouse pathology; conference summary; histopathology; databases

On 3–7 October 2016 the 15th annual workshop, *Pathology of Mouse Models of Human Disease*, was held at the High Seas Conference Center at The Jackson Laboratory in Bar Harbor, ME. The objective of this workshop was to cover phenotyping mouse models of human disease from the pathologist's perspective and to provide veterinary and human pathologists and pathology residents an overview of the latest technologies ranging from creating mouse models with genetic engineering technologies to evaluating them at the molecular, physiological, and histopathological levels. The meeting discussed the use of mice for modelling human disease for understanding the causes and pathogenesis (mechanisms) of disease, developing therapies, and methods of prevention. Discussions included all disease classifications – genetic, infectious, immune mediated, degenerative, aging, cardiovascular, cancer, and many others, focusing on specific models developed by the faculty.

The laboratory mouse has been critical to biomedical research since Clarence Cook Little defied the thoughts of the day nearly a century ago by creating the first inbred mouse strain¹. Over the last 50 years the laboratory mouse has become the standard biomedical research model organism to study for a wide variety of human diseases. While fish, worms, flies, and other non-mammalian species also serve this purpose, most lack critical anatomical structures or physiological processes found in humans and mice, which limits many types of

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Declaration of Conflict of Interest: Dr. Sundberg has a research contract with BIOCON LLC which has no relevance to this meeting. The other authors state no conflicts of interest.

investigations, especially translational studies. Over 60% of the National Institutes of Health (NIH)-funded research involves rodents, with mice representing 80–90% of the animals used². Detailed characterization of the mouse genome and extensive sets of tools available for genetic modifications also assure continuous use of the mouse as the leading model organism.

Spontaneous (naturally occurring) mutations in mice were, for many years, the unique, albeit relatively rare, source of new mouse biomedical models. The advent of genetically engineered mice (GEMs), which includes transgenesis (moving genes from one species to another or overexpressing a gene), targeted mutagenesis (so-called knockout mice), inducible models with or without molecular markers, and more recent endonuclease modified models, continue to make the laboratory mouse a very utilitarian biological tool. Breakthroughs using mouse models have provided crucial insight into the pathogenesis of numerous diseases affecting all organ systems. These technologies evolved from small scale projects within principal investigator's research laboratories, to large-scale international projects such as the Knockout Mouse Project (KOMP) which aims to create GEMs where ultimately every known protein coding gene in the mouse is inactivated³. Other large-scale projects include aging studies^{4, 5}, mutagenesis strategies^{6, 7}, and new approaches to generate genetically diverse outbred stocks (diversity outcross)⁸ and inbred strains (collaborative cross)⁹. Accurate evaluation and interpretation of these mice requires clinical evaluation, gross necropsy, and histopathological phenotyping¹⁰. Comparison of the diseases these mice develop to human disease, to find the best fit, the so-called "Cinderella effect"¹¹, involves collaboration between veterinarians, who understand the mouse disease and lesions, and physicians, who deal with the human patients. While the technologies to create mutant mice have become more or less routine, there remains a critical shortage of expert pathologists to do the requisite pathology-based phenotyping in which accurate interpretation of lesions are made combined with comparisons with human diseases¹².

Veterinary pathologists are trained in the gross and histopathology of multiple species but have limited knowledge of human pathology, and their experience with laboratory mice is generally restricted to the diagnosis of infectious disease in standard domestic and research animals. Many veterinary pathologists gain expertise in toxicologic pathology while evaluating rodent tissues for the pharmaceutical and chemical industries, but, in general, they are not trained in the nuances of mouse genetics or the types of lesions to be expected in GEMs. By contrast, physicians have extensive knowledge of human disease but are not well versed in the intricacies of mouse anatomy, pathology, and genetics or the concept of comparative pathology. Both groups, physicians and veterinarians, have the basic skills to generate high quality evaluation of mouse models, but all need the confidence they can do this.

To address this issue, the first large meeting, *Pathology of Genetically Engineered Mice*, was held in 1999 at the NIH in Bethesda, Maryland. This meeting resulted in the production of a well-regarded textbook¹³, and additional books (Table 1) and reviews have subsequently provided traditional resources. Many pathologists working with mice do so in small groups or in isolation at their institutions. The small workshop format of the *Pathology of Mouse Models of Human Disease Workshops*, consisting of 20–25 participants and 15 or more

faculty (Figure 1), is designed to encourage interaction among all participants, and has resulted in the development of many collaborations and, perhaps more importantly, confidence for the attendees to seek consultation with the faculty. Variations in this format are now commonly used in similar meetings around the world, often involving the organizers of this series.

The workshop format has evolved to include open evening discussions on cases or research projects using whole slide scanned images. Presentations cover mouse genetics and genetic nomenclature, didactic sessions covering specific diseases and organ systems, embryonic lethal analyses, stem cell and regenerative medicine, technologies for creating GEMs, and the most current physiological and imaging systems to systematically evaluate mouse models. Wet labs on necropsy procedures or new technologies were provided. The core faculty, consisting of experts in their respective areas of mouse pathology from 6 different veterinary and medical colleges and research institutions, described the latest breakthroughs in their fields. The workshop also included discussions on grantsmanship, manuscript writing, and dealing with editors. Dr. Matthew H. Kaufman (University of Edinburgh in Scotland) was a regular speaker on mouse embryology for many years^{14, 15}. He was well known as one of the pioneers in stem cell culturing methods¹⁶. In his memory, the third annual Professor Kaufman Stem Cell Lecture was given by Dr. Rudolf Jaenisch (Whitehead Institute, MIT) during the 2016 course.

Speakers not only lectured on their own work but provided group and individual demonstrations on the use of mouse-centric databases such as The Mouse Genome Informatics Database (<http://informatics.jax.org/>); the Mouse Tumor Biology Database (<http://tumor.informatics.jax.org/>); Mouse Phenome Database (<http://phenome.jax.org/>), Pathbase (<http://pathbase.net/>); the Mouse Disease Information System (MoDIS)^{17, 18}.

These annual workshops provide a state-of-the-art overview of the pathology of GEMs and other mouse models of human disease as well as spontaneous diseases affecting aging inbred strains and results of experimental manipulations. More importantly, the workshops allow for the integration of this field with other research areas such as genetics and molecular biology. Of even greater significance, the workshops promote and strengthen effective working relationships between veterinary and human pathologists, in which they join forces to make the most accurate histopathologic interpretations and the most creative uses of these fantastic biomedical tools. These meetings will continue to be held the first full week of October and at the High Seas Conference Center at The Jackson Laboratory in Bar Harbor, Maine.

Acknowledgments

The authors thank Erin McDevitt and Charles Wray, Courses and Meetings Department, The Jackson Laboratory, who provided critical logistical support to hold these workshops. This workshop series was supported directly or indirectly by grants from the National Institutes of Health (R13 OD010920; R01 CA089713, R01CA197160, R01CA182413), Midcareer Awards in Mouse Pathobiology (K26 RR000173 JPS; K26 RR017595, AYN), NYSTEM (C028125 and C029155, AYN), and Howard Hughes Medical Institute (HHMI).

Abbreviations

GEMS	genetically engineered mice
KOMP	knockout mouse project
MoDIS	Mouse Disease Information System
NIH	the National Institutes of Health in the United States

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Figure 1.

Participants in the 2016, 15th annual Pathology of Mouse Models of Human Disease course outside the High Seas Conference Center in Bar Harbor, ME. Front row - Sara Santagostino, Ana Vieira, May Tse Pui-ying, Kelli Boyd, Jerry Ward; Second row – Nadine Stokar, Alexandria Schauer, Alex Nikitin, Frances Henson; Third row – Jennifer Peirick, Harm Hogenesch, Steve Davison, Piper Treuting; Fourth row – Dustin Graham, Tim Helms, John Sundberg, Ryan Schafbuch; not present – Lauren Himmel, Pankaj Kumar, Ahn Diep, Kuldeep Singh, and Peter Vogel.

Table 1

Textbooks relevant for pathologists studying animal model of human disease

Editors	Title	Publisher
Bannsch P, Gossener W	Pathology of Neoplasia and Preneoplasia in Rodents. Vol 1 and 2	Stuttgart: Schattauer; 1997
Bolon B	Pathology of the Developing Mouse: A Systematic Approach.	Boca Raton, FL: CRC Press; 2015
Croy BA, Yamada A T, DeMayo FJ, et al.	The Guide to Investigation of Mouse Pregnancy	London, Elsevier; 2014
Frith CH, Ward JM	Color Atlas of Neoplastic and Non- neoplastic Lesions in Aging Mice	Amsterdam: Elsevier; 1988
Fox JG, Barthold SW, Davisson MT, et al.	The Mouse in Biomedical Research. Vol 1. History, Wild Mice, and Genetics. 2 nd ed.	San Diego, CA: Academic Press; 2007
Fox JG, Barthold SW, Davisson MT, et al.	The Mouse in Biomedical Research. Vol 2. Diseases. 2 nd ed.	San Diego, CA: Academic Press; 2007
Fox JG, Barthold SW, Davisson MT, et al.	The Mouse in Biomedical Research. Vol 3. Normative Biology, Husbandry, and Models. 2 nd ed.	San Diego, CA: Academic Press; 2007
Fox JG, Barthold SW, Davisson MT, et al.	The Mouse in Biomedical Research. Vol 4. Immunology. 2 nd ed.	San Diego, CA: Academic Press; 2007
Green EL	Biology of the Laboratory Mouse. 2 nd ed.	New York, NY: Dover Publications; 1968
Haschek WM, Rousseaux CG, Wallig MA	Handbook of Toxicologic Pathology. 2 nd ed.	San Diego, CA: Academic Press; 2013
Hedrich HJ	The Laboratory Mouse. 2 nd ed.	London: Academic Press; 2012
Holland EC	Mouse Models of Human Cancer	Hoboken, NJ: Wiley-Liss; 2004
Iwaki T, Yamashita H, Hayakawa T	A Color Atlas of Sectional Anatomy of the Mouse	Tokyo: Maruzen Publishing Company; 2001
Jones TC, Hackel DB, Migaki G	Handbook: animal models of human diseases	Washington, D.C.: Armed Forces Institute of Pathology, 1972.
Jones TC, Mohr U, Hunt RD	Monographs on Pathology of Laboratory Animals: Endocrine System	Berlin: Springer-Verlag, 1983
Jones TC, Mohr U, Hunt RD	Monographs on Pathology of Laboratory Animals: Respiratory System	Berlin: Springer-Verlag, 1985
Jones TC, Mohr U, Hunt RD	Monographs on Pathology of Laboratory Animals: Urinary System	Berlin: Springer-Verlag, 1986
Jones TC, Mohr U, Hunt RD	Monographs on Pathology of Laboratory Animals: Genital System	Berlin: Springer-Verlag, 1987
Jones TC, Mohr U, Hunt RD	Monographs on Pathology of Laboratory Animals: Nervous System	Berlin: Springer-Verlag, 1988
Jones TC, Mohr U, Hunt RD	Monographs on Pathology of Laboratory Animals: Integument and Mammary Glands	Berlin: Springer-Verlag, 1989
Jones TC, Mohr U, Hunt RD	Monographs on Pathology of Laboratory Animals: Hematopoietic System	Berlin: Springer-Verlag, 1990
Jones TC, Mohr U, Hunt RD	Monographs on Pathology of Laboratory Animals: Cardiovascular and Musculoskeletal System	Berlin: Springer-Verlag, 1991
Jones TC, Mohr U, Hunt RD	Monographs on Pathology of Laboratory Animals: Eye and Ear	Berlin: Springer-Verlag, 1991
Jones TC, Popp JA, Mohr U	Monographs on Pathology of Laboratory Animals: Digestive System, 2 nd edition	Berlin: Springer-Verlag, 1997

Editors	Title	Publisher
Kaufman MH	The Atlas of Mouse Development. 2nd ed.	San Diego, CA: Academic Press; 1992
Kaufman MH, Bard JBL	The Anatomical Basis of Mouse Development.	San Diego, CA: Academic Press; 1999
Kaufman MH, Nikitin AY, Sundberg JP	Histologic Basis of Mouse Endocrine System Development: A Comparative Analysis.	Boca Raton, FL: CRC Press, 2010
Maronpot RR	Pathology of the Mouse: Reference and Atlas.	Vienna, IL: Cache River Press; 1999
McInnes, EF	Background Lesions in Laboratory Animals: A Color Atlas	Edinburgh, UK: Saunders (Elsevier), 2012
Mohr U	International Classification of Rodent Tumours: The Mouse.	Berlin, Germany: Springer-Verlag; 2001
Mohr U, Dungworth CC, Capen CC, et al.	Pathobiology of the Aging Mouse. Vol 1 and 2.	Washington, D.C.: ILSI Press; 1996
Percy DH, Barthold SW	Pathology of Laboratory Rodents and Rabbits. 4th ed.	Ames, IA: Iowa Wiley Blackwell; 2016.
Papioannou VE, Behringer RR	Mouse Phenotypes. A Handbook of Mutation Analysis	Cold Spring Harbor, NY: Cold Spring Harbor Press; 2005
Popesko P, Rajitov V, Hork J	A Color Atlas of Anatomy of Small Laboratory Animals	London: Wolfe Publishing, Ltd., 1992.
Proetzel G, Wiles MV	Mouse Models for Drug Discovery. 2 nd ed.	New York, NY: Humana Press; 2016
Ruberte J, Carretero A, Navarro M	Morphologic Mouse Phenotyping. Anatomy, Histology, and Imaging	Madrid: Editorial Medica Panamericana; 2016
Scudamore CL	A Practical Guide to the Histology of the Mouse.	Oxford, UK: John Wiley & Sons; 2013
Silver LM	Mouse Genetics	New York, NY: Oxford University Press; 1995
Smith RS, John SWM, Nishina PM, et al.	Systematic Evaluation of the Mouse Eye. Anatomy, Pathology, and Biomethods	Boca Raton, FL: CRC Press; 2002
Sundberg JP	Handbook of Mouse Mutations With Skin and Hair Abnormalities: Animal Models and Biomedical Tools.	Boca Raton, FL: CRC Press; 1994
Sundberg JP, Boggess D	Systematic Approach to Evaluation of Mouse Mutations.	Boca Raton, FL: CRC Press; 2000
Sundberg JP, Ichiki T	Genetically Engineered Mice Handbook.	Boca Raton, FL: CRC Press; 2006
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