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Training mouse pathologists: 16th annual workshop on the pathology of mouse models of human disease

John P. Sundberg¹, Kelli Boyd², Harm Hogenesch³, Alexander Yu. Nikitin⁴, Piper M. Treuting⁵, and Jerrold M. Ward⁶

¹The Jackson Laboratory, Bar Harbor, ME

²Departments of Comparative Medicine and Pathology, Vanderbilt University, Nashville, TN

³Purdue University College of Veterinary Medicine, West Lafayette, IN

⁴Cornell University College of Veterinary Medicine, Ithaca, NY

⁵Departments of Comparative Medicine and Pathology, University of Washington, Seattle, WA

⁶Global VetPathology, Montgomery Village, MD

The 16th 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 on 1-6 October 2017. This has become a regular, small, and focused meeting aimed at training the next generation of pathologists to develop, phenotype, and validate mouse models of a wide variety of human diseases. The faculty discussed the use of mice for modeling human diseases 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, cancer, and many others, concentrating on specific models developed by the faculty, and usually focused around an organ system.

The laboratory mouse has been critical to biomedical research for well over a century. Worms, flies, fish, and other non-mammalian species also serve this purpose; however, most lack critical anatomical structures or physiological processes found in humans that are present in mice¹. These anatomical and physiological differences between mammals and lower vertebrates and invertebrates limit many types of investigations, especially translational studies. Over 60% of the National Institutes of Health-funded research involves rodents. Mice represent 80-90% of the animals used in biomedical research². Detailed characterization of the mouse genome^{3,4} combined with extensive sets of tools available for genetic modifications^{5,6}, especially using CRISPR/Cas9 to create precise models for specific human mutations in mice, assures continuous use of the mouse.

Address correspondence to: John P. Sundberg, D.V.M., Ph.D., The Jackson Laboratory, 600 Main Street, Bar Harbor, ME 04609-1500, USA; john.sundberg@jax.org.

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Spontaneous mutations in mice, while relatively rare, were a unique source of new mouse biomedical models and they still are. However, with the advent of genetically engineered mice (GEMs), including transgenesis (moving genes from one species to another or overexpressing a gene), targeted mutagenesis (so-called knockout mice which can be complete nulls or hypomorphic alleles), inducible models with or without molecular markers, and more recently endonuclease modified models (which include CRISPR/Cas9), continue to make the laboratory mouse a very useful biomedical research tool. These types of mouse models continue to provide insight into the pathogenesis of numerous human diseases affecting all organ systems. While traditionally these technologies were used to address specific questions in relatively small scale, highly focused projects, they have evolved into large-scale international projects such as the Knockout Mouse Project (KOMP, in the USA) which aims to create GEMs where ultimately every known protein coding gene in the mouse is inactivated⁷⁻⁹. Other large-scale projects include aging studies^{10,11}, mutagenesis strategies^{12,13}, and novel inbred strains (collaborative cross)¹⁴⁻²¹ and outbred stocks (diversity outcross)²²⁻²⁶. Expertise in clinical evaluation, gross necropsy, and histopathological phenotyping of all of these types of mice is required to truly utilize these resources²⁷. In order to find the best fit, the so-called “Cinderella effect”²⁸, involves collaboration between those who understand the mouse disease and lesions (veterinarians), and those who deal with the human patients (physicians). While the technologies used to create GEMS are relatively routine, often provided by an institutional or commercial service, there remains a shortage of expert pathologists, be they veterinarians or physicians, to do the requisite pathology-based phenotyping to obtain an accurate diagnosis of lesions combined with comparisons with human diseases²⁹.

To address these issues, we initiated mouse pathology meetings on a large scale with a meeting titled *Pathology of Genetically Engineered Mice* in 1999 held at the National Institutes of Health in Bethesda, Maryland. Subsequent meetings in this style were held in Stockholm, Sweden, and Kumamoto, Japan. While reaching a wide audience, this format was not suitable for intense, focused training, nor did it provide the opportunity for attendees to meet, much less get to know the faculty. To better approach this, we developed a small workshop format titled *Pathology of Mouse Models of Human Diseases*. Attendees are limited to 20-25 with 15 or more faculty (Figure 1) who are encouraged to stay throughout the workshop. This approach is designed to encourage interaction among all participants and has resulted in numerous collaborations. It also results in the attendees gaining confidence to consult with the faculty in the future because they have come to know them personally.

The workshop format continues to evolve to include organized evening discussions based on case reports or research projects presented by attendees. These may use Powerpoint® presentations, whole slide scanned images, or projected images from a microscope. Open times in some evenings are scheduled to enable participants to work directly, one-on-one, with the faculty on difficult cases, mutant phenotyping, or just to review study sets with some of the world's experts in the field.

Formal presentations during the day covered mouse genetics and genetic nomenclature, didactic sessions on 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. Optional wet labs on specialty necropsy procedures or new technologies were also provided. The core faculty, consisting of experts in their respective areas of mouse pathology, described the latest breakthroughs in their fields. The workshop also included discussions on resources at the NIH and around the country that NIH supports, grantsmanship (given by Dr. Franziska Grieder, Director, Office of Research Infrastructure Programs, NIH), manuscript writing, and submission to journals (given by Dr. Dustin Graham, Nature Research).

Dr. Matthew H. Kaufman (University of Edinburgh in Scotland) was a regular speaker on mouse embryology for many years^{30,31}. He was well known as one of the pioneers in stem cell culturing methods³². In his memory, the fourth annual Professor Kaufman Stem Cell Lecture was given by Dr. Dennis Roop (Professor of Dermatology and Director of the Gates Stem Cell Center, University of Colorado) during the 2017 course.

In addition to the faculty speakers, informatics experts at The Jackson Laboratory, or speakers who developed these tools, were on site to provide group and individual demonstrations on the use of mouse-centric databases, including 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/>); and the Mouse Disease Information System (MoDIS) for medical record keeping for the pathologist^{33,34}.

These annual workshops provide a state-of-the-art overview of the histopathology and underlying genetics of a wide variety of diseases in the laboratory mouse demonstrating how these can be used to not only understand the pathophysiology of diseases in all mammals including humans, but also their use as preclinical tools to test drug efficacy. The core organizing committee participates annually to maintain the high quality of the program. Their topics vary every year by being either completely different, or expanding on previous work with new discoveries. The remaining faculty members rotate to cover different organ systems or technologies. Thus, there is consistency as well as variety at each meeting. Most importantly, these workshops integrate pathological analyses of the mice with other research areas, including genetics and molecular biology. These workshops promote effective collaborative relationships between participants and demonstrate the importance of veterinary and human pathologists working together to make the most accurate interpretations of these mice, which are, without question, fantastic biomedical tools.

The 2018 meeting will again be held the first full week of October and at the High Seas Conference Center at The Jackson Laboratory in Bar Harbor, Maine.

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Figure 1.

Participants in the 2017, 16th annual Pathology of Mouse Models of Human Disease course outside the High Seas Conference Center in Bar Harbor, ME. Front row – Sarah Linn, Angela Chen, Kelli Boyd, Jerry Ward; Second row – Jessica Bailey, Alison Mustonen, Christine Goeopfert, Elena Demeter, Matthew Stachler, Franziska Grieder; Third row – Monica Estrada, Patricia Coutinho de Souza, Margaret Martinez, Tiffany Lyle, Katja Steiger; Fourth row – Peter Vogel, Jimmy Tarrant, David Coleman, William Sills, Michael Martinez, Harm Hogenesch, John Sundberg, Piper Treuting, Paul Schofield; Not present – Omkara Veeranki. Photograph by Erin McDevitt, The Jackson Laboratory.