How to phenotype a mouse

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Genetic technologies empower the mouse as a research tool but leave most researchers who work with them faced with the difficult task of analyzing their complex phenotypes. Recent articles document a shocking shortage of comparative pathologists (Barthold et al., 2007; Cardiff and Altrock, 2007; Cardiff, 2007; Valli et al., 2007; Bolon et al., 2008; Cardiff, 2008; Cardiff et al., 2008; Couto and Cardiff, 2008; Schofield et al., 2009), who are trained to recognize disease in the mouse. Because of this shortage, scientists bravely interpret their own slides without a mouse pathology consult or training. Papers document inadvertent errors and accuse researchers of ‘do-it-yourself’ (D.I.Y.) pathology (Bolon et al., 2008; Cardiff et al., 2008; Ince et al., 2008; Warren et al., 2009). Scientists are in a difficult position. Without access to comparative pathologists, how can disease models be validated with confidence? How will science move forward without D.I.Y. pathology? How does D.I.Y. pathology influence conclusions that are published in the literature?

I recognize that scientists are making the best of a difficult situation when they analyze the influence of their genetic mutations on mouse pathobiology. In the last 20 years, I have worked with hundreds of researchers who use mouse models. They are competent, conscientious scientists. In most cases, they have more experience and expertise in their model than I. But since their knowledge of mouse pathology is frequently limited, it can lead to misinterpretations that often find their way into publication. With the increasing development of mouse populations (Austsin et al., 2004; Grimm, 2006a; Grimm, 2006b; Nature Publishing Group, 2007), this situation promises to become worse before it gets better. The NIH-initiated Knockout Mouse Project (KOMP) will create thousands of new, genetically modified mouse strains that will need analysis and require even more comparative pathology expertise (Couto and Cardiff, 2008; Schofield et al., 2009). The relative number of people who are properly trained to analyze this pipeline of new models will dwindle even more.

Given this pending glut of genetically engineered mice, the shortage of comparative pathologists who are familiar with genomics requires immediate attention. The need for genomic pathologists is increasing (Cardiff, 2008). The solution requires the cooperation of the entire scientific community. Private and public sectors must recognize the need and provide appropriate economic incentives and supporting training programs. Pathologists must recruit and train a new generation of genomic pathologists. However, these are long-term, costly solutions.

The field is faced with important questions: Can long-term and costly solutions keep up with the need for comparative pathologists? Do interim, less costly solutions exist? Will laboratory staff continue to provide the necessary services, and will they be trained appropriately to do so? According to the Priorities for Mouse Functional Genomics Research Across Europe (PRIME) report, 94% of the initial observations and contacts with mice involve ‘staff’, namely graduate students, fellows and technicians (Schofield et al., 2009). Our experience in North America is consistent with these findings (Cardiff et al., 2008). Principal investigators rarely have physical contact with the mice produced in their lab and virtually never pay salaries for necropsies to be carried out by trained professionals. As a result, the personnel characterizing new mouse models often have limited training to guide them. The histology and microscopic examination is strictly...
D.I.Y. Since this will not change in the near future, the challenge is to train staff members appropriately in basic pathobiology so that they can function confidently as ‘parapathologists’.

Fig. 1. Whole slide image (WSI) displayed over the internet using a standard browser. (A) This image illustrates the overview [see ‘POI’ (point of interest)] of a hematoxylin and eosin (H&E)-stained mouse mammary fat pad viewed at a ‘low’ magnification (0.6×) (see ‘ZoomScale’). Notice the annotation in the ‘Note’ field on the right, stating that the slide shows ‘Pten+/– × NeuNT Early MIN and Tumors’. Other information from the database is recorded in the fields below the WSI. The red arrow points to the MIN (mammary intraepithelial neoplasm) shown in B. The cursor arrow points to the region shown in B. (B) This image illustrates the Erbb2-type MIN (see ‘POI’) in the same H&E-stained mouse mammary fat pad at a higher magnification (40×) (see ‘ZoomScale’).
Scientists can use interim solutions to upgrade their knowledge of mouse pathology to deal with the short-term issue. Students, fellows and technical staff can become a trained workforce of pathology-extenders with enough understanding of the processes to know when to call upon a comparative pathology expert! The modeling community needs a cadre of ‘staff’ with an operational knowledge of mouse pathobiology. If this is a serviceable solution, pathology educators will have to broaden their focus to include training of graduate students, fellows and technicians, and not just fellow pathologists.

There is also a shortage of appropriately trained faculty, which precludes most local and independent ‘homegrown’ programs (Cardiff et al., 2008). Furthermore, the standard faculty-focused, location-dependent curricula and workshops are expensive, often require extensive travel, and, clearly, have not served the scientific community. The old educational models are insufficient to meet the modeling community’s needs for mouse phenotyping.

To meet this immediate need, a group of over 40 concerned comparative pathologists have formed an organization aimed at solving the problems of correctly phenotyping model organisms. The Center for Genomic Pathology is a non-profit organization composed of educators and practitioners in comparative pathology for the purpose of teaching genomic pathology (http://ctrgenpath.net).

An enabling technology also exists that overcomes many of the limiting factors. Both long- and short-term goals for staff training can be met effectively using modern internet-based educational technologies (http://ctrgenpath.net/static/GNP100_Information_Session/player.html). Modern media enables distance learning, interactive conferencing over vast distances with whole slide imaging (WSI), and instant access to experts (Fig. 1). First, the currently sparse and geographically dispersed experts can be connected and coordinated using the internet. For example, we have assembled a faculty of world-expert comparative mouse pathologists who have agreed to provide educational material,
conferences and consultation over the internet (http://ctrgenpath.net). Second, WSI provides instant access on the user end to a seemingly endless archive of digitized and annotated slides (http://imagearchive.compmed.ucdavis.edu/). WSIs are the basis for internet-based interactive telepathology, which is the modern form of a ‘slide conference’ (Fig. 2). The traditional 35 millimeter ‘postage stamp’ image is no longer the ‘coin of the

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**Fig. 3. An illustration of the basic principles for publication of WSIs as supplemental data.** When visiting this website, one can see the entire slide by clicking on the specific publication (http://imagearchive.compmed.ucdavis.edu/publications).

**Fig. 4. Introduction to Pathobiology of the Mouse, Part A.** This online course is designed to provide the basic concepts and vocabulary for parapathologists. The course can be found at http://ctrgenpath.net/static/GNP100_Information_Session/player.html
realm’ for teaching or publication (http://imagearchive.compmed.ucdavis.edu/publications) (Fig. 3). The user has internet access to remote images for asynchronous study and synchronous consultation. Third, a new generation of web-savvy students are familiar with the internet and feel comfortable obtaining information and attending classes using the techniques of distance learning. We have partnered with the UC Davis Extension to produce the appropriate curricula (http://extension.ucdavis.edu/unit/health_sciences/) (Fig. 4). So, the modern problem is met with a modern solution. We do not have to discard the positive aspects of traditional teaching methods, but support them with the speed and convenience of newer technologies. The program depends on your recognition, understanding, endorsement and support, and we hope that you might find it useful.

REFERENCES