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Editorial: Best Pathology Practices in Research Using Genetically Engineered Mice

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The recent advent of high-throughput transgenic and gene targeting technologies has accelerated the generation of new genetically engineered mouse (GEM) lines for research and testing. As an example, the International Mouse Knockout Consortium has proposed to systematically mutate every gene in the mouse genome, thereby creating more than 20,000 new embryonic stem cell lines from which null mutant (''knockout'') mice can be made to explore gene function in vivo.[2,4,6] An enormous number of mice will need to be characterized in the coming decades if this remarkable resource is to yield a rich harvest of scientific information.

The recent explosion in the use of GEM in research has led to two issues of serious concern to the members of the American College of Veterinary Pathologists (ACVP). The first issue is the continued publication of erroneous descriptions and interpretations of mutant mouse phenotypes by untrained and inexperienced investigators.[3] The answer to this problem is to ensure that all GEM characterizations are performed by a qualified comparative pathologist. The second issue, as noted in recent commentaries in *Nature*[4] and elsewhere,[1,3] is that the need for comparative pathology expertise cannot be met by the current ranks of research pathologists. The solution to this latter dilemma is to augment the number of well-trained comparative pathologists.

The participation of veterinary pathologists in research involving GEM should be dramatically increased. The emphasis on comparative biology and medicine in veterinary pathology training programs provides the mindset and knowledge required of true comparative pathologists. Moreover, an experienced veterinary pathologist has the expertise to identify the salient phenotypic features of new mouse models and to discern how differences in age, sex, strain background, disease status, and husbandry practices might contribute to this phenotype. Finally, veterinary pathologists are skilled at understanding the pathophysiology of disease and integrating information from numerous sources and across species to achieve a unique perspective on the overall biology of an animal model and its relevance to human disease. These broad skills and comparative outlook are critical tools in the development and validation of GEM and other translational research models. A major impediment to full use of veterinary pathology skills in research using GEM, however, is that support for primary characterization or phenotyping of GEM is available primarily as part of awards for hypothesis-driven research. This approach necessarily targets specific phenotypes or conditions that the GEM is expected to model and restricts thorough characterization of new GEM lines.

With these considerations in mind, we encourage all scientists using these mice to accurately describe GEM lines as well as the relevant control mice in the scientific literature, to evaluate all organ systems rather than just an expected organ of interest, and to report the absence of apparent anatomic or functional findings (''negative'' phenotypes). We urge researchers to recognize and use the unique comparative capabilities of veterinary pathologists in the development and validation of GEM models of human disease, even if such comparative pathology expertise must be sought in the form of external collaborators or qualified contract researchers. We urge the editors of all scientific journals to require that authors support their phenotypic findings by providing descriptive detail regarding GEM, including relevant protocols, correct nomenclature for manipulated genes, complete strain background information, husbandry details, and pathogen status, and by documenting comparative pathology expertise of the author.

In addition, journals should take care that submitted manuscripts reporting GEM pathology information are reviewed by at least one referee with expertise in mouse pathology.

To produce the veterinary pathologists required to meet the increasing need for comparative pathology expertise, we advocate that the entire scientific community using GEM work together to support efforts aimed at increasing the number of veterinary pathologists who receive formal training in comparative pathology, specifically the characterization of GEM. To succeed, this effort cannot be limited to attendance at the occasional short course on GEM pathology or confined only to those individuals fortunate enough to train at an institution with one or more comparative pathologists in residence. Funding must be made available to facilitate regular interactions among qualified comparative pathologists and trainees, perhaps using the power of the Internet to create a ''virtual academy'' that simultaneously expands training opportunities while limiting real costs.[3] We strongly encourage ACVP members with GEM expertise to participate actively in or even lead this initiative.

Finally, we recognize that even if the number of comparative pathologists is increased, many researchers might still lack ready access to their services and expertise. Few biomedical research institutions, regardless of the volume of animal research, have established phenotyping cores or have otherwise made available the necessary comparative pathology expertise by establishing appropriate faculty and staff positions. This may be because the cost is viewed as prohibitive. However, those few such cores that currently exist have shown that, if adequately capitalized and properly managed, they are well utilized and cost-effective. Therefore, we encourage institutions having significant animal research programs to establish and support such laboratories. Furthermore, grant proposals involving creation and characterization of GEM should request funds specifically for pathology support.

References

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