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Selecting appropriate animal models and strains: Making the best use of research, information and outreach

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Abstract
Of the 3Rs, Replacement is the most often considered. While utmost effort should be given to developing and using an in vitro alternative, of equal importance is identifying the most appropriate animal model. The final decision is not between animal and non–animal, but also which animal. Discussion includes the issues involved in the appropriate choice of animal model, along with ideas for solutions and outreach.

Worldwide, before animal research is approved, animal welfare legislation requires consideration of alternatives. Consulting literature sources and conducting searches in bibliographic databases are the commonly recognized methods to insure compliance.

Coupled with the difficulty in locating useful and relevant alternatives information is the misunderstanding of the 3Rs and regulations. Considering and locating information on appropriate animal models and strains is even less well understood. The UCDavis Center for Animal Alternatives Information web–based resource, "Bibliographic Searching Tools on Disease Models: Locating Alternatives for Animals in Research", offers search examples and suggested options, acting as a springboard for consideration of the best model. Arranged by both disease and model, the scientist is offered a new way to look at the research.

Keywords: 3Rs, animal model, animal strain, databases, alternatives

Introduction

Arguably the single most essential element in animal-based research, identifying and selecting the most appropriate animal model is also the most challenging. If after making the best use of the available research and published literature it is determined that there is no non-animal alternative, the very next step is determining the most appropriate animal model. While this process of consideration and concern is a common experience internationally, this paper will discuss and describe what has been done at the University of California, Davis, in an effort to assist scientists with this area.

When discussing the 3Rs, invariably Replacement is the R most often considered. While primary and utmost effort should be given to developing and using in vitro alternatives, the other 2Rs – Reduction and Refinement – are essential considerations in research as well and are too often overlooked.

Replacement is the ultimate alternative. However, the final decision is not always, or even usually, between animal and non-animal; instead, it is which animal? Which strain? For the success and validity of the research, it is crucial to identify the most appropriate animal model. Selecting the best model "reduces and refines" and improves research.

This discussion will raise the issues around the appropriate choice of animal model, along with ideas for solutions and outreach.

Selecting a model

Colleagues at the World Congress have discussed searching by species differences and the importance of appropriate strain selection (Allen, 2007; Savenije, 2007). This is an area that is finally being recognized for its increasing importance.

Worldwide, before animal research is approved, most animal welfare legislation requires consideration of alternatives. Consulting literature sources and conducting searches in bibliographic databases are the commonly recognized methods to insure compliance (Grune, 2004). As information professionals, we make every effort to help scientists meet these requirements and locate useful information. Searching the literature for alternatives, for relevant studies, for the latest developments and techniques, includes searching for

and considering the animal model. When the mouse is determined to be the best option, full consideration must then be given to the strain.

The preponderance of mice in laboratories is due to the explosion in number of engineered strains, the genetic creation of disease models, and the strain-specific models. While mice have become, by far, the most commonly used laboratory animal model, at the same, the number of strains of mice has exploded. The laboratory mouse, with its thousands of inbred, specialized, and mutant strains, serves as the primary animal model for exploring genetic variation and human biology. Specialized searching approaches are necessary for locating information regarding mouse models and strains; specialized searches are required for studies involving strains of mice.

Current publications, such as "The relevance of genetically altered mouse models of human disease" by Bhogal and Combes and "The program for phenotyping of genetically modified animals at AstraZeneca" by Berg and Bohlooly, illustrate the importance of considering phenotype and behavior in genetically modified animals (Bhogal, 2006; Berg, 2006). This concern is reflected in the literature, of which these two articles are just examples.

Strain differences allow for such things as genetic background variation in mouse strains and genetic mutation; for example, making one excessively vulnerable to obesity and type 2 diabetes. Genetic background variation in mouse strains can be shown, illustrating mutant cells and offspring that can then be screened for germline transmission of the mutant allele.

Two other articles, "Mouse phenome research: implications of genetic background" by Yoshiki and Moriwaki and "Genetically altered mice: phenotypes, no phenotypes, and faux phenotypes" by Barthold discuss the research challenges associated with these genetically engineered mice (Yoshiki, 2006; Barthold, 2004). These strain-level concerns are not commonly recognized or considered by the researcher when selecting a model for the study.

Searching: Mouse models

Locating relevant information regarding most appropriate animal models and strains is facilitated by PubMed's Medical Subject Headings tree structure (National Library of Medicine, 2008). PubMed offers search terms to assist with identifying models and strains, examples including the MeSH terms *mice, inbred strains* and *disease models, animal.* However, MeSH is unfortunately not readily understood nor commonly used by scientists when searching. Coupled with the difficulty in locating useful and relevant alternatives information are the general misunderstandings and misconceptions about the 3Rs and the related regulations. Considering and locating information on appropriate animal models and strains are even less well understood and represent another level of complexity.

In addition to PubMed, there are resources and databases created by organizations, programs, and centers working in this area; many have compiled information relevant and useful in the selection of models.

One example is the Mouse Biology Program at the University of California, Davis (University of California, Davis, 2007a). MBP has become a leader, and continues to grow, with particular strength in the biological sciences, veterinary medicine, and human medicine. The research and resulting resources on all aspects of mouse biology are on the forefront of discovery and understanding.

The Trans-NIH Mouse Genomics and Genetics Resources Coordinating Group Knockout Mouse Project, called KOMP, provides information on projects and funding, as well as resources (National Institutes of Health, 2007a). The primary purpose is to generate a comprehensive and public resource cataloging all of the mutants available in the most widely used mouse strain, C57BL/6.

The Mouse Phenome Database, MPD, based at the Jackson Laboratory, is a database of mouse strain characterizations (Mouse Phenome Project, 2007). Phenotype and genotype data presented on this web site are contributed by researchers or obtained from open public sources. The database is a collection of baseline phenotypic data on commonly used and genetically diverse inbred mouse strains and enables investigators to identify appropriate strains. It continues to evolve and its potential immeasurable. Information on the website is arranged by strain, project, investigator, intervention, and subject area.

Related, and also found on the Jackson Laboratory website, is the Mouse Genome Informatics (MGI) site (Mouse Genome Informatics, 2008). It provides integrated access to data on the genetics, genomics, and biology of the laboratory mouse.

Searching: Best model

When considering the most appropriate model, be it an animal model or non-animal alternative, the approach to searching the literature is murky. In addition to the mouse-focused sites above, there exist other resources, from general to specific, each with its own strength and purpose. Each website and database may be useful, dependent on the need, the study, or the disease. Among these web-based resources are AltWeb, in particular the Pain and Humane Endpoints databases (Center for Alternatives to Animal Testing, 2007); ANZCCART, in particular the Fact Sheet on Pain (Australian and New Zealand Council for the Care of Animals in Research and Teaching, 2007); Ensembl Genome Browser (Ensembl,

2007); International Mouse Strain Resource, IMSR (International Mouse Strain Resource, 2007); Mouse Models of Human Cancers Consortium (National Institutes of Health, 2007b); Isogenic Info (Festing, 2007); and, the UKCCCR Guidelines (UK Coordinating Committee on Cancer Research, 1997).

There are a few resources offering unusual depth that warrant particular mention, including the "Alternatives" section on the Animal Welfare Information Center (AWIC) website (USDA, 2007). It provides information and links to techniques, methods, procedures, and models. As new resources become available, AWIC may be relied on to evaluate them and post accordingly, keeping us up to date on the latest developments.

The Institute of Laboratory Animal Research (ILAR) hosts an Animal Models and Strains database that is both searchable and uniquely helpful (ILAR, 2007). It is supported by the National Academy of Sciences, providing scientific and reliable search results.

NIH Model Organisms for Biomedical Research organizes and presents nonmammalian models and the related research. (National Institutes of Health, 2007c) The site provides ideas and inspiration, as well as resources and information. It reports current studies and very often includes access to specialized databases.

The National Cancer Institute (NCI) provides access to an immense library of information, including specific resources focused on mouse models and resources (National Cancer Institute, 2007a). Specifically, the Mouse Models of Human Cancers Consortium (MMHCC) Emice website has a Mouse Model Database among its many databases, resources and projects (National Cancer Institute, 2007b). The NCI MMHCC also supports the related Mouse Repository, a searchable database of strains and related health reports (National Cancer Institute, 2007c).

The Jackson Laboratory (JAX) collection of websites includes a variety of resources and databases (Jackson Laboratory, 2007). Primary among those are the sites under Mice and Services (Mouse Strain Information, Mouse Service Information, and Mice Literature), Research Resources, and Mouse Genome Informatics.

Discussion

As described previously, there are numerous appropriate and valuable information resources and databases. Identifying which to use in any particular case, however, can be a challenge. The UC Davis Center for Animal Alternatives Information webpage, *Bibliographic Searching Tools on Disease Models*, was created to assist the scientist with their search efforts. (University of California, Davis, 2007b) The online interactive resource is intended as a helpful user-friendly guide. It offers search examples and suggested options, acting as a springboard for consideration and identification of the best model. It is also functions as an online tool in conjunction with the book Sourcebook of Models for Biomedical Research (Conn, 2008). The web-based resource is arranged into three sections. The first section helps to identify potential models and alternatives, and is followed by two sections, one arranged by disease and the last arranged by specific models used in biomedical research.

The first section on animal model selection provides access via links to various databases and resources that encourage the consideration of the most appropriate model for that particular study. The following section is arranged by disease; for example, next to the Alzheimer's entry are links with embedded searches to help identify potential models used in Alzheimer's research. These stored searches are available in four publicly available databases: PubMed, NCBI, Toxline, and DTIC. Individual links are also provided in lists of potentially useful databases and resources, both free---such as PrimateLit and FishBase, and proprietary---such as Aquatic Sciences and Fisheries Abstracts and Zoological Record (University of California, Davis, 2007b).

The section arranged by specific models lists research models, like fruit flies, fish, and mice, followed by suggested free databases, relevant proprietary databases, and free embedded searches. For example, with the model "sea urchin embryo", the stored searches are in the PubMed, Toxline, and HSDB databases, and include the subject areas of cellular activity, cellular and early development, transcription, and human and animal toxicity studies. (University of California, Davis, 2007b) Once these searches are initiated, they can then be expanded or narrowed as needed. The embedded search links provide the first step, providing immediate access and immediate search results.

The website, from its organization and arrangement to the embedded searches, offer the scientist a new way to look at research, and a prompt to reconsider what might be the best model for their proposed research.

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References

Allen, T. (2007) A guide to bibliographic and specialist databases and websites for alternative methods in life science research, 6th World Congress on Alternatives and Animal Use in the Life Sciences, oral presentation, August 22, Tokyo, Japan.

Australian and New Zealand Council for the Care of Animals in Research and Teaching. (2007) ANZCCART: Fact Sheets, Website accessed January 2, 2008, http://www.adelaide.edu.au/ANZCCART/publications/facts.html

Barthold, S.W. (2004) Genetically altered mice: Phenotypes, no phenotypes, and faux phenotypes, Genetica, 122(1), 75-88.

Berg, A.L. and Bohlooly, Y.M. (2006) The program for phenotyping of genetically modified animals at AstraZeneca, Experimental and Toxicological Pathology, 57(5-6), 383-4.

Bhogal, N. and Combes, R. (2006) The relevance of genetically altered mouse models of human disease, Alternatives to Laboratory Animals: ATLA, 34(4), 429-54.

Center for Alternatives to Animal Testing. Johns Hopkins University. (2007) AltWeb: Databases, Website accessed January 2, 2008, http://altweb.jhsph.edu/databases.htm

Conn, P.M. (Ed.) (2008) Sourcebook of models for biomedical research, Humana Press, Totowa, NJ.

Ensembl. (2007) Ensembl Genome Browser, Website accessed January 2, 2008, http://www.ensembl.org

Festing, M.F.W. (2007) Isogenic.Info, Website accessed January 2, 2008, http://www.isogenic.info

Grune, B., et al. (2004) Report and recommendations of the international workshop "Retrieval approaches for information on alternative methods to animal experiments", Altex, 21(3):115-127.

ILAR. (2007) ILAR: Institute for Laboratory Animal Research, Animal models and strains, Website accessed January 2, 2008, http://dels.nas.edu/ilar_n/ilarhome/models.shtml

International Mouse Strain Resource. (2007) IMSR: International Mouse Strain Resource, Website accessed January 2, 2008, http://www.informatics.jax.org/imsr

Jackson Laboratory. (2007) The Jackson Laboratory, Website accessed January 2, 2008, http://www.jax.org/

Mouse Genome Informatics. (2008) MGI: Mouse Genome Informatics, Website accessed January 2, 2008, http://www.informatics.jax.org/

Mouse Phenome Project. (2007) MPD: Mouse Phenome Database, Website accessed January 2, 2008, http://www.jax.org/phenome

National Cancer Institute. (2007b) Mouse Models of Human Cancers Consortium: Emice, Website accessed January 2, 2008, http://emice.nci.nih.gov/

National Cancer Institute. (2007c) Mouse Models of Human Cancers Consortium: Mouse Repository, Website accessed January 2, 2008, http://mouse.ncifcrf.gov/

National Cancer Institute. (2007a) NCI, Website accessed January 2, 2008, http://www.cancer.gov/

National Institutes of Health. (2007c) Model Organisms for Biomedical research, Website accessed January 2, 2008, http://www.nih.gov/science/models/

National Institutes of Health. (2007b) Mouse Models of Human Cancers Consortium, Website accessed January 2, 2008, http://www.nih.gov/science/models/mouse/resources/hcc.html

National Institutes of Health. (2007a) NIH Knockout Mice Project (KOMP), Website accessed January 2, 2008, http://www.nih.gov/science/models/mouse/knockout/

National Library of Medicine. (2008) MeSH: Medical Subject Heading Terms, Website accessed January 2, 2008, http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh

Savenije, B. (2007) Searching for alternatives: a service by the 3R Research Centre, 6th World Congress on Alternatives and Animal Use in the Life Sciences, oral presentation, August 22, Tokyo, Japan.

UK Coordinating Committee on Cancer Research. (1997) UKCCCR guidelines for the welfare of animals in experimental neoplasia (second edition), London, Website accessed January 2, 2008, http://www.ncrn.org.uk/csg/animal_guides_text.pdf

University of California, Davis. (2007a) Mouse Biology Program, Website accessed January 2, 2008, http://mbp.compmed.ucdavis.edu/

University of California, Davis. (2007b) University Library. UCDavis Center for Animal Alternatives Information. Bibliographic searching tools on disease models, Website accessed January 2, 2008, http://lib/dept/animalalternatives/diseasemodels.php

USDA. (2007) National Agricultural Library. Animal Welfare Information Center: AWIC, Website accessed January 2, 2008, http://awic.nal.usda.gov

Yoshiki, A. and Moriwaki, K. (2006) Mouse phenome research: Implications of genetic background. ILAR Journal, 47(2), 94-102.