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Where's the mouse info?

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The laboratory mouse has long been the species of choice for many animal models of human diseases. In part, this is due to the long-standing genetic resources available for the mouse, but now also the development of powerful new techniques for generation of mutations, analysis of complex traits, and high throughput data gathering, have made the mouse the preeminent model for the study of human biology and disease.³⁴

With the completion of the mouse genome sequence, it is now possible to rapidly generate knockouts and knock-in mutations anywhere in the genome, either constitutively or conditionally using *Cre*- and *Flp*-mediated recombination, alterations in gene, or locus copy number. Complex trait analysis now permits the underlying spontaneous genetic predisposition to multigenic diseases to be elucidated. The increased sophistication and miniaturization of physiological monitoring and diagnostic instrumentation mean that the depth of phenotype data that can be collected is unprecedented.

Parallel with this rise is the burgeoning need for “mouse pathologists”, veterinary or medical pathologists who can interpret the histopathologic changes that occur primarily in genetically engineered inbred strains of mice,^{8,36} an important aspect of mutant characterization generally referred to as “phenotyping” by molecular biologists and others. Both veterinary pathologists and MD pathologists are capable of performing these functions because of their basic training in mammalian anatomy, normal histology, and pathology. Many pathologists are hesitant to undertake mouse pathology phenotyping because they did not obtain specific training in mouse biology and pathology (although a number of specialized courses are available in the US and elsewhere),⁴¹ or they are insecure with the fundamental anatomical differences between mice and the domestic mammals/humans that they are familiar with. Anatomical, phenotyping, and both generalized and specific pathology information, can be found in many books and review articles^{2-4,7,11-14,17-24,27-33,38,40,42,46,47} or, using the modern approach, a great deal of this information is actually online⁶ or can be searched for in Pubmed. The major topics of interest to pathologists trying to evaluate mutant mice can be broken down into 1) access to software for record keeping, 2) phenotyping approaches, 3) general information on the biology, pathology, or other special aspects of mice, and lastly, 4) where to actually find the

mice in repositories around the world. Rather than list or describe all of the current online resources, we present here the key website addresses of major databases in the field but also on those that identify and coordinate these types of websites.

While many websites host lists of URLs, there are a few that are specifically designed to coordinate this effort into a single site. The Mouse Resource Browser (MRB) (<http://bioit.fleming.gr/mrb>)⁴⁸ is an example of a database that specifically identifies most active websites dealing with mouse biology, pathology, phenotyping, genetics, etc. and provides links and technical information on the resources. MRB currently hosts a list of 223 resources divided into 45 categories. The information contained about each resource is manually curated and divided into four separate areas. The “General” section of MRB contains information such as URL(s), contact information, and related links. The Ontologies & Standards tab includes information regarding implementation by a resource of internationally accepted standard ontologies and minimum information standards for biological investigations.⁴⁵ MRB hosts a collection of these ontologies for download, both within and outside the Open Biological Ontologies framework,³⁷ together with an index of minimum information standards for experimental descriptions. The third section “Technical” holds valuable technical information for each resource such as the server technology used, relational database management system(s) utilized, programming language(s) of implementation, schema descriptive documents or actual database dumps and most importantly information on a resource’s programmatic access, the integration and interoperability services. Whilst the latter are unlikely to be of immediate interest to pathologists, as more data mining and manipulation tools become available programmatic access to this information is increasingly important. An excellent example is shown by the Mouse Disease Information System (MoDIS) data capture tool described below.

Many of the sites listed by MRB offer valuable resources for information but several are not complete, offer only selected information on a subject, may provide services only, or no information online for free. Pubmed (<http://www.ncbi.nlm.nih.gov/sites/entrez?holding=janllib>) can also serve as a great resource for publications on mouse biology and pathology with many papers older than one year retrievable as PDF files for no charge in many but not all journals.

In 2006 several International projects were initiated with the goal of knocking out all of the protein coding genes in the mouse genome. The International Knockout Mouse Consortium (IKMC) represents four major high-throughput gene-targeted mutagenesis programs currently underway around the world: the NIH-sponsored Knockout Mouse Program (KOMP) and state-funded Texas A&M Institute for Genomic Medicine (TIGM) in the U.S., the Genome Canada-funded North American Conditional Mouse Mutagenesis (NorCOMM) Program in Canada, and the European Union Conditional Mouse Mutagenesis (EUCOMM) Program in Europe.^{1,9} This is rapidly generating a large number of mouse based resources, including phenotype and gene function data, and collections of bioresources (knockout mice, embryonic stem (ES) cell clones, targeting vectors).

The IKMC is currently served by the KOMP-DCC (Data coordination centre; <http://www.knockoutmouse.org/>) and bioresources distributed through the KOMP repository (<http://www.komp.org/>). The EUCOMM project database also can be queried at <http://www.eucomm.org/> through which EUCOMM derived mice and ES cells can be ordered. In the imminent future the IKMC International Data coordination centre will provide a portal through which all these resources and contextual information can be accessed.

Information on mouse biology in general and pathology specifically, can be found in many locations. The Mouse Genome Informatics (MGI, <http://www.informatics.jax.org/>)¹⁰ is the

gold standard for all aspects of mouse biology and genetics from which several very specialized databases can be accessed including the Mouse Phenome Database⁵ mentioned above as well as the Mouse Tumor Biology Database (<http://tumor.informatics.jax.org/mtbwi/index.do>).²⁵ One of but the major values of MGI is to provide a centralized reference for the latest gene names and symbols for spontaneous and genetically engineered mouse genes. It also provides mouse genetic nomenclature standards and links to have new gene symbols assigned. This is absolutely essential for accurate descriptions of mouse models of human diseases and is essential to follow when submitting manuscripts to major journals including this one.⁴³ A major international effort to not only assemble digital images of lesions that occur naturally or as a result of genetic manipulation but also to develop a standardized nomenclature for mouse pathology terms (MPATH) is available through Pathbase (<http://www.pathbase.net/>).³⁵ This can be linked to diagnostic or phenotyping programs to provide a “virtual second opinion”,^{39,44} a great training tool for pathologists new to the field.

Repositories have been developed all over the world to maintain live colonies of laboratory mouse strains, stocks, and mutations. Many also cryopreserve embryos, sperm, embryonic stem cells, DNA, and other biological specimens. Most vendors, both commercial and nonprofit, have websites that detail what they distribute. However, the International Mouse Strain Resource (IMSR; <http://www.informatics.jax.org/imsr/index.jsp>) provides a centralized resource on where to start to look for specific strains. In addition, information can be found on inbred strain history, derivation, and specific attributes in a website titled Inbred Strains of Mice and Rats (http://www.informatics.jax.org/external/festing/search_form.cgi).

Record keeping is always an issue with diagnostic workups and even more so for large scale, high throughput, phenotyping programs. On a small scale, the Mouse Disease Information System (MoDIS) (<http://research.jax.org/faculty/sundberg/index.html>) is a tool that is available at no cost and works on the Access database (Microsoft, Redman, WA).^{39,44} MoDIS is currently under development as a data capture tool for large international phenotype databases (<http://www.euromphenome.org>). Other large-scale databases to collect and analyze physiological phenotyping data are in development but not yet publically available. The MoDIS software was designed by pathologists for pathologists and integrates a “virtual second opinion” option that is particularly useful for pathologists entering the field.^{39,44} When installed properly and linked to Pathbase (see below, <http://www.pathbase.net/>), it will automatically code diagnoses. When the links are followed one can find an expert definition, and from there links can be followed to representative photomicrographs of similar lesions reported in genetically engineered mice (GEMs) or inbred strains (natural disease) by other pathologists participating in the database curation. Additional free software programs are available for mouse colony management (<http://colonymanagement.jax.org/>).

Phenotyping evaluations other than anatomic pathology, including but not limited to clinical pathology, behavioral, and physiological phenotyping have been developed especially for laboratory mice. This is further expanded by a wide range of highly specialized imaging devices. Information on how to perform these types of studies can be found in the Mouse Phenome Database (<http://phenome.jax.org/pub-cgi/phenome/mpdcgi?rtn=docs/home>), which also includes the data generated,⁵ and the Europhenome Mouse Phenotyping Resource (<http://www.euromphenome.org/>).²⁶ Systematic phenotyping of mutant mice has now become an urgent priority for the community and through the efforts of the International Mouse phenotype database integration consortium (Interphenome)¹⁵ much of this information is being made available though the databases cited above. A review of phenotypic databases can be found in Hancock et al. (2007).¹⁶

It is beyond the scope of this note to list all resources but The Mouse Resource Browser (MRB, <http://bioit.fleming.gr/mrb/>), as described above, was developed to serve as a centralized site for finding this information online. The major sites in the field, based on their constant updating and strict adherence to mouse nomenclature standards, are listed here to provide starting points for those entering the field.

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