Mouse Models of Human Cancers Consortium (MMHCC) from the NCI

Cheryl Marks

Through extensive discussion with a broad representation of researchers from the cancer research community, the National Cancer Institute (NCI) identified the crucial need for vastly improved animal model systems to inform all aspects of cancer research and to improve patient outcomes. The resulting collaborative mouse cancer modeling program, the NCI-Mouse Models of Human Cancers Consortium (NCI-MMHCC), began in September 1999. For the last decade, the Consortium has combined expertise from many aspects of basic, translational, clinical, and human and mouse genetics research to derive entirely new generations of genetically engineered mouse models (GEMMs) of cancer for all major cancers, and for many malignancies for which animal models did not previously exist. In June 2009, the NCI will renew this cooperative group to address the new challenges of ensuring that mouse models are appropriately and effectively integrated into discovery and translational cancer research.

Mouse models offer abundant research opportunities because the newest GEMMs are excellent simulations of the corresponding human diseases. Researchers use them for in-depth cross-species comparisons of the molecular, biological and functional properties of cancers. These analyses produce important discoveries about human biological markers that can distinguish among previously unrecognized patient groupings, affording better patient stratification for therapy and disclosure of novel targets. The application of a variety of in vivo imaging modalities to GEMMs reveal functional and molecular changes during cancer initiation, progression, invasion, metastasis and response to therapy, heralding a new era of discovery for early detection and for validating surrogate markers of response. Testing standard-of-care therapy in GEMMs illustrates how well these models reflect clinical outcome and the heterogeneity of the tumor response. Sophisticated mouse genetics resources enable a more thorough understanding of how interactions among genes and environmental effectors contribute to cancer susceptibility, disease progression, response to interventions and the potential toxicities of those interventions.

The breadth of research areas within the Consortium program will serve to connect its science to other research constituencies in cancer susceptibility, biology, prevention and therapy. Within the Consortium, groups working by disease site will also provide outlets for communication with the broader community. During the decade of support for this program, the Consortium has worked with the NCI Center for Bioinformatics and Information Technology to develop a communications and informatics infrastructure to convey progress in animal modeling and their applications to cancer research. This infrastructure now enables the merger of preclinical research and agent testing under the aegis of the Cancer Biomedical Informatics Grid (caBIG). The next stage of development involves integration of preclinical research with outcomes from NCI-sponsored clinical and prevention trials, and of mouse genetics with epidemiological research. An integrated infrastructure will permit the development of appropriate imaging strategies, the discovery of surrogate markers prior to the initiation of clinical trials, and patient stratification. The possible outcomes of this integrated approach will be improved prognosis, novel combination therapies and response biomarkers, and reliable means to define when to discontinue a particular treatment.

The bioinformatics resources that the NCI supports include a cancer models database (http://cancermodels.nci.nih.gov), containing information on more than 4700 mouse, rat and zebrafish models; a histology images database (http://cancerimages.nci.nih.gov) of mouse and corresponding human tumors; a laboratory information management system (http://caelmir.compmed.ucdavis.edu) for individual animal drug testing data; and the *e*MICE website (http://emice.nci.nih.gov) that houses links to all the NCI's preclinical models programs and information resources. The NCI Mouse Repository (http://mouse.ncifcrf.gov) deploys fully developed mouse cancer models and 'tool' strains free-of-charge to scientists worldwide.

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Congratulations to recent DMM Research Presentation Grant awardees

DMM Research Presentation Grants provide $1000/£500 to the first named author of a Research Article or Research Report that has been approved for publication in DMM. The grants are offered for a limited time to contribute towards travel and other expenses incurred by the author in presenting the work from their DMM publication at a major meeting. Recent recipients of this grant include **Cristina Santoriello** and **Mikala Egeblad**.

Dr Egeblad recently presented her work, which uses spinning disk confocal microscopy to understand the dynamics of host cells in tumors using mouse cancer models. At the American Association for Cancer Research's (AACR) Special Conference on

Mouse Models of Cancer, she showed how this new technology reveals differences in cell behavior in different parts of an in vivo tumor. This technology allows for a real-time look into the tumor microenvironment and is now being extended to understand the response of cancer and host cells to drug treatment.

Dr Santoriello uses zebrafish to model Costello syndrome, a rare genetic disease that results from activating mutations in the *H-RAS* gene. She will use the grant award to present her work at the 16th International Society of Developmental Biologists Congress in September. She found that transgenic fish that express oncogenic *H-RAS* throughout the germline develop a complex phenotype resembling that of Costello syndrome. Along with her colleagues, she demonstrated that some of these phenotypes are the result of oncogene-induced senescence, which affects mature proliferating cells in the heart and brain – two of the most affected organs in Costello patients. This suggests that an oncogene-induced response triggers cellular senescence during development, which might contribute to brain and cardiac defects in Costello patients.

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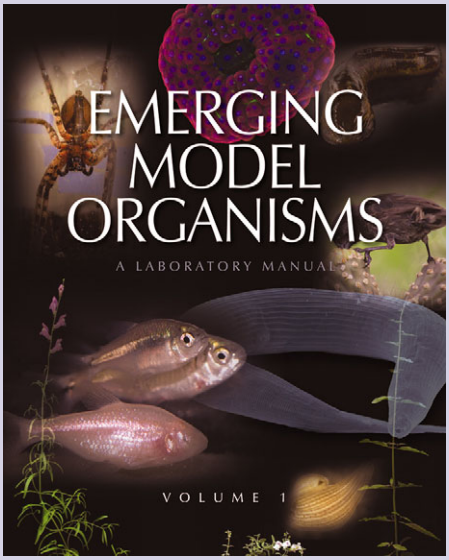
USEFUL RESOURCES

New models made accessible for the masses

Emerging Model Organisms is a laboratory manual that will help scientists expand their work to new and relevant genetic or physiologic systems. This new book presents profiles and protocols for a wide variety of model organisms that are anything but ordinary. Each of the 23 chapters in Volume 1 focuses on a particular organism or group of related organisms, and begins with discussion of the organisms' background, utility in research, distribution sources and husbandry information. Key protocols on maintaining and working with the organism are provided. These detailed instructions allow the reader to have quick access to the essential information that is necessary for using these unique models. Additional resources include information on related species, genomic resources and Internet databases.

The first volume includes chapters on animals ranging from comb jellies (Ctenophora) and planarians, to Japanese quail and opossum (*Monodelphis domestica*). Chapters on plants, such as the moss *Physcomitrella patens* and the tomato *Solanum lycopersicum* are included as well. Organisms planned for inclusion in Volume 2 include Aplysia, ants, squid and rabbit.

The chapters in this book are also being published in instalments in the journal *Cold Spring Harbor Protocols. CSH Protocols* is only available by institutional subscription, but several articles that are featured in this series of Emerging Model Organisms are freely available online each month. More information can be found at: www.cshprotocols.org/emo



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