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Validation of transgenic mammary cancer models: goals of the NCI Mouse Models of Human Cancer Consortium and the mammary cancer CD-ROM⋆

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The generation of genetically altered mouse models for human cancer has provided tremendous insights into the mechanisms of oncogenesis and systems for pre-clinical testing of chemopreventive and chemotherapeutic agents. It has been 18 years since the first published report of a transgenic mouse model for mammary cancer in which the *myc* oncogene was over-expressed in the mammary epithelium using the mouse mammary tumor virus (MMTV) long terminal repeat. Since the seminal publication of that study, the number of transgenic mouse models of mammary cancer alone has well exceeded 100 and continues to grow. Indeed, much work still needs to be done to further define the interactions of multiple genes in the process of oncogenesis through the crossing of transgenic mice which harbor different genetic alterations.

While such studies identify oncogenic mechanisms, it is critical that these models be assessed for their fidelity in serving as surrogate systems to understand and treat human breast cancer. The concept of transgenic model validation is idealized in that no single mouse model will likely capture all features of human mammary cancer to satisfy all of the criteria of molecular biologists, pharmacologists or clinicians. To this end, a major goal of the National Cancer Institute (NCI) Mouse Models of Human Cancer Consortium (MMHCC) is to attempt to fully characterize important genetically engineered mouse models of human cancer to define in what ways such models are similar or unlike human cancers.

The MMHCC was established by the NCI in 1999 and is composed of 20 cooperative agreement grants supporting over 100 investigators from over 40 institutions with the primary purpose of developing better models for various forms of human cancer and validating their similarities to the human diseases. In addition, a major effort is underway to improve the dissemination of information and research materials to the entire scientific community through the development of a comprehensive website (http://emice.nci.nih.gov/) and a repository of mouse cancer models (http://emice.nci.nih.gov/). As the MMHCC website grows, it will include a comprehensive and searchable cancer-models database, information, and activities related to organ-site-specific cancers and advanced technologies, useful teaching tools and protocols and links to other important sources of information related to transgenic and knock-out technologies, including the MMHCC cancer-models repository.

The first step in the process of model validation has been to assess the histopathology of mouse models for human cancers and relate the types of lesions which develop in mice to those which occur in the human disease. This was the goal of the Annapolis Workshop on the Comparative Pathology of Mouse

⋆CD-rom included in this issue.

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Models of Mammary Cancer sponsored by the NCI in which both veterinary and human pathologists reviewed over 100 mouse models of breast cancer. The work presented in the CD-ROM (*Mammary Cancer in Humans and Mice – A Tutorial for Comparative Pathology* by Cardiff et al.) included with this issue of *Transgenic Research* is a compilation of the analyses of the Annapolis Workshop and provides a comprehensive overview of the types of lesions observed in a large number of mouse mammary cancer models, a new system for lesion classification and a comparison to lesions found in human breast cancer.

Based upon the success of the Annapolis workshop, the MMHCC is sponsoring similar workshops to better define the histopathology of cancers from numerous organ sites in order to standardize nomenclature and relate the mouse lesions to those of human cancers. The results of these workshops will be published on the MMHCC website and scientific journals, and made available as CD-ROMs. It is anticipated that in the near future, other measures of model validation will be assessed, including gene expression profiles, genomic alterations, and responses in the setting of pre-clinical testing.

The MMHCC is committed to enabling the entire mouse modeling community to benefit from new technologies, reagents, and information to improve models for human cancers. Databases related to phenotypes, histopathology, gene expression profiling, genomics, and pre-clinical testing will be developed and integrated to give all scientists a comprehensive characterization of mouse models and how they relate to human cancer. All members of the scientific community are strongly encouraged to take full advantage of these new resources.