

INVITED PRESENTATION

Chemical Mutagenesis of the Mouse Germline: New Models for Genetic Diseases and for Dissecting Basic Biological Processes. E. M. Rinchik,^{1,2} D. R. Miller,¹ D. K. Johnson,¹ C. T. Culiati,¹ E. J. Michaud,¹ and members of the Tennessee Mouse Genome Consortium. ¹Life Sciences Division, Oak Ridge National Laboratory, PO Box 2009, Oak Ridge, Tennessee 37831-8077; ²Department of Biochemistry, Cellular, and Molecular Biology, University of Tennessee, Knoxville, TN 37996.

Phenotype- and gene-driven mouse-mutagenesis strategies are being used for functional annotation of DNA sequence and for dissecting complex biological pathways. *N*-ethyl-*N*-nitrosourea (ENU)-induced, point mutations are being recovered in chromosomal regions using marked chromosomal inversions. These strategies allow easy detection of chromosomally pre-mapped recessive mutations, including deleterious ones, without any molecular genotyping; and yield numerous pedigrees, each having multiple mice homozygous for the same mutant chromosome, for broad, multi-site screening for neurobehavioral defects (by the Tennessee Mouse Genome Consortium; <http://tnmouse.org>), for ascertaining statistically sensitive phenotypes, and for establishing aging colonies to be screened for later-onset recessive abnormalities. Complementing this “regional”-mutagenesis approach is DNA sequence-driven recovery of ENU-induced allelic series of mutations in any gene in the genome. We have generated a bank of DNA, tissues, and sperm from 4,000 individual C57BL/6J mice, each heterozygous for a different load of paternally induced ENU point mutations. High-throughput heteroduplex analysis is used to identify mutations in pre-selected genes, with mutant mice being recovered from the corresponding frozen sperm. Thus, this “Cryopreserved Mutant Mouse Bank (CMMB)” is providing an important resource in an integrated genetic/genomic approach for whole-organism functional annotation of the mammalian genome. [Research sponsored by the Office of Biological and Environmental Research, US Dept of Energy, under contract DE-AC05-00OR22725 with UT-Battelle, LLC; and by the National Institutes of Health (MH61971 and ES11023).]