

Screening for age-onset abnormal phenotypes and increased longevity in ENU-mutagenized mice.

Dabney Johnson<sup>1</sup> and The Tennessee Mouse Genome Consortium

<sup>1</sup>Life Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831

The Tennessee Mouse Genome Consortium, supported by a cooperative of NIH institutes, is performing a large-scale, regional ENU-screen for mice displaying recessive abnormalities in behavior and the central nervous system. Point mutations induced by ENU likely mimic subtle human-to-human genetic variation, including variation that modifies longevity and age-related functional decline. The design of our screen offers an opportunity to maintain many parallel cohorts of animals homozygous for the same mutagenized chromosome, allowing for a screen for heritable differences in how individuals age. For each pedigree, animals are screened at seven weeks after birth. In addition, eight naïve animals from each pedigree are set aside for rescreening at 18 months. Age-onset phenotypes of interest include early morbidity, mortality, and progressive neuromuscular or neurological abnormalities. The first of 150 pedigrees will reach 18 months of age by Fall, 2002, with a steady-state of additional pedigrees analyzed thereafter. Germ cells from each pedigree are cryopreserved early so that late-onset mutations can be recovered if fertility is compromised by age. We are likewise initiating a pilot study to evaluate aging pedigrees for increased longevity by maintaining 100 pedigrees for an additional 10 months. Growth-rate data will be collected for these very old pedigrees starting early in life and continuing until 28 months. Levels of insulin, Igf-1, cholesterol, and triglycerides, ability to maintain body temperature in the cold, and bone density and body-fat content will also be monitored.

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