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Laboratory of Experimental Animal Science

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The teaching staff in the Laboratory of Experimental Animal Science consists of a professor, associate professor and instructor. In addition, four postgraduate and four undergraduate students study on the basis of their own theme. We teach the experimental science concerned with disease mechanisms of animal models, the gene manipulation and the morphological analysis. Our current research theme are as follows :

1. The ability of a host to resist infection with a wide range of viral, bacterial and parasitic pathogens is strongly influenced by a lot of genetic factors. The *Bcg* gene on mouse chromosome 1 regulates priming/activation for antimicrobial activity. A candidate gene for *Bcg* expressed in macrophage has been identified as the natural resistance-associated macrophage protein (*Nramp 1*) by positional cloning and full-length sequence analysis. Macrophages are concerned with antimicrobial activity by numerous cytokine-induced nitric oxide (NO) production. We are investigating the relationships among antimicrobial activity, NO production and TNF- $\alpha$  contribution using *Nramp* congenic mice and TNF- $\alpha$  knock out mice.

2. The mouse *Mx 1* and *Mx 2* genes on chromosome 16 encode both interferon IFN- $\alpha/\beta$  inducible proteins which confer resistance to influenza virus and rhabdo virus infections, respectively. The standard laboratory mouse strains all carry the *Mx 1*<sup>-</sup> and *Mx 2*<sup>-</sup> alleles, and are therefore sensitive to the above virus infection. We searched several strains established from wild mice around the world, and found that almost wild-origin strains have *Mx 1*<sup>+</sup> and *Mx 2*<sup>+</sup> alleles by means of sequence analysis, reverse transcription polymerase chain reaction (RT-PCR)

and immunofluorescence staining. We are now studying the sequence analysis of exon and promoter region and the antimicrobial activity of *Mx 1*<sup>+</sup> and *Mx 2*<sup>+</sup> genes.

3. Jumbled spine and ribs (*Jsr*) is an autosomal dominant mutation that results in malformation of the axial skeleton. The vertebrae of mutant mice are shorter than those of normal mice and show various abnormalities. In addition, several ribs are fused at their proximal region because of fusion of thoracic vertebrae. We localized the *Jsr* mutation on distal chromosome 5 and constructed a high-resolution map. Based on histological analysis of mutant embryo, *Jsr* is hypothesized to be caused by abnormal development of primordial cells in the axial skeleton. We are now trying to clone the *Jsr* gene by positional cloning.

4. The sterility of interspecific hybrids such as mules and leopons, is a well-known phenomenon. In mice, the interspecific or intersubspecific hybrid sterility has been occasionally found in matings between laboratory mice and wild mice induced by Hybrid sterility (*Hst*) genes. One of them, *Hst-3*, which controls the sterility of interspecific hybrids between laboratory mice and *Mus spretus* originated from Spanish wild mice. For detailed analysis of this *Hst-3* gene, we made congenic mice C57BL/6-*Hst-3*. The aim of this study was to analyze the developmental breakdown during spermatogenesis in the sterile mice, and also to clone a novel gene associated with spermatogenesis by PCR-select subtraction method.

5. We found a new X-linked dominant mouse mutation, which exhibits phenotype such as hyperkeratotic skin, reduced viability, a tendency to be smaller and lighter weight than the normal sibs during weaning age in affected females, and prenatal lethality in affected males. An subspecific backcross between affected females and wild-origin strain males was designed to map the locus. This mutant showed no recombination

with microsatellite markers on cenromere of chromosome X. The gene position and phenotype of this mutant were very similar to those of *Td*. Therefore, the gene was designated as Tattered-Hokkaido (*Td<sup>ho</sup>*). Prenatal lethality of

male mutants was also investigated, and it was found that the male mutants died between E12.5 and E14.5. We are now studying the cause of death of male mutants.