Technology and Development Team for Mouse Phenotype Analysis

: Japan Mouse Clinic

[2008.4~]
[~2008.3: Shiroishi Research Collaborative Group]

Team Leader
Shigeharu WAKANA, Ph.D.

Goal

We will construct a systematic and comprehensive phenotypic platform including about 400 items based on our understanding of human diseases, and perform various phenotypic examinations of mouse resources mainly deposited in RIKEN BioResource Center. It is expected that new phenotypes evaluated as human disease model can be found from mouse resources (Tg and KO strains etc.) by Japan Mouse Clinic. We are cooperating with the Euro-American large-scale mouse phenotypic analysis project, European Mouse Disease Clinic (EUMODIC), and the Mouse Phenome Project (MPP) for international contribution to mouse phenotypic analysis improvement. Furthermore, we contribute to the infrastructure development of the mouse resources to upgrade the added value by the correspondence of mouse phenotypic data to the clinical data of human disease.

Activities

1. We have started the construction of a comprehensive and detailed phenotypic analysis platform "Japan Mouse Clinic", using two phenotypic pipelines: a fundamental/in-depth pipeline and a behavior-oriented pipeline, for mouse resources mainly deposited in RIKEN BioResource Center.
2. We are constructing standard operating procedures (SOPs) for phenotypic examinations and are cooperating with the Euro-American large-scale mouse phenotypic analysis project, EUMODIC, MPP, and so on. We contribute to the infrastructure development of the mouse resources to upgrade the added value by the correspondence of phenotypic data obtained from Japan Mouse Clinic to the clinical data of human disease.

Members

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Wakana, Suzuki(C), Shibukawa, Ozaki, Yamada, Nakamura, Kamiya
Shinogi, Nishimura, Yokoyama, Morita, Kushida

Kiyohashi, Matsumoto, Hachisu, Sugita, Iijima, Yamaguchi
Abe, Ogamino, Ishii, Ishizuka
Noto, Horie, Shimizu, Kojima, Murayama, Kawato
Nakajima, Aoki, Okada, Hashimoto, Harada

Specific Aims

1. Establishment of an entire system for Japan Mouse Clinic

We aim to establish the entire system for Japan Mouse clinic constructed using a sequence of processes, namely, receipt of examination requests, introduction and production of mouse resources, comprehensive phenotypic examinations, phenotypic data analyses, and publication of data in a website.

2. Construction of a pipeline for 'fundamental screen' in Japan Mouse Clinic

We aim to reconstruct standard operating procedures and develop statistical methods for pipeline 1 of Japan Mouse Clinic's 'fundamental screen' of open field test (7 weeks old), modified SHIRPA (8 weeks old), hematological test (9 weeks old), clinical biochemical test (11 weeks old), and pathologic test (26 weeks old), and 'in-depth screening' of rota-rod test (12 weeks old), auditory brainstem response (ABR) test (13 weeks old), insulin tolerance test (ITT) (13 weeks old), oral glucose tolerance test (OGTT) (14 weeks old), measurement of lactate in blood (17 weeks old), adipocytokine and clinical biochemical tests (glucose- and adipose-related) (18 weeks old), funduscopy (19 weeks old), electroretinography (ERG) (20 weeks old), blood pressure determination (21 weeks old), dual-energy X-ray absorptiometry (DEXA) (23 weeks old), and echocardiography (25 weeks).

3. Behavior-oriented pipeline

Generally, results of behavioral analyses are influenced by pretest experiences. Additionally, a multidirectional assay platform is necessary in the assessment of behavioral characteristics. Thus, it is necessary to construct pipeline 2, which is oriented toward behavioral characterization. Pipeline 2 is composed of behavioral test batteries A and B. Behavioral test battery A is a comprehensive behavioral assay platform that includes light/dark transition test (8 weeks), open-field test (9-10 weeks), rota-rod test (10 weeks), home-cage activity test (11 weeks), passive avoidance test (12 weeks), tail suspension test (14 weeks), hot-plate test (15 weeks), and tail flick test (17 weeks). If marked phenotypes are detected in behavioral test battery A, detailed analysis chosen from behavioral test battery B, which includes prepulse inhibition test (10 weeks), object exploration test (11 weeks), and fear conditioning test (12 weeks), will be performed. We reconstruct SOPs of these tests and a statistical analysis system.

4. Systematic introduction and production of mice using reproductive technologies

Introduction is performed by in vitro fertilization (IVF) using fresh or cryopreserved sperm from a male or cryopreserved embryo. In the carefully planned production of the mouse clinic individuals , we perform IVF or natural mating.

5. Development of accelerated speed congenic strains using reproductive technologies

Almost all genetically engineered mutant mice had a mixed 129 and C57BL/6 (B6) genetic background. To reduce genetic background effects in phenotyping, congenic strains are very important. In general, to transfer mutation onto a homogenous B6 background, we backcross mutant mice to B6 mice. However, using traditional methods (i.e., natural mating), this takes between 2 and 3 years. Therefore, to shorten the period, we have introduced reproductive technology, that is, round spermatid injection (ROSI; under the direction of Dr. Ogura of RIKEN BRC, Tsukuba Institute). This method can significantly reduce the period (congenic strain development in half the time) of creating congenic mouse strains. Furthermore, to investigate the genetic background of a congenic mouse strain by whole genome scan, we have established a rapid detection system by utilizing SNPs Genotyping using TaqMan assay.

6. Establishment of reliable sperm freezing/thawing new system for C57BL/6 strain

Most genetically engineered strains are maintained on the C57BL/6(B6) genetic background. However, the fertilizing ability of cryopreserved spermatozoa of strains with this background is very low compared with that of other inbred strains. The cause of this phenomenon is still unclear. Our aim is to develop a reliable sperm freezing/thawing new system for the C57BL/6 strain.

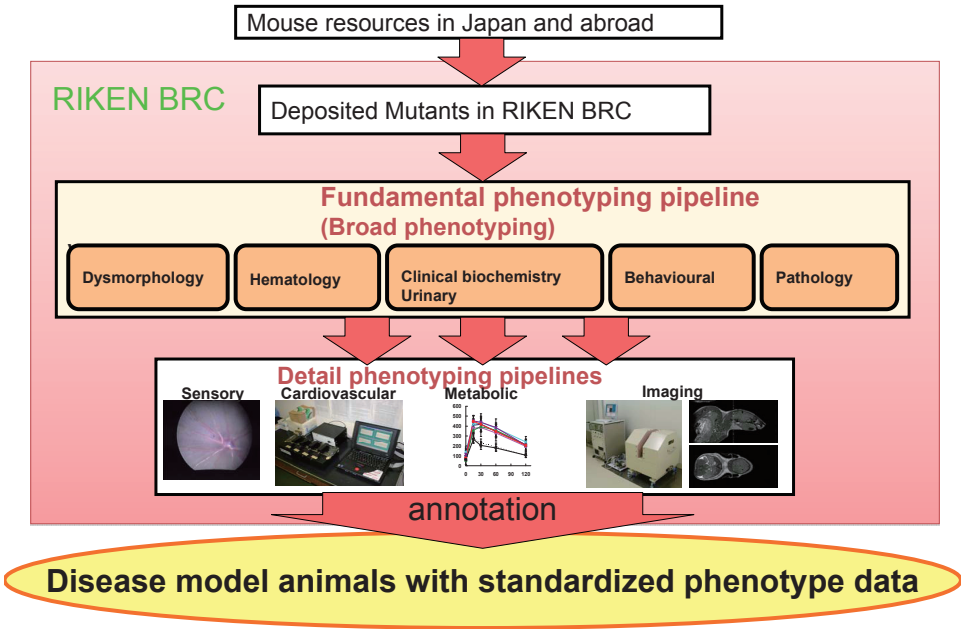

Figure 1. Overview of Japanese Mouse Clinic in RIKEN BRC

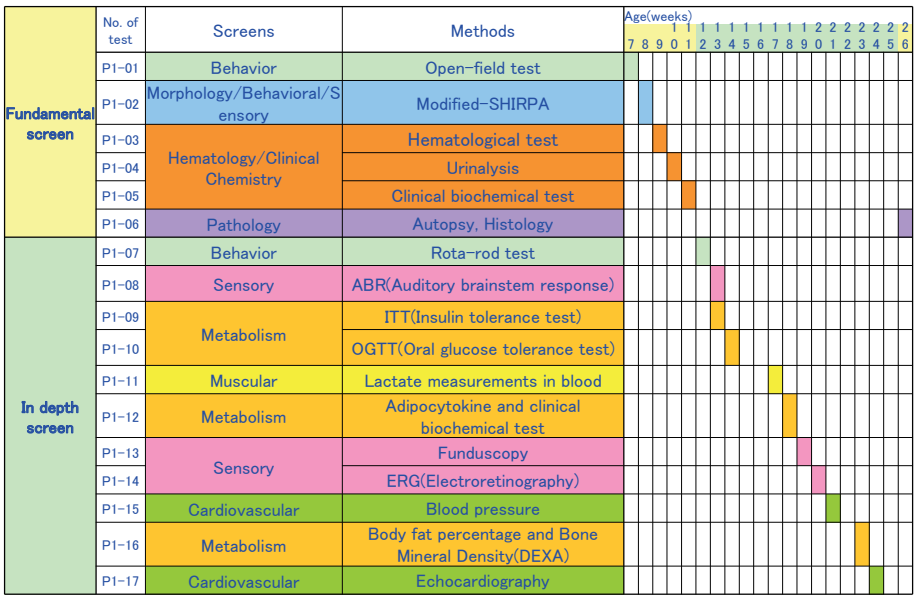

Figure 2. The workflow of pipeline 1 in Japan Mouse Clinic -fundamental screen-

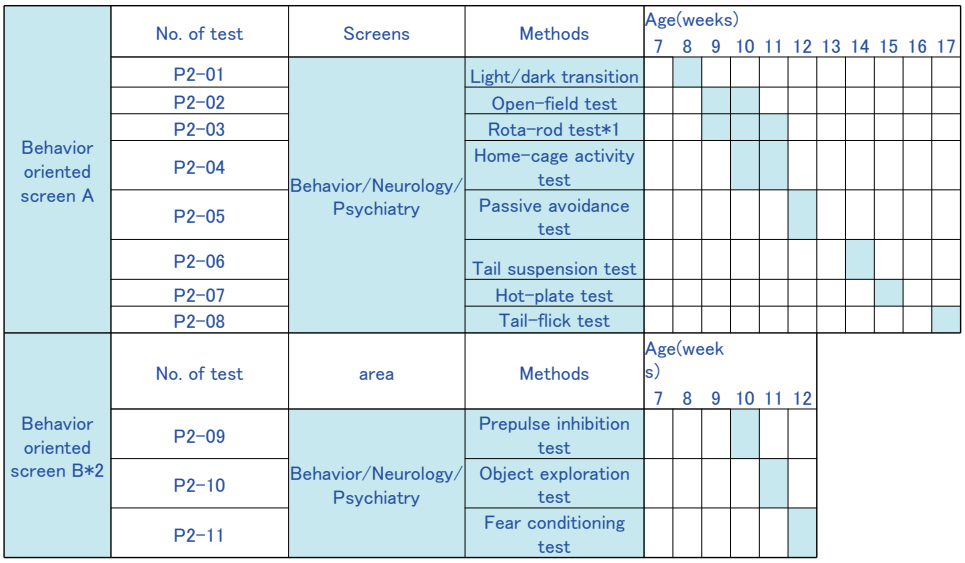

Figure 3. The workflow of pipeline 2 in Japan Mouse Clinic -behabioral screen-

Publications

【Original Papers】(*Peer reviewed journals)

1. Gondo Y., Wakana S., Masuya H.: "Trend in the large-scale mouse mutagenesis projects in the world." Jikkennigaku 26, 2130-2135 (2008) in Japanese.

2. Kaminuma E., Masuya H., Miura I., Motegi H., Takahashi K., Nakazawa M., Matsui M., Gondo Y., Noda T., Shiroishi T., Wakana S., Toyoda T.: "Objective evaluation measures of marker selection in large-scale SNP genotyping." Journal of Bioinformatics and Computational Biology, 6:905-917 (2008).*

3. Sakuraba Y., Kimura T., Masuya H., Noguchi H., Sezutsu H., Takahasi K.R., Toyoda A., Fukumura R., Murata T., Sakaki Y., Yamamura M., Wakana S., Noda T., Shiroishi T., Gondo Y.: "Identification and characterization of new long conserved noncoding sequences in vertebrates." Mammalian Genome (*in press*).*

Oral Presentations

【International Conferences】

1. Furuse T., Wada Y., Hattori K., Yamada I.,, Kushida T., Shibukawa Y., Masuya H., Kaneda H., Miura I., Kobayashi K., Shiroishi T., Yuasa S., Wakana S.: "Genetic and phenotypic analyses of an ENU-induced mouse mutant that shows AD/HD-like behavior." 22nd International Mammalian Genome Conference, Prague, Czech Republic, Nov. 2-5 (2008).

2. Masuya H., Tanaka N., Waki K., Kobayashi N., Toyoda T., Shiroishi T., Wakana S., Mizoguchi R.: "Statistical inference for mammalian omic data integration on the Semantic Web." 22nd International Mammalian Genome Conference, Prague, Czech Republic, Nov. 2-5 (2008).

3. Tanaka N., Waki K., Mizoguchi R., Kobayashi N., Toyoda T., Shibukawa Y., Kushida T., Yamada I., Furuse T., Wakana S., Masuya H.: "Development of interigent infrastructure for description of experimental protocols with Semantic Web technology." 22nd International Mammalian Genome Conference, Prague, Czech Republic, Nov. 2-5 (2008).

4. Wakana S., Suzuki T., Masuya H., Miura I., Kobayashi K., Kaneda H., Furuse T., Yamada I., Motegi H., Toki H., Inoue M., Minowa O., Tanaka N., Noda T., Shiroishi T., Obata Y.: "A plan of Japanese Mouse Clinic in RIKEN BRC." 22nd International Mammalian Genome Conference, Prague, Czech Republic, Nov. 2-5 (2008).

5. Suzuki T., Sato H., Ikeda K., Masuya H., Yokoyama H., Nishimura S., Kaneda H., Miura I., Kobayashi K., Toki H., Minowa O., Kurihara Y., Shiroishi T., Wakana S.: "Genetic analyses of inherited retinal degeneration model mouse in ENU mutagenesis." 22nd International Mammalian Genome Conference, Prague, Czech Republic, Nov. 2-5 (2008).

6. Ono T., Akamatsu N., Shitara H., Ishii R., Taya C., Yamada I., Shibukawa Y., Kushida T., Furuse T., Watabe K., Wakana S., Yonekawa H..: "Mice deficient in *alivin1/amigo2* show enhanced locomotor activity and reduced fear and anxiety." 22nd International Mammalian Genome Conference, Prague, Czech Republic, Nov. 2-5 (2008).

7. Murata T., Umemura N., Nakayama E., Yamaguchi T., Nakahara A., Karouji K., Ishitsuka Y., Kotaki H., Fukumura R., Makino S., Nakai Y., Toki H., Motegi H., Kaneda H., Noda T., Wakana S., Gondo Y.: "Molecular and mouse level analyses of multiple point mutations of beta-catenin gene obtained by ENU-based Gene-driven mutagenesis." 22nd International Mammalian Genome Conference, Prague, Czech Republic, Nov. 2-5 (2008).

【Domestic Conferences】 Total 28