Mutagenesis and Genomics Team

[2008.4~]

Team Leader

Yoichi GONDO, Ph.D.

Goal

Efficient mutagenesis technologies and mutation detection systems are indispensable for developing biological resources. Genomewide mutation discovery is also a key for the quality control of developed bioresources. We of the Mutagenesis and Genomics Team are developing a high-throughput, high-resolution mutation discovery system for detecting unknown newly arisen mutations in the whole genome of higher eukaryotes. At the same time, we are also developing useful mutagenesis infrastructure and technology and provide useful bioresources such as mouse models of human diseases to the research community. We are using a potent mutagen, ethylnitrosourea (ENU) to induce point mutations in the mouse genome. The mutation discovery system will enable us to detect randomly induced single-base substitutions in target genes. Contrary to ordinary genetics, it is called “reverse genetics” or “gene-driven mutagenesis”, which generates mutant mouse lines for understanding the biological function of the gene and genome. Mutant mice carrying mutations in candidate genes for human diseases allow us to elucidate the mechanism of the diseases.

Activities

1. Population and quantitative genomics research as a new information biology
   - 1-1. Development of a large-scale phenotype database
   - 1-2. Development of a large-scale genotype database
2. Development of mutant mouse library system
3. Development of high-throughput mutation discovery system
4. Development of next-generation gene-targeting system

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Specific Aims

1. Population and quantitative genomics research as a new information biology

Note: The most notable achievement during the initial stage of the team's research was the establishment of a high-throughput discovery system of ENU-induced point mutations in the whole mouse genome, which made it possible to conduct ENU-based gene-driven mutagenesis together with the mutant mouse library. These are described in Section 2-4 in detail.

As a new information biology, population and quantitative genomics research based on genetics was started to directly elucidate the biological function of the genomic DNA sequences at the organism level. Without prior knowledge of gene functions or complex interactions among genes and gene products at the molecular level, even a single base change (mutant genotype) may be directly reflected in the trait of the organism (mutant phenotype) based on genetics. Namely, "MUTANT" provides an ultimate tool as a *bona fide* biosimulator for the functional annotation of gene and genome networks.

To achieve our objectives, it is essential to construct a robust genomewide database for phenotypes as well as for genotypes on a large scale (Fig. 1). The Population and Quantitative Genomics Team (PQG), which is the origin of the Mutagenesis and Genomics Team, started their project by constructing a relational ORACLE database when the team was founded in April 2000 in the Bioinformatics Group (Project Director: Akiyoshi Wada, Ph.D.) of RIKEN Genomic Sciences Center (GSC). We have started our project to develop databases for the mouse mutagenesis programme as a model system. The ultimate objective is to directly associate the genotype with the phenotype and *vice versa*. The entire system will then be integrated to a knowledge-based database. Necessary infrastructures for these objectives are also developed, e.g., LAN, a server-client system, a comprehensive phenotype screening platform, and a high-throughput SNP

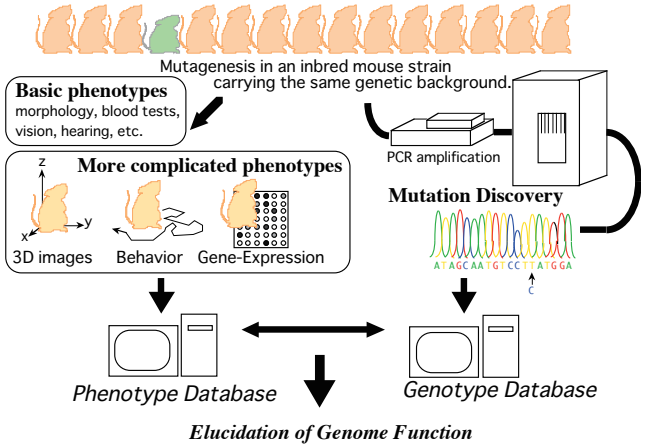

Figure 1. Population and Qunatitative Genomics Research as a new information biology.

and single-base substitution detection system. In particular, interdisciplinary collaborations with various research groups and researchers have been a key to conducting the project.

During the early phase of the team's activities, we established a base for the ENU-based gene-driven mutagenesis as a new reverse genetics. When the RIKEN GSC was reorganized in April 2005, the Population and Quantitative Genomics Team was integrated into the Functional Genomics Research Group (Project Director: Toshihiko Shiroishi, Ph.D.; Deputy Project Director: Yoichi Gondo, Ph.D.). It then focused and expanded on ENU-based gene-driven mutagenesis, which we now call next-generation gene targeting.

1-1. Development of a large-scale phenotype database

We have constructed three major database platforms as multiuser and multitask systems for ENU mouse mutagenesis to efficiently compile the phenotypic data of mutant mice: (1) mouse husbandry management system, (2) mouse mutant screening system and (3) mouse mutant management system.

The phenotype DB for the mouse mutagenesis project has thus far been compiled in a total volume of 2 million data points by screening 200 traits of approximately 20,000 G1 mice derived from ENU-treated male parents (G0). All the systems developed are now enhanced for practical application in the Japan Mouse Clinic.

(1) Mouse husbandry management system

By introducing a bar coding system, GUI platforms for compiling data directly from ~250 client computers to the ORACLE database have been developed. In the SPF-grade mouse area, the touch-panel method is occasionally used to facilitate data input, particularly the identification of each mouse, cage, shelf, rack and room by researchers and technical staffs. This package takes care of all processes such as purchase, identification labeling, husbandry, and mating.

(2) Mouse mutant screening system

In random ENU mouse mutagenesis, the primary identification of mutants depends on their phenotype. Thus, it is a phenotype-driven approach. After a large number of mutagenized mice are produced, candidate mice are then subjected to a series of phenotype screens for, at most, 78 months in the SPF facility. This software package helps researchers and technical staffs to conduct mouse identification, phenotyping experiments, data recording, and relocation of the mice for the next schedule. It also connects the stand-alone-type automated phenotype analysis system to the ORACLE database by constructing an automated data-transfer protocol. A 2D-image API package system for compiling and analyzing X-ray images and other 2D images has also been developed.

(3) Mouse mutant management system

When mutant candidates are nominated by the phenotyping platform, they are registered into the ORACLE database; then this software package manages the confirmation of the heritability and backcrossing for the mapping of the causative gene.

1-2. Development of a large-scale genotype database

In phenotype-driven ENU mouse mutagenesis, the mapping and positional cloning are the final steps in mutant establishment. Thus, we anticipated a huge lag to construct the genotype database. Therefore, we started to identify ENU-induced base substitutions in the G1 mouse genome independently without knowing any phenotype. RIKEN ENU mouse mutagenesis put emphasis on the isolation of mutant strains carrying late-onset phenotypes, which may well represent common human diseases. Such mutants may quickly die or become sterile immediately after the onset of phenotypes; thus, it is necessary to keep the strain as frozen sperm before the onset. For this reason, we decided to cryopreserve all the G1 sperm in liquid nitrogen tanks when they become 12 weeks old before we started the project. We

then started to isolate their genomic DNA as well. The dual archives of G1 sperm and genomic DNA are key resources for ENU-based gene-driven mutagenesis and we call them the mutant mouse library (Fig. 2). Details of ENU-based gene-driven mutagenesis will be described in Section 2 – 4.

At the same time, candidate mutants with their rough mapping data were accumulated by the phenotype-driven approach. We contributed to the identification of causative ENU-induced mutations and responsible genes by designing appropriate PCR primers and directly sequencing candidate genomic DNA sequences.

2. Mutant mouse library system

(1) Cryopreservation of G1 male sperm

We stored approximately 10,000 G1 males as frozen sperm in liquid nitrogen tanks. To cost-effectively store frozen sperm, we developed a new sample storage system with a high capacity (Fig. 3). In this storage system, we can store 51,200 samples with 3 sets of duplicates in a single 430-L liquid nitrogen tank.

(2) Genomic DNA extraction from G1 males

During or after the sperm cryopreservation, the testes or other organs of the G1 males were also frozen for genomic DNA extraction. We have already isolated genomic DNA from about 8,000 G1 males as the genomic DNA archive (Fig. 2). To apply various mutation discovery systems, the isolated genomic DNA samples were bar-coded and placed into 96-well plates. To handle a large number of samples and plates, we introduced robotics systems.

3. High-throughput mutation discovery system

Even in an era of the post-human genome project, it still often takes years to identify responsible genes and causative mutations in the human genome by positional cloning. It is exactly the same situation for the mouse genome. To enhance the pace of mutation discovery as well as to make ENU-based gene-driven mutagenesis, which was considered to be impossible at that time, feasible and practical, we have been trying to construct a high-throughput mutation discovery system by introducing and comparing several point-mutation detection systems (Fig. 4).

To discover newly induced single-base-pair substitutions in

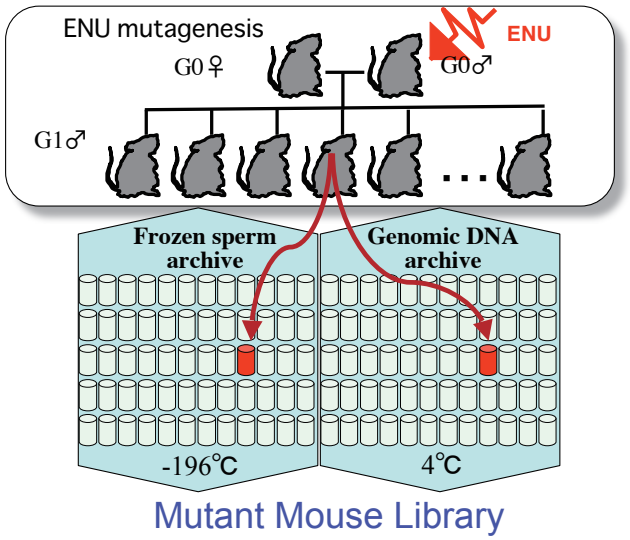

Figure 2. Construction of mutant mouse library

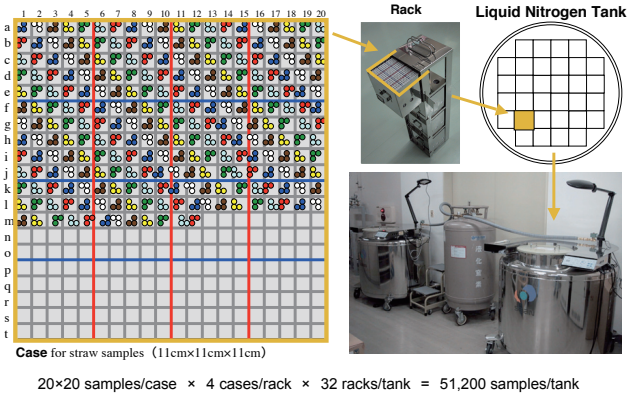

Figure 3. High-density sample storage case system

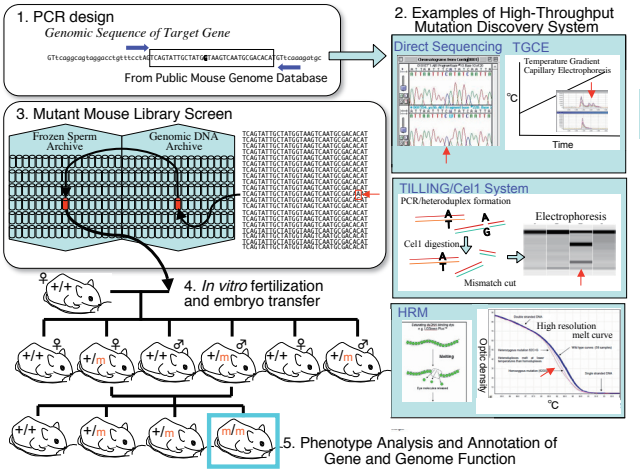

Figure 4. High-throughput mutation discovery system and a new reverse genetics

the mouse genome, PCR primer design is the very first step in amplifying the target DNA sequence. When we started this approach in 2000 that is before the completion of the human and mouse genome projects, quite a few cDNA sequences were already deposited in the public database but only a handful genomic sequences with complete exon-intron information were available. Thus, we had to start collecting such genomic sequences from the public database for mouse genes. By 2002, we had already designed PCR primers for more than 50 mouse genes. To accelerate PCR design and make ENU-based gene-driven mutagenesis available to the research community, we announced the availability of the system through an open WEB site in September 2002. Thereafter, the number of users constantly increased and currently the number of target genes exceeds 300. We have so far compared several mutation discovery systems as follows:

(1) Direct sequencing

This is the simplest straightforward mutation discovery system; however, the cost-performance and throughput of such a system were considered to be insufficient that time. By collaborating with TaKaRa Shuzo Co., we conducted a preliminary trial to detect ENU-induced mutations in G1 genomic DNA samples. As a result, we identified 19 ENU-induced mutations by directly sequencing 20 Mb of G1 genomic DNA. This is the very first discovery of ENU-induced mutation rate per base pair. When we made a poster presentation of this result at the 15th IMGC at Edinburough in 2001, the organizer chose our poster for a special oral presentation. Our finding of the ENU-induced mutation rate at the DNA sequence level for the first time provided key parameters to make ENU-based gene-driven mutagenesis possible. For instance, the mutation discovery system should have a resolution power of one mutation/Mb. Although we succeeded in identifying ENU-induced mutation, direct sequencing was not good enough for conducting the mutation discovery on a large scale. One major reason was obviously cost performance. Moreover, we found that the development of a software package for detecting one mutation/Mb is not an easy task. The number of false positives by one-pass direct sequencing was very large. Based on the preliminary trial, TaKaRa Shuzo Co. withdrew from the collaboration. Thereafter, we conducted ~10 Mb screening by ourselves and ~15 Mb screening in collaboration with the Sequence Technology Team at GSC by direct sequencing. We consistently identified one ENU-induced mutation/Mb throughout the trials.

(2) Temperature gradient capillary electrophoresis (TGCE)

G1 mice heterozygously carry ENU-induced mutations, as shown in Fig. 2. Thus, the PCR products encompassing an ENU-induced mutation form heteroduplex DNA after denaturation followed by renaturation. We tried using several heteroduplex detection systems for a primary high-throughput mutation discovery. The first one was the TGCE system, which has a high-precision temperature control system for 96-capillary electrophoresis. The heteroduplex DNA changes its double-strand structure at lower temperatures than its homoduplex counterpart. This slight conformation difference between the heteroduplex and heteroduplex gives the distinct electrophoresis pattern difference shown in Fig. 4. We found that the TGCE system gives very reproducible results without false positives, which is ideal for a primary screening system. To further enhance the throughput of the TGCE system, we adopted a multiplex loading of 4 samples/capillary simultaneously. By combining this application in the PCR step, namely, multiplex PCR by mixing 4 PCR primer pairs together in a single PCR, we succeeded in increasing the number of samples by fourfold more per analysis and in reducing genomic DNA amount and running cost by fourfold. TGCE with multiplex PCR made ENU-based gene-driven mutagenesis practical. It identifies 100–150 base substitutions yearly. However, the system takes time and manpower to maintain hardware performance. The detection rate of mutations is roughly 70% of that by direct sequencing. The design of multiplex PCR primer pairs for four samples is also time-consuming.

(3) Cycling gradient capillary electrophoresis (CGCE)

As shown above, the detection of point mutations by TGCE is occasionally inefficient. To enhance the resolution of the heteroduplex signal, the cycling application of a temperature gradient was developed. In theory, even a slight difference in electrophoresis mobility between the homoduplex and heteroduplex signals could be magnified at each cycle of temperature shift. In addition, we can continue capillary electrophoresis by repeating the same temperature cycling, making automated multiple sample loading at appropriate

intervals possible. Such automated consecutive sample loading should be much simpler and easier than the design of multiplex PCR for the TGCE system. However, no CGCE systems have been made commercially available yet. We have tried to add a thermal controller to the RISA system and other capillary electrophoresis systems, but have not consistently obtained good performance yet (data not shown).

(4) TILLING/Cel1 digestion

This method uses the endonuclease Cel1 that specifically digests a single-base pair mismatch. After PCR and heteroduplex formation, the sample is digested with Cel1 followed by electrophoresis to detect samples containing any heteroduplex (Fig. 4). The original PCR fragment is cut at the point of mismatches, giving rise to the corresponding multiple electrophoresis bands. The size of the digested bands, therefore, gives a rough estimate of the location of ENU-induced mutations from one end of the PCR fragment. This method has a high resolution power for detecting a minor fraction of heteroduplex DNAs. Thus, it is possible to mix several samples together by pooling several genomic DNA samples of G1 mice. Obviously, the pooling of the genomic DNA samples is much simpler than the multiplex PCR design of the TGCE system. The commercially available TILLING/Cel1 digestion system utilizes a slab-gel electrophoresis system with fluorescent PCR primers. We used a modified TILLING/Cel1 digestion system using a capillary electrophoresis system with ethidium bromide staining to detect DNA fragments. With this modified system, no fluorescent PCR primers are necessary, making the long-term storage of primers possible in addition to the lower cost. The use of capillary electrophoresis requires much less manpower than that of the slab gel system. Interestingly, the use of ethidium bromide staining for detecting DNA fragments gave a much lower S/N ratio than that of the fluorescence-labeled detection system. We have so far succeeded in detecting heteroduplex signals using the modified TILLING/Cel1 digestion method by pooling up to eight genomic DNA samples. We are currently investigating the reproducibility, resolution and throughput of the system.

(5) High-resolution melting (HRM)

The HRM system detects heteroduplex DNA fragments efficiently but requires no electrophoresis. Double- and single-stranded DNAs with exactly identical sequences give different optical densities. The HRM method detects this optical density difference during a temperature gradient shift (Fig. 4). The manufacturer claims an efficient detection with HRM by pooling more than 10 genomic DNA samples. In theory, nanochannel devices should also be applicable to the HRM detection of heteroduplex DNA fragments, which could handle 10,000 reaction samples within 1 h or even less. Nanoscale analyses also save the use of the limited amount of genomic DNA in the mutant mouse library.

4. Next-generation gene-targeting system

Combining the mutant mouse library and high-throughput mutation discovery systems, we succeeded in developing the next-generation gene-targeting system, by using a random mutagenesis with ENU. We have made this system open to the research community since September 2002. The number of users is constantly increasing and the total number of target genes is 308 as of December 2008, of which about 75% are those requested by users (Fig. 5). The availability and list of target genes can be viewed at
www.brc.riken.go.jp/lab/mutants/genedriven.htm.

As described in Section 2, ENU induces one single-base substitution per Mb on average. Thus, one G1 genome carries approximately 3,000 ENU-induced point mutations in its 3,000 Mb of the mouse genome. In the 10,000-G1-mutant mouse library, 30 million ENU-induced mutations have already been accumulated. Approximately 1–2% of the mouse genome contains protein coding sequences; thus, 0.3–0.6 million ENU-induced mutations in the mutant mouse library reside in protein coding sequences. A summary of the mutations discovered by our team has already revealed that 60% and

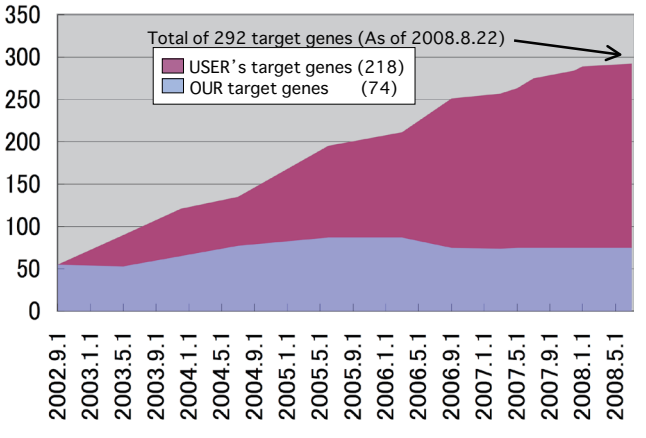

Figure 5. Use of the next-generation targeting system at RIKEN

10% of ENU-induced mutations in protein coding sequences are missense and knockout-equivalent mutations, respectively. Thus, in the RIKEN mutant mouse library, 180,000–360,000 missense mutations and 30,000–60,000 knockout-equivalent mutations exist. Considering that the total number of mouse genes is 30,000, we may be able to identify 6–12 missense mutations and 1–2 knockout-equivalent mutations per gene (Gondo, 2008). Note that ENU preferentially targets T as expected but that mutations induced in the entire genome are distributed according to a Poisson distribution, indicating neither hot nor cold mutation spots with ENU in the whole genome (Sakuraba et al. 2005; Takahasi et al. 2007). Only a bias of ENU-induced mutations was identified between the transcribed and nontranscribed sequences (Takahasi et al. 2007).

We have thus far discovered more than 500 ENU-induced mutations from the mutant mouse library. Roughly 70 mutant strains have been revived from the frozen sperm archive by the in vitro fertilization and embryo transfer method. The recovered mutant strains have been provided to requesting users for phenotype analyses to elucidate the gene and genome function. Disc1 mutant lines for schizophrenia and depression models (Clapcote et al. 2007), Nat1 mutations exhibiting a diminished enzymatic activity (Erickson et al. 2008), and a series of mutations in a highly conserved genomic DNA sequence affecting the expression of the sonic hedgehog gene as a cis-regulatory element (Masuya et al. 2007) are some of such examples.

To accelerate phenotype detection and to shorten the time-consuming mouse experiments, we have also been conducting feasibility experiments using molecular phenotyping or tissue culture systems as a rapid primary phenotype screening. As mentioned above, only 1–2% of the mouse genome comprises protein-coding sequences. Thus, the elucidation of the biological roles of noncoding sequences is also a significant issue for functional genomics. To systematically facilitate such functional studies of noncoding genomic DNA sequences, we have extracted about 600 long conserved noncoding sequences (LCNSs) between human and mouse genomes. We designed PCR primers for some of the LCNS and have already discovered ENU-induced mutations (Sakuraba et al. 2008). The mutation rates found in coding sequences and noncoding sequences are very identical, indicating that LCNSs are not mutational cold spots. This implies the LCNSs are evolutionarily conserved because of selective constraints (Sakuraba et al. 2008). Mutant strains of LCNSs are also available for practical functional studies.

In the near future, the next-generation DNA sequencer should make the resequencing of whole-genome DNA samples of the mutant mouse library feasible. Then, all accumulated ENU-induced mutations will be cataloged and made available for functional studies by the research community.

Publications

【Original Papers】(*All peer reviewed journals)

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2. Takahasi K. R., Tajima F.: "Evolution of coadaptation in a two-locus epistatic system." Evolution: International Journal of Organic Evolution 59, 2324-2332 (2005).*

3. Masuya H., Inoue M., Wada Y., Shimizu A., Nagano J., Kawai A., Inoue A., Kagami T., Hirayama T., Yamaga A., Kaneda H., Kobayashi K., Minowa O., Miura I., Gondo Y., Noda T., Wakana S., Shiroishi T.: "Implementation of the modied-SHIRPA protocol for screening of dominant phenotypes in a large-scale ENU mutagenesis program." Mamm. Genome 16, 829-837 (2005).*

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12. Masuya H., Sezutsu H., Sakuraba Y., Sagai T., Hosoya M., Kaneda H., Miura I., Kobayashi K., Sumiyama K., Shimizu A., Nagano J., Yokoyama H., Kaneko S., Sakurai N., Okagaki Y., Noda T., Wakana S., Gondo Y., Shiroishi T.: “A Series of ENU-induced single base substitutions in a long-range cis-element altering Sonic hedgehog expression in the developing mouse limb bud.” Genomics 89, 207-214 (2007).*

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Oral Presentations

【International Conferences】

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12. Gondo Y.: "Future of ENU mouse mutagenesis with gene-driven approach." International Mouse Mutagenesis Symposium "Trends in Functional Genomics: Mouse Models and Mutagenesis." Yokohama, Mar. (2006). (Organizer)

13. Gondo Y.: "Forward and reverse genetics with ENU mouse mutagenesis at RIKEN." Monterotondo Mouse Biology Meeting, (EMMA, EMBL Monterotondo), Monterotondo, Italy, Apr. (2006). (Invited)

14. Wakana S., Masuya H., Wada Y., Kaneda H., Suzuki T., Furuse T., Kobayashi K., Miura I., Minowa O., Inoue M., Motegi H., Toki H., Gondo Y., Noda T., Shiroishi T.: "A large scale mouse ENU mutagenesis project (2006-1): Overview." 20th IUBMB International Congress of Biochemistry and Molecular Biology and 11th FAOBMB Congress, Kyoto, Jun. (2006).

15. Motegi H., Ohtaki M., Satoh K., Inoue M., Toki H., Wakana S., Gondo Y., Minowa O., Shiroishi T., Noda T.: "A large scale mouse ENU mutagenesis project (2006-2): An analysis of the large amount of accumulated non-ENU treated control data from blood tests on three laboratory mouse strains." 20th IUBMB International Congress of Biochemistry and Molecular Biology and 11th FAOBMB Congress, Kyoto, Jun. (2006).

16. Miura I., Masuya H., Wada Y., Furuse T., Inoue M., Minowa O., Motegi H., Toki H., Kobayashi K., Kaminuma E., Toyoda T., Gondo Y., Noda T., Wakana S., and Shiroishi T.: "A large scale mouse ENU mutagenesis project (2006-3): Establishment of highthroughput gene mapping system by the use of SNPs markers in the mouse." 20th IUBMB International Congress of Biochemistry and Molecular Biology and 11th FAOBMB Congress, Kyoto, Jun. (2006).

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31. Kaneda H., Taguma K., Suzuki C., Ozaki A., Nakamura C., Hachisu A., Masuya H., Wada Y., Suzuki T., Furuse T., Kobayashi K., Miura I., Minowa O., Inoue M., Motegi H., Toki H., Sakuraba Y., Takahasi K. R., Murata T., Fukumura R., Gondo Y., Noda T., Wakana S., Shiroishi T.: "Improvement of embryo-transfer for DBA/2J strain and IVF-based mouse reproduction in the RIKEN mouse mutagenesis program." 2nd International Mouse Mutagenesis Symposium "Trends in Functional Genomics: Mouse Models and Mutagenesis." (Korea

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35. Gondo Y.: "ENU Mouse Mutagenesis Phase II at RIKEN." The Mouse Mutagenesis Workshop, Dec. 5, 2006, Boston, USA, Dec.(2006). (Invited)

36. Gondo Y.: "Mouse mutagenesis project at RIKEN." International Knockout Mouse Consortium Steering Committee Meeting, (European Commission), Brussels, Belgium, Mar. (2007). (Invited)

37. Gondo Y.: "Mouse is a bona fide biosimulator to elucidate mammalian genome function." the RIKEN-NTU Joint Workshop "From Genomics Towards Genomic Medicine." School of Biologycal Sciences (SBS), Nanyang Technological University, Singapore, May (2007). (Invited)

38. Gondo Y.: "Mouse models to elucidate genome function." Edinburgh-RIKEN Workshop on International Systems Biology: Progress and Issues, (University of Edinburgh and RIKEN), Edinburgh, UK, Sep. (2007). (Invited)

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42. Masuya H., Yoshikawa S., Heida N., Kobayashi N., Arikuma T., Toyoda T., Mizoguchi R., Noda T., Gondo Y., Wakana S., Shiroishi T.: "Development of informational infrastructures to share mouse phenotipe and experimental procedures of phenotyping platform with multiple institutions." 21st International Mammalian Genome Conference (IMGC2007), (IMGC), Kyoto, Oct.-Nov. (2007).

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Nishida K., Wakana S., Shiroishi T.: "Establishment of Enu-Induced Dominantly Inherited Retinal Degeneration in Mice." 21st International Mammalian Genome Conference (IMGC2007), (IMGC), Kyoto, Oct.-Nov. (2007).

44. Toki H., Saiki Y., Yamamoto N., Sakuraba Y., Motegi H., Inoue M., Kaneda H., Minowa O., Wakana S., Gondo Y., Shiroishi T., Noda T.: "Mutant Models for Esophageal Carcinogenesis in RIKEN Mouse Enu-Mutagenesis Project." 21st International Mammalian Genome Conference (IMGC2007), (IMGC), Kyoto, Oct.-Nov. (2007).

45. Motegi H., Tsuboi Y., Kikuchi J., Hirayama T., Wakana S., Shiroishi T., Gondo Y., Noda T.: "NMR based metabolic disease model mouse screening in ENU mutagenesis program." 21st International Mammalian Genome Conference (IMGC2007), (IMGC), Kyoto, Oct.-Nov. (2007).

46. Inoue M., Motegi H., Sakuraba Y., Toki H., Wakana S., Gondo Y., Minowa O., Shiroishi T., Noda T.: "Novel mouse models of diabetes mellitus generated by the RIKEN ENU mutagenesis project." 21st International Mammalian Genome Conference (IMGC2007), (IMGC), Kyoto, Oct.-Nov. (2007).

47. Noda T., Motegi H., Inoue M., Toki H., Minowa O., Sakuraba Y., Fukumura R., Murata T., Makino S., Takahasi K. R., Nakai Y., Miura I., Kobayashi K., Kaneda H., Furuse T., Suzuki T., Masuya H., Gondo Y., Wakana S., Shiroishi T.: "Recent Progress in the RIKEN ENU-Mutagenesis Project." 21st International Mammalian Genome Conference (IMGC2007), (IMGC), Kyoto, Oct.-Nov. (2007). (Invited)

48. Gondo Y.: "Trends in large scale mouse mutagenesis." The 21st International Mammalian Genome Conference (IMGC2007), (International Mammalian Genome Society), Kyoto, Oct.-Nov. (2007). (organizer and chairman)

49. Gondo Y.: "ENU mouse mutagenesis project." 2nd AMMRA Annual Meeting, (Asian Mouse Mutagenesis and Resource Association), Nanjing, China, Nov. (2007). (Invited)

50. Murata T., Sakuraba Y., Takahasi K. R., Fukumura R., Makino S., Karouji K., Nakahara A., Yamaguchi T., Nakayama E., Uemura N., Kimura T., Fujimoto N., Tsuchihashi K., Nakamura K., Kaneda H., Wakana S., Noda T., Shiroishi T., Gondo Y.: "Establishing multiple mutant mouse lines of coding (beta-catenin) and non-coding region (LCNS: long conserved noncoding sequence) using ENU-based Gene-driven mutagenesis and Knockout mouse." 2nd AMMRA Annual Meeting, Nanjing, China, Nov. (2007).

51. Gondo Y.: "ENU mutagenesis and human psychiatric disease models." 3rd International Mouse Mutagenesis Conference/2nd AMMRA Annual Meeting/4th Conference for Developmental Biology Society of Jiangsu, (Asian Mouse Mutagenesis and Resource Association), Nanjing, China, Nov. (2007). (Invited)

52. Makino S., Sakuraba Y., Kotaki H., Yamaguchi T., Murata T., Fukumura R., Nakai Y., Takenouchi K., Kaneda H., Hui C., Wakana S., Noda T., Shiroishi T., Gondo Y.: "Screening for point mutations in Hedgehog signaling genes, Smoothened and Sufu, from the ENU-mutagenized mouse genome archive." 41st Annual Meeting for the Japanese Society of Developmental Biologists (Jointly sponsored by the International Society of Developmental Biologists), Tokushima, Japan, May (2008).

53. Murata T, Sakuraba Y, Fukumura R., Makino S., Takahashi K., Nakai Y., Kaneda H., Fujimoto N., Tsuchihashi K., Karouji K., Nakahara A., Yamaguchi T., Nakayama E., Uemura N., Kotaki H., Nakamura K., Noda T., Wakana S., Shiroishi T., Gondo Y.: "ENU-based Gene-Driven Mouse Mutagenesis, yet another reverse genetics infrastructure for coding as well as non-coding regions." 41st Annual Meeting for the Japanese Society of Developmental Biologists (Jointly sponsored by the International Society of Developmental Biologists), Tokushima, Japan, May (2008).

54. Gondo Y.: “RIKEN mustant mouse library for a new reverse genetics.” Recent Progress in Mouse Genetics and Mutation, Paris, France, Jun. (2008). (invited)

55. Gondo Y.: “RIKEN Mutant Mouse Library: Establishment of Diseases Models by Sequence-based Screening.” The XX-th International Congress of Genetics, Berlin, Germany, Jul. (2008). (selected for concurrent session)

56. Gondo Y.: “Trends and Direction of ENU mouse mutagenesis.” The Third Asian Mouse Mutagenesis and Resoource Association (AMMRA) Meteting, Daejeon, Korea, Oct. (2008). (Invited)

57. Fukumura R.: “High-throuput mutation discovery system for ENU-based gene targeting in the mouse.” The Third Asian Mouse Mutagenesis and Resoource Association (AMMRA) Meteting, Daejeon, Korea, Oct. (2008). (Invited)

【Domestic Conferences】 Total 77