Gene Engineering Division

Head, Kazunari K. YOKOYAMA

Goal

The Gene Engineering Division (RIKEN DNA Bank) is a non-profit resource archive that provides genetic resources, technical services and educational program to qualified investigators of private industry, government and academic organizations around the world. RIKEN DNA Bank has been selected as a central facility to collect, preserve and deliver the DNAs of animals and microorganisms by the National BioResource Project sponsored by Ministry of Education, Culture, Sports, Science and Technology of JAPAN (MEXT). Our division undertakes research to ensure the authenticity of the genetic materials in the collection, and to improve and standardize the methods of characterization, maintenance, preservative and distribution of genetic materials. We distribute cloned DNAs, gene libraries (cDNA, phage, cosmid, BAC, phosmid, YAC library), vectors, hosts, recombinant viruses and ordered library-sets from human, mouse, microorganisms, viruses and other animal cells. Our division also performs and sponsors research to improve and standardizes for the advancement, validation and application of scientific knowledge.

History

RIKEN DNA Bank was established in June 1987 when a committee of scientists recognized a need for a central collection of recombinant DNA that would serve scientists in Asia. In 2001, RIKEN BioResource Center (RIKEN BRC) was established and then DNA Bank was reorganized to a Division of Gene Engineering. In 2002, our division was recognized as the central archive for collection of "Animal DNA and Microorganism DNA" in the National BioResource Project (NBRP) program, sponsored by MEXT.

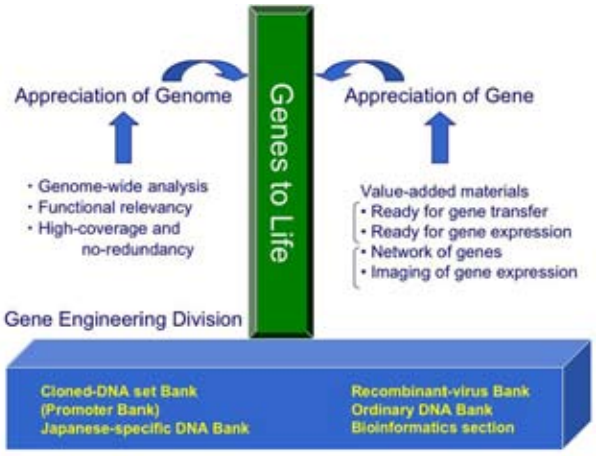


Fig. 1. Goal of Gene Engineering Division

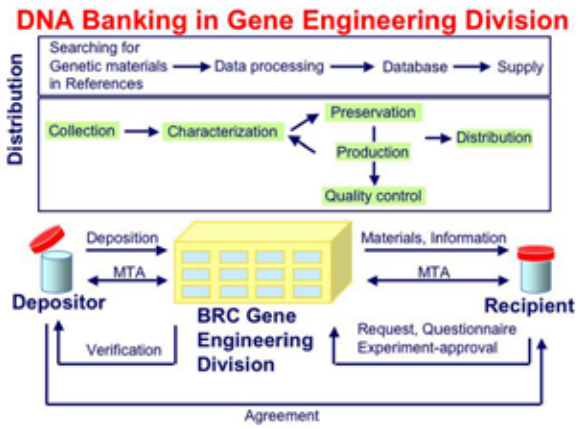


Fig. 2. Schematic Representation of Banking Network

Activities

1. Collection, preservation and distribution of genetic resources

The Gene Engineering Division (RIKEN DNA Bank) is divided into six sections for DNA Banking:

(1) Cloned-DNA Set Bank handling cloned collection of full-length cDNAs which were assembled with the specific research areas like hormons, cytokines, apoptosis, cell cycle, signal cascades, transcription factors, replication factors, ubiquitination and so on. These representative cloned sets were isolated from cDNA libraries, phage, cosmid, BAC, YAC, PAC, P1 and phosmid libraries.

(2) Japanese-specific DNA Bank handling human HLA class I clones which are unique to Japanese and SEREX clones coding cancer antigens of Japanese origin and other clones for Japanese heredity.

(3) Recombinant-virus Bank handling the recombinant viruses which were constructed by inserting the full length cDNA into the viral vectors and generated the viral particles as resources. The viruses are examined their qualities by methods developed in our division. The DNA fragments derived from human and mouse full length cDNA libraries were used as the donor of recombinant viruses.

(4) Promoter-Bank handling the promoter DNA-fragments fused to the reporter genes such as luciferase, lacZ, GFP and Cre recombinase. The transgenic promoter-Cre mice are also generated by collaborating with Animal Resource Center in Tsukuba University and in Experimental Animal Division of RIKEN BRC.

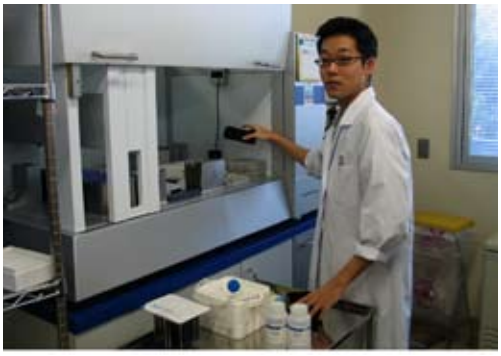
(5) Basic domain of DNA Bank handling individual cDNAs, genome DNA clones and vectors as well as host cells.

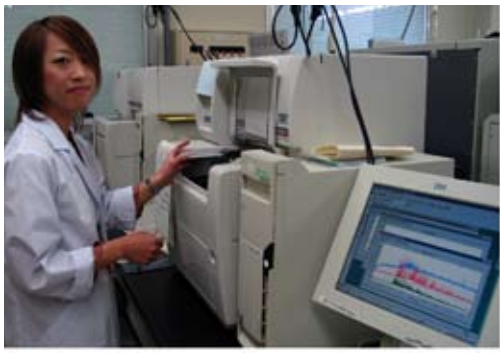
(6) Bioinformatics section handling the informatics of our genetic resources for DNA Banking.

We distributed the genetic resources to only qualified investigations who are associated with certain research, medical or educational organizations. We also reported the activities of our division by an annual report and qualified by the “Resource Committee” every year. We also discussed about a future plan of our mission. The “Resource Ethics Committee” ensured the banking activity of genetic resources of human, which was held every year. The “Advisory Council” is to be held to evaluate the activities of RIKEN BRC every other year. We are evaluated not only the activities of our DNA-Banking but also the research activities of developing technologies related to DNA-Banking.

2. Development of new technology to ensure the authenticity of the genetic materials

The development and the improvement of methods for standardization and characterization of genetic resources are also conducted in our Division. Three technologies as described below are necessary to be developed; 1) Identification of the mutation sites in the genetic resources; 2) Preparation of the novel vectors for the controled expression system of the genes; 3) Preparation of the novel adenovirus vectors for human gene therapy and their efficacies ; 4) Preparation of the artificial reporter vector with different *cis*-elements ; 5) Development and validation of new gene-transferring system using targeted promoter/ enhancer and 6) Development of new system to study gene expression in eukaryotic cells and animals.


Operation of the automated DNA extraction-machine.


Reconfirmation of nucleotide sequence of DNA.

3. Education and training of scientists.

Our division performs the training program for scientists and young students to teach the best use of adenoviral vectors

Members

Head

Kazunari K. YOKOYAMA, Ph. D. (2001. 4 ∽)

Senior Research Scientist

Takehide MURATA, Ph. D. (2001. 4 ∽)　Makoto KIMURA, Ph. D. (2003. 7 ∽)

Research Scientist

Jianzai PAN, Ph. D. (2005. 4 ～)

BRC Collaborative Researchers

Koji NAKADE, Ph. D. (2004. 1 ～)　Bing Bing LIU, M. D., Ph. D. (2004. 2 ～)

Yong WANG, Ph. D. (2005. 8 ～)

BRC Cooperative Researchers

Hong TANG (2004. 3 ～ 2005. 2)　Shigeo SAITO, Ph. D. (2001. 4 ～)

BRC Technical Staffs

Kumiko INABE (2002. 4 ～)　Miho TERASHIMA (2003. 1 ～)

Takahito YAMASAKI (2003. 4 ～)　Yukari KUJIME (2004. 4 ～)

Megumi HIROSE (2004. 4 ～)　Sanae YAMAOKA (2004. 4 ～)

Visiting Members

Kazuko UENO (Science Service Co., Inc.) (Secretary) (2001. 4 ～)

Miyuki YAMAMOTO (Science Service Co., Inc.) (2003. 6 ～)

Student Trainees

Mariko WAKAYAMA (Univ. of Tsukuba) (2002. 4 ～)

Michiya NOGUCHI (Univ. of Tokyo) (2003. 4 ～)

Rei KAWASHIMA (Univ. of Tsukuba) (2005. 4 ～)

Yusuke IDE (Univ. of Chiba) (2005. 4 ～)

Emiko SEO (Univ. of Tsukuba) (～ 2005. 3)

Shunsuke TANIGAWA (Univ. of Kagoshima) (～ 2004. 12)

Noguchi, Kawashima, Ohtou, Inabe, Takahashi, Hattori, Yamaoka, Nakajima
Fujisawa, Kimura (A), Hirose, Terashima, Sato, Katsuya, Hiraguri
Wang, Yamamoto, Ide, Liu, Ueno, Kujime, Yamasaki
Nakade, Pan, Murata, Yokoyama, Kimura (M)

Specific aim

I. Collection, preparation and distribution of genetic materials.

1. Banking system

We have collected the following number of the genetic materials; host 82, vector 104, cloned DNA 2,350, Nakamura-White RELP marker clone 123, human genomic YAC clone 35,712, mouse 15 K cDNA clone 15,000, mouse 7.4 K cDNA clone 7,407, mouse cDNA clones 45,216, cDNA library 47, mouse BAC cloned library 210,592, human SEREX clone 584, Japanese HLA class I 40, recombinant virus 457, Japanese maccaque genome library 200,064 and human genome library 399,456.

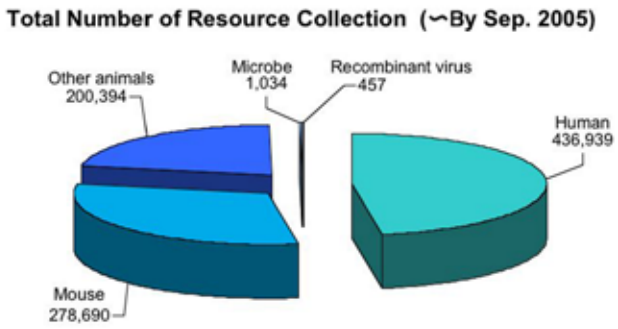


Fig. 3. Total Number of Resource Collection (～ By Sep. 2005)

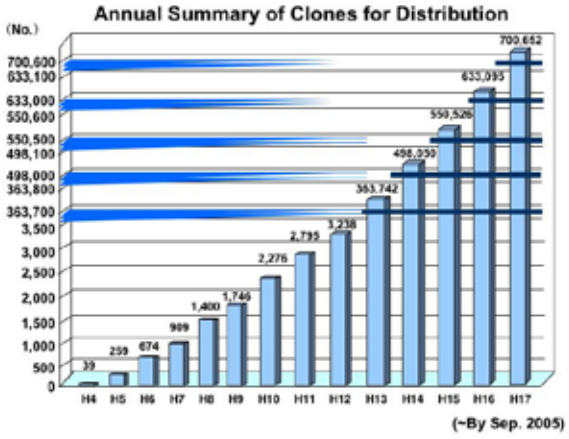


Fig. 4. Annual Summary of Clones for Distribution

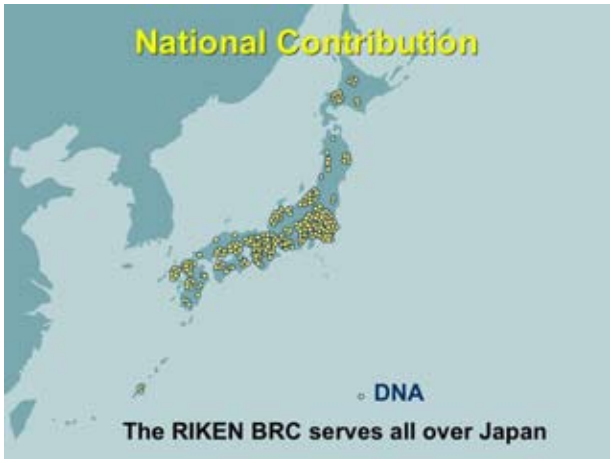


Fig. 5. National Contribution

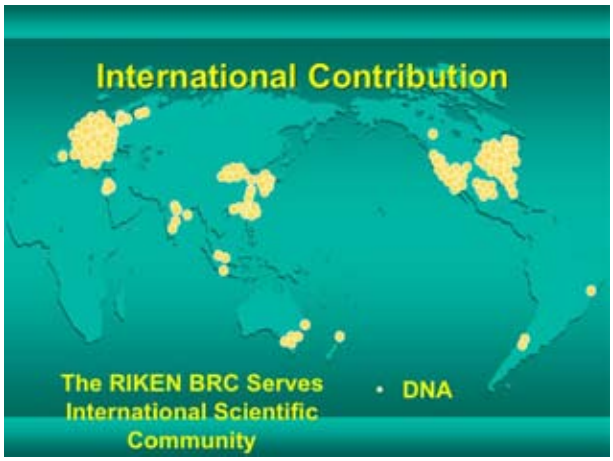


Fig. 6. International Contribution

II. Development of technology

We have performed the following research projects to develop a new technology for the DNA-Banking.

1. Detection of mutation of DNA samples

We have developed the novel techniques to detect the mutation of genetic resources with a higher sensitivity and reproducibilities. These techniques are used for the validation of quality of genetic resources.

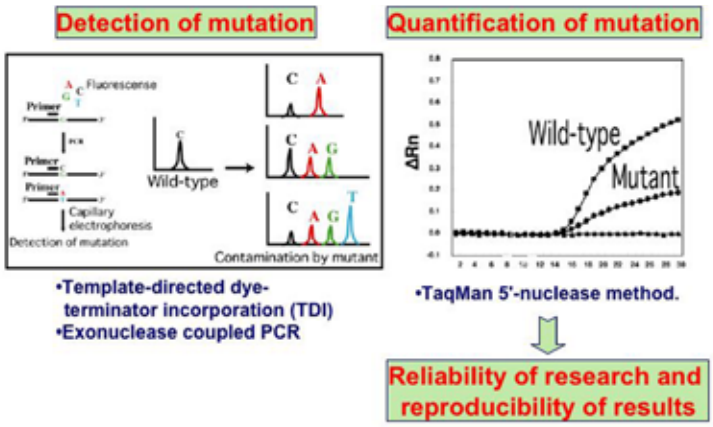


Fig. 7. Development of Technologies for Detection of Mutation and Replecement of Gene

2. Development of controlled expression system of genes with modification enzymes

Recent progress of the recombinant DNA technology focused upon the modification system of genes such as epigenesis, protein degradation, phosphorylation and addition of sugar and lipid moieties to the core proteins and DNAs. We have developed the new two vectors or one vector system to modify the gene products with the genes encoding methylation/demethyation, kinase/phosphatase, acetylase/ deacetylase, ubiquitination/ deubiqutination, smolation/desmolation and sugar/ lipid related enzymes.

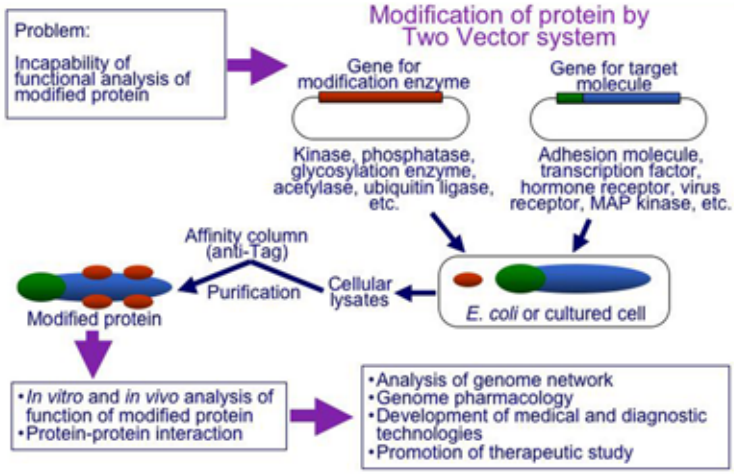


Fig. 8. Development Gene Transfer Vector for Postgenome Research

3. Development of targeted system of gene delivery using the specific promoter and generation of transgenic mice with the controlled gene expression

We have developed the regulated gene expression system using DNA fragments of specific promoters and the reporter constructs like tissue-specific promoters and generated novel transgenic mice with Cre-loxP cassette with tissue specific promoter (with the collaboration with Tsukuba University and the Experimental Animal Division of BRC).

4. Application of adenovirus vectors for cancer gene therapy, regeneration biology and molecular biology

We have developed the novel gene-delivery system to cancerous cells and embryonic stem cells as well as modeled animals using the tumor suppressor genes and suicide genes. We developed the efficient system for gene-transfer using the novel adenoviral vectors with E1-Rb mutants, chimeric fibers and modified fibers for the gallblatter cancer, biliary tract cancer and liver cancer (with the collaboration with Tsukuba University and Sapporo Medical University). We also focused on the embryonic stem cells for the gene delivery of modified adenoviral vectors.

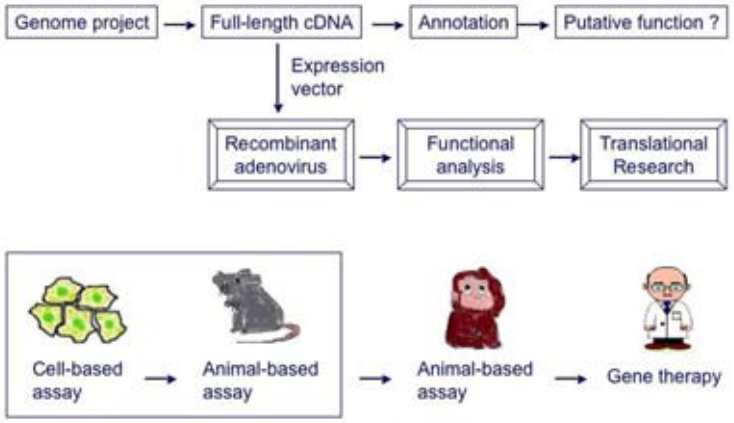


Fig.9. High Expression System in Eukaryotic Cells

5. Development of gene expression system and evaluation system of expressed genes in eukaryotic cells and animal models

We have developed the novel strategy to evaluate the gene expression in chromatin and evaluate the system for expressed gene products in cells. We focused the DNA transcription factors AP-1 family and the chromatin modified factors such as histone acetylation, methylation as well as smolation in eukaryotic cells and modeled animals.

6. Efficacy of artificial promoter vectors

The controlled reporter system with the DNA-binding sites (*cis*-elements) of transcription factors have been developed and we examined their efficacies for various cells including neoplastic cells, normal diploid cells, embryonic stem cells as well as germ cells.

III. Evaluation of activities of the "National BioResource Project (NBRP)".

The NBRP-committee evaluated our mid-term banking activities of RIKEN BRC with the highest score "S".

IV. Introduction and distribution of our banking activities

We have set up the homepages (http://www.brc.riken.jp/dna/en/index.html) and delivered e-mail news, catalogs and other related notices of our DNA-Bank in RIKEN BRC for public use, which are available to researchers around the world. We also introduced our banking activities in several annual national meetings such as Molecular Biology, Biochemistry, Cancer, Gene-Therapy as well as some international conferences like Cold Spring Harbor meethings.

Publications

(* Peer reviewed journal)

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3. Jin, C., Li, H., Horikoshi, M., Sun K. L. and Yokoyama, K.: Role of histone acetyltransferase and deacetylase in the retinoic acid-induced differentiation of F9 cells. Chapter 15, Food factors for disease prevention and health promotion (ed. By F. Shahidi, C-T, HO, Watanabe, S., Osawa, T.). ACS, Washington DC., USA, 163-178 (2003). *

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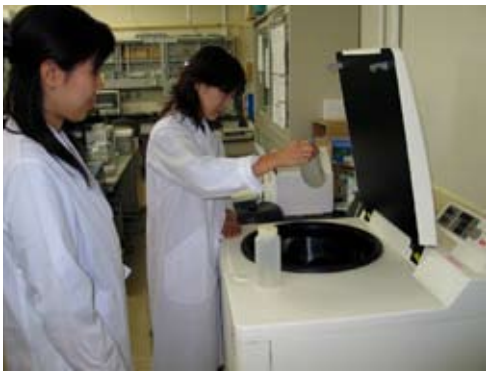

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10. Kishikawa, S., Murata, T., Ugai, H., Yamazaki, T., and Yokoyama, K.: Control elements of Dnmt1 gene are regulated in cell-cycle dependent manner. Nucleic Acids Res. Suppl. 3, 307-308 (2003).*

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12. Yokoyama, K.: Role of histone modification during the differentiation of embryonic carcinoma F9 cells. Recent Res. Dev. Cancer. 5, 89-100 (2003).*

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14. Suzuki, E., Murata, T., Watanabe, S., Kujime, Y., Hirose, M., Pan, J., Yamazaki, T., Ugai, H., and Yokoyama, K.: A simple method for the simultaneous detection of E1A and E1B in adenovirus stocks. Oncology Reports 11, 173-178 (2004).*

15. Wu, C-X., Zhao, W-P., Kishi, H., Dokan, J., Jin, Z-X., Wei, X-C., Yokoyama, K., and Muraguchi, A.: Activation of mouse RAG-2 promoter by Myc-associated zinc finger protein (MAZ). Biochem. Biophys. Res. Commu. 317, 1096-1102 (2004).*

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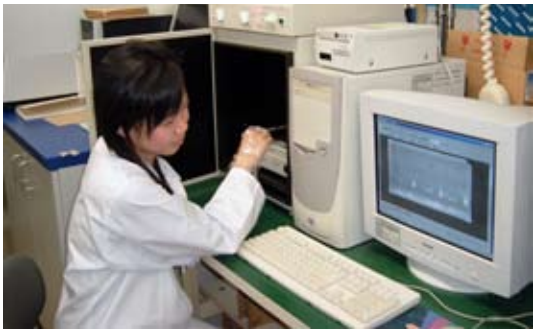
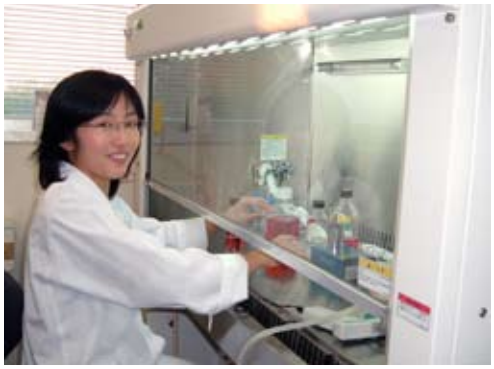


Detection of the DNA fragments.



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24. Yokoyama, K., Murata, T., Ugai, H., Suzuki, E., Terashima, M., Kujime, Y., Inamoto, S., Hirose, M., Inabe, K., and Yamasaki, T.: Recombinant Virus BANK for gene delivery. Science 307, 1722 (2005).*

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Oral Presentations

1. Yokoyama, K., Ugai, H., and Murata, T.: "Spontaneous mutations in the human gene for p53 in recombinant adenovirus during multiple passages in 293 cells" "Vector Targeting strategies for gene therapy" Cold Spring Harbor Meeting, Cold Spring Harbor, NY, pp.47, March (2003).

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