2

Present and Future of Bioresources (Biological Genetic Resources)

AKIHIRO HASEGAWA AND SHIN-ICHI MOGI
Life Science and Medical Research Unit

2.1 Introduction

As it is often said, "no resource, no research," bioresources are inevitable in the life science area. Since bioresource includes various things, such as experimental animals and plants, model animals and plants, embryos, cells, tissues and organs, their collection, storage and supply must be carried out on a national basis.

Since the old days, bioresources have been collected and stored mostly from a naturalistic point of view. In recent years, gene functional analysis has become the dominant subject of research in the life science area, and the accumulation of resources has led to the determination of genomic sequences in various organisms. The determination of the genomic sequence in a species drastically increases the efficiency of gene function analysis in that species, so strategic maintenance of resources linked with the genome research is desirable.

To date, bioresources in Japan have been scattered among individual university laboratories, etc., and the information on their locations has not been open to the public for a long time. Therefore, smooth utilization of the bioresources within research communities was relatively difficult. In order to promote smooth utilization of the bioresources, organizations for storing and supplying bioresources, as well as systems such as contracts, etc., that ensure smooth transfer of materials, will play important roles.

This report summarizes the current status of bioresources in the life science area, and discusses bioresource maintenance adapted to genome research and politic measures for supporting resource centers, etc., for supplying high-quality bioresources.

2.2 What is bioresource?

2.2.1 Materials included in bioresource

The definition for the term "bioresource" has never been made explicit by any public organization in their science and technology policies. Nevertheless, in the area of life science, "bioresource" is generally acknowledged as a term representing research materials such as "strains, populations, tissues, cells, DNAs, etc., that are used as materials for research and development." Moreover, materials applied via fundamental research stages, such as food or feed plant species (varieties) and environment-cleaning micro-organisms, and human-related materials such as cells and tissues used in the medical area, are also included in bioresources (Table 1).

Table 1: Materials included in bioresources

Research materials	Strains, populations, tissues, cells, DNAs, etc., used as materials for research and development
Applied materials	Food and feed varieties, livestock, environment-cleaning organisms
Human-related materials	Human-related materials such as cells, tissues, etc.

Source: The material prepared by Professor Yuji Kohara of the National Institute of Genetics

Table 2: Classification of bioresources from the researchers' viewpoints

Classification	Materials
Produced during the research process	— Mutants — Transgenic organisms
Collected for conducting research	— Materials produced by researchers in the past (Escherichia coli, nematodes, Drosophila, mice, etc.)

Source: The material prepared by Professor Yuji Kohara of the National Institute of Genetics

2.2.2 How bioresources are generated

In recent years, studies for analyzing gene functions dominate the research in the life science area. In the process of such genome studies, various mutants and transgenic organisms (organisms artificially produced via genetic engineering) have been produced in large numbers.

Furthermore, when researchers attempt to elucidate a life phenomenon via gene functional analysis, they often collect species possessing certain characteristics concerning the target phenomenon from species generated by researchers in the past or from natural populations, and search the genes, etc., related to such characteristics. Therefore, species generated by researchers in the past or natural populations are stored by the researchers or resource centers, etc., as valuable bioresources.

Meanwhile, after researchers publish their research results, mutants and transgenic organisms generated during the research process are provided to other researchers as common research materials of the research community to ensure reproducibility of the results and enable comparisons of research results. Therefore, it is widely accepted that after researchers publish their works, they must store the bioresources generated during the research process and share them with other researchers.

2.2.3 Bioresource centers

When collection and management of bioresources are consigned to individual university laboratories, etc., some problems may arise, such as:

— Heavy burdens on researchers for collecting and managing materials over a certain size, over a certain period;

— Loss or quality deterioration of materials due to personnel changes in researchers, etc.; and

— Little chance of exploiting valuable bioresources within research communities due to difficulties in accessing information concerning bioresource locations.

Therefore, bioresource centers that are capable of collecting, managing and supplying bioresources should be established for each biological species or research area to realize unified supplying of bioresources to the research communities.

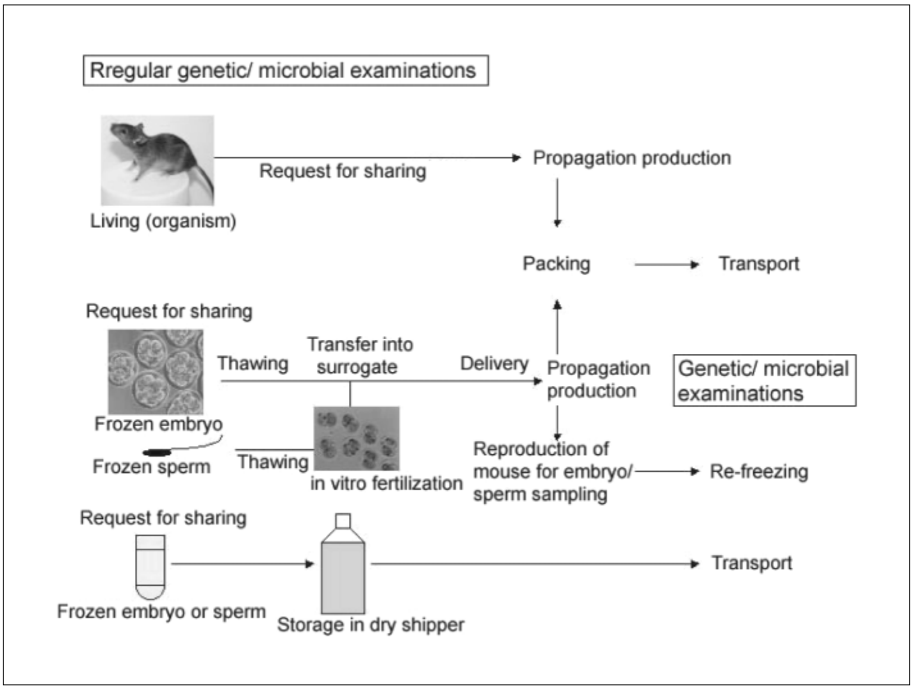
A bioresource center requires a large amount of labor and cost for maintaining and managing a great number of animals, microorganisms and other living organisms. As can be seen from the example of dealing with mice, supplying genetically or pathologically superior resources requires regular genetic or microbial examinations, as well as techniques for managing frozen embryos and sperms and propagation techniques such as in vitro fertilization. Consequently, the staff members must be highly specialized in such techniques (Figure 1). These techniques differ among various bioresources, depending on the species or levels of materials such as individuals, cells and DNAs. Therefore, bioresource centers must retain specialized staff members for each kind of bioresource.

In addition to supplying high-quality bioresources, bioresource centers are expected to lead the research community by:

— Reorganizing research results such as constructing genetic maps and assigning names to genes; and

— Supporting research from a comprehensive point of view by summarizing all data, ranging from the genetic backgrounds of the resources to the results of studies conducted using the resources.

Figure 1: Process for sharing mouse strains



Source : The material prepared by the Bioresource Center of The Institute of Physical and Chemical Research

All in full liaison with the research community and with authorized researchers playing the central role. This means that a bioresource center is not merely a research-supporting organization, but is the core of the academic area.

2.2.4 Bioresource and intellectual property rights

Recently, there are many cases where the results obtained from a genome research or other fundamental research directly lead to industrial applications. As a consequence, intellectual property rights are actively applied for bioresources, and certain restrictions (e.g., prohibition of direct application to profit-making activities, and prohibition of transfer to a third party) are imposed on the other parties in bioresource transfer contracts (MTA: Material Transfer Agreement). Meanwhile, researchers, especially from the standpoint of the developers of the resources, are demanding the development of new means to protect intellectual property rights on the resources themselves, which extends beyond the range of intellectual property rights covered by the existing patent laws.

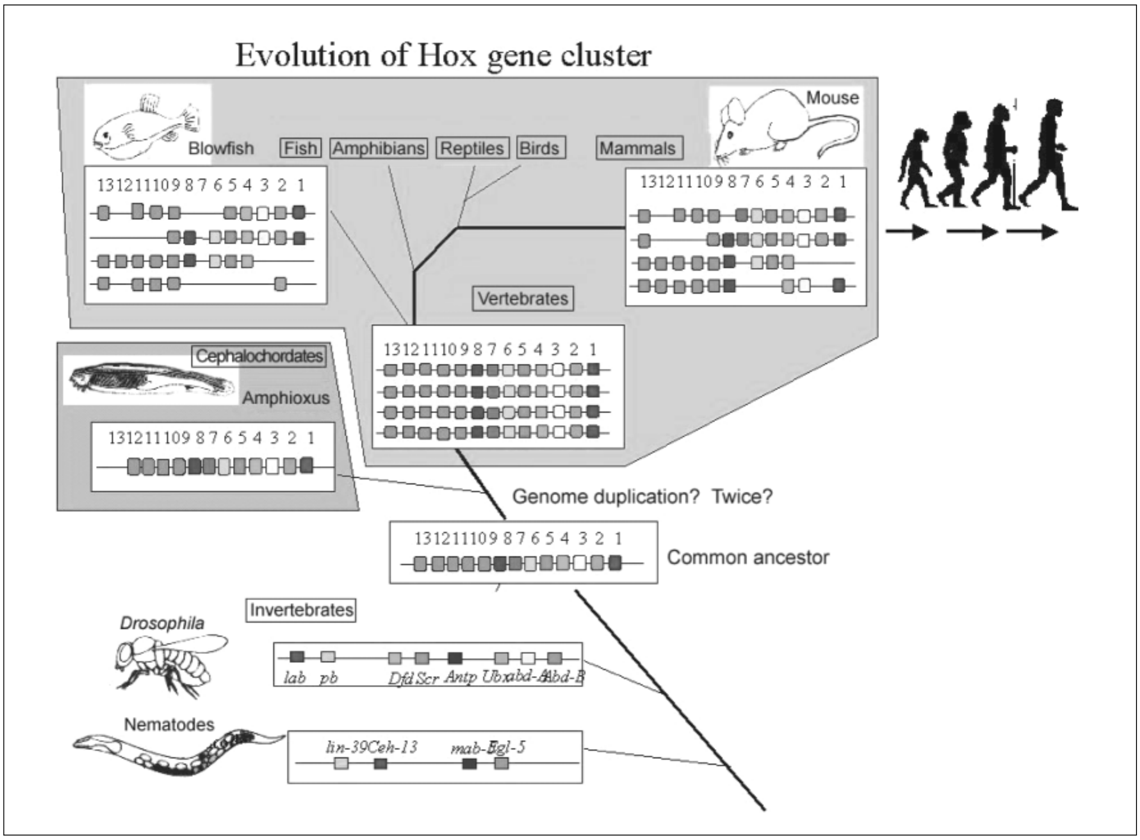
On the other hand, a reinforcement of intellectual property rights imparted to resource developers may raise the price of the resources or hinder smooth access to the resources by the research community. Many researchers warn, "Excessive assertion of intellectual property rights for bioresources may deprive life science of novel discoveries."

2.3 Importance of bioresources in the genome age

Genome sequences, the integral part of the genetic information of organisms, have been identified in microorganisms including pathogens, industrially useful bacteria and yeast that have been genetically studied in detail. Subsequently, genomes for multicellular organisms such as nematodes and *Drosophila* have been sequenced, and mammalian genomes have also been roughly sequenced (draft sequence) in mice and human beings.

In recent years, comparative genomic analyses among various organisms have led to a hypothesis that the evolution of organisms can be explained as the evolution of genomes. For instance, the comparison of the Hox gene family that controls morphogenesis among various species has revealed that invertebrate genomes had duplicated twice resulting in a 4-fold increase as they evolved

Figure 2: Evolution of organisms and Hox gene



Source: The material prepared by Professor Yuji Kohara of the National Institute of Genetics

into vertebrates (Figure 2). The basic structures of Hox genes are similar between fish and mammals, suggesting that the gene composition has not changed drastically since the appearance of vertebrates.

Once the entire genomes are sequenced for various organisms, the diversity of organisms may be revealed at a molecular level, based on the sequence comparison of not only the specific genes but also the entire genome. In addition, since a gene whose function has been revealed in a certain species has its homologues (genes with closely related structures) in various other species, the efficiency of gene function analysis should be drastically increased by comparative genomic analysis among species whose genomes have been sequenced. In other words, animals, plants and even microbes can be used as model organisms for elucidating the functions of human genes.

For a model organism with established experimental systems, bioresources such as mutants must be reorganized in linkage with genome sequences. Elucidation of various life phenomena with such model organisms is inevitable for technical development in the medical and industrial areas, so the importance of bioresource is increasing more and more in the genome age.

2.4 Current status of bioresource organizations and the related policies

2.4.1 History of bioresource organizations in Japan

With a few exceptions, the great number of various biological resources in our country and their information are collected by individual universities or specialized organizations based on their own standpoints. Most of them have been available for internal use only, leaving few open to the public.

Organizations of bioresources and the related information bases are important research bases in the area of life science. Such recognition among researchers and administrative departments has led to the suggestion of "the organization of research and development bases" as a policy for the Science and Technology Basic Plan decided by the Cabinet in July 1996, based on the Science and

Table 3: Organization of bioresources in universities, etc.

1997	Cultured cells: Institute of Development, Aging and Cancer, Tohoku University
"	Barley: Research Institute for Bioresources, Okayama University
"	Silkworm: Faculty of Agriculture, Kyushu University
"	Mouse, rice, Escherichia coli: National Institute of Genetics
1999	Drosophila: Kyoto Institute of Technology

Source: The material prepared by Professor Yuji Kohara of the National Institute of Genetics

Technology Basic Law. Specifically, "improvement of the information infrastructure" was mentioned, in addition to "improvement of research and development facilities and equipment" and "the promotion of a research-informational infrastructure." Concerning the "improvement of the information infrastructure," it has been declared that "it is important to organize, collect, store and accumulate standards, evaluation methods for examinations, bioresources, genetic resources, materials, etc., for the stable, efficient promotion of research and development activities, etc. Moreover, the above-mentioned standards, materials, etc., must be supplied widely to promote their broad diffusion throughout the country."

In association with such movement for bioresources in universities, etc., which have accounted for a major portion of the bioresources used in the life science area in our country, the Science Council announced "A report on the application of bioresources for academic research" in June 1996, and bioresource centers for each kind of bioresource was established as university affiliates, etc. (Table 3).

Combined with the establishment of bioresource centers, construction of databases and networks concerning bioresources was initiated to reinforce the intellectual basis. The National Institute of Genetics established the Genetic Resource Information Center in 1997, and started their Genetic Resource Information Databank Division the following year. In cooperation with the Resource Conservation Division, the center is constructing and disclosing a bioresource information database (SHIGEN: SHared Information of GENetic resources), mainly targeting bioresource centers.

Meanwhile, databases for the bioresources, including applied and human-related materials presented Table 1, have been enriched in the gene bank of the National Institute of Agrobiological Science under the Ministry of Agriculture, Forestry and Fisheries, the Japan Health Science Foundation, the National Institute of Health Science and the National Institute of Infectious Diseases under the Ministry of Health, Labor and Welfare, and the National Institute for Environmental Studies under the Ministry of the Environment.

2.4.2 The National Bioresource Project

The projects mentioned in Section 2.4.1 have advanced the organization of bioresource in the life science area to a certain extent. Yet, the progress in genome research has increased the importance of the organization of intellectual bases in the life science area. Taking this into consideration, the Ministry of Education, Culture, Sports, Science and Technology started the National Bioresource Project from 2002.

Among the bioresources such as experimental animals and plants, stem cells such as ES cells (embryonic stem cells) and gene materials of various organisms, this project aims at establishing a system for the systematic collection, storage, supplying, etc., of materials that need to be strategically organized under government control. The goal is to establish a bioresource organization system at the world's highest level by 2010.

As shown in Table 4, in 2002, core bases for each of the 23 resources are to be established for systematic collection, storage, supplying, etc., of the resources, as well as information centers for summarizing and providing information on the locations of various resources and genetic information. The total project expense for 2002 is 4.4 billion yen.

Table 4: Summary of the National Bioresource Project

I. Core Base Establishment Program		
Experimental Animals	— Mouse (development • storage • supplying)	RIKEN BRC
	— Mouse (mutagenesis)	RIKEN GSC
	— Rat	Animal Experiments of the Faculty of Medicine, Kyoto University
	— *Drosophila*	Kyoto Institute of Technology
	— Nematodes	Tokyo Women's Medical University
	— *Xenopas*	Amphibian Laboratory, Hiroshima University
	— Silkworms	Faculty of Agriculture, Kyushu University
	— Cyprinodont	Bioscience Center, Nagoya University
Experimental Plants	— *Arabidopsis*	RIKEN BRC
	— Rice	National Institute of Genetics
	— Wheat	Faculty of Agriculture, Kyoto University
	— Barley	Research Institute for Bioresources, Okayama University
	— Algae	National Institute for Environmental Studies
	— *Chrysanthemum*	Plant Gene of Hiroshima University
	— Morning glory	Faculty of Science, Kyushu University
Microbes	— Pathogenic microbes	Research Center for Pathogenic Fungi and Microbial Toxicoses, Chiba University
	— *E. coli*	National Institute of Genetics
	— Yeast	Faculty of Science, Osaka City University
Primates	— Japanese macaque	National Institute for Physiological Sciences, Okazaki National Research Institute
	— Chimpanzee (investigation)	Faculty of Agriculture, Tokyo University
Cells/ DNAs	— Animal and plant cultured cells, tumor cells, DNAs, etc.	RIKEN BRC
Human cultured cells	— ES cells	Institute for Frontier Medical Science, Kyoto University
	— Standard human cultured cell strains (investigation)	Institute of Development, Aging and Cancer, Tohoku University
II. Information Center Establishment Program		National Institute of Genetics

Source: The material prepared by the Life Science Section, Ministry of Education, Culture, Sports, Science and Technology

2.4.3 Main bioresource centers overseas

Bioresource organization is most advanced in the United States among other foreign countries. There, large-scale core bases were already established during the early period. In most cases, Japanese researchers cannot conduct their research and development without the resources supplied from the U.S. and other foreign countries.

Jaxon Laboratory, one of the world's largest bases in the U.S. for supplying experimental mice that are widely used in basic and applied research in the life science area, was founded in the 1930s. ATCC (American Type Culture Collection), known as a microbe-supplying base in the U.S., also has a long history with its foundation back in the 1920s. These institutions are non-profit organizations, receiving financial support from NIH.

At Jaxon Laboratory, the total project expense for 2000 was 88.1 million dollars (approximately 50% shared by NIH, mouse sales earnings were 34.2 million dollars), and the number of staff members was 1,022 (260 of which were researchers). None of the core bases in Japan has a scale comparable to this. Furthermore, Jaxon Laboratory possesses over 2,700 mouse lines, supplying about 2 million mice to universities, etc., per year. On the other hand, merely 619 mouse lines (as of July 2002) have been submitted to the Bioresource Center of The Institute of Physical and Chemical Research (RIKEN BRC), which is the largest core base in Japan.

2.5 Conclusion

In our country, the Ministry of Education, Culture, Sports, Science and Technology has started the National Bioresource Project as its policy from 2002. The establishment of the core bases for individual organisms and a genetic resource center network that links them are currently in progress, with the academia playing the leading role. Researchers in universities, etc., are also expecting that the project will improve, to a certain extent, the situation in which bioresources have been scattered among individual university laboratories, etc., preventing their effective use within the research

Table 5: Main Bioresource Centers Overseas

U.S.	Europe
• **NIH(National Institutes of Health)** Financially supports institutions storing research resources for research and projects • **NCI(National Cancer Institute, NIH)** General support • **NCRR (National Center for Research Reources, NIH)** Supports resources for research ranging from medical to general biological studies • **ATCC (American Type Culture Collection)** Virus, bacteria, cells, fungi, cultured plants, protista, and yeast • **CCR(Coriell Cell Repositories)** Human cells derived from human hereditary diseases • **FGSC (Fungal Genetics Stock Center, University of Kansas Medical Center)** Shares fungi • **CDC (Centers for Disease Control and Prevention)** Pathogenic microbes • **JAX (Jackson Laboratory)** Mice • **ZFIN (Zebrafish Information Network, University of Oregon)** Zebra fish • **Fly stock(Bloomington Drosophila Stock Center, Indiana University)** *Drosophila stock center* • **National Resource for Aplysia Facility, University of Miami** Sea hare • **National Resource Center for Cephalopod, The University of Texas Medical Branch** Cephalopoda • **CABRI (Common Access to Biotechnological Resources and Information)** Summarizes information from bioresource institutions in Europe	(U.K.) • **UKNCC (United Kingdom National Culture Collection)** Union of 10 institutions collecting microbes, animal cells, and plant cells • **CABI (CAB International)** Provides genetic resources and identification and examination services for various species • **CAMR (Centre for Applied Microbiology & Research)** Provides biological and medical research resources • **ECACC(European Collection of Cell Cultures)** Shares animal cultured cells • **NCIMB (National Collection of Industrial and Marine Bacteria)** Shares industrial and marine microbes • **NCTC(National Collections of Type Cultures)** Bacteria, fungi, micoplasma, plasmids, and transposons (Holland) • **CBS (Fungal Biodiversity Center - Utrecht, The Netherlands)** Institution collecting fungi, yeast and bacteria (Germany) • **DSMZ(German Collection of Microorganisms and Cell Cultures)** Collects microbes and animal cultured cells (France) • **Institut Pasteur** Mainly microbes and plasmids (Belgium) • **Belgian Co-ordinated Collections of Micro-organisms (BCCM)** Holds and shares fungi and yeast strains as type strains

Source: The material prepared by Dr. Hiroshi Mizusawa of the National Institute of Health Science

communities.

Meanwhile, the prices of bioresources are unstable, being affected by the research trend in the life science area. Since the education of human resources for handling the bioresources requires the promotion of policies on a long-term basis, future follow-up is inevitable.

When promoting the policies, the following points must be considered.

2.5.1 Short – and long-term, balanced support policies

In the life science area, the main research subject has changed from phenomenon to phenomenon along with time. Consequently, the values of the bioresources have also changed. For example, mutants and transgenic organisms are artificially produced in large amounts in the process of genome research, but once they accomplish their roles as tools for analyzing gene functions, they are no longer valued. Furthermore, such materials can be reproduced if required in some cases. Therefore, support policies with time limits are urgently required for such materials.

On the other hand, there are many irreplaceable resources that cannot be artificially produced, such as natural subspecies and related species. Therefore, a good balance between short- and long-term policies is required, such as developing an inexpensive, resource-storing technique while promoting permanent collection and management of the resources.

2.5.2 Continuous support policies concerning human resource education

As mentioned in Section 2.2.3, bioresources; (1) shows uniqueness in their maintenance and propagation techniques for individual species, and (2) are highly valued for the information on their genetic backgrounds. Therefore, it is important to educate specialists for maintaining and managing the resources.

In policies such as the National Bioresource Project, resource centers that are affiliates of universities or other public research institutions are exclusively employed as the core bases, and the government offers the financial support required for collecting and supplying the bioresources. On the standpoint of educating specialists, not only short-term financial support but also mid- to long-term support policies for ensuring human resources are required.

Bioresource centers in the U.S. and European countries not only have large-scale facilities but also have well-established personnel systems for technicians to allow their promotion. Holding technicians in high esteem encourages the education of human resources specialized in bioresource management. There is a differentiation of roles between researchers and technicians, where the roles for good researchers are to map out policies for resource management or to give instructions to the technicians.

2.5.3 Bioresources and genome information

Currently, information concerning bioresource management is mainly centered on the location of resources, and the genetic information of the resources is only partly included. Furthermore, information on bioresources accompanying the information on genomes, such as their genomic sequences (e.g., information on the kind of bioresource from which the genomic data was obtained), lacks uniformity in the style of description and is not necessarily well established.

Assuming that gene function will be analyzed in various species in the future, genomic data will become closely linked with the information on the traits at an individual level, so information on bioresources accompanying genome information should become more and more important.

As a conclusion, for databases of genomic data such as the sequence data, it is important to contemplate how to organize an ontology*1 concerning bioresource information.

Acknowledgment

The present report was prepared based on the lecture "Current Status of Bioresources and Domestic Policies" given by Professor Yuji Kohara, head of the Genetic Resource Information Center, vice director of the National Institute of Genetics, on July 25, 2002 at the National Institute of Science and Technology Policy, and supplemented by information obtained through research conducted by the authors.

Finally, we would like to thank Professor Kohara for kindly offering guidance and the related materials during the preparation of this manuscript.

Glossary

*1 Ontology

Well-disciplined vocabulary or description method, free of unique concepts or terms defined for individual research subjects.

(Original Japanese version: published in September 2002)