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Risk Management of Microbial Genetic Resources in the BCRC/FIRDI of Taiwan

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Abstract

Microorganisms, their cells and replicable parts (e.g. genomes, plasmids, viruses, and complementary DNAs) are the tools for biotechnology and underpin the life sciences. They provide a major source of genetic information to solve problems in agriculture, industry, plant and animal sciences, and human health. The total number of microorganisms is unknown, and they are difficult to study *in situ*. Microorganisms that are isolated from natural and manmade environments are typically conserved in microbial resource centers (MRCs). It has been over two decades since 1982, when the Bioresource Collection and Research Center of the Food Industry Research and Development Institute (BCRC/FIRDI) initiated the work of microbial resource collection and preservation in Taiwan. In 2001, the quality management system of BCRC/FIRDI was audited and determined to be compliant with ISO 9001:2000 requirements. Being a multifunctional MRC, the BCRC/FIRDI implements access and benefit sharing (ABS) by establishing a biological material transfer mechanism and being involved in benefit-added biological material development. The BCRC holds three domains of bioresources: microbial resources, cellular resources, and genetic resources. In order to ensure the availability, integrity, and traceability of all records concerning these bioresources, we developed a workflow management system. The first step in risk management processes is to identify vulnerabilities and threats and then to assess the possible damage to determine where proper countermeasures should be implemented. All challenges require efforts not only from individual MRCs, but also from cooperation among MRCs, particularly internationally. In the future, the BCRC will continue to provide high-quality cultures, and genetic information facilities and techniques. The BCRC aims to support and promote partners engaged in general and applied research to enable them to accelerate their research and contribute to the development of the bio-industry in Taiwan.

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Introduction

Microorganisms, their cells, and replicable parts (e.g., genomes, plasmids, viruses, and complementary DNAs) are the tools for biotechnology and underpin the life sciences. They provide a major source of genetic information to solve problems in agriculture, industry, plant and animal sciences, and human health. The diversity of microorganisms plays a major role in maintaining the biosphere and provides vast resources for mankind. The total number of microorganisms is unknown, and they are difficult to study *in situ*. They may be transferred across borders by wind, water, and the movements of animals and humans. They are unlikely to be depleted by sampling; however, the loss of hosts can lead to the loss of dependent microbial species. Microorganisms that are isolated from natural or manmade environments are typically conserved in microbial resource centers (MRCs), be they public-service MRCs or specialized research MRCs. For the purposes of describing new taxa and acting as essential reference standards for future study and use, the conservation and accessibility of type strains (those on which the taxonomic description is based) and other representative isolates are fundamental. Furthermore, the *ex situ* conservation of all isolated microorganisms that have been studied and reported in the scientific literature would equally be important if science is to progress. The uncertainties associated with the re-isolation of strains underline the need for deposition in an MRC, where conservation skills and ready accessibility to specimens tagged with a conserved and unique reference number are provided. Without this, scientists would constantly need to conduct the skilled and expensive processes of isolation, characterization, and identification at the beginning of each new study. Careful documentation of all conserved materials and the availability of such data are essential tasks of MRCs.

Roles of MRCs

MRCs are the custodians of microbial diversity and play a key role in the storage and supply of authentic reference materials for research and development. MRCs are often regarded as living libraries and represent dynamic institutions of learning, research, scientific culture, and information. MRCs must be established with utility, particularly to serving scientific, industrial, agricultural, environmental, and medical research, and development of biotechnological applications, while providing protection for intellectual property. The benefits of the conservation and sustainable use of microbial resources, emphasized by the *Convention on Biological Diversity* (CBD), highlight the role of MRCs as *ex situ* protectors of

biodiversity. They also offer an important interface among governments, industry, and the public, helping policy makers and the public understand the value of conserving microbial resources.

Development of an MRC in Taiwan

The development of a microbial resource collection of Taiwan began in 1978. The idea of establishing an MRC was initially discussed at the first National Science Conference formally held in the same year. At the meeting, one important item was on the agenda: to preserve microbial cultures for industry.

In 1982 when the second National Science Conference was held, four science projects included ”Biotechnology” and ”Food technology” were added as the 7th and 8th national policy research projects. The Culture Collection and Research Center (CCRC) was then established in the Food Industry Research and Development Institute (FIRDI), a non-for-profit independent research institute, to support the project of the Ministry of Economic Affairs (MOEA) for industrial purposes in 1982.

It has been over two decades since 1982, when the CCRC/FIRDI initiated the work of microbial resources collection and preservation. The CCRC/FIRDI then became a member of the World Federation for Culture Collections (WFCC) in 1984. In 1987, on the initiative of the Council of Agriculture (COA) of the Executive Yuan, a long-term "Agricultural Microorganisms Bank" project was also assigned to the CCRC. An amendment to the Patent Law in 1994 allowed public ownership of microbial patents. The MOEA designated the CCRC/FIRDI as the national depository for microbial-related patent applications with the support of the government Intellectual Property Office (IPO). In 1998, the CCRC became a core facility of the National Health Research Institute (NHRI) as a cell bank to support the development of biomedical research. In 2001, the CCRC initiated a microbial genome project. The CCRC was then renamed in 2002 as the Bioresource Collection and Research Center (BCRC).

Challenges and opportunities for MRCs

It is time for changes in traditional culture collections. Operations of microbial collections have changed over the last decade as a result of advancements in bioinformatics and in the ability to present electronic data over the internet. In addition, the huge gap between the discovery of new microorganisms and their potential numbers in nature has stimulated an interest in microbial diversity and harnessing their genes, properties, and

products. Therefore, implementation of international criteria for quality management is now essential for MRCs to provide reliable and high-quality microbial resources and authentic information. MRCs now need to provide access to genes and genetic elements with associated information. Long-term and stable preservation of microbial resources is a crucial obligation of MRCs.

The CCRC was renamed in 2002 as the BCRC in accord with the expansion of collections of cells and genetic resources. Simultaneously with the name change from CCRC to BCRC, the center was reorganized into five working fields: (1) microbial resources, (2) cellular resources, (3) genetic resources, (4) development of bioresources, and (5) services for bioresources. The center was also subdivided into 13 working groups (Table 1). The functions and service platform of BCRC in Taiwan is shown in Figure 1.

Table 1. Structural framework of the BCRC/FIRDI

Working field	Working group
Microbial resources	Bacteria and yeasts
	Filamentous fungi
	Mushrooms
Cellular resources	Human and animal cell lines
	Stem cells
Genetic resources	Gene bank
	Functional genomics
	Bioinformatics
Development of bioresources	Genetic resource development
	Microbial resource development
	Fermentation
	Bioengineering processes
Services for bioresources	Bioresource services

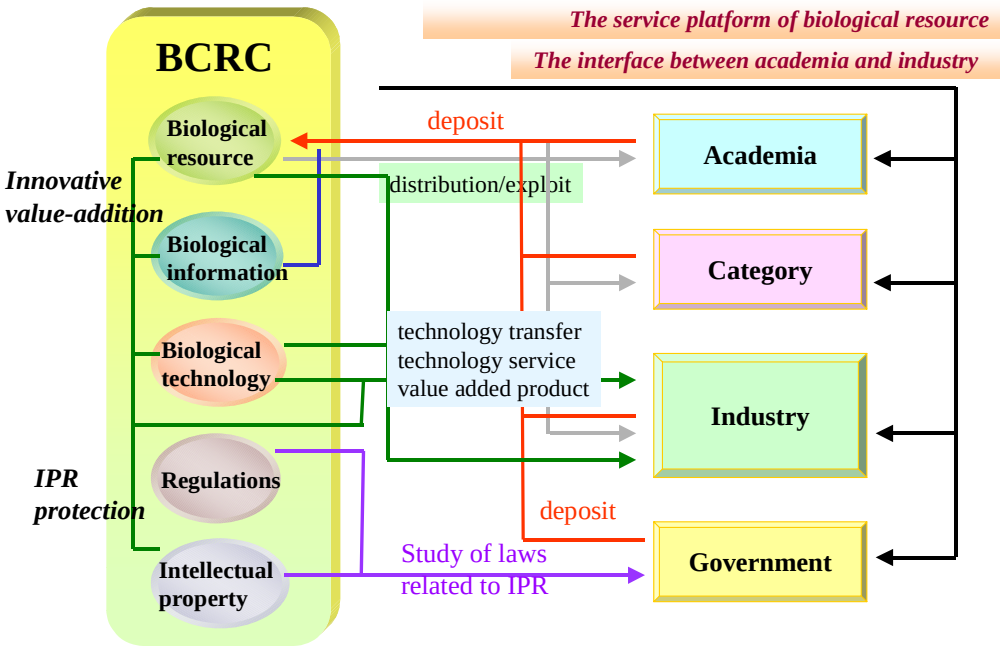

Figure 1. The functions and service platform of the BCRC/FIRDI in Taiwan

Establishment of an ISO quality management system at the BCRC/FIRDI

In 2001, the quality management system of the BCRC/FIRDI was audited and found to be compliant with ISO 9001:2000 requirements. The quality management system includes (1) a patent-related biological material depository, (2) contract microbial identification and tests, (3) cultivation and preservation of animal and human cells, (4) collection, preservation, and distribution of microbial resources, and (5) collection, preservation, and distribution of genomic and complementary DNA libraries.

The quality policies of BCRC in ISO 9001 include biodiversity, systematic management, professional services, and quality at the international level (Table 2).

Table 2. Quality policy statement of the BCRC/FIRDI

Biodiversity
1. Conserving biodiversity in the sprit of the *Convention on Biological Diversity* (CBD).
2. Offering services based on the diverse collection of bioresources.
Systematic management
1. Establishing documentation systems and standard operation procedures for all service processes.
2. Establishing an efficient, low-cost, and satisfaction-guaranteed management system.
Professional services
1. Establishing techniques for professional services.
2. Establishing service credibility.
Quality at the international level
1. Establishing a quality management system that meets ISO 9001 standards to achieve an international level of quality.
2. Ensuring satisfaction with products and services to establish a bioresource collection and research center of international standards.

Risk management of bioresource information and MRCs

The BCRC holds three domains of bioresources: microbial resources, cellular resources, and genetic resources. In order to ensure the availability, integrity, and traceability of all records concerning these bioresources, we developed a workflow management system to collect and manage all documents, information, and tasks from one participant to another for actions according to the procedural rules of deposition, preservation, storage, and distribution that are ISO 9001:2000 certified. To date, 891,701 bioresources are being held in the BCRC, and 971,645 related data are stored in the in-house database. External and internal users access the data through the internet and intranet. More than 650,000 man-hours are used to browse bioresource-related information per year. Therefore, information security is an important on-going issue for the BCRC. Risk management processes in terms of security should be considered.

The first step in risk management processes is to identify vulnerabilities and threats and then to assess the possible damage to determine where proper countermeasures should be implemented. The assets associated with information should be quantitatively and qualitatively measured, which will be helpful in determining the proper plan to reduce the

aspects affected by different threats. In the computerized environment of the BCRC, it is easy for web users such as hackers, employees, and contractors to exploit system vulnerabilities to cause harm to the network, databases, or online services. The tangible value of information assets is estimated to be at least TWD 4 billion. If there was irreversible impairment of the assets, they could be reconstructed. But the impact due to the loss of data, information, and intellectual property on BCRC's business and reputation would be inestimable. The best practice for BCRC's business continuity is to address each risk individually.

Countermeasures implemented by the BCRC are to reduce overall risks to an acceptable level. With strategies of building up prevention controls by monitoring safeguards such as firewalls, antivirus software, and vulnerability scanners, the risk from hackers and viruses can be reduced. To prevent unwanted incidents, all possible disasters are predicted, and annual disaster drills are planned and executed in case those events do actually occur. Once a disaster occurs, in order to rescue computer servers from irreversible damage, a recovery solution to reset and return the servers to their original configurations from a backup site is required. The damage can also be ameliorated by executing viable alternatives such as switching to mirrors which are synchronized with the production and which serve as a redundant environment to maintain the system performance during an emergency.

Access control by employees and contractors is hard to deal with using IT tools. Access authorities are defined according to the skill identification and management responsibilities. The system will look at some types of access control matrixes or compare security labels to verify that a subject may indeed access the requested resource and perform the attempted actions. But training and awareness programs should continually be implemented to prevent security incidents by staff members. The BCRC also executes regular monitoring and review procedures by auditors to determine and measure the effectiveness of its risk management. The last approach is to accept the risk, face the potential costs of damage, and then institute appropriate corrective controls to eliminate the cause of nonconformities in order to prevent a recurrence.

The major risks and strategic plans for risk management of an MRC by the BCRC/FIRDI in Taiwan are summarized in Table 3.

Table 3. Risk management of a microbial resource center by the BCRC/FIRDI

Type of risk	Risk	Strategy for risk management	
Collection of microbial genetic resources (MGRs)	Loss of local MGRs with unique properties	Exploit	Set up a special collection system to facilitate the collection of local MGRs
	Loss of scientific research achievements	Share	Publish "regulations for grants, deposits, and distribution of biological material"
	Limitations on the distribution of international bioresources	Enhance	Set up a service platform for bioresource distribution; Assist the importation of international bioresources
	Limitations on the acquisition and benefit-sharing of bioresources	Exploit	Actively participate in international cooperation (e.g., MOSAICS) to establish standards
	Limitations on isolation and preservation abilities	Enhance Share	Develop new isolation and preservation technologies; Promote cooperation with local research communities
Preservation of MGRs	Limitations on the preservation ability	Mitigate Enhance Exploit	Employ multiple types of preservation to reduce risks; Establish new preservation technologies; Establish a banking system for genetic resources
	Limitations on the identification and authentication abilities	Enhance	Develop new identification technologies

	Quality control	Enhance	The BCRC has received ISO Standard 9001 accreditation since 2001 and has maintained its quality assurance system with no nonconformities; Incorporate BRC guidelines
	Management of facilities	Mitigate Transfer Enhance	Establish backup systems to reduce risks; Acquire maintenance contracts for risk transfer; Maintain the best practices by continually renewing facilities
	Resource management	Transfer Enhance	Purchase insurance for the storage environment; Incorporate the ISO 9001:2000 quality assurance system
	Information technology ability	Enhance	Develop a workflow management system to collect and manage all documents and information; Build up prevention controls by monitoring safeguards
Distribution of MGRs	Distribution control for potentially hazardous microorganisms	Enhance	Develop a material transfer mechanism for appropriate management of access to and transfer of microbial resources
	Convention on Biological Diversity Quarantine regulations	Exploit Enhance	Actively participate in establishing standards (e.g., patent depository, regulations on genetic resources); Set up a service platform for bioresource distribution
	Packaging and transport control	Enhance	Comply with international regulations
	Customer relationship Management	Share	Create the greatest benefits for MRCs by customized and value-added technological services

Establishment of a biological material transfer mechanism at the BCRC/FIRDI

Being a multifunctional MRC, the BCRC/FIRDI implements ABS by establishing a biological material transfer mechanism and being involved in benefit-added biological material development.

For the transfer mechanism, the BCRC/FIRDI enacted a “regulation for deposits, donations, and distribution of biological materials” in 2003. The regulation, including material transfer agreements, sets out basic contract terms among biological material providers, recipients, and the BCRC/FIRDI. First, providers are encouraged to obtain prior informed consent from the country of origin. Second, providers may further define the terms they require, such as benefit-sharing provisions. The terms required by providers bind the recipients. The mutually agreed-upon benefit-sharing terms between providers and recipients are made possible by the bridge of the BCRC. Third, further transfer of materials from recipients to any third party is prohibited. Limiting further transfer to third parties can shorten the transfer chain along which microbial resources may be lost to monitoring of the transfer.

Along the microbial resource transfer chain, from an *in situ* resource origin to an *ex situ* resource isolator to an MRC to an *ex situ* resource user, being an important collector and provider for *ex-situ* microbial resources enables an MRC to monitor and track the resource flow (Figure 2). Thus, an MRC can play a role in realizing the ABS concept. First, an MRC can encourage prior informed consent by requiring proof of that consent when acquiring microbial resources from a provider. Second, by using a material transfer agreement in a biological resource center (BRC), the bridge of the MRC can facilitate the creation of mutually agreed-upon terms between providers and users of microbial resources.

Using molecular characterization of 852 of groundnut accessions using 21 SSR markers, we secured allele information on rare and unique alleles for hypogaea, and fastigiata cultivar groups and wild species accessions and accessions of geographic origin – Africa, America, Asia, Europe, and Oceania. The gene diversity in groundnut composite collection was 0.819. Wild relatives were more diverse than sub-species hypogaea and fastigiata. Groundnut accessions from Americas were more diverse followed by Asia and the gene diversity was minimum in germplasm accessions from Oceania.

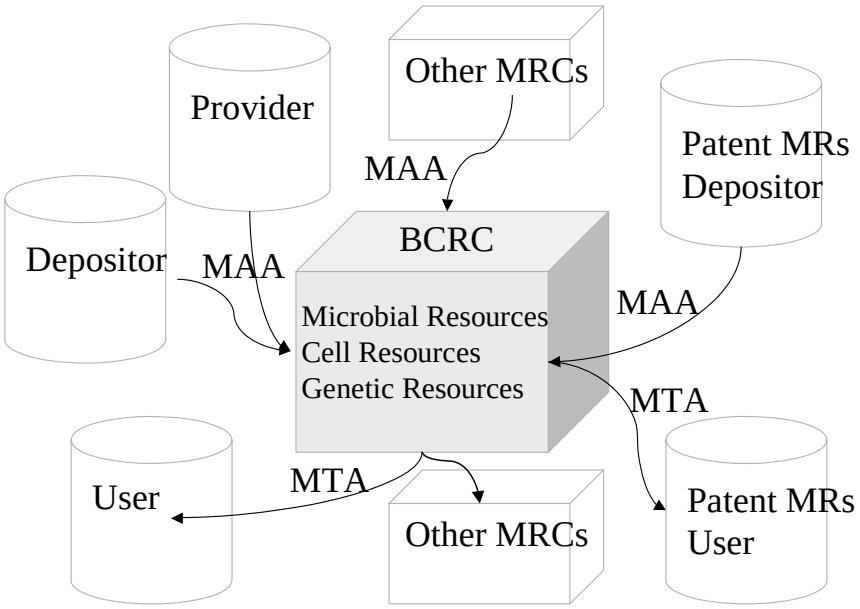

Figure 2. Transfer of microbial resources (MRs) from providers to users through the BCRC material transfer mechanism

The FIRDI was designated the national authority for the deposition of patent-related biological materials with the support of the government IPO in 1994. The patent-related depository work is processed based on “The Regulations and Rules of Microorganisms Deposits for Patent Purposes” and the standard operation procedure (SOP) of the quality control system (ISO 9001:2000). After acceptance of each case, the institute tests the deposited microorganisms for viability and then preserves them. To ensure the safety and confidentiality of the deposition, microorganisms and related documents and the storage room are operated under strict managerial regulations. Patented microorganisms are available to the public for research purposes upon request until the patent is granted. At the end of September 2008, the BCRC/FIRDI had accepted over 1500 microorganisms deposited for patent purposes of various types and from various countries.

As to issues of the transfer of microbial resources, there are national regulations about importation controls of microbial materials in Taiwan (Table 4).

Table 4. Importation controls of microorganisms and related materials in Taiwan

Governing issues	Plant protection	Animal protection	Human protection	Environmental protection
Governing authorities	Plant Division, The Bureau of Animal and Plant Health Inspection and Quarantine (BAPHIQ), Council of Agriculture, Executive Yuan	Animal Division, The Bureau of Animal and Plant Health Inspection and Quarantine (BAPHIQ), Council of Agriculture, Executive Yuan	Centers for Disease Control (CDC), Department of Health, Executive Yuan Bureau of Medical Affairs, Department of Health, Executive Yuan	Environmental Protection Administration, Executive Yuan
Related laws and regulations	*Plant Protection and Quarantine Act*	Statue for Prevention and Control of Infectious Animal Disease	*Communicable Disease Control Act* Regulations Governing Management of Infectious Biological Materials and Collection of Specimens from Patients of Communicable Diseases Statute For Transplantation Of Human Organs	*Environmental Agents Control Act* Regulation Governing Experimental Research for the Purpose of Developing Environmental Agent Using Genetic Engineering Microbial Preparations

Perspectives

Intellectual property rights (IPRs) are one of the efforts required from MRCs. Numerous challenges still remain in facilitating the exchange of microbial resources and technologies. For example, restrictions affecting access to microbial resources must be managed to accelerate the exchange process. Monitoring and tracking of microbial resources are priorities for realizing access and benefit sharing, and consequently can encourage resource exchanges. All challenges require efforts not only from individual MRCs, but also from cooperation among MRCs, particularly internationally. In the future, the BCRC will continue to provide high-quality cultures, and genetic information facilities and techniques. The BCRC aims to support and promote general and applied research partners to enable them to accelerate their research and contribute to the development of the bio-industry in Taiwan.