



Significance and future role of microbial resource centers



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ABSTRACT

Isolated strains constitute the basis for microbial systematics as well as for numerous applications in biotechnology, pharmacology, agronomy and public health. Microbial resource centers (mBRCs) are institutions capable of safeguarding, maintaining and distributing authenticated microbial strains, their genomic DNA and the associated data in a quality-controlled manner. They allow the deposit and distribution of type strains that form the basis of microbial taxonomy. Beyond taxonomy, deposited strains enable follow-up scientific studies and lead to a significantly improved recognition of scientific work. Considerable added value is generated through the labor-intensive steps of enrichment, enrichment screening, isolation, characterization, conservation and long-term storage of microbial strains. Here, a microbial strain is calculated to attain a value of 9836 Euro through its isolation and another 918 Euro through its deposit, adding up to a total value of 10,754 Euro. mBRCs provide a highly cost-effective way of preserving this value of microbial strains. A considerable future challenge of mBRCs will be to secure a larger fraction of strains that are isolated in research labs worldwide. mBRCs provide the expert knowledge and the cultivation and preservation skills crucial to access the large fraction of uncharted microbial diversity. mBRCs also provide the expertise and support the depositors of microbial resources to meet new legal challenges after implementation of the Nagoya Protocol. A suitable roadmap is described that allows mBRCs to meet the new demands emerging in science, technology and economy through an integration of novel technology, expansion of their duties and establishing an improved global mBRC network.

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Introduction

In microbial systematics, the classification and identification of microorganisms is founded on the comparison of physiological, biochemical and molecular characteristics of isolated strains (polyphasic approach [46]). In contrast to most multicellular organisms, microbial systematics thus relies on the availability of live cultures instead of the preserved specimen that usually suffice for plants and animals. Microbial strains are also instrumental for understanding and interpreting genome sequences, for elucidating novel biochemical reactions and metabolic pathways, and as reference organisms for microbial ecology research.

Aside from their fundamental relevance for the basic sciences, live microorganisms are required for numerous practical applications. Clinically relevant viruses, bacteria and fungi (e.g. strain

collectives recovered from outbreaks) are needed to analyze and reconstruct the emergence and dispersal of human pathogens, to identify their source and eventually to find an effective treatment of the associated infectious diseases [44]. Bacterial and fungal bioresources continue to be the prime source of novel bioactive compounds or lead structures [21]. About 60% of marketed pharmaceuticals are either derived directly from natural products or represent chemically modified derivatives [36]. Many more additional compounds are expected to occur in nature but still await their detection [28]. The development of novel medical treatments such as phage therapy [16] or the application of probiotics [6] relies on the availability of suitable and active microbial resources. Other isolates bear the potential for novel developments in the bioeconomy sector or provide solutions for problems in environmental protection and food safety. Thus, novel types of cultured microorganisms enable the decontamination of groundwaters [33] or have been applied as biological pesticides [43]. An appropriate knowledge of the systematics of these microorganisms is a precondition for their successful application.

The term ‘microbial resources’ has been coined to denote taxonomically defined, physiologically well-characterized, genetically

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stable, authenticated, well-documented, quality-controlled and long-term preserved strains of viruses, bacteria, archaea, fungi or protists. The term acknowledges that microbial strains constitute important assets for science, research and development. Microbial resources and the associated data have also been termed ‘microbial commons’ to emphasize that they typically are shared by a group of people who also participate in the decisions about their use [9]. Microbial resource centers (microbial domain Biological Resource Centers sensu OECD, mBRCs) are institutions capable of safeguarding, maintaining and distributing these microbial resources and the associated data. They maintain expert knowledge of microbial cultivation and systematics and protect the intellectual property that is associated with microbial strains. Through the implementation of quality assurance procedures, their legal expertise with regard to property rights, biosafety and biosecurity, as well as their scientific and database services, mBRCs fulfill many more tasks than conventional culture collections and play a pivotal role not only for bacterial systematics but also for the development of a sustainable bioeconomy [37]. This article highlights the current impact and challenges of mBRCs and describes a suitable roadmap that allows mBRCs to meet the new demands emerging in science, technology and economy.

Microbial resource centers lay the foundation for scientific progress

In microbial systematics, the role of mBRCs is well established. In order to decode microbial diversity and to classify and correctly name microorganisms, the type strains of validly described taxa constitute a basic prerequisite. It is mandatory to render this type permanently available and easily accessible for follow-up studies and future comparisons.

For the domains *Bacteria* and *Archaea*, the International Code of Nomenclature of Bacteria (previously, The Bacteriological Code) denotes the principles and rules for naming taxa, thereby regulating the valid description of species [26]. Alterations to the Code are adopted by the relevant authority, the International Committee on Systematics of Prokaryotes (ICSP), and are compiled online (<http://www.bacterio.net/-code.html>). According to Rule 18 of the Code, a verbal description, a preserved non-viable specimen, or an illustration does not qualify as the type for a species or subspecies description. Instead, types must be deposited as live, and replication-competent cultures in two recognized collections located in two different countries. Documents certifying the deposition and availability of type strains must be submitted for the publication of a valid description of a bacterial or archaeal species. Culture collections that qualify for the deposit of type strains are members of the World Federation of Culture Collections (WFCC) [57]. To date, 647 culture collections from 70 countries have registered [59].

Genome comparisons become increasingly important for the delineation of bacterial taxa and it is foreseeable that the valid description of novel bacterial species will be based on their entire genome instead of just the 16S rRNA gene sequences as is current practice [46]. In addition, genome sequences of validly described species permit an in-depth comparison with so-far-uncultured bacteria in natural populations. A large part of future taxonomic work is thus expected to be conducted *in silico*. mBRCs will play a key role in this transition since they will be capable of providing standardized and high-quality genomic DNA of existing type strains to feed coordinated sequencing programs (e.g., the GEBA project of the DOE Joint Genome Institute, CA, USA [61]) which will allow to build up the necessary sequence database. Beyond this transitional phase, however, the DNA banks of mBRCs will enable laboratories that are not specialized in cultivation to easily access microbial diversity for subsequent genetic work (e.g., heterologous

expression). This will be particularly important for fastidious or slow growing bacterial strains that require knowledge of specific cultivation techniques. In order to prepare for these new tasks, a considerable fraction of mBRCs (58% of the largest culture collections registered by the WFCC) have already established dedicated DNA banks (e.g., see the European Microbial DNA Bank Network; www.microdnabank.eu/microdnabank/Availability). While high-molecular-weight, quality-controlled genomic DNA is likely to be a constituent of the deposited material of type strains in the near future, it appears unlikely that a deposit of genomic DNA can serve as type material on its own (compare [46] in this special issue) since subsequent physiological investigations require live bacterial strains.

However, besides serving as reference centers for taxonomical work, microbial resource centers are of vital importance for the biological sciences in general. Taking the Leibniz-Institute DSMZ as an example, a total of 11,020 scientific publications that were published over the last 30 years referred to strains held in the DSMZ collections (WDCM Analyzer for Bio-Resources Citation database; <http://abc.wfcc.info/index>). Of these, 63% of the publications appeared in journals that are not dedicated to bacterial systematics, thus demonstrating the need for and the scientific value of well-curated microbial resources for research. Particularly over the last 15 years, publications based on DSMZ strains have been increasing steadily, reaching 1055 papers (referencing 1531 strains) in 2013 alone. No doubt the scientific value of microbial resources will continue to increase.

Well-curated and preserved microbial resources are especially valuable since they permit innovative follow-up scientific studies once novel experimental techniques become available. For example, microbial resource centers supplied the isolated representatives of bacterial lineages previously not covered by whole genome analysis. Next-generation genome sequencing of these strains subsequently led to the discovery of a plethora of novel protein families and new types of functional proteins [61]. Another notable example is the revival of the long-lost homoacetogenic *Clostridium acetium* [60] from a 34-year-old stock culture that was still available [4]. This strain then became a valuable model for subsequent microbiological studies [35].

Furthermore, scientific articles associated to deposited strains receive >220% more citations than controls [15]. Thus, the access to a larger fraction of cultured microbial diversity clearly fosters future scientific work. Also, the improved recognition of own research results should provide a major incentive for scientists to rapidly deposit and secure their newly isolated microbial resources in public culture collections.

Microbial resource centers maintain the value of live isolates

Given that microbial strains constitute important assets for science and commercial applications, can a monetary value be assigned to them when they are still present in their natural habitat *in situ* or when they are maintained *ex situ* as pure culture isolates? This monetary value of microorganisms has implications for (1) the valuation of microbial systematics and diversity research, (2) the assessment of the financial requirements and cost effectiveness of mBRCs, (3) the valuation of a nation's microbial resources for consideration in national accounting systems and (4) the fair and equitable access and benefit-sharing (ABS) within the framework of the Nagoya Protocol and the Convention on Biological Diversity (CBD).

Undoubtedly, microorganisms that fulfill key functions in the environment are of direct economic relevance. In the case of arbuscular mycorrhiza, the economic value of microbial phosphorous mobilization can readily be estimated by the cost of phosphorus fertilization that is required to sustain similar levels of plant

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