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Microbiological Research Under the Nagoya Protocol: Facts and Fiction

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The Nagoya Protocol is based on concepts of biological diversity that are hardly applicable to microorganisms. Because of this incongruence, the Nagoya Protocol threatens future microbial research, potentially defeating its original purpose. Countries with appropriate regulations can promote science and their bioeconomy through international collaboration and simultaneously gain a competitive advantage.

Political Motives and Legal Framework of the Nagoya Protocol

The Convention on Biological Diversity (CBD; www.cbd.int) was signed in 1992 in the face of large-scale species extinction and driven by the need for a more sustainable use of biodiversity. The CBD treats biodiversity as a valuable global asset and recognizes the sovereignty of a state over its biological resources and the associated traditional knowledge. It attempts to resolve the dual interests of developing and industrialized countries by supporting conservation and sustainable use of biodiversity, sharing of benefits, and the transfer of knowledge and technologies through scientific cooperation. To harmonize the implementation of the CBD among signatories, the *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity* (in short, Nagoya Protocol or NP; Box 1) was adopted in 2010 in Nagoya, Japan. The NP seeks to create predictable conditions and legal certainty for the use of genetic resources. It specifies means for the sharing of benefits and defines mechanisms of compliance: signatory states are obliged to ensure the legal use of foreign genetic resources and the benefit sharing within their jurisdiction and to punish violations. The NP entered into worldwide force on October 12, 2014.

Are Concepts of the Nagoya Protocol Commensurate with the Biology of Microorganisms?

Based on current scientific knowledge on the biology of microorganisms, we offer here three reality checks on central concepts which underlie the NP.

NP Concept 1: Provider Countries Host Unique and Unmatched Biodiversity

The majority of biodiversity hotspots are located in developing countries [1], which has raised expectations that the latter can serve as providers of genetic resources and obtain monetary and non-monetary benefits when genetic resources are exported and used in industrialized countries. Yet, the scientific definition of biodiversity hotspots is based on high diversity and habitat loss of vascular plants as a proxy for all biodiversity.

Scientific Facts Biodiversity hotspots and local endemisms have not been detected for many microorganisms which display a biogeography very different from macroorganisms. For example, bacterial diversity was fourfold higher in a Canadian soil than the 5000 bacterial species detected in a Brazilian oxisol with similar acidity [2]. In sharp contrast to animals and plants, bacterial diversity does not decline with elevation in Eastern Peru [3]. Microorganisms have very high dispersal rates and can cross the Atlantic within 3 days [4]. In addition, they feature very large population sizes. Accordingly, microbes tend to be cosmopolitan; recent whole-genome analysis has confirmed high sequence identity (97 to > 99%), similar gene content (up to 93%), and identical secondary metabolites of bacterial strains isolated up to 18 000 km apart [5,6]. As another example, *Streptomyces carpaticus* strains isolated from coastal habitats in Indonesia, Madagascar, Sao Tomé, Portugal, Sicily, and Mexico all produced the same cytotoxic compound (Ikarugamycin) [7]. Geography-dependent differences in sequences have only been detected in very isolated, island-type, environments like geothermal hot springs and are limited (e.g., 1% of all sequence positions), and selectively neutral [8,9]. Similarly, multiple groups of fungi are cosmopolites. Others, such as the plant-associated (ectomycorrhizal) fungi, differ in species composition between geographic regions, but their functions do not show any biogeographic pattern. Even if bacterial species were limited to certain (larger) regions, their functions are likely to be found in other species because of the frequent lateral gene transfer that can move complex traits [10] and entire biosynthetic pathways between bacterial lineages [11]. These facts negate the macroorganism concepts of diversity hotspots, local endemism, and potential extinction for microbes. Consequently, the political expectation that microbiologists must seek out individual provider countries to access unique microbial biodiversity is not scientifically supported. In fact, developing and industrialized countries are of similar attractiveness for microbial bioprospecting as 1 gram of a single soil type from Europe or North America already contains five times more bacterial species than are currently validly described, and as the diversity of the ectomycorrhizal fungi or of several other noncosmopolitan fungal groups is actually highest in temperate or boreal ecosystems.

NP Concept 2: Genetic Resources Are a Natural Capital Which Can Be Directly Evaluated and Often Even Monetized to Promote the Domestic Bioeconomy and Conservation Alike

A central mechanism of the CBD and the NP is to create economic incentives for the protection and sustainable use of biodiversity by capturing the value of genetic resources (and associated traditional knowledge). Highly publicized biopiracy

Box 1. Key Elements of the Nagoya Protocol and Their Implementation

The Nagoya Protocol applies for all genetic resources under the jurisdiction of a member state, except for human materials. Consequently, regions outside the sovereign territories of states, such as the open ocean, the deep sea, and Antarctica are exempted. Complicance with the Nagoya Protocol requires the user to legally acquire and document any genetic resource, declare and prove due diligence through traceability, risk assessment and risk mitigation procedures, and enable inspections by national authorities. Each signatory state can determine its own access policy or can provide free access to its own genetic resources and the associated traditional knowledge (as is the case for, e.g., Germany). However, most states grant access only after receiving sufficient information on, and agreeing to, the planned work (prior informed consent, PIC), and through a contractual agreement stating the conditions for using genetic resources and for benefit sharing (Mutually Agreed Terms, MAT). In practice, numerous countries cover the latter aspects through a Material Transfer Agreement (MTA) which specifies the origin, provider, recipient, and the modalities of use and distribution of the genetic resource.

Within their territories, states grant access and enforce compliance through their national authorities. These bodies include National Focal Points responsible for the national policy, National Competent Authorities coordinating the implementation of the Nagoya Protocol and providing the PICs, and Checkpoints monitoring the actual usage of genetic resources. All agreements for work under the Nagoya Protocol are bilateral between user and provider (represented by its National Competent Authority). If work does not encompass individual organisms, for example, in ecological research, access and benefit sharing does not need to be considered. However other types of permit (e.g., sampling permit or export permit) may be required. The flow chart in Figure I depicts a typical procedure for establishing research on genetic resources under the Nagoya Protocol in a foreign country.

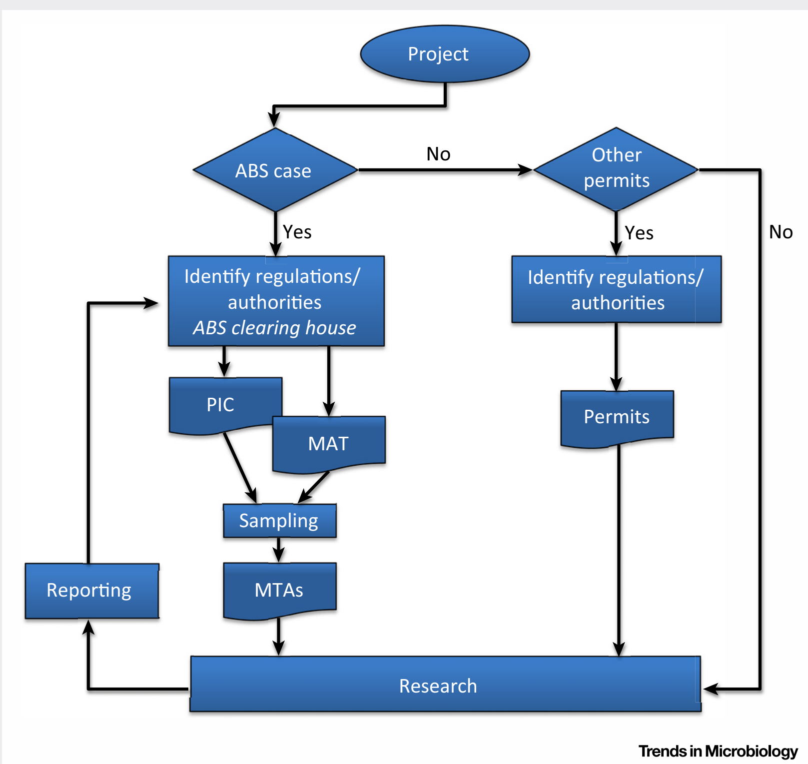

Figure I. Flow Chart Depicting a Typical Procedure for Establishing Research on Genetic Resources Under the Nagoya Protocol. Whether a new (international) project is an 'ABS case' depends on whether the country in question is a Party to the NP, which can be determined in real-time on the ABS Clearinghouse website. If the country is not a party to the NP, there may still be other national legislation that is relevant. Notably, Antarctica and international waters (usually > 100 km offshore) are currently excluded from the NP. All NP-related documents must be maintained for at least 20 years following the initial access and/or use of the genetic resource.

litigation cases [12] demonstrate that provider countries sometimes assume that commercial application is straightforward and that genetic resources have an inherent value which must be carefully negotiated for all use cases.

Scientific facts Microorganisms are in unlimited supply. Based on economic principles, the monetary value of microbes in natural samples is therefore negligible (see references in [7]). Instead, microorganisms require a substantial financial investment for isolation and characterization prior to any use. The isolation of a single bacterial strain incurs average costs of about 10 000 Euros in Europe and 5000 Euros in India [7]. Up to 100 000 uncharacterized strains are statistically needed to yield one single pharmaceutical product. The tremendous costs of isolating this number of strains (1 billion Euros) need to be added to the downstream development costs. Unsurprisingly, industry has largely given up on such untargeted screening campaigns for natural compounds. Economic theory predicts that microbial genetic resources still buried in a natural sample will find hardly any customers. In addition to a better knowledge of the microbial diversity actually present in a country, the financial demand for initial isolation must therefore be factored into realistic negotiations of benefit sharing.

NP Concept 3: Independent of the Type of Use, the Key Measures for Fair Benefit Sharing Are to Strictly Control the Access to Genetic Resources, Control Their Dissemination, and Tightly Regulate International Export

In the NP, the term 'use' covers all scientific, noncommercial, and commercial activities, including basic research. The term 'genetic resources' covers not only the genetic materials themselves, but also natural biochemical compounds that are produced by the genetic resources. Some developing countries also restrict the dissemination of nucleic acid or amino acid sequence information (e.g., their deposit in public databases), although this