COMMENT

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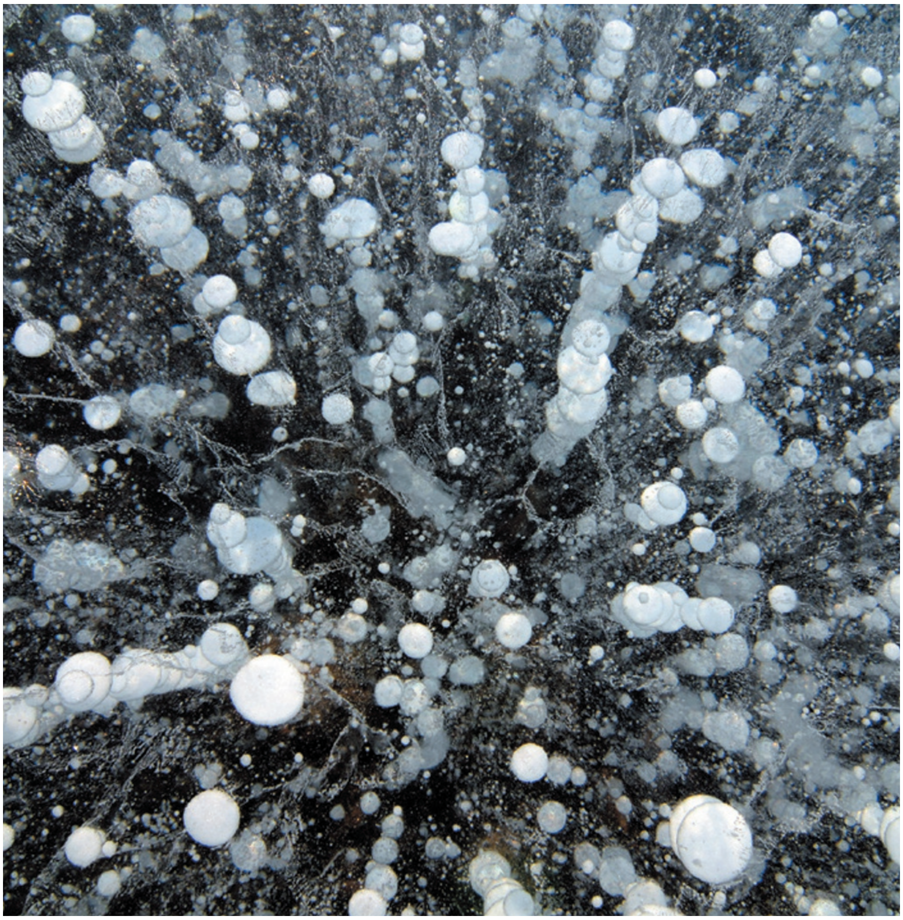

CLIFF LEIGHT/GETTY

Even extreme environments such as Antarctic ice lakes host microbes.

Create a global microbiome effort

Understanding how microbes affect health and the biosphere requires an international initiative, argue **Nicole Dubilier**, **Margaret McFall-Ngai** and **Liping Zhao**.

Microbes have been discovered on Earth wherever anyone has looked for them, from the boiling waters of Yellowstone's hot springs in Wyoming to the depths of cold, dark Antarctic lakes under 800 metres of ice. A holistic understanding of the role of Earth's microbial community and its genome — its microbiome — in the biosphere and in human health is key to meeting many of the challenges that face humanity in the twenty-first century, from energy to infection to agriculture.

Recognizing this, a group of leading US scientists this week proposes[1] the creation of a Unified Microbiome Initiative (UMI). The UMI would bring together researchers and representatives from public and private agencies and foundations to study the activities of Earth's microbial ecosystems.

The UMI is conceived as a US initiative; springing from meetings sponsored by the White House Office of Science and Technology Policy and the Kavli Foundation of Oxnard, California. But Earth's biome is not defined by national borders, and efforts to unlock its secrets should go global.

We believe that to be successful, microbiome research will require a coordinated effort across the international community of biologists, chemists, geologists, mathematicians, physicists, computer scientists and clinical experts. As three scientists working in three countries — Germany, China and the United States — we call for an International Microbiome Initiative (IMI) supported by funding agencies and foundations around the world, in addition to the UMI. This would ensure the sharing of standards across borders and disciplines, and bring cohesion to the multitude of microbiome initiatives that exist.

MICROBIAL REVOLUTION

Science is only just realizing the full importance of the microbial world. This is thanks to developments such as low-cost high-throughput sequencing; advances in sample preparation that allow researchers to sequence genomes from individual cells as well as from microbial communities; improvements in computing power and imaging technologies; and the development of bioinformatics tools to help make sense of the data.

Thus biologists are gaining insight into the identity and function of microbes that cannot be grown in the laboratory — the vast majority of Earth's microbiome. Currently only 35 bacterial and archaeal phyla are recognized on the basis of classical approaches to microbial taxonomy. Sequencing efforts in the past few years have pushed the number closer to 1,000 (ref. 2).

Newfound groups of bacteria are throwing old assumptions about the tree of life into question, and revealing vast holes in our ▶

understanding of the planet's biosphere and its evolution. The discovery in 2003 of giant viruses with hundreds or even thousands of genes shattered the existing definition of living organisms[3]. (Viruses had long been considered to straddle the line between living and non-living things because of their extreme reliance on host genes.)

It is also becoming clear that microbes provide ecosystem services that are crucial to local and global sustainability. The microbiota in and on crops, trees and other plants, and in the soils in which these grow, provide nitrogen, phosphorus and other essential nutrients. They break down pollutants and suppress the activity of pathogenic microbes. Recognizing the untapped power of soil and plant microbiomes in enhancing agricultural productivity, companies such as Monsanto are investing millions of dollars in research and development in this area.

Microbes in the oceans produce 50% of the oxygen we breathe, and — through photosynthesis — remove roughly the same proportion of carbon dioxide from the atmosphere. They also remove up to 90% of methane from the world's oceans. Over the past decade, research cruises such as Tara Oceans and the Global Ocean Sampling Expedition have sampled, sequenced and analysed the ocean's microorganisms. These have provided insight into the roles that marine bacteria, archaea, viruses and eukaryotic microbes have as global primary producers that provide nutrition at the base of the food chain; remineralization (the transformation of organic molecules into inorganic forms); and the deposition of carbon on the sea floor.

Some of the most profound insights in the crucial role of microbes for human well-being have emerged from analyses of the microbes on and in our bodies — their genomes, transcriptomes, proteomes and metabolomes. (These are analyses of genes, RNA molecules, proteins and chemical metabolites). Complex gut communities, for instance, protect us from disease, provide nutrition, and affect our development even before birth[4].

STUMBLING BLOCKS

There are two major stumbling blocks to advancing our understanding of microbes' role in the biosphere. First is the fragmentation of the life-sciences field. Second is a lack of coordination among the various microbiome research endeavours under way.

Disciplinary silos are problematic because any attempt to understand anything about plants or animals needs to be rooted in microbiology. For example, for decades, circadian rhythms in the mammalian gastrointestinal system were studied in the context of human physiology and gene expression. Yet in the past two to three years, biologists have discovered that daily cycles in the motility of the gut — the production of digestive enzymes, gene expression in gut cells and so on — rely on the activities of gut microbiota. Compounds produced by microbes either cause changes in the gut directly or pass into the host's bloodstream and influence the central nervous system, possibly through neural, hormonal and immune pathways[5].

The first hint of this came from the discovery (led by one of us, M.M.-N.) that bioluminescence and other products of the marine luminous bacterium *Vibrio fischeri* regulate the expression of a circadian cryptochrome gene in squid[6]. This highlights the value of investigating host–microbe relationships from all branches of the tree of life, including those in which only a single symbiotic species is involved.

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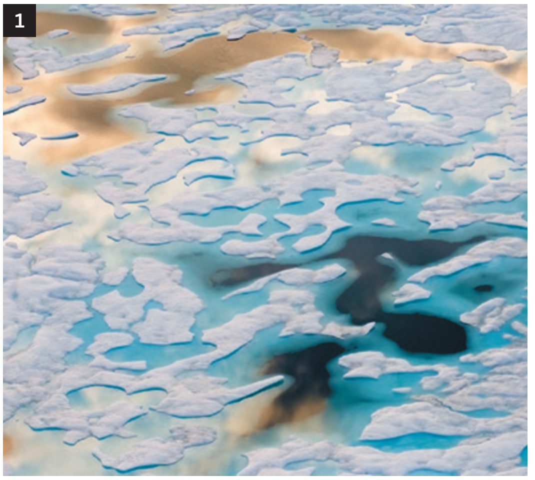

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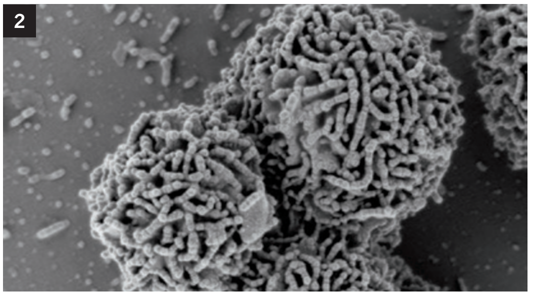

PROJECT PROBLEMS

Since a 2005 workshop in Paris, at least eight programmes have been established to study the human microbiome. These include the US Human Microbiome Project, the Canadian Microbiome Initiative, MetaHIT (involving the European Union and China) and the Human Metagenome Consortium in Japan.

These initiatives have generated vast amounts of data that are not easily comparable. For example, many studies on human microbiota identify species (or operational taxonomic units) and map evolutionary relationships using the 16S ribosomal RNA gene. Differences between the primers (which provide a starting point for the DNA synthesis) used to amplify this gene can have a big effect on the sequence data ultimately obtained. And estimates of species numbers can vary by two to three orders of magnitude, even when applied to the same sample, because different software packages are being used to analyse the amplified genes[7].

This lack of consistency in approaches means that effective comparisons and interpretations of human microbiota studies are often not possible. The International Human Microbiome Consortium, established in 2008, and the International Human Microbiome Standards project, launched in 2011, have attempted to address some of these

GOING GLOBAL

Four functions of an International Microbiome Initiative

Guidelines. Create a working group to oversee the development and implementation of guidelines for the study of microbiomes, drawing on and developing those already established by other initiatives such as the Earth Microbiome Project. The group would set standards for methods, data analysis, data sharing and intellectual-property rights, and would partner with funding agencies and publishers to ensure that researchers follow the agreed guidelines.

Priorities. Develop a common research agenda, with the goal of enabling comparative analyses that range from local to global scales. For instance, one priority could be to increase the number and diversity of people sampled in studies of the human microbiome.

Tools. Identify new cross-disciplinary methods for microbiome studies. Examples include imaging techniques ranging from confocal advances to cryotomography — which can resolve subcellular structure and reveal microbial cell function — and ways to monitor the production and exchange of microbial metabolites.

Forums. Establish platforms for the discussion and exchange of research within and between nations, the development of programmes for training the next generation of microbiome scientists, and the establishment of outreach projects to educate and engage the general public. A good model is the Ocean Sampling Day's citizen's science campaign, which recruits citizens to help obtain environmental data.

Microbes such as *Planococcus halocryophilus* (2), cyanobacteria (4) and *Arthrobacter crystallopoietes* (5) are found everywhere from soils (6) to the Arctic's Chukchi Sea (1) to Yellowstone's Grand Prismatic Spring (3).

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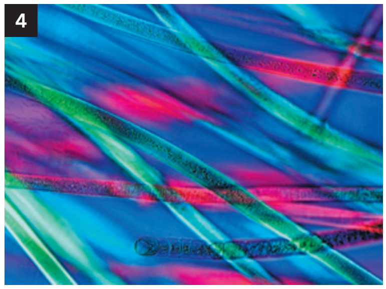

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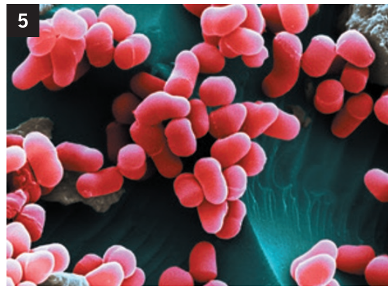

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1. STEVEN KAZLOWSKI/GETTY; 2. N. C. S. MYKYTCZUK *ET AL. ISME J.* **7**, 1211–1226 (2013)/NPG; 3. PETER ADAMS/JAI/CORBIS; 4. MAREK MIS/SPL; 5. EYE OF SCIENCE/SPL; 6. FRANS LEMMENS/ALAMY

issues. But, especially in the case of the standards project, many national research projects were already well under way. Both initiatives are struggling with issues about data sharing and differences between national policies in ownership and property rights.

GLOBAL SOLUTION

We think that an IMI could do a better job. The study of any microbiome demands myriad collaborations. These should involve basic and applied biologists, including those with expertise in microorganisms or in higher organisms; informaticians and mathematicians, who can develop methods that extract information from the mountains of sequence data; and chemists, physicists and engineers. Physical scientists are needed to find new ways to measure and manipulate the compounds that microbes produce and exchange with their biotic and abiotic surroundings.

An IMI would be pivotal in bringing together all these experts and allow scientists to move beyond cataloguing, which has characterized much of microbiome work so far. And, it would be limiting to recruit such a vast range of intellectual, scientific and technological expertise from one country alone.

IMI participants could use comparative approaches to reveal the factors that underlie the structure and function of microbiomes on local to global scales. An example of the potential of comparative approaches comes from studies of Native Americans[8] and African hunter-gatherers[9]. It seems that these groups have a much higher diversity of microbial partners (a known correlate with better health) than do people living in industrialized societies.

By pooling data from scientists from around the world, an IMI would generate much more knowledge than could one country alone. Thanks to the falling costs of sequencing machines, individual labs will probably soon produce more data than the conventional large sequencing centres, such as the Joint Genome Institute in Walnut Creek, California. Yet for any one laboratory, sample sizes might be restricted, and researchers might have only limited bioinformatics capacity.

An IMI could encourage the integration of data across institutions and nations. This is especially important for countries that may not have the funds to invest in their own global-scale projects. For example, cloud-computing platforms would allow people to upload and analyse sequencing data as soon as they are available. The IMI could also control and organize access to metadata (the associated host disease phenotype data, for a human gut microbiota sample, for instance) without which meaningful interpretation of the data is not possible. This could also be a way to safeguard the intellectual property of researchers, funding bodies and nations.

> ***"We urge scientists to help make an IMI happen by sharing their data."***

Most importantly, an IMI is essential when it comes to solving problems that affect the biosphere. Although processes involving microbiomes vary from place to place, the impact of such processes can often be felt globally. Potent greenhouse gases, such as nitrogen oxides produced by denitrifying bacteria in overfertilized Chinese farming lands or methane released by archaea in the millions of ruminant animals in Australia and New Zealand, may have contributed substantially to global warming. Billions of tonnes of human-made toxic chemicals have overwhelmed the degrading and recycling capacity of microbiomes. And the imprudent use of antibiotics has contributed worldwide to epidemics of chronic diseases, such as obesity, diabetes and cancer. The solutions to some of these problems may come out of local research, but an IMI is essential for ensuring that comparable data are produced from efforts throughout the international scientific community.

We do not have all the answers when it comes to designing an IMI. In fact, we think that the first step to launching such a project should be the bringing together of leading microbiome researchers from across the globe to discuss its goals. However, even at this stage, some elements seem crucial (see 'Four functions of an International Microbiome Initiative').

As long as communities are prepared to start afresh and conform to new ground rules, we believe that an IMI could succeed where other efforts to achieve standardization and coordination have struggled. Such a project would be ahead of the curve, because the tools needed to explore the world's microbes have only recently become available. Also, if multiple working groups with representatives from across the life sciences were established — similar to those set up by an effort to assess marine organisms called the Census of Marine Life — an IMI could be much broader in scope than any pre-existing programme.

Finally, an IMI would be able to solve the data sharing and intellectual-property issues that have been stumbling blocks for previous efforts, by organizing and controlling access to the metadata that are so essential for interpreting results, publishing papers and filing patents.

It is crucial that the IMI is launched quickly to avoid corrective actions having to be applied after-the-fact to national efforts. We invite private foundations that have been pivotal in mounting international research efforts to support an IMI. These include the Gordon and Betty Moore Foundation with its Marine Microbiology Initiative, the Alfred P. Sloan Foundation with its Census of Marine Life, the Kavli Foundation with its Brain Initiative, and the Bill & Melinda Gates Foundation with its Global Health Program.

We also encourage national funding agencies to open up their programmes to international collaborations and to adopt any standards established by an IMI. Finally, we urge scientists to help make an IMI happen by sharing their data.

So much can be gained by creating an IMI. Further uncoordinated national microbiome programmes will almost certainly waste research efforts and taxpayers' money. Let's transcend national silos and gain universal insights that will benefit all humankind. ■

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KAROL KOZLOWSKI/ALAMY

The world's oldest continually operational university was founded in Fes, Morocco, in AD 859.

Revive universities of the Muslim world

To boost science, higher-education institutes must give students a broad education and become meritocratic, say **Nidhal Guessoum** and **Athar Osama**.

The Islamic civilization lays claim to the world's oldest continually operational university. The University of Qarawiyyin was founded in Fes, Morocco, in AD 859, at the beginning of an Islamic Golden Age. Despite such auspicious beginnings, universities in the region are now in dire straits, as demonstrated by a report we have authored, released this week (see go.nature.com/korli3).

The 57 countries of the Muslim world — those with a Muslim-majority population, and part of the Organisation of Islamic Cooperation (OIC) — are home to nearly 25% of the world's people. But as of 2012, they had contributed only 1.6% of the world's patents, 6% of its academic publications, and 2.4% of

CORRECTION

Reference 1 in the Comment 'Create a global microbiome effort' (N. Dubilier *et al. Nature* **526,** 631–634; 2015) gave incorrect page numbers. It should have read: Alivisatos, A. P. *et al. Science* **350,** 507–508 (2015).