

NEW BUSINESS OPPORTUNITIES CREATED BY MICROBIAL COMMUNITIES

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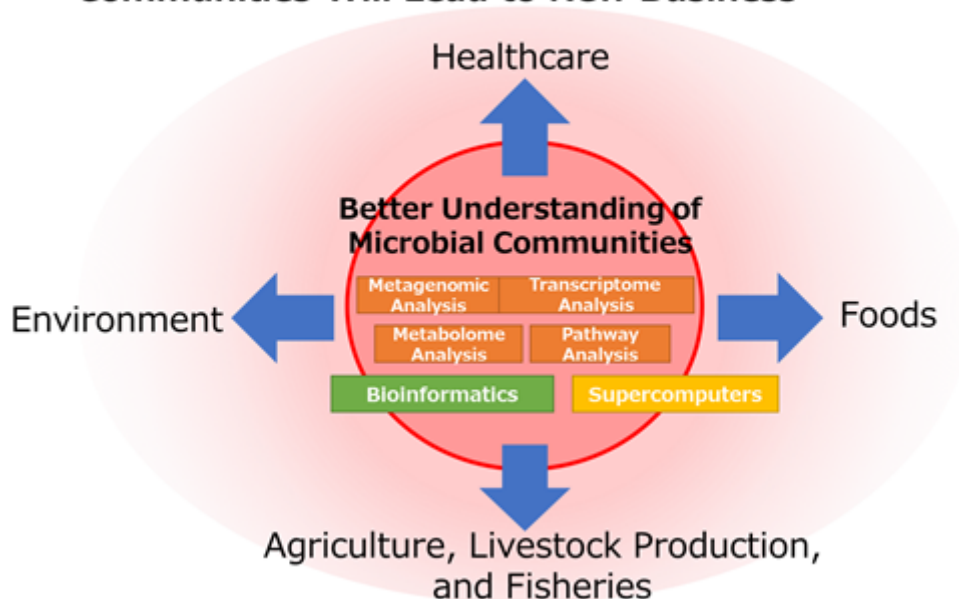
RICH DIVERSITY OF MICROBIAL COMMUNITIES

The use of microorganisms dates back several thousand years. The manufacturing process of fermented foods, such as cheese, bread, and wine, was established long before the 10th century BC. After many years, various products using microbes, including industrial enzymes and antibiotics, were created in the 19th and 20th centuries. Note, however, that these products have used less than 1% of microorganisms living in the environment, with the remaining 99% left unused. Up to the 20th century, research on microbes centered on those that can be isolated and cultured, while those for which it was difficult to do so or those for which methods had not been established were rarely subjects for study. As such, it was largely unknown before this century began what kind of microbes exist in the world and what their functions are.

In 2004, Dr. J. Craig Venter, a pioneer in genomic research, carried out “metagenomic analysis” of DNA sequences derived from the entire microbial population of a specific region of the sea (i.e., without cultivating each microbe) and revealed the kinds and proportion of marine microorganisms present. The project attracted great attention as a new method to analyze microorganisms. With the arrival of next-generation sequencing technologies that make genomic sequencing faster and cheaper, metagenomic approaches are increasingly being used. Meanwhile, data obtained from such next-gen sequencers are statistically processed. The processing of a vast amount of data took more than two weeks in the past, but it now takes only six minutes thanks to supercomputers’ processing speed and capacity.

With the huge advances in analysis technologies, we have come to know that microbes exist in diverse locations of the earth (including the human body, animals and plants, soil, marine water, and the atmosphere) by forming a community where they interact with each other, and it is difficult for them to exist alone. It was also revealed that such communities coexist with animals and plants, and influence each other. By focusing on and utilizing the positive impact of microbial communities on human beings, animals, and plants, companies can create new business in several areas, such as healthcare, foods, agriculture, livestock production, fisheries, and the environment (Chart 1).

Chart 1: Better Understanding of Microbial Communities Will Lead to New Business



Our particular focus is on emerging business opportunities in foods (utilization of enteric microbial communities) and agriculture (that of plant-microbe communities).

UTILIZATION OF ENTERIC MICROBIAL COMMUNITIES – KEY FACTORS FOR PERSONALIZED WELLNESS

Health Benefits Provided by Enteric Microbes

Probiotics are live microorganisms that have a positive effect on health, such as lactic acid bacteria and bifidobacterium. According to market research company Euromonitor, the market for yogurt, supplements, and sour milk drinks (lactobacillus drinks, etc.) containing probiotics expanded from USD 30 billion in 2010 to USD 40 billion in 2016. It may top USD 50 billion by 2020, with particularly strong growth expected in Asia and North America.

Major factors behind this anticipated growth include significant progress in scientific research on probiotics. Recent research outcomes show that microbial communities that inhabit the human intestinal tract, including probiotics, affect not only the digestive system, but also the immune, nervous, and endocrine systems, by transmitting substances to/from the intestine. The correlation and causation between enteric microbes and various diseases, such as digestive disorders, allergy, obesity, diabetes, cancer, multiple sclerosis, liver illness, autism, and asthma, are being clarified.

Based on such study results, major manufacturers of probiotics products, including Danone (based in France), Probi (Sweden), Chr. Hansen (Denmark), Yakult Honsha, Morinaga Milk, and Meiji Holdings, have started to develop new products, such as supplements to alleviate stress, powdered milk formulas to reduce allergic responses, yoghurt to prevent colds, and supplements to combat celiac diseases.

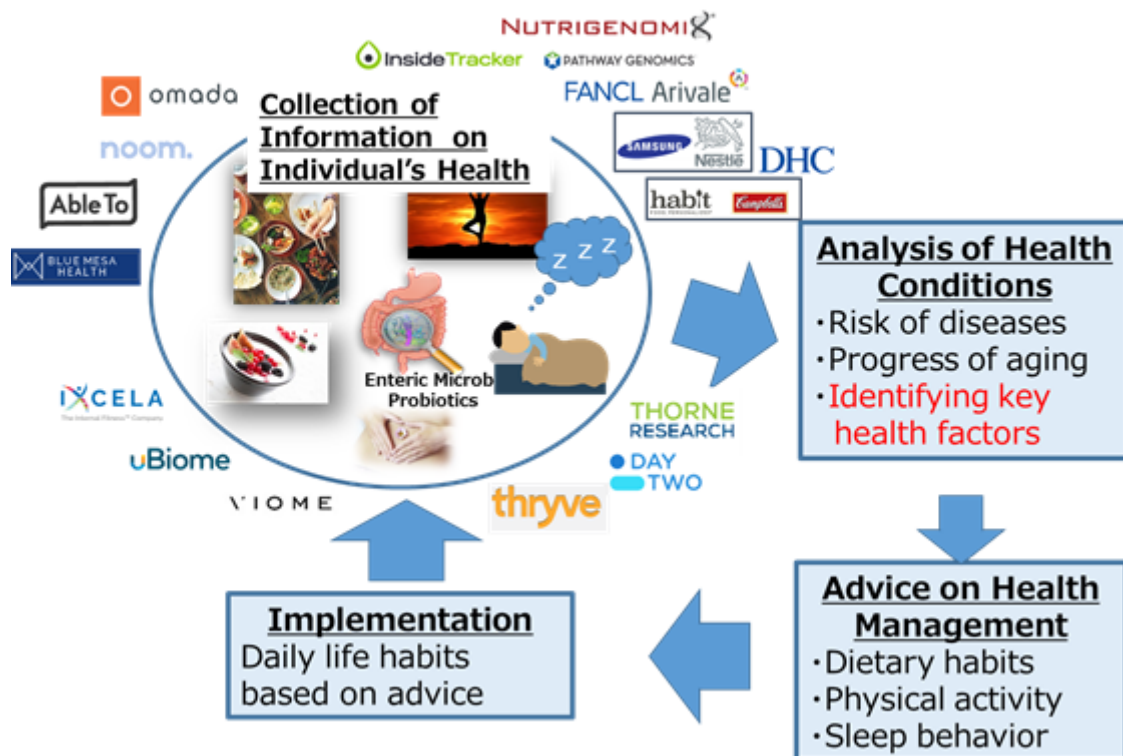
Some companies are also developing cutting-edge personal care products. For example, probiotics companies Hyperbiotics (based in the US), AB-Biotics (Spain), and BioGaia (Sweden) developed tablets to prevent tooth decay and reduce gum inflammation. British Beauty Bay created probiotics skincare products, and French

leading personal care company L'Oréal is exploring effects of probiotics on recovery of skin damage caused by UV rays.

Business Opportunities in Personalized Nutrition and Personalized Wellness

In the food sector, new business opportunities related to personalized nutrition are attracting attention. Chart 2 illustrates the concept of personalized nutrition, in which information on an individual's health is collected/analyzed and used to offer advice on health management.

Chart 2: Image of Personalized Nutrition



So far, the collection/analysis of information has focused on genetic and lifestyle information, including physical activity, sleep behavior, and dietary habits. Going forward, personalized nutrition business that analyzes enteric microbial communities and offers probiotics products to improve their conditions will likely expand. The number of genes of enteric microbes is said to be 2-20 million vs. only about 20,000 in the case of human genes. As such, information on human genes may be insufficient to understand health and diseases. Better understanding of enteric microbial communities will be a key factor to control health conditions.

In the personalized nutrition business, providing functional foods and other solutions can be one of the main earnings sources. A number of probiotics, including but not limited to lactic acid bacteria and bifidobacteria, have been found. Synergy effects between these probiotics and prebiotics (oligosaccharide, dietary fiber, etc.), which are food for probiotics, also warrant attention. Companies engaged in the personalized nutrition business need to hold a variety of probiotics and prebiotics as a portfolio, rather than relying on a single microorganism, in order to deliver optimal solutions. They also need to provide scientific evidence including clinical data to promote the health benefits. For players in the food sector, it is worth considering collaborating on R&D with those in the healthcare sector.

As mentioned above, probiotics and prebiotics can be used for cosmetics and oral care products. General trading companies, which deal with a wide range of products, should not limit the scope of their personalized nutrition business to foods, but aim to expand into the wellness business, including personal care products.

Of note, the use of new probiotics and prebiotics may be regulated from the viewpoint of safety, depending on the country or region. Therefore, it is necessary to find a consultant who has expertise in each region and facilitate communication with regulators for a smooth startup of the business.

MICROORGANISMS LIVING IN THE PLANT (PHYTOBIOME) – REVOLUTION IN AGRICULTURE –

Benefits of Utilization of Plant-Microbe Communities

An enormous number and variety of microorganisms live in, on, or around a plant. They form a community, interact with the plant, and are deeply involved in each step of the plant's growth, from sprouting to harvest. It is well known that some microorganisms provide benefits to the plant. For example, certain microorganisms help a plant grow faster. The rhizobia of leguminous plants have the ability to fix nitrogen and convert it to ammonium nitrogen, which is used for bio-fertilizer.

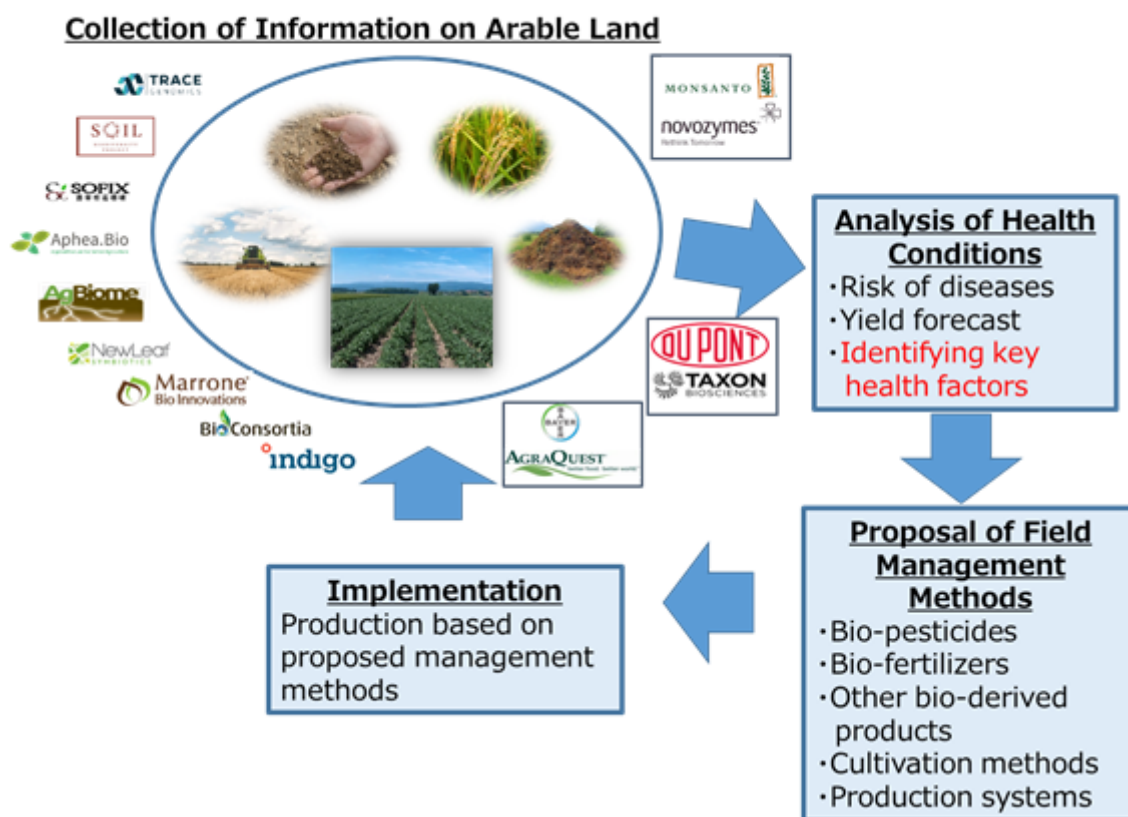
The progress in analysis techniques will enable us to look at the overall picture of microbial communities and understand the structure and behaviors of microorganisms more precisely. By selecting microorganisms that have a significant influence on communities, we can promote the activities of microbial communities, enhance their growth, and control pest and disease, which will contribute to the healthy development of a plant.

Amid technological innovations, major agrochemical and seed companies have already started to focus on the microbial communities of plants. For example, Monsanto and Novozymes formed a partnership (the BioAg Alliance) in 2013 and launched growth enhancers and other products. Meanwhile, DuPont acquired US startup company Taxon, which is strong in analysis of microbial communities, in April 2015. It is establishing a microbial genomics platform and developing a technique to effectively select microorganisms. Bayer Cropscience acquired AgraQuest, a supplier of biological pest management solutions, in 2012. It also started a joint venture in 2017 with Ginkgo Bioworks, which breeds microbes, to develop technologies for nitrogen fixation.

Business Opportunities in Agricultural Design

Agricultural design using microbial communities has received a lot of attention. As shown in Chart 3, agricultural design is to collect/analyze information on health conditions of arable land, propose management methods suitable for each field, and grow agricultural products based on such proposal.

Chart 3: Image of Agricultural Design



The adoption of agricultural design using microbial communities could lead to optimization of the cultivation environment, substantial reduction in the use of agrochemicals, and production of high value-added products (e.g., antioxidant-rich crops). It will significantly affect existing agrochemical and fertilizer business and may drastically change the way agriculture is conducted.

One of the business models using agricultural design is to propose/offer field management methods as a total package solution. Microbial communities interact with plants and work as partners of plants for their healthy growth. We see the need for proposing/offering solutions to activate microbial communities and thereby facilitate healthy development of plants. For example, we can provide bio-pesticides and bio-fertilizers, seeds treated by such materials, as well as chemical fertilizers and pesticides which generate synergy effects with bio-pesticides and bio-fertilizers. We can also propose cultivation methods and offer total solution packages to optimize the cultivation process. Agricultural design brings innovation to agriculture, and potential providers of total package solutions, which will probably include seeds companies, agrochemical manufacturers, and agricultural machinery makers, should work together with farm producers. They need to expand their portfolio of products and services that affect microbial communities, as their solutions need to deal with various crops, diseases and pests, as well as growing environments.

While agricultural design enables eco-friendly production and the production of value-added agricultural products like functional crops, such products are not always accepted by consumers. As such, it is necessary to capture consumer demand and provide what they want. If general trading companies conduct business involving agricultural design, they need to engage in not only production, but also distribution and retail so that they can capture consumer demand and look at the overall food supply chain. They are also expected to support

farm producers, as it is necessary to optimize cultivation methods and secure higher profits for producers in order to promote the idea of agricultural design.

Cross-Disciplinary Measures/Efforts

As described above, microbial communities offer new business opportunities related to the “health of human beings” and the “health of soil and plants”. Of note, there are moves to connect these opportunities. Agri Garden School & Academy, an agriculture business school established in Fukuoka Prefecture in 2014, is working to grow farm products that make people healthy by utilizing microbial communities, with the aim of creating a multidisciplinary industry covering medicine, agriculture, and science. Meanwhile, Tokyo University of Agriculture and Showa University concluded a comprehensive cooperative agreement in August 2018 to promote cooperation in the fields of medicine, agriculture, and biotechnology.

In promoting cooperation between agriculture and medical fields, the utilization of microbial communities is keenly anticipated. On the medical front, some bacteria have mutated into drug-resistant bacteria due to improper use of antibiotics, including excessive use, and antibiotics are not effective against such drug-resistant bacteria. In agricultural, livestock and marine products, synthetic chemicals including antibiotics are also excessively used, leading to the emergence of drug-resistant bacteria. Drug-resistant bacteria derived from livestock and farmed fish spread to the surrounding environment via their excrement, but the activities of drug-resistant bacteria are restrained if microbial communities function well. As such, we see more business opportunities to develop/sell products that replace some antibiotics and help maintain microbial communities. Such products will probably include probiotics, bio-pesticides, vaccines, and bacteriophages (a group of viruses that infect specific types of bacteria, including drug-resistant bacteria).

In order to maintain and utilize microbial communities, the medical, foods, agriculture, livestock, and fishing industries should work together. General trading companies, whose business fields cover these areas, can play the role of connecting players in various fields. This cross-sectoral approach has something in common with the “One World, One Health” concept. This is the slogan declared by health experts from around the world who met at the Rockefeller University in 2004. It is based on the idea that it is important to establish a holistic approach to maintain ecosystem integrity for the benefit of humans, animals, plants, soil, and water. Microbial communities will not only lead to business opportunities in the future, but also help solve global issues and contribute to society.

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