Yakult's research activities: The inheritance and practice of Shirota-ism

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Figure 1: Analysis of intestinal epithelial cells with a confocal laser scanning microscope. The induction of Th17 cells by segmented filamentous bacteria was visualized using a technique called immunofluorescence.

We contribute to the health and happiness of people around the world through our pursuit of excellence in life sciences and our research and experience in microorganisms.

Yakult's business activities began with founder Dr Minoru Shirota's pursuit to build a body that is resilient to disease. The origins for Dr Shirota's beliefs are in the philosophy of Shirota-ism, which encompasses the concepts of preventive medicine, the idea that a healthy intestinal tract leads to a long life, and to offer products at a price that everyone can afford. Shirota-ism has withstood the test of time and continues in the research and development activities at the Yakult Central Institute.

Here we describe our efforts to address the ultimate challenge: to understand the significance of gut microbiota in maintaining human health and to share the results of our probiotic studies.

FROM THE INTESTINAL TRACT TO THE ENTIRE BODY

The Yakult Central Institute fulfils its aim to support the foundation of probiotic research by scientifically verifying the effect that microbes inhabiting the intestine have on the human body from both clinical and non-clinical perspectives. The human intestinal tract contains approximately 1,000 different species of bacteria that form the gut microbiota. Gut microbiota have a variety of physiological effects on the host. Research on gut microbiota has rapidly developed on an international scale in recent years. The influences of gut microbiota on the host are not limited to intestinal diseases, but can also have an effect on cancer and mental health. The Yakult Central Institute uses a variety of methods, including the latest gene sequencing analysis and technology to isolate intestinal bacteria. The research is helping Yakult scientists to discover how the type and composition of intestinal bacteria are connected to the onset of illness and to elucidate the functions of gut microbiota, including the effects on the health of the host, from the perspective of preventive medicine.

ADVANCED RESEARCH CAPABILITIES

Through our research on gut microbiota we have shown that *Bifidobacterium longum*

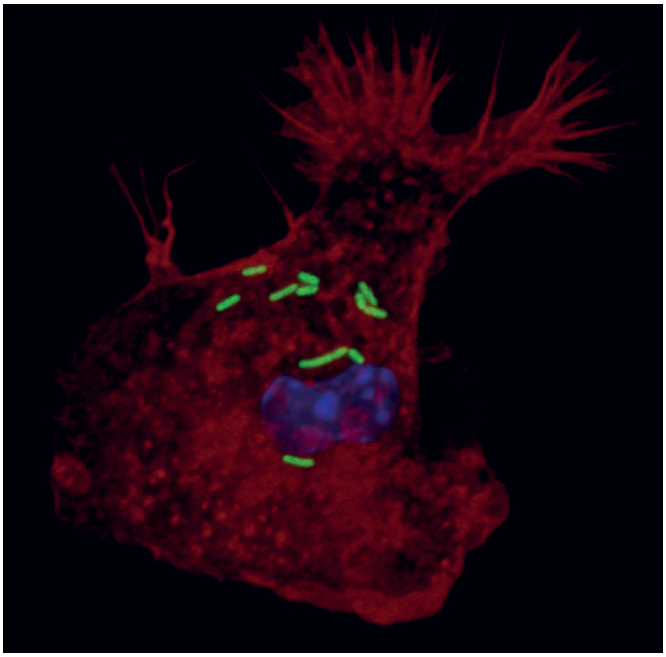

Figure 2: *Lactobacillus casei* strain Shirota (stained green) incorporated in a macrophage (the cytoplasm is stained red and the nucleus is stained blue). Findings suggested that the macrophage is key to the immune regulation of *L. casei* strain Shirota.

is passed on from mother to newborn during vaginal delivery[1]. We also demonstrated that segmented filamentous bacteria (intestinal bacteria present in a wide range of mammals) are involved in the induction of Th17 cells, which are helper T cells that play an important part in the cellular immune response[2] (**Fig. 1**). Additionally, Yakult Central Institute has established a system that enables precise and extensive analysis of gut microbiota called YIF-SCAN®[3]. Based on genetic sequences that are unique to each species of intestinal bacteria, YIF-SCAN® selectively quantifies the bacteria, enabling us to rapidly identify a wide range of bacteria, from highly populous bacteria to those that are relatively few in number.

LACTOBACILLUS CASEI STRAIN SHIROTA HAS BEEN DEMONSTRATED TO REGULATE IMMUNITY IN THE BODY

PROPRIETARY PROBIOTICS

The idea of using microorganisms such as *Lactobacilli* and *Bifidobacterium* as probiotics to contribute to human health has gathered increasing attention in recent years. The concept is identical to the ideas of 'preventive medicine' and 'a healthy intestinal tract leads to a long life' that were advocated by the company's founder, Dr Shirota. The Yakult Central Institute has focused on the potential of microorganisms since it was founded and continues its tireless research to develop products aimed at contributing to people's health. Among the probiotics investigated at the institute are *Lactobacillus casei* strain Shirota and *Bifidobacterium breve* strain Yakult, and through safety studies and long-term consumption trials we have confirmed that these probiotics survive digestive juices such as gastric fluid, reach the intestines alive, and produce beneficial effects[4,5].

EFFECTS ON CANCER AND INFECTIOUS DISEASES

Research has shown that lactic acid bacteria can be beneficial to human health. The probiotic *L. casei* strain Shirota is one example and ingestion of this strain has been shown to regulate immunity in the body, including through the maintenance and restoration of natural killer activity, which plays a vital part in innate immunity[6] (**Fig. 2**). Some reductions in the risk of bladder[7], colon[8] and breast cancer[9] have been reported. *L. casei* strain Shirota is also known to be effective in reducing the incidence and mitigating the symptoms of various infectious diseases, such as gastroenteritis caused by acute infantile diarrhoea[10], upper respiratory tract infection[11] and norovirus[12].

LEVERAGING THE POWER OF PROBIOTICS

The results of research activities at Yakult Central Institute are applied to fields beyond product development. One example of our research accomplishments is synbiotic therapy, which is utilized in medicine. Synbiotics is a combination of probiotics and prebiotics, which functions to help increase the number of beneficial bacteria in the intestines. Synbiotic therapy is being used in medical institutions, and there are numerous reports of its usefulness in preventing postoperative infection, assisting the recovery of immune functions and improving nutritional conditions. The therapy has been particularly helpful in this respect for gastroenterological surgery, where there is a high risk of microbial infection[13].

YAKULT DNA: DR MINORU SHIROTA AND SHIROTA-ISM

In 1930, Dr Minoru Shirota (**Fig. 3**) of the department of microbiology at the school of medicine at Kyoto Imperial University, Japan, showed for the first time that the reinforced culture of a lactic acid bacterium was beneficial for human health. The bacterium was named *L. casei* strain Shirota after taking the name of Shirota.

When Shirota began researching the therapeutic uses of *Lactobacilli* in preventive medicine, microbiological research in the field of medicine was in its early days. Successful identification of the Shirota strain was 23 years after the Russian scientist Ilya Mechnikov, who was jointly awarded the 1908 Nobel prize in physiology or medicine with Paul Ehrlich for their work on immunity, announced yoghurt's eternal life agenda[14]. Because of his research and achievements, Dr Shirota could be described as a pioneer of preventive medicine.

Shirota established the ideas behind his research activity to investigate preventive medicine that would help to maintain healthy intestines and to ensure that products could be sold at a price that everyone could afford. This philosophy is continued as Shirota-ism by the research and development activities at the Yakult Central Institute. The concept of probiotics, meaning symbiosis with microorganisms, is to suppress the growth of harmful bacteria in the intestine by the action of useful microorganisms to maintain intestinal health and prevent the onset of illness.

As the state-of-the-art research institute in the field of probiotics, the Yakult Central Institute is pursuing life sciences to advance and develop its research and contribute to human health.

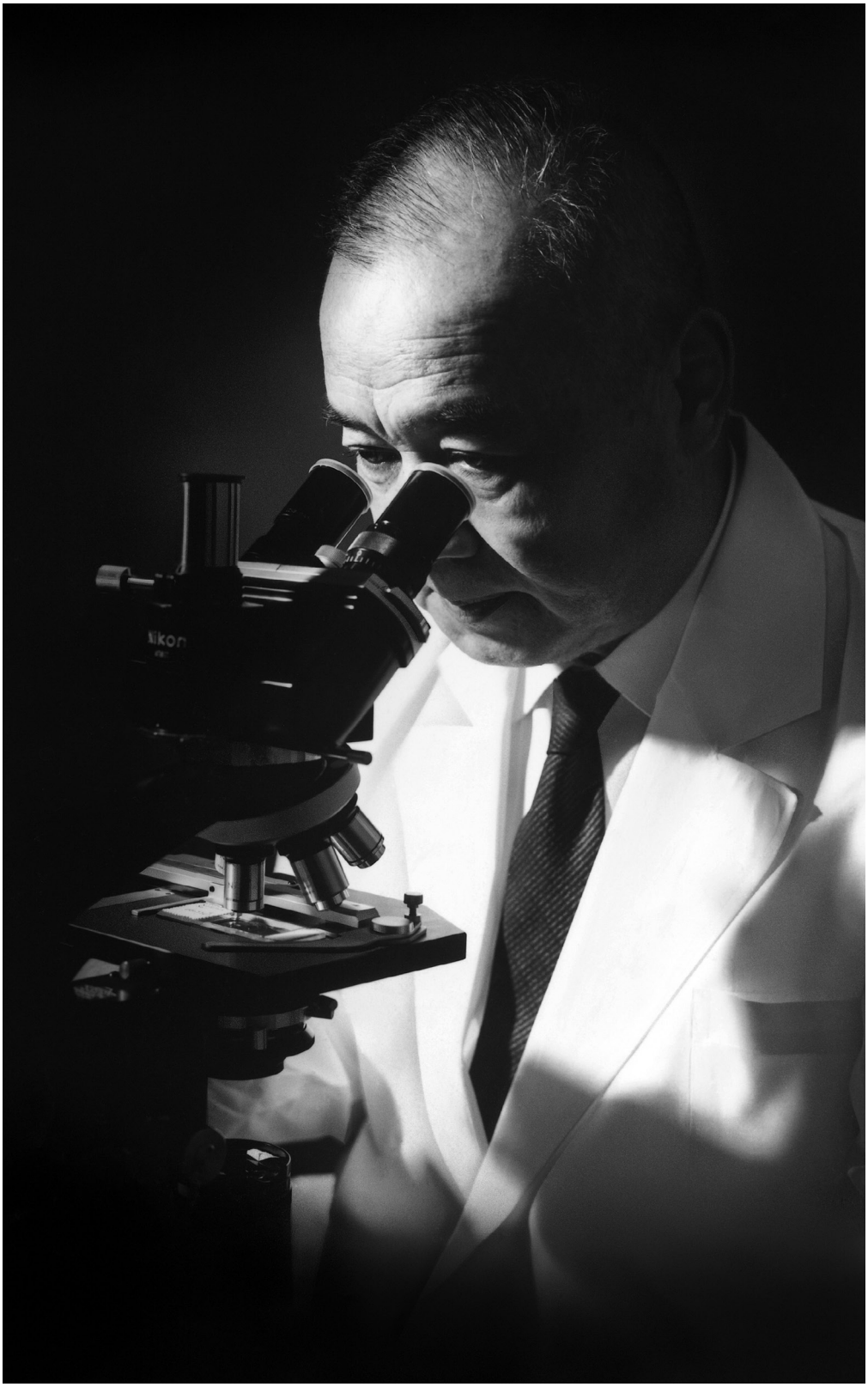

Figure 3: Dr Minoru Shirota (1899–1982).

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