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

Yakult

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

In 1935 Yakult was established. Five years earlier, with the passionate desire to "deliver good health to as many people as possible", Dr. Minoru Shirota M.D., Ph.D. who was founder of Yakult succeeded in fortifying and culturing a strain of beneficial lactic acid bacteria that could reach the intestines alive, and set about providing it in the form of a drink. Since then, the fruit of his passionate desire has continued to spread across the globe and, as of fiscal 2019, Yakult's dairy products are consumed daily by 40 million people in 40 countries and regions. Yakult is imbued with this passionate desire from our founding and it is part of everything we do, including the development, manufacture and sales of pharmaceuticals and cosmetics.

Under our corporate philosophy of "we contribute to the health and happiness of people around the world through pursuit of excellence in life science in general and our research and experience in microorganisms in particular," we will continue to work for the benefit of our stakeholders, and first and foremost, our customers.

THE BEGINNING OF YAKULT: THE PURSUIT OF PREVENTIVE MEDICINE LEADS TO A FOCUS ON THE POWER OF MICROORGANISMS

Yakult was born out of the passion of Minoru Shirota, M.D., Ph.D (**Fig.1**). In the early 20th century, when the future Dr. Shirota was still a young man, poor hygiene and nutrition led to the deaths of many people in Japan from infectious diseases such as cholera and dysentery. Disturbed by this reality, the young man set his sights on medicine and began studying at Kyoto Imperial University (now Kyoto University) in 1921. He started down the path of microorganism research, focusing on preventive medicine, which places emphasis not on treating illnesses, but on trying to prevent them. As part of his research, he discovered that lactic acid bacteria suppress harmful bacteria in the intestines. In 1930, he succeeded in strengthening and culturing a strain of lactic acid bacteria that could survive digestive juices, such as gastric fluid and bile, reach the intestines alive, and produce beneficial effects. This strain is now known as *Lactobacillus casei* strain Shirota. With the goal of providing this lactic acid bacteria to as many people as possible, Dr. Shirota developed an affordable and delicious fermented milk drink and released it under the name of Yakult in 1935. This marked the start of Yakult, which has since found popularity all around the world.

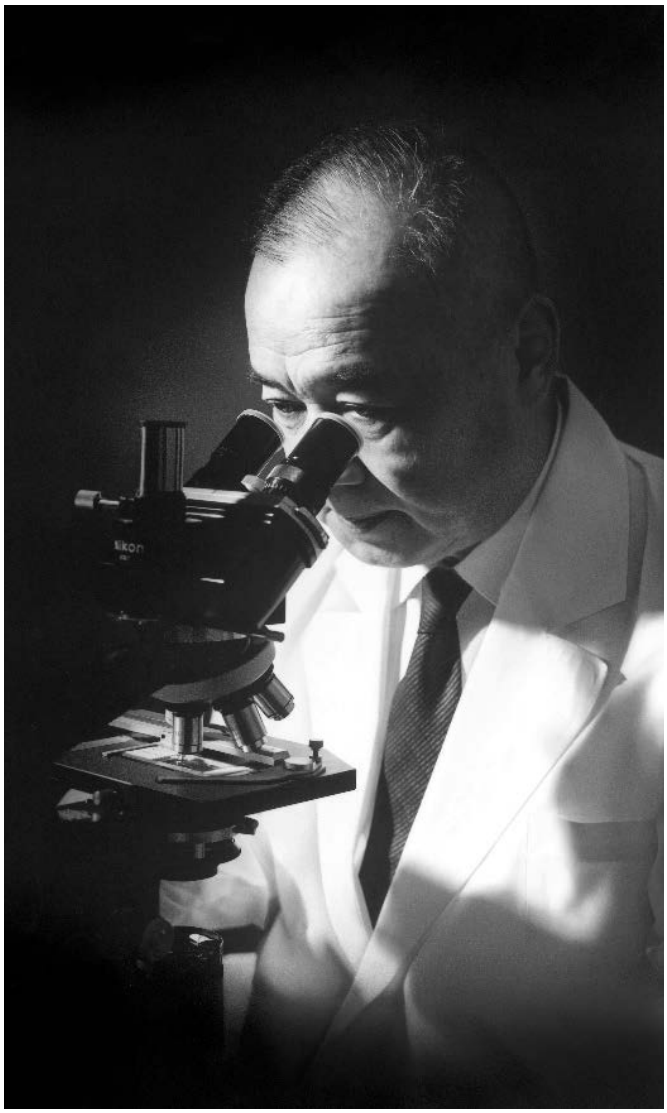

Figure 1. Dr Minoru Shirota (1899–1982).

SHIROTA-ISM: DR. SHIROTA'S IDEAS REMAIN AT THE HEART OF ALL OUR BUSINESS ACTIVITIES

Dr. Shirota proposed certain key ideas, such as preventive medicine, which together, we call Shirota-ism. This serves as the foundation and the guide for all of our business activities so that by "caring enough to make home deliveries", we also strive for the ideals of "sincerity" and "harmony

among people".

The ideals of the company's founder have endured to the present day, unchanged by time and today Shirota-ism is still at the heart of Yakult.

Since its founding, Yakult has consistently pursued research tapping into the potential of probiotics. With the goal of contributing to the healthy lives of as many people as possible, we will continue to devote our efforts to discovering new powers of microorganisms and using those powers to further contribute to health.

YAKULT'S PROBIOTICS: MAKING USE OF OUR CAREFULLY SELECTED, PROPRIETARY MICROORGANISMS

The idea of using microorganisms such as lactobacilli and bifidobacteria as probiotics to contribute to the health of people, has gathered an increasing amount of attention in recent years. This concept is identical to the "preventive medicine" and "a healthy intestinal tract leads to a long life" ideas advocated by the company's founder, Dr. Shirota. Yakult has focused on the potential of microorganisms since its founding and through tireless research continues to develop products aimed at contributing to people's health. Among these probiotics are *Lactobacillus casei* strain Shirota. As a result of a number of safety studies as well as long-term consumption studies as part of the company's research activities, we have been able to confirm that these probiotics survive digestive juices such as gastric fluid, reach the intestines alive, and produce beneficial effects[1].

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RESEARCH AND DEVELOPMENT ACTIVITIES AT YAKULT: ELUCIDATING THE FUNCTION OF PROBIOTICS AND DEVELOPING PRODUCTS THAT CONTRIBUTE TO THE HEALTH AND HAPPINESS OF PEOPLE

Product development at Yakult, including for foods, cosmetics, and pharmaceuticals, is founded on research and development. In order to realize preventive medicine and contribute to people's health, we focus on beneficial microorganisms, particularly the intestinal microbiota, and investigate the relationship between the intestinal microbiota and overall health from a variety of angles, including molecular biology, immunology, physiology, and nutrition. We use the results of these efforts in the development of food, cosmetics, and pharmaceutical products. We are also focused on investigating microorganisms and natural products whose functions have so far escaped notice and are proactively researching these as potential new ingredients.

The Yakult Central Institute is the company's hub for research and development, and is comprised of seven buildings with advanced research equipment and facilities (Research Administration Building, Basic Research Building, Food Research Building, Pharmaceutical and Cosmetic Research Building, Quality and Technical Development Building, Common Use Facility Building, and Energy Supply Building). In this enriched environment, we conduct a wide range of research including basic research, applied research focused on the development of food, cosmetic and pharmaceutical products, and an analysis business dedicated to safe production and environmental protection.

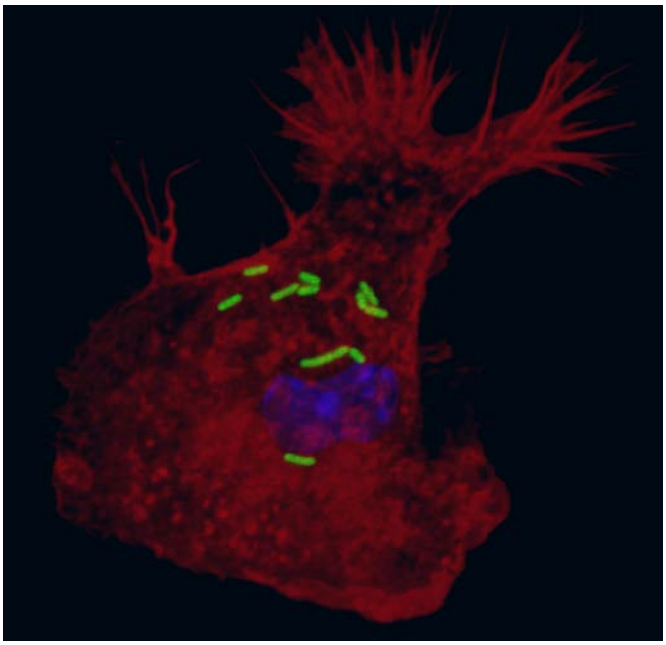

Figure 2. *Lactobacillus casei* strain Shirota (stained green) incorporated in a macrophage (the cytoplasm is stained red and the nucleus is stained blue). Findings suggested that the macrophage is the key to the immune regulation of *Lactobacillus casei* strain Shirota.

RESEARCH AND ACHIEVEMENTS IN A VARIETY OF AREAS: YAKULT HAS MAINTAINED ITS FOCUS ON PROBIOTICS WITH THE AIM OF ELUCIDATING THE BENEFITS OF LACTIC ACID BACTERIA AND INTESTINAL BACTERIA

Since its founding Yakult has been engaged in basic research of probiotics and intestinal microbiota, which are now the topics interesting many researchers in the world. Yakult has collaborated with other research institutions in recent years as part of its focus on exploring the further potential of probiotics.

Years of research has shown that lactic acid bacteria bestow a variety of benefits. The probiotic *Lactobacillus casei* strain Shirota is a case in point. Ingestion of this strain has been demonstrated to regulate immunity in the body, including through the maintenance and restoration of NK activity, which plays a vital role in immunosurveillance[2] (**Fig.2**). It also helps to rid the body of harmful mutagens, potentially reducing the risk of cancer[3]. Some reductions in the risk of bladder[4], colon[5] and breast cancer[6], among others, have been reported. *Lactobacillus casei* strain Shirota is also known to be effective in reducing the incidence and mitigating the symptoms of infectious diseases, such as infectious gastroenteritis caused by acute infantile diarrhea[7], upper respiratory tract infection[8] and norovirus infection[9]. Recent studies also showed that intake of probiotics alleviated stress related symptoms[10,11].

LEADING THE WORLD IN THE ELUCIDATION OF THE TRUE STATE OF INTESTINAL MICROBIOTA AND INTESTINAL BACTERIA WITH ADVANCED RESEARCH CAPABILITIES

We have produced many results in our research on intestinal microbiota. The Institute confirmed using the latest way that the bifidobacteria in the mother transmit to the intestines of newborns[12]. The Institute also demonstrated that segmented filamentous bacteria (SFB), which

Figure 3. Analysis of intestinal epithelial cells with a confocal laser scanning microscope. The induction of Th17 cells by segmented filamentous bacteria was visualized with immunofluorescence technique.

are intestinal bacteria present in same mammals, are involved in the induction of Th17 cells, a type of T cell that plays an important role in the defense system against the extracellular pathogens[13] (**Fig.3**). Yakult also developed YIF-SCAN®, a system that enables highly efficient analysis of intestinal microbiota[14]. Based on genetic sequences unique to each species of intestinal microbiota, YIF-SCAN® selectively quantifies the bacteria, enabling rapid, precise analysis of a wide range of bacteria, from abundant bacteria to those relatively few in number.

The results of research activities at Yakult are applied not only to product development, but in a number of different fields as well. One of our research accomplishments that is now utilized in the medical field is synbiotic therapy. Synbiotics combines probiotics and prebiotics, which function to help increase the beneficial bacteria in the intestines and strengthen gut barrier. Synbiotic therapy is currently being used in medical institutions, where there have been 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 opportunistic infection[15].

It is expected that improving the intestinal environment will have a positive effect on the reduction of antibiotics use and the response rate of the anticancer drug.

We remain actively engaged in joint research with other cutting edge organizations, including the Japan Aerospace Exploration Agency, a National Research and Development Agency. We also launched joint research operations with the Tohoku Medical Megabank Organization, a National University Corporation, in April 2018. This latter cooperation aims to help clarify the physiological significance of the intake of fermented milk drinks in terms of preventive medicine, and create new forms of preventive and therapeutic medicine that target intestinal microbiota. The cooperation is expected to extend through the end of 2020.

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