Japan’s Nitto Pharmaceutical Industries, Ltd. (Nitto Pharma) has developed an extensive library of over 400 strains of enterobacteria over its 70-year history, all of which live in the human digestive tract. Now, under the NOSTER brand, the company is working with domestic and international partners to apply this knowledge to create health care products for treating intestinal tract inflammation, preventing diabetes, and reducing allergies. Noster is Latin for “our,” underscoring Nitto Pharma’s mission to develop products that benefit everyone.

Green and spacious company environment
Nitto Pharma is located a short 30-minute train ride from Kyoto Station in a quiet residential area with narrow, cobbled streets lined with sakura trees. Walking through the entrance to the company’s premises reveals meticulously manicured lawns decorated with seasonal flowers, surrounded by small buildings with wooden facades. The view is more like that of a flower garden in a mountain retreat than a cutting-edge R&D hub at one of Japan’s top biopharmaceutical companies.

“The green and relaxing nature of these premises reflects our motto of being a ‘family-friendly company’ with the aim of contributing to the rich and happy spiritual lives of our employees and to humanity’s health and happiness,” says Kohey Kitao, managing director and head of R&D at Nitto Pharma. “This philosophy is embedded in NOSTER, our new brand of biopharmaceutical medicinal and nutritional products.”

Producing metabolites outside the human body
Many kinds of microorganisms are present in the human intestine. These intestinal bacteria metabolize the food we eat into compounds useful for human health, including health-promoting short-chain fatty acids and amino acids, the building blocks of proteins. Nitto Pharma is conducting R&D into mass-producing bacterial metabolites, which it refers to as “postbiotics,” through fermentation technology. The metabolites produced are used as raw materials for not only pharmaceutical products but also health care supplements and so-called functional foods—foods that have a positive effect on human health.

“We cultivate live lactic acid bacteria and microorganisms for producing high-quality pharmaceuticals and functional foods for health care,” says Yasunori Yonejima of Nitto Pharma’s R&D Division. “We devise ways of protecting the microorganisms—such as coating them in oil—so that they survive the harsh conditions in the stomach and reach the gut, where the byproducts of their metabolism act to improve the health of patients.” Yonejima and his colleagues, including Koichi Yamada, manager of Nitto’s Development Planning Section, are leading the company’s search for novel useful microorganisms and products for the NOSTER brand.

Beyond probiotics
With these new products, Nitto Pharma is taking conventional probiotics a step further, and currently supplying seven strains of probiotics, including lactic acid bacteria, as part of the NOSTER brand that can be used as raw materials to produce functional foods.

The three main themes behind the company’s move into postbiotics, exemplified by its NOSTER products, are:

1. Searching for new microorganisms for pharmaceuticals and functional foods
The company is isolating and collecting useful microorganisms, mainly in the Kyoto area near the company’s headquarters, such as lactic acid bacteria from fermented foods like pickles. It will continue to expand these activities and fieldwork with the aim of establishing a library of 1,000 strains of bacteria.

2. Enhancing research on functionality of microorganisms
Kyoto is home to many famous universities and research institutes, including Kyoto University. The company takes advantage of this proximity and collaborates with academia to advance evidence-based research into intestinal bacteria. A recent example of joint research is a collaboration with Jun Kunisawa at the Laboratory of Vaccine Materials and Laboratory of Gut Environmental Systems, National Institutes of Biomedical Innovation, Health and Nutrition, on the correlation between intestinal bacteria and disease, with the intention of developing new drugs.

3. Conducting postbiotics research
Postbiotics are products that benefit human health through ingestion of live microorganisms, typified by lactic acid bacteria. The examples currently under development are functional fatty-acid metabolites and exopolysaccharides, as described below.
Recent results of Nitto Pharma’s postbiotics research

Nitto Pharma is pursuing cutting-edge research on the functional fatty acid HYA (10-hydroxy-cis-12-octadecenoic acid) in collaboration with Jun Ogawa and Shigenobu Kishino of Kyoto University, who first discovered the metabolic pathways showing that HYA is produced by lactic acid bacteria from linoleic acid found in vegetable oil.

Notably, recent proof-of-concept clinical trials conducted by the company showed that food in the form of HYA in gelatin-coated capsules inhibited the rise of postprandial blood glucose levels (1), and Nitto is working with Ikuo Kimura of Tokyo University of Agriculture and Technology to clarify the underlying mechanisms that lie behind these results. “This is an important finding for the prevention of diabetes,” says Kitao. “Furthermore, related in vivo experiments showed that HYA protects the intestinal barrier. So we have an innovative new drug in the form of a functional food.”

Based on the promising results of these trials, Nitto Pharma is carrying out preliminary tests for producing the large quantities of HYA that will be necessary to move it from the lab to the market. There are two main issues to consider for the commercialization of HYA: first, its purity, and second, ensuring efficient means for mass production. With these factors in mind, Nitto Pharma researchers successfully produced HYA with 50% purity (HYA50) from safflower oil. The process starts by combining lactic acid bacteria with safflower oil, followed by washing and purification, centrifugal refining known as “degumming,” and finally filtration for decoloration.

HYA50 is sufficiently pure for the production of functional foods; drug applications for HYA would require over 99.9% purity. For use in functional foods, the company manufactures gelatin-coated HYA capsules, HYA oil produced by a transesterification reaction, and HYA powder generated by spray drying.

“We plan to launch functional food products starting in 2019,” explains Kitao. “Clinical trials for HYA drugs will take longer, so we are expecting to move into production in about 10 years.”

New applications in health care

Hidenori Matsui of Kitasato University has reported on the anti-helicobacterial action of HYA, thereby opening up the possibility of HYA-based antibacterial medication that does not affect other useful bacteria in the gut. Specifically, reports from the 23rd Annual Meeting of the Japanese Society for Helicobacter Research showed that giving mice drinking water mixed with HYA for three weeks protected them from infection with two strains of Helicobacter pylori (2). The company plans to pursue this line of research so that it can develop a range of health care products based on HYA.

Research and development of bacterial exopolysaccharides

Nitto Pharma is also conducting postbiotics research on bacterial exopolysaccharides (EPSs)—metabolites of lactic acid bacteria. The company has used its Leuconostoc mesenteroides NTM048 of lactic acid bacteria—discovered in green peas—to produce large quantities of an EPS they refer to as “leucosaccharides.”

Initial experiments done in collaboration with Kenji Yamamoto of Ishikawa Prefectural University show that leucosaccharides promote the secretion of IgA antibodies, thereby enhancing immunity of the intestinal mucosa. Additional research undertaken with Takuya Suzuki of Hiroshima University revealed that leucosaccharides also alleviate symptoms of the chronic skin disease psoriasis.

These results are expected to lead to improvements in immune system balance in humans.

These are only early examples of the search by Nitto Pharma researchers for practical uses of leucosaccharides and the potential benefits of leucobacteria.

R&D driven by open innovation and international collaboration

Nitto Pharma has had a very favorable response from industry contacts in the United States regarding its development of postbiotics and its core expertise in producing lactic acid bacteria. “Our vision of being the ‘world’s best biotech company’ is based on open innovation and international collaboration,” says Kitao. “We are now actively pursuing the formation of collaborative relationships with partners in the U.S. This global and innovative strategy reflects the essence of the inclusive nature of the NOSTER brand.”

For further information, see the Nitto Pharmaceutical Industries, Ltd. website: www.nitto-pharma.co.jp/en

References