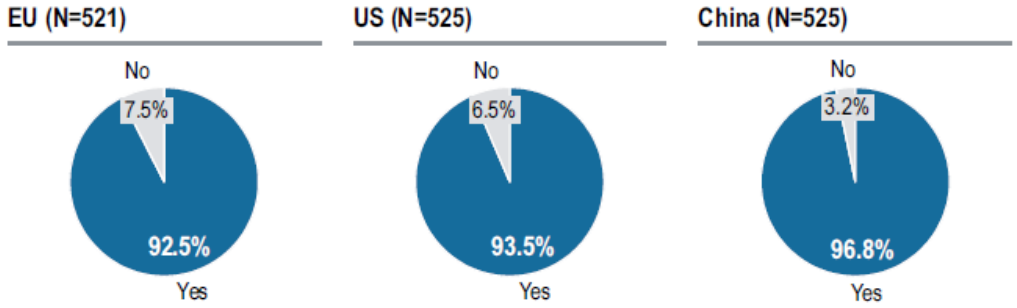
What can be expected from this technology

* Abbreviation of “Human Milk Oligosaccharides”

Manufacturing and supplying human milk oligosaccharides (HMO*) to contribute to the health and well-being of people around the world

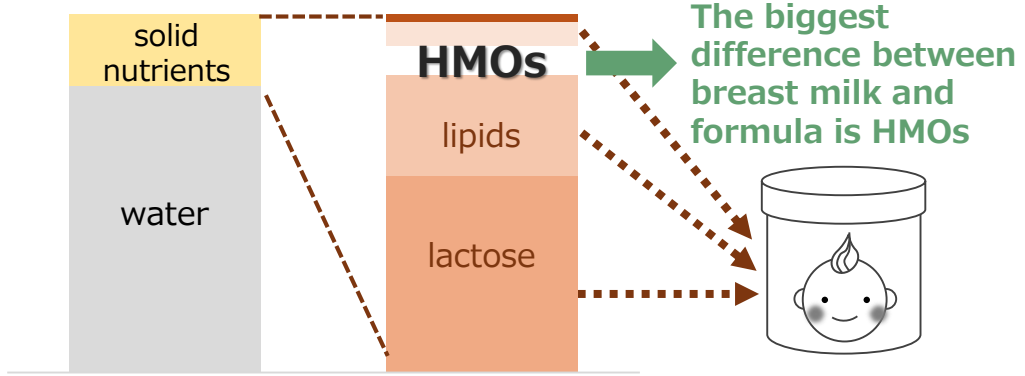
There is a need for milk powder that is similar to breast milk

Q. Do you want a formula that is similar to breast milk*?



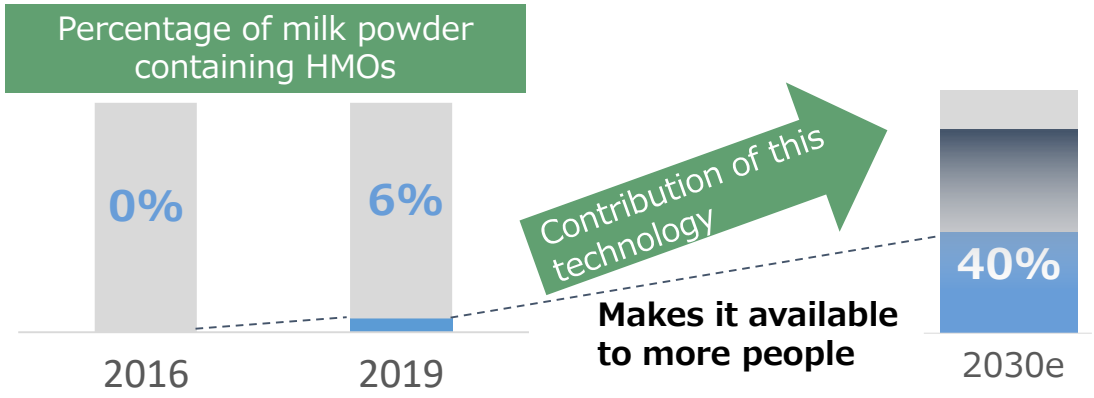
More than 90% of respondents want formula that is similar to breast milk

Nutrients in breast milk

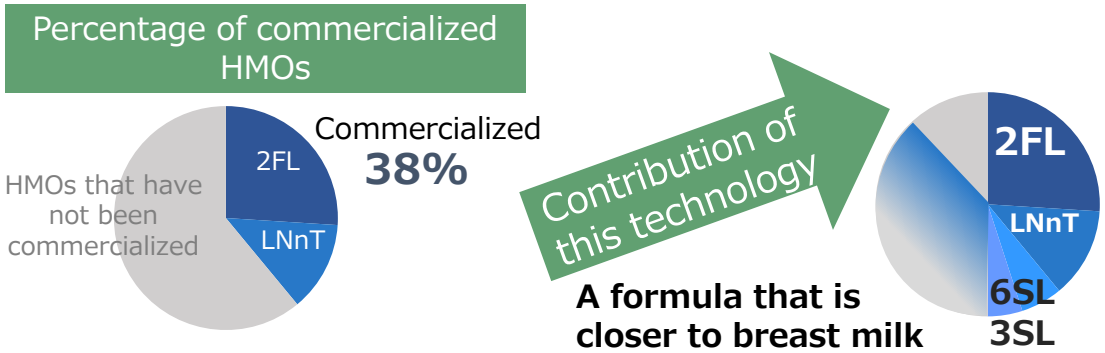


Greater variety of HMOs for larger population

■The percentage of formulas containing HMOs is still low.*



■ We still haven't covered HMOs in breast milk.**



* In-house data,
** Percentage accounted for by commercialized HMOs, 2FL and LNnT, out of breast milk HMOs

What can be expected from this technology

* Abbreviation of “Human Milk Oligosaccharides”

Manufacturing and supplying human milk oligosaccharides (HMO*) to contribute to the health and well-being of people around the world

HMOs found to be valuable for the health of adults as well

Recent years have seen the publication of an increasing number of functional studies on HMOs In particular, the effects of 6SL & 3SL on brain function is attracting attention.

* WHO Web site

Example of social issues to be solved: dementia

Dementia: Approximately 50 million people worldwide suffer from dementia.
Ten million people develop dementia every year.
One of the major causes of disability and dependency among older people worldwide*.

Technology overview 1: using innovative biotechnology to establish a process for the mass production of HMO

Challenges of conventional technology

Existing production method:
Chemical synthesis
- Expensive
- Complex process

What Kyowa Hakko Bio has made possible

Innovative production method:
Fermentation
- Low-cost
- Simple process

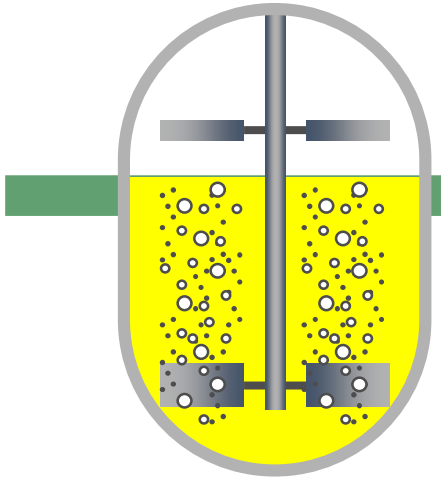
= enables large-scale production

Simple ingredients

- Sugars
- Materials for culture media

HMO-producing bacteria

Simple production method



Mass production

Technology overview 2: three types of HMO processes established thus far (2FL, 6SL, 3SL)

Strain Development

Developing Production Process

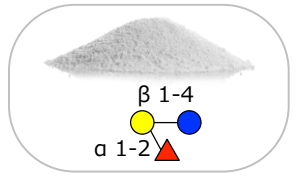
High content in breast milk

Technological breakthrough

2’-fucosyllactose (2FL)-producing bacteria

Fermentation and purification process appropriate for 2FL

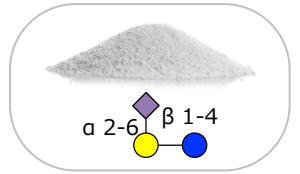
2FL product



6’-sialyllactose (6SL)-producing bacteria

Fermentation and purification process appropriate for 6SL

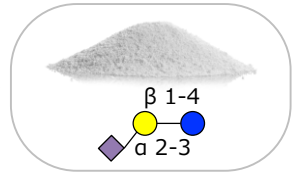
6SL product



3’-sialyllactose (3SL)-producing bacteria

Fermentation and purification process appropriate for 3SL

3SL product



Background of this technology (1): Kyowa Hakko Bio's strain development

2000 World's first microorganism-based HMO production process developed

Technology for inducing **high-yield** production by microorganisms

Metabolic engineering

1956 Developed the world's first amino acid fermentation method

1990 Developed biological production process for nucleic acids

Technology for inducing the production of **new substances** by microorganisms

Genetic engineering

2003 *C. glutamicum** genome determined

2004 Dipeptide synthase discovered

* A type of amino acid-producing bacteria

Applications filed for more than 14 HMO process patents

PATENT PROTECTED

Technologies accumulated by Kyowa Hakko Bio

Background of this technology (2): production process development by Kyowa Hakko Bio

Developing a process suitable for the production of raw materials for products to be consumed by infants, which require high quality similar to pharma-grade products

Fermentation process

The manufacturing process precisely controls the culture parameters of bacteria, which are sensitive to minute changes in raw materials and temperature, and controls impurities less than 0.1%

Purification process

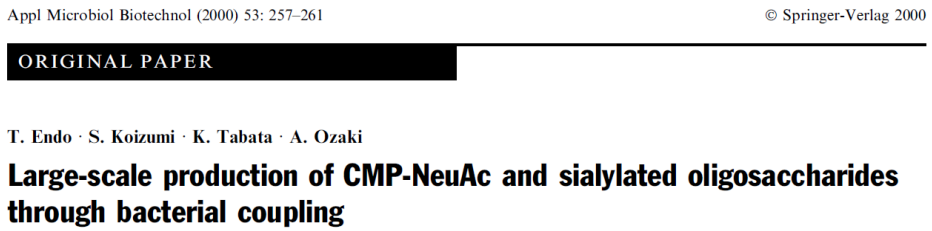
Our highly controlled refining process leverages our experience in pharmaceutical manufacturing, and is intended to ensure a steady supply of high-purity products

Uniqueness of this technology

Established the **world's first*** industrial-level HMO production system

Kyowa Hakko Bio is the first company in the world established an industrial-level production system for HMOs*

More than 140 citations since 2000**



Appl Microbiol Biotechnol (2000) 53: 257–261 © Springer-Verlag 2000

ORIGINAL PAPER

T. Endo · S. Koizumi · K. Tabata · A. Ozaki

Large-scale production of CMP-NeuAc and sialylated oligosaccharides through bacterial coupling

We have been pursuing a competitive edge by applying for production process patents

2FL production process: employs one proprietary patented technology

6SL production process: employs six proprietary patented technologies

3SL production process: employs six proprietary patented technologies

PATENT PROTECTED

* Tetsuo Endo et. al.,Appl. Microbiol. Biotechnol. 53, 257-261 (2000), https://link.springer.com/article/10.1007/s002530050017,
** Google Scholar

6SL and 3SL are not yet supplied at industrial level

Future possibilities

Bringing more varieties of HMOs and their health value to the world

The presence of as many as 250 different HMOs has been reported in breast milk
Only two types, however, are commercially available in the world today

We are researching production methods for more types of HMO
than just the ones whose commercialization has been scheduled (2FL, 6SL and 3SL)

Bringing formula that resembles breast milk more closely to babies around the world

Bringing the health value of breast milk to adults through health foods and beverages