Human Milk Oligosaccharides for Infant Food, and Functional Food Applications

 Novel functional food ingredients with multiple health benefits as old as human mankind

Mr. Glyn Brookman
About Jennewein Biotechnologie
Leading producer of a comprehensive portfolio of human milk oligosaccharides and scarce monosaccharides for the use as functional health ingredients.

*Founded in 2005,* Jennewein Biotechnologie GmbH started with the vision to develop *novel production processes* for complex oligosaccharides. In particular our focus was right from the very beginning on *human milk oligosaccharides (HMO)* with the aim to *produce these oligosaccharides in very large quantities* at *low cost* and at *food-grade quality* for the use in *infant formula and as a functional food ingredients.*

Although the *oligosaccharides* produced by Jennewein Biotechnologie are *known from natural sources* such as human milk, *no production processes was available,* which *proved economical viable,* i.e. allowing large-scale production at food-grade quality and at economically feasible costs.

Products currently produced by Jennewein Biotechnologie includes, besides various HMOs, nucleotide-activated monosaccharides such as GDP-fucose, CMP-sialic acid, and the monosaccharides *L-Fucose* and *Sialic-acid,* which are also *key building-blocks for the chemical synthesis of human milk oligosaccharides.*

*L-Fucose* and *Sialic-acid* are also found in human milk as *free monosaccharides.*
About Jennewein Biotechnologie
Human milk oligosaccharides (HMOs) have first been discovered in the late 19th century. The interest in these human specific carbohydrates was driven by the observation that the survival rate of breast-fed infants was considerably higher compared with bottle-fed infants.

A major breakthrough for infant survival was the discovery of microorganisms and their importance to infant health by the pediatrician Theodor Escherich in 1886 and his observation that specific milk carbohydrates play a key role in the growth of these intestinal bacteria.

In the following decades research advanced by pediatricians and microbiologists studying the health benefits of human milk and chemists characterizing the carbohydrates abundant in human milk. This research led to a characterization of more than 150 different human specific saccharide structures found in human milk and the discovery of various health benefits ranging from a bifidogenic / prebiotic factor, reducing infection to brain development.

These advances resulted in a growing interest to synthetically produce these human specific saccharides. In the mid 20th century several chemical synthesis were developed which, however, were later abolished due to uneconomic high cost and lack of scalability.
What‘s in Human Milk

Specific composition of human mother‘s milk.

Human breast milk is a complex mixture of carbohydrates, fats, proteins and other molecules that provide the primary source of nutrients for newborns and infants, as well as a number of additional protective and health-promoting factors. Human milk oligosaccharides (HMOs) represent the third most abundant solid component in human breast milk.

Amount and composition of HMOs vary between women and over the course of lactation. It is reported that colostrum contains as much as 20-25 g/l of HMO. As milk production matures and total milk consumption by the infant per day increases, HMO concentrations decline to 5-20 g/l. Scientific research assumes that breastfed infants receive about 15 g of HMOs per day or more.¹

Human Milk Oligosaccharides
A structural diverse family of complex neutral and acidic lactose based oligosaccharides
Comparative Analysis of human and dairy animal milk

Human milk is unique with regard to amounts and structural diversity of oligosaccharides present.
Functional Benefits of Human Milk Oligosaccharides
The Sweet Secret of Human Milk

Human milk oligosaccharides (HMOs) are health promoting sugars and function as effective decoys for human pathogens.

By synthesizing soluble complex oligosaccharides similar to cell standing oligosaccharides, nature developed a **highly efficient and effective system of protection** against a broad range of pathogens – viruses, bacteria and toxins.

Human milk oligosaccharides **resembles sugar molecules present on the surface of human cells**. These surface-bound sugars are used by pathogens to connect to and hence infect the human cell. By intake of human milk oligosaccharides, the organism benefits from the fact that these **oligosaccharides are structurally similar to the surface-bound sugars used by bacteria and viruses** to infect the organism.

**Pathogens connect to human milk oligosaccharides instead of binding to human cells**. Once a pathogen has bound, the body eliminates the molecule without the latter being infected. Thus, these specific oligosaccharides are a **decoy for pathogens** aiming for attachment and infection of human cells using an oligosaccharide as receptor or coreceptor. This natural protection mechanism is scientifically well described and proven. Nature applies this protection system successfully in **human mother’s milk**.
Broad Field of Application

Health promoting benefits qualify HMOs as a functional ingredient in products ranging from infant nutrition over medical nutrition to functional food products.

Infant Nutrition
- Closer to human milk
- Infant health / protection against viral and bacterial infection
- Supporting healthy development of infants and small children from gut to brain
- ....

Medical Nutrition
- Supporting/reestablishing digestive health
- Protecting against viral and bacterial infection
- Protecting against nosocomial infections
- Reducing the risk / alleviate adverse effects of a therapy
- ....

Food Supplements
- Protecting against viral and bacterial infection
- Supporting digestive health
- Supporting brain development and function
- ....

Functional Food
- Protecting against viral and bacterial infection
- Supporting digestive health
- Supporting brain development and function
- ....
Portfolio of Human Milk Oligosaccharides

Jennewein Biotechnologie offers the most abundant HMOs in human milk.

<table>
<thead>
<tr>
<th>Human milk oligosaccharides</th>
<th>Reported natural concentration (g/L)</th>
<th>Scientific insights on functional benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>2’-Fucosyllactose (CAS No. 41263-94-9)</td>
<td>2.43 ± 0.26</td>
<td>• Inhibition of various diarrhea causing bacteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prebiotic effects</td>
</tr>
<tr>
<td>3-Fucosyllactose (CAS No. 41312-47-4)</td>
<td>0.86 ± 0.10</td>
<td>• Inhibition of various diarrhea causing bacteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prebiotic effects</td>
</tr>
<tr>
<td>Lacto-N-tetraose (CAS No. 14116-68-8)</td>
<td>1.09 ± 0.47</td>
<td>• Antiadhesive antimicrobial effect <em>Entamaeba histolytica</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prebiotic effect</td>
</tr>
<tr>
<td>Lacto-N-neotetraose (CAS No. 13007-32-4)</td>
<td>0.17 ± 0.03</td>
<td>• Inhibition of pneumococcal adherence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prebiotic effect</td>
</tr>
<tr>
<td>Lacto-N-triose</td>
<td>n.a.</td>
<td>• Prebiotic effect</td>
</tr>
<tr>
<td>6’-Sialyllactose (CAS No. 35890-39-2)</td>
<td>0.3 ±0.03</td>
<td>• Brain development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Influenza virus</td>
</tr>
<tr>
<td>3’-Sialyllactose (CAS No. 37449-93-7)</td>
<td>0.3 ±0.1</td>
<td>• Brain development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Influenza virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inhibition of <em>H. pylori</em></td>
</tr>
</tbody>
</table>
Large-scale 2’-Fucosyllactose Production

Jennewein Biotechnologie possesses the first large-scale commercial production facility for HMOs and manufactures 2’-Fucosyllactose.

In 2013 Jennewein Biotechnologie GmbH started to build the first fully dedicated commercial production facility for 2’-FL at Rheinbreitbach (near Bonn). Facility is an approved facility for infant food production (FDA registered food facility), which is also ISO 22000, Kosher and Halal certified.
2’-Fucosyllactose Fermentation is run at Jennewein Biotechnologie at a 225 m³ Fermentation-Scale
2′-Fucosyllactose

The first HMO used in Infant Formula and Medical Nutrition products
2‘-Fucosyllactose
The first Infant Formula containing 2‘-Fucosyllactose went on market in September 2016.
Product Portfolio of Jennewein Biotechnologie GmbH

Jennewein Biotechnologie GmbH developed processes for several Mono- and Oligosaccharides.
Registration of HMO Cocktails
Currently Jennewein Biotechnology is working on the registration of two HMO mixes, containing the most dominant HMOs in human milk, for infant formula applications.
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HMO Mix
Comprising the most dominant HMOs found in human milk at physiological concentrations.

<table>
<thead>
<tr>
<th>HMO</th>
<th>Final conc. in IF</th>
<th>Mix %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2’-FL</td>
<td>3 g/l</td>
<td>52%</td>
</tr>
<tr>
<td>3-FL</td>
<td>0,75 g/l</td>
<td>13%</td>
</tr>
<tr>
<td>LNT</td>
<td>1,5 g/l</td>
<td>26%</td>
</tr>
<tr>
<td>3’-SL</td>
<td>0,2 g/l</td>
<td>3.5 %</td>
</tr>
<tr>
<td>6’-SL</td>
<td>0,3 g/l</td>
<td>5.2 %</td>
</tr>
<tr>
<td>Total</td>
<td>5.75 g/l</td>
<td>100 %</td>
</tr>
</tbody>
</table>
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