What can be expected from this technology
Contribute to the brain health of people around the world in the fields of food & beverages to pharmaceuticals

Citicoline is a compound found in the body

**Citicoline** is needed for the maintenance of cell membranes in the brain and neurons

Cell membrane damage and quality deterioration as a result of trauma to the brain and aging

Decline in brain function

Maintenance of brain function

Kyowa Hakko Bio’s citicoline

Global market needs and main applications

Number of stroke victims: 13.7 million*

Chances of having a stroke: one in four people over the age of 25.**

65 years and older in Europe and the US: 18%,*** about one in six.

An ingredient for active pharmaceutical ingredients

An ingredient for health foods

*World Stroke Organization “Learn about stroke”
*** World Population Prospects 2019
What can be expected from this technology

Contribute to the brain health of people around the world in the fields of food & beverages to pharmaceuticals

**Pharmaceutical** use as treatments for brain disease

- For the patients
  - Use as a treatment for stroke*
  - Other benefits
    - Brain dysfunction from accidental trauma**
    - Glaucoma treatment ***
  - A wide range of dosage forms, including injections, oral formulations and eye drops

**Health foods to maintain cognitive decline**

- For the middle-aged and elderly
  - Support for improving cognitive function as it declines with age
  - Studies on the effectiveness of citicoline for the elderly has been published in academic journals****

**Use in **food and beverages** to support brain power and skills**

- For young and mature customers
  - Helping those who want to improve their work performance and efficiency
  - Can be widely applied to convenient beverages and processed foods

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* Curr Opin Investig Drugs 2(12), 1757-1762 (2001)
** From the Drug Interview Form
*** Nutrients 12(3), 793 (2020)
About this technology

Technology overview 1: established an innovative method for the mass production of citicoline based on an unique technology

**Challenges of past technologies**

The main technique used was chemical synthesis

Expensive, low-volume production

Difficult to ensure a steady, low-cost supply of citicoline for wide population

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**What Kyowa Hakko Bio has made possible**

- We have designed an original process combining the nucleic acid fermentation technology developed over many years and microorganisms with enhanced enzymatic activity
- We have established a process that enables high quality product manufacturing in a plant scale
- Kyowa Hakko Bio, with its extensive knowledge of microorganisms, is uniquely able to provide citicoline inexpensively and in large quantities by using a production method based on its established know-how that is difficult to imitate.
About this technology

Technology overview 2: a biological process combining conventional and new technologies

**Nucleic acid fermentation technology**
- allowing simultaneous control of two microorganisms

**Production process developed by leveraging manufacturing technologies for active pharmaceutical ingredients**

**Inexpensive raw materials**
- Orotonic acid
- Choline chloride

**A simple process**
- Nucleic acid-producing bacteria
- Citicoline biosynthesis-enhancing bacteria

**Fermentation and purification process suitable for citicoline**

**Citicoline products**

*Kyowa Hakko Bio is the only company that can provide a stable supply of citicoline with this technology*
About this technology

The History of Kyowa Hakko Bio and citicoline

1956
Kyowa Hakko developed the world's first microorganism-based amino acid fermentation technology

1970s
Citicoline produced via chemical synthesis began to be distributed on the world’s markets as a pharmaceutical product

1990
Kyowa Hakko Bio began producing citicoline through fermentation

2003
Kyowa Hakko Bio started to actively promote citicoline under brand name Cognizin

2016
Cognizin has been introduced to a major, well-known health food brand in the US.

2016-2020
Demand for energy drinks is on the rise
Citicoline's concept - improved attention and concentration - meets market needs

Future
We are planning to expand areas where Cognizin can be used as a food ingredient
The uniqueness of this technology

Provide added value in the form of citicoline produced by Kyowa Hakko Bio

<table>
<thead>
<tr>
<th>Creation</th>
<th>Production</th>
<th>Sales</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technical Research Laboratories</strong></td>
<td><strong>Manufacturing high quality pharmaceutical grade products in an appropriate facility environment</strong></td>
<td><strong>As an active pharmaceutical ingredient</strong>&lt;br&gt;• Supplying to China, Europe, India and Southeast Asia</td>
<td><strong>Hospitals</strong>&lt;br&gt;Treatment of patients</td>
</tr>
<tr>
<td>• Evaluation for improvements to manufacturing process, etc.</td>
<td></td>
<td><strong>As a food/health food</strong>&lt;br&gt;• Branded citicoline&lt;br&gt;• Raising awareness on social media and websites (Twitter, Instagram, Facebook, etc.)&lt;br&gt;  *Mainly in the U.S. and Europe</td>
<td><strong>Foods and health foods</strong>&lt;br&gt;Effective dose of citicoline based on clinical studies</td>
</tr>
<tr>
<td><strong>R&amp;I Center</strong></td>
<td><strong>Health benefits backed by science</strong></td>
<td><strong>Investigate competitor, customer and market trends to reconsider productivity and obtain new data.</strong></td>
<td><strong>Foods and health foods</strong>&lt;br&gt;Health and happiness</td>
</tr>
<tr>
<td>• Conduction of fundamental to clinical research in cooperation with research institute</td>
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*Papers****
Uniqueness of this technology

Effectiveness and application of citicoline scientifically proven by Kyowa Hakko Bio

Examples of Effects of citicoline intake

- Clinical trials in healthy individuals
- Decreased omission error when operating a computer*
- Improved finger tapping test **
  \[1 \text{ Number of times a button is tapped}\]
- Combined with other well-known ingredients
  - Combination with DHA
  - Further cognitive improvement can be expected***

Proposals for new markets and areas

- Providing Citicoline to people seeking better focus across generation
- Improve the work productivity of remote workers in their new lifestyle and maintain their focus
- E-sports market, where finger tapping tasks and focus are important

For the evolution of your mind!

* Food and Nutrition Sciences, 3: 769-773 (2012)
** J Atten Disord, 23(2), 121-134, (2019)
Future vision

Contribute to support the brain health of more people

Kyowa Hakko Bio provides citicoline as branded ingredient for brain health backed by scientific evidence

Expanding the number of countries and regions where citicoline can be used as an ingredient for foods and health foods via ingredient registration procedures

High-quality, safe citicoline for “pharmaceutical”, and proven Cognizin brand citicoline for “foods and health foods”