Kirin Group R&D Day
Aiming to Solve Social Issues Worldwide
with Kirin's Fermentation and Biotechnology

Discovery and Promise of
Lactococcus Lactis Strain Plasma

Special Guest: Yasuhiro Nishizaki
Senior Executive Director, Tokai University Tokyo Hospital

Daisuke Fujiwara
Deputy General Manager, Health Science Department
Kirin Holdings Company, Limited

October 6, 2020
Kirin Holdings Company, Limited
Speakers

Dr. Yasuhiro Nishizaki
Hospital Senior Executive Director and Medical Examination Center Director, Tokai University Tokyo Hospital
Chief Professor, Department of Clinical Health Science, Tokai University School of Medicine
Director, Life Care Center, Graduate School of Medicine, Tokai University
Vice President, Japan Society of Health Evaluation and Promotion
Director, The International Health Evaluation and Promotion Association
Board Chairman, NPO inc. Center for Healthy Longevity Research and Education
Specialties: gastroenterology and hepatology, preventive medicine, anti-aging medicine

Daisuke Fujiwara
Kirin Holdings Company, Limited
Deputy General Manager, Health Science Department
Ph.D. Agriculture
Visiting lecturer,
Graduate School of Agricultural and Life Sciences, The University of Tokyo
The Kirin Group has been engaged in immunological research for 35 years. In addition to its pharmaceutical business, encompassing therapeutic antibody and other products, the Group has made significant contributions to the field of immunology over the years. For example, the Group has been involved in the establishment of LIAI — the world's most advanced public immunology research center.

**Therapeutic antibody in the field of immunology**

**One of the leading public immunity laboratories in the U.S.**

Established in 1988 with funding from the Kirin Group
### Social issues we wanted to solve

<table>
<thead>
<tr>
<th>Means</th>
<th>Antibiotics</th>
<th>Vaccines, anti-viral drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target scope</td>
<td>○ Effective for a wide range of issues</td>
<td>× Only effective on specific viruses</td>
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- Are any means available that are **effective against a wide spectrum of viruses** instead of a single one?
- Might there be a convenient way to help through diet rather than with drugs?

1) Credit: Rocky Mountain Laboratories, NIAID, NIH
2) w:User:Graham Beards
Developing a subject based on cutting-edge science

There is a hierarchy to anti-viral immunity, with pDCs serving as “control towers”

Instructions and orders

Viral infection control

What if there was a lactic acid bacterium that activates the pDC?
Discovery of *Lactococcus lactis* strain Plasma

**Before**

Researchers around the world believed
Lactic acid bacterium to be unable to activate pDC

**Kirin’s discovery**

In 2012, we reported the unprecedented discovery of a lactic acid bacterium that can activate pDC

Numerous lactic acid bacteria stored in strain banks

Comparison of pDC activation by lactobacilli

**PLoS One, 2012**

No other commercially available lactobacilli exerts any effect

*Lactococcus lactis* strain Plasma

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Effects of *Lactococcus lactis* strain Plasma as seen by the eye (microscopic observation)

Addition of *Lactococcus lactis* strain Plasma activates “pDCs”, the control tower of anti-viral immunity

Green: pDC
Red: virus
Contributing to the development of academic research by studying the subject in its entirety, from basic mechanisms to clinical application, and presenting the data externally

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The world’s first lactic acid bacteria that strengthens the foundation of immune cells

- It is increasingly important to strengthen the body’s natural immunity to fight viruses in the course of daily life.

- Our researchers will provide explanations.

- What is immunity?
  - A mechanism for eliminating viruses, bacteria and other pathogens through both innate and acquired immunity
  - Main types of immunity: Innate immunity, Adaptive immunity
  - Innate immunity
    - First line of defense
    - Effective immediately
    - Common sense
  - Adaptive immunity
    - More powerful and long-lasting
    - Responds to specific pathogens

- What can be expected from this technology
  - Control infectious disease risk and solve the problem of infectious diseases in areas with poor sanitary conditions
  - New treatment: Phage
  - Nutritional supplements

- Dietary habits greatly affect immunity
  - Lactic acid bacteria are known to be closely linked to immunity

- Background of this technology
  - In the past, the accepted knowledge in immunology was that lactic acid bacteria activate only some immune cells (KCs).

- Forging a relationship with lactic acid bacteria and the intestinal flora
  - To be effective, it is necessary to positively modulate immune cells and support immunity.

- Ingestion of Lactobacillus acidophilus strain Plasma® reduced the risk of influenza and colds
  - We asked 200 people to consume either a milk-based drink containing Lactobacillus acidophilus strain Plasma® or a milk-based drink without Lactobacillus acidophilus strain Plasma® for 3 months.
  - Analysis of their physiological condition, symptoms, and subjective evaluation

See the poster presentation for more information. Our researchers will provide explanations.
Immunoregulation by *Lactococcus lactis* strain Plasma

**L. lactis Plasma**

*Plasma* lactobacilli

**Group of lactobacilli**

**Lumen**

**Villi**

**Plasmacytoid dendritic cells**

1. Taken by mouth
2. Absorbed in the small intestine
3. Activates plasmacytoid dendritic cells in the small intestine

**Intestinal tract**


Hypothesized mechanism of pDC activation in the small intestine upon oral ingestion of *L. lactis* Plasma. *L. lactis* Plasma is taken up by Peyer’s patches (masses of immune tissue found in the small intestine), and controls immune response to viruses by activating pDCs.
Overview of a clinical trial conducted at Tokai University School of Medicine

Method
Subjects: Tokai University students and faculty (18-39 years old)
Period: December 2013 to March 2014 (winter)
Outcomes: Upper respiratory tract symptoms (cold and flu-like symptoms)
Anti-viral immunity index (interferon-alpha)

Results
- Cases of upper respiratory symptoms in the winter months were reduced
- Increased expression of antiviral genes in the blood

Conclusions
Issues in the medical field: overworked healthcare professionals

Distribution of working hours per week for doctors and others year, full-time employees


Risk factors for viral infection in winter

(1) Spread due to dry conditions
(2) Temperature facilitating growth
(3) Less time spent in the sun

- Dry outside air in winter
- More drying due to heating

<table>
<thead>
<tr>
<th>Droplet transmission</th>
<th>Airborne transmission</th>
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<tbody>
<tr>
<td>Moisture</td>
<td></td>
</tr>
<tr>
<td>- Larger than 5 μm in diameter</td>
<td></td>
</tr>
<tr>
<td>- Fall velocity 30-80 cm/sec</td>
<td></td>
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<tr>
<td>Coughing, sneezing, talking, tracheal aspiration</td>
<td></td>
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<tr>
<td>Usually a short distance; &quot;about 1 meter&quot;</td>
<td></td>
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<tr>
<td>Droplet nuclei</td>
<td></td>
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<tr>
<td>- 5 μm or less in diameter</td>
<td></td>
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<tr>
<td>- Fall velocity 0.06-1.5 cm/sec</td>
<td></td>
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<tr>
<td>Dispersed over a wide area via air flow</td>
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33°C We feel great!


Vitamin D is activated in the body following exposure to ultraviolet light

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The Kirin Group's approach to employee health management

FANCL's Health and Exercise Instructor Ono explains how you can turn your everyday life into a workout with just a few changes in "the way you walk".

1. Stand up straight.
   • Picture standing a little taller.
   • Focus your effort on a spot about three fingers below the navel.

2. Let your arms swing forward naturally, and make a conscious effort to swing them backwards.
   • Swing your arm backwards, pulling your shoulders back.
   • Relax and let your arm swing forward.

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Emerging risk of viral infections in Asia

Dengue fever
Chikungunya fever

Effects on the dengue virus (non-clinical studies)

Relative virus titer

- day 0
- negative
- 1 µL
- 10 µL
- 100 µL
- Ctrl
- LC-Plasma

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ANTIVIR RES
Strengthen global expansion capabilities by accurately identifying regional health issues and continuously and strategically pursuing high-quality R&D that fits each region's needs.

North America

Collaborating with local partners to develop a BtoB business

Asia

Selling soft drinks with immune function labeling in Vietnam

Launched a new business development acceleration program in Singapore

Kyowa Hakko Bio Global sales offices

Growth of the immunity market in the U.S.

The U.S. immunity market is expected to grow 1.5x year-on-year in 2020 due to rising consumer awareness of immunity.
The challenge of creation for the future

Contributing to health and well-being through immunological research

Our goal is to contribute to the well-being of people around the world by advancing research on immunity, which is closely related to the preservation of health, based on the fermentation technology we have developed over the years.
よろこびがつなぐ世界へ  Joy brings us together