



**KIRIN**

Joy brings us together

**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



## 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**



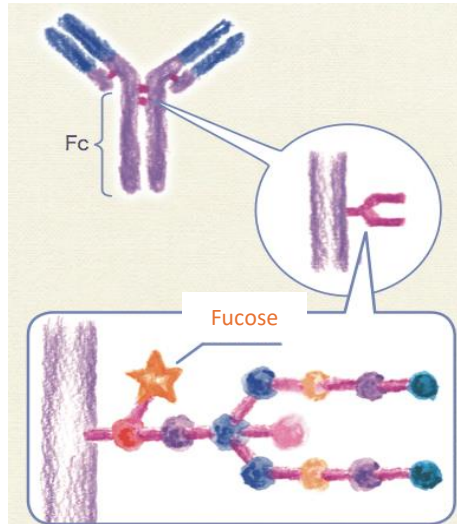
## Daisuke Fujiwara

Kirin Holdings Company, Limited  
Deputy General Manager,  
Health Science Department  
Ph.D. Agriculture  
Visiting lecturer,  
Graduate School of Agricultural and Life Sciences,  
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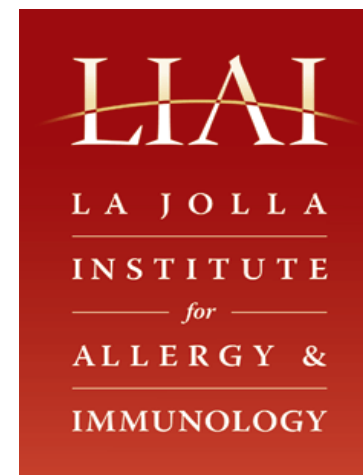
# The Kirin Group and Immunity Research

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

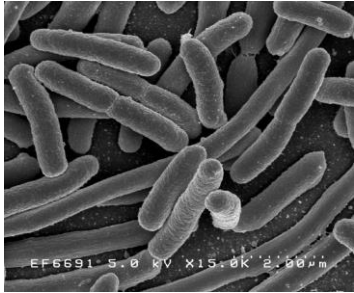
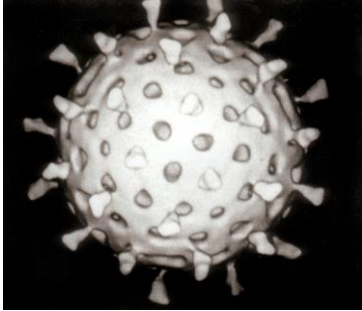


## One of the leading public immunity laboratories in the U.S.



**Established in 1988  
with funding from  
the Kirin Group**

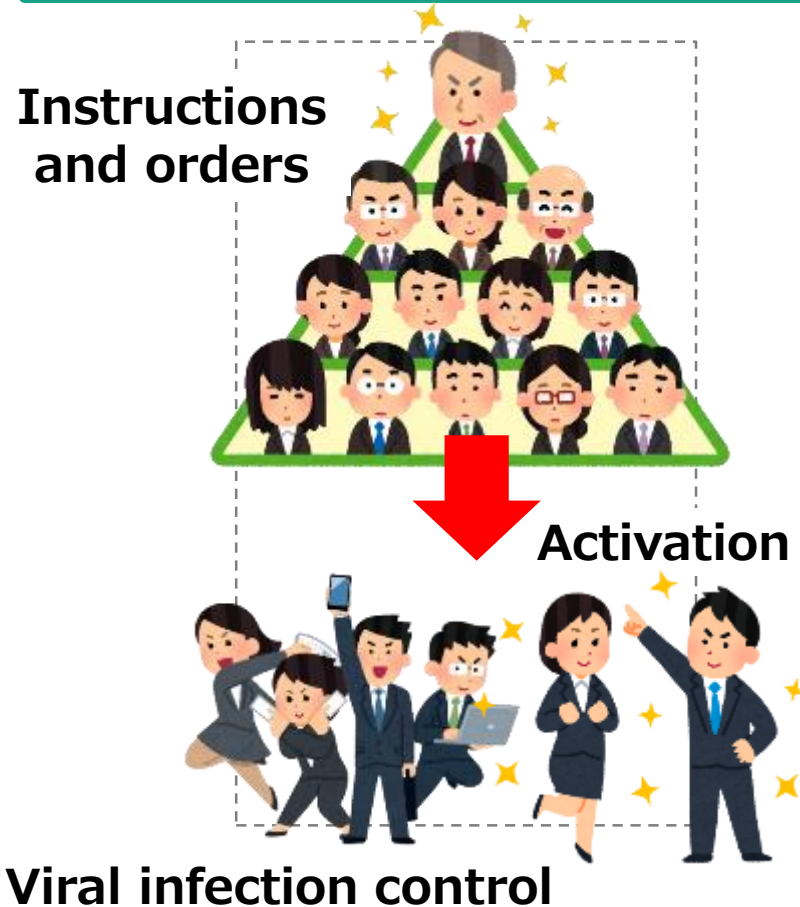
# Social issues we wanted to solve

	<p>Bacteria</p>  <p>1)</p>	<p>Virus</p>  <p>2)</p>
Means	Antibiotics	Vaccines , anti-viral drugs
Target scope	<p>○</p> <p>Effective for a wide range of issues</p>	<p>×</p> <p>Only effective on specific viruses</p>

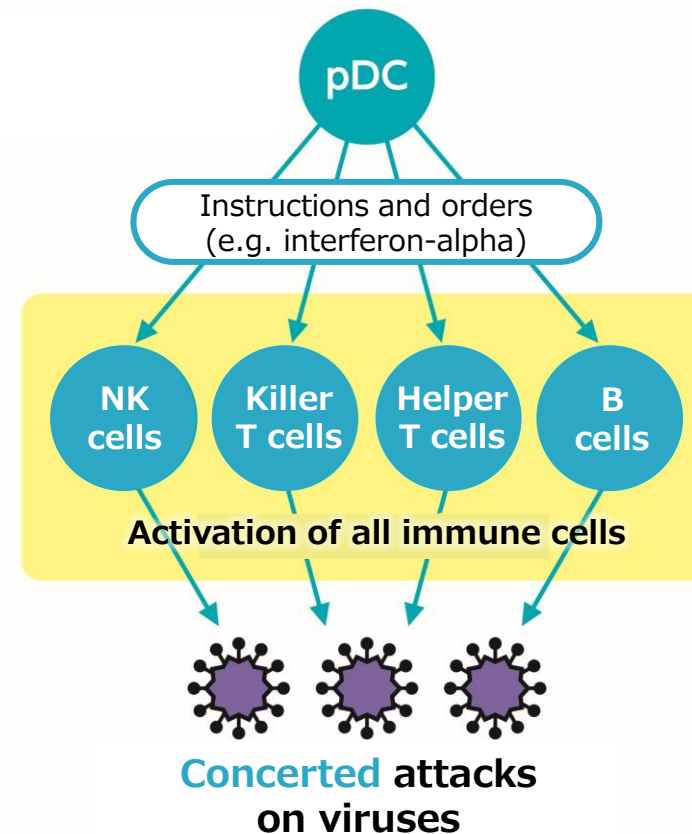
- Are any means available that are effective against a wide spectrum of viruses instead of a single one?
- Might there be a convenient way to help through diet rather than with drugs?

# Developing a subject based on cutting-edge science

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



"Control tower" of the immune system



What if there was a lactic acid bacterium that activates the pDC?

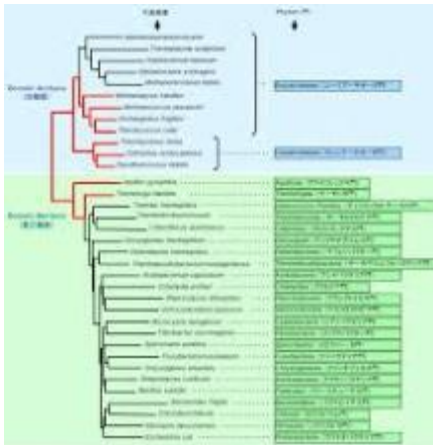
# Discovery of *Lactococcus lactis* strain Plasma

## Before

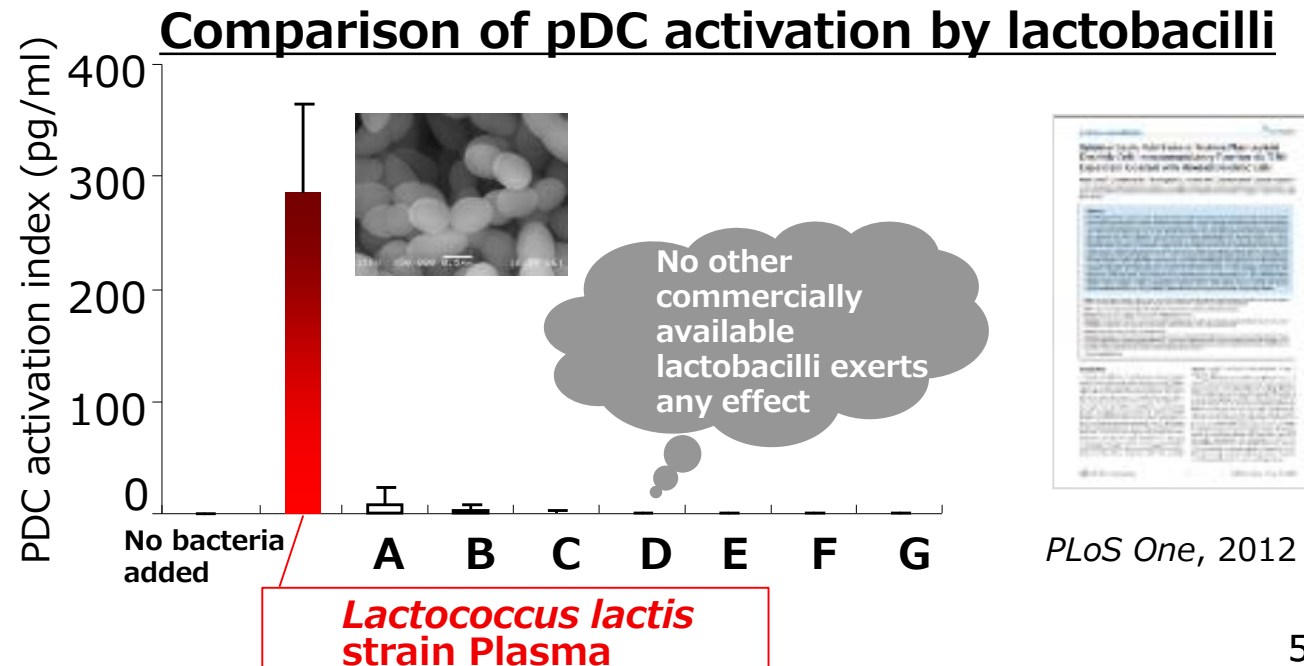
Researchers around the world believed  
Lactic acid bacterium to be unable to activate pDC

## 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

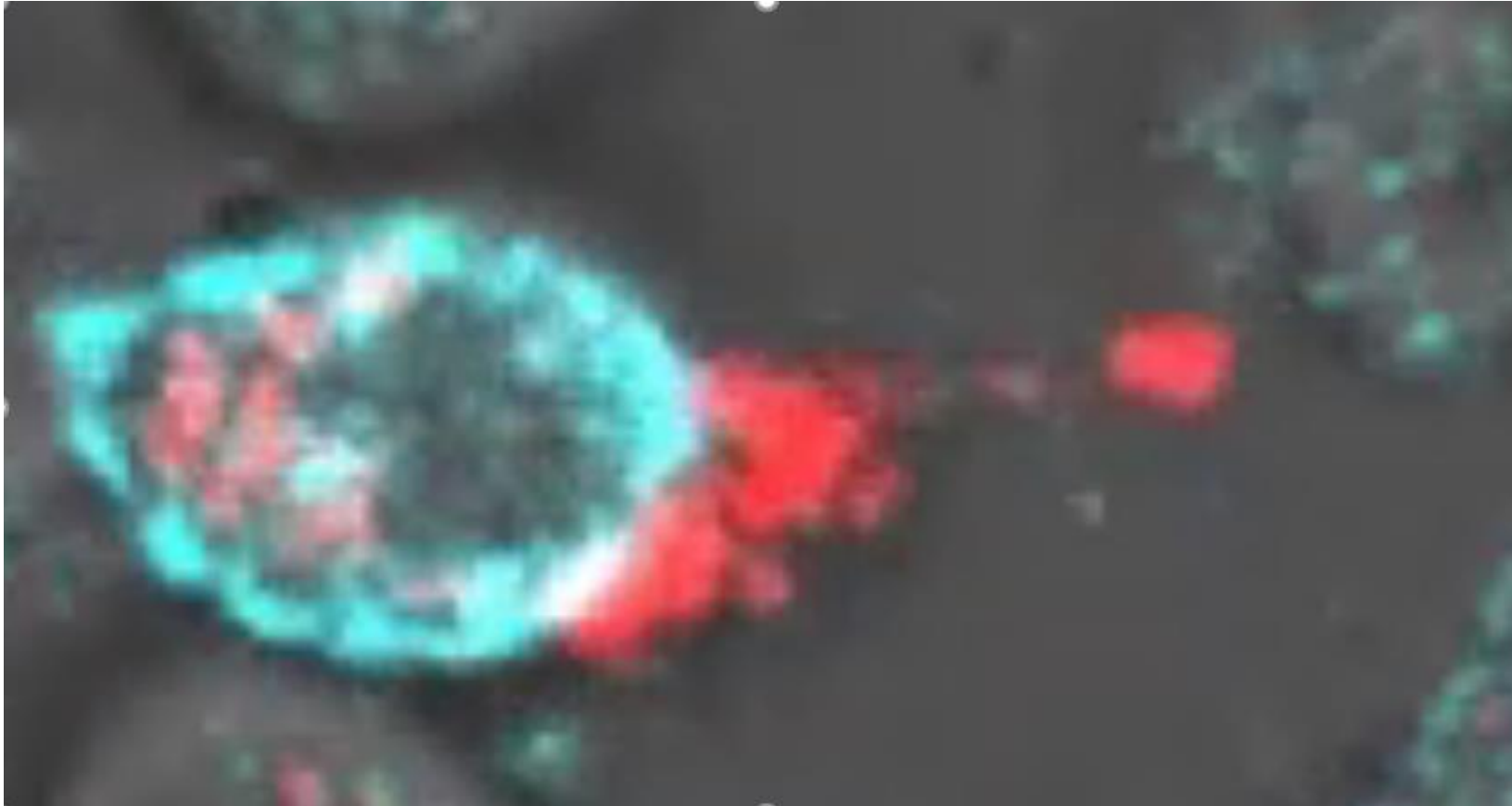


PLoS One, 2012



# 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

# List of evidence for *Lactococcus lactis* strain Plasma

1. Jounai K, Ikado K, Sugimura T, Ano Y, Braun J, Fujiwara D. (2012) Spherical lactic acid bacteria activate plasmacytoid dendritic cells immunomodulatory function via TLR9-dependent crosstalk with myeloid dendritic cells. PLoS One 7: e32588.
2. Sugimura T, Jounai K, Ohshio K, Tanaka T, Suwa M, Fujiwara D. (2013) Immunomodulatory effect of *Lactococcus lactis* JCM5805 on human plasmacytoid dendritic cells. Clin Immunol 149: 509–518.
3. Jounai K, Sugimura T, Ohshio K, Fujiwara D. (2015) Oral administration of *Lactococcus lactis* subsp. *lactis* JCM5805 enhances lung immune response resulting in protection from murine parainfluenza virus infection. PLoS One. 6: e0119055.
4. Fujii T, Tomita Y, Ikushima S, Horie A, Fujiwara D. (2015) Draft genome sequence of *Lactococcus lactis* subsp. *lactis* JCM 5805T, a strain that induces plasmacytoid dendritic cell activation. Genome Announc 3 : e00113-15
5. Sugimura T, Takahashi H, Jounai K, Ohshio K, Kanayama M, Tazumi K, Tanihata Y, Miura Y, Fujiwara D, Yamamoto N. (2015) Effects of oral intake of plasmacytoid dendritic cells-stimulative lactic acid bacterial strain on pathogenesis of influenza-like illness and immunological response to influenza virus. Br J Nutr. 3:1-7.
6. Suzuki H, Kanayama M, Fujii T, Fujiwara D, Sugimura K (2015) Effects of the beverage containing *Lactococcus lactis* subsp. *lactis* JCM5805 on anti-viral immune responses and maintenance of physical conditions -a randomized, double-blind, placebo-controlled, parallel-group Trial— Jpn Pharmacol Ther. 43:1465–72.
7. Tanaka K, Suzuki H, Kanayama M, Fujii T, Fujiwara D, Nozawa H, Sugimura K. (2015) The safety evaluation of long-term or excessive intake of the beverage containing *Lactococcus lactis* subsp. *lactis* JCM 5805 and resistant maltodextrin -a randomized, double-blind, placebo-controlled, parallel-group trial—Jpn Pharmacol Ther. 43:1711–27.
8. Suzuki H, Ohshio K, Fujiwara D. (2016) *Lactococcus lactis* subsp. *lactis* JCM5805 activates natural killer cells via dendritic cells. Biosci Biotech Biochem. 80: 798-800
9. Shibata T, Kanayama M, Haida M, Fujimoto S, Oroguchi T, Sata K, Mita N, Kutsuzawa T, Ikeuchi M, Kondo M, Naito K, Tsuda M, Nishizaki Y, Ishii N. (2016) *Lactococcus lactis* JCM5805 activates anti-viral immunity and reduces symptoms of common cold and influenza in healthy adults in a randomized controlled trial. J Func Food. 24: 492-500.
10. Sakata K, Sasaki Y, Jounai K, Fujii T, Fujiwara D. (2017) Preventive effect of *Lactococcus lactis* subsp. *lactis* JCM 5805 yogurt intake on influenza infection among schoolchildren. Health 9: 756-762
11. Fujii T, Jounai K, Horie A, Takahashi H, Suzuki H, Ohshio K, Fujiwara D, Yamamoto N. (2017) Effects of heat-killed *Lactococcus lactis* subsp. *lactis* JCM 5805 on mucosal and systemic immune parameters, and antiviral reactions to influenza virus in healthy adults; A randomized controlled double-blind study. J Func Food. 35: 513-521.
12. Jounai K, Sugimura T, Morita Y, Ohshio K, Fujiwara D. (2018) Administration of *Lactococcus lactis* strain Plasma induces maturation of plasmacytoid dendritic cells and protection from rotavirus infection in suckling mice. Int Immunopharmacol., 56: 205-211.
13. Kanayama M, Kato Y, Tsuji T, Komano Y, Hashimoto A, Kanauchi O, Fujii T, Fujiwara D. (2018) Enhancement of immunomodulative effect of lactic acid bacteria on plasmacytoid dendritic cells with sucrose pantothenate. Sci Rep., 8: 3147.
14. Sugimura T, Jounai K, Ohshio K, Suzuki H, Kirisako T, Sugihara Y, Fujiwara D. (2018) Long-term administration of *Lactococcus lactis* strain Plasma accelerates senescence and prolongs the lifespan of mice. Int Immunopharmacol., 58:166-172.
15. Tsuji R, Komano Y, Ohshio K, Ishihara Y, Kanauchi O. (2018) Long-term administration of pDC stimulative lactic acid bacteria, *Lactococcus lactis* strain Plasma, prevents immune-senescence and decelerates individual senescence. Exp Gerontol., 111: 10-16.
16. Suzuki H, Jounai K, Ohshio K, Fujii T, Fujiwara D. (2018) Plasmacytoid dendritic cell stimulative lactic acid bacteria and pantothenate enhance immune response in mice. J Phys Res Commun., 503: 1315-1321.
17. Kato Y, Kanayama M, Yanai S, Nozawa H, Kanayama M, Yamamoto N, Fujiwara D. (2018) Safety evaluation of long-term or excessive intake of the beverage containing *Lactococcus lactis* strain Plasma in mice. Food Nutr Sci., 9:403-419.
18. Komano Y, Shimada K, Naito H, Fujikawa K, Ishihara Y, Fujii T, Kokubo T, Daida H. (2018) Efficacy of heat-killed *Lactococcus lactis* JCM 5805 on immunity and fatigue during consecutive high intensity exercise in male athletes: a randomized, placebo-controlled, double-blind trial. J Int Soc Sports Nutr., 15:39.
19. Suzuki H, Tsuji R, Sugamata M, Yamamoto N, Yamamoto N, Kanauchi O. (2019) Administration of plasmacytoid dendritic cell stimulative lactic acid bacteria is effective against dengue virus infection in mice. Int J Mol Med., 43:426-434
20. Tsuji R, Yamamoto N, Yamada S, Fujii T, Yamamoto N, Kanauchi O. (2018) Induction of anti-viral genes mediated by humoral factors upon stimulation with *Lactococcus lactis* strain Plasma results in repression of dengue virus replication *in vitro*. Antiviral Res., 160:101-108.
21. Kokubo T, Komano Y, Tsuji R, Fujiwara D, Fujii T and Kanauchi O. (2019) Plasmacytoid dendritic cell-stimulative lactic acid bacteria, *Lactococcus lactis* strain Plasma, relieves exercise-induced fatigue and aids recovery via immuno-modulatory action. Int J Sport Nutr Exer Metabol., in press.
22. Horie A, Tomita Y, Ohshio K, Fujiwara D, Fujii T. (2019) Characterization of genomic DNA of lactic acid bacteria for activation of plasmacytoid dendritic cells. BMC Microbiol., in press.
23. Tsuji R, Fujii T, Nakamura Y, Yazawa K, Kanauchi O. (2019) *Staphylococcus aureus* epicutaneous infection is suppressed by *Lactococcus lactis* strain Plasma via IL-17A elicitation. J Infect Dis., in press.
24. Sugimura T, Jounai K, Ohshio K, Fujiwara D. (2019) Plasmacytoid dendritic cell dysfunction caused by heat stress is improved by administration of *Lactococcus lactis* strain Plasma in mice. Biosci Biotech Biochem. , in press.
25. Kokubo T, Wakai S, Fujiwara D, Kanauchi O, Jonai K, Ichikawa H, Takuma M, Kanaya Y, Shiraoka R. (2020) Lactococcus Lactis Strain Plasma Improves Subjective Physical State and Presenteeism: A Randomized, Open-label Crossover Study Among Healthy Office Workers. Prev Nutr Food Sci, in press

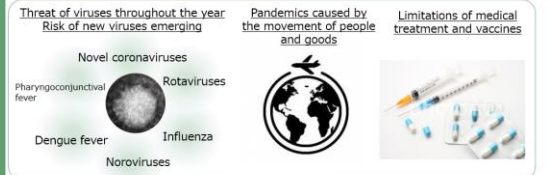
**25 scientific papers,  
including 10 human clinical trials**

**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**



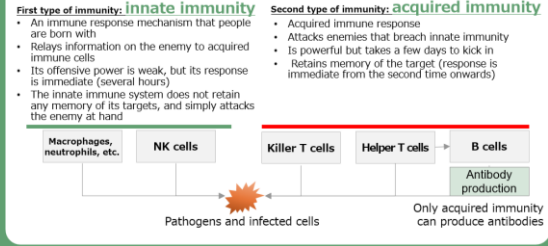
# The world's first lactic acid bacteria that strengthens the foundation of immune cells

What can be expected from this technology  
Control infectious disease risk and solve the problem of infectious disease in areas with poor sanitary conditions

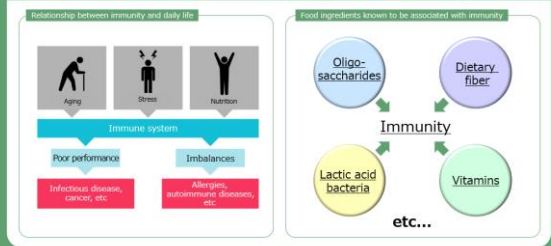


It is increasingly important to strengthen the body's natural immunity to fight viruses in the course of daily life.

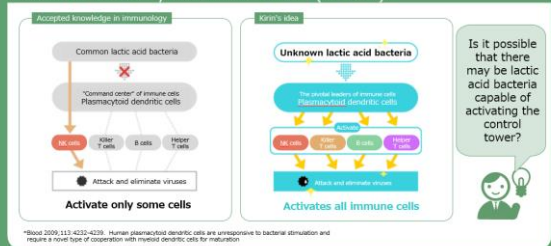
What is immunity?  
A mechanism for eliminating viruses, bacteria and other pathogens through both innate and acquired immunity



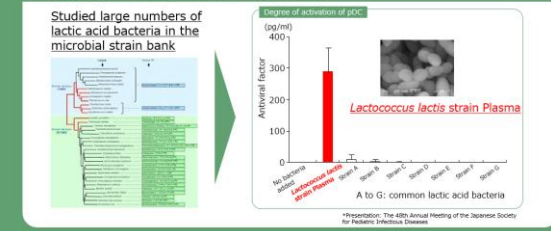
Immunity and food  
Dietary habits greatly affect immunity  
Lactic acid bacteria are known to be closely linked to immunity



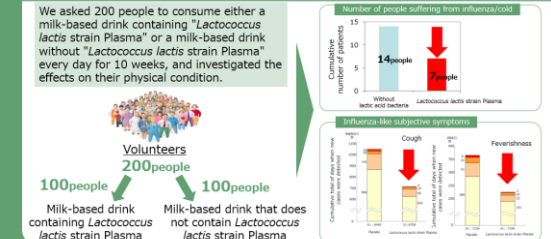
Background of this technique  
In the past, the accepted knowledge in immunology was that lactic acid bacteria activate only some immune cells (NK cells).



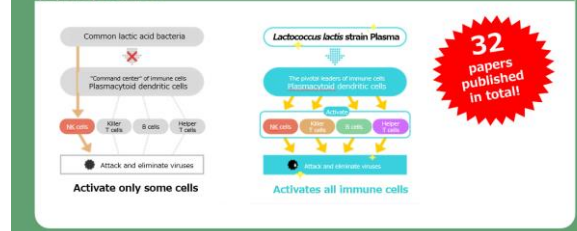
About this technology  
By questioning accepted knowledge and studying large numbers of lactic acid bacteria, we discovered "Lactococcus lactis strain Plasma" — a type of bacteria that activates the control tower



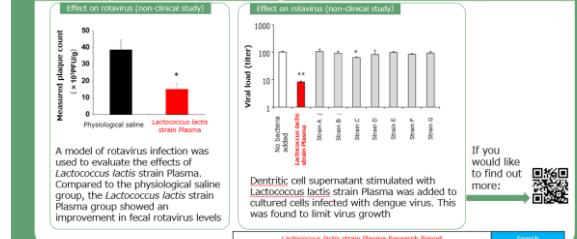
About this technology  
Ingestion of "Lactococcus lactis strain Plasma" reduced the risk of influenza and colds



Uniqueness of this technique  
Lactococcus lactis strain Plasma are highly rated by experts for their unique ability to activate the "control tower," with numerous scientific papers published



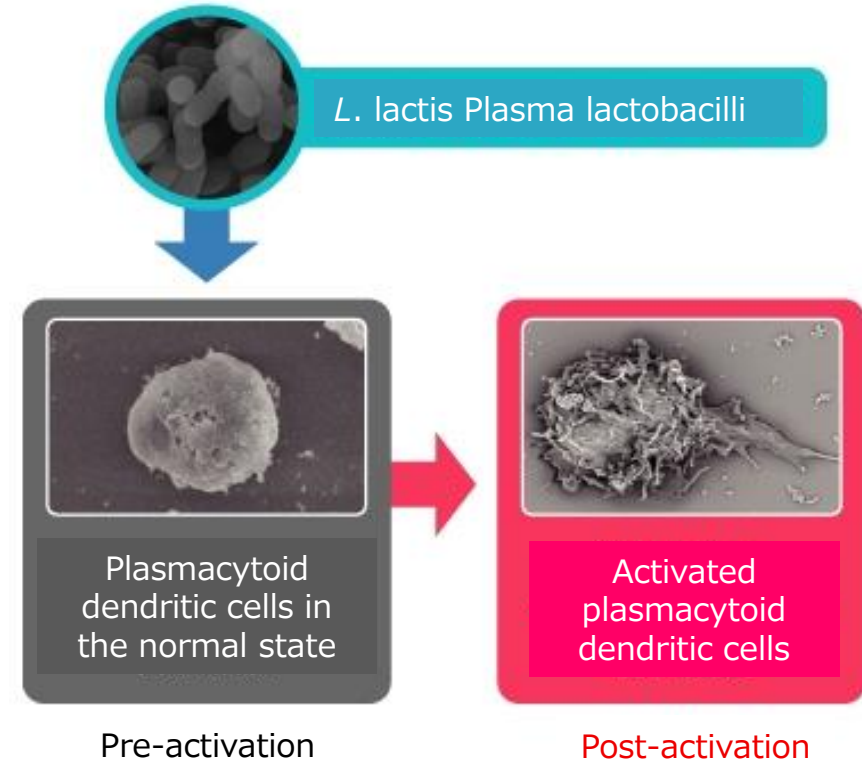
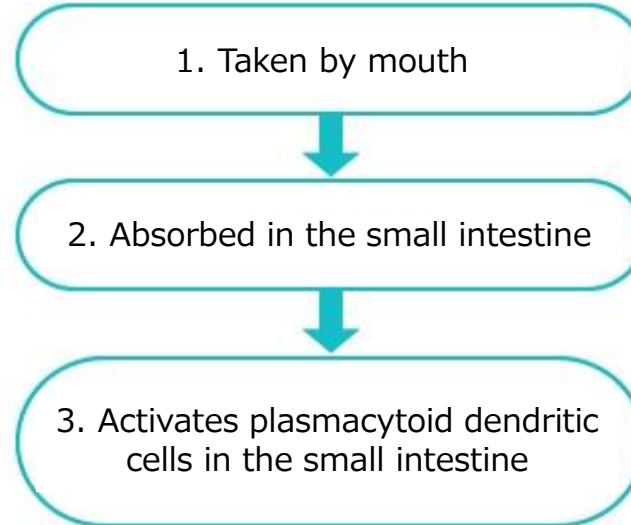
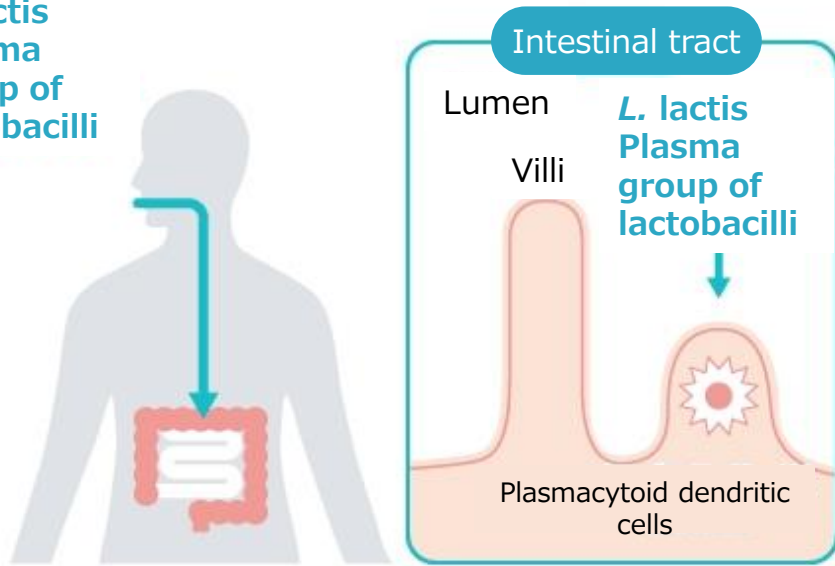
Future potential  
Since Lactococcus lactis strain Plasma activate the "control tower," they can be expected to be effective against various viruses



See the poster presentation for more information.  
Our researchers will provide explanations.

# Immunoregulation by *Lactococcus lactis* strain Plasma

*L. lactis*  
Plasma  
group of  
lactobacilli



Source : PLoS One Vol 10: e0119055, 2015.

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

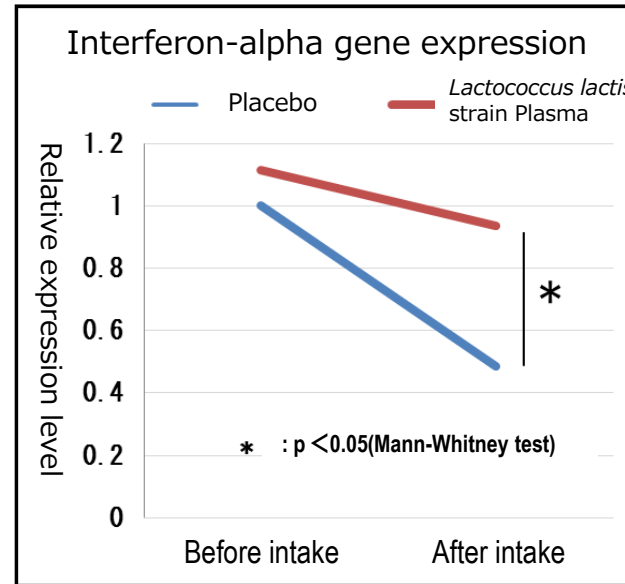
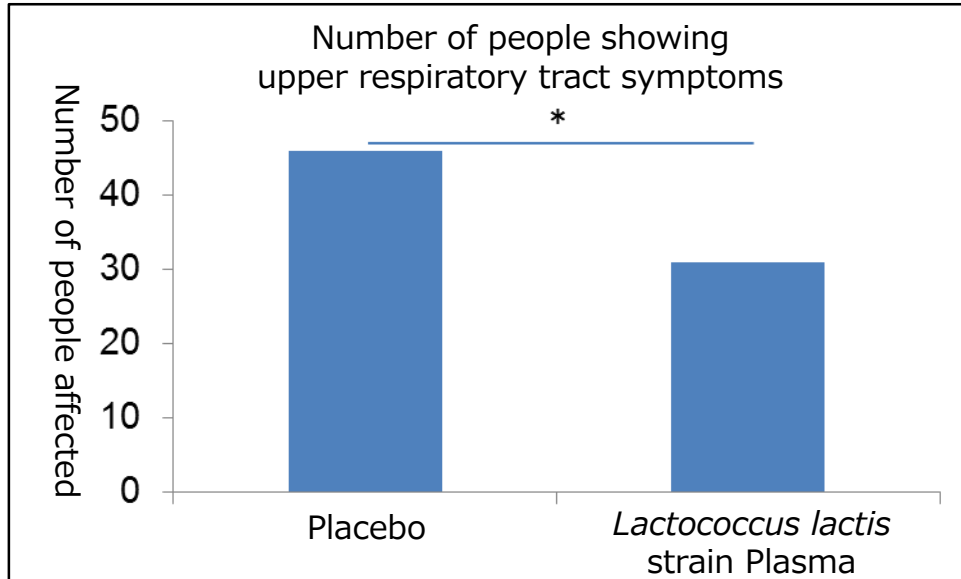


## Method

**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



## Conclusions

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



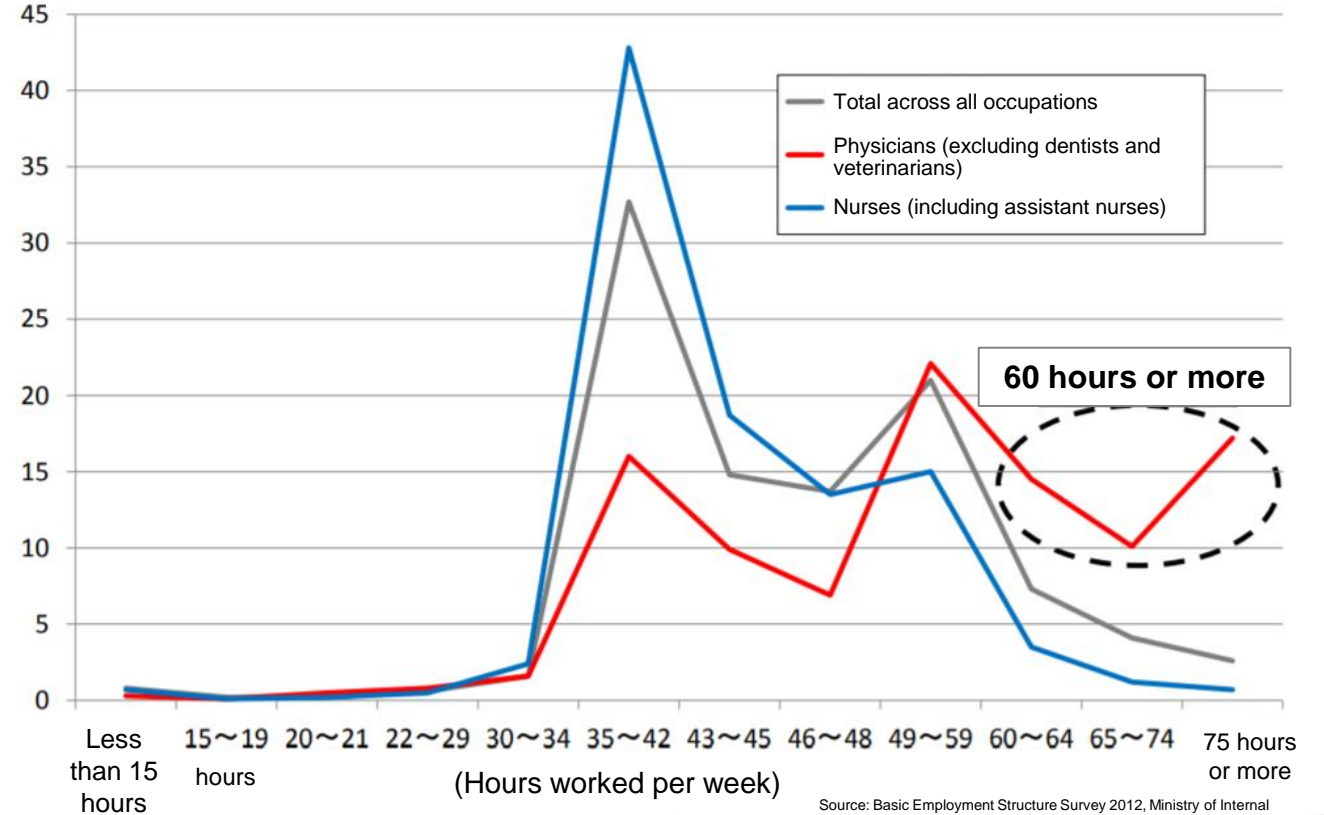


# Issues in the medical field: overworked healthcare professionals



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

(Percentage of respondents, %)



Source: Basic Employment Structure Survey 2012, Ministry of Internal Affairs and Communications  
More than 200 days of work per year, full-time employees

6

Source: Document 3: Physicians' Working Conditions, 1<sup>st</sup> Document on the Reform of the Working Style of Physicians, Ministry of Health, Labour and Welfare

<https://www.mhlw.go.jp/file/05-Shingikai-10801000-Iseikyoku-Soumuka/0000173612.pdf>



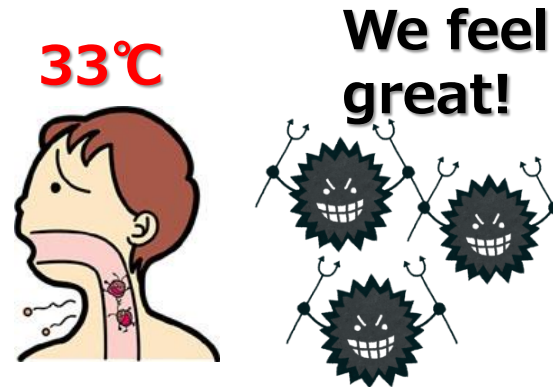
## (1) Spread due to dry conditions



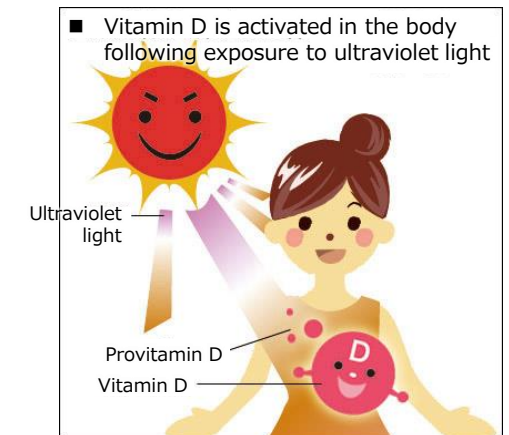
飛沫 droplet	飛沫核 droplet nuclei
<p>Moisture</p> <ul style="list-style-type: none"><li>• Larger than 5 <math>\mu\text{m}</math> in diameter</li><li>• Fall velocity 30-80cm/sec</li></ul> <p>Coughing, sneezing, talking, tracheal aspiration Usually a short distance; "about 1 meter"</p>	<ul style="list-style-type: none"><li>• 5 <math>\mu\text{m}</math> or less in diameter</li><li>• Fall velocity 0.06-1.5cm/sec</li></ul> <p>Dispersed over a wide area via air flow</p>
<b>Droplet transmission</b>	<b>Airborne transmission</b>

<https://www.anzen.mofa.go.jp/sars/pdf/k-6.pdf>

## (2) Temperature facilitating growth



## (3) Less time spent in the sun



# The Kirin Group's approach to employee health management



FANCL This Makes Sense!  
Educational Video Service

## The right way to walk

FANCL  
正直品質。

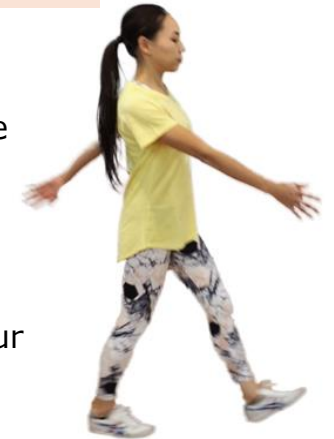
Straighten your back and swing your arms

### 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.

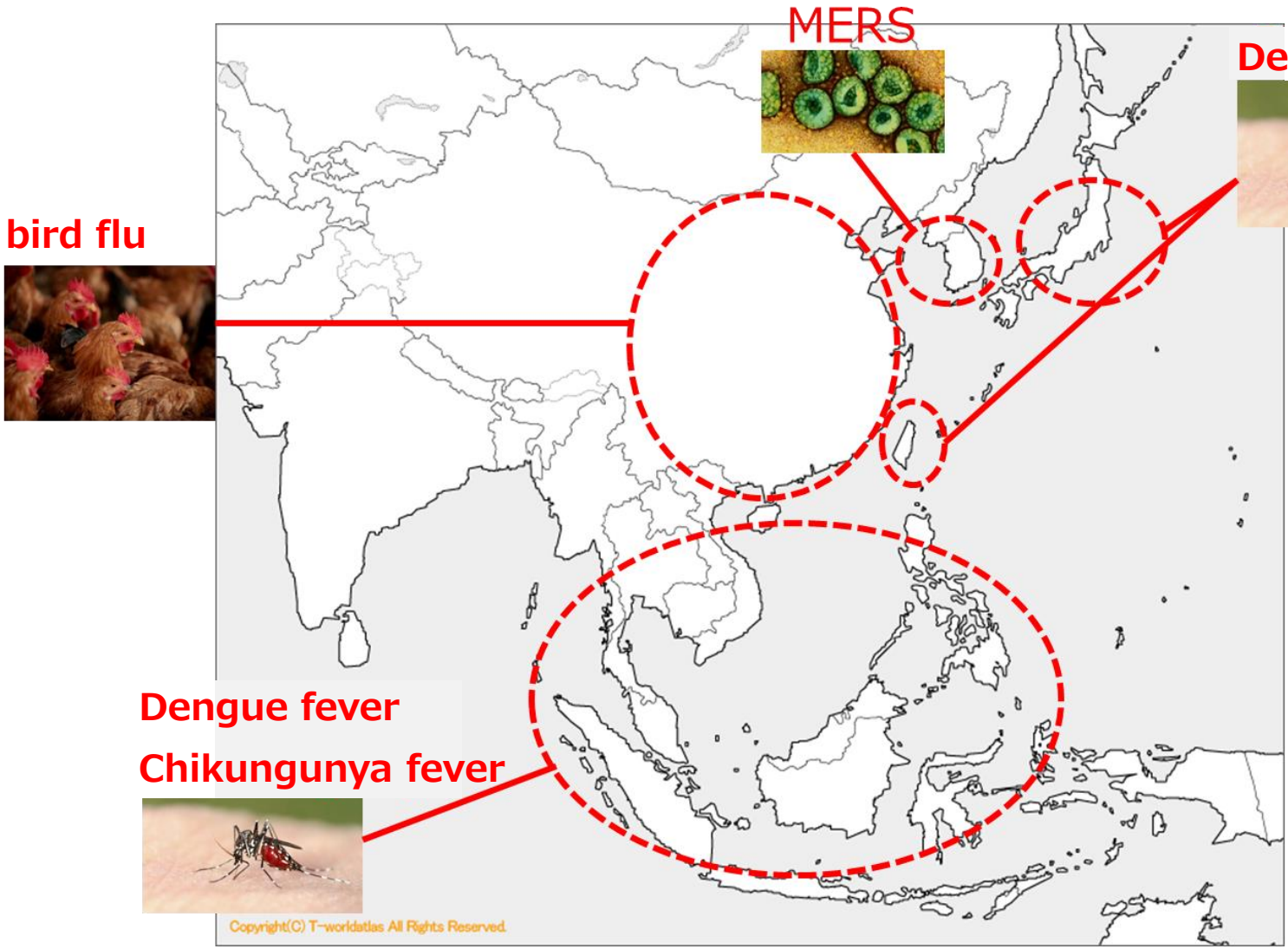
- Swing your arm backwards, pulling your shoulders back.
- Relax and let your arm swing forward.



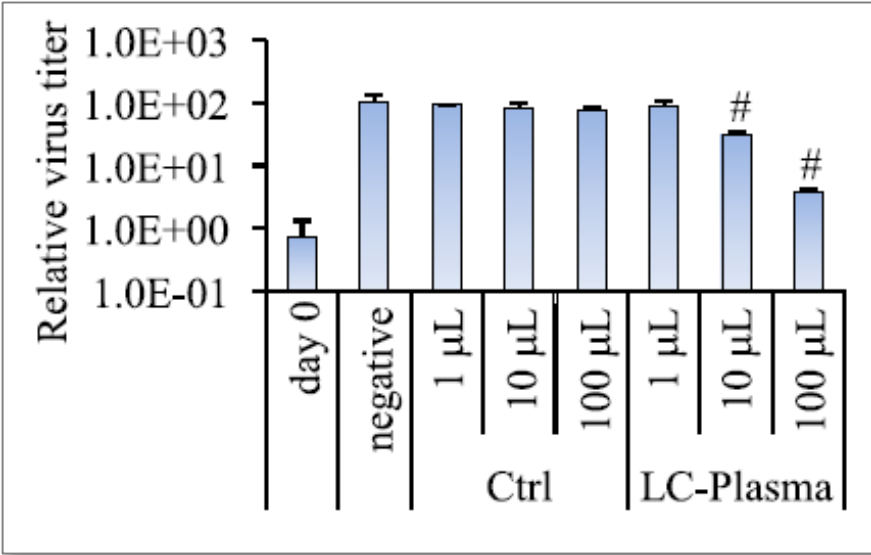
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FANCL's Health and Exercise Instructor Ono explains how you can turn your everyday life into a workout with just a few changes in "the way you walk".

# Emerging risk of viral infections in Asia



**Effects on the dengue virus (non-clinical studies)**



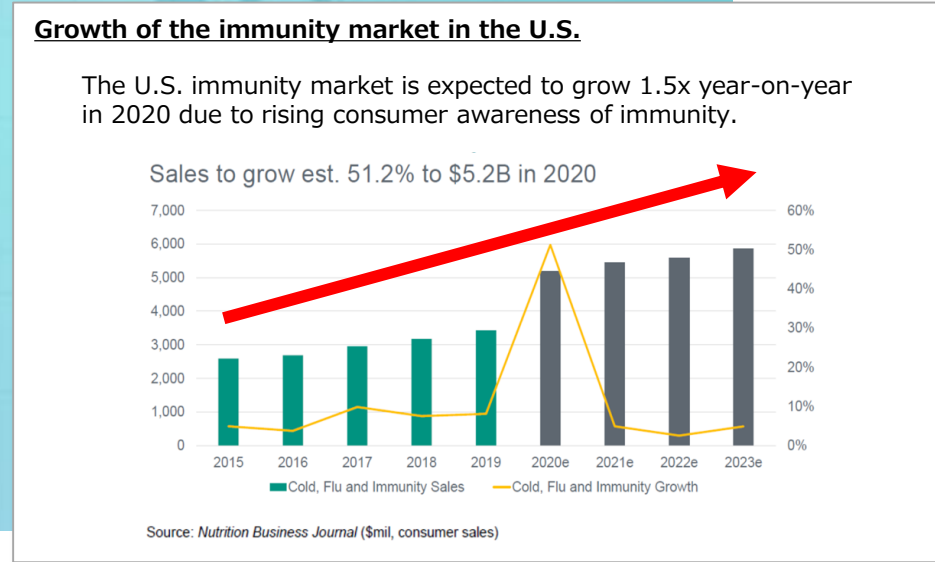
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# Global Business Strategy



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



## 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