




Immunity: Mastering the Market

Postbiotic Immune Activation with IMMUSE™ LC-Plasma
An Innovative Approach to Immune Health

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Company Overview

Date of Incorporation	February 23 rd , 1907
Number of Group Companies	281
Number of Employees	31,040

Kirin Holdings Company, Ltd.



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Dietary Supplement & Nutrition Products


Glutathione


By the addition of your mind!


Maximum Performance Blend


Supports a healthy heart









<p>Amino Acids</p> <ul style="list-style-type: none"> L-Arginine L-Arginine + L-Citrulline (VELOX®) L-Citrulline L-Glutamine <p>New Product Development</p> <p>Human Milk Oligosaccharides (HMOs)</p> <ul style="list-style-type: none"> 2'-Fucosylactose 3'-Sialyllactose Sodium Salt 6'-Sialyllactose Sodium Salt 	<p>Nucleic Acids</p> <ul style="list-style-type: none"> Citicoline (Cognizin®) <p>Postbiotics</p> <p>Kirin Holdings Co. Ltd., Product Offering:</p> <ul style="list-style-type: none"> Lactococcus Anfidis strain Plasma (IMMUSE™) Lactocaseibacillus paracasei KW3110 (EYEMUSE™) <p>Peptides</p> <ul style="list-style-type: none"> L-Alanyl-L-Glutamine L-Glutathione Reduced (Setria®) L-Glutathione + L-Citrulline (Setria® Performance Blend) 	<p>Vitamins</p> <ul style="list-style-type: none"> Vitamin K₂ <p>Vitamin B Derivatives</p> <p>Kyowa Pharma Chemical Co. Product Offerings:</p> <ul style="list-style-type: none"> Vitamin B₁₂ derivatives Pantesin® L080 Pantesin® HF55 <p>Vitamin B₆ derivatives</p> <ul style="list-style-type: none"> Pyridoxal-5'-phosphate
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Learning objectives 


- Understand the functional benefits and formulation advantages of postbiotics.
- The unique mechanism of action of IMMUSE™, *Lactococcus lactis* strain Plasma (LC-Plasma).
- The importance of plasmacytoid dendritic cells within the immune system.

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Agenda 

- What are postbiotics?
 - Definition of postbiotics
 - Benefits of postbiotics
 - Immune modulation by postbiotics
- Examples of immune modulation by postbiotics
 - IMMUSE™, a novel postbiotic to activate the immune system

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What are postbiotics? 

Probiotics
"live microorganisms which when administered in adequate amounts confer a health benefit on the host." WHO 2001


Prebiotics
"non-digestible food ingredients that were beneficial to the host through their selective stimulation of specific bacteria within the colon." ISAPP 2017

Postbiotics
"preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" ISAPP 2021

Antibiotics

Synbiotics
Mixture of Probiotics and Prebiotics

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ISSAP definition 

The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics

- Published May 2021
- The term postbiotic was chosen by the panel as a composite of ‘biotic’, defined as “relating to or resulting from living organisms”, and ‘post’, a prefix meaning ‘after’. Together these terms suggest ‘after life’; that is, non-living organisms.
- We propose that a postbiotic is a “preparation of inanimate microorganisms and/or their components that confers a health benefit on the host”

Salmiminen, S., Collado, M.C., Endo, A. et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nat Rev Gastroenterol Hepatol* 18, 649–667 (2021). <https://doi.org/10.1038/s41575-021-00440-6>

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Functions of probiotics 

Probiotics

- Reduction of cholesterol
- Immune modulation
- Anti-inflammation
- Gut-barrier improvement
- Improvement of constipation
- Modulation of Gut microbiota
- Amelioration of Stress related symptom
- H. Pylori* control
- Blood pressure management
- Cancer risk reduction

Open Vet J. 2020 Jul-Sep; 10(3): 323–330
Nutrients 2021, 13, 1225

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Nutrients 2021, 13, 1225

Postbiotics are comparable to probiotics with several benefits


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Examples of immune modulation

Title	Heat-killed strain	Function	Issue
Beneficial effect of a diet containing heat-killed <i>Lactobacillus paracasei</i> K71 on adult type atopic dermatitis	<i>L. paracasei</i> K71	Atopic dermatitis	J Dermatol .2011 Feb;38(2):131-9
The effects of non-viable <i>Lactobacillus</i> on immune function in the elderly: a randomised, double-blind, placebo-controlled study	<i>L. paracasei</i> MCC1849	Improvement of Vaccine effect	Int J Food Sci Nutr .2016;67(1):67-73.
The efficacy and safety of heat-killed <i>Lactobacillus paracasei</i> for treatment of perennial allergic rhinitis induced by house-dust mite	<i>L. paracasei</i> 33	Improvement of allergy	Pediatr Allergy Immunol .2005 Aug;16(5):433-8.
Efficacy of oral administration of a heat-killed <i>Lactobacillus gasseri</i> OLL2809 on patients of Japanese cedar pollinosis with high Japanese cedar pollen-specific IgE	<i>L. gasseri</i> OLL2809	Improvement of allergy	Biosci Biotechnol Biochem .2009 Sep;73(9):1971-7.
Immunoprotective effects of oral intake of heat-killed <i>Lactobacillus pentosus</i> strain b240 in elderly adults: a randomised, double-blind, placebo-controlled trial	<i>L. pentosus</i> b240	Reduction of common cold	Br J Nutr .2013 May 28;109(10):1856-65.
Daily intake of heat-killed <i>Lactobacillus plantarum</i> L-137 augments acquired immunity in healthy adults	<i>L. Plantarum</i> L-137	Enhance Th1 response	J Nutr .2006 Dec;136(12):3069-73.
Heat-killed <i>Lactobacillus gasseri</i> can enhance immunity in the elderly in a double-blind, placebo-controlled clinical study	<i>L. gasseri</i> TMC0356	Enhance natural defence	Benefit Microbes .2015;6(4):441-9.
A Double-Blind, Randomized, Placebo-Controlled Trial of Heat-Killed <i>Pedococcus acidilactici</i> K15 for Prevention of Respiratory Tract Infections among Preschool Children	<i>P. acidilactici</i> K15	Support anti-infectious immune system	Nutrients .2020 Jul 3;12(7):1989.

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Immune cells in the intestine

About 70 ~ 80% of immune cells are in the intestine (Kagnoff, 1987) 

⇒ It is reasonable that postbiotics can modulate immune cells in the small intestine

Small intestine

Many immune cells

Few microbiome

⇔

Postbiotics

Large intestine

Less immune cells

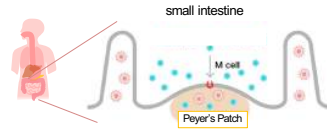
Most if microbiome

⇔

Probiotics

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Immune cell/postbiotics interaction




- Orally administered postbiotics will go to the small intestine where a lot of immune cells reside
- M cell, a special cell to pick up large particle in the small intestine, will convey postbiotics to immune cell rich reason (Payer's Patch)
- Postbiotics interact with immune cells in PP

Drug Discov Today. 2005 Sep 1;10(17):1145-57
Biotechnol Biochem. 2009 Jul;73(7):1561-5

It is considered that the small intestine is the main place where postbiotics interact with immune cells

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Benefit of postbiotics 


Postbiotics are comparable to probiotics with several health benefits, and immune function is the most known one

+

Easy to handle

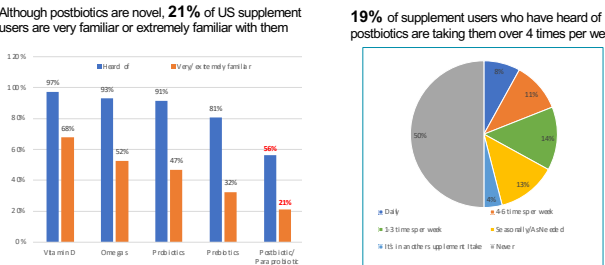
- No need to care for viability
- Postbiotics are generally stable in room temperature
- Applicable to variety of product forms

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Consumer Recognition of Postbiotics 

Although postbiotics are novel, **21%** of US supplement users are very familiar or extremely familiar with them

19% of supplement users who have heard of postbiotics are taking them over 4 times per week




Supplement	Hard of	Very familiar or extremely familiar
Vitamin D	97%	68%
Omega-3	92%	52%
Probiotics	92%	47%
Prebiotics	81%	32%
Postbiotics	56%	21%

Frequency	Percentage
Daily	2%
3-3 times per week	13%
1-2 times in another supplement	50%
4-4 times or more per week	19%
5 or more times per week	16%
Never	1%

N=1,000, Dietary supplement users live in the USA. ITC Insights 2021 Consumer Supplements Survey

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IMMUSE™
 innovative immune support ingredient

Broad Range Immune Support



IMMUSE™
 Immune Support

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What is IMMUSE™?


IMMUSE™

IMMUSE is a branded form of *Lactococcus lactis* strain Plasma

After the culturing, cells were heat-treated (= postbiotics)

Specially chosen bacterial strain to provide broad-range immune support

Marketed in Japan since 2012, and launched in the US in 2020



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Activate the "Right" Immune Cells

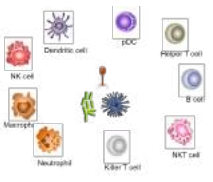

IMMUSE™

It is important to activate the "right" immune cells

Like an army, the immune system is composed of various immune cells, each one has its own role.

To fight against invaders, our immune cells need to be organized as a system.

The key is to activate the "right" immune cells

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pDCs, a Leader of Immune System

Plasmacytoid dendritic cells (pDCs) are the "right" immune cells to activate

- pDCs detects invaders
- pDCs secrete IFN- α , an important signal molecule to activate other immune cells
- pDCs induce broad range immune activation

KYOWA

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Researchers' Challenge

Current ingredients for immune activation mainly target NK cells. Researchers in Kirin decided to find a novel food ingredient that can activate pDCs, which are the right immune cells to activate more comprehensive immune support

KYOWA

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Discovery of IMMUSE™

Researchers tested several hundreds of microbial strains and finally found one special strain, *Lactococcus lactis* strain Plasma (IMMUSE™).

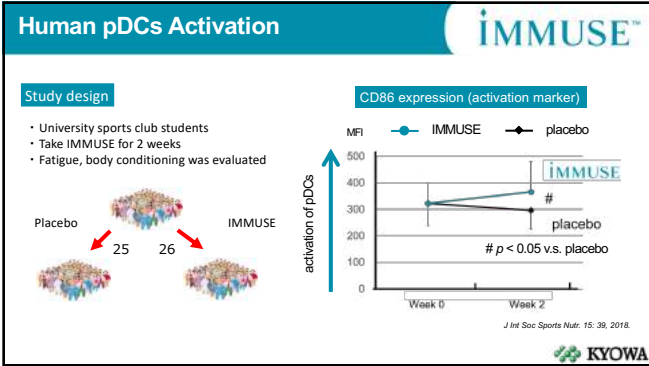
Type I Interferon production from pDCs

Condition	IFN- α (pg/ml)
control	~0
IMMUSE+	~300
A	~10
B	~10
C	~10
D	~10
E	~10
F	~10
G	~10

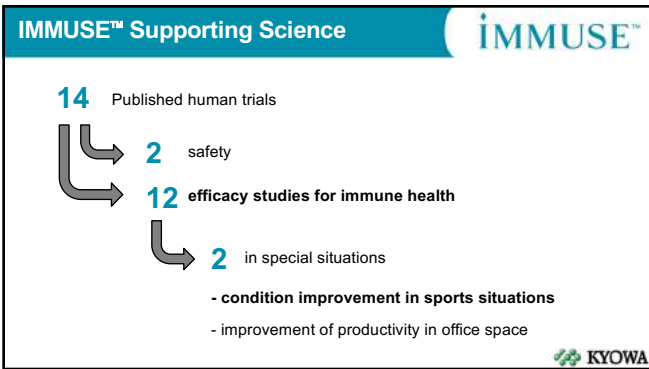
Conventional LAB cannot activate pDCs. Only IMMUSE do

KYOWA

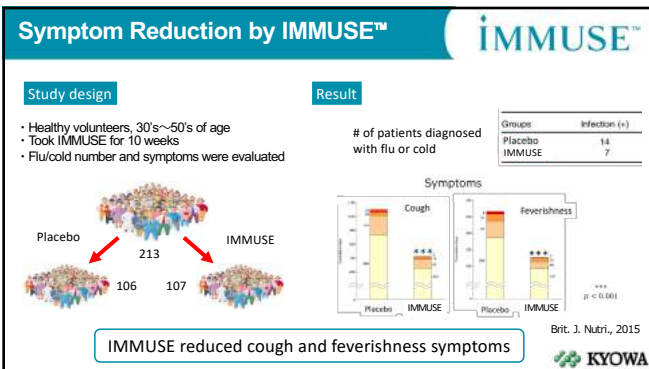
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Symptom Reduction by IMMUSE™

Study design

- Healthy volunteers, 18-39 of age
- Placebo 205
- IMMUSE 192
- Took IMMUSE for 12 weeks
- Severity of cold-like symptoms were evaluated

Result

Table 3 Cumulative number of incident days of each symptom with its severity grade during the intake period.

Symptoms	IMMUSE	Placebo	IMMUSE	Placebo	p-value*	
Incidence on remaining weeks (n)	IMMUSE	1808	4016	588	23	0.016
	Placebo	1807	4016	588	23	0.016
Sore throat (n)	IMMUSE	404	514	33	17	<0.001
	Placebo	404	514	33	17	<0.001
Cough (n)	IMMUSE	196	233	14	26	0.001
	Placebo	196	233	14	26	0.001
Runny nose (n)	IMMUSE	328	345	32	19	0.047
	Placebo	328	345	32	19	0.047
Headache (n)	IMMUSE	17	18	0	0	0.800
	Placebo	17	18	0	0	0.800
Stomach pain (n)	IMMUSE	10	12	0	0	0.800
	Placebo	10	12	0	0	0.800
Chills (n)	IMMUSE	10	12	0	0	0.800
	Placebo	10	12	0	0	0.800

* The statistical analysis of incident days of each symptom is based on the chi-square test.
 † For each symptom, the percentage of occurrence with each severity grade was compared between the placebo and IMMUSE groups by the Fisher test.

J. Func. Food, 2016

Scores of cough and sore throat were significantly reduced

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Incident Case Reduction by IMMUSE™

Study design

- Healthy volunteers
- Placebo 19
- IMMUSE 19
- Took IMMUSE for 4 weeks
- Cumulative incidence days per week were measured

Result

Table 1 Transition of the cumulative incidence days per week during intake period.

1st week	Symptoms, -		Symptoms, +		Chi-square test
	IMMUSE group	Placebo group	IMMUSE group	Placebo group	
1st week	60	64	40	46	p = 0.467
2nd week	64	105	27	28	p = 0.125
3rd week	63	83	38	30	p = 0.220
4th week	100	100	33	33	p = 0.884

* Chi-square test was used for statistical analysis. Residuals: 1. 1st/2nd week: IMMUSE group n = 13 (19 subjects) + 7 days and placebo group n = 13 (19 subjects) + 7 days. Data of 1st week placebo group: n = 13 (19), 2nd week: 1st/2nd week: IMMUSE group n = 13 (19), 3rd week: 1st/2nd week: IMMUSE group n = 13 (19), and 3rd week placebo group n = 13 (19) were deleted because of blank record.

Clin Immunol, 2013

IMMUSE reduced cumulative incidence days in the 4th week

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Incident Case Reduction by IMMUSE™

Study design

- School children in Shizuokushi town
- Took yogurt drink with IMMUSE for 10 weeks
- Number of student diagnosed with flu was measured and compared with neighboring town

Result

Cumulative rate of absence from flu

School Type	Neighboring town (%)	Shizuokushi (%)
Elementary school	~35	~25
Junior high school	~25	~15
total	~30	~20

Health, 2017

IMMUSE reduced absence from flu compared to neighboring town

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IMMUSE™ for Sport Club Students

Study design

- University sports club students
- Take IMMUSE for 2 weeks
- Cumulative days of incidence and the fatigue level of students were evaluated

Result

Table 3 Number of subjects and cumulative days of URTI during intervention period

	Placebo	LC-Plasma	p-value*
Number of subjects	11	11	0.958
Number of incidences (days)	56	306	<0.001
	LC-Placebo [†]	306	

Comparison of the cumulative number of subjects and days of URTI. *Two-tail subject and incidence were compared between the placebo and LC-Plasma groups by Chi-square test. †The adjusted result of the LC-Plasma group (symptoms required) was calculated as 32.

IMMUSE™ reduced cumulative incident days and fatigue level during intensive training

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Supporting Claims

Immune support

- IMMUSE provides clinically researched immune support
- IMMUSE activates pDCs
- IMMUSE proactively supports the immune system.
- Immune support for year-round health
- IMMUSE is an immune activator
- IMMUSE activates the immune system
- IMMUSE gets your immune system ready
- IMMUSE Stimulates your body's natural defenses

Immune support during training

- Immune support for exercise (high intensity training)
- Get your immune system ready for training
- Supports exercise performance by activating immune system

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IMMUSE™ Feature & Benefits

- Recommended Dose**
50 mg/day
- Solubility**
Freely soluble in water
- Taste**
Neutral taste when added to water
- Stability**
Stable at room temperature
Stable in liquids and to high heat

Patented | GRAS | Vegetarian | Allergen Free | Clinically Studied | Non-GMO

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Any Questions? **IMMUSE™**

For More Information please contact:
info@kyowa-usa.com

immusehealth.com 
