HOWARU益生菌在婴幼儿消化和免疫健康的功效性研究新进展
Efficacy of HOWARU probiotic strains on infants and toddlers" digestive and immune health

What are probiotics?
什么是益生菌？

"Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host"

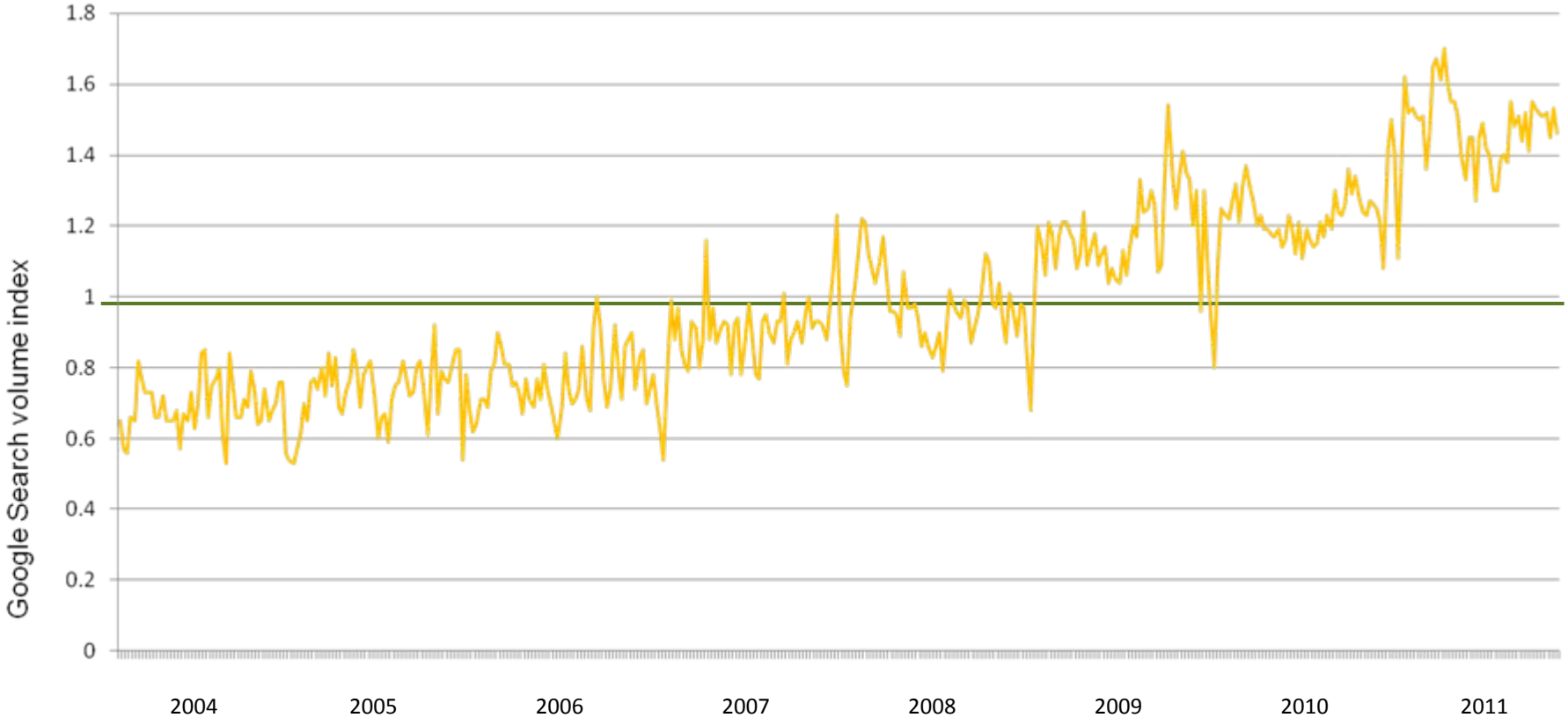
益生菌：活的微生物，当摄入充足的数量，对宿主产生一种或多种有论证的功能性健康益处. *(FAO/WHO 2002)*

主要内容

- 益生菌市场状况及趋势回顾

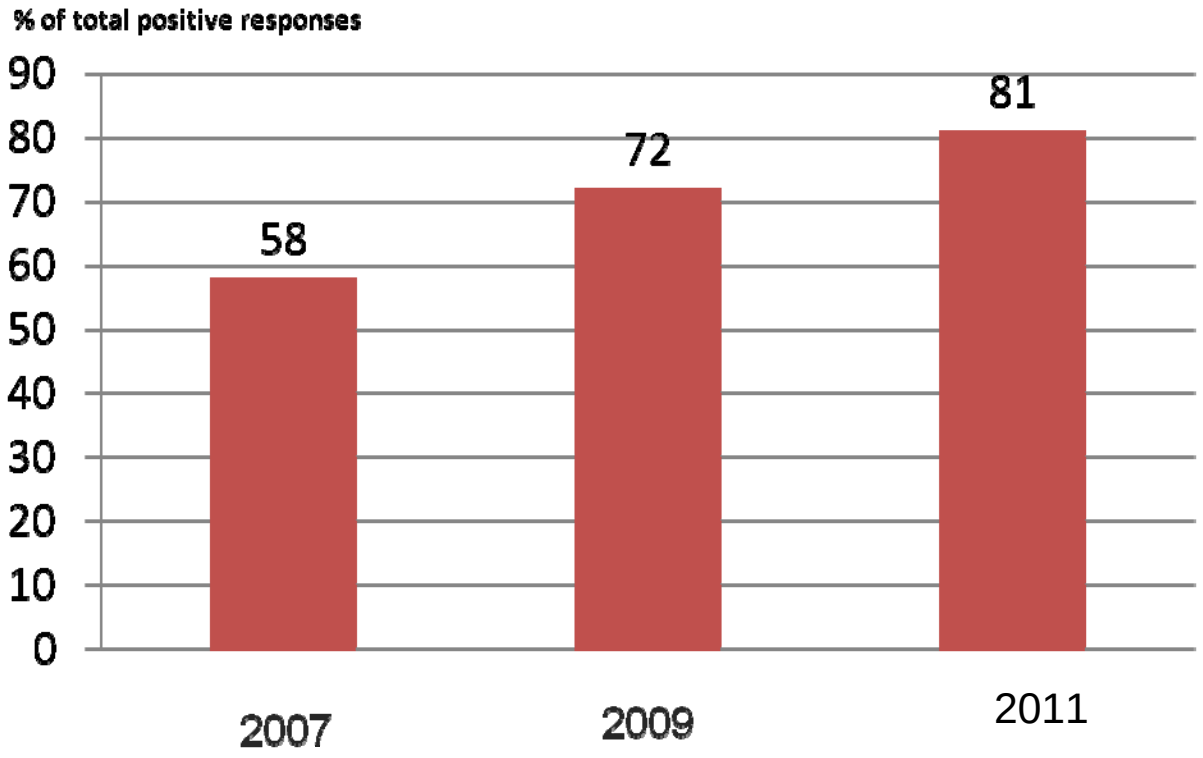
- 杜邦-丹尼斯克 益生菌---本地的产品、法规和技术服务
- 杜邦-丹尼斯克 益生菌在婴幼儿健康的功效性研究新进展

消费者越来越关注益生菌
2004 -2011年间，Google™的“益生菌”检索量翻了2倍



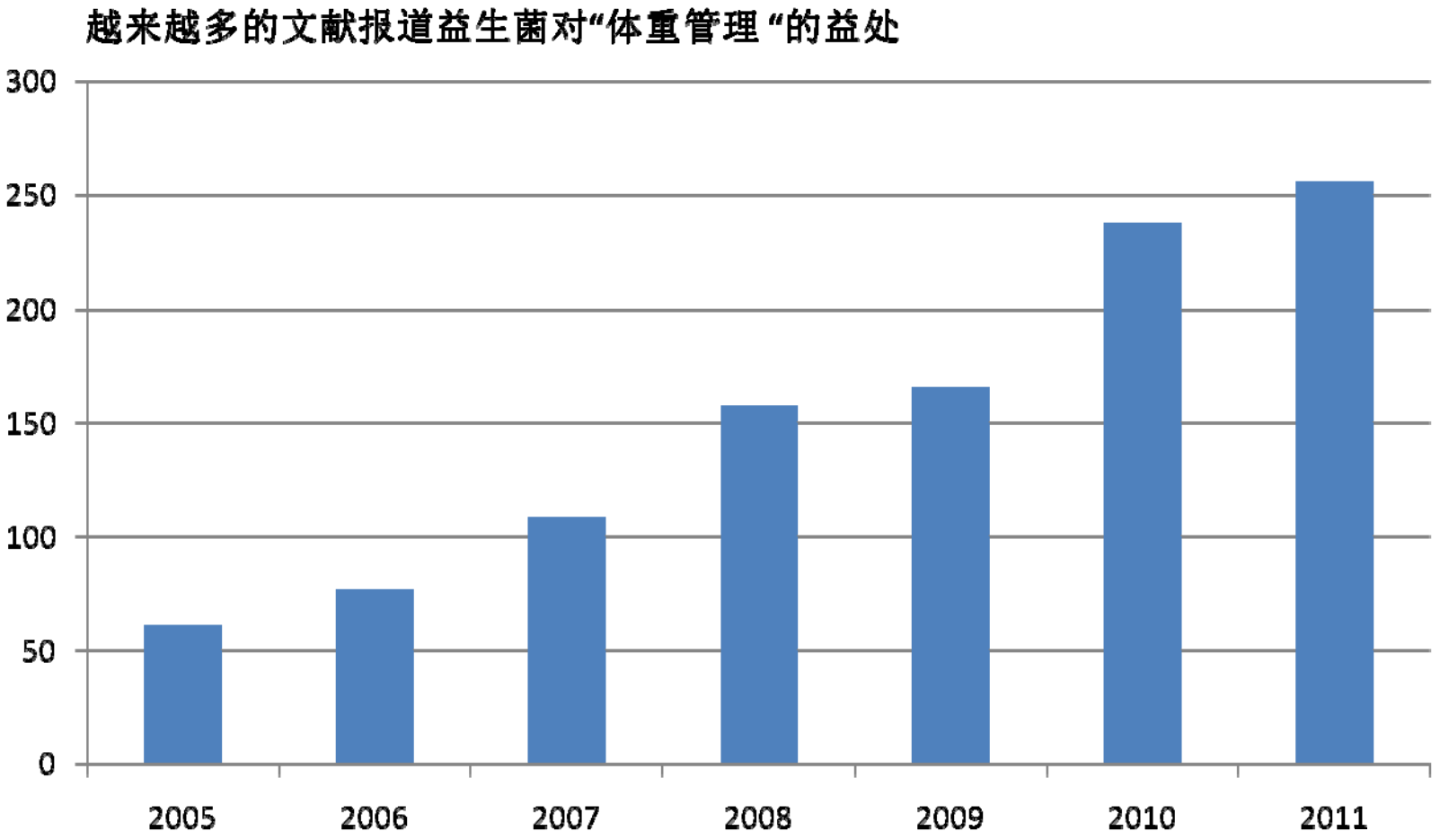
益生菌有益于消化健康，已被越来越多的美国消费者认知

“我确信益生菌有益于消化健康"



Source: International Food Information Council (IFIC), on line survey, 1000 adults March & April 2011

益生菌有益于人体健康

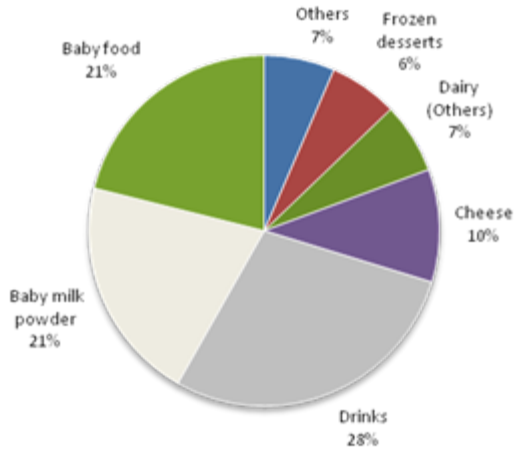


Source: PubMed

全球食品工业领域益生菌的发展趋势

在食品与饮料领域，酸奶占益生菌新产品的75%，且近三年增长平稳

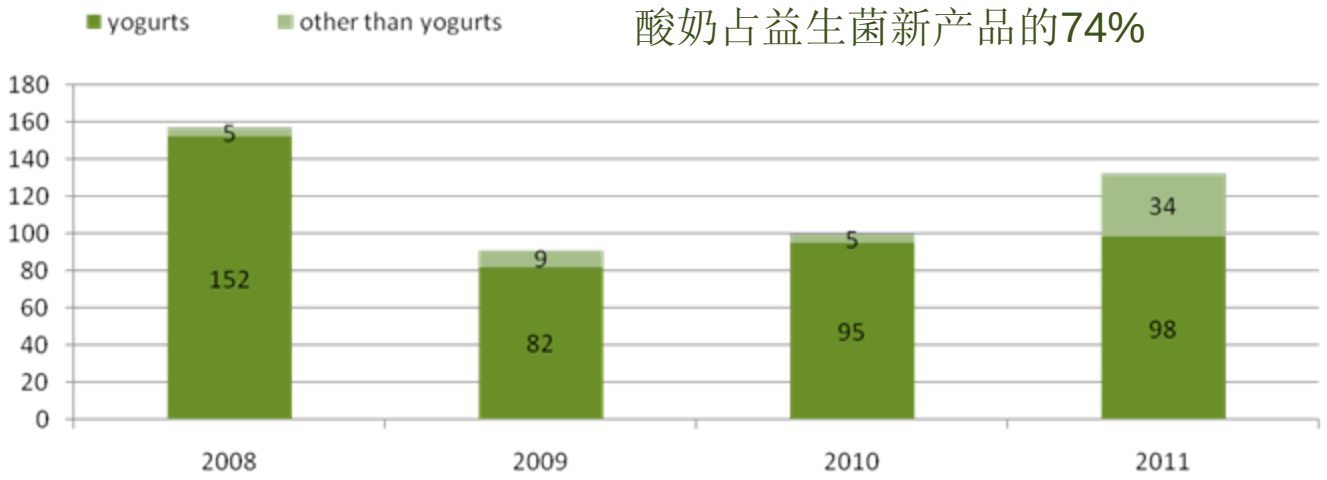
其余25%的益生菌新产品构成如下：



21%	**Baby food** – Cereals, biscuits desserts, juices...
21%	**Baby milk powder** – From 0 to 4+ years old...
28%	**Drinks –** Nectar, fruit juices, beverage mixes...
10%	**Cheese –** Hard cheese, processed cheese, ...
7%	**Dairy (others) –** Milk, cream, kefir, curds....
6%	**Frozen desserts –** Dairy & water based ice creams...
7%	**Others –** Bakery, breakfast cereals chocolate...

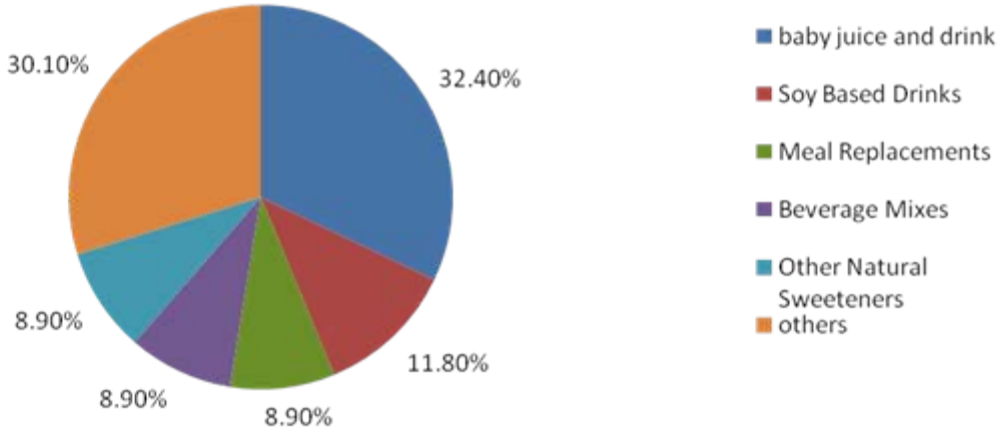
Source: Mintel GNPD - 2011

中国食品市场益生菌的发展趋势



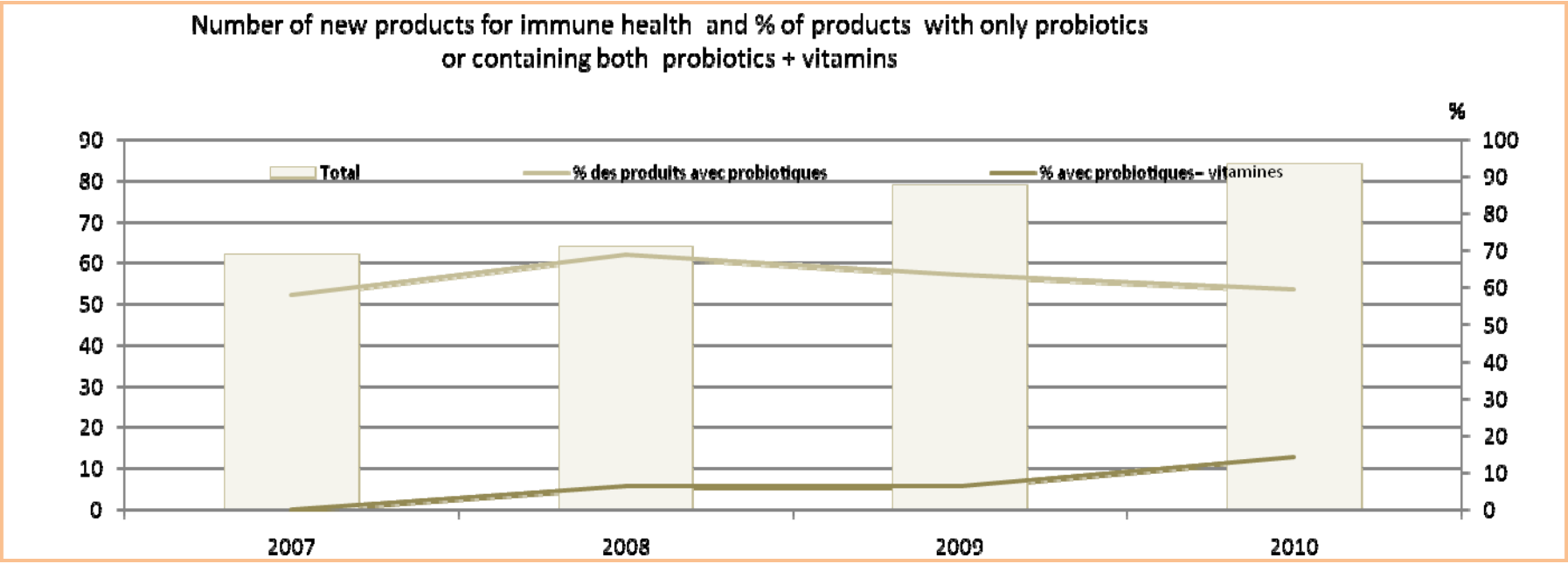
酸奶占益生菌新产品的74%

其余26%的益生菌新产品构成如下：



Source: Mintel GNPD - 2011

欧洲产品趋势：益生菌+维生素类的产品有益于免疫健康



Emmi – Russie
Avril 2010
LGG + vitamine B6 + acide folique

Danone – Espagne
Juillet 2010
Nouvelle formulation avec vit E et B6

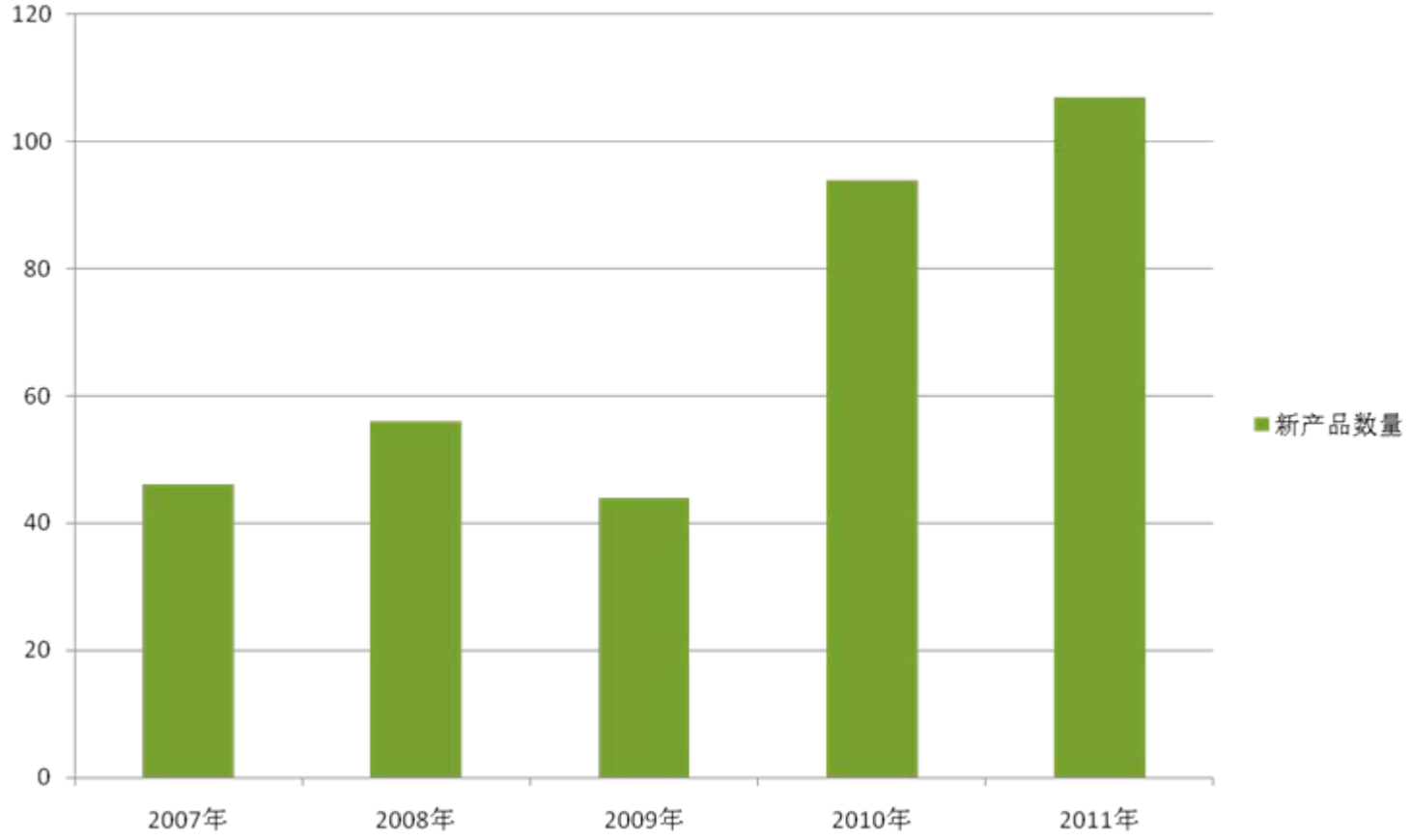
Danone – Nederlands –Mai2011
« Boisson laitière parfum fruits des bois contient des fruits, des vitamines ajoutées B6 et D.
Aide à renforcer le système immunitaire »

Granarolo – Italie
Juillet 2011
Probiotique LGG + vitamine B6

Source: GNPD, Allégation: Functional –Immune System, Jan 2007-Dec 2010

全球食品工业领域婴幼儿益生菌产品的发展趋势

（单位:个）



Source: Mintel GNPD - 2011

新产品——含益生菌的食品及饮料

Nestlé Cerelac “Céréale Infantile” avec Fruits (Infant Cereal with Fruits) 适用于4-6个月的婴儿，不含糖及麸质。此款谷类产品含益生菌(bifidus BL)及8种维生素 **来促进消化，促进微量元素铁锌的吸收，提高机体自身防御能力**。

USA - Goodbelly Splash 芒果口味的益生菌果汁饮料，功能诉求是：**健康消化，天然免疫**。每瓶含200亿活的益生菌（植物乳杆菌+双歧乳杆菌Bi07）

Mintel GNPD - 2011

满足不同人群需求的益生菌果汁饮料

美国

瑞典

芬兰

婴幼儿新产品---配方奶粉

Töpfer Lactana Kinder Bio Folgemilch (Organic Follow-On Milk for Kids) 适用于1-4岁的婴幼儿，含维生素及矿物质，此款配方奶粉含双歧杆菌**来促进消化，促进微量元素的吸收。**

Hipp Plus Praebiotik + Probiotik Folgemilch (Prebiotic + Probiotic Follow-up Milk)适用于6-12个月的婴儿，含维生素及矿物质，不含麸质，此款配方奶粉含乳酸菌及益生元**来促进消化。**

婴幼儿新产品---谷物类

Happybellies Organic Super Cereals适用于0-4岁的婴幼儿，不含麸质，绝对素食主义。此款谷物类产品含益生菌(嗜酸乳杆菌、乳双歧杆菌）及低聚果糖，**来促进消化，提高机体免疫功能**。

英氏益生菌营养米粉适用于0-4岁的婴幼儿，含维生素及矿物质，此款米粉含益生菌(乳酸杆菌）及低聚果糖，**来促进消化，提高机体免疫功能**。

婴幼儿新产品---酸奶


fresh'n fruity
my first
probiotic yoghurt
with soft fruit pieces
BEST BEFORE 14/07/11
100g

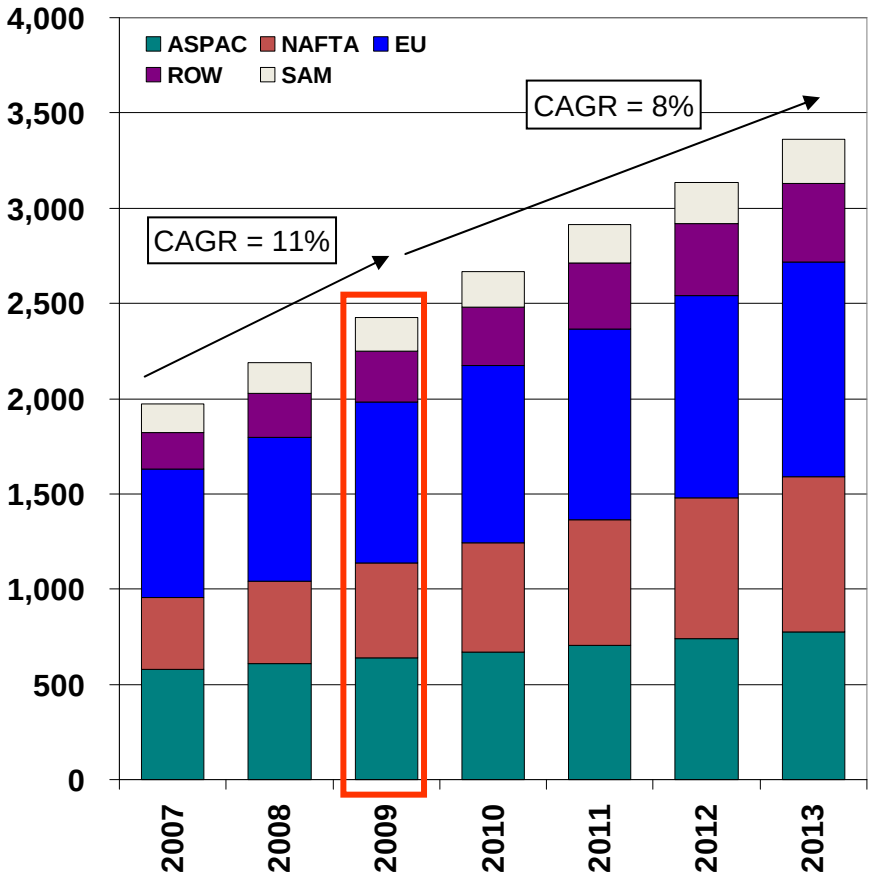

MADETA
Lipánek
BABY:)
OD 1 ROKU
1+
Probiotický
jogurt
Jablko +Mrkev


6x100g
fresh'n fruity
12+
months
With 100% natural ingredients, no added sugar and natural probiotic Bifidus Immun™, this is an ideal food for your toddler. As a Mum and Nutritionist, it is a yoghurt I proudly sign my name to.
apple yoghurt
mango yoghurt
peach yoghurt

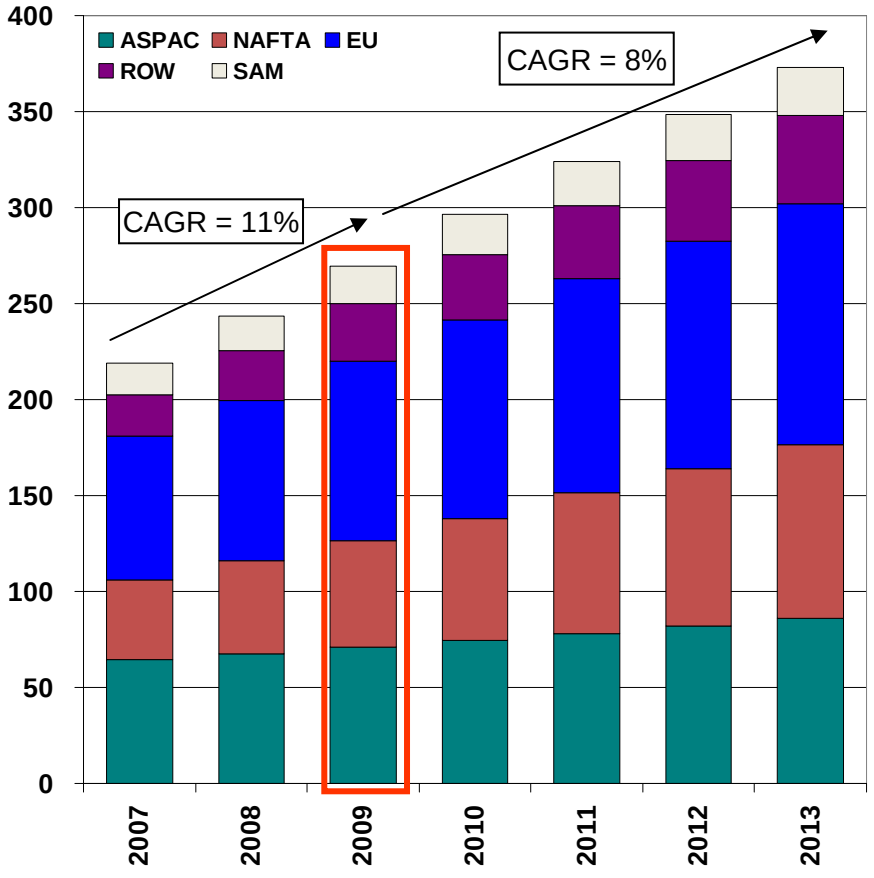

MADETA
lipánek
BABY:)
1+
Probiotický
jogurt
Jablko
+Mrkev

益生菌膳食补充剂整体市场容量

2011年益生菌补充剂市场
28亿美元 (零售层面)



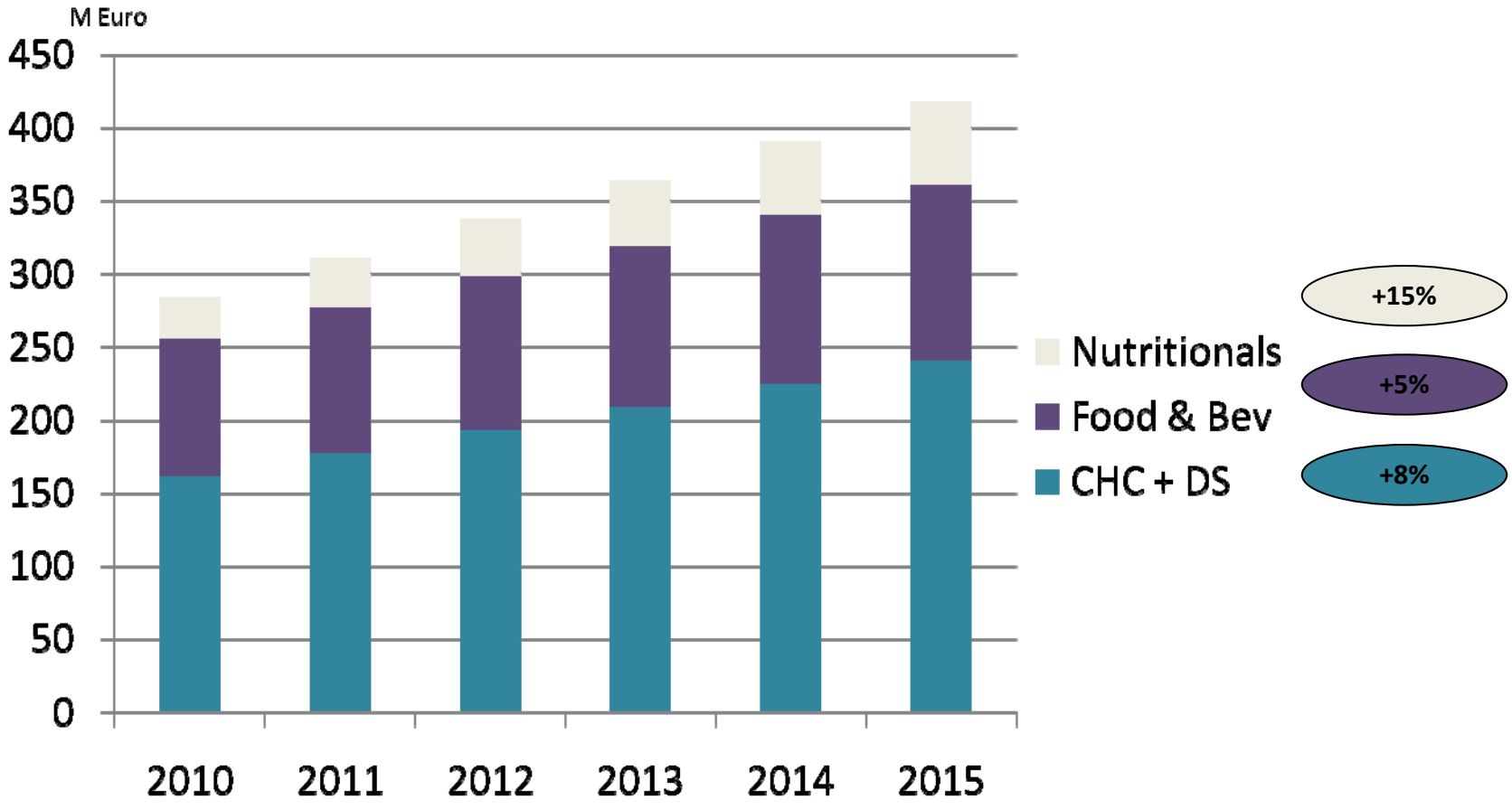
2011年益生菌配料市场
3.26亿美元 (B2B 层面)



Source: Euromonitor; IMS Health:
Danisco Market Assessment

食品以外的益生菌市场

益生菌市场总值估计在3亿欧元，其中膳食补充剂及非处方药市场增速高于食品及饮料行业，营养品市场的增速最迅猛



免疫增强是膳食补充物市场新的驱动力

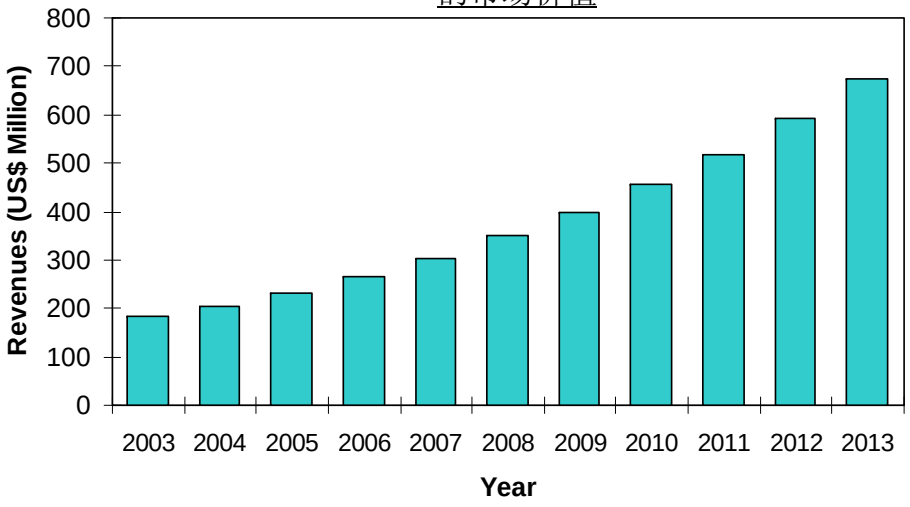
现今，消费者日益关注他们的饮食习惯与健康之间的影响，

具有增强身体自然抵抗力的膳食补充物的市场需求。

膳食补充物

- 消费者已经非常熟悉益生菌的概念，特别是它们具有增强身体自然抵抗力方面的好处
- 因此，益生菌膳食补充物市场呈两位数的快速增长

北美和欧洲益生菌膳食补充物的市场价值



Sources: Frost & Sullivan

发展迅速的美国膳食补充剂市场

以美国*Ultimate Flora* 益生菌产品为例

市场更关注活菌数

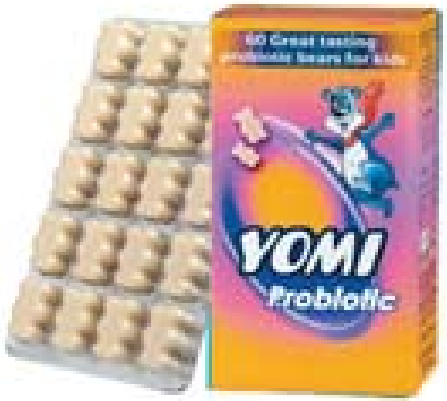
“益生菌的活菌数越高，对你健康越有利！”

国外市场新品上市

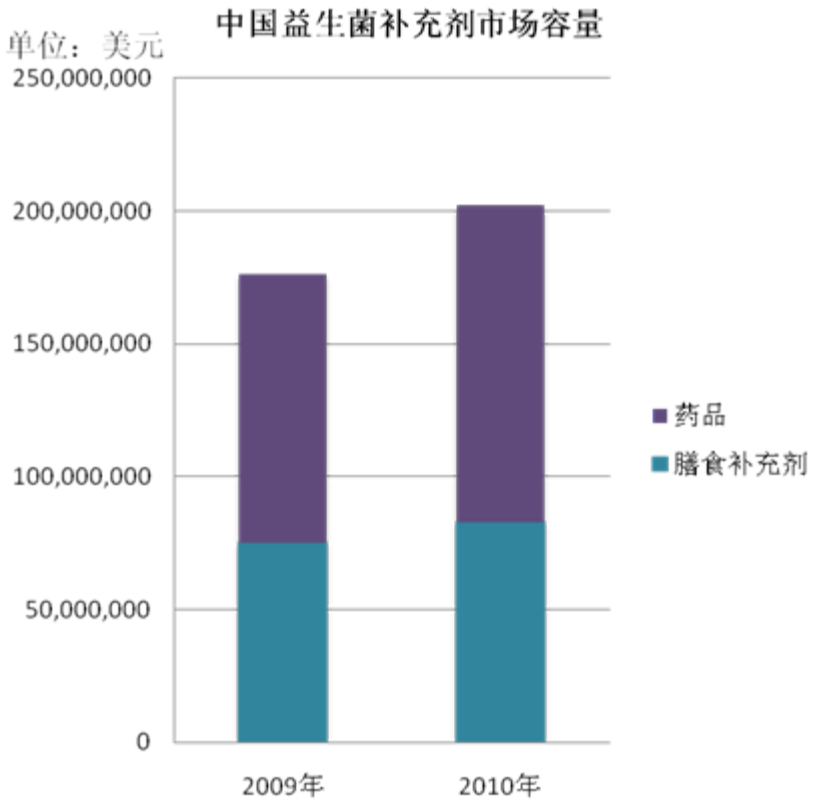
HOWARU Probiotic Yogurt Bears 益生菌小熊糖果

- 儿童为主要消费者
  以美味的方式摄取每天需要的益生菌
  - 香草味和草莓味，还有无糖的形式
- 每个含益生菌10亿
- HN019 & NCFM 1:1– “Balance” 平衡的概念
- 平衡概念的宣称
  - 平衡机体对肠道健康和免疫健康的需求
  - 维护儿童的消化和免疫健康

- 上市的品牌
  - Czech Republic in Summer 2010
  - US – GNC in early 2011 (focus adults)
  - US – Atrium Innovations (focus kids)
  - Italy – Montefarmaco (pending)
  - Multiple opportunities in ASPAC



中国益生菌膳食补充剂市场容量



- 2010年，中国益生菌补充剂市场容量为2.02亿美元，其中药品接近1.2亿美元。
- 2010年，益生菌膳食补充剂市场总量为8260万美元
- 2010年，益生菌膳食补充剂市场同比增长10.4%，药品市场同比增长17.9%。

中国的膳食补充剂领域，益生菌是提高儿童机体免疫力方面最重要且增长迅速的新兴市场

Biostime is the pionneer and leader on this market

For Danny Baby products, we have two different formula for first and second age.

总结

益生菌有利于人体健康的报道不断增多

膳食补充剂 &营养品市场细分增长快速，尤其是亚洲市场

配方上追求在种和菌株上的多样化和差异化

菌数增多的趋势

法规部对保健品产品功效的严格控制

量身定做的“ 功效”研究

主要内容

- 益生菌市场状况及趋势回顾

- 杜邦-丹尼斯克 益生菌介绍---本地的产品、法规和技术服务
- 杜邦-丹尼斯克 益生菌在婴幼儿健康的功效性研究新进展

杜邦健康与营养平台

消化健康	免疫健康	体重控制	骨骼健康	口腔健康	心血管健康
Diarrhea General transit IBS	General immune support Cold & flu	Metabolic syndrome Satiety	Osteoporosis Child bone development	Dental caries Gum disease	Endothelial function Hypertension
HOWARU® Premium Probiotics HOWARU® Restore Litesse® Polydextrose OsmoAid™ Lactitol	HOWARU® Premium Probiotics HOWARU® Protect HOWARU® Balance	Fructofin® OsmoAid™ Lactitol Litesse® Polydextrose XIVIA™ Xylitol Enzymes Cultures	ActivK™ Vitamin K2	XIVIA™ Xylitol	ActivK™ Vitamin K2 PinVita™ Phytosterols

HOWARU® premium probiotics · floraFIT® custom probiotics · Litesse® the better fiber · activK · XIVIA™ · betaPOWER™ Natural Betaine · PinVita™ science at heart

100多年历史的杜邦-丹尼斯克菌种部
---世界最大的冷冻干燥菌种供应商

全球最大的冷冻干燥益生菌生产商, 全面的菌种产品和应用，多样化的益生菌选择

超过100年的菌种生产历史，在全球有9家工厂，包括法国全球最大的冷冻干燥菌种工厂，中国北京的工厂----亚洲唯一的菌种工厂

位于芬兰的丹尼斯克营养健康中心-
唯一自有营养健康中心的菌种供应商；独有Enteromix®仿生研究设备，模拟真实肠道系统，进行益生菌功效的深入研究

专利技术保证益生菌的高存活性 （US patent 6,653,062 November 25, 2003)

US006653062B1

(12) United States Patent
DePablo et al.

(10) Patent No.: US 6,653,062 B1
(45) Date of Patent: Nov. 25, 2003

引领益生菌市场的发展历史

1974

Introduced frozen probiotics for milk supplementation

1984

Launched freeze-dried probiotics for dietary supplement market

1990

Initiated probiotic supplementation of yogurt starters

1994

Entered animal probiotic market

Introduced probiotics for toddler/ follow-on formula supplementation

2004

Supplying medical food containing probiotics

First supply of turn key finished format

2009

First sale of turn-key finished format in Europe

2010

First sale of turn-key finished format in Asia

Launched our first turn-key finished format in the FDM channel

健康与营养上海研发中心

拥有1000平方米的研发中心

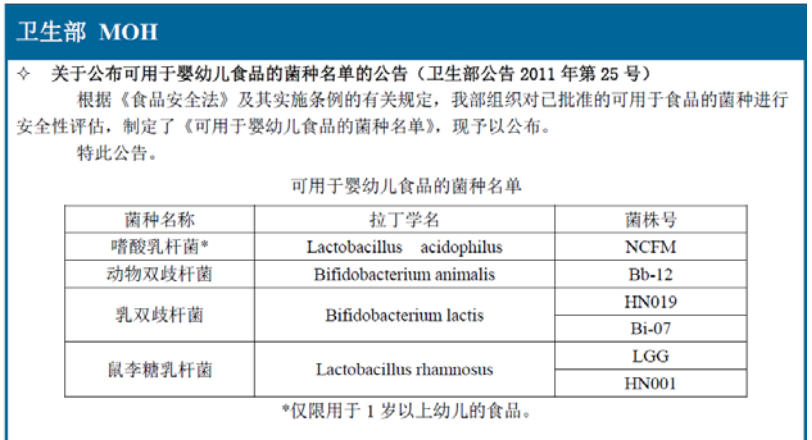
北京的菌种工厂---提供含益生菌的最终产品

益生菌生产商唯一在中国拥有可生产含益生菌普通食品及保健食品生产资质的企业

服务中国的技术及法规支持

- 位于上海的上游研发及应用支持实验室为中国客户提供
  - 配方开发
  - 活菌数检测
  - 保质期稳定性跟踪
  - 本地临床试验的进行-----提供中国人群的功效数据
  - 软宣传的权威机构认证

- 法规服务：2位专职的法规人员在北京为产品的申报提供支持——新资源批准的用于婴幼儿的益生菌，六株中丹尼斯克占了四株



卫生部 MOH

✧ 关于公布可用于婴幼儿食品的菌种名单的公告（卫生部公告 2011 年第 25 号）

根据《食品安全法》及其实施条例的有关规定，我部组织对已批准的可用于食品的菌种进行安全性评估，制定了《可用于婴幼儿食品的菌种名单》，现予以公布。

特此公告。

可用于婴幼儿食品的菌种名单

菌种名称	拉丁学名	菌株号
嗜酸乳杆菌*	Lactobacillus acidophilus	NCFM
动物双歧杆菌	Bifidobacterium animalis	Bb-12
乳双歧杆菌	Bifidobacterium lactis	HN019
		Bi-07
鼠李糖乳杆菌	Lactobacillus rhamnosus	LGG
		HN001

*仅限用于 1 岁以上幼儿的食品。

两大益生菌品牌

floraFIT® custom probiotics

是目前市场上最稳定的菌株，为创造独一无二的质构提供了无限可能

HOWARU® premium probiotics

经多个临床研究验证，对人体健康有益的单菌株以及混合菌株品牌

- 不同销售渠道保持均一的稳定性
- 新产品的创新及应用
- 销售及技术的个性化支持
- 法律及法规的专业支持
- 杰出的制造标准
- 可代加工终产品

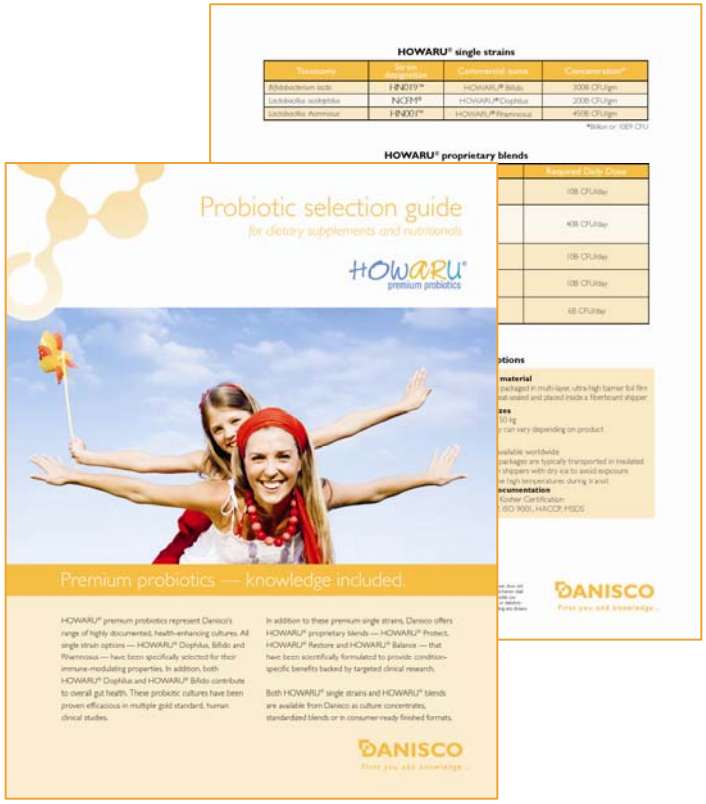
FloraFIT® 为客户定制配方提供了无限可能

Flexible. Stable. Proven.

floraFIT® custom probiotics

Strain Range	Bif. breve Bb-03™ Bif. bifidum Bb-06™ Bif. lactis Bl-04™ Bif. longum Bl-05™ Lb. acidophilus La-14™ Lb. brevis Lbr-35™ Lb. bulgaricus Lb-64™ Lb. casei Lc-11™	Lb. paracasei Lpc-37™ Lb. plantarum Lp-115™ Lb. rhamnosus Lr-32™ Lb. salivarius Ls-33™ Lb. gasseri Lg-36™ Lc. lactis Ll-23™ St. thermophilus St-21™
Features	Single strains or custom blends	
	Available as concentrates or standardized blends of any combination	
	• *In vitro* and *in vivo* characterization • Some strains involved in animal and/or human clinical studies	

HOWARU® 为客户提供经临床验证对健康有益的各种配方



HOWARU® premium probiotics

Product Range	HOWARU® Dophilus HOWARU® Bifido HOWARU® Rhamnosus HOWARU® Protect HOWARU® Balance/ Balance Plus/ Balance Kids HOWARU® Restore
Features	Single strains or blends
	Single strains available as concentrates or standardized blends. Multi-strain blends available in clinically tested formulation only.
	• In vitro and in vivo characterization • Animal studies • Substantial human clinical documentation of efficacy

益生菌发展的三大核心因素

功效

为特殊健康要求提供配方，并经独一无二的筛选管道及临床疗效评估不断发展

稳定

根据客户需求，为定制商品调整货架期

应用

扩大益生菌产品的应用领域

功效平台

功效

为特殊应用条件提供配方，并经独一无二的筛选管道及临床疗效评估不断发展

- 全球功效网络平台支持对特定功效的产品研发进入临床试验阶段
- 唯一拥有营养与健康研发中心的益生菌供应商
- 经临床试验研究证实的多菌株的复配研发
- 与客户成为合作伙伴
- 对益生菌作用机制的研究，已深入至基因水平，处于全球领先水平

全球合作品牌

EUROPE

CHINA

USA & CANADA

TAIWAN

MALAYSIA

SOUTH AFRICA

NEW ZEALAND

主要内容

- 益生菌市场状况及趋势回顾

- 杜邦-丹尼斯克 益生菌---本地的产品、法规和技术服务
- 杜邦—丹尼斯克 益生菌在婴幼儿健康的功效性研究新进展

临床研究(1)---呼吸道感染

百年品牌的中国情结

2007年5月，丹尼斯克结束了在浙江金华的试验。---这是益生菌供应商在中国的第一个临床试验。

“中国孩子需要提高免疫力和抵抗力，他们的需要比其他地方的孩子更为迫切。

PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

PROBIOTICS REDUCE INCIDENCE AND DURATION OF RESPIRATORY TRACT INFECTION SYMPTOMS IN 3- TO 5-YEAR-OLD CHILDREN

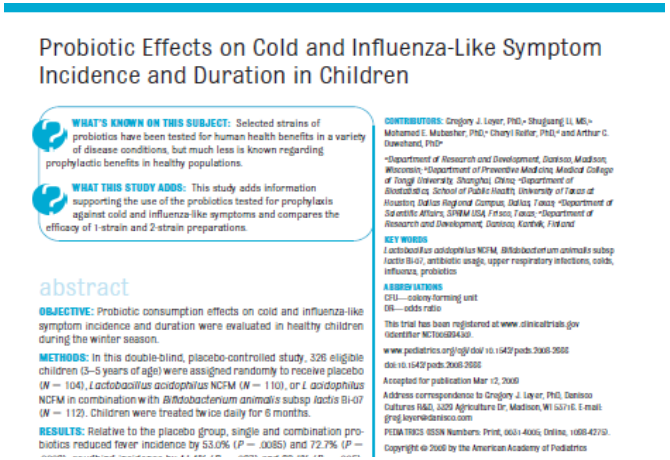
Arthur Ouwehand, Greg Leyer and Didier Carcano

Pediatrics 2008;121:S115

DOI: 10.1542/peds.2007-2022JJJ

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://www.pediatrics.org



Probiotic Effects on Cold and Influenza-Like Symptom Incidence and Duration in Children

WHAT'S KNOWN ON THIS SUBJECT: Selected strains of probiotics have been tested for human health benefits in a variety of disease conditions, but much less is known regarding prophylactic benefits in healthy populations.

WHAT THIS STUDY ADDS: This study adds information supporting the use of the probiotics tested for prophylaxis against cold and influenza-like symptoms and compares the efficacy of 1-strain and 2-strain preparations.

abstract

OBJECTIVE: Probiotic consumption effects on cold and influenza-like symptom incidence and duration were evaluated in healthy children during the winter season.

METHODS: In this double-blind, placebo-controlled study, 326 eligible children (3–5 years of age) were assigned randomly to receive placebo ($N = 104$), *Lactobacillus acidophilus* NCFM ($N = 110$), or *L acidophilus* NCFM in combination with *Bifidobacterium animalis* subsp *lactis* BI-07 ($N = 112$). Children were treated twice daily for 6 months.

RESULTS: Relative to the placebo group, single and combination probiotics reduced fever incidence by 53.0% ($P = .0085$) and 72.7% ($P =$

CONTRIBUTORS: Gregory J. Leyer, PhD,[a] Shuguang Li, MS,[b] Mohamed E. Mubasher, PhD,[c] Cheryl Reifer, PhD,[d] and Arthur C. Ouwehand, PhD[e]

[a]Department of Research and Development, Danisco, Madison, Wisconsin; [b]Department of Preventive Medicine, Medical College of Tongji University, Shanghai, China; [c]Department of Biostatistics, School of Public Health, University of Texas at Houston, Dallas Regional Campus, Dallas, Texas; [d]Department of Scientific Affairs, SFNRM USA, Frisco, Texas; [e]Department of Research and Development, Danisco, Kantvik, Finland

KEY WORDS

Lactobacillus acidophilus NCFM, *Bifidobacterium animalis* subsp *lactis* BI-07, antibiotic usage, upper respiratory infections, colds, influenza, probiotics

ABBREVIATIONS

CFU—colony-forming unit

OR—odds ratio

This trial has been registered at www.clinicaltrials.gov (identifier NCT00689403).

www.pediatrics.org/cgi/doi/10.1542/peds.2008-2688

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临床研究(1)---感冒

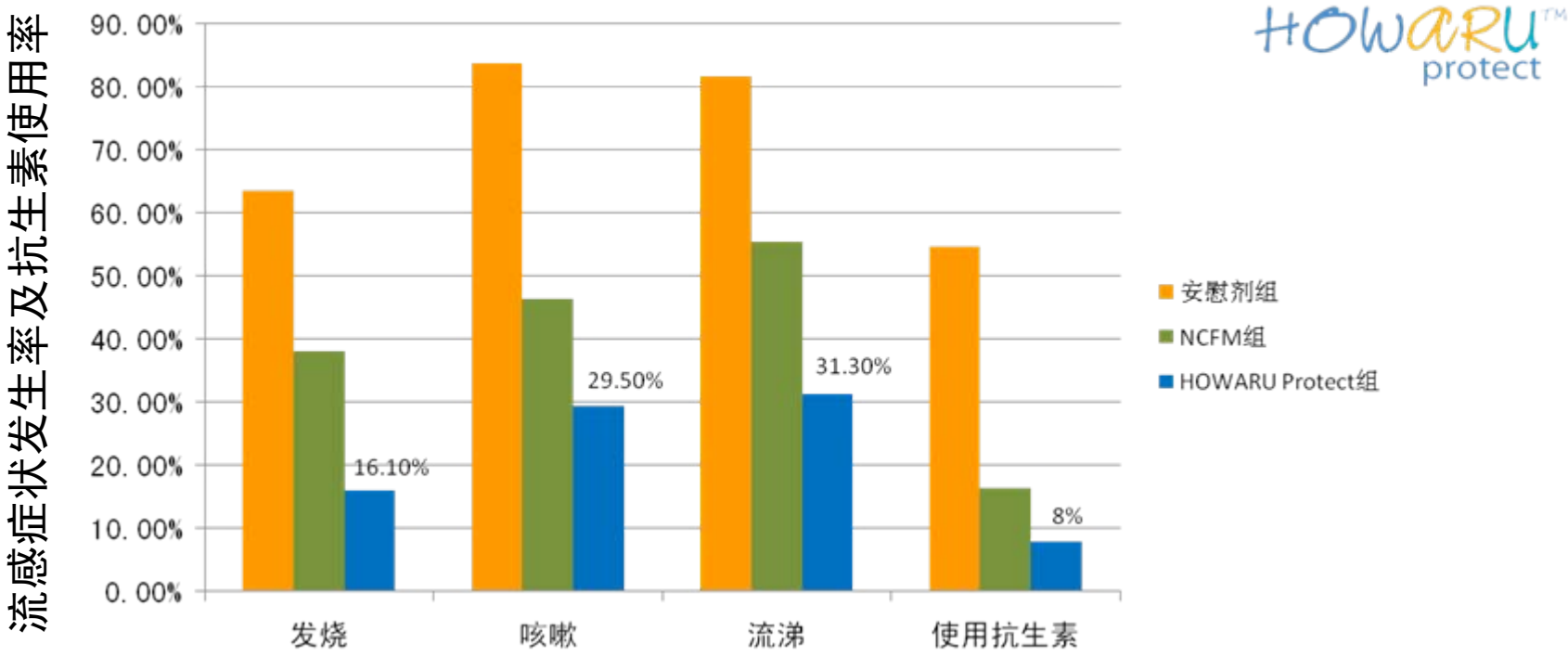
研究目的:
确定益生菌的每日剂量对感冒的发生与发病持续时间之间的关系

HOWARU protect

- 研究对象: 326名在浙江金华日托幼儿园的3-5岁的儿童
- 试验设计: 在11月到来年5月间，对326名儿童进行随机、 双盲、对照的临床试验研究，予口服益生菌，每天2次，持续6个月。
- 试验分组: - L.acidophilus组: n=110 NCFM Does= $1.0*10^{10}$CFU/d
  - Comination组: n=112 NCFM+Bi-07 Does= $1.0*10^{10}$CFU/d
  - 安慰剂组: n=104
- 评价指标: 上呼吸道感染的相关症状、流感症状持续的天数、抗生素的使用情况、儿童在日托班的缺席天数

Leyer GJ, Li S, ME, Reifer C, Ouwehand AC. 2009. Probiotic effects on cold and influenza-like symptom incidence and duration in children. Pediatrics 124:e172-e179.

临床研究结果---益生菌可改善感冒的临床症状



- 临床研究显示：试验期六个月内，服用益生菌的儿童发烧、咳嗽及流涕症状的发生频次显著少于安慰剂组，同时，使用抗生素的频次也显著降低。
- NCFM组：发烧以及咳嗽的发生率，与对照组相比，有显著性差异，P<0.05。
- HOWARU Protect组：所有症状均显著降低，同时使用抗生素的频次与对照组相比，有显著性差异，P<0.01。

临床研究结果---益生菌缩短感冒症状持续时间

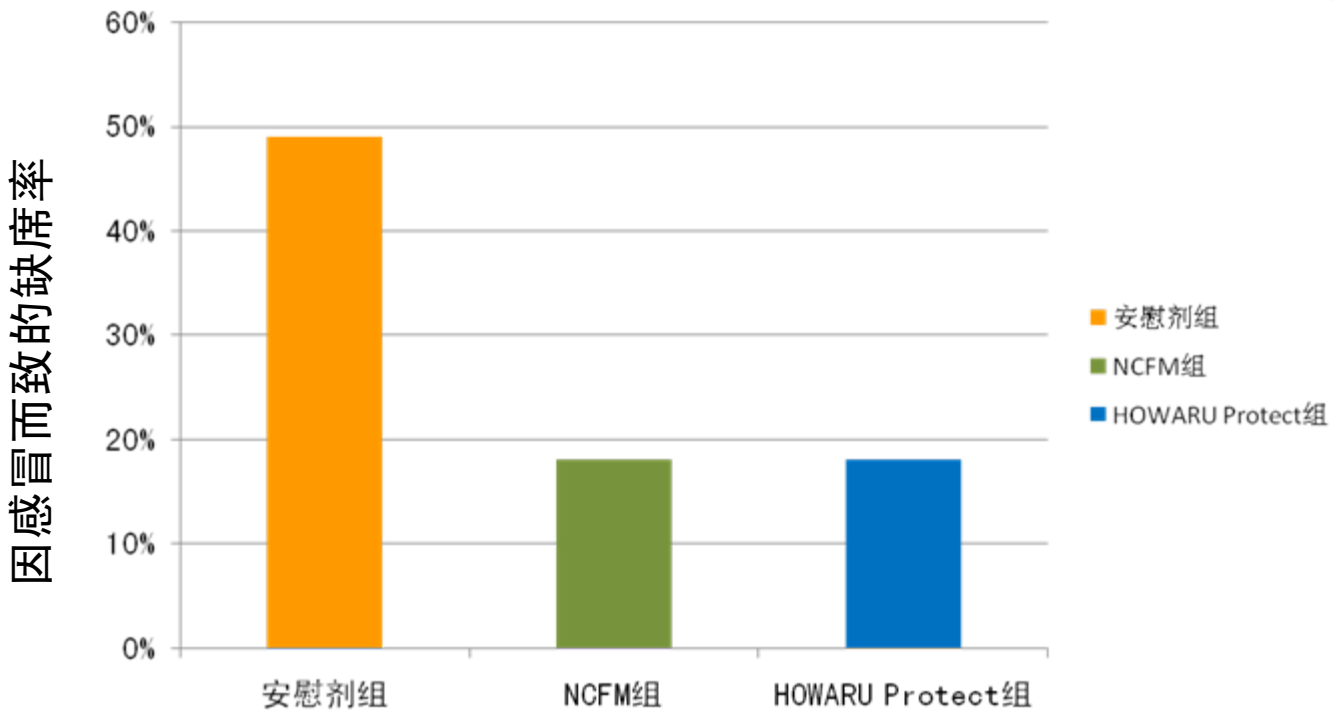
HOWARU™ protect

TABLE 5 Symptom Duration According to Study Group During 6-Month Follow-up Period

	Symptom Duration		
	Placebo	*Lactobacillus acidophilus*	*L acidophilus*/ *Bifidobacterium lactis*
N	104	110	112
Mean ± SD, d	6.5 ± 7.3	4.5 ± 4.7	3.4 ± 3.7
Reduction vs placebo, %	NA	31.8	47.7
25th percentile, d	1	1	1
50th percentile, d	4	3	2
75th percentile, d	10	6	5

- 临床研究显示：试验期六个月内，服用益生菌的儿童发烧、咳嗽及流涕症状的持续时间，均显著少于安慰剂组， P<0. 05。

临床研究结果---益生菌减少感冒而致的缺席率



- 益生菌可显著减少因感冒而致≥1天的缺席率，与安慰剂组相比，均有显著性差异（P<0.05）。

上海市营养学会

HOWARU™ Protect 对学龄前儿童流感类症状及发作持续时间改善效果的临床研究

医学评审报告

评审[2009]第 002 号

项目名称	HOWARU™ Protect 对学龄前儿童流感类症状及发作持续时间改善效果的临床研究			
申请人	丹尼斯克（中国）有限公司			
医学评审会成员				
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侯建星	男	副会长	宝山区红十字会	侯建星

试验医学评审会意见

专家意见：

经专家组论证，认为本试验符合 GCP 原则，严格按照试验方案执行，试验结果：

丹尼斯克独特的和可追踪的专利保护的菌株配方可

- ✓ 减少了发生感冒症状的人数
- ✓ 减少感冒和流感症状（发烧、咳嗽、流鼻涕）
- ✓ 缩短感冒和流感症状的持续时间

根据试验结果提示，HOWARU™ Protect 配方可增强儿童对感冒和流感的抵抗力。

试验结果达到预期的试验目的。

试验医学评审会会主任（签名）：

2009 年 10 月 30 日

上海市营养学会
地址：上海市南昌路 47 号
电话：021-53828965

- HOWARU Protect可增强儿童对感冒和流感的抵抗力：
  1，减少发生感冒症状的人数；
  2，减少感冒和流感症状（发烧、咳嗽、流鼻涕）；
  3，缩短感冒和流感症状的持续时间。

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PROBIOTICS REDUCE INCIDENCE AND DURATION OF RESPIRATORY TRACT INFECTION SYMPTOMS IN 3- TO 5-YEAR-OLD CHILDREN

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感冒和流感---最频繁发生的疾病

- 感冒和流感是最频繁发生的传染性-接触性传染疾病，导致人类痛苦

- 一个巨大的消费群体期待功能性食品或膳食补充物来减少感冒和流感症状的发生和缩短发病时间

- 伤风感冒的高感染性*:
  - 儿童每年感染6至10次
  - 对于成年人，每年感染2至3次
- 发病持久性*:
  - 感冒的平均持续时间：7天
  - 轻度感冒: 2或3天
  - 重度感冒:超过14天

- 多种表现性症状:
  - 打喷嚏 sneezing
  - 流鼻涕 runny nose
  - 咳嗽 cough
  - 喉咙痛痒 sore or scratchy throat
  - 喉咙肿痛沙哑 hoarseness
  - 头痛 headache
  - 发烧 feverishness
  - 寒意 chilliness…

→ 由于能够使感冒和流感症状减少和缩短发病时间，HOWARU™ Protect打开了一个崭新的提供免疫增强益处的市场领域。

** Gwaltney, J.M.Jr. 2000. The Common Cold. In Principles and Practices of Infectious Diseases, 5th ed. G.L. Mandell, J.E. Bennett, and R. Dolin, editors. Churchill Livingstone, New York. 651-656.*

免疫增强是膳食补充物市场的推动力

膳食补充物

2 项诉求能够帮助“免疫增强”膳食补充物市场保持成长：

- **清晰的功效性声明**，归功于所选择的高品质活性配料
- **针对明确专门的健康情况**，能够设计产品的差异性

- 产品: Bion 3
- 加工商: Merck
- 声明: 健康催化剂
  - 激活免疫细胞的一些参数
  - 减轻感冒和流感型症状的程度
- 配料:
  - 益生菌,维生素，矿物质和植物提取物
- 上市: 欧洲/亚洲 – 2000年

- 产品: Fluaway
- 生产商 : Nature Nutrition - Gunler
- 配料:
  - 益生菌，维生素，矿物质，植物提取物，乳制品， β –葡聚糖
- 上市: 墨西哥 - 2007

→ 新的备有临床文献支持的益生菌所具有的独特的健康益处能够帮助开发市场，打开一个全新的针对特殊健康状况的细分的市场，例如针对感冒和流感。

Sources: Datamonitor – Frost & Sullivan

美国ABC新闻“早安美国” 健康专栏于2009年7月27号介绍 Howaru protect

The ABC News program Good Morning America (GMA), has highlighted the health benefits of Danisco’s HOWARU Protect probiotic formulation. GMA’s health segment was timed to match the publication in Pediatric of Danisco’s clinical study results. Entitled “Probiotic Effects on Cold and Influenza-Like Symptom Incidence and Duration in Children” the benefits of HOWARU® Protect were clinically shown to maintain immune health in children.

http://abcnews.go.com/video/playerindex?id=8181505 “用酸奶对抗流感“

临床研究(2)---呼吸道感染

研究目的:

分析益生菌加益生元对因呼吸道细菌感染而服用抗生素治疗的儿童患者的影响

- 研究对象: 140位1-6岁患呼吸道细菌感染的儿童入组，其诊断包括：扁桃体炎、咽炎、中耳炎、支气管炎及轻度肺炎。

- 试验设计: 对140位因呼吸道细菌感染而服用抗生素治疗的儿童患者进行随机、 双盲、对照的临床试验研究，在患者服用抗生素期间予每天服用含合生剂的营养补充剂，连续服用至抗生素治疗后14天，其余治疗方案遵医嘱。

- 试验分组: - PS组: n=50 含益生菌加益生元的营养补充剂 低聚果糖Does=3.5g/L，混合益生菌(嗜酸乳杆菌+双歧乳杆菌)=1*109CFU/d
  - P组: n=43 营养补充剂
  - 安慰剂组： n=47 水果味饮料

- 评价指标: 体重、营养指标、粪便样本细菌构成。

Schrezenmeir J, Heller K, McCue M, Llamas C, Lam W, Burow H, Kindling-Rohracker M, Fischer W, Sengespeik HC, Comer GM, Alarcon P. 2004. Benefits of oral supplementation with and without synbiotics in young children with acute bacterial infections. Clin Ped. 43: 239-249.

临床研究结果---益生菌可促进儿童的能量摄入

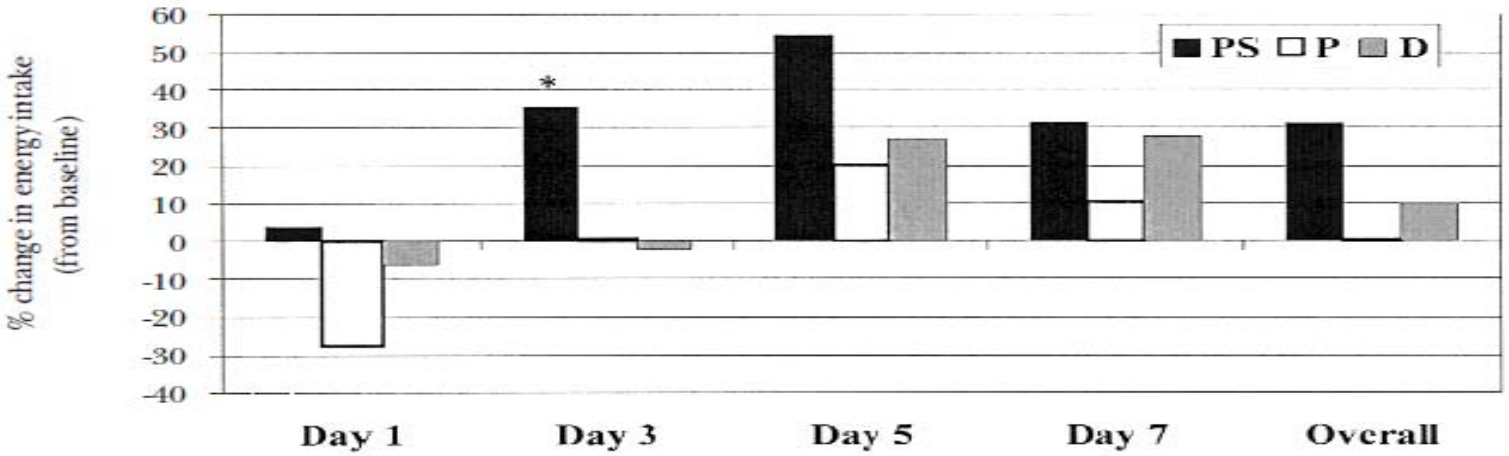


Figure 1. Energy intake (food + formula): change from baseline. Bars represent mean % change in energy intake from baseline. PS = Nutritional supplement with synbiotics; P = Nutritional supplement without synbiotics; D = Fruit-flavored drink.*PS is significantly greater than P ($p = 0.049$) and D ($p = 0.023$).

- Day 3，PS组儿童的能量摄入显著高于P组和安慰剂组，两者有显著性差异，$P<0.05$。

临床研究结果---益生菌可增加儿童的体重

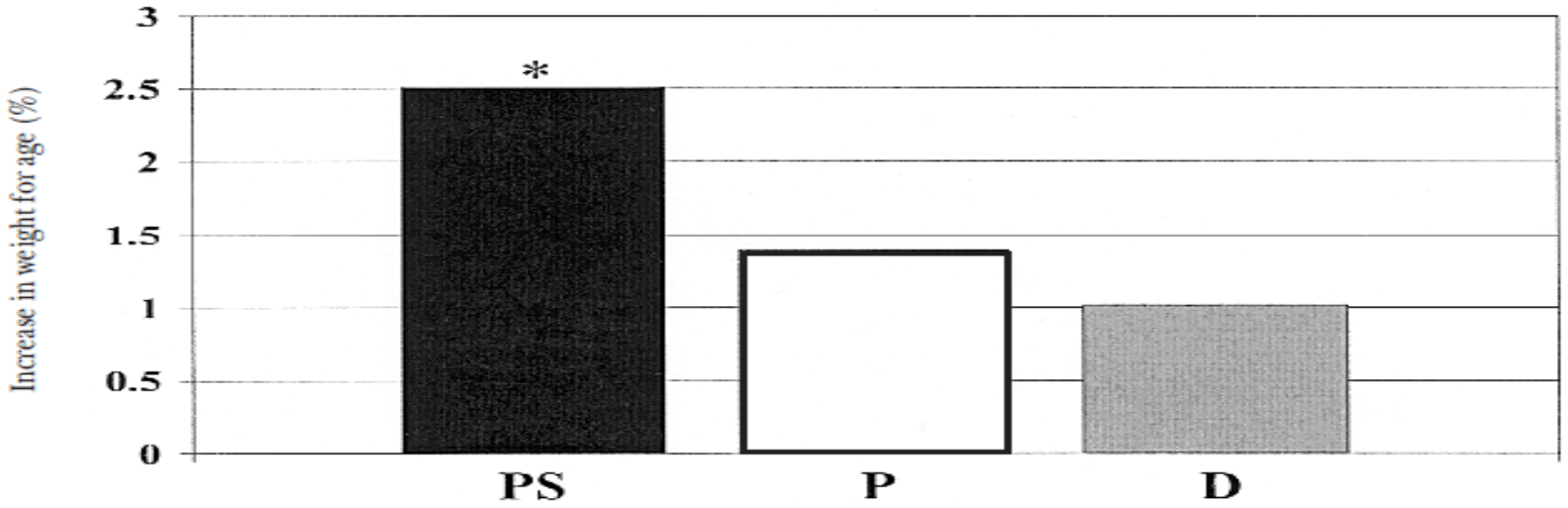


Figure 2. Increases in weight for age with formula intake at end of antibiotic therapy. Bars represent increases in weight for age (%). PS = Nutritional supplement with synbiotics; P = Nutritional supplement without synbiotics; D = Fruit-flavored drink. *PS is significantly ($p = 0.01$) greater than D.

- 随着抗生素治疗的进程，在治疗结束后测量儿童患者的体重与治疗前相比，PS组的体重增长更显著，显著高于P组与安慰剂组，P=0.01。

临床研究结果---益生菌可改变肠道微生态环境

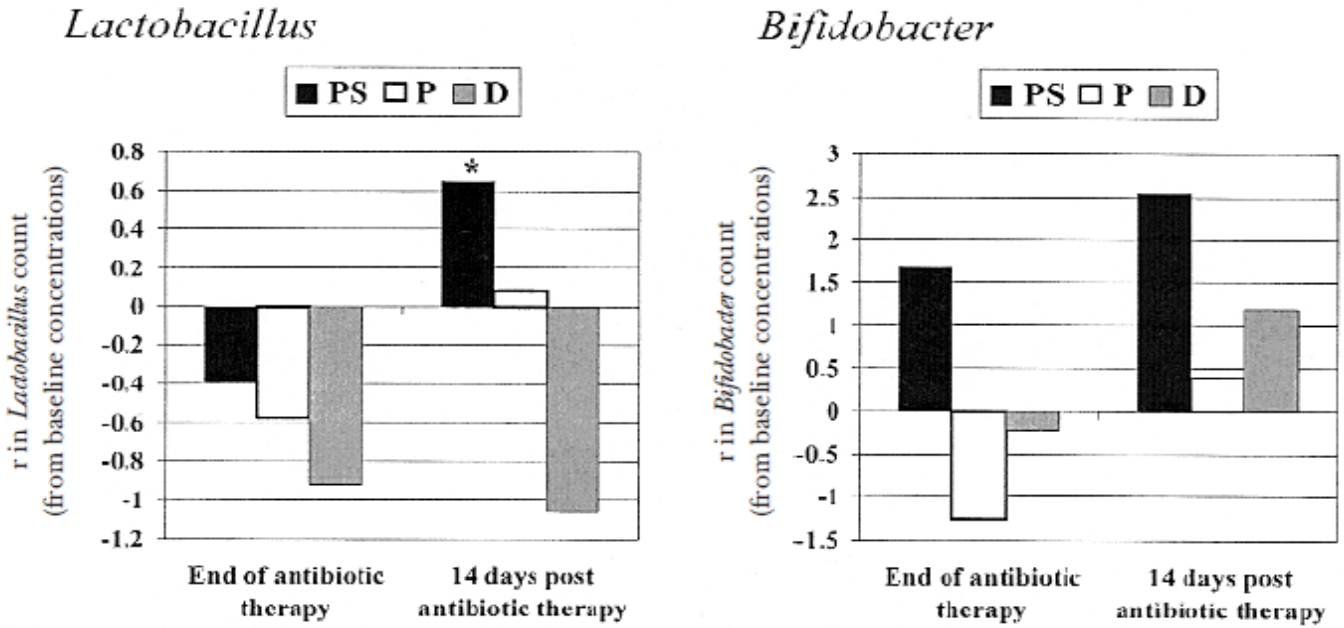


Figure 7. Effects of nutritional supplements with or without synbiotics on *Lactobacillus* and *Bifidobacter* stool content.

- 粪便微生物检测结果显示：抗生素治疗后，乳酸杆菌与双歧乳杆菌的数量与治疗前相比，显著降低；
- 抗生素治疗后14天，PS组的乳酸杆菌数量快速增长，与对照组相比，两者有显著性差异，$P<0.05$；
- 呼吸道感染时间长，易复发的儿童患者，可通过长期服用益生菌，从健康的肠道微生态环境中受益。

临床研究(3)---遗传过敏性湿疹

研究目的:

分析不同益生菌菌株，在孕妇分娩前干预，对新生儿脐血及母乳中免疫因子的影响

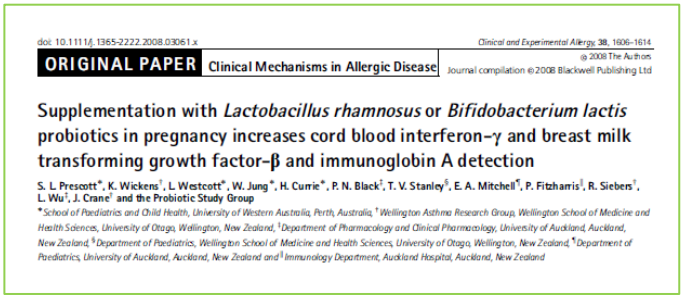
- 研究对象: 105位新西兰惠林顿及奥克兰地区的孕妇入组，其孕妇本人或胎儿的生父曾被诊断为哮喘、过敏性鼻炎或者湿疹。

- 试验设计: 对105位孕妇进行随机、双盲、对照的临床试验研究，在分娩前2-5周每天服用含益生菌的膳食补充剂，连续服用至产后6个月，其新生儿则连续服用至2岁。

- 试验分组: - L.rhamnosus组: n=34 HN001 Does= $6*10^9$CFU/d

  - B.lactis组: n=35 HN019 Does= $9*10^9$CFU/d

  - 安慰剂组: n=36



doi: 10.1111/j.1365-2222.2008.03061.x Clinical and Experimental Allergy, 38, 1606–1614

ORIGINAL PAPER Clinical Mechanisms in Allergic Disease

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Supplementation with *Lactobacillus rhamnosus* or *Bifidobacterium lactis* probiotics in pregnancy increases cord blood interferon-γ and breast milk transforming growth factor-β and immunoglobin A detection

S. L. Prescott*, K. Wickens†, L. Westcott*, W. Jung*, H. Currie*, P. N. Black‡, T. V. Stanley§, E. A. Mitchell¶, P. Fitzharris§, R. Siebers†, L. Wu†, J. Crane‡ and the Probiotic Study Group

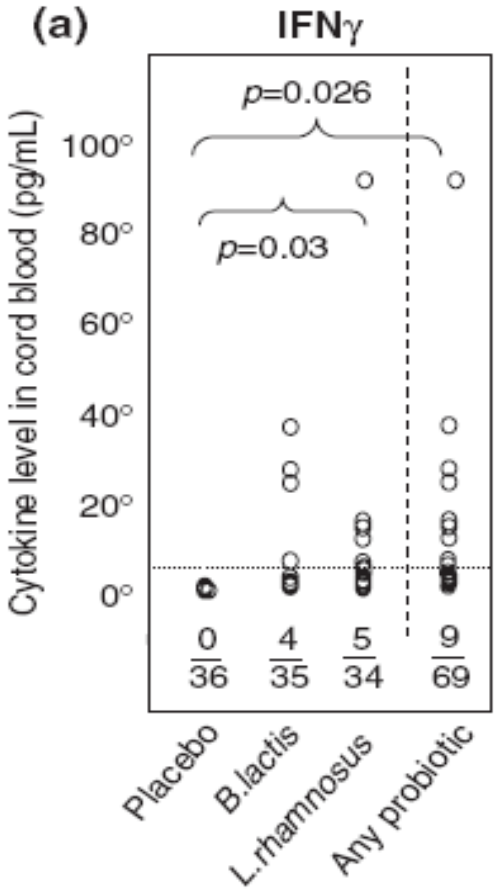
*School of Paediatrics and Child Health, University of Western Australia, Perth, Australia, †Wellington Asthma Research Group, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand, ‡Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand, §Department of Paediatrics, Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand, ¶Department of Paediatrics, University of Auckland, Auckland, New Zealand and ||Immunology Department, Auckland Hospital, Auckland, New Zealand

- 评价指标: 湿疹评估：用SPT法评估皮疹情况

  母乳生化指标：IL-5, IL-6, IL-10, IL-13, TGF-β 1, IFN-γ , TNF-α

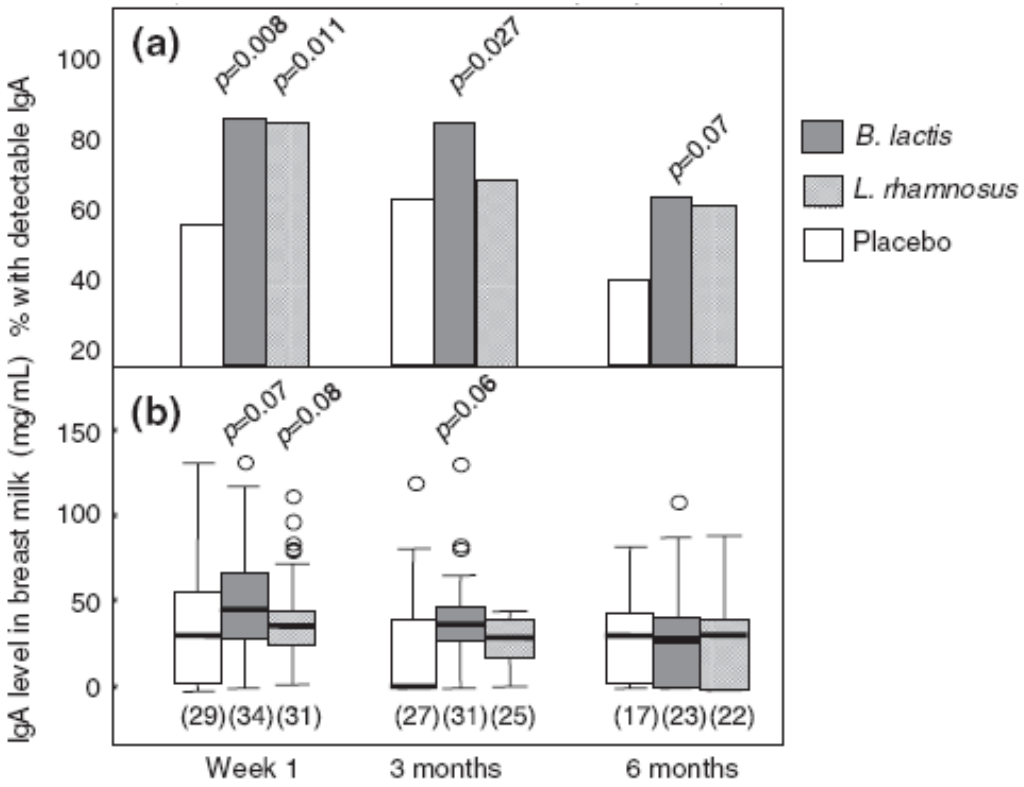
Prescott SL, Wickens K, Westcott L, Jung W,Currie H, Black PN, Stanley TV, Mitchell EA, Fitzharris P, Siebers R, Wu L, Crane J; Probiotic Study Group.2008. Supplementation with Lactobacillus rhamnosus or Bifidobacterium lactis probiotics in pregnancy increases cord blood interferon-c and breast milk transforming growth factor-b and immunoglobin A detection. Clin Exp Allergy. 38: 1606-14.

临床研究结果---益生菌提高脐血IFN-γ的含量



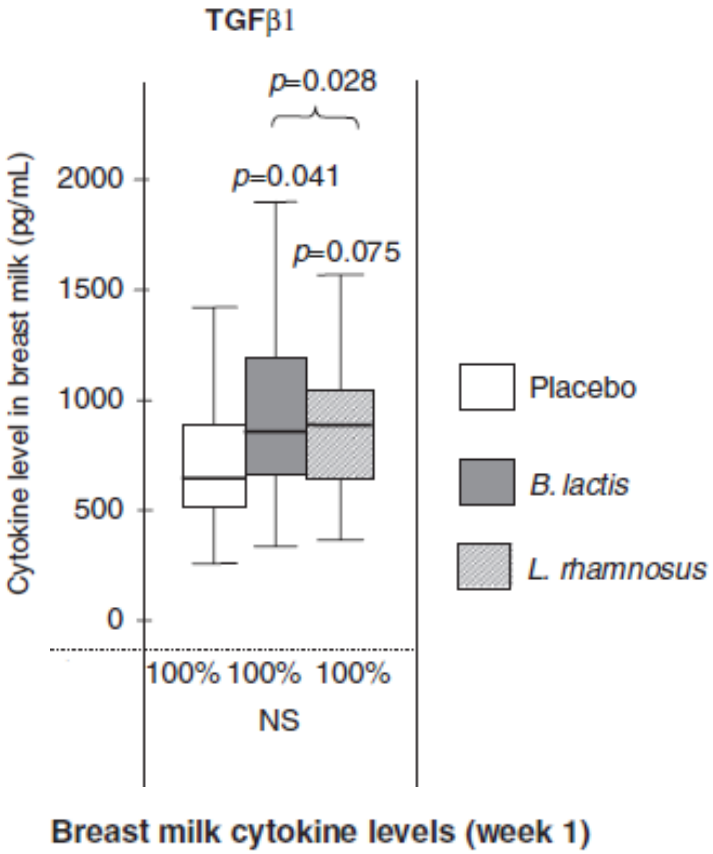
- 临床研究显示：对孕妇进行产前益生菌的干预，可提高新生儿脐血中IFN-γ的含量，尤其是HN001 组，与安慰剂组对相比，两者有显著性差异，P<0.05。
- 大量试验研究表明：脐血IFN-γ的指标提示可减少新生儿过敏症发生率，同时亦可减少随后的哮喘发生率。

临床研究结果---益生菌增加母乳IgA 的含量



- 图表(a): 经益生菌干预后，HN001组及HN019组 均显著提高产妇母乳中IgA的检测率，与安慰剂组相比，有显著性差异。
- 图表(b): 经益生菌干预后，HN001组及HN019组 均显著提高产妇母乳中IgA的含量，与安慰剂组相比，有显著性差异。
- 大量文献支持：IgA 被认为可保护婴儿肠道免受致病菌和过敏原的侵害，降低暴露在过敏原中的危险。

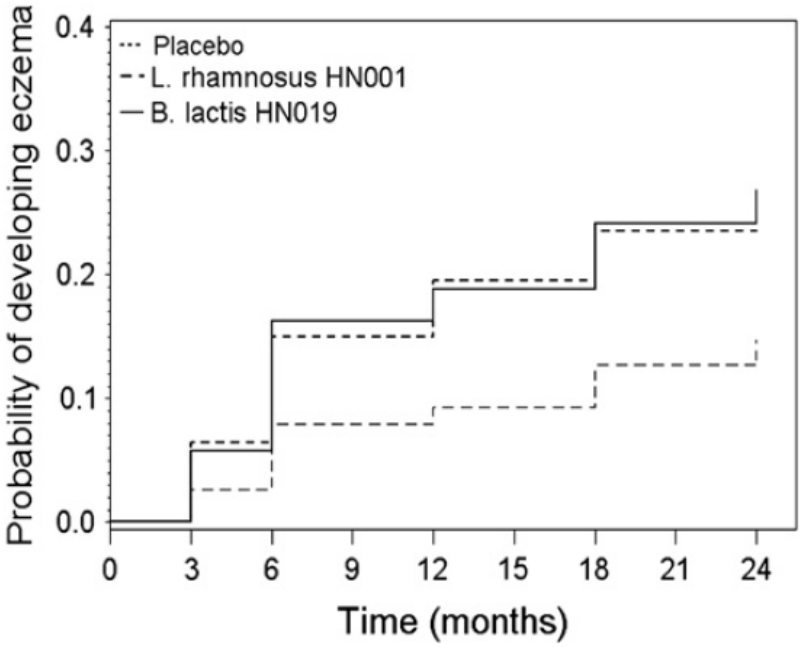
临床研究结果---益生菌提高母乳TGF-b_1的含量



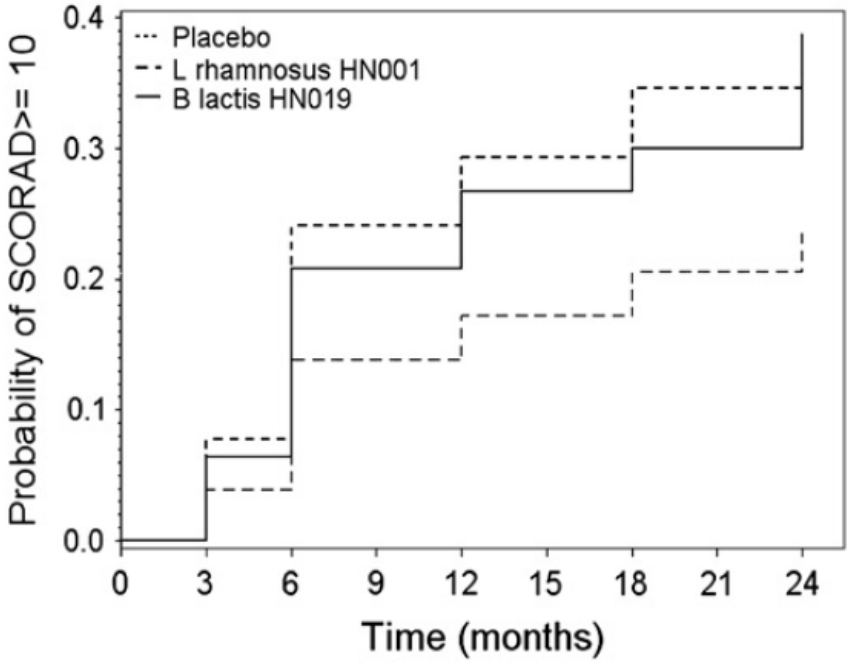
Breast milk cytokine levels (week 1)

- 经益生菌干预后，产后第一周的母乳中TGF-β_1的含量显著增高，HN001组及HN019组，与安慰剂组相比，均有显著性差异。
- 大量研究表明：TGF-β_1可提高人体对过敏原的耐受性，从而避免过敏症状的发生。

临床研究结果---HN001降低过敏性湿疹发生率



- 经鼠李糖乳杆菌HN001干预后，可显著降低两岁内遗传过敏性湿疹的发生率。



- 经鼠李糖乳杆菌HN001干预后，遗传过敏性湿疹的患病儿童症状显著减轻。

临床研究(4)---过敏性皮炎

研究目的:

分析不同益生菌菌株，对过敏性皮炎儿童患者严重性的影响

- 研究对象: 50位丹麦哥本哈根诊断为过敏性皮炎的儿童入组，年龄为7-24个月，其中90%的儿童，其父母或其中的一位兄弟姐妹有过敏史。

- 试验设计: 对50位过敏性皮炎的儿童患者进行随机、双盲、对照的临床试验研究，予每天服用含益生菌的膳食补充剂，连续服用8周，其余治疗方案遵医嘱。

- 试验分组: - 嗜酸乳杆菌NCFM组: n=17 Does=10^{10}CFU/d

  - 双歧乳杆菌Bi-07组: n=17 Does=10^{10} CFU/d

  - 安慰剂组: n=16

- 评价指标: 湿疹评估：用SCORAD法评估皮疹情况

  生化指标：血清IgE、血清ECP、IFN-γ、IL-10、IL-31、粪便钙卫蛋白。

R Gobel, N Larsen, C Molgaard, M Jakobsen and KF Michaelsen.2010. Probiotics to young children with atopic dermatitis: a randomized placebo-controlled trial.Int J Prob Preb.Vol.5;No.2:53-60,2010.

临床研究结果---Bi-07可缓解AD的临床症状

TABLE 2. Change in SCORAD index between baseline and after intervention (N = 50, mean ± SD). ** Significant difference between baseline and after intervention in the Bi-07group in post hoc analysis

GROUP	BASELINE ±SD	AFTER INTERVENTION ±SD	DIFFERENCE	P
Bi-07 (N = 17)	22.5 ± 11.0	15.8 ± 8.9	-6.7	0.009**
NCFM (N = 17)	20.6 ± 13.1	17.6 ± 10.5	-3.0	0.22
Placebo (N = 16)	20.2 ± 8.3	14.7 ± 9.7	-5.5	0.09

- 经Bi-07干预后，过敏性皮炎儿童患者的SCORAD指数较试验前，两者有显著性差异，P<0.05。
- NCFM组及安慰剂组，干预起点与结束后SCORAD指数对照，两者均无统计学差异。

临床研究(5)---桦树花粉过敏症

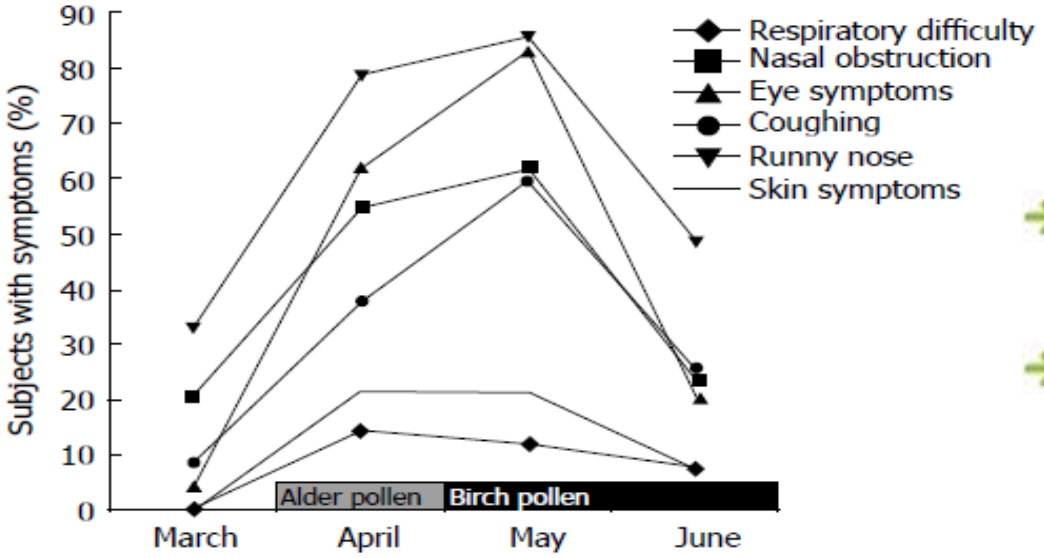
研究目的:

分析肠道微生态环境的改变对桦树花粉过敏症状的影响，以及在此过程中益生菌的作用

- 研究对象: 47位诊断为桦树花粉过敏症的芬兰儿童入组，平均年龄为9岁，所有儿童患者均对桦树花粉过敏，有过敏性鼻炎的症状。
- 试验设计: 在3-6月，对47位桦树花粉过敏症的儿童患者进行随机、双盲、对照的临床试验研究，予每天服用含益生菌的胶囊，连续服用8周，其余治疗方案遵医嘱。
- 试验分组: - 试验组组: n=24 混合益生菌（25%NCFM+75%Bi-04） Does=$5*10^9$CFU/d
  - 安慰剂组: n=23 麦芽糊精
- 评价指标: 过敏症状评估、鼻液及静脉血嗜酸性粒细胞计数、免疫因子分析、肠道微生物检测（菌株类别、数量及微生物活性）

Ouwehand AC, Nermes M, Collado MC, Rautonen N, Salminen S, Isolauri E. Specific probiotics alleviate allergic rhinitis during the birch pollen season. World J Gastroenterol. 2009 15: 3261-3268.

临床研究结果---益生菌可缓解鼻部症状



- 在桦树花粉季节，4-5月过敏症状高发，突出表现为鼻塞及流涕现象。
- 经益生菌干预后，4-5月间，患者的鼻塞及流涕现象显著减轻。

- 4-5月间，儿童患者鼻粘膜中嗜酸性粒细胞数量较前显著增加，经益生菌干预后，试验组测得的嗜酸性粒细胞数量与对照组相比，两者有显著性差异，P<0.05。

Table 2 Number of subjects with nasal eosinophilia *n* (%)

Month	Placebo	Probiotic
March	14 (63.6)	17 (70.8)
April/May	19 (95.0)	12 (57.1)[1]
June	12 (60.0)	12 (60.0)

[1]*P* = 0.013 compared to placebo group.

临床研究结果---益生菌对机体免疫应答的影响

Table 4 Fecal immune markers; before, during and after the birch pollen season

	Visit 1 (March)		Visit 2 (April/May)		Visit 3 (June)	
	Placebo	Probiotic	Placebo	Probiotic	Placebo	Probiotic
Fecal IgA (μg/g)	157.0 (105.0-278.8)	157.0 (114.0-371.0)	233.0 (136.0-288.8)[1]	155.0 (44.5-336.5)[1]	203.0 (99.0-388.0)[1]	135.0 (63.4-325.3)[1]
Fecal calprotectin (μg/g)	21.6 (9.5-58.6)	14.3 (10.7-30.1)	21.1 (12.6-46.7)	16.2 (13.1-31.8)	22.1 (10.9-53.2)	15.5 (12.0-31.5)

[1]Significantly different between groups; $P < 0.05$. Data are expressed as median (interquartile range).

- 在桦树花粉季节，患者的粪便检测结果显示：安慰剂组IgA较前显著增高；而益生菌的干预可减缓IgA的增高，其IgA的值与安慰剂组对照，两者有显著性差异，P<0.05。
- 儿童患者鼻部症状的改善，及IgA的指标都说明了：特定配置的益生菌(NCFM+Bi-04)的干预，可抑制由花粉过敏而引起的机体向Th2型免疫应答的转变。

临床研究结果---益生菌影响肠道微生态环境

Table 5 Alteration of the fecal microbiota composition during the birch pollen season

	March		April/May		June	
	Placebo	Probiotic	Placebo	Probiotic	Placebo	Probiotic
Eubacterium[4]	2.7×10^9 (0.3×10^9)	2.5×10^9 (0.4×10^9)	1.8×10^9 (1.0×10^9)	1.6×10^9 (0.2×10^9)[2]	2.00×10^9 (0.2×10^9)	1.9×10^9 (0.3×10^9)
Bifidobacterium[4]	5.0×10^8 (5.0×10^8)	3.5×10^8 (3.3×10^8)	2.1×10^8 (0.4×10^8)[2]	1.6×10^8 (0.3×10^8)[1]	2.50×10^8 (0.4×10^8)	2.0×10^8 (0.2×10^8)
Bacteroides[4]	4.9×10^8 (3.5×10^8)	5.4×10^8 (3.2×10^8)	2.3×10^8 (0.4×10^8)[2]	1.7×10^8 (0.3×10^8)[1]	1.30×10^8 (0.2×10^8)	1.5×10^8 (0.4×10^8)
Clostridium[4]	1.4×10^8 (1.0×10^8)	1.5×10^8 (0.3×10^8)	0.7×10^8 (0.2×10^8)[2]	0.8×10^8 (0.2×10^8)[1]	1.30×10^8 (0.3×10^8)[2]	1.6×10^8 (0.2×10^8)[1]
Akkermansia[4]	1.3×10^8 (0.2×10^8)	1.3×10^8 (0.2×10^8)	1.2×10^8 (0.2×10^8)	1.1×10^8 (0.1×10^8)	0.90×10^8 (0.2×10^8)	1.1×10^8 (0.2×10^8)
B. lactis[5]	2.6×10^7 (1.7×10^7)	1.5×10^7 (1.3×10^7)	0.1×10^7 (0.1×10^7)	11.2×10^7 (4.2×10^7)[1,3]	0.01×10^7 (0.05×10^7)	2.6×10^7 (1.0×10^7)[1,3]
L. acidophilus NCFM[5]	1.0×10^6 (0.8×10^6)	0.7×10^6 (0.5×10^6)	0.2×10^6 (0.1×10^6)[1]	3.5×10^6 (1.3×10^6)[3]	0.02×10^6 (0.1×10^6)	4.2×10^6 (2.4×10^6)[3]

[1]Significantly different from previous time point; $P < 0.01$. [2]Significantly different from previous time point; $P < 0.05$. [3]Significantly different from placebo; $P < 0.01$. [4]Determined by fluorescent *in situ* hybridization (FISH). [5]Determined by quantitative real-time PCR. Data are expressed as mean (SE), microbes/g feces.

- 在桦树花粉过敏的高峰季节，儿童患者的粪便检查显示：双歧杆菌、梭状芽胞杆菌、及类杆菌均显著减少。
- 4-6月间，混合益生菌(NCFM+Bi-04)的干预，可显著增加粪便中嗜酸乳杆菌及双歧乳杆菌的数量，与对照组相比，两者有显著性差异，P<0.05。

临床研究(6)---低体重儿童

研究目的:

测定含益生菌的营养粉对营养不良的儿童患者减少疾病发生率的有效性及耐受性

- 研究对象: 626位来自巴西、墨西哥、葡萄牙及西班牙等13个研究中心，1-6岁足月分娩的低体重儿童患者（因摄入量过少而体重不足）。
- 试验设计: 对626位低体重儿童患者进行随机、 双盲、对照的临床试验研究，予每天服用含益生菌加益生元的营养粉，连续服用4个月，其余治疗方案遵医嘱。
- 试验分组: - 试验组: n=310 含合生剂的营养粉（嗜酸乳杆菌+双歧乳杆菌）Does=$6*10^7$CFU/g

  - 对照组: n=316 营养粉
- 评价指标: 试验期间患病率，患病天数及每日能量摄入量

Fisberg M, Maulén-Radován IE, Tormo R, Carrascoso MT, Giner CP, Martin FA, et al. 2002.Effect of oral nutritional supplementation with or without synbiotics and sickness and catch-up growth in preschool children. Int Pediatr. 17: 216-222.

临床研究结果---益生菌可降低患病率

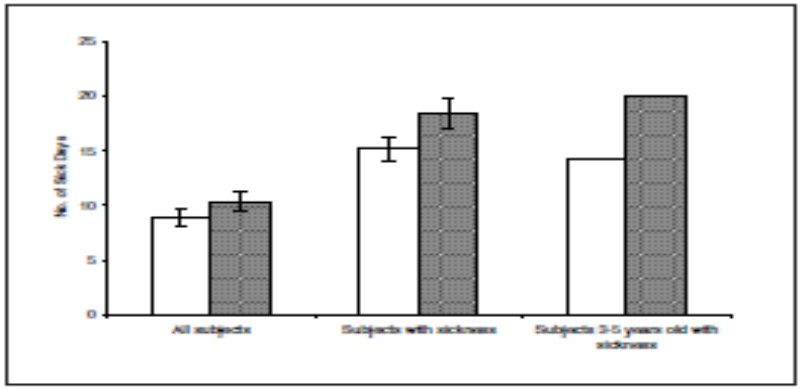


Fig. 1 - Mean (SEM) number of sick days in the experimental (with synbiotics) group (open bars) and control (without synbiotics) group (solid bars). *Significantly lower in the experimental group ($p<0.05$).

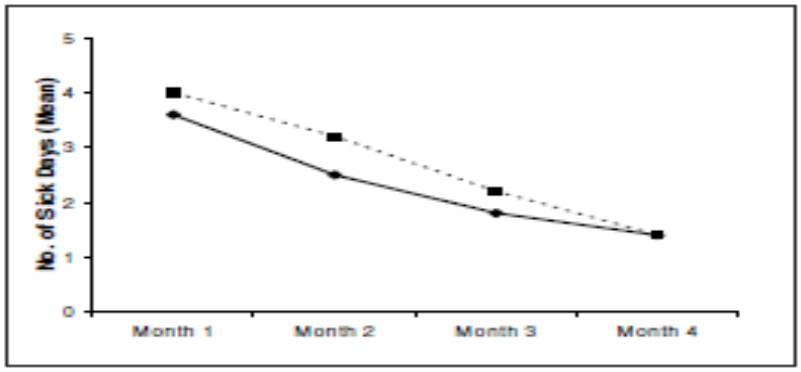


Fig. 2 - Summary of sick days per month in the experimental (with synbiotics) group (—◆—) and the control (without synbiotics) group (—■—). For both groups, trend related to baseline, $p<0.01$.

- 试验结果表明：试验组中3-5岁的低体重儿童平均患病的天数为14.2天，显著低于对照组20.1天，两组数据有显著性差异，P<0.05；
- 低体重儿童每月患病天数显著降低，两组前后对照，均有显著性差异，P<0.01；
- 在试验前三个月，1-2岁的低体重儿童患病天数减少率较3-5岁的儿童更高，

临床研究结果---益生菌可降低便秘发生率

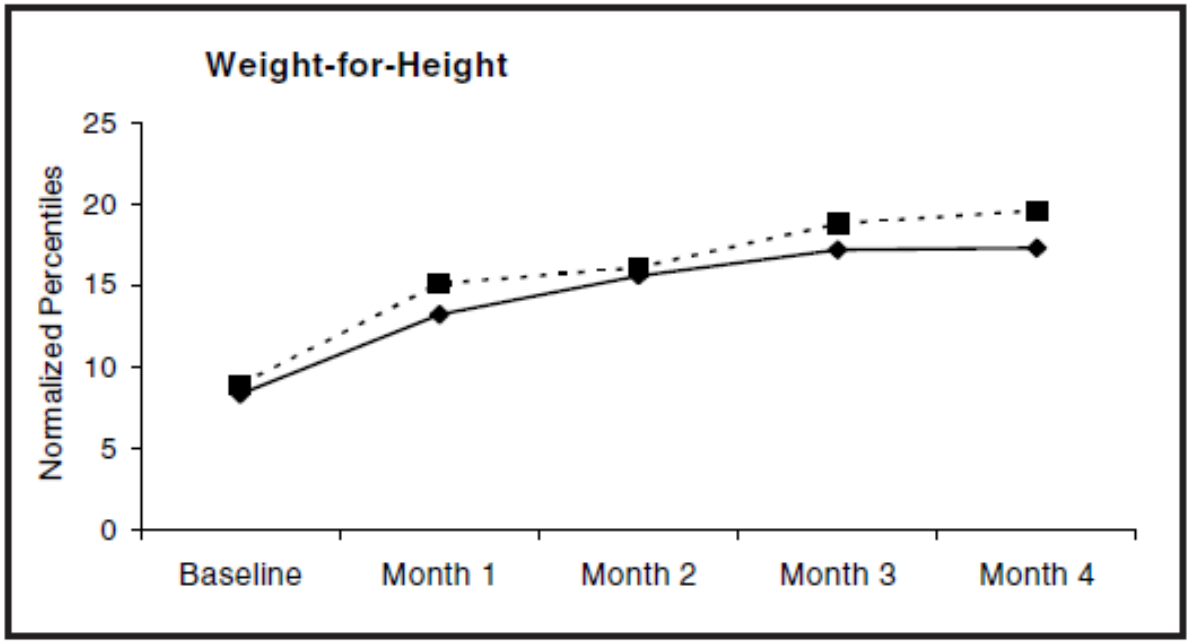


Fig. 3 - Mean (SEM) normalized percentiles for weight-for-height in the experimental (with synbiotics) group (—◆—) and the control (without synbiotics) group (—■—). For both groups, trend related to baseline, p<0.001.

- 试验后，两组低体重儿童的生长率（体重/身高）与试验前相比，均有显著性差异，P<0.01；
- 试验组低体重儿童的便秘天数，与对照组相比显著减少，两者有显著性差异，P=0.02；

临床研究结果---试验后低体重率显著降低

Oral Supplementation with or without Synbiotics

Table 4 - Shift Table from Baseline to the End of Study in Weight for Height in Percentile

	End of Study				
Baseline	Below -2 SD	-2 SD - -1SD	-1 SD - median	Above median	Total
Below -2 SD	13	37	6	1	57
-2 SD - -1 SD	10	138	121	12	281
-1 SD - median	0	4	9	6	19
Above median	0	1	0	0	1
Total	23	180	136	19	358

- 试验后，两组儿童的体重均显著增加，与试验前相比，低体重率（体重/身高）显著降低；

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2010 Scientific Achievement Awards - US journal

Danisco receives award for innovation on HOWARU® probiotics

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Danisco: Excellence in Probiotics

Its ingredients can be found in every second ice cream and cheese product, every third box of detergent, and every fourth loaf of bread produced globally. It employs 6,800 people in 40 countries, boasts more than 10,000 customers worldwide, and brings in roughly $8 billion annually. Yet, in the world of probiotics, ingredient supplier **Danisco** is hardly a household word.

"Danisco has been a quiet giant," notes Anthony Almada of IMAGINutrition. "It has one of the most researched probiotic strains in the world, and has really raised the bar when it comes to scientifically assessing what probiotics can do in humans. Still, people don't know much about it."

That might soon change as the 20-year-old, Denmark-based company rolls out a host of new condition-specific probiotic strains and blends in its branded *HOWARU* line, and further extends its reach into supplements and functional foods with additional strains and innovative stabilization technologies.

All of this stems from a long-standing commitment to solid research, both by Danisco and by its recent acquisitions, according to Scott Bush, vice president of marketing for Danisco's Health and Nutrition Division. "We are now seeing the results of our decision to spend heavily on clinical work," says Bush, noting that while probiotics remain a small portion of Danisco's overall sales, that's poised to change. "Probiotics is one of the fastest growing businesses within Danisco. It's very important strategically as we strive to become a bigger player in health and nutrition."

Known best as a supplier of enzymes, natural sweeteners, emulsifiers, pectin and gums for processed foods, Danisco came to probiotics in 2001, when it licensed two strains—now contained in its *HOWARU Bifido* and *HOWARU Rhamnosus* branded ingredients—from the **New Zealand Dairy Board**. Three years later, Danisco paid $490 million to acquire **Rhodia Food Ingredients**—a leading probiotics producer.

With the acquisition came staff, including Bush, with three decades of expertise in the field of probiotics, and exclusive marketing rights to Lb acidophilus NCFM, one of the most studied probiotics strains in the world. Danisco got to work, using a novel approach to research that would turn out to be a game-changer for the probiotics industry.

"There was a one-strain-does-it-all mentality out there for a long time," says Bush. "Danisco was the first company to embrace a condition-specific approach to probiotic health benefits." Seven years later, Danisco has sponsored 18 human clinical studies and collaborated on four more, testing specific strains for everything from gut health, to cold and flu prevention, to allergy relief, to gum health. Armed with solid research, the company is now taking new branded formulas to market, and emphasizing ones that have yet to receive the attention they deserve.

> *There was this one-strain-does-it-all mentality for a long time. We were the first company to embrace a condition-specific approach to probiotic health benefits.*
>
> —Scott Bush, Danisco

In July, 2009, a study of 326 children published in the prestigious journal *Pediatrics* showed that kids taking Danisco's *HOWARU Protect* probiotic formula (a blend of Lactobacillus acidophilus NCFM and Bifidobacterium lactis Bi-07) reduced their fever, coughing and runny nose incidence significantly; missed fewer school days; and took fewer antibiotics. Shortly thereafter, Danisco made the formula commercially available. It is now present in immune-support supplements on the shelf in New Zealand, Australia and Malaysia, and company officials expect to see products containing *HOWARU Protect* on U.S. shelves in 2011.

Another 2009 study, published in the *Journal of Medical Microbiology* found that, when patients suffering from gut stress—often from antibiotic use—took Danisco's *HOWARU Restore* formula (a different blend of lactobacillus and bifidobacterium strains), beneficial bacteria levels were quickly restored to pre-stress levels.

In addition to its pre-formulated, ready-to-market *HOWARU* line, Danisco also produces an older, markedly less-hyped *FloraFIT* line of custom probiotics, aimed at manufacturers "looking to develop their own unique formulation," says Bush. To date, it makes up the bulk of the company's probiotic sales.

Specific strains aside, Danisco has moved the field of probiotics forward in another major way, according to Almada. "Danisco has been able to improve the stability of these bugs in ways that make them more consumer friendly and green," he says.

Armed with an exclusive license from the **Wisconsin Alumni Research Foundation**, Danisco developed stabilizing technology that allows manufacturers to create probiotic products that can remain unrefrigerated on the shelf and stay fresh for as long as 18 months. "Doing a clinical study is great," says Bush, "but if you don't have strains that you can deliver in stable format to the consumer, it doesn't matter a whole lot. As probiotics start to move into food, drug and mass, refrigeration is more of an issue. To really market quality probiotics that meet label claim at the end of shelf life, you need to be room-temperature stable."

Between its *FloraFit* line, its *HOWARU* line, and its stabilization techniques, Danisco touches a clear majority of probiotic products produced in the United States. As the company moves forward scientifically, using genomics to explore more effective, stable strains, there will no doubt be more news, and more market share, to come. "We are starting to really understand, mechanistically, how and why probiotics work, and this can pave the way for more targeted applications," says Bush.

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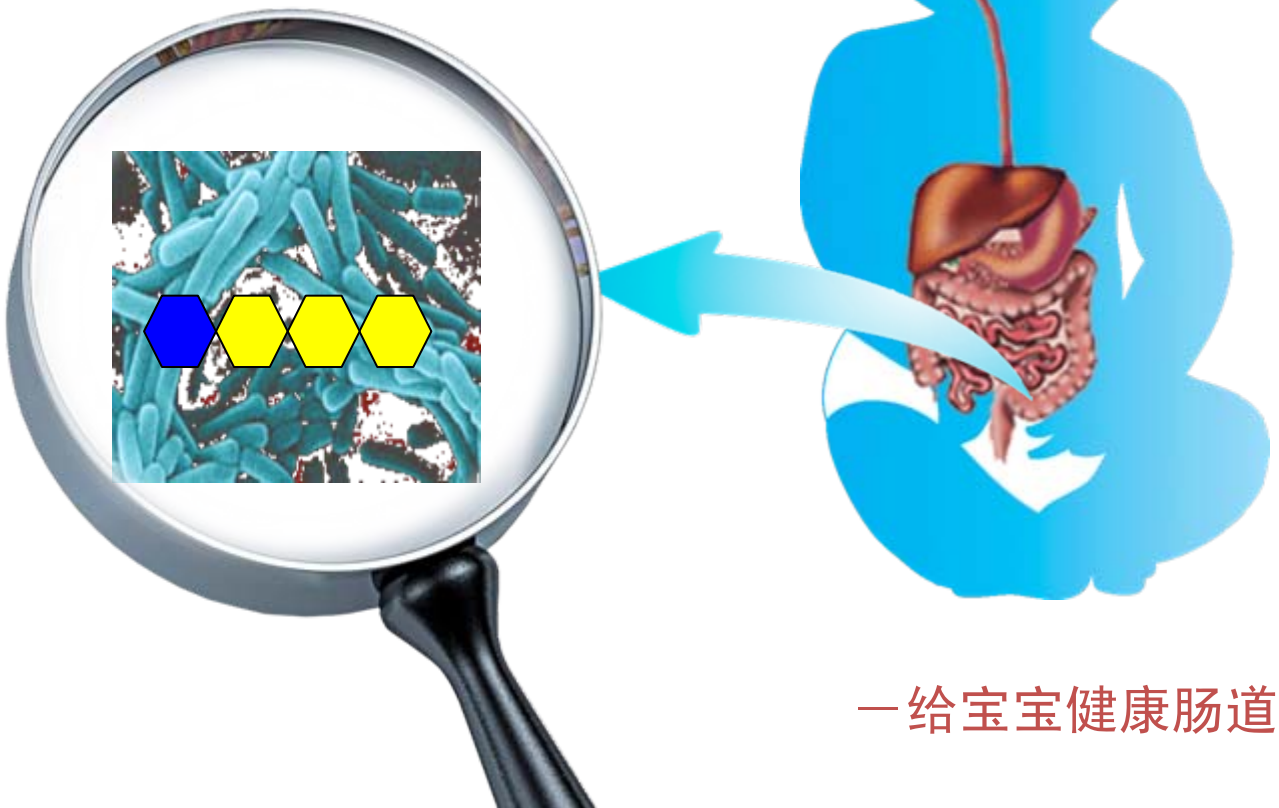

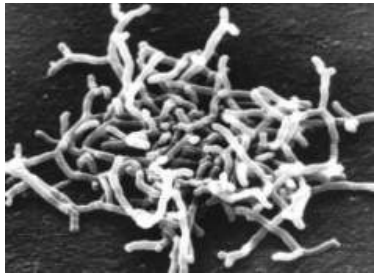

—给宝宝健康肠道，提高宝宝抵抗力