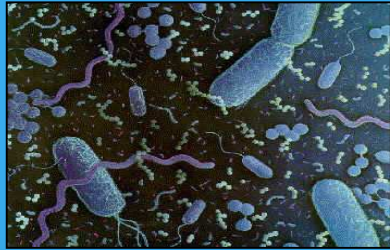




Department of Medical and Surgical Sciences  
University of Otago Rheumatology Research Unit



# Probiotics. What Should you Know?



Simon Stebbings

University of Otago School of Medicine

# An Introduction to Probiotics in Rheumatic Disease

- What are probiotics and should we care?
- The Bacteriology of the Intestine
- How might probiotics exert a therapeutic benefit?
- Is there any clinical evidence that probiotics work?
- Are they safe?
- The Probiotic Industry: snake oil salesmen?
- What relevance do probiotics have to Rheumatologists?
- Developing Research into probiotics in Rheumatic Disease: An Otago Perspective

# What are Probiotics?

World Health Organization definition

‘Live microorganisms which when administered in adequate amounts confer a health benefit on the host’

In practice most bacteria studied are intestinal commensals

- *L. Casei*
- *L. acidophilus*
- *L. Bulgaricus*
- *B. brevis*
- *B. infantis*
- *Strep. salivarius*

# History of Probiotics

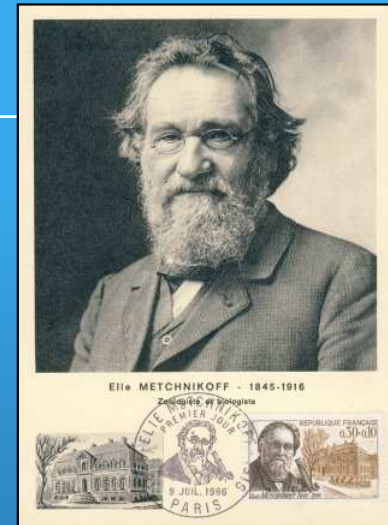
Founding Father of Probiotics and a multi-billion dollar industry.

**Ilya Mechnikov (1845-1916). Nobel Prize**

- ‘Putrefying bacteria promoted disease’

Advocated total colectomy to eradicate

- Converted to yoghurt by observing the long healthy life of Bulgarian Peasants
- Healthy lactobacilli inhibited souring of milk in hot climates and could prevent putrefaction in bowel
- Credited with Introducing Yoghurt to the West from the Ottoman Empire



# The gut and past perceptions

- Until the 1960's majority of gut bacteria were thought to be lactobacilli, clostridia and enterococci - easily cultured
- Now realised vast majority of bacteria in lower intestine are obligate anaerobes (  $O_2$  =death!). *Bacteroides* and *bifidobacteria* are largest species
- 40% colonic bacteria cannot be cultured. Techniques introduced 1990's - allowed comprehensive analysis of microbiota- using molecular identification 16S rRNA
- A complex ecosystem, uniquely adapted to the individual and highly resistant to change.

# How Might Probiotics work?

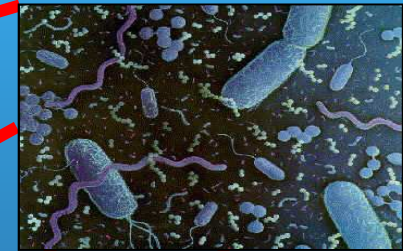
## Probiotics

1 Composition of Gut Bacteria

2 Leakiness of the Gut Wall

3 Adhesion of Bacteria

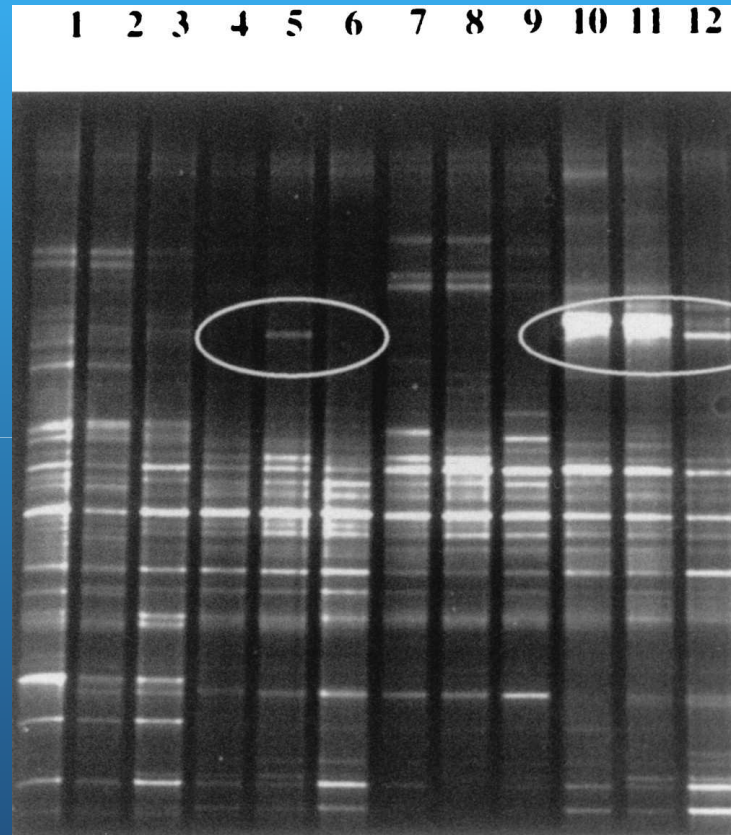
4 Response of the Immune System



# What happens to probiotic bacteria after they are ingested?

- Surprisingly most probiotic bacteria survive transit through the gut
- Lactobacilli are acid tolerant: yoghurt and the vagina
- Probiotics do not colonise the intestine permanently and are only detectable for as long as they are consumed
- The human enteric microbiota is remarkably resilient to change

## PCR-DGGE profiles *L.rhamnosus*- DR-20

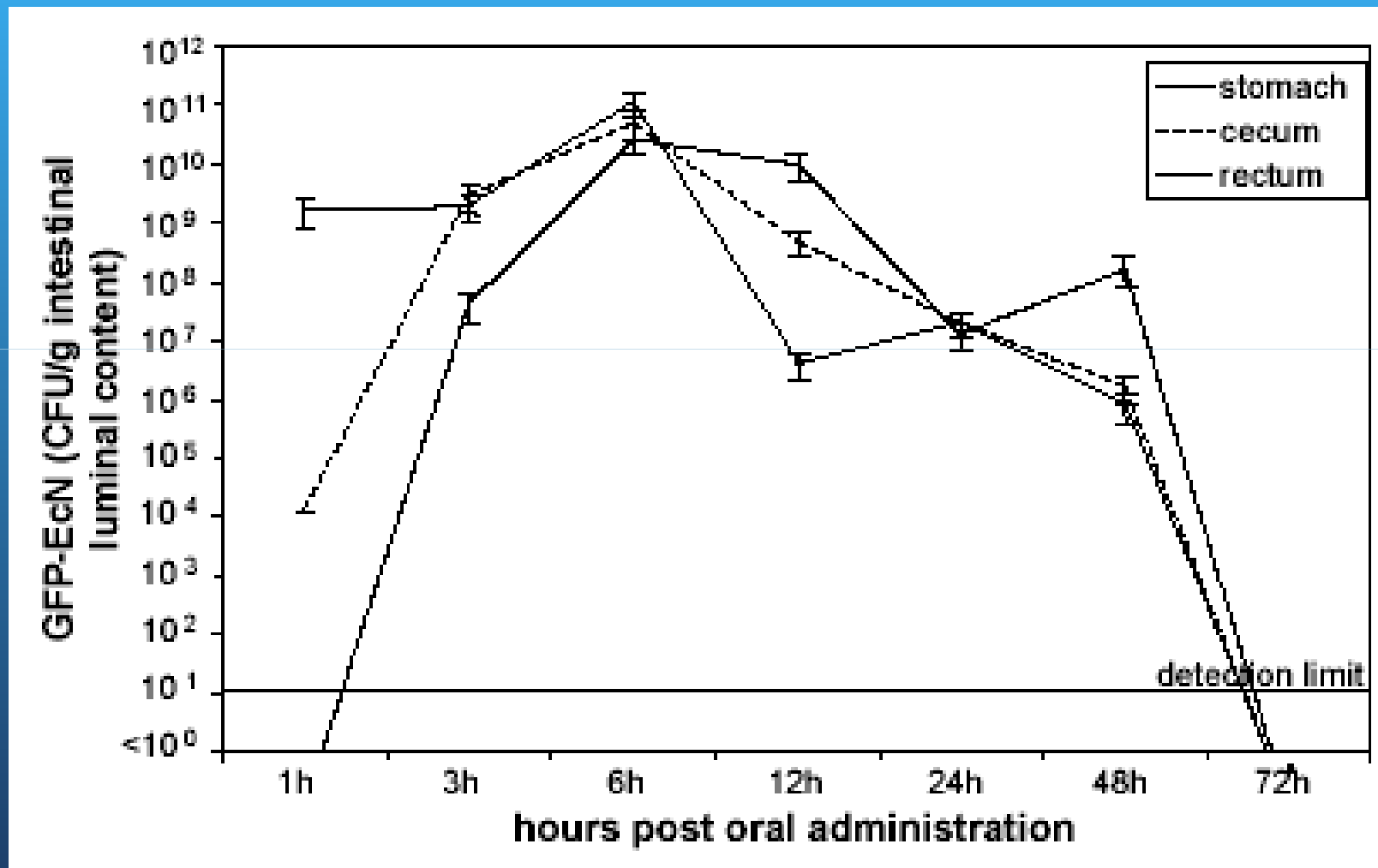


Faecal samples. Showing 3 samples from 4 subjects and controls. Test and posttest period samples [1-3, and 7-9 controls]



# Where do they go?

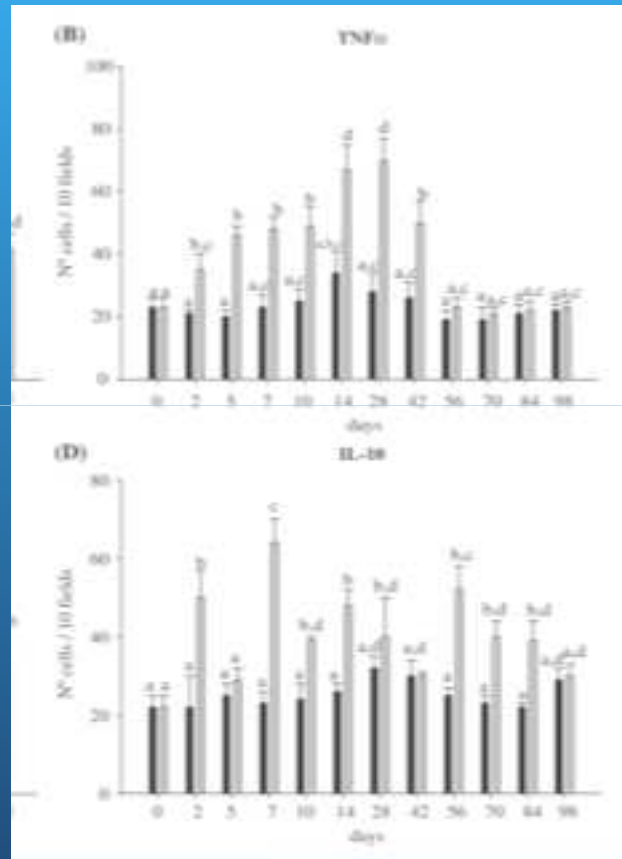
Follow-up After Oral Administration of One Dose of Probiotic



So?

- They don't hang around in the gut for long.
- In that case are they a waste of time?

# Cytokine Profiles in BALB/c Mice Treated with Probiotic



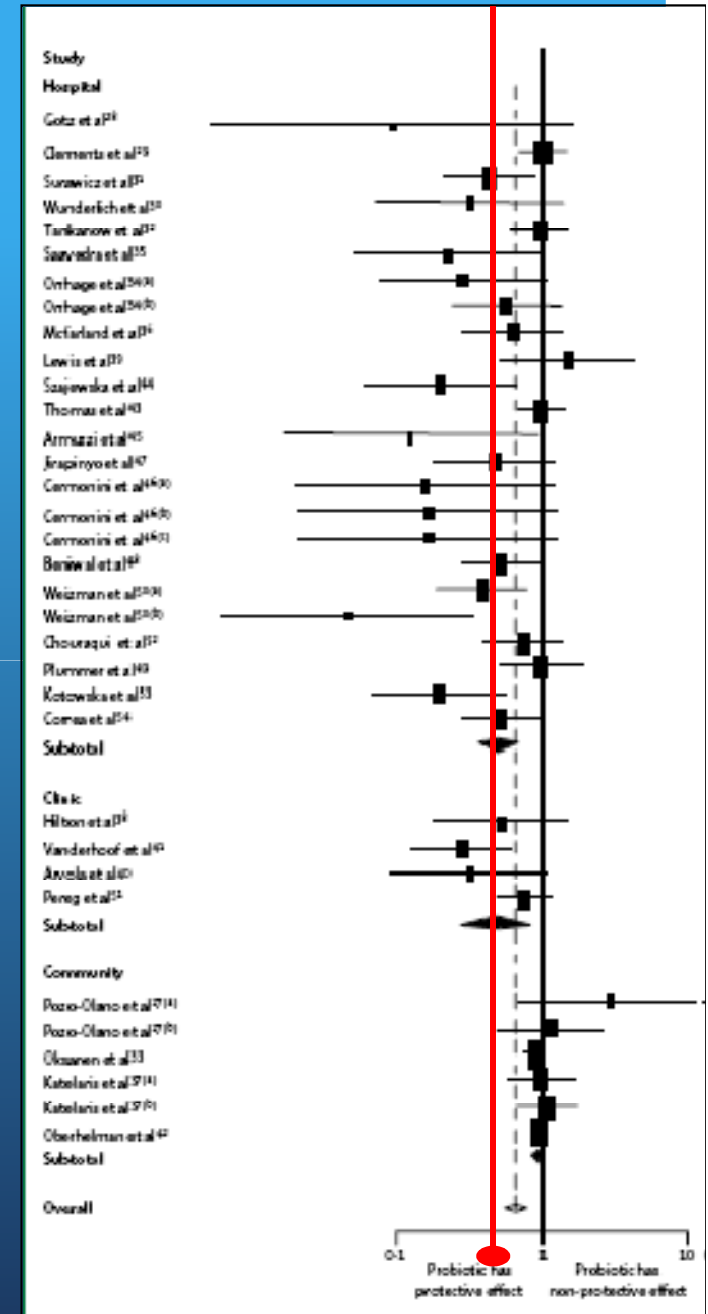
↑  
Increased levels of TNF following probiotic

↑  
Increased levels of IL-10 following probiotic

**Well that's all very good for  
Rodents what about People?**

# Prevention of antibiotic-associated Diarrhea

Meta-analysis: Probiotics reduces duration and severity of hospital acquired antibiotic induced Diarrhea



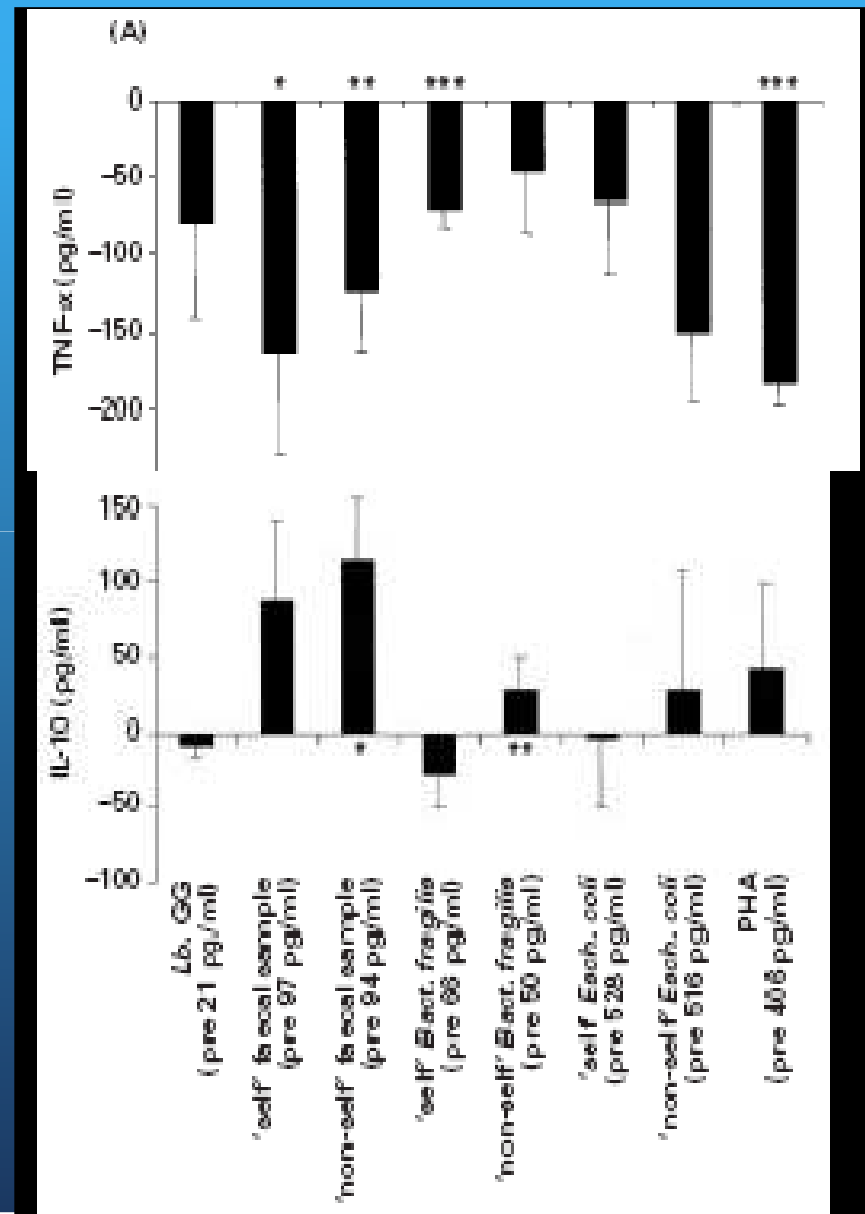
# Clinical Evidence for Immunomodulation

pro-inflammatory →

vs.

anti-inflammatory →

In IBD Probiotics affect cytokine profiles of PBMC



# Ulcerative Colitis

30 patients  
endoscopically active UC  
sulphasalazine + steroids

*bifidobacterium*

placebo

2 months

20% relapse

93.3% relapse

Cui, 2004

Index	BIFICO group		Placebo group	
	Pretreatment	Post-treatment	Pretreatment	Post-treatment
IL-1	0.41±0.09	0.53±0.11	0.38±0.12	1.20±0.08 <sup>d</sup>
TNF-α	0.79±0.06	0.35±0.12 <sup>b</sup>	0.86±0.05	1.40±0.18 <sup>d</sup>
IL-10	0.76±0.32	1.11±0.21 <sup>b</sup>	0.54±0.26	0.45±0.04 <sup>d</sup>

<sup>a</sup>P<0.05, <sup>b</sup>P<0.01 vs post-treatment; <sup>c</sup>P<0.05, <sup>d</sup>P<0.01 vs control.

**Aren't Probiotics Simply  
Part of the Complementary  
and Alternative Medicines  
Health Scam?**



# Commercial Development of Probiotics

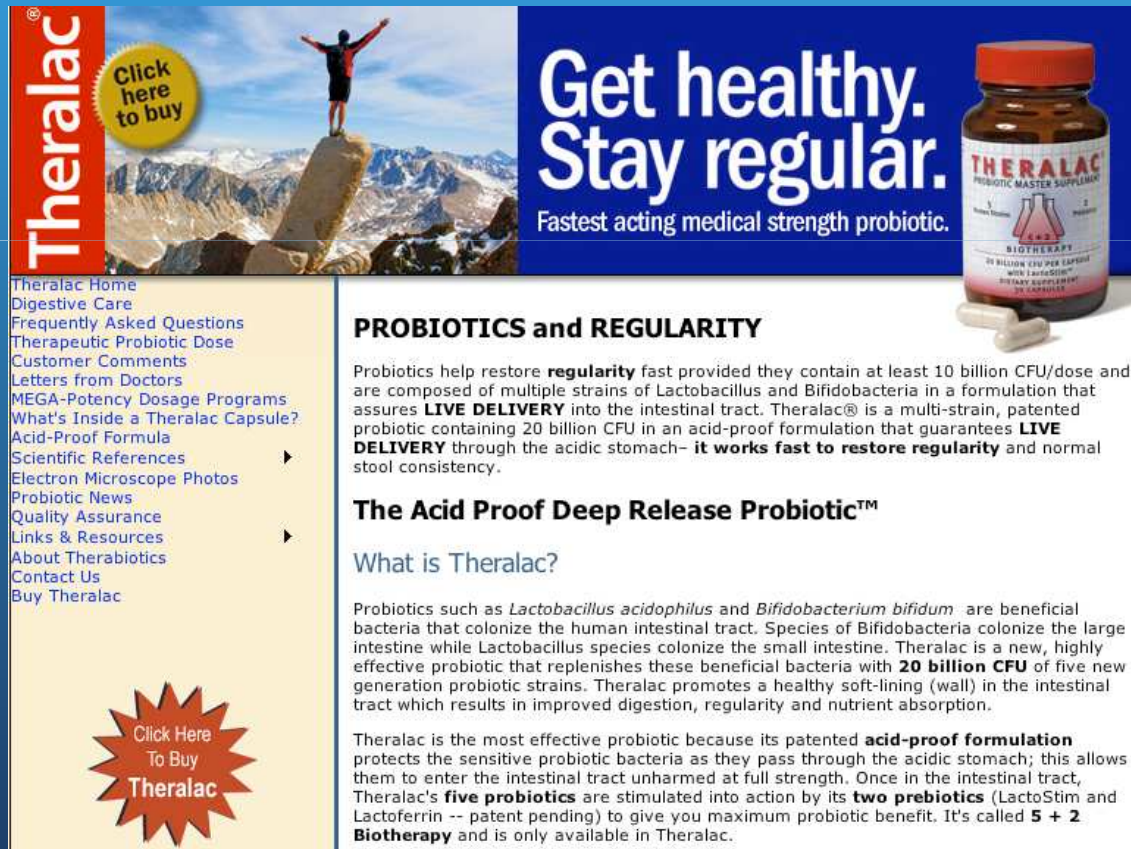
- Probiotics are one of the fastest growing functional food products worldwide.
- The US probiotics market is forecast to more than double in value from \$143.9 million in 2006 to \$394 million by 2010
- Fonterra in NZ have been developing probiotics since 1996 and screened >2000 bacteria. Commercialised *Lactobacillus rhamnosus* HN001 and *Bifidobacterium lactis*.

# What Can Probiotics do for me: according to the internet?

## Why Does Your Digestive System Need Probiotics?

From the day you were born your digestive tract has been introduced to a steady stream of bacteria – some helpful, some harmful. One key to intestinal health is maintaining a balance of helpful bacteria and harmful bacteria, thus avoiding digestive imbalance.\*

Unfortunately, many factors (see list below) can disturb your intestinal balance and decrease the level of beneficial bacteria or naturally occurring probiotics (healthy bacteria). There is good news, however. A daily regimen of a probiotic supplement, such as Sustenex, can boost beneficial bacteria levels to help restore intestinal balance.\*



**Theralac**  
Click here to buy

**Get healthy. Stay regular.**  
Fastest acting medical strength probiotic.

**PROBIOTICS and REGULARITY**

Probiotics help restore **regularity** fast provided they contain at least 10 billion CFU/dose and are composed of multiple strains of Lactobacillus and Bifidobacteria in a formulation that assures **LIVE DELIVERY** into the intestinal tract. Theralac® is a multi-strain, patented probiotic containing 20 billion CFU in an acid-proof formulation that guarantees **LIVE DELIVERY** through the acidic stomach– **it works fast to restore regularity** and normal stool consistency.

**The Acid Proof Deep Release Probiotic™**

**What is Theralac?**

Probiotics such as *Lactobacillus acidophilus* and *Bifidobacterium bifidum* are beneficial bacteria that colonize the human intestinal tract. Species of Bifidobacteria colonize the large intestine while Lactobacillus species colonize the small intestine. Theralac is a new, highly effective probiotic that replenishes these beneficial bacteria with **20 billion CFU** of five new generation probiotic strains. Theralac promotes a healthy soft-lining (wall) in the intestinal tract which results in improved digestion, regularity and nutrient absorption.

Theralac is the most effective probiotic because its patented **acid-proof formulation** protects the sensitive probiotic bacteria as they pass through the acidic stomach; this allows them to enter the intestinal tract unharmed at full strength. Once in the intestinal tract, Theralac's **five probiotics** are stimulated into action by its **two prebiotics** (LactoStim and Lactoferrin -- patent pending) to give you maximum probiotic benefit. It's called **5 + 2 Biotherapy** and is only available in Theralac.

Theralac Home  
Digestive Care  
Frequently Asked Questions  
Therapeutic Probiotic Dose  
Customer Comments  
Letters from Doctors  
MEGA-Potency Dosage Programs  
What's Inside a Theralac Capsule?  
Acid-Proof Formula  
Scientific References  
Electron Microscope Photos  
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Click Here To Buy Theralac

‘Restoring the balance’

# Theories of Medicine 400BC - 2008: What Goes Around Comes Around



‘Restoring the balance’

The Four Humours:

Blood

Phlegm

Black bile

Yellow Bile

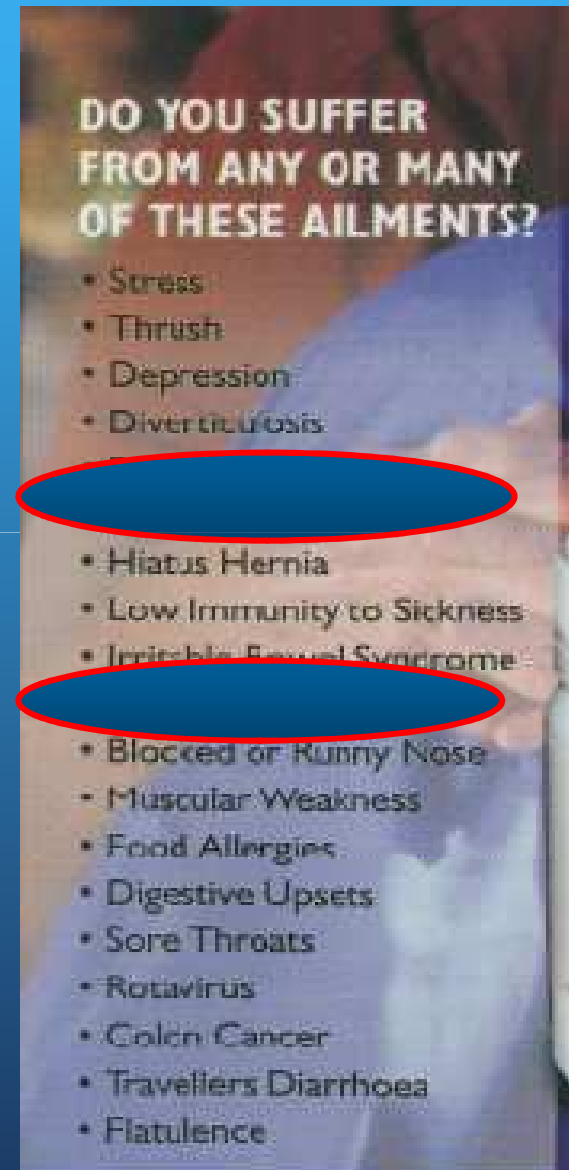
Galen 120 AD- accepted  
medical model that put back  
medicine 1500 years.

Every Man in His Humour is a 1598 Ben Jonson. A play  
where each character is characterized by a particular  
humour- satire



# Health Claims that target our Patients

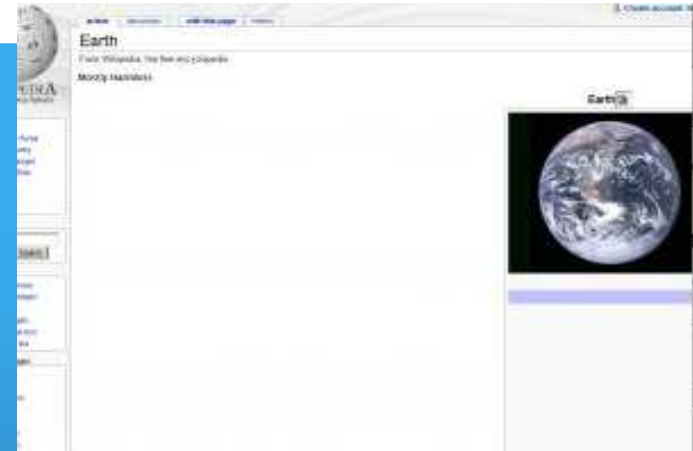
- ‘Boosts the immune system’
- ‘Improves arthritis’
- ‘Improves rheumatism’
- ‘Reduces the side effects of Steroids’



# Probiotic Skepticism

- Unreliable content of commercial products even from reputable companies
- Study of 21 probiotics claiming up to 60 billion live organisms
- 8 contained > 1% of claimed no. (ie were not probiotic!)
- Many companies refer to 'acidophilus' or fail to specify the strain of bacteria ( eg L. acidophilus NCFM®)

# Are Probitics Safe?



- Like the Earth in HitchHiker's Guide 'mostly Harmless'
- 20 billion doses are taken globally each year
- 4 reported adverse events in literature
- Safe in immuno-compromised - eg HIV
- **Study:** Probiotic prophylaxis severe acute pancreatitis (ICU)
  - 16% in probiotics group died, compared with 6% in the placebo group (relative risk 2.53).
  - 9 in probiotics group developed bowel ischaemia (8 with fatal outcome), c/w none in placebo group (p=0.004).

*Besselink Lancet 2008; 371:651-659*

# Probiotics and Arthritis in Humans

## Probiotics in Spondyloarthropathy

- Randomised controlled internet based trial of a probiotic in SpA
- 147 pts recruited from a weblink on the NASS website
  - Diagnosis confirmed by GP or Rheumatologist - pts had to have 'sacroiliitis'
  - Randomised to probiotic (L.salivarius, B. infantalis, B.bifidum cfu 10<sup>9</sup>) or placebo
- Outcomes - self assessment VAS- global well being  
Disease activity, function, bowel symptoms



# Probiotics and Arthritis in Humans (2)

- 96 of 147 completed 3 month trial
- 11 adverse events (6 and 5 ) - cramps, indigestion, dizziness
- 65% completed all questionnaires
- No significant difference between groups for any of the parameters

Brophy: *BMC Musc Dis* 2008

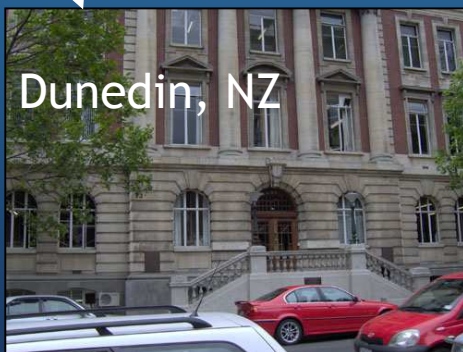
# Probiotic Research in Otago



Collaboration with BLIS Technologies:  
BLIS BioRestore in ankylosing spondylitis

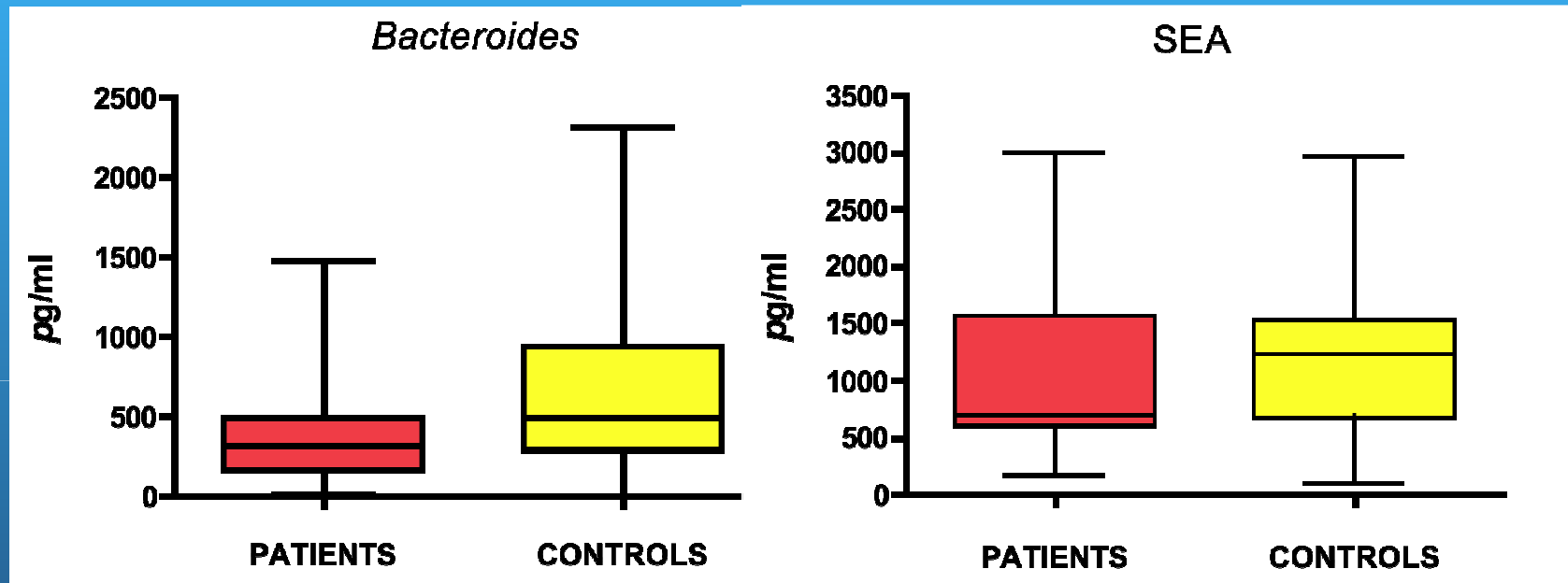


*Strep. salivarius* K12  
*L. acidophilus*  
*B. lactis*  
*L. rhamnosus*



Collaboration with the Department of  
Gastroenterology, School of Pharmacy, Dept of Human  
Nutrition

# IL-10 production during T-cell proliferation



P < 0.001

P > 0.05

AS have lack of anti-inflammatory activity with regard to *Bacteroides*?

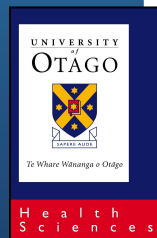
# A Double Blind Randomised Controlled Trial of an Orally administered Probiotic in the Treatment of Spondyloarthritis

Spondylarthritis -ESSG criteria  
n = 2 x 32

BLIS BioRestore®/Placebo  
3/12

BASDAI, BASMI, BASFI, BASG, SDI, VAS pain scales,  
CRP, MASES Enthesitis Index, DISQ, Stool chart

DGGE profiles, Gastroduodenal and intestinal  
permeability assessment, faecal calprotectin,  
Serum cytokines levels



BLIS Technologies LTD

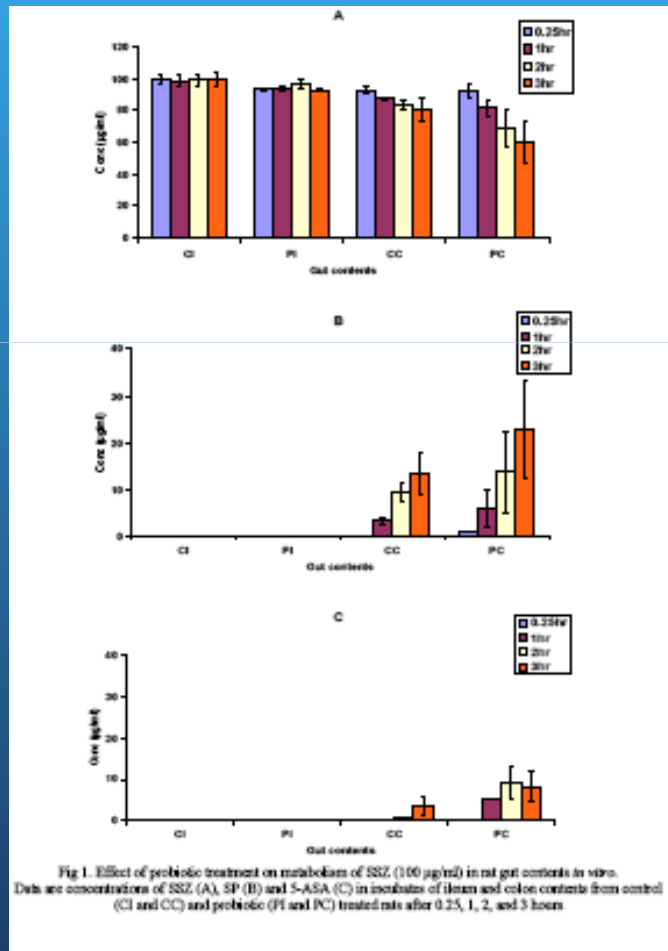
Products

Company

Science

ARTHRITIS  
NEW ZEALAND  
ENABLING A BETTER QUALITY OF LIFE

# Effects of Giving Probiotics to rats taking Sulfasalazine. A potential interaction in our patients?



SSZ levels fall

SP increases

5-asa increases

# Sulphasalazine Treatment and Probiotics -humans

- 12 patients with RA taking stable doses of Sulfasalazine
- One week of probiotic therapy
- Measure serum, urinary and faecal concentrations of SSZ and metabolites at 1 and 4 weeks.
- Concentration SSZ in plasma increased by 23% after probiotic treatment whereas SP and 5-ASA concentrations were decreased by 9 % and 6 % respectively. However the differences were not statistically significant.
- The mean urinary concentration of SSZ remained unchanged during the trial indicating no effect of probiotics on SSZ absorption
- No adverse events

# Summary

- Probiotics appear to be a potential therapy for a number of conditions
- Limited evidence mostly from animal models suggests possible mechanisms of action
- Very little robust clinical evidence is available
- Probiotics are a hugely profitable industry, with many unsubstantiated claims made - some of which target our patients
- Potential for benefit and harm ( perhaps including adverse interactions with widely used therapies) may involve our patients

# Research Group

## Rheumatology:

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## Gastroenterology:

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## BLIS Technologies:

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Paul Fawcett

Hee Ji Lee



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## Immunology:

Assoc Prof Margaret Baird

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