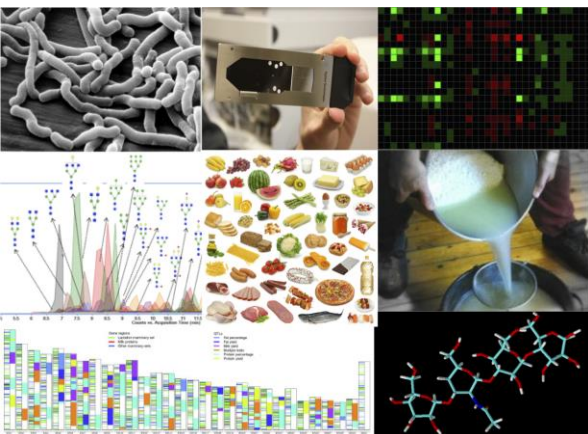


A serene sunset scene over a calm body of water. The sky transitions from a deep blue at the top to a bright orange and yellow near the horizon, where the sun is setting. The water reflects the colors of the sky, creating a shimmering effect. A dark silhouette of trees and land is visible along the horizon line. The text is overlaid in the upper half of the image.

# Milk's Future: Capturing Value in Genetic Traits

# Foods for Health Institute

Building the Science,  
Technologies and Education to  
Guide Diet and Health and  
Create Value for Agriculture in  
the 21<sup>st</sup> Century



FOODS  
FOR HEALTH  
INSTITUTE



# Disclosures



# Diet & Health - Oops

We should be enjoying the best health in history and some are,

.....but most are not



Jaring Timmerman Roger Gentilhomme

# The horror of 60 years of Science Funding

To cure the  
diseases of  
middle  
aged rich  
men



# Value of Milk

## The price of milk as a beverage

- Sacramento airport:
- Water \$2.49
- Milk \$2.25

**Value of Milk?**  
**According to price,**  
**California farmers lower**  
**the value of water by**  
**passing it through their**  
**cows!**



**Value?**

**Lets put that  
price in  
context**



**Value of Milk?  
Cheaper than Water!**

**It must be toxic?**

# Airport reality

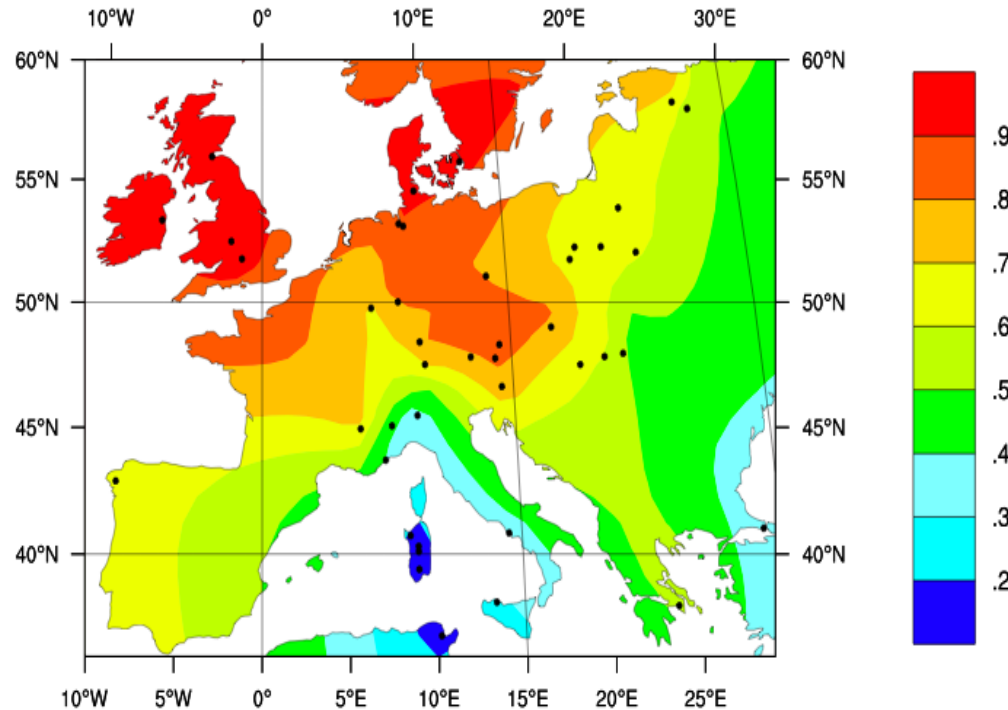
**You are about to be literally tied to a chair for hours:**

- **Bone turnover**
- **Muscle atrophy**
- **Immune Senescence**
- **Physiological Performance**

**What would help:  
MILK!**



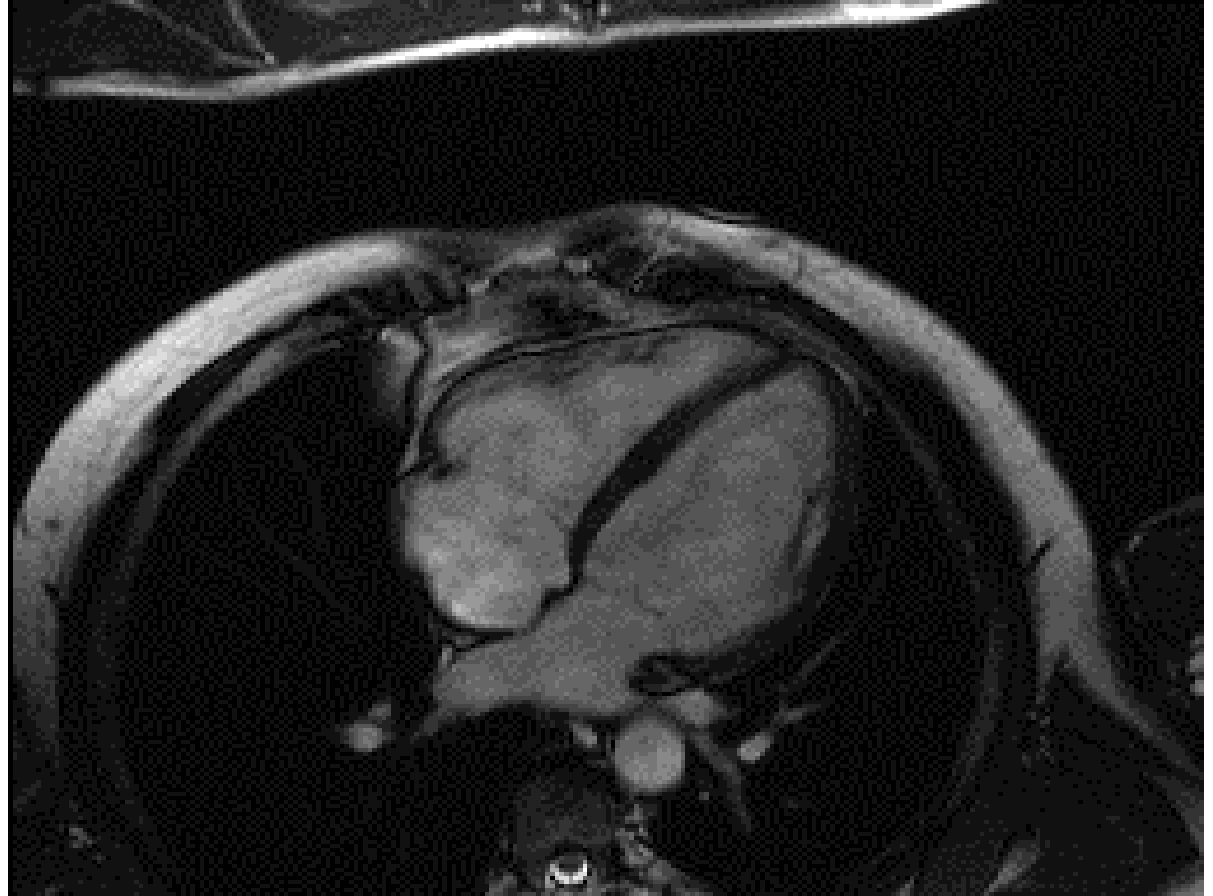
# Human gene variants enabled Lactase Persistence into adulthood



- **Europe:** 1 known variant
- **Africa:** 4 known variants: 3 African, 1 European origin
- *Lactase mutation occurred often in human history*

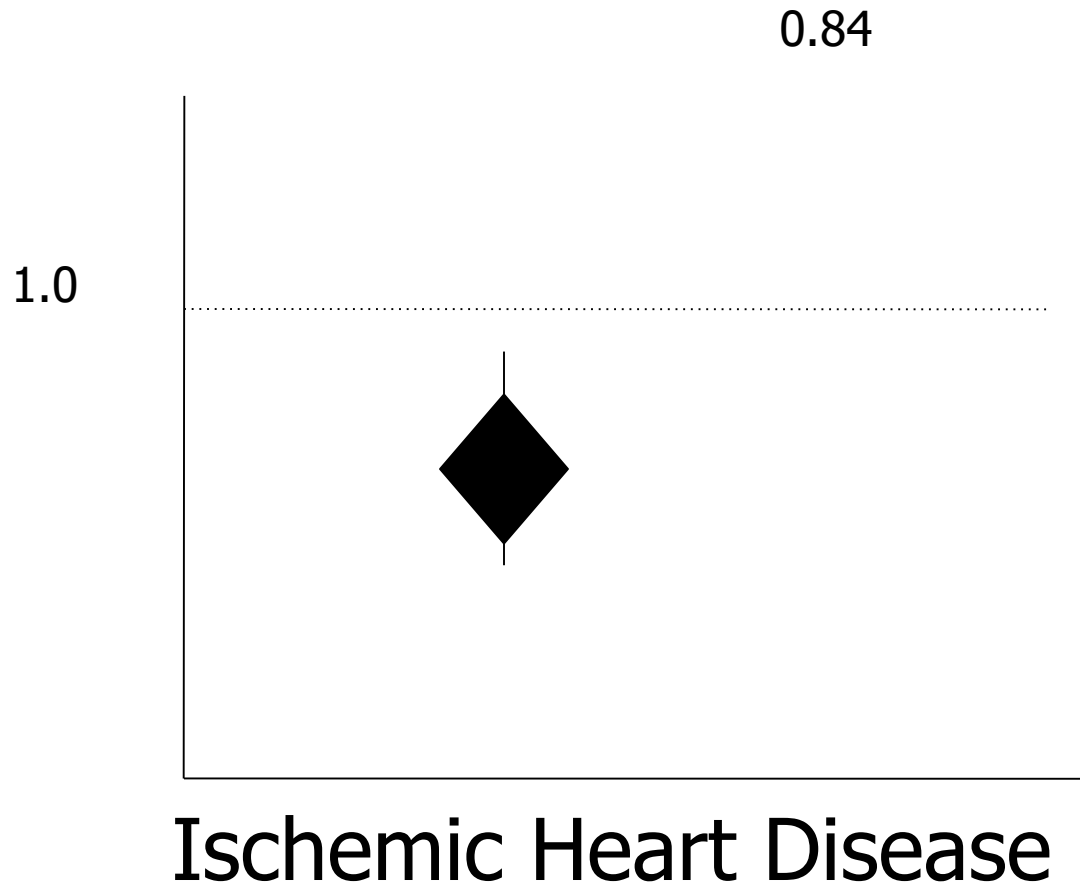
# The Elephant in the room

Does  
milk  
cause  
heart  
disease  
?



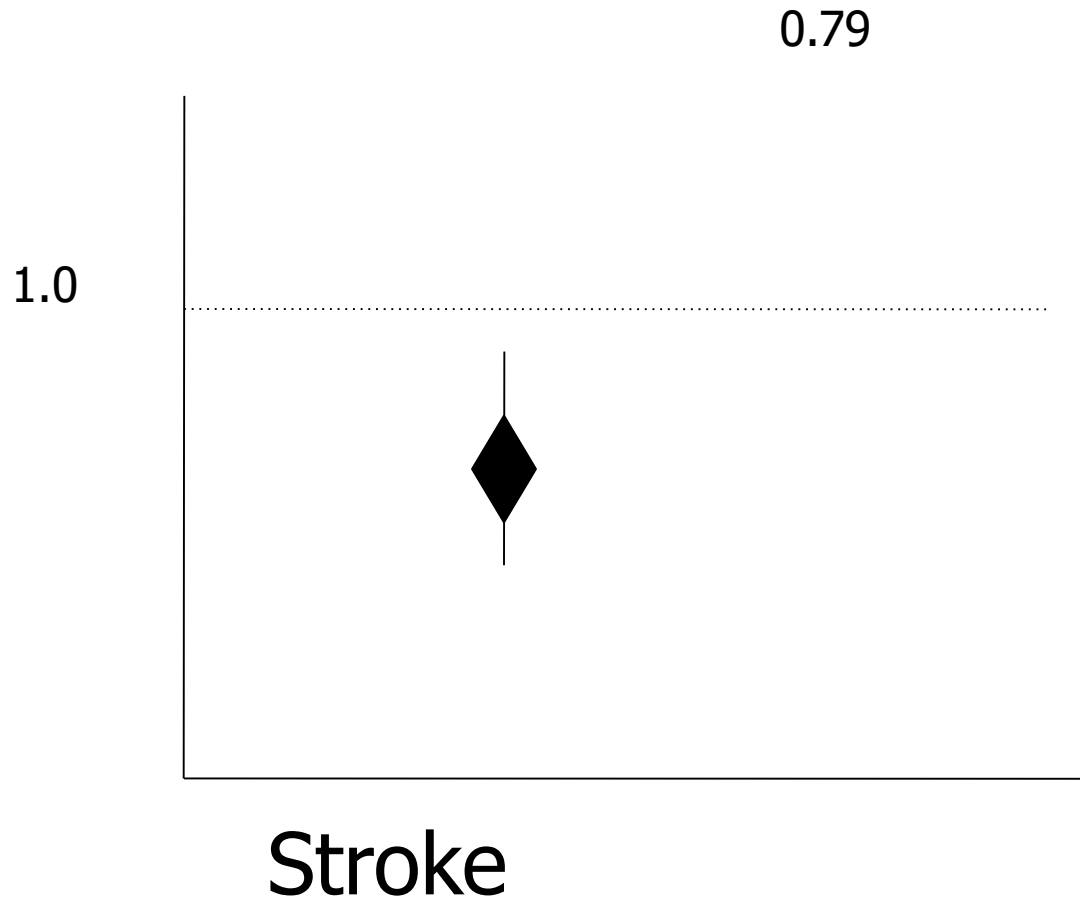
# Relative Risk of Death by:

*Elwood et al., 2008*



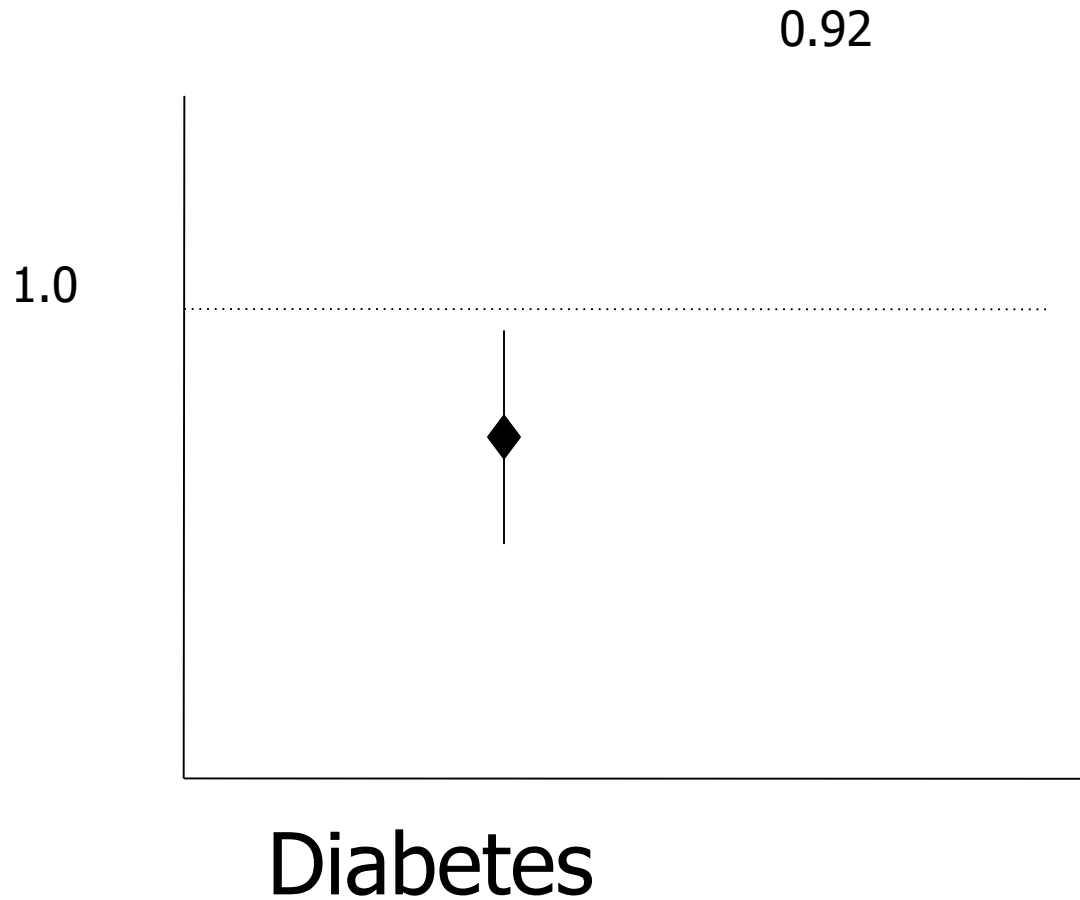
# Relative Risk of Death by:

*Elwood et al., 2008*



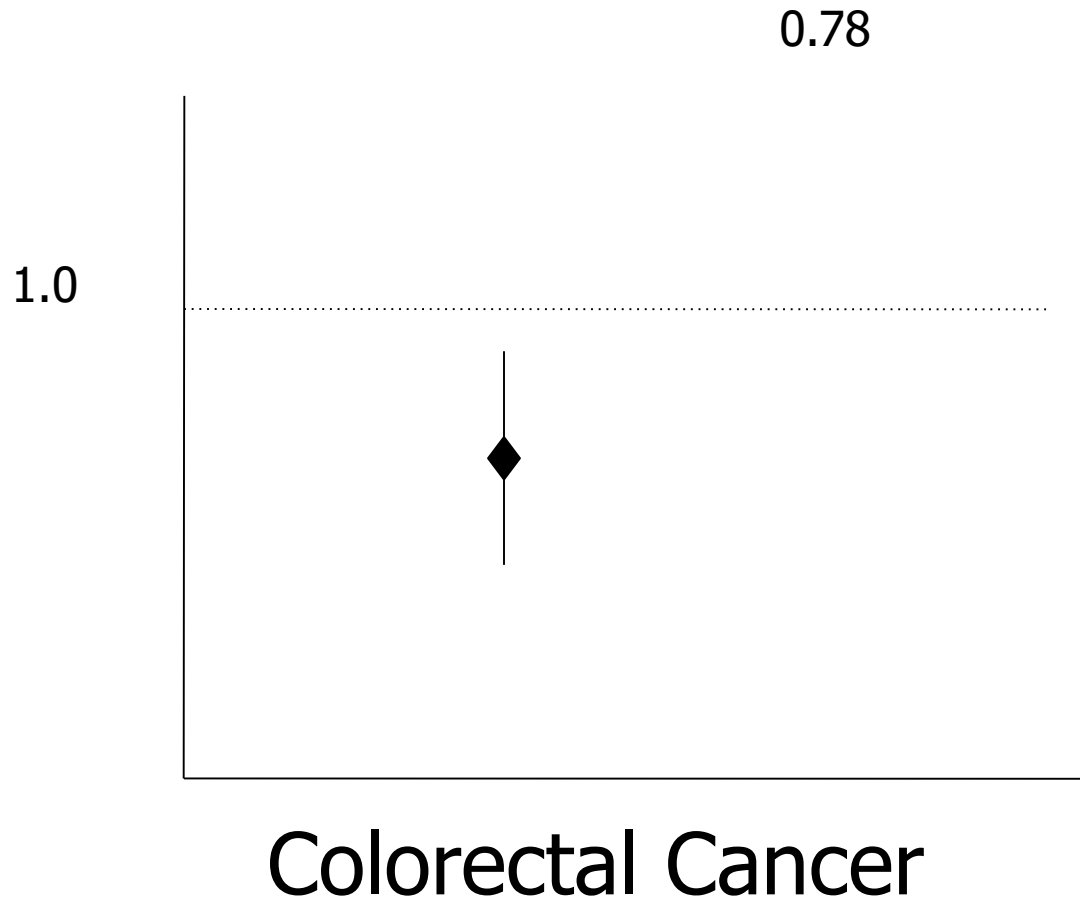
# Relative Risk of Death by:

*Elwood et al., 2008*



# Relative Risk of Death by:

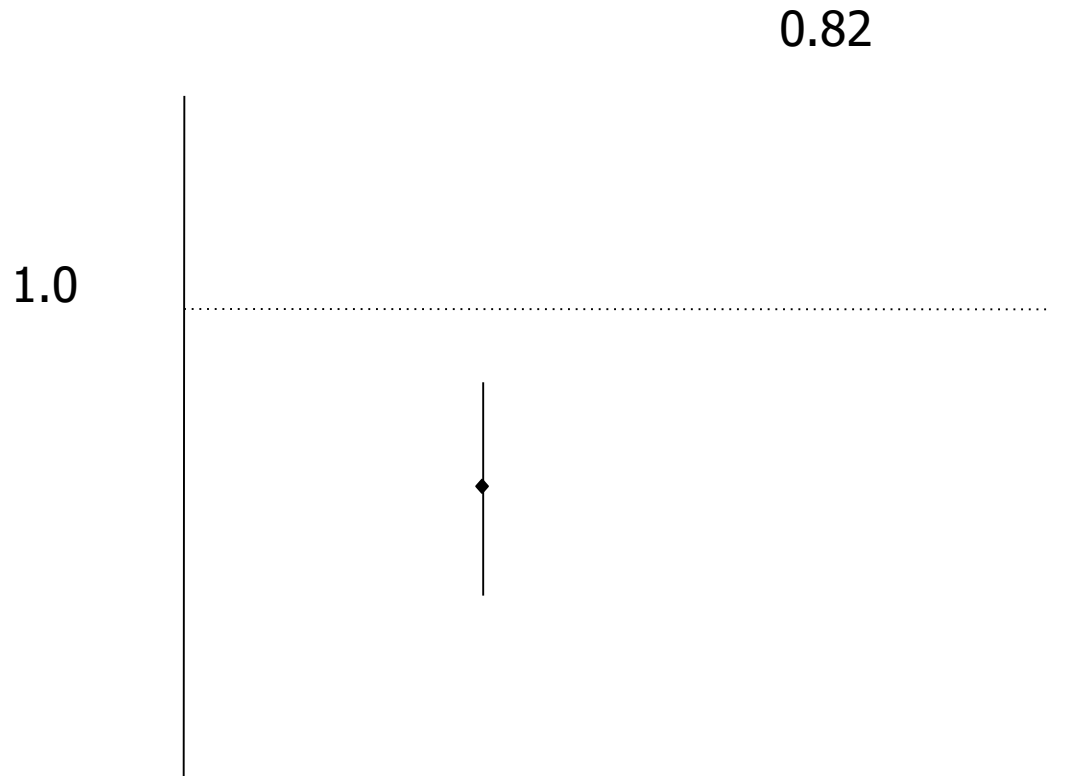
*Elwood et al., 2008*





# Relative Risk of Death by:

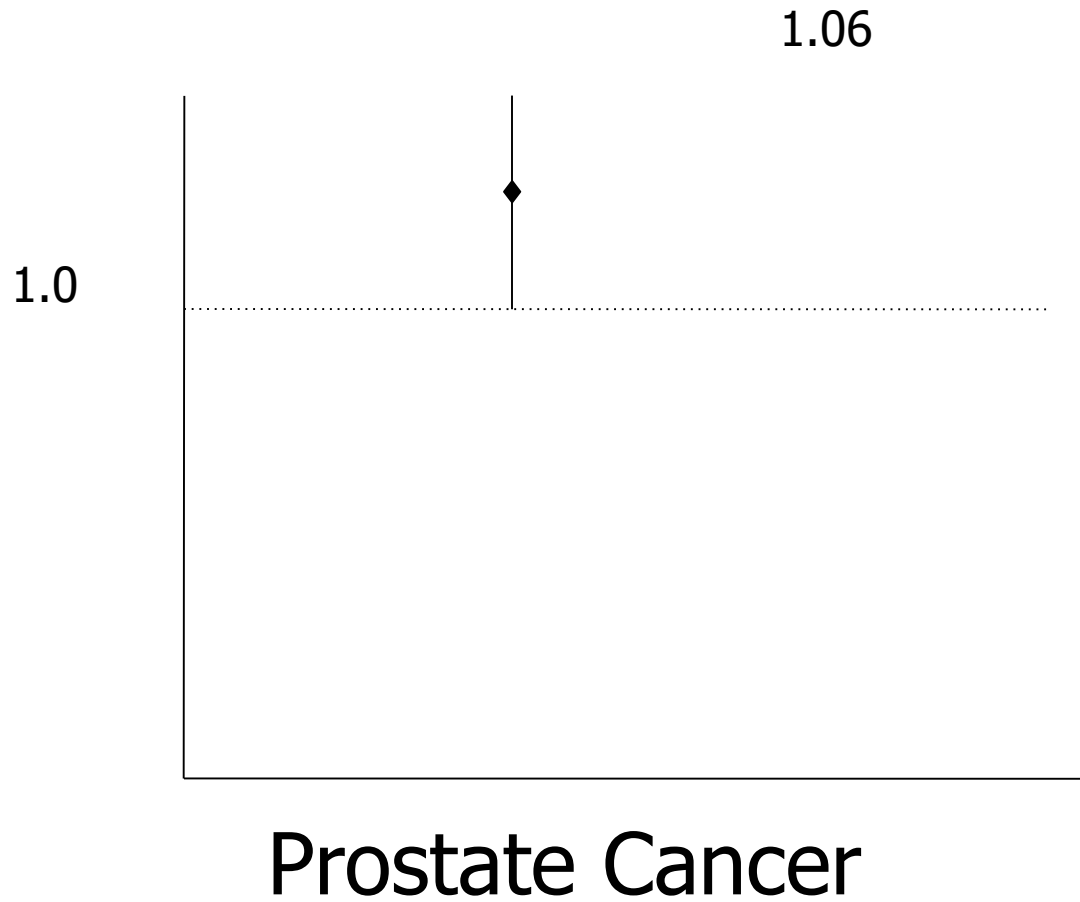
*Elwood et al., 2008*



Bladder Cancer

# Relative Risk of Death by:

*Elwood et al., 2008*



# Real Value of Milk

Individuals who drink milk throughout their lives are:

Taller

Leaner

Stronger

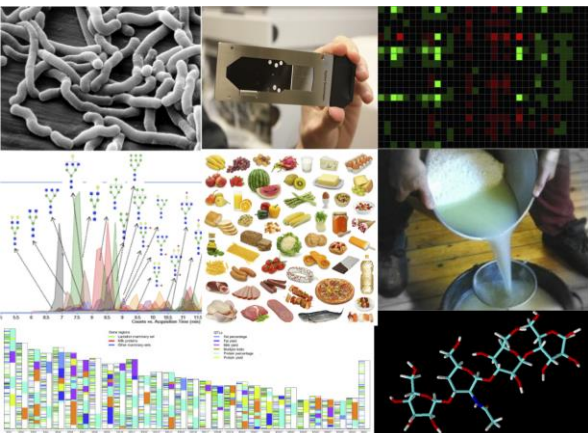
Break fewer bones at all ages

Live longer

# Foods for Health Institute

What should we eat

What should we grow



FOODS  
FOR HEALTH  
INSTITUTE

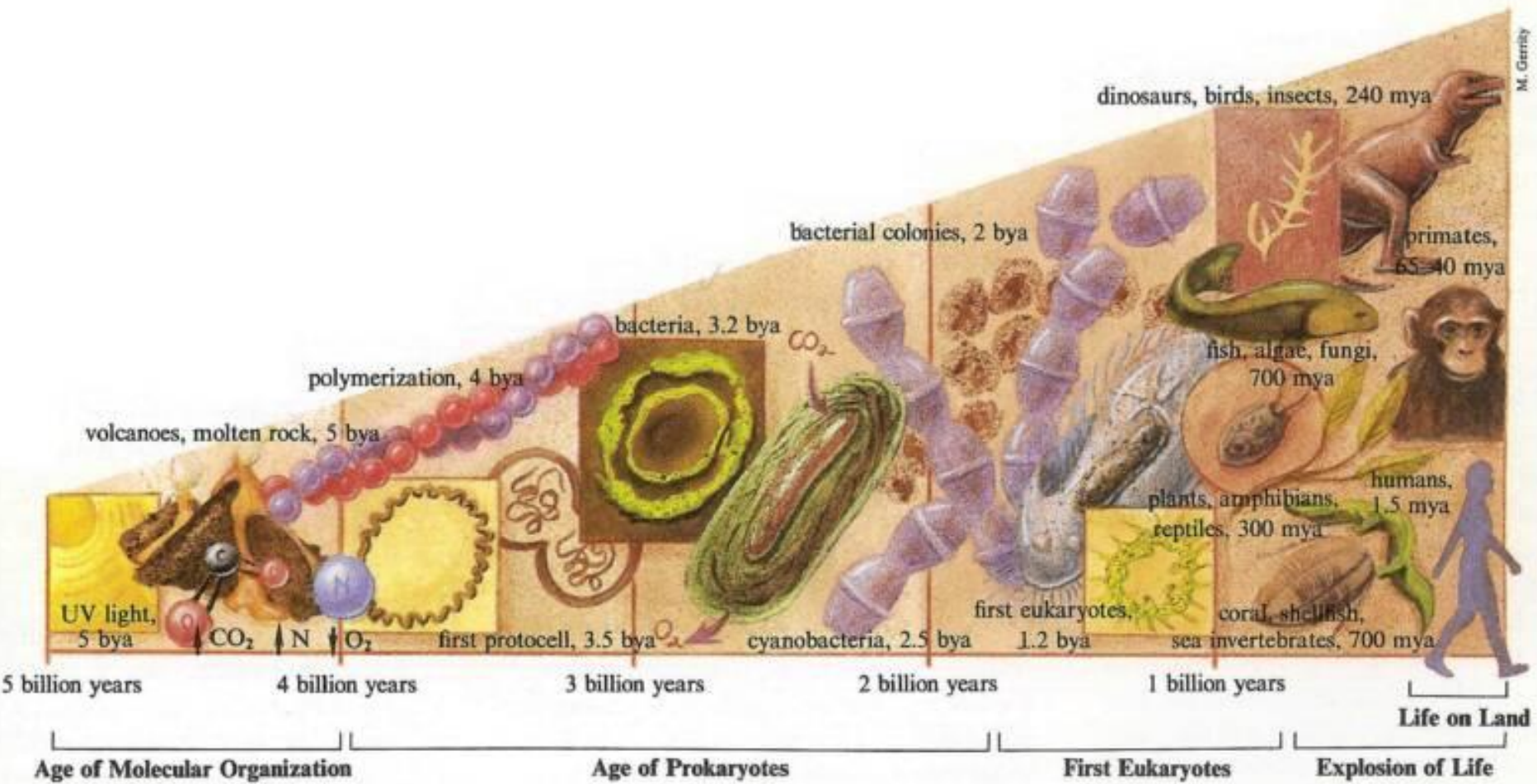
# Evolutionary Nutrition



**What evolved under the Darwinian Pressure to be Nourishing?**

# Evolution

M. Gerrity



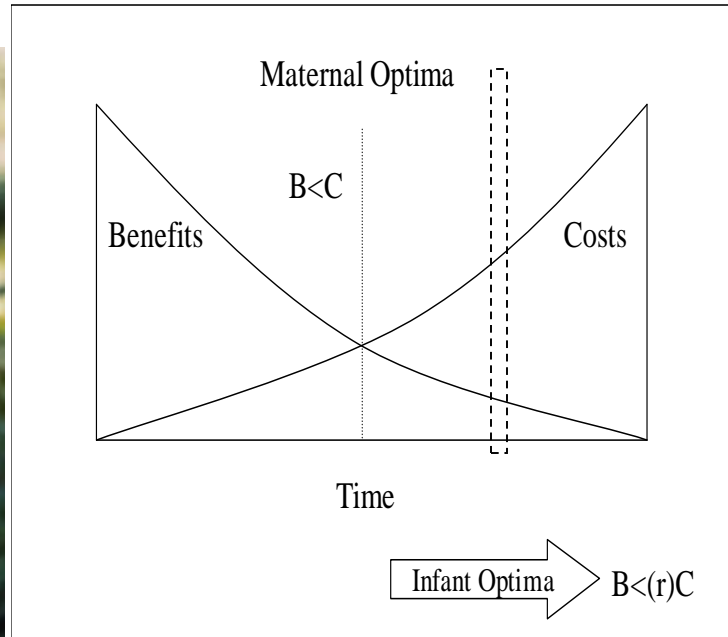
**Key**  
millions of years ago = mya  
billions of years ago = bya

# Darwin Awards: The willful removal of genetic material



# Lactation

## The Darwinian Engine of Nutrition



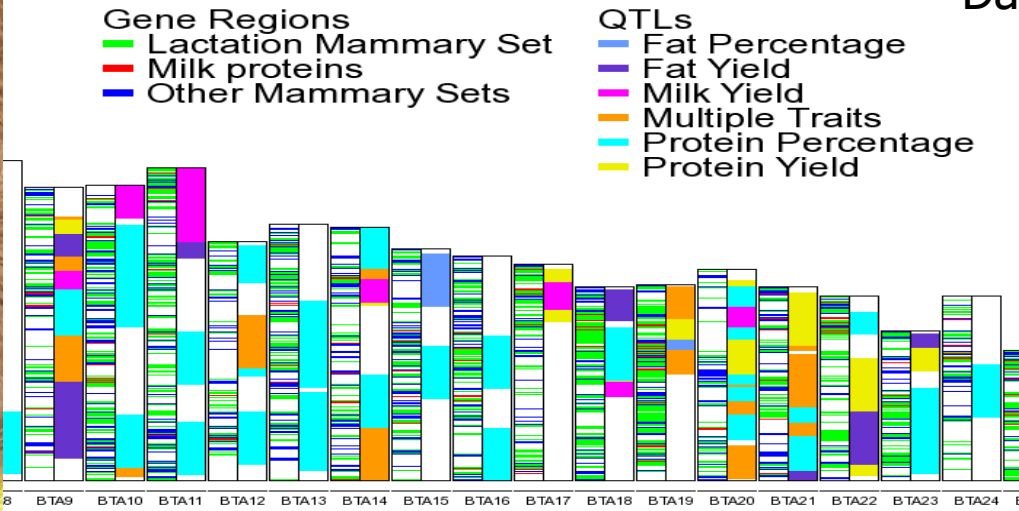
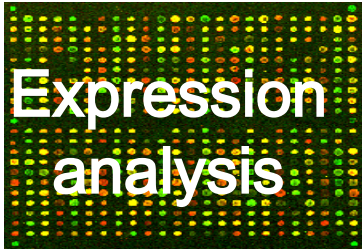
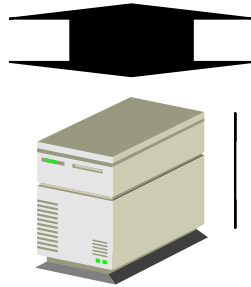
Evolutionary a cost – benefit solution for Health



# Milk Genomics Consortium

Coordinating world wide resources to assemble, annotate and validate the subset of mammalian genomes responsible for milk: The Milk Genome

Health



Danielle Lemay UCD





INTERNATIONAL  
**MILK GENOMICS**  
CONSORTIUM

A close-up photograph of a splash of white milk against a white background.

# **SPLASH!**

## **milk science update**

### **Kangaroo Tips for Human Preemies**

by [Danielle Lemay and Kevin Nicholas](#) in [SPLASH! milk science update: October 2013 issue](#)

All of the breakthroughs in milk research, summarized, interpreted and explained



# The Thematic principle

Concept: **“Evolutionary Nutrition”**

Example: milk, the Rosetta stone of nourishment



Mechanistic targets for health and prevention

▪

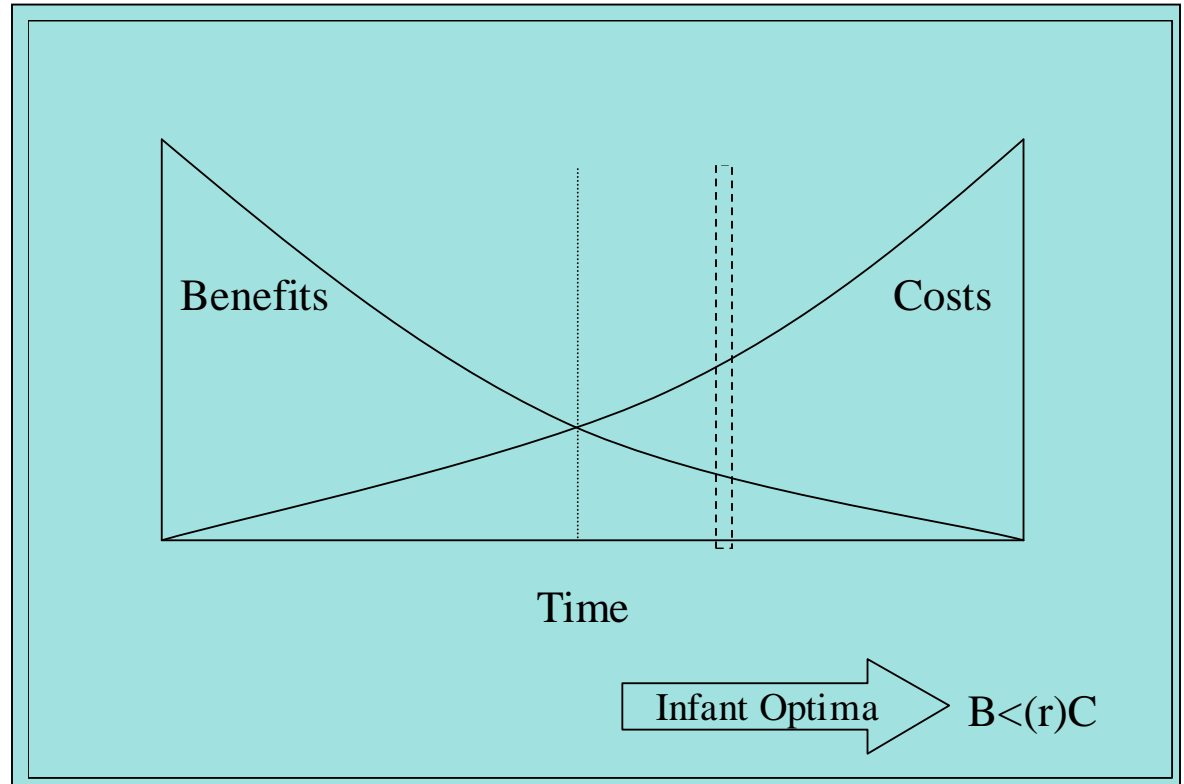
# **Proof of Principle: 1**

## **milk's view of**

### **Bacteria**

# Lactation

## The Darwinian Engine of Diet, Health & Sustainability



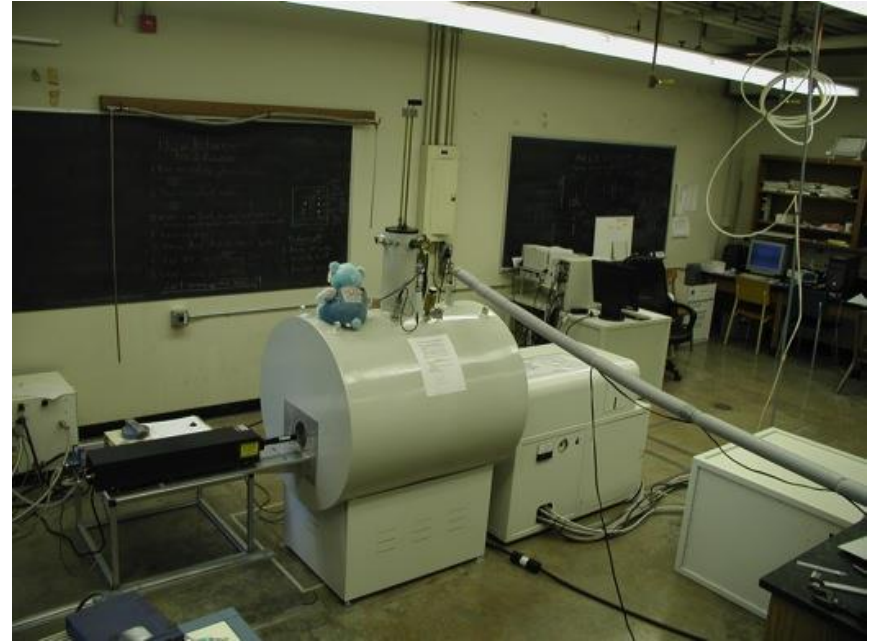
# Functions of Milk?

The 3<sup>rd</sup> most abundant class of biomolecule in human breast milk is un-digestible by humans!

- What are they?



# Milk Oligosaccharides

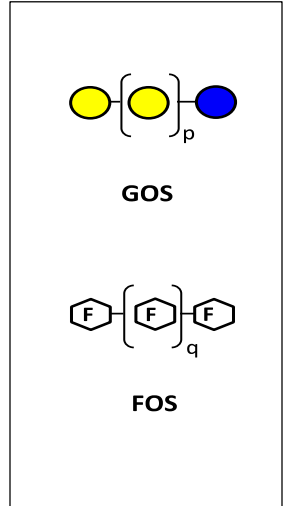
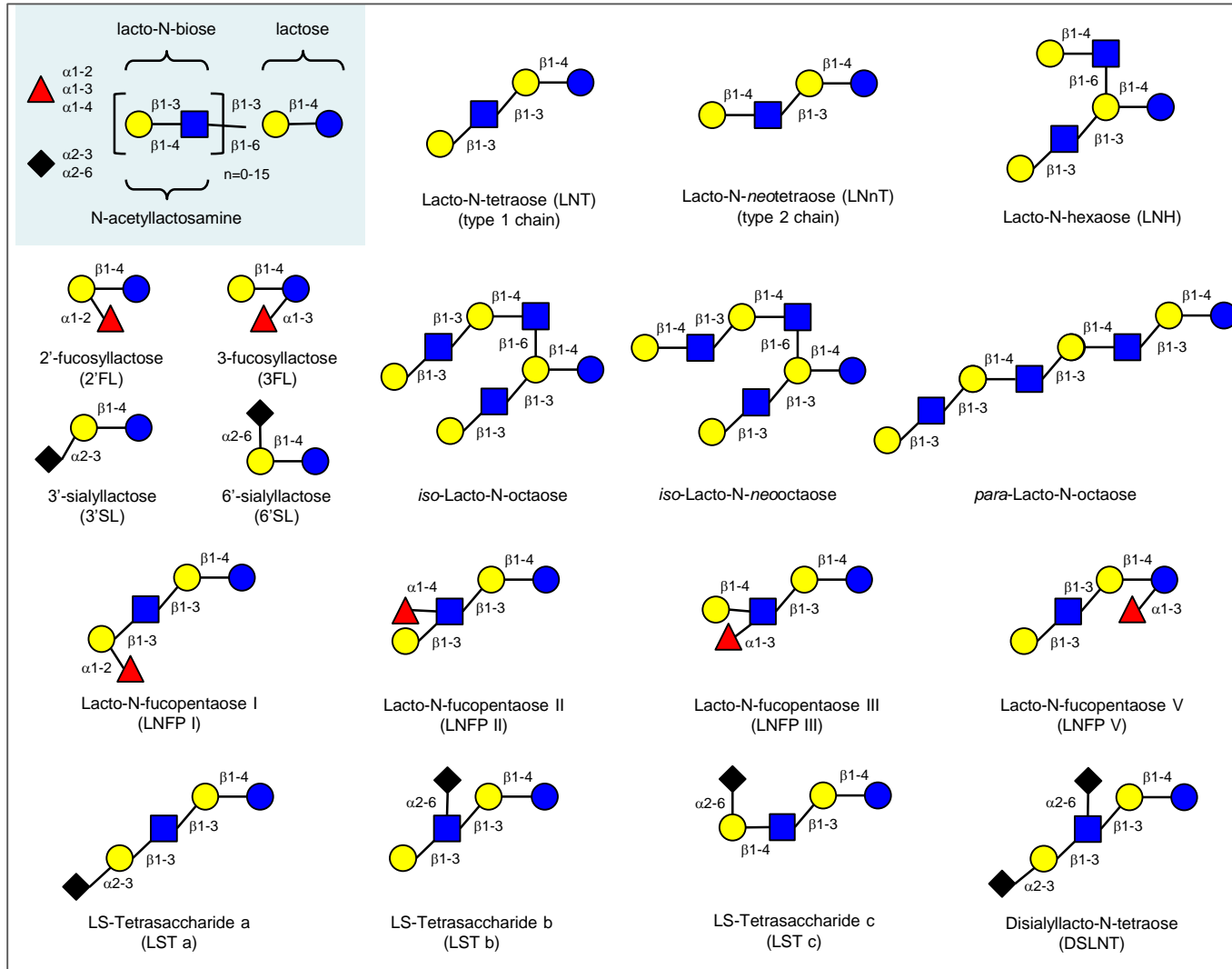


Carlito Lebrilla

- World's Leading Analytical GlycoChemist

# HMO Structural Diversity

# FOS/GOS



150 – 200 different HMO

Courtesy of Lars Bode



# Functions of Milk?

The 3<sup>rd</sup> most abundant class of biomolecule in human breast milk is un-digestible by humans!

■ Why?

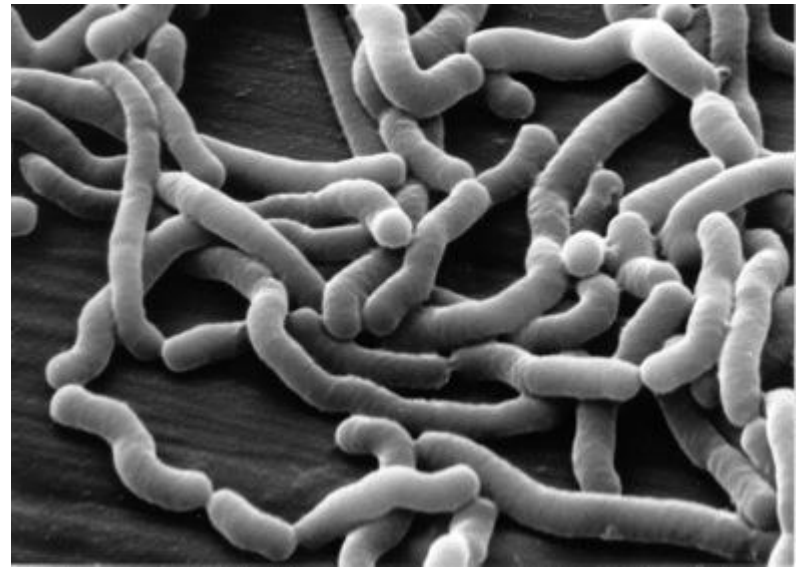
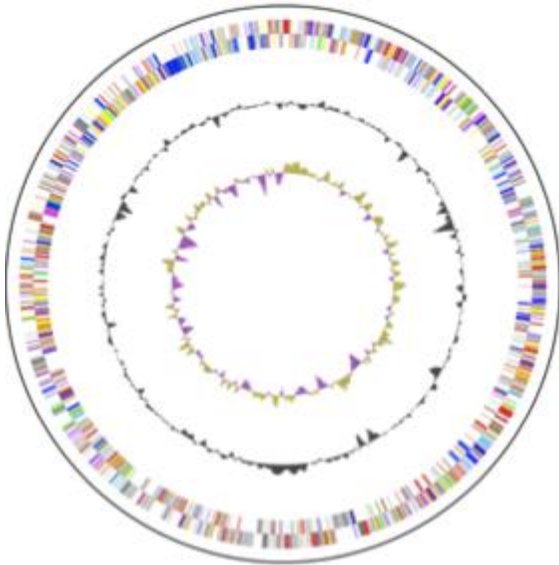


# Bacteria?

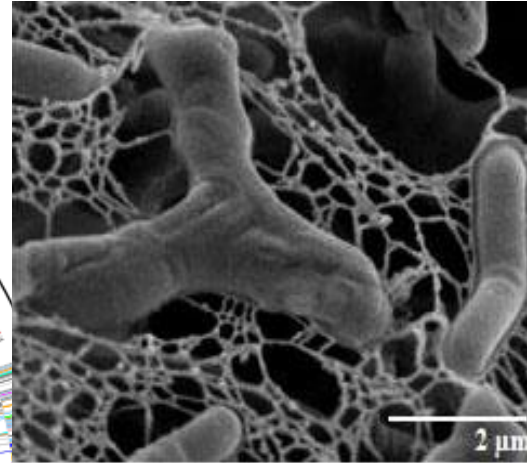


## David Mills

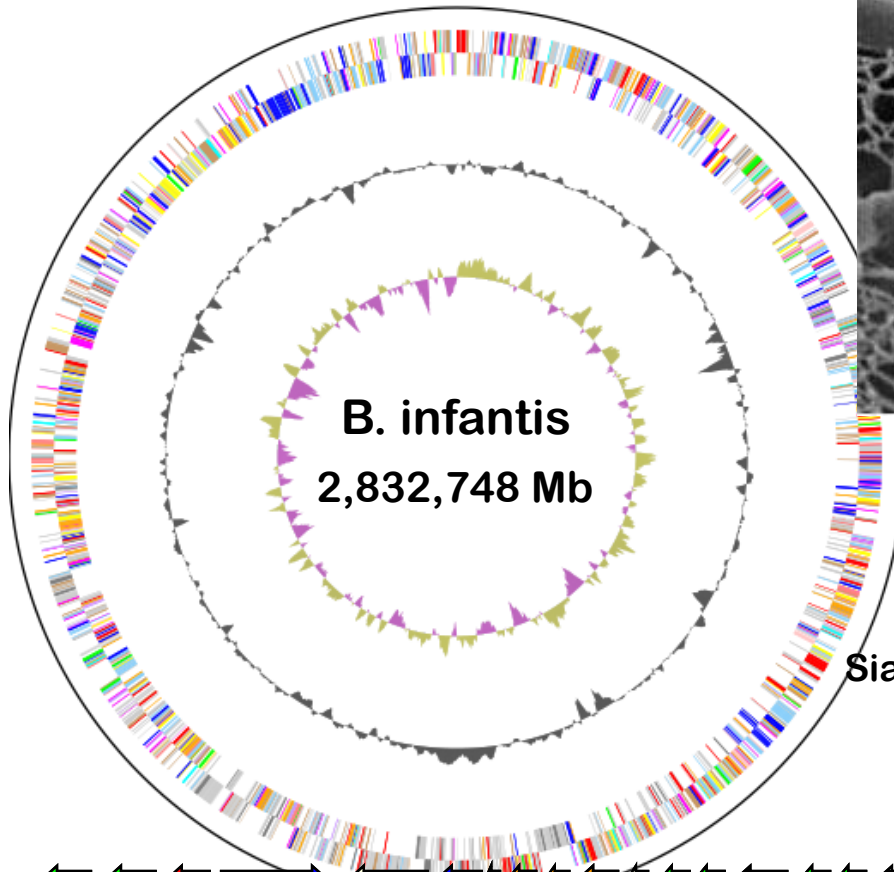
Structure, Function and Health  
Benefits of Food Borne Bacteria



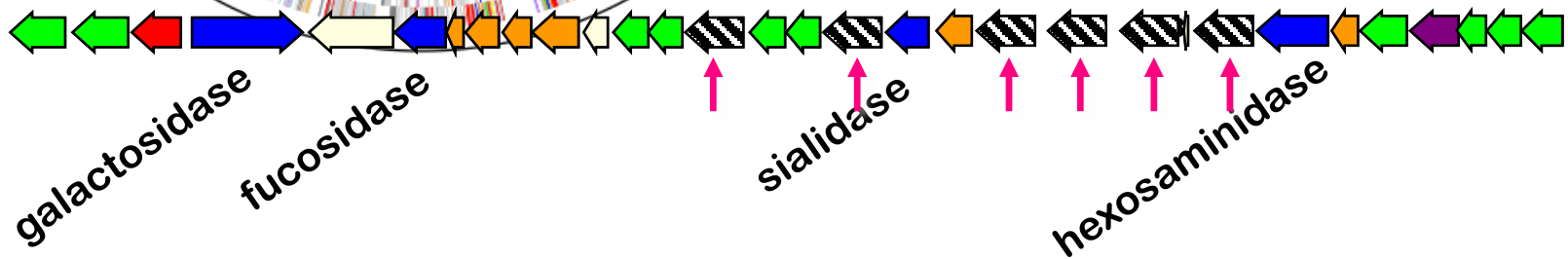
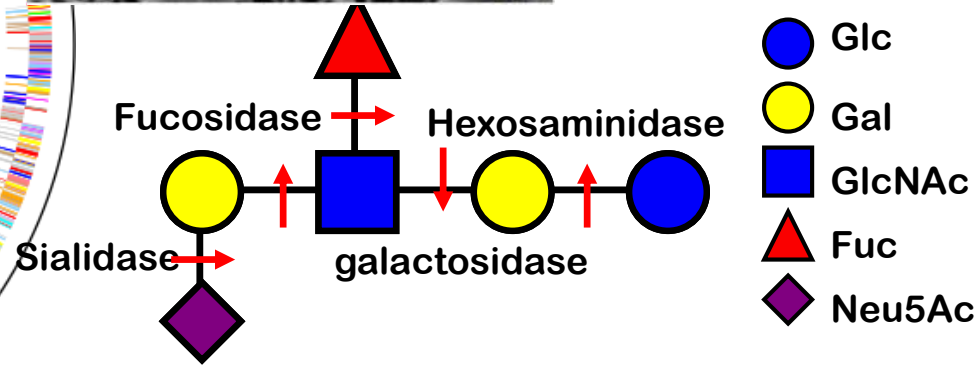
# *Bifidobacterium Infantis*



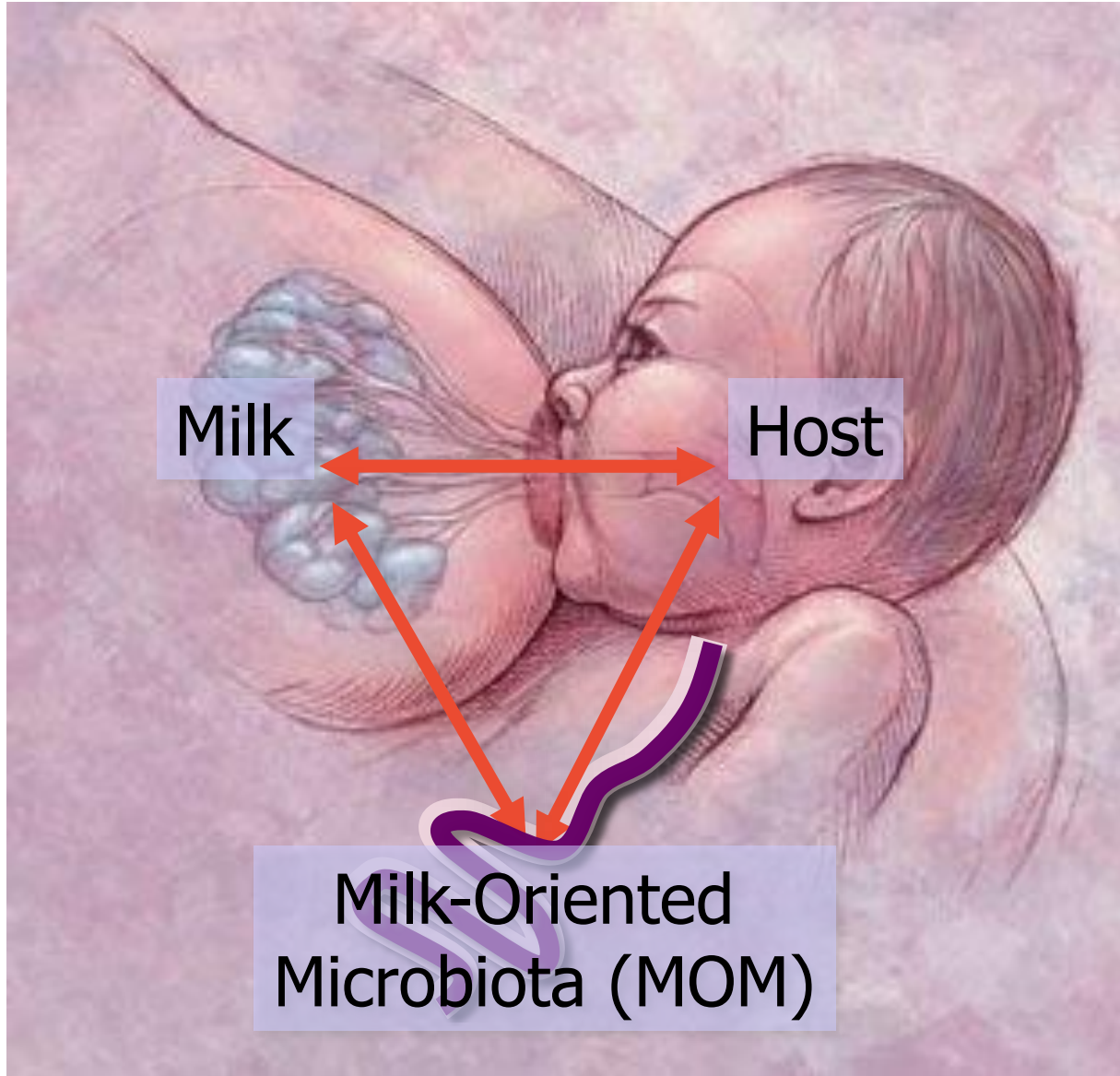
**JGI**  
DOE JOINT GENOME INSTITUTE  
US DEPARTMENT OF ENERGY  
OFFICE OF SCIENCE



**B. infantis**  
2,832,748 Mb



# Tripartite Evolutionary Relationship

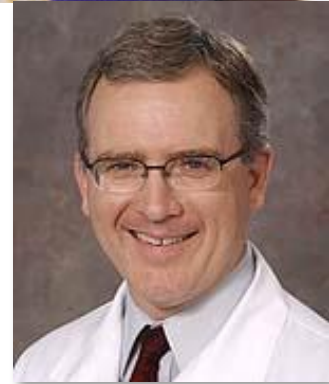


# Customers?

Premature Infants  
Necrotizing  
Enterocolitis



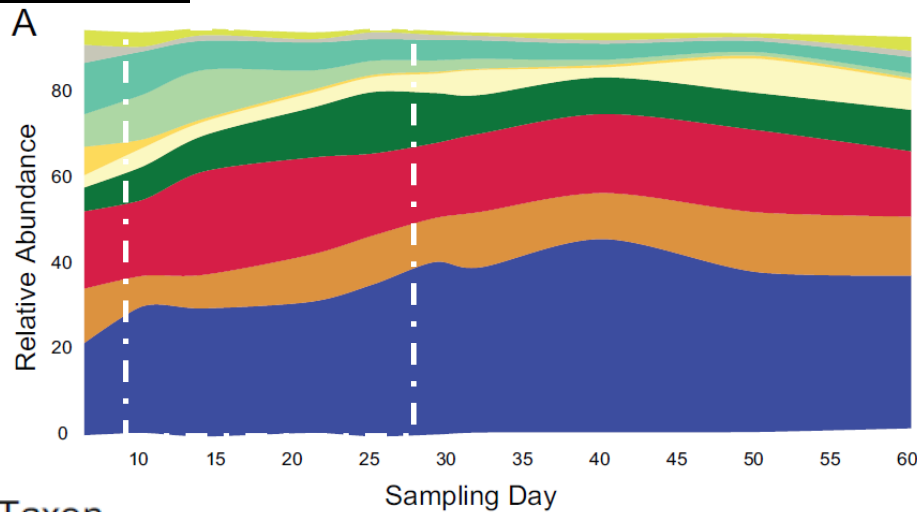
Combination of human  
milk oligosaccharides  
plus *Bifidobacterium*  
*longum* subsp. *infantis*:



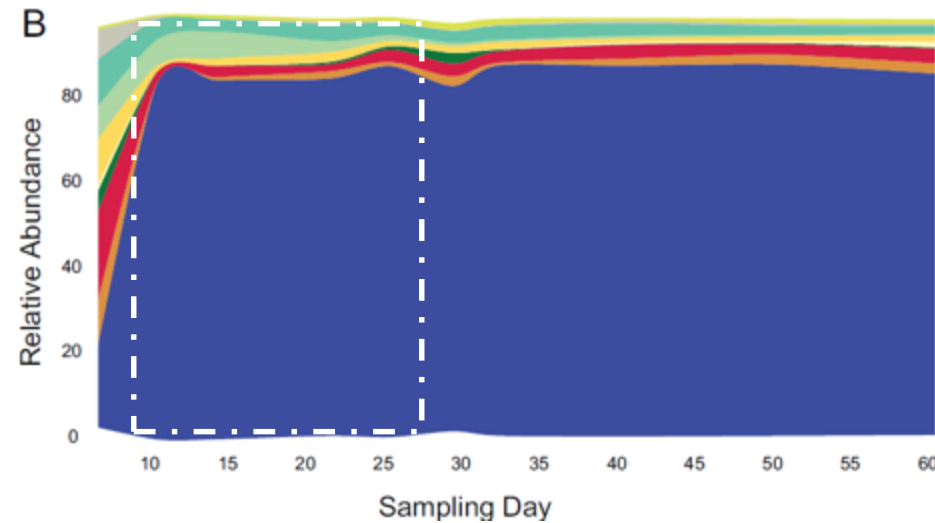
Mark Underwood

# Results: microbial colonization

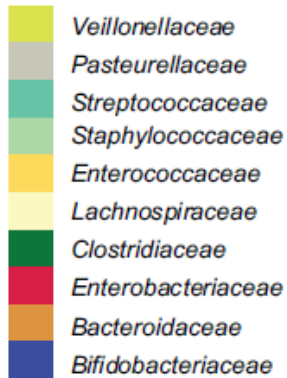
UNS



EVC001

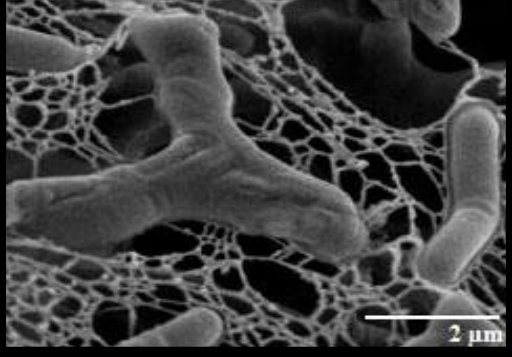


Taxon



- Restored gut microbiome
- Significantly reduced populations of Enterobacteriaceae and Clostridiaceae
- Lowered Inflammation

Dominate the microbial community in the lower intestine

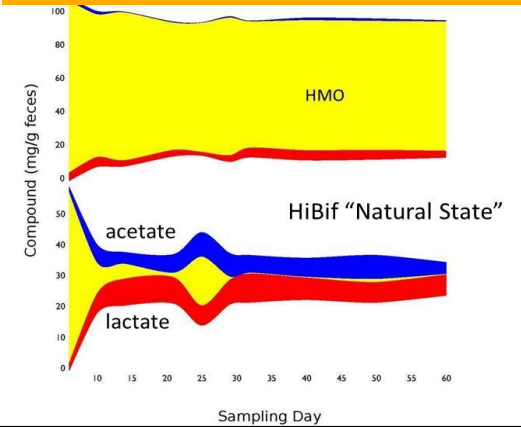


**UC DAVIS**  
FOODS FOR HEALTH INSTITUTE

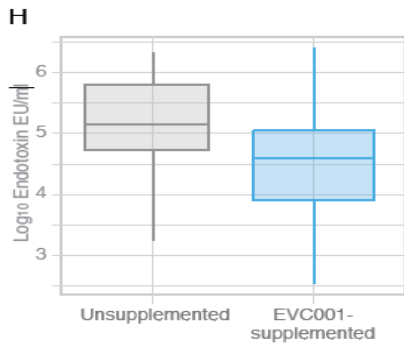
» Human Studies > Lactation Study



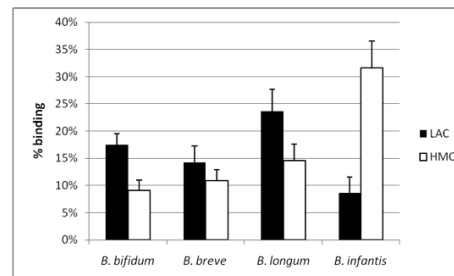
Fuel the intestine and beyond



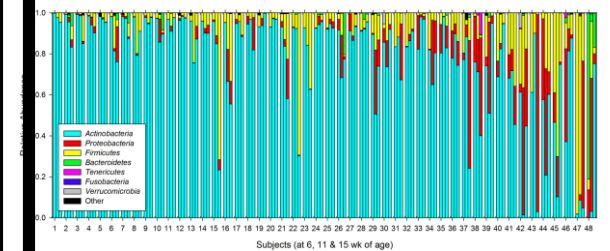
Regulate activation of innate Immunity



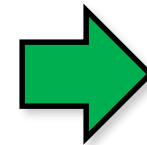
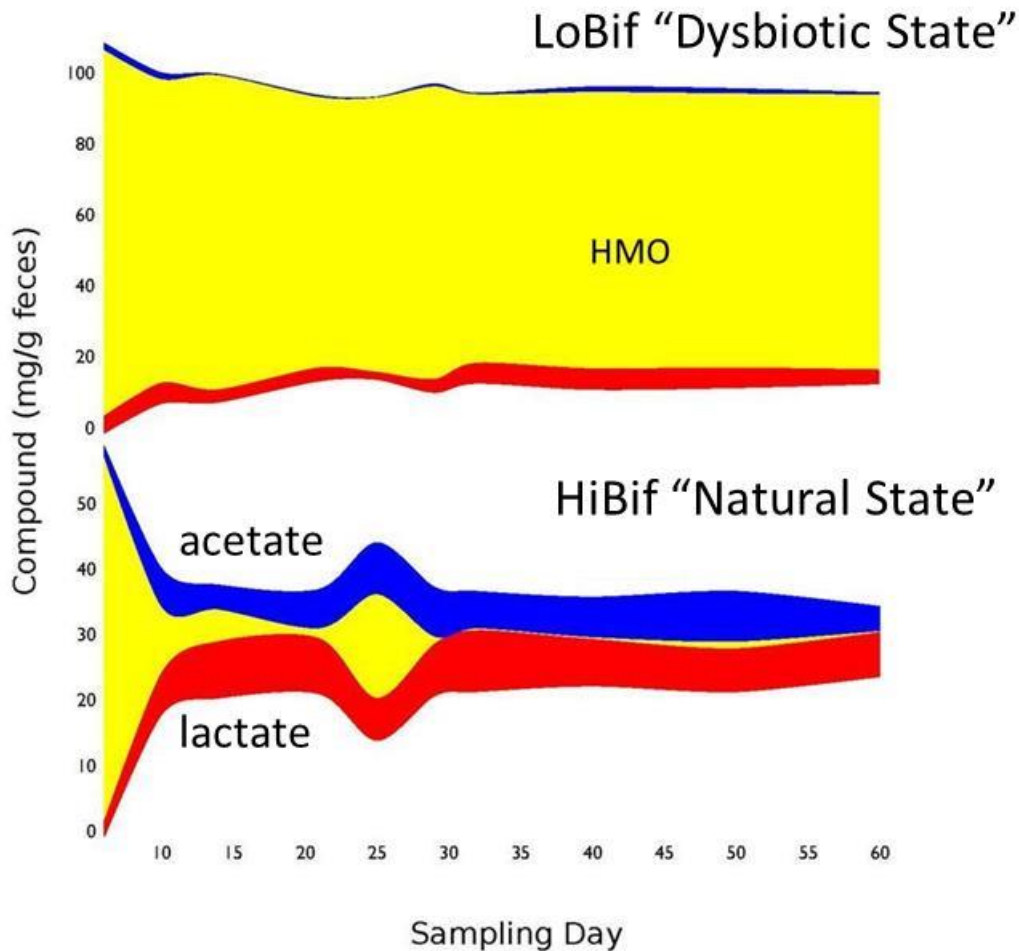
Guide the development of Intestinal barrier Functions



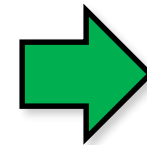
Educate and guide acquired immunity



# Hi-Bif babies: a different “colonic terroir”



pH = 6.0  
Stools: 33% watery  
Frequency: 4.0/d



pH = 4.5  
Stools: 20% watery  
Frequency: 1.8/d



# Mammals have embraced bacterial transfer



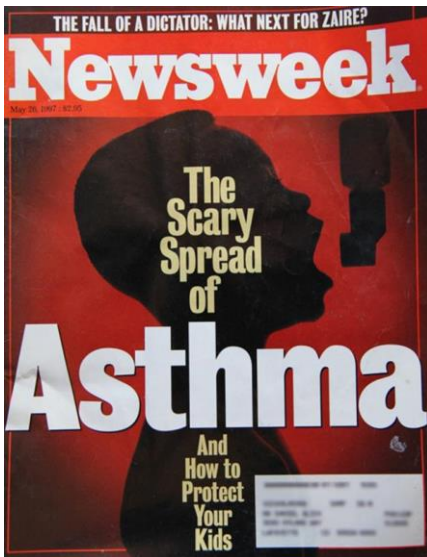
# Modern Life has stopped microbial transfer



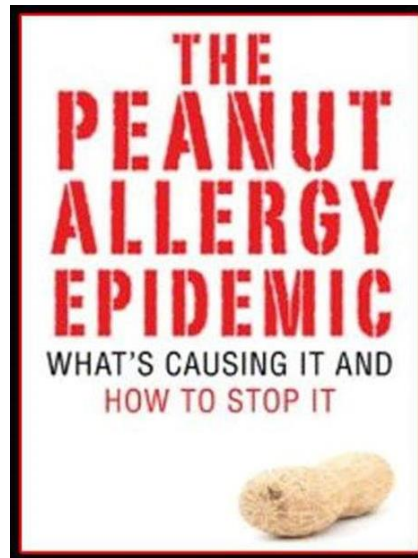
SHIT!



# Something you already know



5x



4x



5x



Tim Brown CEO

Establishing, restoring,  
and maintaining  
a healthy human  
gut microbiome

# Evivo



Hey, baby!  
Evivo was made just for you.

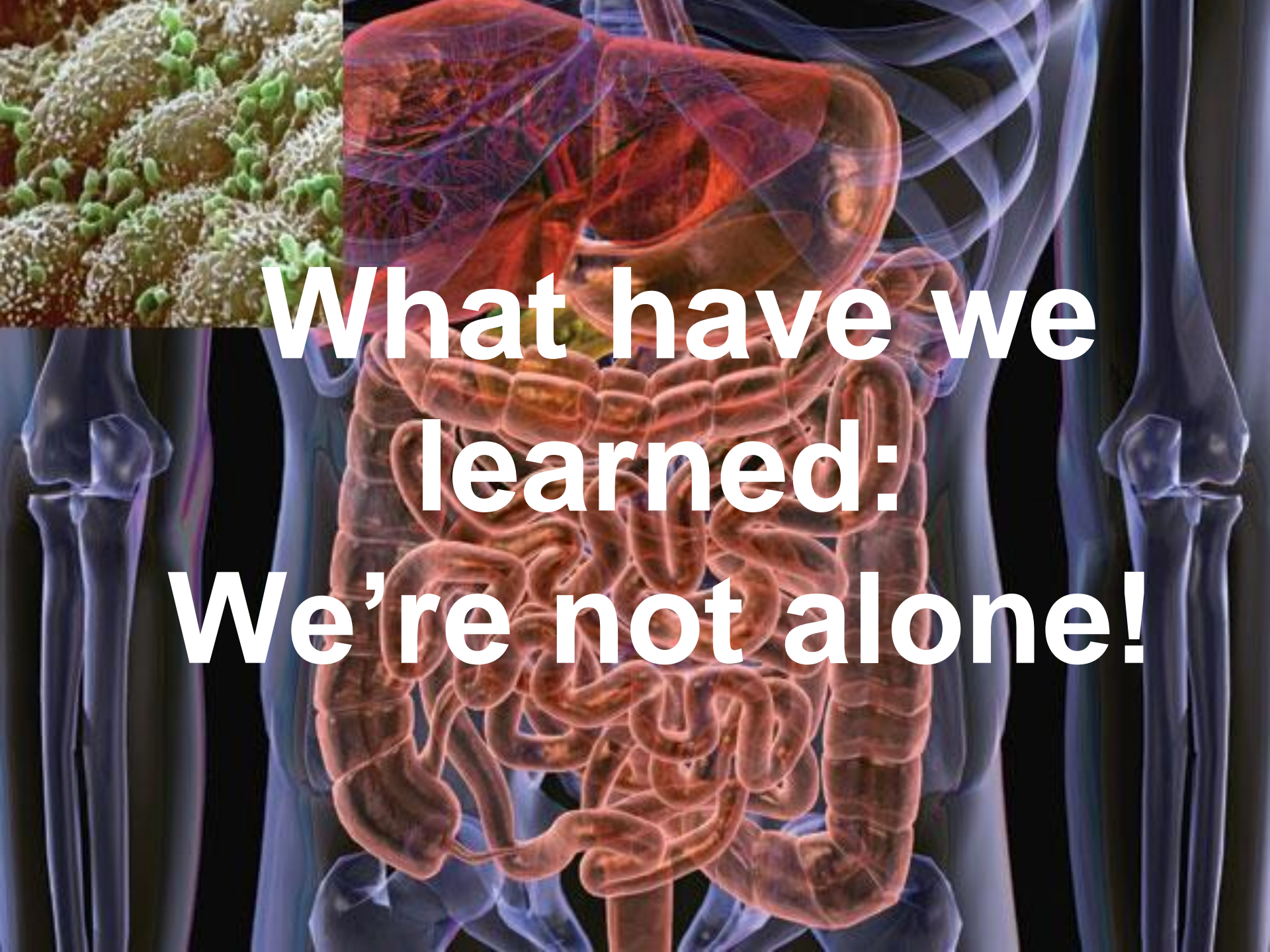
Introducing Evivo. The first and only baby probiotic of its kind. Evivo contains the good bacteria *B. infantis*, which fully utilizes breast milk to protect baby's gut from potentially harmful bacteria linked to higher risk of colic, eczema, allergies, diabetes, and obesity.



Save \$10 on any Starter Kit 2+ Mo

EVIVO™



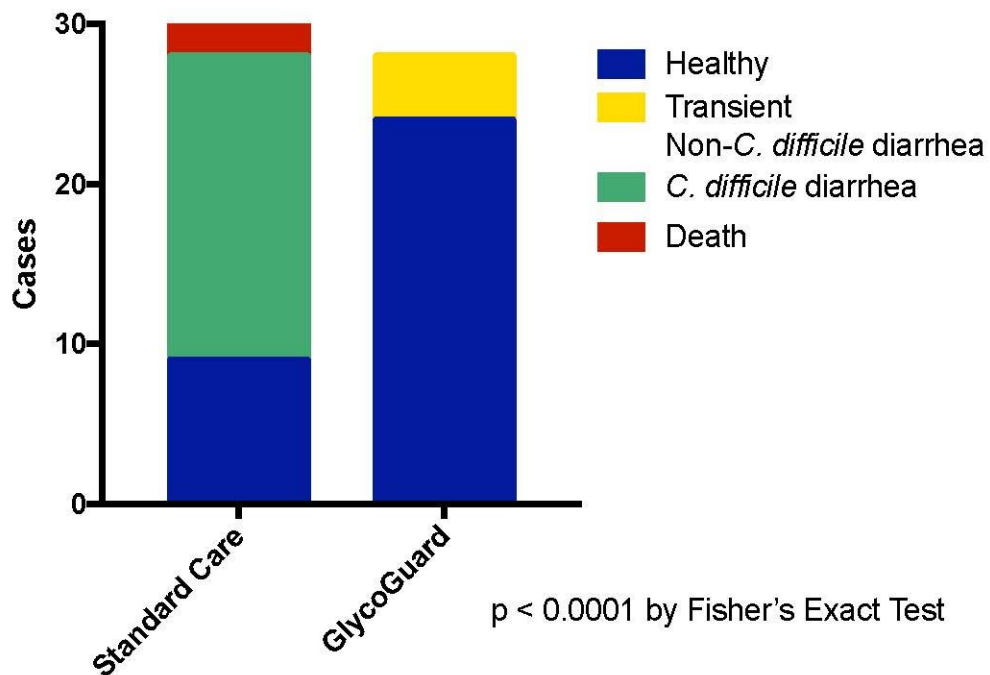


**What have we  
learned:  
We're not alone!**

# Gut Health Across Mammalian Species



GlycoGuard Reduces *Clostridium difficile* Diarrhea in Nursing Foals



GlycoGuard to be launched at AAEP Dec 3-7 Orlando

Confidential



# **Not only Babies**

**By understanding the  
mechanisms of milk we gain  
a detailed understanding of  
diet and health for  
EVERYONE**

# Opportunity: **BioProfessionals**

## Our minions!



## Need Food!



## Business Opportunities

# UCD Milk Processing



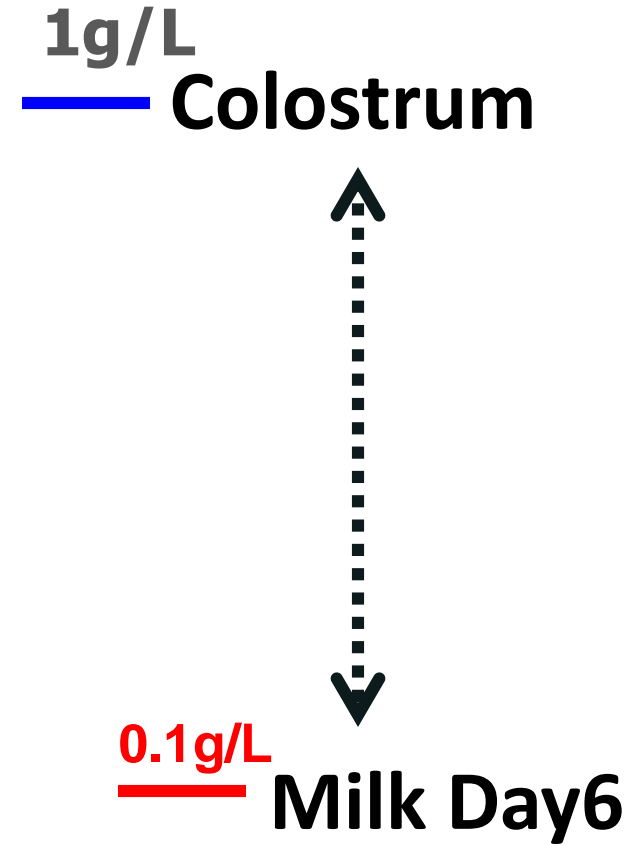
Daniela Barile  
Asst Prof FST



- Pilot-scale filtration from MMS AG Systems
- Fourier Transform Advanced IR MilkoScope
- Speed vacuum MiVac Quattro Concentrator
- Industrial freeze dryer

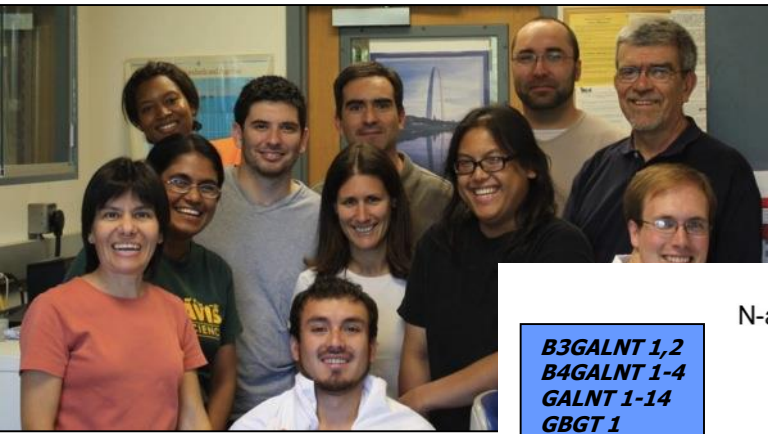


# Bovine milk oligosaccharides

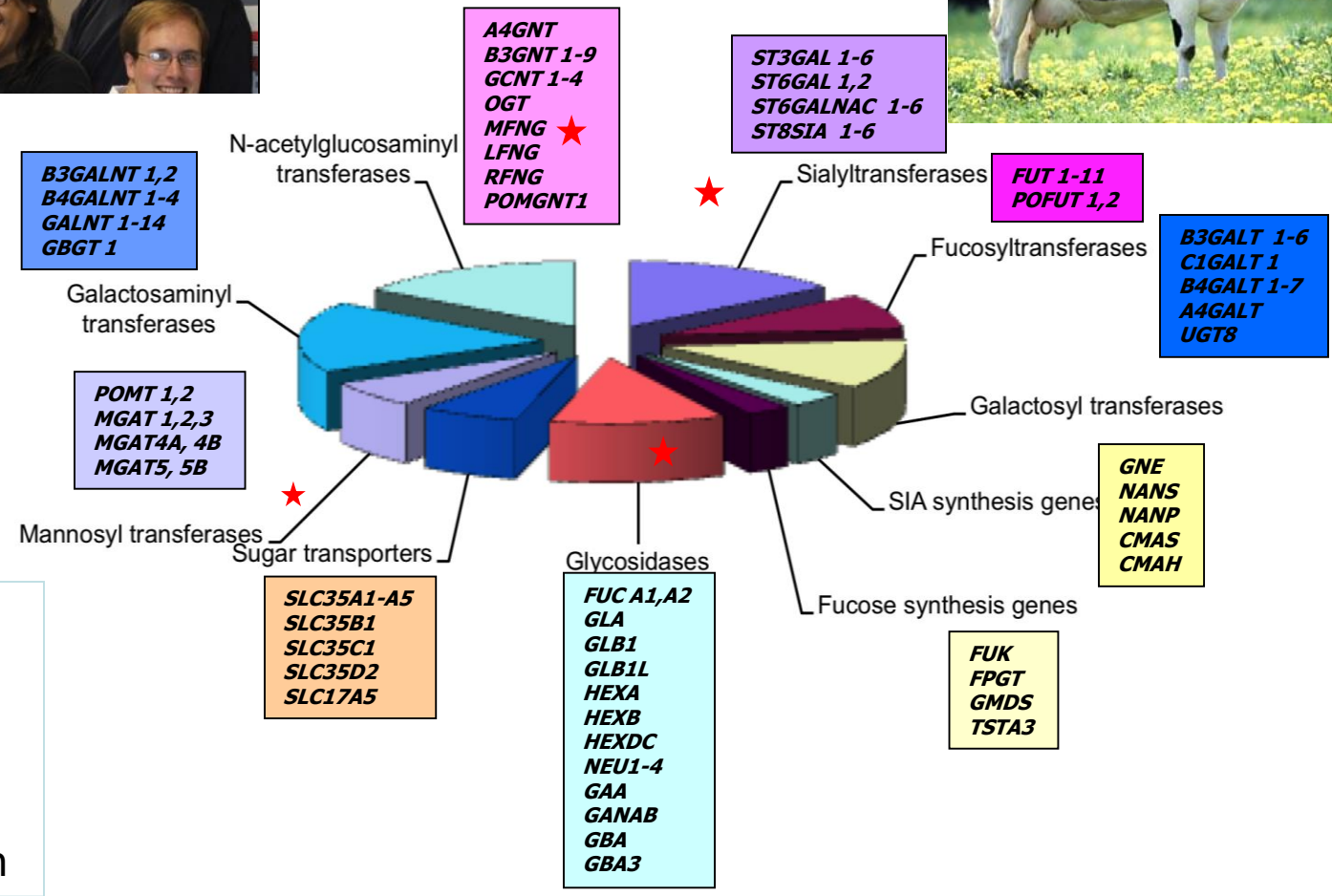


Retention Time (min)

# Oligosaccharide Biology in Bovine



Medrano Lab



SNP in coding regions  
 ↓  
 Genotyping array  
 ↓  
 Association study in 500 cows

# Opportunity: 'Bugs' of Health

Personal microbiome management:  
premature infants to weaning  
from athletes to hospitals



# Opportunity: 'Bugs' of Delight

From chocolate to coffee, wine to beer, yogurt to cheese, bread



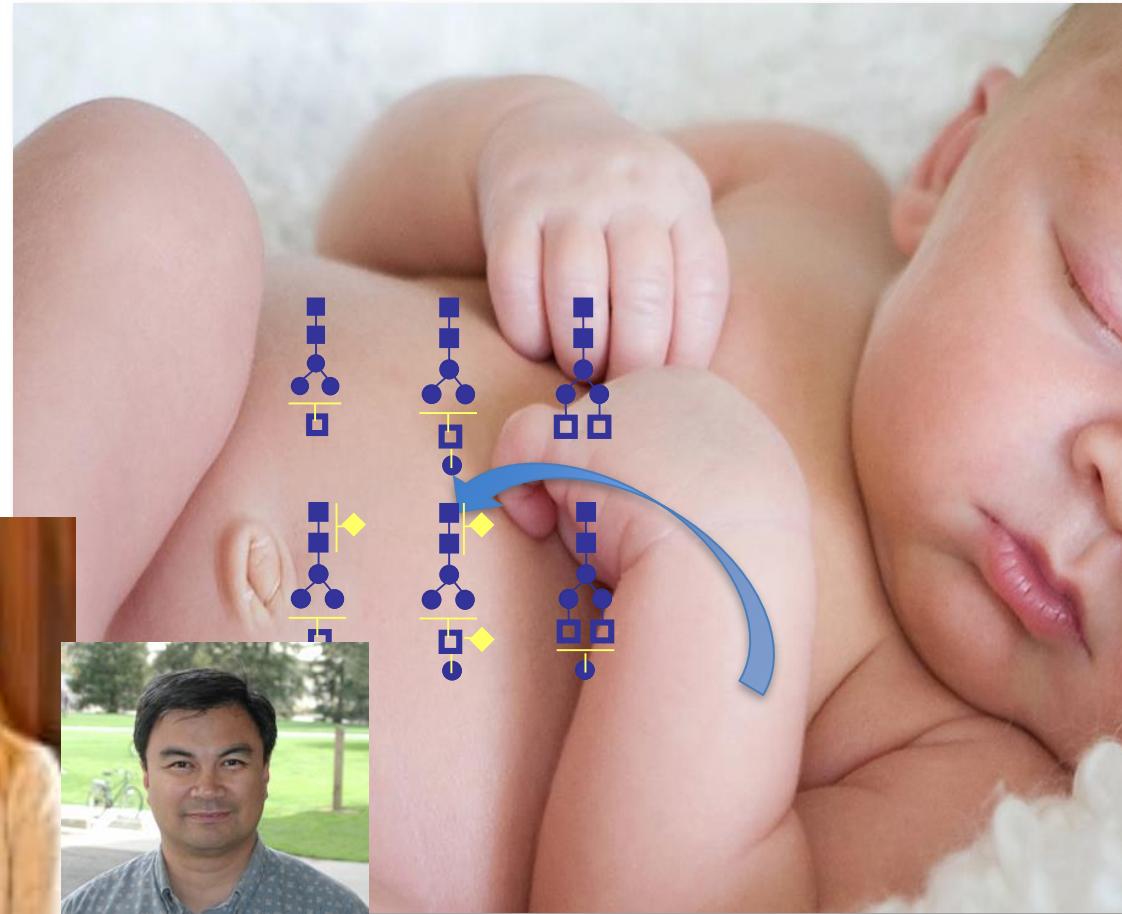
# **Proof of Principle: 2 milk's view of protein**





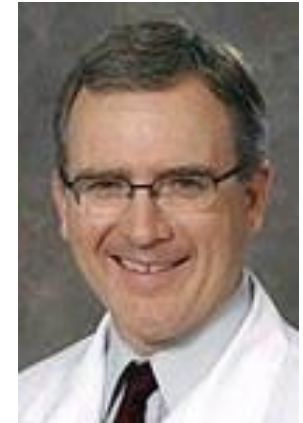
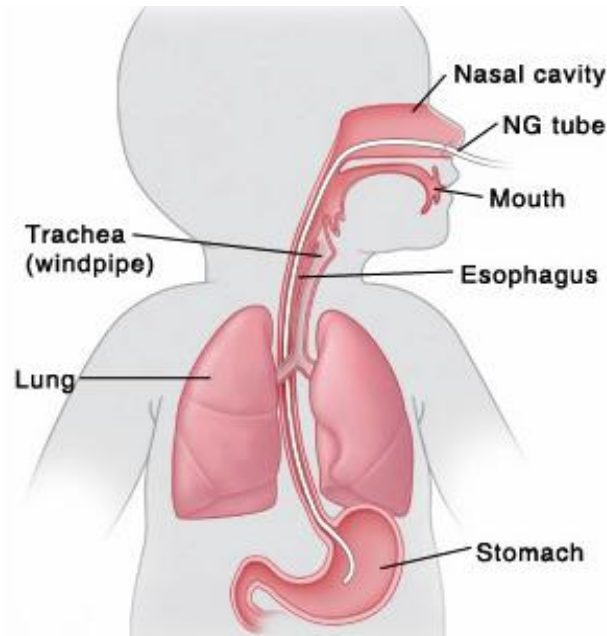
# Infant Digestomics

## Infant Digestion as a Bioreactor



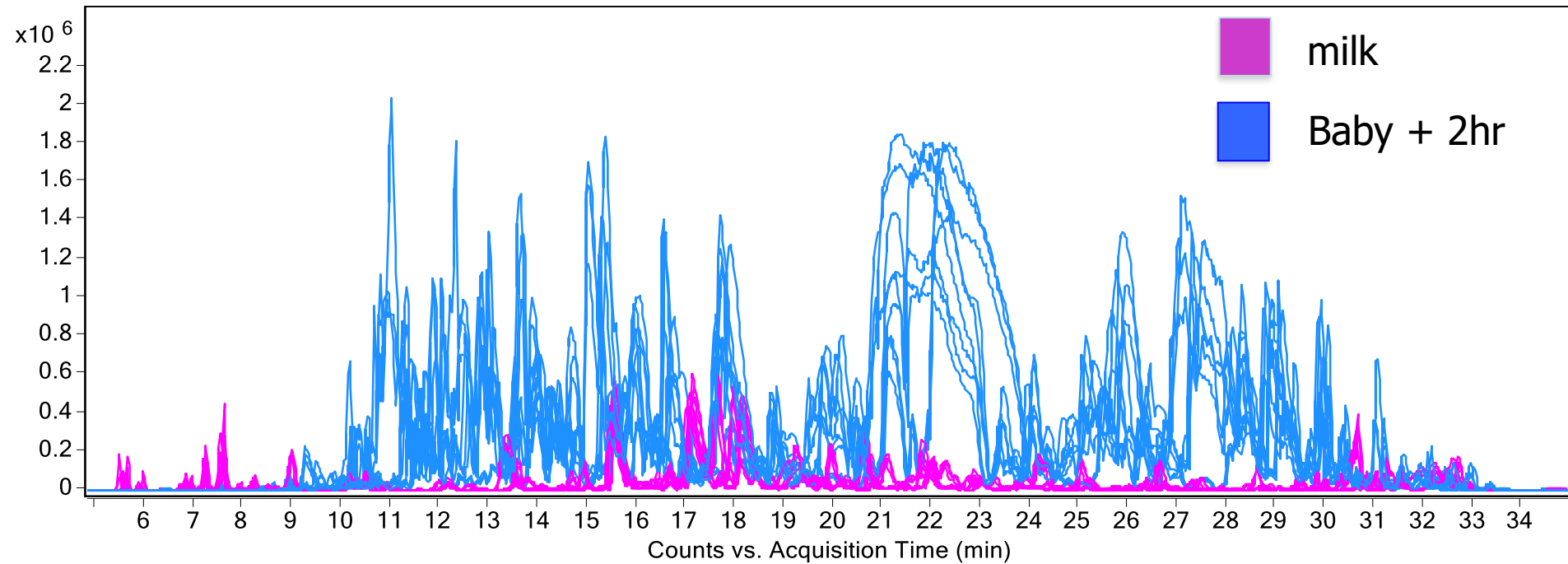
# Sample collection

- Neonatal Infant Care Unit
- Feed milk
- Gastric drop (after 2 h digestion) via feeding tubes



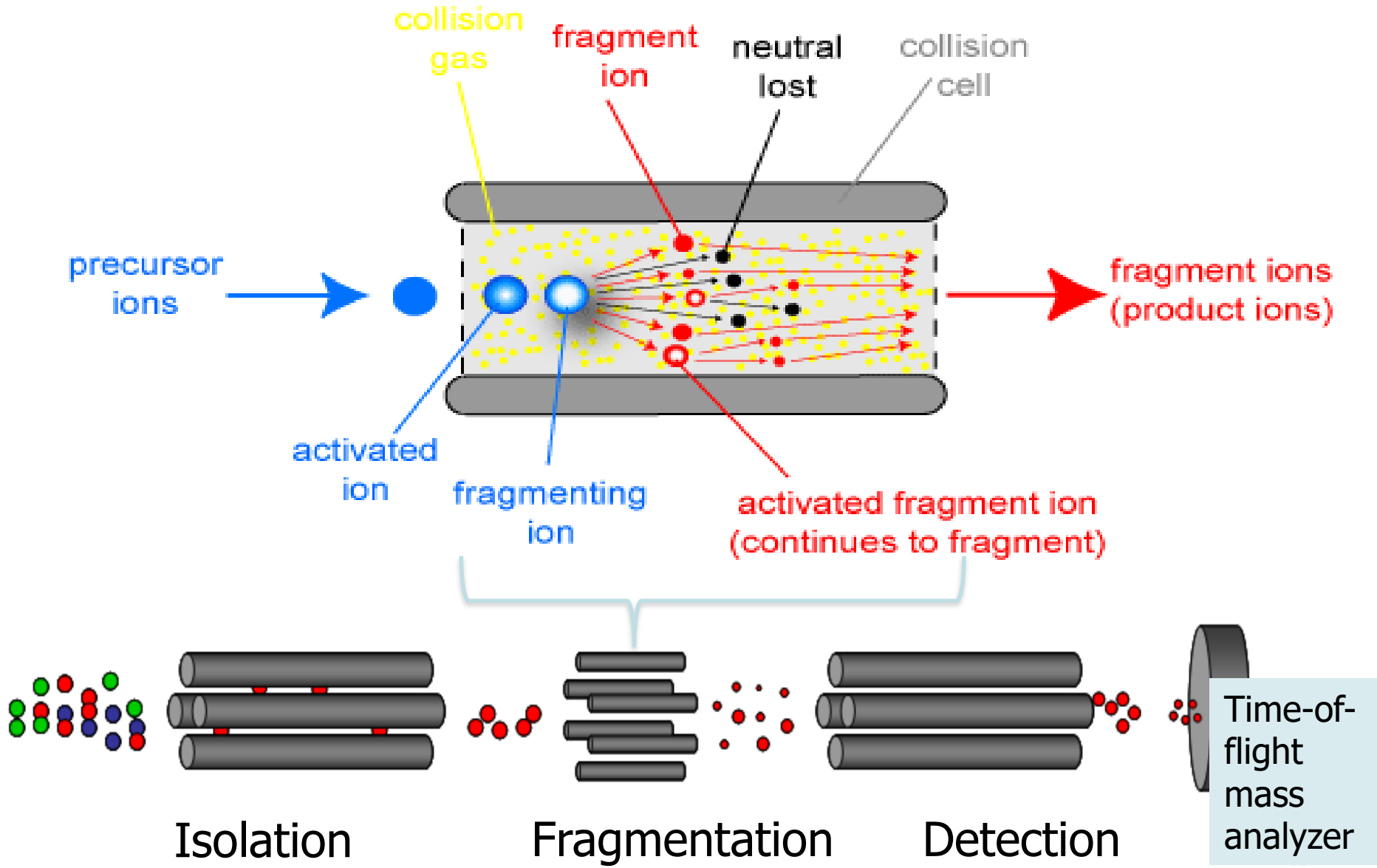
Dr. Mark Underwood  
UC Davis Medical  
School  
Department of  
Pediatrics

# Peptides in the stomachs of babies



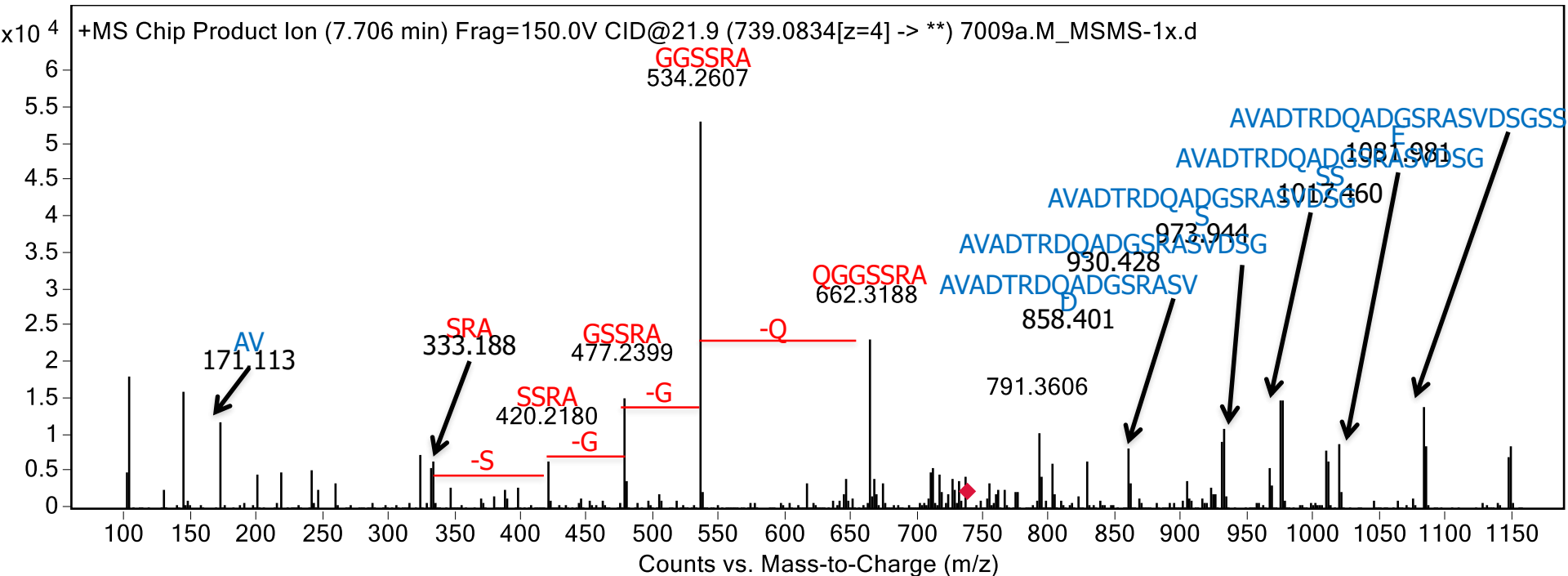
(Dallas et al., 2014, JN)

# What are the peptides? Ask Carlito!



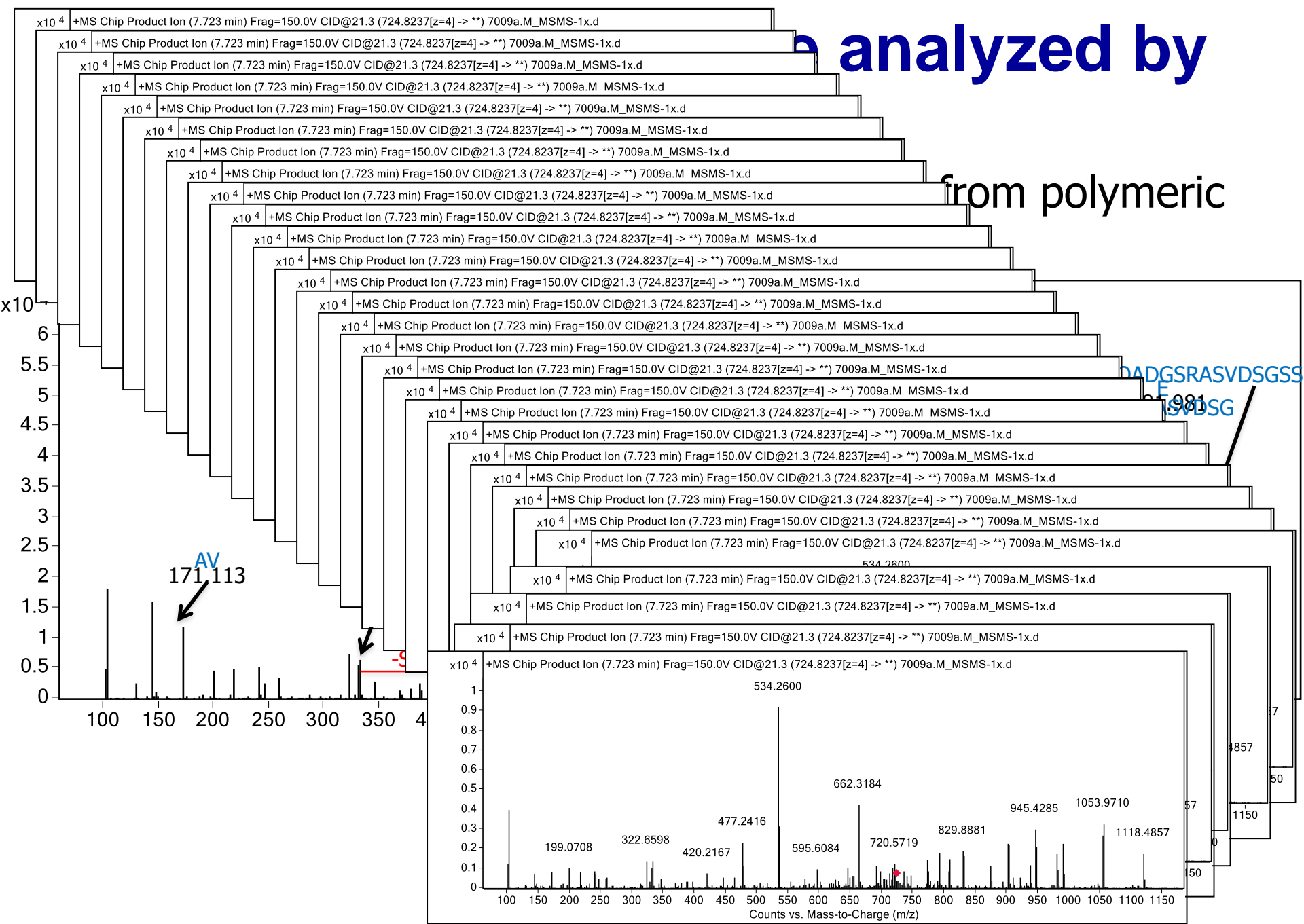
# Tandem spectra can be analyzed by hand.

AVADTRDQADGSRASVDSGSSEEQGGSSRA from polymeric immunoglobulin receptor

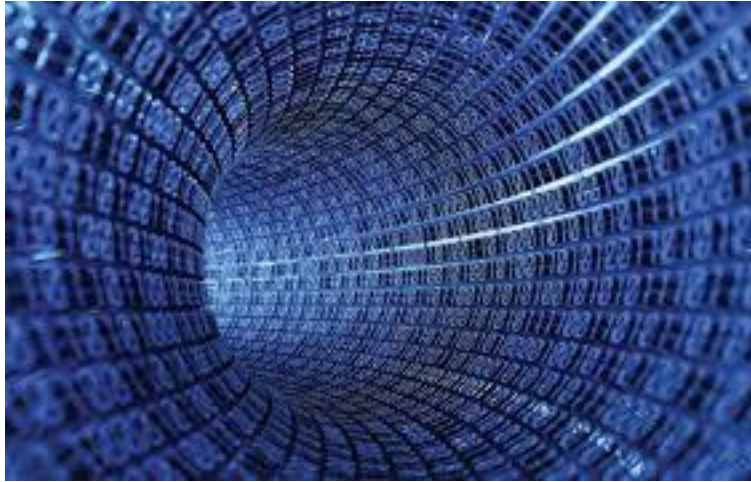


# analyzed by

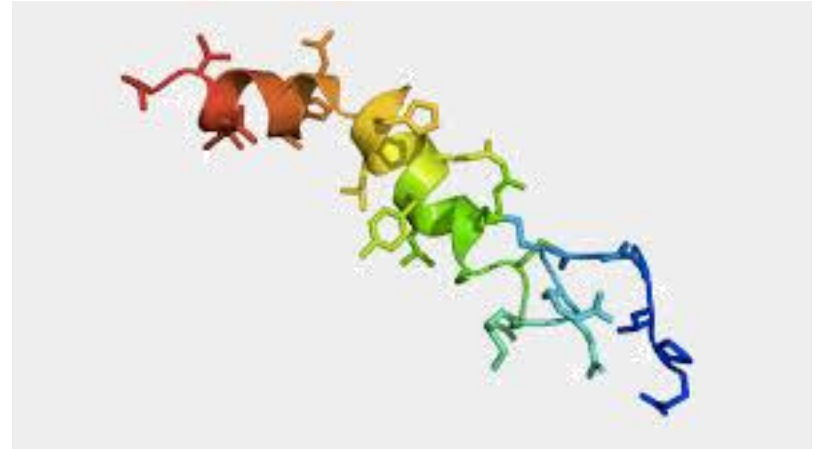
# from polymeric



# What does all this tell us



Database of proteins



Database of peptides

Where did the peptides originate?

How were they released?

# What enzymes can do this?

## Active Enzymes:

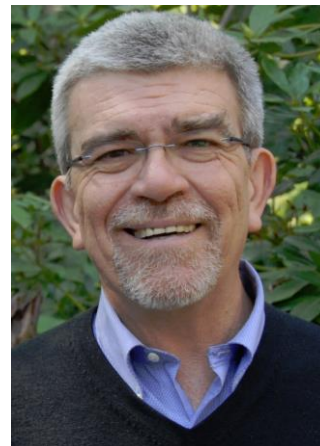
- plasmin
- elastase
- cathepsin D
- glutamyl endopeptidase
- proline endopeptidase

Enzyme	Number					
	in lactation cows	in lactation sheep	Total cows	Upper change within the protein	Lower change observed	Class expression given in BPM
Plasma	128	260	388	0	212	11
Plasma 1*	128	260	388	0	212	11
Cathepsin D	18	52	70	0	36	24
Chymotrypsin	48	24	72	0	48	11
Trypsin	11	29	40	0	26	13
Plasma 1 pH 7.5	11	47	58	0	42	10
Class 1 cathepsin*	17	21	38	0	19	5
Plasma 1 pH 7.5	14	31	45	0	28	16
Chymotrypsin	3	12	15	0	10	4



Nora Khaldi

All except plasmin showed mRNA expression in milk



Juan Medrano

Category	Enzyme	Gene symbol <sup>1</sup>	Day 15 <sup>2</sup>	Day 90 <sup>2</sup>	Day 200 <sup>2</sup>
Cathepsins	Cathepsin B	CTSB	1262.0	1462.3	1052.5
	Cathepsin D	CTSD	786.0	4007.6	4645.6
	Cathepsin Z	CTSZ	222.0	1048.3	1034.0
	Cathepsin H	CTSH	122.0	136.0	645.1
	Cathepsin S	CTSS	89.1	107.2	642.0
	Cathepsin C	CTSC	65.3	376.1	446.4
	Cathepsin K	CTSK	62.1	376.8	389.8
	Cathepsin A	CTSA	66.8	432.5	334.0
	Cathepsin F	CTSF	22.1	76.2	103.3
	Cathepsin W	CTSW	16.7	25.3	32.2
	Cathepsin L2	CTSL2	15.5	13.5	13.0
	Cathepsin O	CTSO	0.8	3.7	4.4
Cathepsin L1	CTSL1	0.8	0.8	0.1	
Cathepsin G	CTSG	0.0	0.0	0.0	
Elastase	Elastase 1	ELAI	0.4	3.2	1.2
	Elastase 2B	ELAI2B	0.0	0.1	0.1
Plasminogen pathway	Plasminogen	PLG	0.0	0.0	0.0
	Urokinase-type plasminogen activator	PLAU	18.7	218.8	12.2
	Tissue plasminogen activator	PLAT	62.4	346.3	91.3
	Plasminogen activator inhibitor	SEIWFZ1	1.9	4.2	4.8
	Plasmin inhibitor	SEIWFZ2	3.6	76.7	19.5

(Khaldi et al., 2014, JAFC)

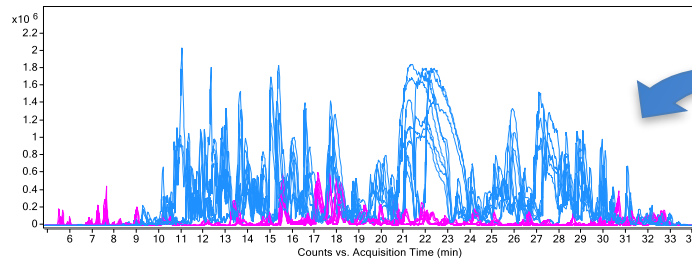




# Infant Digestomics

## Milk is Self-Digesting!

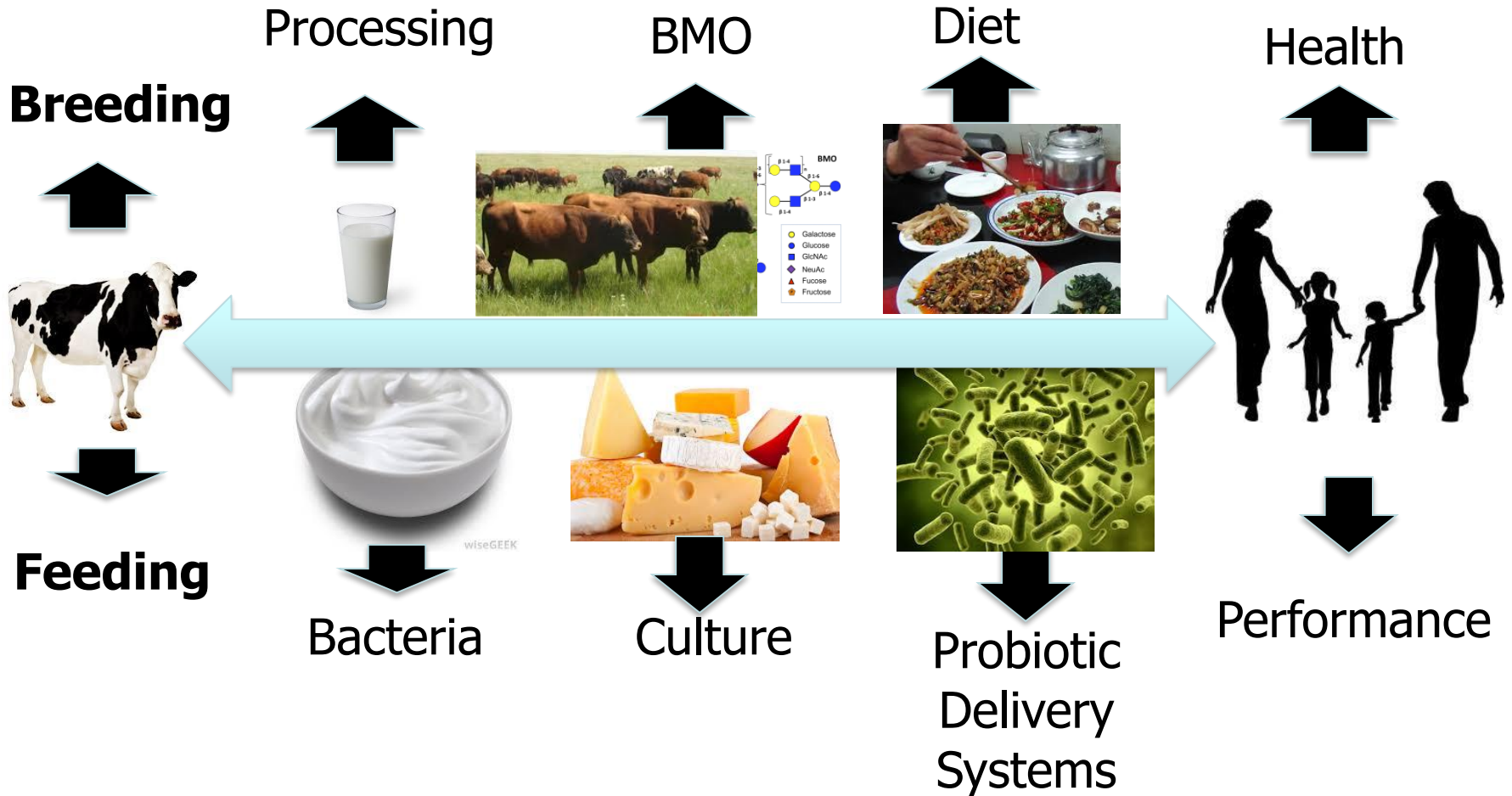
- Detailed milk peptidomics reveal just how much mom's help babies



An anatomical illustration of the human digestive system. The background shows a semi-transparent human torso with the skeletal structure in blue. The digestive organs are highlighted in a reddish-orange color. In the top-left corner, there is a microscopic inset showing the intricate, villous structure of the intestinal lining. Overlaid on the center of the image is the text: 

**What have we  
learned:  
Digestion isn't  
easy!**

# Innovating at every step from farm to fork



# Dairy's future?

## The cornerstone to personalized health



# Recommendations

## **Own Lactation!**

Dairy should lead the world in Human milk support

## **Make Health Measurable**

Dairy should lead the world in health diagnostics support

## **Prepare for Disruption**

Dairy should lead the world on data transparency

# **Future**

**What will be**

**What could be**

# The Global Brand Model



Good Model for Multinational Food  
Bad Model for Agriculture  
Horrible Model for Human Health

# Health is about the entire diet not just a food

- Food is not like drugs!
- You cannot solve the problems of a bad diet with one food item.

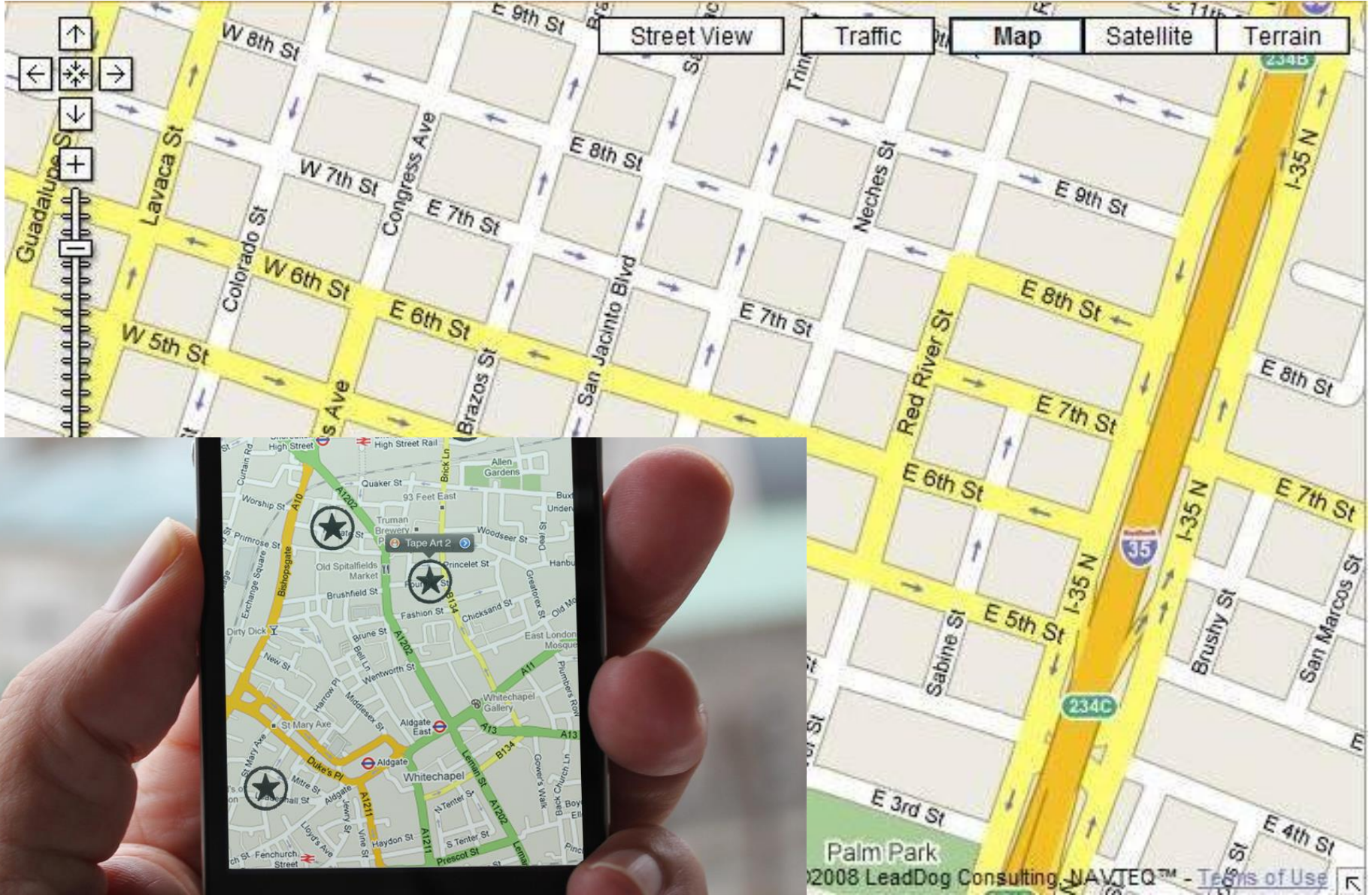




# **Knowledge Based Diet & Health**

**What does a knowledge based system look like**

# Transportation: Google Maps



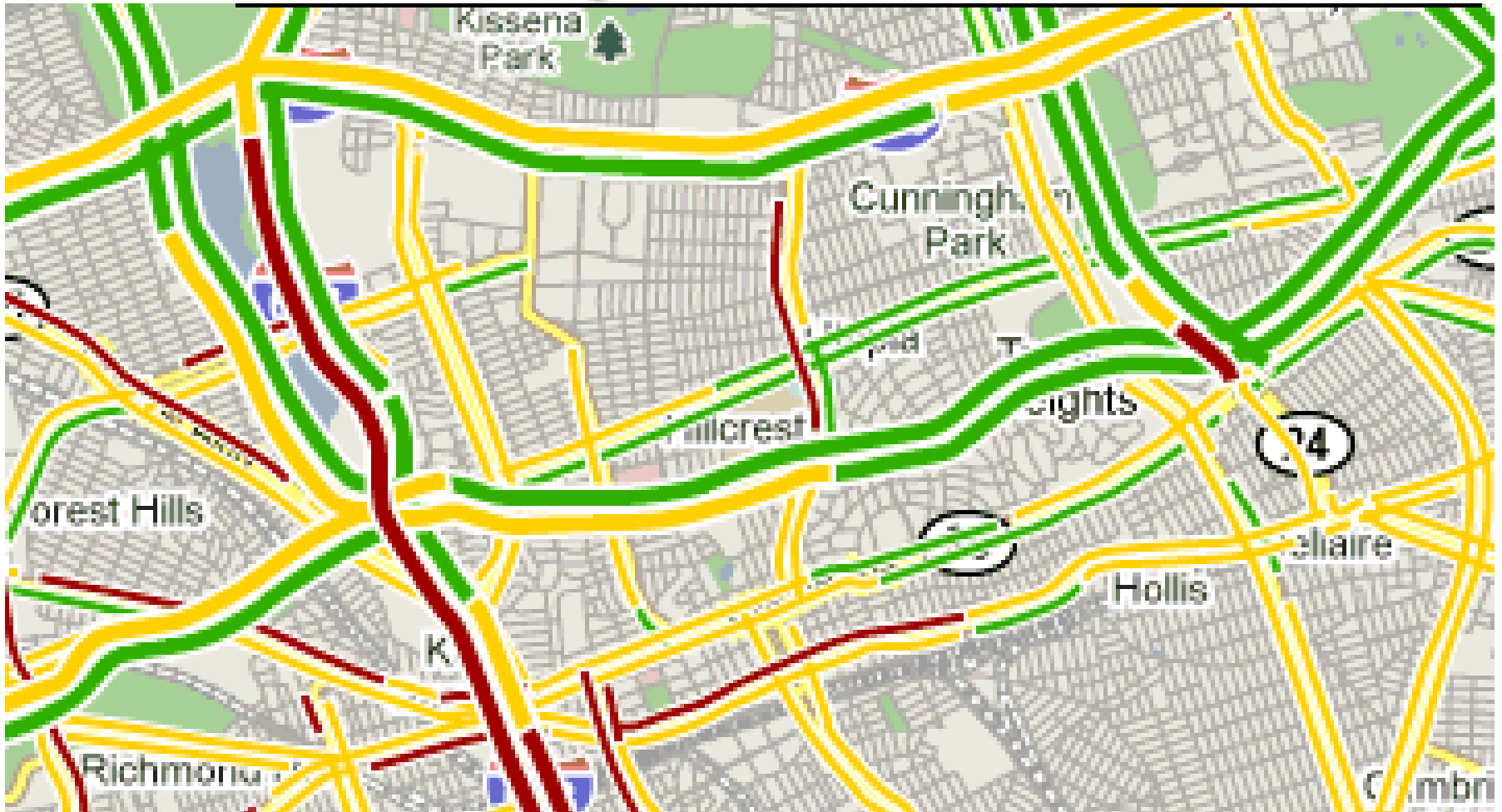
# Transportation: Google Maps

# Personal



# Transportation: Google Maps

## Dynamic



# Transportation: Google Maps

## Annotated

hotels near New York, NY

Check-in  Nights

**A** [Pennsylvania Hotel](#) [- more info](#) **\$129**▼  
 401 7th Avenue, New York, NY - (212) 290-2224  
★★★★☆ 2364 reviews  
Sponsored  
\$129 Priceline  
\$129 Expedia  
"Before booking I informed with friends and never created a great ..."

**B** [Gramercy Park Hotel](#) [- more info](#) **\$395**▼  
 2 Lexington Avenue, New York, NY - (212) 920-3300  
★★★★☆ 350 reviews  
"Positive: The staff and location were excellent. Room was very ..."

**C** [Millenium Hilton New York Hotel](#) [- more info](#) **\$239**▼  
 55 Church Street, New York, NY - (212) 693-2001  
★★★★☆ 1397 reviews  
"It was overall a nice place to stay. Rooms were clean and views were ..."

**D** [Embassy Suites Hotel New York City](#) [- more info](#) **\$289**▼  
 102 North End Avenue, New York, NY

The map shows the New York City area with several hotels marked with red pins labeled A, B, C, and D. Pin A is located in the Penn Station area, Pin B is in the Midtown East area, Pin C is in the Lower East Side area, and Pin D is in the East Village area. The map also shows major roads like I-495, I-278, and I-95, and landmarks like Central Park and the Hudson River.

# **Value Proposition of Google Maps**

**Where am I?**

**Where do I want to go?**

**How do I get there?**

# Health Knowledge

**What is my Health Status  
now?**

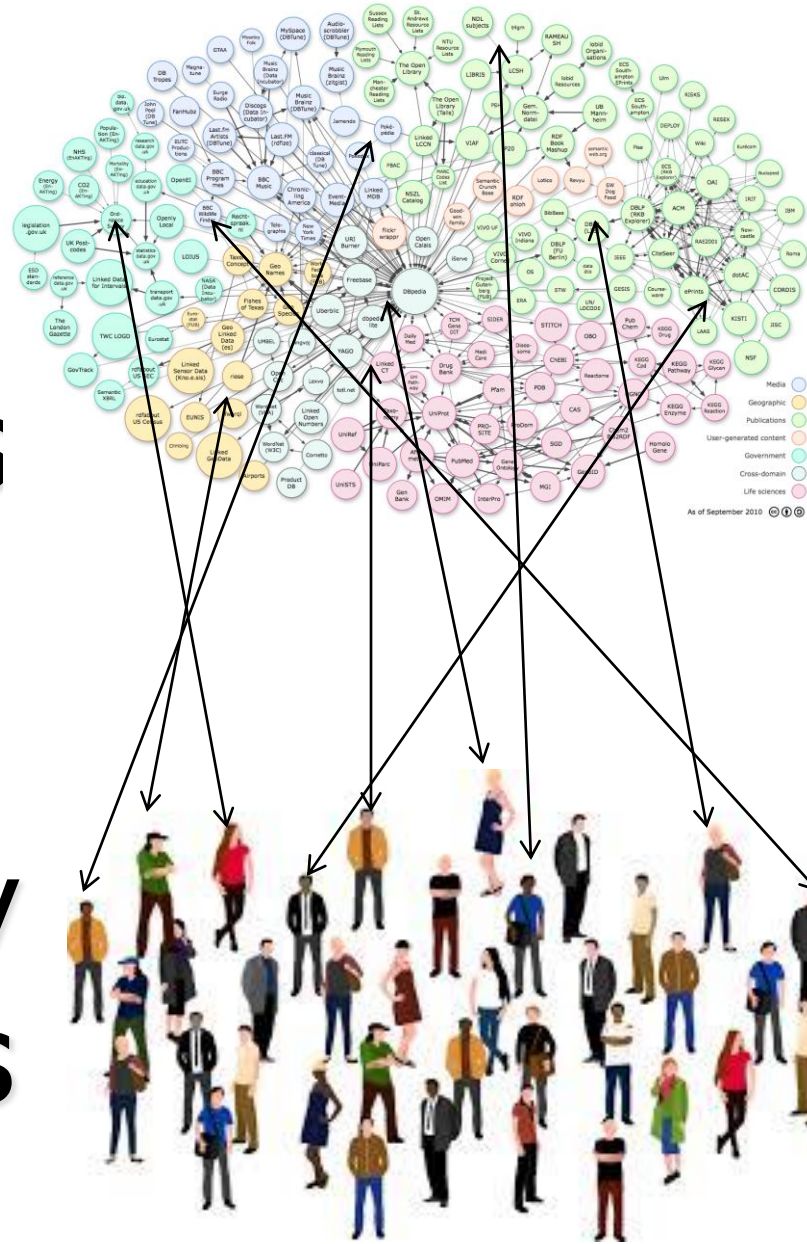
**What would I like it to  
be?**

**How do I get there?**

# How it works

Annotated  
Database of  
Food Chemicals

Interrogated by  
individual users





# Dairy

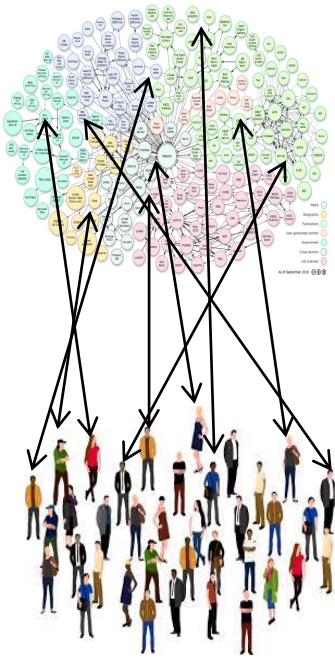
Why would Dairy want to move  
to a Knowledge-based, Diet-  
centric Food System?

National Academy of Science,  
Institute of Medicine's  
History!!

# What will we gain?

## Precision:

- ✓ Health
- ✓ Delight
- ✓ Safety
- ✓ Inventory
- ✓ Performance
  - ✓ Ethics
- ✓ Nourishment



**What COULD  
the future be**

**Global  
Aspirational**

**BIG**



# GOALS

## **Autoimmunity:**

allergy, eczema,  
psoriasis, asthma,  
diabetes, arthritis,  
lupus, MS, IBD,  
celiac,...

# GOALS

## **Inflammation:**

Cardiovascular  
disease, arthritis,  
IBD, hepatitis,  
glomerulonephritis,

...

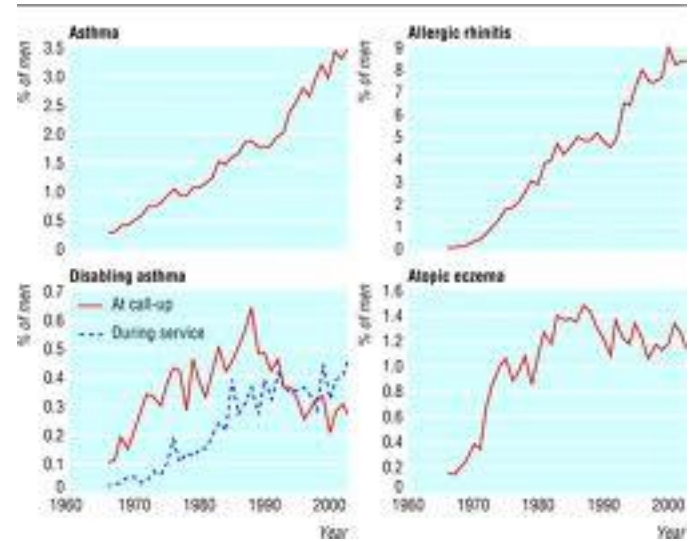
# GOALS

## **Metabolic Control:**

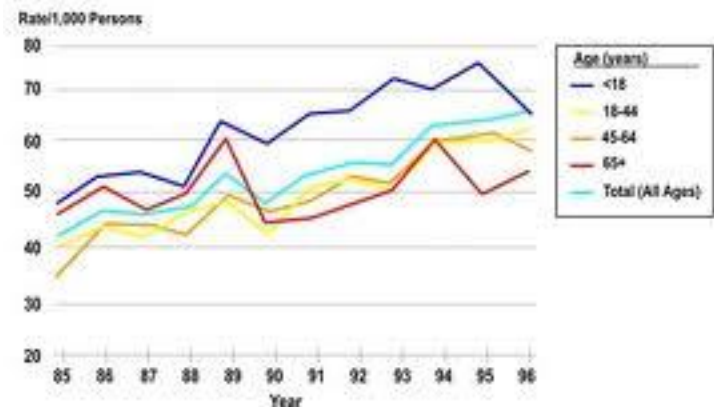
Obesity, Diabeties,  
Steatohepatitis,...

# Allergy/Atopy

The world is suffering through increasing incidence and severity of autoimmunity



Trends in Prevalence of Asthma By Age, U.S., 1985-1996





# Allergy/Atopy

Atopic disease is inexplicably getting more frequent and severe



Raw milk is tantalizingly protective



# Immune Defense

Is it possible to enhance immune surveillance yet inhibit inflammation?

Breast milk supports the developing immune system and inhibits inflammation



# Inflammation

Inflammation  
drives all non-  
communicable  
degenerative  
diseases



# Intestinal Microbiota

Pathogenic bacteria make up a finite proportion of the intestinal microbiota.

Their activation and proliferation promotes inflammatory activation of intestinal cells



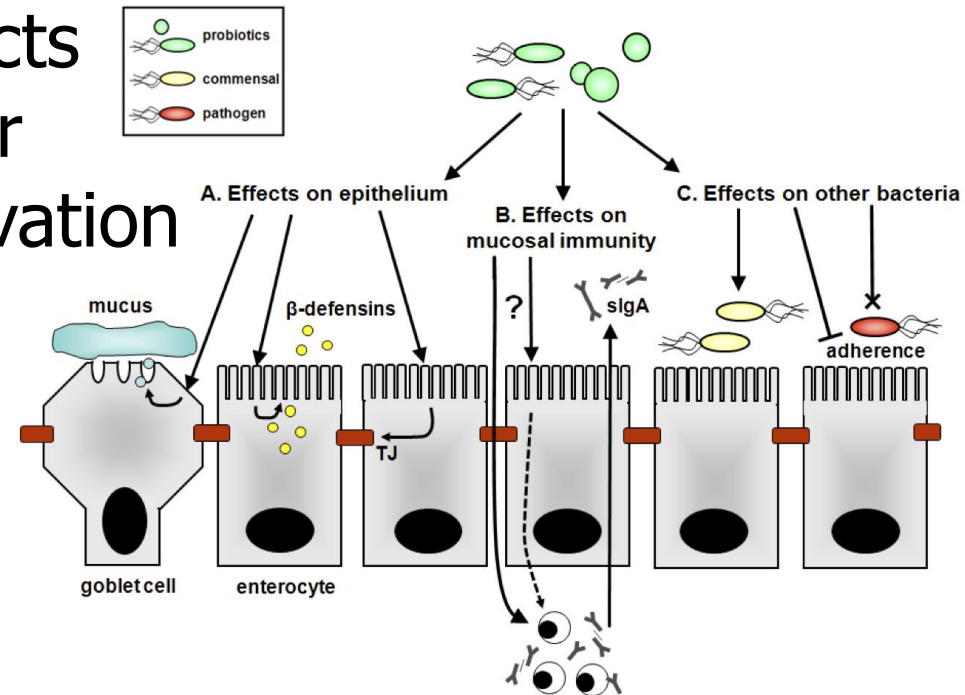
*Commensal bacteria displace pathogens, secrete antimicrobial agents, and guide immune and epithelial function and development in the host*

# Barrier Integrity

The integrity of cell junctions in the gut is critical to maintaining a barrier to the translocation of biomolecules into circulation

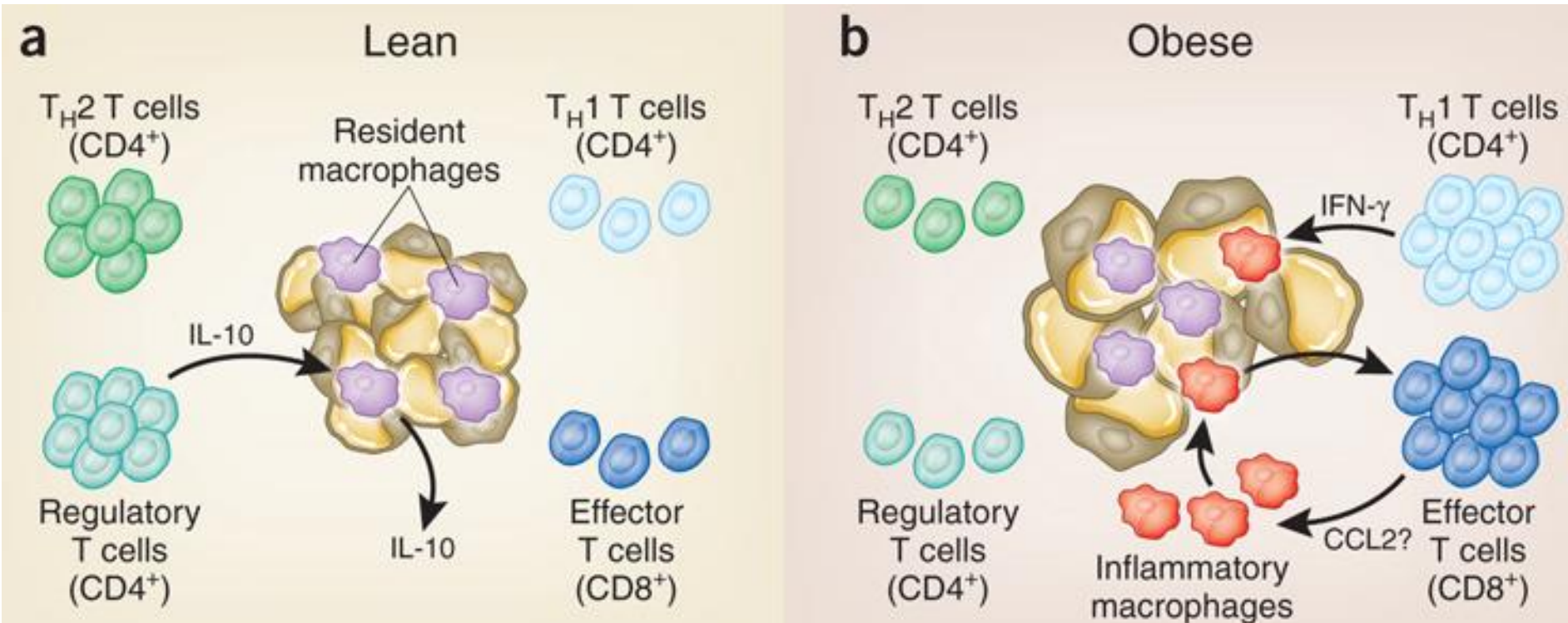
Migration of bacterial products through the epithelial barrier promotes inflammatory activation of circulating cells

*Commensal bacteria and ingested milk components restore barrier integrity*



# Adipose Dysfunction

'Excess' adipose stimulates resident macrophages that recruit a net inflammatory distribution of immune cells into the tissue.



# Dairy's future?

## A cornerstone to personalized health



# The cow as the center of science and industry in the 21<sup>st</sup> Century

Safety

Sustainability



Health

Quality





**Thank You**