

# Brain Development, Nutrition and the Gut-Brain Axis in Premature Newborns

4° Congreso Argentino de Neonatología

Buenos Aires 22-24 Mayo 2019

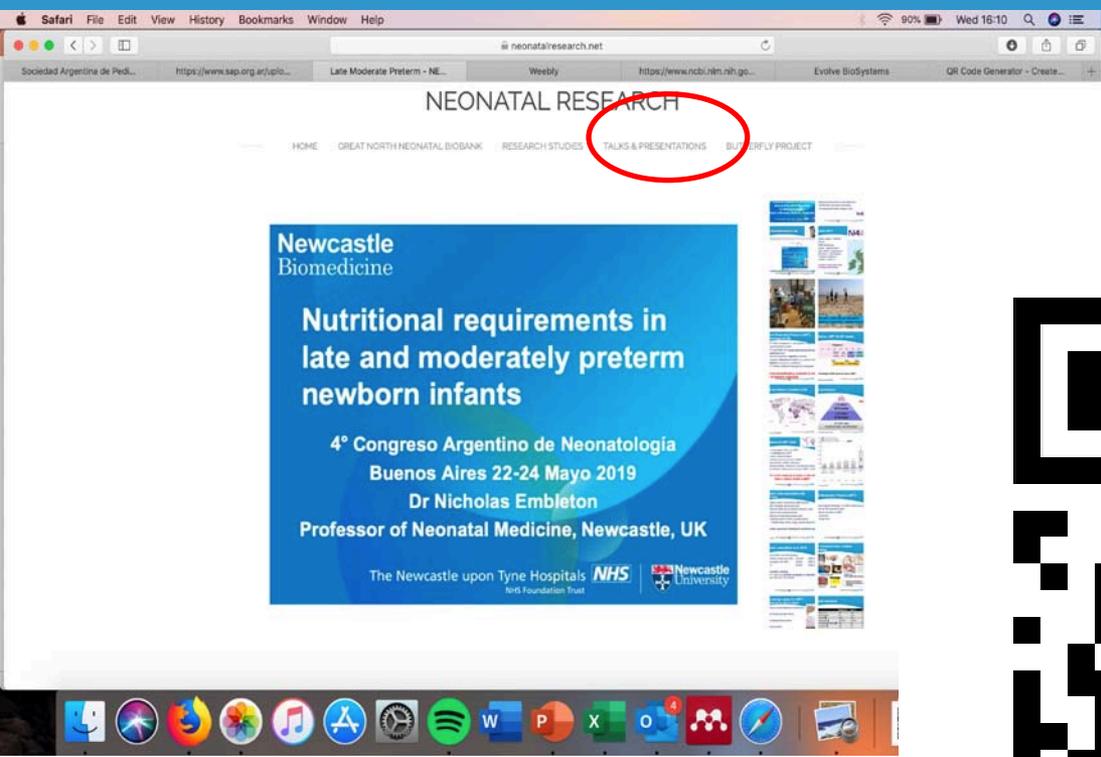
Dr Nicholas Embleton

Professor of Neonatal Medicine, Newcastle, UK

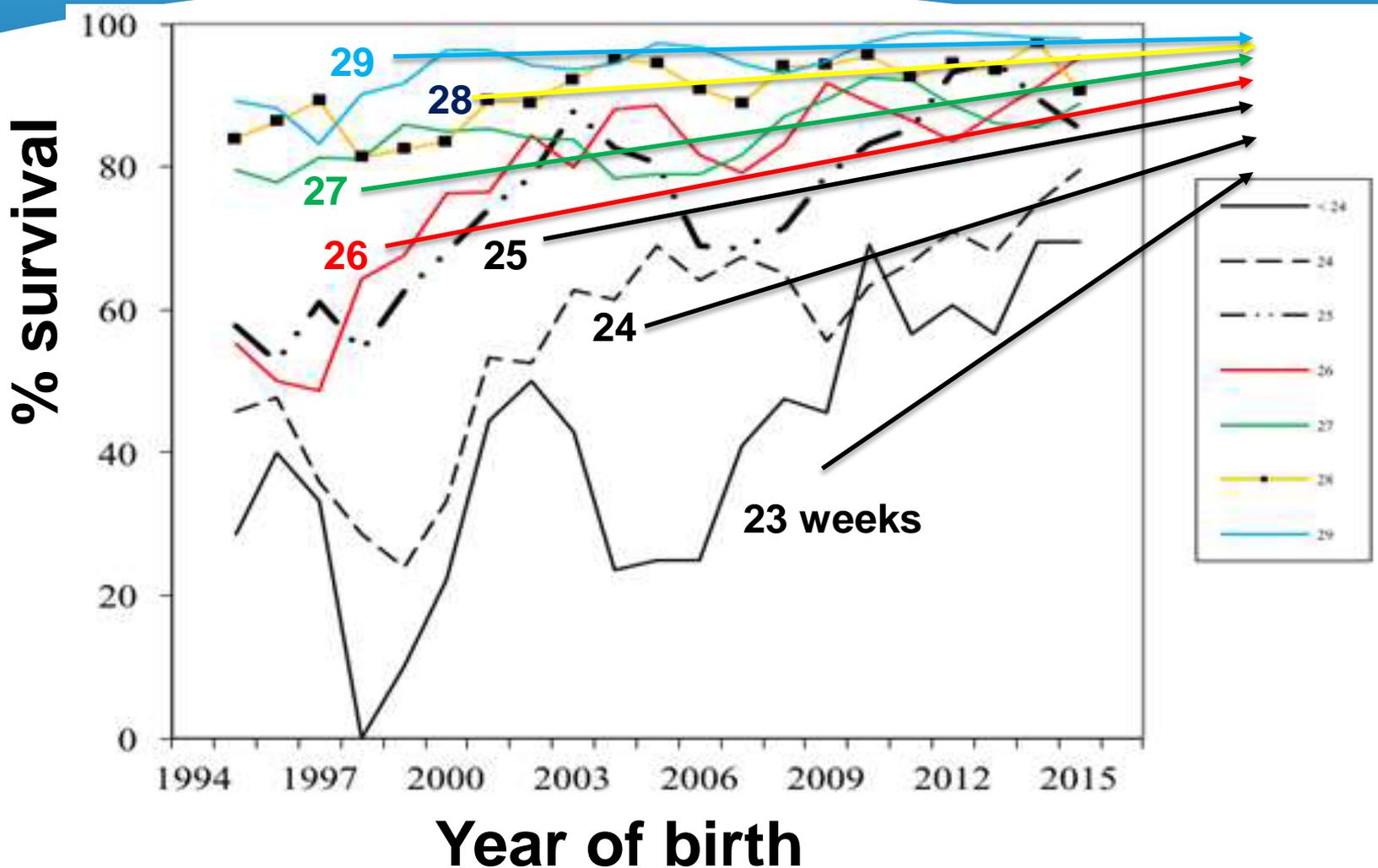
# Structure of the talk

- Survival & brain development in preterm infants
- Nutrition and nutrients
- Microbes
- Gut brain axes
- How does nutrition affect the brain
- Malnutrition in NICU – why so common?
  
- Talk is “Data Light” – if you want references email me [nicholas.embleton@ncl.ac.uk](mailto:nicholas.embleton@ncl.ac.uk) or visit our website [www.neonatalresearch.net](http://www.neonatalresearch.net)

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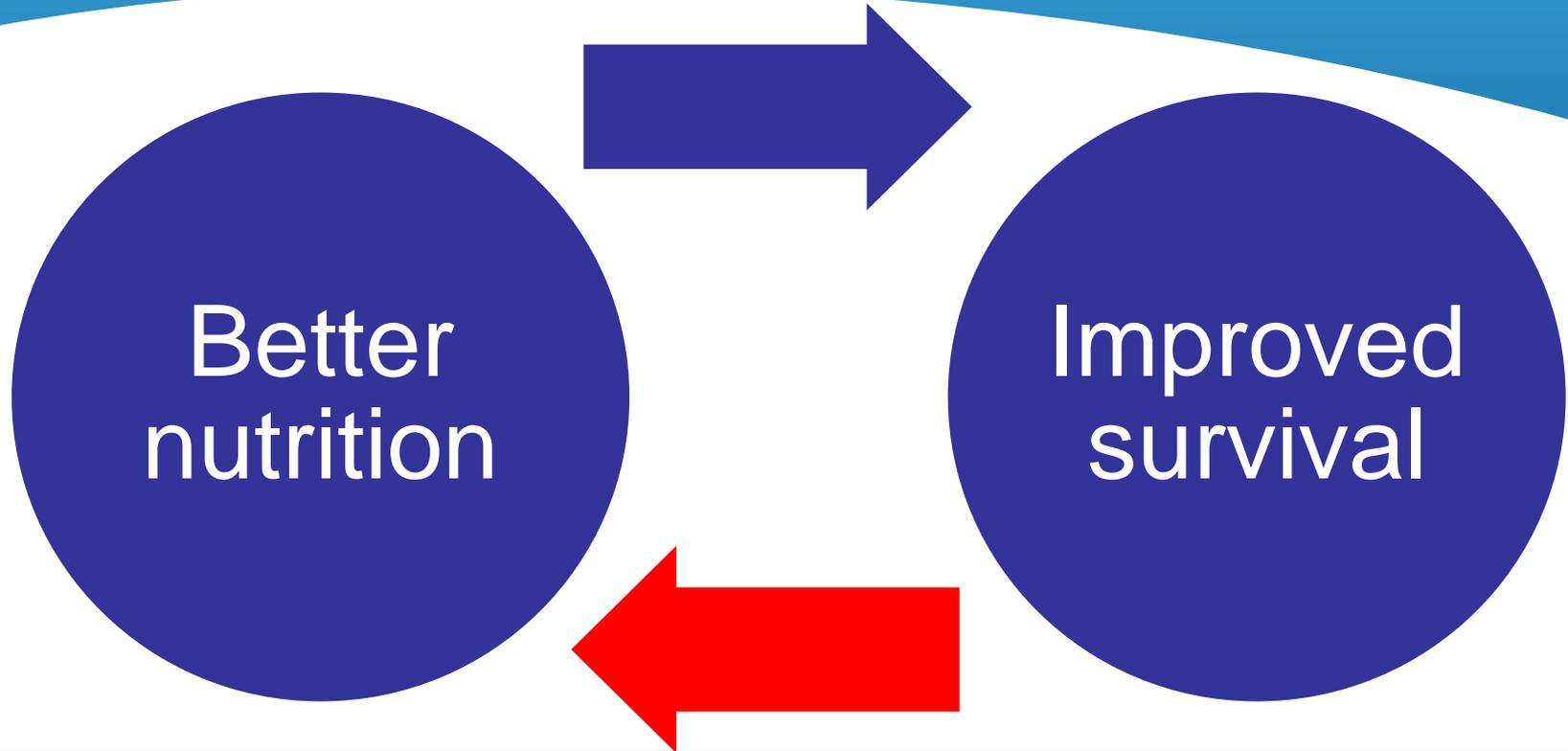


# Increasing survival of preterm infants



Newcastle Neonatal Unit – liveborn & admitted

# Better nutrition: key to improved survival



**Improved survival: nutritional needs become more important & complex**



# NUTRITION = more than 'nutrients'

## NUTRITION

### NUTRIENTS

*proteins, fats,  
micronutrients etc.*

### FUNCTIONAL COMPONENTS

*HMOs, growth factors,  
enzymes etc.*

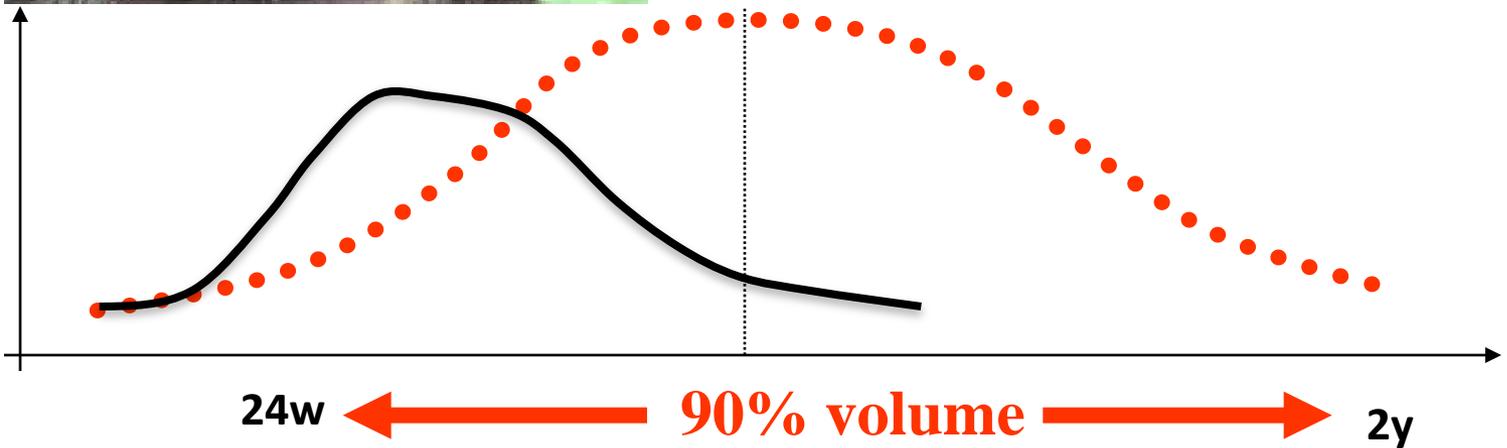
### MICROBES

*Breastmilk, environment,  
probiotics*

### 'TECHNICAL' & SOCIO-BEHAVIORAL

*Tubes, bolus, kangaroo,  
breastfeeding, taste, sensory*

# Brain growth in early life is rapid



# Nutrient requirements are very high

## Risk of abnormal brain development is high

**Tour de France**  
7000Kcal/day  
100kcal/kg/day

↑ 20 - 30%

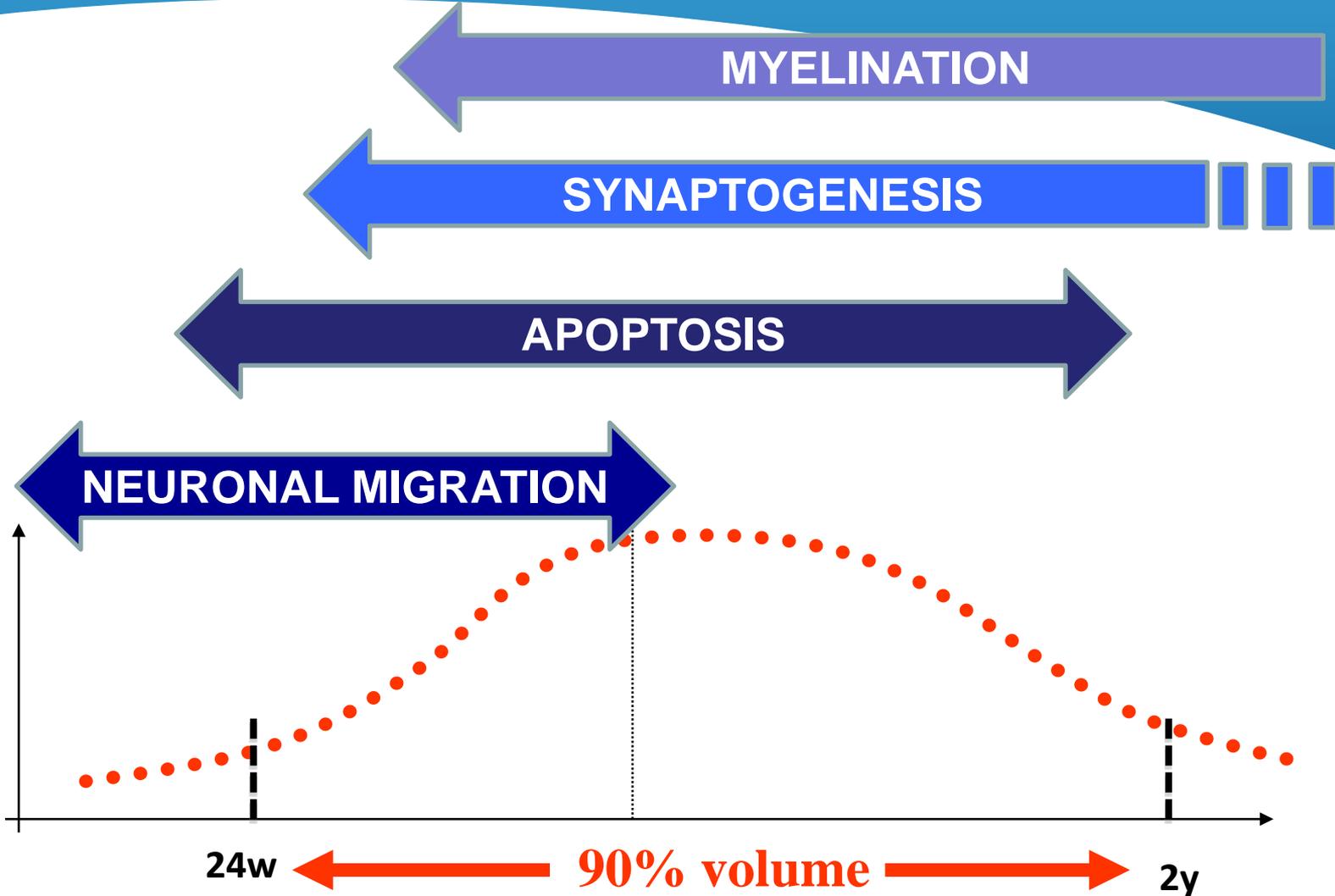
**NICU**

120-130kcal/kg/day

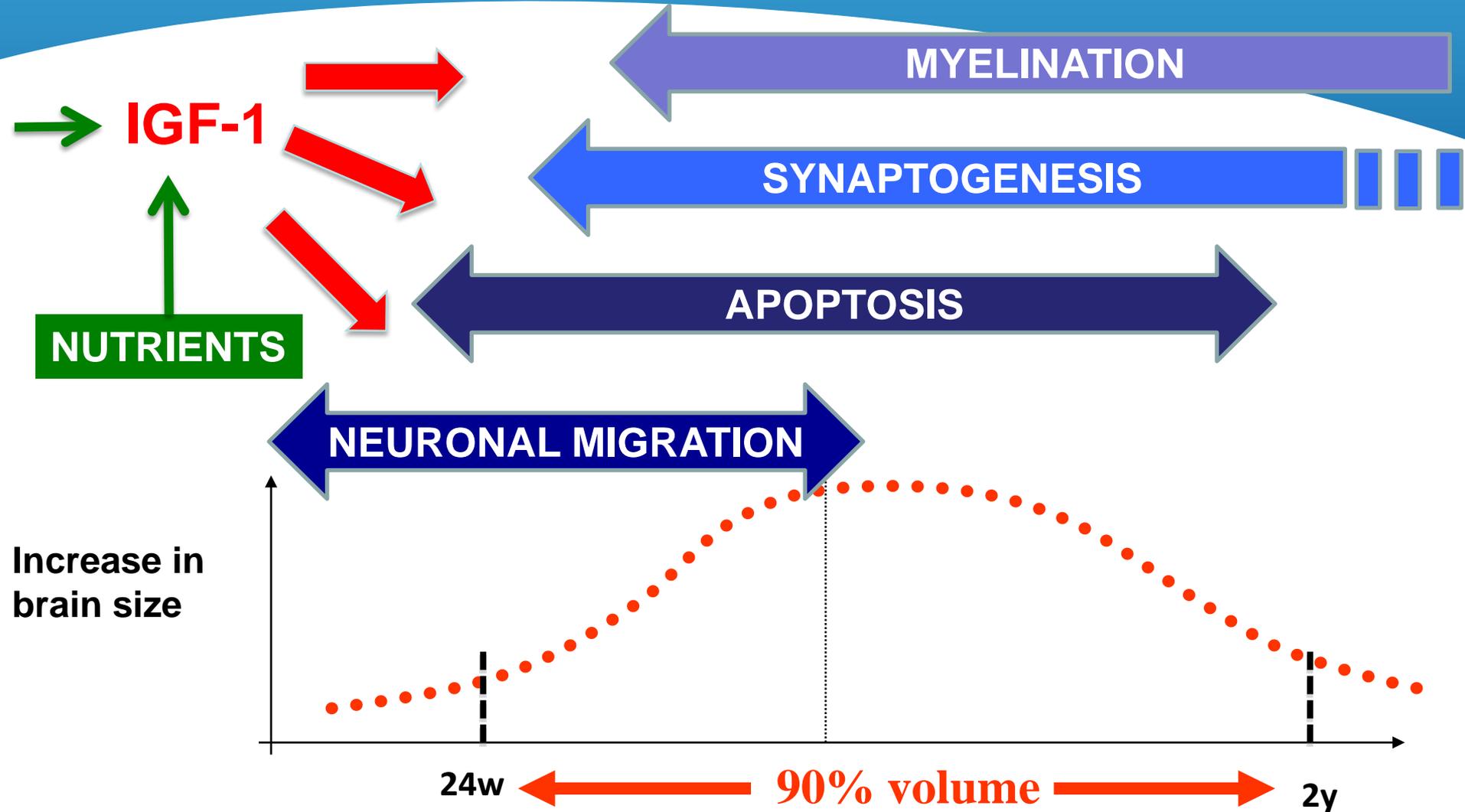


**More than half of all energy  
expenditure is the brain**

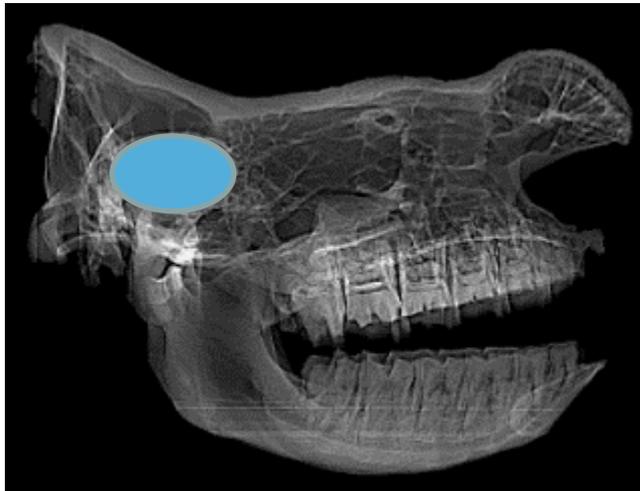
# Neuronal development proceeds in sequence



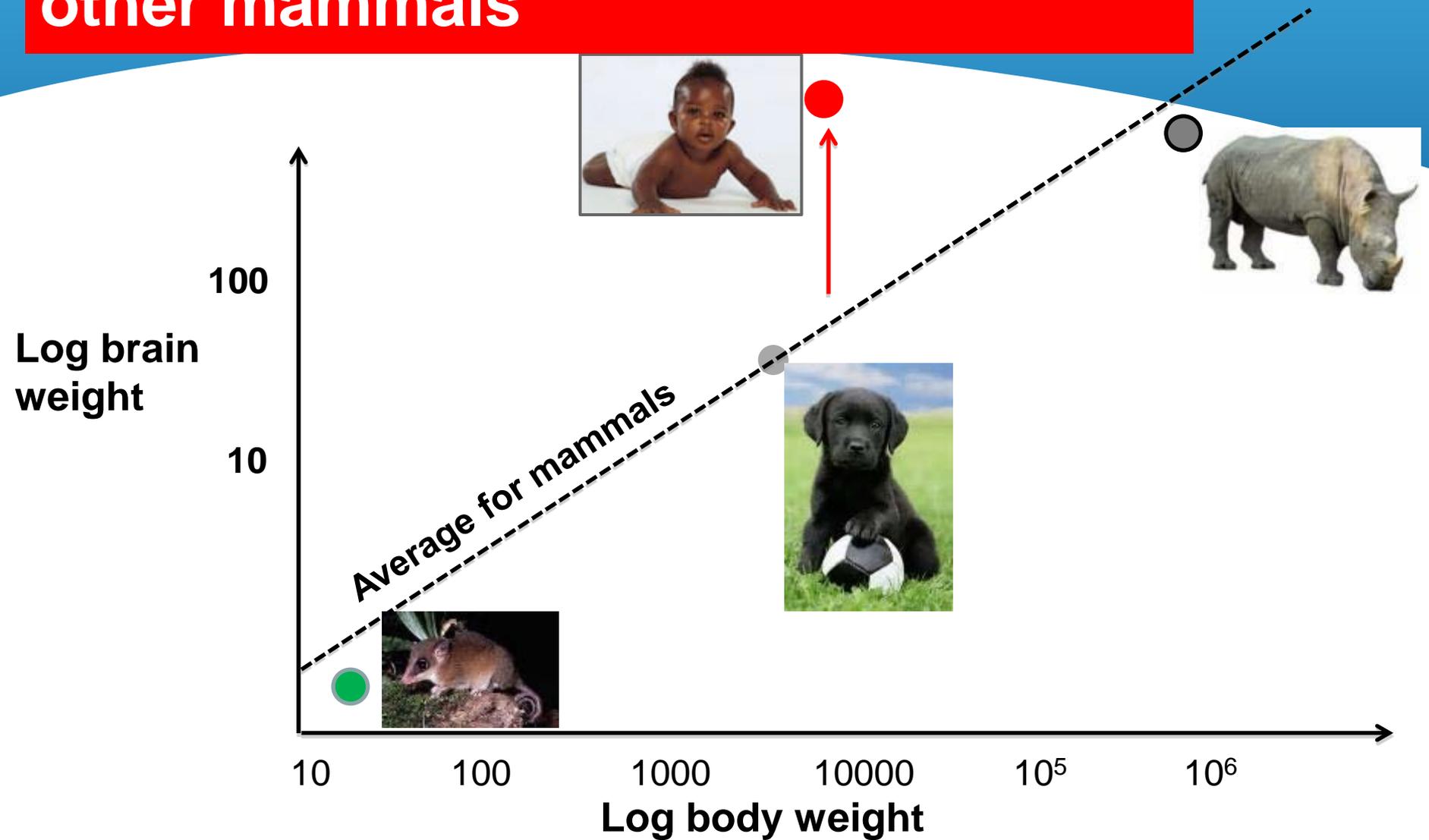
# Neuronal processes influenced by growth factors, signaling & gene expression



# Humans: it's all about the brain



# Human brain: 10-20x as large as other mammals



# Complexity of brain development

**Multiple anatomic  
regions**

**Unique developmental  
processes**

**Time-coordinated  
development of key areas**

**Neural circuits mediate  
complex behaviors**

# We are full of microbes

- 80% antibody producing cells located in gastrointestinal tract
- Gut = most important part of the immune system
- Microbial > human **cells (2:1)**
- Microbial >>> human **genes (100:1)**



# Are we human?



**We have more than 1000 different types of micro-organisms living inside our bodies**



**We have more than 300x as many microbial genes as human genes**



# We are full of microbes

- Humans are a “superorganism”
- Many metabolic & immune processes
- Human development **impossible** without microbes
- ~1.5kg microbes



# Human evolution like a “tug of war” NEC is similar...



Manage beneficial  
microbes

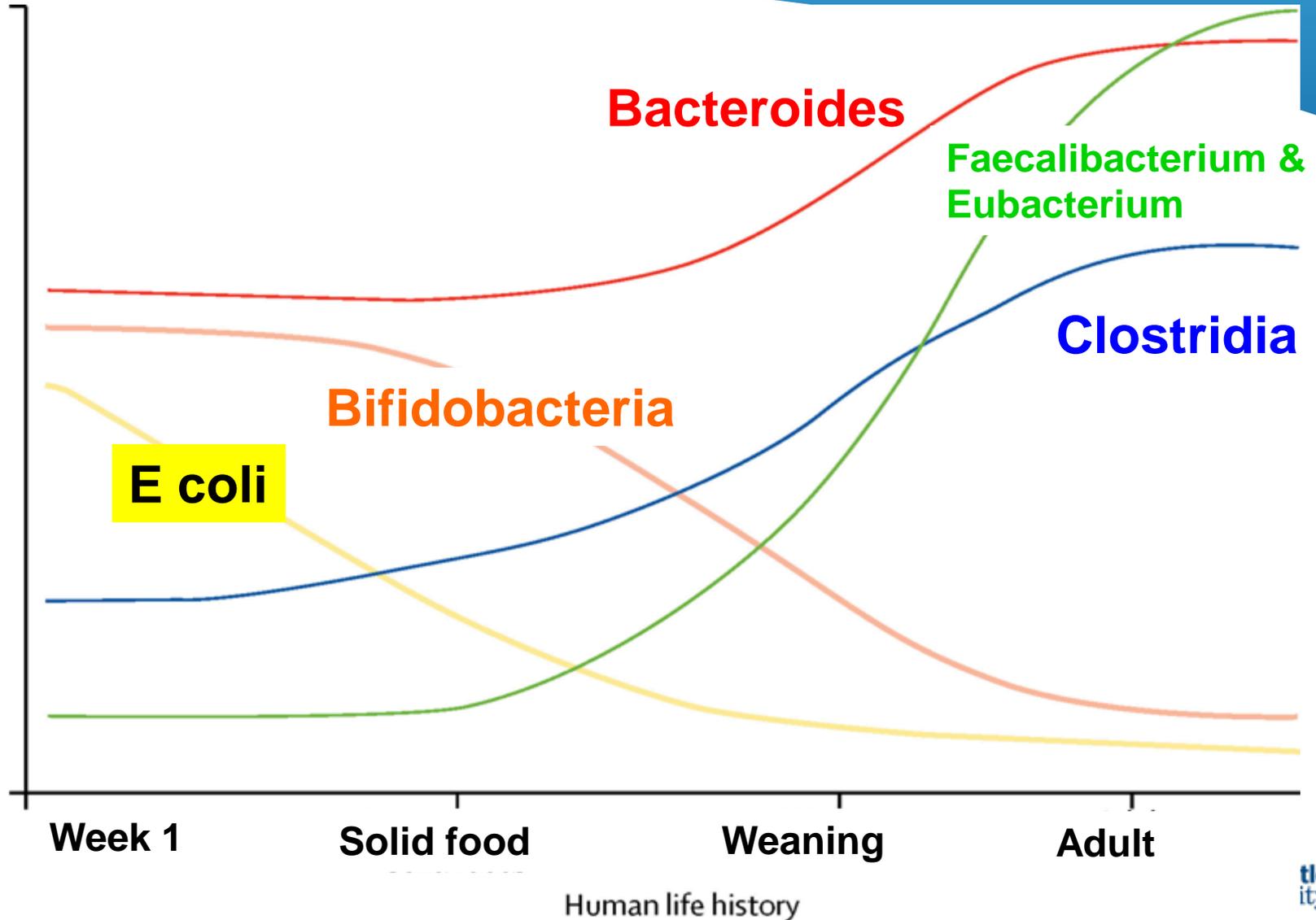
Exclude harmful  
microbes

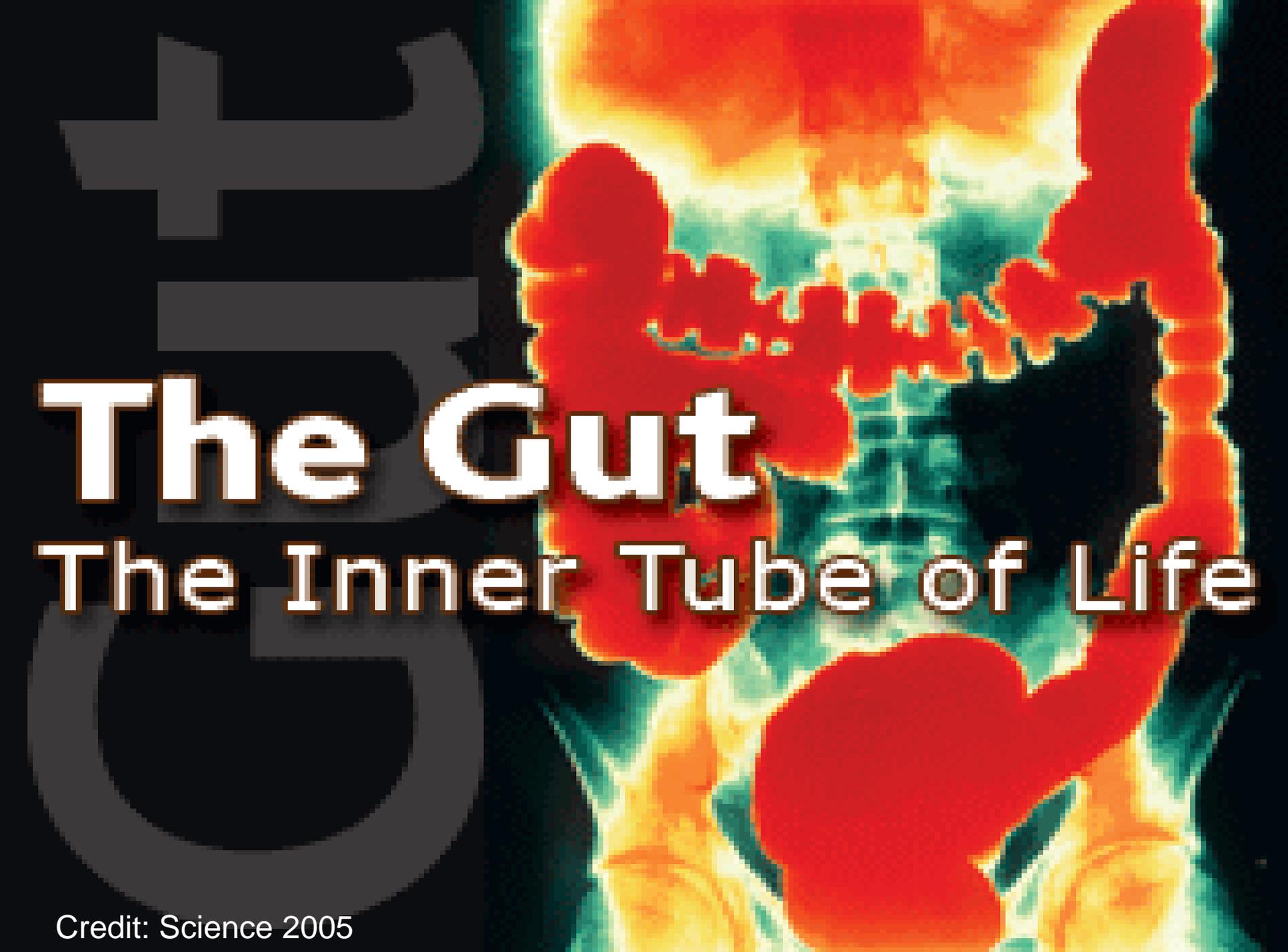


Preterm birth: a similar challenge

*Tolerance* v *Activate immunity*

# Human life-course: baby to adult

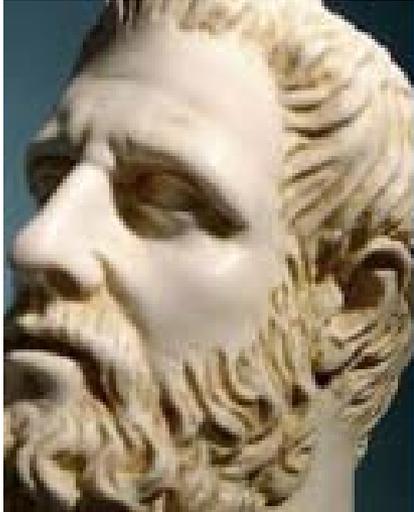




# The Gut

## The Inner Tube of Life

# We have always known that the gut interacts with the brain



"ALL DISEASE  
BEGINS IN  
THE GUT!"  
-HIPPOCRATES

Always trust your gut.  
It knows what your head  
hasn't yet figured out.

—Yogi Berra



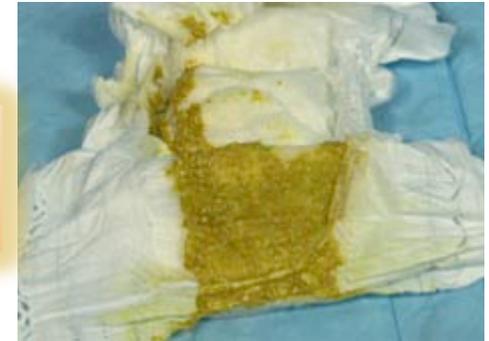
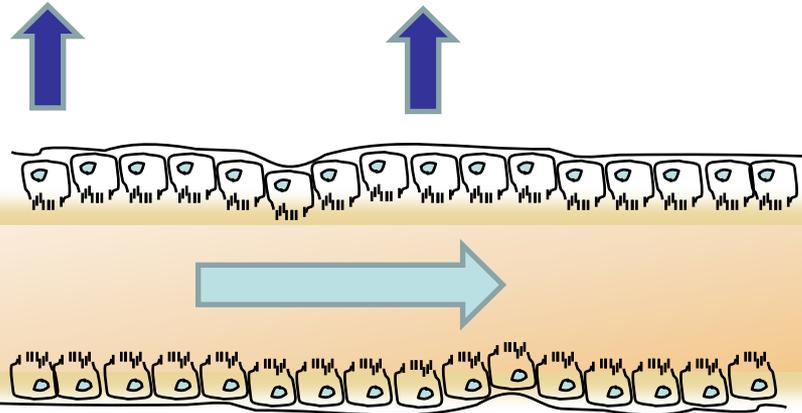
TRUST  
YOUR  
GUT



# Gut – just for nutrition?

Drink milk → absorb nutrients → make stool?

**Fluid**      **Nutrients**

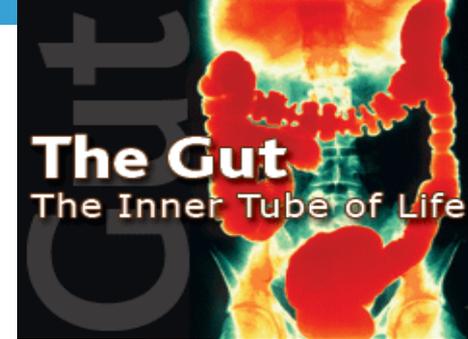


**Food**

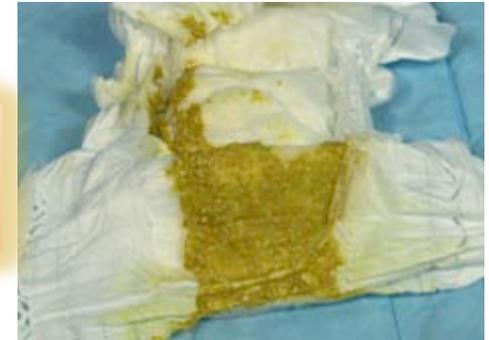
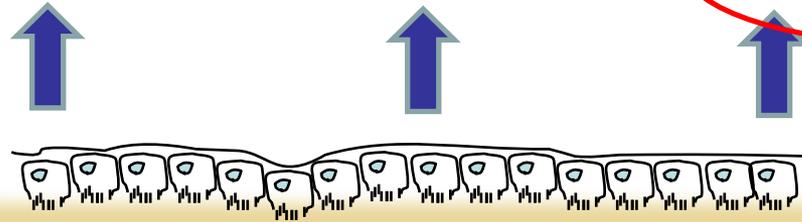


**Waste**

# Breast milk: developmentally regulated maternal-infant biochemical signalling pathway



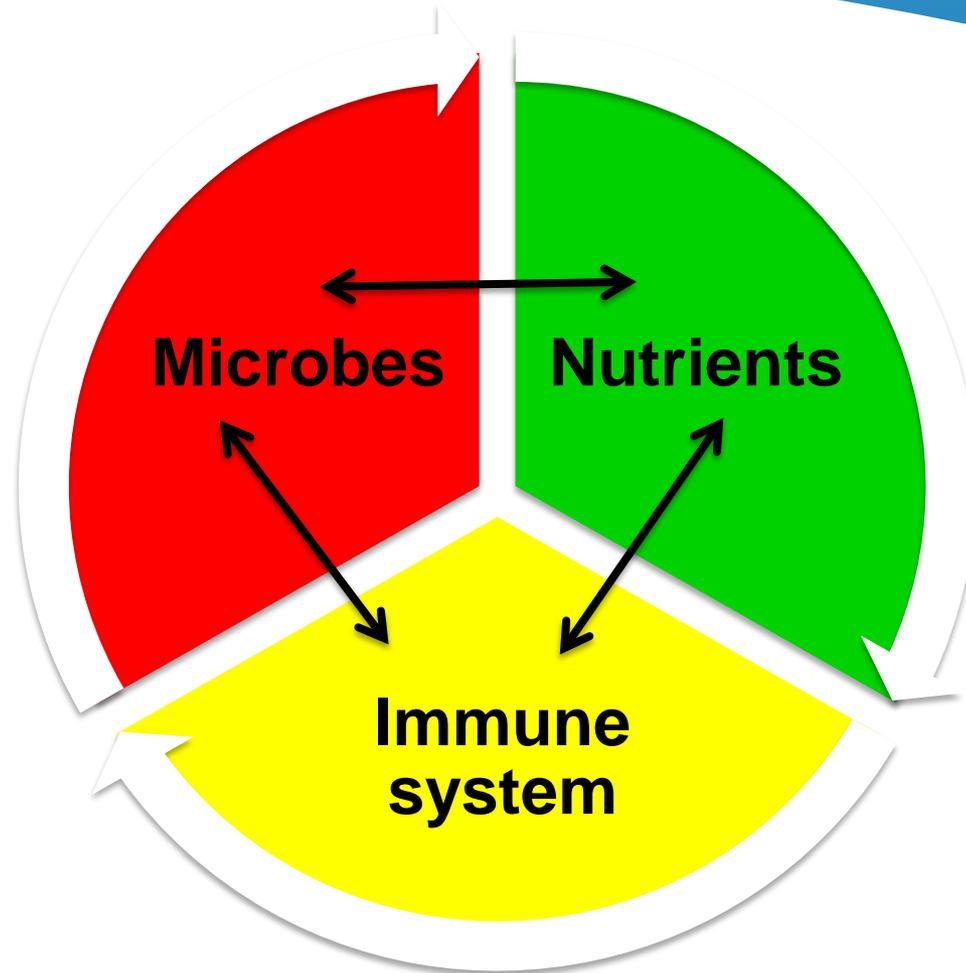
**Fluid**      **Nutrients**      **Metabolites**



**Immune**      **Hormones**      **Microbes**

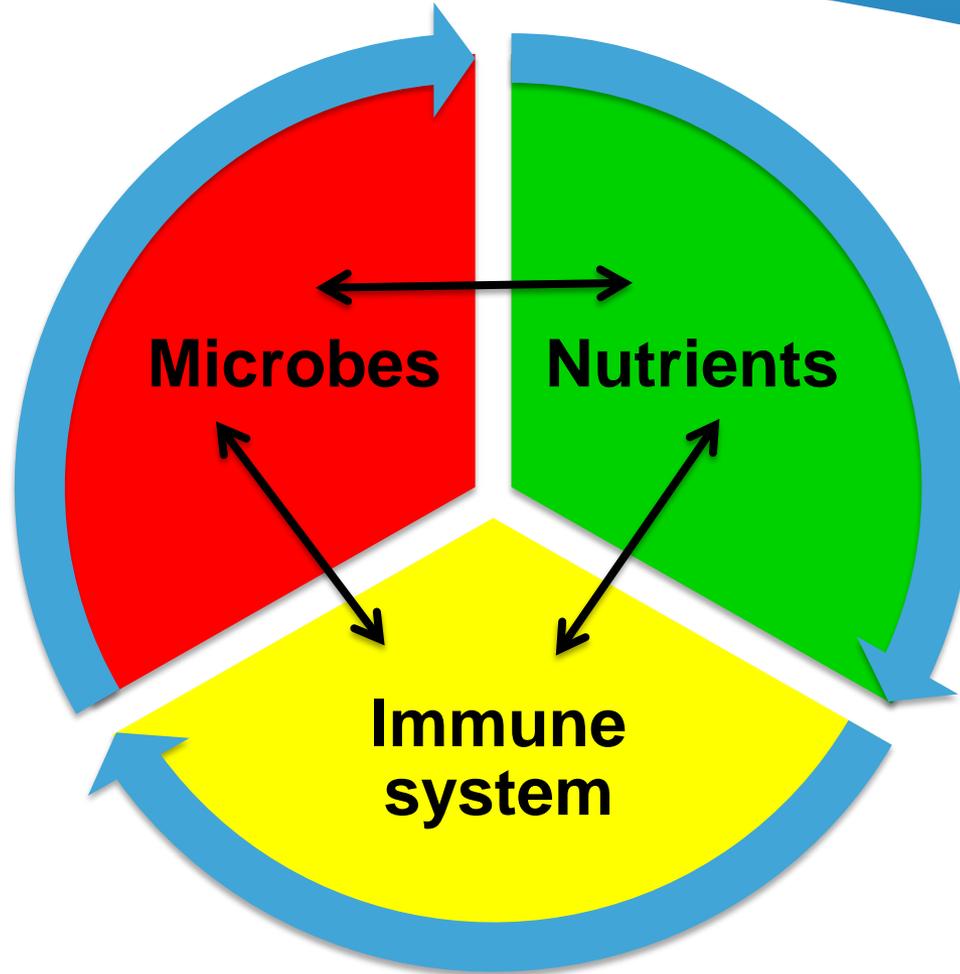
**Food**

# Gut interactions: nutrition, microbes and immunity = gut 'health'



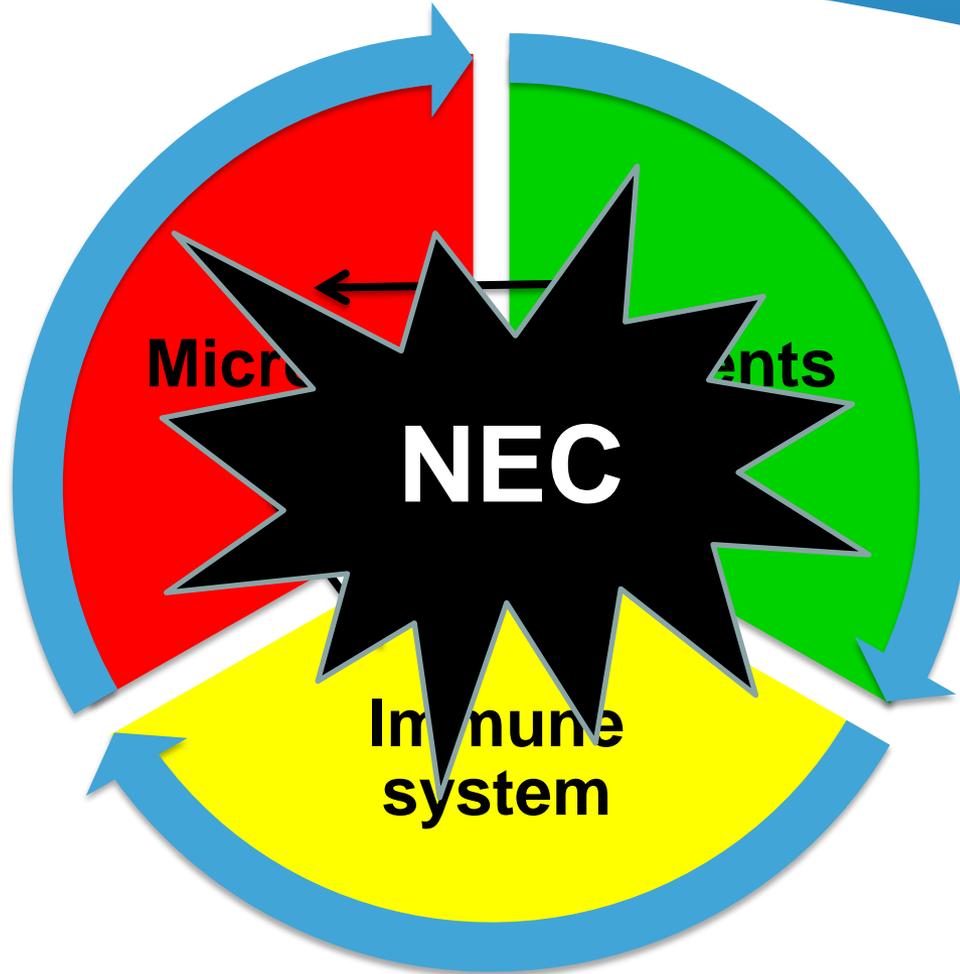
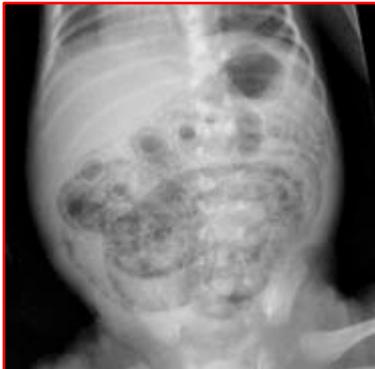
# Mechanisms & effects change over the life-course

## Life-course



# NEC: breakdown of interactions between microbes, metabolites & immune system

**NEC**



# Our first contact with the microbial world

El nacimiento. Bienvenido al mundo

cuando el bebé esté listo para nacer, la mujer se agachará y el bebé se arrastrará hacia afuera para que pueda ser liberado a la naturaleza.

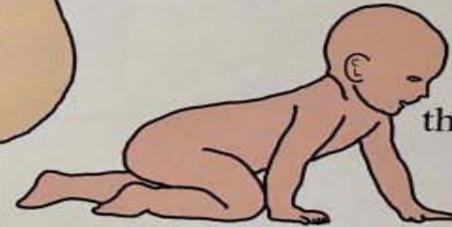
the birthing - welcome to the world

out you come  
little one

Vamos  
bebe!



when the baby is ready to be born  
the woman will crouch down and  
let the newborn crawl out of her  
so it can finally be released  
into the wild



thank you

Gracias!

Textbook of Obstetrics  
Fantasy land c.2018



# Early colonisation is key life event

## “Birth seeds, breastmilk feeds”

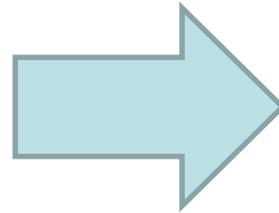


# Early colonisation is key life event



Anaerobes – most abundant early on

- *E coli*
- *Bifidobacteria*
- *Bacteroides*

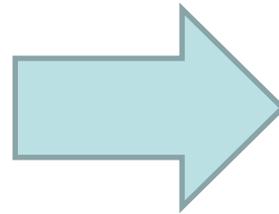


**“Pioneer” species  
sustain low oxygen  
environment**

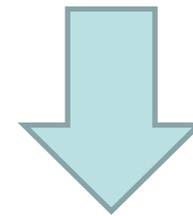
# Early colonisation is key life event



- Anaerobes – most abundant early on
- *Bifidobacteria*
  - *Bacteroides*



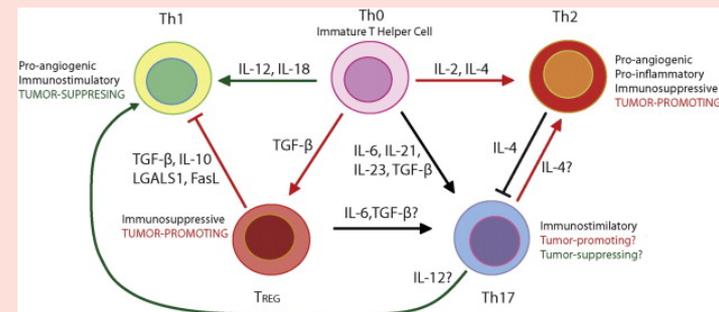
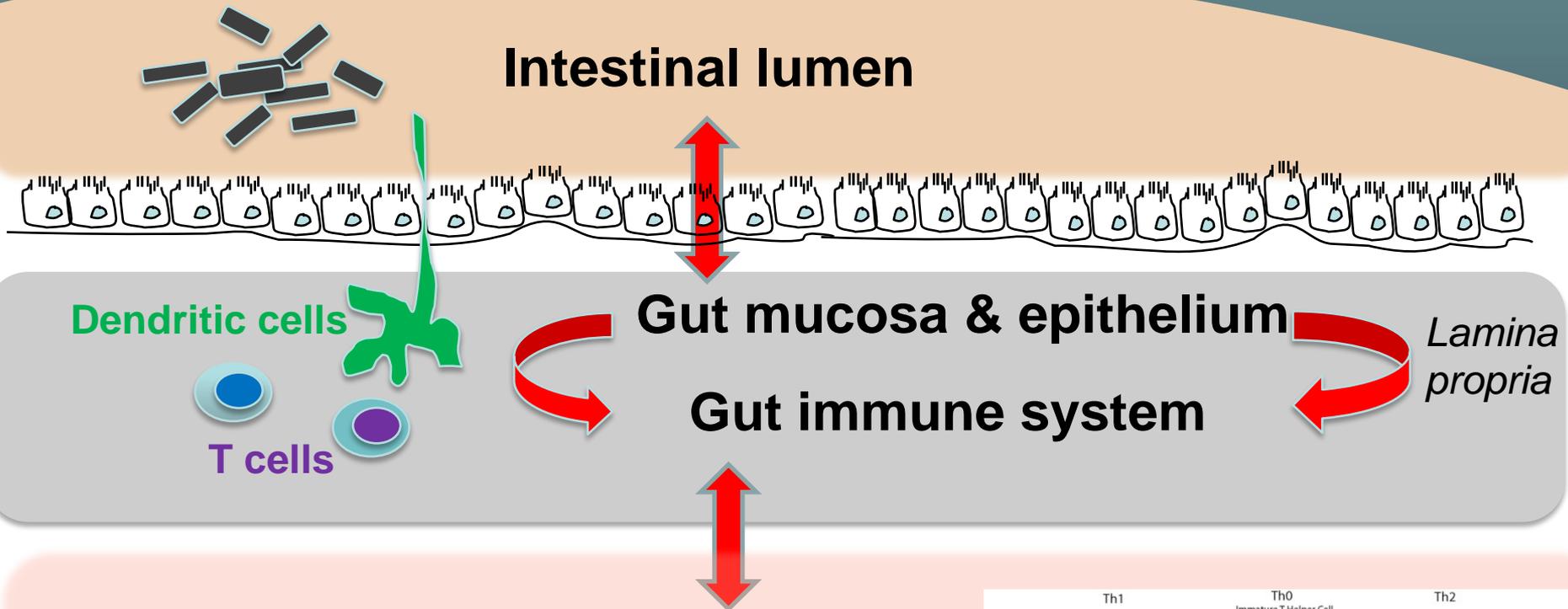
**“Pioneer” species  
sustain low oxygen  
environment**



**“2<sup>nd</sup> wave” of colonisation**

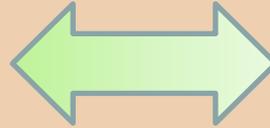


# Anti-infective & immune aspects: what happens in the gut?

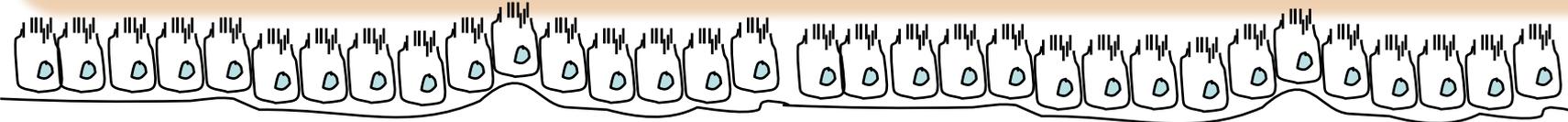


# There is a continual interaction between microbial communities and metabolites

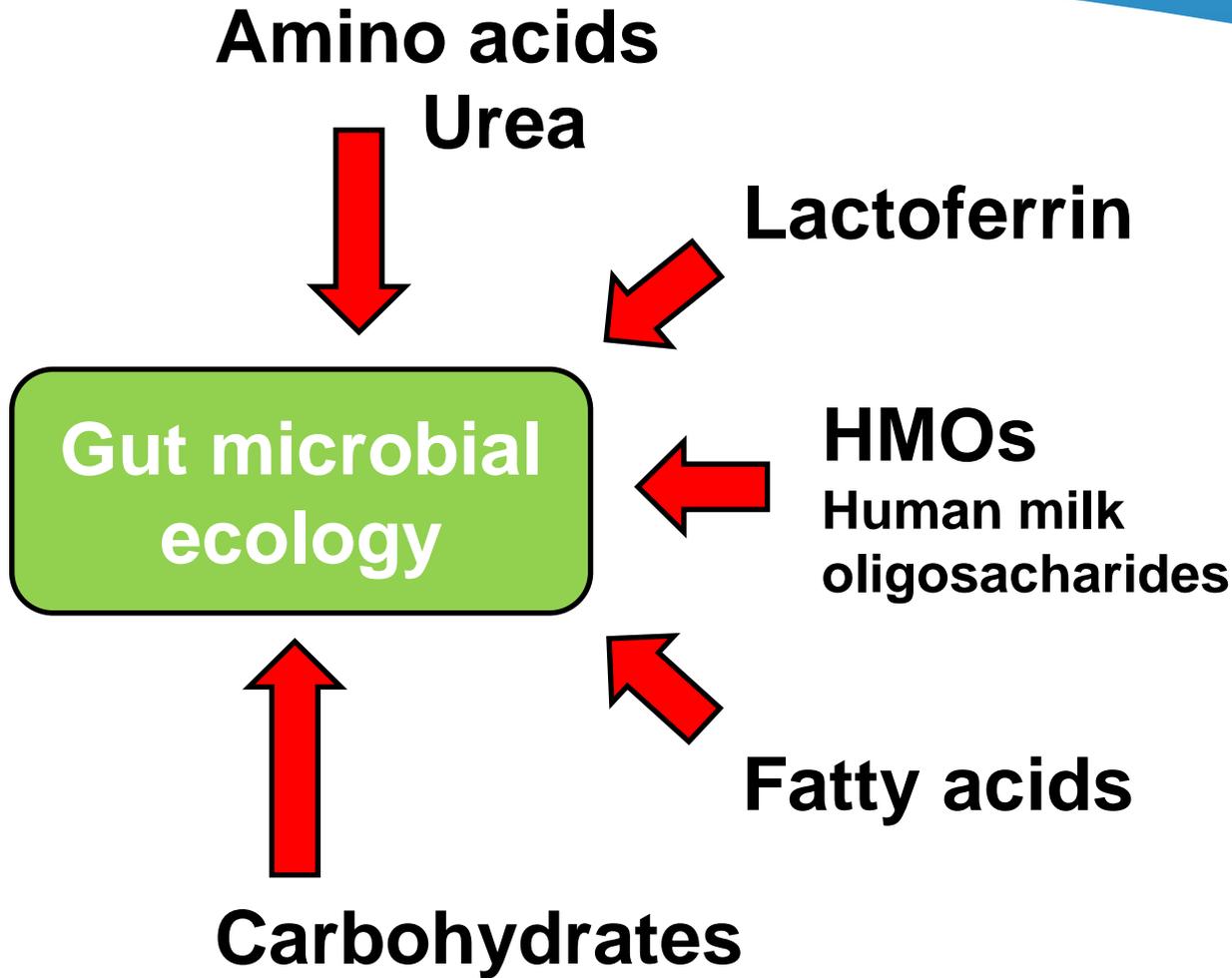
Gut microbial  
communities



Nutrients &  
metabolites



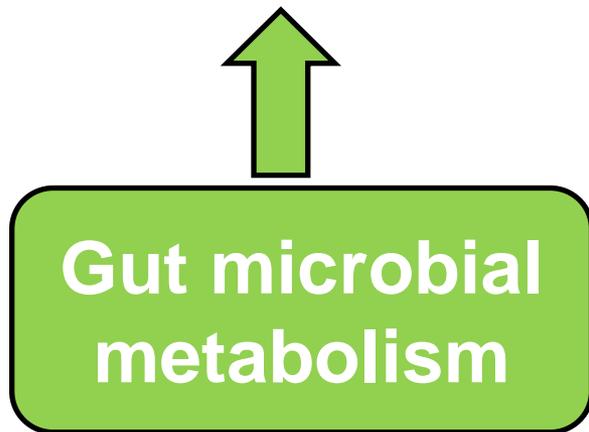
# Key nutrients promote microbes



# Microbes produce key nutrients

## *Host-microbe immuno-metabolic axes*

Short chain fatty acids  
e.g. butyrate



Amino acids  
& peptides

Bile acids

Choline, Vit B & K

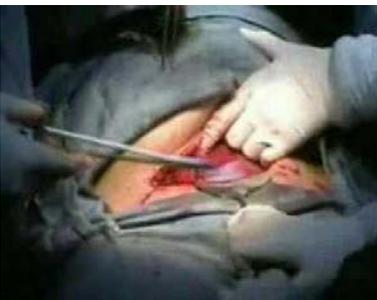
Signalling  
molecules

Molecules with anti- or pro-  
inflammatory effects

# Healthy term infant – birth seeds microbes & genes: essential for immune, gut and brain development



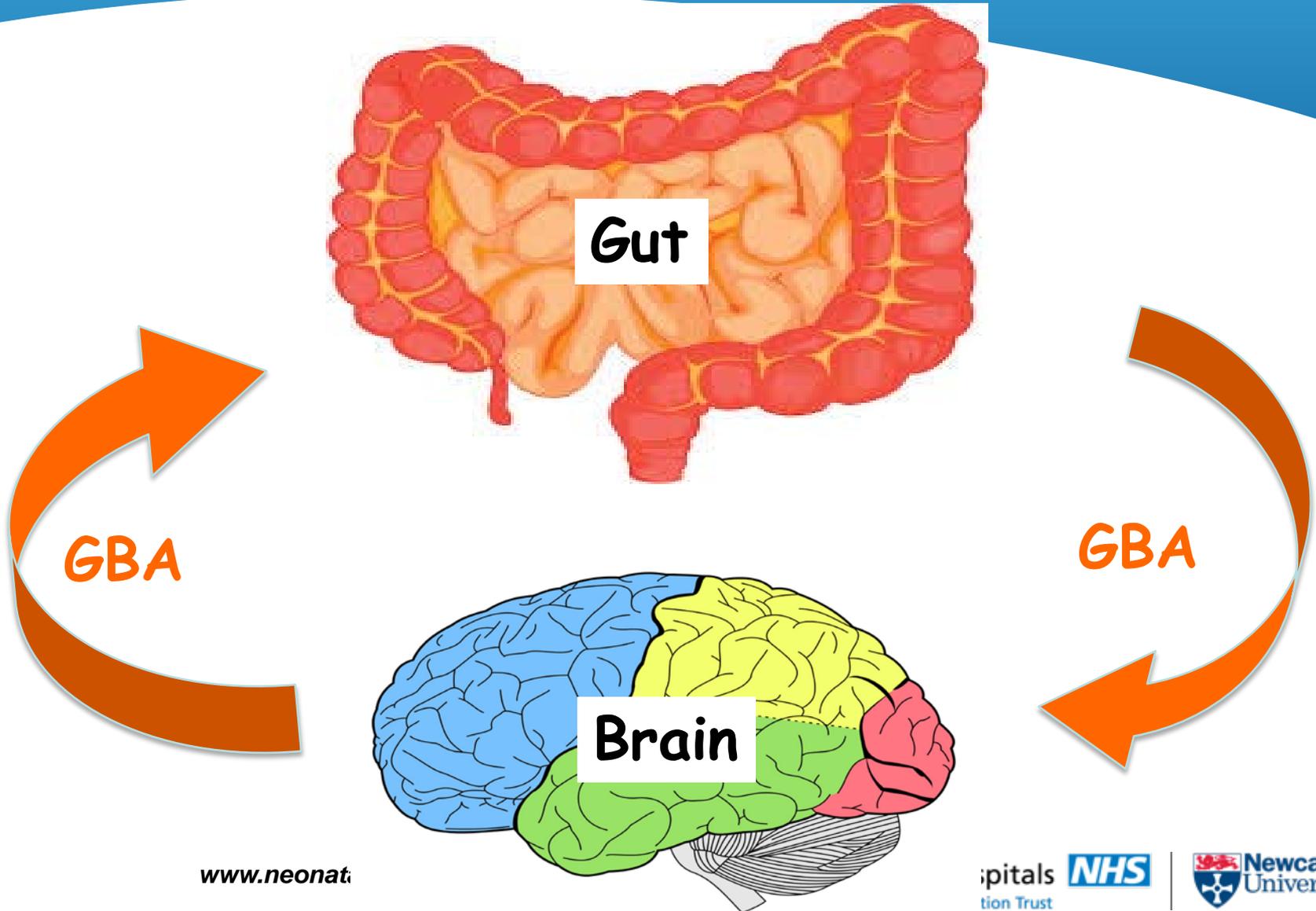
# Birth seeding, breast milk feeding: very different in preterm infants



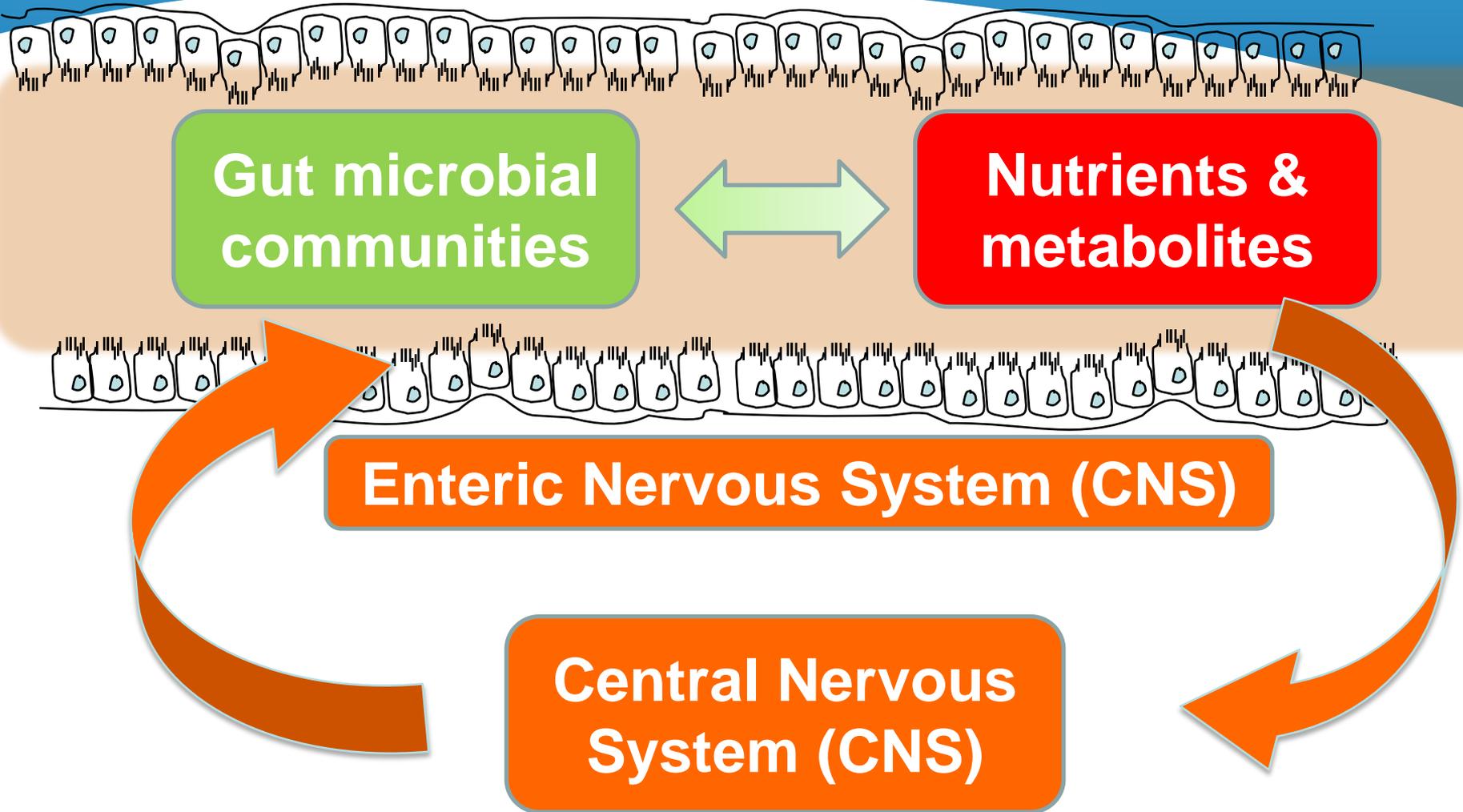
# Nutrition and microbes

- Easy to appreciate importance in preterm infants
  - NEC and sepsis
  - Growth, nutrient assimilation
  - Brain development & signalling
  - Immune function
- NUTRITIONAL STATUS - not simply nutrients
- What is the “Gut Brain Axes (GBA)”?

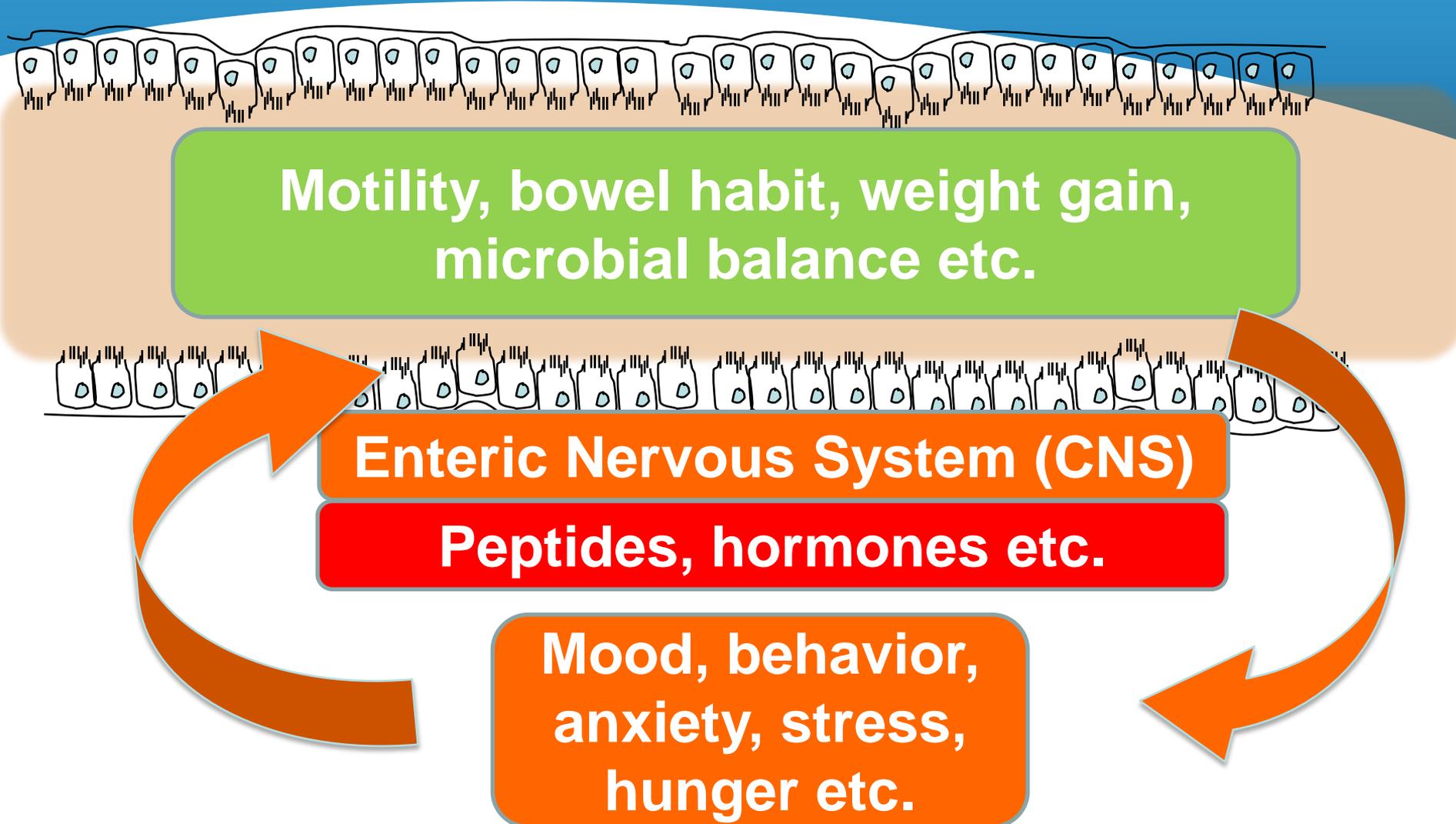
# What is the Gut-Brain Axes (GBA)?



# Gut-Brain Axes (GBA): bi-directional biochemical and neural signaling pathway



# Multiple GBA pathways: neurotransmitters, hormones, peptides, vagus nerve etc.



Motility, bowel habit, weight gain, microbial balance etc.

Enteric Nervous System (CNS)

Peptides, hormones etc.

Mood, behavior, anxiety, stress, hunger etc.

*Sherman et al. 2015*

*Grenham et al. 2011*



# Multiple organ systems and elements

Microbial and host-derived metabolites:  
cytokines, peptides, SCFAs etc.

Smooth  
muscle

ENS

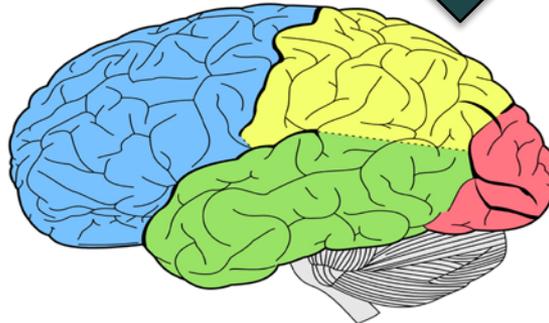
Gut immune  
cells

Adrenal

Vagus  
nerve

Neurotransmitters  
Peptides  
Cytokines

Hypothalamus  
Pituitary

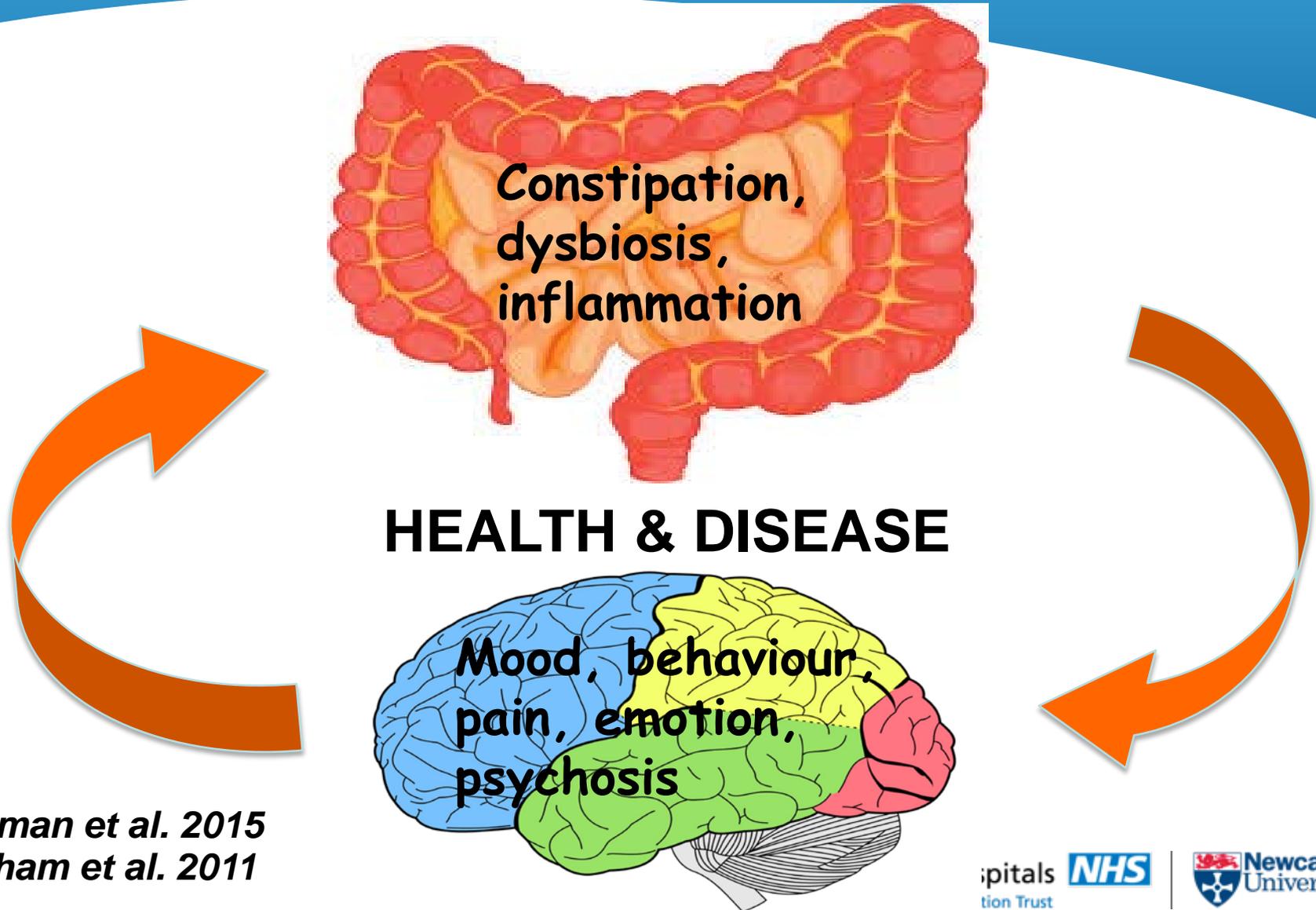


Sherman et al. 2015

Grenham et al. 2011

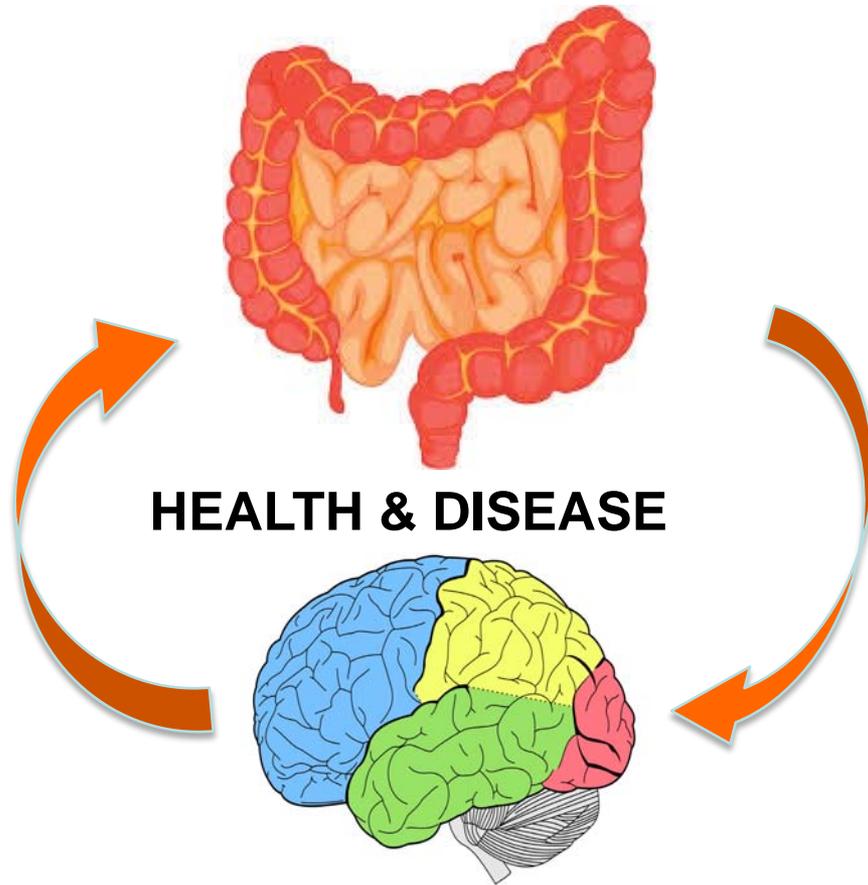
www.neonatalres  
Impro

Lots of data from adults: stress, anxiety, psychosis, Parkinson's disease etc.



*Sherman et al. 2015*  
*Grenham et al. 2011*

# GBA: Multiple areas of potential importance to preterm infants

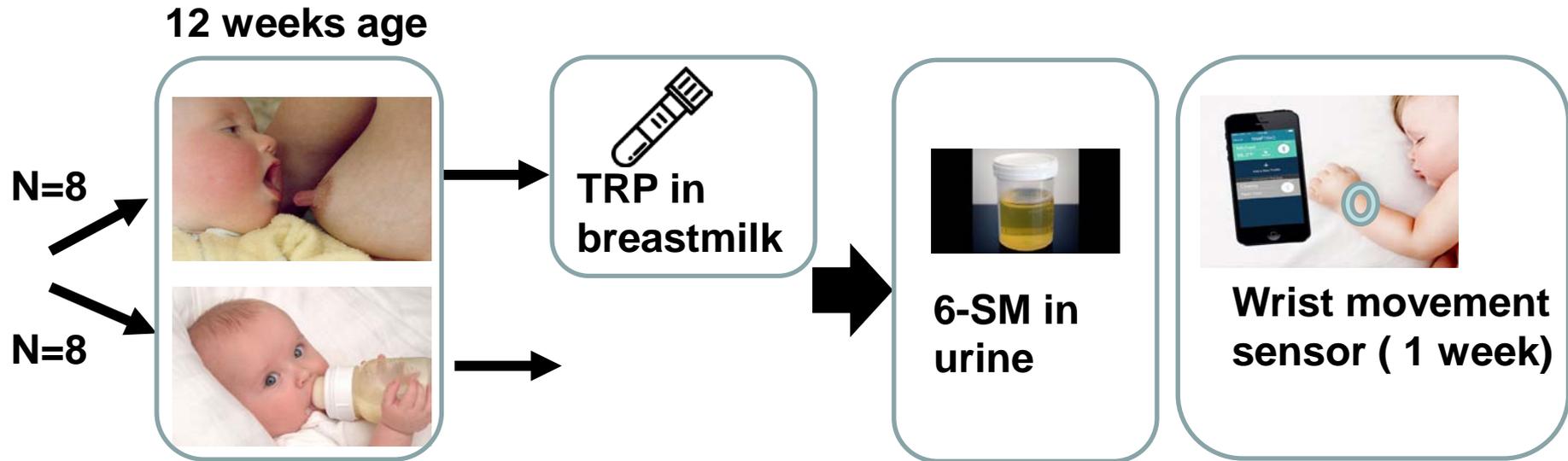


**Gastric emptying / residuals**  
**Motility / abdominal distension**  
**Pain / discomfort**  
**Stool patterns**  
**Hormones / growth**  
**Gene expression**  
**Pro/anti-inflammatory signals**  
**Cytokines**  
**Brain impact of NEC / sepsis etc.**  
**Brain connectome**  
**Nutrient absorption**  
**Sleep patterns**

# Gut brain axes 'at work'

## Breastmilk & tryptophan (TRP)

- Breastfed: better sleep patterns than formula-fed

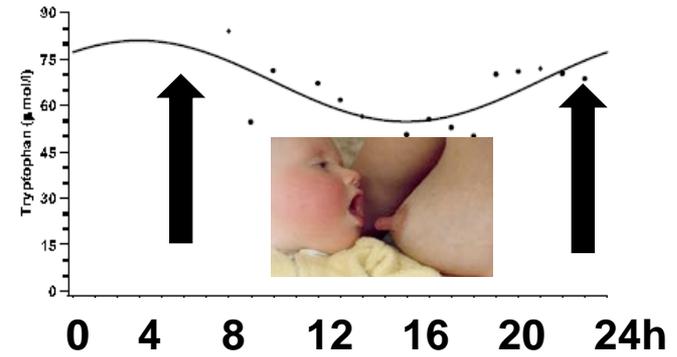


6-SM = 6-sulfatoxymelatonin is metabolite of melatonin excreted in urine

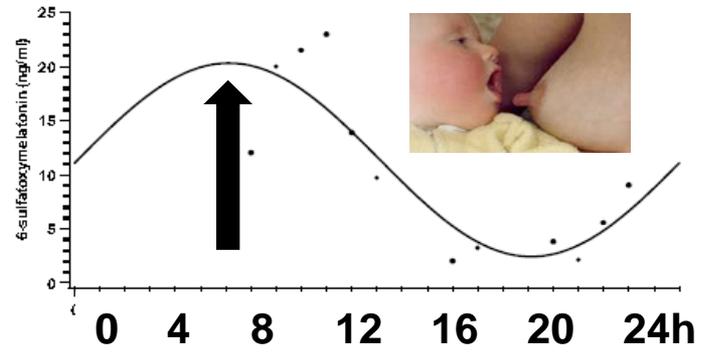
# Breastmilk & sleep

- Actual sleep, and sleep efficiency significantly higher in breast fed infants
- Temporal relationship: urinary 6-SM & breast milk TRP

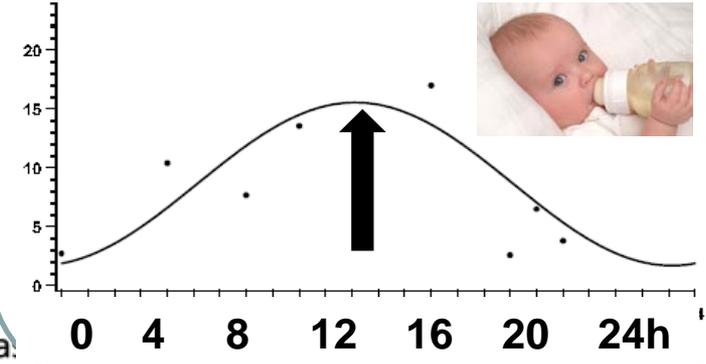
### TRP in breastmilk



### BF: Urine 6-SM peaks 06.00



### Form: Urine 6-SM peaks 12.00



# Nutrition & brain development in preterm infants: at least 6 mechanisms

Nutrients for tissue  
substrate

**Macro- and micronutrients**

Energy to drive the  
system

**Carbohydrate, lipids & ...protein**

Signalling &  
growth factors

**Energy intake, BCAA → IGF-1 etc.**

Impacts on gene  
expression

**Folate, B12, iron, choline etc.**

Gut microbes &  
metabolites

**Prebiotics, HMOs, probiotics**

Prevention of  
disease

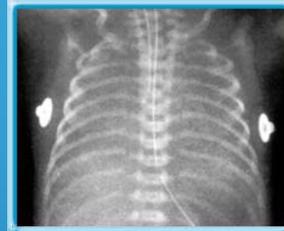
**Breastmilk reduces NEC & sepsis**

# Summary

- Brain growth is rapid
- Nutrient requirements are very high
- Microbes are important
- NEC & sepsis are important causes of death
- Premature infants have worse neurodevelopment

***So why is poor growth & nutrition so common on the NICU?***

# Why is poor nutrition so common? Focus is what we can see and measure



Jaundice & phototherapy  
How high?

Central lines –  
yes/no? when?

Fluids  
60-90-120?

Inotropes  
Which ones?

Heart rate

**Malnutrition is invisible**

Oxygen  
saturation  
85-90-95%?

CPAP, BiPAP or  
Hi-flow

Blood pressure  
How low?

AC PSV VG VT VC HFOV TCPL

**No machine with loud alarm if nutrient  
intakes are inadequate**

Temperature

Blood gases

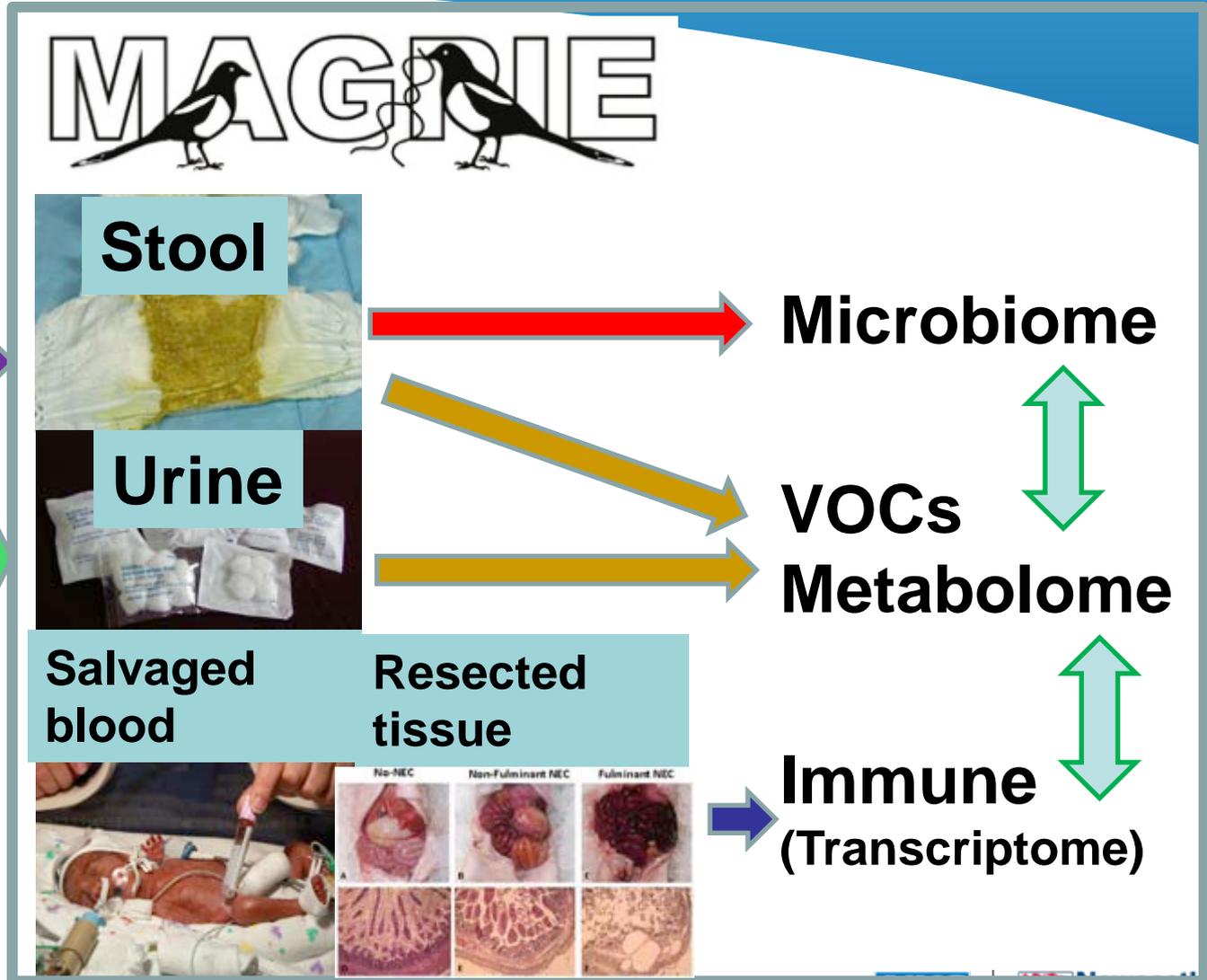
Lactate,  
CRP?

# Nutrition, microbes, metabolism, immunity ...it's all about the brain

- Preterm infants – what are our key aims?
  - Survival
  - ....with good brain development
- Poor motor and cognitive outcome
  - The most important adverse outcome of prematurity
- Good nutrition with **mother's own BREASTMILK**:
  - Feeds the brain with macro- and micronutrients
  - Encourages healthy microbial development
  - Promotes long-term health
  - Prevents disease (especially NEC and sepsis)

**NUTRITION IS MORE THAN NUTRIENTS!**

# Newcastle Neonatal Nutrition Network (N4)



# Final slide - 8 practical ways to improve gut health in preterm infants



# Muchas Gracias!

[www.neonatalresearch.net](http://www.neonatalresearch.net)



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