The gut microbiota and SES in preterm infants in the Chicago area

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Prematurity

- What is full term? 37-40 weeks gestation
- What is prematurity? < 37 weeks gestation
- What is the limit of viability? 22-23 weeks gestation

Prematurity

Full Term, 40 weeks

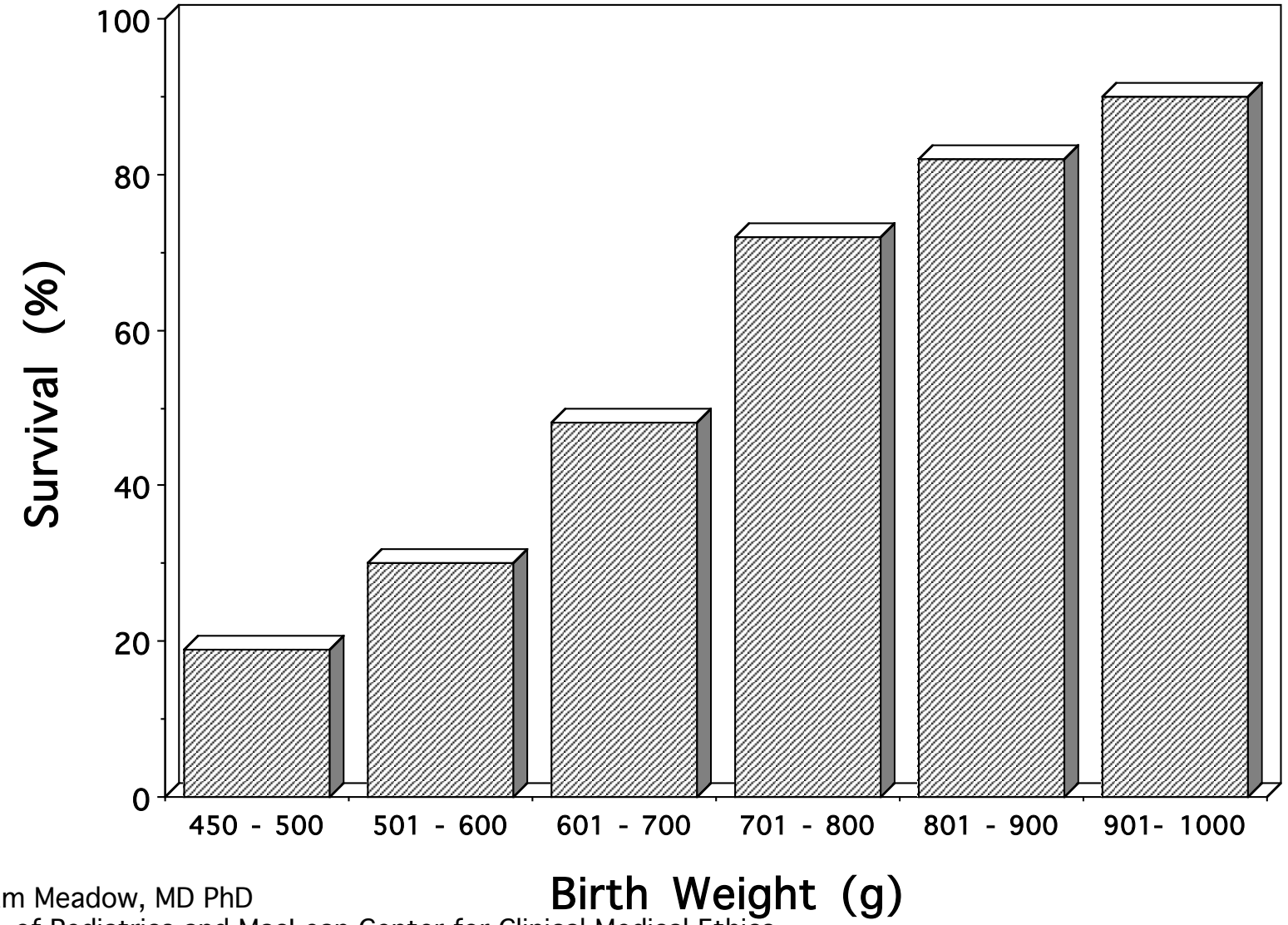
Premature, 23 weeks

Smallest Survivor

Birth weight 8.6 oz

12 oz.

Survival vs Birth Weight for ELBW Infants



William Meadow, MD PhD
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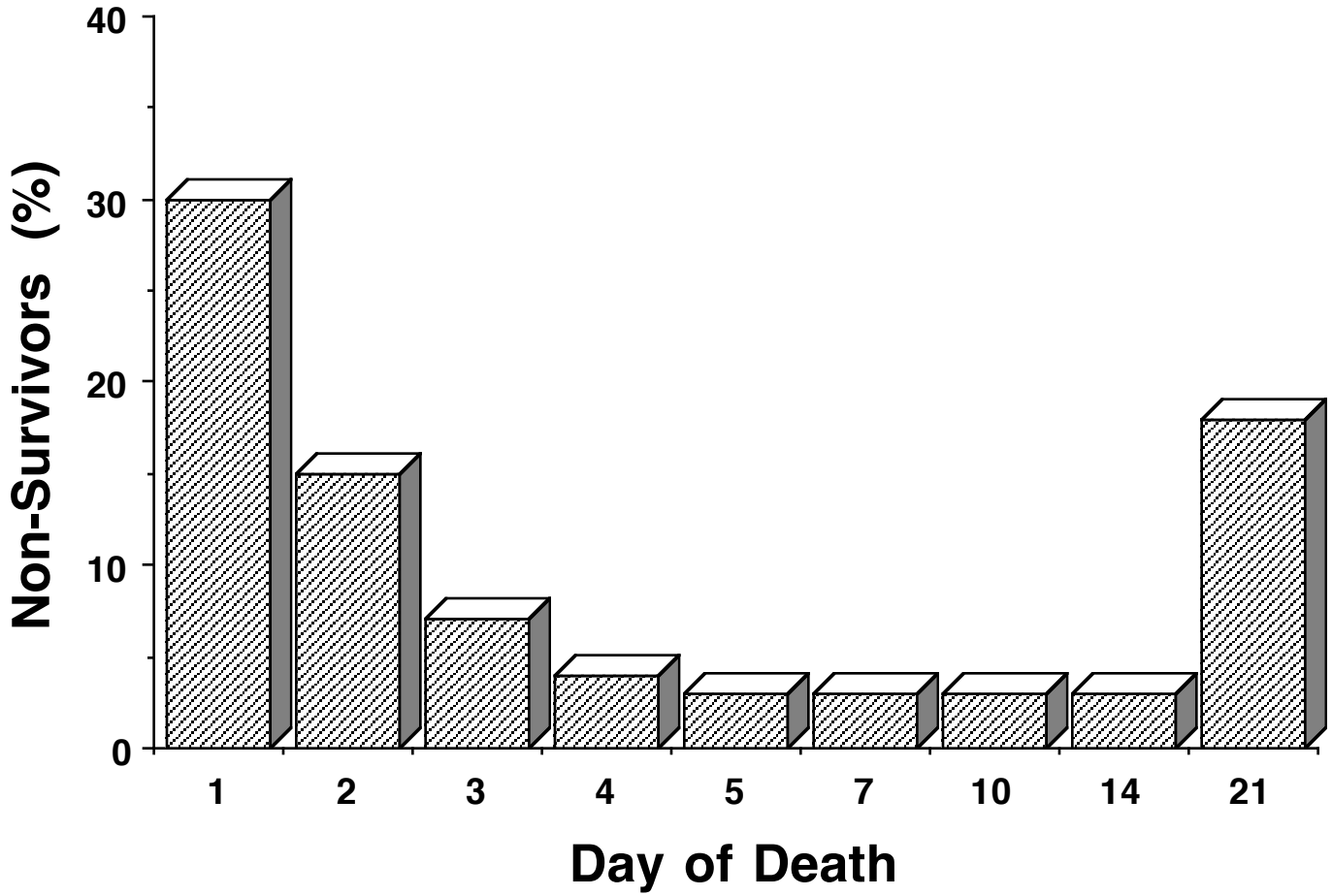
The University of Chicago

Day of Death for ELBW Non-Survivors



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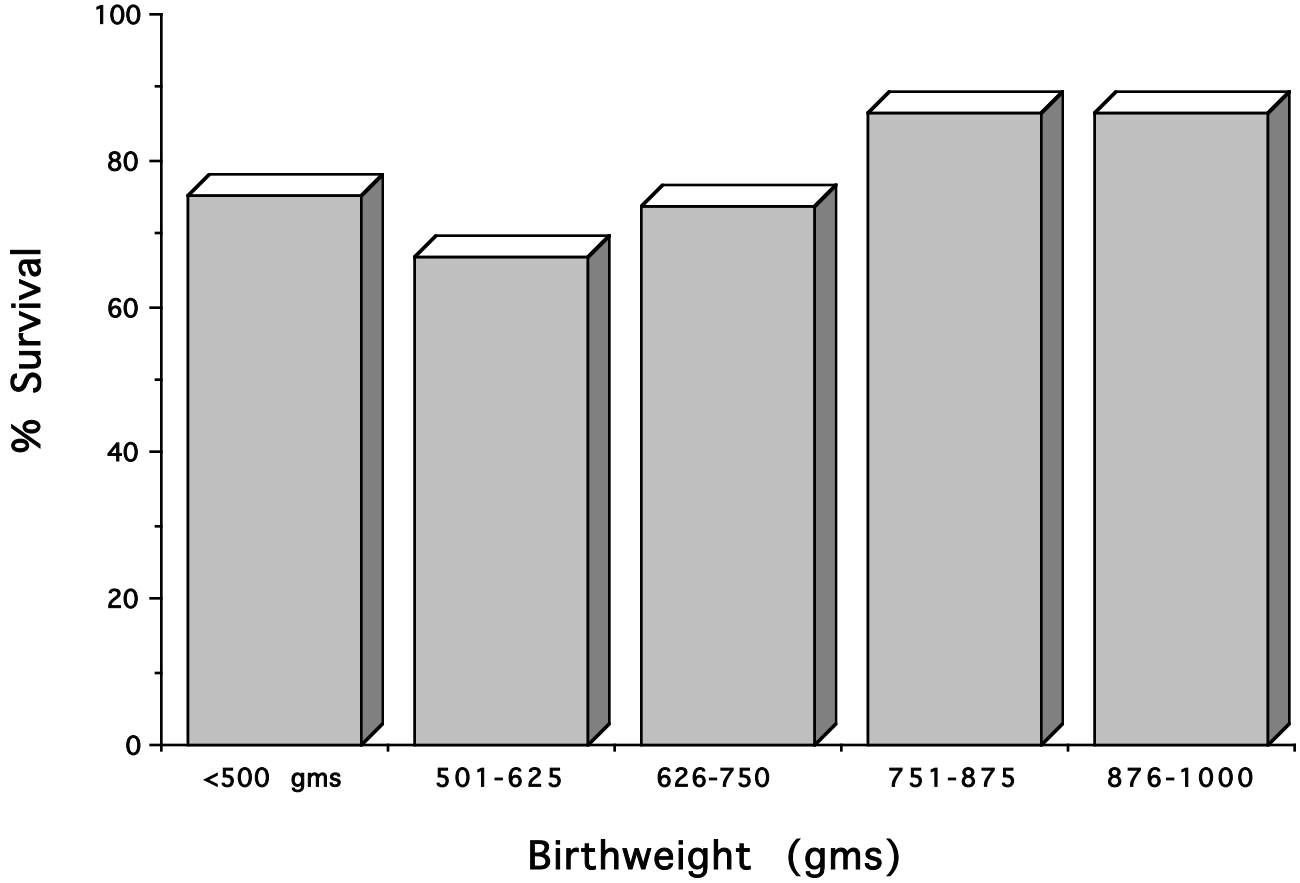
Survival as a function of birthweight for all patients alive on Day 4 (n = 249)



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The Preterm Infant - 12% of births

Disproportionately account for:

40% of children who have cerebral palsy (CP)

25% of children with hearing impairment

35% of those with vision impairment.

The NICU

NICU

Antibiotics

Delayed Feeding

Breast Milk vs. Formula

H2 Blockers

Opioids

Instrumentation

The Value of Preterm Infant Environmental Health Cohorts
The Canary in the Coal Mine

Annemarie Stroustrup, MD, MPH[1,2]; Susan L. Teitelbaum, PhD[2]; Judy L. Aschner, MD[3]

» Author Affiliations | Article Information

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Like the canary in the coal mine—or asthmatics in air pollution studies—children born preterm may serve as a sentinel population owing to increased susceptibility to the sometimes modest effects of common toxicants, improving study power and decreasing necessary sample size.

Necrotizing Enterocolitis (NEC)-

Inflammatory bowel necrosis that primarily afflicts premature infants after the initiation of enteral feeding.

Risk Factors

- Prematurity
- Bacterial Colonization
- Enteral Feeding
- Hypoxia/Altered intestinal blood flow

NEC and Neurologic Outcome

Neurodevelopmental and Growth Outcomes of Extremely Low Birth Weight Infants after NEC Hintz, et al Pediatrics 2005

Multicenter, retrospective analysis 1995-1998

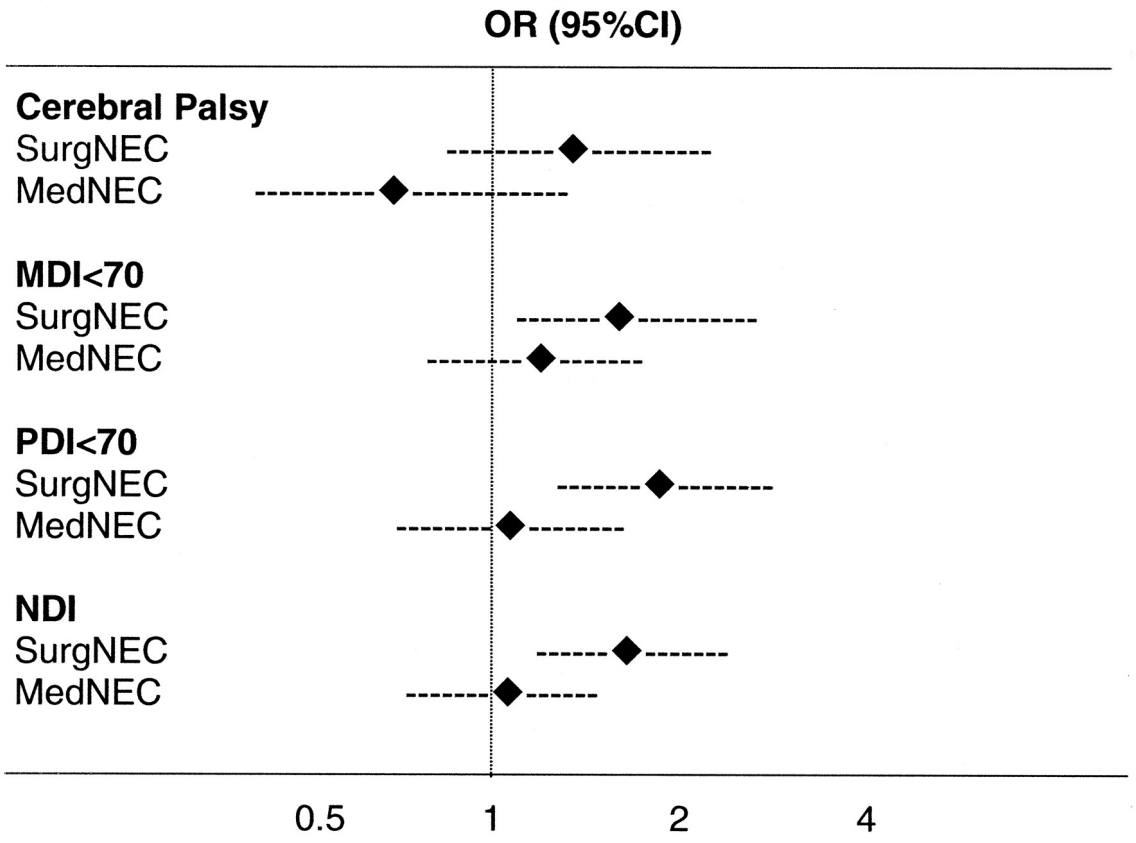
Infants in NICHD Neonatal Network <1000gm

5553 ELBW entered into registry

2948 infants evaluated at 18 and 22 months

- 124 – surgically managed NEC
- 121 – Medically managed NEC

Neurodevelopmental Outcome associated with NEC



SurgNEC

PVL 14% vs. 7%
BPD 57% vs. 43%
CP 24% vs 15%
Decreased growth all parameters

Hintz, S. R. et al. Pediatrics 2005;115:696-703

PEDIATRICS®

Hypothesis:

Enteral feeding results in colonization of the uniquely susceptible premature intestine with pathogenic bacteria, resulting in an exaggerated inflammatory response.

FASEB 2001; 15: 1398-1403

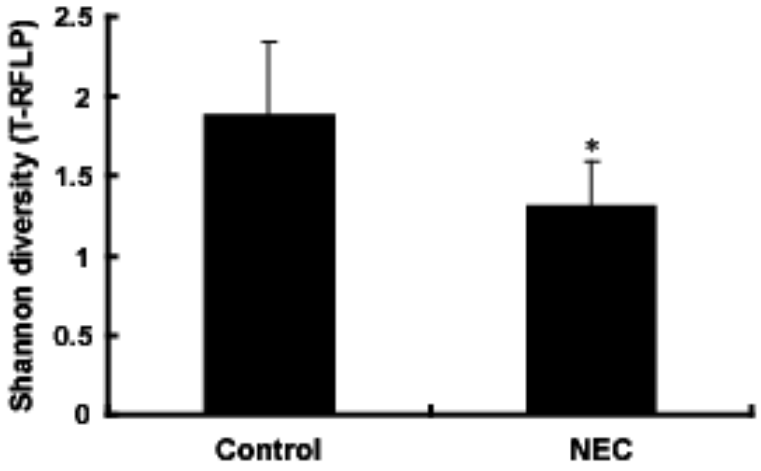
Question:

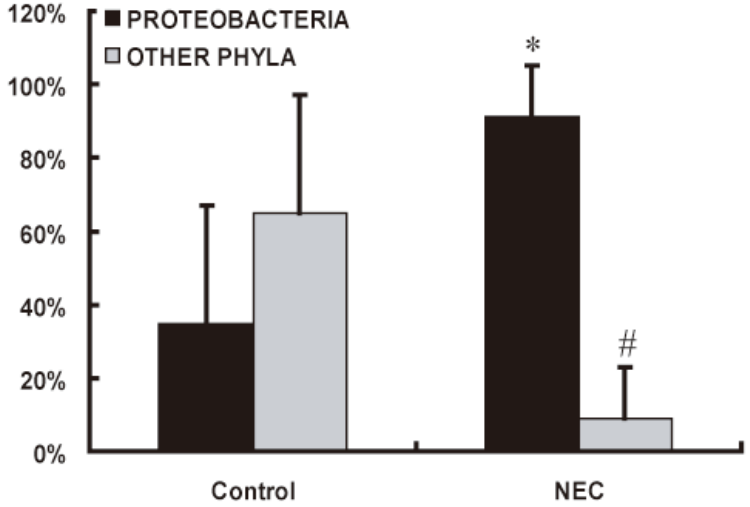
- Can microbiome analysis be used to identify the pathogenic bacteria associated with NEC?

Methods:

- 20 patients - 10 with NEC 10 control
  - 4 sets of twins
- Analysis of fecal samples prior to onset of NEC by 16S rRNA sequencing

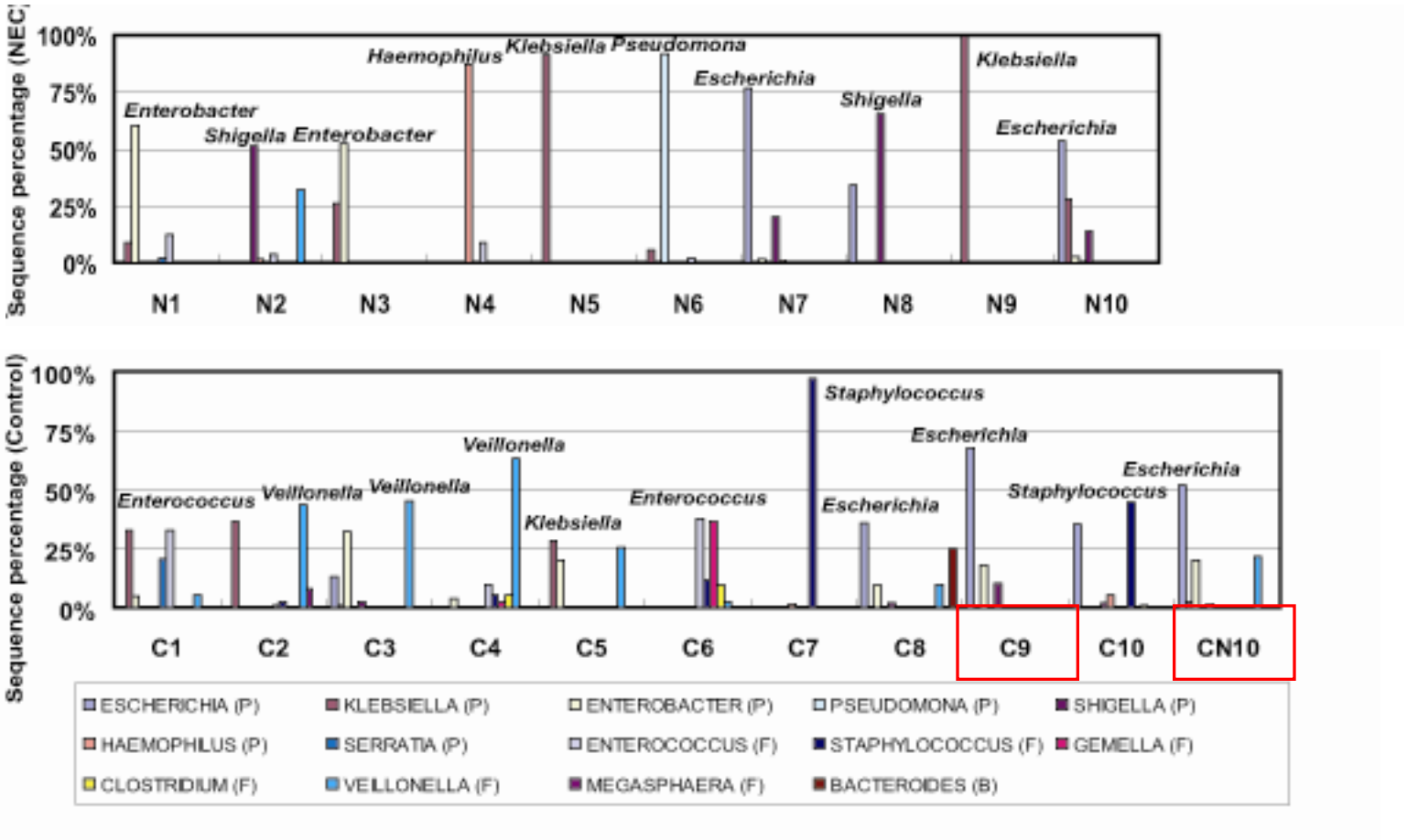
Bacterial Diversity and NEC





Wang et al ISME 3(8):944-54, 2009.

Bacterial Colonization and NEC



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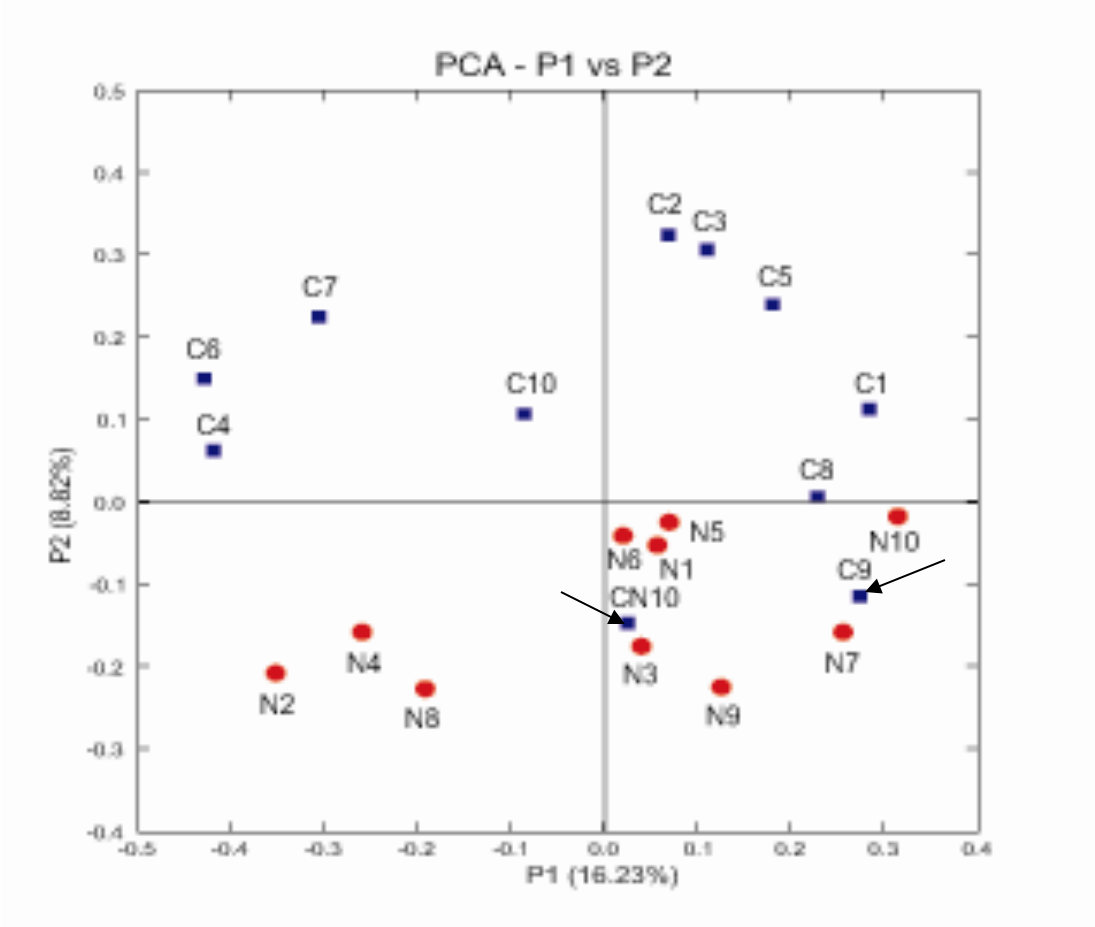
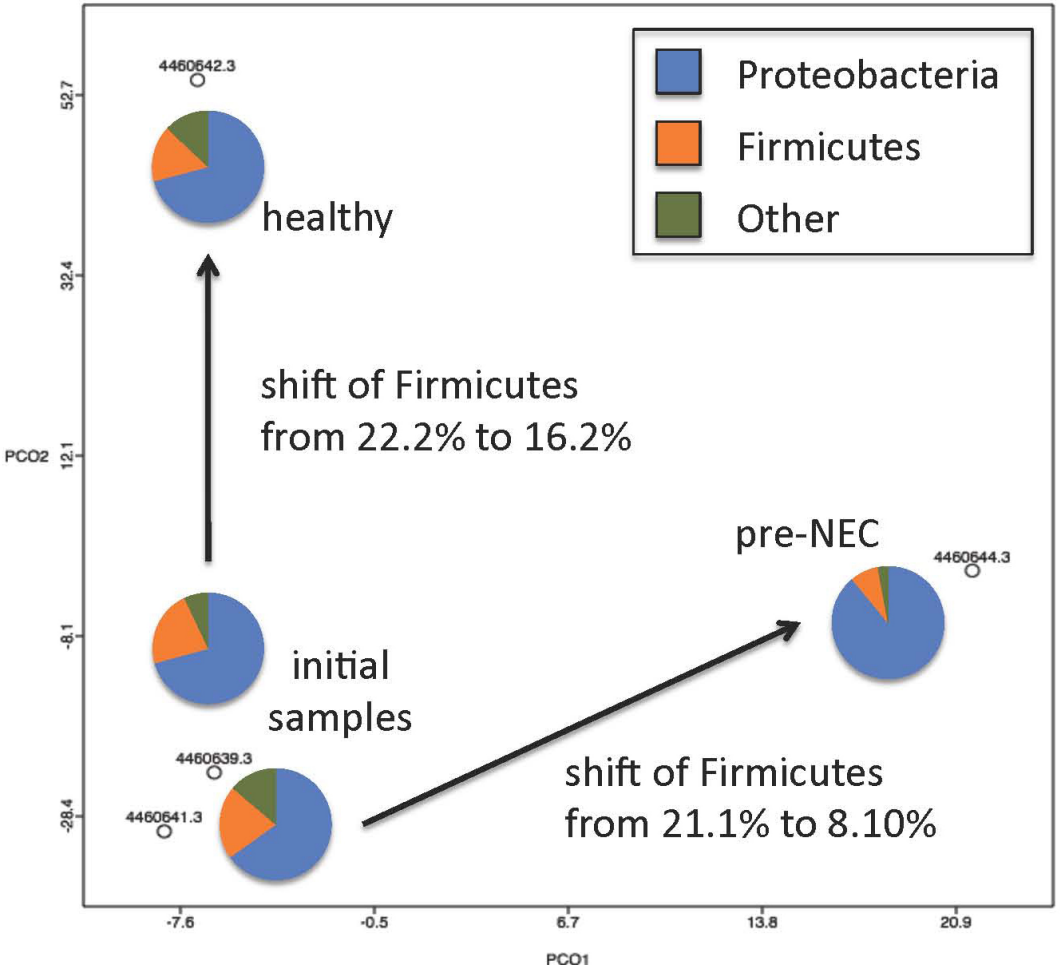
Bacterial Colonization and NEC



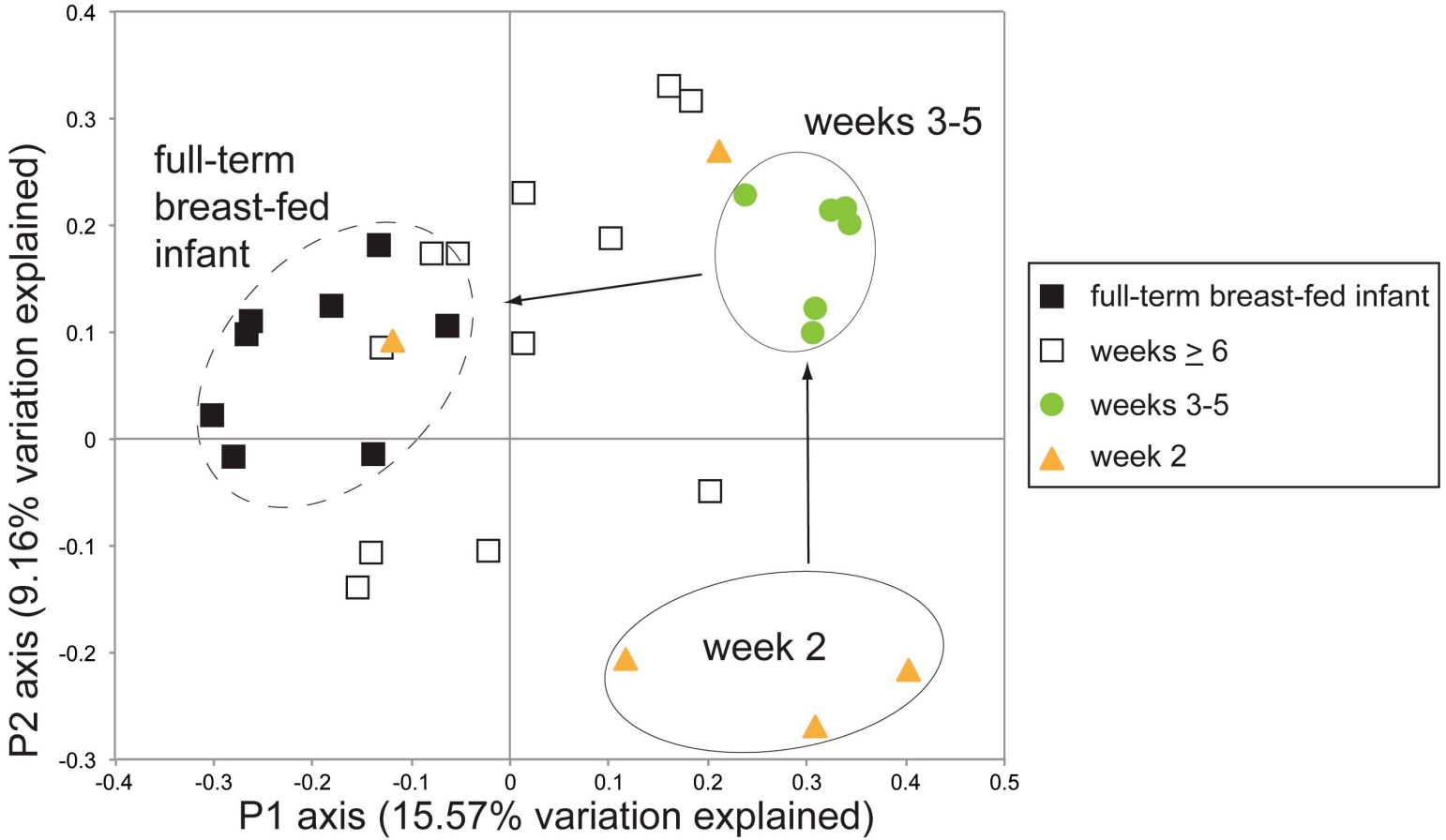
Wang et al ISME 3(8):944-54, 2009.

Shift in Microbiome



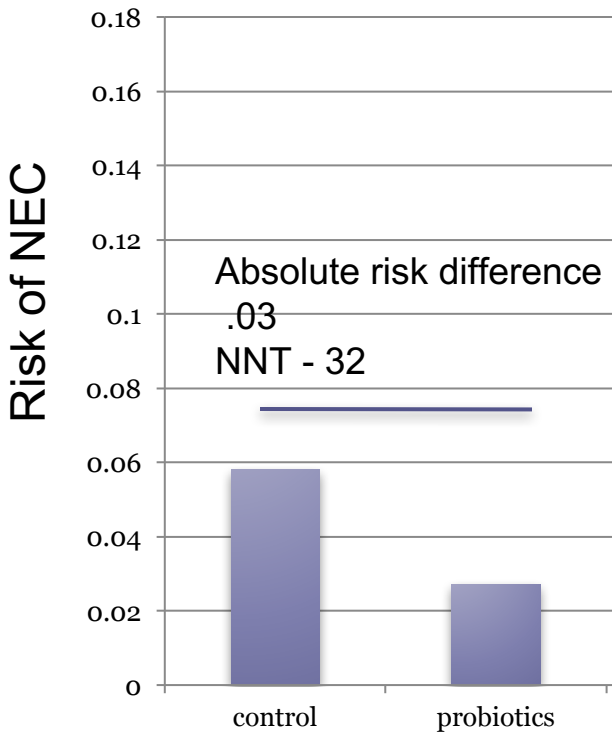
Claud et al. Microbiome, 2013

Temporal progression of the preterm infant microbiota



Claud et al. Microbiome, 2013

Modification of the early microbiome and NEC



AlFaleh K and Anabrees J The Cochrane Collaboration 2014;
Cotten et al Pediatrics 2009 January; 123: 58-66;
Meinzen-Derr et al J Perinatol 2009 January; 29 (1): 57-62

Prematurity

Full Term, 40 weeks

Premature, 23 weeks

Host development coincides with microbiome development

Growth in the Neonatal Intensive Care Unit Influences Neurodevelopmental and Growth Outcomes of Extremely Low Birth Weight Infants

Richard A. Ehrenkranz, MD[a], Anna M. Dusick, MD[b], Betty R. Vohr, MD[c], Linda L. Wright, MD[d], Lisa A. Wrage, MPH[e], W. Kenneth Poole, PhD[e], for the National Institutes of Child Health and Human Development Neonatal Research Network

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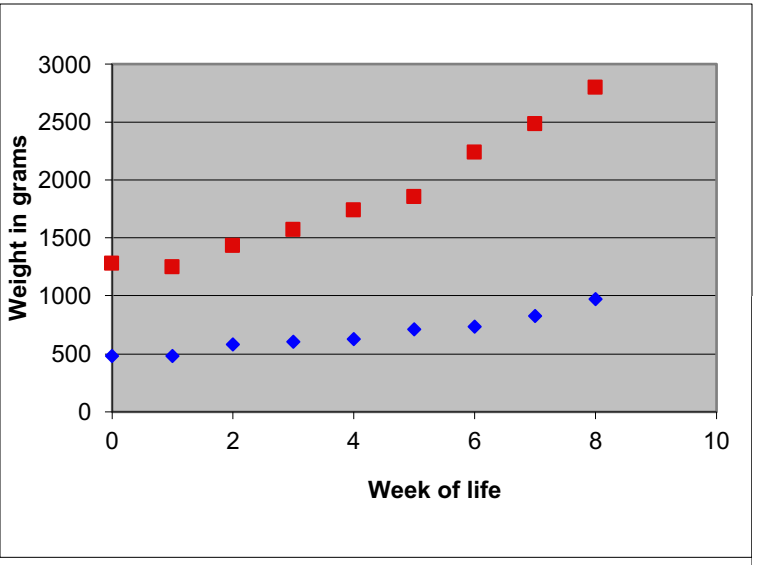
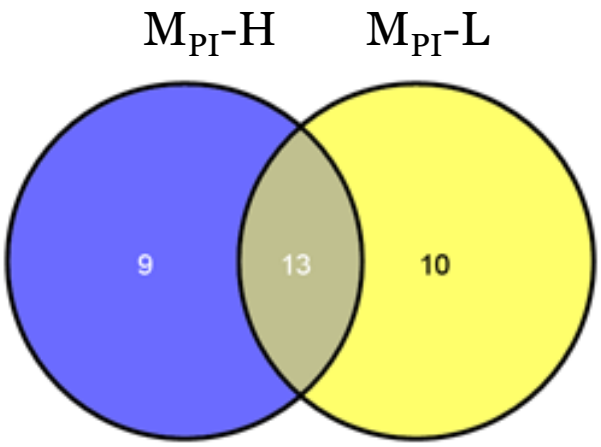
The authors have indicated they have no financial relationships relevant to this article to disclose.

CONCLUSIONS. These analyses suggest that growth velocity during an ELBW infant's NICU hospitalization exerts a significant, and possibly independent, effect on neurodevelopmental and growth outcomes at 18 to 22 months' corrected age.

Pediatrics 2006

Preterm Infant Microbiota (M_{PI})





Good weight gain M_{PI}-H 12 do

Pyrosequencing ID	% of Total Flora
Comamonas sp	21
Weissella confusa	13
Leuconostoc citreum	10
Comamonas testosteroni	10
Lactococcus sp	10
Acinetobacter sp	3
Citrobacter sp	3
Lactococcus lactis	3
Delftia sp	2
Polaromonas sp	2
Alcaligenes sp	2
Enterococcus italicus	1
Streptococcus sp	1
Chryseobacterium bovis	1
Lactococcus raffinolactis	1
Aeromonas sp	1
Arcobacter butzleri	0.5
Brevundimonas sp	0.5
Fusobacterium sp	0.5
Bacteroides sp	0.5
Veillonella sp	0.5
Weissella cibaria	0.5

Poor weight gain M_{PI}-L 6 do

Pyrosequencing ID	% of Total Flora
Comamonas sp	16
Weissella confusa	15
Leuconostoc citreum	12
Lactococcus sp	12
Comamonas testosteroni	11
Citrobacter sp	6
Delftia sp	4
Lactococcus lactis	4
Acinetobacter sp	3
Streptococcus sp	2
Enterobacter sp	2
Lactococcus raffinolactis	1
Leuconostoc sp	1
Flavobacterium sp	1
Stenotrophomonas maltophilia	1
Ralstonia sp	0.5
Moraxella osloensis	0.5
Veillonella sp	0.5
Pseudomonas sp	0.5
Acidovorax sp	0.5
Achromobacter sp	0.5
Weissella cibaria	0.5
Kordia sp	0.5

Transfer of infant microbiome to germ free mice

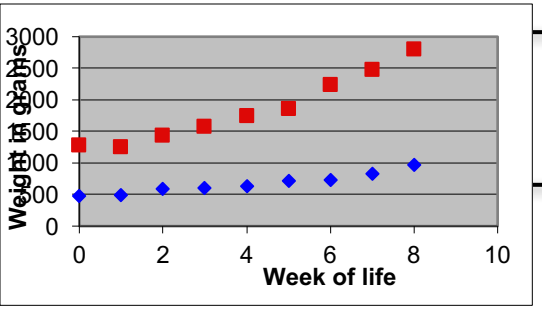
Fecal lysate from infant

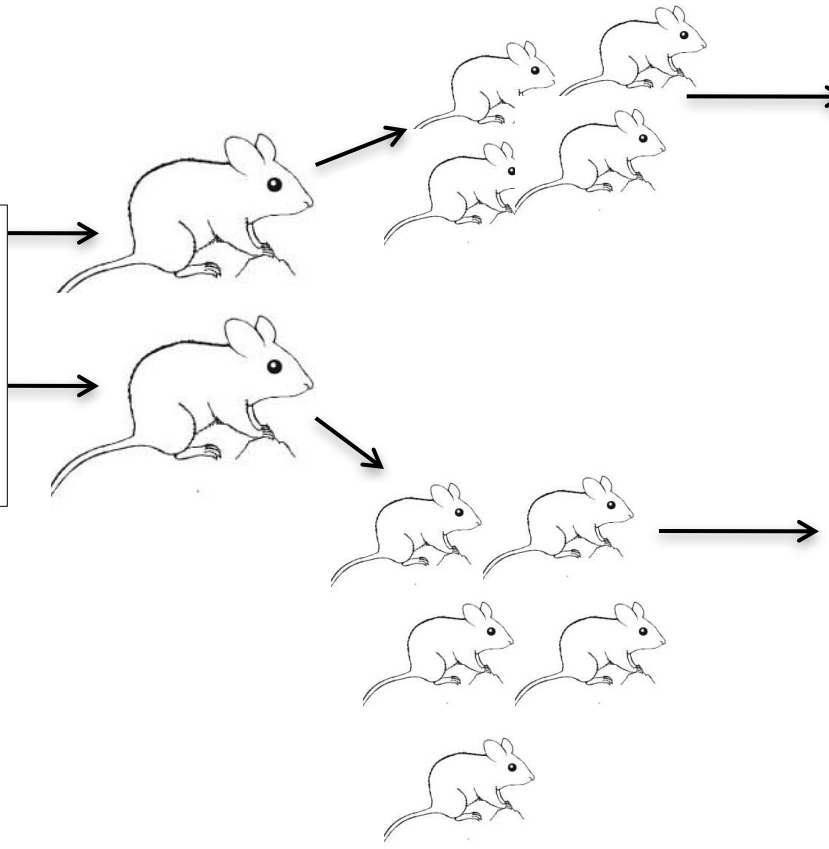
Germ free pregnant dam C57/Bl6

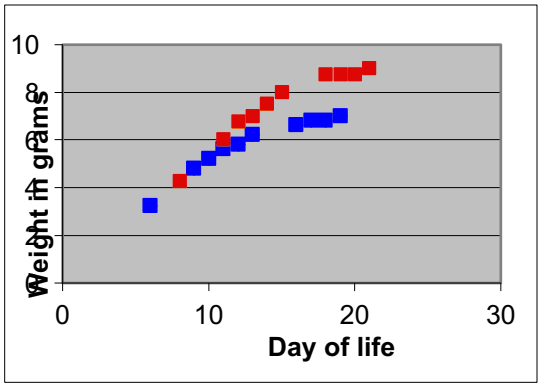
Litter

Daily weight

Wean

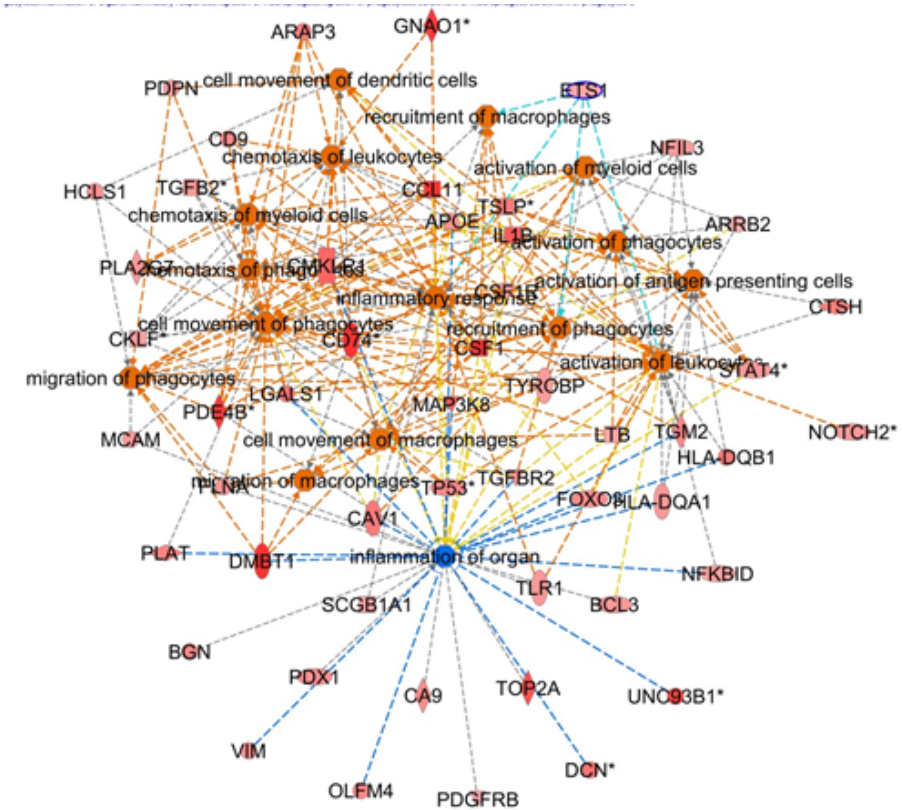




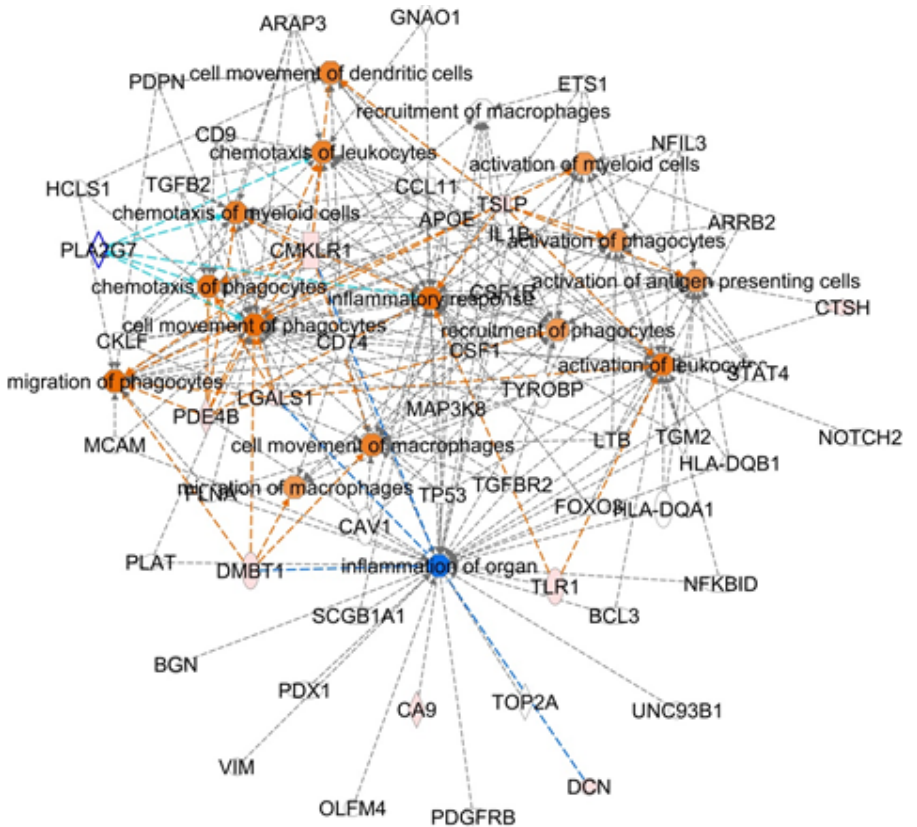


Inflammatory Response Related Networks

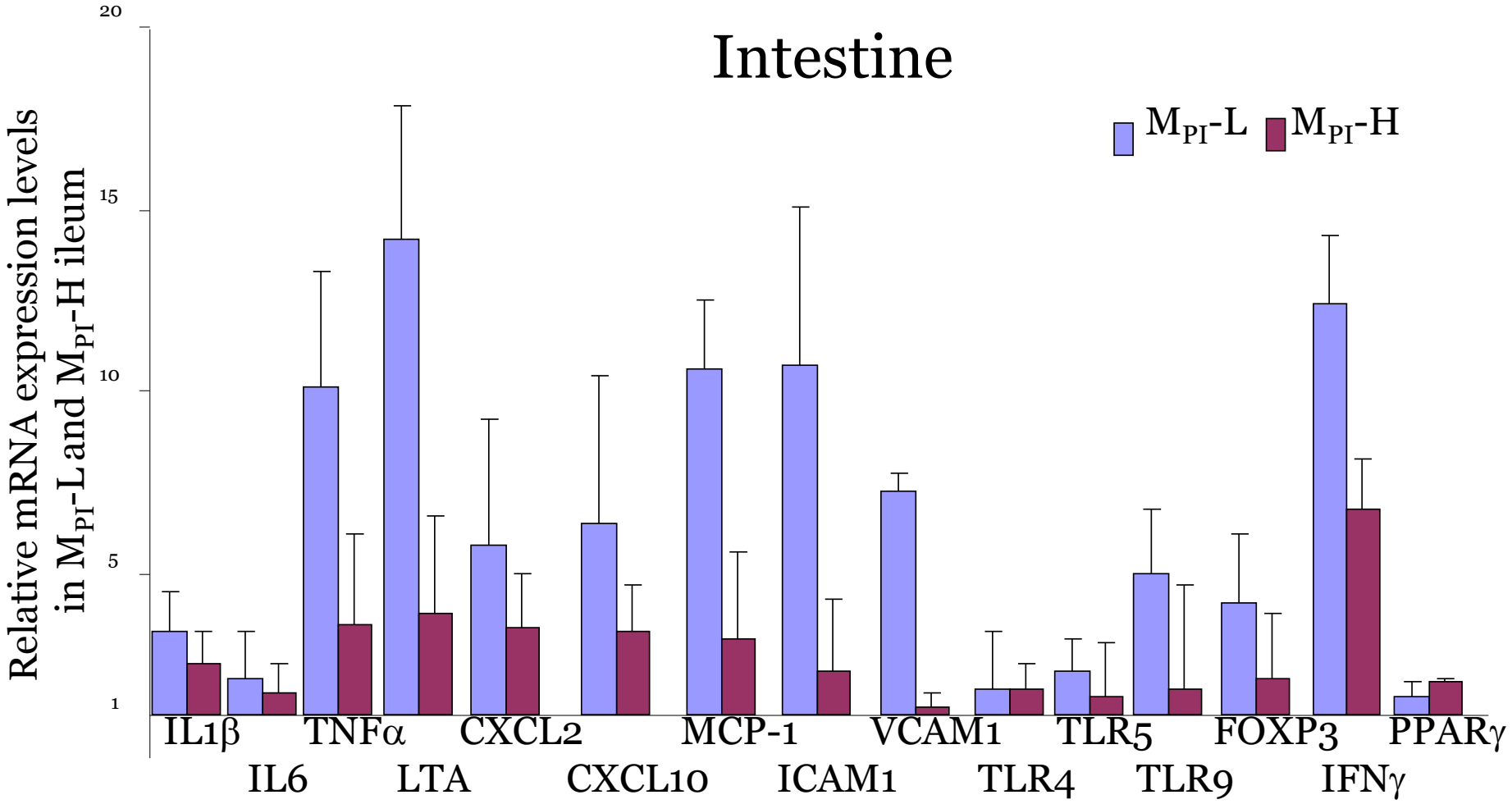
M_{PI}_L



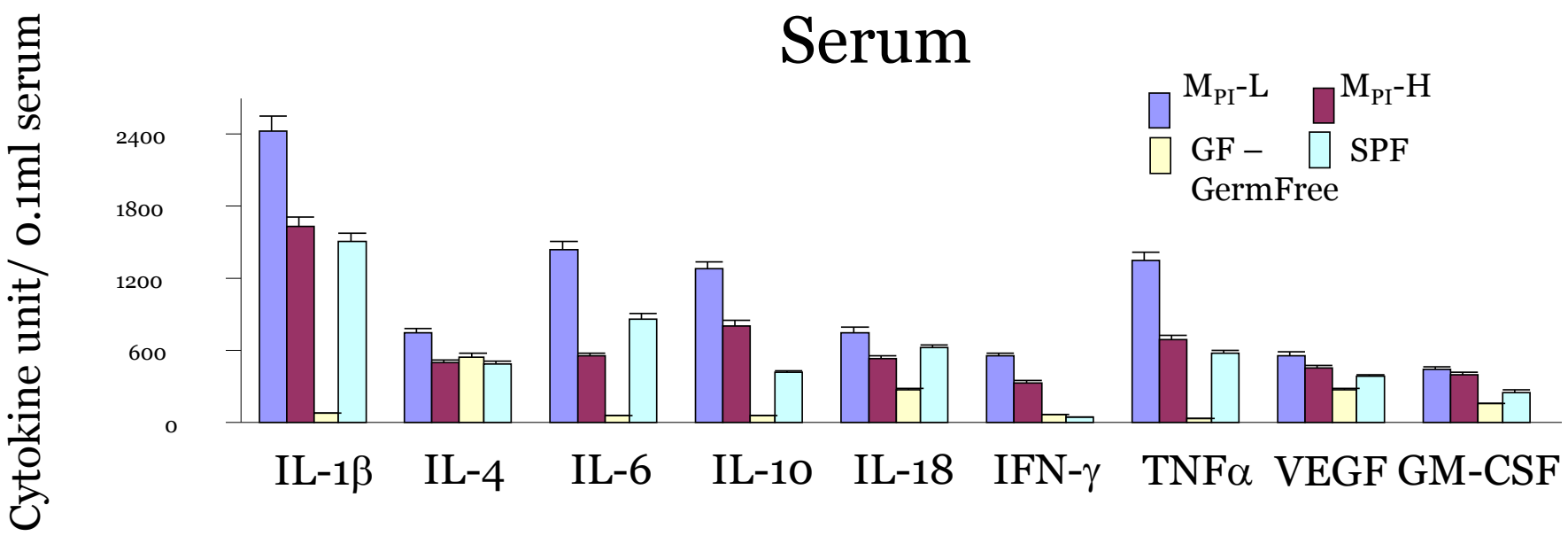
M_{PI}_H



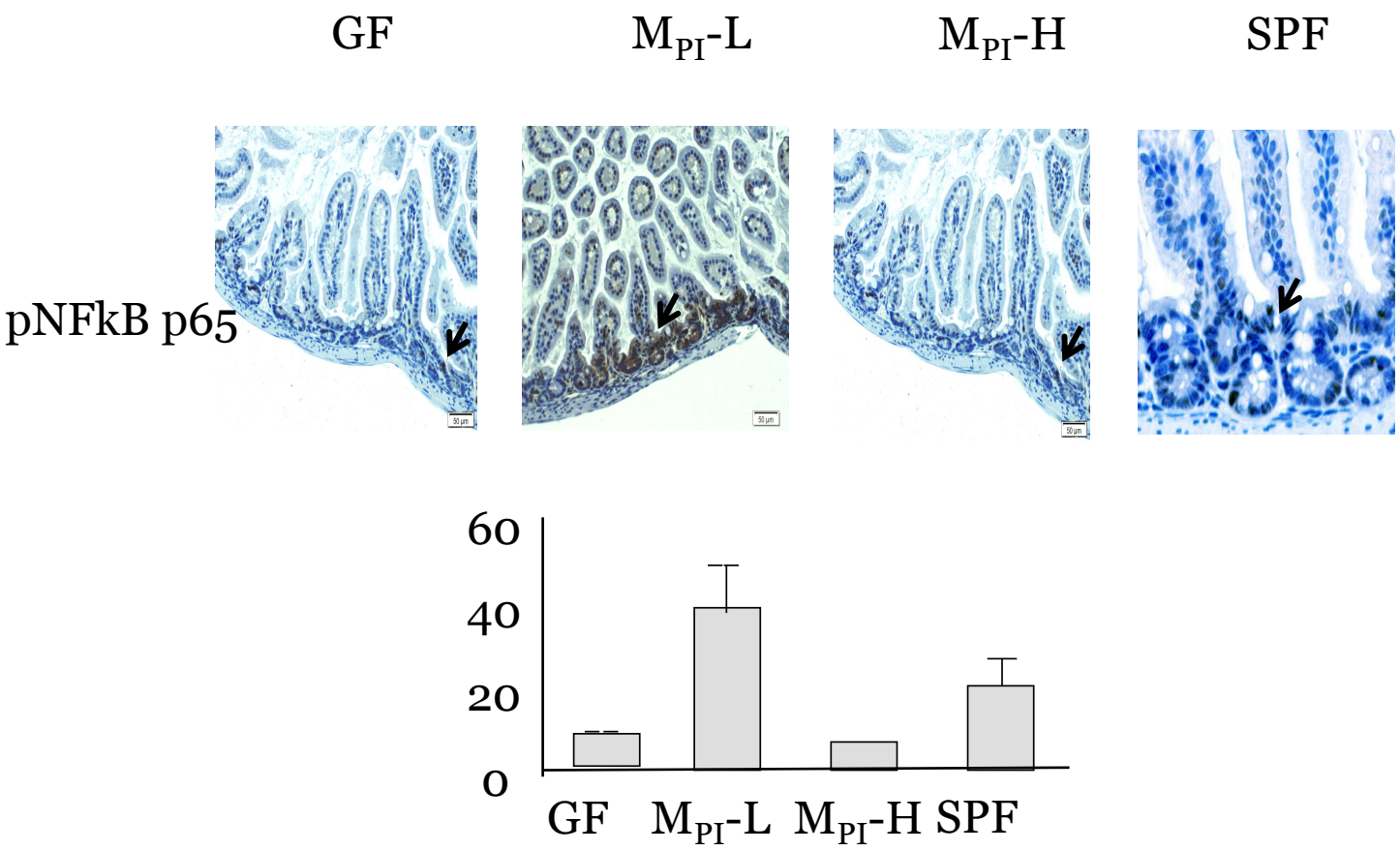
PCR validation of Microarray



Cytokine Expression

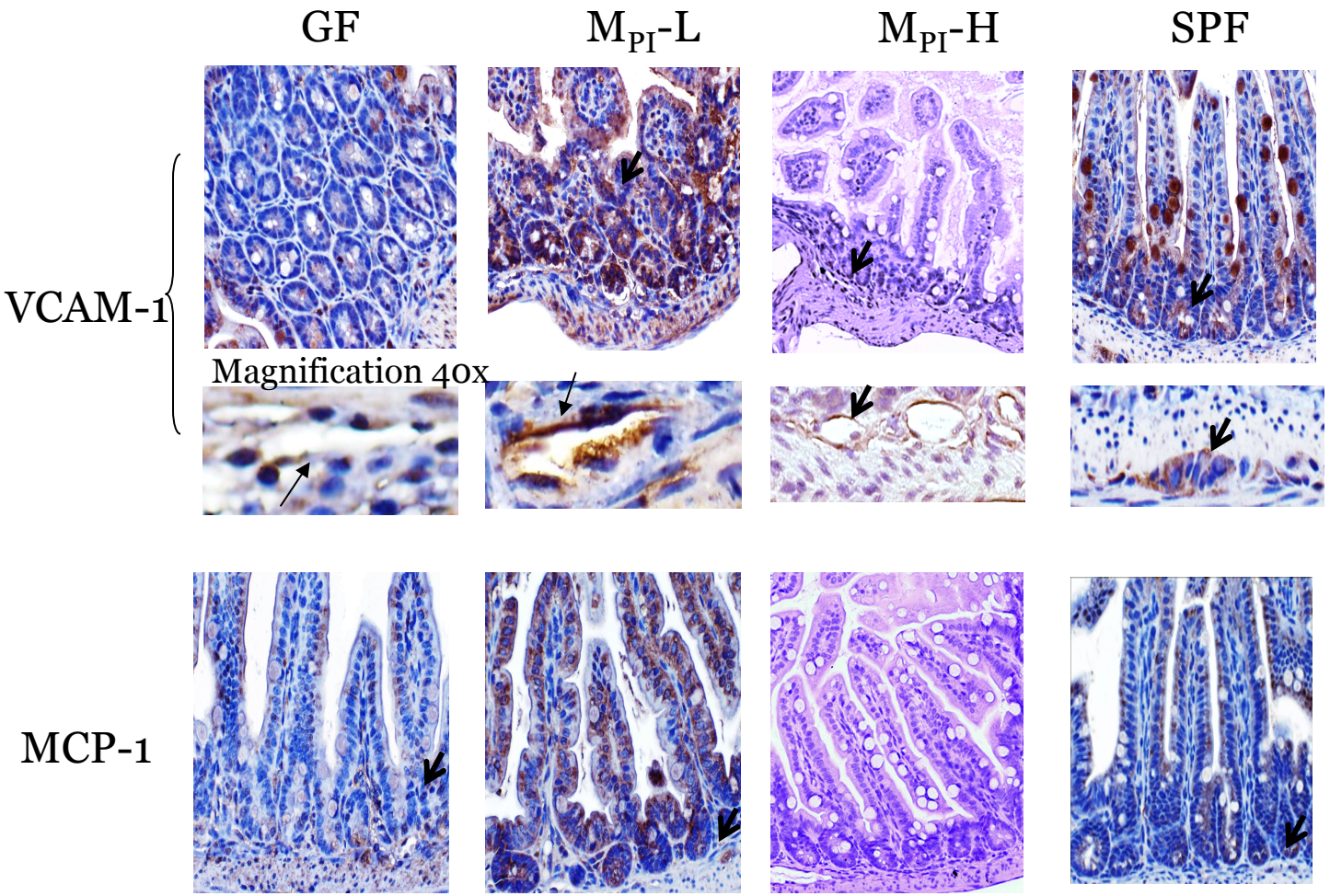


NF-κB Activation



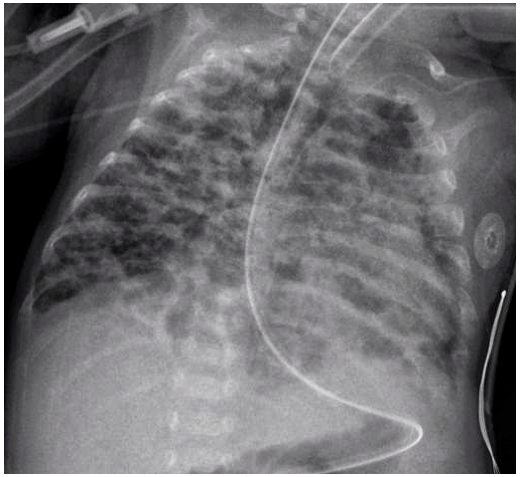
Labeling index for pNFκB p65 nuclear translocation

NF-κB Dependent Cytokines

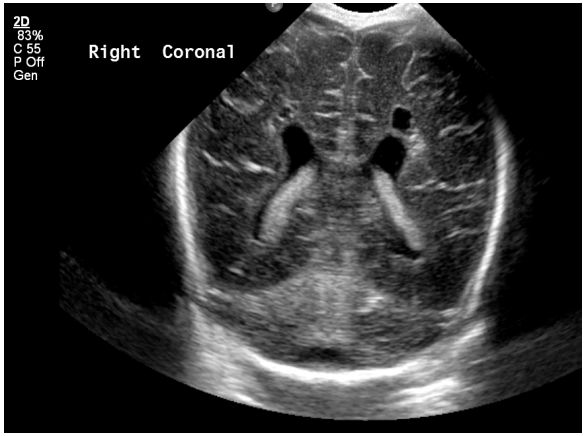


Inflammation and Prematurity

NEC



BPD



PVL

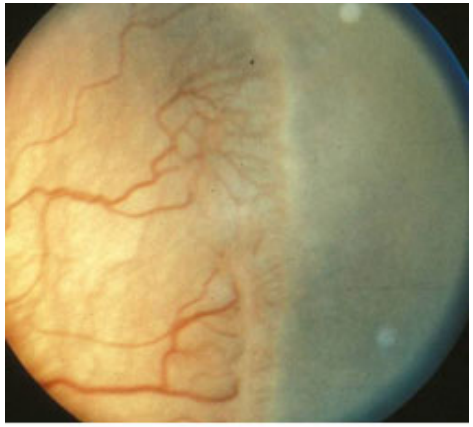


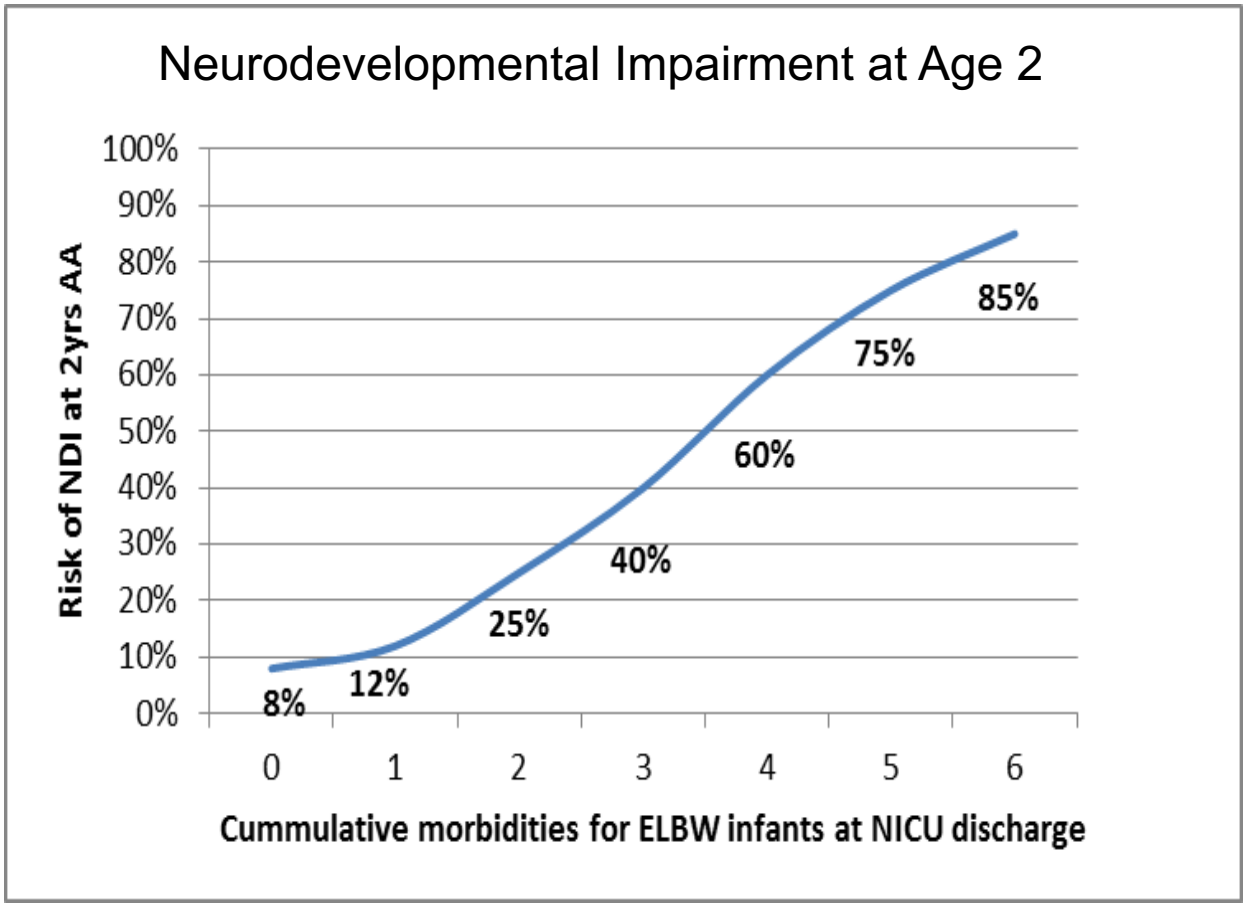
Fig. 3 Stage 3 ROP.

ROP

Neurodevelopmental Outcome in Preterm infants

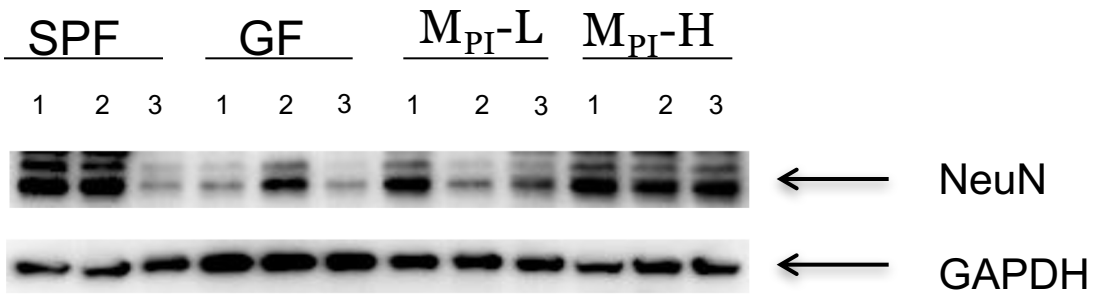
Morbidities

1. Bronchopulmonary dysplasia
2. Necrotizing Enterocolitis
3. Intraventricular Hemorrhage
4. Periventricular Leukomalacia
5. Retinopathy of Prematurity
6. Sepsis

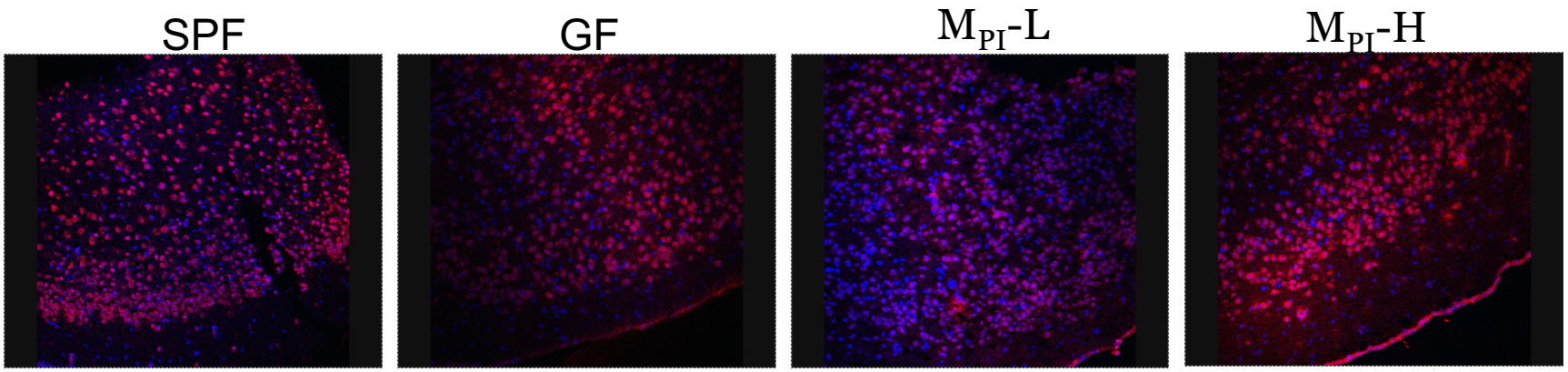


Regulation of cortex neuronal development by gut microbiota.

A.

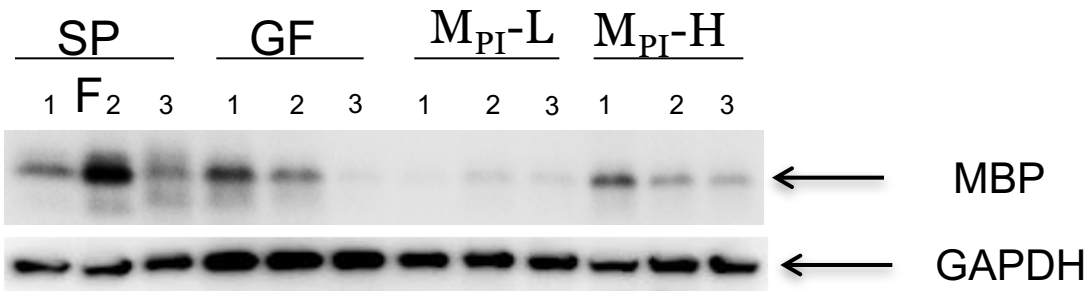


B.

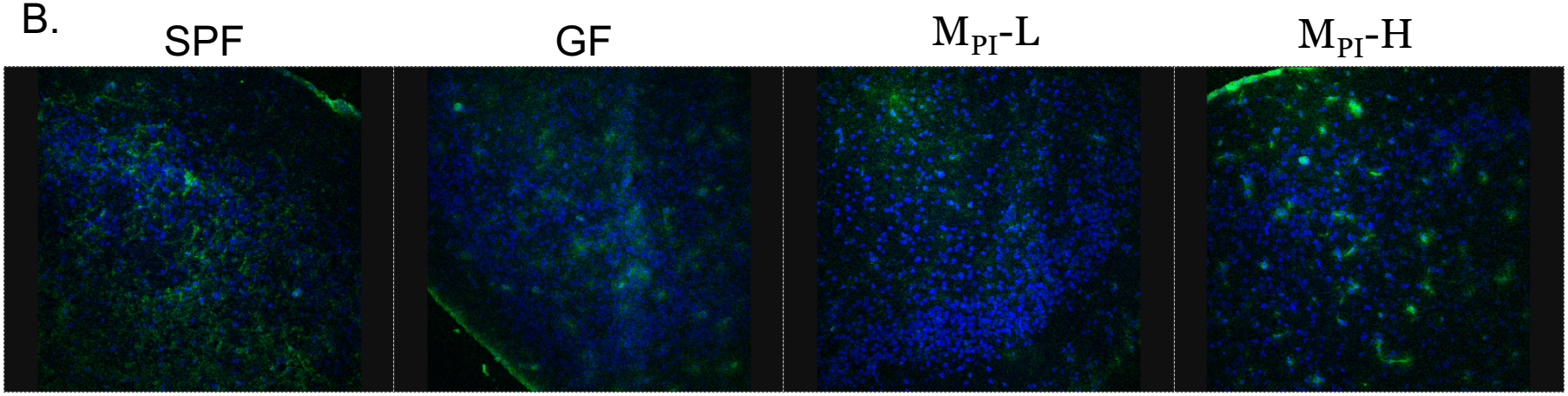


Regulation of cortex myelination by gut microbiota.

A.



B.



DAPI

MBP

IGF1

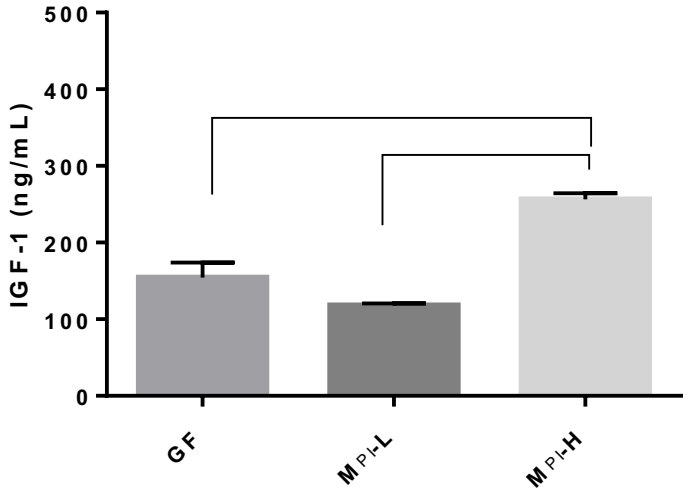
- We have established that certain microbiota colonization normalized the growth in GF mice (M2).
- Mutation(s) in the *igf*-1 gene or in the *igf1r* gene are found to be associated with severe body growth failure, microcephaly, and developmental delay.
- In rodents, *igf-1* gene disruption results in reduced brain size, CNS hypomyelination and loss of hippocampal granules and striatal parvalbumin-containing neurons.
- GF mice have lower circulating IGF-1 comparing to SPF mice.
- IGF1 crosses the blood brain barrier

Hypothesis

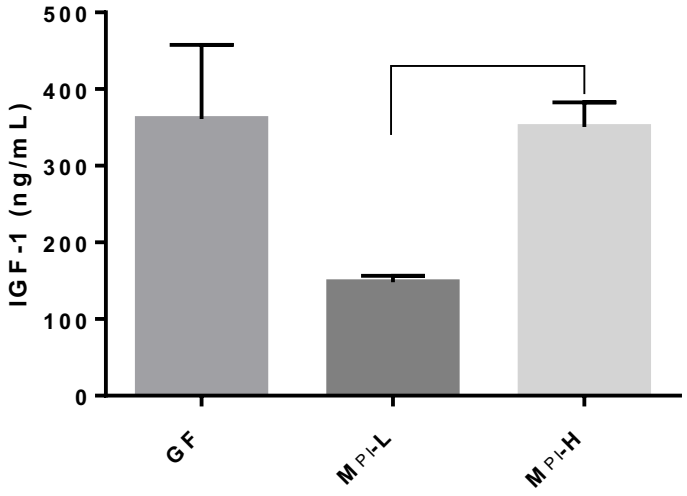
- Microbial colonization can modulate brain development through regulation of IGF1.

Microbiome influences serum IGF-1

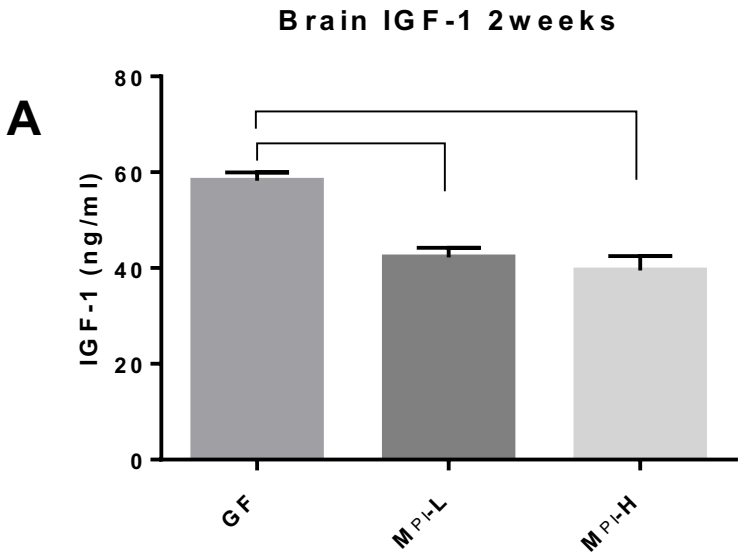
A

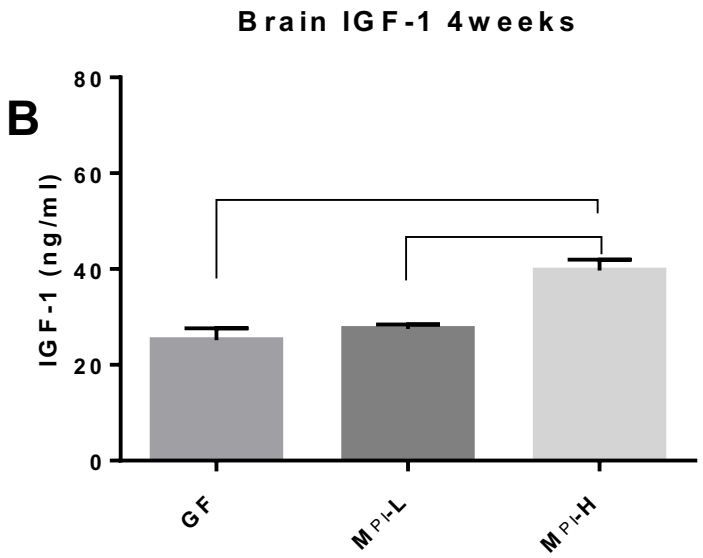


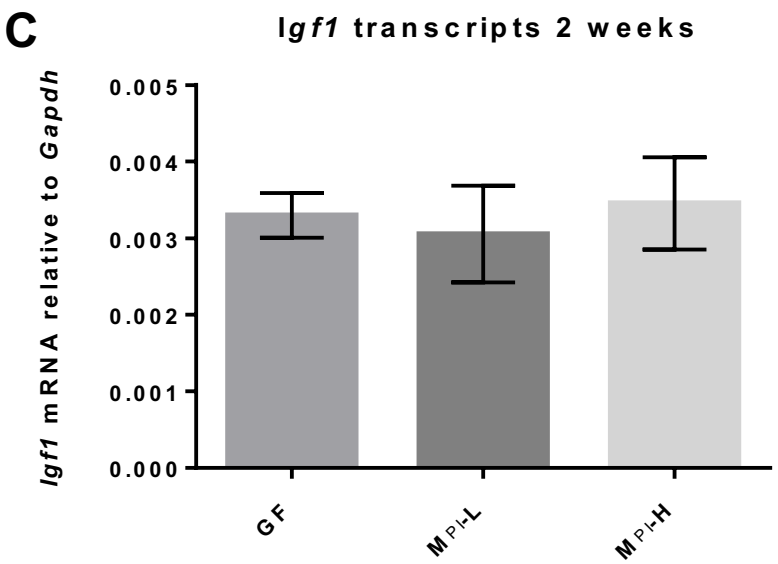
B

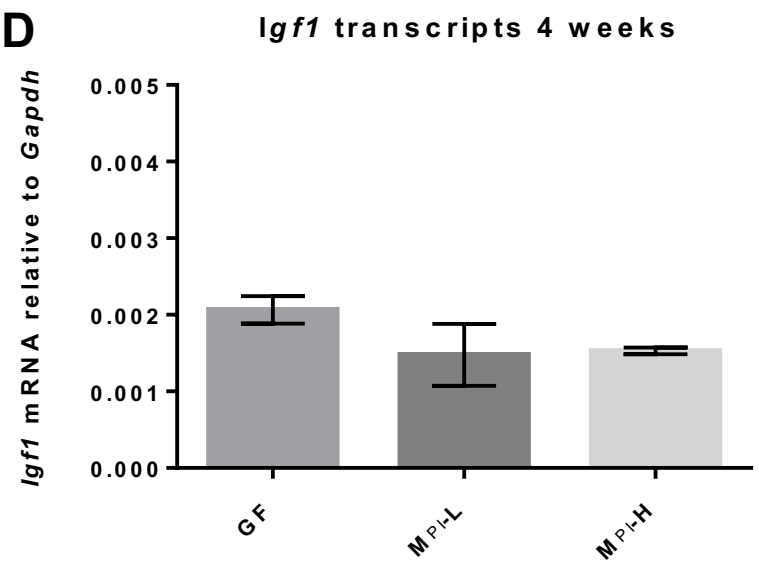


Alterations in brain IGF-1

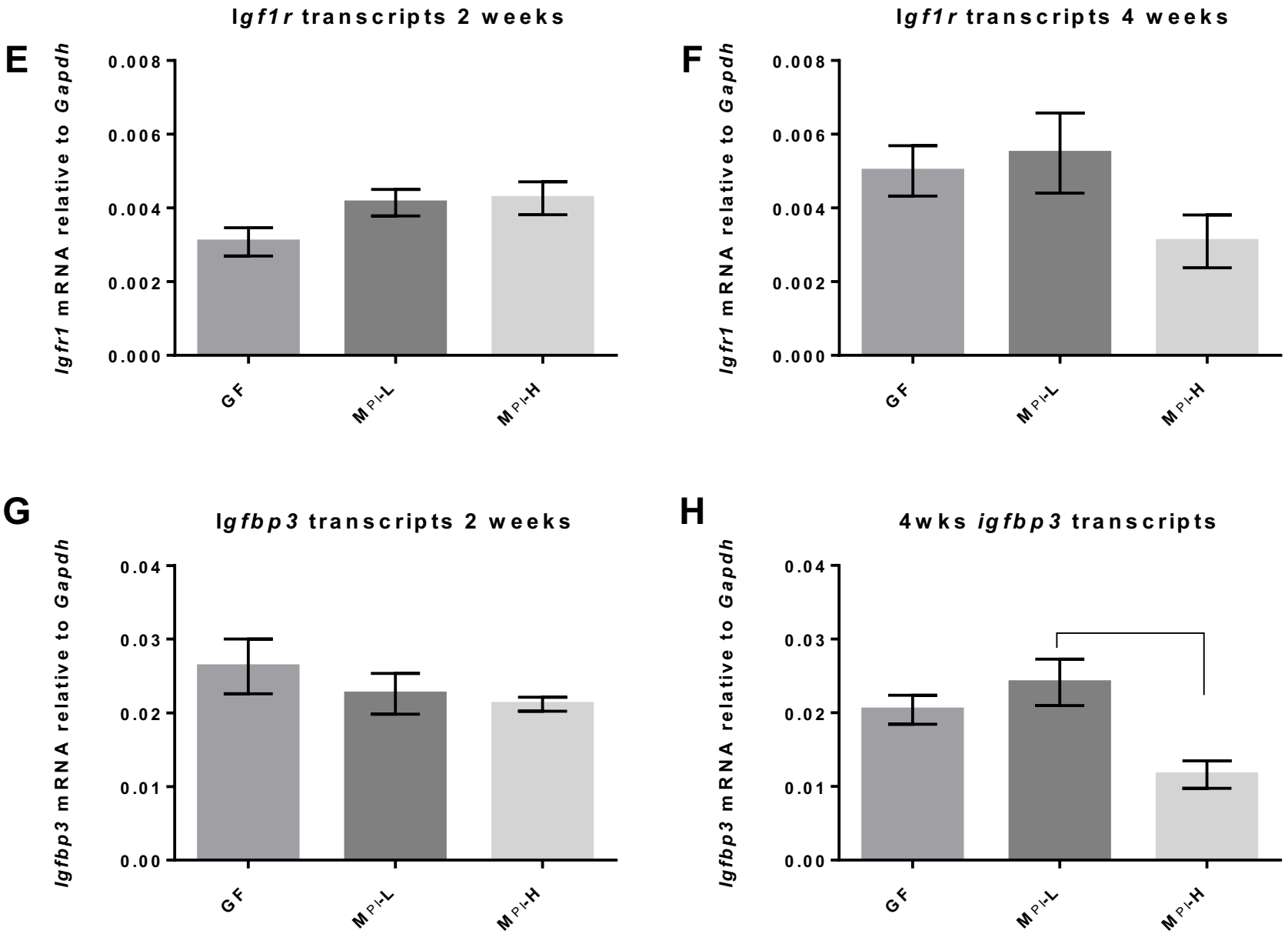




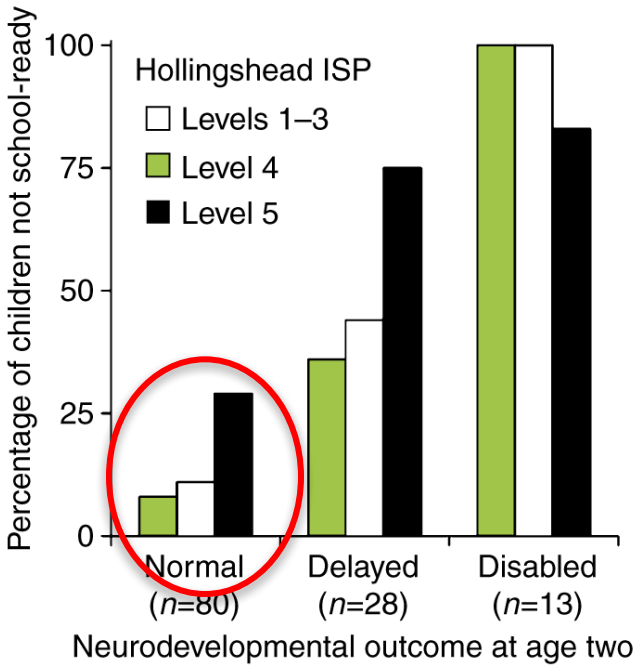


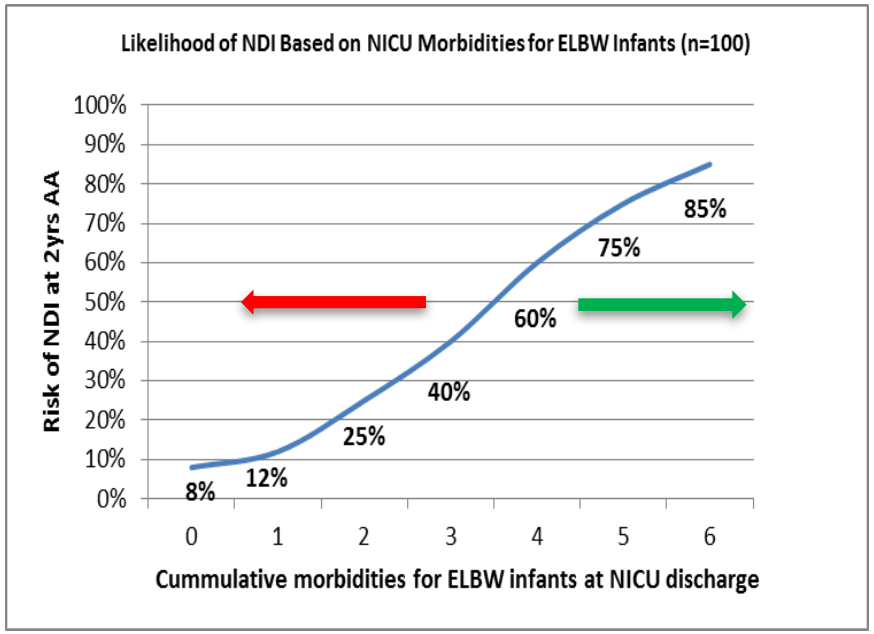


Alterations in brain IGF1r and IGFBP3



Effect of socioeconomic status on Neurodevelopment





Patrianakos-Hoobler et al Dev Med Child Neurol. 2010 Apr;52(4):379-85

Microbiome?

National Institutes of Health
Turning Discovery Into Health

ENVIRONMENTAL INFLUENCES ON CHILD HEALTH OUTCOMES (ECHO) PROGRAM

Environmental influences on Child Health Outcomes (ECHO) Program

- Director's Page
- Planning
- Governance
- Program Components
- Funding
- Announcements

NIH officially launches the ECHO program with more than $150 million in awards

Learn about the new ECHO program components and awardees

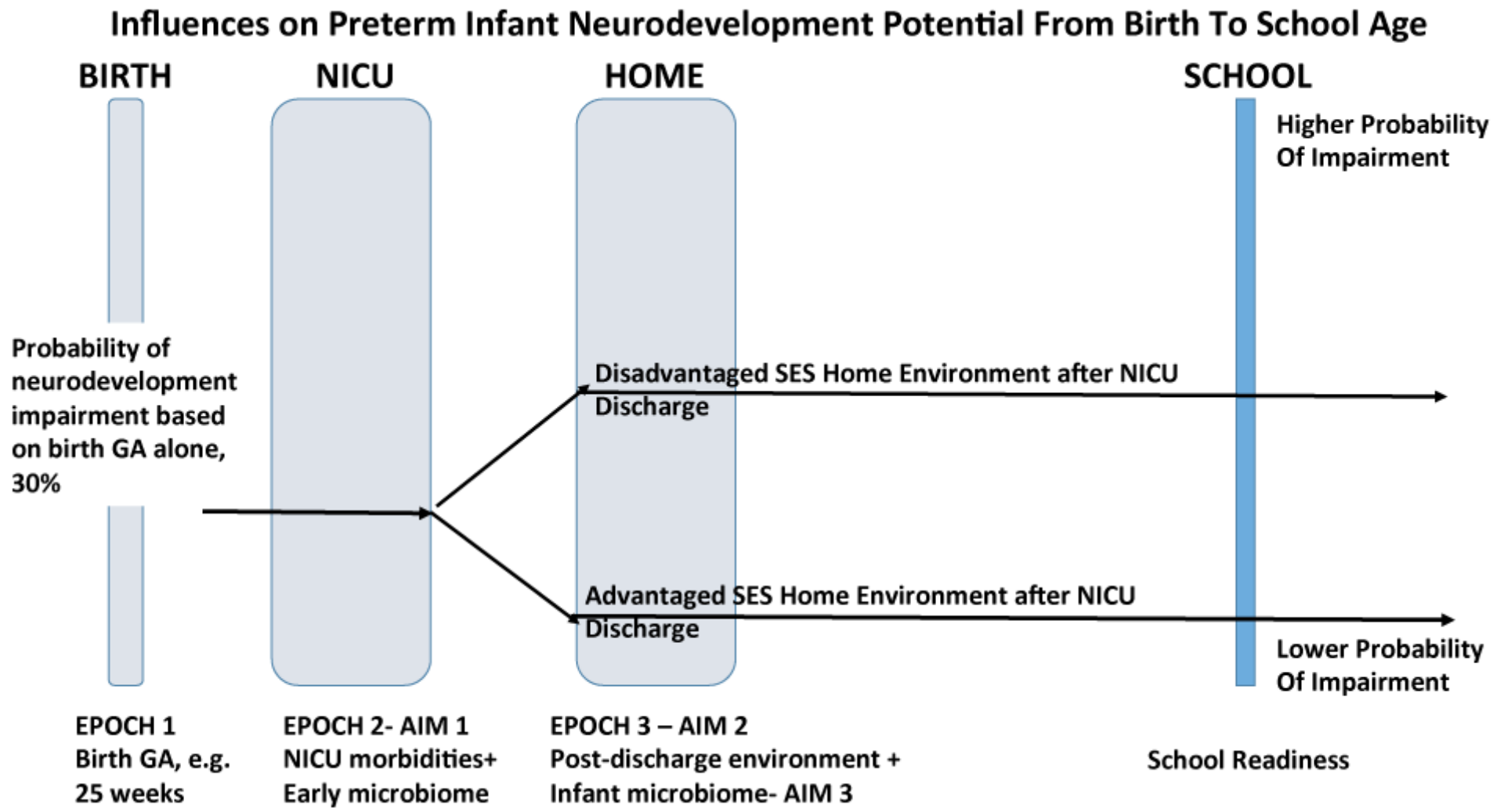
Related Information

About the ECHO Program

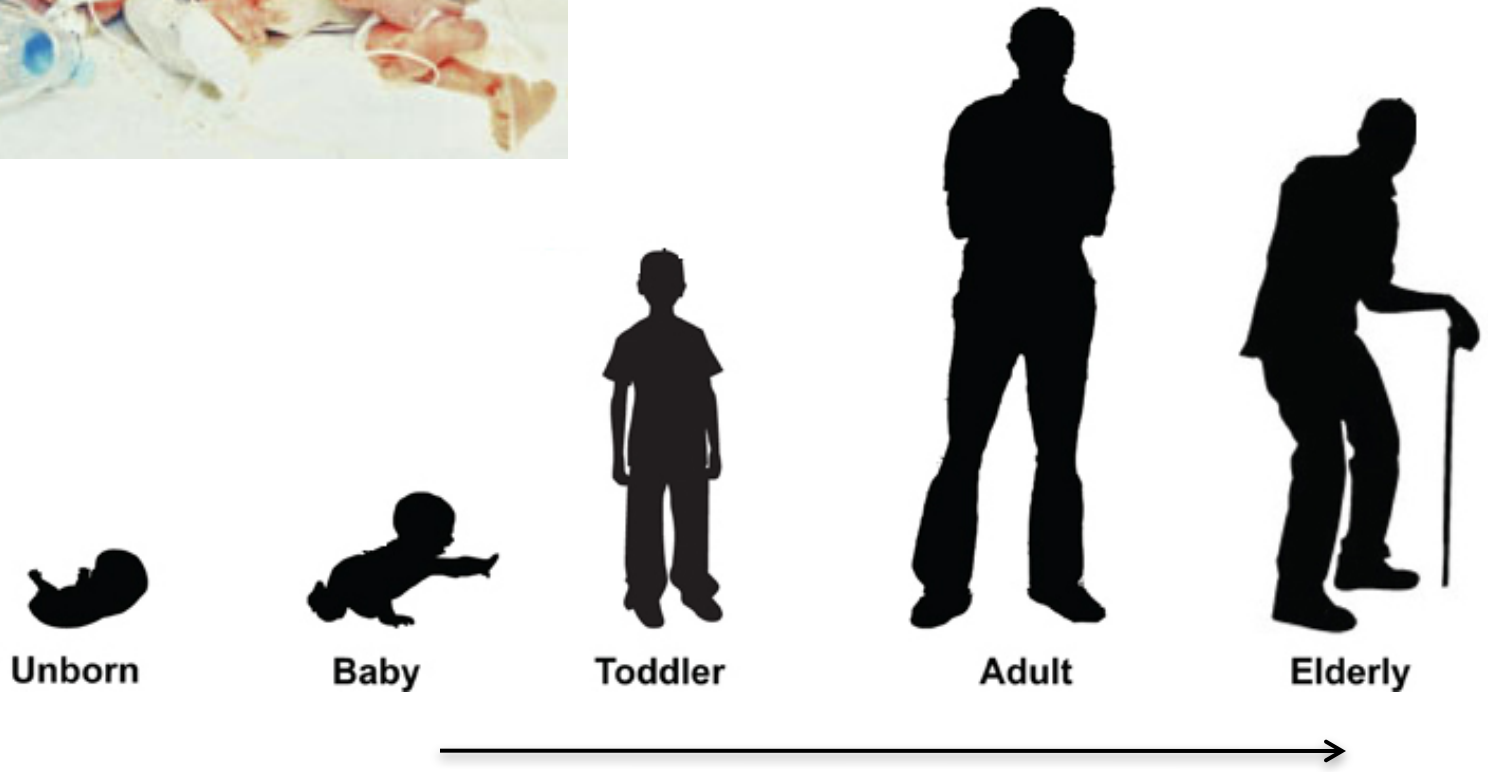
The means by which poverty alters neurodevelopment are unknown.

The microbiome is influenced by environment and in turn influences brain development.

We hypothesize that the microbiome is a biologic effector of the influence of SES and environment on neurodevelopment.


Influences on Preterm Infant Neurodevelopment Potential From Birth To School Age
BIRTH
NICU
HOME
SCHOOL
Higher Probability Of Impairment
Probability of neurodevelopment impairment based on birth GA alone, 30%
Disadvantaged SES Home Environment after NICU Discharge
Advantaged SES Home Environment after NICU Discharge
Lower Probability Of Impairment
EPOCH 1
Birth GA, e.g. 25 weeks
EPOCH 2- AIM 1
NICU morbidities+ Early microbiome
EPOCH 3 – AIM 2
Post-discharge environment + Infant microbiome- AIM 3
School Readiness

The Microbiome is Modifiable



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