Permeabilità Intestinale-Zonulina Dipendente E Composizione/Funzione Del Microbioma Intestinale Nella Patogenesi Delle Malattie Infiammatorie Croniche: Il Futuro Della Medicina Personalizzata E Preventiva.

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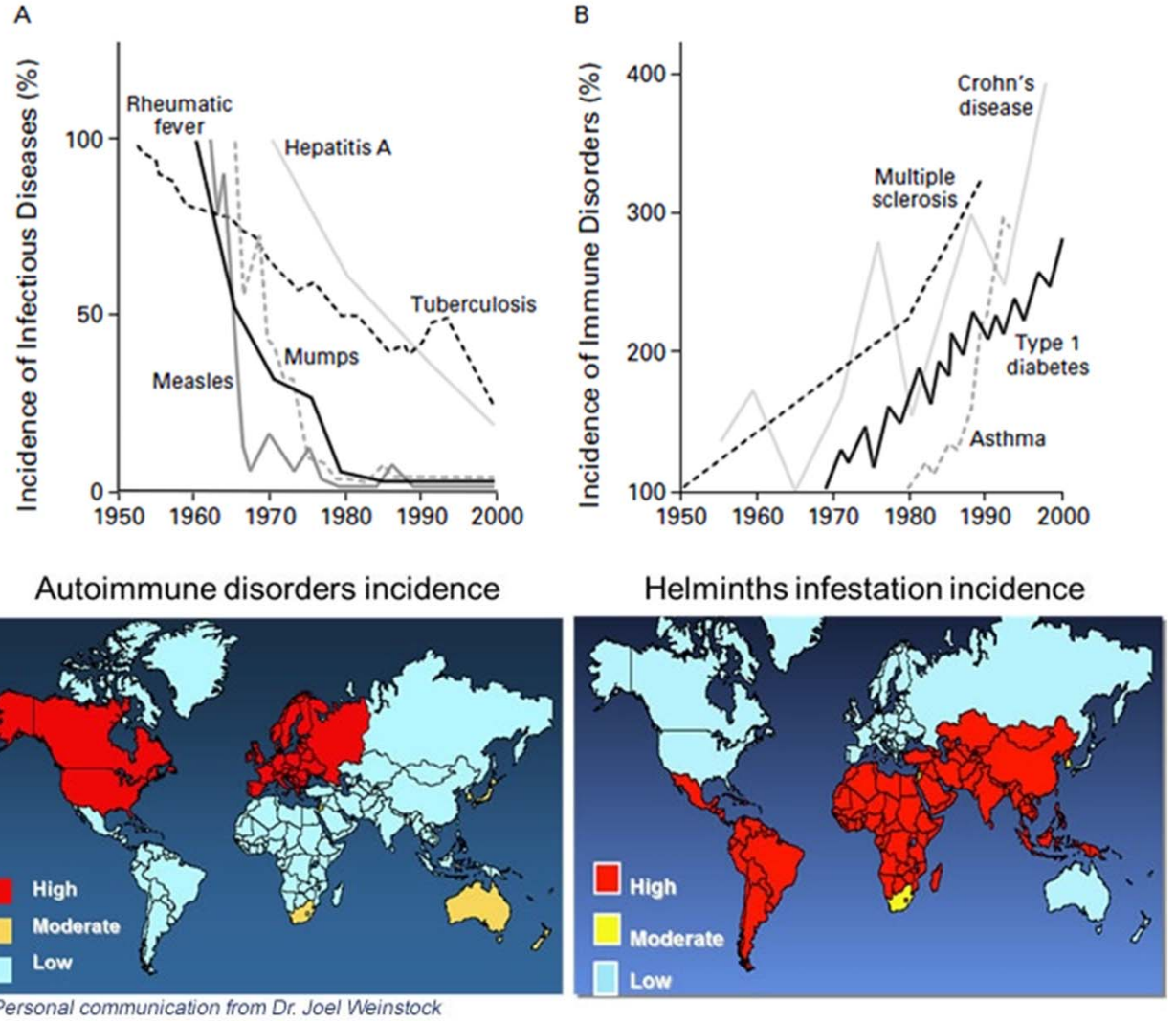
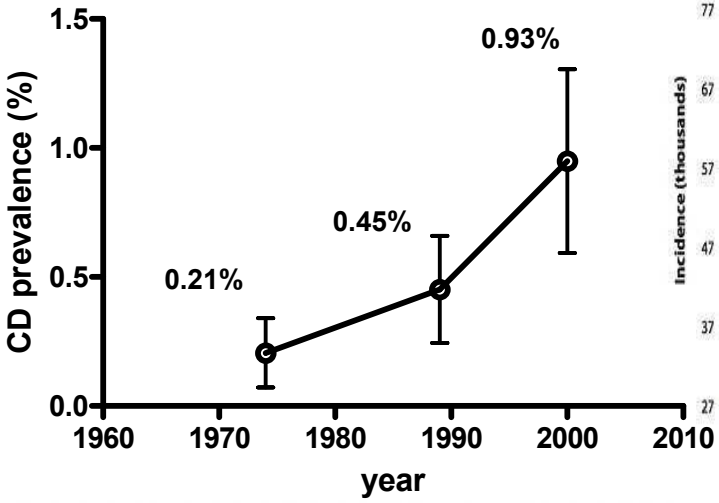
The Epidemics of Chronic Inflammatory Diseases (CID) In The Western Hemisphere: The Hygiene Hypothesis

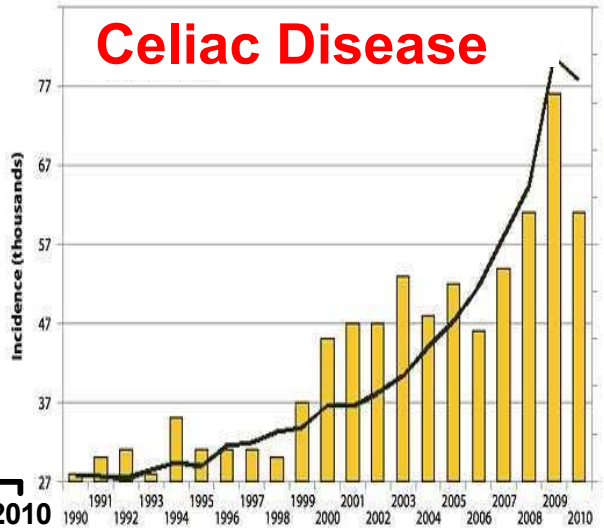


Personal communication from Dr. Joel Weinstock

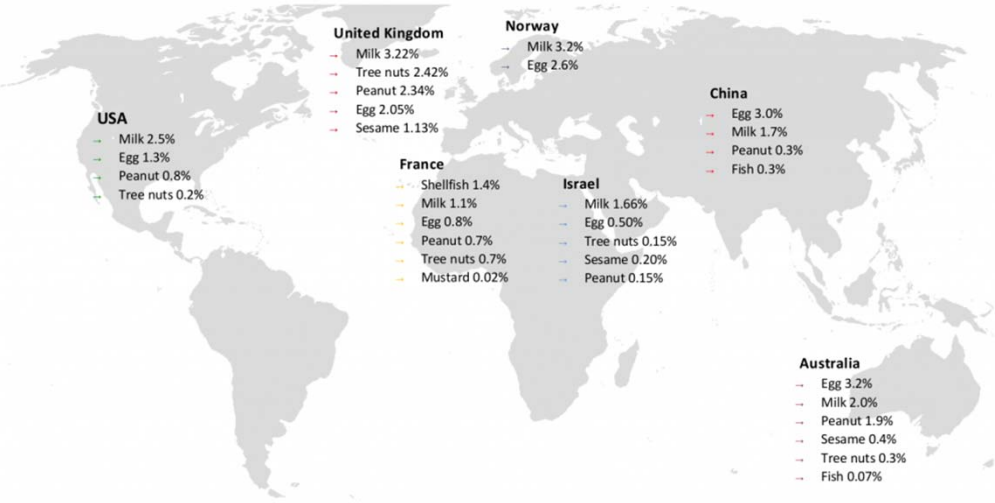
The Epidemics of CID In Western Countries

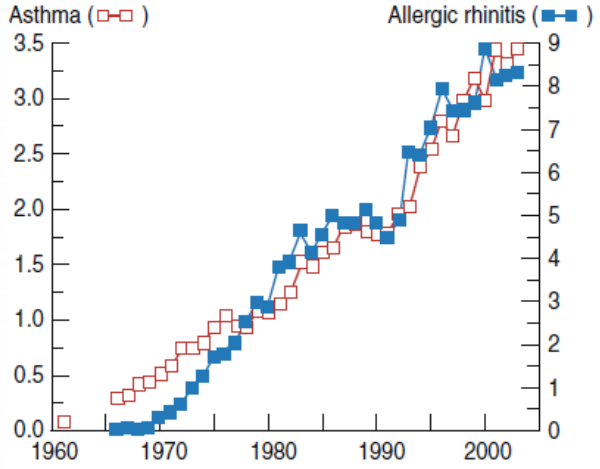


Celiac Disease

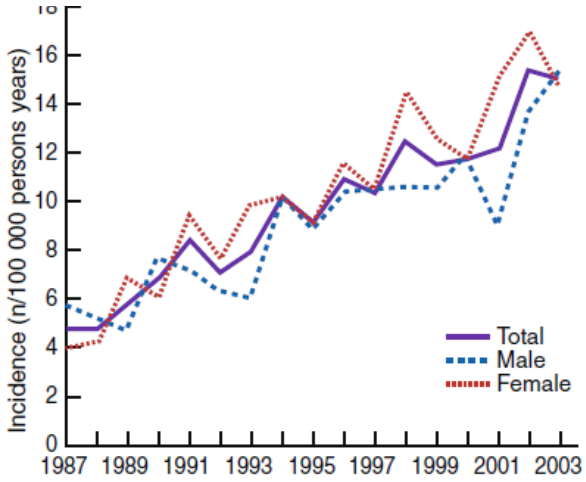


Allergies





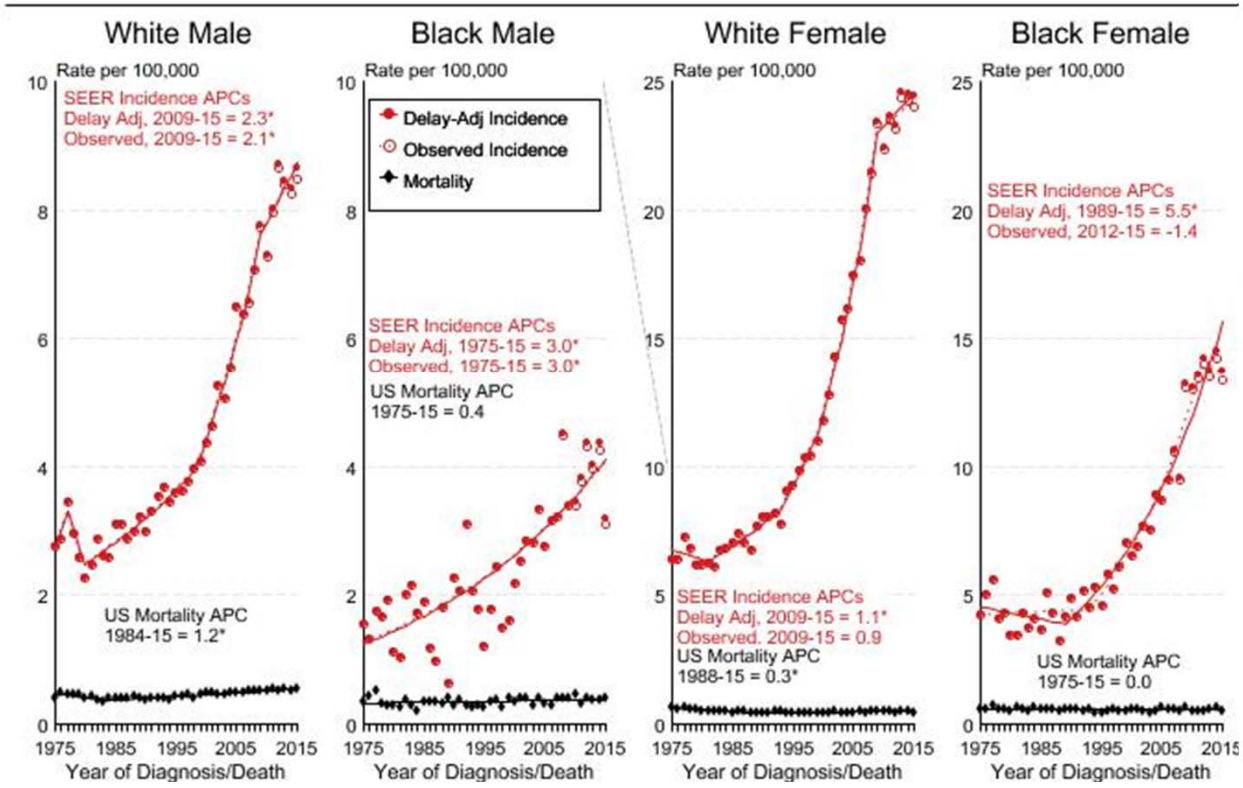
IBD



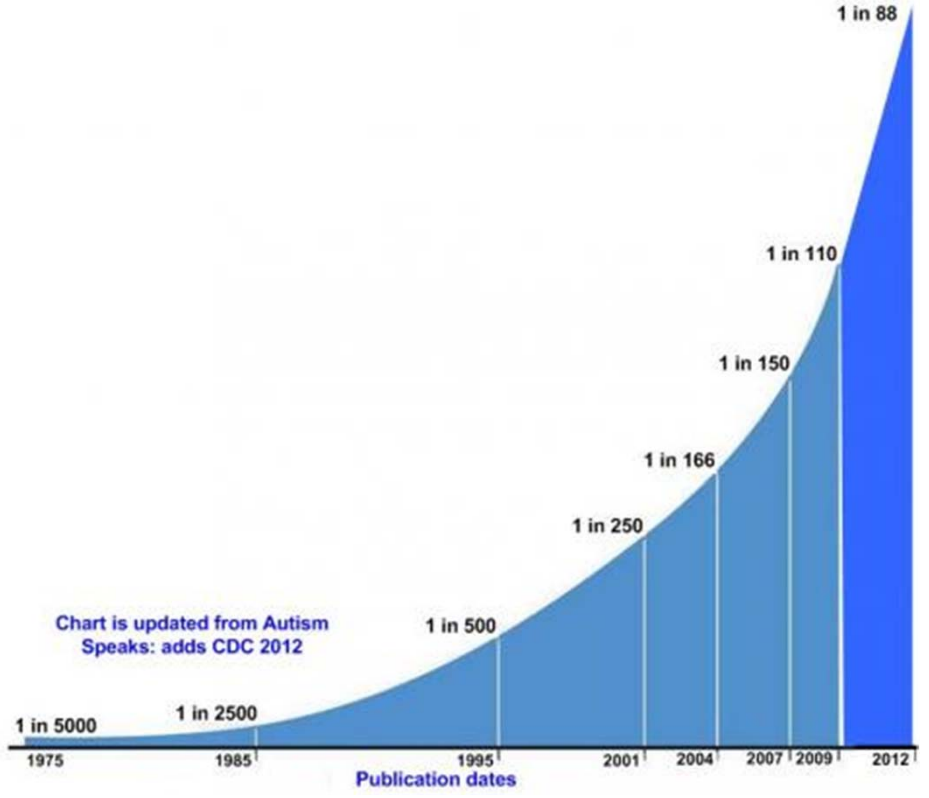
The Epidemics of CID In Western Countries

Cancer

Surveillance, Epidemiology, and End Results (SEER) Observed Incidence, SEER Delay Adjusted Incidence, and US Death Rates Cancer of the Thyroid, By Race and Sex

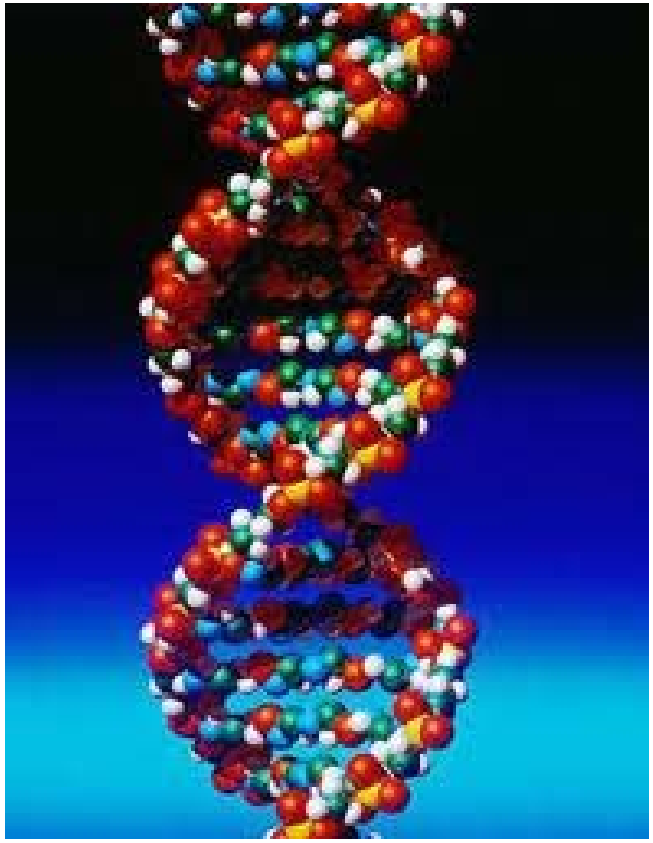


Autism

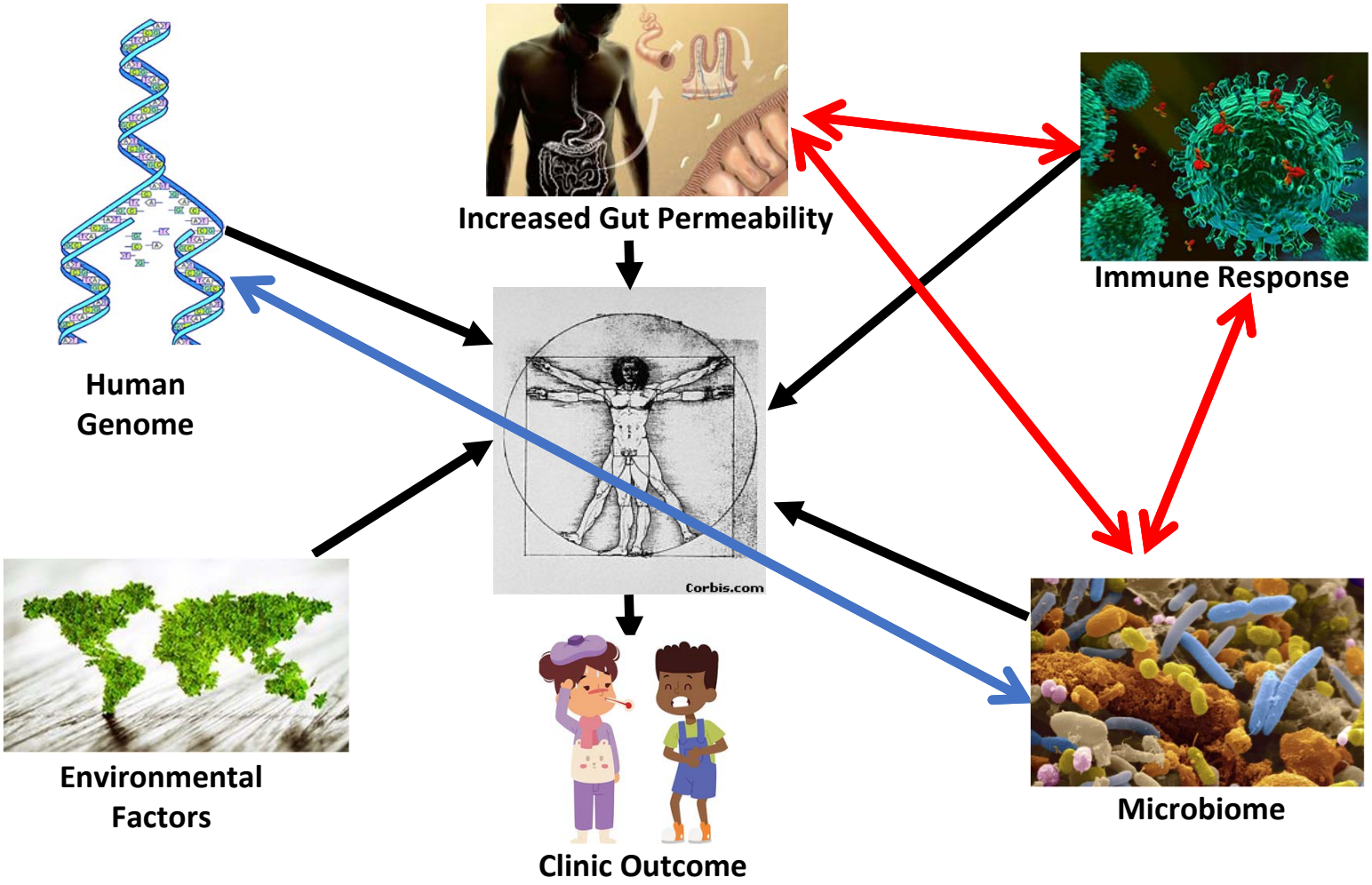


Pathogenesis CID

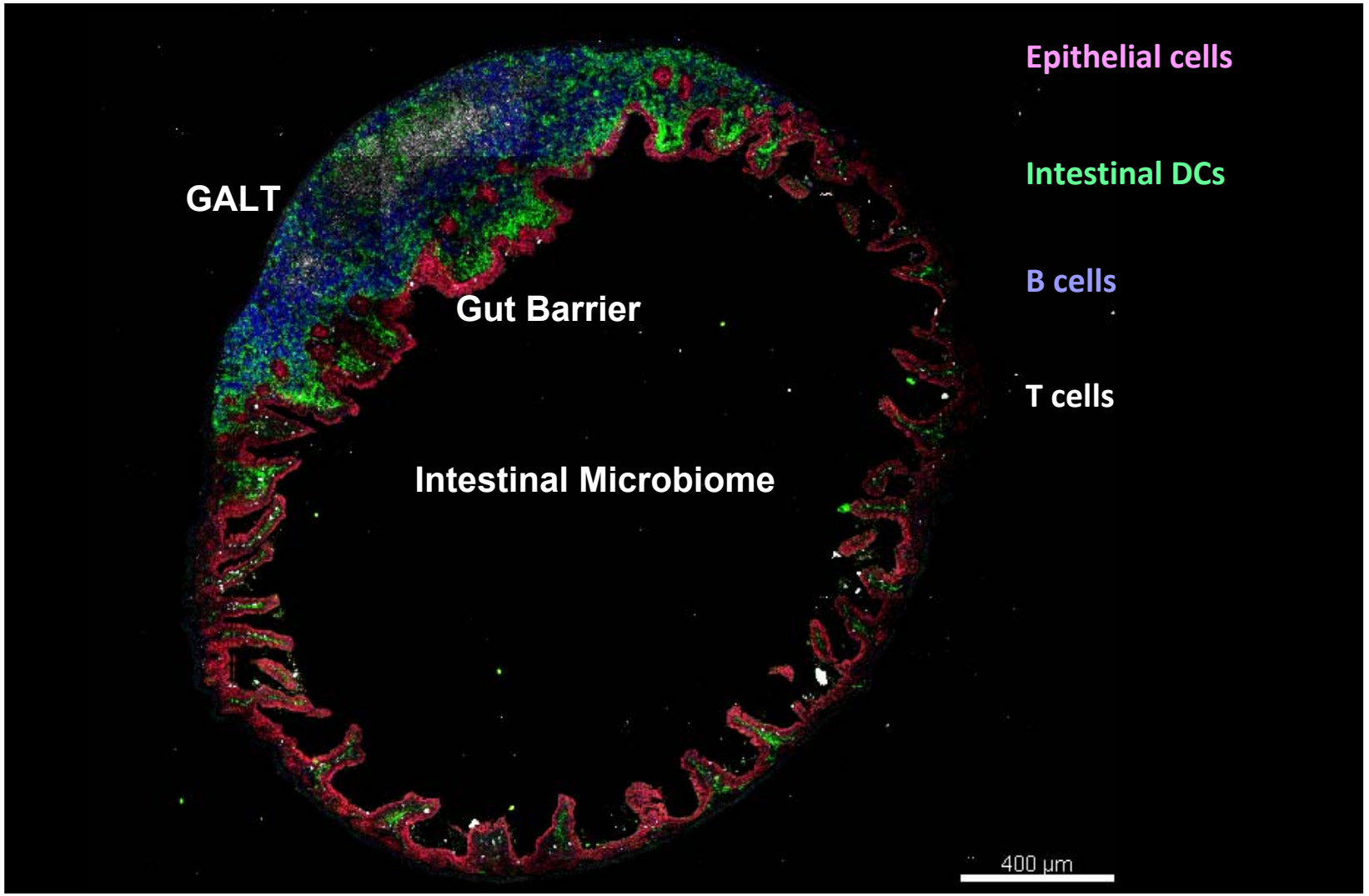
We May Be "*Predisposed*", but Are Not Born "*Destined*" to Develop Chronic Inflammatory Diseases



The Yin and Yang Between Tolerance and Immune Response Leading To CID

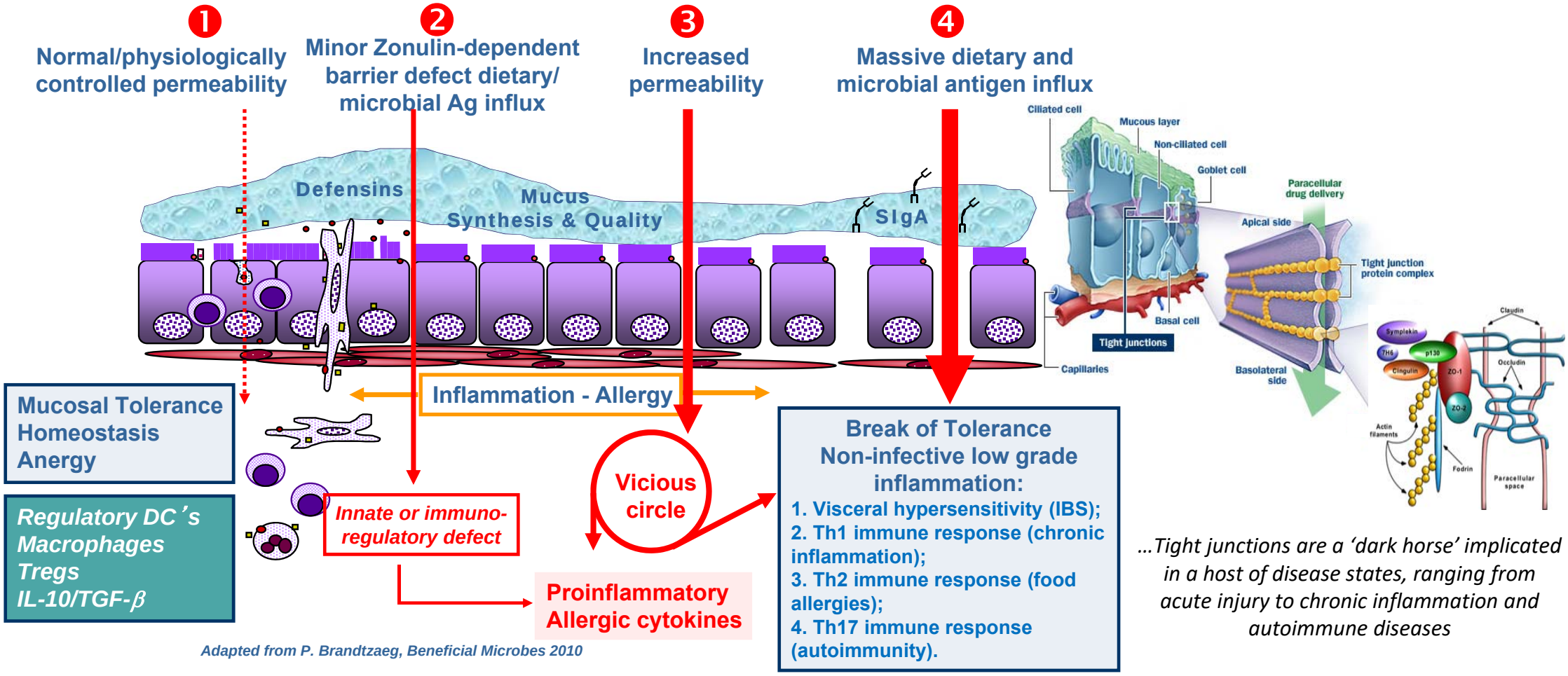


Gut Barrier-Microbiome-Immune System Triangulation Play a Key Role in Maintaining The Immune Homeostasis



Excessive and Inappropriate Inflammatory Process Associated to a Zonulin-Dependent Dysfunction of Barriers:

Loss of Mucosal Immune Homeostasis

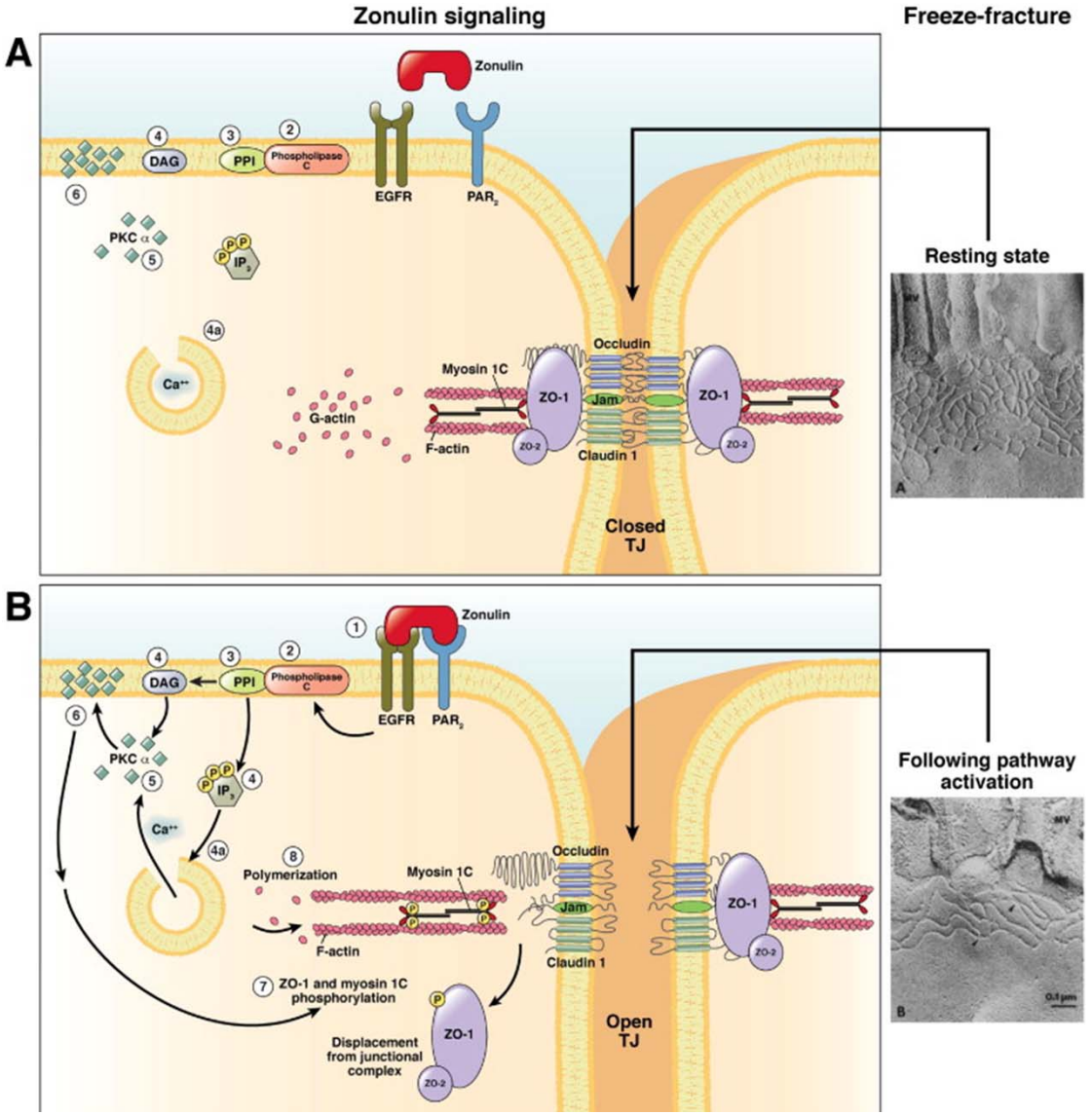


Adapted from P. Brandtzaeg, Beneficial Microbes 2010

…Tight junctions are a 'dark horse' implicated in a host of disease states, ranging from acute injury to chronic inflammation and autoimmune diseases

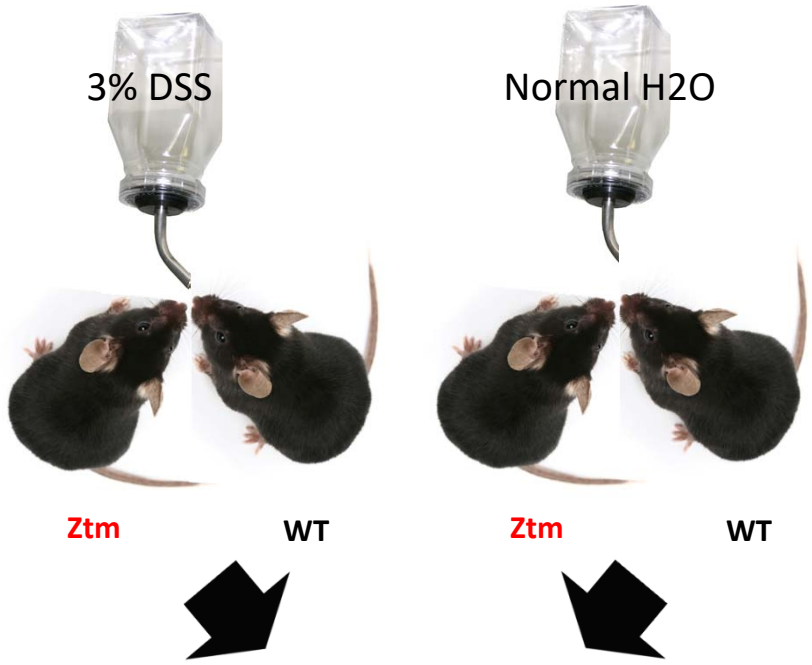
Literature Report On Zonulin Association With CID

Disease	Model	Zonulin Shown to be Involved
Aging	Human	YES
Ankylosis spondylitis	Human	YES
Autism	Human	YES
Celiac Disease	Human	YES
Colitis/IBD (Crohn's disease)	Human	YES
Colitis	Mouse	YES
Fe metabolism in heart transplant	Human	NO
Glioma	Human	YES
Glioma	Cell	YES
Irritable bowel syndrome	Human	YES
HIV	Human	YES
Multiple sclerosis	Mouse	YES
Necrotizing Enterocolitis (NEC)	Rat	YES
Nonalcoholic fatty liver disease	Human	YES
Non-Celiac Gluten Sensitivity	Human	YES
Obesity/Insulin resistance	Human	YES
Post-surgery Sepsis	Human	YES
Post-surgery Sepsis	Mouse	YES
Psoriasis	Human	NO
Sepsis	Human	YES
Type 1 diabetes	Human	YES
Type 2 diabetes	Human	YES

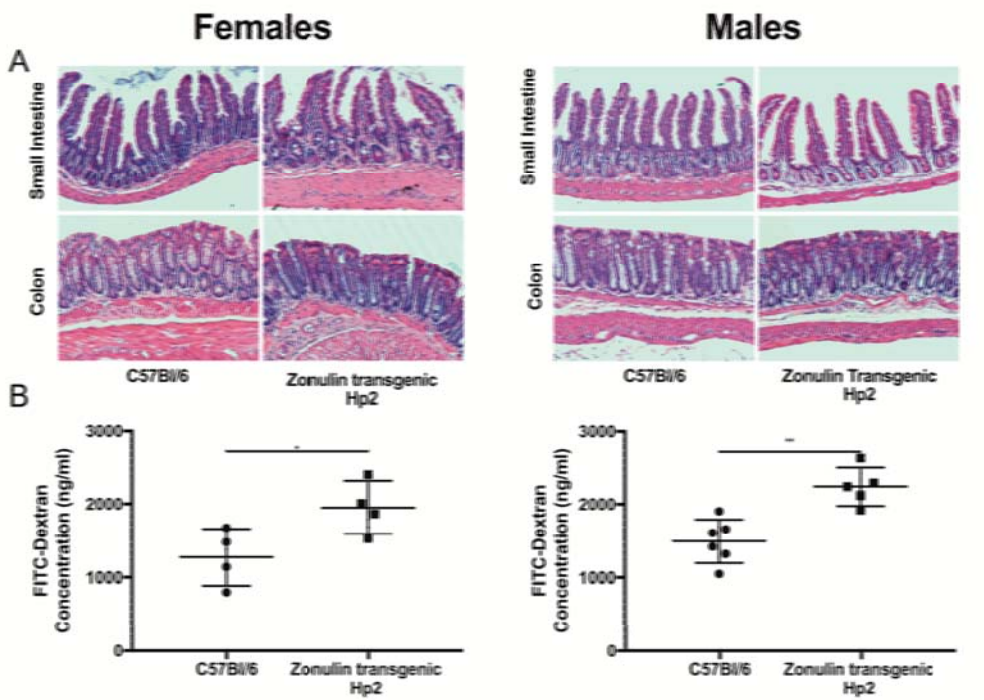


How Zonulin-Mediated Increased Ag Trafficking Leads to Chronic Inflammation:

Insights From The Zonulin Trangenic Mouse (ztm) Model



Daily Body Weight after 7 days all mice are put on Normal drinking water

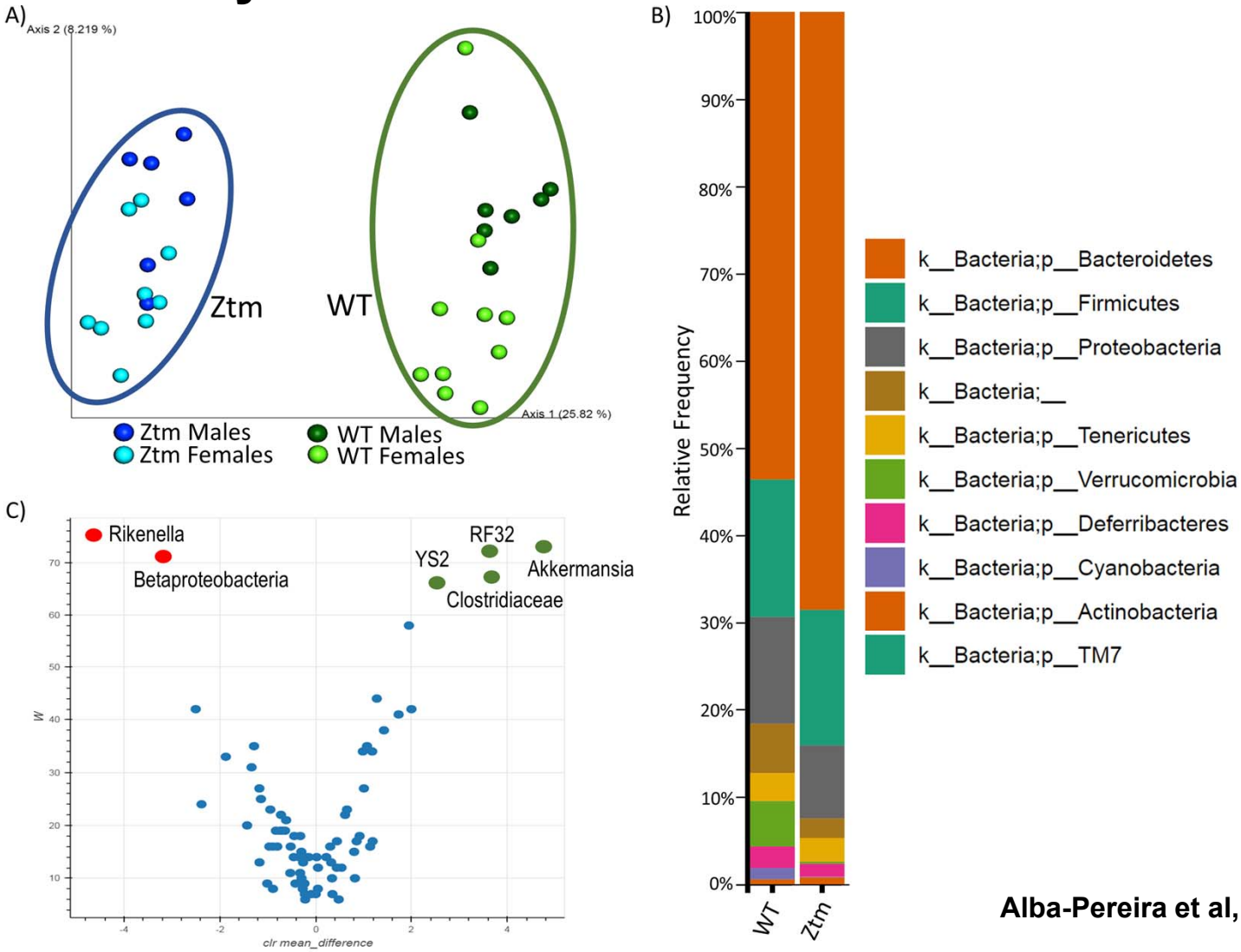


Zonulin transgenic Hp2 mice are phenotypically normal despite increased small intestinal permeability

*p<0.05

Sturgeon C et al. Ann NY Acad Sci 2017

Ztm Showed Dysbiosis Characterized by Increase pro-inflammatory Rikenella And Decreased Akkermansia



Alba-Pereira et al, Front Immunol 2019

Ztm Showed No Differences in Adaptive Immune Profiling, But Differences in Innate Immune Cell Subsets

Ztm and Ztm$_{bWT}$ showed:

-Increase in IL7R^{+}ROR$\gamma\tau^{+}$ innate lymphoid cells in the small intestine (no changes in the colon);

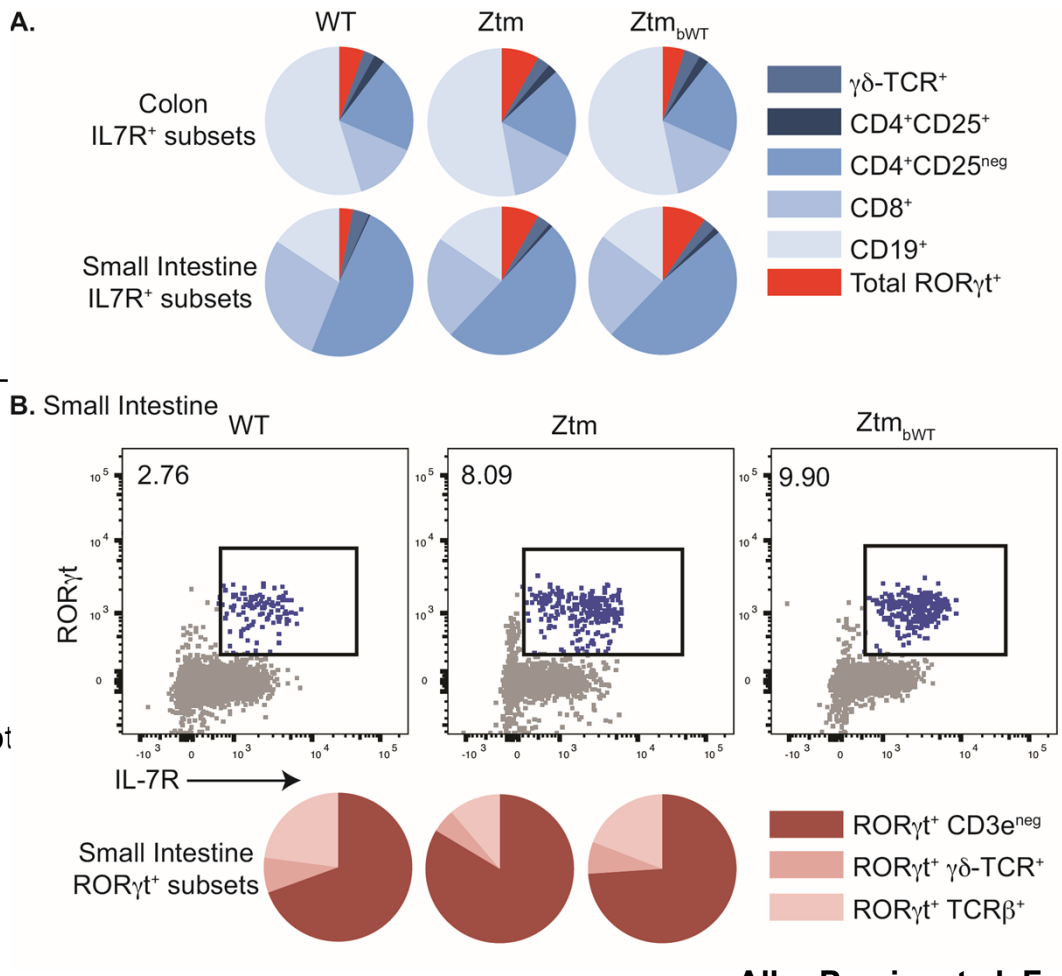
- Decreased frequency and numbers of invariant NKT (iNKT) cells (involved in mucosal immunity);

- Increased ROR$\gamma\tau$ expressing subset of iNKT cells (NKT17 cells). NKT17 cells and $\gamma\delta$-17 T cells are pro-inflammatory innate-like T cell subsets that produce IL-17 and have been implicated in the pathogenesis of various autoimmune diseases, including CD and T1D;

-Increased splenic plasmacytoid dendritic cells.

Combined, these these data suggest that altered gut permeability increases frequency of IL-17 producing T cells in mucosal tissue and in secondary lymphoid organs of Ztm mice.

The fact that the engraftment of WT microbiota did not affect the immune phenotype in Ztm$_{bWT}$ suggests that the increased antigen trafficking through an impaired gut barrier more than the function of an imbalanced microbiota primarily imprints the development of the immune system in the Ztm.

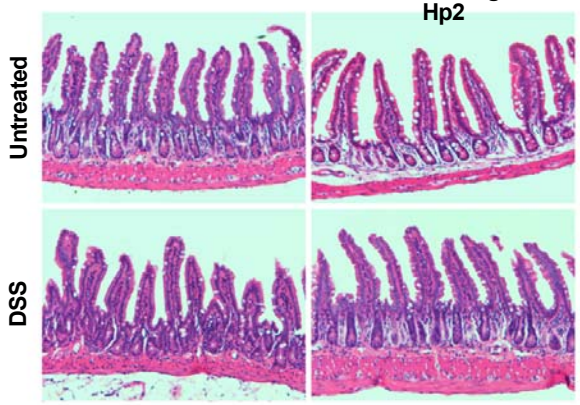


Alba-Pereira et al, Front Immunol 2019

Ztm Showed Increased Morbidity (Colonic Mucosal Damage) And Mortality (70%) Following DSS-Induced Colitis

3% DSS

A



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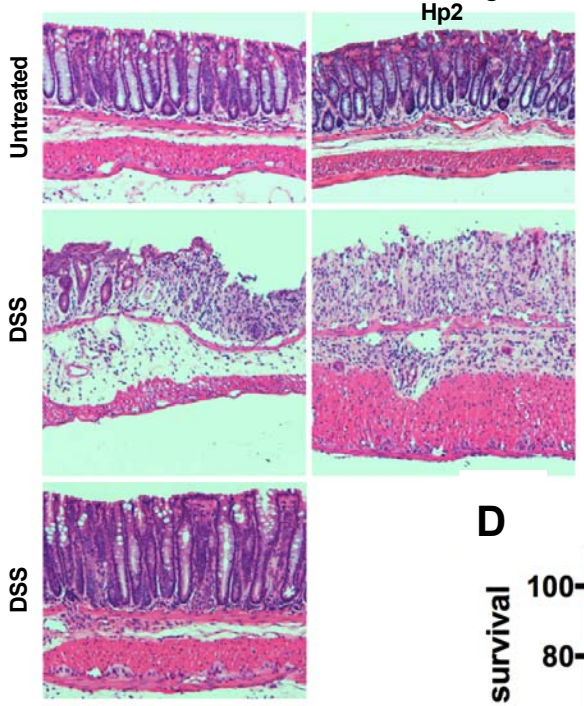
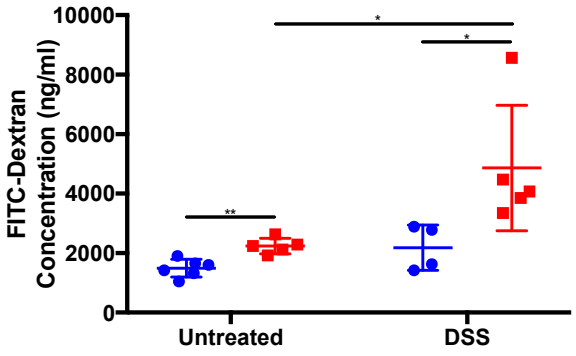
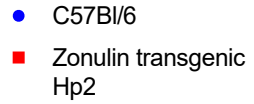


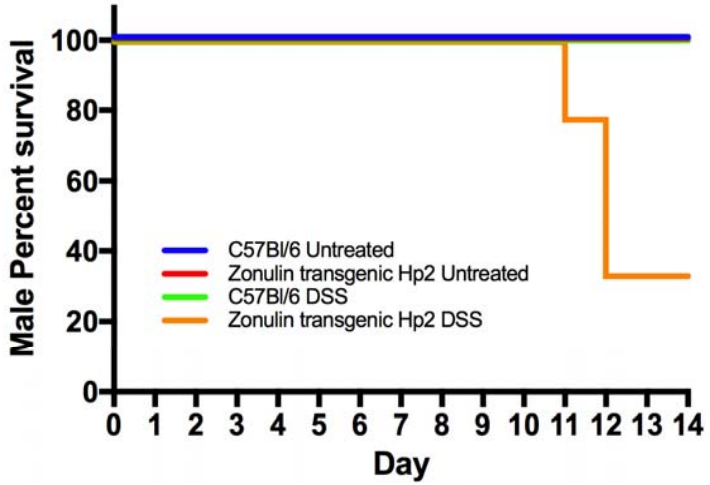
C

in vivo - FITC-dextran





D

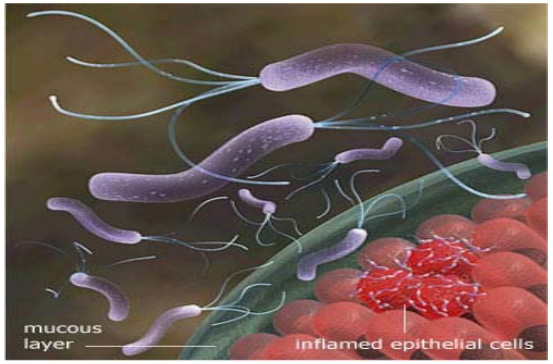


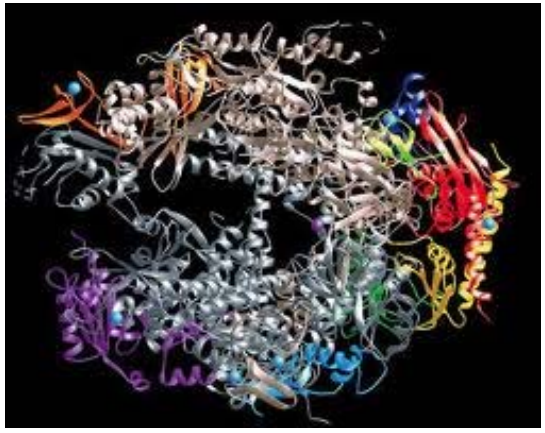
Sturgeon C et al. Ann NY Acad Sci 2017

Environmental Triggers Causing Zonulin Release

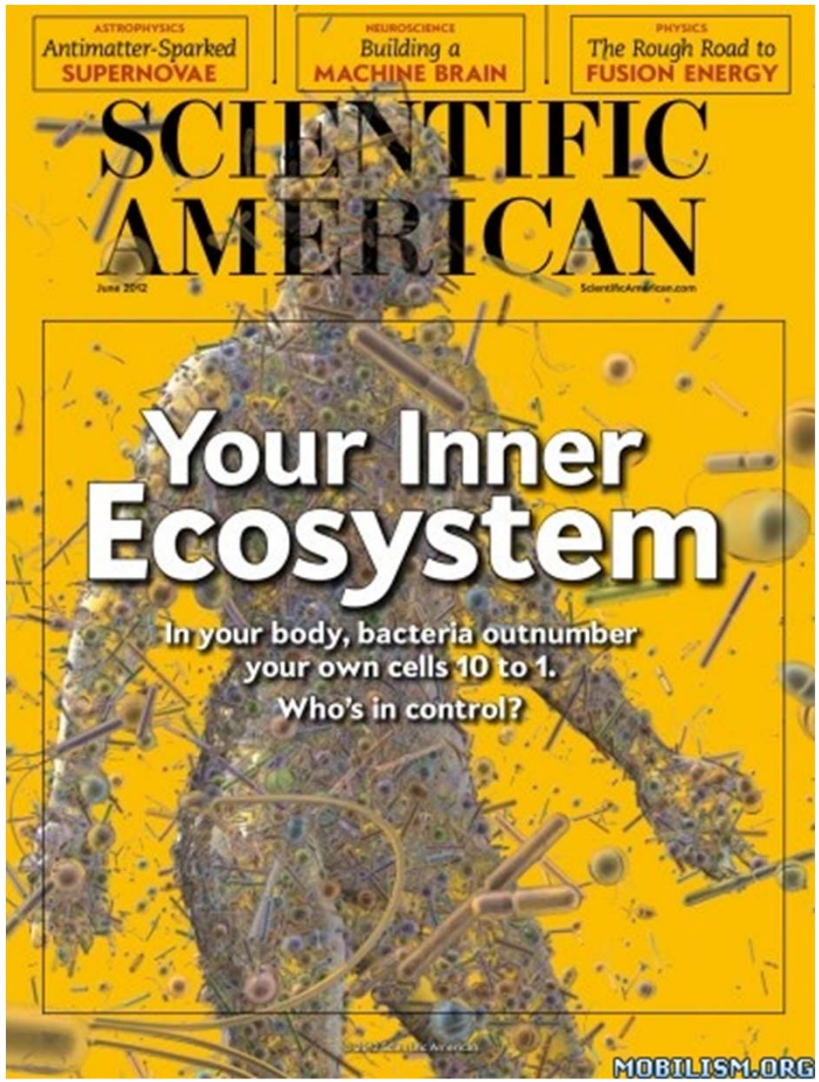
Gluten

Gut Microbiome





The Changing Face Of Gut Microbes



The Microbiome Is Essential To Health

100 TRILLION

The human microbiome is made up of more than 100 trillion bacteria, fungi, protozoa, and viruses that live in and on the human body

>10,000 different species of bacteria are resident in the human intestinal microbiota (400-500/person)

2-5x More

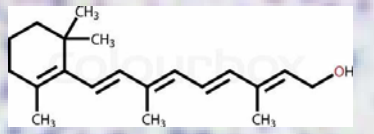
Microbial cells than human cells and the majority live in our gut

150x More

Genes than the human genome

Energy From Food

Regulates Metabolism



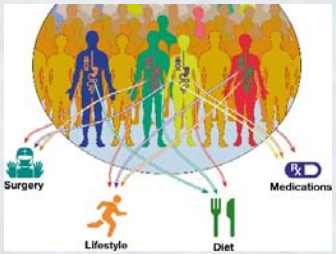
Producing Essential Vitamins

Regulate Immune System

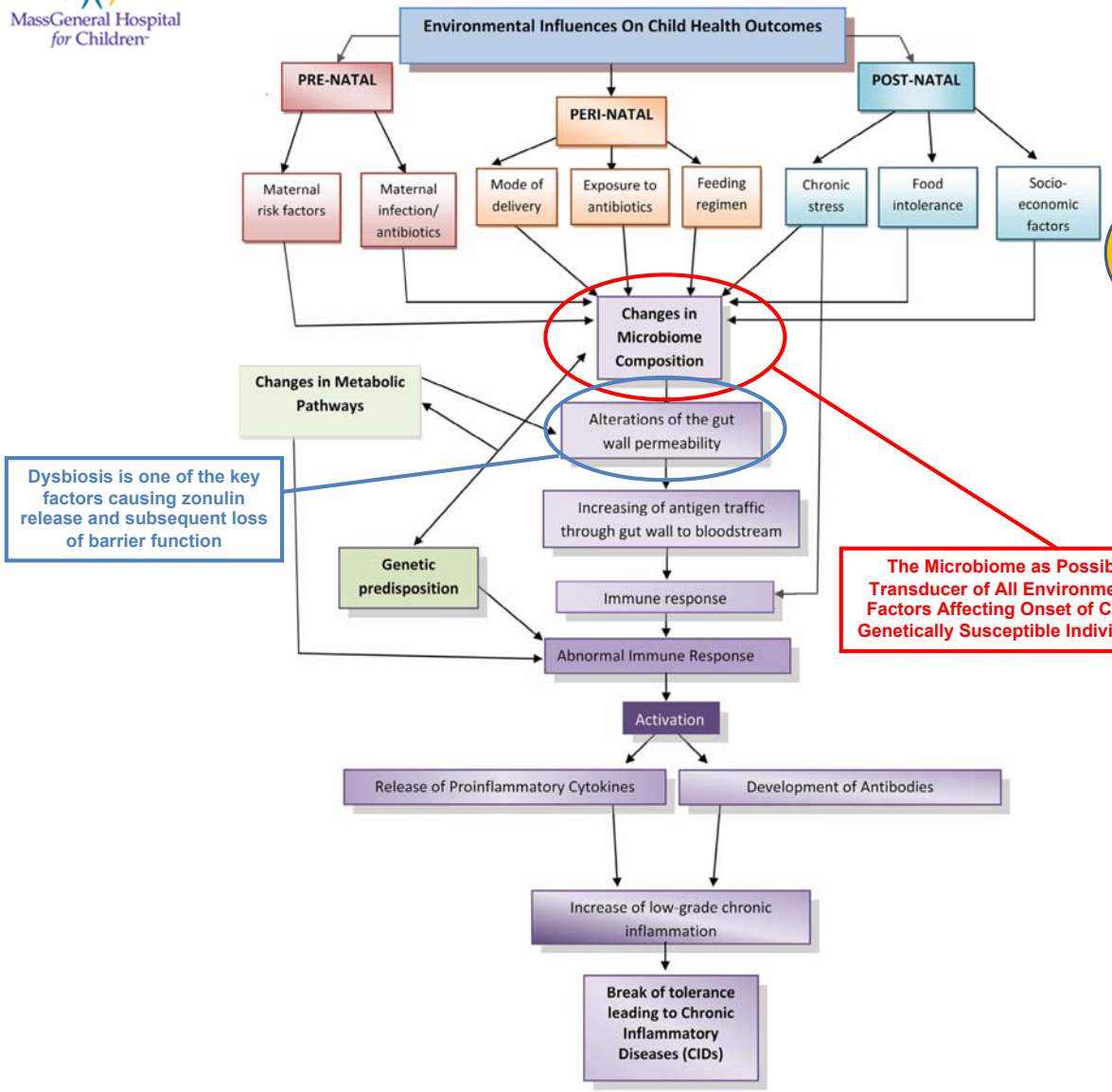
Protection from pathogenic bacteria

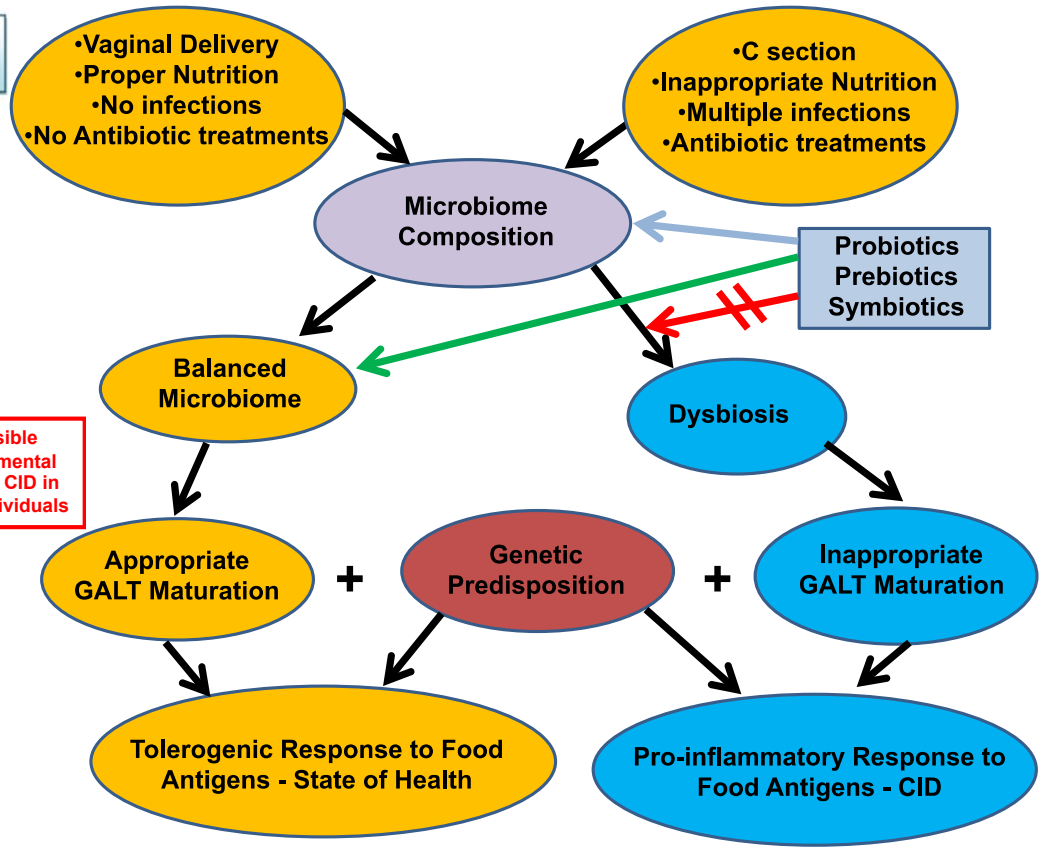
Symbiotic

Personalized



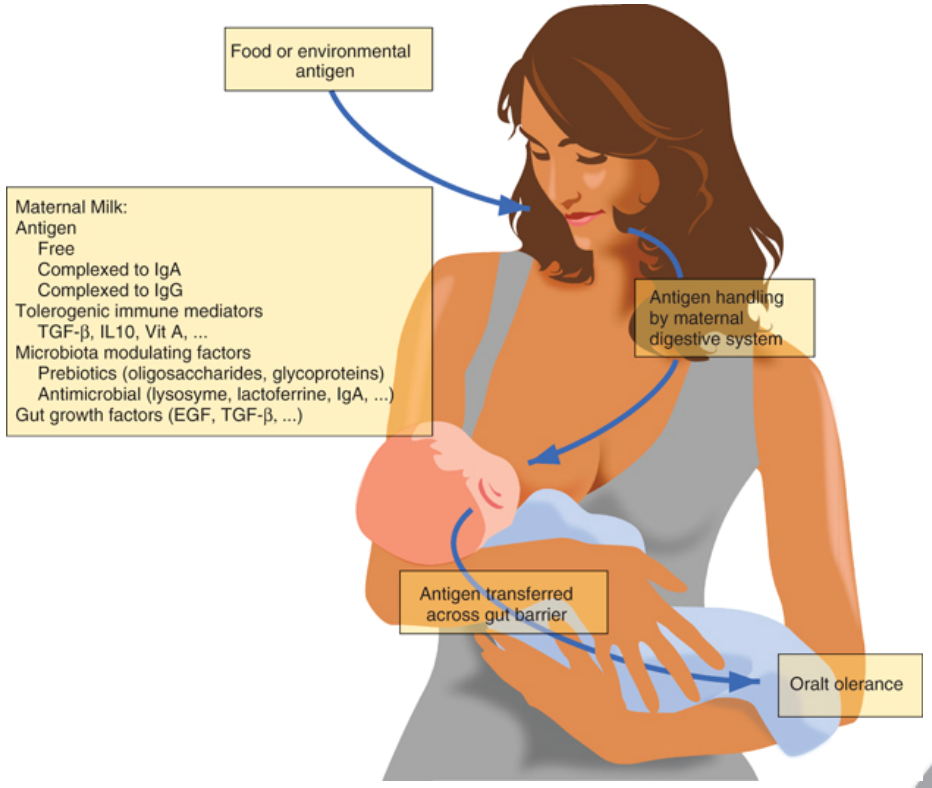
Why The First 1000 Days Of Life Are Instrumental For Clinical Destiny





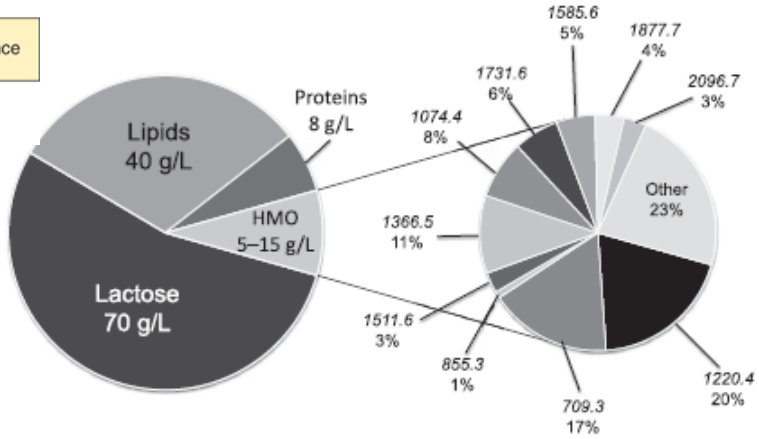
Martin VJ, et al J Pediat 2017

Role of Breastmilk



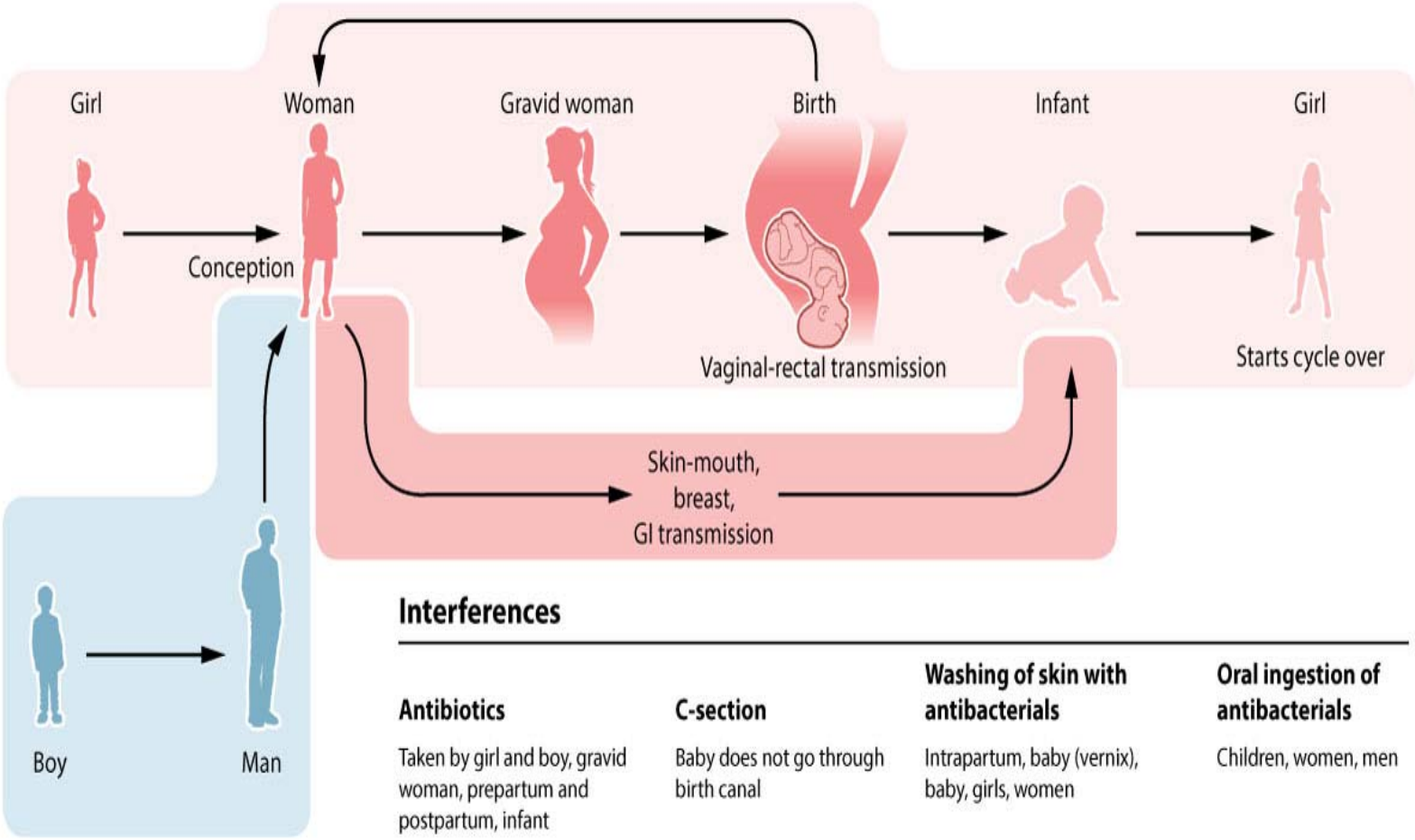
http://www.nature.com

Impact of human milk glycobiome on the infant intestinal microbiota



Zivkovica AM, et al. *PNAS* 2011;108: 4653-58

Cycle of Microbiota Transmission



Interferences

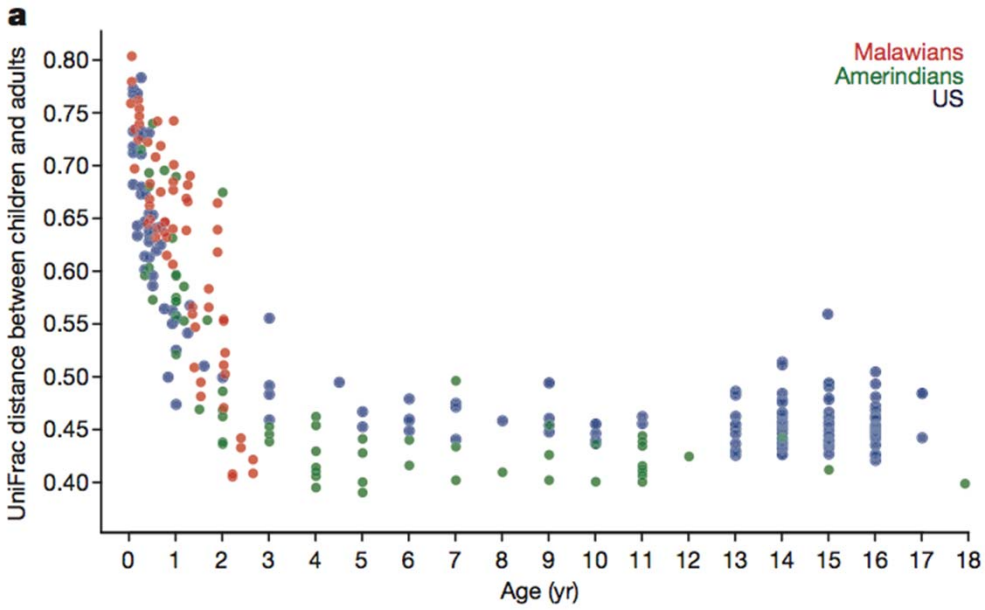
Antibiotics	C-section	Washing of skin with antibacterials	Oral ingestion of antibacterials
Taken by girl and boy, gravid woman, prepartum and postpartum, infant	Baby does not go through birth canal	Intrapartum, baby (vernix), baby, girls, women	Children, women, men

Dominguez-Bello et al Science Trans Med 2015;7:307-39
Fischbach et al Cell 2016;164:1288-1300

Baby's first bacteria

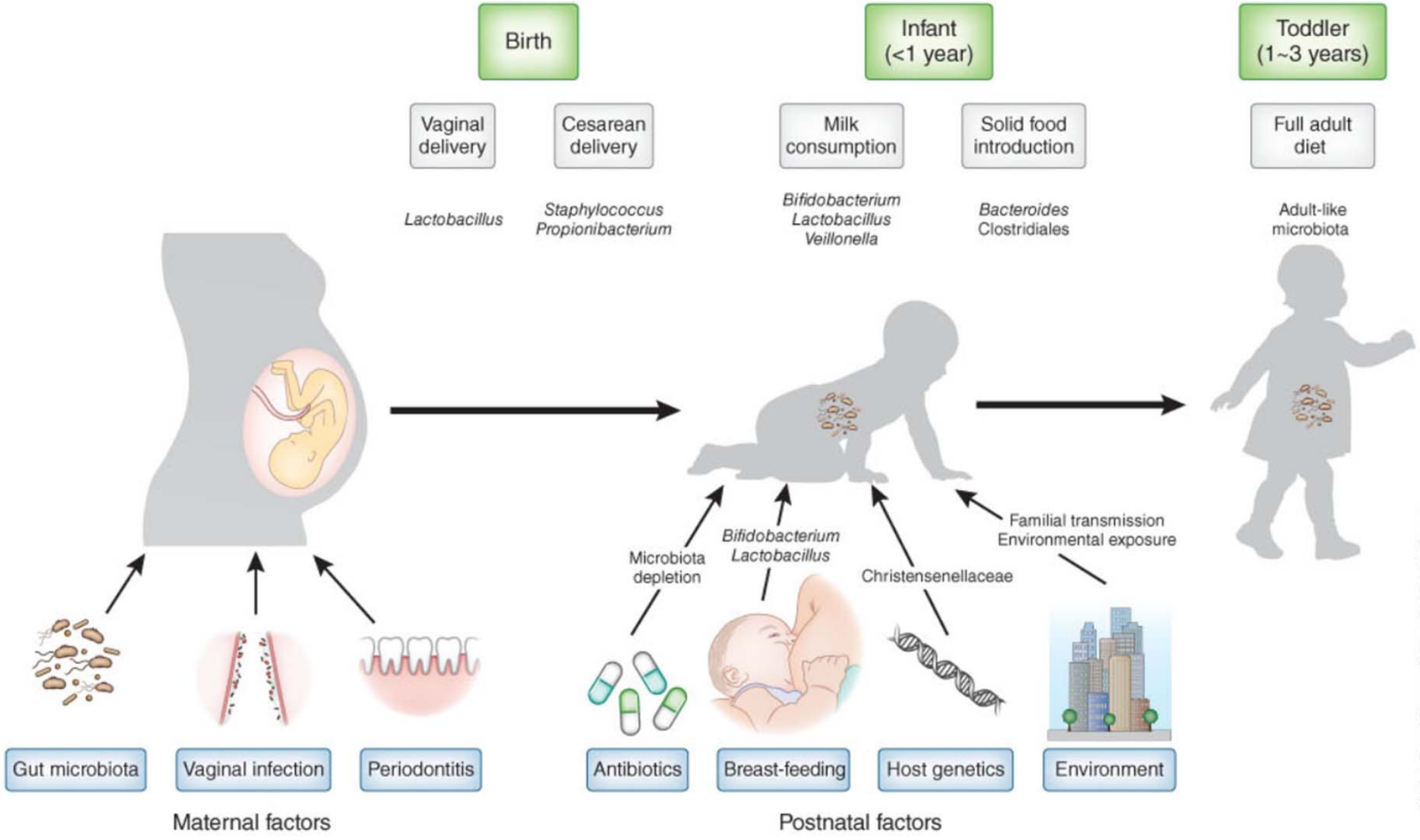
THE WOMB WAS THOUGHT TO BE STERILE. SOME SCIENTISTS ARGUE IT'S WHERE THE MICROBIOME BEGINS.

- Exactly when an infant is first exposed to microbes is still under debate
- Largest microbial transfer occurs at birth
- Microbial colonization of the newborn intestine contributes to the development of the host's immune function
- The first 1-3 years of an infant's microbiome development is characterized by chaotic and dramatic shifts until stabilization at approximately age 3



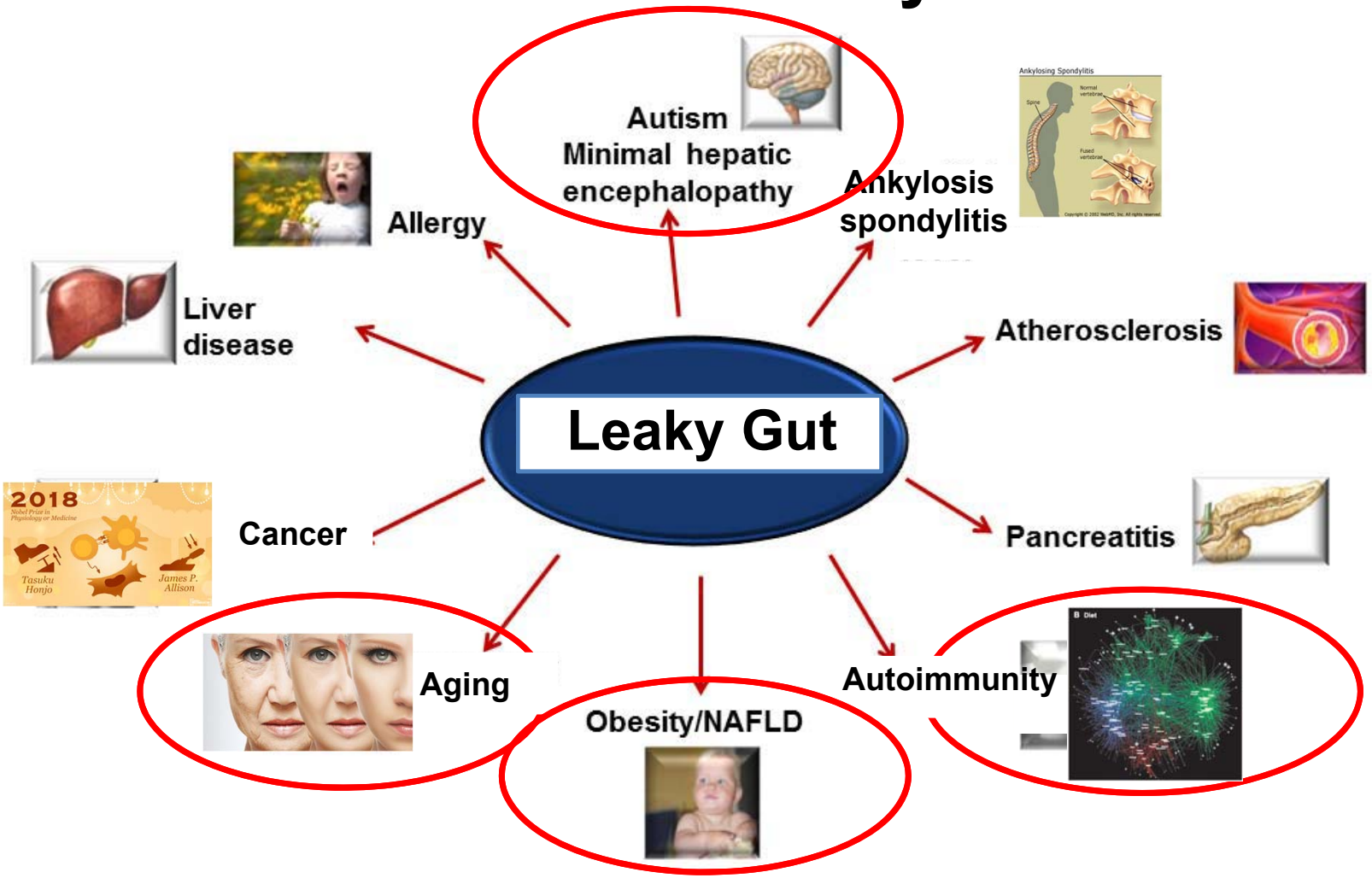
Nature, News Feature 1/18/2018
Yatsunenko, *Nature* ,2012

The Effect of Environmental Factors on Gut Microbiome Dysbiosis and Subsequent Changes to Metabolite Profiles May Be Particularly Important In Early Life



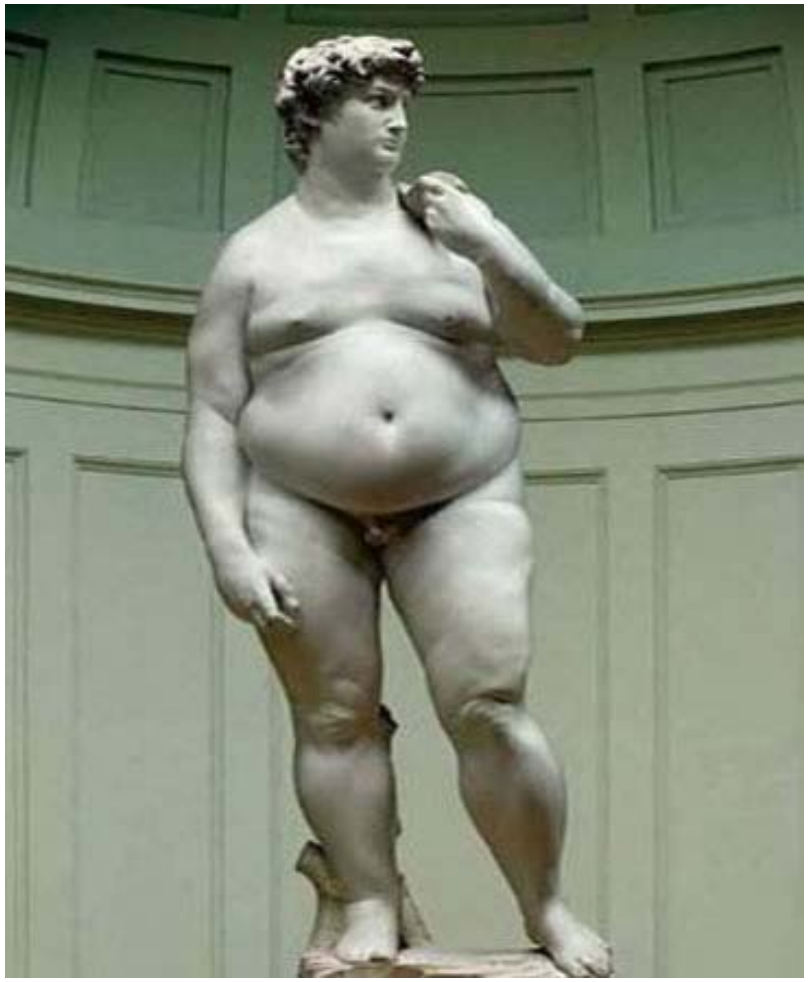
Tamburini, *Nature* 2016.

Role of Gut Permeability In Chronic Inflammatory Diseases

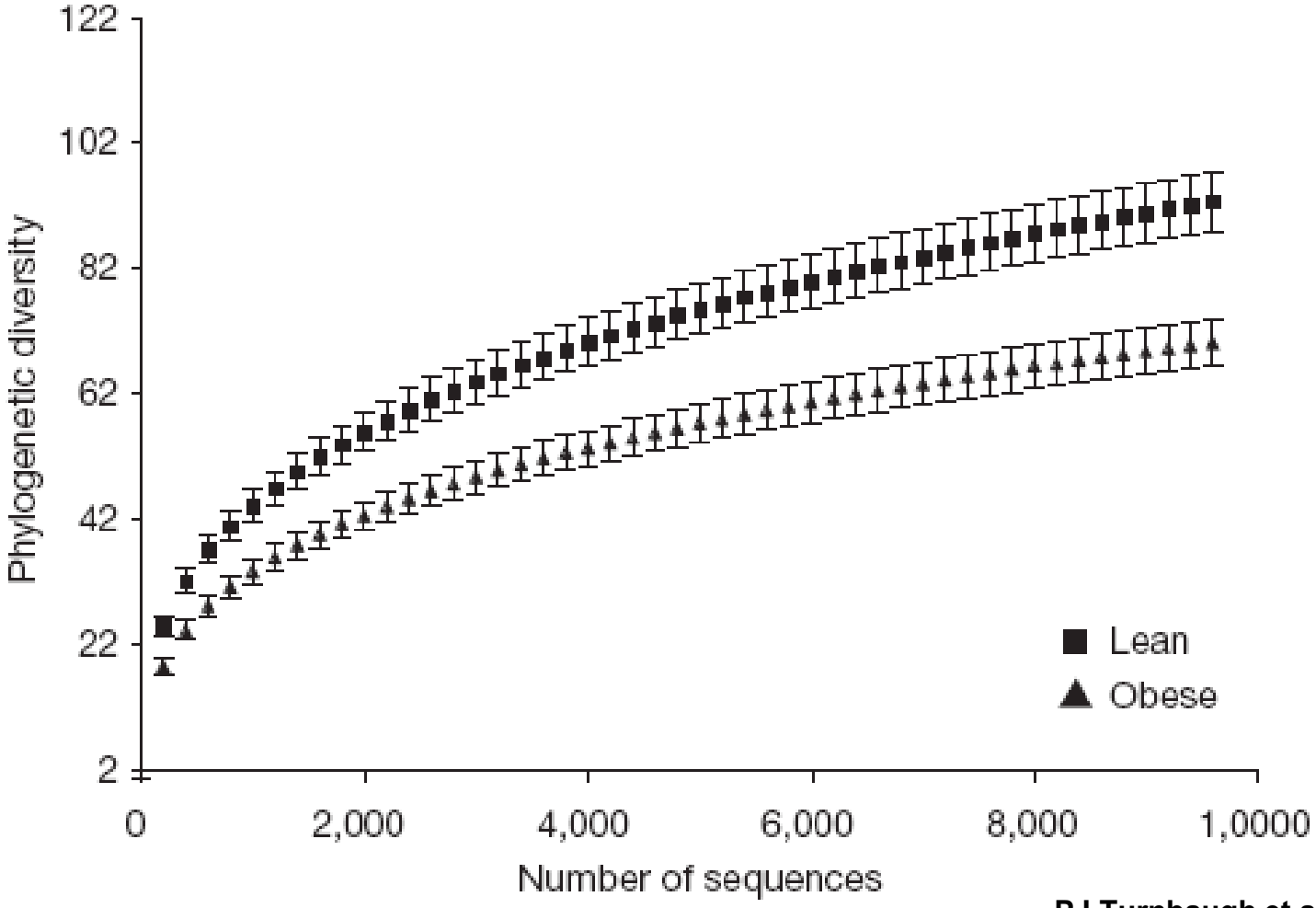


MassGeneral Hospital for Children

Obesity

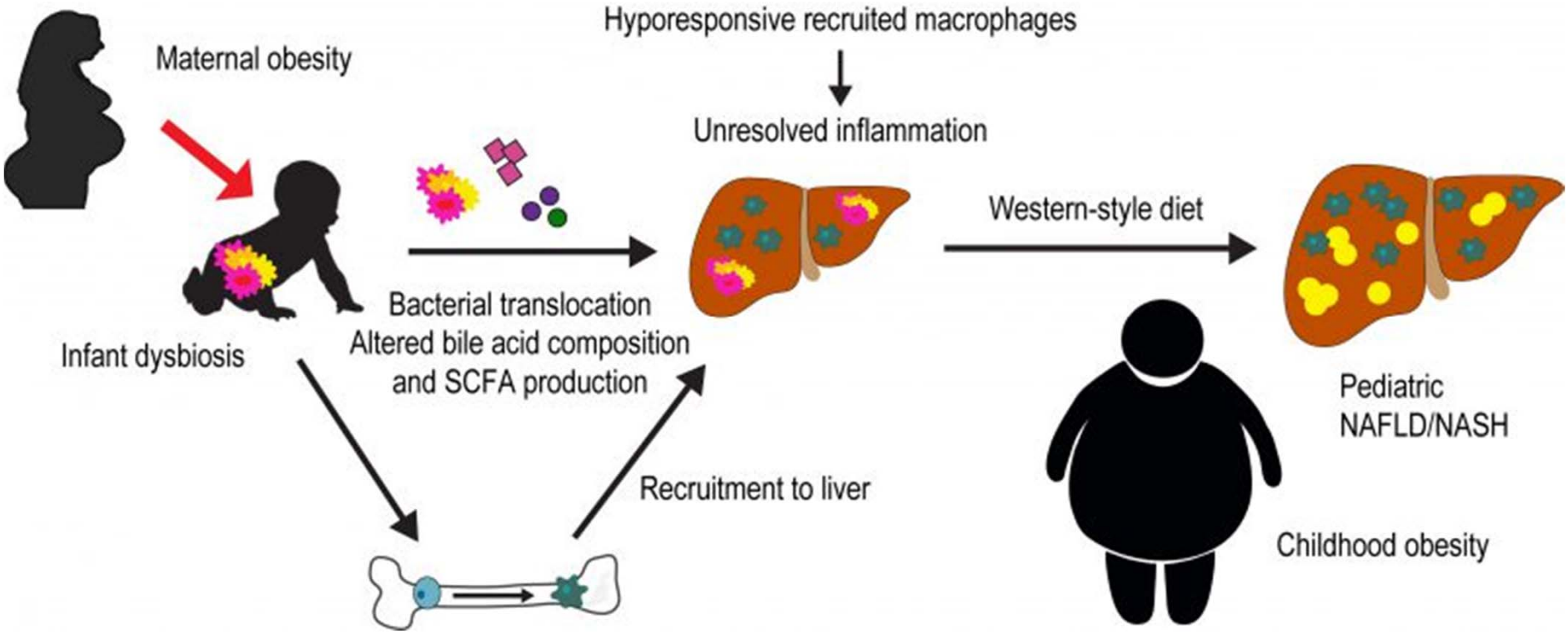


Core Microbiome in Obese And Lean Twins: Missouri Adolescent Female Twin Study



PJ Turnbaugh et al. Nature 2009;457:480-484

Why A Leaky Gut Together With Dysbiosis Can Make Us Fat



RATIONALE

An increase in intestinal permeability is considered to be associated with gut inflammatory tone and development of obesity, fatty liver (typical of obese subjects) and type 2 diabetes

OPEN ACCESS Freely available online

PLoS one

Circulating Zonulin, a Marker of Intestinal Permeability, Is Increased in Association with Obesity-Associated Insulin Resistance

José María Moreno-Navarrete, Mònica Sabater, Francisco Ortega, Wifredo Ricart, José Manuel Fernández-Real*

Department of Diabetes, Endocrinology and Nutrition, Institut d'Investigació Biomèdica de Girona (IdIBGi), CIBEROBN (CB06/03/010) and Instituto de Salud Carlos III (ISCIII), Girona, Spain

Abstract

Zonulin is the only physiological mediator known to regulate intestinal permeability reversibly by modulating intercellular tight junctions. To investigate the relationship between intestinal permeability and obesity-associated metabolic disturbances in humans, we aimed to study circulating zonulin according to obesity and insulin resistance. Circulating zonulin (ELISA) was measured in 123 caucasian men in association with inflammatory and metabolic parameters (including minimal model-measured insulin sensitivity). Circulating zonulin increased with body mass index (BMI), waist to hip ratio (WHR), fasting insulin, fasting triglycerides, uric acid and IL-6, and negatively correlated with HDL-cholesterol and insulin sensitivity. In multiple regression analysis, insulin sensitivity ($p = 0.002$) contributed independently to circulating zonulin variance, after controlling for the effects of BMI, fasting triglycerides and age. When circulating IL-6 was added to this model, only BMI ($p = 0.01$) contributed independently to circulating zonulin variance. In conclusion, the relationship between insulin sensitivity and circulating zonulin might be mediated through the obesity-related circulating IL-6 increase.

Citation: Moreno-Navarrete JM, Sabater M, Ortega F, Ricart W, Fernández-Real JM (2012) Circulating Zonulin, a Marker of Intestinal Permeability, Is Increased in Association with Obesity-Associated Insulin Resistance. PLoS ONE 7(5): e37160. doi:10.1371/journal.pone.0037160

Editor: Massimo Federici, University of Tor Vergata, Italy

J Clin Res Pediatr Endocrinol. 2016 Dec 23. doi: 10.4274/jcrpe.3682. [Epub ahead of print]

The Relationship of Serum Zonulin Level with Clinical and Laboratory Parameters in Childhood Obesity.

Küme T, Acar S, Tuhan H, Çatlı G, Anık A, Gürsoy Çalan Ö, Böber E, Abacı A.

Abstract

OBJECTIVE: The aim of this study was to investigate the relationship between zonulin and clinical laboratory parameters in childhood obesity.

METHODS: The study included obese children with a body mass index >95th percentile and healthy children who were similar age and gender distribution. Clinical (body mass index, waist circumferences, mid arm circumference, triceps skin fold, percentage of body fat, systolic blood pressure, diastolic blood pressure) and biochemical (glucose, insulin, lipids, thyroid function tests, cortisol, zonulin and leptin levels) parameters were measured.

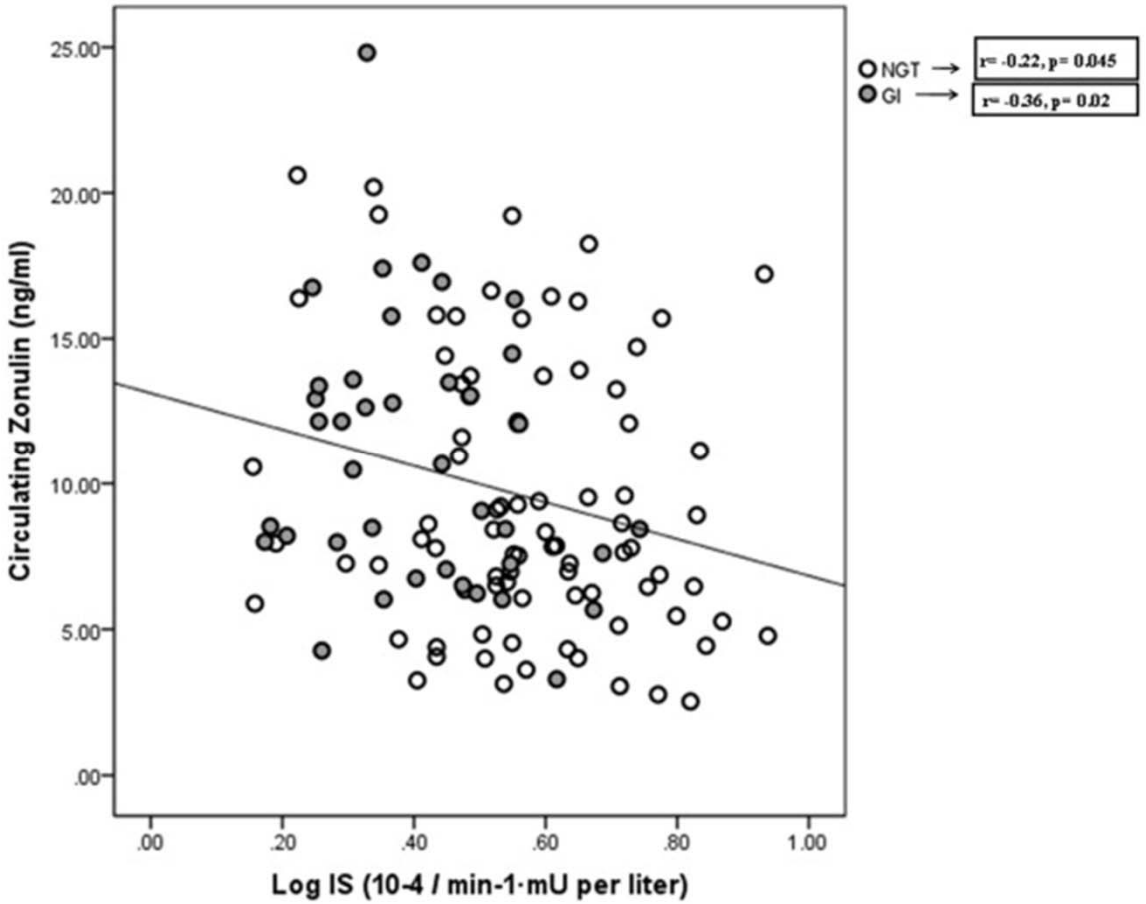
RESULTS: A total of 43 obese subjects (23 males, mean age: 11.1±3.1 yrs) and 37 healthy subjects (18 males, mean age: 11.5±3.5 yrs) were included in this study. Obese children had significantly higher insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, zonulin and leptin levels than those of the healthy children ($p < 0.05$), while glucose levels were not different ($p > 0.05$). Comparison of the obese children regarding the insulin resistance showed no statistically significant differences for zonulin levels ($p > 0.05$).

CONCLUSION: To the best of our knowledge, the present study is the first study to compare serum zonulin levels between obese and non-obese children. The results of the study showed that zonulin was significantly higher in obese children when compared to healthy children, which is indicating a potential role of zonulin in the obesity etiopathogenesis and related disturbances.

PMID: 28008865 DOI: 10.4274/jcrpe.3682

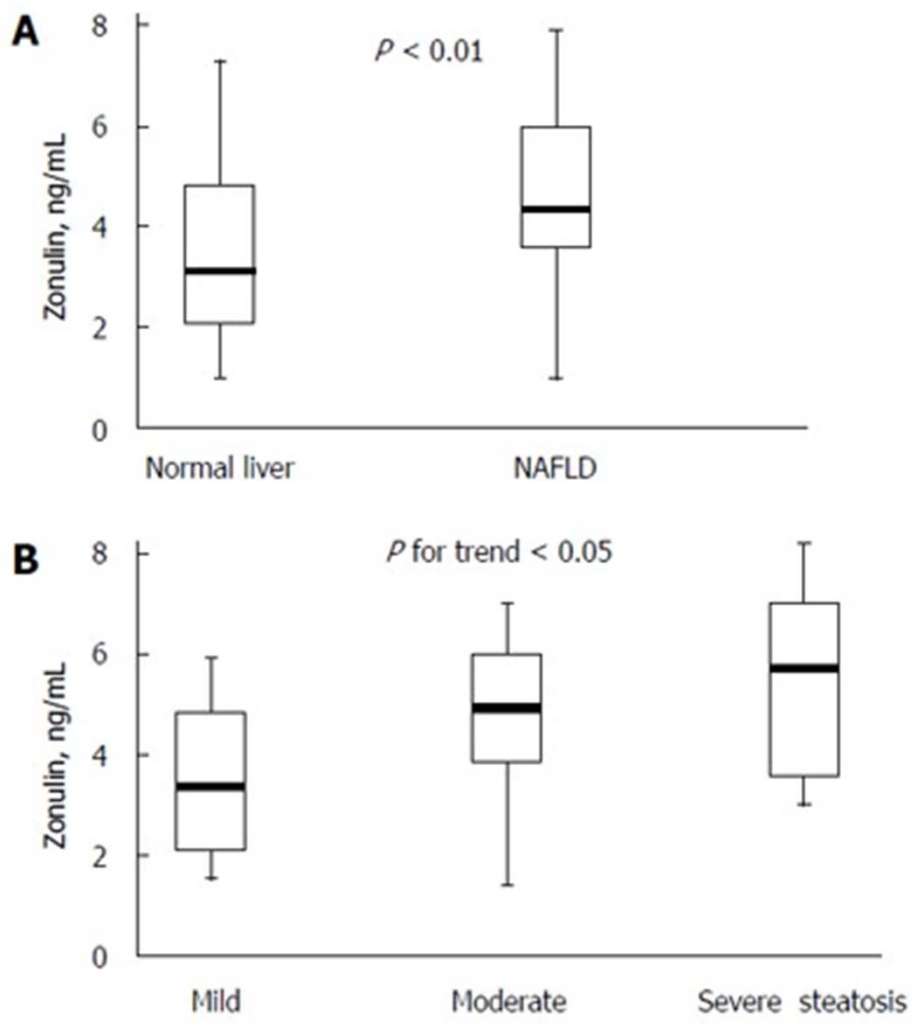
[PubMed - as supplied by publisher] Free full text

Circulating Zonulin, a Marker of Intestinal Permeability, Is Increased in Association with Obesity-Associated Insulin Resistance



The correlation between insulin sensitivity and circulating zonulin in participants with normal glucose tolerance (NGT, n = 82) and with glucose intolerance (GI, n = 41).

Increased Circulating Zonulin In Children With Biopsy-Proven Nonalcoholic Fatty Liver Disease

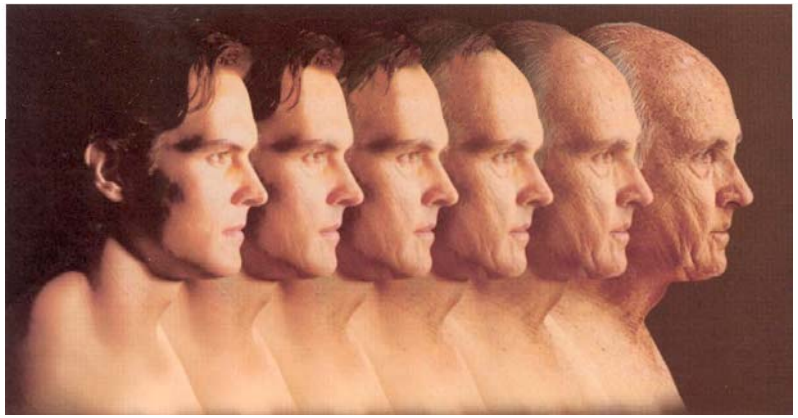


Zonulin levels for obese children.
A: Zonulin levels for obese children with and without nonalcoholic fatty liver disease (NAFLD);

B: Zonulin levels for obese children with NAFLD according to severity of steatosis.

World J Gastroenterol. 2014 Dec 7; 20(45): 17107–17114.

Inflamm(Aging)



- Aging is a syndrome of changes that are deleterious, progressive, universal and thus far irreversible. Aging damage occurs to molecules (DNA, proteins, lipids), to cells and to organs.

- Aging is the accumulation of changes in a person over time. Aging in humans refers to a multidimensional process of physical, psychological, and social change.

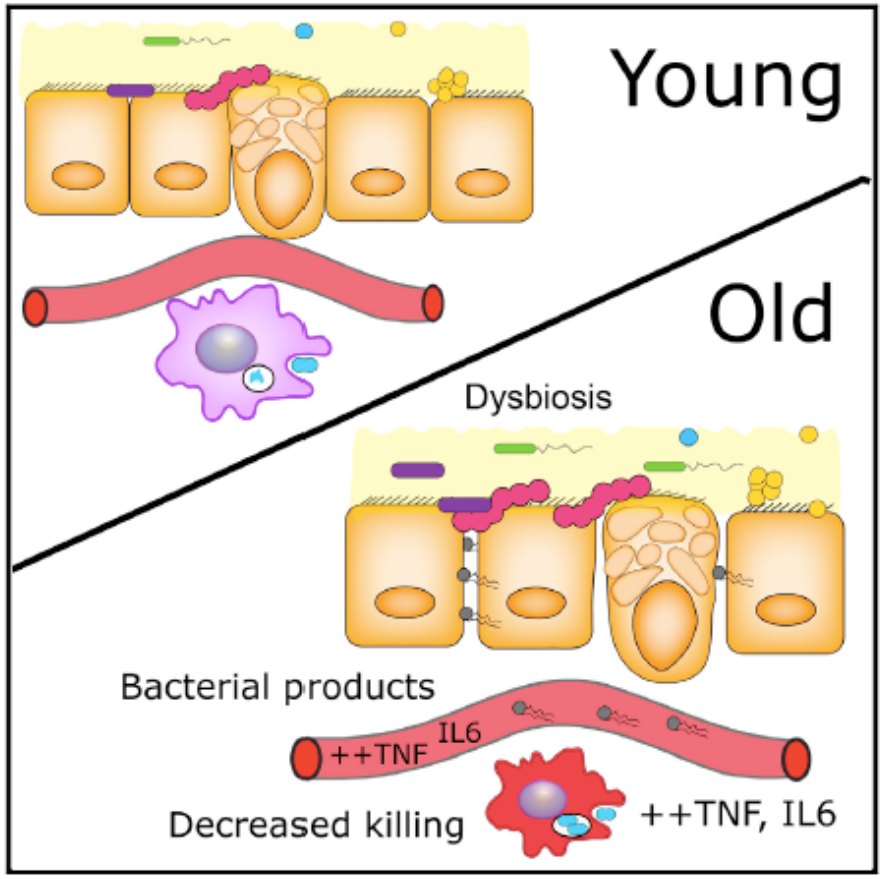
- Research shows that even late in life, potential exists for physical, mental, and social growth and development.

- Recent scientific successes in rejuvenation and extending a lifespan of model animals give hope to achieve negligible senescence, reverse aging or at least significantly delay it.

Cell Host & Microbe

Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction

Graphical Abstract



Authors

Netusha Thevaranjan, Alicja Puchta, Christian Schulz, ..., Elena F. Verdú, Michael G. Surette, Dawn M.E. Bowdish

Correspondence

bowdish@mcmaster.ca

In Brief

Systemic inflammation increases with age, but the underlying causes are debated. Using young and old germ-free and conventional mice, Thevaranjan et al. demonstrate that age-related microbiota changes drive intestinal permeability, age-associated inflammation, and decreased macrophage function. Reducing TNF levels rescues microbiota changes and protects old mice from intestinal permeability.

Theories of Aging

1. **The free radical theory (oxidative stress):** Free radicals can damage nucleic acids, proteins or lipids. For biological systems, oxygen free radicals are the most important, in particular superoxide ($\cdot O_2^-$), nitric oxide ($\cdot NO$) and the hydroxyl radical ($\cdot OH$).

2. **Cellular senescence and apoptosis theory:** The relationship between cellular aging and the aging of the whole organism is complex. Cellular "immortality" is essential for stem cells, but an "immortal" somatic cell is cancerous. Apoptosis is programmed cell suicide — a genetically ***controlled cell death*** that causes cells to shrink and be eliminated without the tissue traumas associated with inflammation that accompanies ***uncontrolled cell death*** (necrosis).

3. **The immune system theory of aging**: According to this theory, many aging effects are due to the declining ability of the immune system to differentiate "foreign" from "self" proteins. There is evidence that histocompatability genes, genes affecting DNA repair and genes for SOD production — all of which affect longevity — are located close together on human chromosome 6.

4. **Inflammation and aging:** With aging the body contains increasing quantities of pro-inflammatory cytokines. Aging is associated with increasing activity of the pro-inflammatory transcription factor NF-kB

5. **Intestinal permeability and aging:** Several reports both in animal models and humans link gut permeability to non-infective chronic inflammation leading to senescence. In fruit fly the increase in intestinal permeability is the best predictor of imminent death, even more than the actual age of the insect.

Intestinal barrier dysfunction links metabolic and inflammatory markers of aging to death in *Drosophila*

Michael Rera[a,1], Rebecca I. Clark[a,1], and David W. Walker[a,b,2]

[a]Department of Integrative Biology and Physiology and [b]Molecular Biology Institute, University of California, Los Angeles, CA 90095

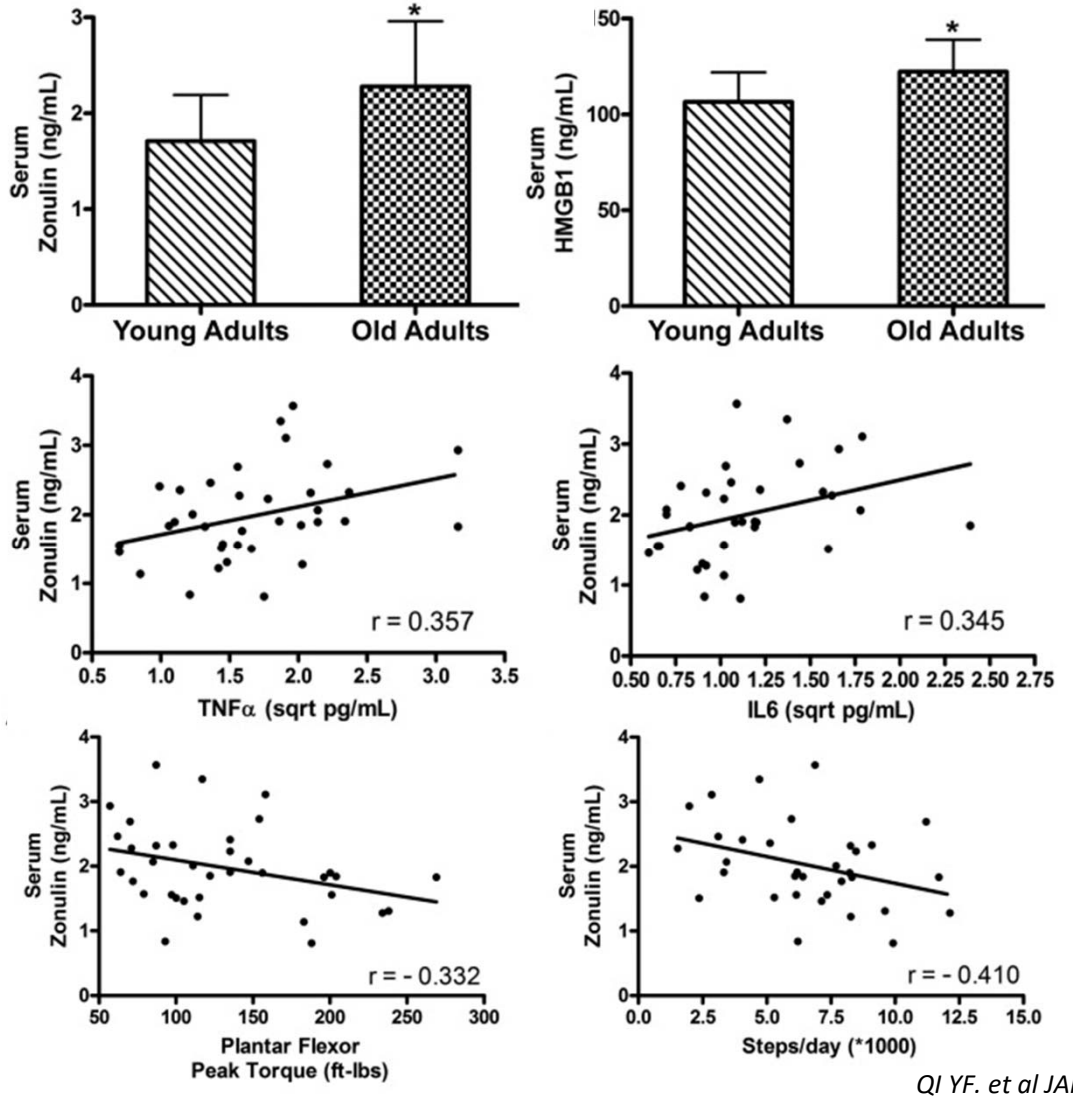
Edited by David S. Schneider, Stanford University, Stanford, CA, and accepted by the Editorial Board November 10, 2012 (received for review September 13, 2012)

Aging is characterized by a growing risk of disease and death, yet the underlying pathophysiology is poorly understood. Indeed, little is known about how the functional decline of individual organ systems relates to the integrative physiology of aging and probability of death of the organism. Here we show that intestinal barrier dysfunction is correlated with lifespan across a range of *Drosophila* genotypes and environmental conditions, including mitochondrial dysfunction and dietary restriction. Regardless of chronological age, intestinal barrier dysfunction predicts impending death in individual flies. Activation of inflammatory pathways has been linked to aging and age-related diseases in humans, and an age-related increase in immunity-related gene expression has been reported in *Drosophila*. We show that the age-related increase in expression of antimicrobial peptides is tightly linked to intestinal barrier dysfunction. Indeed, increased antimicrobial peptide expression during aging can be used to identify individual flies exhibiting intestinal barrier dysfunction. Similarly, intestinal barrier dysfunction is more accurate than chronological age in identifying individual flies with systemic metabolic defects previously linked to aging, including impaired insulin/insulin-like growth factor signaling, as evidenced by a reduction in Akt activation and upregulation of dFOXO target genes. Thus, the age-dependent loss of intestinal integrity is associated with altered metabolic and immune signaling and, critically, is a harbinger of death. Our findings suggest that intestinal barrier dysfunction may be an important factor in the pathophysiology of aging in other species as well, including humans.

in aged mammals (9) and *Drosophila* (10–13). Moreover, we (13) and others (14–16) have shown that the intestine represents an important target organ with respect to genetic interventions that promote longevity in both *C. elegans* and *Drosophila* (17). One interpretation of these findings is that maintaining intestinal integrity is an important determinant of health and viability at the organismal level; however, given that most assays of intestinal homeostasis are based on imaging techniques that require killing the flies (10–12), it has not been possible to determine how the onset of intestinal degeneration in individual flies relates to other aspects of aging and/or subsequent mortality.

We recently developed a noninvasive assay to determine intestinal integrity in individual flies (13). In the present work, we used this assay to further explore the role of intestinal barrier dysfunction in *Drosophila* aging. Our results show that loss of intestinal integrity accompanies aging across a range of *Drosophila* genotypes and environmental conditions. Interventions that extend lifespan, such as reduced temperature or dietary restriction, delay the onset of intestinal barrier defects, whereas loss of subunit b of mitochondrial complex II (*sdhB*) accelerates the onset of intestinal barrier defects and shortens the lifespan. Critically, intestinal barrier dysfunction is a better predictor of age-onset mortality than chronological age. Furthermore, we show that flies with intestinal barrier dysfunction display increased expression of antimicrobial peptides (AMPs), impaired IIS and reduced metabolic stores compared with age-matched animals without intestinal barrier defects. Thus, in a population of aging flies, we can now identify individuals showing systemic metabolic defects,

Serum Zonulin Concentrations Among Healthy Young and Older Adults Correlate With Inflammatory And Aging Markers



QI YF. et al JAMDA 2017;18:810e1-810e4

Aging and Disease
www.aginganddisease.org
Volume 9, Number 2; xxx-xx, April 2018
http://dx.doi.org/10.14336/AD.2017.0630

Short Communications

Serum Zonulin and Endotoxin Levels in Exceptional Longevity versus Precocious Myocardial Infarction

Pedro Carrera-Bastos[1,2], Óscar Picazo[2], Maelán Fontes-Villalba[1,2], Helios Pareja-Galeano[3,4,*], Staffan Lindeberg[1], Manuel Martínez-Selles[5], Alejandro Lucia[3,4], Enzo Emanuele[6]

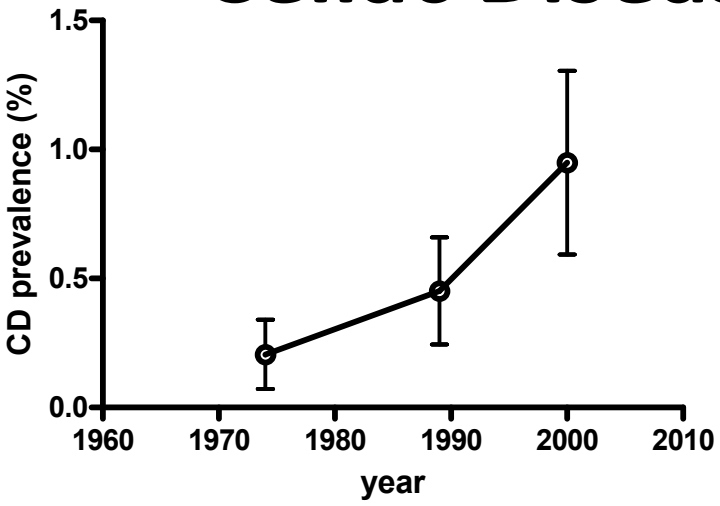
[1]Clinical Research Center, Faculty of Medicine, Center for Primary Health Care Research, Lund University, Malmö, Sweden.
[2]NutriScience – Education and Consulting, Lisbon, Portugal.
[3]European University of Madrid, Spain.
[4]Research Institute of Hospital 12 de Octubre ('i+12'), Madrid, Spain.
[5]Servicio de Cardiología, Hospital Universitario Gregorio Marañón, CIBERCV, Universidad Europea, Universidad Complutense, Madrid, Spain
[6]2E Science, Robbio, Pavia, Italy.

[Received March 23, 2017; Revised May 3, 2017; Accepted June 30, 2017]

ABSTRACT: Endotoxemia-induced inflammation has been associated with insulin resistance and atherosclerosis, ultimately increasing the risk of coronary heart disease. Increased intestinal permeability is an important event leading to endotoxemia. This study aims to elucidate the possible association between endotoxin (lipopolysaccharide) and zonulin (a biomarker of intestinal permeability) levels and the risk of coronary heart disease, and thus healthy aging. Serum levels of zonulin, lipopolysaccharide and soluble CD14 (a protein that binds lipopolysaccharide) were measured in disease-free centenarians, young healthy controls and patients with precocious acute myocardial infarction. Disease-free centenarians had significantly lower levels of serum zonulin ($P<0.01$) and lipopolysaccharide ($P<0.001$) than young patients with acute myocardial infarction, and had significantly lower concentrations of serum lipopolysaccharide than young healthy controls ($P<0.05$). No significant differences were found for soluble CD14 between groups. Our findings may stimulate further research into the role played by intestinal permeability and endotoxemia not only in coronary heart disease but also in lifespan modulation.

Autoimmunity: Celiac Disease

Celiac Disease Can Be Triggered At Any Age



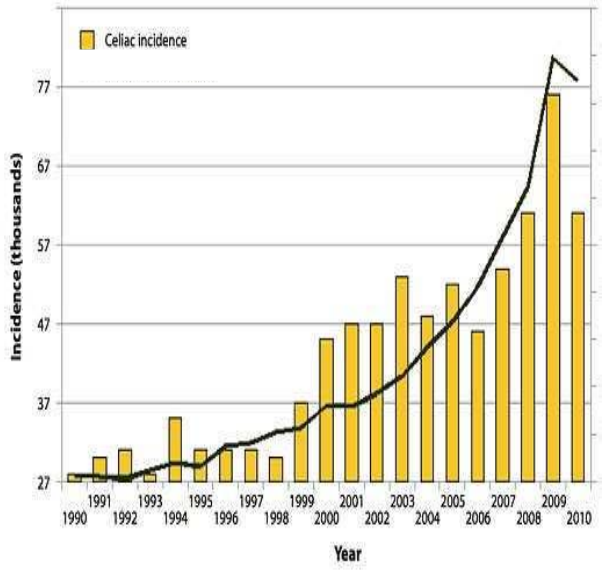


Figure 1. Hospital discharge diagnosis (any) of celiac disease ICD-9 579 and glyphosate applications to wheat (R=0.97 Sources: USDA:NASS; CDC. (Figure courtesy of Nancy Swanson).

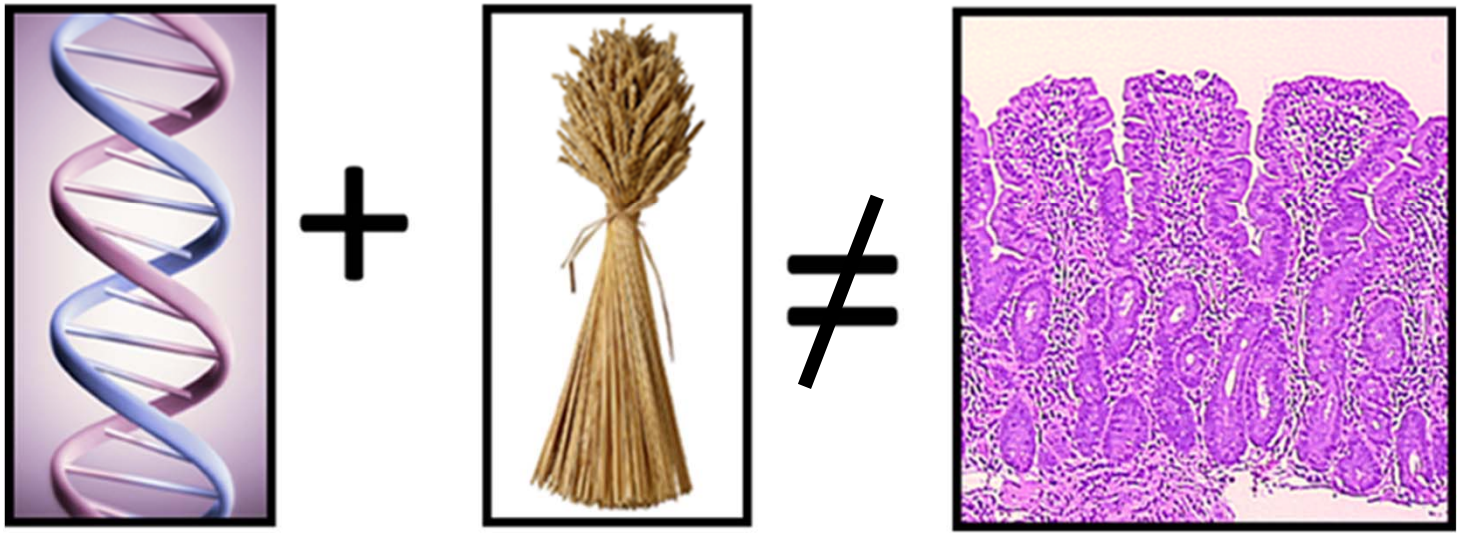
Annals of Medicine, 2010; 42: 530–538

informa
healthcare

ORIGINAL ARTICLE

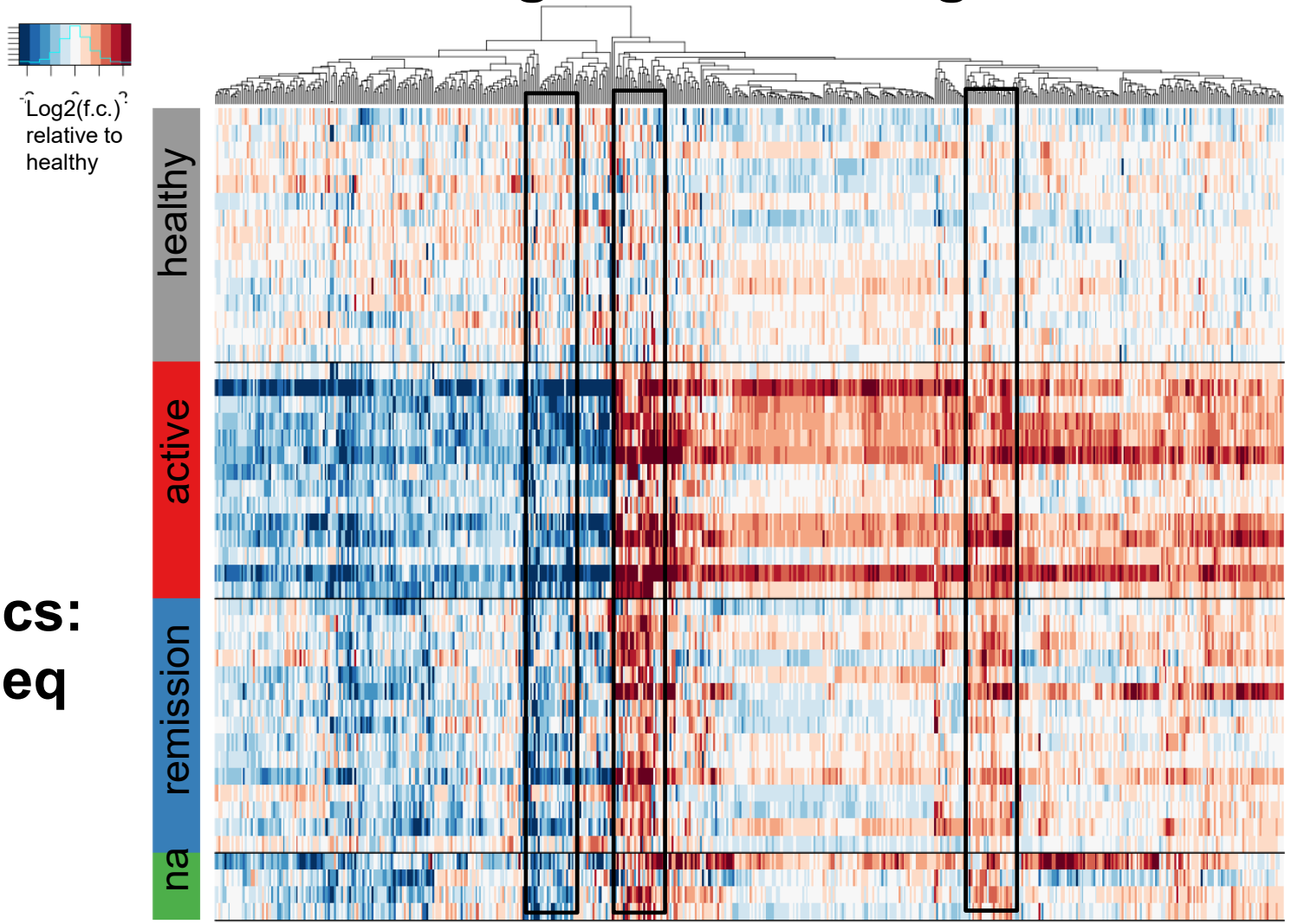
Natural history of celiac disease autoimmunity in a USA cohort followed since 1974

CARLO CATASSI[1,2], DEBBY KRYSZAK[1], BUSHRA BHATTI[1], CRAIG STURGEON[1], KATHY HELZLSOUER[3], SANDRA L. CLIPP[3], DANIEL GELFOND[4], ELAINE PUPPA[1], ANTHONY SFERRUZZA[5] & ALESSIO FASANO[1]



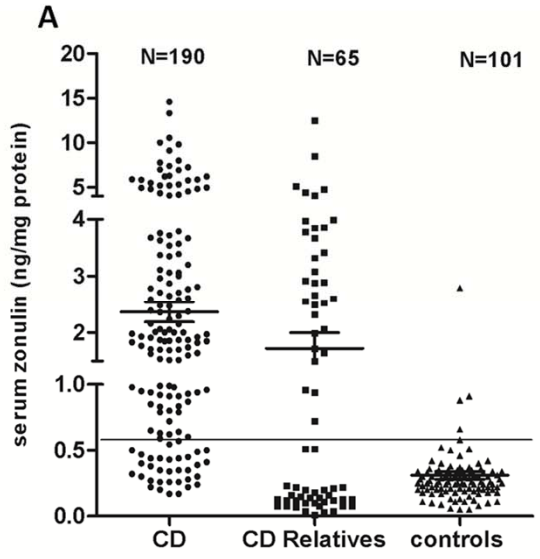
Majority Signatures in the Active State Diminished in Remission, Although Residual Signatures Do Exist.

Genetics: RNASeq

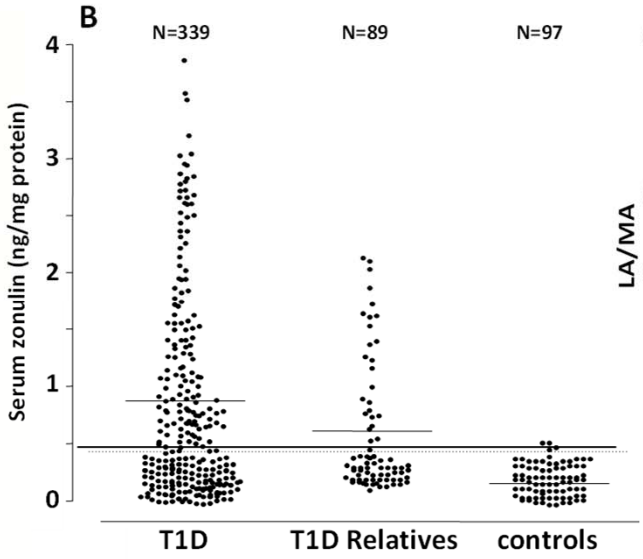


Serum Zonulin Levels and Their Correlation With Intestinal Permeability In Celiac Disease and Type 1 Diabetes

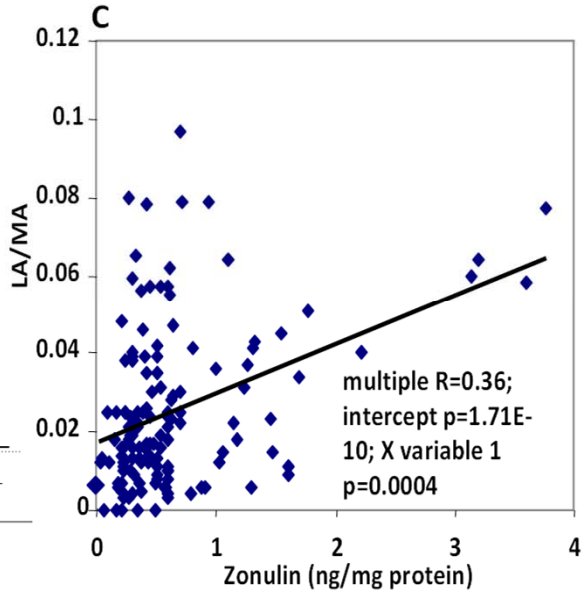
Celiac Disease



Type 1 Diabetes



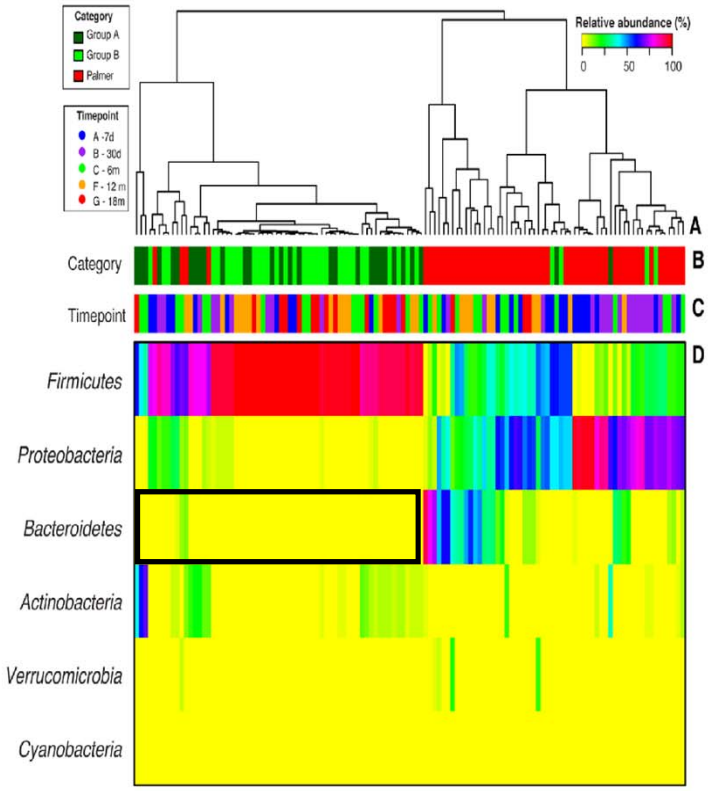
Zonulin-LA/MA

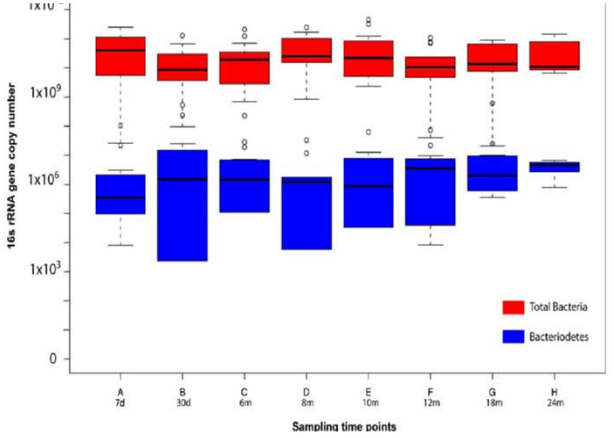


Sapone et al Diabetes 2006; 55:1443-9

Proof of Concept of Microbiome-Metabolome Analysis and Delayed Gluten Exposure on Celiac Disease Autoimmunity in Genetically At-Risk Infants

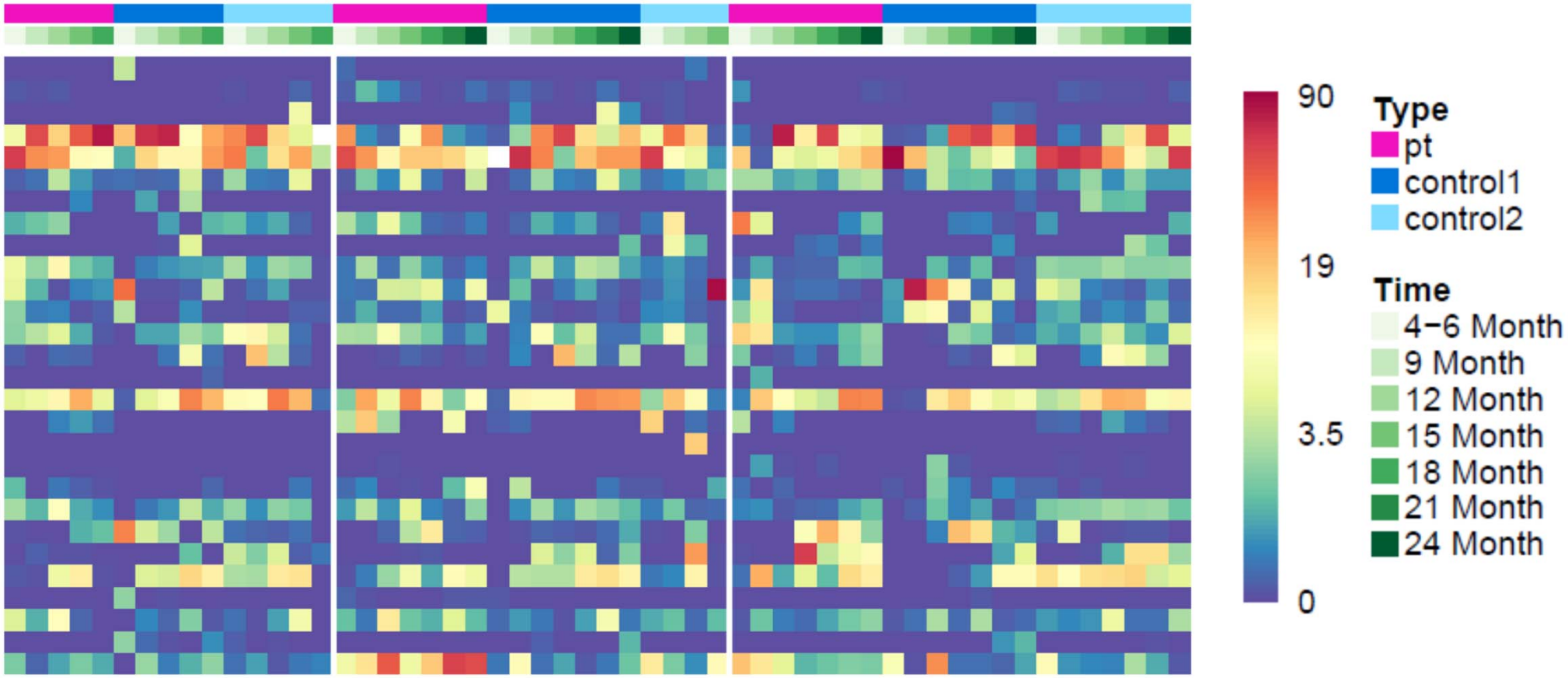
Maria Sellitto[1¤], Guoyun Bai[2], Gloria Serena[1], W. Florian Fricke[2], Craig Sturgeon[1], Pawel Gajer[2], James R. White[2], Sara S. K. Koenig[2], Joyce Sakamoto[2], Dustin Boothe[1], Rachel Gicquelais[1], Deborah Kryszak[1], Elaine Puppa[1], Carlo Catassi[1,3], Jacques Ravel[2]*, Alessio Fasano[1]*





Infants genetically predisposed to CD were characterized by a low abundance of Bacteroidetes (undetectable to 1%) combined with abundance of Firmicutes and abrupt decrease in Lactobacilli during the pre-clinical phase of CD.

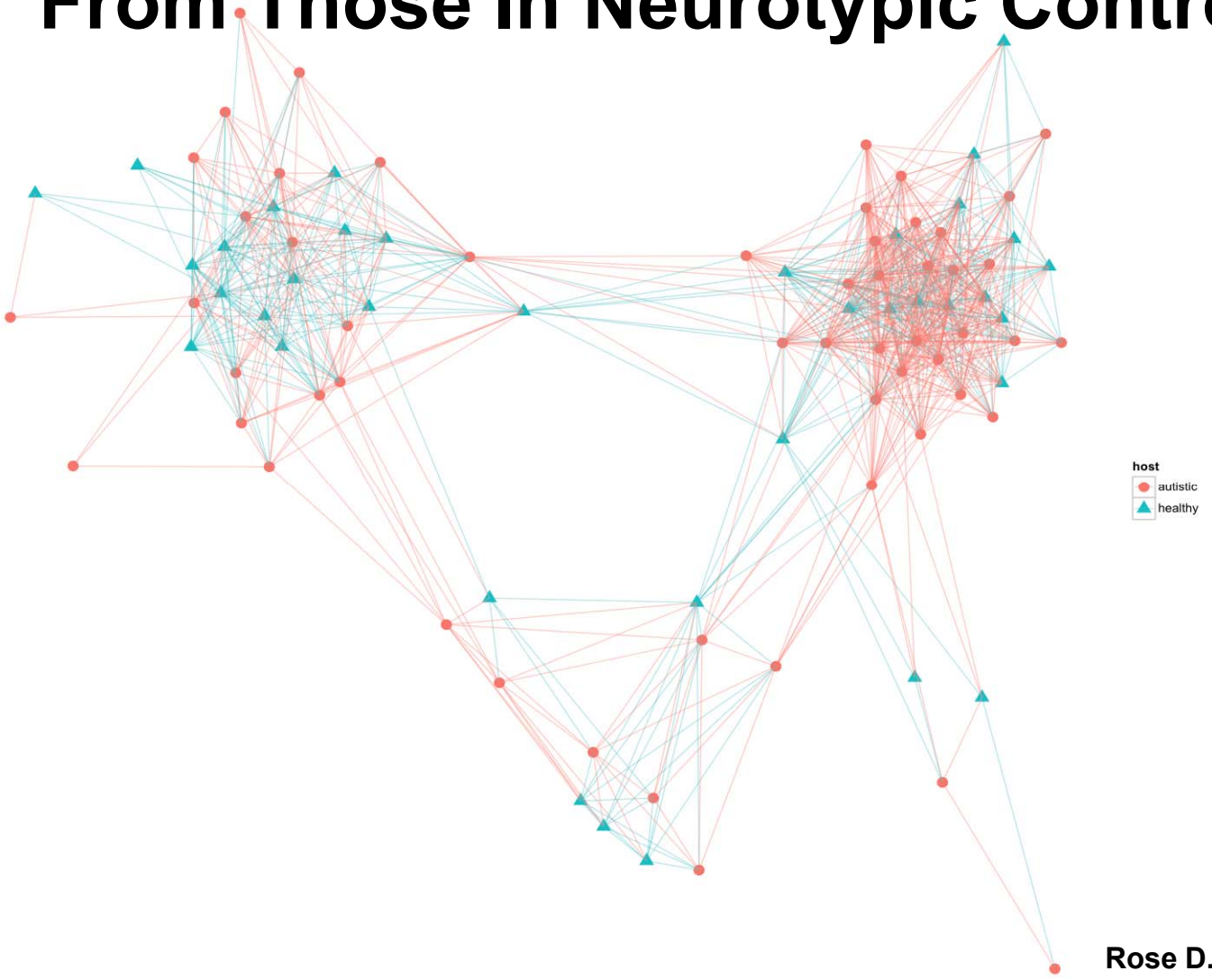
Identifying A Microbial Signature Predictive Of Celiac Disease: Epigenetic Changes In Immune Function



ASD


MAY 15, 2006
POP! GOES SCHOOL SODA ■ EXCLUSIVE: NINTENDO'S NEW GAME
TIME
NEW INSIGHTS INTO THE HIDDEN WORLD OF
AUTISM
BY CLAUDIA WALLIS

Microbial Communities In ASD Are Different From Those In Neurotypic Controls

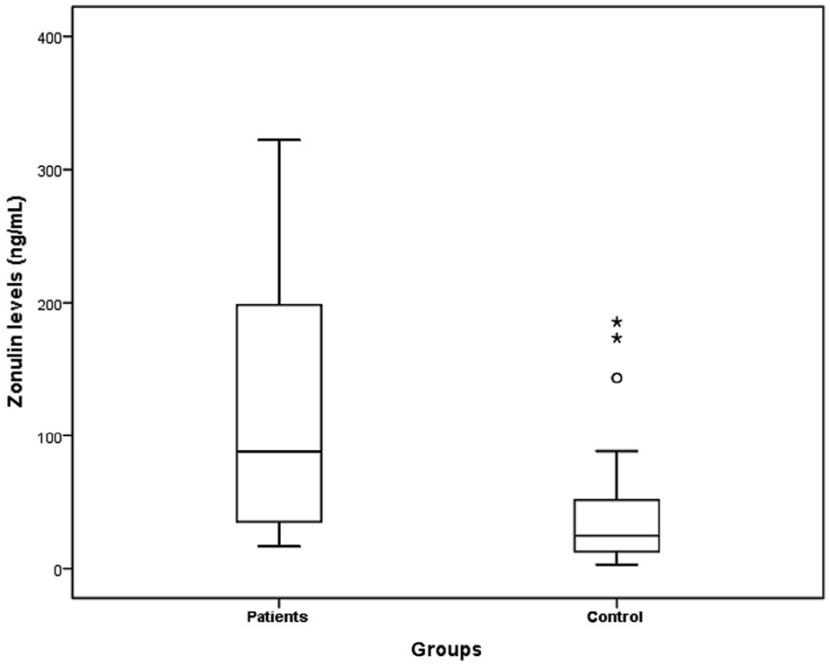


Rose D.R. et al Brain, Behav, immun 2018

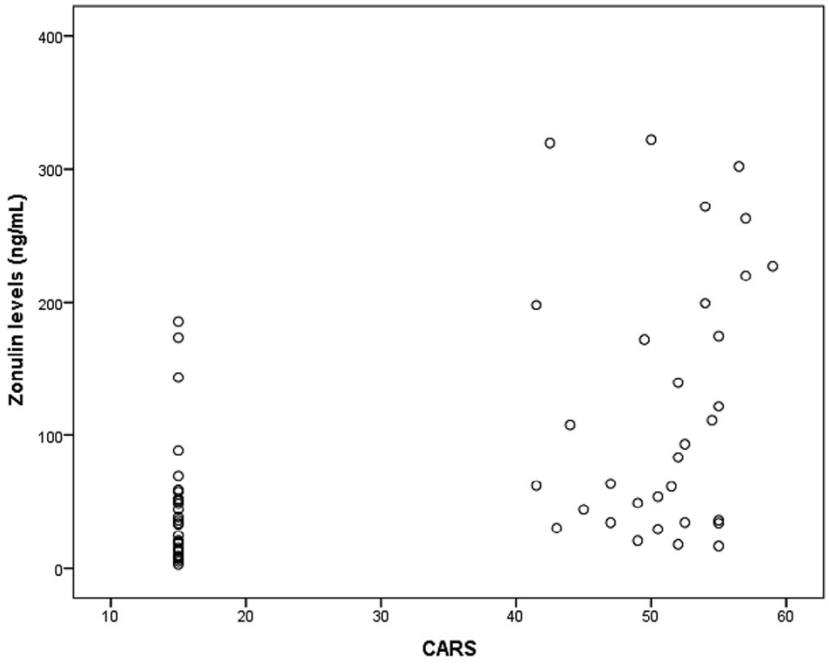
ORIGINAL ARTICLES
www.jpeds.com • THE JOURNAL OF PEDIATRICS
2017

Increased Serum Zonulin Levels as an Intestinal Permeability Marker in Autistic Subjects

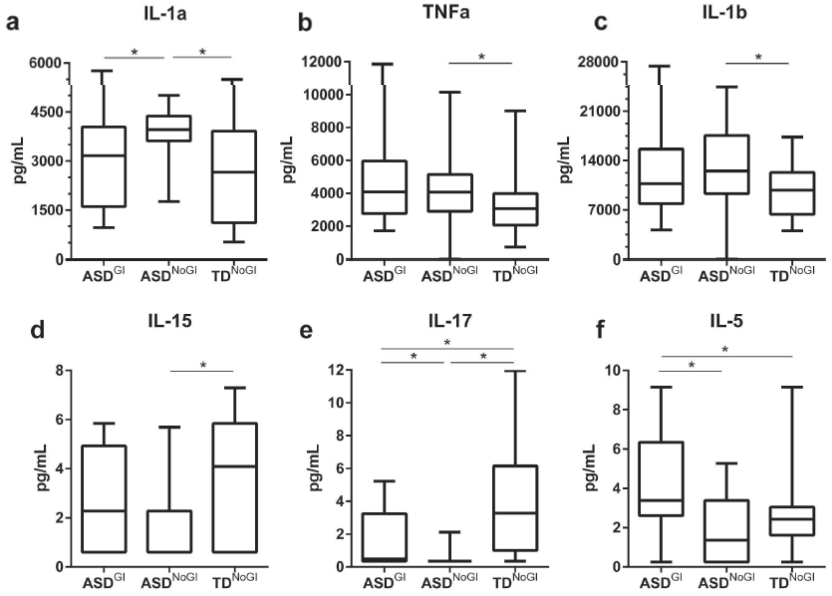
Erman Esnafoglu, MD[1], Selma Cırrık, PhD[2], Sema Nur Ayyıldız, MD[3], Abdullah Erdil, MD[4], Emine Yurdakul Ertürk, MD[4], Abdullah Daglı, MD[4], and Tevfik Noyan, MD[3]



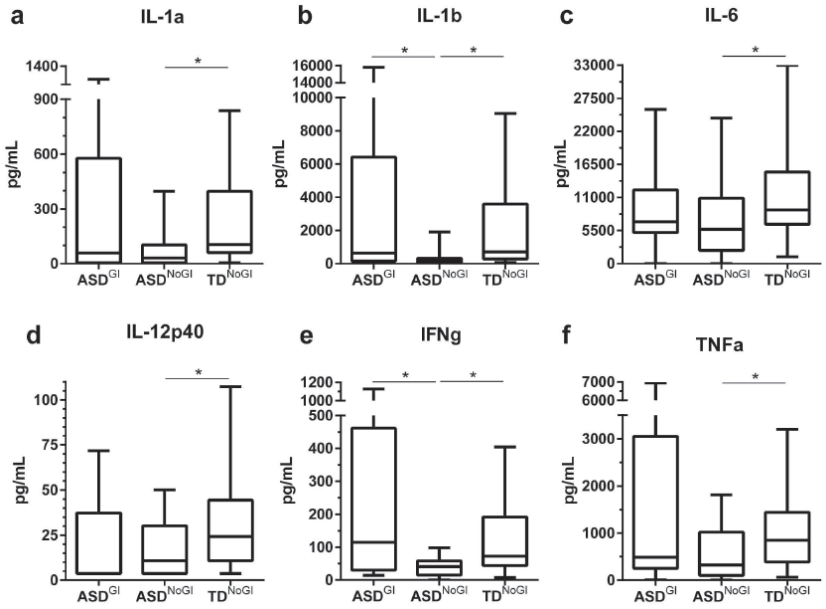
Distribution of serum zonulin levls in ASD patients and controls *p<0.001



Scattergram of zonulin levels according to Childhood Autism Rating Scale (SCAR)



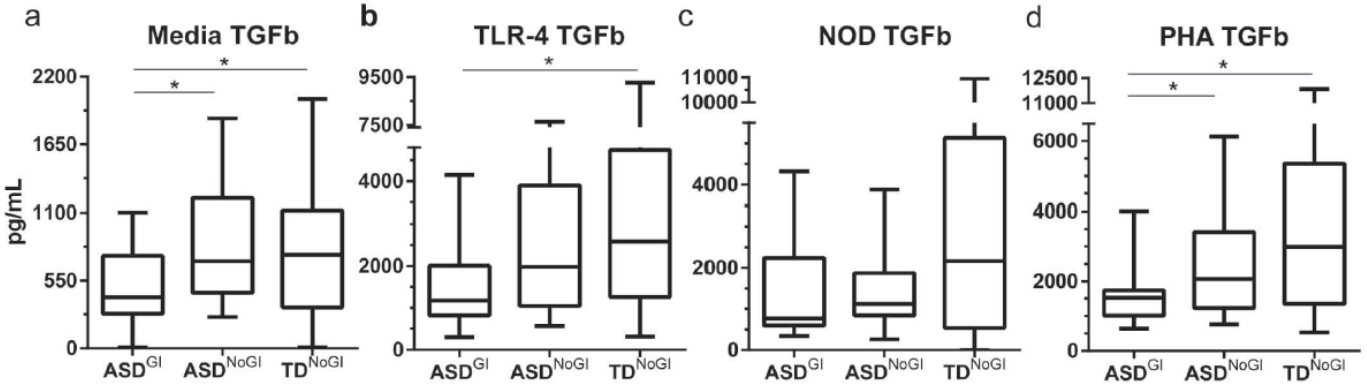
Immune Cells From ASD Children Produce More Pro-Inflammatory Cytokines When Stimulated With TLR4 Agonist



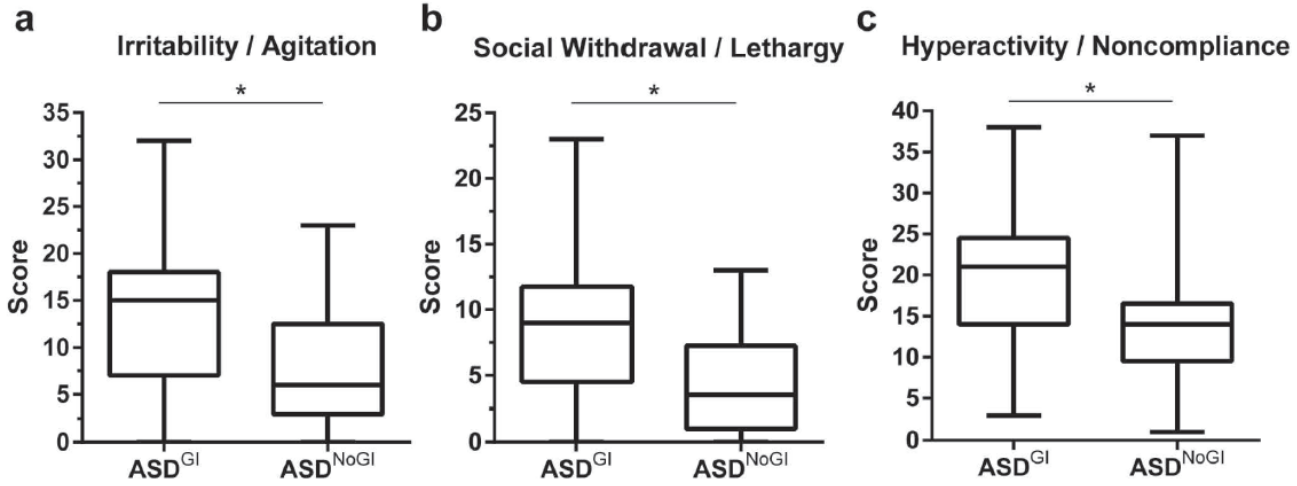
Immune Cells From ASD Children Produce More Pro-Inflammatory Cytokines When Stimulated With NOD Agonist

Rose D.R. et al Brain, Behav, immun 2018

Immune Cells From ASD Children With GI Symptoms Produce Less Anti-Inflammatory Cytokines



Behavioral Measures In ASD Children +/- GI Symptoms

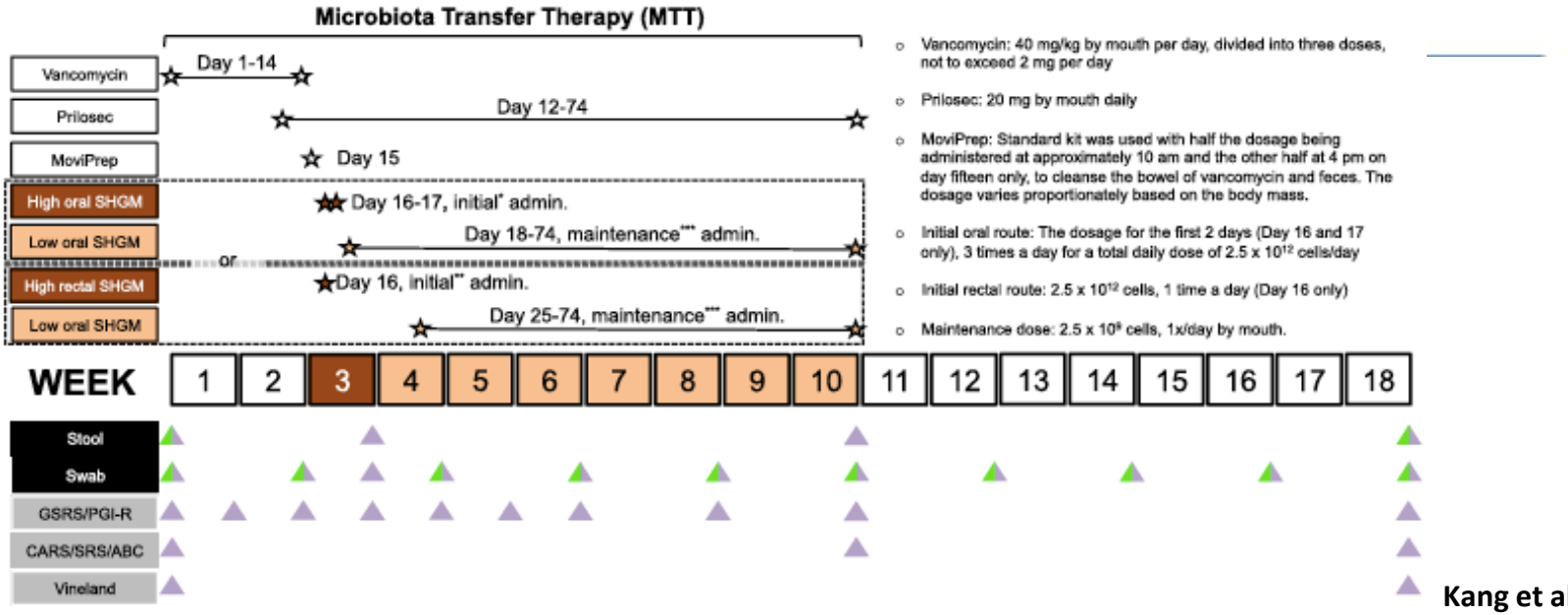


Rose D.R. et al Brain, Behav, immun 2018

RESEARCH Open Access

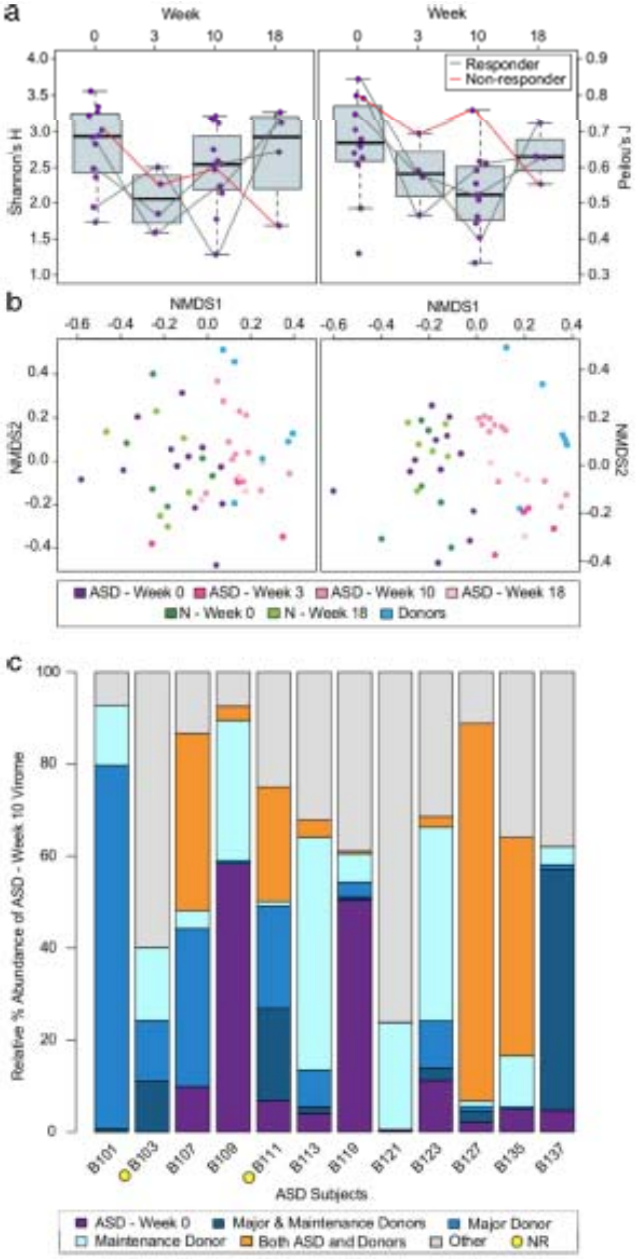
Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

Dae-Wook Kang[1†], James B. Adams[2†], Ann C. Gregory[3,15†], Thomas Borody[4], Lauren Chittick[5,15], Alessio Fasano[6], Alexander Khoruts[7,8,9], Elizabeth Geis[2], Juan Maldonado[1], Sharon McDonough-Means[10], Elena L. Pollard[2], Simon Roux[5,15], Michael J. Sadowsky[8,11], Karen Schwarzberg Lipson[12], Matthew B. Sullivan[3,5,15,16*], J. Gregory Caporaso[12,13*] and Rosa Krajmalnik-Brown[1,14*]



Kang et al *Microbiome*, 2017

Stool Microbiome and Virome Changes With Fecal Microbiota Transplant



Conclusive Remarks:

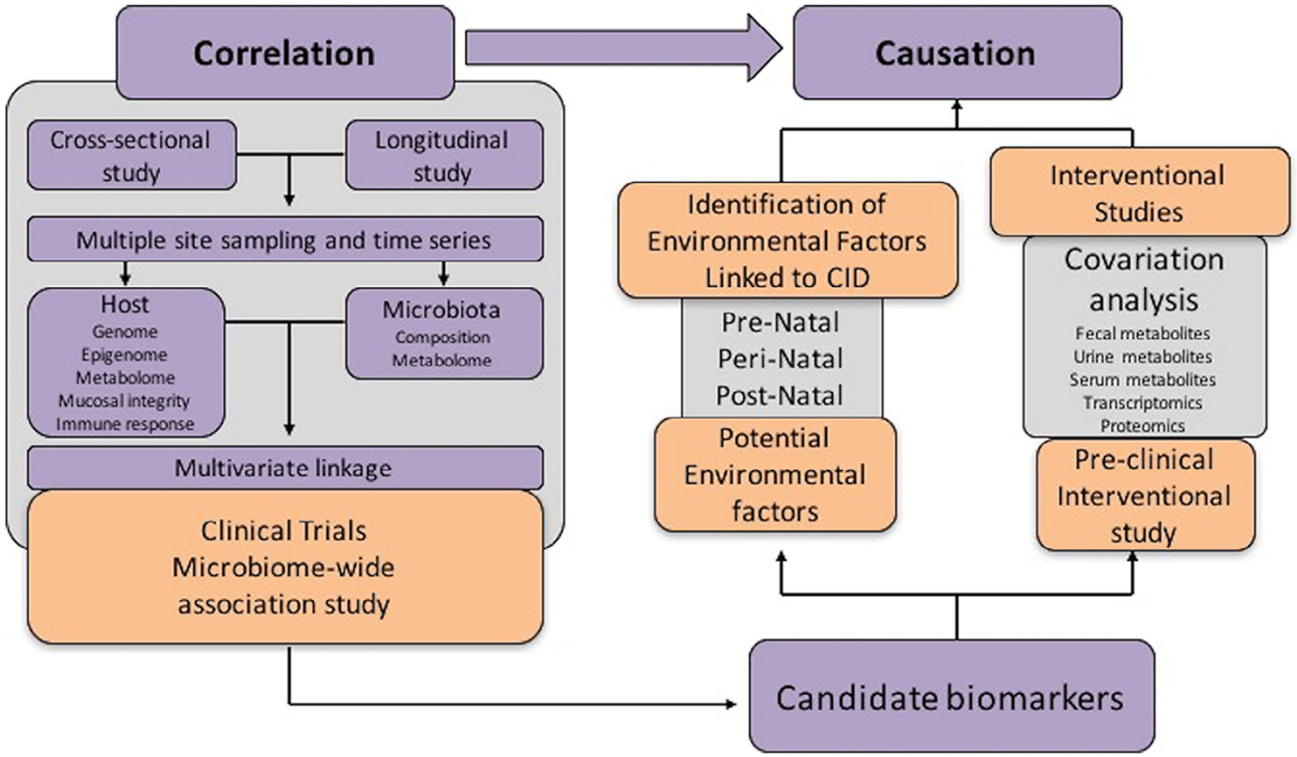
- This small open-label clinical trial showed that the Gastrointestinal Symptom Rating Scale revealed an approximately 80% reduction of GI symptoms at the end of treatment and persisted for 8 weeks after treatment.
- Similarly, clinical assessments showed that behavioral ASD symptoms improved significantly and remained improved 8 weeks after treatment ended.
- Bacterial and phage deep sequencing analyses revealed successful partial engraftment of donor microbiota and beneficial changes in the gut environment.
- Specifically, overall bacterial diversity and the abundance of Bifidobacterium, Prevotella, and Desulfovibrio increased following MTT, and these changes persisted after treatment stopped (followed for 8 weeks).
- This exploratory, extended-duration treatment protocol thus appears to be a promising approach to alter the gut microbiome and virome and improve GI and behavioral symptoms of ASD.

Kang et al *Microbiome*, 2017

THE JOURNAL OF PEDIATRICS • www.jpeds.com COMMENTARY

Transitioning From Descriptive to Mechanistic Understanding of the Microbiome: The Need for a Prospective Longitudinal Approach to Predicting Disease

Victoria J. Martin, MD, Maureen M. Leonard, MD, MMSc, Lauren Fiechtner, MD, MPH, and Alessio Fasano, MD



Martin VJ, et al J Pediat 2017

Celiac Disease Genome, Environment, Microbiome, and Metabolomic Studies

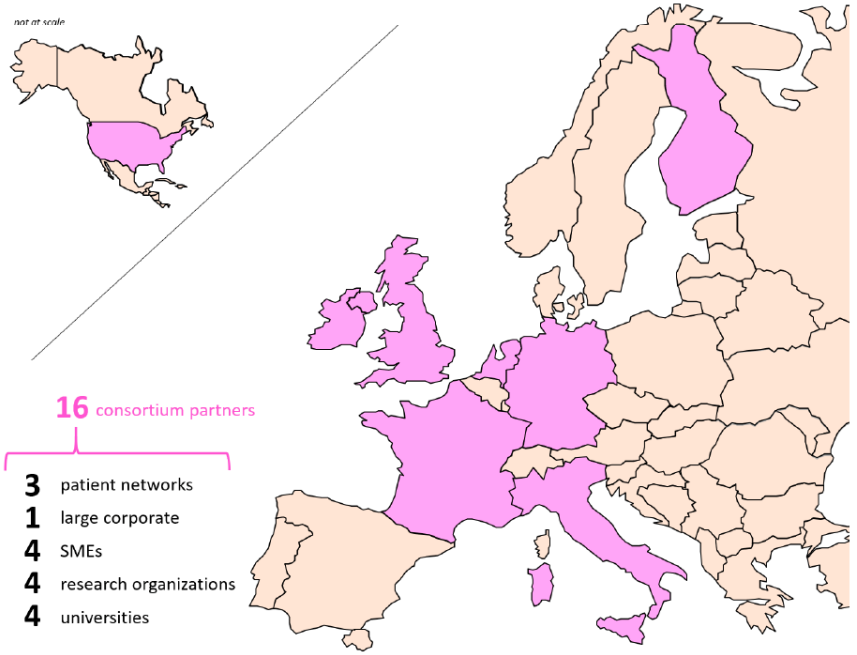
www.CDGEMM.org

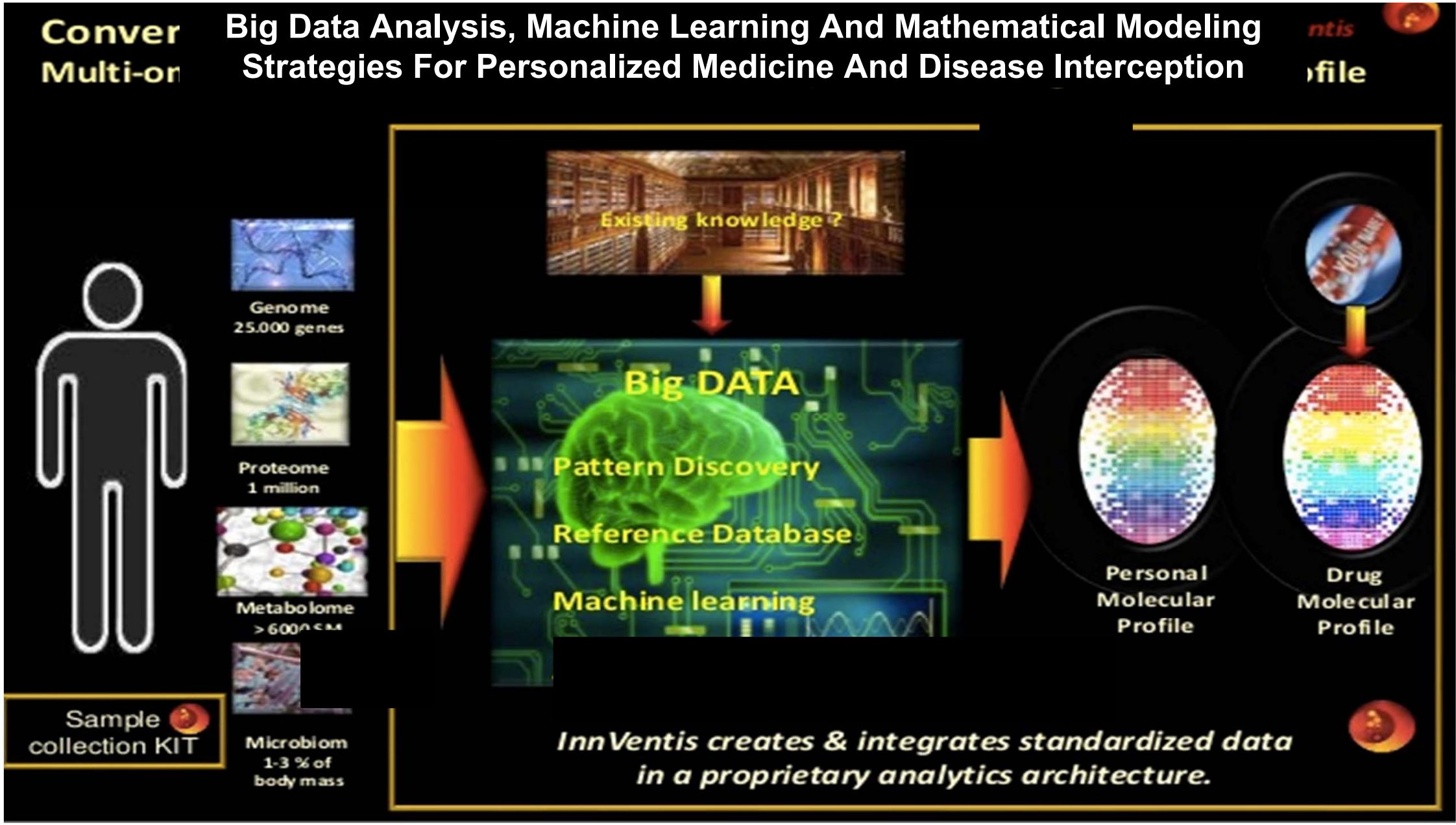
Genome, Environment, Microbiome, and Metabolomic in Autism (GEMMA)

#	Acronym	Participant legal name	Type	Country
#1	EBRIS	European Biomedical Research Institute Salerno	Research	Italy
#2	NUT	Nutricia Research B.V.	Industrial	Netherlands
#3	MED	Medinok	SME	Italy
#4	BMS	BM Systems	SME	France
#5	EUF	Euformatics Oy	SME	Finland
#6	THE	Theoreo SRL	SME	Italy
#7	ICAN	National University of Ireland Galway Irish Centre for Autism & Neurodevelopmental Research	Patient Network	Ireland
#8	ASL	Azienda Sanitaria Locale Salerno	Patient Network	Italy
#9	MGH	Massachussets General Hospital for Children Harvard Medical School	Patient Network	USA
#10	CNR	Consiglio Nazionale delle Ricerche	Research	Italy
#11	INRA	Institut National de la Recherche Agronomique	Research	France
#12	INSERM	Institut National de la Santé et de la Recherche Médicale	Research	France
#13	UU	Utrecht University	Academic	Netherlands
#14	UTA	Tampereen Yliopisto	Academic	Finland
#15	ICL	Imperial College	Academic	UK
#16	JHU	John Hopkins University	Academic	USA

Facts:

- 12.4 M Euros budget;
- 16 Partners (14 EU, of which 5 Italian, 2 US)
- A total of 2,400 subjects to be enrolled;
- More that 17,000 biospecimens to be collected;
- AI applied to mathematical modeling ASD




Conver
Multi-or
Big Data Analysis, Machine Learning And Mathematical Modeling
Strategies For Personalized Medicine And Disease Interception
ntis
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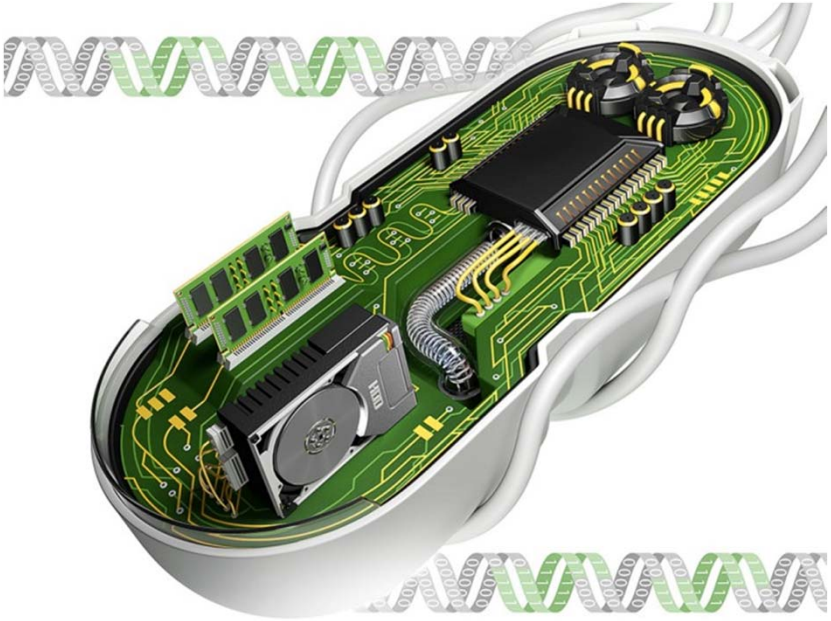
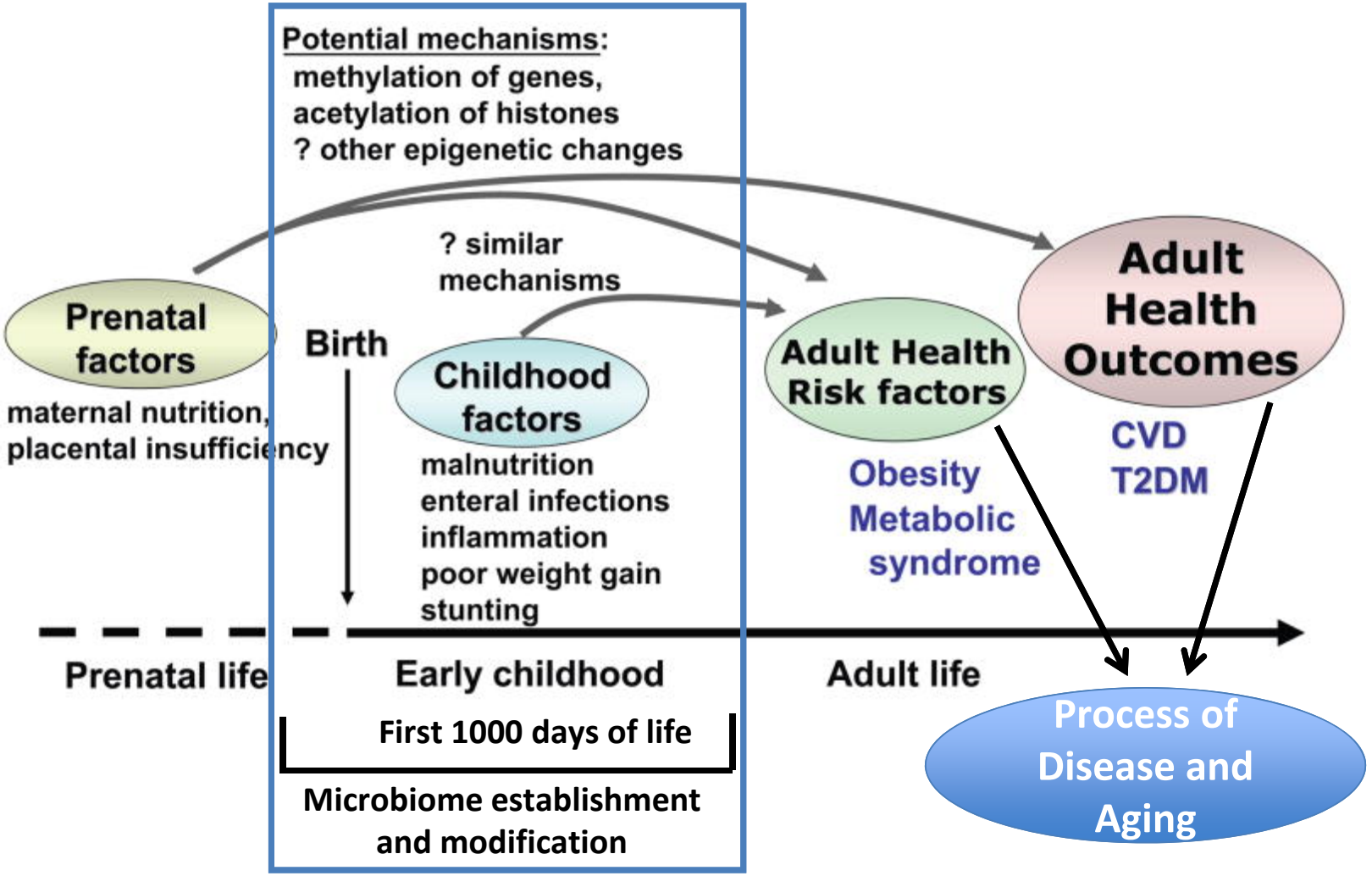
Existing knowledge ?
Genome
25.000 genes
Proteome
1 million
Metabolome
Microbiom
1-3 % of
body mass
Big DATA
Pattern Discovery
Reference Database
Machine learning
Personal
Molecular
Profile
Drug
Molecular
Profile
Sample
collection KIT
InnVentis creates & integrates standardized data
in a proprietary analytics architecture.

MIT Team Creates Genetic Circuits From Bacteria That Remember Logical Functions



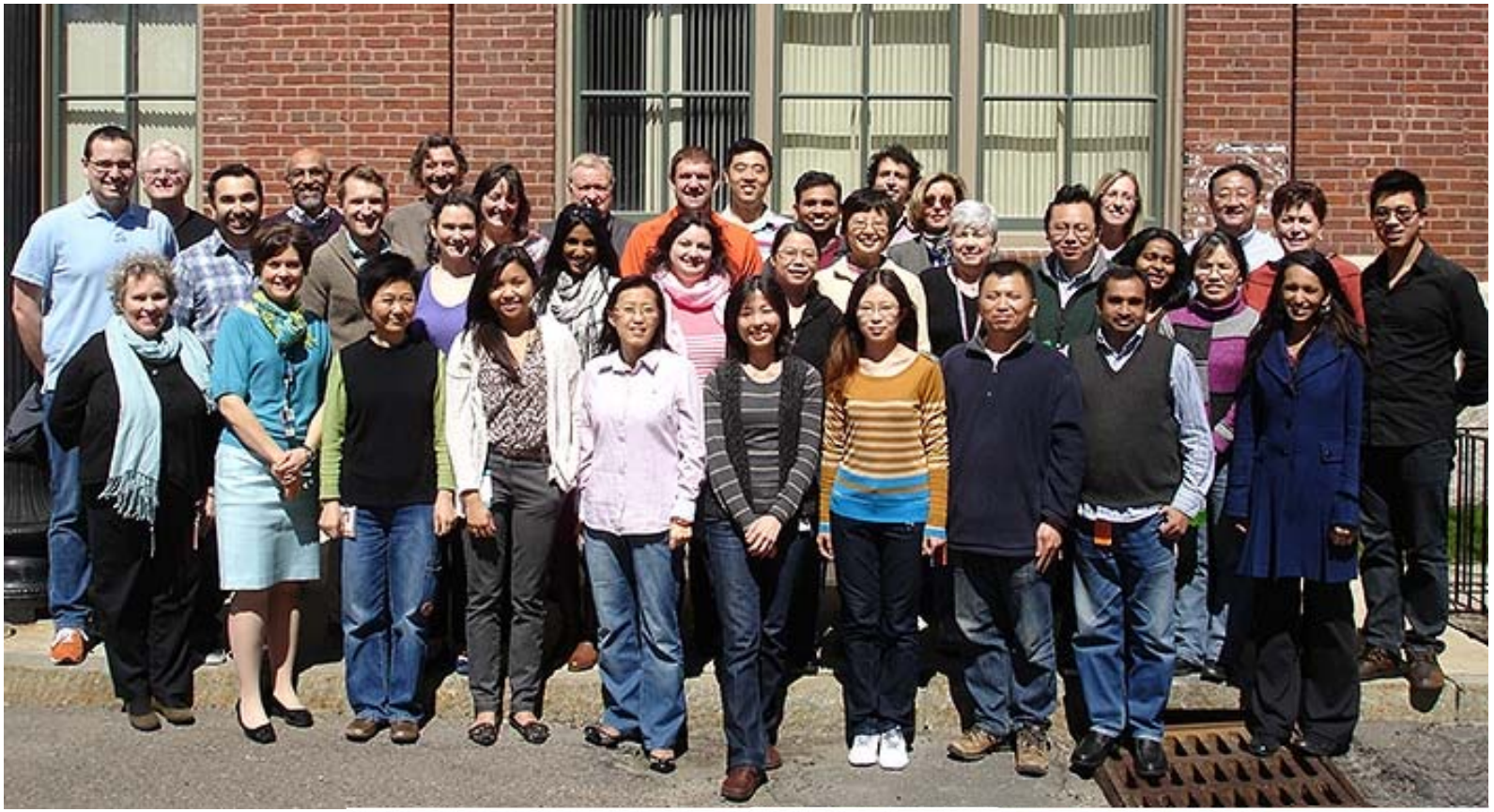
A team of engineers from MIT has created genetic circuits in bacterial cells that can not only perform logic functions, but also remember the results. These functions can then be encoded within the cell's DNA and can be passed on in other cells for dozens of generations.

Modeling the Effects of Early Childhood Microbiome Composition On Entire Lifespan



Acknowledgments

The MIBRC Crew



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