MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA
Changing What's Possible

– Our Newest Organ or Oldest ? –

The Human Microbiome

What we all need to know

Michael G. Schmidt, Ph.D.

AIOB 22 October 2021

Herman Becks, Founder's Lecture

Disclosures

- *Member of the Scientific Advisory Board of MicroGenDx*
- *Fully vaccinated, 23 February 2021*
- Also unrelated to this talk, I am supported by an Award No.2020-V7-GX-K002 from the Office for Victims of Crime, Office of Justice Programs, US Department of Justice.
- *The opinions, findings, and conclusions or recommendations expressed in this presentation are those of the author and do not necessarily reflect the views of the Department of Justice or the Office for Victims of Crime." nor those of my employer, the Medical University of South Carolina*

Learning Objectives

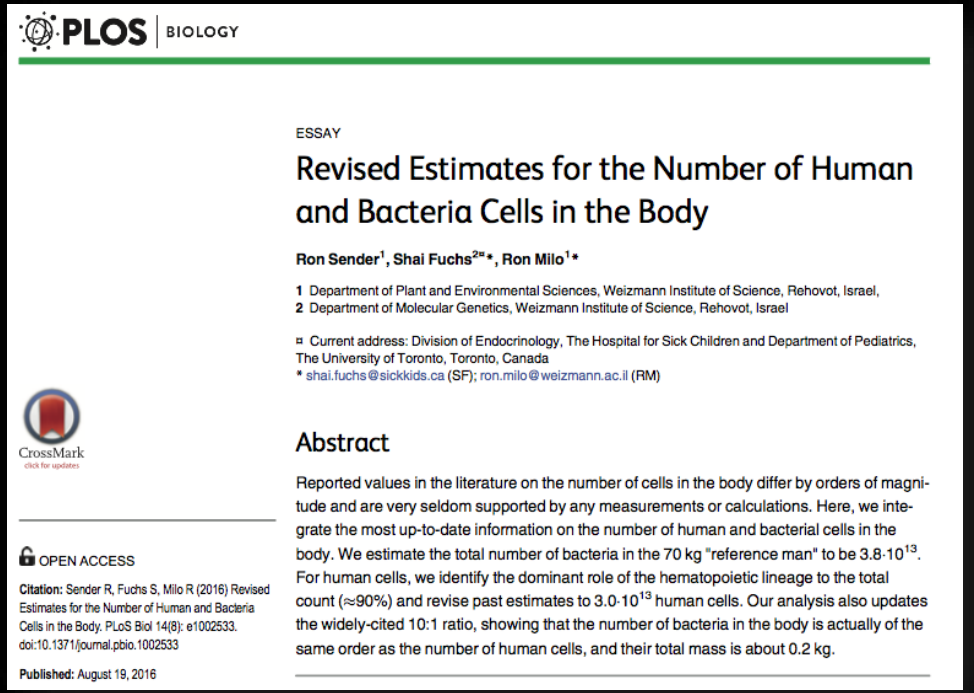
1. Understand how perturbations to the host such as the introduction of antibiotics, birth mode and diet can shape maturation of the microbiome during ~~early~~ life
2. Evaluate whether absence of one microbe can result in the development Autism Spectrum Disorder (ASD)
3. Analyze the role that microbes play in first 100 days of human life to the future development of a chronic inflammatory immune disorder recognized as Asthma

Summary

- The first birthday gift we each received was identical in name and given freely from our mothers
- It was literally delivered precisely at the time of our birth, providing us with an inter-generational hand-off that serves as the foundation for our 13th organ system, our microbiome., if you will, *that one more thing*
- Today, we will explore how perturbations made to this, our 13th organ system, or ***microbiome***, can profoundly influence our lives.

Human Microbiome

- *What do we know?*
  - You are 1 part human & 1 part microbe – formerly it was thought it was 10 parts microbe:1 part human



PLOS | BIOLOGY

ESSAY

Revised Estimates for the Number of Human and Bacteria Cells in the Body

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OPEN ACCESS

Citation: Sender R, Fuchs S, Milo R (2016) Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLoS Biol 14(8): e1002533. doi:10.1371/journal.pbio.1002533

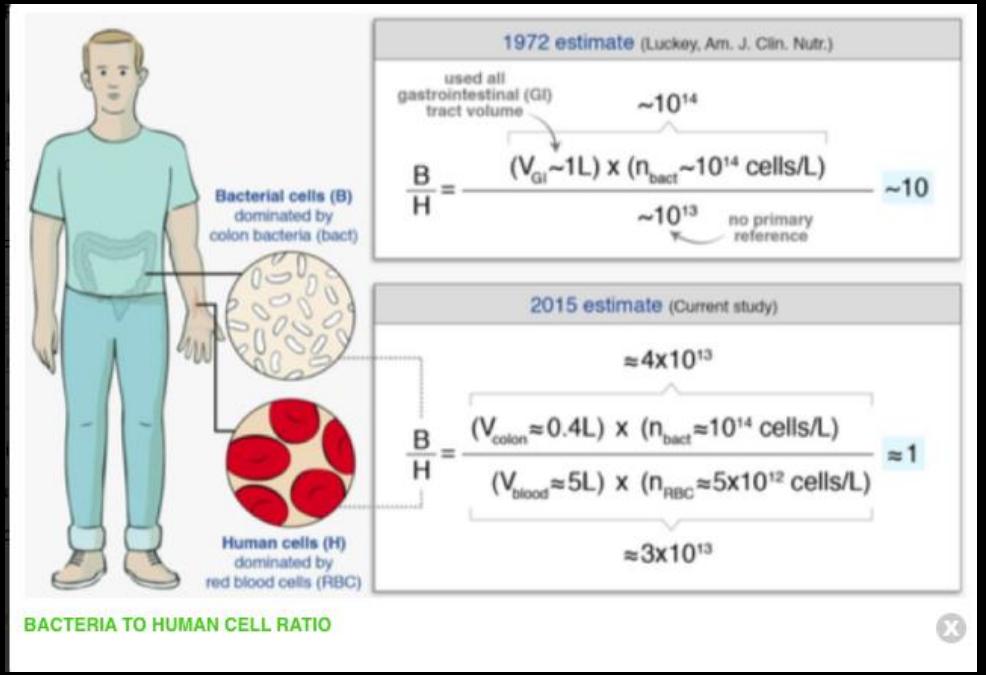
Published: August 19, 2016

Abstract

Reported values in the literature on the number of cells in the body differ by orders of magnitude and are very seldom supported by any measurements or calculations. Here, we integrate the most up-to-date information on the number of human and bacterial cells in the body. We estimate the total number of bacteria in the 70 kg "reference man" to be $3.8 \cdot 10^{13}$. For human cells, we identify the dominant role of the hematopoietic lineage to the total count (≈90%) and revise past estimates to $3.0 \cdot 10^{13}$ human cells. Our analysis also updates the widely-cited 10:1 ratio, showing that the number of bacteria in the body is actually of the same order as the number of human cells, and their total mass is about 0.2 kg.

Human Microbiome

- What do we know?
  - You are 1 part human - 1 part bacteria - formerly thought it was 10 parts bacteria::1 part human



Today

Our journey will take us into the world of the human microbiome and explore why I believe this needs to be our *next moon shot*.

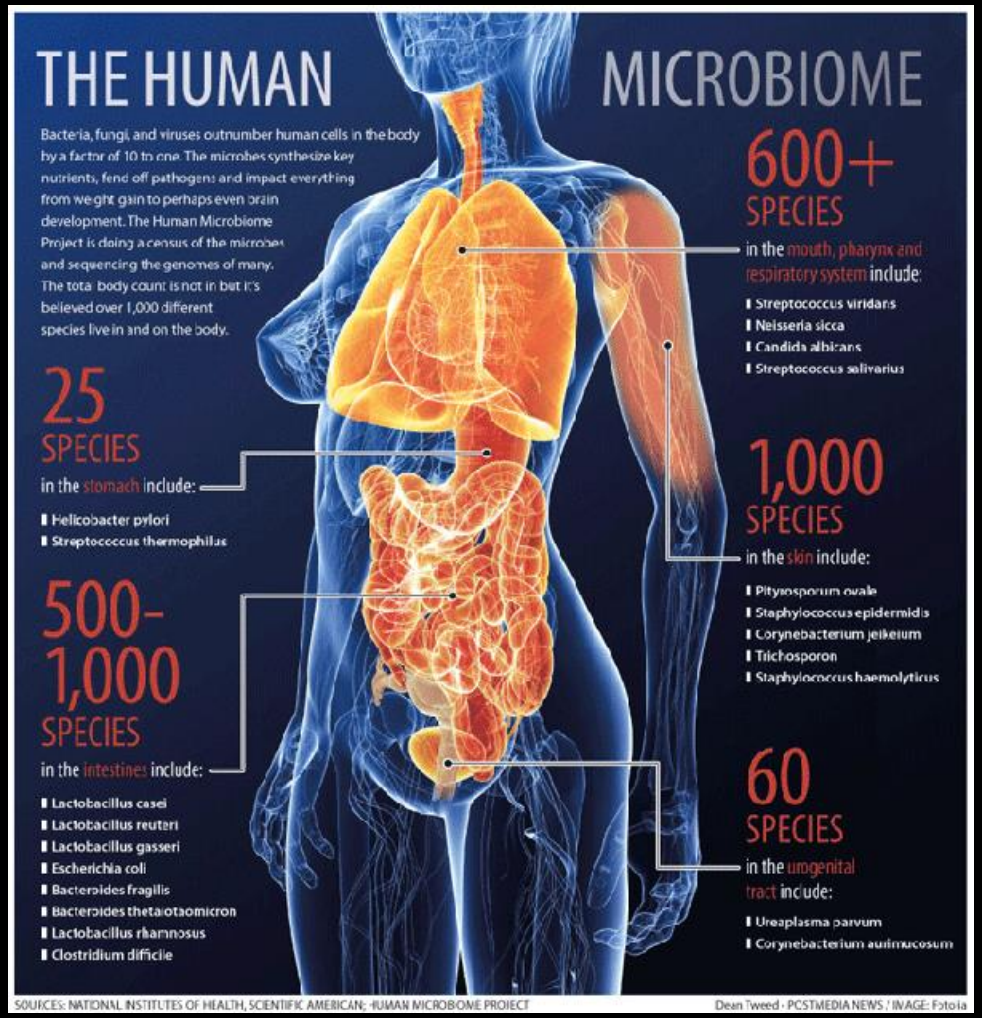
We'll do this in three parts, with some fun facts along the way to help you retain what we're going to experience.

With the end goal being that you achieve an awareness of how the microbiome is paramount to human health.

Consider the following as background

Did you know?

- At this moment 2 to 6 pounds of microbes are living in and on you?
  - *Who are they?*
  - *Where are they?*
  - *What do they do?*
  - *Are they good or bad?*
  - *Can they be dragooned for good?*



Where do our bacteria come from?

Human Microbiome

– ***Fun Facts for future figuring or trival pursuit championships...***

Your belly button can harbor over 2,300 species of bacteria

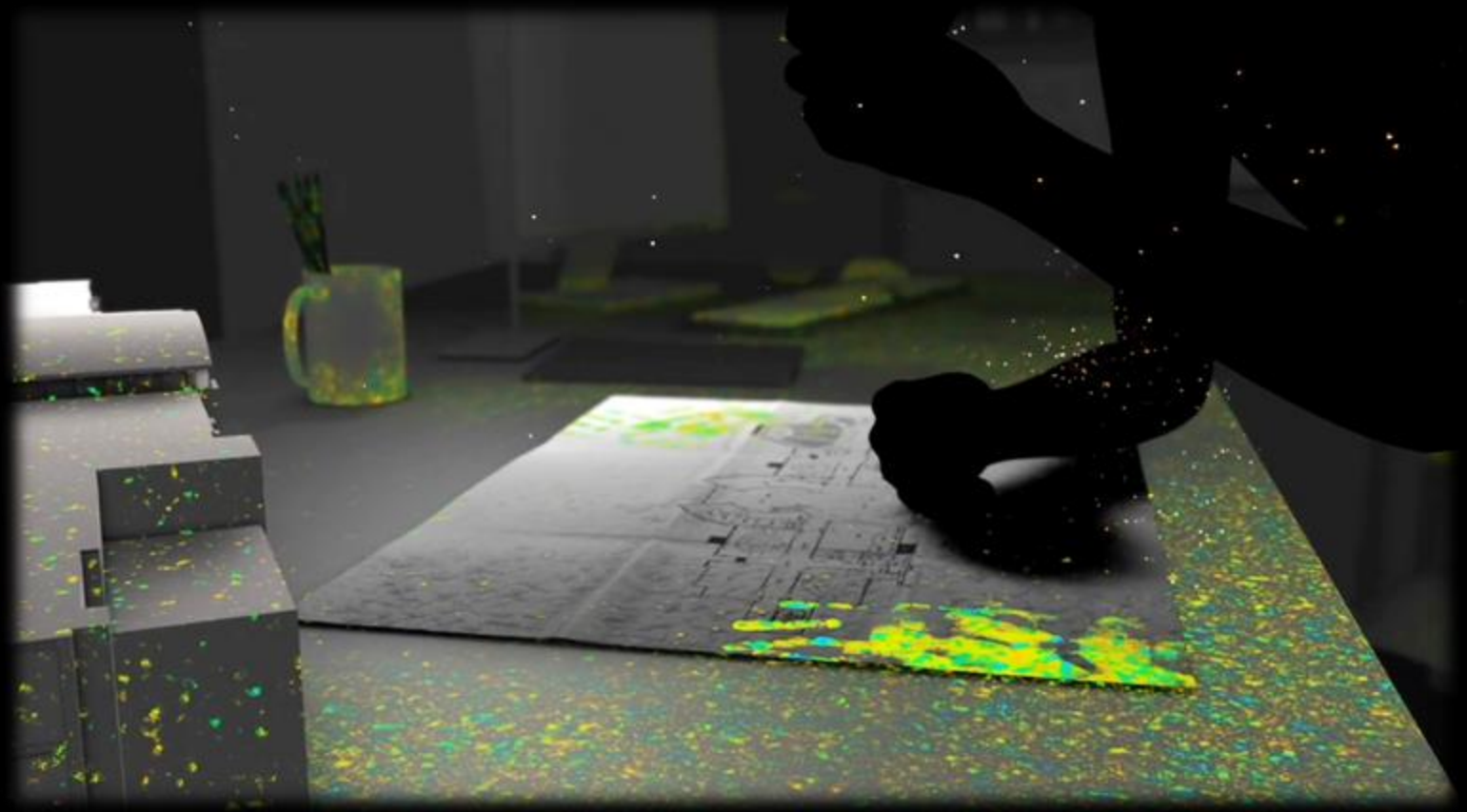
Where do our bacteria come from?

Mostly, from Mom

With

Some, from Family and friends

With



some from the environment and diet

Even the Molly the dog

INFLUENCE OF DOGS ON THE HUMAN MICROBIOME

µBiome

1

Bacteria from a dog's fur and paws is easily transferred to the skin of humans living in the same space. A 2013 study at the University of Colorado showed that adults share more microbes with their own dogs than they do with dogs owned by other people.

Perhaps more unexpectedly, the same study showed that simply owning a dog has an impact on the sharing of microbes between one person and another living in the same place.

Cohabiting couples who owned dogs had more bacteria in common with each other than couples who didn't have dogs.

2

UCSF scientists who conducted a study in 2013 suggested that living with a dog in infancy may lower a child's risk of developing asthma and allergies, largely as a result of exposure to what they call "dog-associated house-dust".

The researchers' hypothesis was that babies and small children need to be exposed to harmless bacteria in order to "train" their developing immune systems.

3

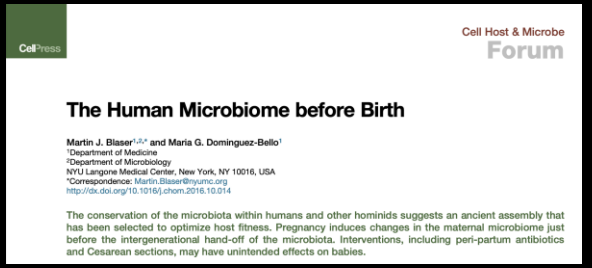
Just as fascinating, and perhaps already a candidate for one of the year's most heart-warming ideas, is a current University of Arizona study that's exploring whether dogs can directly improve the health of older people.

They've adopted unwanted dogs from the Humane Society, then given them to people over 50 who've either never owned a dog, or who haven't had one for a while.

Their theory is that good bacteria from the dogs may be transferred to their new owners, along with other health-boosting benefits.

SOURCE:
http://phys.org/news/2015-03-friend-medicine.html
http://www.popsci.com/science/article/2013-04/humans-share-microbiomes-their-dogs-study-finds
https://health.ucsd.edu/news/features/Pages/2015-05-07-mans-best-germs-your-health-and-your-dog.aspx

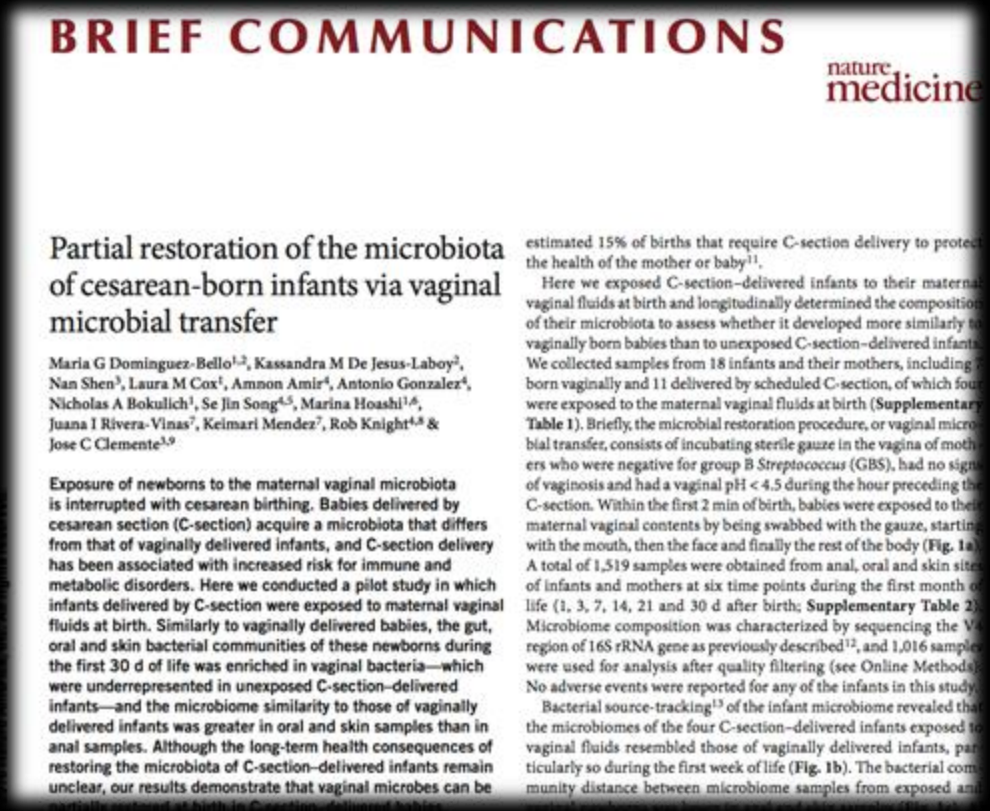
What we know



- *The human microbiome before birth*
  - *Blaser, MJ and Dominguez-Bello, MG*
  - *Bottom line…*
  - *The conservation of the microbiota within humans and other hominids suggests an ancient assembly that has been selected to optimize host fitness.*
  - *Pregnancy induces changes in the maternal microbiome just before the inter-generational hand-off of the microbiota.*
  - *Interventions, including peri-partum antibiotics and Cesarean sections, may have unintended effects on babies.*

Your first microbial encounter…

- Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer
- Nature Medicine 22, 250–253 (2016) doi:10.1038/nm.4039



BRIEF COMMUNICATIONS

nature medicine

Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer

Maria G Dominguez-Bello[1,2], Kassandra M De Jesus-Laboy[3], Nan Shen[3], Laura M Cox[1], Amnon Amir[4], Antonio Gonzalez[4], Nicholas A Bokulich[1], Se Jin Song[4,5], Marina Hoashi[1,6], Juana I Rivera-Vinas[7], Keimari Mendez[7], Rob Knight[4,8] & Jose C Clemente[3,9]

Exposure of newborns to the maternal vaginal microbiota is interrupted with cesarean birthing. Babies delivered by cesarean section (C-section) acquire a microbiota that differs from that of vaginally delivered infants, and C-section delivery has been associated with increased risk for immune and metabolic disorders. Here we conducted a pilot study in which infants delivered by C-section were exposed to maternal vaginal fluids at birth. Similarly to vaginally delivered babies, the gut, oral and skin bacterial communities of these newborns during the first 30 d of life was enriched in vaginal bacteria—which were underrepresented in unexposed C-section–delivered infants—and the microbiome similarity to those of vaginally delivered infants was greater in oral and skin samples than in anal samples. Although the long-term health consequences of restoring the microbiota of C-section–delivered infants remain unclear, our results demonstrate that vaginal microbes can be

estimated 15% of births that require C-section delivery to protect the health of the mother or baby[11].

Here we exposed C-section–delivered infants to their maternal vaginal fluids at birth and longitudinally determined the composition of their microbiota to assess whether it developed more similarly to vaginally born babies than to unexposed C-section–delivered infants. We collected samples from 18 infants and their mothers, including 7 born vaginally and 11 delivered by scheduled C-section, of which four were exposed to the maternal vaginal fluids at birth (**Supplementary Table 1**). Briefly, the microbial restoration procedure, or vaginal microbial transfer, consists of incubating sterile gauze in the vagina of mothers who were negative for group B *Streptococcus* (GBS), had no signs of vaginosis and had a vaginal pH < 4.5 during the hour preceding the C-section. Within the first 2 min of birth, babies were exposed to their maternal vaginal contents by being swabbed with the gauze, starting with the mouth, then the face and finally the rest of the body (**Fig. 1a**). A total of 1,519 samples were obtained from anal, oral and skin sites of infants and mothers at six time points during the first month of life (1, 3, 7, 14, 21 and 30 d after birth; **Supplementary Table 2**). Microbiome composition was characterized by sequencing the V4 region of 16S rRNA gene as previously described[12], and 1,016 samples were used for analysis after quality filtering (see Online Methods). No adverse events were reported for any of the infants in this study.

Bacterial source-tracking[13] of the infant microbiome revealed that the microbiomes of the four C-section–delivered infants exposed to vaginal fluids resembled those of vaginally delivered infants, particularly so during the first week of life (**Fig. 1b**). The bacterial community distance between microbiome samples from exposed and

However for the most part, its Mom

Mom mouth
Mom vagina
Baby (vag. deliv.)
Mom skin
Baby (ces. deliv.)

11 C-section babies with 4 of babies receiving a vaginal wipe

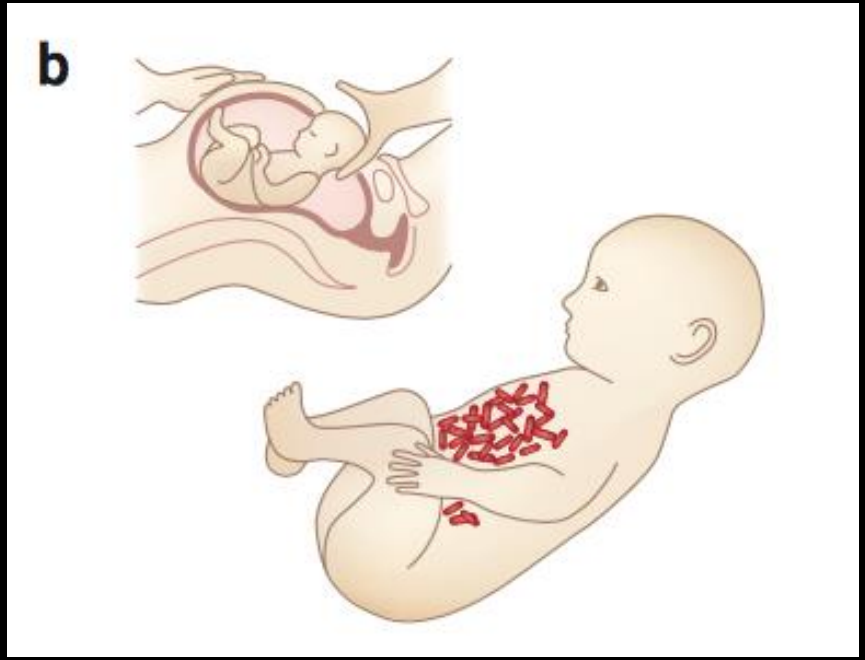
7 Vaginal-birth deliveries and vaginal microbiota

PC2: 9.8%

PC1: 12%

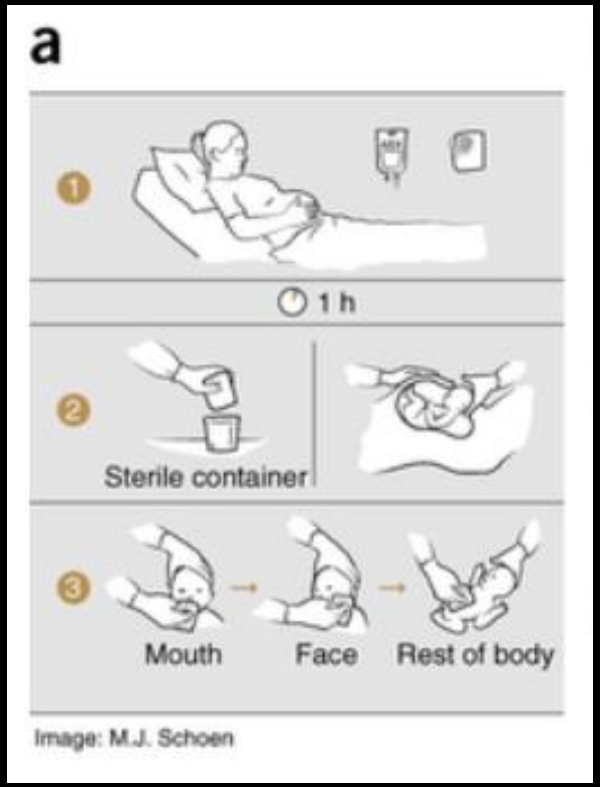
Your first microbial encounter…

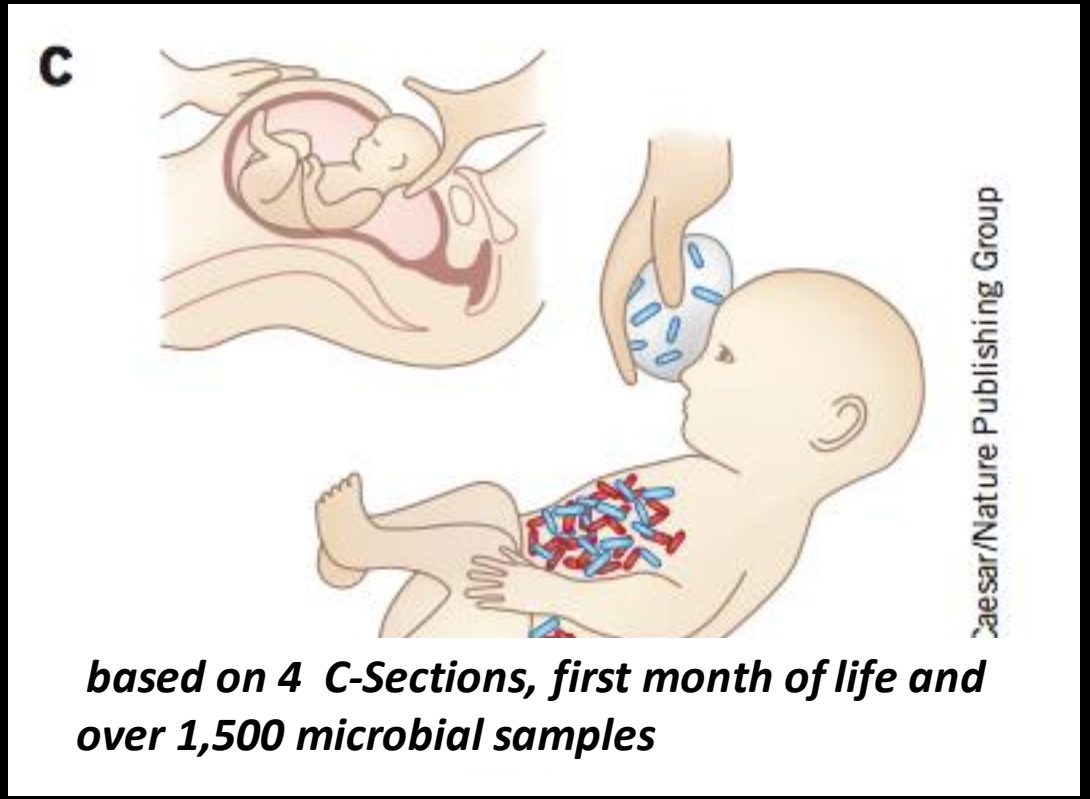
Or, your first microbial encounter…



Be violent, bold, and firm. Laugh at the power of other men, because nobody born from a woman will ever harm Macbeth. Unfortunately for Macbeth, the Scottish nobleman Macduff was *"from his mother's womb/ Untimely ripped,"* and thus not *naturally "born of woman"* (V.vii). Macduff was the only agent capable of destroying Macbeth. He killed Macbeth in battle. *William Shakespeare, Macbeth Act 5, Scene 7*

Will this prevent





based on 4 C-Sections, first month of life and over 1,500 microbial samples

Asthma, Allergies, Type 1 diabetes, Celiac Disease, Obesity?

How long till we get an answer as to body comp, rate of asthma or allergies?

Mom mouth
Mom vagina
Baby (vag. deliv.)
Mom skin
Baby (ces. deliv.)

N=1200 with 3-5 years microbial follow-up

C-section baby and mother's skin

Vaginal-birth baby and vaginal microbiota

It will be much more difficult to determine whether the transfers have any consequences on health. Dominguez-Bello estimates that her team will need to enroll around 1200 children and follow them for at least 3–5 years to explore whether the procedure leads to any differences in body composition or rates of asthma or allergies.

PC1: 12%

- *Antibiotics, birth mode, and diet shape microbiome maturation during early life*

Two studies of more than 80 infants followed for the first 2 to 3 years of life now reveal the effects of birth mode, diet and antibiotic treatment on gut microbiome development (Yassour et al., Bokulich et al.) The investigators show that *antibiotics, cesarean delivery and formula feeding* can alter development of the infant microbiome, *reduce bacterial diversity* and *transiently* increase the presence of antibiotic resistance genes

One more thing…

Home / News & Opinion

C-Sections Tied to "Stunted" Microbiota in Newborns: Study

Research on hundreds of babies finds the delivery method is linked with a greater abundance of taxa more frequently seen in hospitals.

nature
International journal of science

Letter | Published: 18 September 2019

Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth

Yan Shao, Samuel C. Forster, Evdokia Tsaliki, Kevin Vervier, Angela Strang, Nandi Simpson, Nitin Kumar, Mark D. Stares, Alison Rodger, Peter Brocklehurst, Nigel Field & Trevor D. Lawley

Findings highlight

1. **Critical role of the local environment in establishing the gut microbiota in very early life,**
2. **Identify colonization with antimicrobial-resistance-containing opportunistic pathogens as a previously under appreciated risk factor in hospital births**

Take home … 1

- *Antibiotics, birth mode, and diet can shape microbiome maturation during early life*
- ***But to what extent will this have on life?***
  - ***Stay tuned… by the time your ready to have children of your own, we will hopefully have answers***


autism
genetic
symptoms
daily activities
excess of neurons
restricted behavior
hand flapping
independent
interest
skin picking
disorder
defined
valuations
affected
sensory symptoms
differentiate autism
repetitive behavior
systems level
self-injury
variations
complexity
general population
perception
ritualistic behavior
cases
change
help
compulsive behavior
associated
eye poking
emotional
health
health care
evidence
clinical
attention
physical
symptoms
education
examining
nervous system
behavior
repetitive movement
specific
activity
focus
unchanging menu
associated
hand biting
preoccupation
Compulsive behavior
pattern
relative
limited
affected
study reported
family
overconnectivity
unvarying pattern
differentiate autism
interrupted
sensory symptoms
research
clinical
severity

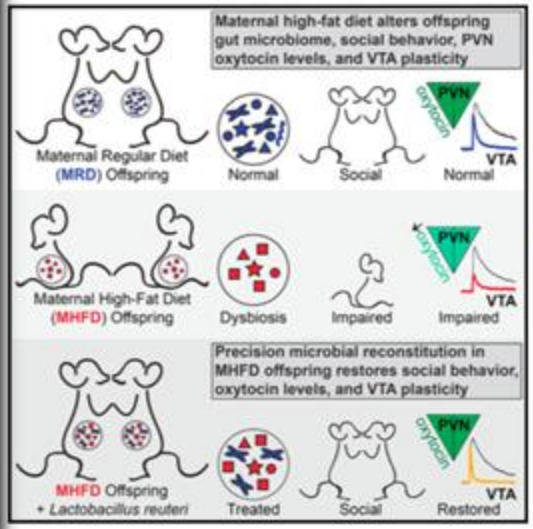
Facts about Autism

- *Autism now affects 1 in 68 children and 1 in 42 boys*
- *Autism prevalence figures are growing*
- *Autism is one of the fastest-growing developmental disorders in the U.S.*
- *Autism costs a family $60,000 a year on average*
- *Boys are nearly five times more likely than girls to have autism*
- *There is no medical detection or cure for autism*
- *$169M goes directly to investigate this condition from the NIH (0.54% of 2018 NIH budget)*

Cell http://dx.doi.org/10.1016/j.cell.2016.06.001

Microbial Reconstitution Reverses Maternal Diet-Induced Social and Synaptic Deficits in Offspring

Graphical Abstract



Authors

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In Brief

A maternal high-fat diet leads to changes in the gut microbiome of offspring and induces behavioral alterations that can be restored via selective reintroduction of a commensal bacterial strain.

Highlights

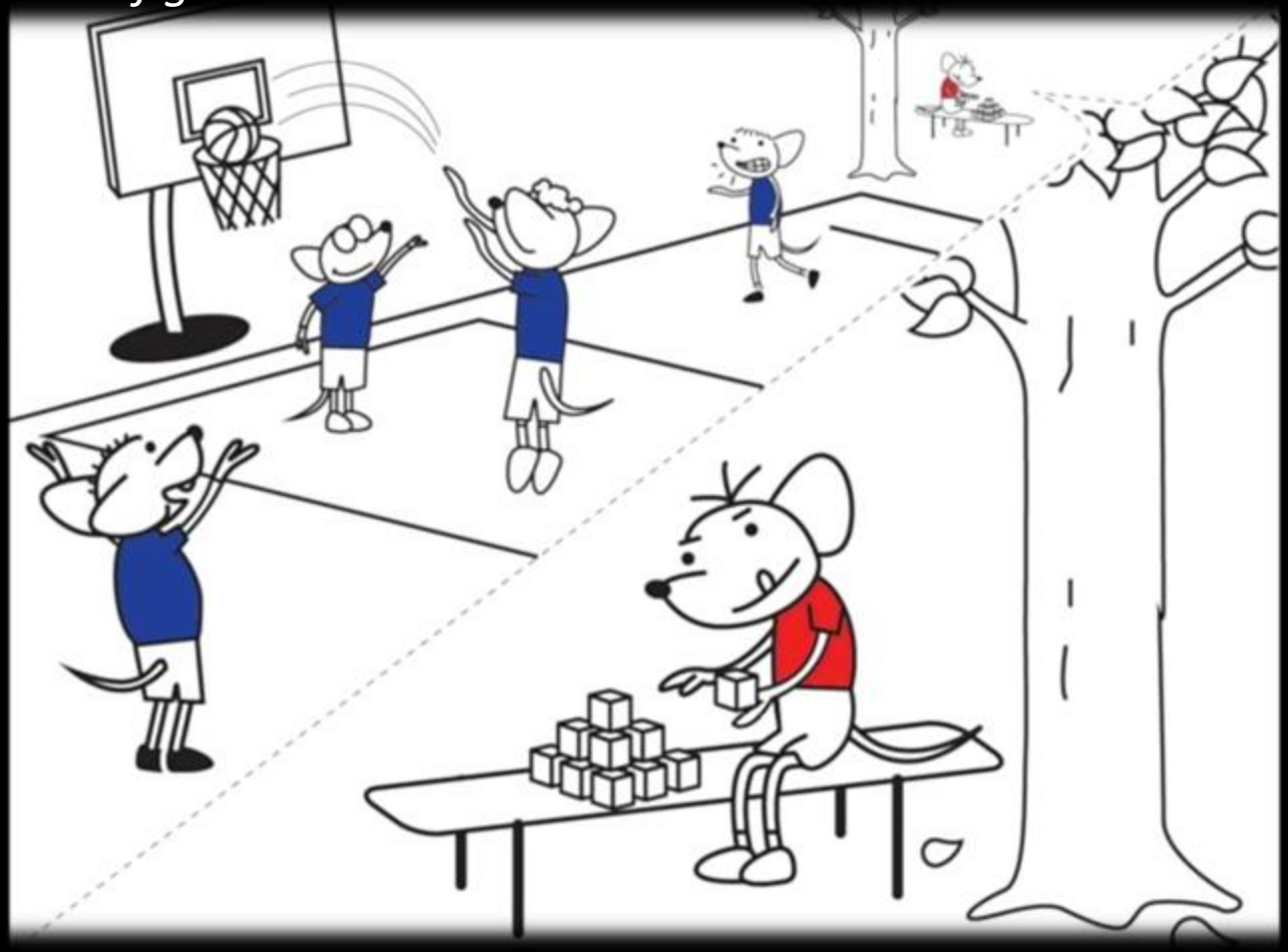
- Maternal high-fat diet (MHFD) induces behavioral alterations in offspring
- MHFD causes alterations in gut microbial ecology in offspring
- MHFD offspring show deficient synaptic plasticity in the VTA and oxytocin production
- *L. reuteri* treatment restores oxytocin levels, VTA plasticity and social behaviors

The inspiration –

- *human epidemiological studies*
  - *maternal obesity during pregnancy could increase children's risk of developing neurodevelopmental disorders, including Autism Spectrum Disorders (ASDs)*

What might be the mechanism?

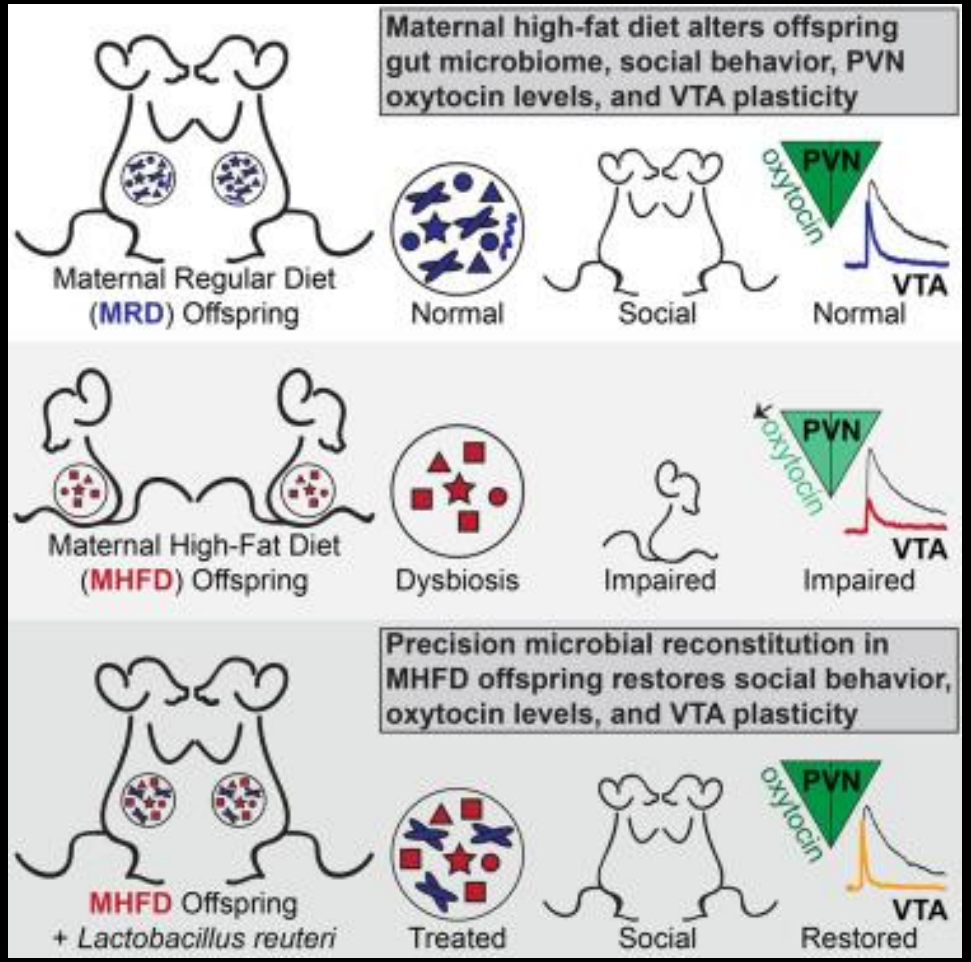
Single species of gut bacteria can reverse autism-related social behavior in mice!



https://www.youtube.com/watch?v=bmR_aQhHJLU

Single species of gut bacteria can reverse autism-related social behavior in mice!

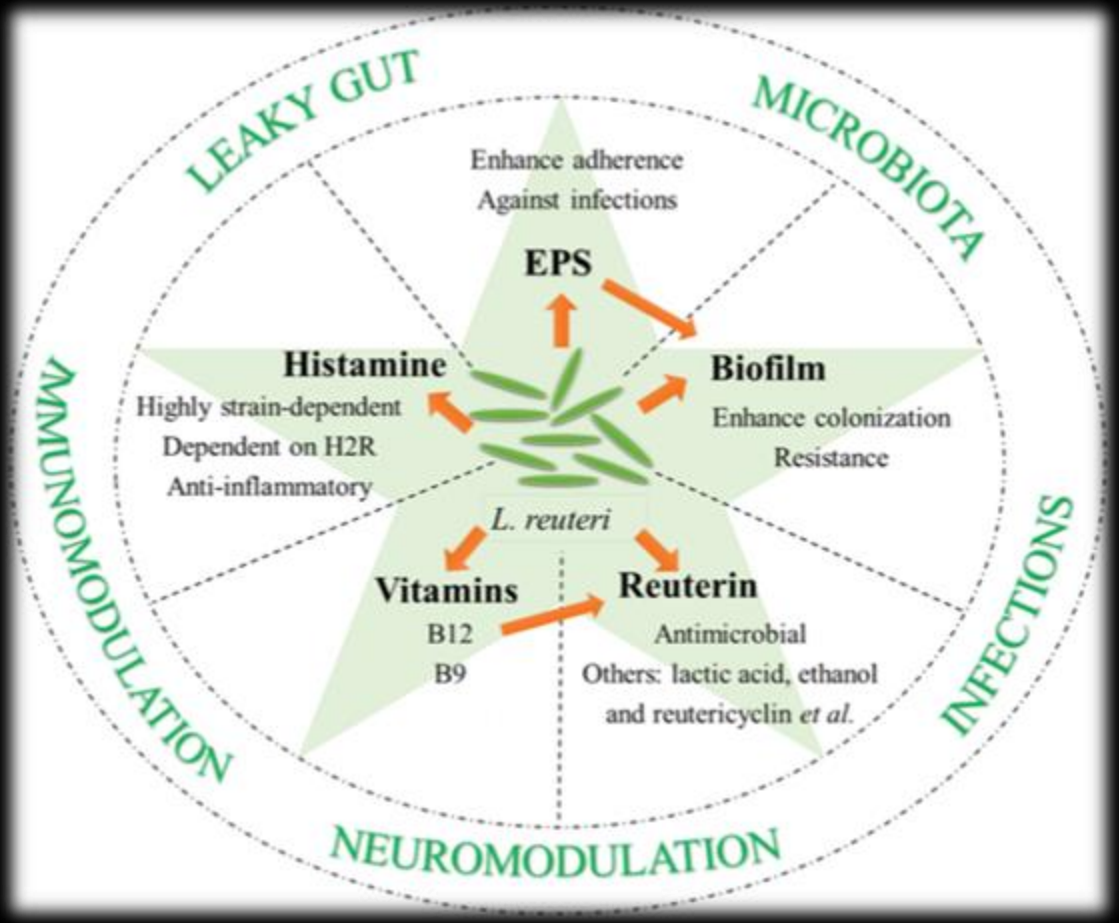
- Maternal high-fat diet (MHFD) induces behavioral alterations in offspring
  - Equivalent of fast food , several times per day, N=60.
- •MHFD causes alterations in gut microbial ecology in offspring
  - Could predict from simply from pattern that the offspring would be impaired! WOW!
- •MHFD offspring show deficient synaptic plasticity in the ventral tegmental area (VTA)and oxytocin production
  - *Attended to Mechanism*
- •*L. reuteri* treatment restores oxytocin levels, VTA plasticity and social behaviors
  - *One microbe, restores activity WOW!*



Lactobacillus reuteri

- *What do we know about L. reuteri in humans?*
  1. Found in GI, UT, Skin and breast milk
     - Abundance varies among humans
     - Can produce antimicrobial molecules
       - Organic acids, EtOH and reuterin
         - » Reuterin induces oxidative stress in cells, most likely by modifying thiol groups in proteins and small molecules
     - Can benefit host immune system
       - Reduce the production of pro-inflammatory cytokines while promoting regulatory T cell development/function
     - Has an ability to strengthen the intestinal barrier
       - Decreases microbial translocation from gut lumen to tissues
  2. Decrease in abundance in humans over the past decades is correlated with an increase in the incidence of inflammatory diseases

- *Niche*
  - Bacterial surface molecules that facilitate binding to the mucus layer …so called mucus binding proteins (MUB)/adhesins
  - Resistant to low pH 2° to gastric acids and bile salts of upper intestine
  - Vitamins (13 needed)
    - B12 (cobalamin) and B9 (folate)



Take home … 2

- *Single species of gut bacteria can reverse autism-related social behavior in mice!*
- *Lactobacillus reuteri*
- *But to does this observation extend to humans?*
  - *For Autism unknown but administration via oral capsule could restore vaginal flora in postmenopausal women*

Take home … 2

Kong et al. Pilot and Feasibility Studies (2020) 6:20
https://doi.org/10.1186/s40814-020-0557-8

Pilot and Feasibility Studies

STUDY PROTOCOL Open Access

Probiotics and oxytocin nasal spray as neuro-social-behavioral interventions for patients with autism spectrum disorders: a pilot randomized controlled trial protocol

Xue-Jun Kong[1,2*], Jun Liu[1,3], Jing Li[4], Kenneth Kwong[1], Madelyn Koh[1], Piyawat Sukjithamapan[3], Jason J. Guo[5], Zhenyu Jim Sun[6] and Yiqing Song[7]

Abstract

Background: Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by impairments in social interaction and communication. Oxytocin (OXT), as a neuropeptide, plays a role in emotional and social behaviors. *Lactobacillus reuteri* (*L. reuteri*) supplementation led to an OXT-dependent behavioral improvement in ASD mouse models. Despite some promising results from animal studies, little is known about the efficacy of supplementation with *L. reuteri*, alone or with exogenous OXT therapy, on social-behavioral functions in ASD patients. This paper presents a protocol for a pilot randomized controlled trial to evaluate the feasibility of conducting a full trial comparing oral supplementation of *L. reuteri* probiotics and intranasal OXT spray to placebo on the effect of social and behavioral functions in ASD patients. The study will also capture preliminary estimates of the efficacy of the proposed interventions in ASD patients.

Methods: This pilot trial is a two-staged, randomized, double-blind, placebo-controlled, parallel-group study. Throughout the study (0–24 weeks), 60 patients with ASD will be randomly assigned to receive either oral *L. reuteri* probiotics or placebo. In the second study stage (13–24 weeks), all participants will receive intranasal OXT spray. As primary outcomes, serum OXT levels will be assayed and social behaviors will be assessed via the Autism Behavior Checklist and the Social Responsiveness Scale which are validated questionnaires, an objective emotional facial matching test, and a new video-based eye-tracking test. Secondary outcomes include the GI-severity-index and Bristol Stool Chart to assess GI function and gut microbiome/short-chain fatty acids. All the outcomes will be assessed at baseline and weeks 12 and 24.

Discussion: This pilot study will provide important information on the feasibility of recruitment, blinding and concealment, treatment administration, tolerability and adherence, specimen collection, outcome assessment, potential adverse effects, and the preliminary efficacy on both primary and secondary outcomes. If successful, this pilot study will inform a larger randomized controlled trial fully powered to examine the efficacies of oral *L. reuteri* probiotics and/or intranasal OXT spray on social-behavioral improvement in ASD patients.

Trial registration: ClinicalTrials.gov, NCT03337035. Registered 8 November 2017.

Keywords: Autism spectrum disorders, ASD, Oxytocin, OXT, Probiotics, Neuro-social behaviors, Randomized controlled trial

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Full list of author information is available at the end of the article

- *Single species of gut bacteria can reverse autism-related social behavior in mice!*
- *Lactobacillus reuteri*
- *But to does this observation extend to humans?*
  - *For Autism unknown but administration via oral capsule could restore vaginal flora in postmenopausal women*

Asthma and the Microbiome

- ✓ ***Globally**, affects over 300 Million*
- ✓ ***Symptoms** – Narrowing and inflammation of airways*
- ✓ *Origin from a synergy between **environmental and genetic factors***
- ✓ *Viral infections with an abundance of Proteobacteria, specifically **Haemophilus and Moraxella***
- ✓ ***Dysbiosis leads to activation of inflammatory pathways and contributes to bronchoconstriction and bronchial hyperresponsiveness***

Asthma and the Microbiome

- Chronic Inflammatory immune disorder of the airways affecting 1:10 children in westernized countries (300 Million people worldwide), 25M in the US (1 in 13 Americans) with Adult Women more likely than Adult Men but more common in boys than girls. Tragically, about 10 deaths per day in US!
- Does it run in families?
  - Yes, variations in two genes, ORMDl3 and GSDML

Environmental Factor
Your Online Source for NIEHS News
SEPTEMBER 2016
NIH National Institute of Environmental Health Sciences

Microbe-rich environments may trigger immune system, prevent asthma

Previous Article | Next Article

By Virginia Guidry

Amish children growing up on farms that use animals have an immune response that may prevent asthma, according to a new study supported in part by NIEHS. The research was published Aug. 3 in the New England Journal of Medicine (NEJM).

The study compared children from two U.S. farming communities, one Amish and the other Hutterite. The two communities have many similarities, including shared genetic heritage, but the Amish use livestock for fieldwork and transportation, and the Hutterites practice industrialized farming with machinery. Previous studies have shown that asthma is rare among Amish children, whereas it is present at typical U.S. levels in Hutterite children.

The researchers saw a key difference in how the children's immune systems functioned. Based on the types of cells and the chemical signals activated, the Amish children actively used their innate immune systems (see sidebar). This response was weaker in the Hutterite children.

"The study augments prior work showing the significant role our environmental exposures play in asthma," said Peter Thorne, Ph.D., in a University of Iowa press release. Thorne is a co-author of the study and director of the NIEHS-funded Environmental Health Sciences Research Center at the University of Iowa. "The big advance is how our study beautifully demonstrated the key role of innate immunity in asthma in two rural populations with similar genetics."

Microbial richness in Amish homes

Thorne's research team used air samplers that did not require electricity in the Amish and Hutterite homes to measure airborne particles and bacterial indicators. The researchers found that the types of bacteria in the two groups of homes were different, and that the levels of endotoxin, a bacterial indicator, were nearly seven times higher in Amish homes.

"The striking differences found in endotoxin levels support the notion that the Amish indoor environment is much richer in microbial exposures than the Hutterite environment," the authors wrote.

Rather than triggering allergic responses, exposure to microbe-rich farm dust seems to prompt the innate immune response to generate a low level of inflammation that prevents the emergence of asthma, according to a NEJM editorial that accompanied the paper. Questions remain as to whether continuous exposure to the dust is required for this protective effect.

Linked Video

Watch a description of the study and findings in this video from NEJM. (1:57)
(Launches in a new window)

"This is a great example of a major discovery arising from a multidisciplinary team of scientists drawn from multiple universities," said Thorne. (Photo courtesy of Tom Langdon)

Innate vs. adaptive immunity

The human immune response includes two main systems, innate and adaptive, which work together to protect people from disease.

The cells of the innate immune system quickly attack foreign microbes. This response activates the adaptive immune response.

The more specialized adaptive immune system can recognize and remember specific bacteria or viruses to provide long-term immunity, but it is slower to respond to new diseases. For example, these cells are the ones that respond to vaccines.

The New England Journal of Medicine

Asthma Risk and Farming

KEY POINTS FROM

Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children

by M.M. Stein et al.

August 4, 2016

Microbe-rich environments may trigger the immune system, prevent asthma

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Innate Immunity in Asthma

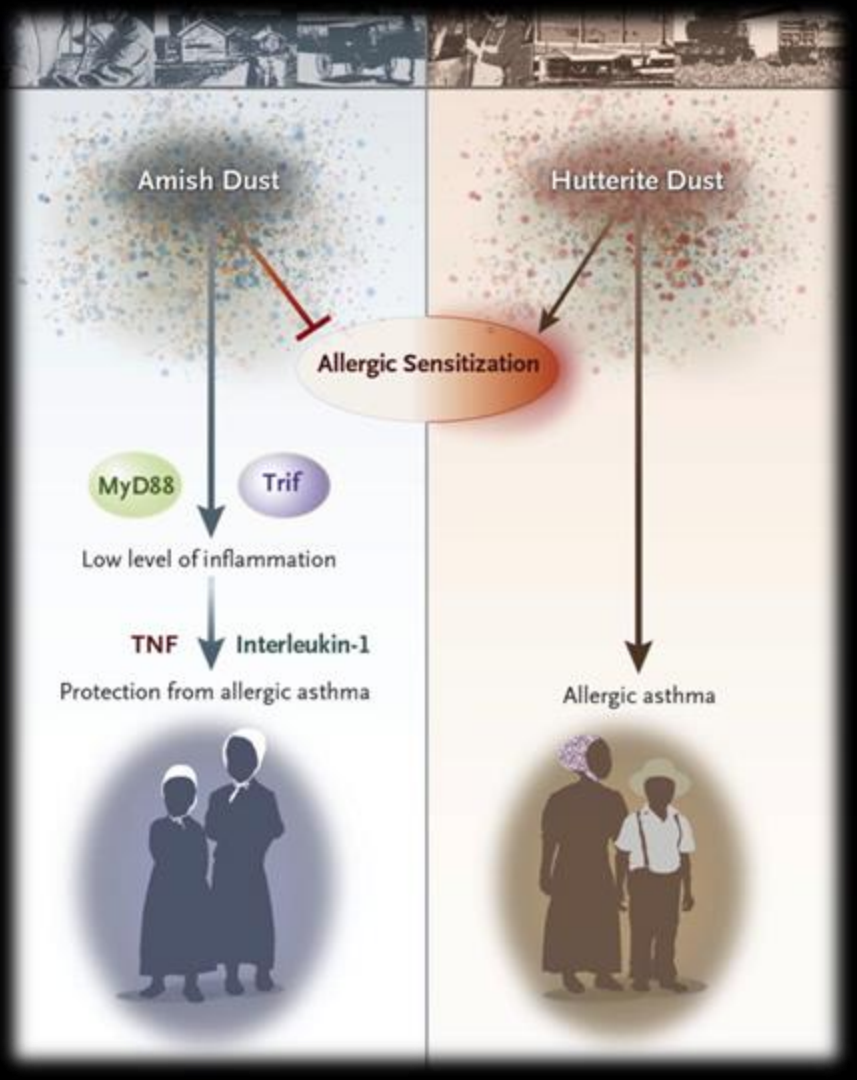
Talal A. Chatila, M.D., M.Sc.

N Engl J Med 2016; 375:477-479 | August 4, 2016 | DOI: 10.1056/NEJMe1607438

It is appreciated that the marked increase in the prevalence of asthma over the past few decades reflects changes in environmental exposures and living conditions associated with modern lifestyles.[1] Of particular interest is the documentation of a protective effect of exposures associated with traditional farming, the influence of which has waned with increased urbanization and the advent of mechanized agriculture.[2] On small family-based farms where children are reared in close proximity to farm animals and their sheds, increased exposure to the microbial products found in these environments, including lipopolysaccharides, has been associated with protection against asthma.[3,4] It remains unclear how exposure to a traditional farming environment confers protection against asthma and whether such protection also applies in the context of large-scale industrialized farming. Stein et al. now advance our knowledge on both accounts in this issue of the *Journal*.[5]

In their study, Stein et al. took advantage of a lifestyle attribute that differentiates two otherwise closely related U.S. populations in which the incidence of asthma is dissimilar. The Amish and the Hutterites are reproductively isolated farming communities that are linked by ancestry, having originated in German-speaking alpine regions of Europe. They also share a similar lifestyle that includes environmental exposures that often affect the risk of asthma, with one notable exception — whereas the Amish have maintained a traditional farming practice that revolves around single-family dairy farms and eschews mechanization, the Hutterites practice large-scale, highly mechanized communal farming. The prevalence of asthma and allergic sensitization among the Amish is low, but among the Hutterites the prevalence of both conditions is strikingly high, similar to that in the U.S. population at large.[6,7] As such, these two communities are ideally suited for analysis of the influence of environmental exposures on susceptibility to asthma.

By studying children from these two communities, Stein et al. confirmed the discrepancy that exists in the communities' incidences of allergy and asthma. The researchers also established the presence of a distinct microbial composition and an increased burden of lipopolysaccharides in dust samples collected from the houses of the Amish as compared with those of the Hutterites. After exposing samples of peripheral-blood lymphocytes from both populations to lipopolysaccharides, the samples from the Amish expressed more innate immunity-related cytokines than those from the Hutterites. The peripheral-blood lymphocytes of Amish children also exhibited a genetic signature



Brief report

Helicobacter pylori infection prevents allergic asthma in mouse models through the induction of regulatory T cells

Isabelle C. Arnold,[1] Nina Dehzad,[2] Sebastian Reuter,[2] Helen Martin,[2] Burkhard Becher,[3] Christian Taube,[2] and Anne Müller[1]

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Atopic asthma is a chronic disease of the airways that has taken on epidemic proportions in the industrialized world. The increase in asthma rates has been linked epidemiologically to the rapid disappearance of *Helicobacter pylori*, a bacterial pathogen that persistently colonizes the human stomach, from Western societies. In this study, we have utilized mouse models of allergic airway disease induced by ovalbumin or house dust mite allergen to experimentally examine a possible inverse correlation between *H. pylori* and asthma. *H. pylori* infection efficiently protected mice from airway hyperresponsiveness, tissue inflammation, and goblet cell metaplasia, which are hallmarks of asthma, and prevented allergen-induced pulmonary and bronchoalveolar infiltration with eosinophils, Th2 cells, and Th17 cells. Protection against asthma was most robust in mice infected neonatally and was abrogated by antibiotic eradication of *H. pylori*. Asthma protection was further associated with impaired maturation of lung-infiltrating dendritic cells and the accumulation of highly suppressive Tregs in the lungs. Systemic Treg depletion abolished asthma protection; conversely, the adoptive transfer of purified Treg populations was sufficient to transfer protection from infected donor mice to uninfected recipients. Our results thus provide experimental evidence for a beneficial effect of *H. pylori* colonization on the development of allergen-induced asthma.

Asthma and the Microbiome

- Gut microbial dysbiosis in human atopic diseases is characterized NOT by GLOBAL changes to the composition of the intestinal microbial population but by taxa-specific shifts
- Impacts- human immune system… which is most plastic during this window

Asthma and the Microbiome

- *Hygiene hypothesis* (Strachan)
  - Are we too clean during our first 100 days?
  - Now includes… mode of birth, abx exp, pets, farm life, etc)
- *Microflora hypothesis*
  - *"it is clear that there is a microbial-immune cell interface, in which cross-talk between microbes and immune cells aids in the development of immune tolerance*
- *Gut-Lung Axis*
  - *How does the gut talk to the lung?*
    - *PAMPs (pathogen associated molecular patterns)*
      - *LPS, Peptidoglycan, CpG*
- *Microbial-derived metabolites… Short chained fatty acids (SCFAs)*
  - *Three major ones – Acetate, Propionate and butyrate (60:20:20) molar ratio*
    - *Modify gene expression in humans through inhibition of histone deacetylases (HDACs) and cytokine and chemokine production, and cell differentiation, proliferation and apoptosis!*

Stiemsma and Turvey
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Allergy, Asthma & Clinical Immunology

REVIEW

Open Access

Asthma and the microbiome: *defining the critical window in early life*

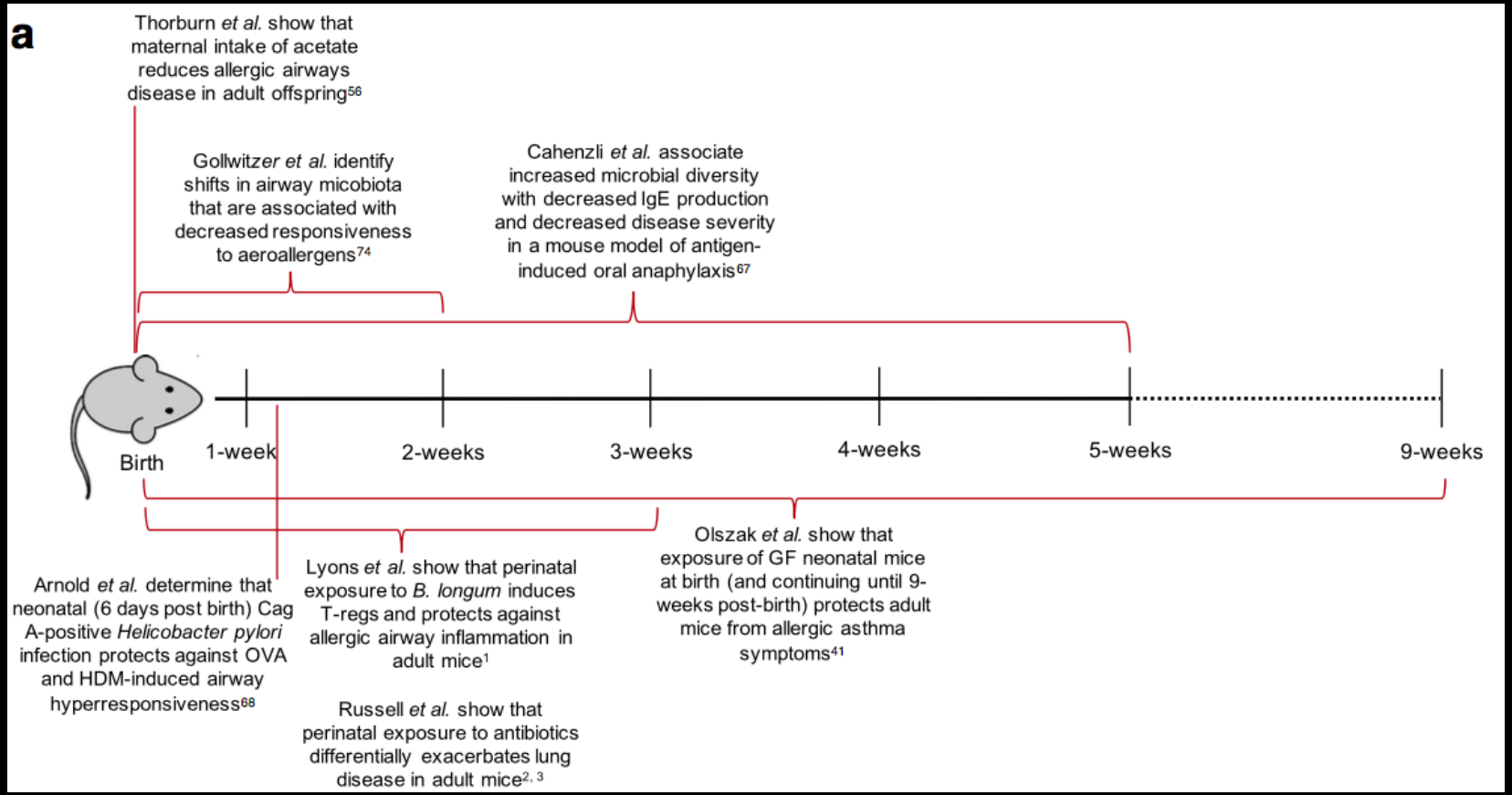
Leah T. Stiemsma[1,2] and Stuart E. Turvey[2,3,4*]

Abstract

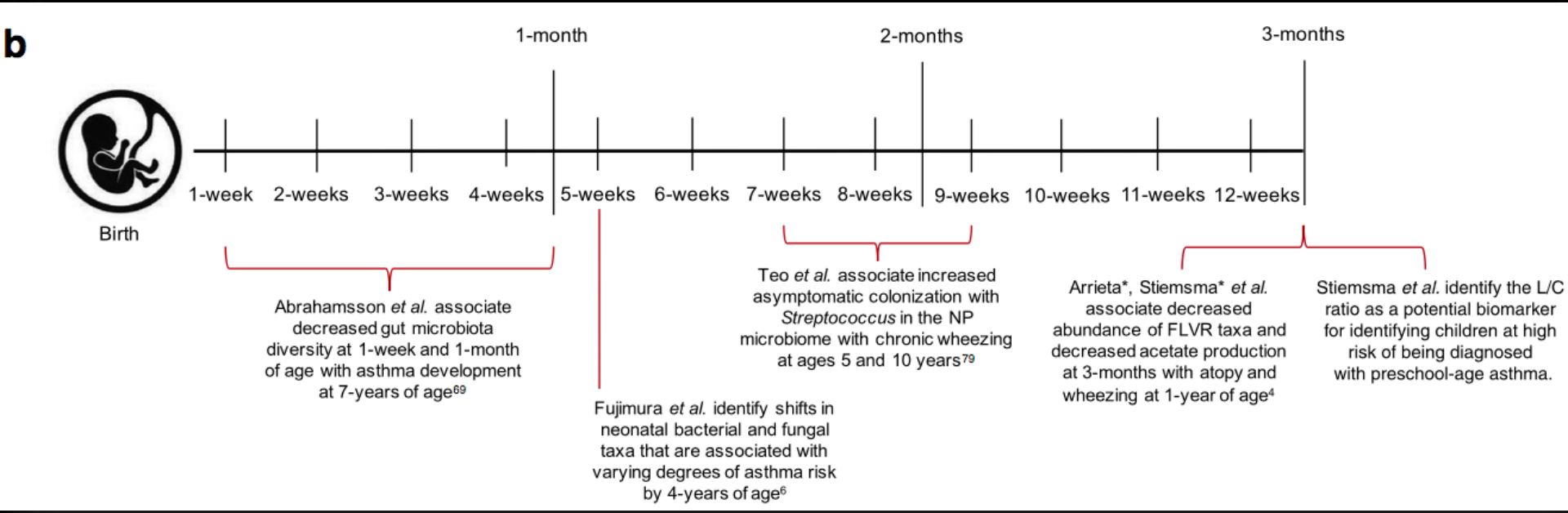
Asthma is a chronic inflammatory immune disorder of the airways affecting one in ten children in westernized countries. The geographical disparity combined with a generational rise in prevalence, emphasizes that changing environmental exposures play a significant role in the etiology of this disease. The microflora hypothesis suggests that early life exposures are disrupting the composition of the microbiota and consequently, promoting immune dysregulation in the form of hypersensitivity disorders. Animal model research supports a role of the microbiota in asthma and atopic disease development. Further, these model systems have identified an early life critical window, during which gut microbial dysbiosis is most influential in promoting hypersensitivity disorders. Until recently this critical window had not been characterized in humans, but now studies suggest that the ideal time to use microbes as preventative treatments or diagnostics for asthma in humans is within the first 100 days of life. This review outlines the major mouse-model and human studies leading to characterization of the early life critical window, emphasizing studies analyzing the intestinal and airway microbiotas in asthma and atopic disease. This research has promising future implications regarding childhood immune health, as ultimately it may be possible to therapeutically administer specific microbes in early life to prevent the development of asthma in children.

Keywords: Microbiota, Asthma, Early life, Critical window, Hygiene hypothesis, Microflora hypothesis

For Asthma, Age is critical



Age is critical

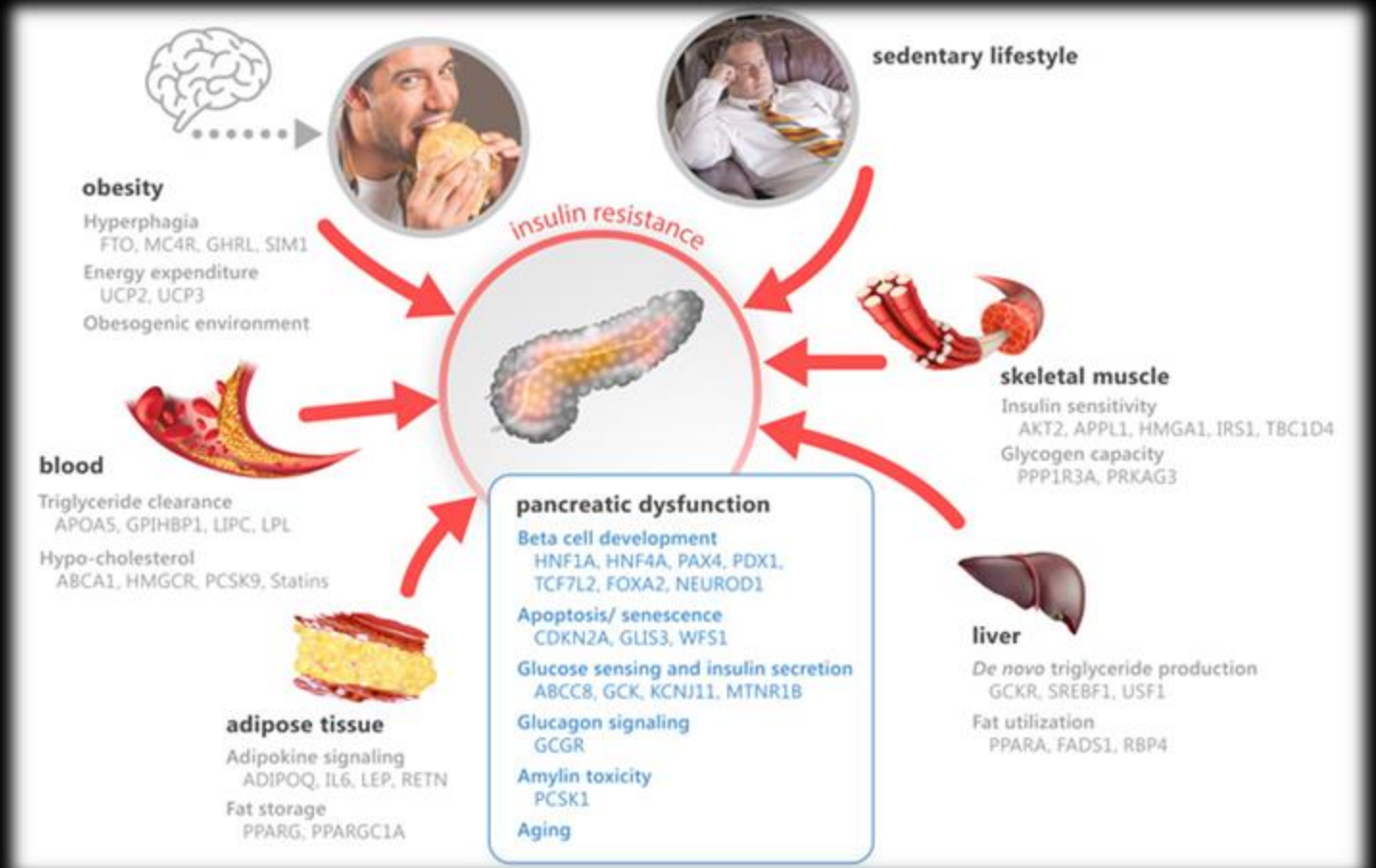


Take Home 3

Asthma and the Microbiome

- Chronic Inflammatory immune disorder of the airways affecting 1:10 children in westernized countries (235 Million people worldwide) with a tragic 9 deaths per day in US!
- Studies suggest that the ideal time to use microbes as preventative treatments or diagnostics for asthma in humans is within the first 100 days of life! Allergy Asthma Clin Immunol. 2017; 13: 3.

What's Next?
Integration and Big Data



Type 2 Diabetes Primary Panel

Your Genes

ABCA1	ABCC8	ADCY3	ADCY5	ADIPOQ	AGPAT1	AKR1B1	AKT2
ANGPTL4	APOA4	APOA5	APOB	APOC2	APOC3	APOE	APPL1
ARAP1	BDNF	BLK	BUD13	C2CD4A	CAPN10	CARS	CCKAR
CDKAL1	CDKN2A	CEL	CELSR2	CETP	COBLL1	CRY2	DGKB
DUSP9	DYRK1B	ENPP1	EPO	FABP2	FABP4	FADS1	FOXA2
FTO	G6PC2	GCGR	GCK	GCKR	GHRL	GLIS3	GLUD1
GNPDA2	GPD2	GPIHBP1	GREM1	HFE	HHEX	HMGA1	HMGCR
HNF1A	HNF1B	HNF4A	IGF1	IGF2BP2	IL6	INS	INSR
IRS1	IRS2	KCNJ11	KCNQ1	KCTD15	KLF11	KSR2	LEP
LEPR	LGR5	LIPC	LIPI	LMF1	LPL	MADD	MAPK8IP1
MC3R	MC4R	MTNR1B	MTTP	NEGR1	NEUROD1	NR0B2	NTRK2
OR4S1	PAX4	PCSK1	PCSK9	PDX1	POMC	PON1	PPARA
PPARG	PPARGC1A	PPP1R3A	PRKAG3	PROX1	PTPN1	RASGRP1	
RBP4	RETN	SEC16B	SH2B1	SHBG	SIM1	SIRT1	SLC2A2
SLC2A4	SLC30A8	SOD2	SREBF1	TBC1D4	TCF7L2	TFAP2B	THADA
TMEM18	TRPM6	TUB	UCP2	UCP3	USF1	VEGFA	WFS1
WNT10B	ZPR1						

Closing thoughts… Microbially Unique

All people have a unique microbiome, because each of us live!

Finally

- *Some will prove wrong but for the most part, our microbes are likely our oldest organ system*

One more thing…

Without our bacteria we would be so much colder, 93.2°F/33°C rather than the 98.6°F/37°C

The Next Moon Shot?

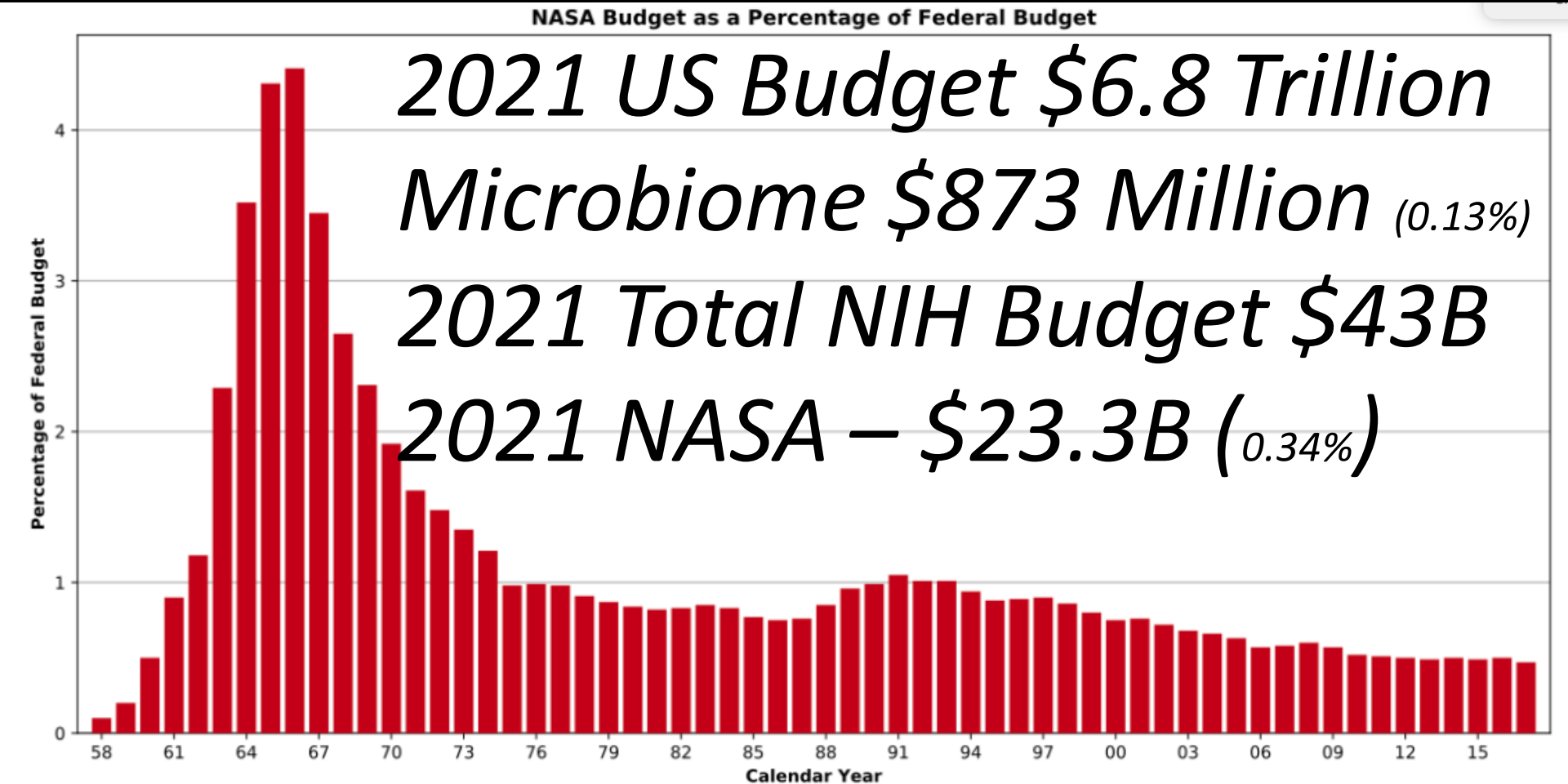
12 September 1962 – 57 years ago… President John F. Kennedy at Rice University, Texas

- We set sail on this new sea because there is new knowledge to be gained, and new rights to be won, and they must be won and used for the progress of all people. For space science, like nuclear science and all technology, has no conscience of its own. Whether it will become a force for good or ill depends on man, and only if the United States occupies a position of pre-eminence can we help decide whether this new ocean will be a sea of peace or a new terrifying theater of war. I do not say that we should or will go unprotected against the hostile misuse of space any more than we go unprotected against the hostile use of land or sea, but I do say that space can be explored and mastered without feeding the fires of war, without repeating the mistakes that man has made in extending his writ around this globe of ours.

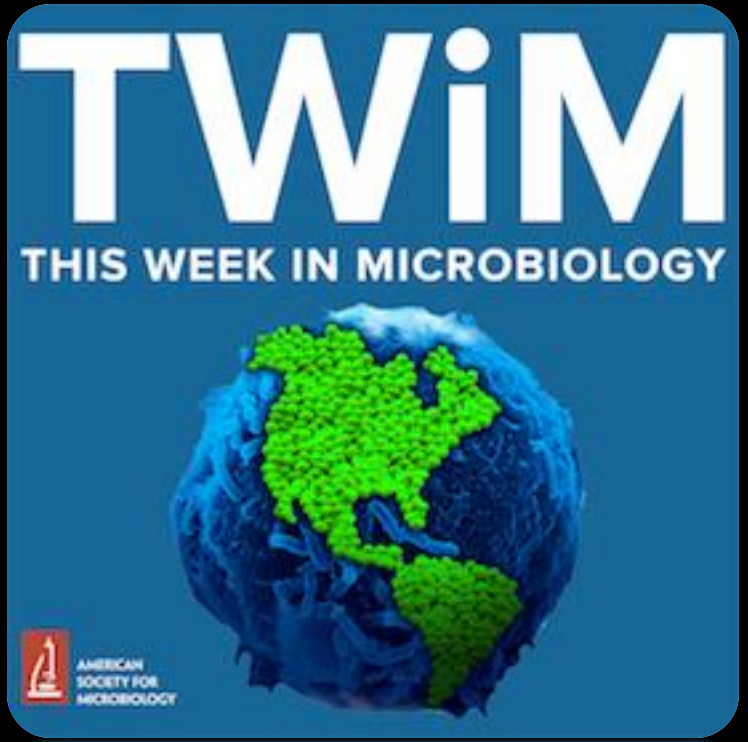
- There is no strife, no prejudice, no national conflict in outer space as yet. Its hazards are hostile to us all. Its conquest deserves the best of all mankind, and its opportunity for peaceful cooperation may never come again. But why, some say, the Moon? Why choose this as our goal? And they may well ask, why climb the highest mountain? Why, 35 years ago, fly the Atlantic? Why does Rice play Texas?[5]

- *We choose to go to the Moon! ...[6] We choose to go to the Moon in this decade and do the other things,[7] not because they are easy, but because they are hard; because that goal will serve to organize and measure the best of our energies and skills, because that challenge is one that we are willing to accept, one we are unwilling to postpone, and one we intend to win ...*

Our Moon Shot, 4.5% of US Fed Budget?



Thank you!



Questions?

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA
Changing What's Possible

– Our Newest Organ or Oldest ? –

The Human Microbiome

What we all need to know

Michael G. Schmidt, Ph.D.

AIOB 22 October 2021

Herman Becks, Founder's Lecture