The Human Microbiome in Health and Disease

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artwork by Scott Draves (www.electricsheep.org)
1. The Epidemic of Non-Communicable Diseases (NCDs)

2. The Completed Self Hypothesis

3. Ramifications of Self Incompleteness for the Immune System

4. The New Target “Organism”:
   a) impact on personalized healthcare and safety
   b) opportunities for probiotic strategies
The Epidemic of Non-Communicable Diseases (NCDs)
Question?

- Allergies (food/asthma/rhinitis/dermatitis)
- Cancer
- Obesity
- Diabetes
- Cardiovascular disease
- Arthritis
- Autism spectrum
- ADD/ADHD
- Celiac disease
- IBD (Crohn’s, UC)
- Lupus
- Autoimmune thyroiditis

- Depression
- Osteoporosis
- Frailty
- Dementia
- Alzheimer’s disease
- Parkinson’s disease
- Hypertension
- Sleep disorders
- PCOS
- COPD
- Chronic kidney disease
- Psoriasis
- Multiple sclerosis
Noncommunicable Diseases and Conditions (NCDs) are the Greatest Threat to Sustainable Healthcare

• Already the Number #1 Cause of Mortality Worldwide (63%)*
• Dramatically Impacts Both Productivity and Quality of Life
• Estimated to Cost 48% of Global GDPs by 2030*
• Most Chronic Diseases are Increasing in Prevalence
• 45.3% of all US adults age 65 and above have two or more chronic diseases: a 20% increase from the previous decade.*

*Joint 2011 report: Harvard School of Public Health and World Economic Forum and NCHS Data Brief Number 100, July 2012
Non-Communicable Diseases Cluster Together

- Inflammation-Related: Inflammatory Bowel Disease, Rheumatoid Arthritis, Colorectal Cancer, Alkylosing Spondylitis, Pediatric Deep Vein Thrombosis, Polyneuropathy
- Autoimmune-Related: Autoimmune Thyroiditis, Hearing Loss, Type 1 Diabetes, Celiac Disease
- Autoimmune-Inflammatory-Related: Psoriasis, Anxiety, Obesity, Lymphoma, Skin Cancer, Metabolic Syndrome, Schizophrenia

- Allergy-Related: Atopic Dermatitis, Allergic Rhinitis, Behavioral Disorders, Olfactory Dysfunction, Overweight Risk
- Childhood Asthma: Otitis Media, Lung Cancer
- Infant Respiratory Infections: Adult Snoring, Cerebral Arteriopathy, Secondary Bacterial Infections
- Infection-Related: Early Immune Activation-Related

Life Course of Comorbid Chronic Diseases With Increased Aging

Dietert, R in (Ed) Weiss, B. *Aging and Vulnerability to Environmental Chemicals.* Royal Soc. of Chemistry Press. 2013
Misregulated Inflammation is a tie that binds non-communicable diseases and conditions (NCDs) together. And A feature of gut microbial dysbiosis

Lipid mediators connected to immune-microbial signaling prove critical in effective control of tissue inflammation.

The Completed Self Hypothesis
Scientific Challenge

If you could pick ONE sign that best distinguishes a lifetime of health from one filled with disease ......what would that be????

[Challenge was issued for an invited paper for a special issue of the physics journal ENTROPY]
My Answer
(upon waking from a dream)

Self completion of the human-microbial superorganism
The Completed Self: An Immunological View of the Human-Microbiome Superorganism and Risk of Chronic Diseases

Entropy 2012, 14 (11), 2036-2065

R Dietert, J Dietert
Self-Completion - The Completed Self

Host-specific, Family-sourced microbiota

2014 documentary film
Wellcome Trust screening
The Complete Human: Three Domains of Life

Domains of Life

- Eukaryota
  - Mammalian
  - Microbial Eukaryotes
- Bacteria
- Archaea

Genomes

- First
  - ~ 25,000 genes
- Second
  - ~ 10 million genes

Superorganism

Majority-Microbial Humans
(based on cell and gene numbers)

Composition

Approximately 90% microbial by cell number

From: Dietert and Dietert Healthcare 3(1), 100-129; 2015.
Archaea – also in your gut
Ramifications of Self Incompleteness for the Immune System

Question
Can you see a day when incomplete seeding of the newborn/infant microbiome has a medical coding?
Our Microbiome Produces a “Fingerprint” of Volatile Organic Compounds (VOCs)

Children living near a sanitary landfill had elevated breath methane correlated with elevated methane producing Archaea in the gut microbiome (unrelated to socio economic status).


Volatile organic compounds (VOCs) in urine can be used to differentiate celiac disease from irritable bowel syndrome based on distinctive microbiome-produced metabolites.

Microbial Dysbiosis and Impending *C. Difficile* Outbreaks

Cliff, the original *C. Difficile* detection dog
http://www.dailymail.co.uk/health/article-2247688/Meet-Cliff-remarkable-super-sniffing-dog-detects-hospital-superbugs.html

Who are you really? and.... How (healthy) are you?
Ramifications of Self Incompleteness

Microbiota are seen as an “Integral Organ”

If they are missing, it analogous to a form of birth defect.

e.g., Clarke et el.,
Minireview: Gut microbiota: the neglected endocrine organ.

Brown JM, Hazen SL. The gut microbial endocrine organ: bacterially derived signals driving cardiometabolic diseases.

Evans et al. The gut microbiome: the role of a virtual organ in the endocrinology of the host.
<table>
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<th>Ineffective Microbiome-Mediated Immune Maturation</th>
<th>Effective Microbiome-Mediated Immune Maturation</th>
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Managing the Human Ecosystem for Effective Immune Maturation and Tolerance
Gut Microbial Dysbiosis – Immune Dysfunction

Invariant NKT cells
- population size –
  regulation of inflammation
  Risk of autoimmune and inflammatory disease

Natural (FoxP3+, CD25+)
T regulatory cells
- maturation and expansion capacity to control Th17 cells
  Risk of autoimmune, allergic and inflammatory disease

Dendritic cells
- maturation promoting T helper balance control of adaptive immune responses
  Risk of allergic and inflammatory disease

Macrophages
- role in inflammation and balance of polarization
  Risk of inflammatory disease, heart disease, and cancer
Modulation of colonic iNKT cells by inhibiting cell proliferation during neonatal development.

Sphingolipids from a Symbiotic Microbe Regulate Homeostasis of Host Intestinal Natural Killer T Cells

Cell, Volume 156, Issues 1–2, 2014, 123 - 133
Diabetes, Obesity, Colitis, Asthma, Celiac disease

Perinatal Period

Birth:
Vaginal vs. Cesarean

Risk of future generations for various immune dysfunction-promoted NCDs

microbiome adjustment as part of adult disease management

microbiome adjustment for pregnancy and to optimize microbiome seeding

healthy microbiome seeding plan

feeding the microbiota for optimized immune and microbial co-maturation
The New Target “Organism”: impact on personalized healthcare and safety, opportunities for probiotic strategies
Responses of the Microbiota to Environmental Exposures

Environmental pollutants (e.g., metals, organics)

Diet

Drugs

1. Sequestration
2. Avoidance/Exclusion
3. Metabolism
4. Specific Signaling
5. Selective Microbe Death
6. Selective Microbe Expansion
7. Translocation

Environmental chemicals, drugs and food additives reported to affect the gut microbiome

- Heavy metals (e.g., cadmium, lead, arsenic)
- Other metals (iron, selenium, zinc)
- PCBs (Choi et al., EHP 2013)
- Particulate matter (PM10) (Kish et al. PloS One 2013)
- Chlopyrifos (Joly et al, ESPRI, 2013)
- High fat diet (Myles et al. Plos One 2014)
- Valproate (de Theije et al. Brain Behav Immun 2013)
- Antibiotics (Ng et al., Nature 2013)
- **Vitamin D (Ooi et al., J.Nutr 2013)
- Food emulsifiers (Chassaing et al. Nature 2015)

**In contrast with antibiotics, Vitamin D is on the list because it affects, but does not necessarily “harm,” the microbiome. Many people are, in fact, deficient in Vitamin D
Current Biomarkers Model for Health Risk Assessment (1987)

From:
National Research Council,
Environ Health Perspect,
74: 3-9, 1987
The Microbiome Filters Virtually All Exposures and Directly Participates in Epigenetic Alterations

Proposed New Environmental Health Assessment Model

Adapted from: Dietert and Silbergeld, Toxicol. Sci. 2015 Apr;144(2):208-16.
Two Examples of Microbiome Status Determining Toxicity

Drugs: Digoxin

- narrow efficacy/toxicity range
- gut microbiota determine actual delivered dose
- adverse outcomes – ineffective drug administration or potentially lethal toxicity


Environmental Chemicals: Arsenic

- sulfur-reducing gut bacteria can convert arsenic into one of its most toxic forms

Unsuspecting Toxicants for the Microbiome

**Food Additives: Emulsifiers**
Polysorbate 80 (PS80), Carboxymethylcellulose (CMC)

In mice, these emulsifiers reduce the gut mucus layer putting bacteria in closer proximity to host cells. This adversely alters the regulation of inflammation and predisposes for later life colitis and metabolic syndrome.

See: Chassaing et al.
The Microbiome in Disease States and Altered Environmental Vulnerability

- Cesarean Delivery
- Antibiotic Use
- Maternal Gestational Weight
- Cadmium Exposure
- Air Pollution

Reduced diversity of gut microbiota and/or altered gut microbe metabolism

- Altered Fatty Acid Production
- Epigenetic Gene Regulation

Obesity/High Body Mass Index

- Altered iron content and distribution in macrophages
- Altered body burden/distribution of arsenic

Altered impact of air pollution on risk of hypertension

From: Dietert and Silbergeld, Toxicol. Sci 144:208-16. 2015;
See also Ginsberg et al. Curr Environ Health Report, 2014
New Horizons: Evaluation and Therapeutics?

- Microbiome Fingerprinting
  - Detailed personalized analysis of the microbiome
- Microbiome Modification
  - Prebiotics and Probiotics
  - Fecal microbiota transfer
  - Direct microbial metabolite treatment
- Microbiome Support, Protection, and Treatment Routes
  - Supportive diet for microbiota instillation and maintenance
  - Avoidance of harmful drugs and chemicals based on superorganism vulnerability (not just mammalian cell sensitivity).
  - New therapeutics that work via the Microbiome

*Timing is everything to avoid perinatally-programmed, life-long immune dysfunction*
Summary

• Failure to self-complete in the newborn may be the single greatest health risk across a lifetime. We need microbiome seeding on every birth plan and active management of our “second genome” (i.e., seed, feed, protect).

• The immune system and the microbiome need to co-mature in a narrow window of development or persistent immune dysfunction and elevated risk of NCDs are likely.

• Safety needs to be based on the whole human. It is the superorganism that needs protection.

• Probiotic strategies offer an core component of future personalized healthcare.
Acknowledgements

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Thank You

Questions?