The Microbiome and Mental Health

Brain & Behavior Research Foundation Webinar
Tuesday, July 11, 2017 2:00 PM - 3:00 PM EDT

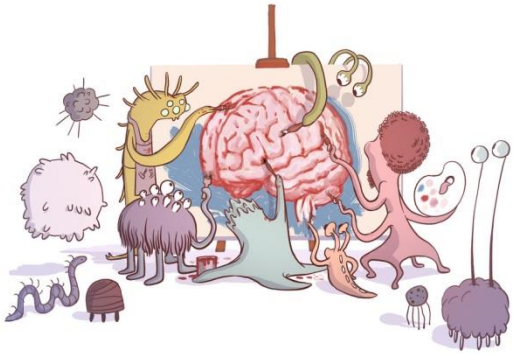

Illustration by Benjamin Arthur for NPR

http://www.npr.org/blogs/health/2013/11/18/244526773/gut-bacteria-might-guide-the-workings-of-our-minds

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Disclosures

- **Presenter(s) has the following interest to disclose:**
  - Member of Scientific Advisory Board (Immodulon Therapeutics, Ltd.)

Outline

- Prevention of mental health disorders
- The Hygiene Hypothesis and psychiatric disorders
- Psychiatric disorders as disorders with a failure of immunoregulation
- Restoration of immunoregulation prevents development of a stress-induced PTSD-like syndrome
- Future directions

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Mental health research

"In contrast to researchers in cancer and heart disease who have sought cures and preventions, biological psychiatrists in both academia and industry have set their sights on incremental and marketable advances, such as drugs with fewer adverse effects."

Insel and Scolnick, 2006, Mol Psychiatry, 11, 11-17

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Major depression is common and becoming more common

"Major depression - Sad Days Indeed",
by Asbjorn Lonvig

Rank Order of Disability-Adjusted Life-Years for the 15 Leading Causes

Rank by Year 1990	Rank by Year 2020	Disease or Injury
1	6	Lower respiratory infections
2	9	Diarrheal diseases
3	11	Conditions arising during the perinatal period
4	**2**	**Unipolar major depression**
5	1	Ischemic heart disease
6	4	Cerebrovascular disease
7	7	Tuberculosis
8	25	Measles
9	3	Road traffic accidents
10	13	Congenital anomalies
11	24	Malaria
12	5	Chronic obstructive pulmonary disease
13	19	Falls
14	39	Iron-deficiency anemia
15	37	Protein-energy malnutrition

Murray and Lopez, 1996, Science, 274: 741-743

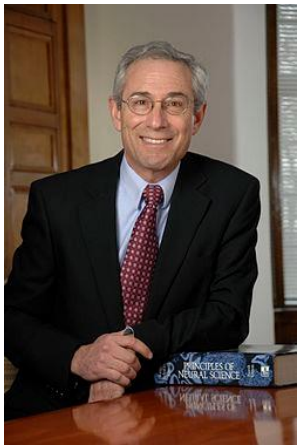
Mental health research

"Psychiatry will need to develop strategies for prevention for each of these disorders."

[schizophrenia, mood disorders, and autism]

Dadu Shin, In, Should I tell my students I have depression?
By Abby L. Wilkerson, New York Times, Dec. 14, 2016

Thomas R. Insel, M.D.
NIMH Director



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Where should we start in search of prevention strategies for psychiatric disorders/optimizing resilience?

Risk factors for psychiatric disorders

- Genetic predisposition
- Environmental influences (ACE, microbial inputs)

Proinflammatory microbial inputs ↓ (+) (–) ↓ Immunoregulatory microbial inputs

- Failure of immunoregulation

↓

↑Inflammation

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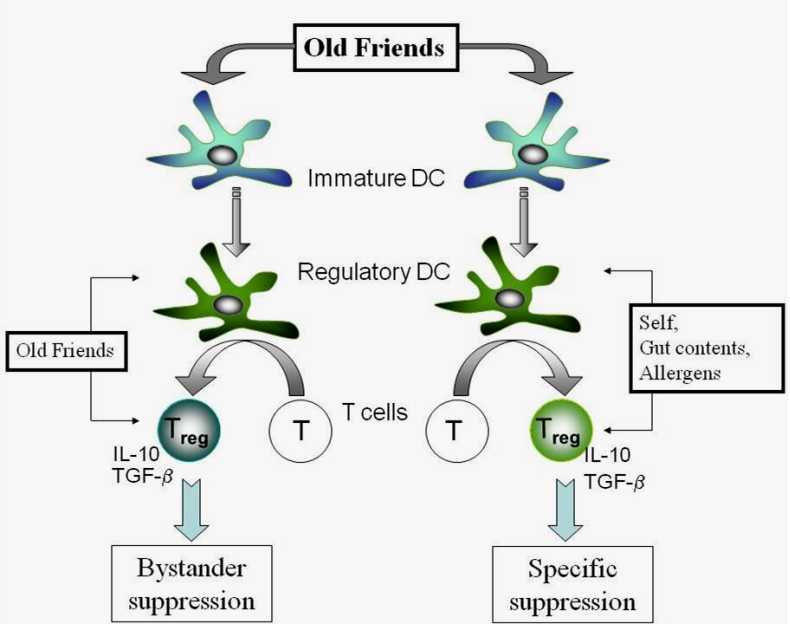
The hygiene hypothesis and psychiatric disorders

"…, some psychiatric disorders in developed countries might be attributable to failure of immunoregulatory circuits to terminate ongoing inflammatory responses."



Rook and Lowry, 2008, Trends in Immunology, 29, 150-158

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The hygiene hypothesis and psychiatric disorders

Depressi
Multiple s
Type 1 d ety
Crohn's gies

(↑IFN-γ) (↑ IL-4,IL-5,IL-13)

Th1 Th2

(adequate levels of IL-10 and TGF-β to terminate inappropriate inflammation)

↑IL-10, TGF-β

Low ratio of regulatory to effector T cells

Normal ratio of regulatory to effector T cells

Image: New York Times, A Cure for the Allergy Epidemic?
By Moises Velasquez-Manoff
Published: November 9, 2013 http://nyti.ms/17V0rRe

Rook and Lowry, 2008, Trends in Immunology, 29: 150-158

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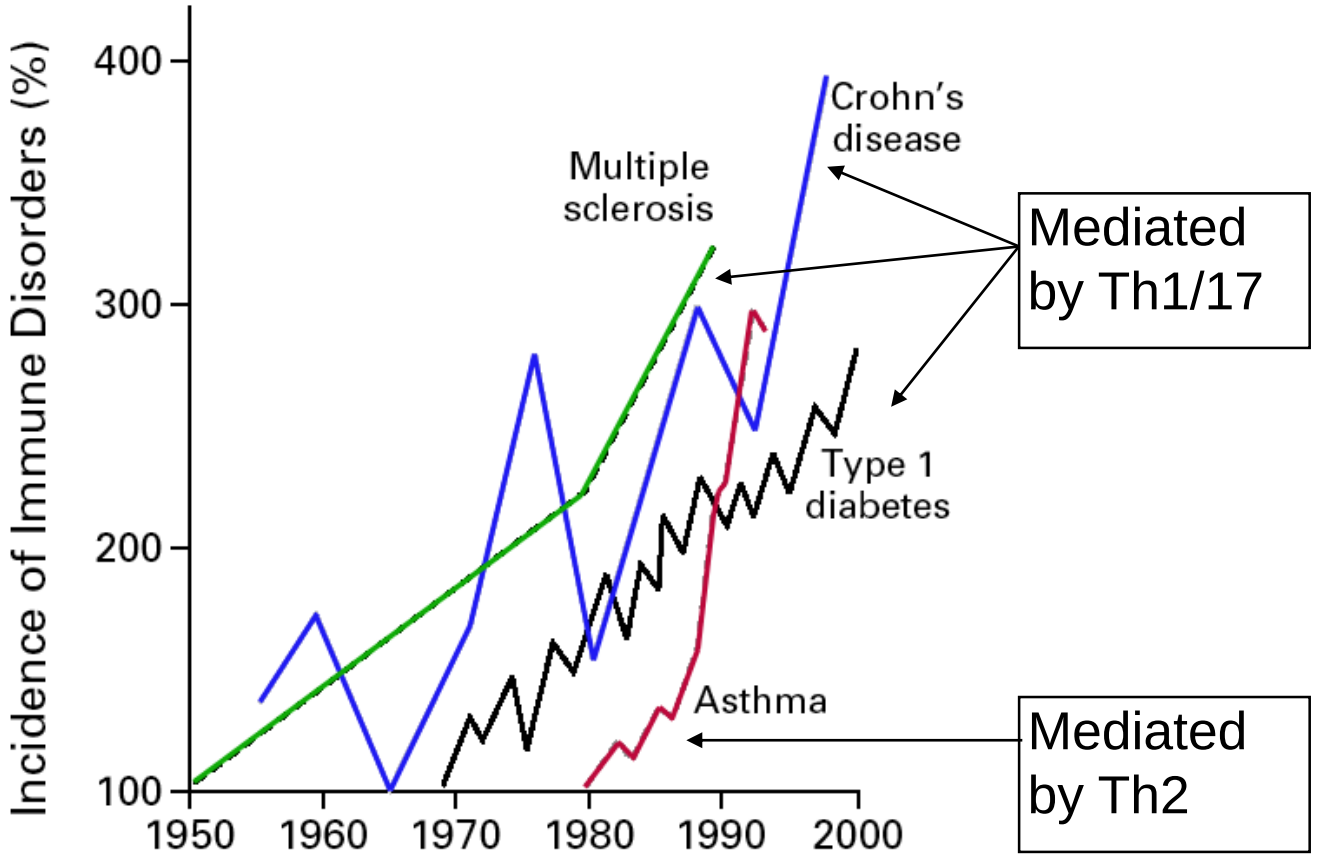
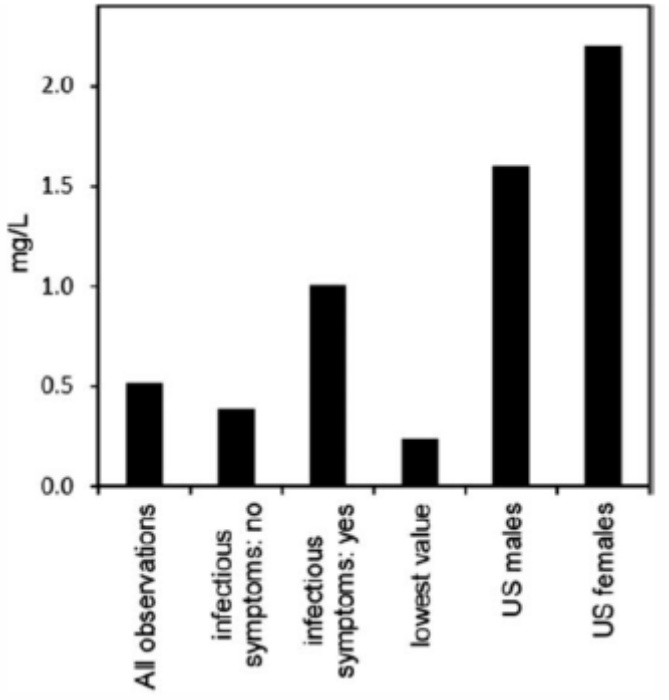
The increasing incidence of immunoregulatory disorders



Bach J-F (2002), New Engl. J. Med. 347:911-920

Serum C-reactive protein (CRP) concentrations are higher in urbanized countries



Median CRP concentrations in lowland Ecuador compared to the United States

Huaorani children in the remote Ecuadorian Amazon

Photo credit: http://vivatropical.com/ecuador/ecuador-climate/
https://www.bostonglobe.com/lifestyle/travel/2014/03/01/introducing-family-amazon/joOzJwkoS07sUIDFqXfNTJ/story.html

McDade et al., 2012, Am J Hum Biol. 24: 675-681

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Reduced Treg in psychiatric disorders

1. Autism	Mostafa et al., 2010, J Child Neurology, 25: 328-335
2. Depression	Li et al., 2010, J Affect Disord, 124: 68-75
3. PTSD	Sommershof et al., 2009, Brain, Behav Immunity 23: 1117-1124

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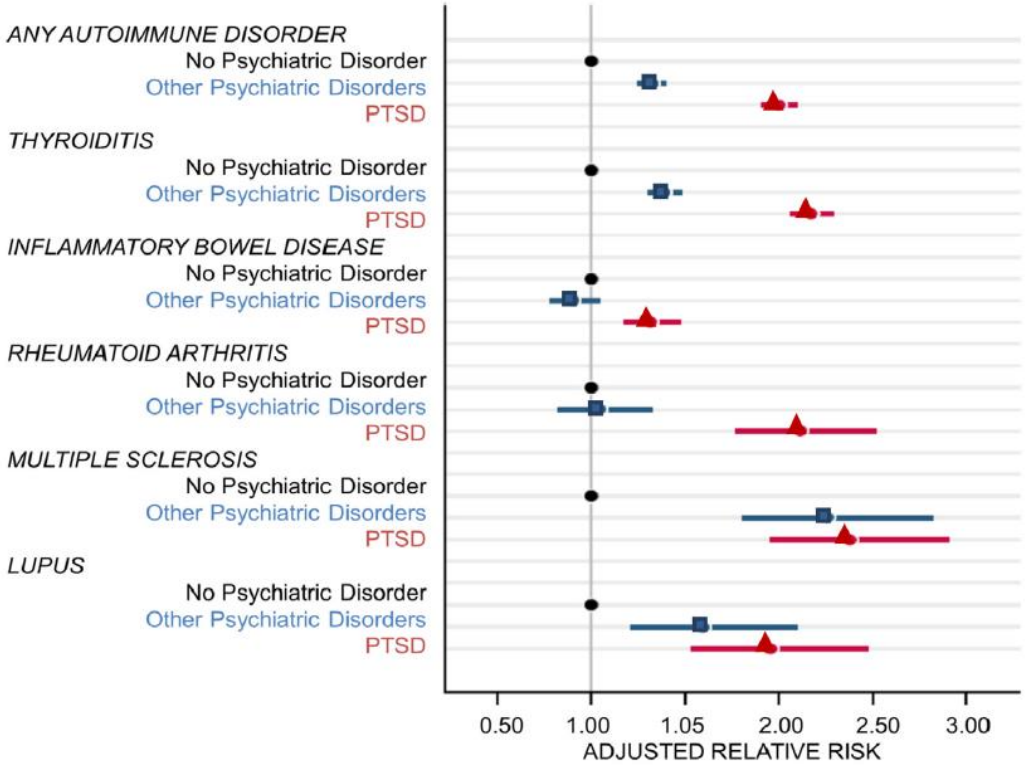
Evidence of inadequate immunoregulation in PTSD: increased risk of autoimmune disorders



O'Donovan et al., 2015, Biol Psychiatry 77: 365-374

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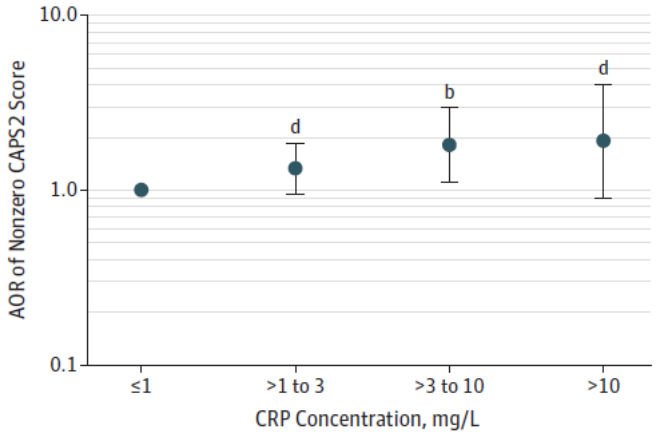
Plasma CRP concentrations before deployment predict Clinician-Administered PTSD Scale (CAPS) scores ~3 and 6 months following deployment

The Marine Resiliency Study, a prospective study of approximately 2600 war zone–deployed Marines



"Adjusting for the baseline CAPS score, trauma exposure, and other relevant covariates, we found baseline plasma CRP concentration to be a highly significant overall predictor of postdeployment CAPS scores (p = 0.002)"

Eraly et al., 2014, JAMA Psychiatr, 71(4): 423-431

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Strategies for prevention: "Old Friends" induce Treg proliferation, Treg activation, and anti-inflammatory cytokine production

Examples of the three overlapping categories of organism implicated in the "hygiene" or "Old Friends" hypothesis
1) **Organisms that form part of the co-evolved human microbiota** that are altered by modern diets, living conditions and antibiotics (e.g. ***Bacteroides fragilis, Lactobacillus reuteri,* isolated from human maternal milk, *Akkermansia muciniphila***)
2) Infections commonly present in early man, usually harmless, transmitted by the fecal-oral route very early in life, that have been depleted since urbanization (e.g. **helminths, hepatitis A virus, *Toxoplasma*, *Salmonella, Helicobacter pylori***).
3) Harmless environmental organisms in mud, untreated water and fermenting vegetable material (**"pseudocommensals": lactobacilli, environmental saprophytes, i.e., *Mycobacterium vaccae***) that are eliminated by the modern city lifestyle.

Rook and Lowry, 2008, Trends in Immunology, 29: 150-158; Rook, Raison, and Lowry, 2011, Microbiologist, 12: 32-36; Rook, Raison, and Lowry, 2014, Clinical and Experimental Immunology, 177: 1-12.

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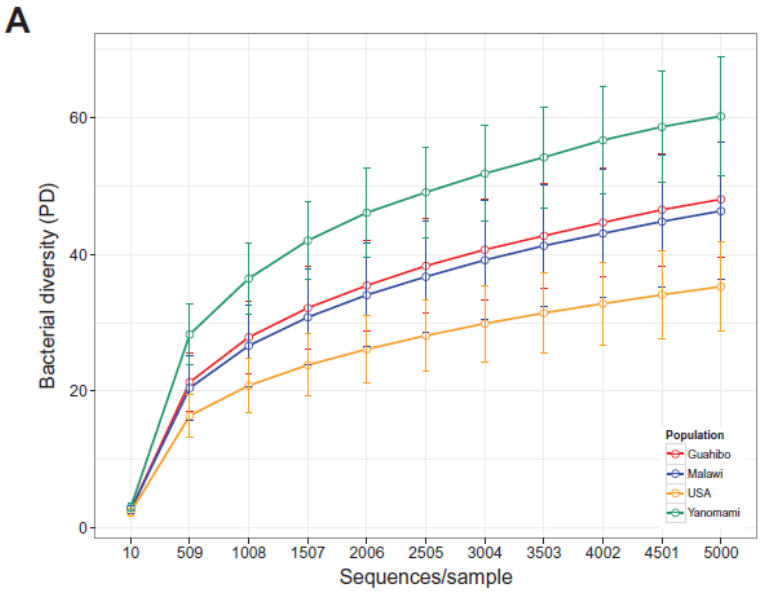
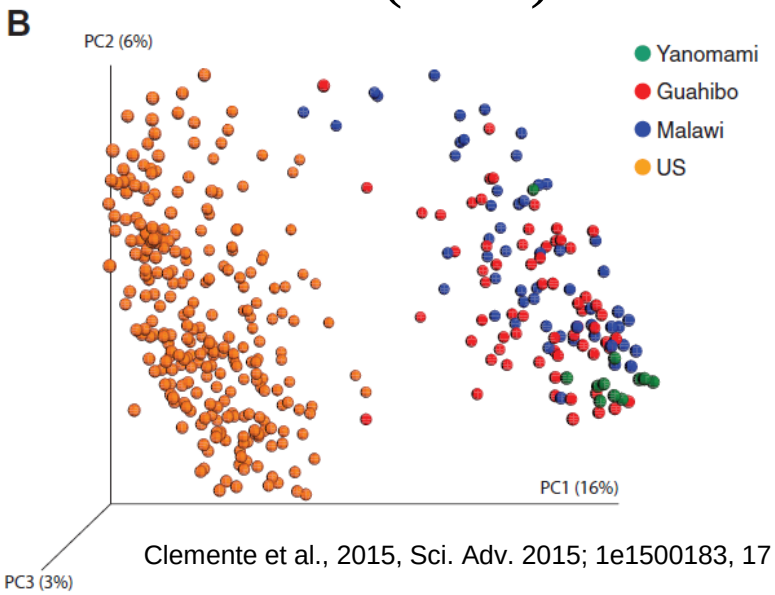
Co-evolved human microbiota:

The microbiome of uncontacted Yanomami Amerindians versus individuals in modern urban societies (USA)





Clemente et al., 2015, Sci. Adv. 2015; 1e1500183, 17 April 2015

Yanomami Amerindians in the remote Venezuelan Amazon: "Their diet consists of wild bananas, seasonal fruits, plantains, palm hearts, cassava, birds, small mammals, small fish, crabs, and frogs."

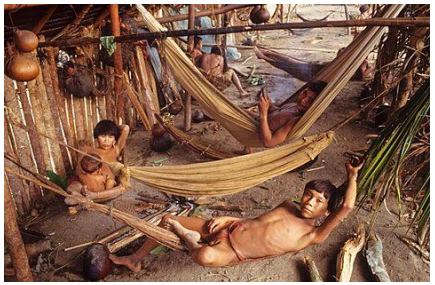


Photo credits: http://www.hardrainproject.com/hrpl?n=9243; © Mark Edwards, Hard Rain Picture Library; Robert Harding; http://blog.mountsinai.org/blog/exploring-diverse-microbes-among-remote-amerindians/

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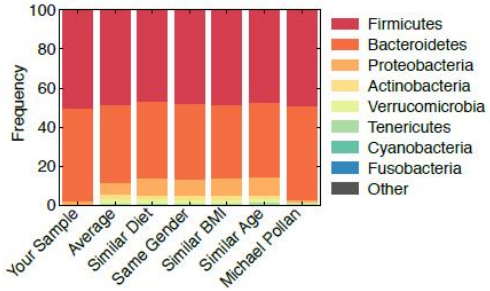
Co-evolved human microbiota:

american gut

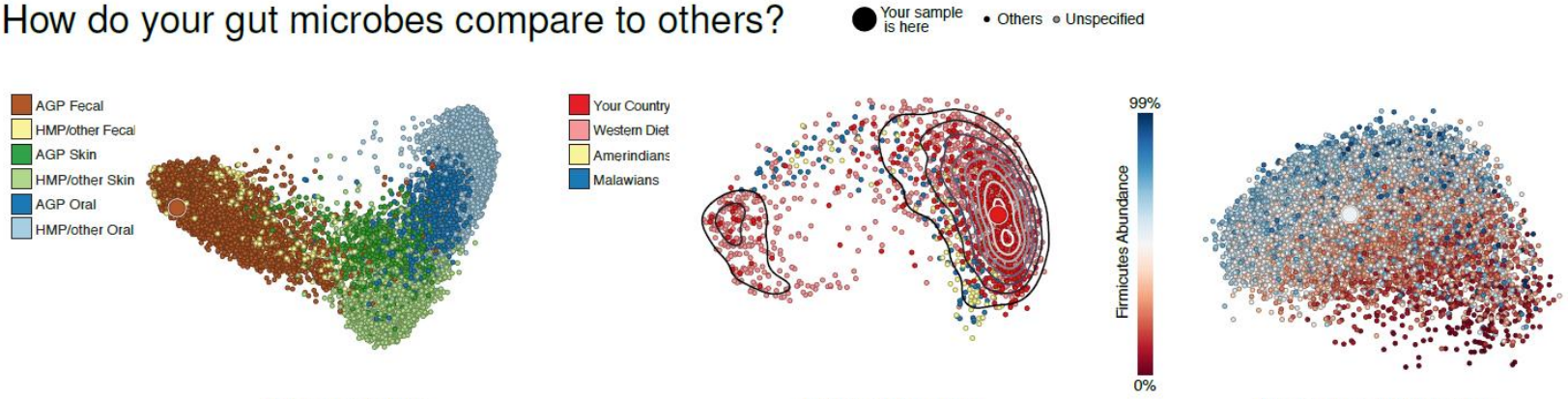
YOUR AMERICAN GUT SAMPLE

CHRISTOPHER LOWRY

What's in your American Gut sample?



How do your gut microbes compare to others?



http://americangut.org/

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Co-evolved human microbiota: Preliminary findings from the American Gut Project

1. The American Gut project has many more samples representing more groups of people than other studies, such as the Human Microbiome Project, Global Gut, or Personal Genome Project.
2. The microbiome changes as we grow! As you get older, your gut microbiome becomes more diverse.
3. Antibiotic usage also affects our microbiomes, by reducing diversity and thereby creating a less healthy gut environment.
4. The more different types of plants a person eats, the higher their gut microbiome diversity.
5. Alcohol consumption also affects microbiome diversity-those who had at least one drink per week had a more diverse microbiome than those who abstained from alcohol.

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Old Infections:

Case study: humans co-evolved with immunoregulatory *Helicobacter pylori*

- The most common bacterial infection worldwide
- Co-evolved with humans at least since humans migrated out of East Africa ~60,000 years ago
- Potent immunoregulatory effects (but a “difficult” Old Friend)

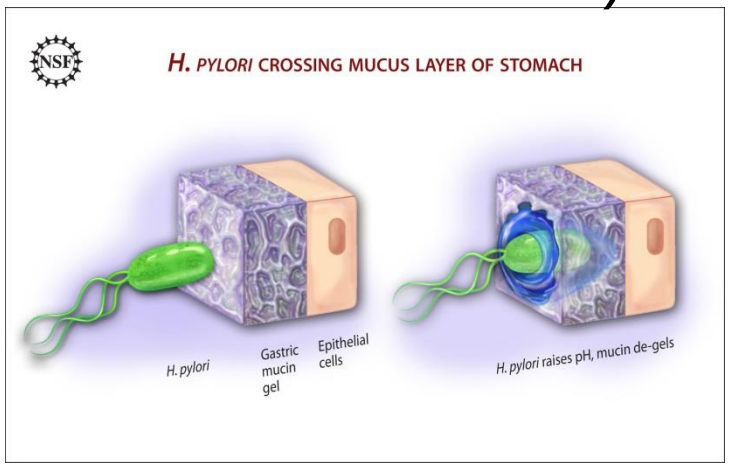

Photo by © Wim van den Heever

Arnold et al., 2012, *Front Cell Infect Microbiol*, 16 February 2012 | doi: 10.3389/fcimb.2012.00010

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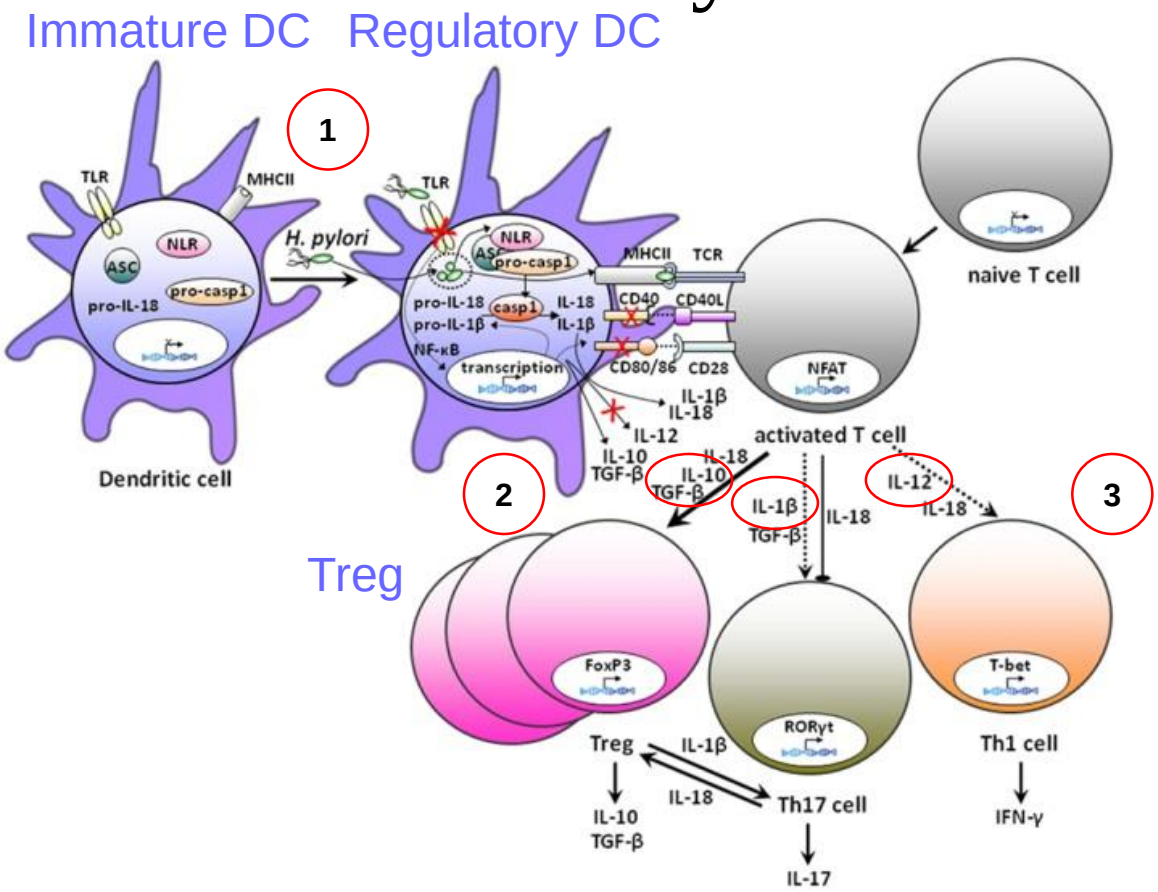
H. pylori induces immunoregulation and production of anti-inflammatory cytokines



1. Exposure to *H. pylori* induces semi-mature DCs with high expression of MHC class II and IL-18, TGFβ and IL-10

2. *H. pylori* experienced DCs induce conversion of naïve T-cells to FoxP3^{+} Tregs via IL-18, TGFβ, and possibly IL-10

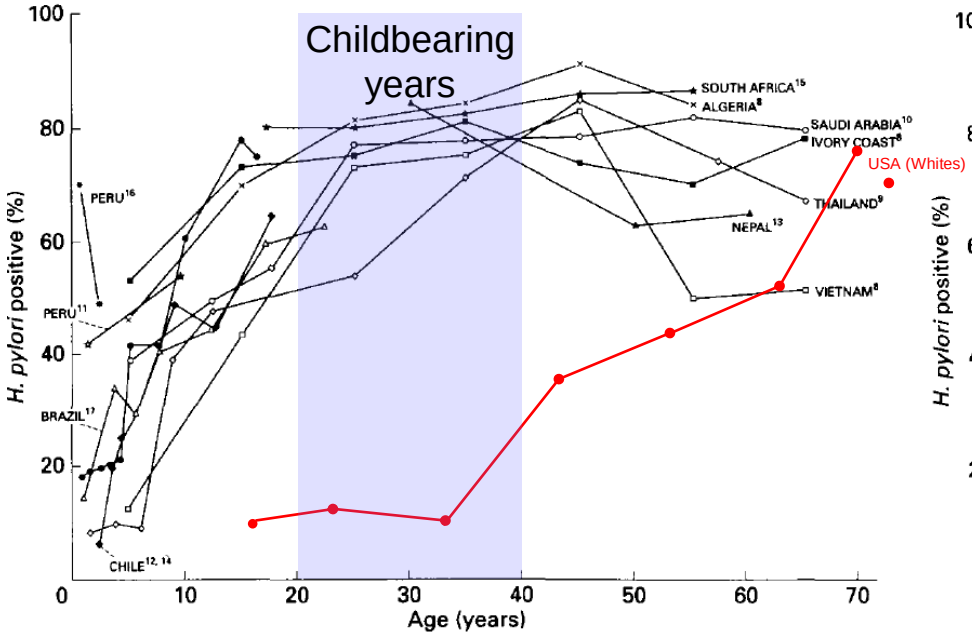
3. *H. pylori* experienced DCs are poor inducers of Th17 and Th1 differentiation

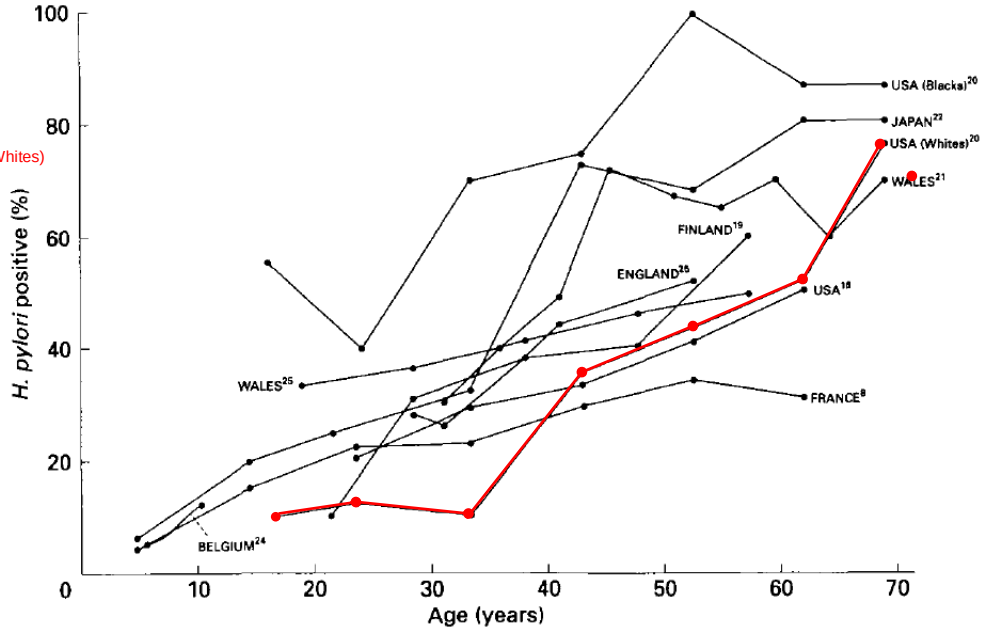
Arnold et al., 2012, *Front Cell Infect Microbiol*, 16 February 2012 | doi: 10.3389/fcimb.2012.00010

H. pylori prevalence is lower in children from developed countries

Childhood *H. pylori* infection is common in developing countries

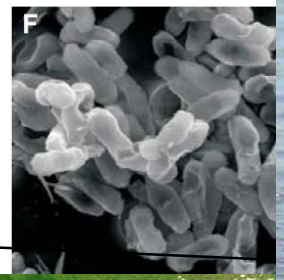
Childhood *H. pylori* infection is uncommon in developed countries





Pounder and Ng, 1995, *Aliment Pharmacol Ther* 9(Suppl.2, 33-39

Environmental pseudocommensals: *Mycobacterium vaccae*, an immunoregulatory environmental saprophyte



John Stanford **Graham Rook** **John Grange**

Photo credits: http://stephenhall.smugmug.com/Africa/Uganda-2012/; http://www.panoramio.com/photo/15354543

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Chronic subordinate colony housing model

Psychoneuroendocrinology 74 (2016) 221–230

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Review

Chronic subordinate colony housing paradigm: A mouse model for mechanisms of PTSD vulnerability, targeted prevention, and treatment—2016 Curt Richter Award Paper

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Reber et al. 2016 *Psychoneuroendocrinology*, 74, 221-230

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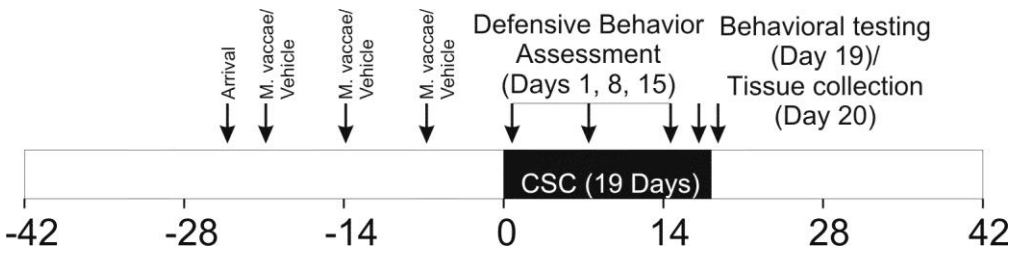
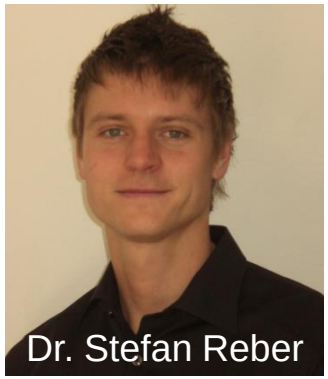
Chronic subordinate colony housing model

Single housed controls (SHC)

Chronic subordinate colony (CSC) housing





Reber et al. 2016 PNAS, 113 (22), E3130-E3139

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Chronic subordinate colony model

submissive behavior

absolute & relative adrenal weight	↑	decreased GC signaling
corticosterone response of adrenal cells (*in vitro* & *in vivo*)	↓	
GC sensitivity (splenocytes, lymph node cells, pituitary)	↓	
anxiety related behavior (EPM, LDB, OF, OA exposure, SPAT)	↑	anxiety
histological damage score (spontaneous colitis)	↑	somatic disorders
risk for inflammation-related colon cancer	↑	
severity of chemically (DSS)-induced colitis	↑	

Reber et al., 2007, Endocrinology 148: 670-682; Reber et al., 2008 Stress 11: 225-34; Veenema & Reber et al., 2008, Endocrinology 149: 2727-2736; Reber et al., 2008, Annals NY Acad Sci 1148: 184-195; Singewald & Reber, 2009, Stress 12:,58-69; Schmidt et al., 2010 in press

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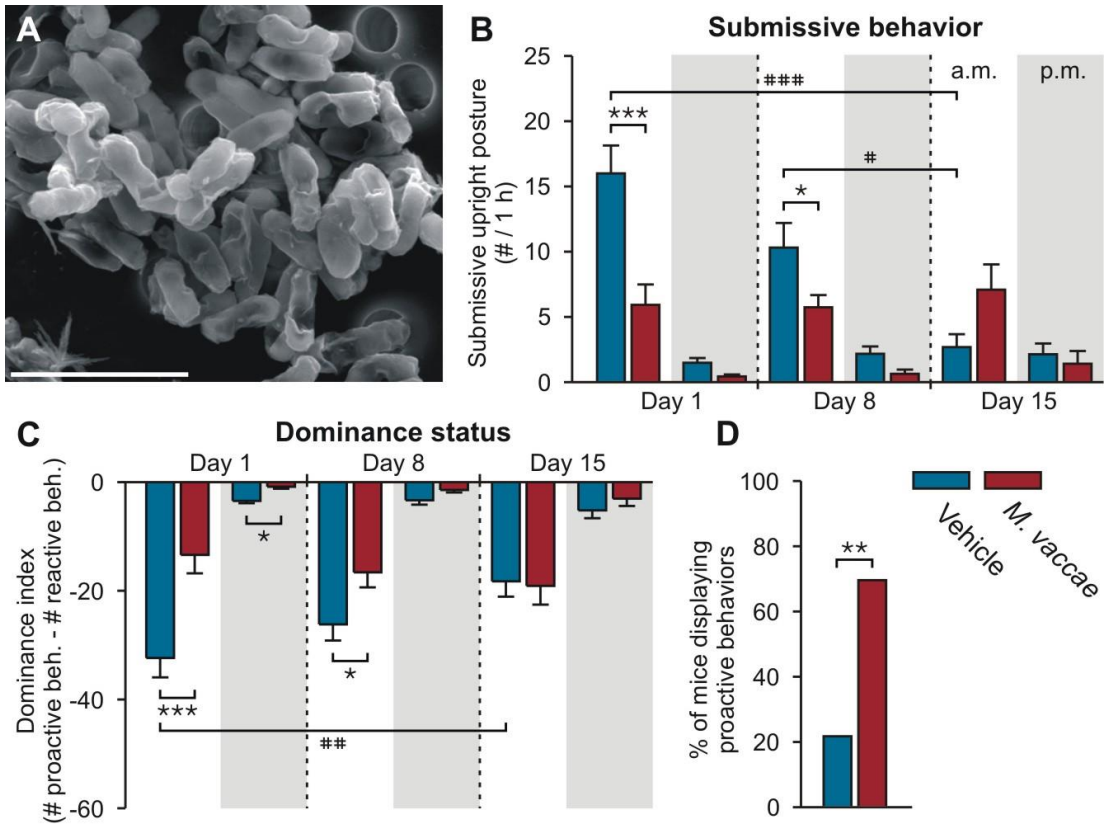
Immunization with *M. vaccae* induces a more proactive coping response to stress



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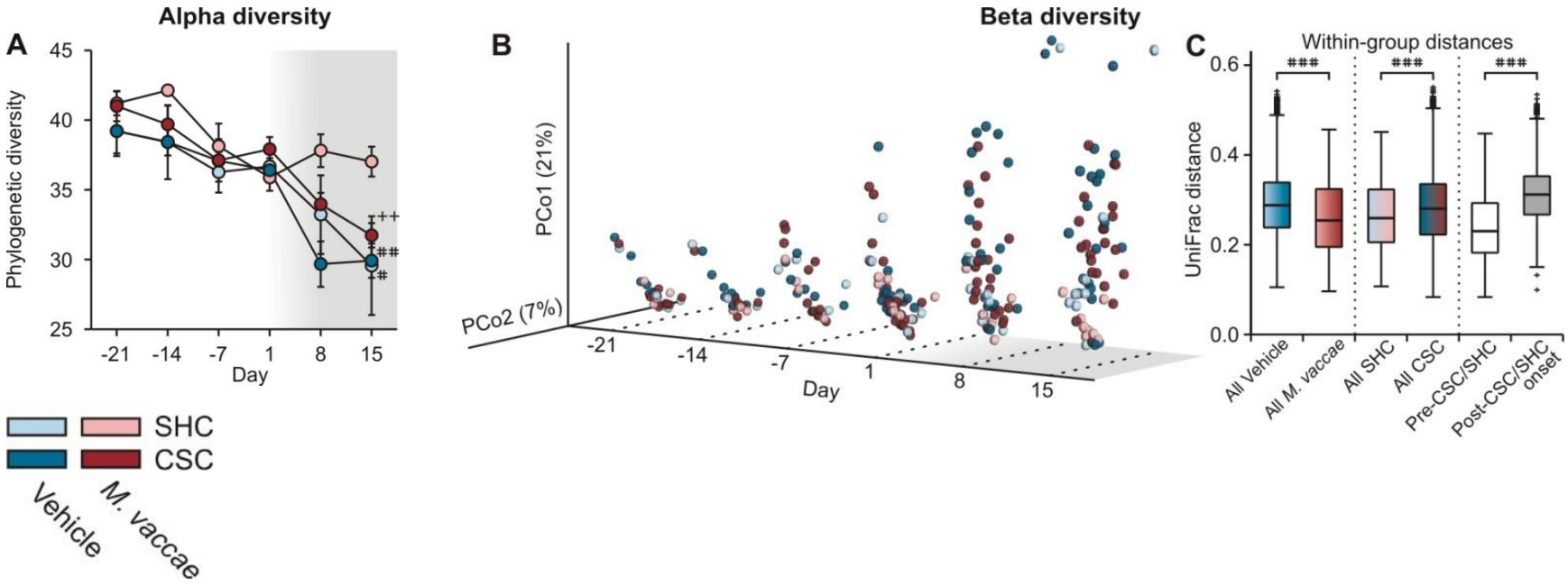
Stress decreases alpha diversity and increases beta diversity of gut microbial communities while *M. vaccae* stabilizes them



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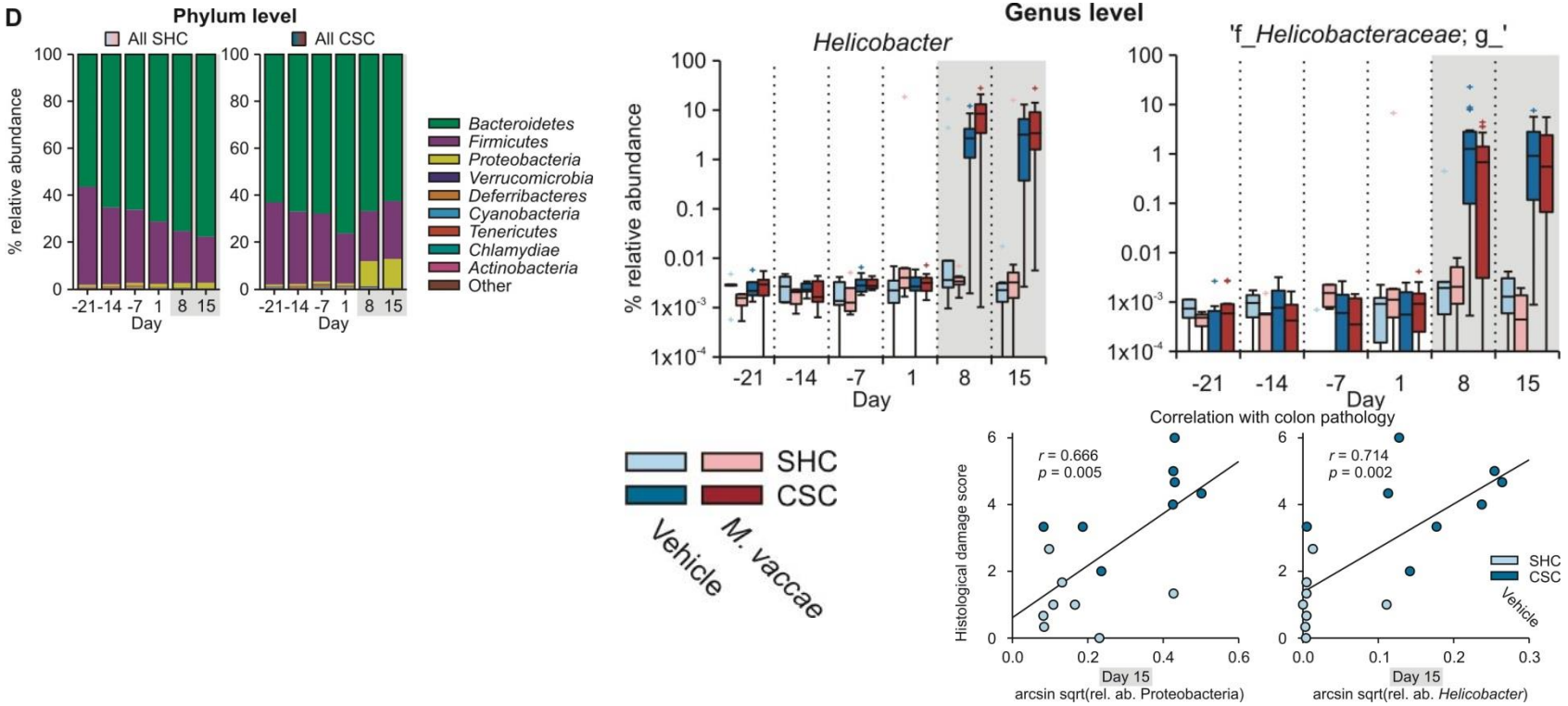
Stress increases *Proteobacteria*, including *Helicobacter* spp., a known colitogenic species



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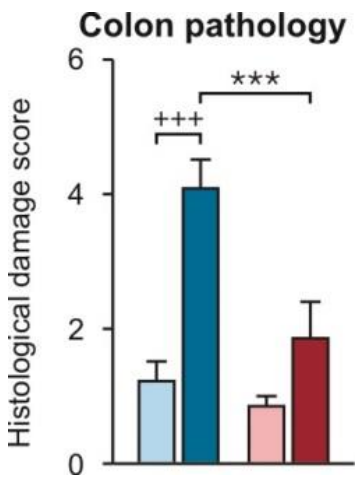
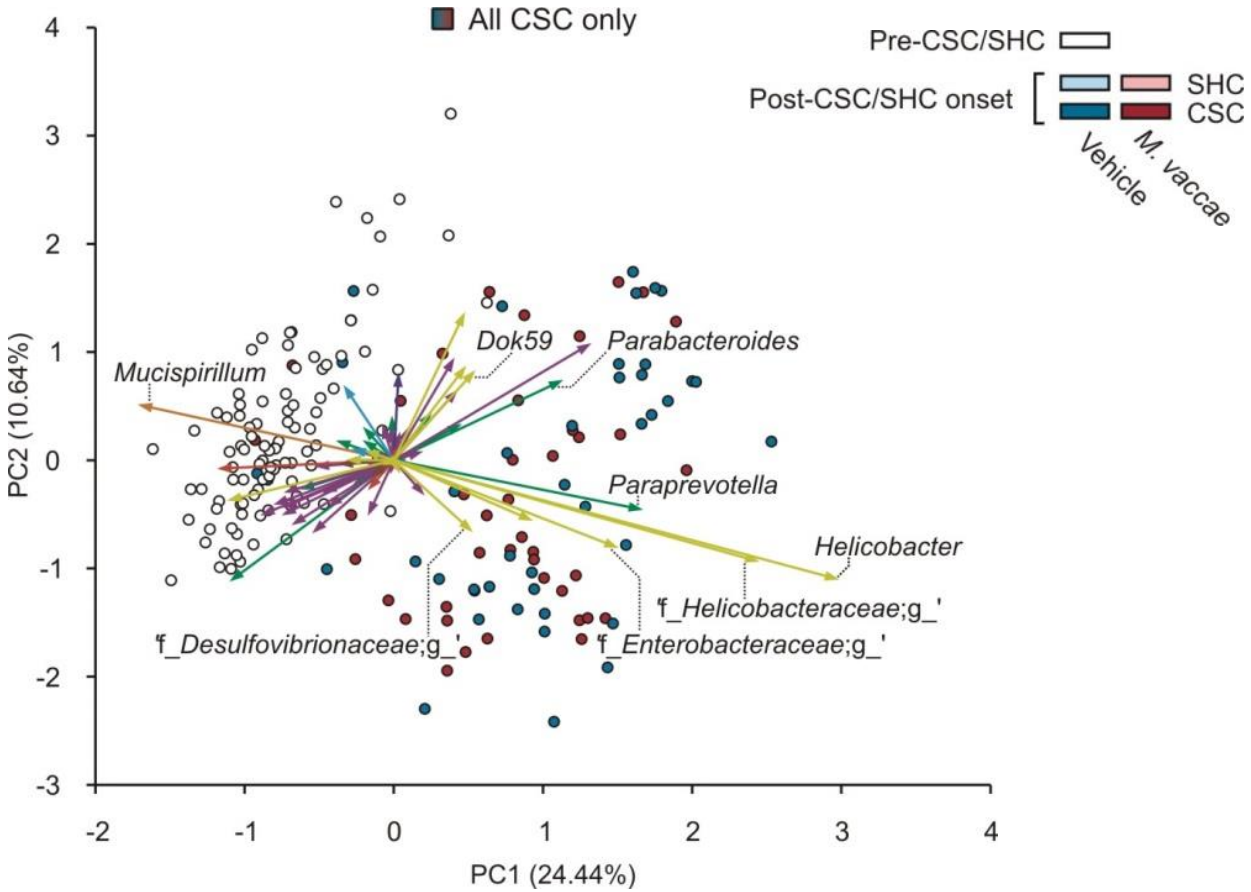
M. vaccae prevents stress-induced colitis, without preventing stress-induced shifts in microbial communities





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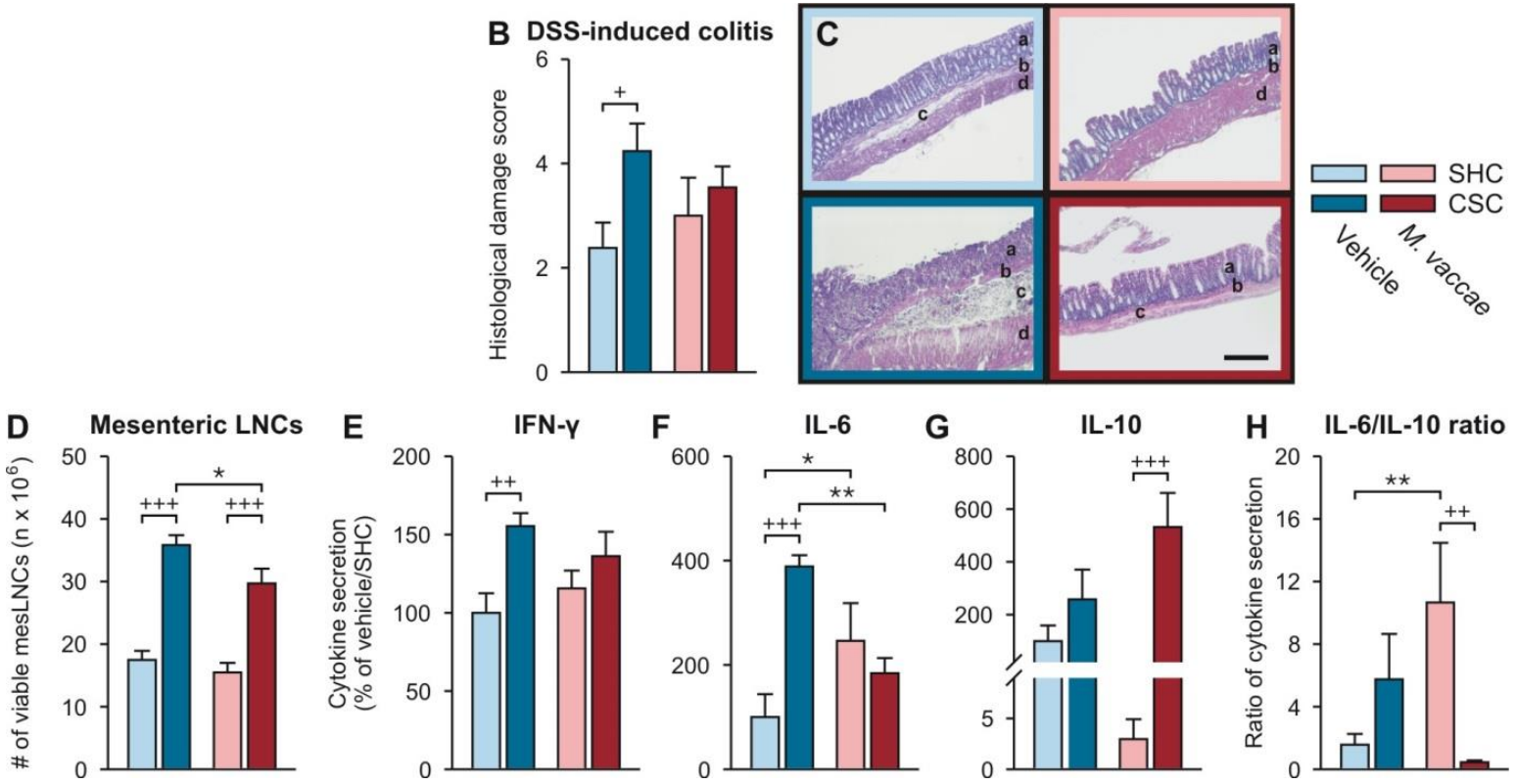
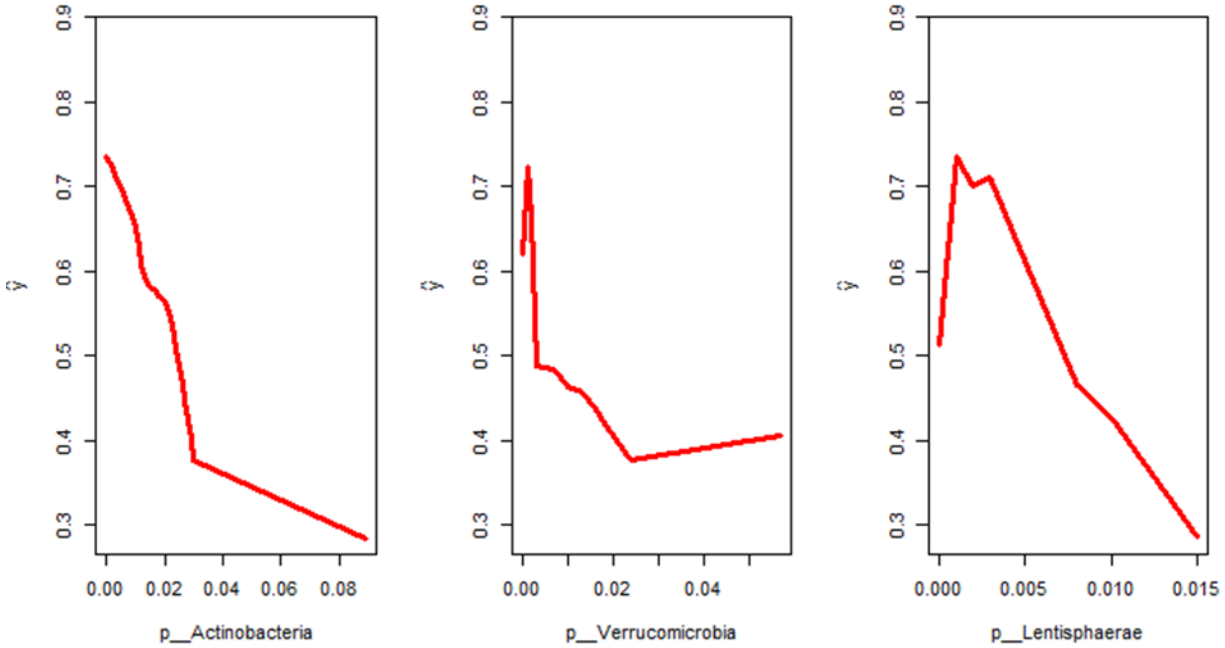
M. vaccae immunization protects against CSC-exaggeration of chemically-induced colitis



Reber et al. 2016 PNAS, 113 (22), E3130-E3139

Pilot study of the gut microbiome of 18 PTSD subjects and 12 trauma-exposed controls in South Africa



Sian
Hemmings
Stellenbosch University

Figure 1. Marginal plots of the predicted values the estimated probability of PTSD from the random forest versus the relative abundance of the three phyla identified as important for distinguishing PTSD status.

Hemmings, et al., 2017, Psychosomatic Medicine, in press

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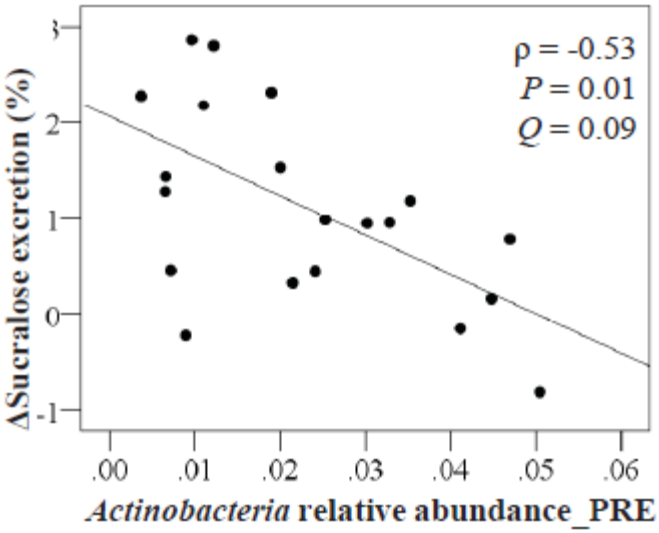
Relative abundance of Actinobacteria is inversely correlated with stress-induced gut permeability

51 km ski march



Karl, et al., 2017, Am J Physiol Gastrointest Liver Physiol (March 23, 2017). doi:10.1152/ajpgi.00066.2017, in press

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Outline

- Prevention of mental health disorders
- The Hygiene Hypothesis and psychiatric disorders
- Psychiatric disorders as disorders with a failure of immunoregulation
- Restoration of immunoregulation prevents development of a stress-induced PTSD-like syndrome
- Future directions

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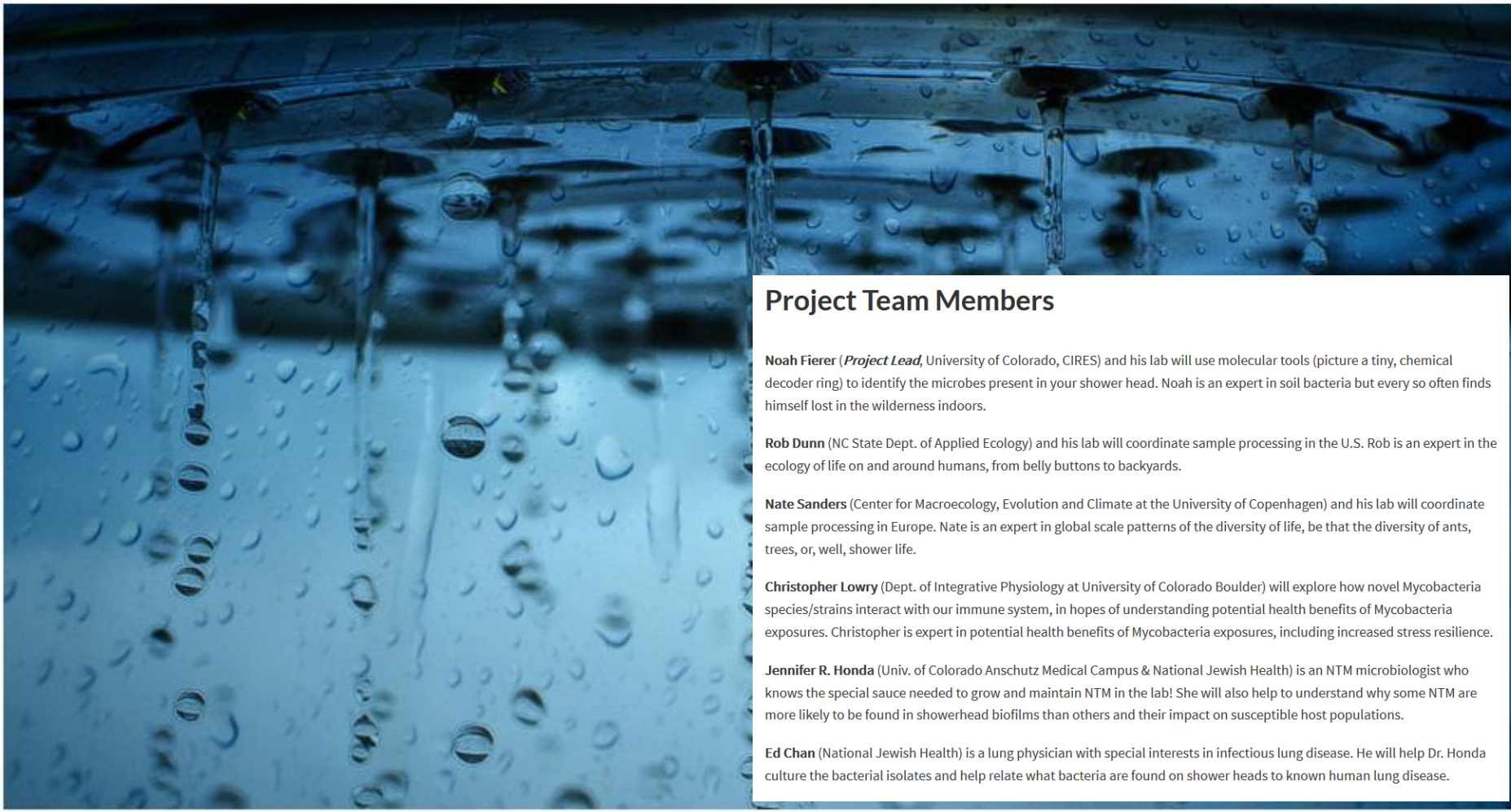

Project Team Members

Noah Fierer (***Project Lead***, University of Colorado, CIRES) and his lab will use molecular tools (picture a tiny, chemical decoder ring) to identify the microbes present in your shower head. Noah is an expert in soil bacteria but every so often finds himself lost in the wilderness indoors.

Rob Dunn (NC State Dept. of Applied Ecology) and his lab will coordinate sample processing in the U.S. Rob is an expert in the ecology of life on and around humans, from belly buttons to backyards.

Nate Sanders (Center for Macroecology, Evolution and Climate at the University of Copenhagen) and his lab will coordinate sample processing in Europe. Nate is an expert in global scale patterns of the diversity of life, be that the diversity of ants, trees, or, well, shower life.

Christopher Lowry (Dept. of Integrative Physiology at University of Colorado Boulder) will explore how novel Mycobacteria species/strains interact with our immune system, in hopes of understanding potential health benefits of Mycobacteria exposures. Christopher is expert in potential health benefits of Mycobacteria exposures, including increased stress resilience.

Jennifer R. Honda (Univ. of Colorado Anschutz Medical Campus & National Jewish Health) is an NTM microbiologist who knows the special sauce needed to grow and maintain NTM in the lab! She will also help to understand why some NTM are more likely to be found in showerhead biofilms than others and their impact on susceptible host populations.

Ed Chan (National Jewish Health) is a lung physician with special interests in infectious lung disease. He will help Dr. Honda culture the bacterial isolates and help relate what bacteria are found on shower heads to known human lung disease.

The Showerhead Microbiome Project

http://robdunnlab.com/projects/showerheads/

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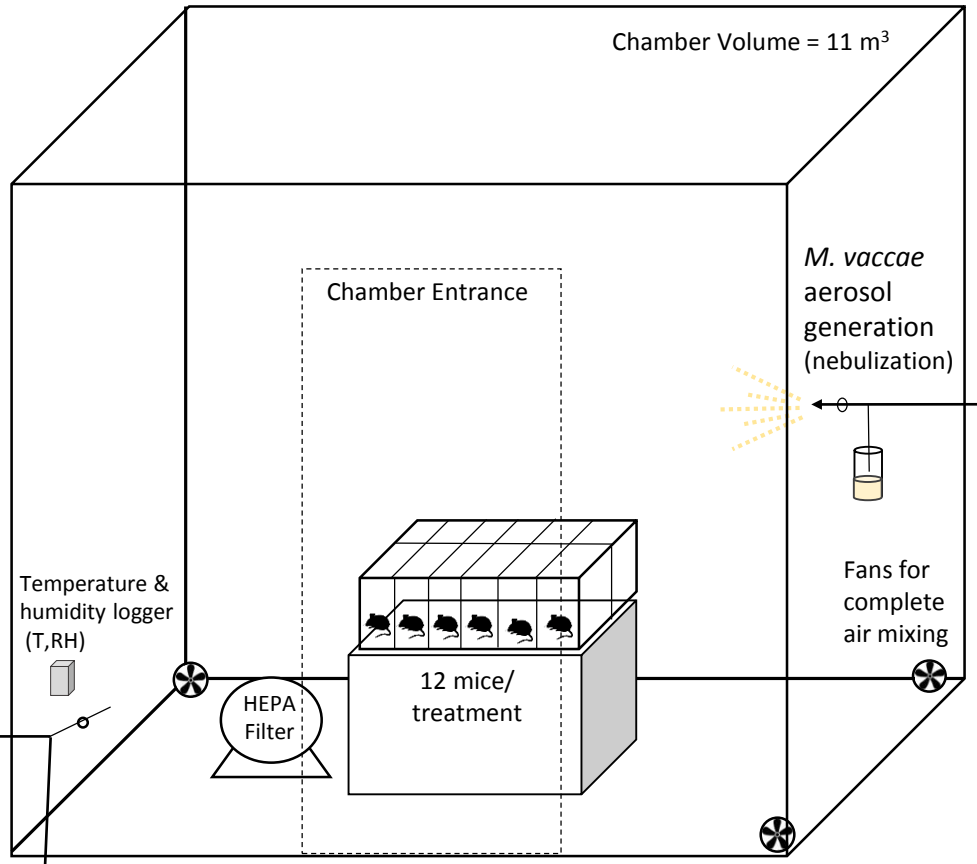
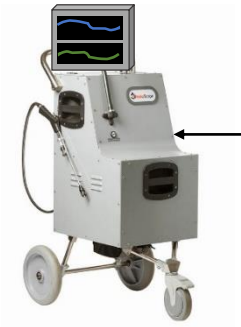
Sealed, well-mixed and controlled chamber for environmental bacteria aerosol exposure studies

Odessa Gomez





InstaScope Bioaerosol Monitor (Tracks aerosol concentration in real-time)

Sequential bioaerosol capture for microscopy enumeration & bioaerosol viability (CFU)

Conclusions

- Exposure to immunoregulatory “Old Friends” has declined dramatically in developed countries in the last 50 years
- Psychiatric disorders are associated with decreased Treg, decreased immunoregulation, and increased inflammation
- Immunization with *M. vaccae* prevents stress-induced inflammation and anxiety/fear
- Microbiome-based nterventions to increase anti-inflammatory/ immunoregulatory signaling might be considered for prevention and treatment of psychiatric disorders

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