2019 Science & Discovery Webinar Series

ME/CFS in the Era of the Human Microbiome: Persistent Pathogens Drive Chronic Symptoms by Interfering With Host Metabolism, Gene Expression, and Immunity

with Amy Proal, Ph.D.

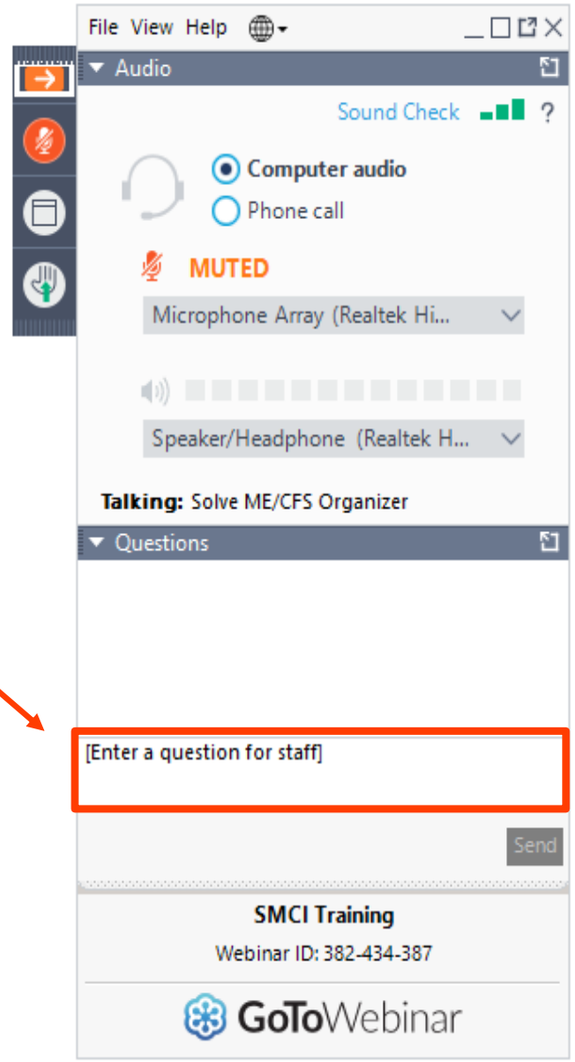
November 14, 2019 | 1:00 PM Eastern

Solve M.E.

www.SolveME.org

About Our Webinars

- Welcome to the 2019 Webinar Series!
- The audience is muted; use the question box to send us questions. Dr. Proal will address as many questions as time permits at the end of the webinar
- Webinars are recorded and the recording is made available on our YouTube channel http://youtube.com/SolveCFS
- The Solve ME/CFS Initiative does not provide medical advice



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Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in the Era of the Human Microbiome: Persistent Pathogens Drive Chronic Symptoms by Interfering With Host Metabolism, Gene Expression, and Immunity

Amy Proal, Autoimmunity Research Foundation/PolyBio

Millions of patients across the globe are suffering with myalgic encephalomyelitis (ME/CFS)

Currently there is **no one disease-specific biomarker** and severely ill patients are often **wheelchair dependent, bedridden** and unable to perform basic tasks of work or daily living.

#millionsmissing

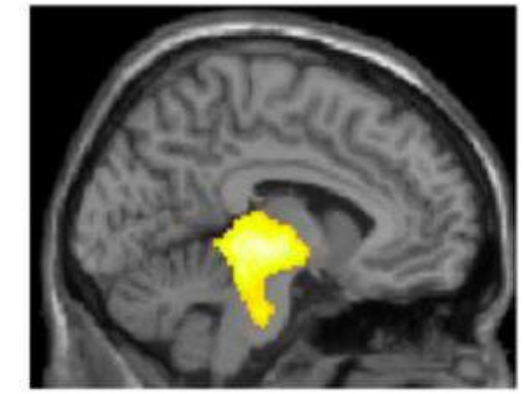
Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Myalgic Encephalomeylitis (ME) = *swelling of the brain*

- Unrelenting fatigue that does not improve with rest
- Post-exertional malaise (cannot recover for several days after exercise)
- Cognitive impairment
- Orthostatic intolerance
- Muscle pain
- Pain in the joints without swelling or redness
- Headaches of a new type, pattern, or severity
- Swollen or tender lymph nodes in the neck or armpit
- A sore throat that is frequent or recurring
- Chills and night sweats
- Visual disturbances
- Sensitivity to light and sound
- Nausea
- Allergies or sensitivities to foods, odors, chemicals, or medications

ME/CFS may be a **neuroinflammatory** disease



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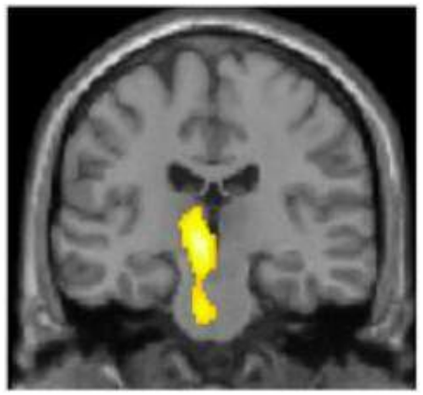

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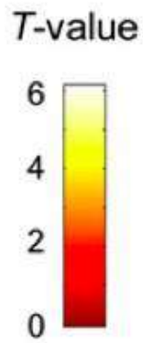

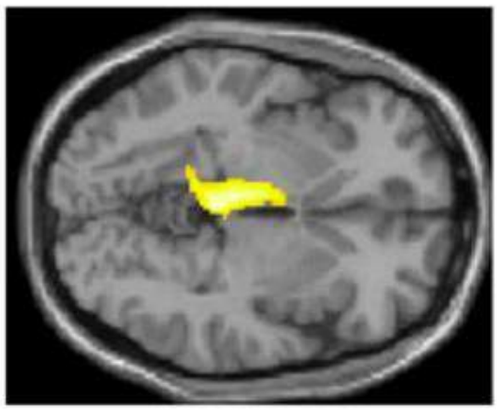

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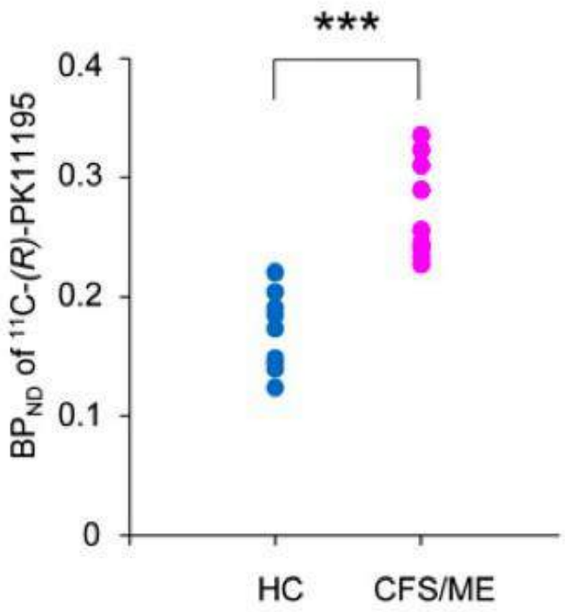


Nakatomi et al. (2014) found increased microglial activation in the brainstem of ME/CFS patients relative to controls.

ME/CFS may be a **neuroinflammatory** disease

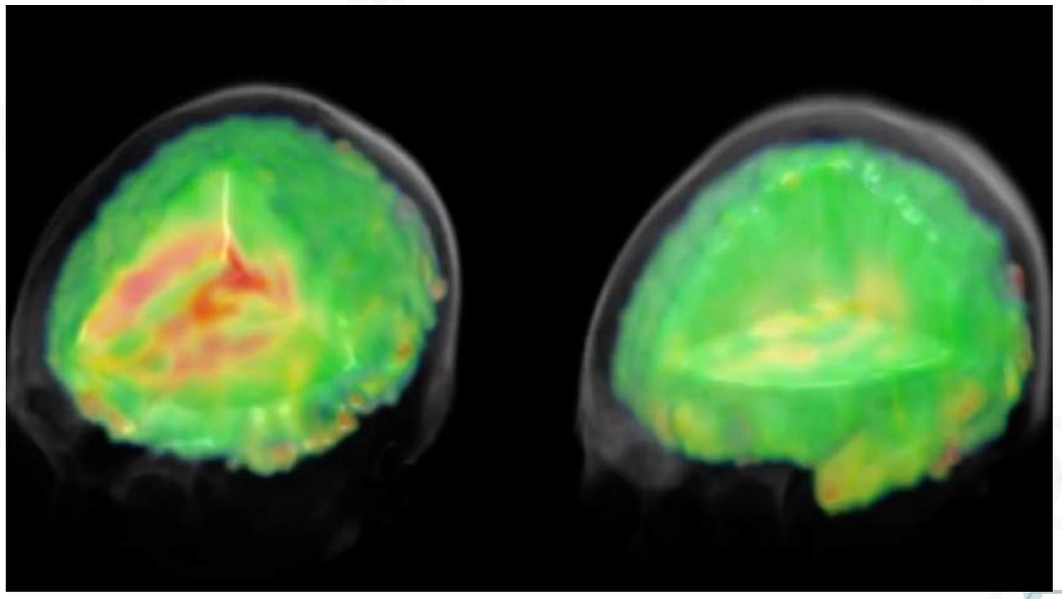
Brain Imaging and Behavior
https://doi.org/10.1007/s11682-018-0029-4

ORIGINAL RESEARCH

Evidence of widespread metabolite abnormalities in Myalgic encephalomyelitis/chronic fatigue syndrome: assessment with whole-brain magnetic resonance spectroscopy

Christina Mueller[1] · Joanne C. Lin[1] · Sulaiman Sheriff[2] · Andrew A. Maudsley[2] · Jarred W. Younger[1]

Choline and lactate are markers of rapid brain cell turnover and neuroinflammation. **Levels of choline/lactate were elevated in the ME/CFS brain** (left) but not in healthy brains (right).



There are also early signs of **heat buildup** (indicating neuroinflammation) in the ME/CFS brain. Five brain regions involved in regulating **fatigue and flu-like symptoms** were most impacted.

Our recent paper explains how persistent infection + microbiome + virome imbalance can contribute to ME/CFS

REVIEW ARTICLE
Front. Pediatr., 04 December 2018 | https://doi.org/10.3389/fped.2018.00373

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in the Era of the Human Microbiome: Persistent Pathogens Drive Chronic Symptoms by Interfering With Host Metabolism, Gene Expression, and Immunity

Amy Proal* and Trevor Marshall

Autoimmunity Research Foundation, Thousand Oaks, CA, United States

EDITED BY

Kenneth J. Friedman
Medical School, Rutgers, The State University of New Jersey, United States

REVIEWED BY

Anju Aggarwal
University College of Medical Sciences, India

Dinesh Upadhya
Manipal Academy of Higher Education, India

The editor and reviewers' affiliations are the latest provided on their Loop research profiles and may not reflect their situation at the time of review.

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The illness ME/CFS has been repeatedly tied to infectious agents such as Epstein Barr Virus. Expanding research on the human microbiome now allows ME/CFS-associated pathogens to be studied as interacting members of human microbiome communities. Humans harbor these vast ecosystems of bacteria, viruses and fungi in nearly all tissue and blood. Most well-studied inflammatory conditions are tied to dysbiosis or imbalance of the human microbiome. While gut microbiome dysbiosis has been identified in ME/CFS, microbes and viruses outside the gut can also contribute to the illness. Pathobionts, and their associated proteins/metabolites, often control human metabolism and gene expression in a manner that pushes the body toward a state of illness. Intracellular pathogens, including many associated with ME/CFS, drive microbiome dysbiosis by directly interfering with human transcription, translation, and DNA repair processes. Molecular mimicry between host and pathogen proteins/metabolites further complicates this interference. Other human pathogens disable mitochondria or dysregulate host nervous system signaling. Antibodies and/or clonal T cells identified in patients with ME/CFS are likely activated in response to these persistent microbiome pathogens. Different human pathogens have evolved similar survival mechanisms to disable the host immune response and host metabolic pathways. The metabolic dysfunction driven by these organisms can result in similar clusters of inflammatory symptoms. ME/CFS may be driven by this pathogen-induced dysfunction, with the nature of dysbiosis and symptom presentation varying based on a patient's unique infectious and environmental history. Under such conditions, patients would benefit from treatments that support the human immune system in an effort to reverse the infectious disease process.

Why study persistent infection in ME/CFS?

When you study ME/CFS through the lens of persistent infection the disease is not a “mystery”

Why study persistent infection in ME/CFS?

The Outbreaks

THE LANCET
LONDON : SATURDAY, MAY 26, 1956

A New Clinical Entity?

IN 1917 VON ECONOMO [1] reported a small outbreak of an illness in which the main features were fever, stupor, and ophthalmoplegia : 2 of his 13 patients died and at necropsy there was evidence of inflammation of the brain substance. During the next two years a great many similar outbreaks were recorded and by 1921 the disease had reached epidemic proportions in almost every country in Europe.[2] In spite of perplexing variations in the clinical picture from case to case, locality to locality, and even from season to season,[2] it soon became clear that for practical purposes a new clinical entity had appeared.[3] In 1924, 5039 cases of encephalitis lethargica were notified in England and Wales alone,[4] but by the beginning of the next decade confirmed cases of this dangerous disease had become sporadic and by 1939 they were extremely rare.[5] By the end of the late war, the centre of interest had shifted to poliomyelitis as by far the most prevalent and disabling infection

		Virus	*C.S.F.*
Group I	Laurent [10] (1947)	Unknown	Usually abnormal
	Kelleher et al.[12] (1949)	Poliomyelitis	
	Curnen et al.[11] (1949)	Coxsackie	
	Jennings et al.[13] (1949)	Poliomyelitis	
	Barrett et al.[9] (1952)	Poliomyelitis	
	Galpine and Macrae [14] (1953) and others	Coxsackie	
Group II	Adelaide [22] (1949)	Unknown	Normal in nearly all cases
	New York State [23] (1950)	Unknown	
	Middlesex Hospital [24] (1952)	Uncertain	
	Coventry [25] (1953)	Unknown	
	Berlin (1954) (Sumner)	Unknown	
	Durban [17] (1955)	Unknown	
	Royal Free Hospital [18] (1955)	Unknown	
	Hampstead (1955) (Ramsay and O'Sullivan)	Unknown	
Group III	Pennsylvania [20] (1945)	Unknown	Abnormal 2/5
	Akureyri, Iceland [19] (1948)	Unknown	Abnormal 8/8
	Cumberland [21] (1955)	Unknown	Unknown

Of the 8 outbreaks in group II, all except that at the Royal Free were initially confused with polio-

ME/CFS is repeatedly tied to signs and symptoms of **persistent infection**

- Most ME/CFS patients present with symptoms after suffering from **a severe bacterial or viral infection**

- These infections often correlate with **travel to a foreign country** or exposure to **pollutants or molds**, suggesting that such pathogens take advantage of factors that compromise the host immune system

- At different points in history, ME/CFS has been called **“Post-Polio Syndrome,” “Chronic Mononucleosis Syndrome”** and **“Post-Viral Syndrome”** due to the fact that chronic symptoms are often noted after acute infection with Polio Virus, Epstein Barr Virus, enteroviruses, influenza or a range of other pathogens

- Severe **flu-like symptoms** (sore throat, swollen lymph nodes etc)

- The **relapsing-remitting** nature of ME/CFS symptoms

- Cytokine activation/immune cell activation in ME/CFS clarifies that the disease is associated with an **inflammatory response**

Trend #1: There are growing number of “post”-infectious chronic conditions

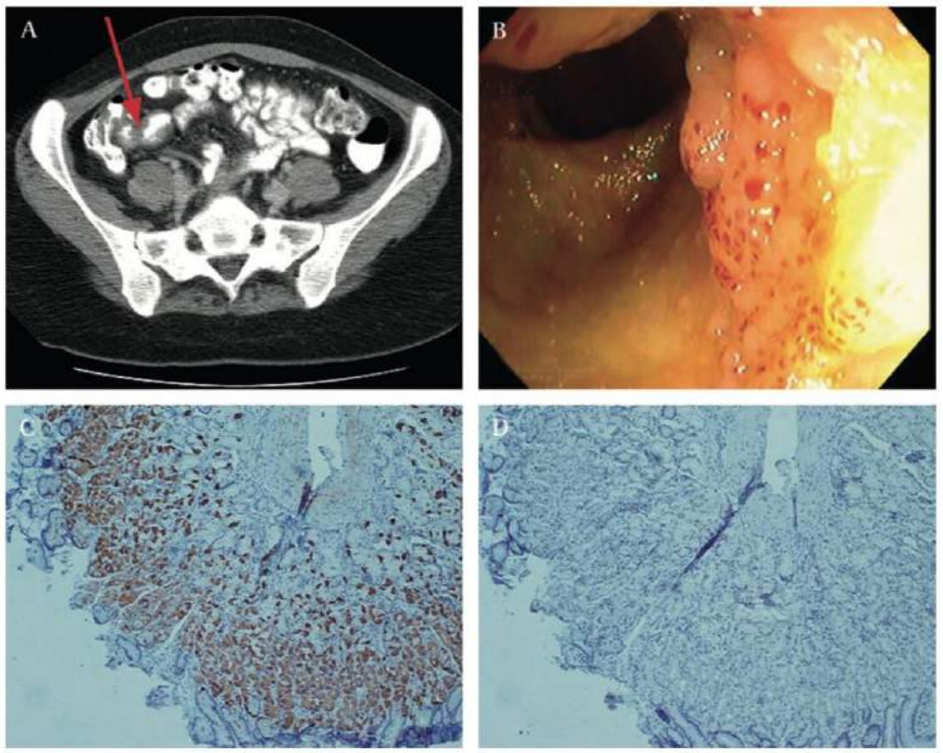
In most cases the infecting organism **can still be detected months + years after initial infection** in certain tissues

Post-Zika
Post-Measles
Post-Ebola
Post-Influenza
Post-Dengue
Post-Polio
Post Treatment Lyme disease (*Borrelia*)

Original article

Acute enterovirus infection followed by myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and viral persistence

J Chia,[1] A Chia,[1] M Voeller,[2] T Lee,[3] R Chang[4]



J Clin Pathol 2010;**63**:165–168. doi:10.1136/jcp.2009.070466

"After acute infections, enteroviruses **can persist in patients resulting in manifestation of ME/CFS.** Chronic enterovirus infection in an immunocompetent host may be an example of a stalemate **between attenuated, intracellular viruses** and an ineffective immune response"

Trend #2: A growing number of neuroinflammatory conditions are now increasingly tied to persistent infection in the blood + brain: Alzheimers, Parkinson's, ALS

Article

Neuron

Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus

Highlights

- Common viral species frequently detected in normal, aging brain
- Increased HHV-6A and HHV-7 in brains of subjects with Alzheimer's disease (AD)
- Findings were replicated in two additional, independent cohorts
- Multiscale networks reveal viral regulation of AD risk, and APP processing genes

Authors

Ben Readhead, Jean-Vianney Haure-Mirande, Cory C. Funk, ..., Michelle E. Ehrlich, Sam Gandy, Joel T. Dudley

Correspondence

joel.dudley@mssm.edu

In Brief

Readhead et al. construct multiscale networks of the late-onset Alzheimer's disease (AD)-associated virome and observe pathogenic regulation of molecular, clinical, and neuropathological networks by several common viruses, particularly human herpesvirus 6A and human herpesvirus 7.

SHARE

RESEARCH ARTICLE | HEALTH AND MEDICINE

Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors

Stephen S. Dominy[1,*,†], Casey Lynch[1,*], Florian Ermini[1], Malgorzata Benedyk[2,3], Agata Marczyk[2], Andrei Konradi[1], Mai Ngu...

+ See all authors and affiliations

Science Advances 23 Jan 2019:
Vol. 5, no. 1, eaau3333
DOI: 10.1126/sciadv.aau3333

ORIGINAL RESEARCH ARTICLE
Front. Neurosci., 26 February 2019 | https://doi.org/10.3389/fnins.2019.00171

Searching for Bacteria in Neural Tissue From Amyotrophic Lateral Sclerosis

Ruth Alonso†, Diana Pisa† and Luis Carrasco*

Centro de Biología Molecular "Severo Ochoa" (CSIC-UAM), Universidad Autónoma de Madrid, Madrid, Spain

Despite great efforts in the investigation, the exact etiology of amyotrophic lateral sclerosis (ALS) is a matter of intensive research. We recently advanced the idea that ALS might be caused by fungal infection. Indeed, fungal yeast and hyphal structures can be directly visualized in neural tissue of ALS patients, and a number of fungal species have been identified in the central nervous system (CNS). In the present work, we tested the possibility that bacterial infections can accompany these mycoses. Our findings establish the presence of bacterial DNA in different regions of the CNS from all ALS patients examined. Specifically, we used PCR and next generation sequencing (NGS) to precisely determine the bacterial species present in ALS tissue. Consistent with these findings, immunohistochemistry analysis of CNS sections using specific anti-bacterial antibodies identified prokaryotic cells in neural tissue. Finally, we assayed for the repeat expansion of the hexanucleotide repeat GGGGCC in C9orf72, which is considered the most common genetic cause of ALS in patients, using DNA extracted from ALS CNS tissue. We failed to find this repeated sequence in any of the eleven patients analyzed. Our results indicate that bacterial DNA and prokaryotic cells are present in CNS tissue, leading to the concept that both fungal and bacterial infections coexist in patients with ALS. These observations lay the groundwork for the use of appropriate therapies to eradicate the polymicrobial infections in ALS.

Virus-like particles and enterovirus antigen found in the brainstem neurons of Parkinson's disease

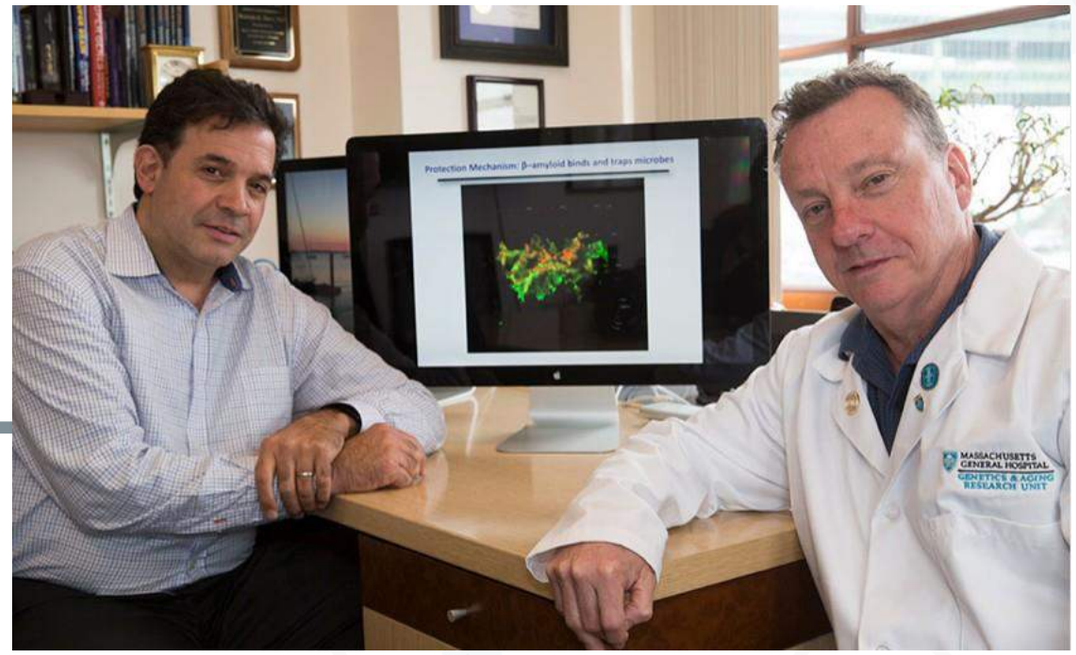
Robert R. Dourmashkin, Sherman A McCall, +4 authors Steven Patterson • Published in F1000Research 2018 •

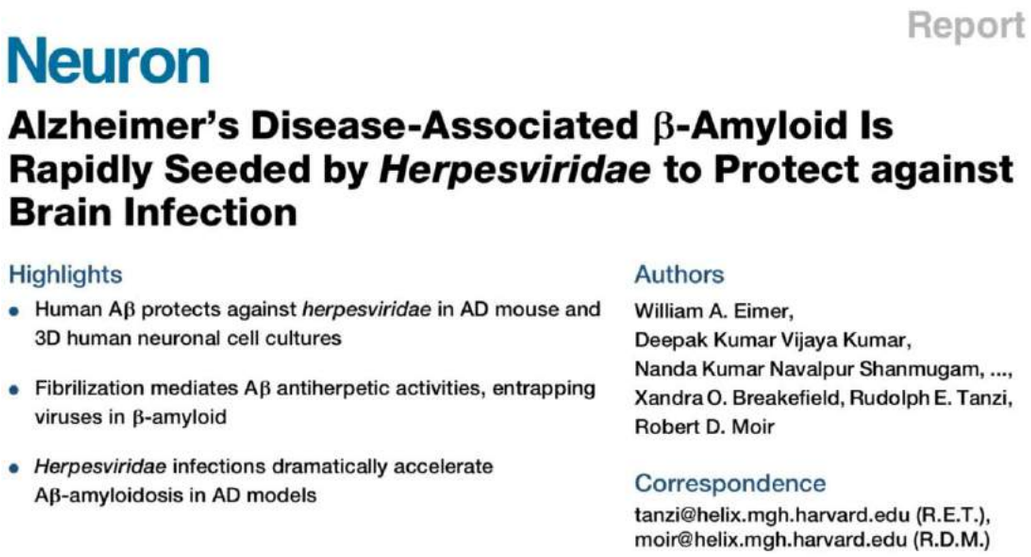
DOI: 10.12688/f1000research.13626.2

Background: In a previous study on encephalitis lethargica, we identified a virus related to enterovirus in autopsy brain material. Transmission electron microscopy (TEM), immunohistochemistry (IHC) and molecular analysis were employed. Our present objective was to investigate, using a similar approach, as to whether virus-like particles (VLP) and enterovirus antigen are present in Parkinson's disease (PD) brainstem neurons. Methods: Fixed tissue from autopsy specimens of late onset PD and... CONTINUE READING

Major breakthrough

Rudy Tanzi + Robert Moir at Harvard show that amyloid beta: Alzheimer's "plaque" may be **a potent antimicrobial peptide** (an important part of the human immune response towards infectious agents in brain and other tissues)





Report

Neuron

Alzheimer's Disease-Associated β-Amyloid Is Rapidly Seeded by *Herpesviridae* to Protect against Brain Infection

Highlights

- Human Aβ protects against *herpesviridae* in AD mouse and 3D human neuronal cell cultures
- Fibrilization mediates Aβ antiherpetic activities, entrapping viruses in β-amyloid
- *Herpesviridae* infections dramatically accelerate Aβ-amyloidosis in AD models

Authors

William A. Eimer, Deepak Kumar Vijaya Kumar, Nanda Kumar Navalpur Shanmugam, ..., Xandra O. Breakefield, Rudolph E. Tanzi, Robert D. Moir

Correspondence

tanzi@helix.mgh.harvard.edu (R.E.T.), moir@helix.mgh.harvard.edu (R.D.M.)

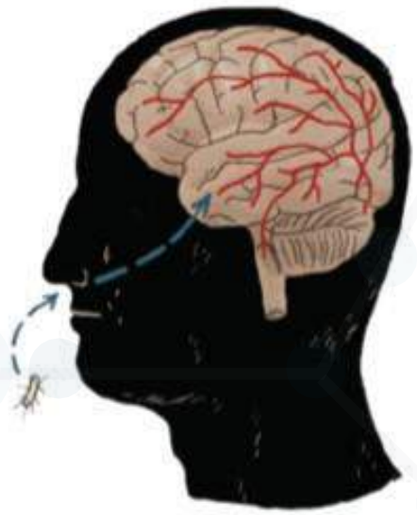
Amyloid beta also **exhibited antimicrobial activity** against a range of common microorganisms with a potency equivalent to, and in some cases greater than, cathelicidin (LL-37). These pathogens **included *Salmonella. typhimurium*, *Candida albicans***

Amyloid traps and neutralizes pathogens in brain tissue

1

Pathogens Enter the Brain

Microbes—bacteria, viruses or fungi—enter the brain. They gain access either through a breach in the blood vessels that supply blood to the brain, or through nerves that lead to the brain, such as those in the nose.



2

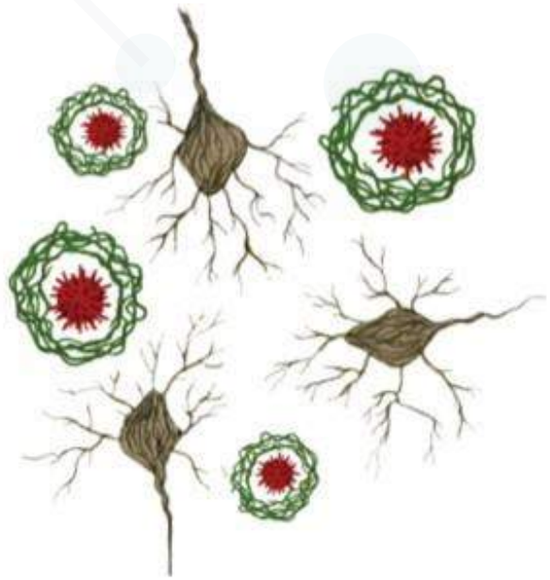
Microbe Encapsulation

Amyloid-beta peptides, short chains of amino acids, attach to the surface of these microbes and entrap them. This leads to the formation of amyloid-beta plaques, which render the microbes ineffective.

3

Plaque Development

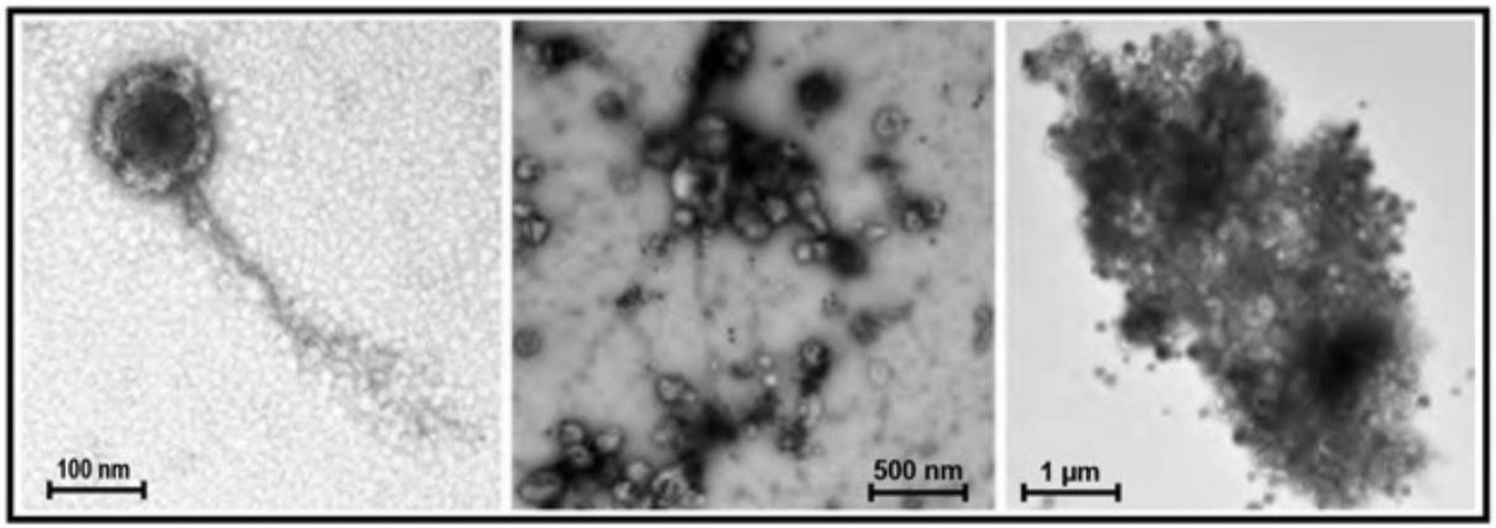
The accumulation of amyloid-beta plaques triggers the formation of tau protein tangles and causes brain inflammation—the pathological processes associated with Alzheimer's disease.



***R Tanzi, R. Moir, Harvard University: amyloid beta plaques form to "fight off" microbes in the brain**

Takeaway

The presence of amyloid in a sample could indicate the presence of specific pathogens



Snare that Virus. *Aβ42 rapidly cocoons viral particles, forming fibrils after 15 minutes (left), nets after 30 (middle), and impenetrable clumps after two hours (right). [Courtesy of Neuron, Eimer et al.]*

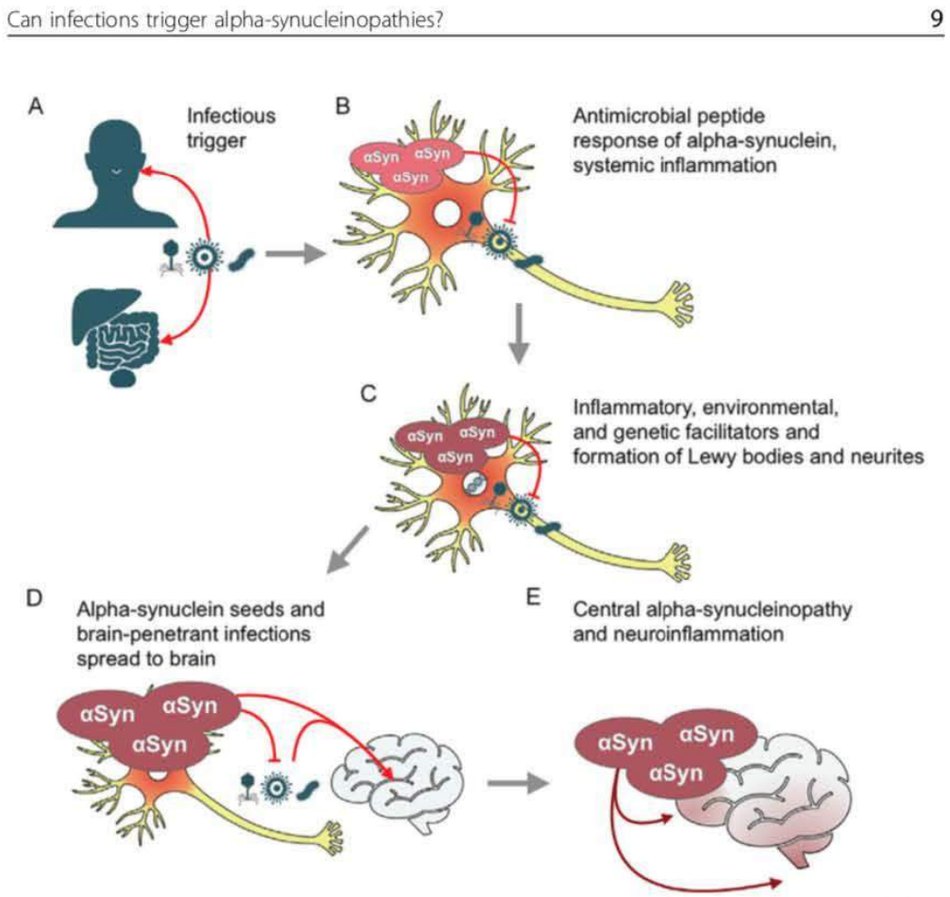
This image shows amyloid beta "entrapping" a herpesvirus

Parkinson's:

Can infections trigger alpha-synucleinopathies?

Christopher T. Tulisiak[a], Gabriela Mercado[a], Wouter Peelaerts[a,b], Lena Brundin[a], Patrik Brundin[a,*]

[a]Center for Neurodegenerative Sciences, Van Andel Research Institute, Grand Rapids, MI, United States
[b]Laboratory for Neurobiology and Gene Therapy, KU Leuven, Leuven, Belgium



Cognitive impairment in ME/CFS can be **extremely debilitating**

"I went from being a company executive to barely reading over the 4th grade level." --Alayne, age 45

"...and all of a sudden I couldn't understand how to find anything. I couldn't write an email, because I couldn't construct a sentence." --Natalie, age 21

"Sometimes when people are talking, it is as if some of the words are in a foreign language. I hear the words. But they don't make sense." --Claire, age 52

One research team has identified amyloid deposits (“plaques”) in the ME/CFS brain

Original research

CNS findings in chronic fatigue syndrome and a neuropathological case report

Kimberly Ferrero,[1] Mitchell Silver,[1] Alan Cocchetto,[2] Eliezer Masliah,[3] Dianne Langford[1]

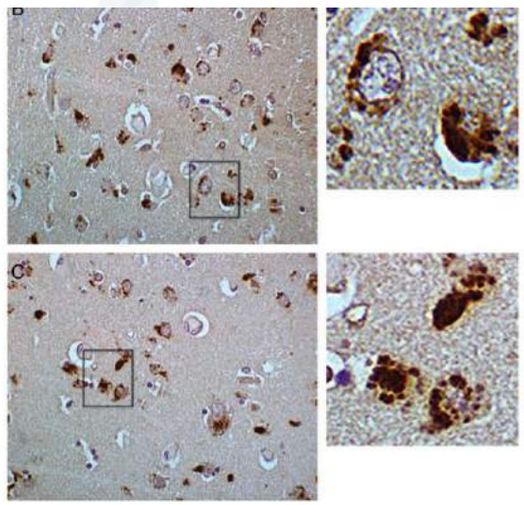


Figure 7 Immunohistochemical labeling of Aβ in frontal cortex white matter of CFS case. (A, B) Immunocytochemical analysis of Aβ deposition using the 4G8 antibody in paraffin sections treated with 80% formic acid. Sections are immunolabeled with antibodies and reacted with 3, 3′-DAB and counterstained with hematoxylin. Images are ×100 magnification. CFS, chronic fatigue syndrome; DAB, diaminobenzidine

What are the new findings?

- Neuropathological autopsy findings from a patient who died with a prior diagnosis of CFS report focal areas of white matter loss, neurite beading, and neuritic pathology of axons in the white matter with axonal spheroids.
- Atypical neurons displaying aberrant sprouting processes in response to injury are observed throughout cortical gray and white matter. Abundant amyloid deposits identical to AD plaques with accompanying intracellular granular structures are observed as well.
- Neurofibrillary tangles are also present in the white matter of the frontal cortex, thalamus and basal ganglia.

A Georgetown University team has already identified amyloid proteins in ME/CFS cerebrospinal fluid

BMC Neurology

BioMed Central

Research article

Open Access

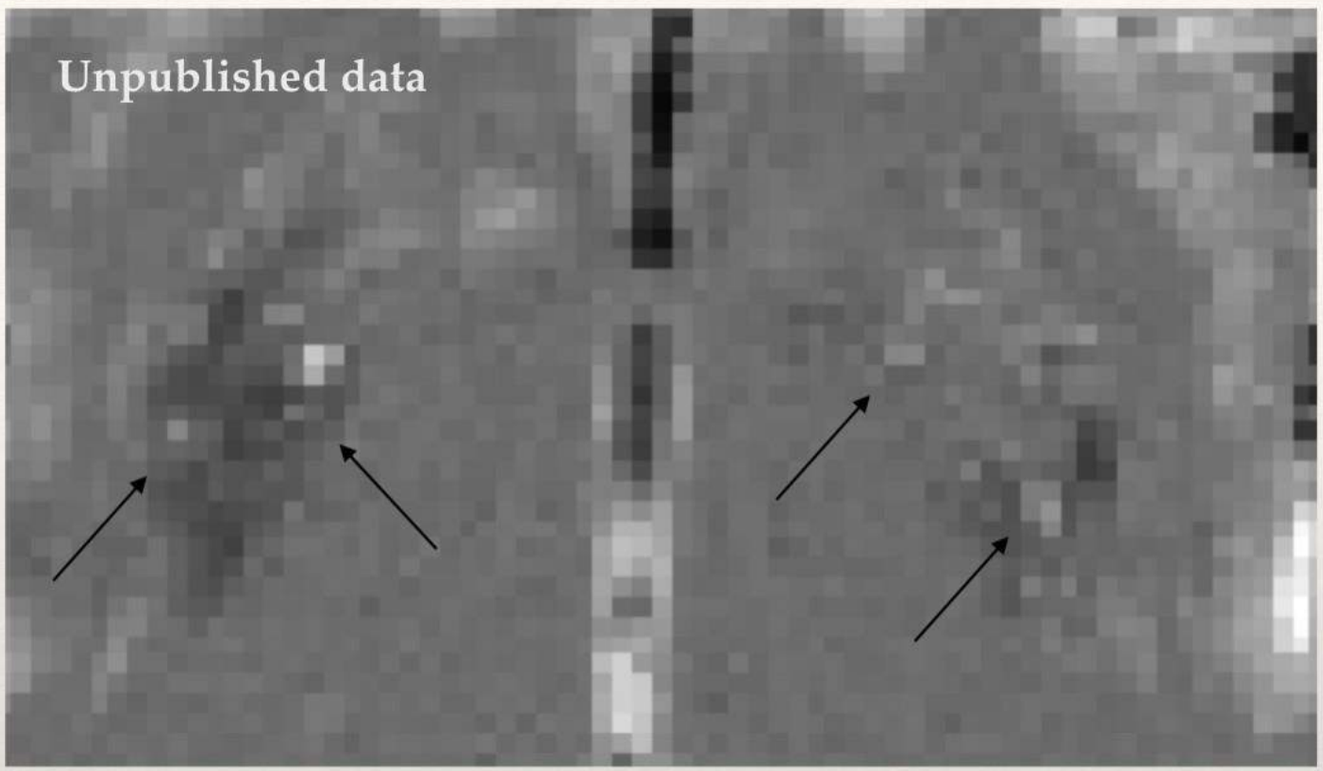
A chronic fatigue syndrome – related proteome in human cerebrospinal fluid

James N Baraniuk*[1], Begona Casado[1,2], Hilda Maibach[1], Daniel J Clauw[3], Lewis K Pannell[4,5] and Sonja Hess S[5]

Address: [1]Georgetown University Proteomics Laboratory, Division of Rheumatology, Immunology & Allergy, Room B-105, Lower Level Kober-Cogan Building, Georgetown University, 3800 Reservoir Road, N.W., Washington DC 20007-2197, USA, [2]Dipartimento di Biochimica A. Castellani, Universita di Pavia, Italy, [3]Center for the Advancement of Clinical Research, The University of Michigan, Ann Arbor, MI, USA, [4]Proteomics and Mass Spectrometry Facility, Cancer Research Institute, University of South Alabama, Mobile, AL, USA and [5]Proteomics and Mass Spectrometry Facility, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892-0508, USA

Conclusion: This pilot study detected an identical set of central nervous system, innate immune and amyloidogenic proteins in cerebrospinal fluids from two independent cohorts of subjects with overlapping CFS, PGI and fibromyalgia. Although syndrome names and definitions were different, the proteome and presumed pathological mechanism(s) may be shared.

Virchow-Robin perivascular spaces: common in Alzheimer's and ME/CFS (early data)



Perivascular spaces (Virchow-Robin)

1. Basal ganglia
2. Parietal cortex
3. Red nucleus of midbrain

***unpublished data from VanElzakker et al.**

Perivascular spaces + activated immune cells in the autism brain

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
AMERICAN NEUROLOGICAL ASSOCIATION
INNOVATORS IN DISCOVERY, EDUCATION, AND CARE

Research Article

T lymphocytes and cytotoxic astrocyte blebs correlate across autism brains

Marcello M. DiStasio MD, PhD, Ikue Nagakura PhD, Monica J. Nadler PhD, Matthew P. Anderson MD, PhD

"Either the T-cells are **reacting normally to a pathogen such as a virus**, or they are reacting abnormally to normal tissue – the definition of an autoimmune disorder."

- Matthew P. Anderson, MD, PhD (Beth Israel Deaconess Medical Center)

Trend #3: The human microbiome

There are vast microbial + viral ecosystems in the human body

These communities extend far beyond the gut and **into nearly all tissue and blood**

Microbiome body sites:

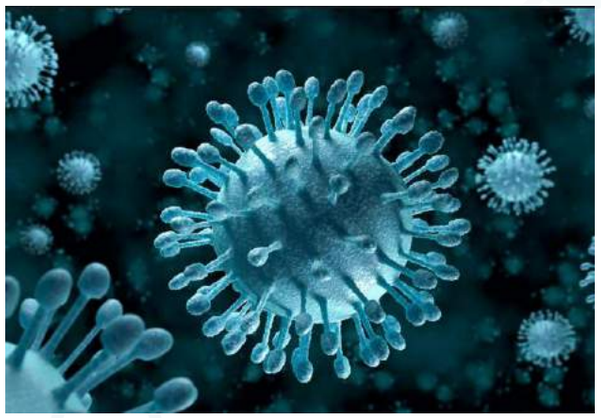
Skin
Oral (mouth)
Gut
Lung
Nasal (nose)
Ocular (eye)
Bladder
Vaginal/Penile
Pancreas
Liver
Circulatory (blood)
Atherosclerotic plaque
Brain (central nervous system)

The human microbiome harbors many different kinds of interacting organisms

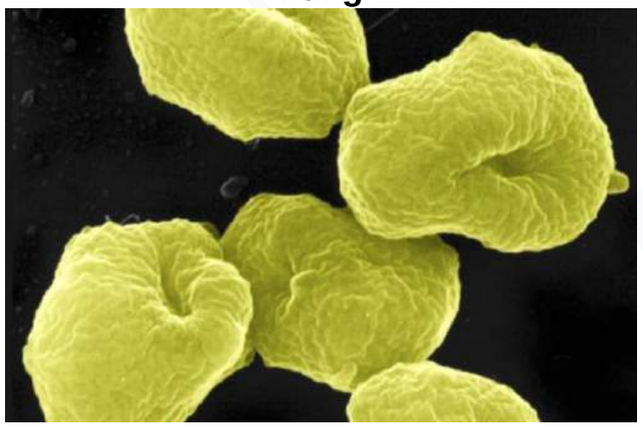
Bacteria

Fungi

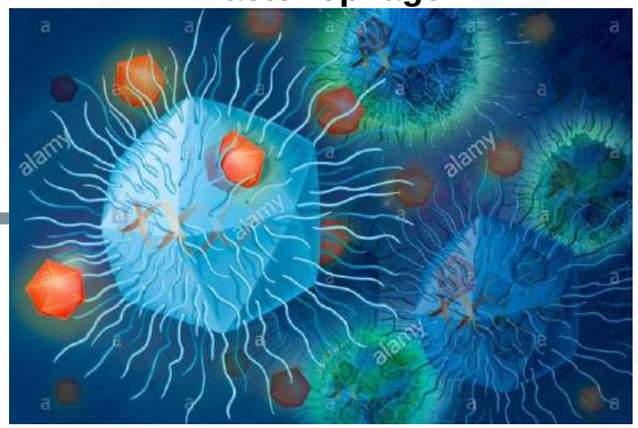
Bacteriophage



Viruses (DNA and RNA)



Archea



Virophage

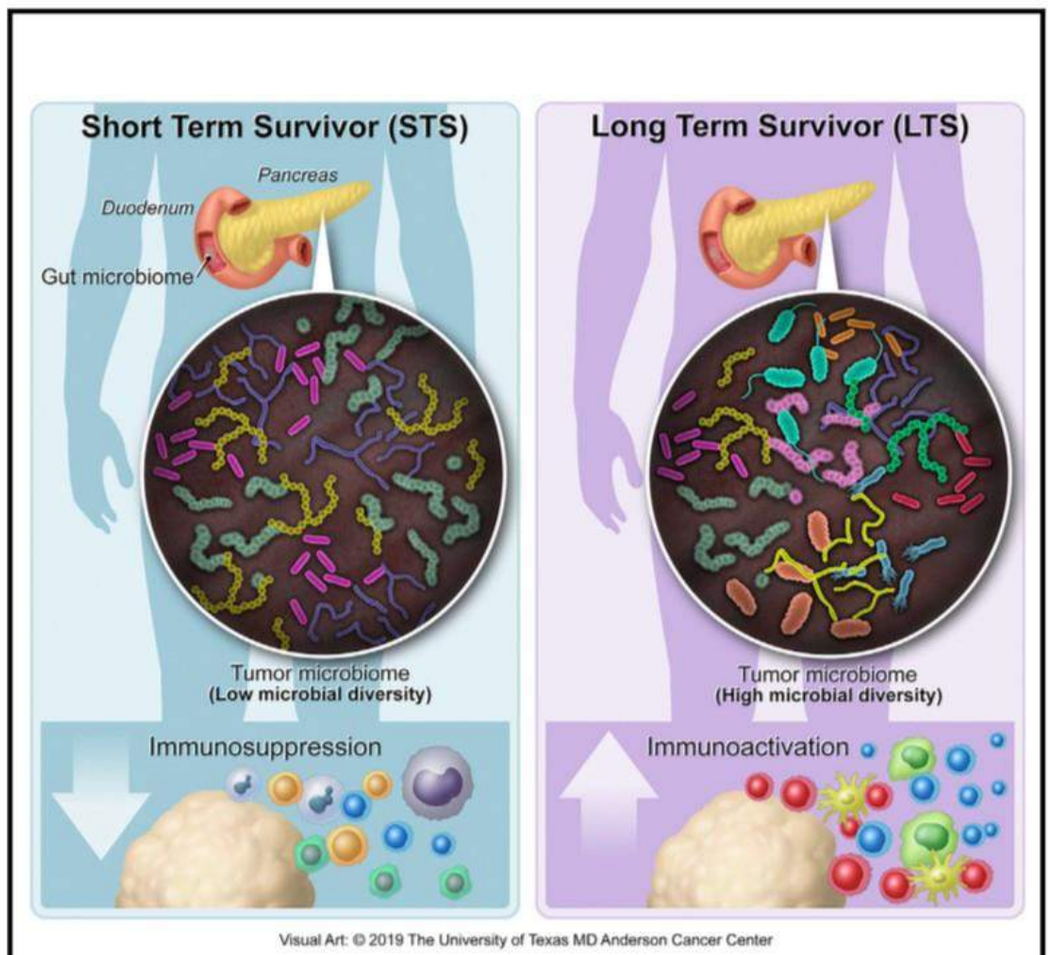
Microbiome communities are not always “good” and can also drive disease

Article

Cell

Tumor Microbiome Diversity and Composition Influence Pancreatic Cancer Outcomes

Graphical Abstract



Authors

Erick Riquelme, Yu Zhang, Liangliang Zhang, ..., Robert Jenq, Jennifer Wargo, Florencia McAllister

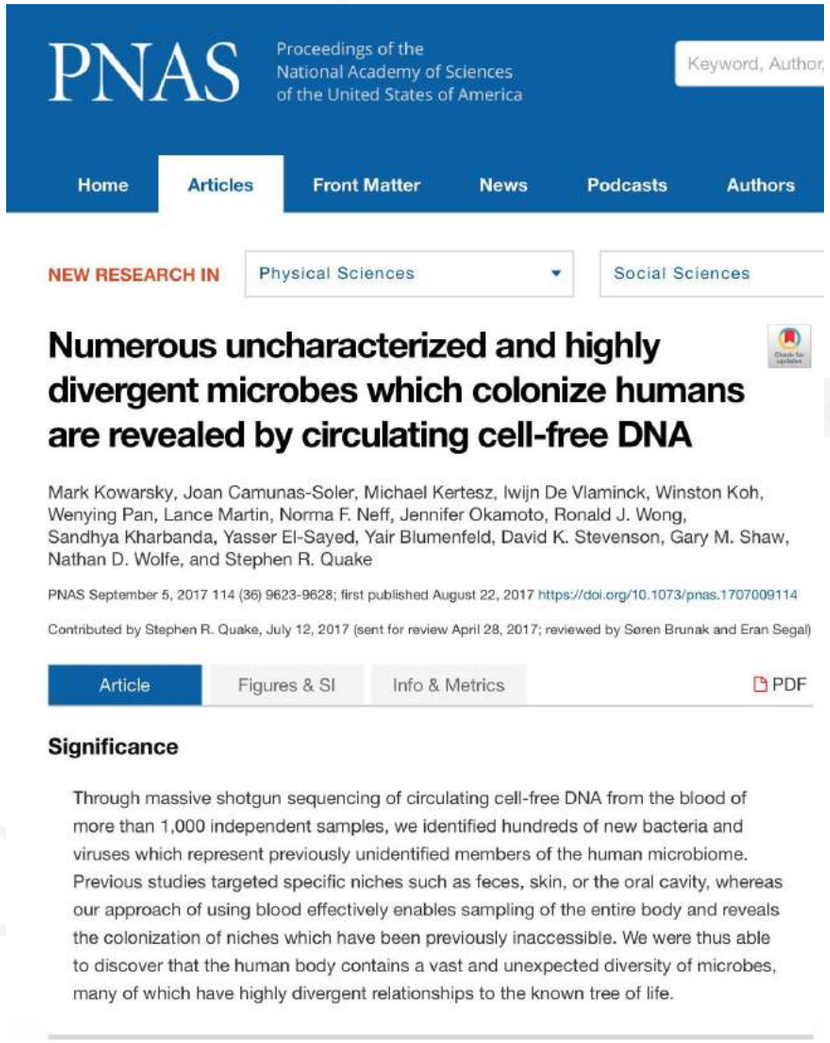
Correspondence

fmcallister@mdanderson.org

In Brief

The distinct tumor microbiome from pancreatic cancer long-term survivors can be used to predict PDAC survival in humans, and transfer of long-term survivor gut microbiomes can alter the tumor microbiome and tumor growth in mouse models.

Vastly more organisms persist in blood than previously believed



PNAS

Proceedings of the National Academy of Sciences of the United States of America

Keyword, Author,

Home | Articles | Front Matter | News | Podcasts | Authors

NEW RESEARCH IN Physical Sciences Social Sciences

Numerous uncharacterized and highly divergent microbes which colonize humans are revealed by circulating cell-free DNA

Mark Kowarsky, Joan Camunas-Soler, Michael Kertesz, Iwijn De Vlaminck, Winston Koh, Wenying Pan, Lance Martin, Norma F. Neff, Jennifer Okamoto, Ronald J. Wong, Sandhya Kharbanda, Yasser El-Sayed, Yair Blumenfeld, David K. Stevenson, Gary M. Shaw, Nathan D. Wolfe, and Stephen R. Quake

PNAS September 5, 2017 114 (36) 9623-9628; first published August 22, 2017 https://doi.org/10.1073/pnas.1707009114

Contributed by Stephen R. Quake, July 12, 2017 (sent for review April 28, 2017; reviewed by Søren Brunak and Eran Segal)

Article | Figures & SI | Info & Metrics | PDF

Significance

Through massive shotgun sequencing of circulating cell-free DNA from the blood of more than 1,000 independent samples, we identified hundreds of new bacteria and viruses which represent previously unidentified members of the human microbiome. Previous studies targeted specific niches such as feces, skin, or the oral cavity, whereas our approach of using blood effectively enables sampling of the entire body and reveals the colonization of niches which have been previously inaccessible. We were thus able to discover that the human body contains a vast and unexpected diversity of microbes, many of which have highly divergent relationships to the known tree of life.

AUGUST 22, 2017

Stanford study indicates that more than 99 percent of the microbes inside us are unknown to science

A survey of DNA fragments circulating in the blood suggests the microbes living within us are vastly more diverse than previously known. In fact, 99 percent of that DNA has never been seen before.

BY NATHAN COLLINS

A new survey of DNA fragments circulating in human blood suggests our bodies contain vastly more diverse microbes than anyone previously understood. What's more, the overwhelming majority of those microbes have never been seen before, let alone classified and named, Stanford researchers report August 22 in the *Proceedings of the National Academy of Sciences.*

"We found the gamut," said Stephen Quake, a professor of bioengineering and applied physics, a member of Stanford Bio-X and the paper's senior author. "We found things that are related to things people have seen before, we found things that are divergent, and we found things that are completely novel."

Stanford Professor Stephen Quake and his lab report a vast array of previously unidentified microbes living inside human beings. *(Image credit: L.A. Cicero)*

Searching for rejection

The survey was inspired by a curious observation Quake's lab made while searching for non-invasive ways to predict whether an organ transplant patient's immune system would recognize the new organ as foreign and attack it, an event known as rejection. Ordinarily, it takes a tissue biopsy – meaning a large needle jabbed into one's side and at least an afternoon in a hospital bed for observation – to detect rejection.

The lab members figured there was a better way. In theory, they might be able to detect rejection by taking blood samples and looking at the cell-free DNA – bits and pieces of DNA circulating freely in blood plasma – contained therein. Apart from fragments of a patient's DNA, those samples would contain fragments of the organ donor's DNA as well as a comprehensive view of the collection of bacteria, viruses and other microbes

“…these novel microbes have potential consequences for human health. They may prove to be the cause of acute or chronic diseases that, to date, have unknown etiology…”

-Stephen Quake, Stanford University

“Seek and ye shall find”

ENU

Translational Psychiatry

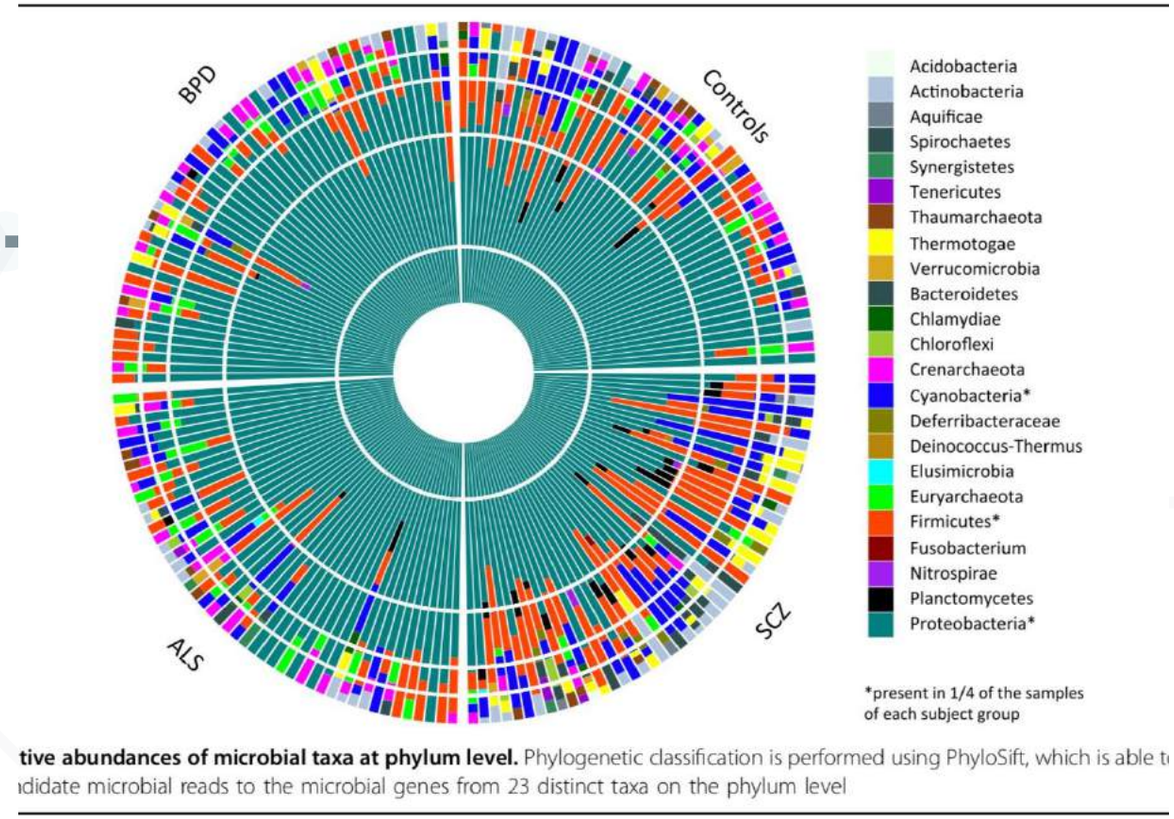
Article | Open Access | Published: 10 May 2018

Transcriptome analysis in whole blood reveals increased microbial diversity in schizophrenia

Loes M. Olde Loohuis, Serghei Mangul, Anil P. S. Ori, Guillaume Jospin, David Koslicki, Harry Taegyun Yang, Timothy Wu, Marco P. Boks, Catherine Lomen-Hoerth, Martina Wiedau-Pazos, Rita M. Cantor, Willem M. de Vos, René S. Kahn, Eleazar Eskin & Roel A. Ophoff

Translational Psychiatry **8**, Article number: 96 (2018) | Download Citation

2865 Accesses | **13** Citations | **161** Altmetric | Metrics »



tive abundances of microbial taxa at phylum level. Phylogenetic classification is performed using PhyloSift, which is able t
ıdidate microbial reads to the microbial genes from 23 distinct taxa on the phylum level

Extensive phyla (families) of bacteria persist in healthy human blood

The composition of these blood microbiome communities changed in patients **with ALS, bipolar disorder and schizophrenia**

PLOS | ONE A Peer-Reviewed, Open Access Journal

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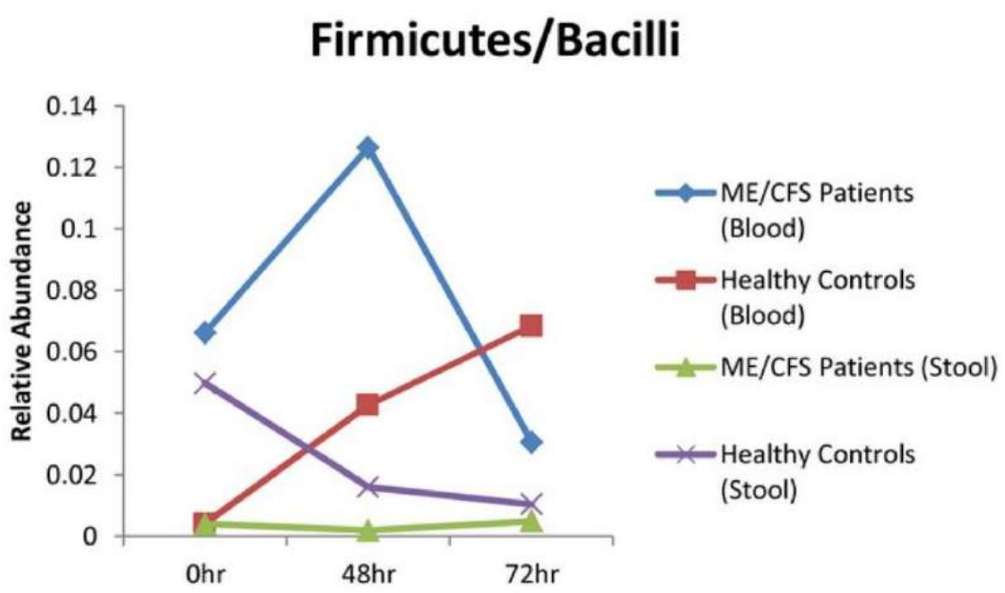
PLoS One. 2015; 10(12): e0145453.
Published online 2015 Dec 18. doi: 10.1371/journal.pone.0145453

PMCID: PMC4684203
PMID: 26683192

Changes in Gut and Plasma Microbiome following Exercise Challenge in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Sanjay K. Shukla, [1,*] Dane Cook, [2,3] Jacob Meyer, [2] Suzanne D. Vernon, [4] Thao Le, [1] Derek Clevidence, [3,¤a] Charles E. Robertson, [5] Steven J. Schrodi, [1] Steven Yale, [6,¤b] and Daniel N. Frank [5]

Microbiome Response to Maximal Exercise



Figure

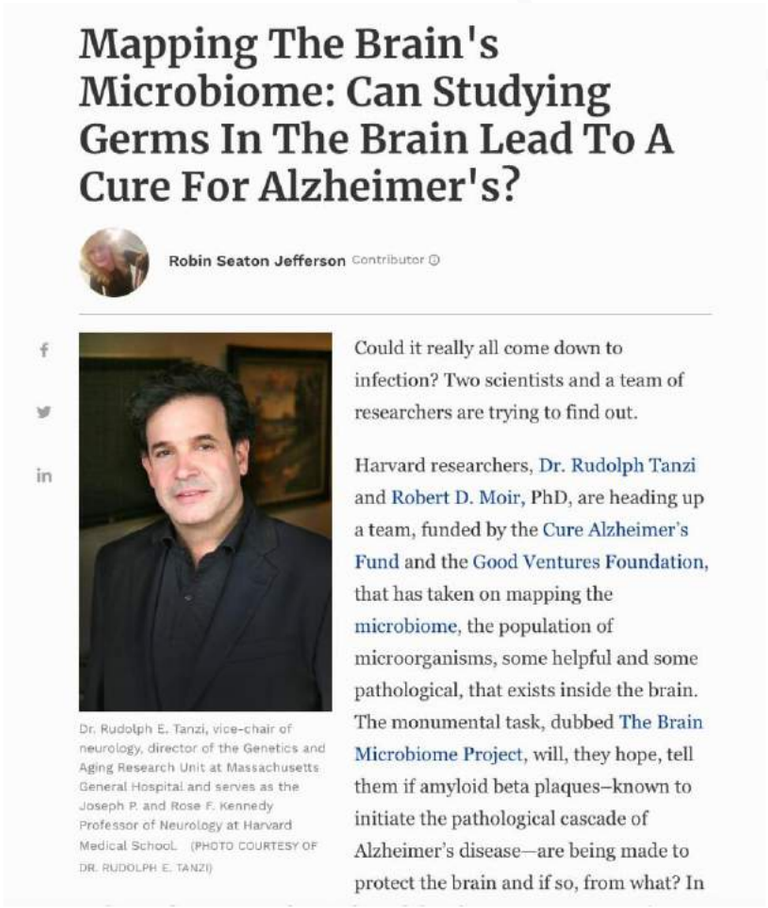
Caption

Fig 2. Changes in the relative abundance of Firmicutes/Bacilli in blood and stool samples before (0 hr) and after maximal exercise.

"Following maximal exercise challenge, there was an **increase in relative abundance of 6 of the 9 major bacterial phyla/genera in ME/CFS patients** from baseline to 72 hours post-exercise compared to only 2 of the 9 phyla/genera in controls."

Major paradigm shift:

The Harvard University Brain Microbiome Project



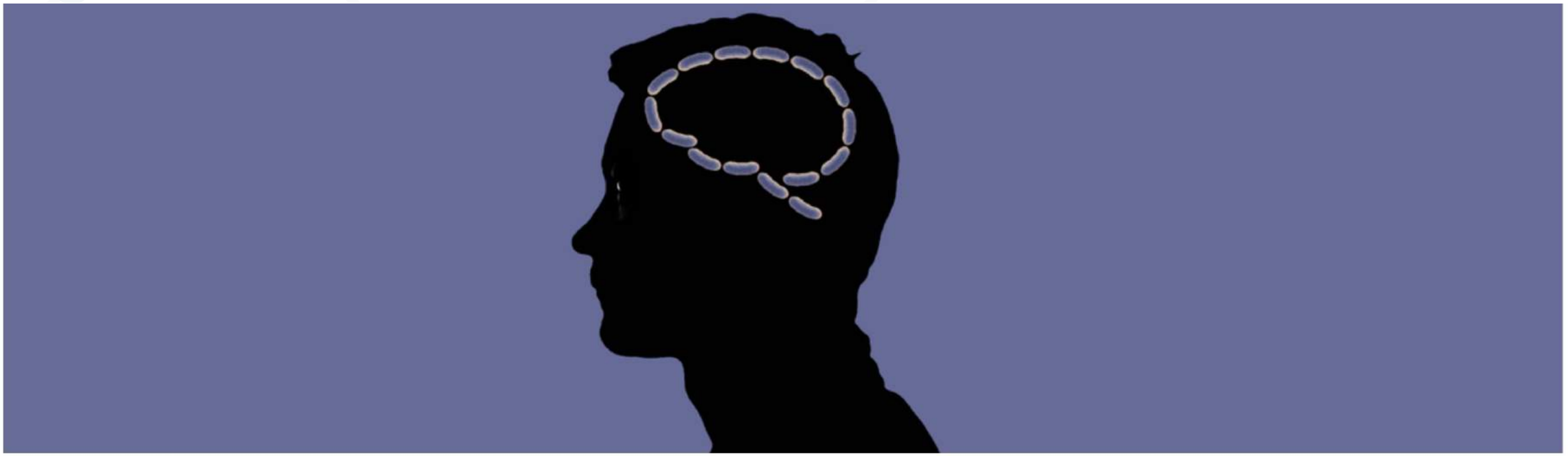
Mapping The Brain's Microbiome: Can Studying Germs In The Brain Lead To A Cure For Alzheimer's?

Robin Seaton Jefferson Contributor

Dr. Rudolph E. Tanzi, vice-chair of neurology, director of the Genetics and Aging Research Unit at Massachusetts General Hospital and serves as the Joseph P. and Rose F. Kennedy Professor of Neurology at Harvard Medical School. (PHOTO COURTESY OF DR. RUDOLPH E. TANZI)

Could it really all come down to infection? Two scientists and a team of researchers are trying to find out.

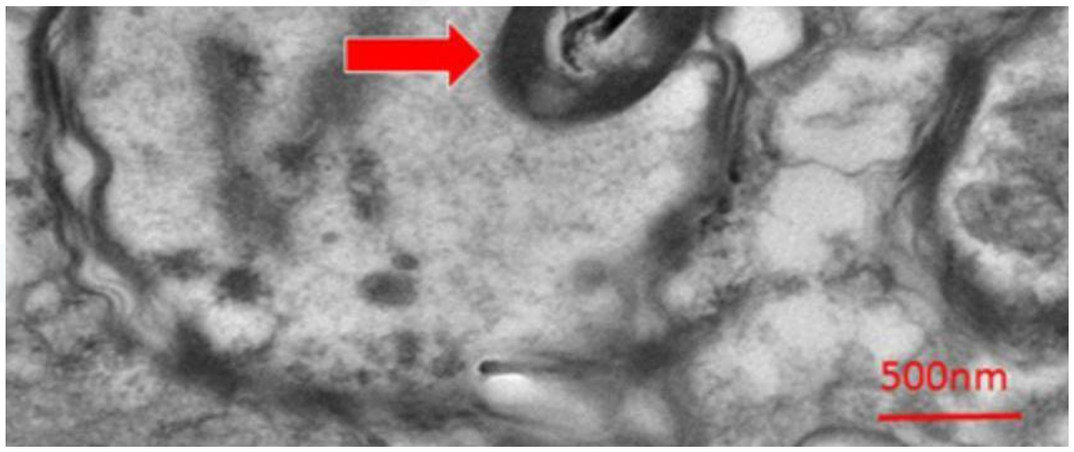
Harvard researchers, Dr. Rudolph Tanzi and Robert D. Moir, PhD, are heading up a team, funded by the Cure Alzheimer's Fund and the Good Ventures Foundation, that has taken on mapping the microbiome, the population of microorganisms, some helpful and some pathological, that exists inside the brain. The monumental task, dubbed The Brain Microbiome Project, will, they hope, tell them if amyloid beta plaques–known to initiate the pathological cascade of Alzheimer's disease—are being made to protect the brain and if so, from what? In



BIOLOGY | NEUROSCIENCE

Are There Bacteria in Your Brain?

A surprising new result catches the attention of the neuroscience community.



"We saw that bacteria like to be inside astrocyte cells around the blood-brain barrier. They also like to be in axons, which are projections between brain regions that conduct information."

-Rosalinda Roberts, University of Alabama Birmingham

The human virome:

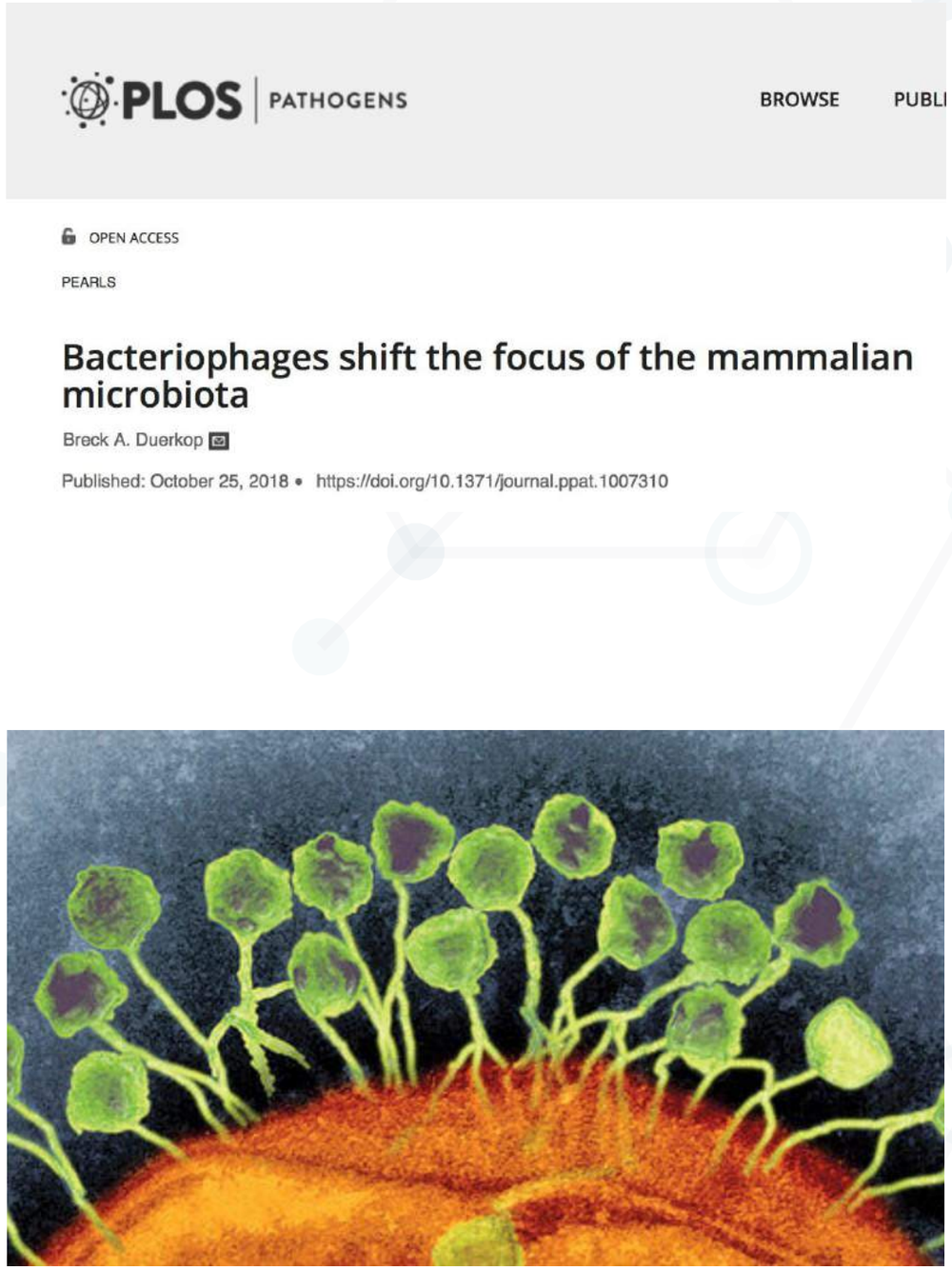
Vast communities of viruses in the human body

Viruses are the **most abundant life form on the planet** and in the human body

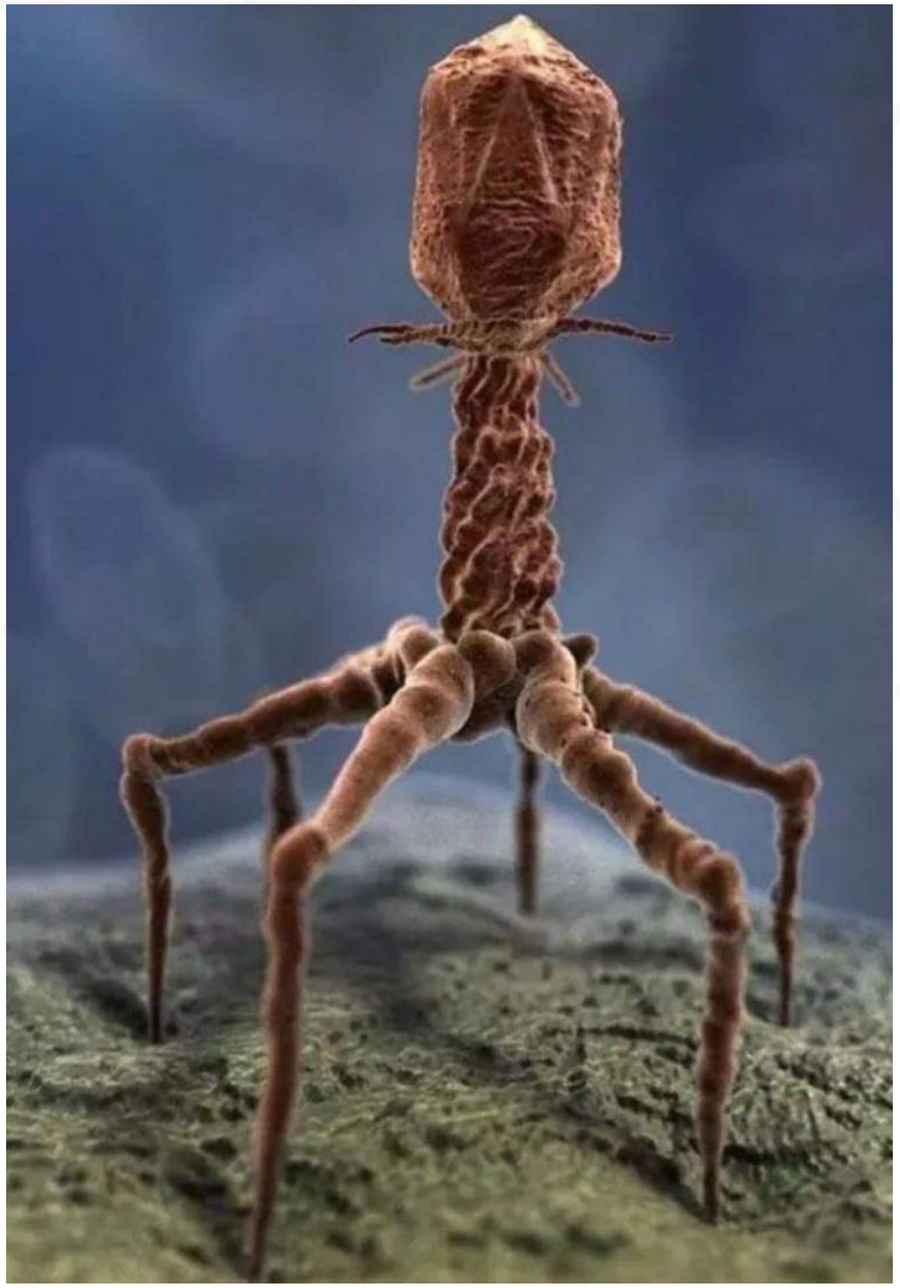
Bacteriophages (phages) are viruses that infect bacteria and modulate their activity

Trillions of phages persists in human tissue and blood

We have identified and characterized **~.001%** of these viruses in the human body.

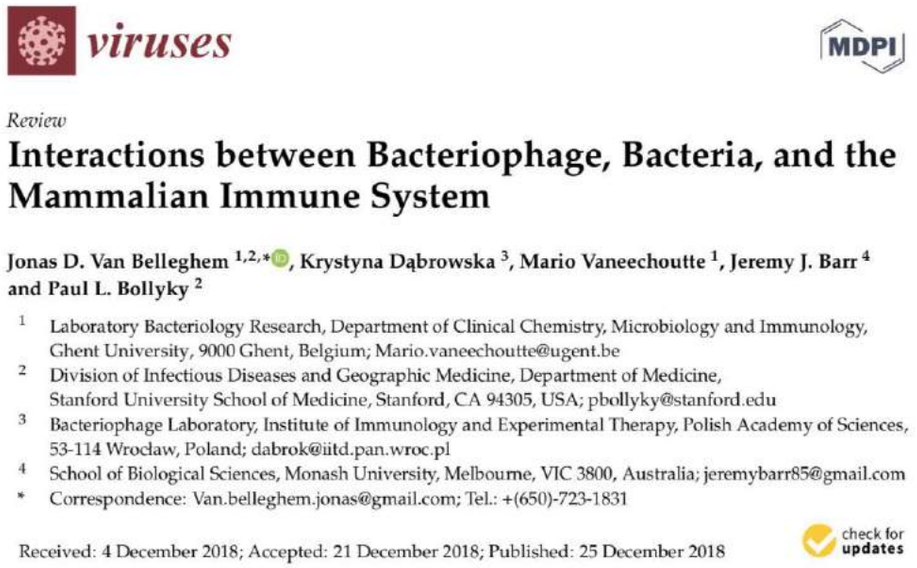


An *e.coli* bacteriophage (computer generated image)



Stanford University Research:

Phages interact with the human immune system



viruses

MDPI

Review

Interactions between Bacteriophage, Bacteria, and the Mammalian Immune System

Jonas D. Van Belleghem [1,2,*], Krystyna Dąbrowska [3], Mario Vaneechoutte [1], Jeremy J. Barr [4] and Paul L. Bollyky [2]

1 Laboratory Bacteriology Research, Department of Clinical Chemistry, Microbiology and Immunology, Ghent University, 9000 Ghent, Belgium; Mario.vaneechoutte@ugent.be
2 Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA; pbollyky@stanford.edu
3 Bacteriophage Laboratory, Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, 53-114 Wrocław, Poland; dabrok@iitd.pan.wroc.pl
4 School of Biological Sciences, Monash University, Melbourne, VIC 3800, Australia; jeremybarr85@gmail.com
* Correspondence: Van.belleghem.jonas@gmail.com; Tel.: +(650)-723-1831

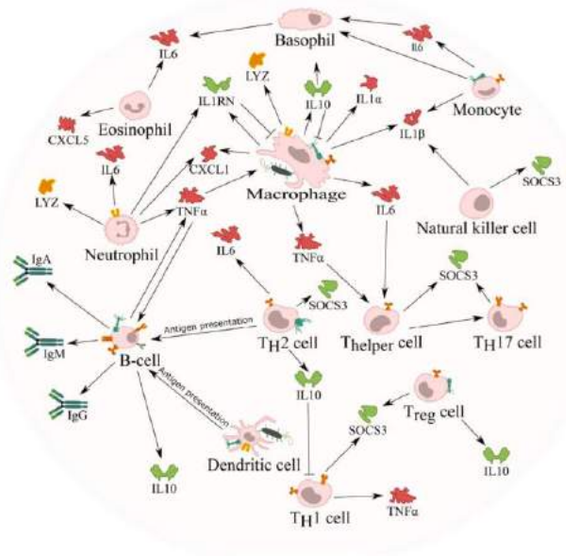
Received: 4 December 2018; Accepted: 21 December 2018; Published: 25 December 2018

Phages **directly interact** with human cells + impact/modulate the human immune response

Provides examples of how phages can modulate innate immunity via phagocytosis and cytokine responses

Phages can impact adaptive immunity via effects on antibody production

Computational modeling predicts that **phages may play important roles** in shaping mammalian-bacterial interactions



Interaction of bacteriophages with human immune cells

“We’ve long known that you’ve got up to 10 quadrillion phages in your body, but we just figured whatever they were doing was strictly between them and your commensal bacteria. Now we know that phages can get inside your cells too, and make you sick”

- Paul Bollyky (Stanford University)

Nikos Kyrpides + David Paez-Espino at Berkeley's Joint Genome Institute have transformed our ability to identify a broad range of known + novel environmental + human viruses thanks to their **"Uncovering the Earth's Virome Project"**

The first paper published on the Project in 2016 increased the number of known viruses on Earth **by 16-fold**

MENU nature

Article | Published: 17 August 2016

Uncovering Earth's virome

David Paez-Espino, Emiley A. Eloe-Fadrosh, Georgios A. Pavlopoulos, Alex D. Thomas, Marcel Huntemann, Natalia Mikhailova, Edward Rubin, Natalia N. Ivanova & Nikos C. Kyrpides

Nature **536**, 425–430 (25 August 2016) | Download Citation

Abstract

Viruses are the most abundant biological entities on Earth, but challenges in detecting, isolating, and classifying unknown viruses have prevented exhaustive surveys of the global virome. Here we analysed over 5 Tb of metagenomic sequence data from 3,042 geographically diverse samples to assess the global distribution, phylogenetic diversity, and host specificity of viruses. We discovered over 125,000 partial DNA viral genomes, including the largest phage yet identified, and increased the number of known viral genes by 16-fold. Half of the predicted partial viral genomes were clustered into genetically distinct groups, most of which included genes unrelated to those in known viruses. Using CRISPR spacers and transfer RNA matches to link viral groups to microbial host(s), we doubled the number of microbial phyla known to be infected by viruses, and identified viruses that can infect organisms from different phyla. Analysis of viral distribution across diverse ecosystems revealed strong habitat-type specificity for the vast majority of viruses, but also identified some cosmopolitan groups. Our results highlight an extensive global viral diversity and provide detailed insight into viral habitat distribution and host–virus interactions.

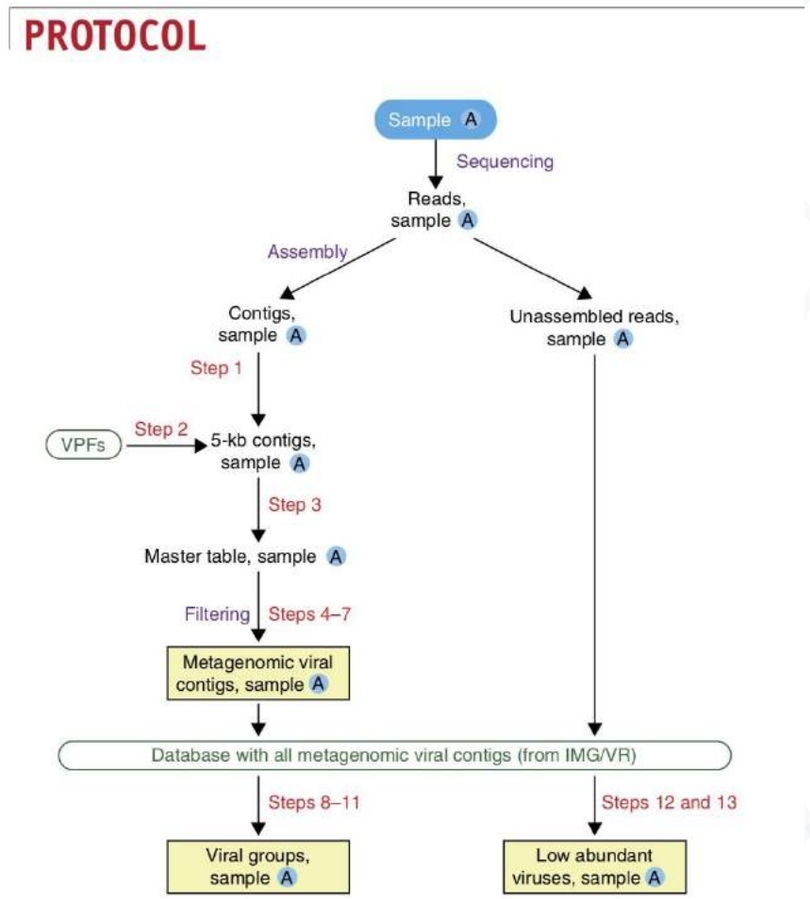
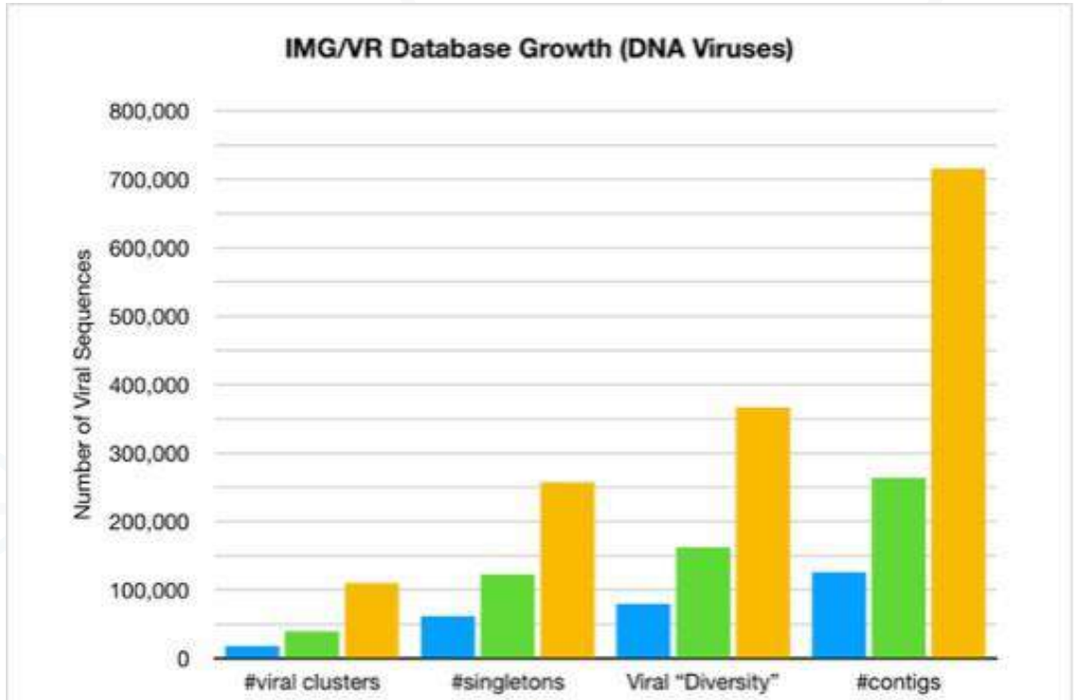


Figure 1 | Overview of the computational workflow. General pipeline of the protocol, showing the different steps required for the detection of abundant and low-abundant metagenomic viral contigs, as well as their classification into viral groups. Viral protein family models (VPFs) and all metagenomic viral contigs from IMG/VR are available through the aforementioned FTP site.

2018: The IMG/VR database **triples in size**



	#viral clusters	#singletons	Viral "Diversity"	#contigs
August 2016	18,470	61,682	80,152	125,842
January 2017	39,701	122,652	162,353	264,064
January 2018	109,968	257,267	367,235	715,672

The JGI IMG/VR database catalogs viruses in Earth's ecosystems including the human body. Viral diversity in IMG/VR has more than tripled since August 2016.

Meanwhile: A typical ME/CFS blood test at the doctor’s office:

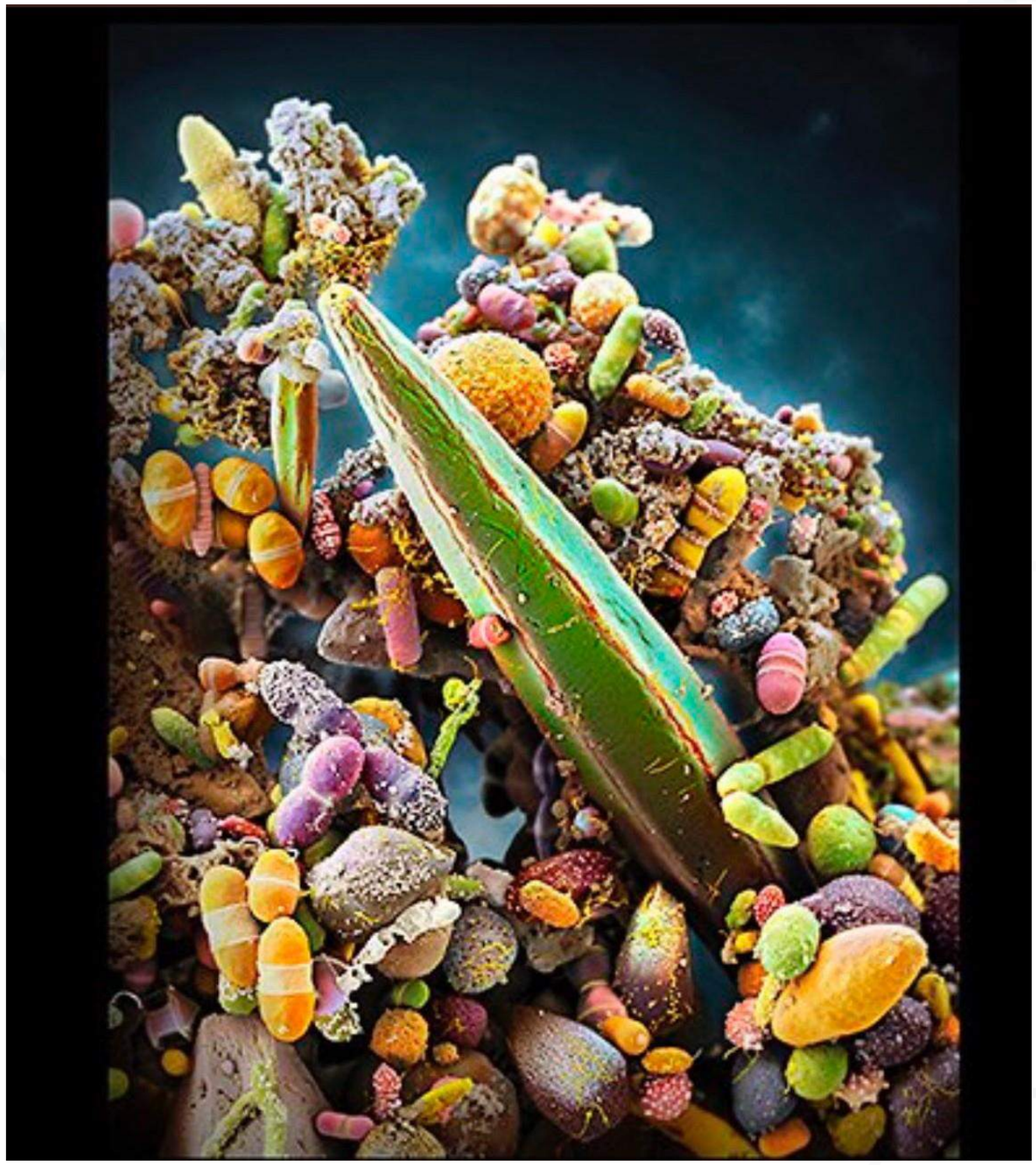
Includes antibody testing
for only 5-10 well-known
viruses, 2-3 bacterial species

Epstein Barr Virus
Cytomegalovirus
Herpes Virus 6
Parvovirus 19
Coxsakie viruses
M. tuberculosis

Polymicrobial disease

ME/CFS-associated pathogens are members of complex microbiome communities

ME/CFS-associated pathogens can now be studied as **interacting members of these microbiome ecosystems**



Interacting bacteria, fungi and virus in the human gut (Image by

The microbiome community a pathogen enters plays a role in determining **if it will survive/persist** in its host

EDITORIAL REVIEW

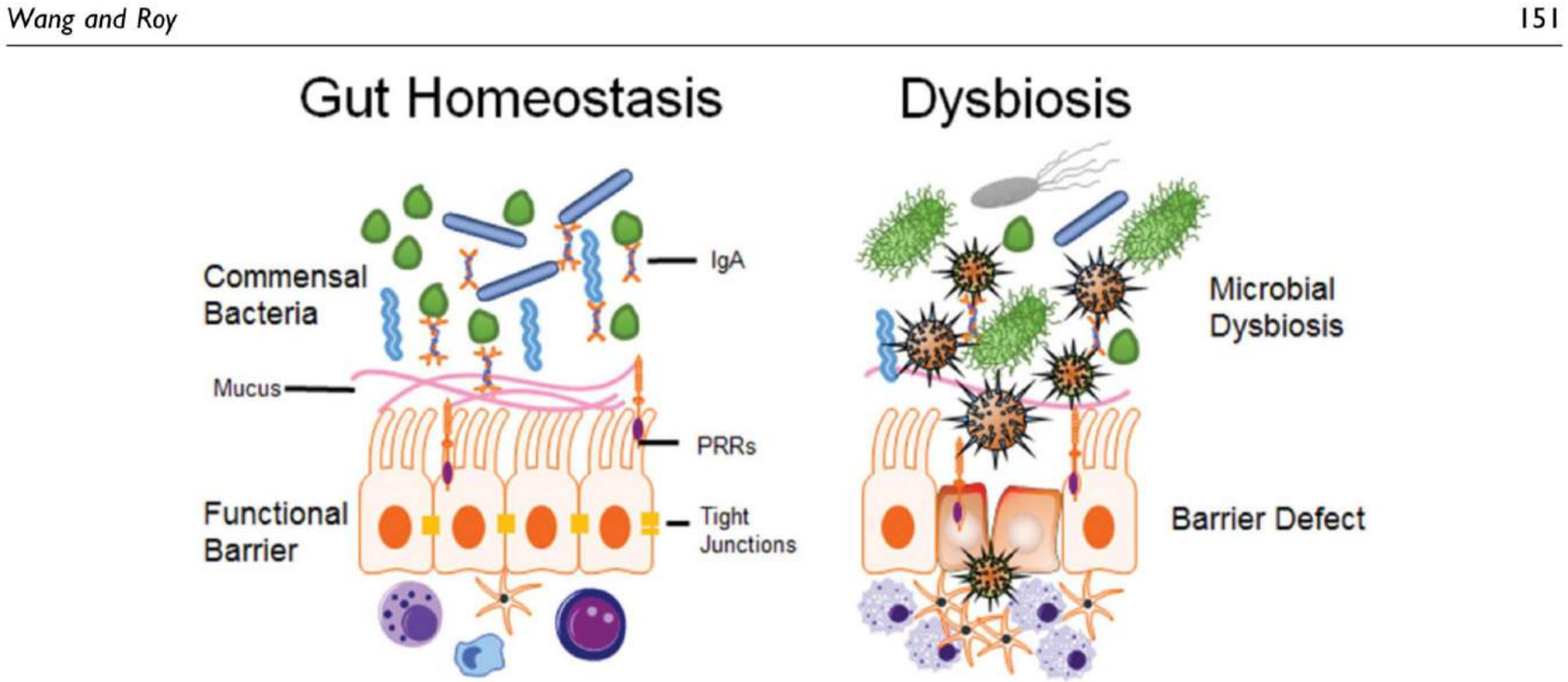
Vaginal microbiota and susceptibility to HIV

McKenna C. Eastment[a] and R. Scott McClelland[a,b,c]

Image: Diego Spitaleri, SEM

Microbiome/virome dysbiosis

Entire communities of organisms **in ME/CFS tissue + blood** may act + signal together to drive symptoms (microbiome/virome dysbiosis)



- Almost every well-studied human inflammatory disease is now tied to microbiome/virome dysbiosis
- Microbiome dysbiosis also happens in microbial + viral communities outside the gut

How does dysbiosis happen?

Microbiome dysbiosis is often **driven by dominant pathogens** whose signaling and activity negatively influences the activity of other nearby organisms

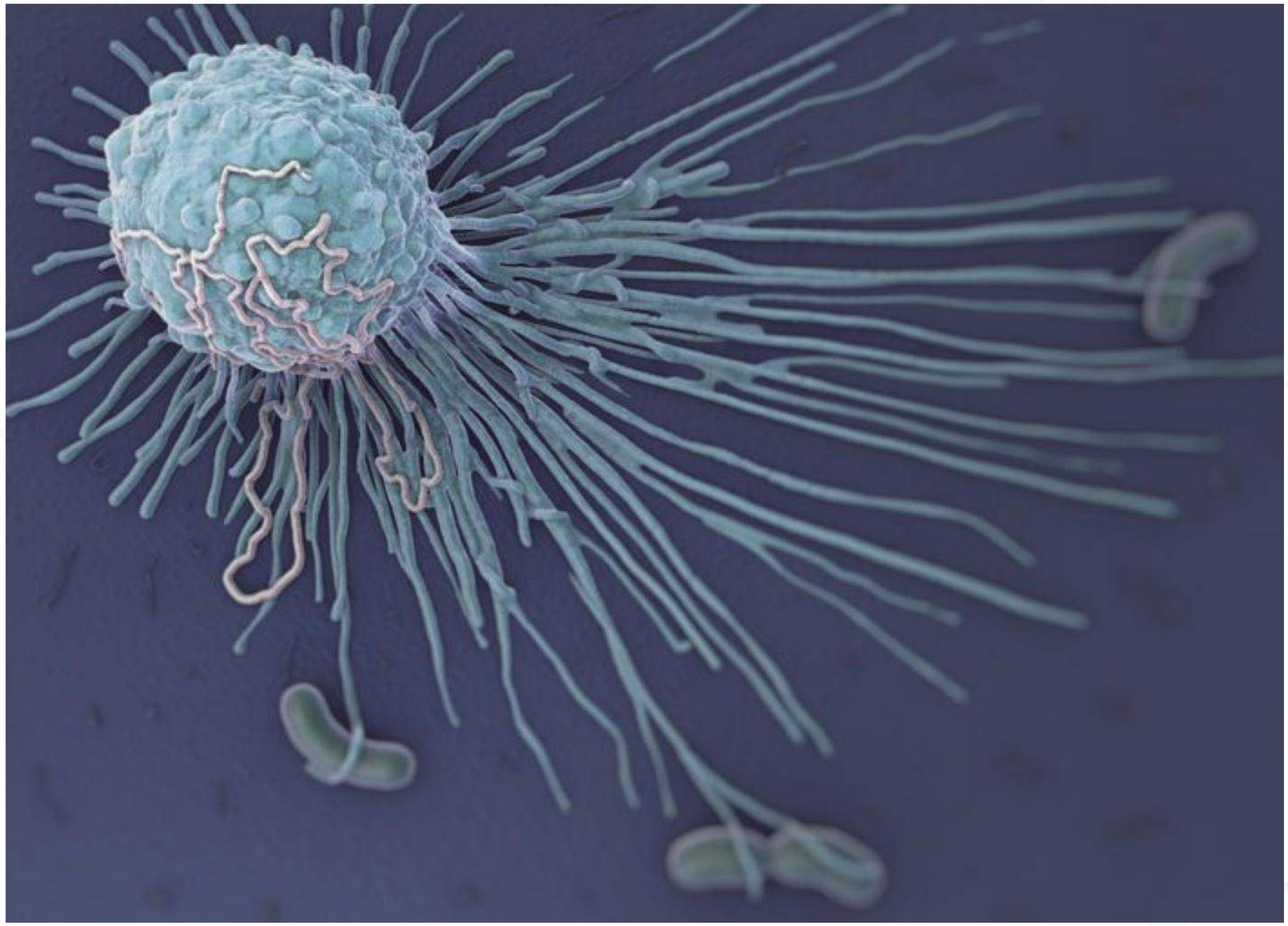
Single criminal vs. a gang of criminals

- Induce biofilm formation
- Virulence factor expression
- Persist inside the cells of the immune system (intracellular)

How does dysbiosis happen?

Immunosuppression

A robust immune response is often capable of controlling pathogen virulence. However, if pathogens overcome the immune response, **or the immune system is suppressed by medications, chemicals, or other environmental factors**, dominant pathogens are more likely to alter their gene expression in a manner that promotes disease.



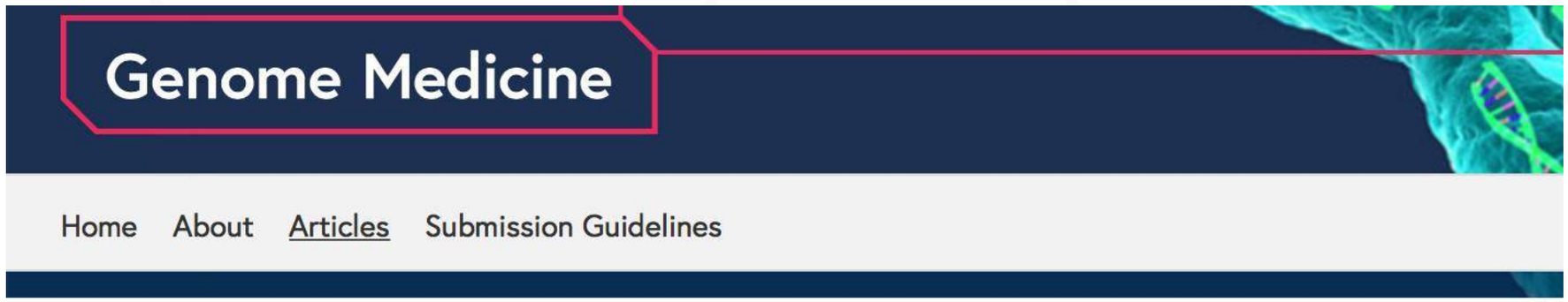
How does dysbiosis happen?

Pathobiont behavior:
Most human “commensal” microbes can change their gene expression (turn genes on/off) to act as pathogens **under conditions of imbalance and/or immunosuppression**

Example: *S. aureus* causes a range of illnesses, from skin infections to life-threatening diseases such as endocarditis and meningitis. However, ~30% of the healthy human population harbors *S. aureus* as a member of the normal nasal microbiome. *S. aureus* virulence in these communities is determined by a number of factors, **including the signaling and competitive strategies employed by neighboring microbes.**

Dysbiosis in driven by changes in organism/pathogen ACTIVITY

Oral microbiome example: different organisms **act together** to drive periodontitis (a complex oral polymicrobial disease)

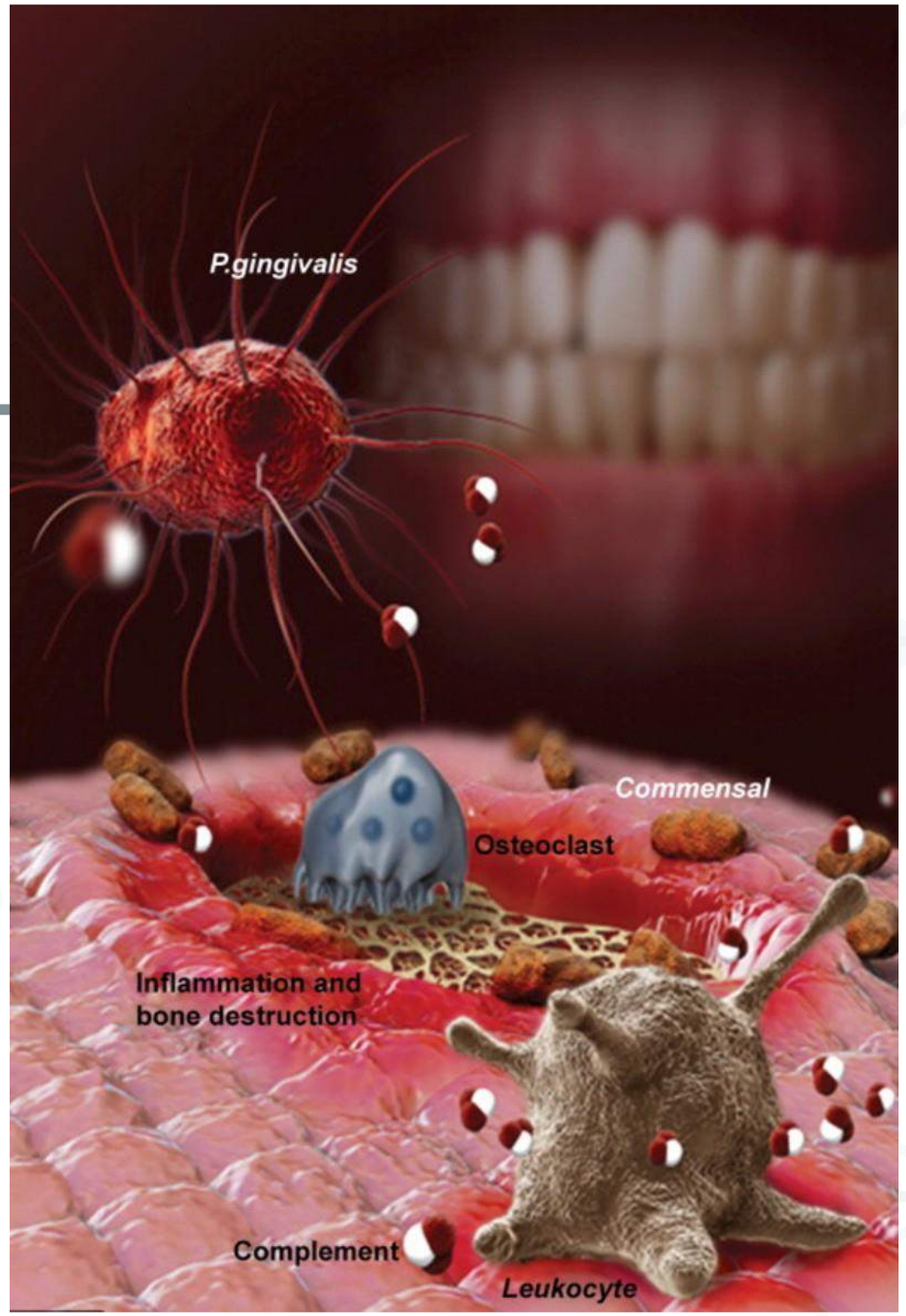


Research | Open Access | Published: 27 April 2015

Functional signatures of oral dysbiosis during periodontitis progression revealed by microbial metatranscriptome analysis

Susan Yost, Ana E Duran-Pinedo, Ricardo Teles, Keerthana Krishnan & Jorge Frias-Lopez ✉

P.gingivalis: the bacterial pathogen often comprises just .01% of periodontal biofilms, **yet impairs innate immune activity so profoundly** that it becomes a central player in biofilm growth and development



Community gene expression changes included:

- pH changes (acidic environment)
- peptidoglycan biosynthesis
- potassium transport
- ciliary motility
- iron transport
- response to oxidative stress

The team concluded that periodontitis progression “is driven by the whole oral microbial community and not just a few select pathogens. In effect, **under conditions of increasing inflammation and imbalance, the entire oral community appeared to *act together as a pathogen*.**

Trend #2: A growing number of neuroinflammatory conditions are now increasingly tied to persistent infection in the blood + brain: Alzheimers, Parkinson's, ALS

Article

Neuron

Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus

Highlights

- Common viral species frequently detected in normal, aging brain
- Increased HHV-6A and HHV-7 in brains of subjects with Alzheimer's disease (AD)
- Findings were replicated in two additional, independent cohorts
- Multiscale networks reveal viral regulation of AD risk, and APP processing genes

Authors

Ben Readhead, Jean-Vianney Haure-Mirande, Cory C. Funk, ..., Michelle E. Ehrlich, Sam Gandy, Joel T. Dudley

Correspondence

joel.dudley@mssm.edu

In Brief

Readhead et al. construct multiscale networks of the late-onset Alzheimer's disease (AD)-associated virome and observe pathogenic regulation of molecular, clinical, and neuropathological networks by several common viruses, particularly human herpesvirus 6A and human herpesvirus 7.

SHARE

RESEARCH ARTICLE | HEALTH AND MEDICINE

Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors

Stephen S. Dominy[1,*,†], Casey Lynch[1,*], Florian Ermini[1], Malgorzata Benedyk[2,3], Agata Marczyk[2], Andrei Konradi[1], Mai Ngu...

+ See all authors and affiliations

Science Advances 23 Jan 2019:
Vol. 5, no. 1, eaau3333
DOI: 10.1126/sciadv.aau3333

ORIGINAL RESEARCH ARTICLE

Front. Neurosci., 26 February 2019 | https://doi.org/10.3389/fnins.2019.00171

Searching for Bacteria in Neural Tissue From Amyotrophic Lateral Sclerosis

Ruth Alonso†, Diana Pisa† and Luis Carrasco*

Centro de Biología Molecular "Severo Ochoa" (CSIC-UAM), Universidad Autónoma de Madrid, Madrid, Spain

Despite great efforts in the investigation, the exact etiology of amyotrophic lateral sclerosis (ALS) is a matter of intensive research. We recently advanced the idea that ALS might be caused by fungal infection. Indeed, fungal yeast and hyphal structures can be directly visualized in neural tissue of ALS patients, and a number of fungal species have been identified in the central nervous system (CNS). In the present work, we tested the possibility that bacterial infections can accompany these mycoses. Our findings establish the presence of bacterial DNA in different regions of the CNS from all ALS patients examined. Specifically, we used PCR and next generation sequencing (NGS) to precisely determine the bacterial species present in ALS tissue. Consistent with these findings, immunohistochemistry analysis of CNS sections using specific anti-bacterial antibodies identified prokaryotic cells in neural tissue. Finally, we assayed for the repeat expansion of the hexanucleotide repeat GGGGCC in C9orf72, which is considered the most common genetic cause of ALS in patients, using DNA extracted from ALS CNS tissue. We failed to find this repeated sequence in any of the eleven patients analyzed. Our results indicate that bacterial DNA and prokaryotic cells are present in CNS tissue, leading to the concept that both fungal and bacterial infections coexist in patients with ALS. These observations lay the groundwork for the use of appropriate therapies to eradicate the polymicrobial infections in ALS.

Virus-like particles and enterovirus antigen found in the brainstem neurons of Parkinson's disease

Robert R. Dourmashkin, Sherman A McCall, +4 authors Steven Patterson • Published in F1000Research 2018 •

DOI: 10.12688/f1000research.13626.2

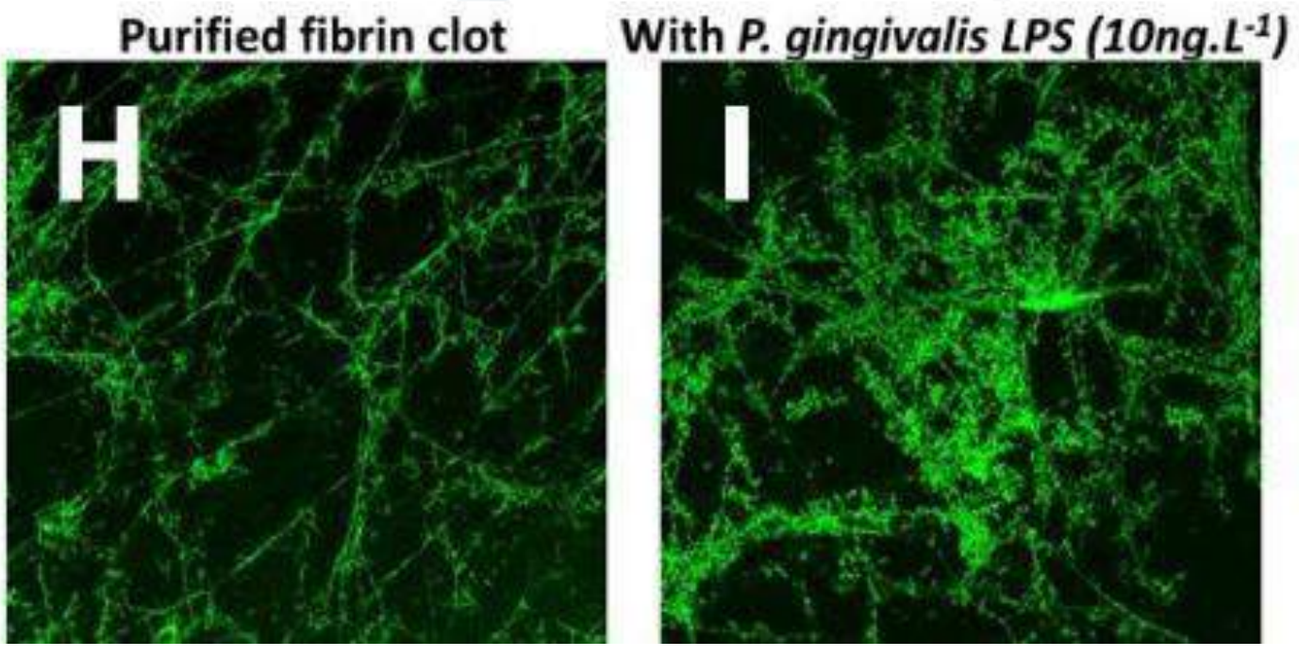
Background: In a previous study on encephalitis lethargica, we identified a virus related to enterovirus in autopsy brain material. Transmission electron microscopy (TEM), immunohistochemistry (IHC) and molecular analysis were employed. Our present objective was to investigate, using a similar approach, as to whether virus-like particles (VLP) and enterovirus antigen are present in Parkinson's disease (PD) brainstem neurons. Methods: Fixed tissue from autopsy specimens of late onset PD and... CONTINUE READING

P. gingivalis in Parkinson's blood

ORIGINAL RESEARCH ARTICLE
Front. Aging Neurosci., 27 August 2019 | https://doi.org/10.3389/fnagi.2019.00210

Parkinson's Disease: A Systemic Inflammatory Disease Accompanied by Bacterial Inflammagens

Büin Adams[1], J. Massimo Nunes[1], Martin J. Page[1], Timothy Roberts[1,2], Jonathan Carr[3], Theo A. Nell[1], Douglas B. Kell[1,2*†] and Etheresia Pretorius[1*†]



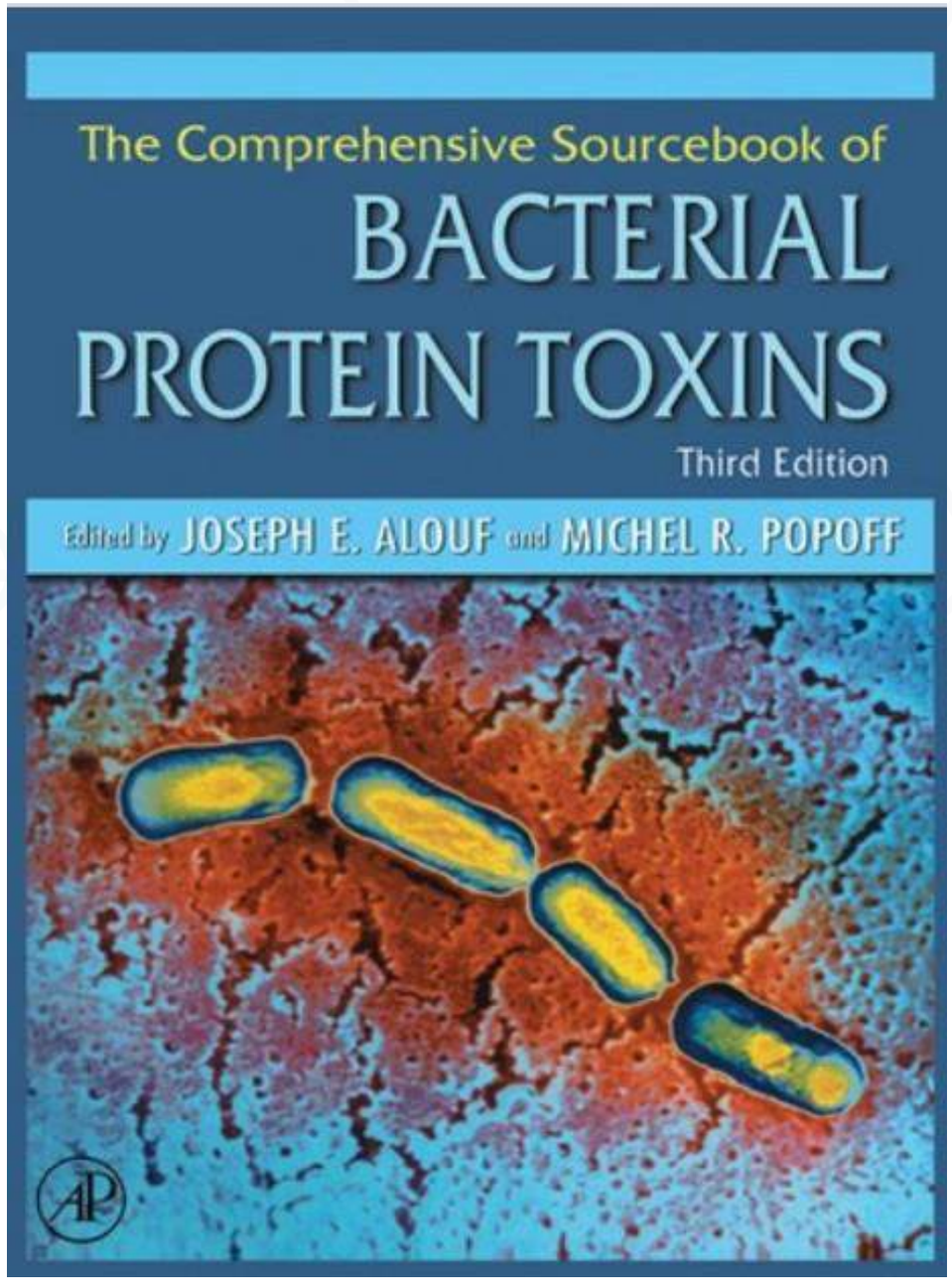
- Our work "serves as a preliminary study **showing a role of *P. gingivalis* LPS** and gingipain protease in abnormal blood clotting observed in our Parkinson's samples"

Takeaways

1.A healthy person and a patient with ME/CFS could harbor the same pathogen and/or communities of pathogens…**but the organisms may be ACTING differently** in the ME/CFS patient

2.It is hard to fully understand the symptoms of a disease without factoring in how a dominant pathogen **influences the activity of other organisms** in its microbiome/virome community

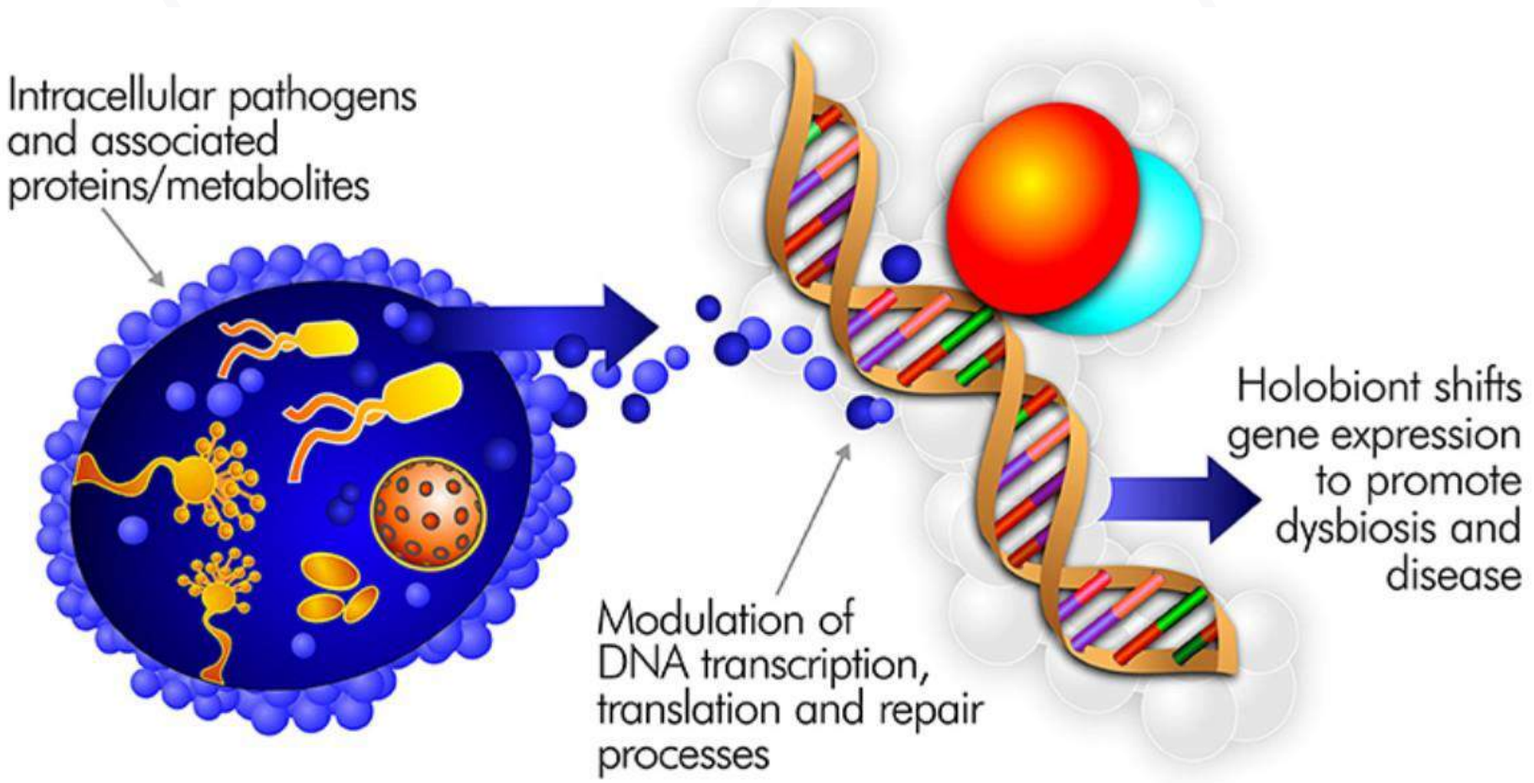
Human organisms/pathogens create a broad range of proteins and metabolites



Dominant pathogens are almost always capable of persisting inside the nucleus of human cells where they:

1. Slow immune response

2.Create proteins/metabolites that Interfere with human transcription/ translation/DNA repair processes and the epigenetic environment



Human signaling pathways are controlled by proteins + metabolites (ligands) binding into receptors

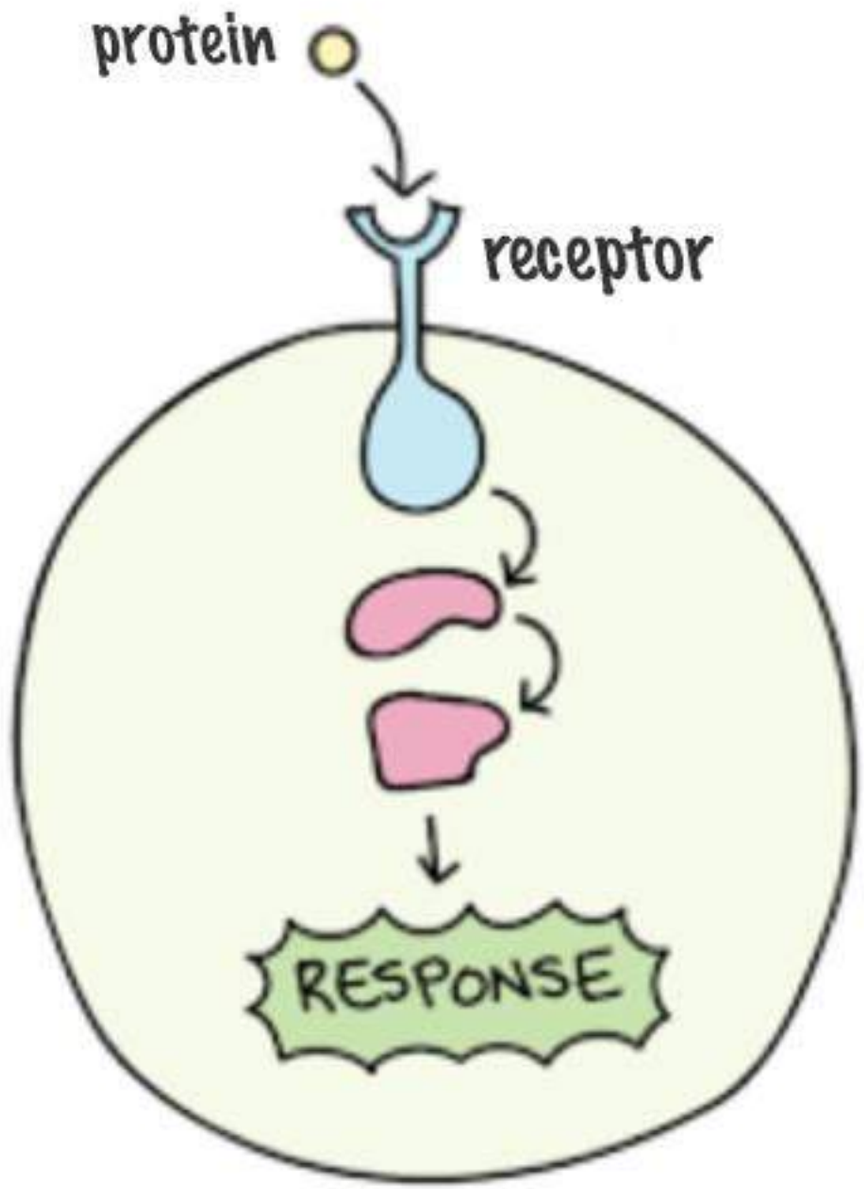


*Image Khan Academy

Molecular mimicry

Microbial proteins and metabolites are often identical or similar in structure to those created by their human hosts.

It follows that proteins/metabolites created by pathogens can dysregulate the activity of human receptors + signaling pathways

Viral, bacterial and fungal proteins + metabolites can directly alter the activity of human signaling pathways

PNAS

Viral insulin-like peptides activate human insulin and IGF-1 receptor signaling: A paradigm shift for host–microbe interactions

Emrah Altindis[a], Weikang Cai[a], Masaji Sakaguchi[a,b], Fa Zhang[c], Wang GuoXiao[a], Fa Liu[c], Pierre De Meyts[d,e], Vasily Gelfanov[c], Hui Pan[a], Richard DiMarchi[c], and C. Ronald Kahn[a,1]

[a]Joslin Diabetes Center, Harvard Medical School, Boston, MA 02215; [b]Department of Metabolic Medicine, Kumamoto University, 1-1-1 Honjo, Chuo-ku, 860-8556 Kumamoto, Japan; [c]Department of Chemistry, Indiana University, Bloomington, IN 47405; [d]Department of Cell Signaling, de Duve Institute, B-1200 Brussels, Belgium; and [e]Department of Stem Cell Research, Novo Nordisk A/S, DK-2760 Måløv, Denmark

Viral/bacteria/fungal proteins + metabolites have also been shown to dysregulate human signaling pathways that control:

Blood pressure, circulatory issues and autonomic function

Natural killer cell activity

Lactate accumulation in blood/brain

Glutamate metabolism

Pain signaling + neuropathy

Mast cell activation

Mitochondrial activity

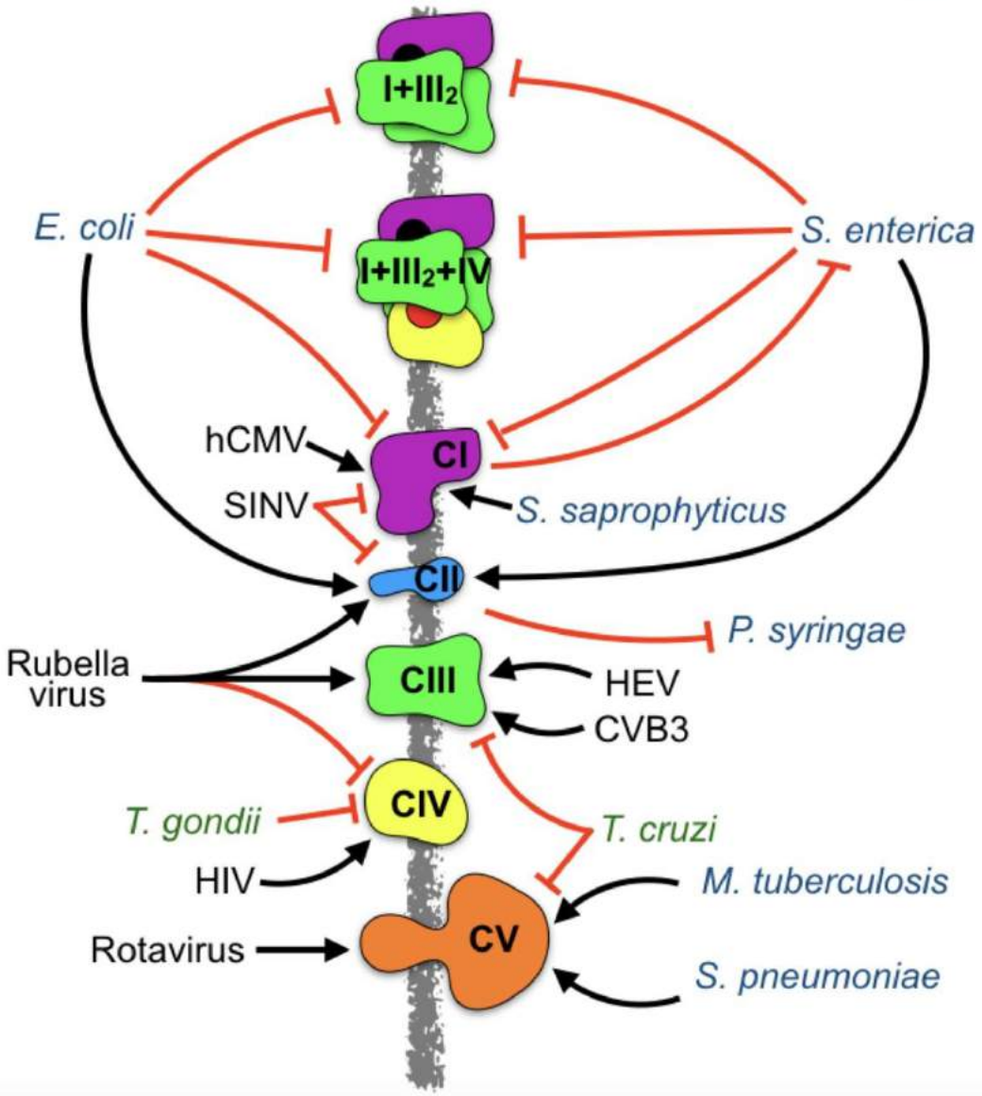
Pathogen/organism activity is characterized by a high level of functional redundancy

Immunometabolism. 2019;1:e190011. https://doi.org/10.20900/immunometab20190011

Review

Roles of Mitochondrial Respiratory Complexes during Infection

Pedro Escoll [1,2,*]*, Lucien Platon [1,2,3], Carmen Buchrieser [1,2,*]*



Pathogens that degrade collagen

FEMS Microbiol Rev. 2012 Nov;36(6):1122-80. doi: 10.1111/j.1574-6976.2012.00340.x. Epub 2012 Jun 18.

Human pathogens utilize host extracellular matrix proteins laminin and collagen for adhesion and invasion of the host.

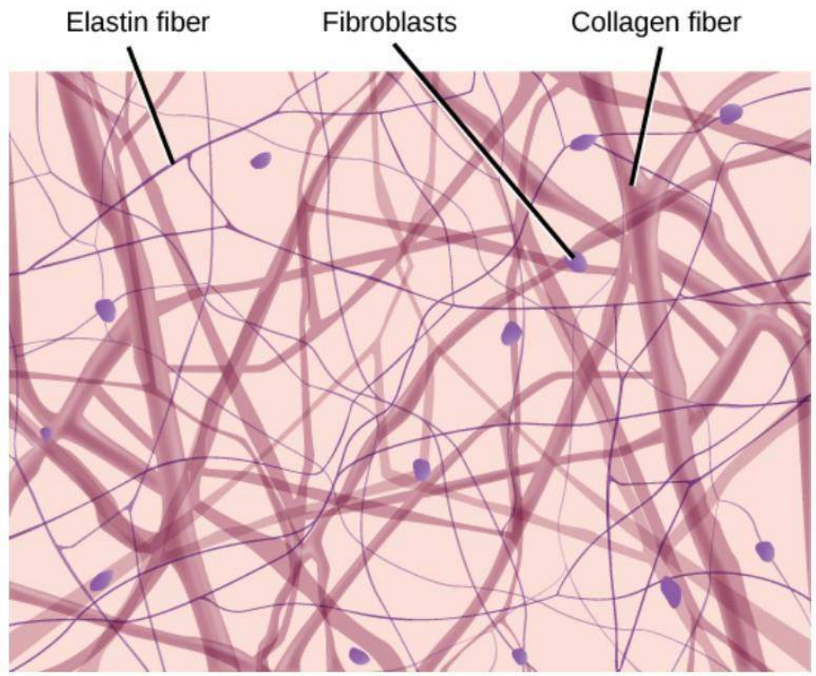
Singh B[1], Fleury C, Jalalvand F, Riesbeck K.

Author information

1 Medical Microbiology, Department of Laboratory Medicine Malmö, Skåne University Hospital, Lund University, Malmö, Sweden.

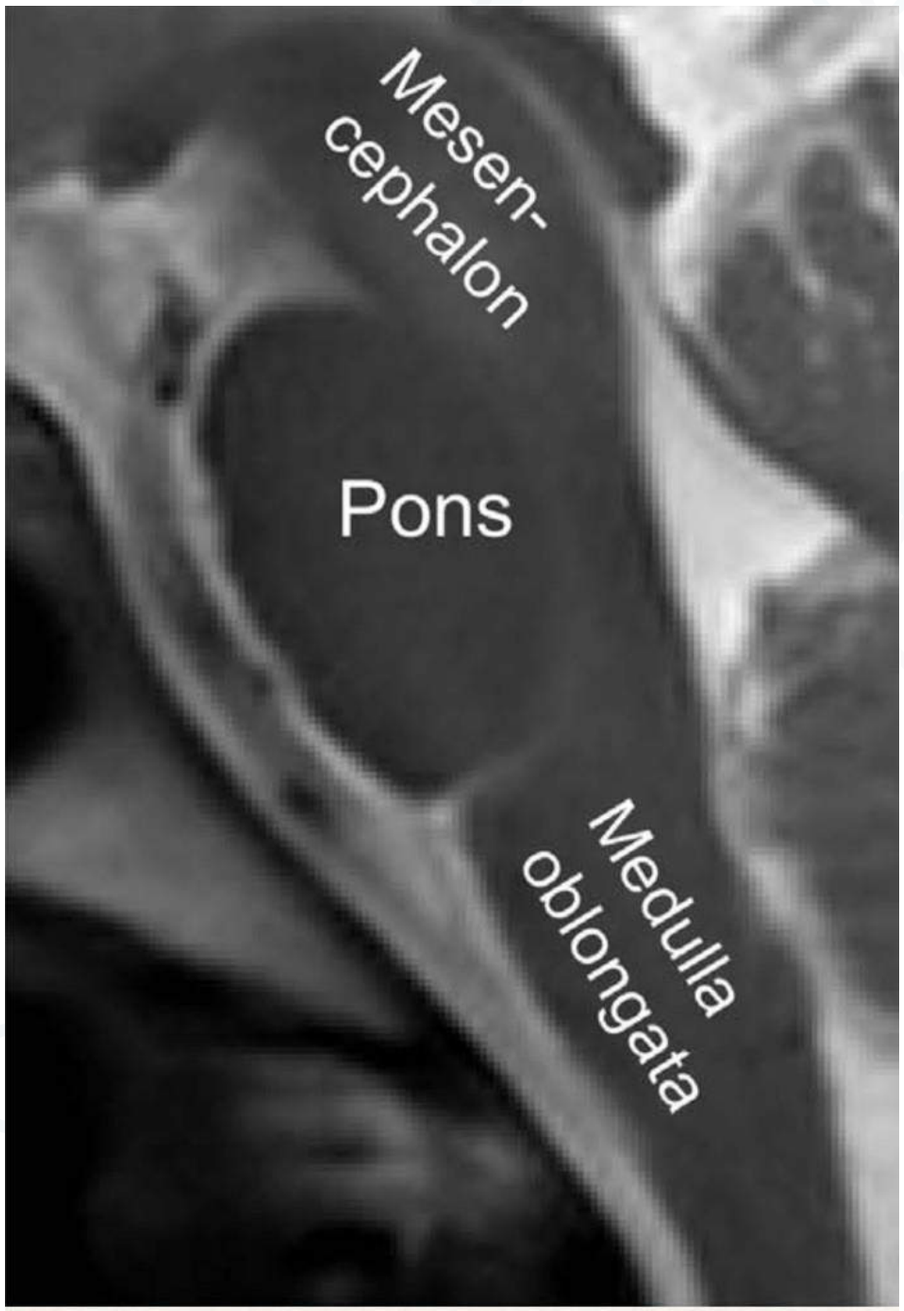
Most pathogens associated with the respiratory, gastrointestinal, or urogenital tracts, as well as with the central nervous system or the skin, **have the capacity to bind and degrade collagen(s) in order to adhere to and invade host tissues**. The major pathogens discussed are:

Streptococcus
Staphylococcus
Pseudomonas,
Salmonella,
Yersinia,
Treponema,
Mycobacterium,
Clostridium,
Listeria,
Porphyromonas and Haemophilus;
Candida,
Aspergillus,
Pneumocystis,
Cryptococcus and Coccidioides; Acanthamoeba,
Trypanosoma and Trichomonas;
retrovirus and papilloma virus.



ME/CFS research goal: better characterize the signaling pathways + tissues + cell types that redundant ME/CFS dominant pathogens can dysregulate

Brainstem area postrema and the vagus nerve



Sclocco R, et al. (2018). Challenges and opportunities for brainstem neuroimaging with ultrahigh field MRI. *NeuroImage 168*, 412-426.

Area postrema lies between pons and medulla, and **is a window in the blood-brain barrier,** allowing immune cells and molecules into the brain

The **vagus nerve that control the "sickness behavior" response** enters at the exits at the brainstem

ME/CFS is a spectrum disorder

C. Immune, gastro-intestinal and genitourinary Impairments

At least one symptom from three of the following five symptom categories

1. Flu-like symptoms may be recurrent or chronic and typically activate or worsen with exertion. *e.g. sore throat, sinusitis, cervical and/or axillary lymph nodes may enlarge or be tender on palpitation*

2. Susceptibility to viral infections with prolonged recovery periods

3. Gastro-intestinal tract: *e.g. nausea, abdominal pain, bloating, irritable bowel syndrome*

4. Genitourinary: e.g. *urinary urgency or frequency, nocturia*

5. Sensitivities *to food, medications, odours or chemicals*

Notes: *Sore throat, tender lymph nodes, and flu-like symptoms obviously are not specific to ME but their activation in reaction to exertion is abnormal. The throat may feel sore, dry and scratchy. Faucial injection and crimson crescents may be seen in the tonsillar fossae, which are an indication of immune activation.*

D. Energy production/transportation impairments: At least one symptom

1. Cardiovascular: *e.g. inability to tolerate an upright position - orthostatic intolerance, neurally mediated hypotension, postural orthostatic tachycardia syndrome, palpitations with or without cardiac arrhythmias, light-headedness/dizziness*

2. Respiratory: *e.g. air hunger, laboured breathing, fatigue of chest wall muscles*

3. Loss of thermostatic stability: *e.g. subnormal body temperature, marked diurnal fluctuations; sweating episodes, recurrent feelings of feverishness with or without low grade fever, cold extremities*

4. Intolerance of extremes of temperature

Notes: *Orthostatic intolerance may be delayed by several minutes. Patients who have orthostatic intolerance may exhibit mottling of extremities, extreme pallor or Raynaud's Phenomenon. In the chronic phase, moons of finger nails may recede.*

Paediatric considerations

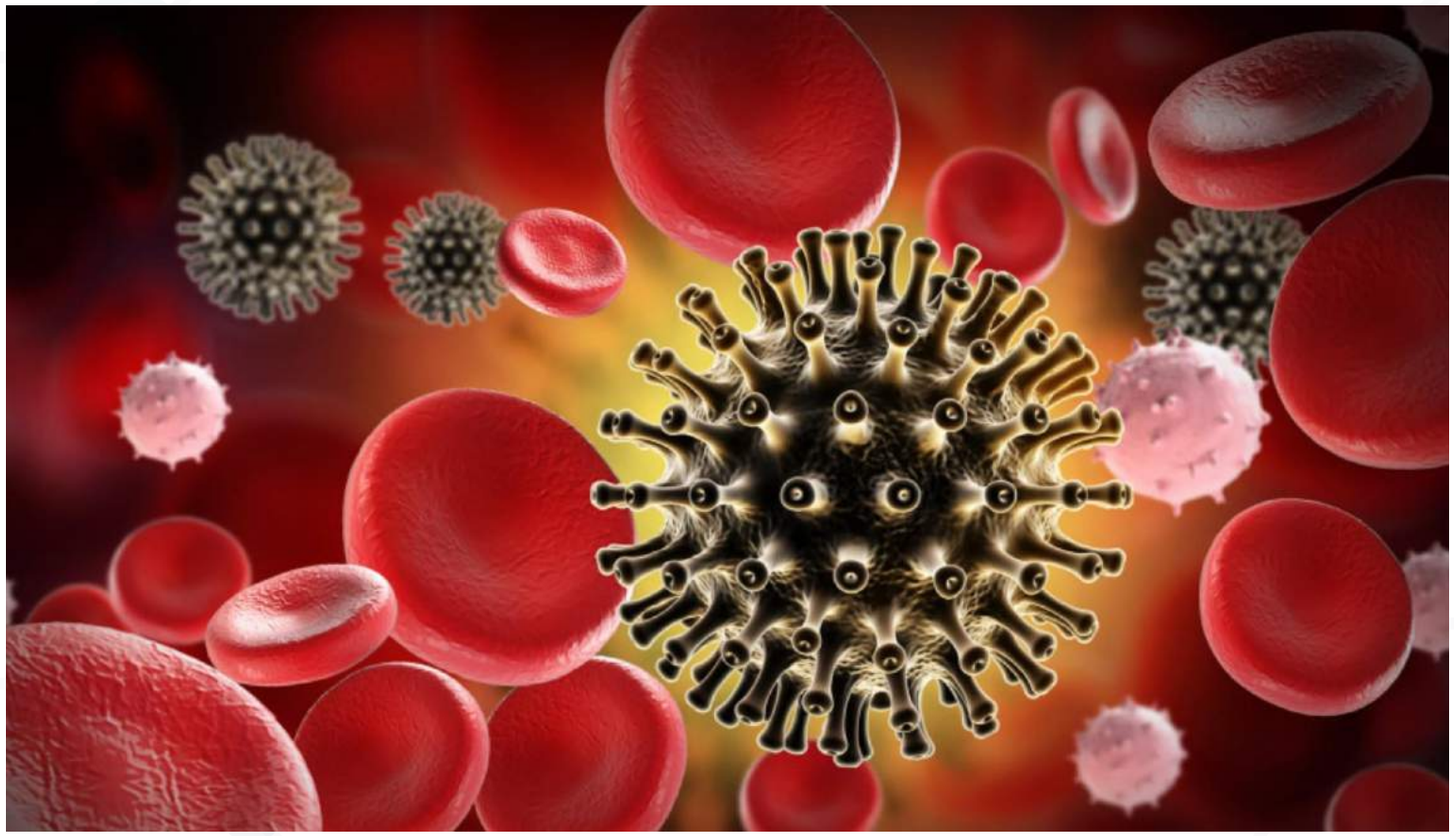
Symptoms may progress more slowly in children than in teenagers or adults. In addition to postexertional neuroimmune exhaustion, the most prominent symptoms tend to be neurological: headaches, cognitive impairments, and sleep disturbances.

1. Headaches: Severe or chronic headaches are often debilitating. Migraine may be accompanied by a rapid drop in temperature, shaking, vomiting, diarrhoea and severe weakness.

2. Neurocognitive impairments: Difficulty focusing eyes and reading are common. Children may become dyslexic, which may only be evident when fatigued. Slow processing of information makes it difficult to follow auditory instructions or take notes. All cognitive impairments worsen with physical or mental exertion. Young people will not

Every patient’s chronic inflammatory symptoms are unique

Even in HIV/AIDS, where an easily detected virus dysregulates immunity, disease symptoms reflect **a mix of those driven by HIV, and those driven by “co-infectious” agents** able to take advantage of the immunocompromised host. No two patients with HIV/AIDS **are expected to harbor the same mix** of these additional persistent bacteria, fungi, and viruses.



- Bacterial infections, including tuberculosis and a serious related disease, Mycobacterium avium complex (MAC)
- Viral infections, such as cytomegalovirus (CMV) and hepatitis C
- Fungal infections, like yeast infections, cryptococcal meningitis, pneumocystis carinii pneumonia (PCP) and histoplasmosis
- Parasitic infections, such as crypto (cryptosporidiosis) and toxo (toxoplasmosis)

Other environmental factors that can contribute to ME/CFS

-mold exposure

-chemical exposures

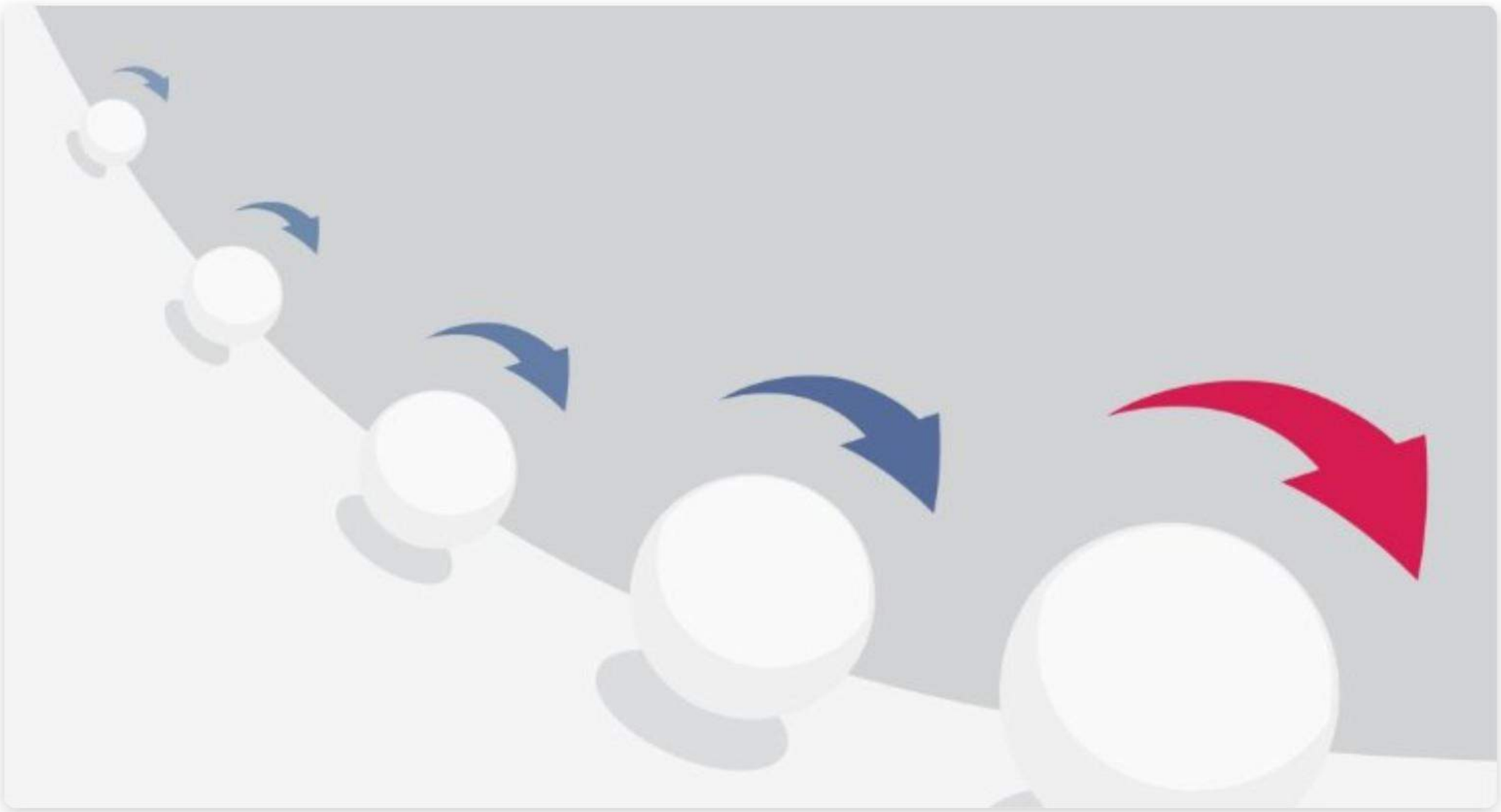
-injuries (especially CNS injuries)

-high levels of stress

-immunosuppressive drugs/supplements

-rare human genome variants

Successive infection as a model for ME/CFS disease development



A successive infection “snowball” could drive many forms of disease

Successive infection as a model for ME/CFS disease development

1. An acquired persistent pathogen, an inherited pathogen and/or environmental exposure dysregulates the host immune system. This makes it easier for microbes + viruses to subvert the immune response **by acting as polymicrobial entities.**

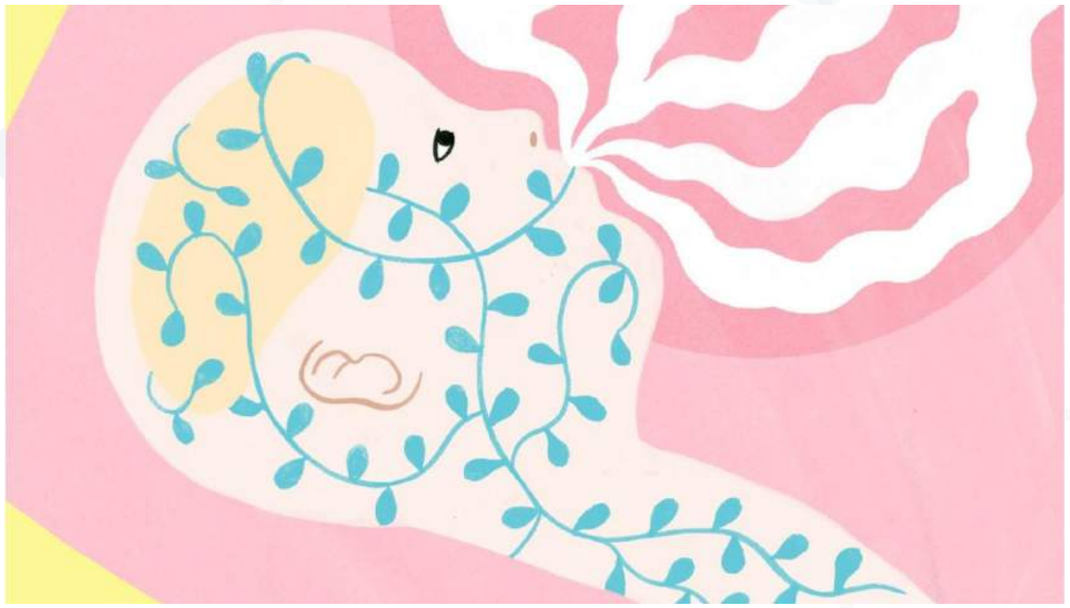
3. Pathobionts alter their gene expression to better promote community-wide virulence. The proteins/metabolites created by these (intracellular) organisms begin to **dysregulate human signaling pathways.** Dysfunction driven by **molecular mimicry** increases. Certain pathogens may **infect mitochondria, central nervous system tissue** etc.

5. Intracellular pathogens **slow the human immune response, causing the host to more easily acquire other infectious agents** or become more sensitive to additional environmental exposures. This creates a snowball effect in which the microbiome + virome in various body cites become increasingly dysbiotic as the strength of the immune response weakens over time.

Successive infection: the importance of inherited organisms

Bacterial, viral and fungal communities are passed in families, especially down the maternal line

-Breast milk microbiome
-Organisms passed in the womb (placenta, amniotic fluid)
-Vaginal microbiome



ORIGINAL RESEARCH ARTICLE
Front. Microbiol., 04 June 2019 | https://doi.org/10.3389/fmicb.2019.01124

Check for updates

The Not-so-Sterile Womb: Evidence That the Human Fetus Is Exposed to Bacteria Prior to Birth

Lisa F. Stinson[1*], Mary C. Boyce[2], Matthew S. Payne[1] and Jeffrey A. Keelan[1]

[1]Division of Obstetrics and Gynaecology, Faculty of Health and Medical Sciences, The University of Western Australia, Perth, WA, Australia
[2]Centre for Integrative Metabolomics and Computational Biology, School of Science, Edith Cowan University, Perth, WA, Australia

Directions for treatment

Treatment is **already changing** in Alzheimer's to include/develop antiviral + antimicrobial medications

Detailed Description

Valacyclovir is a drug approved by the U.S. Food & Drug Administration to treat herpes and shingles. HSV-1 (oral herpes) and HSV-2 (genital herpes) are known to trigger amyloid aggregation and their DNA is commonly found in beta-amyloid plaques, which are a hallmark of Alzheimer's disease. In studies in mice, anti-HSV drugs have reduced accumulation of beta-amyloid and p-tau, another protein found in the brains of people with Alzheimer's disease. This study will test valacyclovir as a possible treatment in slowing or preventing Alzheimer's disease.

Participants will take four to eight coated tablets of either 500 mg of valacyclovir or placebo daily for 78 weeks. Researchers will measure amyloid accumulation on PET scans in multiple regions of the brain, as well as changes in cognitive function and activities of daily living using assessments and tests. Investigators also will obtain measures of beta-amyloid and tau in cerebrospinal fluid from participants who agree to lumbar puncture.

Locations

Name	City	State	Zip	Status	Primary Contact
New York University School of Medicine	New York	New York	10016	Not yet recruiting	Shannon Chen, BA 212-263-5845 Shannon.Chen@nyumc.org
New York State Psychiatric Institute	New York	New York	10032	Recruiting	Julianna Pollina, BS 646-774-8638 julianna.pollina@nyspi.columbia.edu

Lead Sponsor Agency

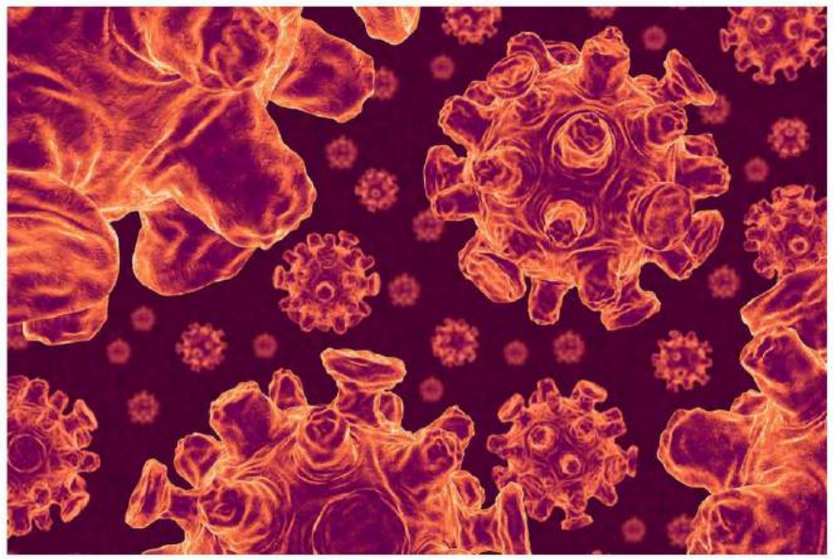
New York State Psychiatric Institute

Collaborator Sponsor

- National Institutes of Health (NIH)

COULD ALZHEIMER'S BE TREATED WITH AN ANTI-VIRAL DRUG?

March 21, 2016 | Penny Dacks, PhD



Directions for treatment

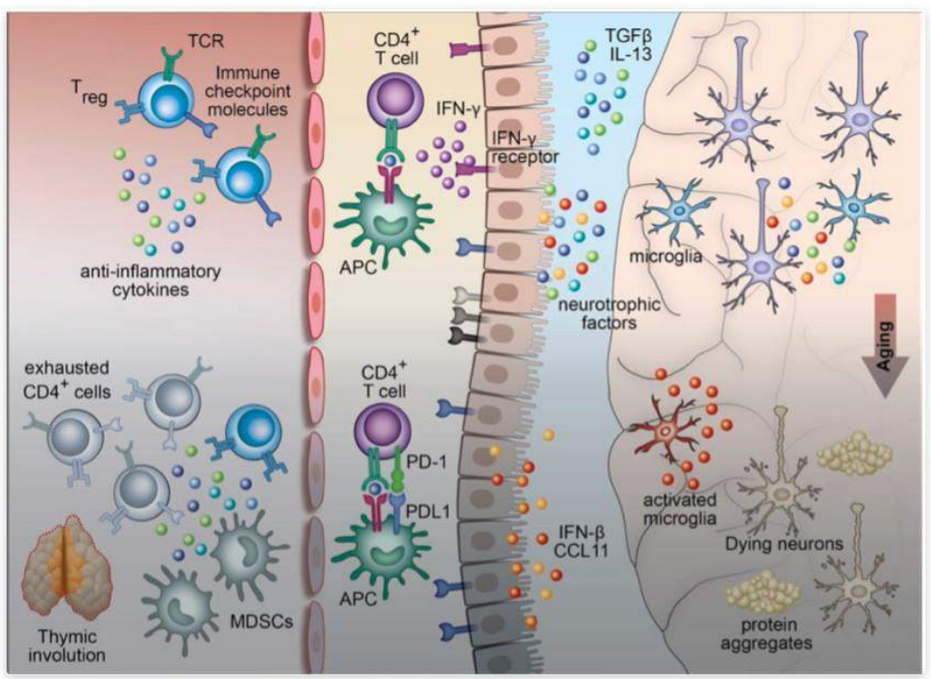
Published Online: 9 October, 2018 | Supp Info: http://doi.org/10.1084/jem.20181737
Downloaded from jem.rupress.org on October 11, 2018

JEM Journal of Experimental Medicine

VIEWPOINT

Targeting neuro–immune communication in neurodegeneration: Challenges and opportunities

Aleksandra Deczkowska[1] and Michal Schwartz[2]



Brain-immune communication points during aging and neurodegenerative disease (Schwartz et al)

Paper highlight: "For decades, it was accepted that the CNS is an "immune-privileged site"… This view ascribed the inflammation in chronic neurodegenerative disease to autoimmunity. As a consequence, ***attempts were made to treat such conditions with immunosuppressive drugs, all of which failed"***

“In conclusion, the **development of a therapy that boosts the immune system in a well-controlled way,** and thereby restores and/or activates brain–immune communication, is an outcome of a general shift toward the perception of the CNS as a tissue that engages in a constant dialog with peripheral immunity. Such an approach is expected to **provide novel treatment modalities in order to harness common immune repair mechanisms** to combat Alzheimer’s disease and perhaps other neurodegenerative diseases.”

Treatment: support the immune system to better target persistent pathogens/manage toxic exposures

Immunologic Research
July 2013, Volume 56, Issue 2–3, pp 398–412 | Cite as

Immunostimulation in the treatment for chronic fatigue syndrome/myalgic encephalomyelitis

Authors | Authors and affiliations

Amy D. Proal, Paul J. Albert, Trevor G. Marshall, Greg P. Blaney, Inge A. Lindseth

Treatment of Autoimmunity
First Online: 11 April 2013

Abstract

Chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) has long been associated with the presence of infectious agents, but no single pathogen has been reliably identified in all patients with the disease. Recent studies using metagenomic techniques have demonstrated the presence of thousands of microbes in the human body that were previously undetected and unknown to science. More importantly, such species interact together by sharing genes and genetic function within communities. It follows that searching for a singular pathogen may greatly underestimate the microbial complexity potentially driving a complex disease like CFS/ME. Intracellular microbes alter the expression of human genes in order to facilitate their survival. We have put forth a model describing how multiple species—bacterial, viral, and fungal—can cumulatively dysregulate expression by the VDR nuclear receptor in order to survive and thus drive a disease process. Based on this model, we have developed an immunostimulatory therapy that is showing promise inducing both subjective and objective improvement in patients suffering from CFS/ME.

Our Organism Identification Project:

The Organism Identification Pipeline: A collaboration between **top global research teams** to standardize the process of using novel, cutting-edge technologies and algorithms **to search for viruses + bacteria + other organisms in the blood/cerebrospinal fluid** of ME/CFS subjects.

JGI
JOINT GENOME INSTITUTE

HARVARD
UNIVERSITY

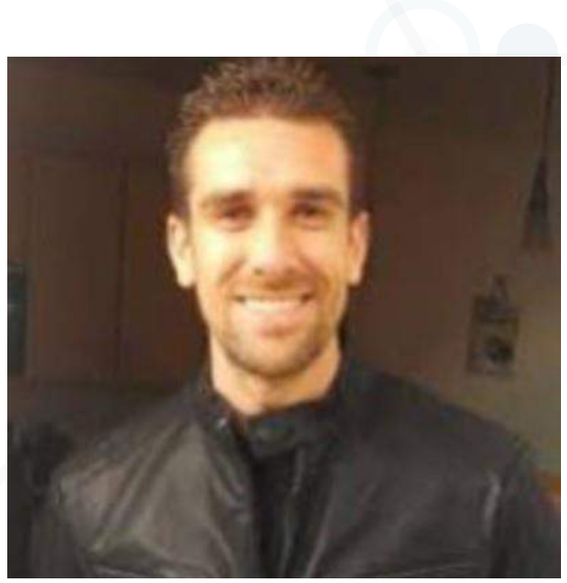
GENESAVVY
Genetic Health Solutions

The Organism Identification Pipeline Team

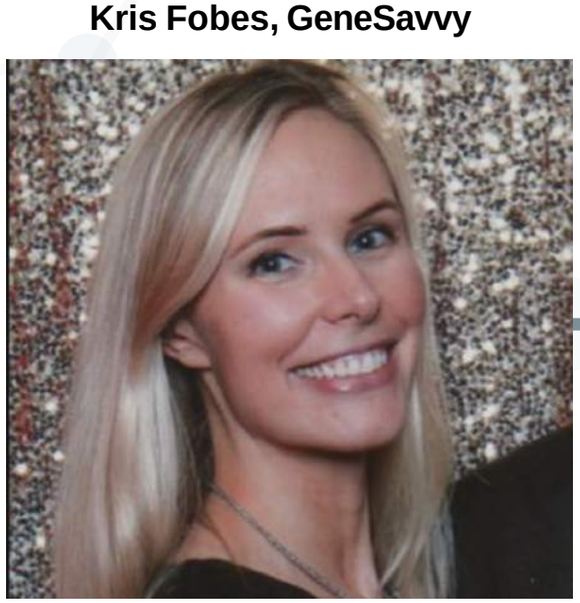
Nikos Kyrpides (Joint Genome Institute Berkeley)

Kris Fobes, GeneSavvy

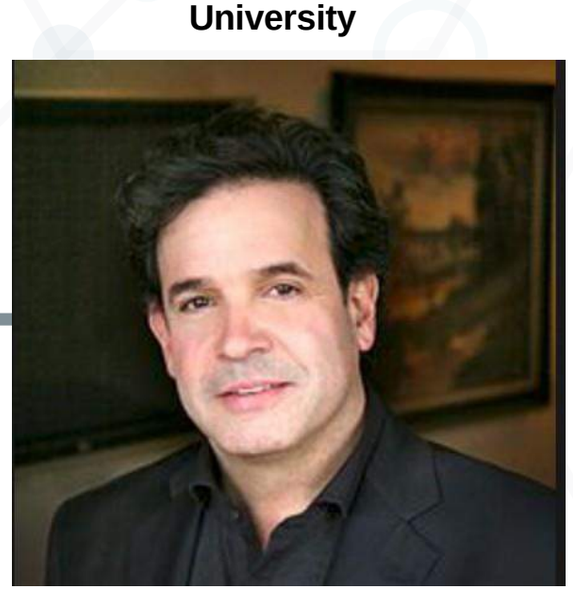
Robert Moir, Harvard University



David Paez-Espino, Joint Genome Institute Berkeley



Amy Proal, Autoimmunity Research Foundation



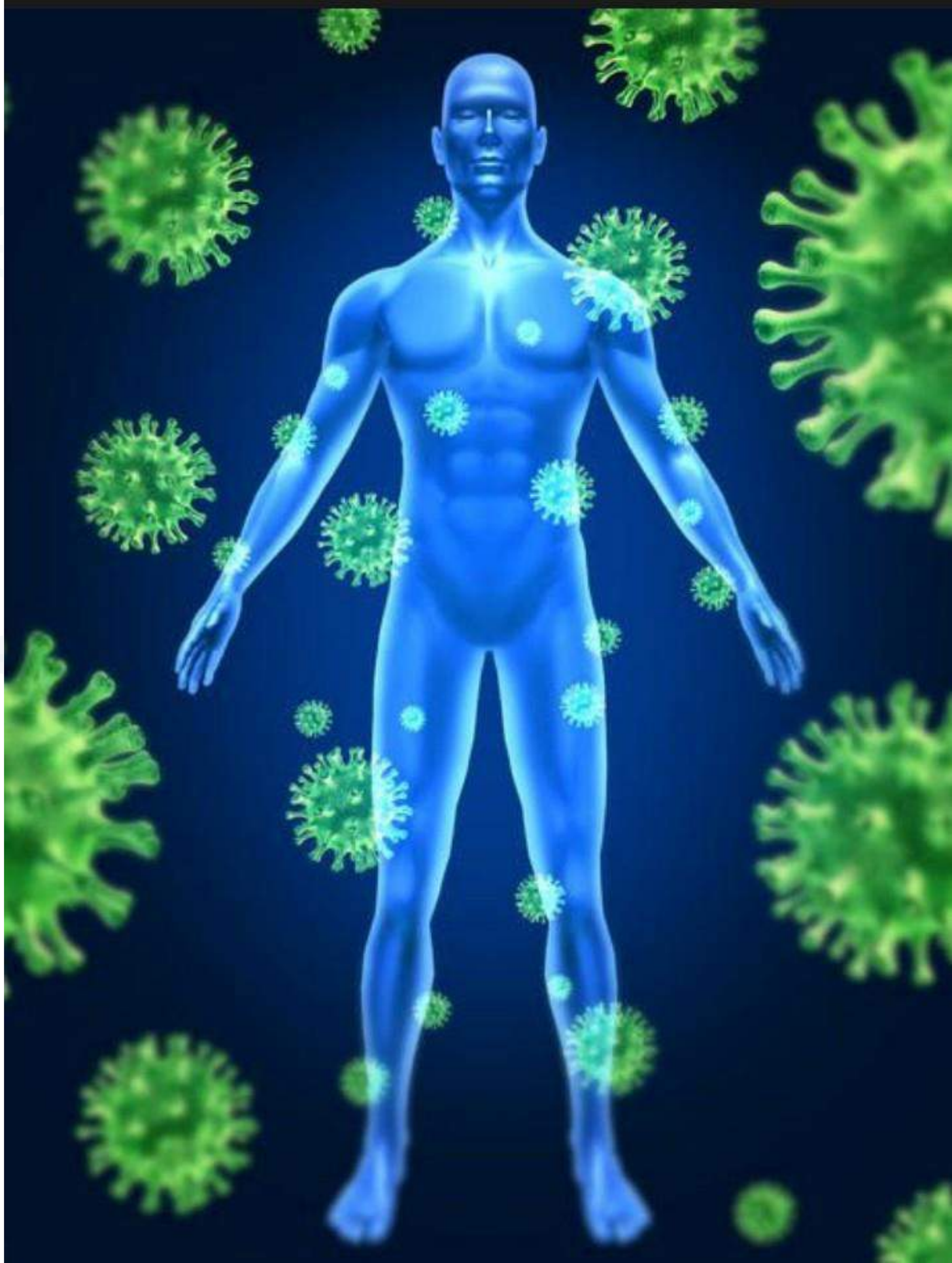
Rudy Tanzi, Harvard University

Organism Identification Pipeline: Part 3

Nikos + David at will use their “Uncovering the Earth’s Virome” technologies to **characterize the microbiome + virome communities in ME/CFS blood**

They will use their existing pipelines **that identify general ss and ds RNA and DNA viruses + phages + specific viral groups.** These include phages, mycoviruses, giant viruses, virophages and even retroviruses

The analysis will also **identify known and novel bacteria + fungi** and use algorithms to predict their relationship to phages. These relationships can then be used to **infer organism activity and microbial ecosystem dynamics**

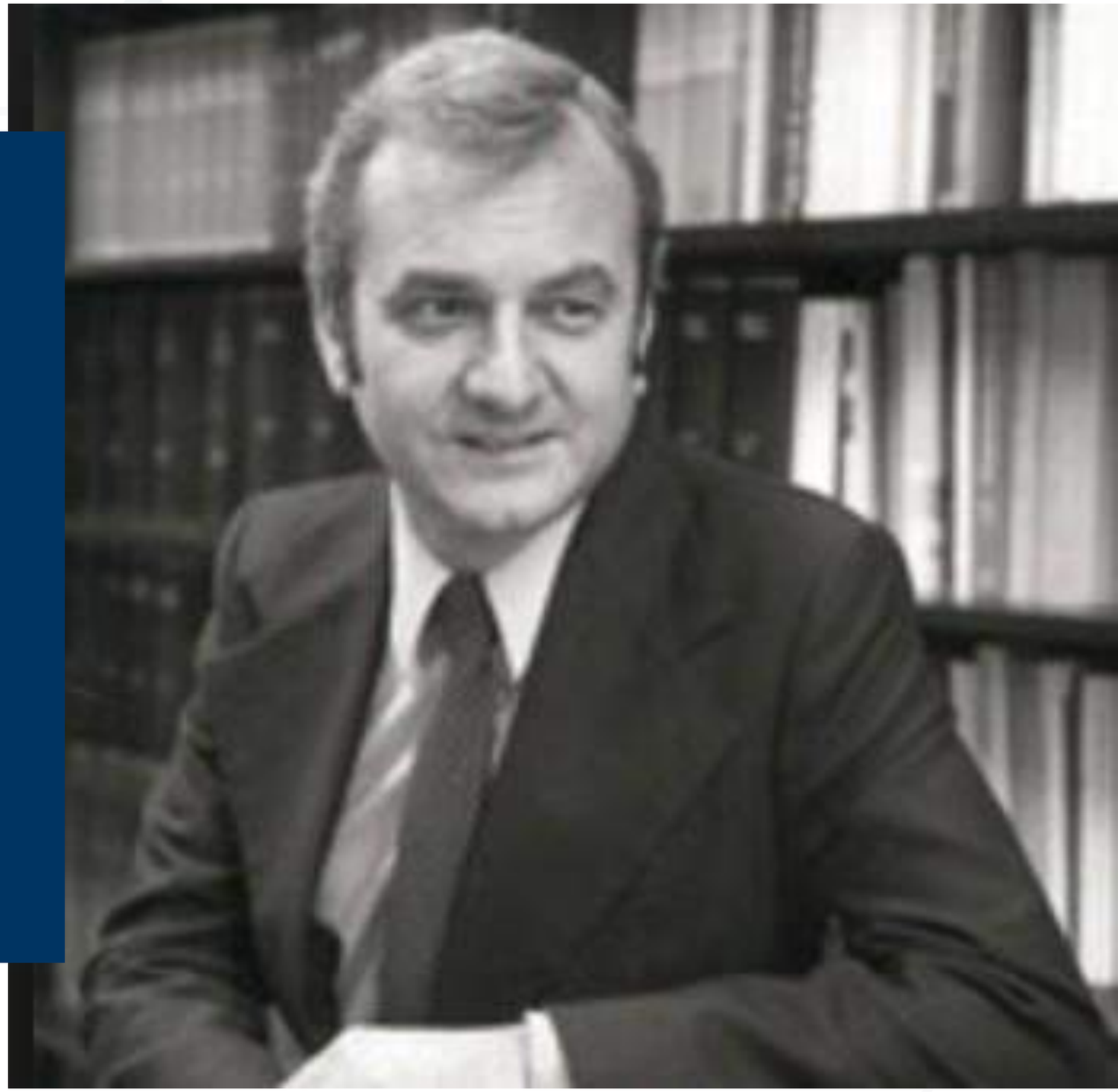


The Organism Identification Pipeline: **Further Benefits for ME/CFS**

- Further establishes ME/CFS as a **serious, biomedical condition**
- Connects researchers all focused on **developing actual treatment** for patients
- Allows us to immediately **apply the latest discoveries** in Alzheimer's, Parkinson's etc to ME/CFS (and vice versa)
- Establishes a pipeline for further analyses **at the lowest possible cost**
- Can serve as **a basis for the development** of accurate microbiome/virome commercial testing
- Sets the stage for collaboration with yet other **cutting-edge** research teams (eg: George Tetz, HMI)\
- Could lead to **increased funding** from private groups like Facebook…or even the NIH
- Will allow samples from **other ME/CFS body sites** to be additionally analyzed for organisms…and/or samples from patients with **related diagnoses such as EDS/fibromyalgia** to be analyzed

“It is unwise to dismiss the pathogenic capacities of any microbe in a patient with a mysterious disease. The so-called “autoimmune” conditions, in which no pathogen can be identified by routine testing are particularly suspect”

-Gerald Domingue, Professor Emeritus Tulane University



A personalized approach to ME/CFS diagnosis and treatment

1.Look for rare human genome variants that predispose towards persistent infection and/or environmental exposure risk

2.Characterize the maternal/inherited microbiome for the presence of inherited pathogens/dysbiotic microbiome + virome communities

3. Document and test for acquired pathogens

4. Document and test for environmental exposures

5.Document and test for microbiome/virome dysbiosis in various body sites

6.Factor in injuries, stress, pregnancies and other complications that can impact patient health

Dysbiosis in driven by changes in organism/pathogen ACTIVITY

Research | Open Access | Published: 11 May 2019

Evolution of the gut microbiome following acute HIV-1 infection

Muntsa Rocafort, Marc Noguera-Julian, Javier Rivera, Lucía Pastor, Yolanda Guillén, Jost Langhorst, Mariona Parera, Inacio Mandomando, Jorge Carrillo, Víctor Urrea, Cristina Rodríguez, Maria Casadellà, Maria Luz Calle, Bonaventura Clotet, Julià Blanco, Denise Naniche & Roger Paredes

Prevalence of fecal virus shedding

	Recent HIV-1 infection	Chronic HIV-1 infection
		ART-naive
Adenovirus	26/49 (53.2%)**	36/71 (50.7%)**
Cytomegalovirus	3/49 (6.1%)	4/71 (5.6%)*
Enterovirus	1/43 (2.4%)	4/19 (21.1%)*
Human herpes virus 6A, 6B, and 8	0/49 (0%)	0/71 (0%)

- loss of bacterial toxonomic richness
- long-term reductions in microbial gene richness

Article | Published: 23 July 2018

Murine colitis reveals a disease-associated bacteriophage community

Breck A. Duerkop, Manuel Kleiner, David Paez-Espino, Wenhan Zhu, Brian Bushnell, Brian Hassell, Sebastian E. Winter, Nikos C. Kyrpides & Lora V. Hooper

Nature Microbiology **3**, 1023–1031(2018) | Cite this article

"We discovered that during colitis the intestinal **phage population is altered and transitions from an ordered state to a stochastic dysbiosis….**Our findings indicate that **intestinal phage communities are altered** during inflammatory disease, establishing a platform for investigating phage involvement in irritable bowel disorder."

Bacterial byproducts in ME/CFS blood

Researchers at Cornell University found that ME/CFS patients **had significantly higher levels of LPS** in their blood than healthy individuals

LPS are large toxic molecules found in the membranes of bacteria

Research | Open Access

Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome

Ludovic Giloteaux, Julia K. Goodrich, William A. Walters, Susan M. Levine, Ruth E. Ley and Maureen R. Hanson

Microbiome 2016 **4**:30
https://doi.org/10.1186/s40168-016-0171-4
Received: 29 February 2016 | **Accepted:** 11 May 2016 | **Published:** 23 June 2016

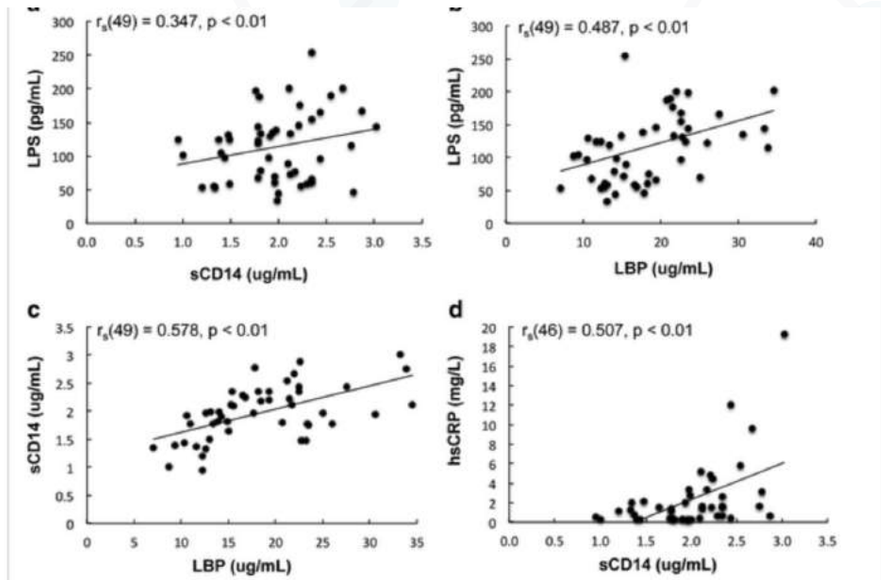


Fig. 2
Correlation between plasma levels of LPS and sCD14 (**a**), plasma levels of LPS and LBP (**b**), plasma levels of sCD14 and LBP (**c**), and plasma levels of hsCRP and sCD14 (**d**) in the ME/CFS population. Spearman's rank test was used to determine correlations

The human holobiont

nature
International journal of science

Letter | Published: 16 May 2018

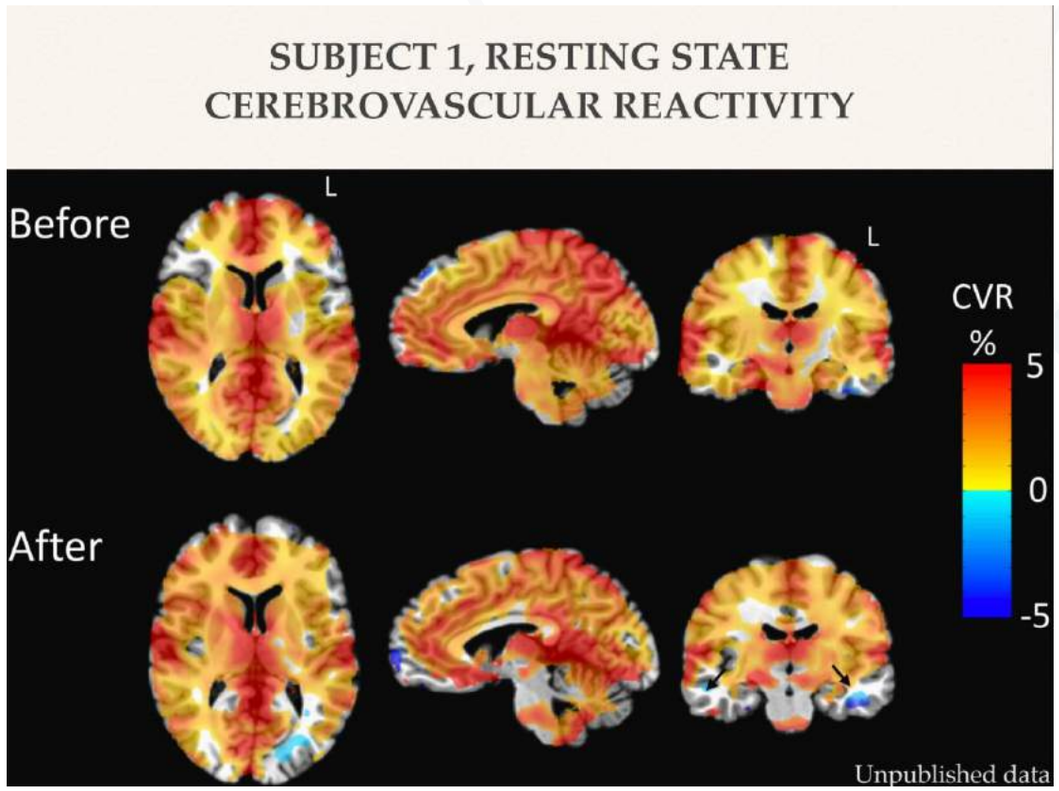
Microglial control of astrocytes in response to microbial metabolites

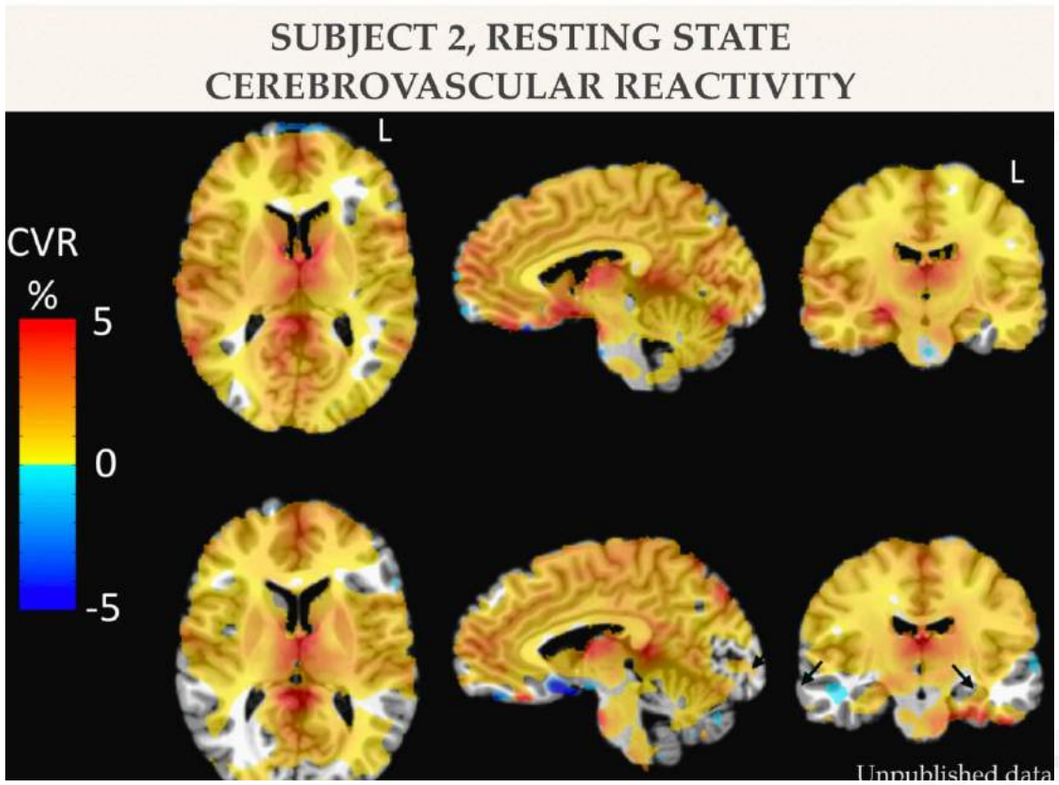
Veit Rothhammer, Davis M. Borucki, Emily C. Tjon, Maisa C. Takenaka, Chun-Cheih Chao, Alberto Ardura-Fabregat, Kalil Alves de Lima, Cristina Gutiérrez-Vázquez, Patrick Hewson, Ori Staszewski, Manon Blain, Luke Healy, Tradite Neziraj, Matilde Borio, Michael Wheeler, Loic Lionel Dragin, David A. Laplaud, Jack Antel, Jorge Ivan Alvarez, Marco Prinz & Francisco J. Quintana

Nature **557**, 724–728 (2018) | Download Citation
14k Accesses | **91** Citations | **600** Altmetric | Metrics »

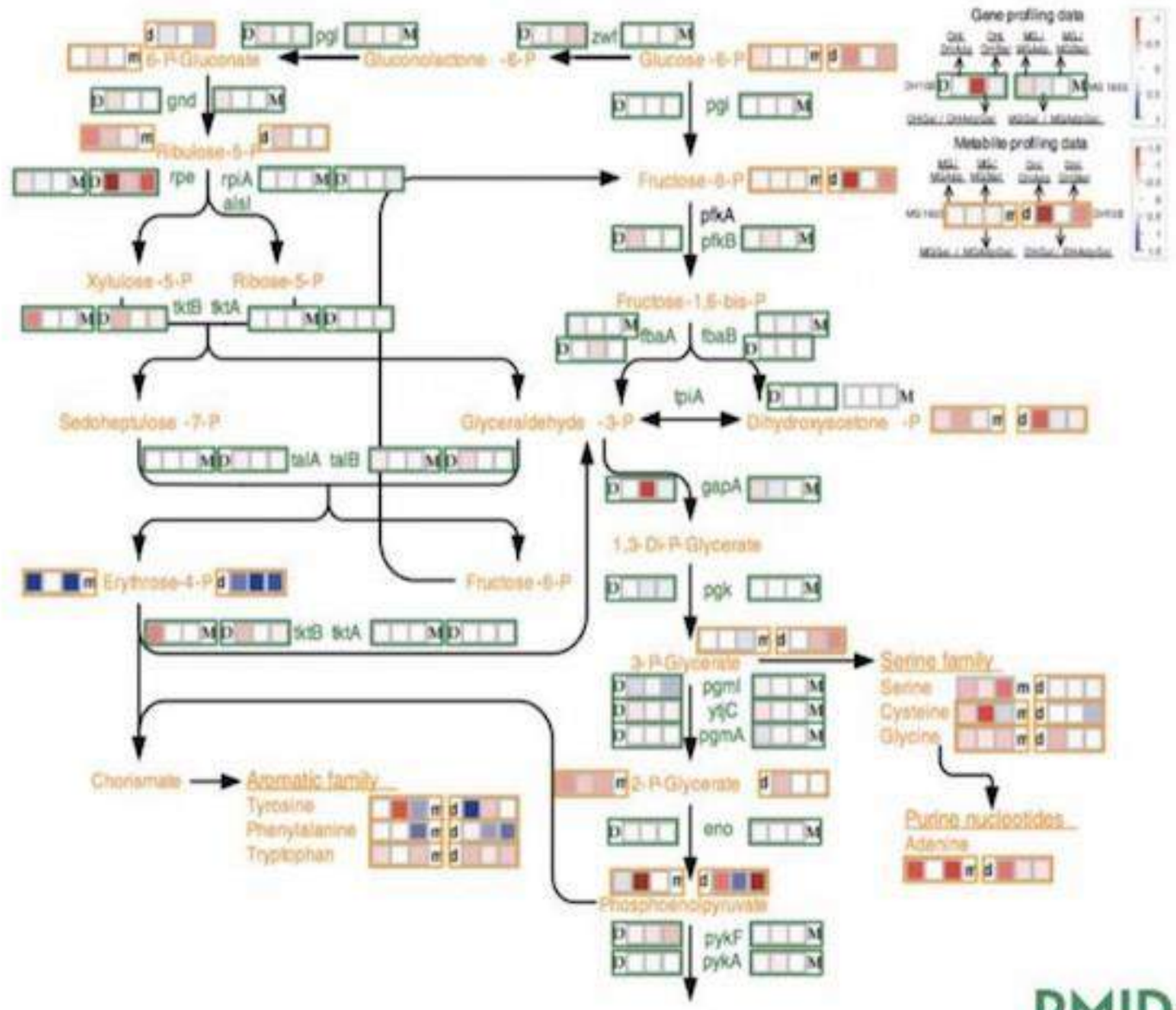
The team found that tryptophan **created by the gut microbiome** interacted with the AHR receptor on microglia/astrocytes. Subsequent changes in gene expression **regulated communication between the two cell types.**

Harvard University pilot data indicates dyregulated **blood perfusion** between the ME/CFS brain/body





E. coli glucose metabolism



PMID: 18402659

How do organisms get into the brain?

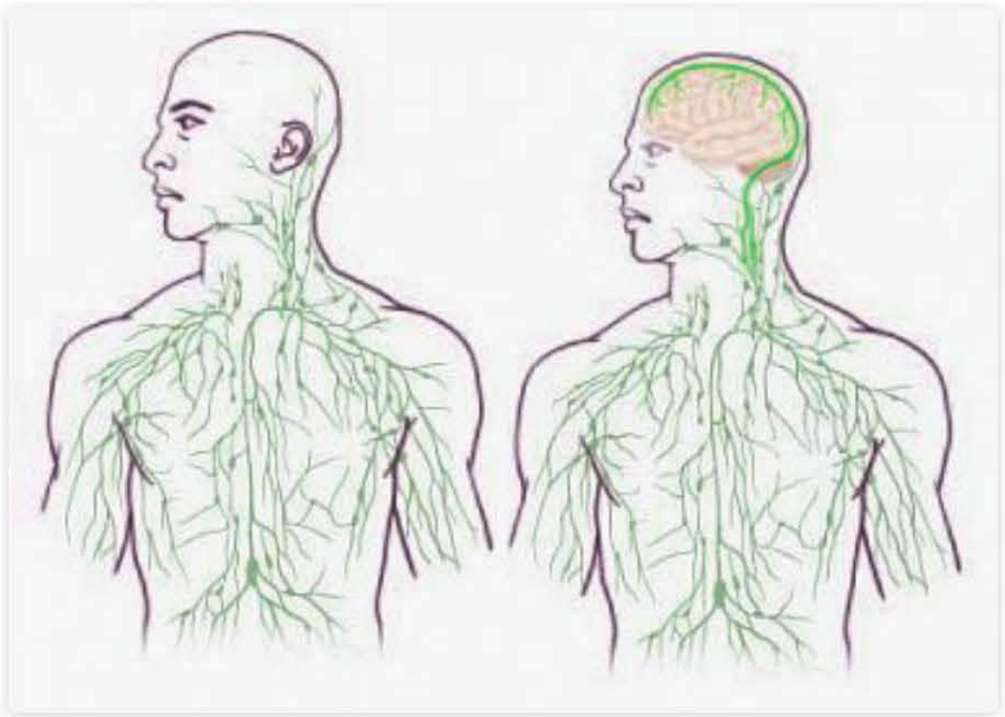
nature
International journal of science

Letter | Published: 01 June 2015

Structural and functional features of central nervous system lymphatic vessels

Antoine Louveau ✉, Igor Smirnov, Timothy J. Keyes, Jacob D. Eccles, Sherin J. Rouhani, J. David Peske, Noel C. Derecki, David Castle, James W. Mandell, Kevin S. Lee, Tajie H. Harris & Jonathan Kipnis ✉

Nature **523**, 337–341 (16 July 2015) | Download Citation ⬇



Maps of the lymphatic system: old (left) and updated to reflect the new discovery.

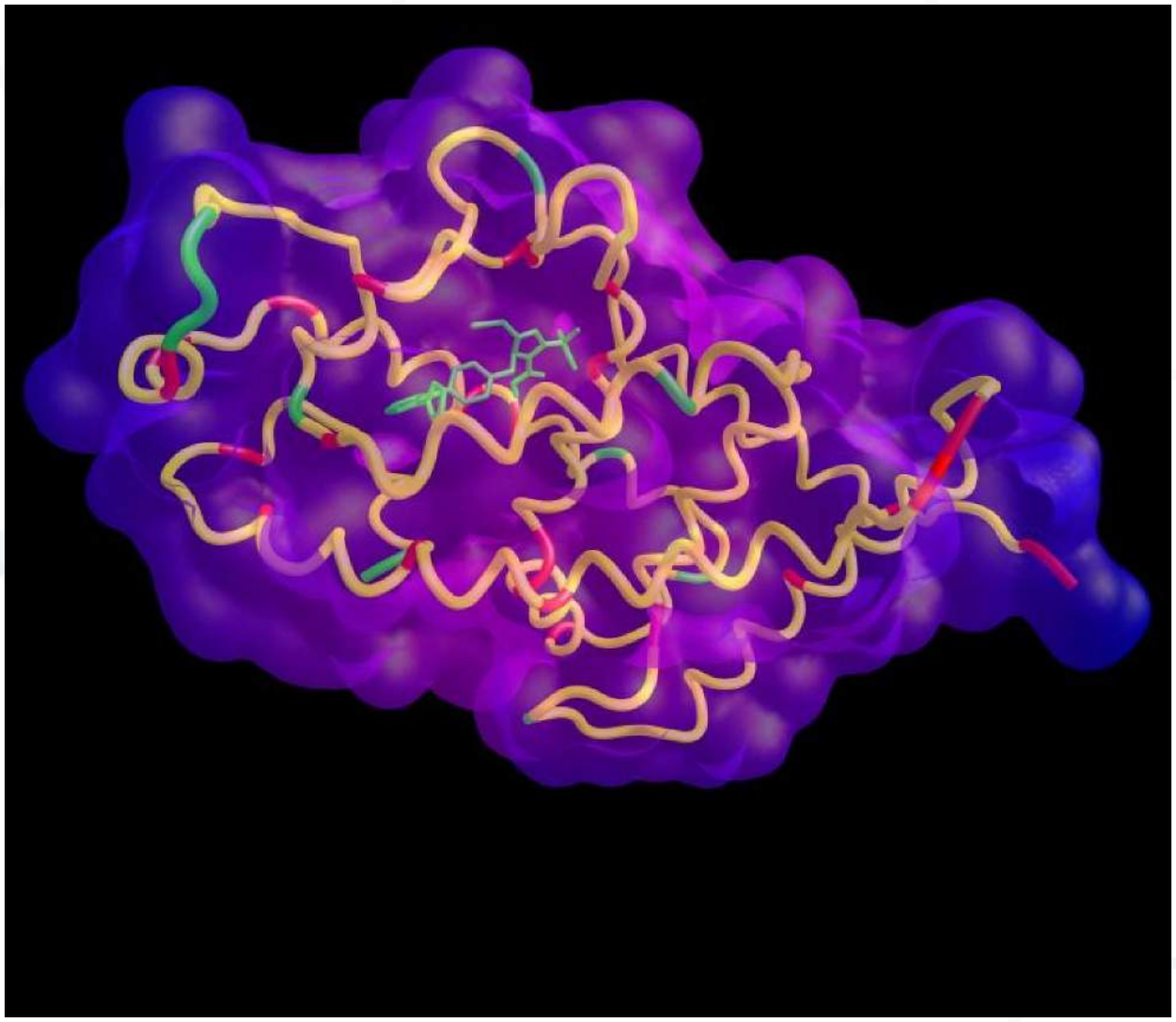
Pathogen/organism activity is characterized by a high level of functional redundancy

The VDR Nuclear Receptor

- Regulates expression of thousands of human genes, many of which regulate inflammatory and cancerous processes

- Controls multiple families of important antimicrobial peptides including cathelicidin (LL-37)

- Controls signaling of TLR2 + TLR4 (proteins that recognize foreign substances + pathogens and alert other parts of the immune response)



Pathogens that dysregulate/slow VDR activity:

- Epstein Barr Virus
- HIV
- *Mycobacterium tuberculosis*
- Cytomegalovirus
- *Borrelia burgdorferi*
- *Mycobacterium leprae*
- Aspergillus fumigatus
- *Chlamydia trachomatis*

- Because disabling the innate immune system via the VDR pathway is such a logical survival mechanism, **other uncharacterized bacteria, viruses or fungi** may have also evolved to dysregulate receptor activity.

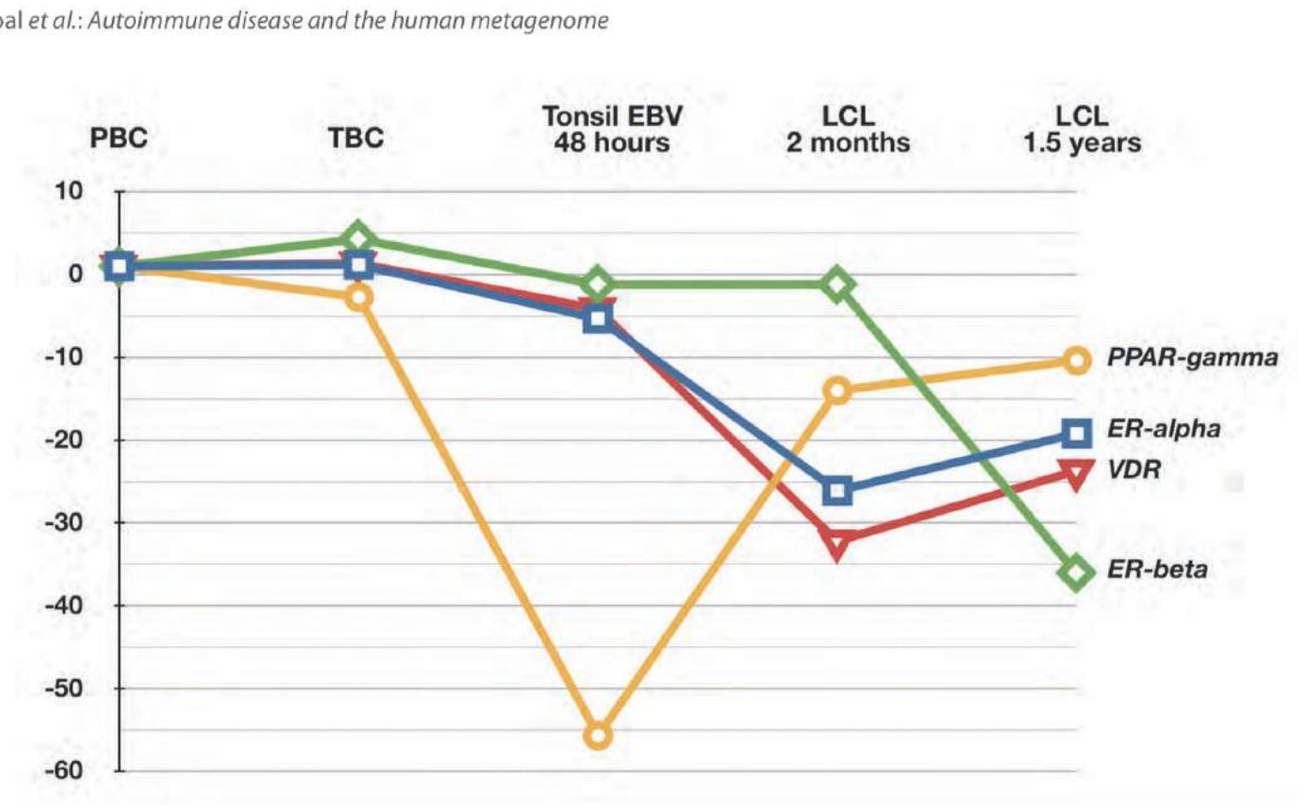
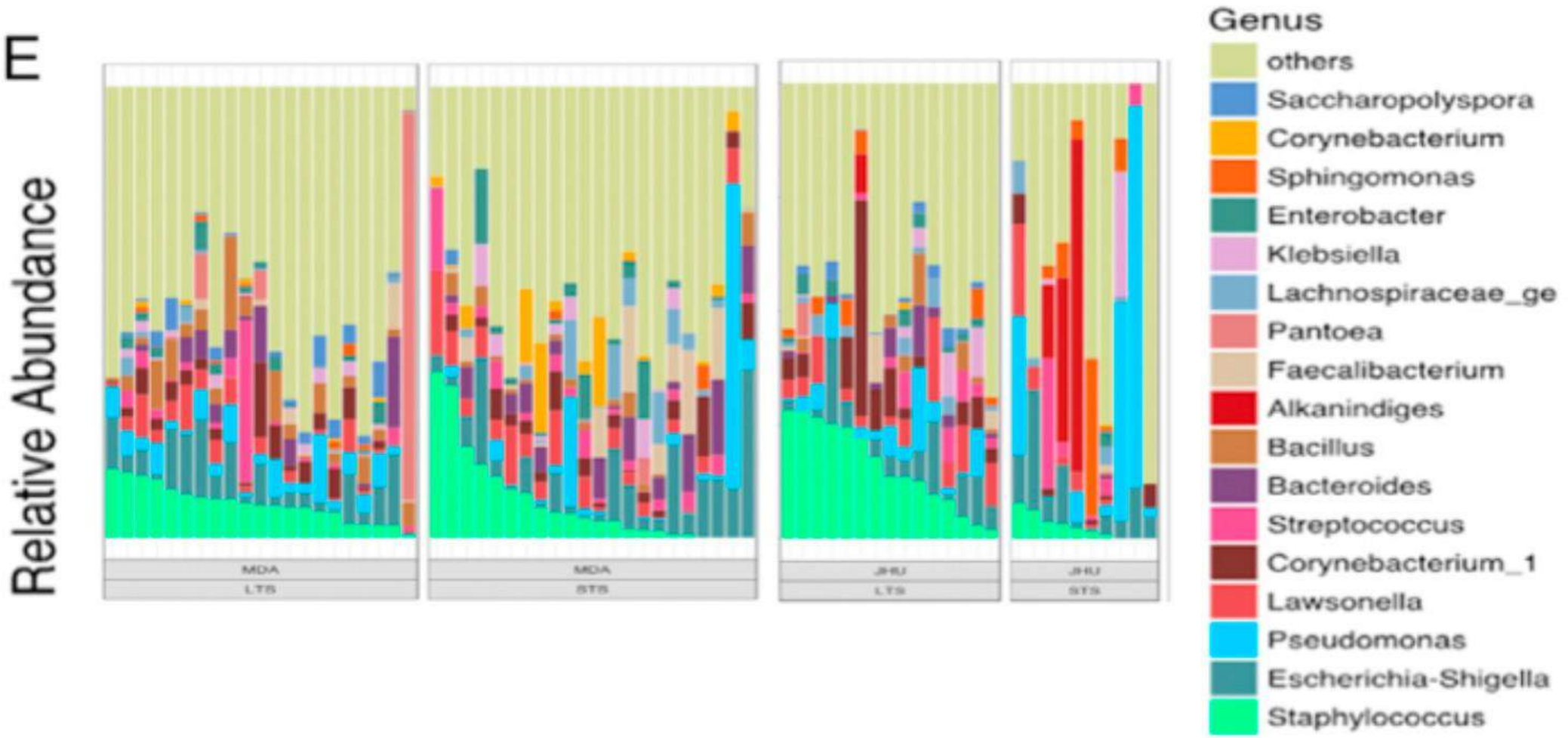


Figure 2. Nuclear receptors mRNA expression is downregulated upon infection of B-cells with EBV [65]

Taxonomic composition based on relative abundance plotted for each tumor (0%–100%).



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Clin Microbiol Rev. 2004 Apr; 17(2): 323–347.
doi: 10.1128/CMR.17.2.323-347.2004
PMCID: PMC387409
PMID: 15084504

Invasion of the Central Nervous System by Intracellular Bacteria

Douglas A. Drevets,[1,*] Pieter J. M. Leenen,[2] and Ronald A. Greenfield[1]

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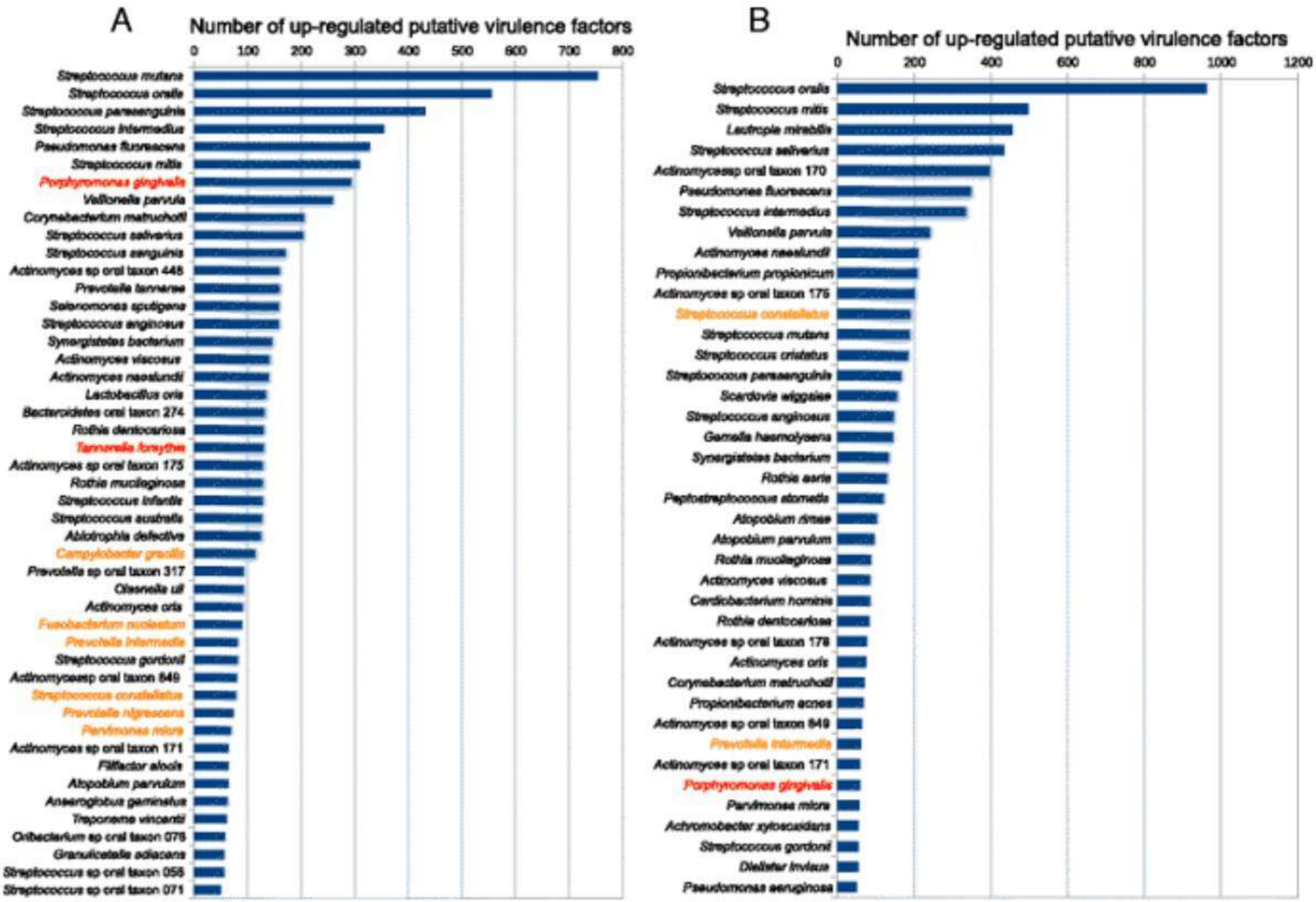
ABSTRACT

Go to:

Infection of the central nervous system (CNS) is a severe and frequently fatal event during the course of many diseases caused by microbes with predominantly intracellular life cycles. Examples of these include the facultative intracellular bacteria *Listeria monocytogenes*, *Mycobacterium tuberculosis*, and *Brucella* and *Salmonella* spp. and obligate intracellular microbes of the Rickettsiaceae family and *Tropheryma whipplei*. Unfortunately, the mechanisms used by intracellular bacterial pathogens to enter the CNS are less well known than those used by bacterial pathogens with an extracellular life cycle. The goal of this review is to elaborate on the means by which intracellular bacterial pathogens establish infection within the CNS. This review encompasses the clinical and pathological findings that pertain to the CNS infection in humans and includes experimental data from animal models that illuminate how these microbes enter the CNS. Recent experimental data showing that *L. monocytogenes* can invade the CNS by more than one mechanism make it a useful model for discussing the various routes for neuroinvasion used by intracellular bacterial pathogens.

Figure 5


A
Number of up-regulated putative virulence factors
0
100
200
300
400
500
600
700
800
Streptococcus mutans
Streptococcus oralis
Streptococcus parasanguinis
Streptococcus intermedius
Pseudomonas fluorescens
Streptococcus mitis
Porphyromonas gingivalis
Veillonella parvula
Corynebacterium matruchotii
Streptococcus salivarius
Streptococcus sanguinis
Actinomyces sp oral taxon 448
Prevotella tannerae
Selenomonas sputigena
Streptococcus anginosus
Synergistetes bacterium
Actinomyces viscosus
Actinomyces naeslundii
Lactobacillus oris
Bacteroidetes oral taxon 274
Rothia dentocariosa
Tannerella forsythia
Actinomyces sp oral taxon 175
Rothia mucilaginosa
Streptococcus infantis
Streptococcus australis
Abiotrophia defectiva
Campylobacter gracilis
Prevotella sp oral taxon 317
Olsenella uli
Actinomyces oris
Fusobacterium nucleatum
Prevotella intermedia
Streptococcus gordonii
Actinomycesp oral taxon 849
Streptococcus constellatus
Prevotella nigrescens
Parvimonas micra
Actinomyces sp oral taxon 171
Filifactor alocis
Atopobium parvulum
Anaeroglobus geminatus
Treponema vincentii
Oribacterium sp oral taxon 078
Granulicatella adiacens
Streptococcus sp oral taxon 058
Streptococcus sp oral taxon 071
B
Number of up-regulated putative virulence factors
0
200
400
600
800
1000
1200
Streptococcus oralis
Streptococcus mitis
Lautropia mirabilis
Streptococcus salivarius
Actinomycesp oral taxon 170
Pseudomonas fluorescens
Streptococcus intermedius
Veillonella parvula
Actinomyces naeslundii
Propionibacterium propionicum
Actinomyces sp oral taxon 175
Streptococcus constellatus
Streptococcus mutans
Streptococcus cristatus
Streptococcus parasanguinis
Scardovia wiggsiae
Streptococcus anginosus
Gemella haemolysans
Synergistetes bacterium
Rothia aeria
Peptostreptococcus stomatis
Atopobium rimae
Atopobium parvulum
Rothia mucilaginosa
Actinomyces viscosus
Cardiobacterium hominis
Rothia dentocariosa
Actinomyces sp oral taxon 178
Actinomyces oris
Corynebacterium matruchotii
Propionibacterium acnes
Actinomyces sp oral taxon 849
Prevotella intermedia
Actinomyces sp oral taxon 171
Porphyromonas gingivalis
Parvimonas micra
Actinomobacter xylosoxidans
Streptococcus gordonii
Dialister invisus
Pseudomonas aeruginosa

Pathobiont behavior could be compared to children misbehaving when the teacher leaves the classroom

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