INFLAMMATION, IMMUNITY, AND THE GUT MICROBIOME IN PARKINSON'S RISK AND PROGRESSION






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NORMAN FIXEL INSTITUTE FOR NEUROLOGICAL DISEASES

DISCLOSURES

- Ex-employee of Xencor Inc. and Co-inventor of DN-TNFs (XPro1595)

- *Industry Collaborations*:
  - INmune Bio
  - Prevail
  - Merck
  - Denali
  - Longevity
  - Biogen/IONIS
  - Amylyx

- *Advisory Boards*:
  - Weston Foundation
  - Quebec Parkinson's Network
  - Alzheimer's Association

- *Grant Review Panels*:
  - NIH Study Section (CNNT)
  - MJ Fox Foundation
  - W. Garfield Weston Foundation
  - Alzheimer's Association
  - Bright Focus Foundation
  - Alzheimer's Drug Discovery Foundation (ADDF)

- *Editorial Boards:*
- *Neurobiology of Disease*
- *Experimental Neurology*
- *Journal of Parkinson's Disease*
- *NPJ Parkinson's Disease*
- *PLoS ONE*

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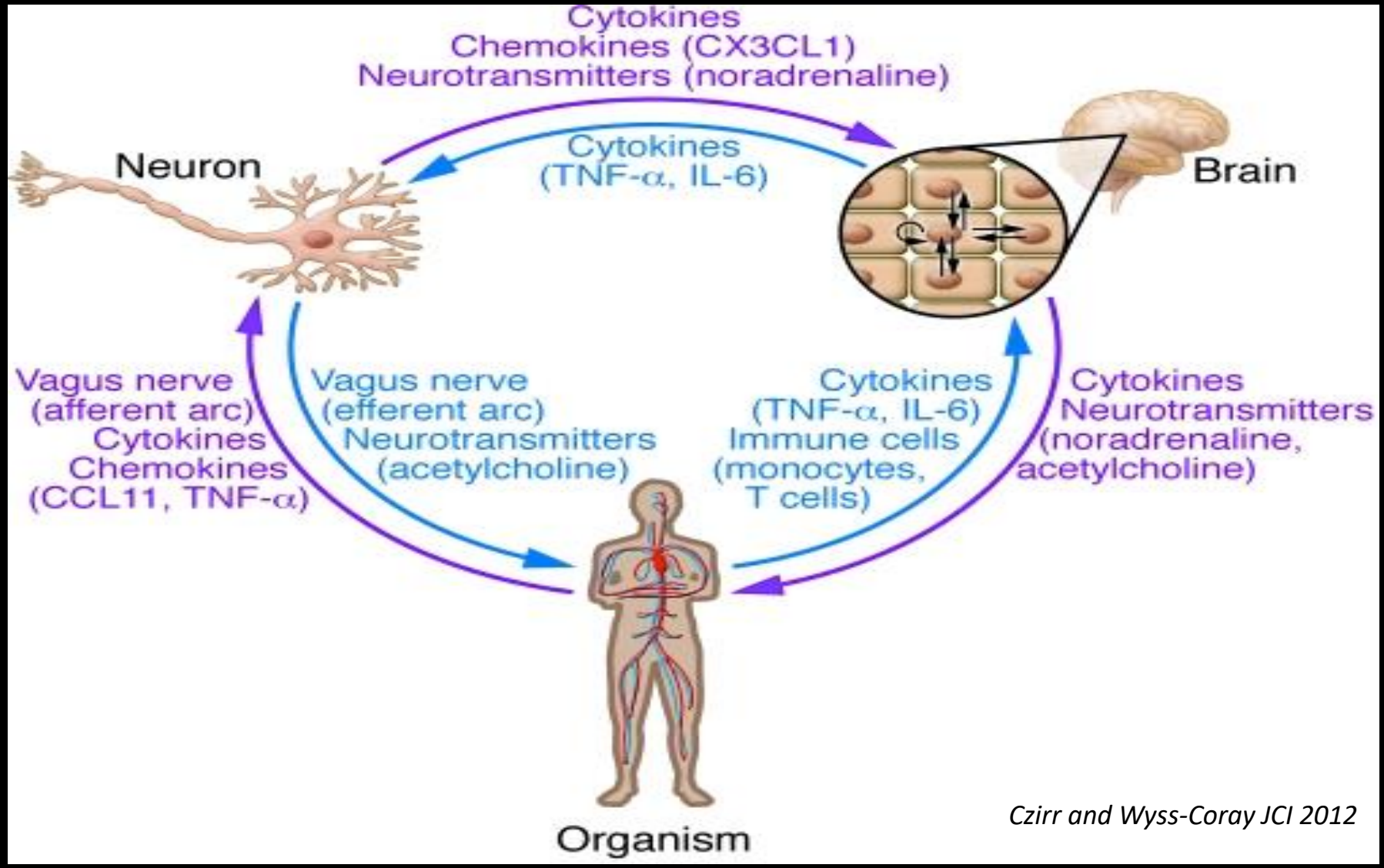
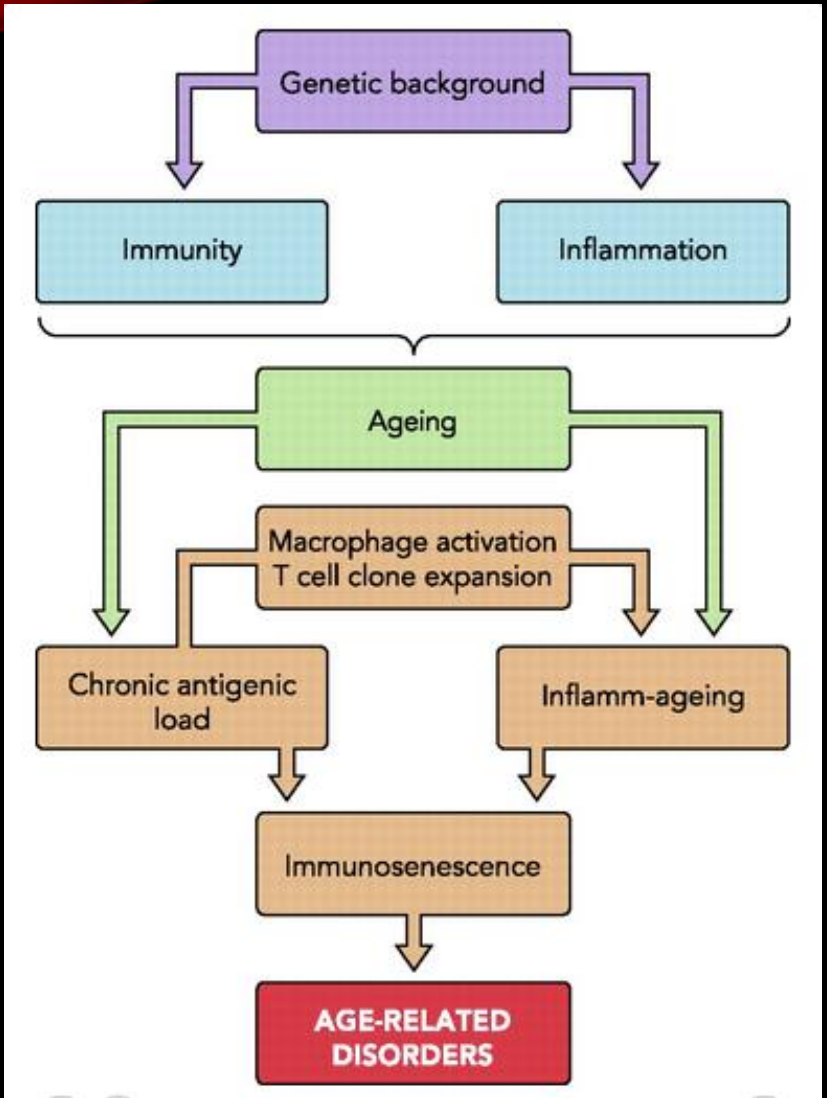
NIH
MJ Fox Foundation
Parkinson's Foundation
Alzheimer's Association
ADDF/AFTD

BIDIRECTIONAL COMMUNICATION BETWEEN THE NERVOUS AND IMMUNE SYSTEMS IS CRITICAL FOR BRAIN HEALTH



Czirr and Wyss-Coray JCI 2012

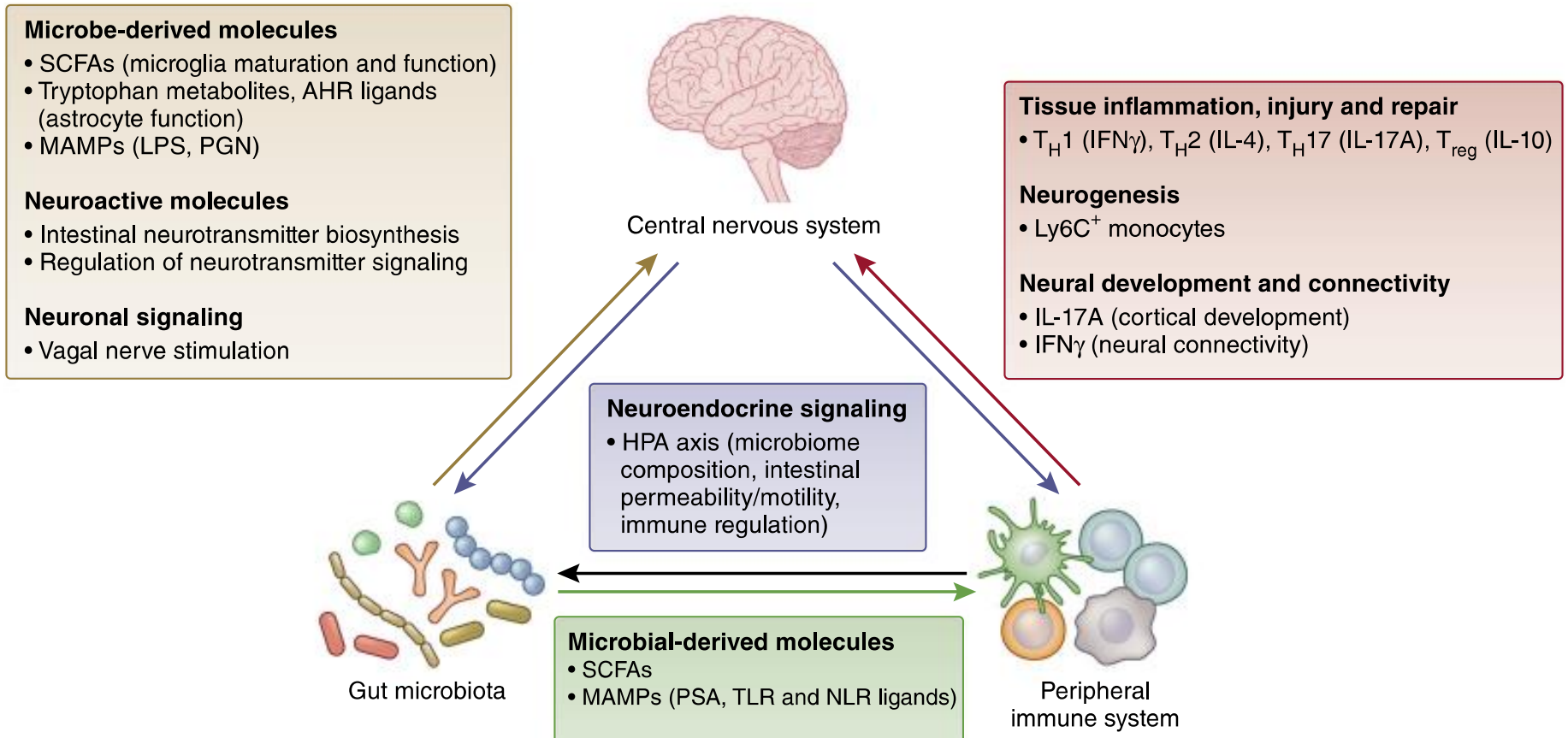
HUMAN LONGEVITY, GENETICS AND INFLAMMATION



Larbi et al 2008

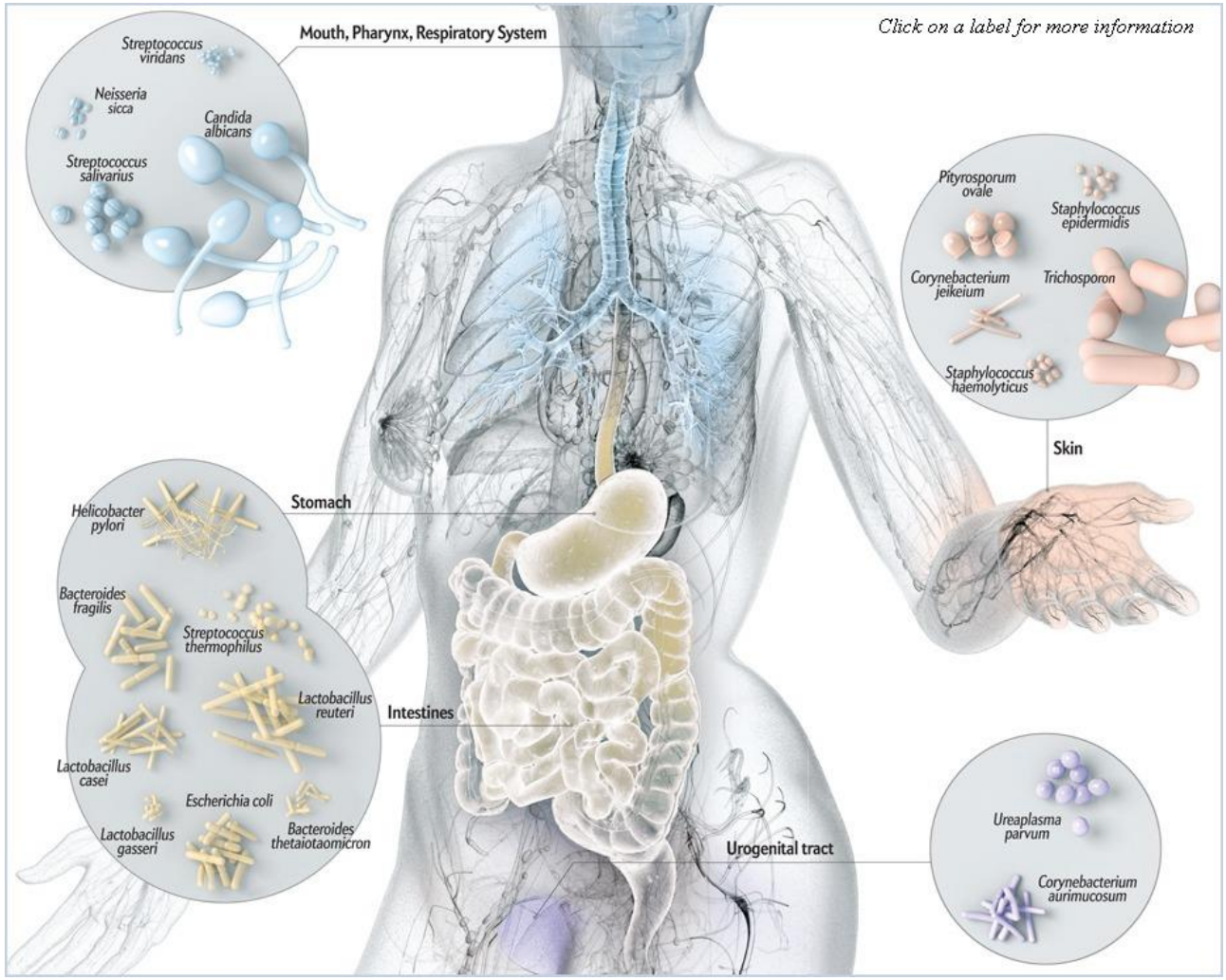
- Evolutionary pressure for genes and gene variants → robust immune responses
- Increased longevity → chronic antigenic load
- Inflamm-aging (increased low-grade chronic inflammation) and immunosenescence (loss of immunocompetence and autoimmunity)
- Age is the #1 risk factor for AD and PD

CNS-Gut-Peripheral Immune System: Novel Targets for Therapeutic Intervention

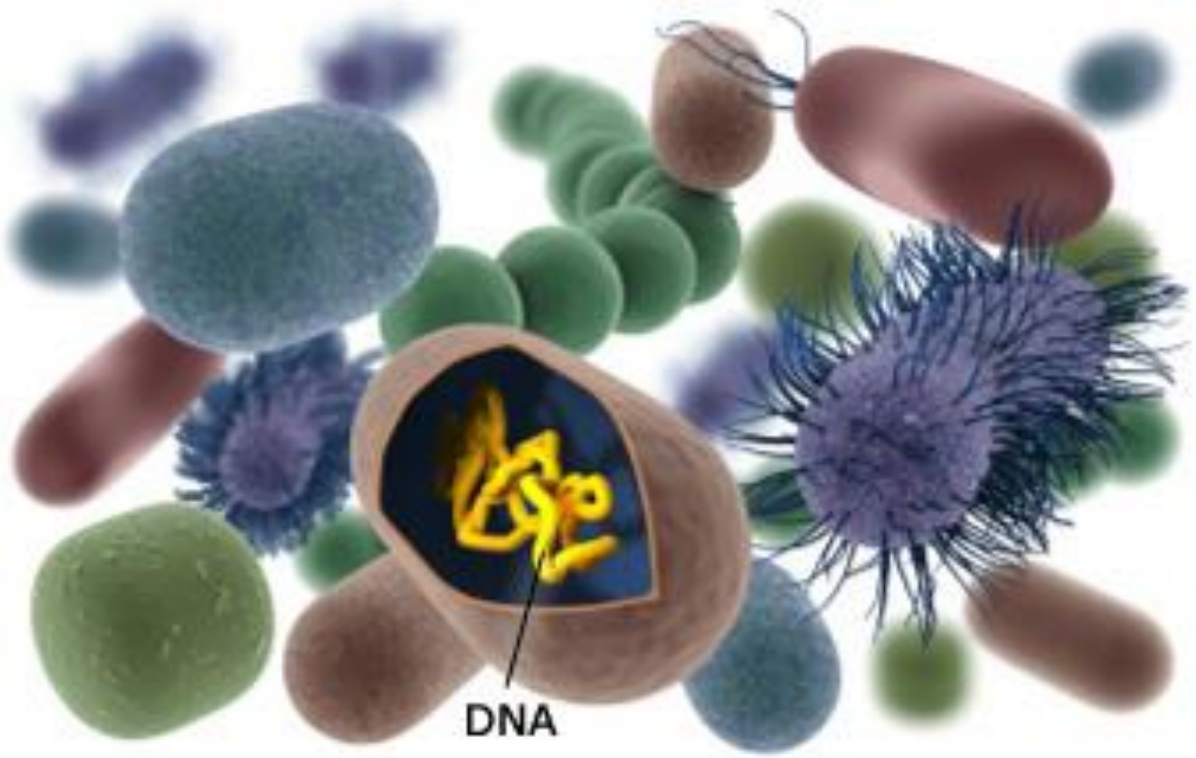


Fung , Olson and Hsiao Nature Neuro 2017

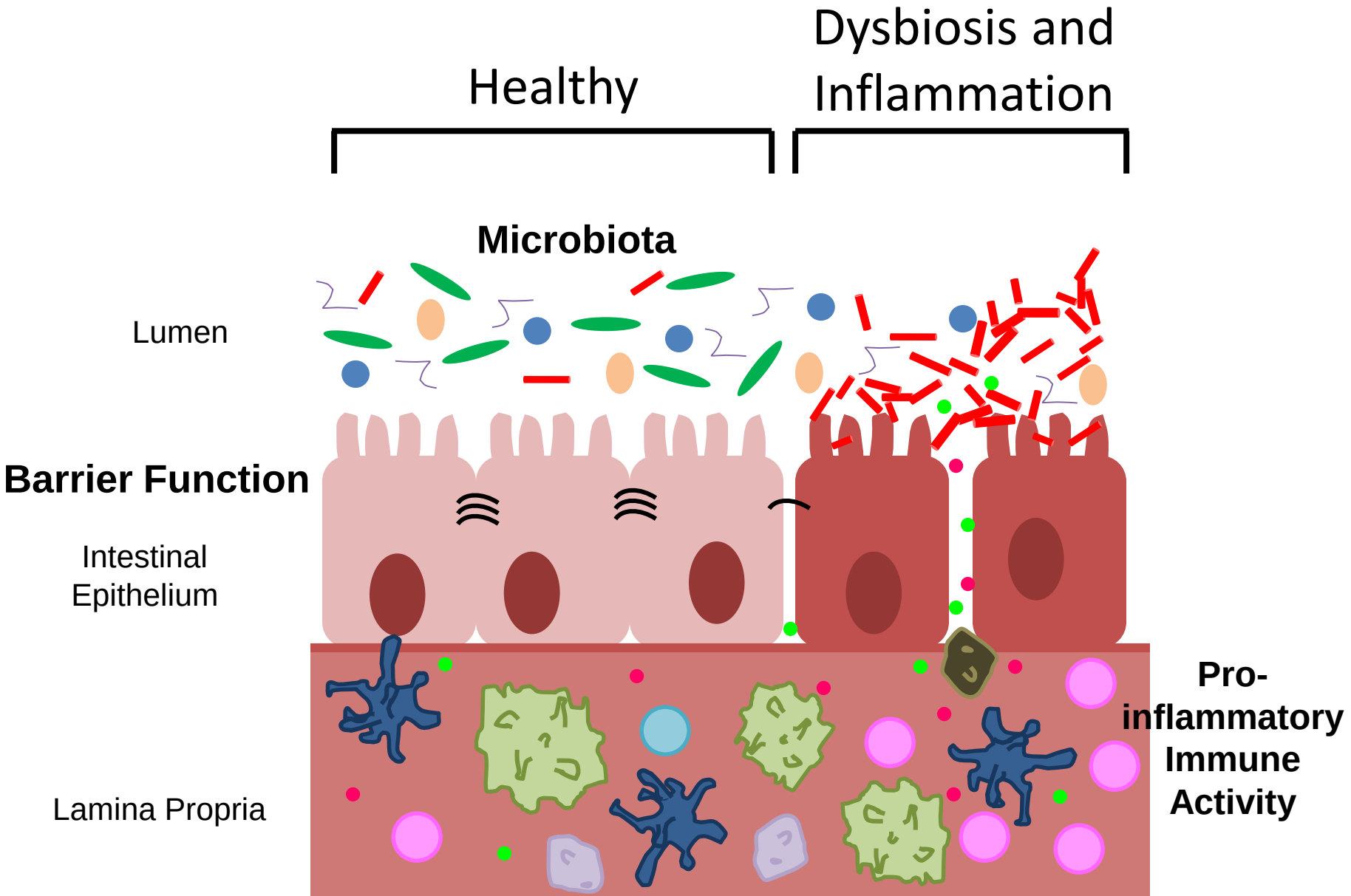
What is the Microbiome?



Bacterial taxa can be identified by sequencing dna



Gut Barrier Critical for Brain Health



WHERE DOES IT COME FROM?

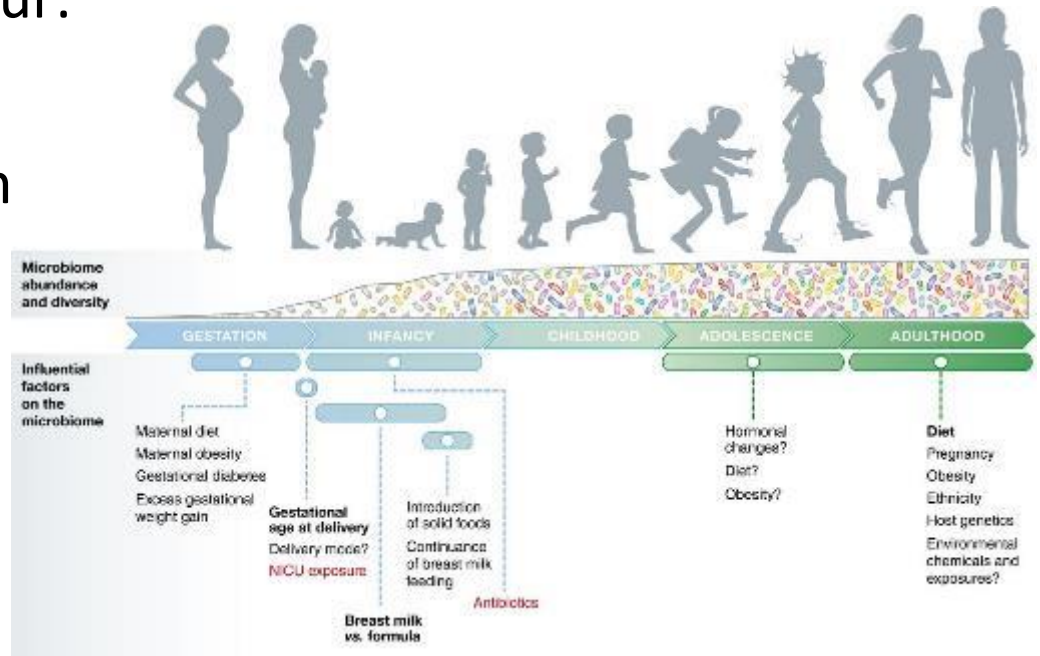
Fetus is traditionally considered sterile

Bacteria is acquired at birth, changes as the human develops/changes.

Bacterial composition is highly variable person to person, throughout a person's life.

Thought to be determined by our:

- Diet
- Genetics/Immune System
- Environment

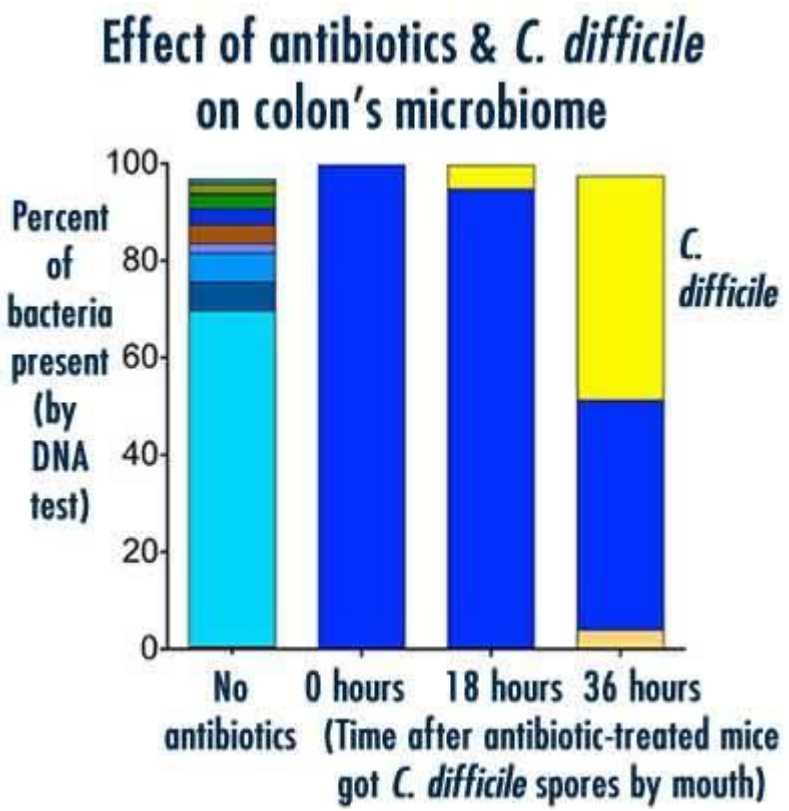


Most bacteria in the microbiota benefit us

- Food digestion
- Wound healing
- Regulate immune system
- Etc.
- Etc.
- Etc.

Antibiotics save lives, but…

- Destroy our microbiota
- Leave “space” for more pathogenic bacteria to colonize and cause disease



The GUT Microbiome has been Demonstrated to play a role in which 10 of these diseases?

- Amphetamine abuse
- Anxiety
- Asthma
- Autism Spectrum Disorder
- Eyesight
- Gut health
- Hair growth
- High blood pressure
- Inheritance patterns of human DNA
- Mathematical ability
- Multiple sclerosis
- Nail growth
- Obesity
- Parkinson’s disease
- Response to cocaine
- Tay-Sachs disease

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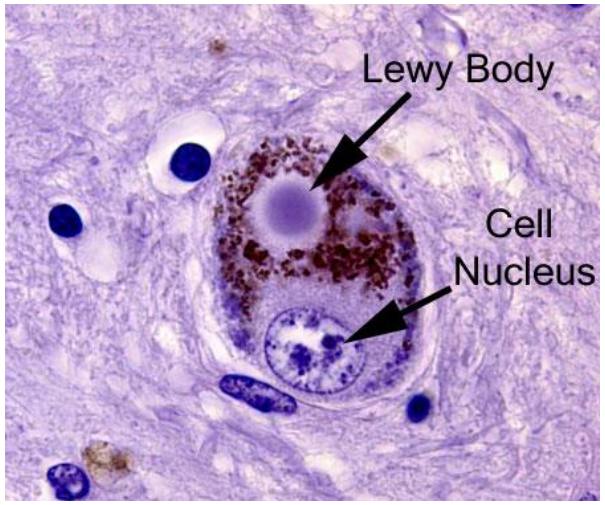
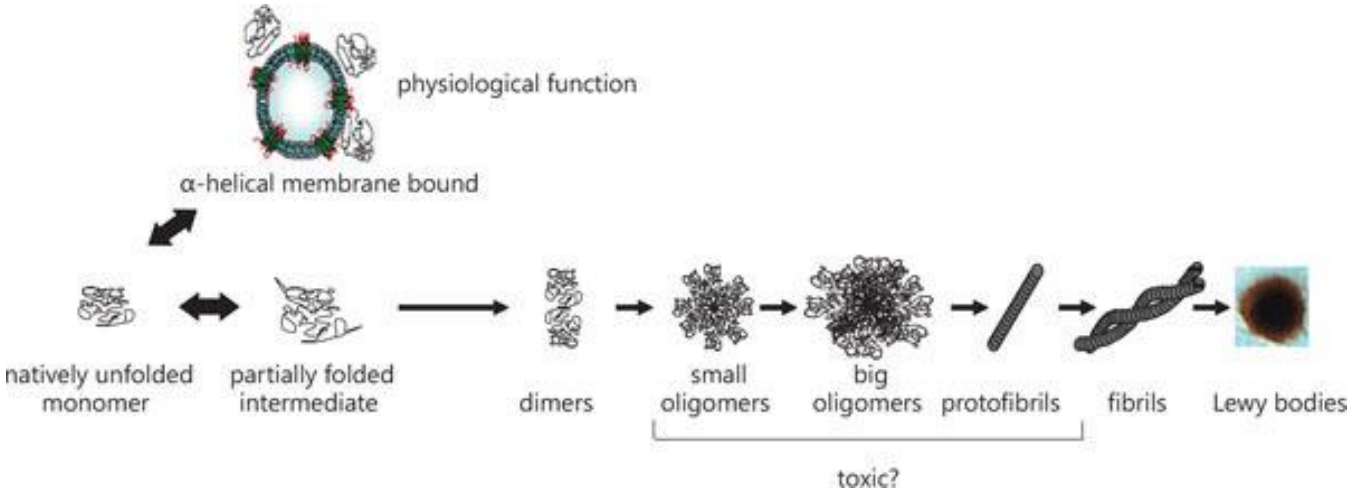
Alpha-synuclein and PD

- Initiating event in α-synuclein aggregation is unknown
- Increased expression of α-synuclein is a factor in aggregation
- 5 *SNCA* mutations of familial PD have been identified (Roberts, 2015)



Houlden, 2012



Eschbach & Danzer, 2013

Unhealthy Aging

Chronic Systemic Inflammatory Disease

(T2D, MetS, Obesity, Atherosclerosis, Arthritis?)

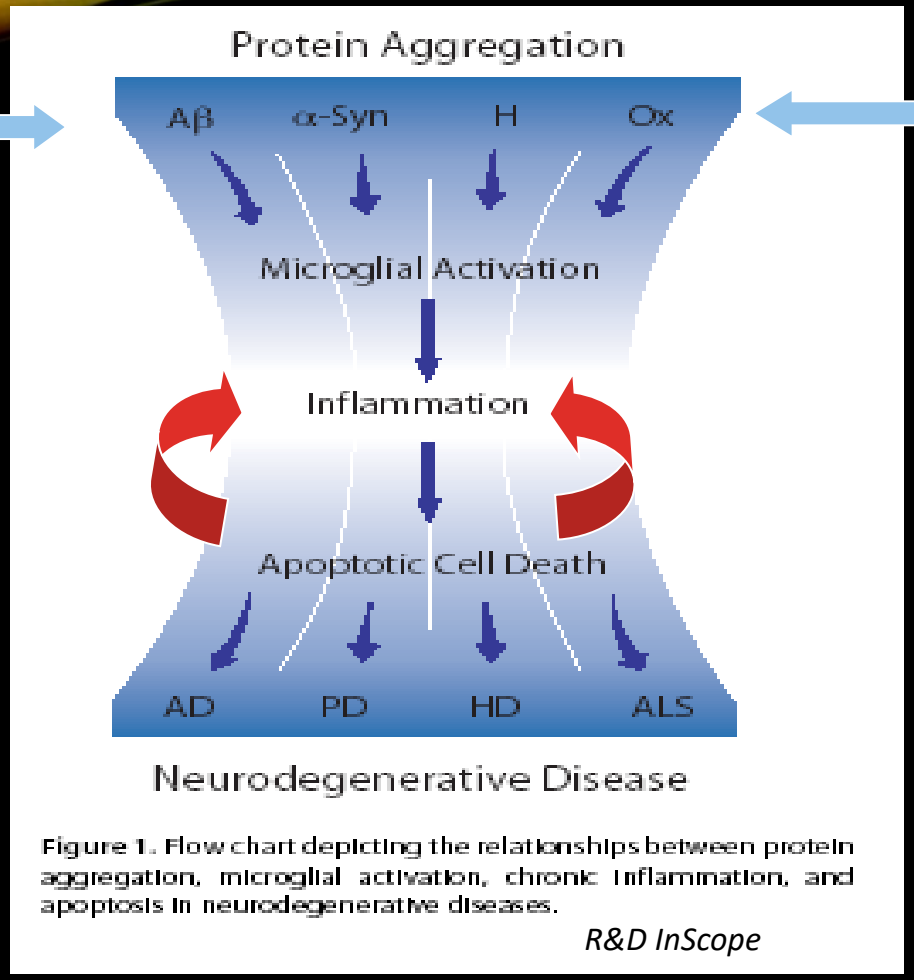


Figure 1. Flow chart depicting the relationships between protein aggregation, microglial activation, chronic inflammation, and apoptosis in neurodegenerative diseases.

R&D InScope

Environmental Exposures

Peripheral Infections

Pesticides

Physical Inactivity

Unhealthy Diet and Gut Dysbiosis

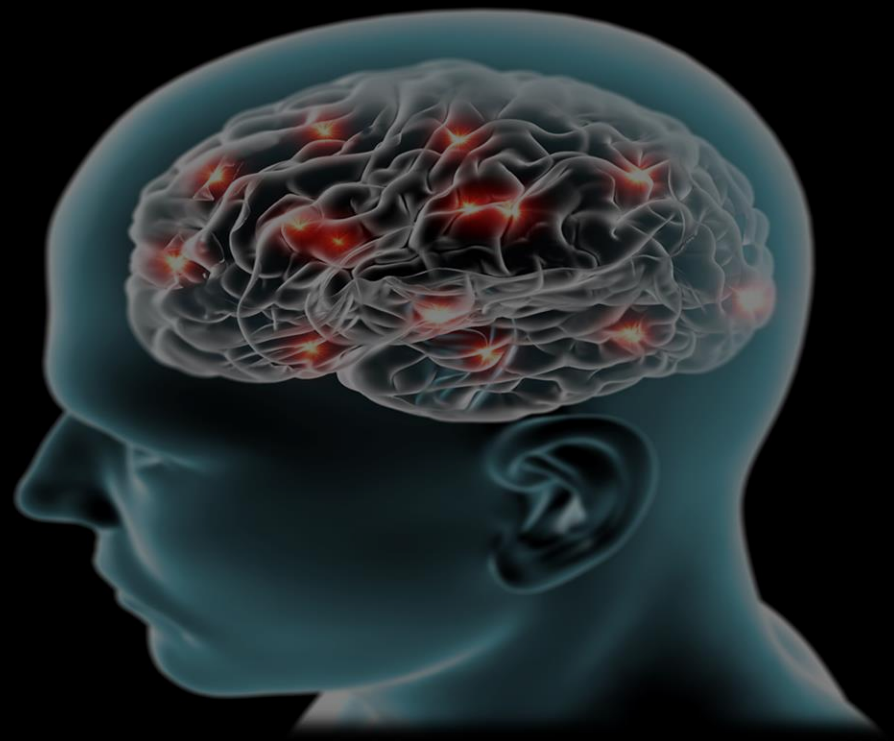
Model Linking Chronic Central or Peripheral Inflammation to Neurodegeneration

INFLAMMATION AND IMMUNE DYSFUNCTION IN PARKINSON'S DISEASE

Neurohistology
Gliosis, Cytokines

Biofluids
Cytokines, Immune cells

Neuroimaging
Microgliosis



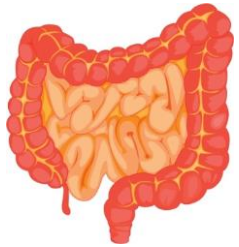
Genetics
Immune Gene SNPs

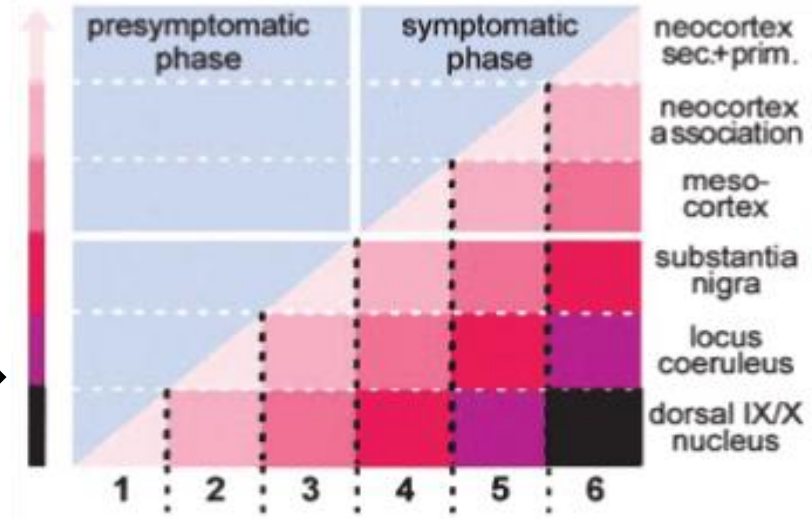
Epidemiology
Infections, NSAIDs, IBD

Parkinson's disease: non-motor symptoms

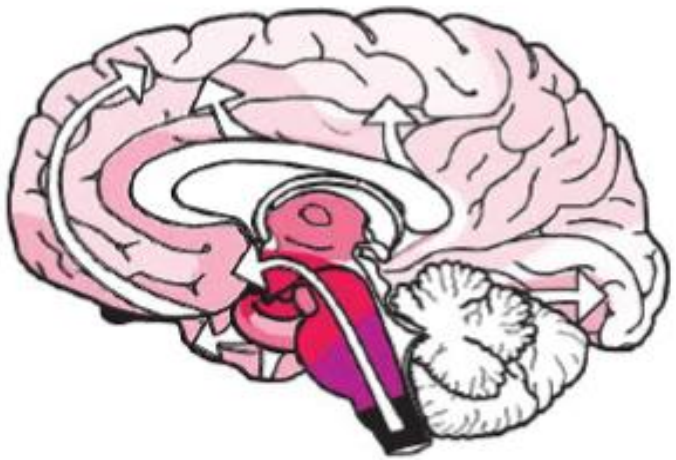
Non-Motor symptoms

- Hyposmia
- Anxiety
- Depression
- Sleep disturbances
- **GI dysfunction**





Some non-motor symptoms are also pre-motor symptoms



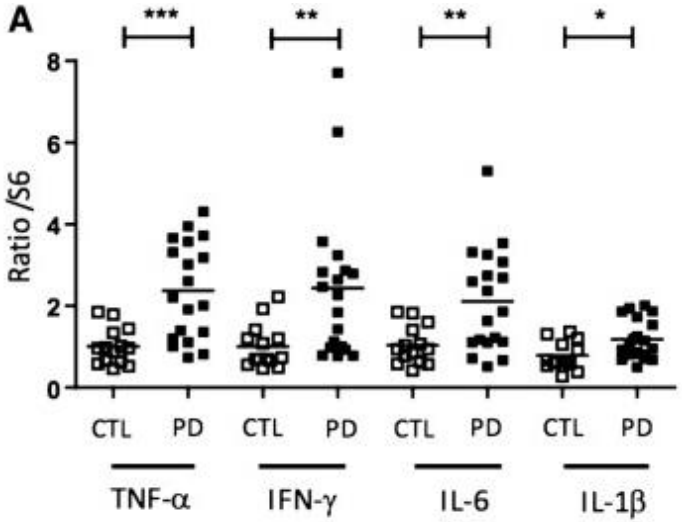
Braak, H., et al. Cell Tissue Res (2004) 318: 121.

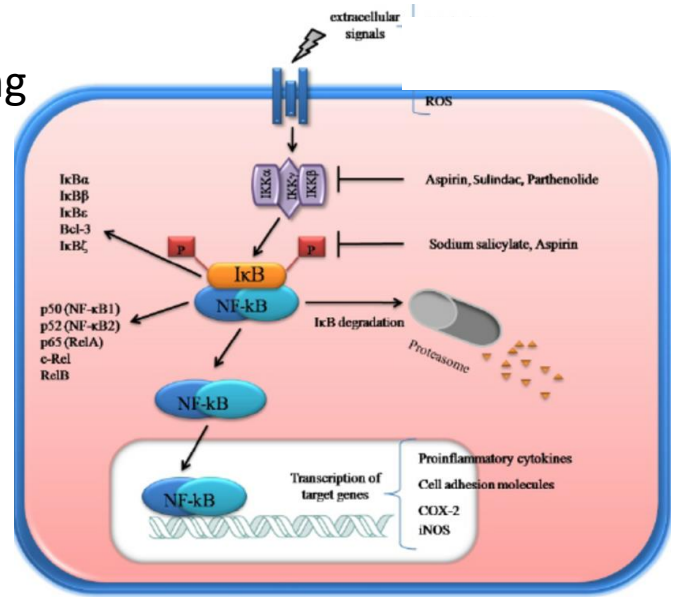
Intestinal inflammation is present in Parkinson's disease

Houser et al., ***Movement Disorders*** 2018

PD patients have:

- ↑ intestinal pro-inflammatory cytokines (TNF, IFNγ, IL-6, IL-1β) (Devos *Neurobiol Dis* 2013)
- ↑ fecal calprotectin and lactoferrin (Mulak *Gastroenterol* 2017, Schwiertz *Parkinsonism Relat Disord* 2018)
- ↑ fecal IL-1α, IL-1β, CXCL8, CRP (Houser *Mov Disord* 2018)
  - All associated with NFκB signaling



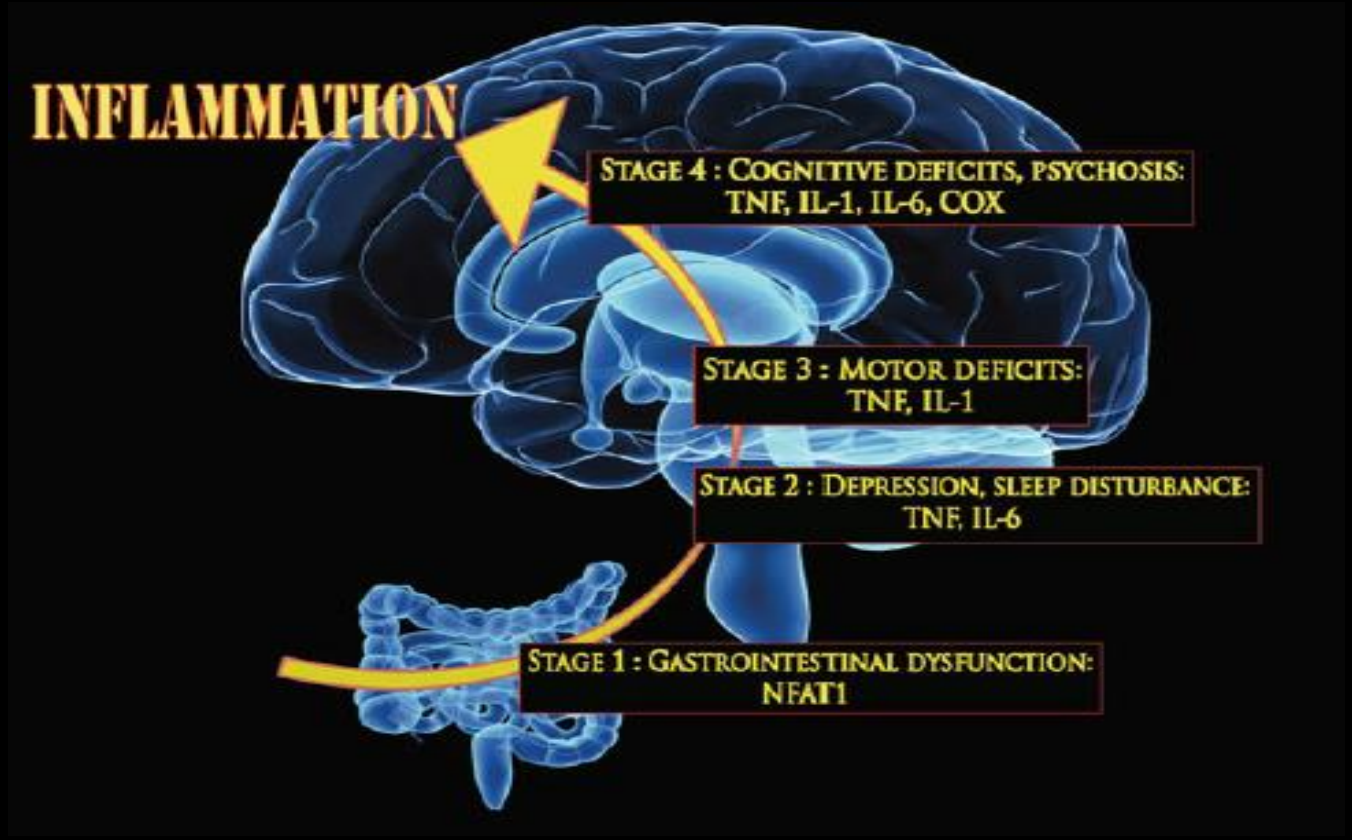


Increased incidence of psychological and gastrointestinal symptoms in PD patients and decreased coffee and alcohol consumption

Question	Response	Subjects		X^2	p
		Controls	*PD Patients*		
Diagnosed or suspected anxiety	Yes	11	41	11.52	0.0007
		10.0%	26.1%		
	No	98	110		
		89.1%	70.1%		
Diagnosed or suspected depression	Yes	24	52	5.147	0.0233
		21.8%	33.1%		
	No	84	95		
		76.4%	60.5%		
Diagnosed or suspected sleep problems, insomnia	Yes	14	61	22.61	0.0001
		12.7%	38.9%		
	No	92	89		
		83.6%	56.7%		
Experienced digestive problems in the past 3 months	Yes	40	101	22.69	<0.0001
		36.4%	64.3%		
	No	58	40		
		52.7%	25.5%		
Currently on medication for digestive problems	Yes	16	47	8.086	0.0045
		14.5%	29.9%		
	No	89	106		
		80.9%	67.5%		

Question	Response	Subjects		X^2	p
		Controls	*PD Patients*		
Diagnosed or suspected IBD, IBS, Crohn's, or colitis	Yes	9	26	4.390	0.0361
		8.2%	16.6%		
	No	101	126		
		91.8%	80.3%		
How much caffeinated coffee do you drink	None	26	40	11.61	0.0205
		23.6%	25.5%		
	<6 cups a week	10	27		
		9.1%	17.2%		
	At least 1 cup a day	13	16		
		11.8%	10.2%		
	1-2 cups a day	36	55		
		32.7%	35.0%		
	3+ cups a day	25	14		
		22.7%	8.9%		
How much alcohol do you drink	None	31	59	19.38	0.0016
		28.2%	37.6%		
	< 2 drinks a week	47	48		
		42.7%	30.6%		
	2-6 drinks a week	8	31		
		7.3%	19.7%		
	1 drink a day	9	7		
		8.2%	4.5%		
	2 drinks a day	12	5		
		10.9%	3.2%		
	3+ drinks a day	3	2		
		2.7%	1.3%		

Chronic inflammation as a driver in multisystem Dysfunction in PD

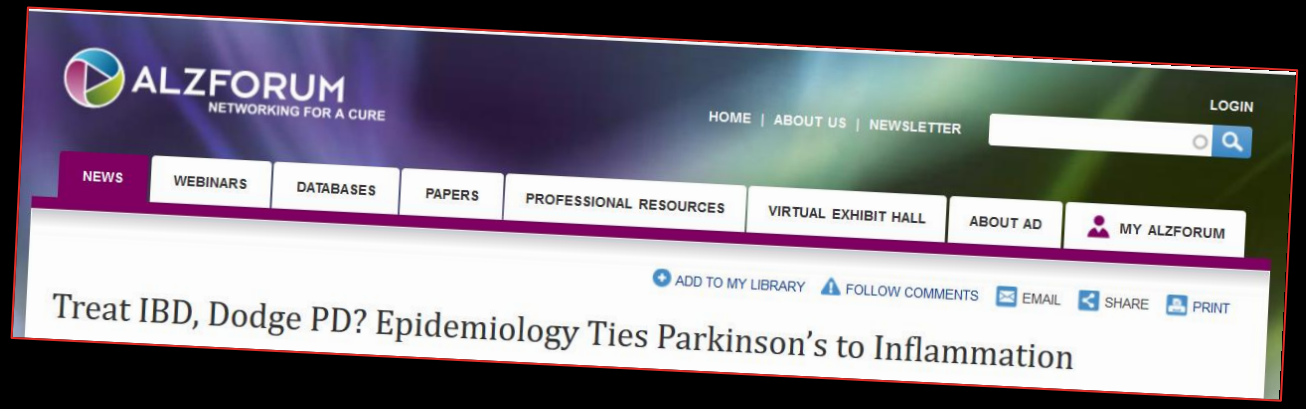


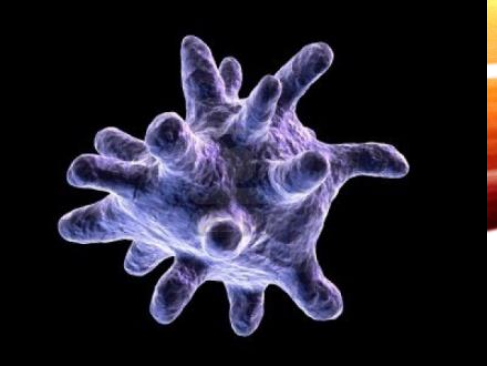
Barnum and Tansey, Curr Neurol Neurosci Rep 2012
MOVEMENT DISORDERS
Neuroinflammation and Non-motor Symptoms: The Dark Passenger of Parkinson's Disease?

IBD AND PD ARE EPIDEMIOLOGICALLY LINKED, AND ANTI-TNF BIOLOGICS REDUCE PD RISK

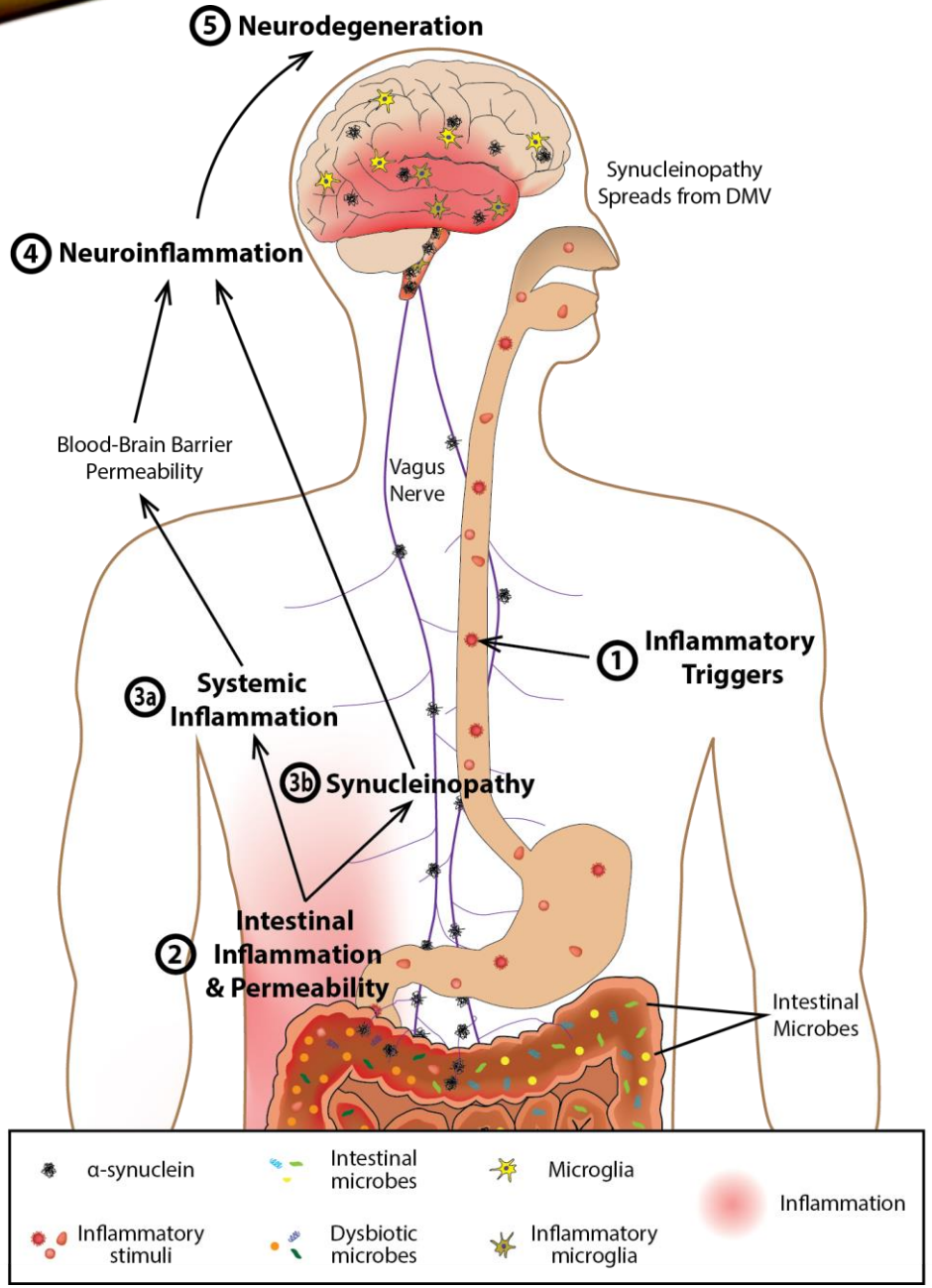
- Patients with IBD are more likely to develop PD (Lin *Inflamm Bowel Dis* 2016, Peter *JAMA Neurol* 2018, Villumsen *Inflamm Bowel Dis* 2018)

- Anti-TNF therapy reduces incidence of PD in IBD patients by 78% (Peter *JAMA Neurol* 2018)





INTESTINAL INFLAMMATION MAY DRIVE PD PATHOGENESIS



Houser, MC and MG Tansey, NPJ Parkinson's Disease, 2017

Gut inflammation may trigger Asyn Upregulation, Aggregation and Propagation to the CNS

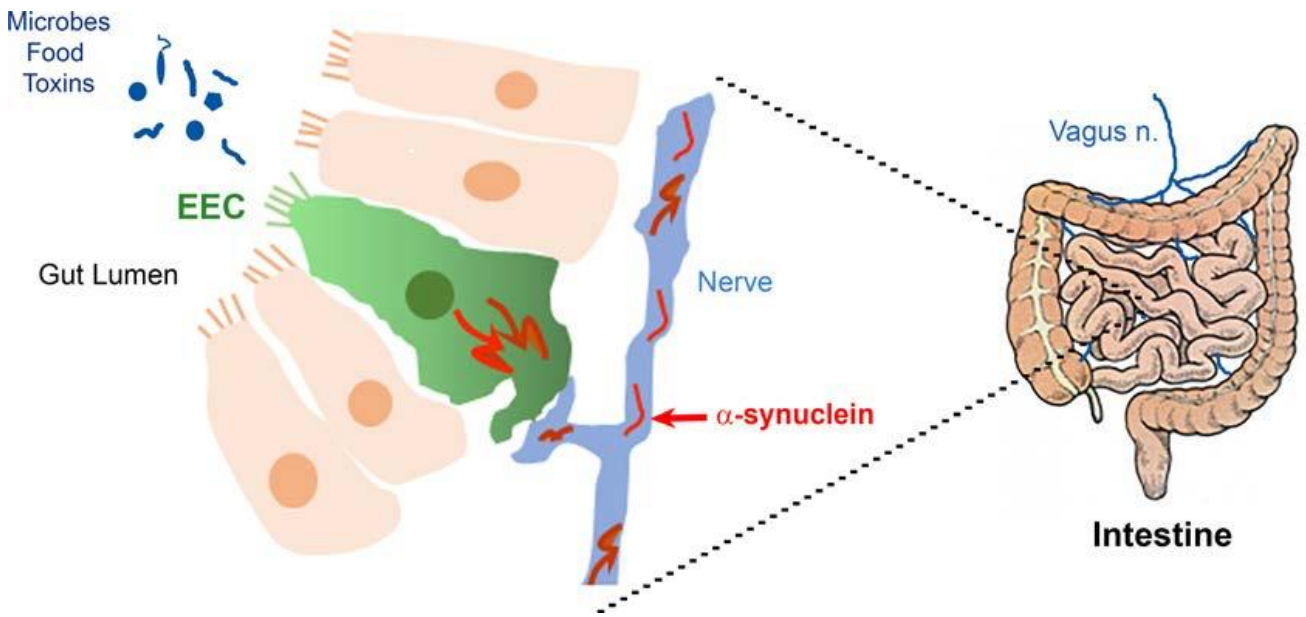


Figure 10. Hypothetical pathway for pathogenic migration of α-synuclein in the gut. The apical surface of enteroendocrine cells (EECs) is exposed to the lumen and thus is in contact with ingested toxins and metabolites produced by gut microbes. The basolateral surface of EECs is in contact with enteric nerves and glia. We propose that toxin uptake by EEC can cause aggregation of α-synuclein inside these cells and this aggregated protein can migrate to enteric nerves, thereby initiating a pathogenic cascade leading to α-synucleinopathies.

insight.jci.org https://doi.org/10.1172/jci.insight.92295

Chandra et al. JCI Insight 2017

Gut microbiota influence peripheral immune cell traffic to CNS

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Monocyte mobilisation, microbiota & mental illness

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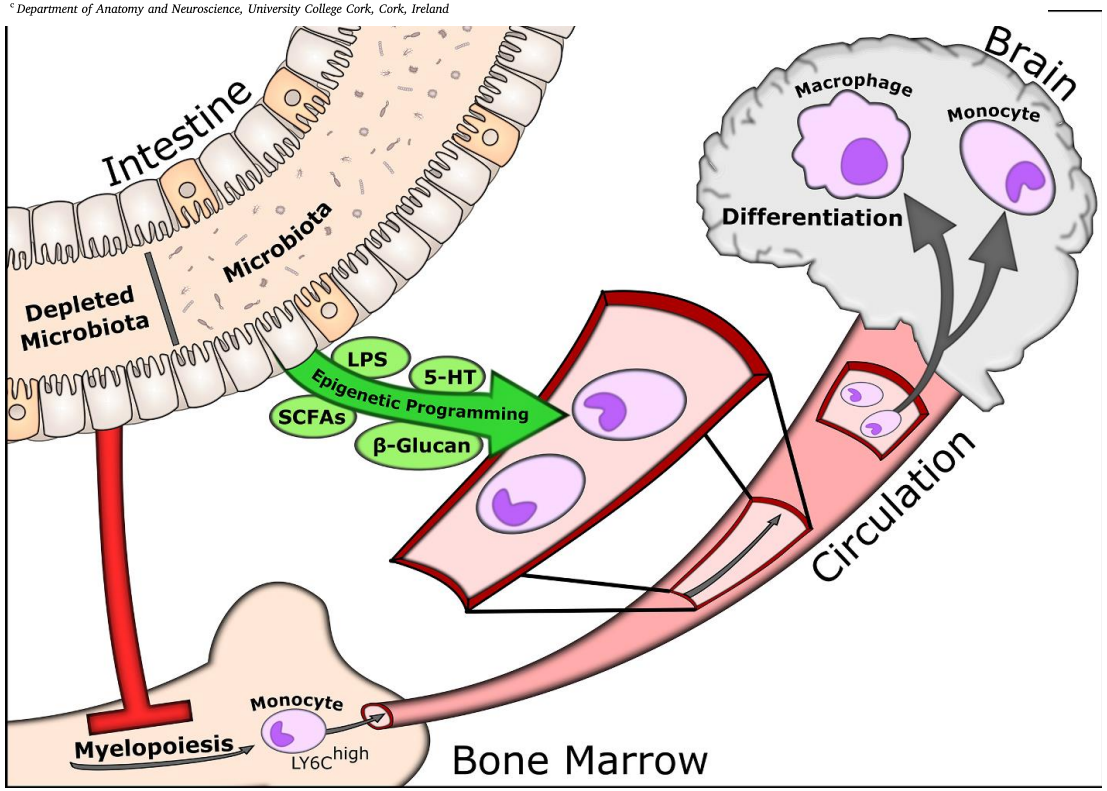


Fig. 2. Pathways in which the microbiota can influence monocyte trafficking to the brain. A depleted gastrointestinal microbiota results in a decreased myelopoiesis and monocyte levels, resulting in reduced monocyte trafficking to the brain. Alternatively, gut microbiota-derived metabolites, such as lipopolysaccharide (LPS), serotonin (5-HT), SCFAs (short-chain fatty acids), and β-glucans, can influence monocyte properties and the macrophages they subsequently differentiate into.

Therapeutic Potential of Microbiota-targeted Strategies to Modulate Central and Peripheral Immunity in Multiple Neurological Disorders or Conditions

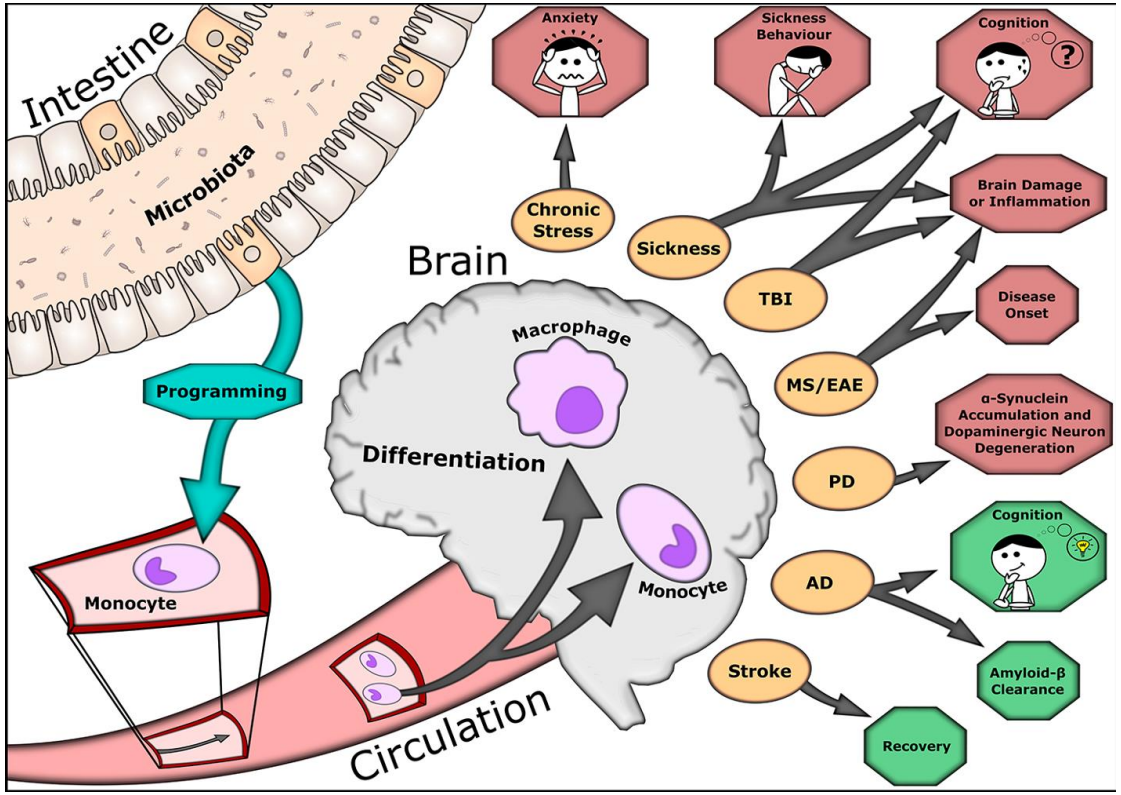
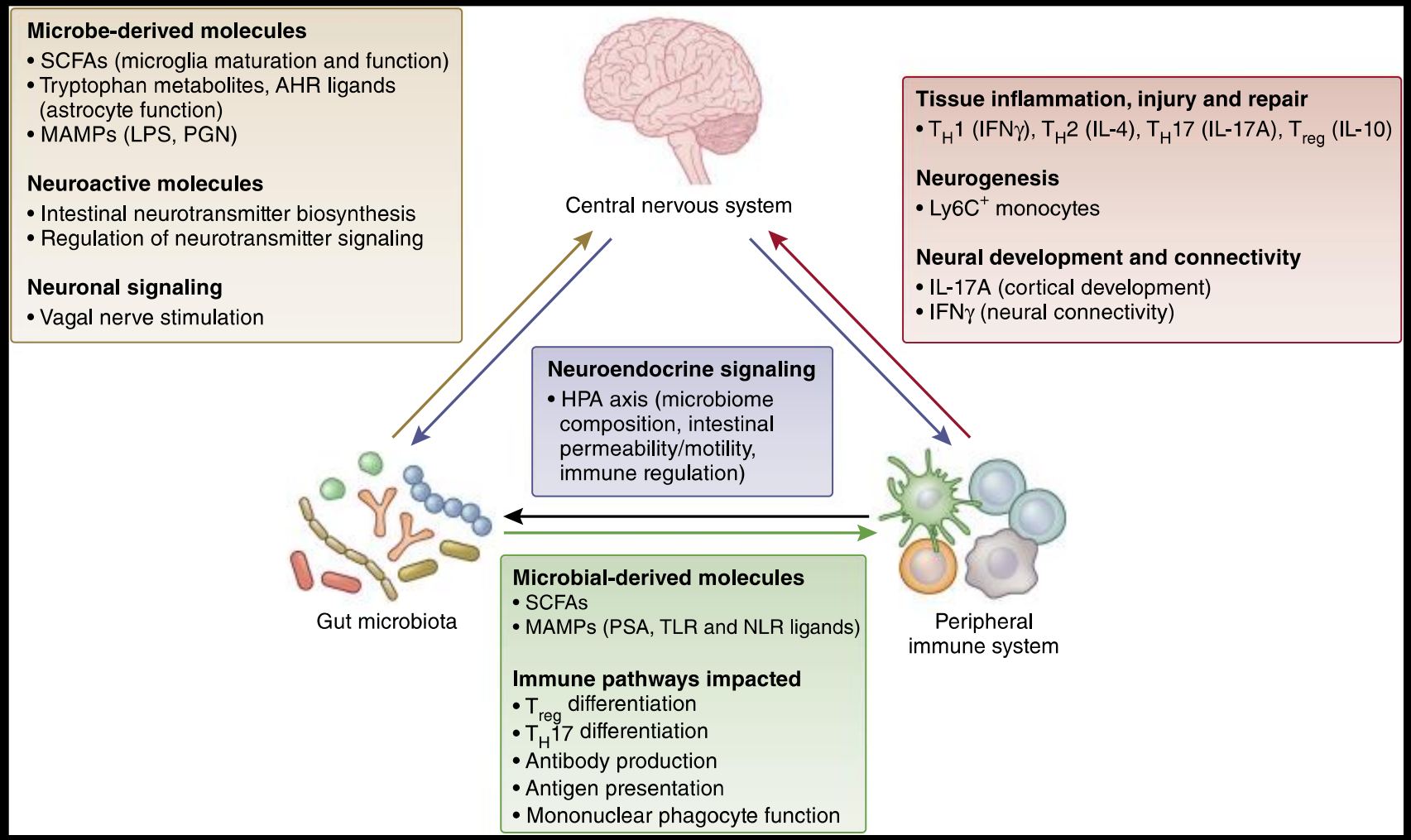


Fig. 3. The therapeutic potential of microbiota-targeted strategies in conditions associated with enhanced monocyte trafficking into the brain. The microbiota can (epigenetically) program circulating monocytes, prior to their trafficking into the brain and subsequent differentiation into macrophages. These monocytes and monocyte-derived macrophages play a causal role in specific aspects of pathophysiology of various disease conditions, such as traumatic brain injury (TBI), experimental autoimmune encephalomyelitis (EAE) and human multiple sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD) and stroke, as well as conditions associated with chronic stress and sickness. Monocytes play a negative role (red boxes) or positive role (green boxes) depending on the disease condition.

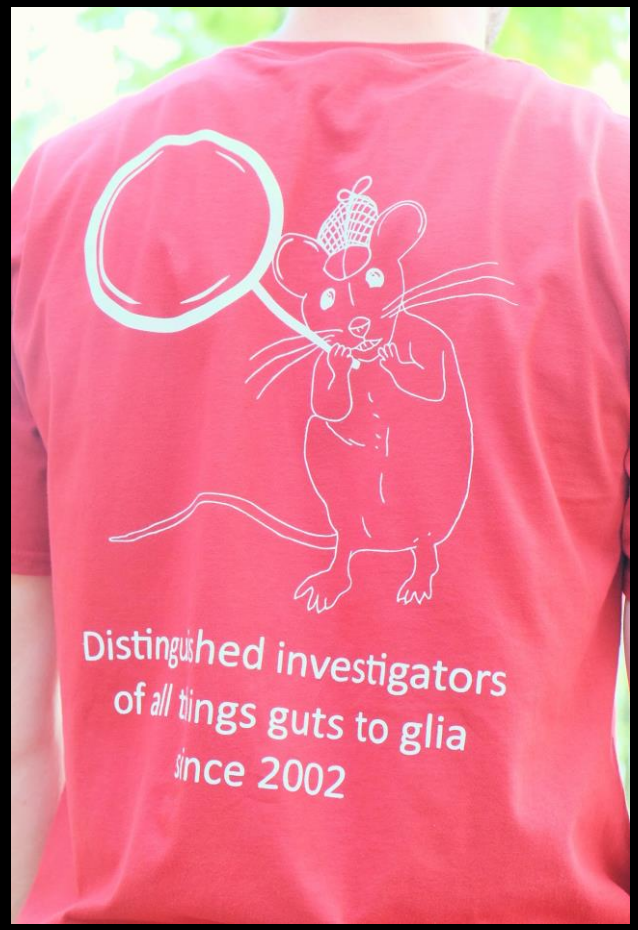
Van de Wouw et al 2019

CNS-Gut-Peripheral Immune System: Novel Targets for Therapeutic Immunomodulatory Interventions?



Fung , Olson and Hsiao Nature Neuro 2017

Questions?


Distinguished investigators
of all things guts to glia
since 2002