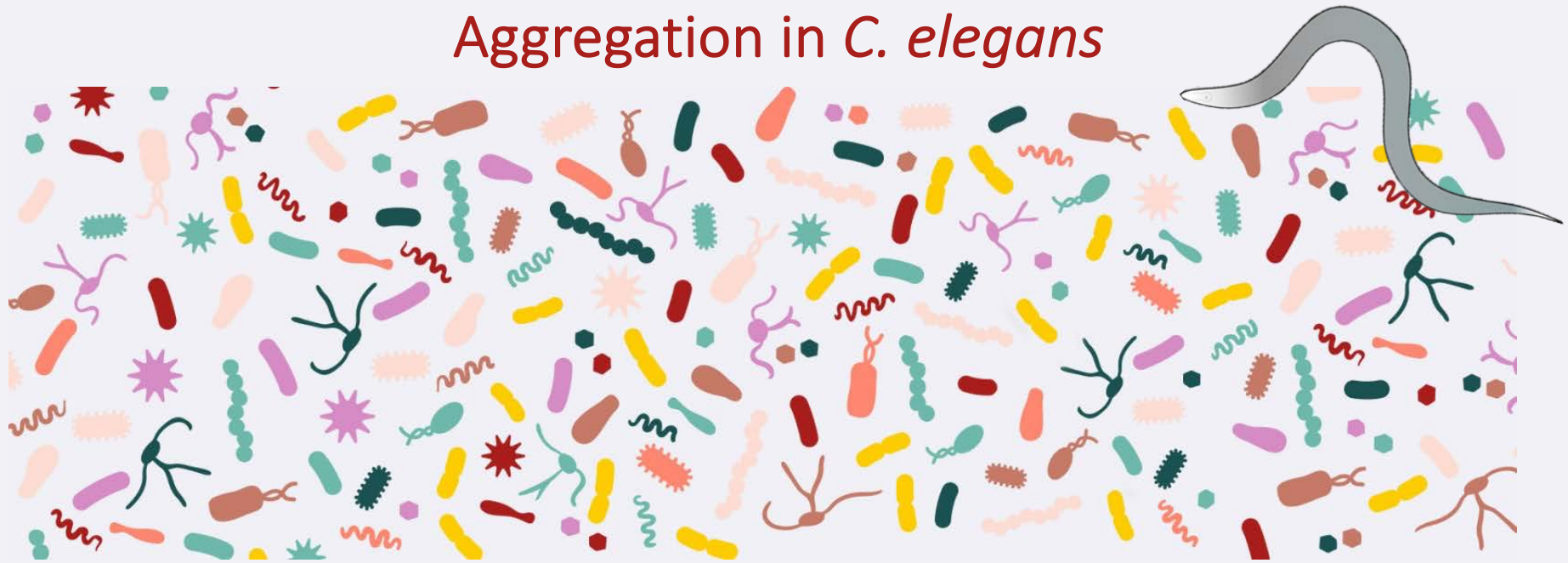


A Probiotic Bacterium Protects against α -Synuclein Aggregation in *C. elegans*



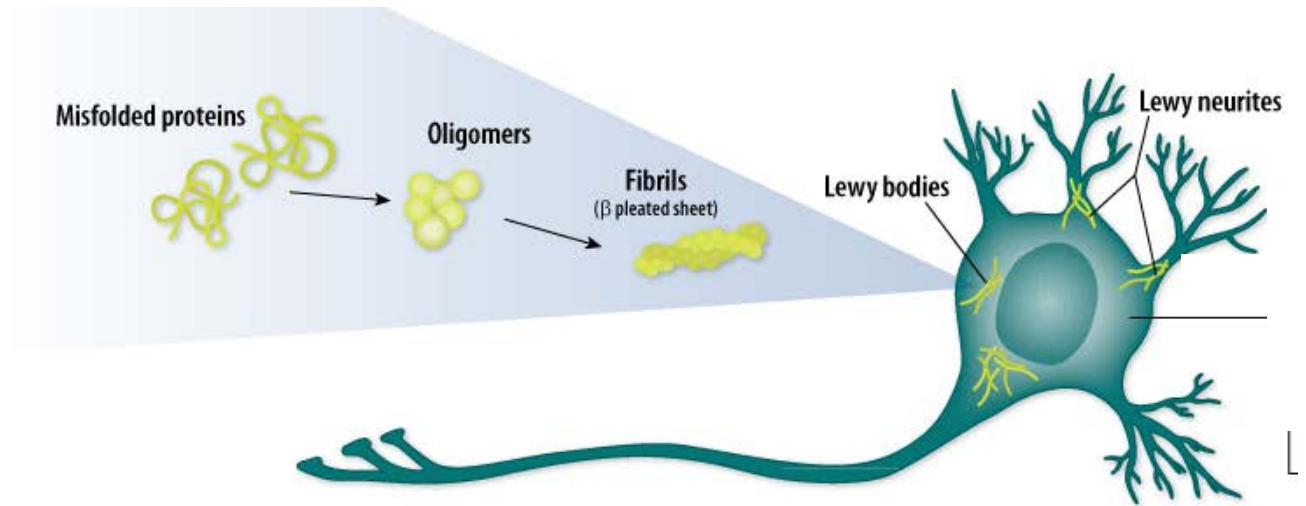
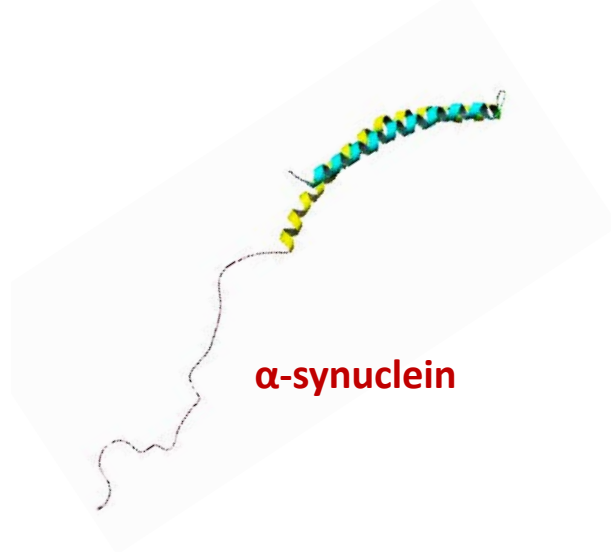
Maria Doitsidou
University of Edinburgh

Maria.Doitsidou@ed.ac.uk

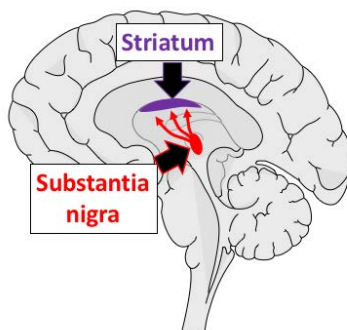


@Doitsidou_lab

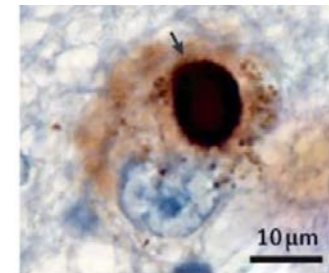
α -synuclein aggregation is central to the pathology of Parkinson's



Loss of dopamine neurons



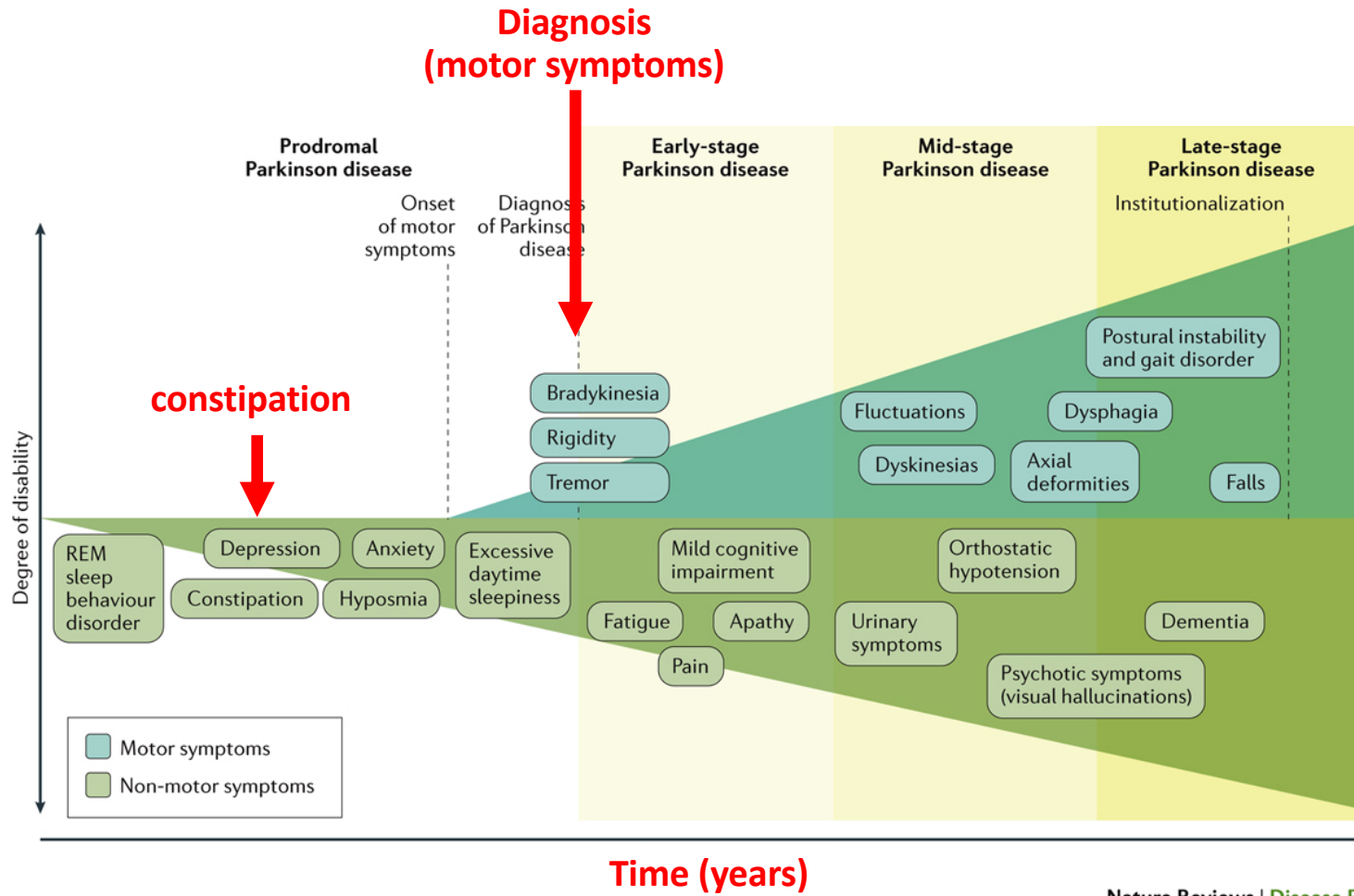
Lewy Bodies



Why is the gut of interest in Parkinson's research?

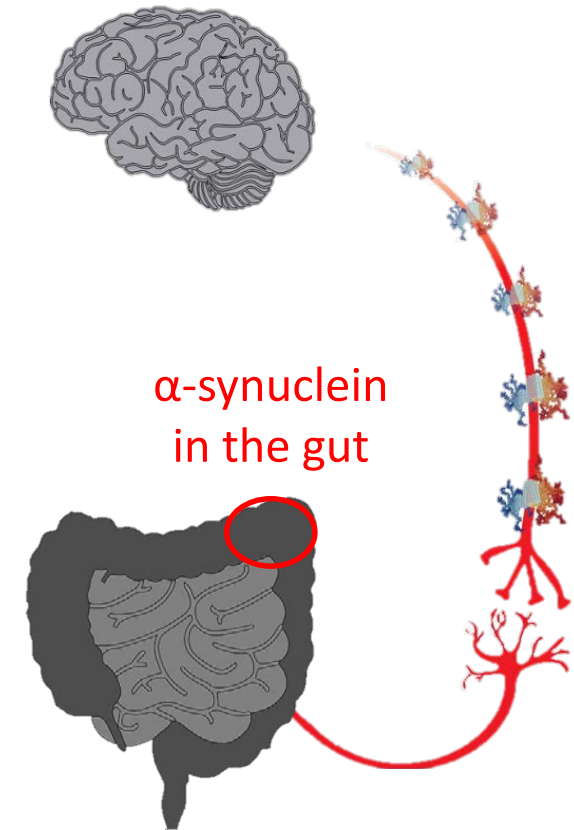
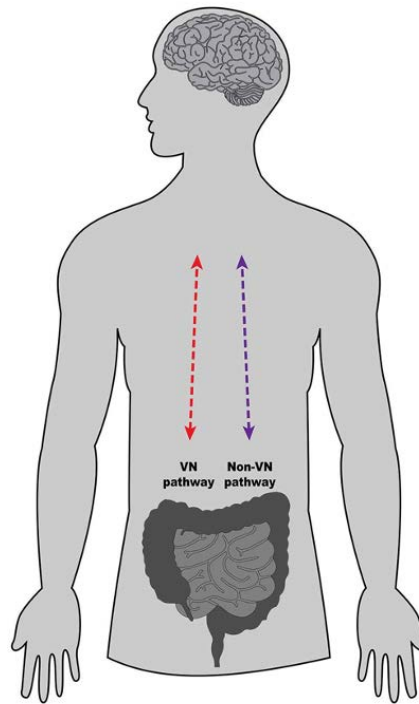
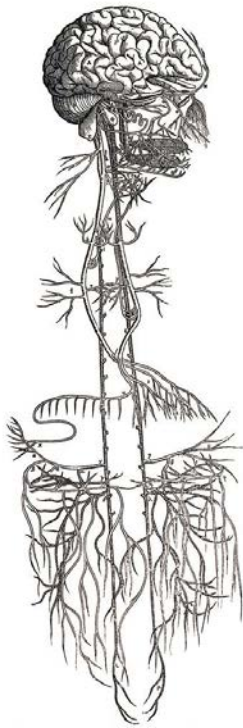
1. Gastrointestinal symptoms in Parkinson's
2. Gut origin of Parkinson's
3. Gut bacteria (microbiota) affect the brain

1. Gastrointestinal symptoms in Parkinson's



2. Gut origin of Parkinson's

Vagus nerve

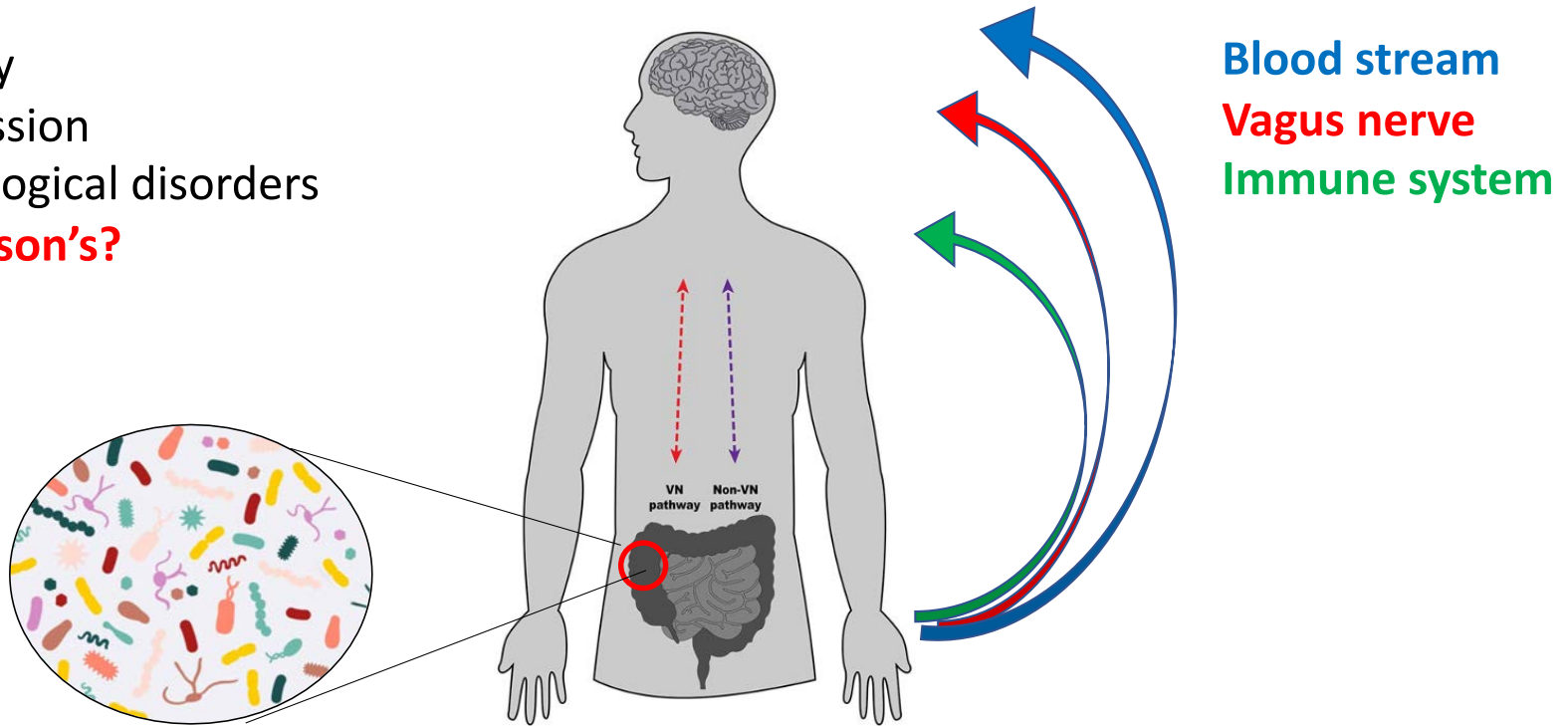


Andreas Vesalius, Book IV, De Fabrica, 1543

Adapted from Santos et al, 2019, Frontiers in Neurology

3. Bacteria in the gut affect the brain

Anxiety
Depression
Neurological disorders
Parkinson's?



Bacteria produce metabolites (chemicals)
e.g. neurotransmitters, hormones, vitamins, etc

Adapted from Santos et al, 2019, Frontiers in Neurology

Gut bacteria influence Parkinson's symptoms in mice

Mice that produce human α -synuclein



Germ free



No motor symptoms!

Sampson et al, 2016, Cell

Article

Cell

Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease

Timothy R. Sampson,^{1,*} Justine W. Debelius,² Taren Thron,¹ Stefan Janssen,² Gauri G. Shastri,¹ Zehra Esra Ilhan,³ Collin Challis,¹ Catherine E. Schretter,¹ Sandra Rocha,⁴ Viviana Gradinaru,¹ Marie-Francoise Chesselet,⁵ Ali Keshavarzian,⁶ Kathleen M. Shannon,^{7,8} Rosa Krajmalnik-Brown,³ Pernilla Wittung-Stafshede,⁴ Rob Knight,^{2,8} and Sarkis K. Mazmanian^{1,10,*}

¹Division of Biology & Biological Engineering, California Institute of Technology, Pasadena, CA 91125, USA

Gut bacteria influence Parkinson's symptoms in mice

Mice that produce human α -synuclein



Faecal transplant

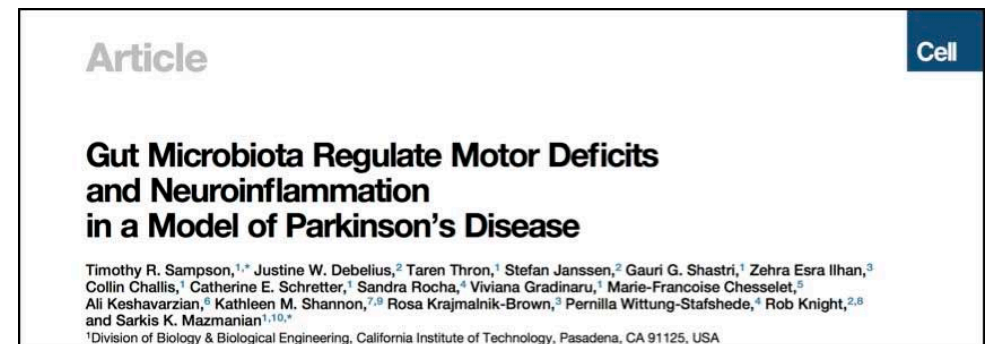


Individuals with Parkinson's



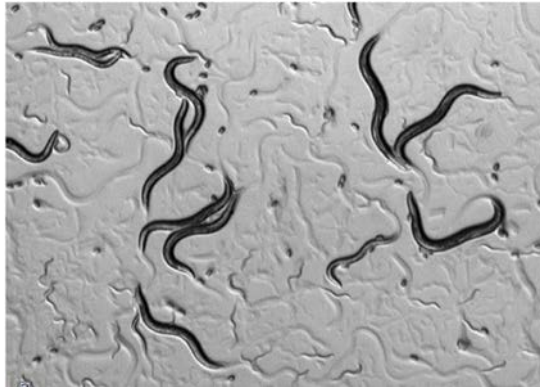
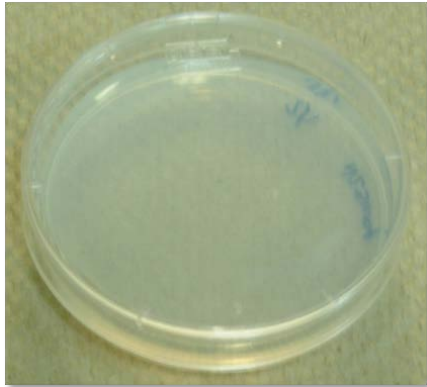
Enhanced symptoms!

Sampson et al, 2016, Cell



The roundworm *C. elegans* as a model to study microbiota

One bacterial species at a time



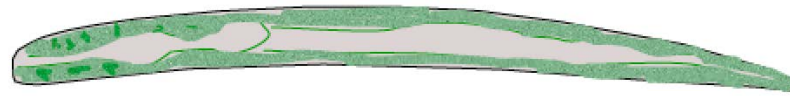
1 mm long



Speed of experimentation

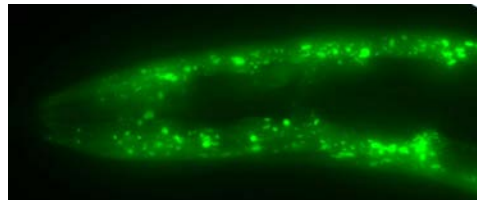
- 3 days generation time
- 3 weeks lifespan
- Large number of offspring
- Transparent

An α -synuclein based aggregation model



C. elegans that produce human α -synuclein::YFP

van Ham TJ, 2008, *PLOS Genetics*



Regular diet (*E. coli*)

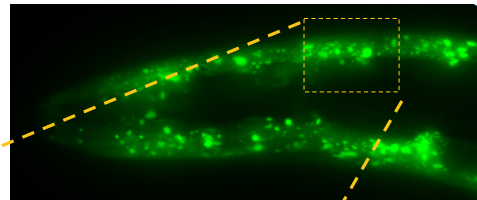


B. subtilis diet protects against α -synuclein aggregation

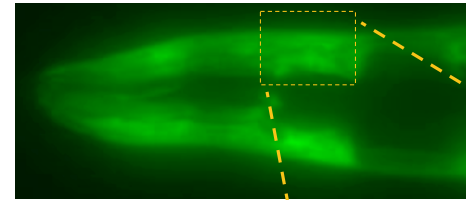


C. elegans that produce human α -synuclein::YFP

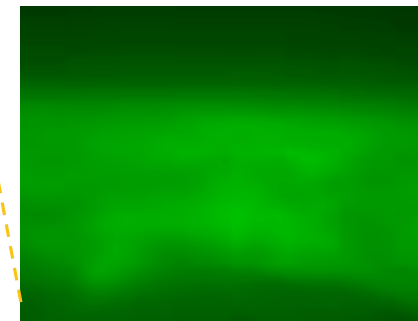
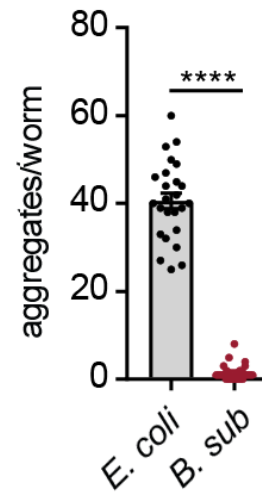
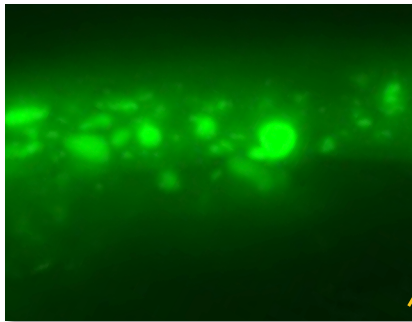
van Ham TJ, 2008, PLOS Genetics



Regular diet (*E. coli*)

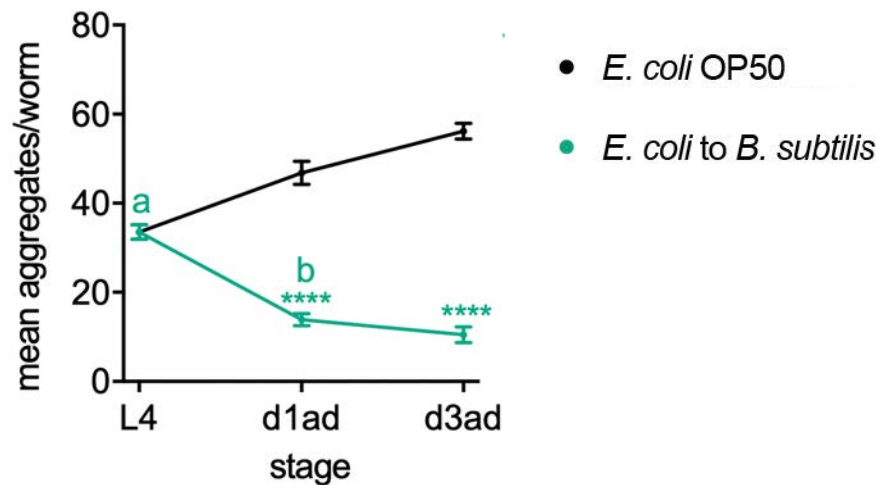
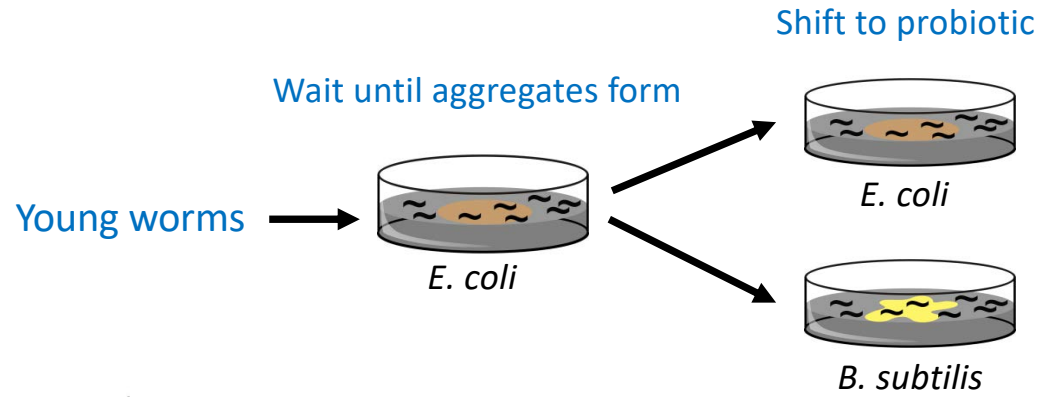


B. subtilis



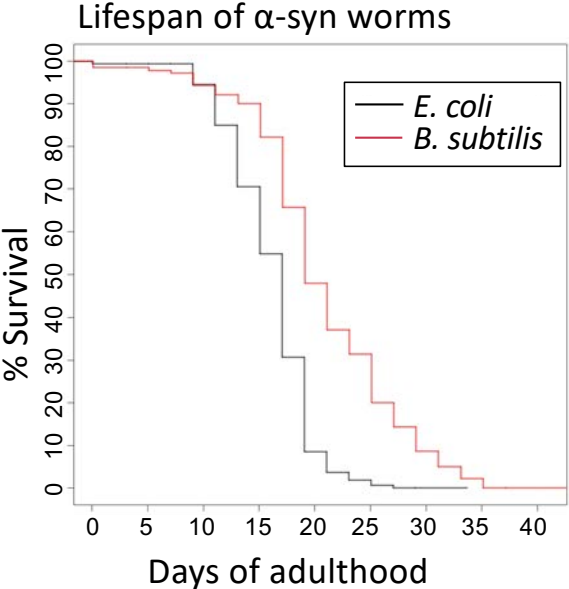
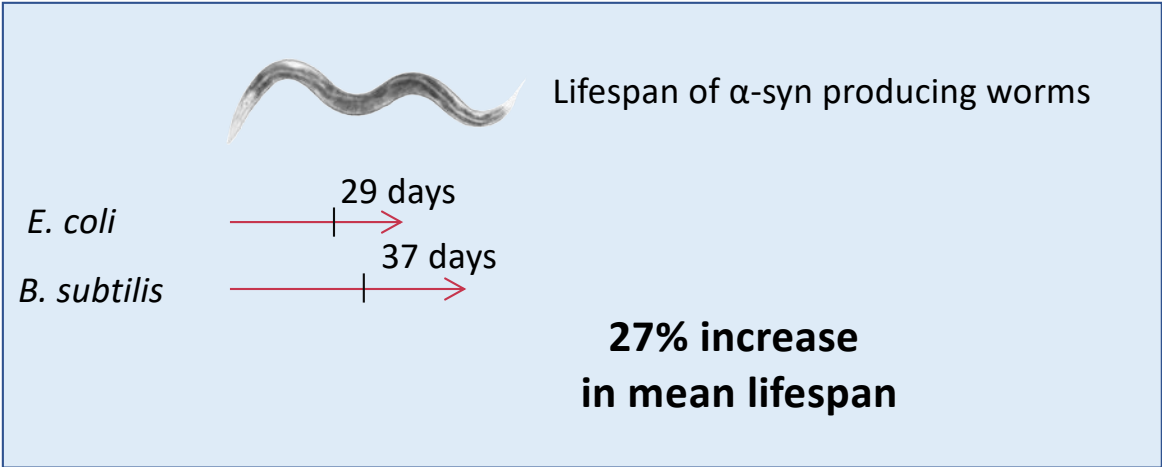
Goya et al, 2020, Cell Reports

Can *B. subtilis* clear already formed aggregates?



***B. subtilis* diet clears
already formed aggregates**

B. subtilis diet extends *C. elegans* lifespan



***B. subtilis* diet also improves locomotion of α -synuclein worms**

Goya et al, 2020, Cell Reports

What causes the protective effect of *B. subtilis*?

Bacteria



Host



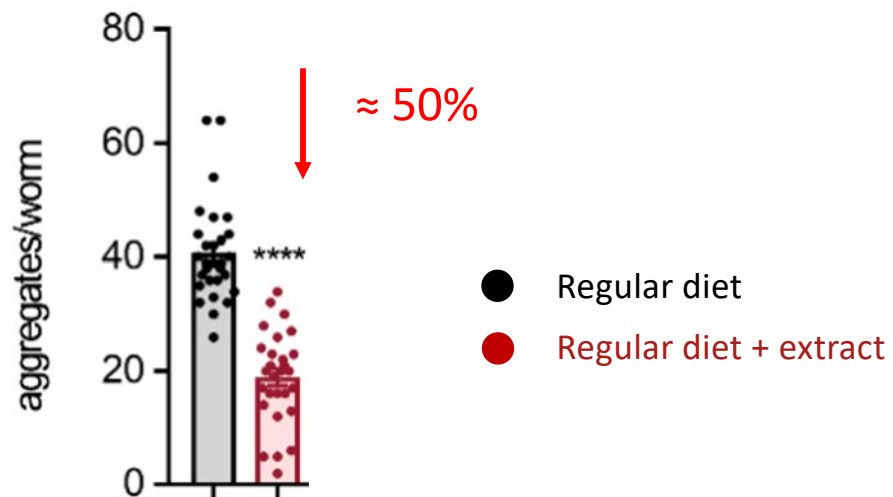
What is the 'protective signal'?

- Protective metabolite(s)

What happens in the host?

- Changes in 2 biochemical pathways
 - Insulin signalling
 - Lipid processing in cells

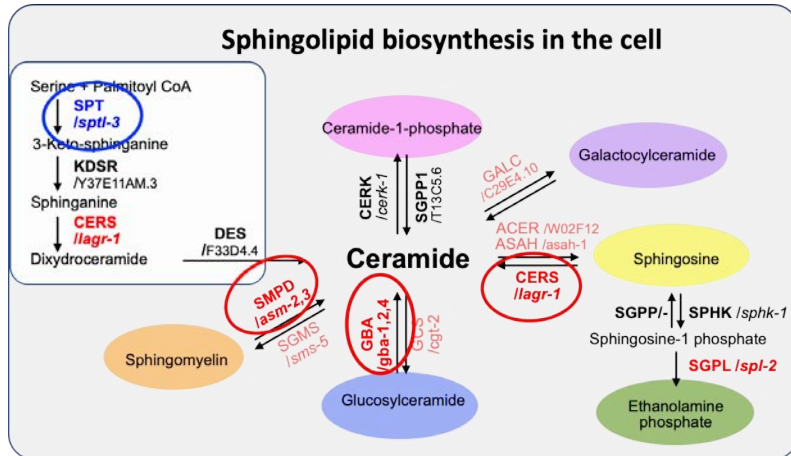
Bacterial metabolites protect against α -synuclein aggregation



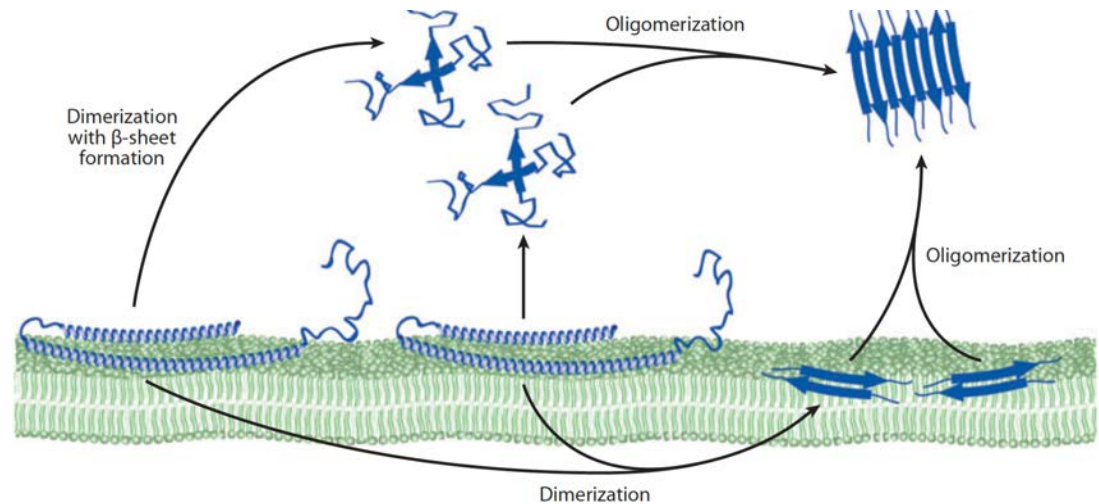
➤ Bacterial extracts are protective

➤ **What is the protective metabolite?**

The probiotic changes how cells process specific lipid molecules called 'sphingolipids'



- α -synuclein associates with lipids in the cell
- Lipid composition alters the likelihood of aggregation
- Sphingolipids are known to play a role in Parkinson's



from Auluck et al., *Annu. Rev. Cell Dev. Biol.* 2010. 26:211–33

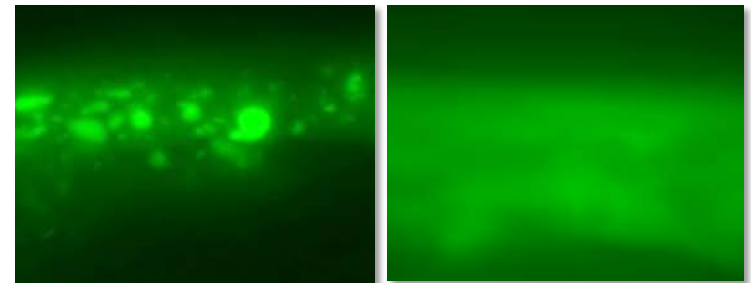
Summary

Cell Reports
Article

OPEN
ACCESS
CellPress

Probiotic *Bacillus subtilis* Protects against α -Synuclein Aggregation in *C. elegans*

María Eugenia Goya,¹ Feng Xue,^{1,5} Cristina Sampedro-Torres-Quevedo,^{1,5} Sofia Arnaouteli,²
Lourdes Riquelme-Dominguez,¹ Andrés Romanowski,³ Jack Brydon,⁴ Kathryn L. Ball,⁴ Nicola R. Stanley-Wall,²
and Maria Doitsidou^{1,6,*}



➤ Protective metabolite

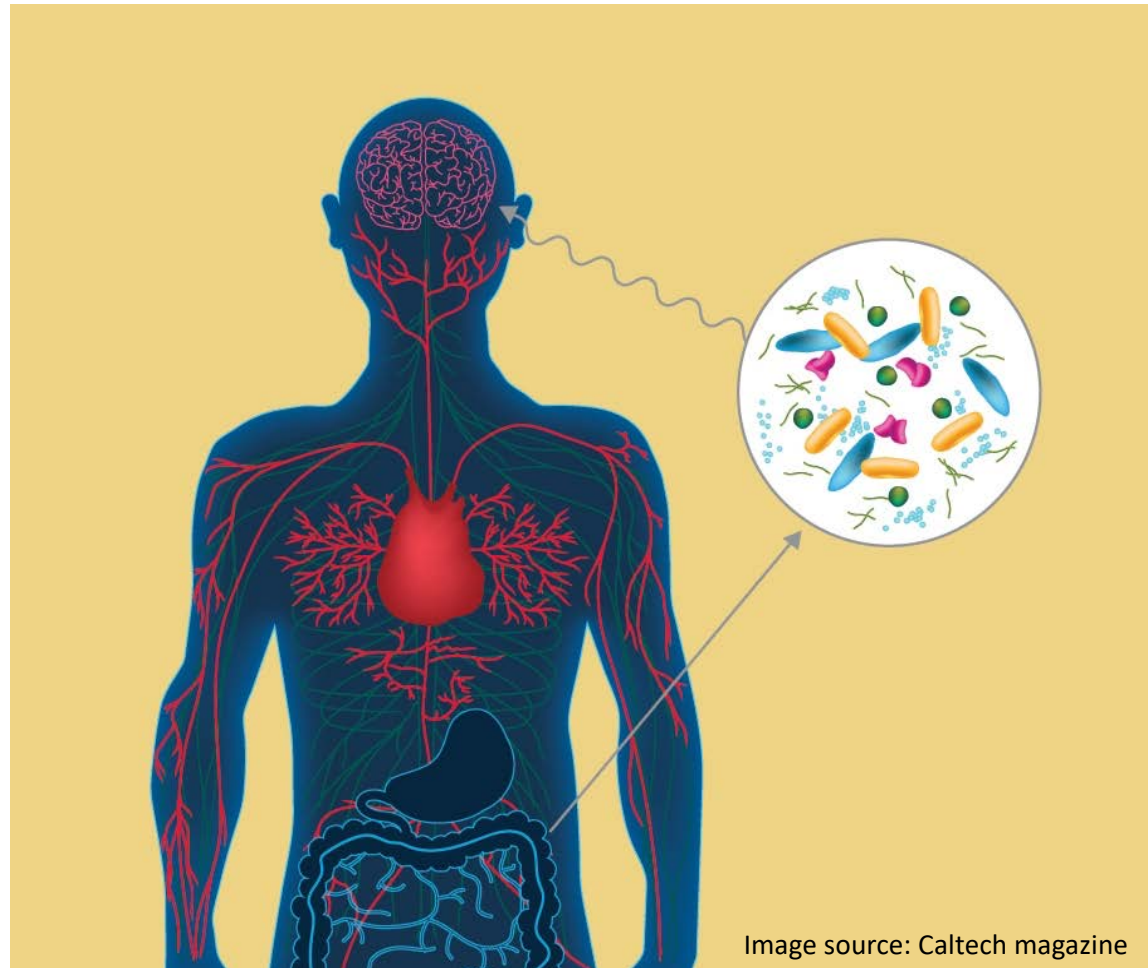
Changes in 2 biochemical pathways

- Insulin signalling
- Lipid processing in cells



The microbiome as a therapeutic target for Parkinson's

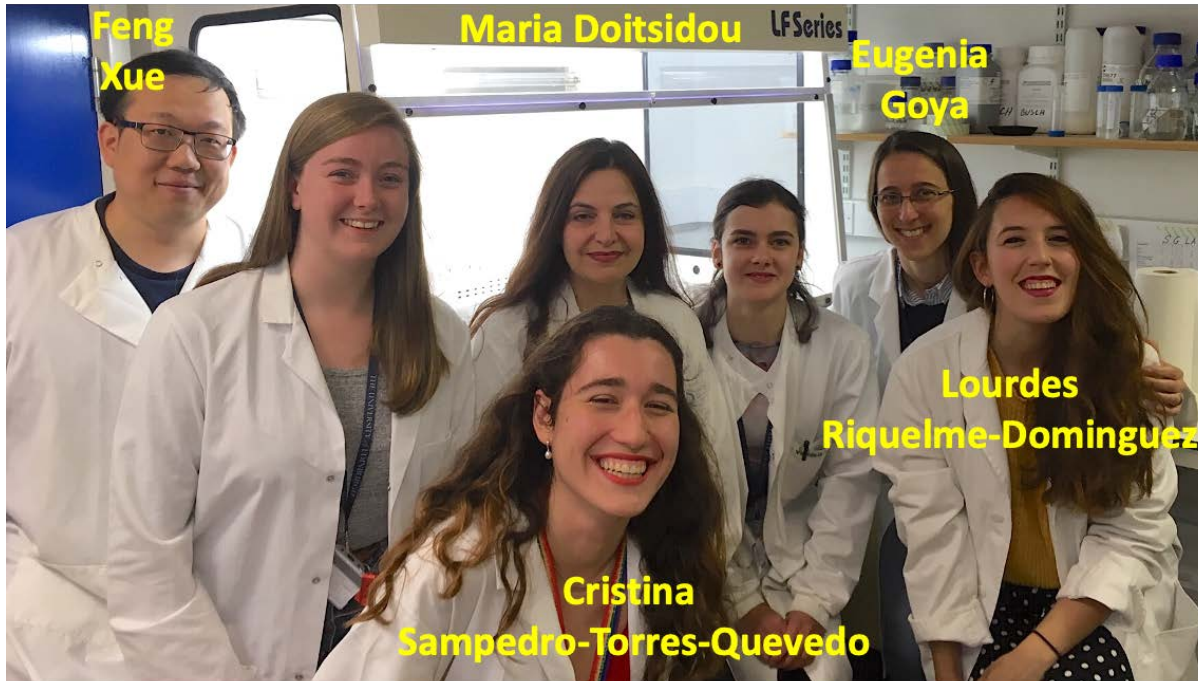
- Enriching beneficial bacteria (probiotics)
- Targeting harmful bacteria
- Bacterial metabolites as basis for drugs
- Host pathways as drug targets





@Doitsidou_lab

The Doitsidou lab



Collaborators:

- Tilo Kunath, UoE
- David Breen, UoE
- Jodi Maple, SUS, Norway
- Guido Alves, SUS, Norway
- Louise Horsfall, UoE

Nicola Stanley Wall (Dundee)



Kathryn Ball, UoE



Nicola Stanley Wall (Dundee)



PARKINSON'S^{UK}
CHANGE ATTITUDES. FIND A CURE. JOIN US.

