

Mechanistic Mining of the Microbiome for Metabolic and Mental health

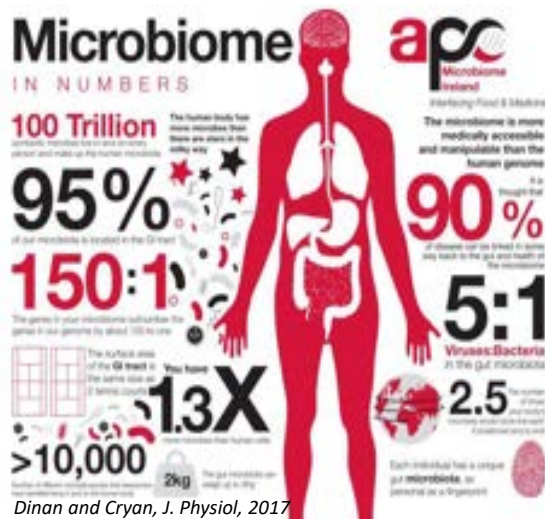
Dr. Harriët Schellekens
Lecturer in Anatomy & Neuroscience

[HSchellekens - Google Scholar](#)

[@harschellekens](#)



Living in a Microbial world...



Varied microbiota composition

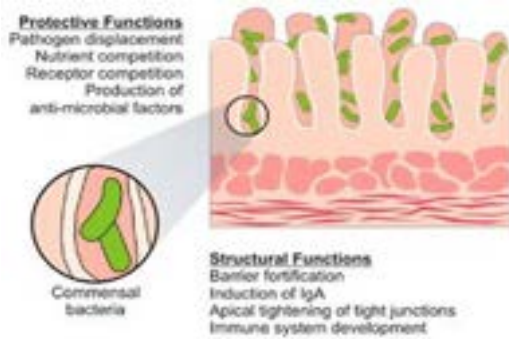


...unique needs across the lifespan



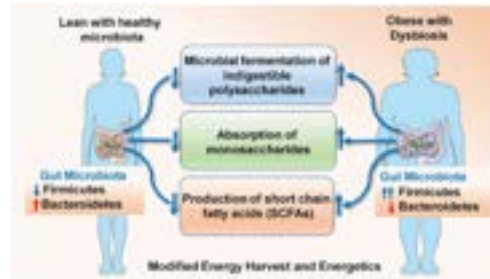
Living in a Microbial world...

Humans and other animals share an mutualistic relationship with resident microorganisms



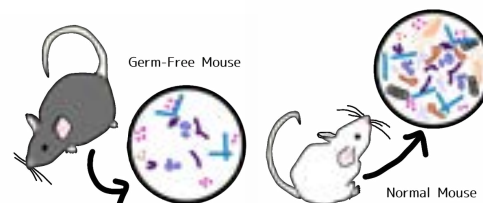
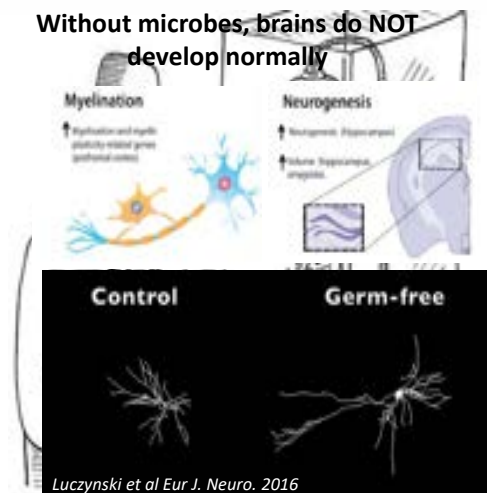
Metabolic Functions:

Synthesis of vitamins
 Fermentation of non-digestible dietary fiber
 Salvage of ENERGY: microbiota contributes to host energy metabolism and alter the way we store fat, how we balance levels of glucose in the blood, and how we respond to hormones that make us feel hungry or full.



MICROBIOTA & NEUROSCIENCE?

Without microbes, brains do NOT develop normally



- Hyperphagic—eat more
- Glucose homeostasis
- Insulin response
- Anxiety
- Dopamine signalling (ghrelin)
- Anxiety, depression, cognition, sociability, fear

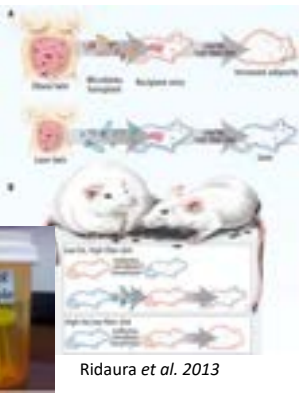
PLEASE PASS THE MICROBIOTA!!



FEACAL MICROBIOTA TRANSPLANT

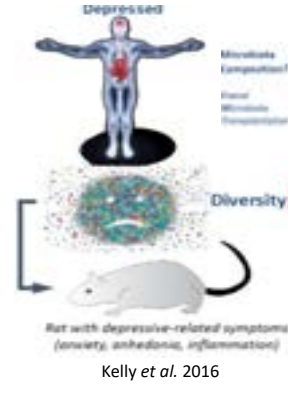


TRANSFORMING FAT TO THIN



Ridaura et al. 2013

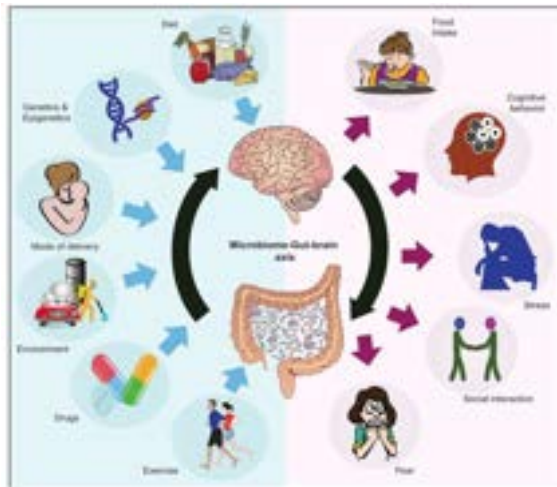
TRANSFERRING THE BLUES



Kelly et al. 2016

✓ FMT has illustrated the *influence of the gut microbiota on our METABOLIC AND MENTAL HEALTH* independently of diet.

MICROBIOTA MEDIATOR OF GUT-BRAIN FUCTION



Many factors can both positively as negatively influence microbiota composition



..basis for microbiota-targeted approaches (diet, drugs, supplements)

Public Health Concern! Obesity & Stress

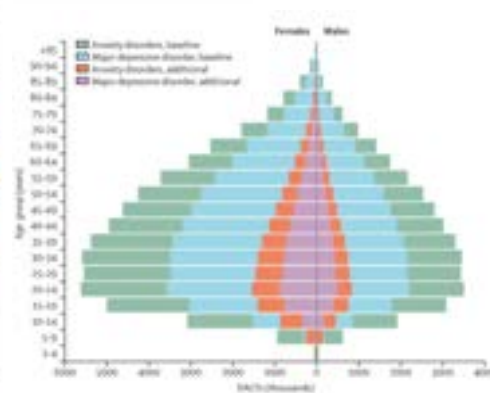
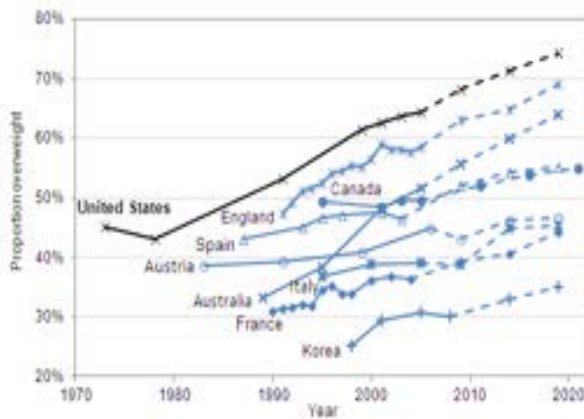


Figure 4 Global burden of major depressive disorder and anxiety disorders by age and sex, 2020

Obesity and anxiety are public health problems that have no effective cure.
Few treatments exist and are mostly unsatisfactory.

PROBIOTICS FOR OBESITY: NOT A MAGIC BULLET!



Microbiota and body weight control: Weight watchers within? March 2022

Serena Bescato^{1,2}, Sarah-Jane Leigh^{1,2}, Aonghus Lawille^{1,2}, Rubén García-Callezas¹, Gerard Clarke^{1,2}, Harriett Schellkens^{1,2}, Julie F. Cryan^{1,2}

“While there are strong relationships between body weight and gut microbiota composition both in preclinical studies, translation is not always there and the gut microbiota alone may not be sufficient to exert beneficial effects in this context.”

Multiple microbiota mechanism likely needed (combining strategies) for translation of anti-obesity and stress-resilience effects in humans.



REVIEW ARTICLE
Finding the needle in the haystack: systematic identification of psychobiotics

Supplementary Information: This article is accompanied by Supplementary Information. For more information on this article please go to the article web page at <https://doi.org/10.1038/s41574-022-00000-0>

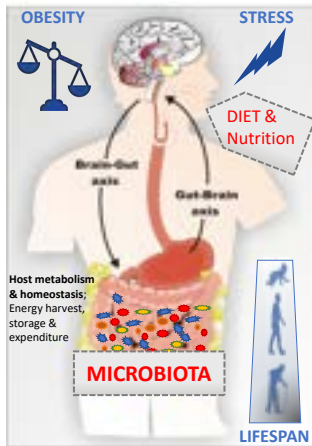
Article published online in Nature Reviews Clinical Oncology on 15 March 2022

Check for updates

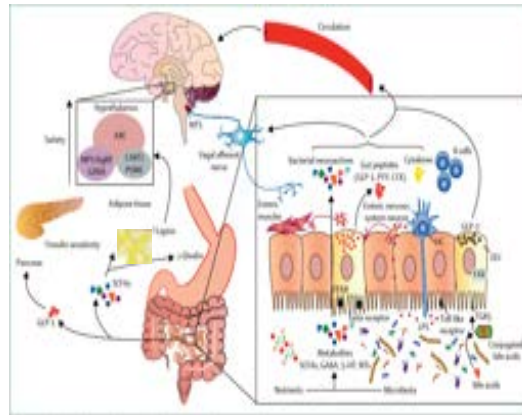
Microbiome-Gut-Brain Axis in Obesity & Stress



GUT-BRAIN AXIS

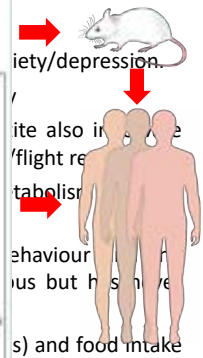


MOLECULAR MECHANISM



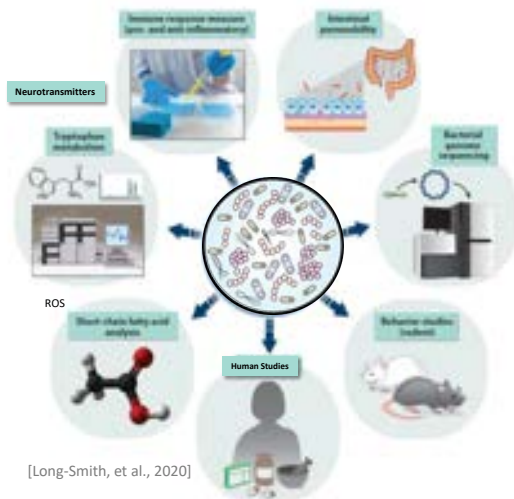
Torres-Fuentes, Schellekens, et al, Lancet Gastro & Hepat 2017

TRANSLATION

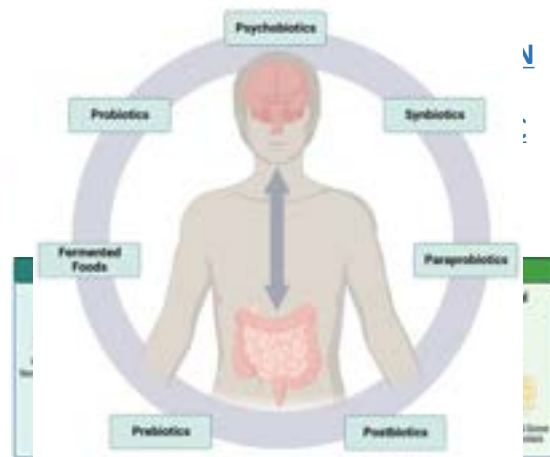


METABOLIC & MENTAL HEALTH

BUGS TO DRUGS: Pharmaceutical approach to mine microbes & metabolites



[Long-Smith, et al., 2020]



[N. Carey, 2023, in prep]

Microbiota Metabolites as GPCR Ligands

nature | <https://doi.org/10.1038/nrn3919> | 1 November 2016

Commensal bacteria make GPCR ligands that mimic human signalling molecules

Chen J, Cohen, David Edelstein, Saeng-Inhaek Kim, Christopher Lammie, Myoung-Ki Aguilera, Richard S. Stead, Alexander J. Peckard, Justin R. Irvine, Amy R. Ehrlich, Ben M. Bray, John P. Kelly, David Holt, George Kaperis, Andrej Bogar, Paula D. Coffey, Craig Maclean, J. Wojciechowski, David A. Clark, P. Breen

Cell Host & Microbe | <https://doi.org/10.1016/j.chom.2018.08.007>

A Microbial Drugstore for Motility

Ashu P. Oryan,^{1,2*} Gerard Clarke,^{1,2} Timothy S. Dinan,^{1,2} and Harriet Schofield-Kern,^{1,2}

¹APC Microbiome Ireland, University College Cork, Cork, Ireland
²Department of Anatomy & Neuroscience, University College Cork, Cork, Ireland
³Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork, Ireland
*Correspondence: a.p.oryan@ucc.ie
<https://doi.org/10.1016/j.chom.2018.08.007>

Cell Host & Microbe | <https://doi.org/10.1016/j.chom.2019.07.009>

The Gut Feeling: GPCRs Enlighten the Way

Shubhi Pandey,¹ Jagannath Mahorana,¹ and Anur K. Shukla^{1,2*}

¹Department of Biological Sciences and Biotechnology, Indian Institute of Technology, Kanpur 208016, India
²Correspondence: ashuk@iitk.ac.in
<https://doi.org/10.1016/j.chom.2019.07.009>

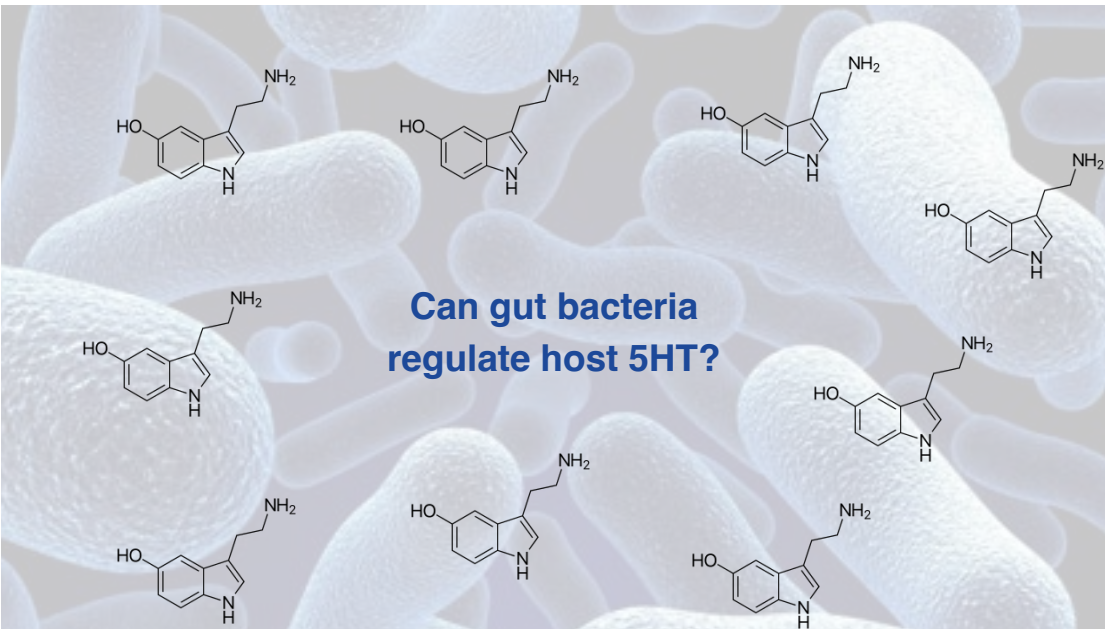
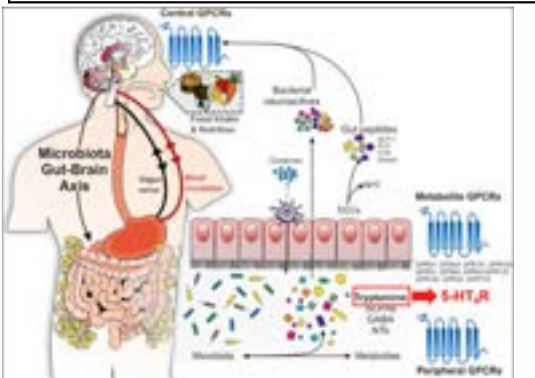
Cell Metabolism | <https://doi.org/10.1016/j.cmet.2017.03.003>

GPCR-Mediated Signaling of Metabolites

Anna Sofie Husted,¹ Mette Traulsen,¹ Olga Rubinek,¹ Jo A. Hjorth,^{1,2} and Toru W. Schwartz^{1,2*}

¹Section for Metabolic Research, Novo Nordisk Foundation Center for Basic Metabolic Research
²Laboratory for Molecular Pharmacology, Department for Biomedical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark
*Correspondence: toru@biomed.ku.dk
<https://doi.org/10.1016/j.cmet.2017.03.003>

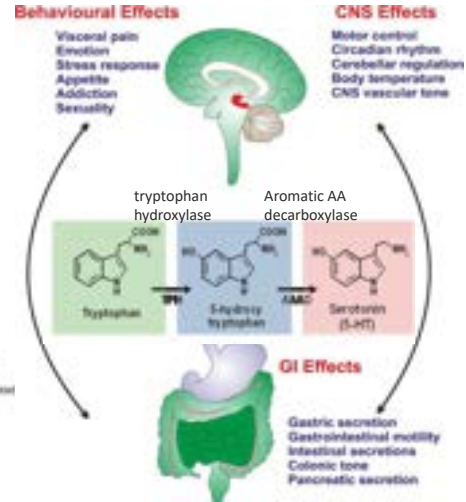
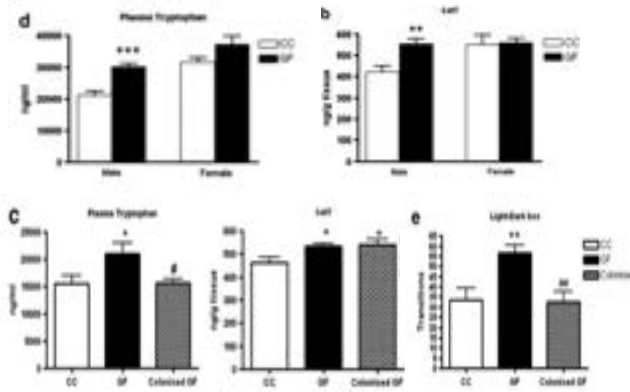
April 4, 2017



Serotonin, Tryptophan and the Brain-Gut-Microbiome Axis



Molecular Psychiatry
 The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner



O'Mahony, et al, Behavioural Brain Research, 2015

Microbiota modulates serotonin signalling



Neuroscience Letters
 Research article
Feeding the developing brain: Juvenile rats fed diets rich in prebiotics and bioactive milk fractions exhibit reduced anxiety-related behavior and modified gene expression in emotion circuits
 Agnieszka Mita^{1,2}, Michelle Gaffney¹, Rachel Fuller¹, Almagul Hibi¹, Courtney A. Beecher¹, Kristina A. Huber¹, Robert E. Thompson^{1,2}, Shany Dzhambazki¹, Brian M. King¹, Monika Frohne-Hagemann¹

Table 4
 Regression between *Lactobacillus spp.* (ln) and 5HT_{2C} mRNA expression in subregions of the prefrontal cortex and striatum, 5-HT_{2A} mRNA in the rostral dorsomedial aspect of the dorsal raphe nucleus (DRN) and 5-HT_{2C} mRNA in the lateral amygdala.

Strains	mRNA Probe	Brain Region	R	P Value
<i>Lactobacillus spp.</i>	5HT _{2C}	Prefrontal cortex (Cingulate)	0.482	0.0074
		Prefrontal cortex (Subthalamic)	0.230	0.0421
		Prefrontal cortex (Prethalamic)	0.436	0.0080
		Dorsomedial Striatum	0.462	0.0036
		Dorsomedial Striatum	0.484	0.0019
		Caudal DRN (Dorsomedial)	0.452	0.0028
		Lateral Amygdala	0.378	0.0004

Lactobacillus modulates 5HT_{2C} expression in amygdala

Effects of regulating gut microbiota on the serotonin metabolism in the chronic unpredictable mild stress rat model
 Huihui Li¹, Peng Wang¹, Lipiao Huang¹, Ping Li¹, Dianfang Zhang¹

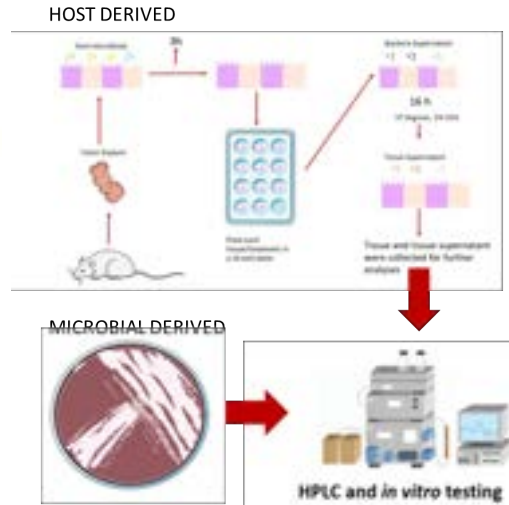
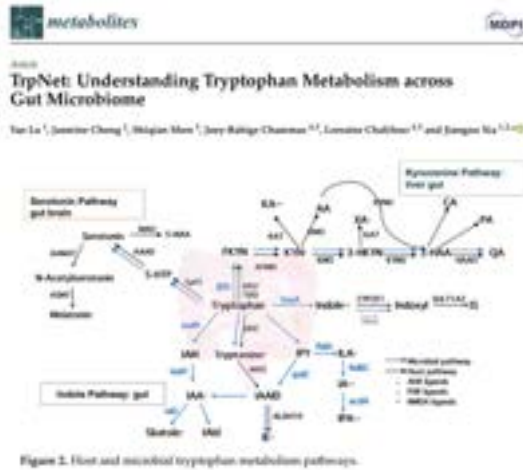
a) Prefrontal subregion: Shows levels of 5-HT, 5-HIAA, and 5-HT/5-HIAA ratio.

b) Dorsomedial striatum: Shows levels of 5-HT, 5-HIAA, and 5-HT/5-HIAA ratio.

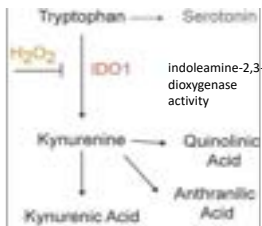
c) Lateral amygdala: Shows levels of 5-HT, 5-HIAA, and 5-HT/5-HIAA ratio.

d) Rostral DRN: Shows levels of 5-HT, 5-HIAA, and 5-HT/5-HIAA ratio.

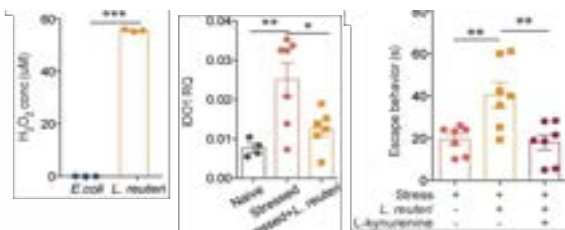
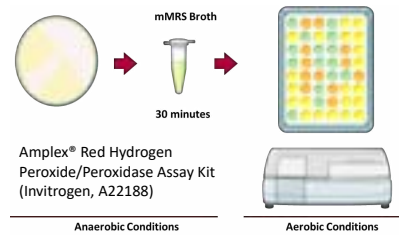
A screening pipeline for Tryptophan metabolism and microbiota interactions



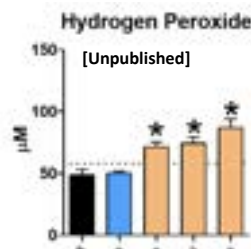
Lactobacillus produces ROS, H2O2



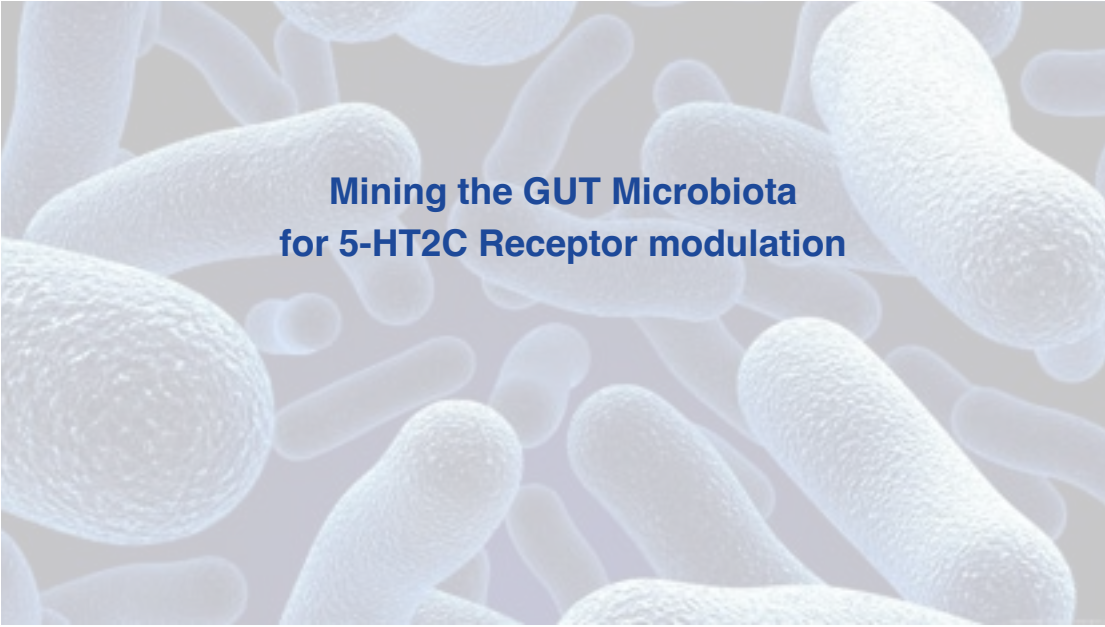
✓ Hydrogen peroxide (H₂O₂), a reactive oxygen species (ROS) implicated in metabolic pathways with neuroactive potential



[Marin.....Gaultier, Scientific reports, 2017]



✓ microbiota player (*Lactobacillus*) may contribute to regulating metabolism and resilience during stress.

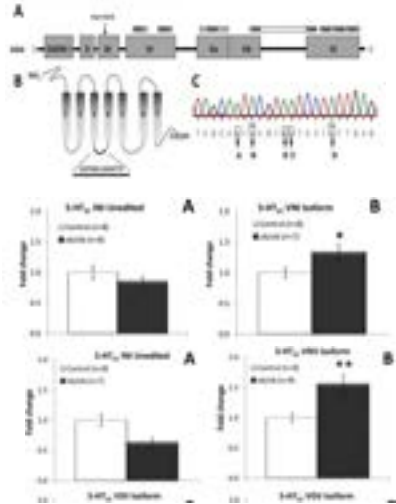


Mining the GUT Microbiota for 5-HT_{2C} Receptor modulation

The 5-HT_{2C} receptor in obesity & stress



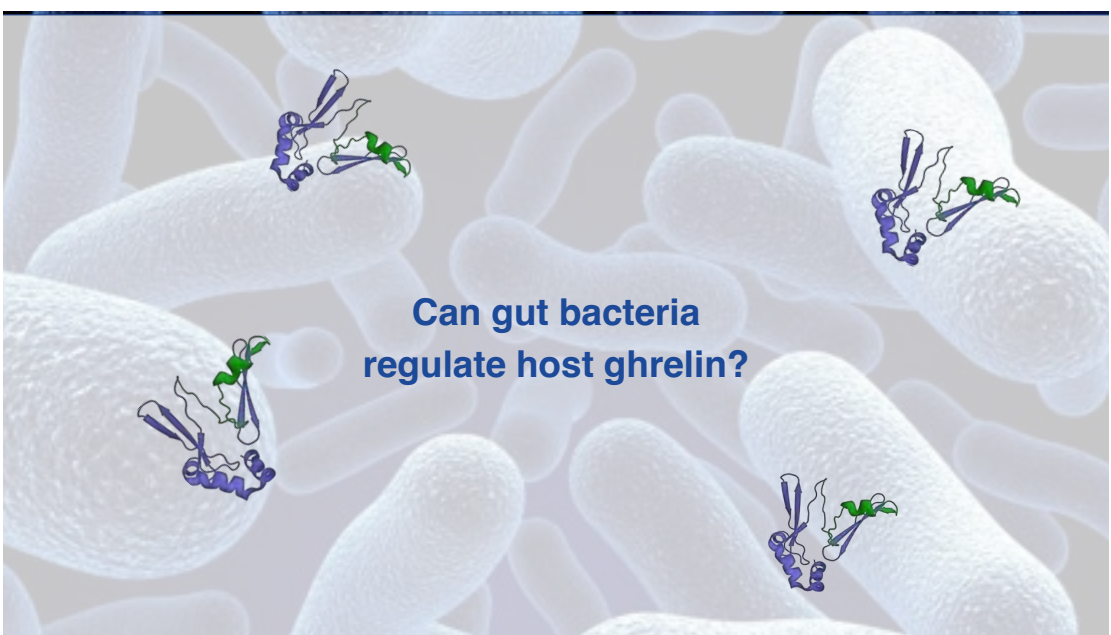
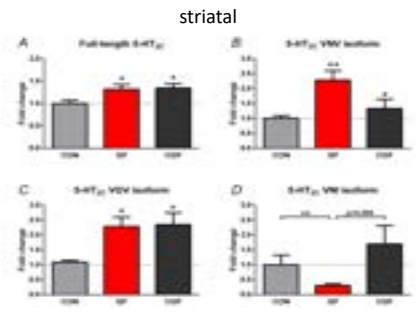
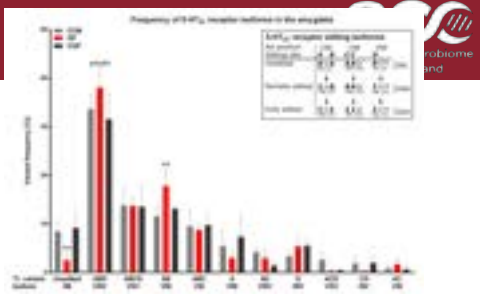
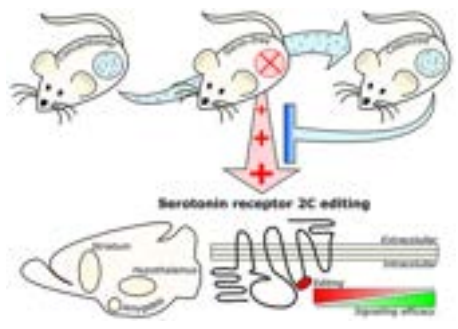
- ✓ Important role in mood, motor, endocrine secretion, addiction and food intake.
- ✓ 5-HT_{2C} is a satiety receptor
- ✓ 5-HT_{2C} **editing** is implicated in obesity (Kawahara, 2008; Schellekens et al. 2012) and stress response (Bhansali et al. 2007; Englander et al. 2005)
- ✓ Editing of the 5-HT_{2C} receptor has been demonstrated to lead to a decreased receptor functioning (Burns et al. 1997, Berg et al. 2008; Olaghere da Silva et al. 2010).
- ✓ Increased editing in hypothalamus and hippocampus of *ob/ob* (leptin deficient obese mouse)



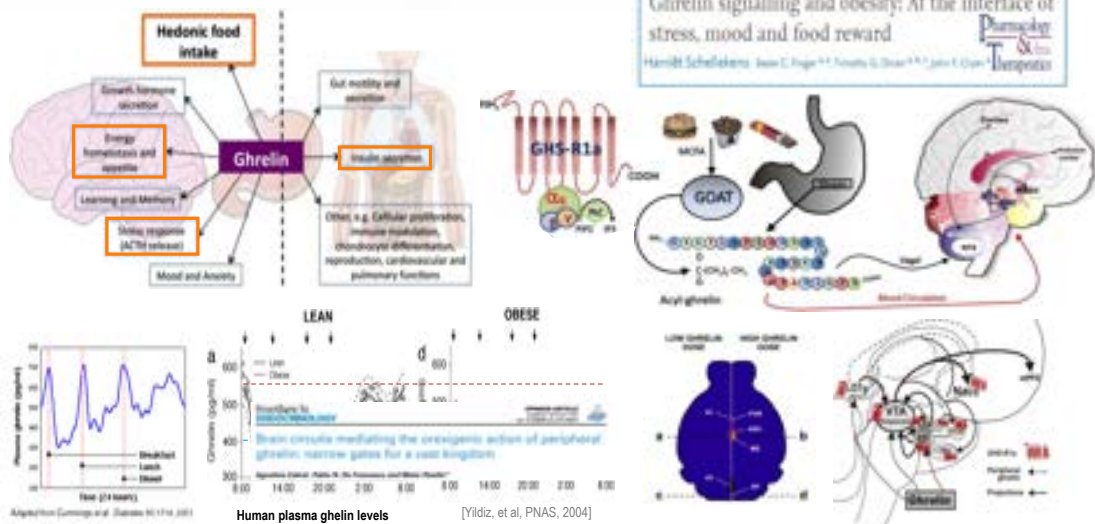
Central 5-HT_{2C} receptor editing in Germ-Free mice

Host Microbiota Regulates Central Nervous System Serotonin Receptor 2C Editing in Rodents
 Michaela M. Wirth, Richard M. Ebling, Anwarul Haque, Francesco Pizzagalli, J. Ross Abel, S. Melissa Pappas, Sharmila Sankar, Daniel Clarke, Marissa J. Chalmers, Timothy L. Dinan, and P. David Slattery

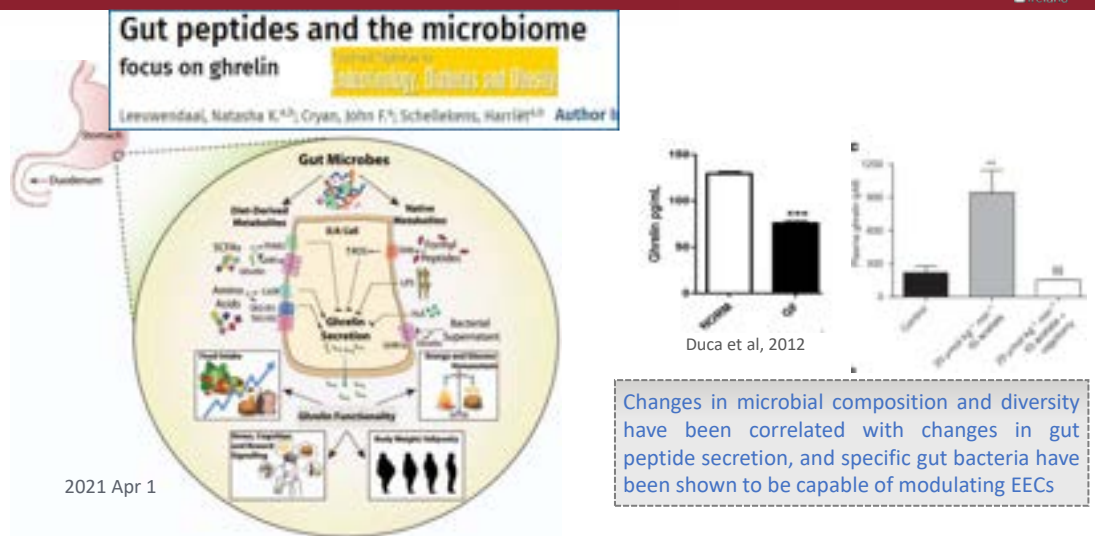
- ✓ Altered 5-HT_{2C} editing in hypothalamus, amygdala and striatum GF mice (absent microbiota!)



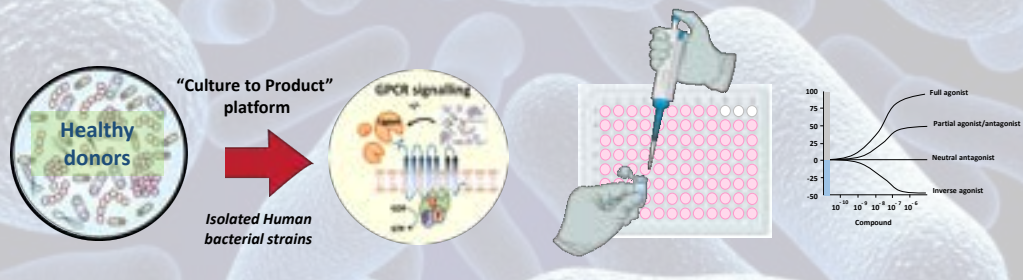
Ghrelin and the GHSR-1a receptor



Ghrelin and the Gut Microbiota



Mining the GUT Microbiota for Ghrelin Receptor modulation

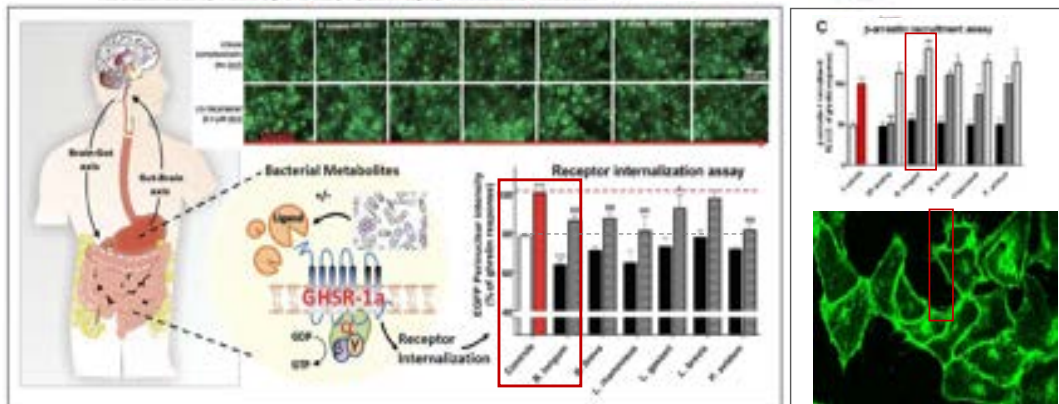


APC1472 has inverse agonist activity & bias towards β -arrestin-mediated ghrelin signaling

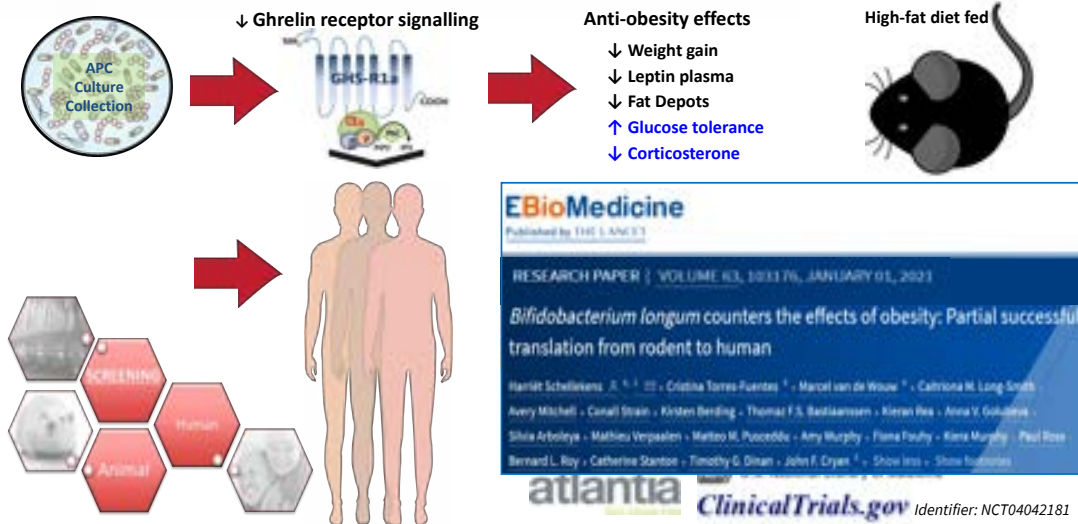
FASEB Short-chain fatty acids and microbiota metabolites attenuate ghrelin receptor signaling

09 October 2018 Carolina Torres-Farinas,^{1,2} Anna V. Golubeva,^{1,2} Alexander V. Zhilov,² Shanna Wallace,^{1,2} Silvia Arboleya,^{1,2} Dmitri B. Pylkovskiy,¹ Sahar El Aidi,^{1,2} Paul Ross,¹ Bernard L. Roth,¹ Catherine Stanton,^{1,2} Timothy C. Dinan,^{1,2} John F. Cryan,^{1,2} and Harriet Schothanus^{1,2}

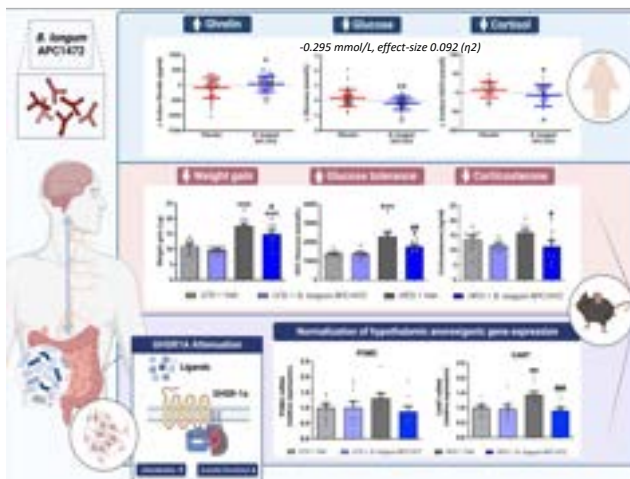
HIGH THROUGHPUT CELLULAR ASSAYS



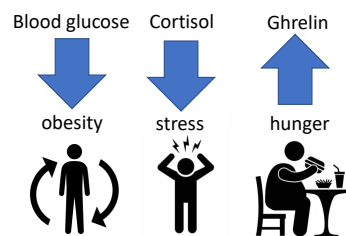
Translational validation of Bifidobacteria Longum APC1472 anti-obesity effects in overweight/obese humans



Bifidobacteria Longum APC1472 a novel bacteria modulating Glucose, cortisol and perceived stress in obesity



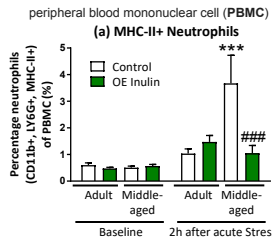
Findings reinforce the concept of the link between OBESITY and STRESS and the potential amelioration of both via microbiome targeted approaches



Normal fasting blood sugar <5.6mmol/L; Prediabetic 5.6 to 7.0 mmol/L.

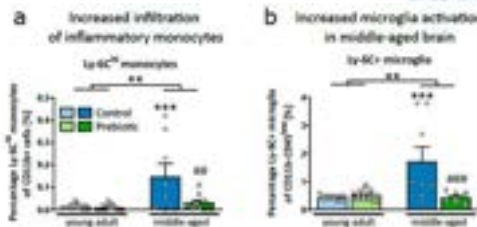
Schellekens, et al. EBioMedicine, The Lancet, 2021

PREBIOTIC (OligofructoseE-Inulin) reverses stress-induced immune priming and microglia activation in middle age



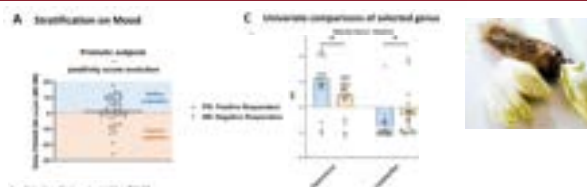
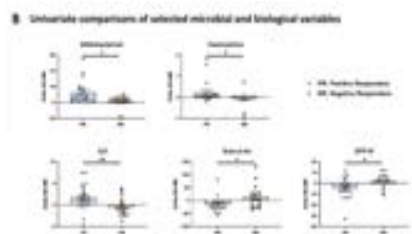
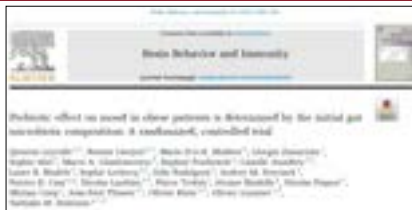
- OE Inulin (modulates)
- The suppresses immune
- **Potent neuroinflammation**
- Prebiotic protects neuroinflammation

Molecular Psychiatry Fibre-not-fast cars as answer to mid-life (microbiome) crisis!
 Article | Published: 16 May 2019
Mid-life microbiota crises: middle age is associated with pervasive neuroimmune alterations that are reversed by targeting the gut microbiome
 Marissa Boehme, Marcel van de Wilt, Thomas F. S. Bastiaansen, Loreto Oliveira-Santos, Gabriela Lynn, Franz Fusch, Anna V. Soldanova, Gerard M. Muloney, Chana Mironis, Kieran V. Sandhu, Karen A. Scott, Gerard Clarke, Catherine Stanton, Timothy G. Dinan, Harvitt Schellekens & John F. Cryan



age
 major
 ated
 g by
 ated

PREBIOTIC (Inulin) improves mood in obesity

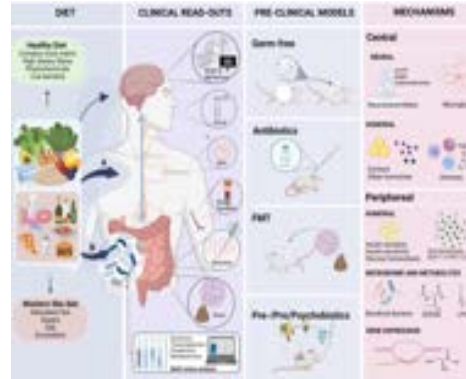
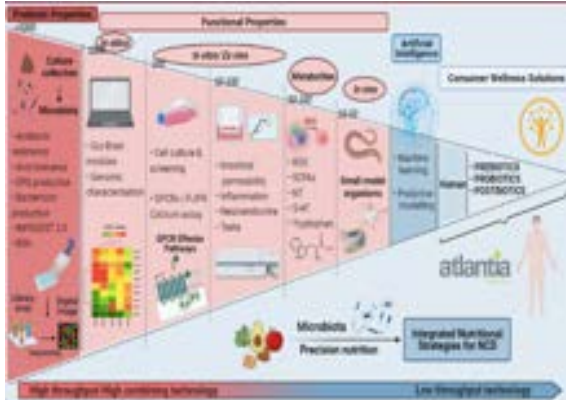


- A randomized, single-blinded, multicentric, placebo-controlled trial (n=106 obese patients), receiving 16 g/d of native inulin or maltodextrin combined with dietary advice to consume inulin-rich or -poor vegetables for 3 months & CR.
- **Inulin supplementation in obese subjects had moderate beneficial effect on emotional competence and cognitive flexibility.**
- **Positive responders** exhibiting **specific microbial signature** -elevated Coprococcus levels at baseline- were more prone to benefit from prebiotic supplementation in terms of mood.
- Positive correlation of positivity score with Bifidobacterium, Haemophilus, IL-8, Dipeptidylpeptidase-4 (degrades incretins like GLP1) and subcutaneous fat mass, which can **predict or mediate the beneficial effects of inulin on behaviour in obesity.**

➢ **Inulin intake may improve mood in obese subjects exhibiting a specific microbial profile.**



The Pipeline: Mechanistic Mining of Microbes



[Harriet Schellekens, et al., Nutritional Neuroscience, 2022]

Human microbiome: Diet, precision **THE IRISH TIMES** medicine and wellbeing
 Conor Purcell talks to Dr Harriet Schellekens of APC Microbiome Ireland
 Sep 11 2021

Schellekens Lab members (current & alumni)

@harschellekens



- C. Cuesta-Marti
- N. Carey (MSc)
- Dr. Cristina Torres
- Dr. M. van de Wouw
- Dr. M. Tufvesson
- Dr L. Wasiewski
- Dr. F. Uhlig
- N. Leeuwendaal
- T. Lipuma (MSc)
- Dr. Marcus Boehme
- Dr. B. Chruscicka
- Dr. S. Menneson
- Dr. M. Schrever
- Dr. D. Kazareva
- Dr.R. O'Connor
- Dr. Wallace-Fitzsimons
- Dr.W. van Oeffelen†
- Dr. K. Howick
- Dr. Daniela Felice
- Dr.T. Becker
- Dr. H. Shaban
- Dr.V. Ramirez
- Connelly(MSc)
- S.Theratile(MSc)
- Dr M. Javaid

Collaborators

- Prof John Cryan
- Prof Ted Dinan
- Prof Catherine Stanton
- Dr Ger Clarke
- Dr. Siohain O'Mahony



Mind your MicroBiome

