Project number: 6565
Funding source: Science Foundation Ireland (SFI)
Date: Oct 2020
Project dates: Oct 2013 – May 2019

Microbiota Transplantation

Microbiome Ireland
Interfacing Food & Medicine

Key external stakeholders:

SFI, research communities, public health agencies and health professionals, policymakers.

Practical implications for stakeholders:

- A fecal microbiota transplant (FMT) (also known as a stool transplant) is the process of transplantation of faecal bacteria from a healthy individual into a diseased recipient. FMT involves restoration of the colonic microflora and natural antibacterials by introducing healthy bacterial flora through infusion of stool, obtained from a healthy donor.
- FMT is a centuries-old procedure however we are trying to study it in the modern era with new technology to make it safer, and scientifically assess it to determine mechanisms of action and to clarify which patients should and should not receive it.
- Results of this study delivered new knowledge on targeting the gut microbiota as a therapeutic strategy in depression, cardiorespiratory diseases, obesity and metabolic syndrome.
- The scientific findings and technological solutions were shared with relevant stakeholders.

Main results:

- We demonstrated that depression is associated with decreased gut microbiota richness and diversity. Fecal microbiota transplantation from depressed patients to microbiota-depleted rats can induce behavioural and physiological features characteristic of depression in the recipient animals, including anhedonia and anxiety-like behaviours, as well as alterations in tryptophan metabolism.
- Faecal microbiota transfer to vehicle- and antibiotic-treated animals disrupted the gut microbiota composition, associated with depressed ventilatory responsiveness to hypercapnia. Faecal microbiota transfer caused significant disruptions to brainstem monoamine neurochemistry, with increased homovanillic acid:dopamine ratio indicative of increased dopamine turnover, which correlated with the abundance of several bacteria of six different phyla.
- Fecal microbiota-transplant from male mice transferred the metabolic syndrome (MS) phenotype to female mice, while antibiotic treatment eliminated the sexual dimorphism in MS, suggesting a causative role of the gut microbiome in this condition.

Opportunity / Benefit:

Findings from this project advance the concept that targeting the gut microbiota may be a viable therapeutic strategy for novel antidepressant development in sub groups of depressed patients and may augment depression prevention strategies. Our research also adds to emerging evidence providing a rationale for manipulation of the gut microbiota as an adjunctive therapy in cardiorespiratory diseases. In addition, we have identified a previously uncharacterized microbiome-based mechanism that sheds light upon sexual dimorphism in the incidence of MS and that suggests novel therapeutic targets and strategies for the management of obesity and MS in males and postmenopausal women.

Collaborating Institutions:

Teagasc, University College Cork, Harvard Medical School.

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Teagasc project team: Prof Catherine Stanton (Project Leader)

External collaborators: University College Cork:
Prof Paul Ross, Prof John Cryan, Prof Ted Dinan and Dr Gerard Clarke

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1. Project background:

The human body contains trillions of bacteria cells. This vast, largely unexplored bacterial community known as the microbiome has been linked to many aspects of human health, from gastrointestinal diseases to obesity. Importantly, disrupting the microbiome with antibiotics can cause disease by wiping out the helpful bacteria in our guts.

A Fecal Microbiota Transplantation (FMT), also known as a stool transplant, is an innovative treatment that involves the process of transplantation of faecal bacteria from a healthy individual into a diseased recipient. FMT involves restoration of the colonic microflora and natural antibacterials by introducing healthy bacterial flora through infusion of stool, obtained from a healthy donor. FMT has in randomized, controlled clinical trials resolved 80-90% of infections caused by recurrent *C. difficile* that does not respond to antibiotics. In this project we also sought to explore FMT's potential role for treating other diseases, such as depression, cardiorespiratory diseases, obesity and metabolic syndrome.

2. Questions addressed by the project:

FMT is a centuries-old procedure however we are trying to study it in the modern era with new technology to make it safer, and scientifically assess it to determine mechanisms of action and to clarify which patients should and should not receive it. We also sought to explore FMT's potential role for treating diseases such as depression, cardiorespiratory diseases, obesity and metabolic syndrome.

3. The experimental studies:

- A Fecal Microbiota transplantation was prepared from a group of depressed patients and controls and transferred by oral gavage to a microbiota-deficient rat model and assessed if a depressive-like phenotype emerged in the treated animals.
- In a second experimental study we sought to determine the cardiorespiratory effects of manipulation of the gut microbiota following a 4-week administration of a cocktail of antibiotics in adult male rats. We subsequently explored the effects of administration of faecal microbiota from pooled control (vehicle) rat faeces, given by gavage to vehicle- and antibiotic-treated rats.
- Understanding the mechanism of the sexual dimorphism in susceptibility to obesity and metabolic syndrome (MS) is important for the development of effective interventions for MS. In a third experimental study fecal microbiota transplantation was used to investigate whether gut microbiota were necessary to mediate sexual dimorphism in MS. FMT with fecal content from donor male mice for 10 weeks was performed on female 10-week-old recipient mice pretreated with an antibiotic cocktail.

4. Main results:

- We demonstrated that depression is associated with decreased gut microbiota richness and diversity. Fecal microbiota transplantation from depressed patients to microbiota-depleted rats can induce behavioural and physiological features characteristic of depression in the recipient animals, including anhedonia and anxiety-like behaviours, as well as alterations in tryptophan metabolism.
- Faecal microbiota transfer to vehicle- and antibiotic-treated animals disrupted the gut microbiota composition, associated with depressed ventilatory responsiveness to hypercapnia. Faecal

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microbiota transfer caused significant disruptions to brainstem monoamine neurochemistry, with increased homovanillic acid:dopamine ratio indicative of increased dopamine turnover, which correlated with the abundance of several bacteria of six different phyla.

- Fecal microbiota-transplant from male mice transferred the metabolic syndrome (MS) phenotype to female mice, while antibiotic treatment eliminated the sexual dimorphism in MS, suggesting a causative role of the gut microbiome in this condition

5. Opportunity/Benefit:

Findings from this project advance the concept that targeting the gut microbiota may be a viable therapeutic strategy for novel antidepressant development in sub groups of depressed patients and may augment depression prevention strategies. Our research also adds to emerging evidence providing a rationale for manipulation of the gut microbiota as an adjunctive therapy in cardiorespiratory diseases. In addition, we have identified a previously uncharacterized microbiome-based mechanism that sheds light upon sexual dimorphism in the incidence of metabolic syndrome and that suggests novel therapeutic targets and strategies for the management of obesity and metabolic syndrome in males and postmenopausal women.

6. Dissemination:

- Kelly, J.R., Borre, Y., O'Brien, C., Patterson, E., El Aidy, S., Deane, J., Ross, P., Stanton, S., Clarke, G., Cryan, J.F., and Dinan, TG. 2016. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. Journal of psychiatric research, 82, pp.109-118.
- O'Connor, K.M., Lucking, E.F., Golubeva, A.V., Strain, C.R., Fouhy, F., Cenit, M.C., Dhaliwal, P., Bastiaanssen, T.F., Burns, D.P., Stanton, C. and Clarke, G., 2019. Manipulation of gut microbiota blunts the ventilatory response to hypercapnia in adult rats. EBioMedicine, 44, pp.618-638.
- Kaliannan, K., Robertson, R.C., Murphy, K., Stanton, C., Kang, C., Wang, B., Hao, L., Bhan, A.K. and Kang, J.X., 2018. Estrogen-mediated gut microbiome alterations influence sexual dimorphism in metabolic syndrome in mice. Microbiome, 6(1), pp.1-22.
- Long-Smith, C., O'Riordan, K.J., Clarke, G., Stanton, C., Dinan, T.G. and Cryan, J.F., 2020. Microbiota-gut-brain axis: new therapeutic opportunities. Annual review of pharmacology and toxicology, 60, pp.477-502.

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