P52 – **Probiotic modulation of the gut microbiota in the 3xTG Alzheimer's Disease mouse model is associated with improvements in cognitive capacity and lipid and inflammatory profiles**

Davies, TS.[1], Masetti, G.[1,2], Michael, DR.[1], Turner, S.[2], Kerry-Smith, J.[1], Amblin, M.[1], Rees, M.[1], Allen, M.1, Glymenaki, M.[3], Li, J.[3], Marchesi, J.[3,4], Good, MA.[2], Plummer, SF.[1], Hughes, TR.[2]

[1]*Cultech Ltd.*

[2]*Division of Infection and Immunity, Cardiff University School of Medicine*

[3]*Faculty of Medicine, Department of Surgery & Cancer, Imperial College London*

[4]*School of Biosciences, Cardiff University*

tomd@cultech.co.uk

Background: Alzheimer's Disease (AD) is a progressive neurodegenerative condition strongly associated with ageing, inflammation and metabolic syndrome. Recent research has shown that AD progression and severity is linked to the gut microbiota through its interactions via the gut-brain-axis. Probiotics are microorganisms which have been shown to provide health benefits to the host and are being targeted to modulate many inflammatory conditions including neurodegeneration.

Objective: To assess the potential impact of probiotic (Lactobacillus and Bifidobacterium) supplementation on gut microbiome composition, cognitive impairment, lipid and inflammatory dysregulation in the 3xTG AD mouse model receiving a high-fat diet (HFD).

Methodology: Three groups of 3xTG mice (n=10/group) were fed a HFD for 12 weeks to promote AD progression. Group 1 received the HFD diet supplemented with Lab4 probiotic (L. acidophilus and Bifidobacterium spp.), group 2 received a HFD diet supplemented with Lab4b probiotic (L. paracasei, L. salivarius and Bifidobacterium spp.) and group 3 received HFD diet as the control. Faecal samples were collected at the baseline and end-point for 16S rRNA next-generation sequencing to identify differentially abundant operational taxonomic units (OTUs) between treatments and to determine changes in alpha- and beta-diversity. Cognitive capacity was assessed at week 11 using novel object recognition tests, nest scoring, open field and olfactory preference analysis. Lipid and inflammatory cytokine analyses were performed on plasma samples from baseline and end-point. Regulation of gene expression was assessed in liver, duodenum, colon and brain tissue samples extracted at the end-point.

Results: The HFD profoundly changed the composition of the gut microbiota of 3xTG mice from the baseline with reduction of the alpha diversity index and an increase in Firmicutes:Bacteroidetes ratio. These HFD-mediated changes were less drastic with Lab4 and Lab4b supplementation compared to the control group. OTUs differentially present in the control group in response to the HFD and AD progression were less abundant in the Lab4 and Lab4b intervention groups. The Lab4 and Lab4b interventions reduced HFD-mediated weight gain over the 12 week period compared to the control. Cognitive impairment was reduced with both Lab4 and Lab4b compared to the control as demonstrated by improved novel object recognition and increased nesting scores. Lower levels of circulating cholesterol and LDL were recorded in the Lab4 and Lab4b groups compared to the control. The expression of circulating pro-inflammatory (TNF-α and KC/GRO) cytokines was also lower with both intervention groups compared to the control.

Conclusions / Implications for practice: Supplementation of HFD-fed 3xTG AD mice with either Lab4 or Lab4b significantly impacted on the composition of the gut microbiota, improved cognitive impairment and plasma lipid composition and also reduced circulating pro-inflammatory cytokine levels when compared to the control group receiving HFD alone. These findings provide a strong justification for further investigation involving either additional genetic models and/or human intervention studies.