Data input form: MouseAGE Database

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Preferred acknowledgement:

Summarise supporting data attached:

APP/PS1 mice were assessed in several experiments at ages from 6-7 months of age. At this age Aβ accumulation was evident and was more pronounced in female compared with male mice. Evidence of microglial activation increased expression of inflammatory cytokines and infiltration of peripheral immune cells were clear from 7 months of age, as was behavioural dysfunction; when explicitly assessed, some of these changes were more pronounced in female, than in male, mice. Increased blood brain barrier permeability and LTP impairment were evident at 13-14 months, though we have not assessed these earlier and at this time, there was evidence that microglia from APP/PS1 mice were more sensitive to inflammatory stimuli.

Ageing / disease: Alzheimer's disease

Model: APP/PS1 mice

Clinically relevant? (Yes or No): Minimally

Explanation of why clinically relevant or not: Provides information on contributing factors in the development of Aβ pathology. Useful for investigating impact of neuroinflammation

Characteristics, timing of appearance of phenotype and phenotypic tests used (attach supporting data when unpublished if available):

PHENOTYPE	TIMING	REFERENCE
Aβ accumulation	6-7 months	Browne TC et al (2013) J Immunol. 190, 2241-2251.
	7 months (only females assessed)	O'Reilly et al (2012) J Neuroimmune Pharmacol, 7, 140–144
	8-9 months (females>males)	Gallagher JJ et al (2011) Neurodegener Dis. 11, 33-41
	12 months	McManus R et al (2014) Neurob Aging. 35, 109-121.
	13-14 months	Kelly RJ et al (2013) J Alz Dis, 37, 63-75 Minogue AM et al (2014) Neurobiol Aging. 31, 1442-1452

		Dempsey C et al (2017) Brain Behav Immun. 61, 306-316 McDonald CM et al. (2016) Brain Behav Immun. 58:191-200
Inflammatory changes (including microglial activation)	7 months (only females assessed) 8-9 months (females>males) 8-9 months (only females assessed) 12 months 13-14 months	O'Reilly et al (2012) J Neuroimmune Pharmacol, 7, 140–144 Gallagher JJ et al (2011) Neurodegener Dis. 11, 33-41 Gallagher JJ et al (2012) J Alz Dis. 28, 147-161 McManus R et al (2014) Neurobiol Aging. 35, 109-121. Kelly RJ et al (2013) J Alz Dis, 37, 63-75 Minogue AM et al (2014) Neurobiol Aging. 31, 1442-1452 McDonald CM et al. (2016) Brain Behav Immun. 58:191-200
Inflammasome activation	15 months	Dempsey C et al (2017) Brain Behav Immun. 61, 306-316
Behavioural dysfunction	7 months (only females assessed) 8-9 months (females only) 14 months 15 months	O'Reilly et al (2012) J Neuroimmune Pharmacol, 7, 140–144 Gallagher JJ et al (2011) Neurodegener Dis. 11, 33-41 McDonald CM et al. (2016) Brain Behav Immun. 58:191-200 Dempsey C et al (2017) Brain Behav Immun. 61, 306-316
Impaired LTP	13-14 months	Kelly RJ et al (2013) J Alz Dis, 37, 63-75
Oxidative changes	8-9 months (only females assessed)	Gallagher JJ et al (2012) J Alz Dis. 28, 147-161
Increased genotype-related microglial sensitivity to inflammatory stimuli Increased sensitivity of macrophages from APP/PS1 mice to inflammatory stimuli	12-14 months >15 months	Jones RS et al (2015) Neurobiol Aging. 36, 2716-2724. Barrett JP et al. (2015) J Alz Dis. 44, 949-962.

Altered microglial metabolism & iron retention	8-9 months (only females assessed) 12 months	Gallagher JJ et al (2012) J Alz Dis. 28, 147-161 Holland R et al (2018) Brain Behav Immun. 68:183-196.
BBB permeability	14 months	Minogue AM et al (2014) Neurobiol Aging. 31, 1442-1452
Infiltrating cells	6-7 months 12 months 13-14 months	Browne TC et al (2013) J Immunol. 190, 2241-2251. McManus R et al (2014) Neurob Aging. 35, 109-121. Kelly RJ et al (2013) J Alz Dis, 37, 63-75 Minogue AM et al (2014) Neurobiol Aging. 31, 1442-1452
T1 & T2 relaxation time changes	13-14 months	Kelly RJ et al (2013) J Alz Dis, 37, 63-75

If applicable, Intervention(s) performed (type, dose, route of administration, frequency):

INTERVENTION	IMPACT	
B Pertussis infection at 4 and 8 months	Increased genotype-related inflammation, infiltration of cells and Aβ accumulation 2 months after infection (mice now 12 months)	McManus R et al (2014) Neurob Aging. 35, 109-121.
FTY720 (0.3mg/kg in drinking water) for 93 days from 10 months. B Pertussis infection 3 days after start of FTY720	FTY720 attenuated infection-induced BBB permeability, astrocytic activation (GFAP), Aβ pathology and T cell infiltration	McManus RM et al (2017) J Neuroimmune Pharmacol. 12, 670-681
MCC950 (10mg/kg ip every second day for 3 months from 12-15 months	Attenuates genotype-related inflammasome activation, Aβ accumulation	Dempsey C et al (2017) Brain Behav Immun. 61, 306-316
AntiTLR2 antibody (1mg/kg iv every 2 weeks from 7 months to 14 months)	Attenuates genotype-related behavioural deficit, infiltrating cells, microglial & astroglial activation and Aβ pathology	McDonald CM et al. (2016) Brain Behav Immun. 58:191-200
Rosiglitazone (6mg/kg/day orally in maple syrup) from7 months for 2 weeks	Attenuates genotype-related behavioural deficit, Aβ pathology and microglial activation	O'Reilly et al (2012) J Neuroimmune Pharmacol, 7, 140–144
Aβ-specific Th1 cells ($15x10^6$ cells/mouse iv) in 6-7 month-old mice	Exacerbates genotype-related Aβ pathology and results in behavioural deficits and microglial activation in APP/PS1 mice	Browne TC et al (2013) J Immunol. 190, 2241-2251.

Phenotype post-treatment (include null or negative results and attach supporting data separately):

References (list below):

Holland R, McIntosh AL, Finucane OM, Mela V, Rubio-Araiz A, Timmons G, McCarthy SA, Gun'ko YK, Lynch MA. (2018) Inflammatory microglia are glycolytic and iron retentive and typify the microglia in APP/PS1 mice. Brain Behav Immun. 68:183-196.

McManus RM, Finucane O, Wilk MM, Mills KHG, Lynch MA (2017) FTY720 attenuates infection-induced enhancement of Aβ accumulation in APP/PS1 mice by modulating astrocytic activation. J. Neuroimmune Pharmacol. 12, 670-681

Dempsey C, Rubio Araiz A, Bryson KJ, Finucane O, Larkin C, Mills EL, Robertson AA, Cooper MA, O'Neill LA, Lynch MA. (2017) Inhibiting the NLRP3 inflammasome with MCC950 promotes non-phlogistic clearance of amyloid-β and cognitive function in APP/PS1 mice. Brain Behav Immun. 61, 306-316.

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Jones RS, Minogue AM, Fitzpatrick O, Lynch MA (2015) Inhibition of JAK2 attenuates the increase in inflammatory markers in microglia from APP/PS1 mice. Neurobiol Aging. 36, 2716-2724.

Barrett JP, Minogue AM, Jones RS, Ribeiro C, Kelly RJ, Lynch MA. (2015) Bone Marrow-Derived Macrophages from AβPP/PS1 Mice are Sensitized to the Effects of Inflammatory Stimuli. J Alzheimers Dis. 44, 949-962.

Minogue AM, Jones RS, Kelly RJ, McDonald CL, Connor TJ and Lynch MA (2014) Age-associated dysregulation of microglial activation is coupled with enhanced BBB permeability and pathology in APP/PS1 mice. Neurobiol Aging. 31, 1442-1452

McManus R, Mills, KHG, Lynch MA (2014) Respiratory infection promotes T cell infiltration and Aβ deposition in APP/PS1 mice. Neurobiol Aging. 35, 109-121.

Kelly RJ, Minogue AM, Lyons A, Jones, RS, Browne TC, McManus R, Costello DA, O'Sullivan C, Connor TJ, Lynch MA (2013) Glial activation in APP/PS1 mice is associated with infiltration of IFNγ-producing cells. J Alz Dis. 37, 63-75

Browne TC, McQuillan K, McManus RM, O'Reilly JA, Mills KH, Lynch MA (2013) IFN-γ Production by amyloid β-Specific Th1 cells promotes microglial activation and Increases plaque burden in a mouse model of Alzheimer's disease. J Immunol. 190, 2241-2251.

Gallagher JJ, Minogue AM and Lynch MA (2013) Impaired performance of female APP/PS1 mice in the Morris water maze is coupled with increased Aβ accumulation and microglial activation. Neurodegener Dis. 11, 33-41

Gallagher JJ, Finnegan ME, Grehan B, Dobson J, Collingwood JF, and Lynch MA (2012) Modest Amyloid Deposition is Associated with Iron Dysregulation, Microglial Activation, and Oxidative Stress. J Alz Dis. 28, 147-161.

O'Reilly J-A and Lynch MA (2012) Rosiglitazone improves s patial memory and decreases insoluble $A\beta_{1-42}$ in APP/PS1 mice. J Neuroimmune Pharmacol, 7, 140–144