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EPSRC
Engineering and Physical Sciences Research Council

Mitochondrial Biochemistry in Ageing

- Brain and Muscle
- Lipidomics, proteomics and enzyme activity
- Old and young mouse
- Neurodegeneration and Parkinson’s disease
- Other model and non-model organisms

How does the biochemical composition of mitochondria change with age?

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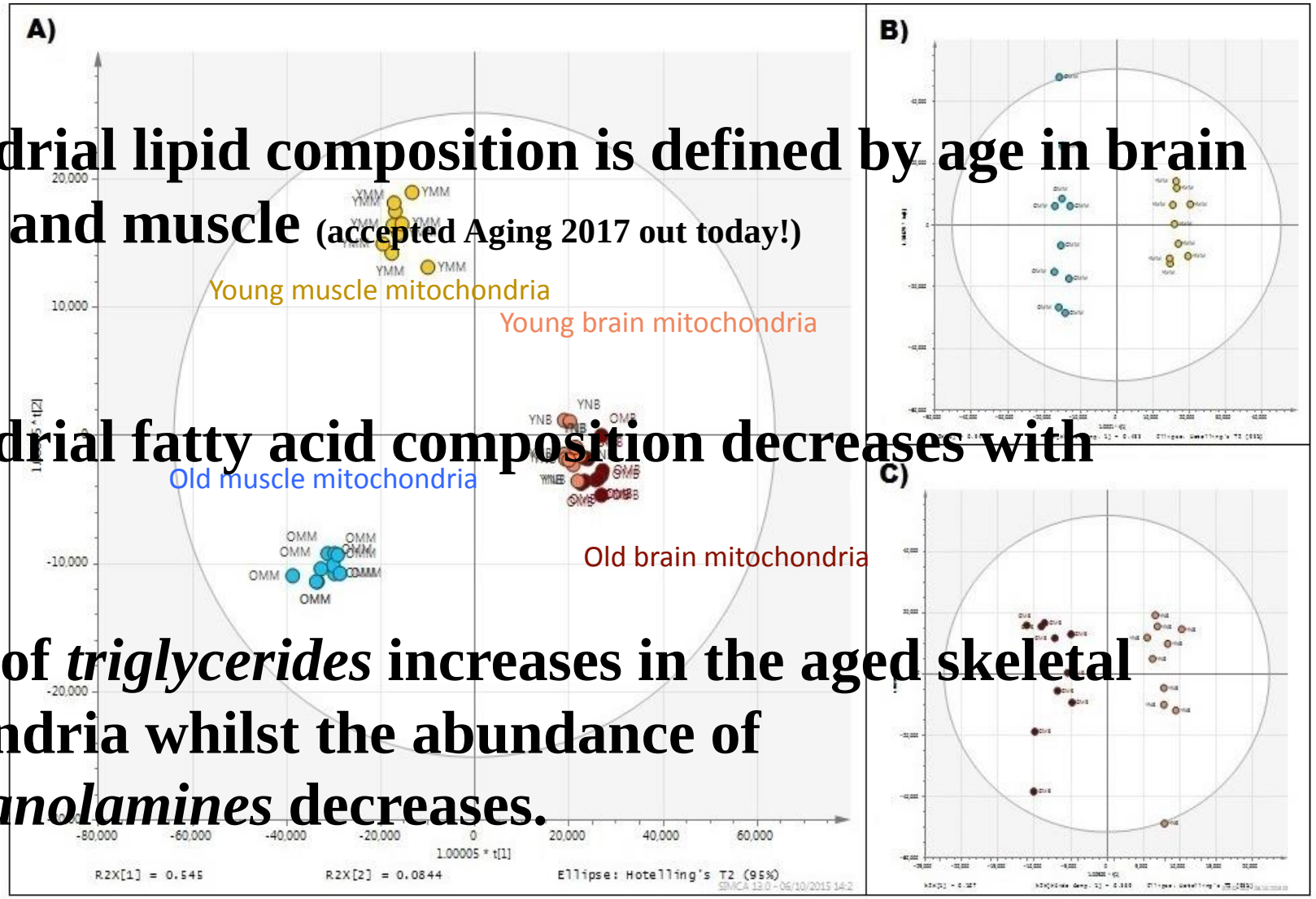
Mouse mitochondrial lipid composition is defined by age in brain and muscle (accepted Aging 2017 out today!)



- **Brain mitochondrial fatty acid composition decreases with ageing.**
- **The abundance of *triglycerides* increases in the aged skeletal muscle mitochondria whilst the abundance of *phosphatidylethanolamines* decreases.**

How do proteins change in the brain and muscle samples with age?

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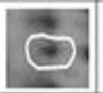
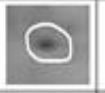
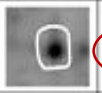
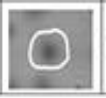
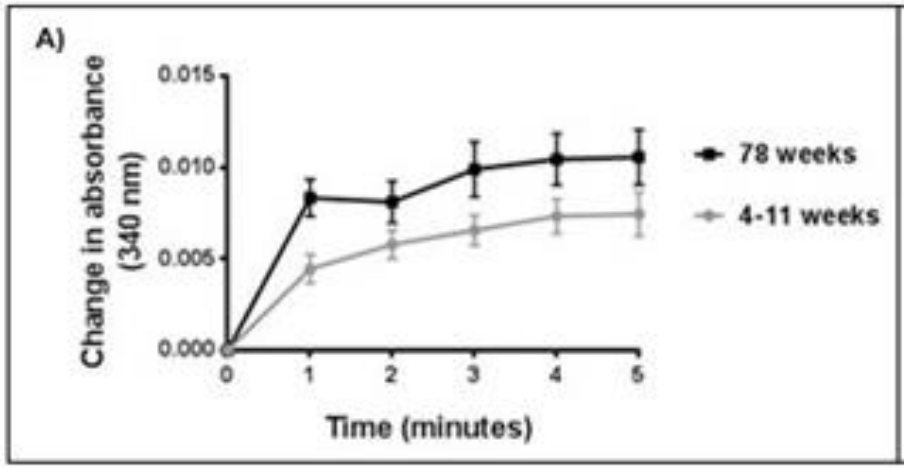
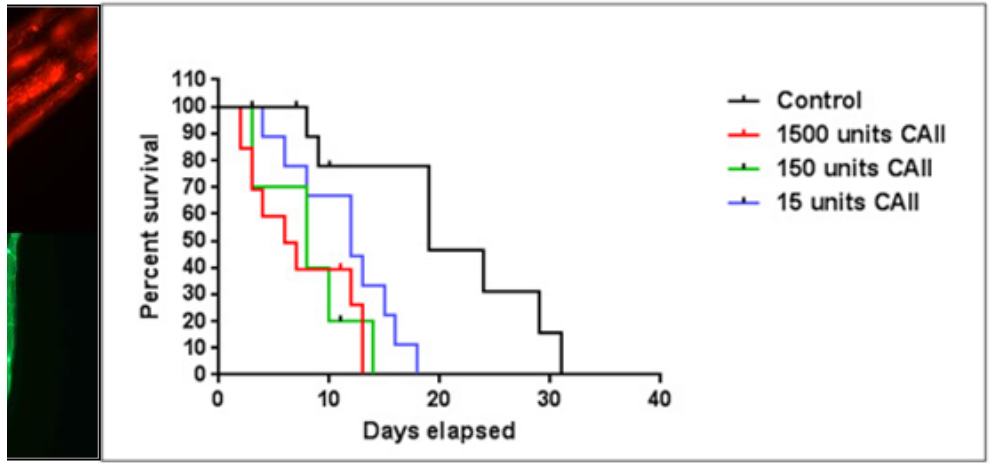
A)

Spot no.	Skeletal Muscle 4-11 weeks	Skeletal Muscle 78 weeks	Protein Identity	MASCOT matched peptide sequence	Anova (p)	Fold change	Expression with age	Mitochondrial Localisation Probability Score	Mitochondrial Localisation Cleavage Site	Mitochondrial Localisation Cleaved sequence
6			Calsequestrin	9.5%	0.012	2.2	Increased	0.0518	25	MGARAVSELRLALLFVLVL GTPRL
26			Voltage-dependent anion channel 1	26%	0.013	1.7	Increased	0.4779	Not predictable	N/A
47			i) ATP synthase subunit O ii) Protein DJ-1	i) 44% ii) 24%	0.047	1.5	Decreased	i) 0.9940 ii) 0.3321	i) 42 ii) 15	i) MAAPAASGLSRQVRSFS TSVVRPFAKLVRPPVQVYGI EGRY ii) MASKRALVILAKGA
29			Carbonic anhydrase III	19%	0.084	2.3	Increased	0.0545	Not predictable	N/A
60			Haemoglobin subunit alpha	21%	0.112	1.4	Decreased	0.0337	Not predictable	N/A

B)

Spot no.	Brain 4-11 weeks	Brain 78 weeks	Protein Identity	MASCOT matched peptide sequence	Anova (p)	Fold change	Expression with age	Mitochondrial Localisation Probability Score	Mitochondrial Localisation Cleavage Site	Mitochondrial Localisation Cleaved sequence
133			Carbonic anhydrase II	7%	0.004	1.6	Increased	0.0117	Not predicatable	N/A
108			Pyruvate dehydrogenase E1	14%	0.047	1.2	Decreased	0.9764	15	MAAVSGLVRRPLRE
75			Alpha-enolase	13%	0.088	1.3	Increased	0.5329	19	MSILRIHAREIFDSRGNP
153			NADH dehydrogenase flavoprotein 2	12%	0.141	1.2	Increased	0.9966	43	MFSLALRARATGLAAQWG RHARNLHKTAVHNGAGGAL FVHRD

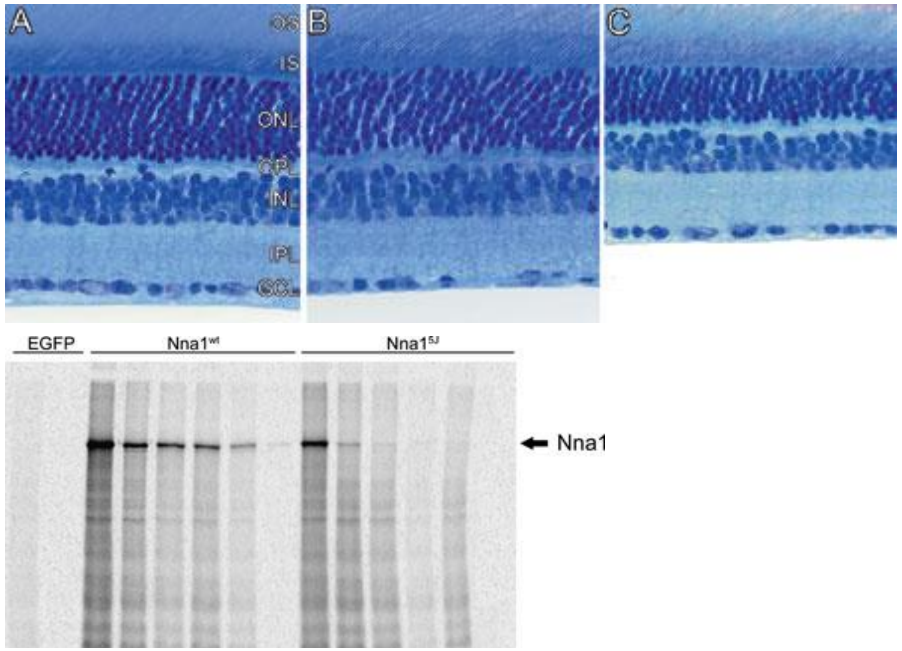


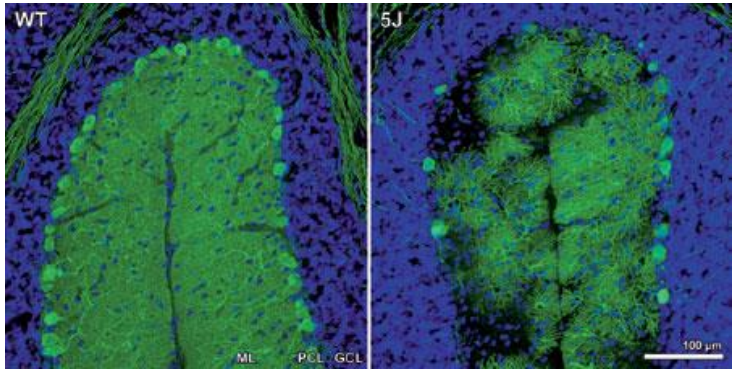


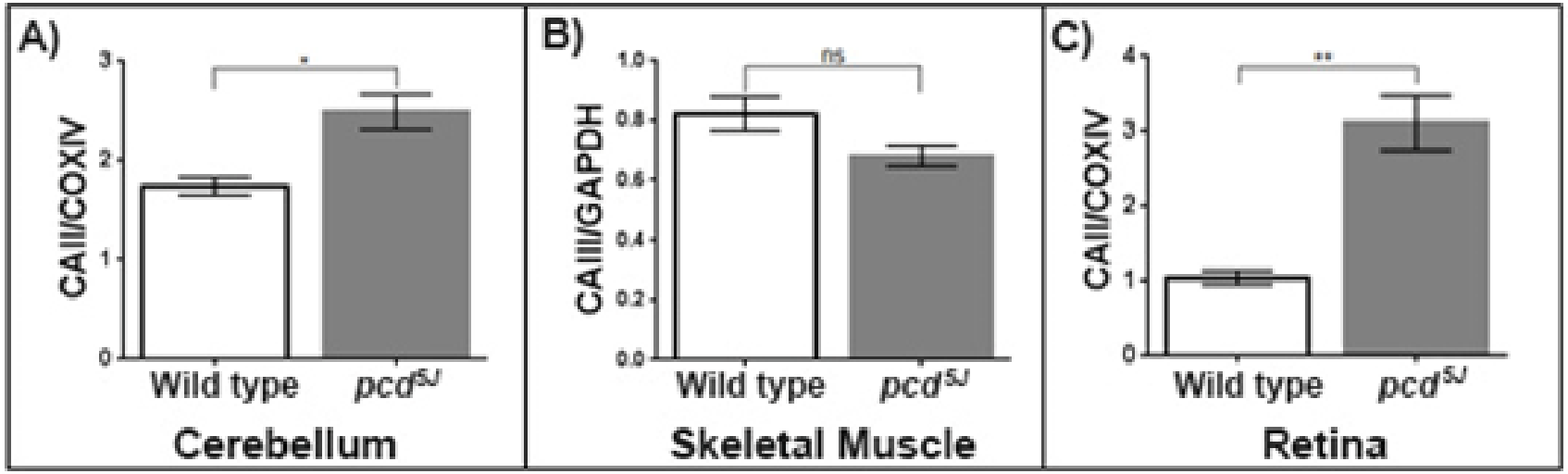
Pollard *et al., Aging 2016*

Purkinje cell degeneration^{5J} and mitochondria

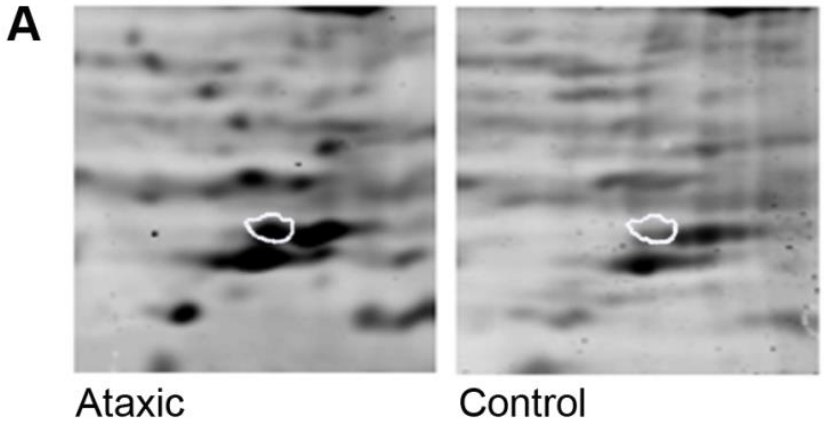
Chakrabarti et al., Neuron 2010

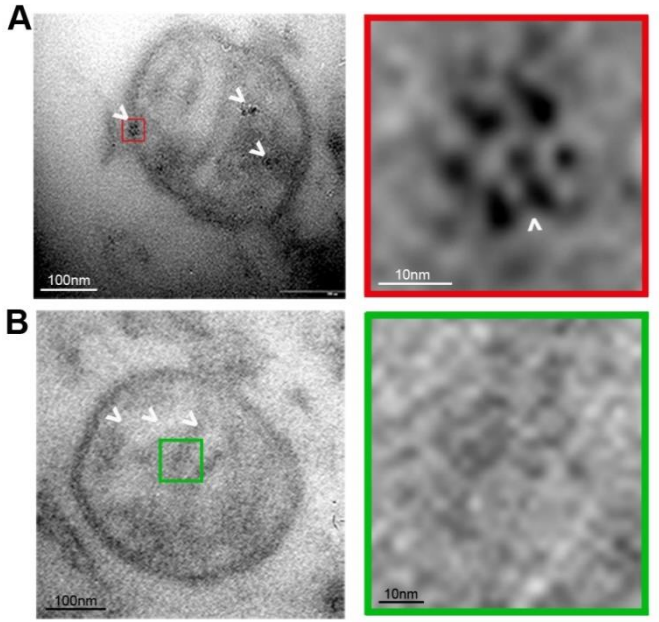


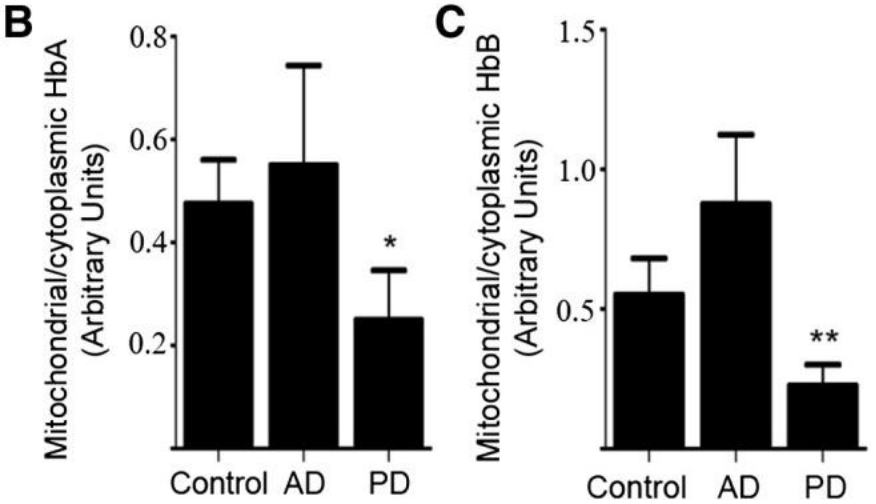


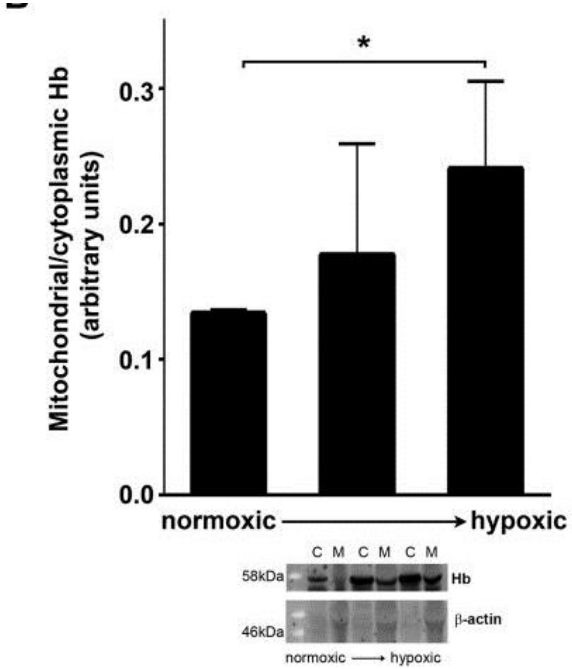


Does this *pcd* model of neurodegeneration tell us anything about human age-related disease?





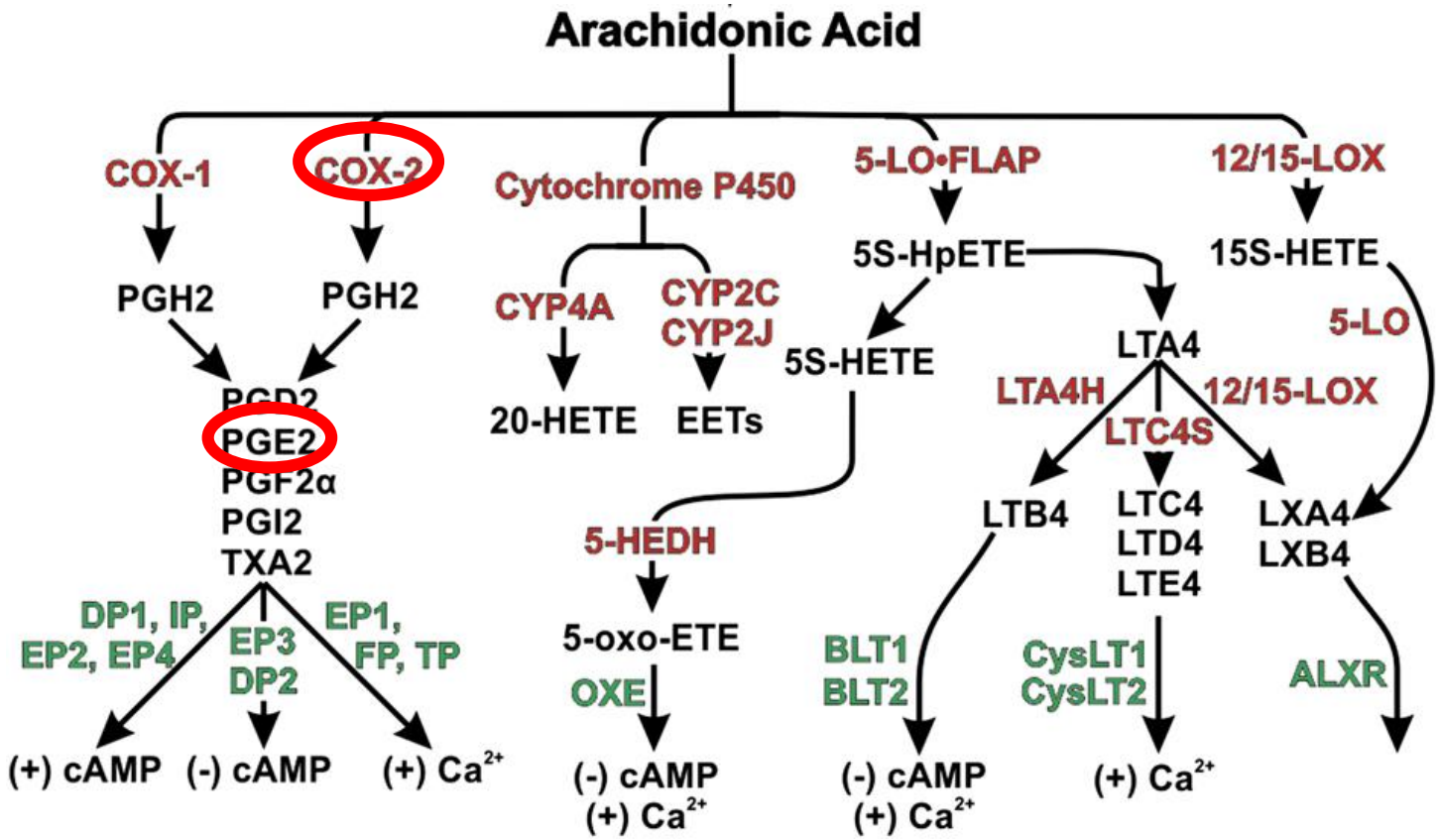


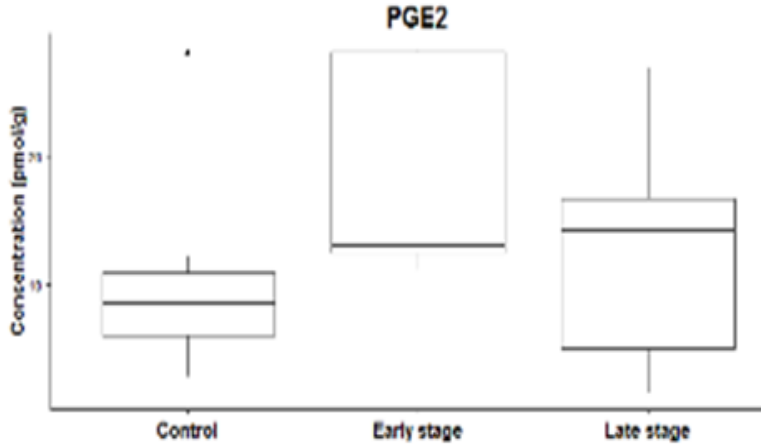


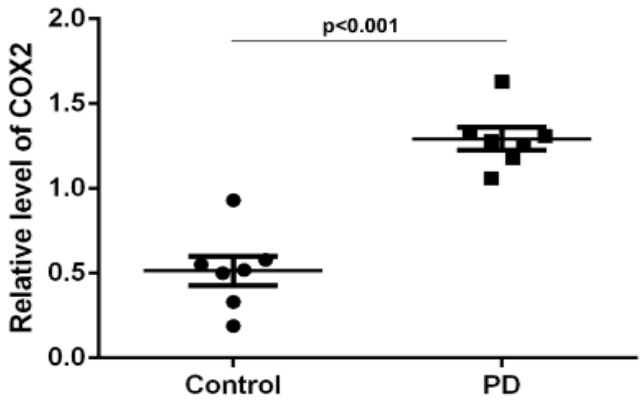
Shephard *et al., Mitochondrion 2014 and 2016*

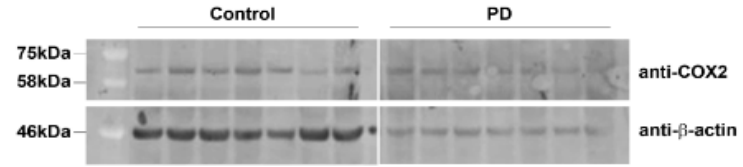
Connecting mitochondrial dysfunction with neuroinflammatory processes In Parkinson's disease

We are using lipidomics to look at specifc pathways

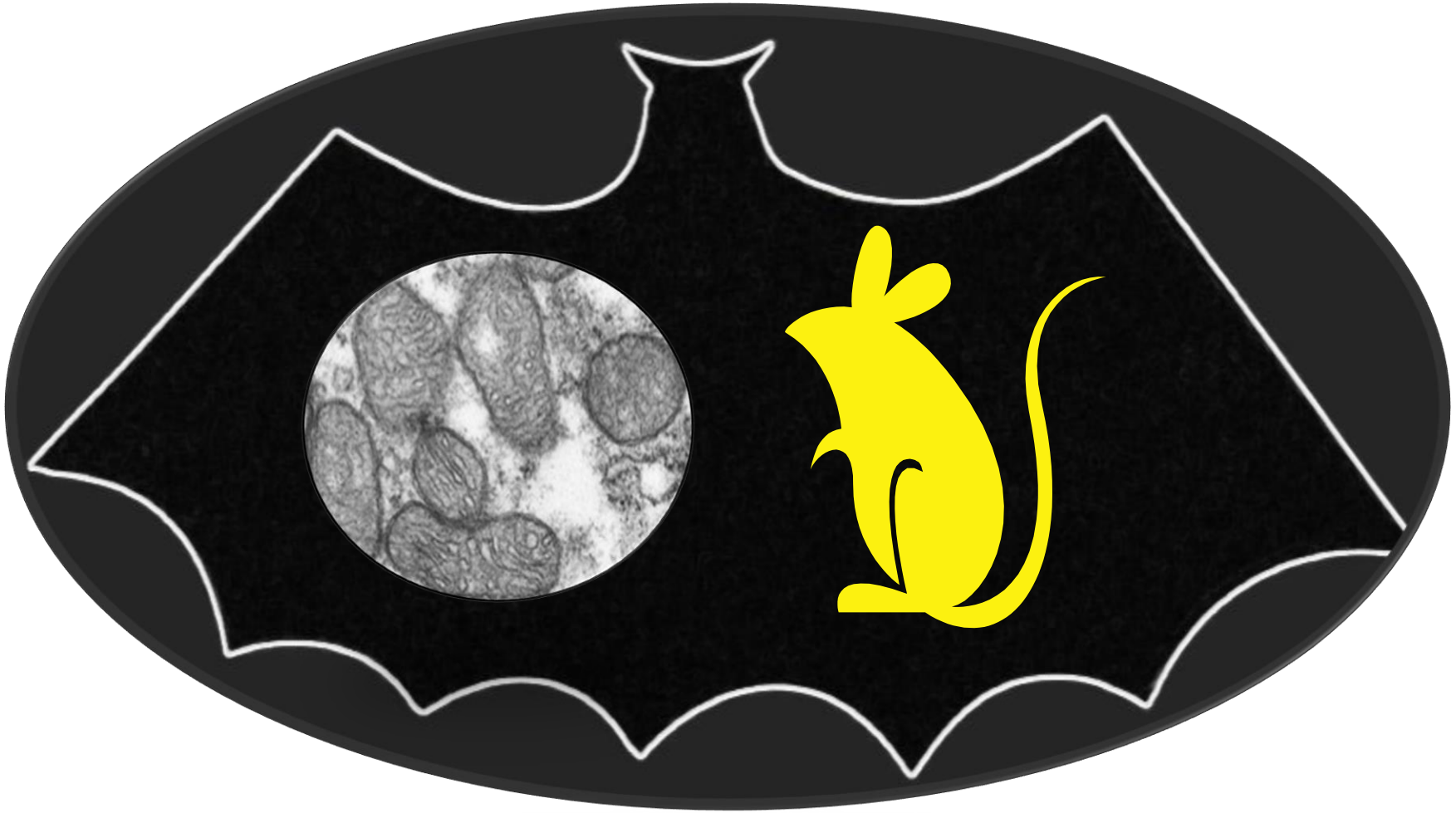






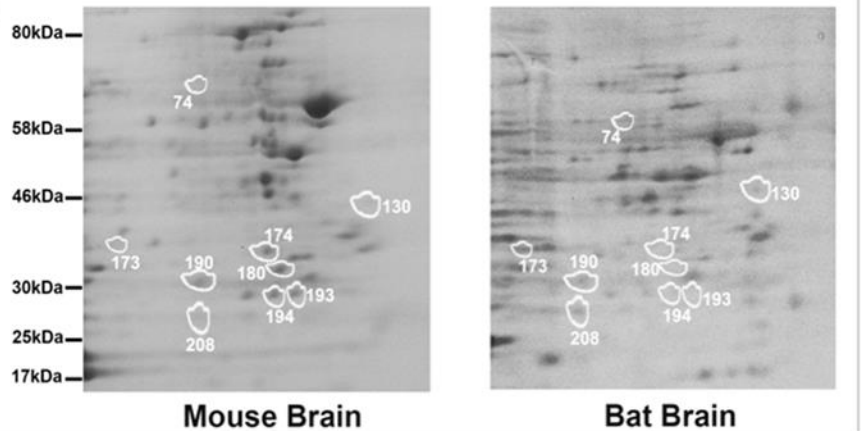


Comparative mitochondrial ageing



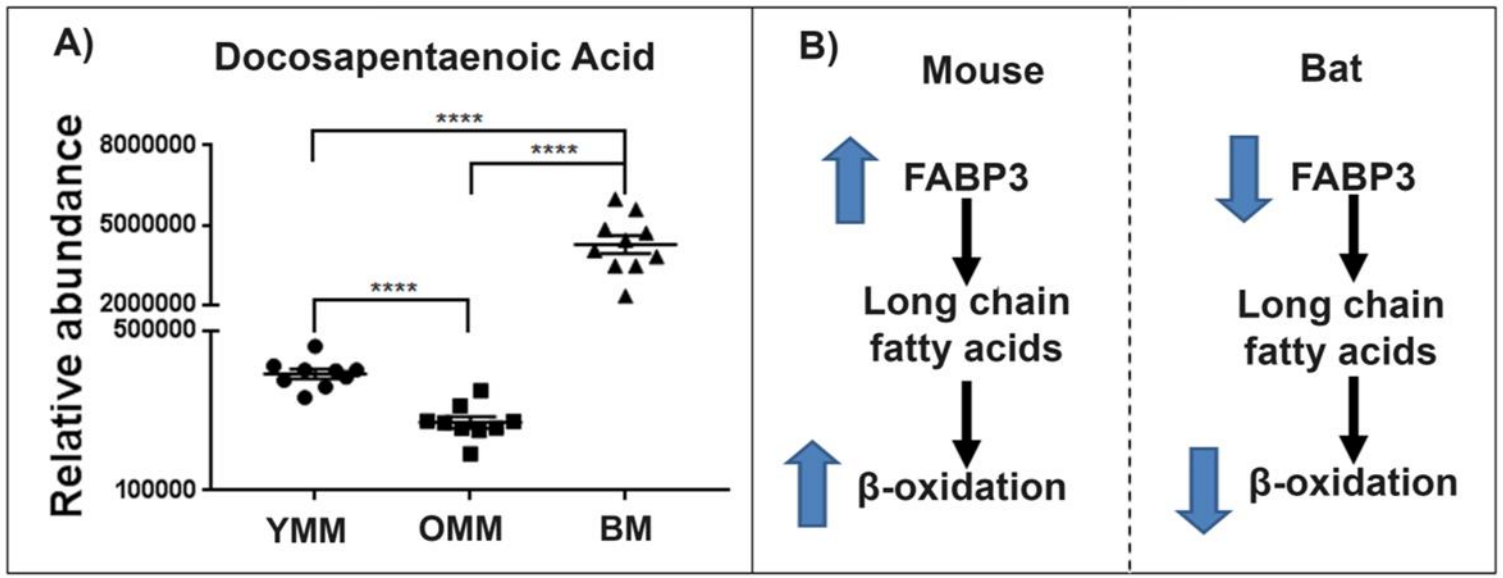
Fatty acid binding protein (FABP3) increases whilst long chain fatty acids (C20 and above) decrease in abundance in the mouse skeletal muscle mitochondria.

A)



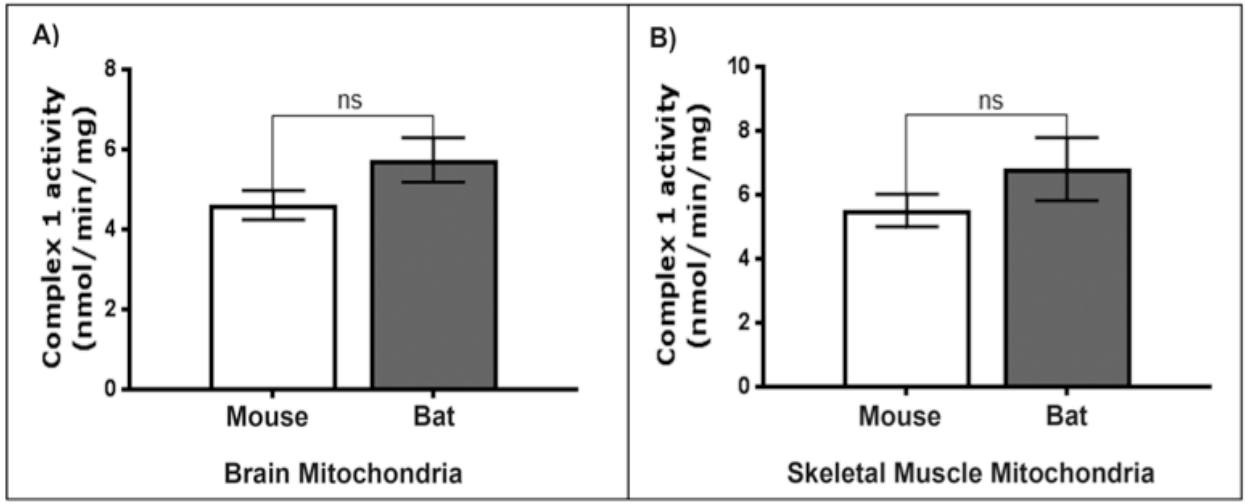
B)

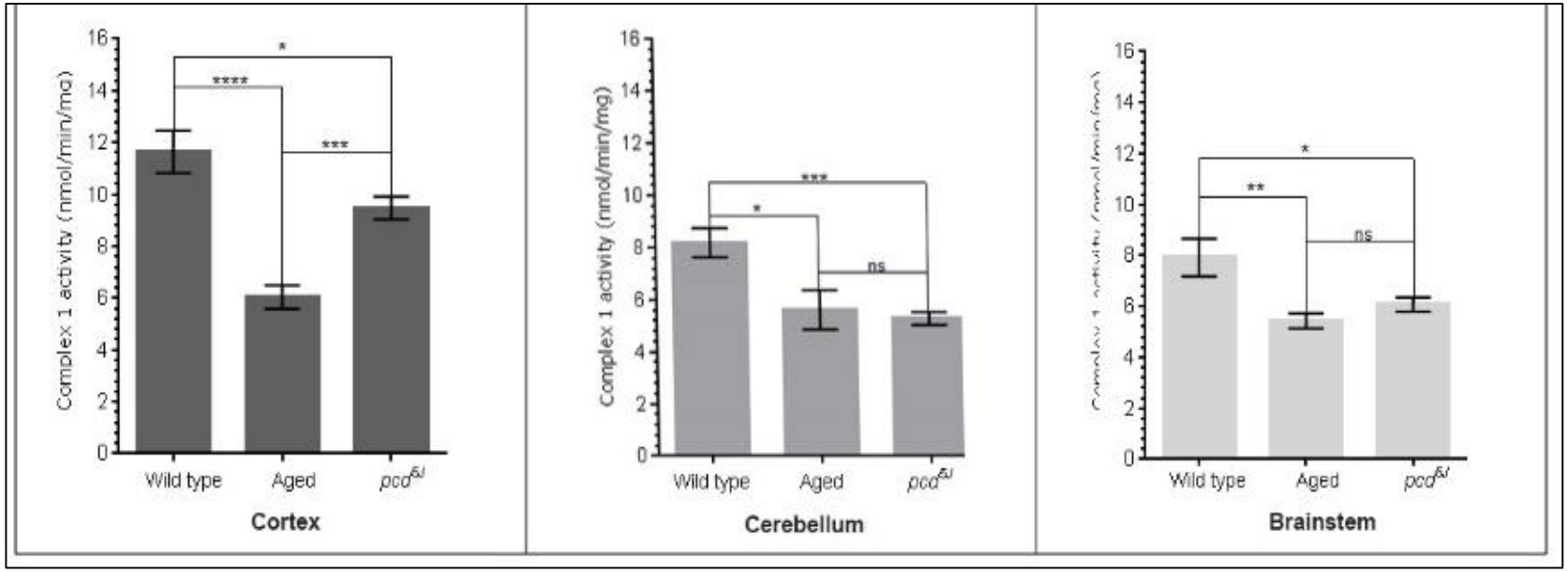
Spot no.	Protein identity	Anova (p)	Fold change	Increased expression in	Mitochondrial localisation signal		
					Probability Score	Cleavage site	Cleaved sequence
194	ATP synthase subunit d	0.0001	2.1	Mouse	0.5089	14	MAGRKLALKTIDW
180	NADH dehydrogenase [ubiquinone] flavoprotein 2	0.0002	2	Mouse	0.9966	43	MFSLALRARATGLAAQW GRHARNLHKTAVHNGA GGALFVHRD
174	NADH dehydrogenase [ubiquinone] iron-sulfur protein 3	0.0002	2.2	Mouse	0.9956	37	MAAAAARVWCRGLLGAA SVGRGAGRPSVLWQHVR RF
190	RAB14 protein	0.0070	1.4	Mouse	0.0198	Not predictable	N/A
208	Myelin basic protein	0.0090	1.5	Mouse	0.3619	Not predictable	N/A
130	Tropomyosin alpha-1 chain	0.0090	1.3	Bat	0.2602	Not predictable	N/A
193	Ras-related protein Rab-1B	0.0120	2.1	Mouse	0.0157	Not predictable	N/A
173	Cytochrome b-c1 complex subunit Rieske	0.0140	1.5	Bat	0.6452	22	MLSVAARSGPFAPV LSATSRG
74	NADH dehydrogenase Fe-S protein 1	0.0260	1.3	Bat	0.6865	24	MLRIPIKRALIGLSN SPKGYVRT



Higher levels of FABP3
- greater risk of type 2 diabetes
- heart failure / stroke
- dilated cardiomyopathy

Complex I activity per mitochondrial unit not significantly different in the bat versus the mouse.

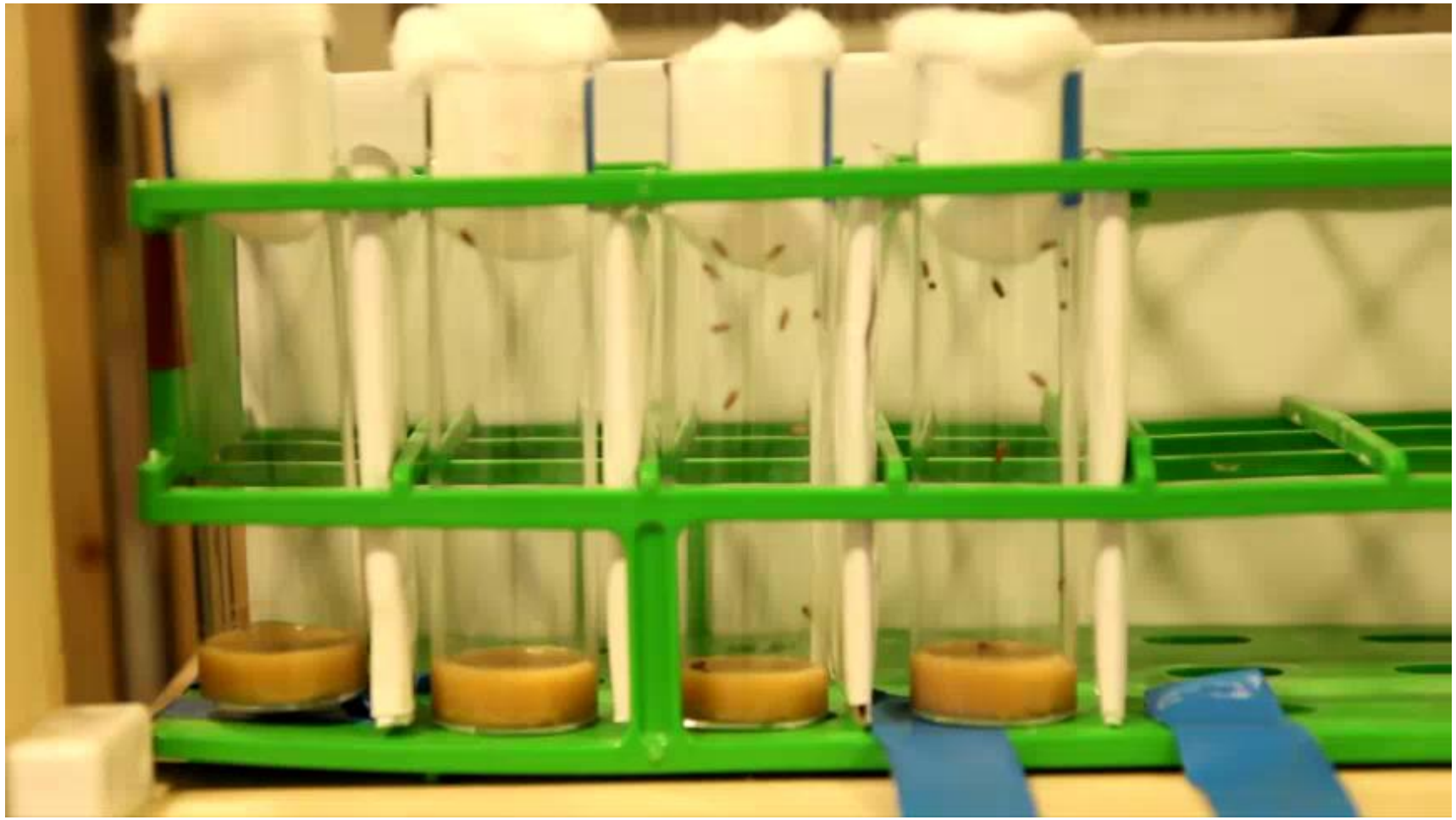


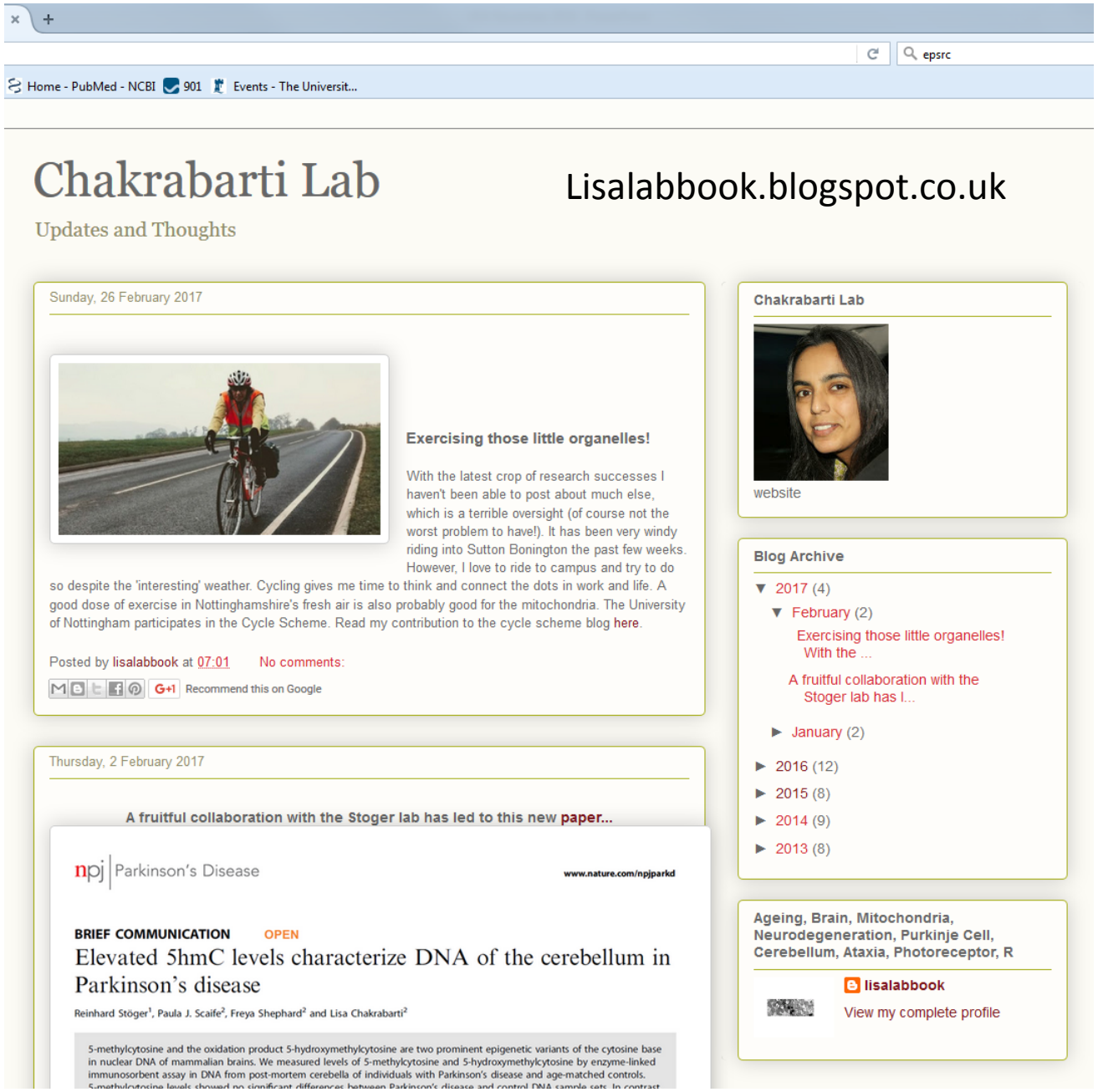


Pollard, Craig and Chakrabarti *PLOS ONE 2016*

UK National cross-country inter-county finals – Loughborough March 2017

Does exercise change the biochemistry of mitochondrial ageing?





We are always looking to collaborate

- Lipidomics, proteomics, enzymes
- Banked human brain tissues
- Model and non-model organisms
- Please come and talk to me and I can tell you more!