CURRICULUM VITAE: Dr. Iain P. Hargreaves

Senior lecturer in Biochemistry*
Honorary Consultant Clinical Scientist[1]
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EDUCATION

From	Degree	Subject	University/Institute
02/04/2015	FRCPath	Clinical Chemistry	Royal College of Pathologists, United Kingdom
20/09/1994	PhD	Biochemistry	University of Liverpool
14/7/1989	BSc	Biochemistry	University of Lancaster

EMPLOYMENT

Dates	Position	Employer	Duties
10/01/1995-03/02.1997	Post-doctoral researcher	Institute of Neurology, London, UK.	Establishment of enzyme assays to assess mitochondrial function.
04/02/1997-16/09/2016	Principal Clinical Scientist	National Hospital, University College of London Hospitals, London, UK.	Running the mitochondrial diagnostic service in the Neurometabolic service and undertaking research into mitochondrial and CoQ10 metabolism
20/09/2016-	Senior lecturer	Liverpool John Moores University, Liverpool, UK.	Lecturing in biochemistry and biomedical sciences. Research into mitochondrial and CoQ10 metabolism.

PUBLICATIONS (Since 2016)

Refereed journals

1. Heaton RA, Heales S, Rahman K, Sexton DW, **Hargreaves I.** The Effect of Cellular Coenzyme Q_{10} Deficiency on Lysosomal Acidification.J Clin Med. 2020 Jun 19;9(6):E1923. doi: 10.3390/jcm9061923.PMID: 32575494

2. Ghosh R, Wood-Kaczmar A, Dobson L, Smith EJ, Sirinathsinghji EC, Kriston-Vizi J, **Hargreaves IP**, **Heaton R**, Herrmann F, Abramov AY, Lam AJ, Heales SJ, Ketteler R, Bates GP, Andre R, Tabrizi SJ. Expression of mutant exon 1 huntingtin fragments in human neural stem cells and neurons causes inclusion formation and mitochondrial dysfunction. FASEB J. 2020 Jun;34(6):8139-8154. doi: 10.1096/fj.201902277RR.

3. Turton N, Heaton RA, Ismail F, Roberts S, Nelder S, Phillips S, **Hargreaves IP.** The Effect of Organophosphate Exposure on Neuronal Cell Coenzyme Q_{10} Status. Neurochem Res. 2020 Apr 18. doi: 10.1007/s11064-020-03033-y.

4. Heaton RA, Heales S, Rahman K, Sexton DW, **Hargreaves I.** The Effect of Cellular Coenzyme Q_{10} Deficiency on Lysosomal Acidification.J Clin Med. 2020 Jun 19;9(6):E1923. doi: 10.3390/jcm9061923.PMID: 32575494

5. Bugiardini E, Bottani E, Marchet S, Poole OV, Beninca C, Horga A, Woodward C, Lam A, **Hargreaves I**, Chalasani A, Valerio A, Lamantea E, Venner K, Holton JL, Zeviani M, Houlden H, Quinlivan R, Lamperti C, Hanna MG, Pitceathly RDS. Expanding the molecular and phenotypic spectrum of truncating MT-ATP6 mutations. Neurol Genet. **2020**; 7,6(1):e381

6. Heaton R, Duderly KE, **Hargreaves IP**. Assessment and the Establishment of a Neuronal Cell Model of CoQ10 Deficiency. Methods Molecular Biology, Vol. 2138 *(In press)*

7. Horga A, Woodward CE, Mills A, Pareés I, **Hargreaves IP**, Brown RM, Bugiardini E, Brooks T, Manole A, Remzova E, Rahman S, Reilly MM, Houlden H, Sweeney MG, Brown GK, Polke JM, Gago F, Parton MJ, Pitceathly RDS, Hanna MG. Differential phenotypic expression of a novel PDHA1 mutation in a female monozygotic twin pair. Hum Genet. **2019**;138(11-12):1313-1322.

8. Ng X, Sadeghian M, Heales S, **Hargreaves IP.** Assessment of Mitochondrial Dysfunction in Experimental Autoimmune Encephalomyelitis (EAE) Models of Multiple Sclerosis. Int J Mol Sci. **2019**; 20(20). pii: E4975. **(Impact factor: 4.33)**

9. **Hargreaves IP**, Mantle D. Supplementation with selenium and coenzyme Q10 in criticallyill patients. Br J Hosp Med (Lond). **2019** 2;80(10):589-593.

10. Keatley K, Stromei-Cleroux S, Wiltshire T, Rajala N, Burton G, Holt WV, Littlewood DTJ, Briscoe AG, Jung J, Ashkan K, Heales SJ, Pilkington GJ, Meunier B, McGeehan JE, **Hargreaves IP**, McGeehan RE. Integrated Approach Reveals Role of Mitochondrial Germ-Line Mutation F18L in Respiratory Chain, Oxidative Alterations, Drug Sensitivity, and Patient Prognosis in Glioblastoma Int J Mol Sci. **2019**; 20(13). pii: E3364.

11. Heaton R, Millchap L, Saleem F, Ganon J, **Hargreaves IP**. Current biochemical treatments of mitochondrial respiratory chain disorders. Expert opinion on orphan drugs. **2019**; 7(6):277-285

12. Horga A, Bugiardini E, Manole A, Bremner F, Jaunmuktane Z, Dankwa L, Rebelo AP, Woodward CE, **Hargreaves IP** , Cortese A, Pittman AM, Brandner S, Polke JM, Pitceathly RDS, Züchner S, Hanna MG, Scherer SS, Houlden H, Reilly MM. Autosomal dominant optic atrophy and cataract "plus" phenotype including axonal neuropathy Neurol Genet. **2019** 1;5(2):e322.

13. Thueson E, Leadon DP, Heaton R, **Hargreaves I**, Bayley WM. Effect of daily supplementation with ubiquinol on muscle coenzyme Q10 concentrations in Thoroughbred racehorses. Comparative Exercise Physiology. **2019** (3):219-226.

14. Foti SC, **Hargreaves I**, Carrington S, Kiely AP, Houlden H, Holton JL. Cerebral mitochondrial electron transport chain dysfunction in multiple system atrophy and Parkinson's disease. Sci Rep. 2019; 25;9(1):6559.

15. Mantle D, **Hargreaves I**. Coenzyme Q10 and Degenerative Disorders Affecting Longevity: An Overview Antioxidants (Basel). **2019**;8(2). Antioxidants (Basel). 2019 16;8(2). pii: E44.

16. Montero R, Yubero D, Salgado MC, González MJ, Campistol J, O'Callaghan MDM, Pineda M, Delgadillo V, Maynou J, Fernandez G, Montoya J, Ruiz-Pesini E, Meavilla S, Neergheen V, García-Cazorla A, Navas P, **Hargreaves I,** Artuch R. Plasma coenzyme Q status is impaired in selected genetic conditions. Sci Rep. **2019**;9(1):793.

17. Mantle D, **Hargreaves IP**. Organophosphate poisoning and coenzyme Q10: an overview.British Journal of Neuroscience Nursing **14**(5):206-214 02 Oct 2018

18. **Hargreaves I,** Mody N, Land J, Heales S. Blood Mononuclear Cell Mitochondrial Respiratory Chain Complex IV Activity Is Decreased in Multiple Sclerosis Patients: Effects of β-Interferon Treatment. J Clin Med. **2018**, 20;7(2). pii: E36.

19. Ahmed ST, Alston CL, Hopton S, He L, **Hargreaves IP**, Falkous G, Oláhová M, McFarland R, Turnbull DM, Rocha MC, Taylor RW. Using a quantitative quadruple immunofluorescent assay to diagnose isolated mitochondrial Complex I deficiency. Sci Rep. **2017**;7(1):15676.

20. Al Shahrani M, Heales S, **Hargreaves I,** Orford M. 14.Oxidative Stress: Mechanistic Insights into Inherited Mitochondrial Disorders and Parkinson's Disease. J Clin Med. **2017**;6(11). pii: E100. doi: 10.3390/jcm6110100.

21. Manole A, Jaunmuktane Z, **Hargreaves I**, Ludtmann MHR, Salpietro V, Bello OD, Pope S, Pandraud A, Horga A, Scalco RS, Li A, Ashokkumar B, Lourenço CM, Heales S, Horvath R, Chinnery PF, Toro C, Singleton AB, Jacques TS, Abramov AY, Muntoni F, Hanna MG, Reilly MM, Revesz T, Kullmann DM, Jepson JEC, Houlden H. Clinical, pathological and functional characterization of riboflavin-responsive neuropathy. Brain. **2017**;140(11):2820-2837**.**

22. Ghose A, Taylor CM, Howie AJ, Chalasani A**, Hargreaves I,** Milford DV. Measurement of Respiratory Chain Enzyme Activity in Human Renal Biopsy Specimens. J Clin Med. **2017;** 19;6(9). pii: E90.

23. Stepien KM, Heaton R, Rankin S, Murphy A, Bentley J, Sexton D, **Hargreaves IP**. Evidence of Oxidative Stress and Secondary Mitochondrial Dysfunction in Metabolic and Non-Metabolic Disorders. J Clin Med. **2017**; 19;6(7). pii: E71.

24. Dyson A, Dal-Pizzol F, Sabbatini G, Lach AB, Galfo F, Dos Santos Cardoso J, Pescador Mendonça B, **Hargreaves I,** Bollen Pinto B, Bromage DI, Martin JF, Moore KP, Feelisch M, Singer M. Ammonium tetrathiomolybdate following ischemia/reperfusion injury: Chemistry, pharmacology, and impact of a new class of sulfide donor in preclinical injury models. PLoS Med. **2017** 5;14(7):e1002310.

25. Bugiardini E, Poole OV, Manole A, Pittman AM, Horga A, **Hargreaves I,** Woodward CE, Sweeney MG, Holton JL, Taanman JW, Plant GT, Poulton J, Zeviani M, Ghezzi D, Taylor J, Smith C, Fratter C, Kanikannan MA, Paramasivam A, Thangaraj K, Spinazzola A, Holt IJ, Houlden H, Hanna MG, Pitceathly RDS. Clinicopathologic and molecular spectrum of RNASEH1-related mitochondrial disease. Neurol Genet. **2017** 2;3(3):e149.

26. Cornelius N, Wardman JH, **Hargreaves IP,** Neergheen V, Bie AS, Tümer Z, Nielsen JE, Nielsen TT. Evidence of oxidative stress and mitochondrial dysfunction in spinocerebellar ataxia type 2 (SCA2) patient fibroblasts: Effect of coenzyme Q10 supplementation on these parameters. Mitochondrion. 2017;34:103-114.

27. Morel J, **Hargreaves I**, Brealey D, Neergheen V, Backman JT, Lindig S, Bläss M, Bauer M, McAuley DF, Singer M. Simvastatin pre-treatment

improves survival and mitochondrial function in a 3-day fluid-resuscitated rat model of sepsis. Clin Sci (Lond). **2017**;131(8):747-758.

28. Sadeghian M, Mastrolia V, Rezaei Haddad A, Mosley A, Mullali G, Schiza D, Sajic M, **Hargreaves I,** Heales S, Duchen MR, Smith KJ. Mitochondrial dysfunction is an important cause of neurological deficits in an inflammatory model of multiple sclerosis. Sci Rep. **2016**;6:33249.

29. Tarry-Adkins JL, Fernandez-Twinn DS, Chen JH, **Hargreaves IP**, Neergheen V, Aiken CE, Ozanne SE. Poor maternal nutrition and accelerated postnatal growth induces an accelerated aging phenotype and oxidative stress in skeletal muscle of male rats. Dis Model Mech. **2016** ; 9(10):1221-1229.

30. McKiernan P, Ball S, Santra S, Foster K, Fratter C, Poulton J, Craig K, McFarland R, Rahman S, **Hargreaves I,** Gupte G, Sharif K, Taylor RW. Incidence of Primary Mitochondrial Disease in Children Younger Than 2 Years Presenting With Acute Liver Failure. J Pediatr Gastroenterol Nutr. **2016**;63(6):592-597.

*I have published a further **93** papers (pre 2016) in peer reviewed journals which are available on PUBMED.*

Book chapters

1. Neerghen V, Dyson A, Wainwright L, **Hargreaves IP**. Statin and Fibrate-Induced Dichotomy of Mitochondrial Function. In: Will Y and Dykens JA, eds. Mitochondrial Dysfunction Caused by Drugs and Environmental Toxicants. Wiley. **2018**: 2-2: 457-473.
2. Neerghen V, **Hargreaves IP**. Secondary coenzyme Q10 deficiency: Causes and consequences. In Grigoryeva S, ed. Coenzyme Q10: Uses, Health Effects and Role in Disease. Nova Science, New York. **2018**. 89-110.

Books

1. Hargreaves, I. P. Mitochondrial Respiratory Chain Disorders: From Clinical Presentation to Diagnosis and Treatment. New York: Nova Science Inc; **2019.**

2. Hargreaves I (ed). Coenzyme Q10: from fact to fiction. New York: Nova Science; **2015**.

PhD STUDENTS:

- **Current PhD students I am currently supervising:**
- PhD in Biochemistry, start date Oct 2017, Robert Heaton, `*Coenzyme Q10 deficiency: The lysosomal paradigm*,` 31.01.2020 - Lead supervisor
- PhD in Biochemistry, start date 31.01.20, Nadia Turton**,** *Longevity through novel dietary strategies for individuals with PKU*,` 31.01.2023- Lead supervisor.

- **PhD students that have completed under my supervision.**

- PhD in Biochemistry at UCL, Mesfer Al Shahrani, `*Mitochondrial function, oxidative stress and Parkinson's disease,*` 2015 Oct- Oct 2018- Secondary supervisor.
- PhD in Biochemistry at UCL, Luke Wainwright, `*Mechanisms*` *of CoQ10 blood brain barrier transport*,` 2015 Oct- Oct 2018- Lead supervisor
- PhD in Biochemistry at UCL, Kate E Duberley, ` *Neurometabolic Implications of Coenzyme $Q_{10}$ Deficiency: Pathogenesis, Detection and Treatment,*` Oct 2010-Oct 2013 – Lead supervisor

RESEARCH

- **A major area of my research is focussed upon CoQ10 metabolism and its involvement in disease:**
- I am interested in the effect of a Q10 deficiency on lysosomal function and together with my PhD student have just submitted a manuscript to the Journal of Clinical Medicine which will be the first to report an impairment of lysosomal function as the result of a CoQ10 deficiency. This result could have important clinical consequences as it indicates that a deficit in cellular CoQ_{10} status may impact upon on lysosomal function as well as its widely described effect on mitochondrial activity- This paper will be used as a basis for further funding.
- After receiving funding from the pharmaceutical company, Pharm Nord in June 2019 I was able to investigate the effect of organophosphate (OP) exposure on neuronal CoQ10 status. The results of this study have for the first time indicated the ability of OP`s to inhibit CoQ10 biosynthesis. This result will have important consequences for the treatment of OP exposure and at present I am writing a paper to ensure this information is available to clinicians as well as contacting Gulf War Syndrome charities to engender further funding for this interesting research.
- My research on neuronal cell CoQ10 deficiency and the effect of this deficiency on mitochondrial function has resulted in 3 highly cited papers (cited 96,46 + 43 times, respectively) as well as invites to chair a session at the United Mitochondrial Disease Foundation Meeting in USA in 2013 and a talk at the International CoQ10 Association meeting in Spain in 2014. My experience and knowledge of CoQ10 metabolism has enabled me to be considered one of the UK`s leading experts on disorders of CoQ10

metabolism and I provide clinical advice on this subject in my capacity as an Honorary Consultant Clinical Scientist.

- As a result of my original work on CoQ10 and its detection I synthesized a unique non physiological internal standard (I.S) and using this I was able to establish the only UK based NHS clinical CoQ10 diagnostic service at the National Hospital in London which is now an NHS England commissioned service. The paper in which I reported the I.S. has received 110 citations to date.
- **The second major area of my research focuses on mitochondrial metabolism:**
- My research on mitochondrial metabolism allowed me together with Prof Simon Heales (UCL) and Dr. John Land (UCL) to establish the MRC diagnostic service based at the National Hospital which is now an NHS England commissioned service and generates an income of 180,000 per year.
- As part of my research into the effect of mitochondrial dysfunction upon cellular antioxidant status I detected evidence of a deficiency in the antioxidant, glutathione in the muscle tissue of patients with mitochondrial disease. The resulting paper has provided support for the importance of cellular glutathione restoration in the treatment of mitochondrial disease.
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- **RESEARCH GRANTS AND INDUSTRIAL SPONSORSHIP OVER THE PAST FIVE YEARS**

- PhD studentship funded by the Liverpool company, **Vitaflo** (Which is part of Nestle Health Care) for the project entitled, ` *Longevity through novel dietary strategies for individuals with PKU*` 31.1.2020, total value of support: £75,000- **I am the Principle Investigator (PI).**
- Research studentship, funded by the pharmaceutical company**, Pharma Nord**, for the project entitled: Title: *Assessment of the effect of organophosphate exposure upon neuronal cell coenzyme Q_{10} status*, June, 2019, total value of support: £4,000 – **I was the PI.**

- Summer studentship, Funded by the British Inherited Metabolic Disease Group (BIMDG), for the project title: ` *Assessment of the coenzyme $Q_{10}$ status and mitochondrial respiratory chain function in a human neuronal cell model of methylmalonic acidemia*,` June, 2018, total value of support:£1,600- **I was the PI.**
- **PhD Studentship funded by Liverpool John Moores University on a project entitled:** ``*Coenzyme Q10 deficiency: The lysosomal paradigm*,` Oct 2017 -Oct 2020. total value of support: £75,000- **I am the Principle Investigator (PI).**

- Investigation to assess the effect of statin therapy upon mouse cerebral CoQ10 + CoQ9 status, funded by the pharmaceutical company, **Pharma Nord**, 2015, total value; £3,000.

- PhD studentship, funded jointly by Ataxia UK and UCL, for the project entitled, ` *Mechanisms` of CoQ10 blood brain barrier transport*,` Oct 2015-2018, total value of support:£75,000- **I was the PI.**