British Infection Association

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BIA Grant Application Form

Please complete within the space provided - The form should be submitted electronically by MS word or .pdf document to the Scientific Affairs Secretary at scientificresearch@britishinfection.org

Please indicate below the scheme to which you are applying

☐ BIA Research Fellowship
x BIA Small Research Project Grant
☐ BIA Clinical Exchange

1. Applicant (complete section 1A as well if applying for BIA Clinical Exchange or research in an overseas centre):

	Applicant (details of current work)	UK Sponsor
Surname	Payne	Chinnery
Forename(s)	Brendan	Patrick
Age	36	
Title	Dr	Prof
Post Held	Clinical Lecturer in Infectious Diseases and Virology	Professor of Neurogenetics
Department:	Department of Infection and Tropical Medicine	Institute of Genetic Medicine
Institution:	Royal Victoria Infirmary	Newcastle University
Address:	Elliott Building Royal Victoria Infirmary Newcastle-upon-Tyne NE1 4LP	Wellcome Centre for Mitochondrial Research Institute of Genetic Medicine Central Parkway Newcastle-upon-Tyne NE1 3BZ
Telephone No:	0191 282 1104	0191 241 8611
Fax No:	0191 282 6276	0191 241 8666
Email:	Brendan.Payne@ncl.ac.uk	Patrick.Chinnery@ncl.ac.uk

1A. Overseas Research training and BIA Clinical Exchange applicants ONLY
Details should be given of the overseas sponsor and/or supervisor.

	Applicant (details of current work)	Sponsor (overseas institution)
Surname		
Forename(s)		
Age		
Title		
Post Held		
Department:		
Institution:		
Address:		
Telephone No:		
Fax No:		
Email:		

2a) Institution/Authority (administering grant if approved):

Newcastle University (will administer grant)
Newcastle-upon-Tyne Hospitals NHS Foundation Trust (co-applicant)

b) Address at which work is to be done:

Royal Victoria Infirmary, Newcastle-upon-Tyne, and
Institute of Genetic Medicine, Newcastle University

3. Title of Investigation:

HIV and Urinary Mitochondrial Dysfunction (a pilot study)

4. Abstract of research (not to exceed 250 words)

This is a pilot study to assess the feasibility of using mitochondrial DNA (mtDNA) analysis of urine as a marker of mitochondrial damage in treated HIV-infected patients. The concept is based on two prior observations. Firstly, we have recently established that some HIV-infected patients with prior exposure to certain nucleoside analogue reverse transcriptase inhibitors (NRTIs) show an increase in mtDNA mutations in skeletal muscle, in an apparent acceleration of that seen during normal ageing. These findings have important implications for the long-term health of such patients as they continue to age. In order to properly study such patients longitudinally we require a non-invasive measure of mtDNA damage. Peripheral blood is not suitable owing to the high cell turnover and the fact that mtDNA mutations are selected against. Secondly, tenofovir disoproxil fumarate (TDF) is one of the most commonly used anti-retroviral agents but causes renal proximal tubulopathy in some patients. Renal biopsy studies suggest this may be caused by mitochondrial toxicity that is specific to tubular epithelial cells, but does not usually manifest systemically. Recent work by colleagues in our mitochondrial diagnostic service shows that mtDNA mutations arising in tubular epithelial cells can be reliably detected in urine, at comparable levels to those seen in skeletal muscle, even in the absence of detectable mutations in peripheral blood. We will therefore investigate whether mtDNA mutations are detectable in the urine of ART-treated HIV-infected patients with a view to their future use as a non-invasive measure of mitochondrial dysfunction in this patient group.

5. Key words:

Human Immunodeficiency Virus
DNA, Mitochondrial
Kidney tubules, proximal
Biomarkers
Anti-retroviral therapy

6. Does this project involve the use of human participants or human tissue? Yes × No ☐
If yes, please attach copies of your submission to the relevant Ethics Committee(s) along with your letter of approval if available. Attention is drawn to the MRC's guidance on good practice when conducting research on human subjects, in particular the guidance pertaining to subjects overseas. If ethical approval has not yet been given, please note that award of any grant will be contingent on the necessary ethical approval having been obtained.

Application for ethical permission is to be submitted to LREC meeting April 2015.

Candidates name: Brendan Payne

7. Proposed starting date:

1.8.2015

8. Breakdown of costs by financial year (1 April to 31 March):

	Financial Year 1 £	Financial Year 2 £	Total £
Fellows salary	-	-	-
Consumables	3527.83	3068.00	6595.83
Travel	-	-	-
Equipment	-	-	-
Grand Total	**3527.83**	3068.00	6595.83

For Small Research Project grant and Clinical Exchange, the Salary section should be left blank

9. Other research grants and grant applications

a) Is this application currently being submitted elsewhere? **Yes ☐ No ×**

If yes, to which organisation, and by what date is a decision expected?

b) Has this, or a similar application been submitted elsewhere over the past year? **Yes ☐ No ×**

If yes, to which organisation, and what was the result

Candidates name: Brendan Payne

10. Declaration:

Applicant:

If an award is made, I

i. **will take all reasonable actions to ensure that the Society's contribution to funding the research is suitably acknowledged in all publications arising from it, and ensure that copies of any such publications are forwarded to the Society.**
ii. **will inform the BIA of any major changes to details set out in the application**

To be signed by:	Signature	Name in block capitals	Date
Applicant		DR BRENDAN PAYNE	23.3.2015
Sponsor		PROF PATRICK CHINNERY	23.3.2015

11. This application should be submitted by/through (1) the Head of Department and (2) the Officer who will be responsible for administering any grant that may be awarded. Each should sign the following declaration:

I confirm that I have read this application and that, if granted, the work will be accommodated and administered in the Department/Institution. The salaries and other costs quoted are correct and in accordance with the normal practice of this institution. I confirm also that this institution is subject to external audit.

	Head of Department	Administrative Authority
Signature:		Armstrong
Title:	Professor	ASSISTANT GRANTS + CONTR MGR
Name and Initials (Block Capitals):	PATRICK F CHINNERY	DONNA ARMSTRONG.
Institution:	Newcastle University	NEWCASTLE UNIVERSITY
Address:	Institute of Genetic Medicine Central Parkway Newcastle-upon-Tyne NE1 3BZ	NEWCASTLE JOINT RESEARCH OFFICE GRANTS & CONTRACTS RESEARCH AND ENTERPRISE SERVICES NEWCASTLE UNIVERSITY & NEWCASTLE UPON TYNE NHS FOUNDATION TRUST FLOOR 2, 16/17 FRANKLINGTON PLACE. NEWCASTLE/TYNE. NE2 4AB.
Date:	31.3.2015	31/03/15

12. Career Intentions - please give your reasons for applying for this fellowship or grant and your long term career aims (no more than 300 words).

I am currently an NIHR Academic Clinical Lecturer (ACL) in Infectious Diseases and Virology. I am committed to developing my career as an independent clinical academic. The crucial next key step on this trajectory will be to secure a substantive post-doctoral level clinical fellowship (Wellcome Trust Intermediate Fellowship or equivalent). Securing such a fellowship will also lead to a tenured position at Newcastle University. In my doctoral research (MRC clinical research training fellowship) I studied the effects of long-term NRTI exposure on mitochondrial DNA (mtDNA) mutations in the skeletal muscle of HIV-infected patients and established for the first time that such patients show an increased accumulation of such mutations. These observations show a proof-of-concept that the ageing process may be altered at the cellular and molecular level in some HIV-infected patients. One key aim of my postdoctoral research is to explore the functional and clinical relevance of these findings. As such, I have established collaborations with large well-characterised patient cohorts. If, as expected, this pilot project is able to detect a signal to suggest that mtDNA mutations in urine are marker of systemic mitochondrial toxicity, this approach will be taken forwards as part of a much larger cohort study. As such, this grant proposal will give me invaluable pilot data to take this part of my fellowship proposal forwards. With these plans for preliminary data in place, I therefore expect to be in a position to submit a strong fellowship application in late 2016.

Candidates name: Brendan Payne

13. Proposed Investigation:
Please print using a standard sized font (no smaller than 10 point) on separate pages. Should not exceed 4 pages for fellowship application and should not exceed 2 pages for Small Research project Grant and Clinical Exchange applications. Extra pages may be used for the reference list.

1. Title:

2. Aims and objectives:

3. Background:

4. Experimental design and methods

5. Potential benefits and application of the findings

6. References:

See attached pages

Title: 'HIV and Urinary Mitochondrial Dysfunction'

Aims and objectives

Primary objective: To explore whether anti-retroviral treated HIV-infected persons have evidence of mitochondrial DNA damage in urine

Secondary objective: To explore the correlates of urinary mitochondrial DNA damage in anti-retroviral treated HIV infected persons

Background

A key consideration in the long-term management of HIV infection is the prevention and detection of non-AIDS comorbidities. Such comorbidities increase with age and overlap with those seen during normal ageing. We intend to perform a pilot study of urine samples from anti-retroviral treated HIV-infected patients to look for molecular evidence of mitochondrial damage.

Progressive accumulation of mitochondrial DNA (mtDNA) damage (mutations) is a well-described feature of normal human ageing, and is likely to contribute causally to the ageing process at the cellular level (1-3). We have recently demonstrated that long-term treated HIV-infected patients show an accelerated accumulation of mtDNA mutations, associated with exposure to certain anti-retroviral drugs, which may plausibly contribute to accelerated senescence in this patient group (4). These changes were identified in skeletal muscle, which necessitates an invasive biopsy. However, recent work from our local colleagues has shown that mtDNA mutations can be readily detected in urine in patients with inherited disorders of mtDNA maintenance, often at comparable levels to those seen in skeletal muscle (5). In contrast, such mutations are rarely detectable in peripheral blood. Furthermore other putative biomarkers of HIV-associated mitochondrial dysfunction (including mtDNA content in blood, magnetic resonance spectroscopy, and serum cytokines) have proved disappointing (6-8). If urinary mtDNA mutations are detectable in the urine of some treated HIV-infected patients, this would provide a convenient means of testing for or monitoring mitochondrial toxicity without recourse to biopsy.

Tenofovir (as tenofovir disoproxil fumarate, TDF) is one of the most commonly used anti-retroviral drugs for the treatment of HIV infection. Although TDF has proved to be safe and efficacious both in clinical trials and post-marketing use, in a proportion of treated patients it does however cause renal tubular dysfunction. Hypophosphataemia is common in HIV-infected TDF-treated patients, and rarely, such patients develop frank Fanconi syndrome. The pathophysiological reasons for these abnormalities of renal phosphate handling remain unclear, however recent work by our group and others have suggested possible explanations (9-15). Firstly, we have identified specific renal proximal tubular transporter proteins which are affected by TDF in an *ex vivo* model of renal tubular epithelium. Secondly, recent evidence suggests that TDF may cause specific mitochondrial dysfunction in the renal tubules (16, 17). Several nucleoside analogue reverse transcriptase inhibitor (NRTI) anti-retroviral drugs cause inhibition of the mtDNA polymerase, pol γ. This leads to mtDNA depletion, the accumulation of mtDNA mutations, and clinical toxicity such as myopathy, neuropathy and lipodystrophy. In contrast, TDF does not cause mtDNA depletion in blood samples or in standard tissue culture systems, and was previously thought to be free from mitochondrial toxicity. However, recent work suggests that TDF may indeed induce a mitochondrial effect which is selective for renal tubular cells (probably due to a very high intra-cellular accumulation of the drug) (18). Such mtDNA damage may therefore be detectable in the cellular fraction of urine as this is known to contain tubular epithelial cells.

In order to address these questions we will initially perform a pilot cross-sectional study of urine from anti-retroviral treated patients.

Experimental design and methods

We will undertake a cross-sectional study of 40 HIV-infected anti-retroviral treated adult subjects. Exclusion criteria will include: severe renal impairment (eGFR <30), known renal tubulopathy unrelated to HIV or anti-viral therapy, diabetes mellitus. The following analyses will be performed:

Serum biochemistry: urea and electrolytes, urate, bone profile, liver function tests, random glucose, bicarbonate, PTH, total vitamin D.

Urine biochemistry: dip stick for glucose, uric acid / creatinine ratio, phosphate / creatinine ratio, protein / creatinine ratio, retinol binding protein.

Urine mitochondrial DNA analyses: mtDNA content, mutational analysis (by long-range PCR and massively parallel sequencing). (Prior work in our group has established that mtDNA mutations are not detectable in the urine of healthy subjects or those with other causes of renal tubular disease.)

Urine cytological analysis: Immunofluorescence confocal microscopy for mitochondrial morphology, and expression of transport proteins in cells expressing proximal tubular cell markers.

Clinical data

Demographic, disease and treatment data will be collected by case-note review: age, gender, country of birth, date of diagnosis of HIV infection, full (lifetime) treatment history (drugs and dates), comorbid medical conditions, all current medication, current CD4 lymphocyte count, nadir CD4 lymphocyte count, current HIV RNA plasma viral load, highest HIV viral load.

Statistical Considerations

The study is exploratory in nature and as such most of the data analysis will be descriptive. Urine and serum biochemistry will be compared with well-characterised laboratory normative values and reported in terms of proportions of subjects falling outwith the normal ranges. In addition we will compare mtDNA markers according to treatment status (including TDF vs. non-TDF treated).

The study is exploratory in nature and as such formal power calculations have not been performed. In general, and in our specific prior experience of mtDNA mutational analyses, a sample size of >30 in a pilot study such as this is required to elicit meaningful signals.

Potential benefits and application of the findings

If we establish as expected that mtDNA mutations are detectable in the urine of anti-retroviral treated subjects this has two key applications depending on which patients show a signal.

Firstly, if a signal is seen in those patients likely to have systemic mitochondrial dysfunction (older patients, those with history of prior exposure to mitochondrially toxic NRTIs), this assay could be explored for the non-invasive measurement of mitochondrial dysfunction in larger studies which can assess the functional effects of mitochondrial damage in ageing HIV-infected subjects. Currently there is no useful non-invasive measure of systemic mitochondrial dysfunction in HIV-infected patients and such a marker would be crucial if such large-scale longitudinal studies are to be feasible in the future.

Secondly, if a signal is seen in TDF-treated subjects this would help to confirm the hypothesis from limited renal biopsy observations that TDF-induced renal tubulopathy may be mitochondrially-mediated. The assay could then be evaluated in a larger study to determine if it is predictive of the development of clinical tubulopathy.

References

1. Bua E, Johnson J, Herbst A, Delong B, McKenzie D, Salamat S, et al. Mitochondrial DNA-deletion mutations accumulate intracellularly to detrimental levels in aged human skeletal muscle fibers. American journal of human genetics. 2006 Sep;79(3):469-80. PubMed PMID: 16909385. eng.
2. Corral-Debrinski M, Horton T, Lott MT, Shoffner JM, Beal MF, Wallace DC. Mitochondrial DNA deletions in human brain: regional variability and increase with advanced age. Nature genetics. 1992 Dec;2(4):324-9. PubMed PMID: 1303288. eng.

3. Taylor RW, Barron MJ, Borthwick GM, Gospel A, Chinnery PF, Samuels DC, et al. Mitochondrial DNA mutations in human colonic crypt stem cells. The Journal of clinical investigation. 2003 Nov;112(9):1351-60. PubMed PMID: 14597761. eng.
4. Payne BA, Wilson IJ, Hateley CA, Horvath R, Santibanez-Koref M, Samuels DC, et al. Mitochondrial aging is accelerated by anti-retroviral therapy through the clonal expansion of mtDNA mutations. Nature genetics. 2011 Aug;43(8):806-10. PubMed PMID: 21706004. Pubmed Central PMCID: 3223397. Epub 2011/06/28. eng.
5. Blackwood JK, Whittaker RG, Blakely EL, Alston CL, Turnbull DM, Taylor RW. The investigation and diagnosis of pathogenic mitochondrial DNA mutations in human urothelial cells. Biochemical and biophysical research communications. 2010 Mar 19;393(4):740-5. PubMed PMID: 20171163.
6. Cherry CL, Nolan D, James IR, McKinnon EJ, Mallal SA, Gahan ME, et al. Tissue-specific associations between mitochondrial DNA levels and current treatment status in HIV-infected individuals. Journal of acquired immune deficiency syndromes (1999). 2006 Aug 1;42(4):435-40. PubMed PMID: 16810110. eng.
7. Payne BAI, Price DA, Chinnery PF. Elevated serum fibroblast growth factor 21 levels correlate with immune recovery but not mitochondrial dysfunction in HIV infection. AIDS RES Ther. 2013;in press.
8. Payne BA, Hollingsworth KG, Baxter J, Wilkins E, Lee V, Price DA, et al. In vivo mitochondrial function in HIV-infected persons treated with contemporary anti-retroviral therapy: a magnetic resonance spectroscopy study. PLoS One. 2014;9(1):e84678. PubMed PMID: 24409305. Pubmed Central PMCID: 3883680.
9. Labarga P, Barreiro P, Martin-Carbonero L, Rodriguez-Novoa S, Solera C, Medrano J, et al. Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir. AIDS (London, England). 2009 Mar 27;23(6):689-96. PubMed PMID: 19262355.
10. Horberg M, Tang B, Towner W, Silverberg M, Bersoff-Matcha S, Hurley L, et al. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naive patients. Journal of acquired immune deficiency syndromes (1999). 2010 Jan;53(1):62-9. PubMed PMID: 19838127.
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12. Gara N, Zhao X, Collins MT, Chong WH, Kleiner DE, Jake Liang T, et al. Renal tubular dysfunction during long-term adefovir or tenofovir therapy in chronic hepatitis B. Alimentary pharmacology & therapeutics. 2012 Jun;35(11):1317-25. PubMed PMID: 22506503. Pubmed Central PMCID: 3443969.
13. Danjuma MI, Mohamad-Fadzillah NH, Khoo S. An investigation of the pattern of kidney injury in HIV-positive persons exposed to tenofovir disoproxil fumarate: an examination of a large population database (MHRA database). Int J STD AIDS. 2014 Mar;25(4):273-9. PubMed PMID: 24067251.
14. Kinai E, Hanabusa H. Progressive renal tubular dysfunction associated with long-term use of tenofovir DF. AIDS research and human retroviruses. 2009 Apr;25(4):387-94. PubMed PMID: 19361280.
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16. Lebrecht D, Venhoff AC, Kirschner J, Wiech T, Venhoff N, Walker UA. Mitochondrial tubulopathy in tenofovir disoproxil fumarate-treated rats. Journal of acquired immune deficiency syndromes (1999). 2009 Jul 1;51(3):258-63. PubMed PMID: 19582894. Epub 2009/07/08. eng.
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Candidates name: Brendan Payne

14. Curriculum Vitae of applicant

Name: Dr Brendan Payne

Degree etc. (subject, class, university, and date):
BMedSci (1st class honours), University of Nottingham, 2000
BMBS (honours), University of Nottingham, 2002
MRCP(UK), 2005
DipHIVMed, 2007
SCE (Specialty Certificate Examination) Infectious Diseases, 2013
PhD, Newcastle University, 2014
FRCPath (Virology), 2014

Posts held (with dates):
3/2014 – present: NIHR Clinical Lecturer in Infectious Diseases & Medical Virology, Newcastle University
9/2011 – 3/2014: Associate (Honorary) Clinical Researcher, Newcastle University
7/2007 – 8/2011: Clinical Research Associate (MRC Clinical Research Training Fellow), Newcastle University
1/2007 – 3/2014: SpR (Type 1) Infectious Diseases & Medical Virology, Northern Deanery
1/2006 – 1/2007: SpR (LAT) Infectious Diseases & G(I)M, Newcastle-upon-Tyne Hospitals
8/2005 – 1/2006: Clinical Fellow Infectious Diseases, Newcastle General Hospital
8/2003 – 8/2005: SHO Medical Rotation, Newcastle-upon-Tyne Hospitals
2/2003 – 8/2003: PRHO Medicine & Infectious Diseases, City Hospital Nottingham
8/2002 – 2/2003: PRHO Surgery, University Hospital Hartlepool

All Publications; also papers in press:
ORIGINAL ARTICLES

1) van der Westhuizen FH, Sinxadi P, Dandara C, Smuts I, Riordan G, Meldau S, Malik A, Sweeney M, Tsai Y, Towers W, Louw R, Gorman G, Payne B, Soodyall H, Pepper MS, Elson J (2015). Understanding the Implications of Mitochondrial DNA Variation in the Health of Black Southern African Populations: The 2014 Workshop. *Human Mutation* [in press]

2) Payne BAI, Gardner K, Blakely EL, Maddison P, Horvath R, Taylor RW, Chinnery PF (2015). Clinical and pathological features of mitochondrial DNA deletion disease following anti-retroviral treatment. *JAMA Neurology* [in press]

3) Nile DL, Brown AE, Kumaheri MA, Blair HR, Heggie A , Miwa S, Cree LM, Payne BAI, Chinnery PF, Brown L, Gunn DA , Walker M (2014). Age-Related Mitochondrial DNA Depletion and the Impact on Pancreatic Beta Cell Function. *PLoS One* 9(12):e115433

4) Gardner K, Payne BAI (joint first author), Horvath R, Chinnery PF (2014). Use of stereotypical mutational motifs to define resolution limits for the ultra-deep resequencing of mitochondrial DNA. *Eur J Hum Genet* [ePub ahead of print]

5) Tzoulis C, Tran GT, Coxhead J, Bertelsen B, Lilleng PK, Balafkan N, Payne BAI, Miletic H, Chinnery PF, Bindoff LA (2014). Molecular pathogenesis of polymerase gamma related neurodegeneration. *Annals Neurol* 76(1):66-81

6) Frith J, Ng WF, Day CP, Payne BAI, Sheerin N, Gorman G, Jones D, Newton JL (2014). Orthostatic intolerance is common in chronic disease – a clinical cohort study. *Int J Cardiol* 174(3):861-3

7) Pfeffer G, Gorman GS, Griffin H, Kurzawa-Akanbi M, Blakely EL, Wilson I, Sitarz K, Moore D, Murphy JL, Alston CL, Pyle A, Coxhead J, Payne BAI, Gorrie GH, Longman C, Hadjivassiliou M, McConville J, Dick D, Imam I, Hilton D, Norwood F, Baker MR, Jaiser SR, Yu-Wai-Man P, Farrell M, McCarthy A, Lynch T, McFarland R, Schaefer AM, Turnbull DM, Horvath R, Taylor RW, Chinnery PF (2014). Mutations in the SPG7 gene cause chronic progressive external ophthalmoplegia through disordered mitochondrial DNA maintenance. *Brain* 137(Pt 5):1323-36

8) Rowley K, Payne BAI, Schmid ML (2014). Determinants of response to repeat hepatitis B vaccination in HIV-infected prior non-responders. *J Infect* 69(1):98-9

9) Payne BAI, Hollingsworth KG, Baxter J, Wilkins E, Lee V, Price DA, Trenell M, Chinnery PF (2014). In vivo mitochondrial function in HIV-infected persons treated with contemporary anti-retroviral therapy: a magnetic resonance spectroscopy study. *PLoS One* 9(1):e84678

10) Payne BAI, D Ashley Price, Patrick F Chinnery (2013). Elevated serum fibroblast growth factor 21 levels correlate with immune recovery but not mitochondrial dysfunction in HIV infection. *AIDS Res Ther* 10(1):27

11) Oosterhout J, Gardner K, Mallewa J, Kaunda S, Kampira E, Payne BAI, Heyderman R, Chinnery PF (2013). Severe toxicity and polymerase-γ gene abnormalities in Malawian adults on stavudine based antiretroviral therapy. *Pharmacogenet Genomics*. 23(11):624-6

12) Payne BAI, Medhi M, Ijaz S, Savage E, Valappil M, Gill ON, Tedder RS, Schwab U (2013). Hepatitis E infection and men who have sex with men, UK. *Emerg Infect Dis*. 19(2):333-5

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REVIEW ARTICLES & BOOK CHAPTERS

1) Payne BAI, Bellamy R (2014). Novel respiratory viruses: what should the clinician be alert for? Clin Med. 14(Suppl 6):s12-s16

2) Payne BAI, Cree L, Chinnery PF (2014). Single cell analysis of mitochondrial DNA. *Methods Mol Biol* [in press]

3) Payne BAI, Gardner K, Coxhead J, Chinnery PF (2014). Deep resequencing of mitochondrial DNA. *Methods Mol Biol* [in press]

4) Payne BAI, Gardner K, Chinnery PF (2014). Mitochondrial DNA mutations in ageing and disease: implications for HIV? *Antivir Ther* [ePub ahead of print]

5) Gardner K, Chinnery PF, Hall PA, Payne BAI (2013). HIV Treatment and Associated Mitochondrial Pathology: Review of 25 Years of in Vitro, Animal, and Human Studies. *Toxicol Pathol* 42(5):811-822

6) Payne BAI, Bellamy R (2009). HIV: treating tuberculosis. *Clin Evid*. 2009 Nov 5

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Current grant support:
Academy of Medical Sciences Starter Grant for Clinical Lecturers: 'Does the clonal expansion of mutations mediate mitochondrial ageing?' Principal investigator, 2 years (1/2014 – 1/2016), £30k.

15. Curriculum Vitae of Sponsor in UK (duplicate for multiple sponsors)

Name: Professor Patrick Chinnery

Degree etc. (subject, class, university, and date):
FMedSci, Academy of Medical Sciences, 2009
FRCPath, Royal College of Pathologists UK, 2007
FRCP , Royal College of Physicians UK, 2006
CCST in Neurology, Specialist Training Authority, 2002
PhD, University of Newcastle upon Tyne, 2000
MBBS (Hons), University of Newcastle upon Tyne, 1992
BMedSci (1st), University of Newcastle upon Tyne, 1989

Posts held (with dates):
2010 – Director, Institute of Genetic Medicine, Newcastle University.
2008 – Director, Newcastle NIHR Biomedical Centre.
2003 – Wellcome Trust Senior Fellow in Clinical Science (2nd renewal).
2004 – Professor of Neurogenetics, Newcastle University.
2002 – Honorary Consultant Neurologist, Newcastle Hospitals NHS Trust.

Do you have assured salary support for the period of the Fellowship or grant? Yes × No ☐

Up to 10 Recent Publications; also papers in press:

(Total publications = 459 h-index = 71 on 1st Jan 2015 (Google Scholar). 19,317 citations.)

1) Pyle A, Smertenko T, Bargiela D, Griffin H, Duff J, Appleton M, Douroudis K, Pfeffer G, Santibanez-Koref M, Eglon G, Yu-Wai-Man P, Ramesh V, Horvath R, Chinnery PF. Exome sequencing in undiagnosed inherited and sporadic ataxias. *Brain* 2015 Dec 12 PMID: 25497598

2) Taylor RW, Pyle A, Griffin H, Blakely EL, Duff J, He L, Smertenko T, Alston CL, Neeve VC, Best A, Yarham JW, Kirschner J, Schara U, Talim B, Topaloglu H, Baric I, Holinski-Feder E, Abicht A, Czermin B, Kleinle S, Morris AAM, Vassallo G, Gorman G, Ramesh V, Turnbull DM, Santibanez-Koref M, McFarland R, Horvath R, Chinnery PF. Use of whole exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain complex deficiency. *Journal of the American Medical Association* 2014;312(1):68-77. PMID:25058219

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Current grant support:

2014 – 2017, Medical Research Council, Clinical research capabilities call: The Newcastle University Single Cell Functional Genomics Unit (£1.98M. PI).

2013 – 2018, Wellcome Trust, Senior Clinical Fellowship (2nd Renewal, 101876/Z/13/Z): Genetic factors modulating the expression of mitochondrial disease (£1.3M. PI).

2013 – 2015, Medical Research Council, Maximising the value of MRC Brain Banks: high-throughput genomic studies to enrich data available to the research community (£1.7M. Newcastle PI).

2013 – 2015, Medical Research Council: High throughput genomics and transcriptions of the human development biology resource (£891K. PI).

2012 – 2015 , EU-FP7-PEOPLE-2012-ITN, Marie Curie Training Network: MEET – Mitochondrial European Educational Training (£425K).

2012 – 2014, Medical Research Council, Efficacy Mechanism Evaluation: Stratifying patients with Leber Hereditary Optic Neuropathy (LHON) for idebenone therapy using mitochondrial DNA analysis (PI £641K)

2012 – 2017, Wellcome Trust, Centre Award: Newcastle Centre for Mitochondrial Research (096919Z/11/Z) (Deputy Director, Co-PI, £4.4M).

16. Statement of support from UK sponsor (not more than 400 words). Candidates for the BIA Clinical Exchange or those intending to undertake a Fellowship Award overseas must ensure that section 16A is also completed.

Candidate

I have worked with Dr Payne for the last several years, first as his PhD supervisor during his MRC Clinical Research Training Fellowship and now as academic sponsor of his NIHR ACL post. During this time he has proved to be a highly motivated and able academic trainee and has delivered a number of high quality outputs, including a first-author paper in *Nature Genetics.* He was awarded the RCPath Trainee Research Medal in Microbiology for his doctoral work. Within his ACL he is making excellent progress towards developing his independent research programme and will be well placed to deliver a competitive application for further fellowship funding within the next 1-2 years. The proposed project as described in this application will make a very meaningful contribution in terms of preliminary data to support the fellowship, and will thus significantly strengthen the application.

Facilities

I am very confident that the proposed project will be readily deliverable within the facilities in our Institute. I can confirm that Dr Payne will be fully supported with bench space and core equipment as well as access to specialist equipment (such as our Illumina MiSeq platform) and will be able to drawn upon the extensive technical expertise available within our group and institute. Dr Payne will have continued academic career development support and mentorship both from myself and from the faculty (for example he is currently enrolled on our 'PI development programme') as well as his external academic mentor.

I have no hesitation in fully supporting this application.

Candidates name: Brendan Payne

16A. Statement of support from overseas sponsor (not more than 400 words).
This statement can be submitted as a faxed, electronic, or hard copy.

Candidates name: Brendan Payne

17. Experiments involving animals

Applicants must have regard to animal welfare and advances in the refinement, replacement and reduction of animal use. The number of animals requested must be fully justified.

a) Do the experiments you propose involve the use of protected animals in regulated procedures under the Animals (Scientific Procedures) Act 1986? (For the information of non-UK applicants, this includes all vertebrates as well as octopus.) **Yes ☐ No ×**

If yes, which species and how many animals?

Are any of the procedures of substantial severity? **Yes ☐ No ☐**

b) Has a project licence, under the terms of the Animals (Scientific Procedures) Act 1986, been granted which authorises the proposed experiments? Yes ☐ No ☐

If yes, please state the name and address of the licensee, Home Office reference and date of issue and attach a copy of the front page of the project licence.

If not, has it been applied for? **Yes ☐ No ☐**

Does each individual carrying out work on animals have a personal licence? **Yes ☐ No ☐**

c) Have all those involved in the care and use of animals before, during and after the experiments, received appropriate training in animal care and in the procedures involved? Has this training included attendance at the relevant courses?

d) Does your institution have an Ethics (or Animal Care and Use) Committee for animal experiments? If so, have the proposed experiments received its approval?

If not, what steps have been taken to gain its approval?

e) Will the animals be conscious for all or part of the experiments? If so, explain why this is necessary, what, if any, discomfort they are likely to experience and how it is ameliorated.

f) If the animals are to be anaesthetized, will they be allowed to regain consciousness? Unless the animals are to be the subject of survival studies, explain why this is being allowed.

g) Does the proposed experimentation on live animals duplicate any other research which has already taken place, or which is known to be currently taking place in any research establishment?

h) Will you be engaging any other establishment to carry out experiments on live animals as part of this research project? If so, please provide full details.