Institution: Brunel University London		
Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Curing Friedreich ataxia using a genetically-altered mouse		
Period when the underpinning research was undertaken: 2007-2017		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
1) Mark Pook	1) Reader in Biomedical Sciences	1) 10/2005-09/2019
2) Sara Anjomani-Virmouni	2-1) Lecturer in Biomedical Sciences 2-2) Post-doc research fellow	2-1) 04/2018-present 2-2) 09/2011-03/2015
3) Sahar Al-Mahdawi	3-1) Honorary Senior Research Fellow	3-1) 11/2019-present 3-2) 03/2006-11/2012
4) Chiranjeevi Sandi	3-2) Senior Research Fellow 4) Research Fellow	4) 09/2007-12/2013
Period when the claimed impact occurred: 1 Aug 2013 to 31 Dec 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Friedreich Ataxia (FRDA) is an inherited progressive neurodegenerative disease which typically causes loss of mobility in childhood and early death from heart failure in early adulthood. Preclinical investigations are the first stage in developing treatment for FRDA. Drs Pook and Anjomani-Virmouni developed and characterised genetically altered mouse models of FRDA for use in these studies. The donation of the mouse model to The Jackson Laboratory (Maine, USA) for distribution worldwide to research groups and pharmaceutical companies (Pharma) provided the basis for 10 different clinical trials which have had a beneficial impact upon FRDA patients and their families.

2. Underpinning research (indicative maximum 500 words)

Friedreich ataxia (FRDA) is a lethal inherited progressive neurodegenerative disease that affects approximately 1,000 individuals in the UK. The estimated prevalence in Europe is in the range of 1 in 20,000 and 1 in 50,000, with some geographical variability (the highest levels observed in northern Spain, south of France and Ireland, and lowest levels in Scandinavia and Russia). Typically, FRDA patients gradually lose the ability to walk from childhood, becoming wheelchair-bound in their teenage years and dying from heart failure in early adulthood. There is currently no effective treatment for this disease.

To provide an essential tool for worldwide preclinical investigations prior to the much more expensive and time-consuming clinical trials since 2005, Dr Pook has been developing genetically altered FRDA mouse models for a milder FRDA phenotype (**Ref 1**) with Drs Chiranjeevi Sandi (then Research Fellow) and Sahar Al-Mahdawi (then Research Fellow). Subsequently, Dr Anjomani-Virmouni has characterised the models that would show some of the characteristic features observed in FRDA patients with mild overall phenotype, which were not conductive to effective preclinical testing (**Ref 2**). In 2015, Dr Anjomani-Virmouni further refined the models to more closely resemble the FRDA phenotype which means that the models are best optimised for investigating the cause and treatment for FRDA disease. This is significant because these models could be used to develop treatment for other neurological conditions or diseases with mitochondrial dysfunctions. (**Ref 3**)

With The Jackson Laboratory (Maine, USA) and other international FRDA research collaborators at Imperial College London and the University of Valencia in Spain, the Pook lab has

characterised the FRDA mouse models to reveal their FRDA-like disease phenotype and determine how they can be best used as a tool for FRDA preclinical studies.

Since 2011, Dr Pook has collaborated with many international FRDA researchers and Pharma who intended to investigate a number of drug compounds as potential FRDA therapies by sharing the mouse models. Different pre-clinical trials were conducted to test the efficacy of different compounds using the Pook mouse models.

The first study (**Ref 4**) tested novel histone deacetylase (HDAC) inhibitors that were generated by the Scripps Research Institute (USA), funded by the pharmaceutical company Repligen Inc. (USA). Beneficial effects of the HDAC inhibitors on the coordination ability and frataxin protein levels of the FRDA mice were observed (Sandi et al 2011), giving support to a subsequent Repligen-sponsored Phase I (human safety trial) FRDA clinical study of the HDAC inhibitor, designated **RG2833,** which took place in Italy from 2012 to 2014.

In collaboration with a researcher from the University of Rome Tor Vergata, Italy, Dr Pook investigated the effects of a compound, **interferon gamma** on a FRDA mouse model (**Ref 5**). The results of this study provided supporting evidence for interferon gamma FRDA Phase 2 (Human safety and efficacy trial) and Phase 3 (Definitive trial) clinical studies sponsored by the Children's Hospital of Philadelphia (USA) from 2013-15 and Horizon Pharma Ireland, Ltd. (Dublin, Ireland) from 2015-18.

Dr Pook and Murdoch Children's Research Institute in Australia identified resveratrol as a potential FRDA therapy (**Ref 6**), leading to a Phase 1/2 clinical trial from 2011-14. In collaboration with Professor Richard Festenstein (Imperial College London), they investigated the effects of nicotinamide on a FRDA mouse model (**Ref 7**), providing supporting evidence for a Phase 2 clinical trial from 2012-14. Other collaborative studies with Gino Cortopassi (UC Davis, USA) identified deficits of Nrf2 expression in FRDA (**Ref 8**), supporting a Phase 2 clinical trial of the NRF2 activator omaveloxolone (RT408) sponsored by Reata Pharmaceuticals (USA) from 2014 to 2018. Collaborative studies with Kevin Kemp and Alistair Wilkins (University of Bristol) using cytokine therapy of our FRDA mouse model (**Ref 9**) have provided evidence to support a Phase 1 trial of granulocyte colony stimulating factor (GCSF) as a novel treatment for FRDA from 2018 to 2019.

Finally, the Pharmaceutical company, Takeda, contacted Dr Pook in 2014-15 and provided funding to investigate the effects of compound TAK-831 on the behavioural phenotype of a FRDA mouse model, thereby supporting a subsequent Phase 2 clinical trial in the USA that was initiated in 2017.

3. References to the research (indicative maximum of six references)

Ref 1: Sahar Al-Mahdawi, Ricardo Mouro Pinto, Ozama Ismail, Dhaval Varshney, Stefania Lymperi, Chiranjeevi Sandi, Daniah Trabzuni, **Mark Pook** (2007) The Friedreich ataxia GAA repeat expansion mutation induces comparable epigenetic changes in human and transgenic mouse brain and heart tissues. Human Molecular Genetics, 17(5): 735–746 https://doi.org/10.1093/hmg/ddm346

Ref 2: **Anjomani Virmouni S**, Sandi C, Al-Mahdawi S, **Pook M** Cellular, molecular and functional characterisation of YAC transgenic mouse models of Friedreich ataxia. PLoS One. 2014;9(9):e107416. Published 2014 Sep 8. doi:10.1371/journal.pone.0107416

Ref 3: **Anjomani Virmouni S**, Ezzatizadeh, V., Sandi, C., Sandi, M., Al-Mahdawi, S., Chutake, Y. and **Pook, M**. A. (2015) A novel GAA repeat expansion-based mouse model of Friedreich ataxia. Dis. Models. Mech. 8: 225-235. PMID: 25681319, doi: 10.1242/dmm.018952

Ref 4: Sandi, C., Pinto, R.M., Al-Mahdawi, S., Ezzatizadeh, V., Barnes, G., Jones, S., Rusche, J., Gottesfeld, J. and **Pook, M.** (2011) Prolonged treatment with pimelic o-aminobenzamide HDAC inhibitors ameliorates the disease phenotype of a Friedreich ataxia mouse model. Neurobiol. Dis. 42: 496-505 PMID:21397024 PMC3107941 doi:10.1016/j.nbd.2011.02.016.

Ref 5: Tomassini, B., Arcuri, G., Fortuni, S., Sandi, C., Ezzatizadeh, V., Casali, P., Condo', I., Malisan, F., Al-Mahdawi, S., **Pook, M.** and Testi, R. (2012) Interferon gamma upregulates frataxin and corrects the functional deficits in a Friedreich ataxia model. Hum. Mol. Genet. 21: 2855-2861 PMID:22447512 PMC3373236 doi:10.1093/hmg/dds110

Ref 6: Li, L., Voullaire, L., Sandi, C., **Pook, M.A.**, Ioannou, P.A., Delatycki, M.B. and Sarsero, Impact case study (REF3) Page 3 J.P. (2013) Pharmacological Screening using an FXN-EGFP Cellular Genomic Reporter Assay for the Therapy of Friedreich Ataxia. PLoS One 8: e55940 PMID:23418481 doi:10.1371/journal.pone.0055940.

Ref 7: Chan, J.P.K., Torres, R., Yandim, C., Law, P.P., Chapman-Rothe, N., **Pook, M.** and Festenstein, R. (2013) Heterochromatinization induced by GAA-repeat hyperexpansion in Friedreich's ataxia can be reversed upon HDAC inhibition by Vitamin B3. Hum. Mol. Genet. 22: 2662-2675 PMID:23474817 doi:10.1093/hmg/ddt115

Ref 8: Shan, Y., Schoenfeld, R.A., Hayashi, G., Napoli, E., Akiyama, T., Iodi-Carstens, M., Carstens, E.E., **Pook, M.A.** and Cortopassi, G.A. (2013) Frataxin deficiency leads to defects in expression of antioxidants and Nrf2 expression in dorsal root ganglia of the Friedreich's ataxia YG8R mouse model. Antioxidants & Redox Signaling 19: 1481-1493 PMID:23350650 doi:10.1089/ars.2012.4537

Ref 9: Kemp, K., Cerminara, N., Hares, K., Redondo, J., Cook, A., Haynes, H., Burton, B., **Pook, M.**, Apps, R., Scolding, N. and Wilkins, A. (2017) Cytokine therapy-mediated neuroprotection in a Friedreich's ataxia mouse model. Ann. Neurol. 81:212-226. doi:10.1002/ana.24846

4. Details of the impact (indicative maximum 750 words)

FRDA mouse models are considered essential for the development of effective drug-based therapy for this lethal disease. Additionally, they have potential in the development of therapies aimed at treating much more common neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease or Huntington's disease.

Murdoch Children's Research Institute states that the FRDA mouse models that have been developed and characterised by Drs Pook and Anjomani-Virmouni are the "best mouse model for Friedreich ataxia." This is because they incorporate the same genetic mutation as FRDA, and as such are available for drug treatment strategies that are aimed at specifically targeting the mutated human frataxin gene. (**Source 5**)

These mouse models have been donated to The Jackson Laboratory (in 2014 and 2016) for cryopreservation and distribution to research groups and Pharma throughout the world to progress their FRDA preclinical research studies and support FRDA clinical trials (**Source 1**). Through the utilisation of the "unique 'humanised' YG8R-derived FA mouse model" Drs Kemp and Wilkins at the University of Bristol have been able to focus on utilising "bone marrow stem cell mobilising drugs as regenerative therapy" for FRDA patients. Their research, using the Pook model, has provided the 'proof-of-concept' basis for clinical trial. (**Source 8**)

Brunel has granted licences to the following Pharma to obtain Pook FRDA mouse models from The Jackson Laboratory for use in their preclinical FRDA studies: RaNA Therapeutics Inc., Cambridge, MA, USA (2015), Biomarin Pharmaceuticals Inc., Novato, CA, USA (2016), Vertex Pharmaceuticals Inc., Boston, MA, USA (2016), Ionis Pharmaceuticals Inc., Carlsbad, CA, USA (2017). Dr Pook has also performed collaborative FRDA mouse model studies with Takeda California Inc. in the development of their compound named TAK-831. As concluded by Dr Jordi Serrats of Takeda California Inc. "Dr. Pook's work with TAK-831 has been instrumental in supporting clinical trials in FRDA patients".

Overall, the results of preclinical studies using the FRDA mouse models developed in the Pook laboratory have provided evidence in favour of proceeding with the following 10 international FRDA clinical studies that have involved a total of 786 FRDA patients:

1. RG2833 Epigenetic Therapy of Friedreich's Ataxia, sponsor Repligen Corporation, Waltham, MA, USA. (20 FRDA patients) (**Source 2**).
2. Interferon Gamma-1b in Friedreich's Ataxia (FRDA), sponsor Children's Hospital of Philadelphia, USA. ClinicalTrials.gov Identifier: NCT01965327 (12 FRDA patients) **(Source 3)**
3. Safety, Tolerability and Efficacy of ACTIMMUNE® Dose Escalation in Friedreich's Ataxia (STEADFAST), sponsor Horizon Pharma Ireland, Ltd., Dublin, Ireland. ClinicalTrials.gov Identifiers: NCT02415127, NCT02593773 (92 and 86 FRDA patients, respectively) **(Source 3)**
4. Long-Term Safety Extension Study of ACTIMMUNE® (Interferon γ-1b) in Children and Young Adults With Friedreich's Ataxia (STEADFAST), sponsor Horizon Pharma Ireland, Ltd., Dublin, Ireland. ClinicalTrials.gov Identifiers: NCT02797080 (38 FRDA patients) **(Source 3)**
5. A Study of Resveratrol as Treatment for Friedreich Ataxia, sponsor Murdoch Childrens Research Institute, Melbourne, Australia. ClinicalTrials.gov Identifier: NCT01339884 (27 FRDA patients) **(Source 4 and 5)**
6. Effect of Nicotinamide in Friedreich's Ataxia, sponsor Imperial College London, UK. ClinicalTrials.gov Identifier: NCT01589809 (40 FRDA patients) **(Source 6)**
7. Study of the Efficacy and Safety of Nicotinamide in Patients With Friedreich Ataxia (NICOFA), sponsor RWTH Aachen University, Aachen, Germany. ClinicalTrials.gov Identifier: NCT03761511 (225 FRDA patients estimated) **(Source 6)**
8. RTA 408 Capsules in Patients With Friedreich's Ataxia – MOXIe, sponsor Reata Pharmaceuticals, Inc., Irving, TX, USA. ClinicalTrials.gov Identifier: NCT02255435 (172 FRDA patients) **(Source 7)**
9. Efficacy, Tolerability, and Pharmacokinetics of Multiple Doses of Oral TAK- 831 in Adults With Friedreich Ataxia, sponsor Takeda Pharmaceuticals, Deerfield, IL, USA. ClinicalTrials.gov Identifier: NCT03214588 (67 FRDA patients) **(Source 9)**

7 of these clinical trials (1-6 and 8) have already reported data regarding safety and efficacy outcomes. They have shown the drug to be well tolerated, with no serious adverse events, but the levels of efficacy varied. The RG2833, resveratrol, nicotinamide and RTA 408 clinical trials (1, 5, 6, 8) have each shown increased levels of frataxin protein and/or improved neurological function as beneficial effects of the drug treatment.

As well as having clinical impact the research carried out by Drs Pook and Anjomani-Virmouni has had impact upon FRDA patients and their families world-wide. A total of 786 FRDA patients have taken part in, or registered to take part in, these clinical trials, providing potential or actual clinical benefits to many FRDA patients and providing psychological benefits to the well-being of the participating FRDA patients and their families.

5. Sources to corroborate the impact (indicative maximum of 10 references)

Source 1: Pook FRDA mouse models available from The Jackson Laboratory:

1.1. Stock No: 031007 | Fxnnull:Y47: https://www.jax.org/strain/031007
1.2. Stock No: 030930 | Fxnnull:YG8s(GAA)~300: https://www.jax.org/strain/030930
1.3. Stock No: 030395 | Fxnnull:YG8s(GAA)>800: https://www.jax.org/strain/030395
1.4. Stock No: 030324 | YG8s(GAA)~300: https://www.jax.org/strain/030324
1.5. Stock No: 024113 | YG8sR: https://www.jax.org/strain/024113
1.6. Stock No: 024097 | Y47R: https://www.jax.org/strain/024097
1.7. Stock No: 012910 | YG22R: https://www.jax.org/strain/012910
1.8. Stock No: 012253 | YG8R: https://www.jax.org/strain/012253

1.9. Stock No: 010963 | Frda-; YG22: https://www.jax.org/strain/010963

1.10. Stock No: 008398 | YG8 rescue mice (YG8R): https://www.jax.org/strain/008398

Sources 2-9: FRDA Clinical Trial information:

Source 2. Soragni E et al. (2014) Epigenetic therapy for Friedreich ataxia. Ann Neurol. 76(4):489-508. doi: 10.1002/ana.24260. Epub 2014 Sep 16. PMID: 25159818

Source 3. Interferon Gamma-1b:

3.1 ClinicalTrials.gov Identifier: NCT01965327
https://clinicaltrials.gov/ct2/show/NCT01965327?cond=Friedreich+Ataxia&rank=6

3.2 ClinicalTrials.gov Identifier: NCT02415127
https://clinicaltrials.gov/ct2/show/NCT02415127?cond=Friedreich+Ataxia&draw=4&rank=22

3.3 ClinicalTrials.gov Identifier: NCT02593773
https://clinicaltrials.gov/ct2/show/NCT02593773?cond=Friedreich+Ataxia&draw=3&rank=18

3.4 Greeley et al (2014) Open-label pilot study of interferon gamma-1b in Friedreich ataxia. Acta Neurol Scand. 132(1):7-15. doi: 10.1111/ane.12337. Epub 2014 Oct 21. PMID: 25335475.

3.5 Lynch et al (2019) Randomized, double-blind, placebo-controlled study of interferon-gamma 1b in Friedreich ataxia. Ann. Clin. Transl. Neurol. https://doi.org/10.1002/acn3.731

Source 4. Resveratrol:

4.1 ClinicalTrials.gov Identifier: NCT01339884
https://clinicaltrials.gov/ct2/show/NCT01339884?cond=Friedreich+Ataxia&draw=3&rank=17

4.2 Yiu et al (2015) An open-label trial in Friedreich ataxia suggest clinical benefit with high-dose resveratrol, without effect on frataxin levels. J. Neurol. 262:1344-1353. doi:10.1007/s00415-015-7719-2.

Source 5. Letter of support from Murdoch Children's Research Institute, Parkville, Australia

Source 6. Nicotinamide:

6.1 ClinicalTrials.gov Identifier: NCT01589809
https://clinicaltrials.gov/ct2/show/NCT01589809?cond=Friedreich+Ataxia&draw=6&rank=45

6.2 ClinicalTrials.gov Identifier: NCT03761511
https://clinicaltrials.gov/ct2/show/NCT03761511?cond=Friedreich+Ataxia&rank=5

6.3 Libri et al (2014) Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study. Lancet. http://dx.doi.org/10.1016/S0140-6736(14)60382-2.

Source 7. RTA 408:

7.1 ClinicalTrials.gov Identifier: NCT02255435
https://clinicaltrials.gov/ct2/show/NCT02255435?cond=Friedreich+Ataxia&draw=3&rank=19

7.2 Lynch et al (2018) Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. Ann. Clin. Transl. Neurol. https://doi.org/10.1002/acn3.660

Source 8.

8.1 GCSF: http://www.bristol.ac.uk/news/2018/april/fa-study-.html

8.2 Letter of support from the University of Bristol.

Source 9. TAK-831:

9.1 ClinicalTrials.gov Identifier: NCT03214588
https://clinicaltrials.gov/ct2/show/NCT03214588?cond=Friedreich+Ataxia&draw=2&rank=13

9.2 Letter of support from Takeda California, Inc., San Diego, USA.