Institution: University of Cambridge

Unit of Assessment: UOA1

Title of case study: Developing accurate diagnostics and new treatments of pulmonary arterial hypertension – a rare and fatal disease of young adults

Period when the underpinning research was undertaken: 2015 to Dec 2019

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:
Nick Morrell	Professor of Cardiopulmonary Medicine	2000-present
Paul Upton	Senior Research Associate	2000-present
Wei Li	Senior Research Associate	2009-present
Stefan Gräf	Senior Research Associate	2012-present

Period when the claimed impact occurred: June 2015-present

Is this case study continued from a case study submitted in 2014? N

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

Pulmonary arterial hypertension (PAH) – severe high blood pressure in the lungs – is a rare disease currently known to affect 6,500 people in the UK and 70,000 in North America, Europe and Japan. This incurable condition usually affects young women, who die within 3-5 years of diagnosis. Cambridge University research showed that mutations in the bone morphogenetic protein type II receptor (BMPR2) pathway causes >25% of PAH cases characterised by particularly severe disease in the youngest patients. This discovery has led directly to routine genetic testing for BMPR2 pathway mutations in PAH patients across the world and the development of new treatments targeting the BMP pathway, commercialised through a University of Cambridge spin-out company. Together, these advances are enabling earlier diagnosis and tailored treatment, bringing hope of a cure to those diagnosed with this terminal disease.

2. Underpinning research (indicative maximum 500 words)

PAH is a rare and incurable disease that affects around 6,500 people in the UK. The condition is usually diagnosed in women (female:male 2.3:1) aged 20-50 years who present with disabling breathlessness. Patients usually die from heart failure within five years of diagnosis. Existing treatments provide symptomatic relief but have little impact on the duration of survival. Until recently, the underlying cause of the great majority of cases of PAH was unknown, severely limiting the development of novel diagnostic and treatment approaches.

Identifying the causes of PAH and their clinical significance: Although prior research had identified mutations in the BMPR2 pathway as an important cause of PAH (Lane et al., 2000; Deng et al, 2000), the extent and clinical significance of these mutations was not known, limiting translation into clinical practice. Therefore, in 2015-2016, Morrell led an international collaborative study that brought together experts from across the world to analyse 1,550 patients with idiopathic, heritable and anorexigen-associated PAH from eight cohorts that had been systematically tested for BMPR2 mutations [1]. These data showed definitively, that 29% of cases of PAH are caused by mutations in *BMPR2* and that these patients present at a younger age with more severe disease. Further, among 1,164 individuals with available survival data, age and sex-adjusted death risk was significantly greater in patients with *BMPR2* mutations than those without (p=0.0011).

Building on these genetic studies, Morrell showed that bone morphogenetic protein type 9 (BMP9) in the blood, potently activates the BMPR2 receptor on the endothelial cells lining lung blood vessels [2]. And, that therapeutic administration of BMP9 to rodents with genetic and non-genetic forms of PAH can restore BMPR2 signalling and reverse the disease [2].

To discover additional genes that might be mutated in PAH among patients with no known cause, Morrell led a European-wide collaboration that performed whole genome germline sequencing of

over 1,038 PAH patients and 6,385 controls [3]. This work identified rare variants of the genes *ATP13A3*, *AQP1* and *SOX17* as important contributors to PAH and provided independent validation of a critical role for Growth Differentiation Factor 2 (GDF2) in the disease. This work also demonstrated that GDF2 mutations reduce the circulating levels of BMP9, providing additional key evidence that BMP9 replacement might serve as a novel therapy of the disease [3, 4].

Cambridge University research has also identified a key link between disordered BMPR2 signalling and aberrant inflammation; thereby providing additional therapeutic targets. In that regard, work led by Morrell using both human samples and laboratory models demonstrated that BMPR2 deficiency promotes an exaggerated inflammatory response *in vitro* and *in vivo*, which can instigate development of PAH [5]. This response includes release of tumour necrosis factor-α that selectively reduces BMPR2, thereby subverting BMP signalling [6]. Together, these data have inspired repurposing of anti-inflammatory drugs as potential treatments of PAH. Between 2015 and 2019 four patents for therapeutic application of BMP9 were awarded in the United States and one in Europe [7]. These potential new treatments represent lead candidate therapies of a cadre of treatments under investigation by the international PAH community led by Morrell [8].

3. References to the research (indicative maximum of six references)
Evidence of research quality: *Research published in peer-review journals. Research was supported by competitively won grants.

[1] *Evans JD, Girerd B, Montani D, Wang XJ, Galie N, Austin ED, …, Di Angelantonio E, Humber M, **Morrell NW**. BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis. ***Lancet Respir Med*** 2016; 4(2):129-37. PMID 26795434.

[2] *Long L, Ormiston ML, Yang X, Southwood M, **Graf S**, Machado RD, …, **Upton PB**, **Morrell NW**. Selective enhancement of endothelial BMPR-II with BMP9 reserves pulmonary arterial hypertension. ***Nature Medicine*** 2015; 21:777-85.

[3] *Gräf S, Haimel M, Bleda M, Hadinnapola C, Southgate L, …, Trembath RC, **Morrell NW**. Identification of rare sequence variation underlying heritable pulmonary arterial hypertension. ***Nature Commun***. 2018; 9(1):1416. PMID:29650961.

[4] *Hodgson J, Swietlik EM, Salmon RM, …, **Li W**, **Gräf S**, **Upton PD**,**Morrell NW**. Characterization of *GDF2* Mutations and Levels of BMP9 and BMP10 in Pulmonary Arterial Hypertension. ***Am J Respir Crit Care Med***. 2020; 201(5):575-585. PMID:31661308.

[5] *Soon E, Crosby A, Southwood M, Yang P, Tajsic T, Toshner M, …, **Upton P**, **Morrell NW**. Bone Morphogenetic Protein Receptor Type II Deficiency and Increased Inflammatory Cytokine Production. A Gateway to Pulmonary Arterial Hypertension. ***Am J Respir Crit Care Med*** 2015;192(7):859-72.

[6] *Hurst LA, Dunmore BJ, Long L, Crosby A, Al-Lamki R, Deighton J, …, **Upton PD**, **Morrell NW**. TNFα drives pulmonary arterial hypertension by suppressing the BMP type-II receptor and altering NOTCH signaling. ***Nature Commun*** 2017; 8:14079. PMID 28084316.

[7] **Patents:** Inventors (all): Nicholas W. Morrell, Wei Li, Paul D Upton; **USA patents**: 20190359668 (2019); 10336800 (2019); 20170209540 (2017); 20170121383 (2017); **European patent:** EP 3166628 A1 (2017)

[8] ***Morrell NW**, Bloch DB, ten Dijke P, Goumans MJT, Hata A, Smith J, Yu PB, Bloch KD. Targeting BMP Signalling in Cardiovascular Disease and Anaemia. ***Nature Rev Cardiol*** 2016; 13 (2): 106-20. *

Competitive grant funding

2019-2024 British Heart Foundation (BHF) Programme grant GBP1,409,223 PI Morrell NW
Targeting the BMP signalling pathway for the treatment of pulmonary arterial hypertension
2019-2023 BHF GBP1,510,822 PI Morrell NW
National cohort study of idiopathic and heritable pulmonary arterial hypertension.
2013-2018 BHF RG/13/4/30107 GBP1,283,492 PI Morrell NW
Targeting the BMP signalling pathway for the treatment of pulmonary arterial hypertension
2013-2023 BHF Special Project no. SP/12/12/29836 GBP1,300,000 PI Morrell NW
National Cohort Study of heritable pulmonary arterial hypertension

2013-18 Medical Research Council (MRC) Experimental Challenge Award GBP3,193,698 PI Morrell NW
Mechanisms underlying the development of pulmonary arterial hypertension

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

Impact on the health and wellbeing of people

Routine genetic testing of patients with PAH: Prior to the research published by Morrell and his colleagues, only patients with PAH who had a positive family history (<5% of cases) had access to routine genetic testing. This meant that around 190 of the 200 people diagnosed with idiopathic or familial PAH in the UK each year had no known underlying cause for their disease; delaying diagnosis and impeding precise and early treatment intervention. Cambridge University-led research has directly influenced clinical recommendations and implemented genetic screening leading to early diagnosis and more appropriate management for patients worldwide [A, B, C, D]. To set this in context, in 2014-2015 no patients with idiopathic PAH in the UK were referred for genetic testing. Currently, at least 25% and in some centres around 50% of PAH patients presenting with idiopathic PAH and no family history are now referred routinely for genetic testing of PAH [H]. A UK PAH centres informal survey in early 2020 showed that all eight National Pulmonary Hypertension Centres discuss the likelihood of a genetic diagnosis with patients and offer referral for genetic counselling and testing. The finding of a mutation in an index case has a major impact on patient prognosis and can help tailor management options. As part of the National Cohort Study of Idiopathic and Heritable PAH, unaffected relatives of PAH patients with a germline mutation are now offered annual screening for PAH. This service has screened over 60 unaffected relatives of BMPR2 index cases, allowing early diagnosis intervention therapy for five newly detected patients[H]. It is well established that early intervention improves survival in PAH patients *(Hachulla & Denton 2010, Burger et al 2019*).

Rapid access to novel treatment and risk-stratified treatments for patients: Widespread genetic testing for the different types of BMPR2 mutation has opened up the possibility of recruiting patients to clinical trials aimed at restoring BMPR2 function. Increasingly, the BMPR2 status of patients is included as part of clinical trial design (Sitbon O et al, Eur Respir J. 2019). Indeed, in January 2020 Morrell's research group received an MRC Developmental Pathway Funding Scheme award to conduct a clinical trial of hydroxychloroquine in PAH patients with BMPR2 mutations, as well as a precision medicine approach using 4-phenylbutyrate in patients with cysteine substitutions in the extracellular domain of BMPR2, based on their preclinical research. These trials are connected to the UK British Heart Foundation (BHF)/MRC PAH Cohort, which is being used to identify patients for precision medicine trials. Their research has also provided a definitive test for those patients that have a particularly poor prognosis, justifying more intensive therapy and early referral for lung transplantation. In addition, the company Acceleron have recently published positive Phase 2 trial data using 'sotatercept', a drug that targets the BMPR2 pathway, in patients with PAH, providing further support for the use of genetic testing [E].

Patient education and empowerment: Significant mechanistic discoveries by Cambridge research has given patients with PAH an understanding of their fatal disease and the prospect of development of a cure a reality. Morrell and his team have presented their findings to UK patient groups) (most recently at the annual UK Pulmonary Hypertension Association meeting May 2019) and their families to raise awareness of genetic testing in this disease. In February 2020, the Pulmonary Hypertension Association (UK) conducted a survey, in collaboration with Morrell, to identify the need for genetic testing in PAH patients (n=211 patients) [F]. One of the key findings was that "74% of respondents said they would want to be referred for genetic testing if they knew there was a chance of their PAH being caused by a faulty gene" [F].

Impact on practitioners and the delivery of professional services

Refining the patient care pathway in the UK: Prior to the Cambridge-led research described in Section 1, the absence of evidence supporting routine genetic testing for *BMPR2* and other mutations in patients with suspected PAH meant that healthcare professionals did not have access to accurate diagnostic tests for most patients. Their research has led directly to a step change in the number of idiopathic and familial PAH patients being tested across the UK (up to 50%). They

have added PAH genetic testing to the NHS testing directory [G]. The finding of a genetic mutation in a patient with PAH immediately establishes the diagnosis of heritable PAH, which means that additional testing to ascertain other causes of PAH become unnecessary, saving resources and time in the NHS [H]. The research suggests that patients with mutations have a particularly poor prognosis and justify more intensive therapy and early referral for lung transplantation. These recommendations have been incorporated into the 2018 international global guidance on the clinical management of PAH [A], and should improve outcomes for these patients.

Genetic testing of PAH across the world: Several European countries have now adopted routine genetic testing in PAH, most notably in France [B], and Germany. In 2019 Morrell established an International Consortium for the Genetics of PAH, a collaborative network of 34 institutions from 10 countries in Europe and North America [I, G], to encourage appropriate genetic testing, to curate causative mutations to inform clinicians, and to provide a platform for further genetic discovery.

Impact on commerce and the economy

Although existing drugs are licensed to treat PAH, their impact on the disease is modest. Based on Morrell's genetic and lab-based research identifying BMP9 as a potential new therapy, patents have been awarded to protect this discovery in the United States and Europe [7]. Working with the University technology transfer office, Cambridge Enterprise, Cambridge academics (Morrell, Upton and Li) established a spin-out biotech company to commercialise the BMP9 approach [J, K]. The venture capital firm, Medicxi, along with Cambridge Innovation Capital and Cambridge Enterprise have invested GBP19,800,000 in the company, Morphogen-IX [K].

In October 2018 the company announced the nomination of its clinical development candidate, MGX292 [L]. The company is now undertaking manufacturing of MGX292 to support planned Phase 1 and Phase 2 studies in patients.

The existing PAH drug market, despite being a rare disease, is worth in excess of USD5 billion per year. As recent national audit data commented: "*While there are currently 12 marketed PAH therapies available, they only serve to slow disease progression. There is no marketed drug that addresses the underlying disease mechanism and targets to cure patients*." The expectation is that the BMP9 approach could be a potential cure, as highlighted in a Guardian article [K].

Morphogen-IX has led to the creation of 10 new jobs. Based on the Babraham Research Campus, the company employs one full time employee, with a subcontract of its drug development activities to a local contract testing research organisation (RxCelerate). The RxCelerate team working with Morphogen-IX comprises 5 senior research scientists, 1 administrator and 3 researchers/technicians. In addition, the company employs consultants in safety, regulatory affairs and manufacturing across the UK.

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

[A] Genetics and genomics of pulmonary arterial hypertension. *Eur Respir J*. 2019;53(1): 1801899. PMID:30545973. This article was a multi-authored output from the 2018 World Symposium on Pulmonary Hypertension. - - references [1] page 5, 1
[B] Genetics of pulmonary hypertension in the clinic. Girerd B, Lau E, Montani D, Humbert M. *Curr Opin Pulm Med*. 2017;23(5):386-391. PMID:28661905 - page 2 references [1]
[C] The revised definition of pulmonary hypertension: exploring the impact on patient management. Simonneau G, Hoeper M. *Eur Heart J Suppl*. 2019;21(Suppl K):K4-K8. PMID: 31857795 – page 3 references [1]
[D] 2015 European Society of Cardiology (*ESC*) / European Respiratory Society (*ERS)* Guidelines for the diagnosis and treatment of pulmonary hypertension. Pages 75, 81
[E] Acceleron results of the Sotatercept PULSAR phase 2 trial. 24 June 2020
[F] Testimonial letter from Pulmonary Hypertension Association UK containing Genetics-PAH online survey results.

[G] (i) National Genomic Test Directory for Rare and Inherited Disease. R188 Pulmonary arterial hypertension,(page 337) (ii) NHS Genomic Medicine Service for R188 Pulmonary arterial hypertension. (page 374)
[H] (i)Testimonial letter from Chair, National Pulmonary Hypertension Centres of UK and Ireland Physicians' committee (ii) National Cohort Study of Idiopathic and Heritable PAH website
[I] International Consortium for the Genetics of PAH. Available from: www.PAHICON.com
[J] 'This could be a real game-changer': protein points to cure for life-limiting disease. The Guardian, 21 June 2015.
[K] Morphogen-IX (i) About Morphogen-IX. (ii) Morphogen-IX raises £18.4M ($23.2M) in a Series B financing. (iii) About Cambridge Innovation Capital. (iv) Morphogen-IX: £18.4m investment will boost PAH medicine – Cambridge Independent article. 27 December 2018 (v)Morphogen-IX announces MGX292 as clinical development candidate. 27 November 2018