Institution: University of Hull

Unit of Assessment: 03 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study:
Chronic cough: defining a "new" disease and producing a novel class of effective drugs

Period when the underpinning research was undertaken: 1998 - to date

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:
Prof Alyn Morice	Project leader (Clinical academic)	1998 – to date
Dr Simon Hart	Senior lecturer (Clinical academic)	2007 – to date
Dr Michael Crooks	Senior lecturer (Clinical academic)	2015 – to date
Ms Caroline Wright	Clinical Trials Co-ordinator	1998 – to date
Dr Laura Sadofsky	Senior lecturer (Pharmacologist, Non-clinical)	2001 – to date

Period when the claimed impact occurred: 2014 – 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Research from the University of Hull has defined the condition of chronic cough as a disease and had the following impact: the work has driven best practice culminating in the full publication of European Respiratory Society guidelines in 2020, the first truly international guidelines as endorsed by the Chinese and Asian Societies; the work has been crucial in driving significant investment in this, until recently, neglected disease, as evidenced by the purchase of Afferent by Merck for >$1 billion to become the market leader in chronic cough treatment. Five lead compounds in international phase 2 and phase 3 trials which all completed recruitment in 2020 are founded on Hull's research.

2. Underpinning research

Research in Hull, led by Professor Alyn Morice since 1999, has established the patterns of presentation and molecular mechanisms that underlie chronic cough (***2.1***); developed methodologies for the disease's objective quantification nationally and internationally (***2.2***); and has undertaken seminal work which has led to the development of a new class of antitussive drugs (***2.3***). The Hull team has worked together with key national (Prof S Birring, Kings College London, Prof L McGarvey, Queens University Belfast) and international collaborators (Prof P Dicpinigaitis, Einstein University, New York, USA) over the past two decades publishing extensively. The key research findings are:

2.1 Epidemiology and disease classification
We have shown that chronic cough is a condition that affects approximately 10% of the UK population; with half reporting that cough interferes with daily life **(1)**, a finding subsequently confirmed by a systematic review of 80 studies worldwide **(2)**. Currently, confusion in how to diagnose chronic cough leads to over-prescription of antibiotics, and the prescription of ineffective, inhaled, medication. We published a survey of such patients showing that they attended an average of six doctors, over a mean time period of 6 years, with multiple, costly, investigations; but always without any relief from their symptoms **(3)**. In 2011 we published the Hull Airway Reflux Questionnaire (HARQ) demonstrating that this could accurately diagnose the condition **(4)**. Over the REF period its usage has become global.

2.2 Adoption of best practice
A major clinical trial published in 2011 by the Hull team demonstrated that reflux cough did not respond to high-dose acid suppression, the previous standard treatment **(5).** This, together with confirmatory work from others, has led to a radical change in the recommendations in the recently published European Respiratory Society (ERS) guidelines. Prof Morice has chaired the four Task Forces, funded by the ERS, on the diagnosis, treatment and assessment of cough (last one held in 2019) involving investigators from the USA, China, Korea, as well as across Europe which has allowed an international consensus to be established.

2.3 Drug development

Hull's research work on the mechanism of cough hypersensitivity has been vital for assessing the clinical importance of putative antitussive agents by both the pharmaceutical industry and the regulatory bodies. Hull has been one of the main centres conducting Phase 2 and 3 trials on the first-in-class drug, gefapixant (AF-219/MK-7264), on behalf of Afferent Pharmaceuticals. The drug is an antagonist of the P2X3 purinergic receptor, which has demonstrated a role for adenosine triphosphate (ATP) in afferent neural pathways of airway hypersensitivity. The emerging evidence of gefapixant's efficacy against chronic cough is high, with approximately two thirds of patients with chronic refractory cough responding. At the request of the US Federal Drug Administration Prof Morice's unit performed a study, published in 2020, demonstrating efficacy with subjective and objective endpoints. The primary endpoint of this study was a unique four modality challenge: ATP, distilled water, capsaicin and citric acid. This study demonstrated, for the first time, that two pathways exist in the human cough reflex; one irritant, nociceptor led, and one purinergic/osmotic, which is responsible for pathological cough **(6)**.

3. References to the research

(1) Ford, A. C., et al. Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. *Thorax* 2006: **61**: 975-979.

(2) Song, W. J., et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *European Respiratory Journal* 2015: **45**(5): 1479-1481.

(3) Everett, C. F., et al. Chronic persistent cough in the community: A questionnaire survey. *Cough.* 2007: **3**(1): 5.

(4) Morice AH, Faruqi S, Wright CE, Thompson R, Bland JM: Cough hypersensitivity syndrome: a distinct clinical entity. Lung. 2011, 189: 73-79.

(5) Faruqi S et al. Chronic cough and esomeprazole: a double-blind placebo-controlled parallel study, *Respirology* 2011: **16**(7): 1150-1156

(6) Morice AH; Kitt MMK; Ford AP; Tershakovec AM; Wu W-C; Brindle K; Thompson R; Thackray-Nocera S; Wright C. The Effect of Gefapixant, a P2X3 antagonist, on Cough Reflex Sensitivity: A randomized placebo-controlled study. *European Respiratory Journal* 2020: **54**(1): 1900439

Research grants 2014-2020

In excess of £1.25 million pounds from the pharmaceutical industry has been awarded to the team since 2014 including for work on cough:

1) AF 219 on the cough reflex. Afferent pharmaceuticals (£202,851)
A Study to assess the effect of AF-219 on cough reflex sensitivity in both healthy and chronic cough subjects (Clinical Trial)

2) BAY1817080 in chronic cough. Bayer pharmaceuticals (£168,410)
Double-blind, placebo-controlled, randomized, two-way crossover administration with four-step dose titration in patients with refractory chronic cough to assess safety, tolerability and efficacy for proof of concept and dose-finding.

3) Synairgen Research Ltd (£48,463)
A randomised, double-blind, placebo-controlled study, in COPD patients with and without a confirmed respiratory virus infection assessing anti-viral biomarker responses and clinical effects of inhaled SNG001 compared to placebo

Prof Morice has also been a co-applicant on two major, multicentre, grants responsible for the analysis of symptom data in chronic obstructive pulmonary disease (COPD).

NIHR Health Technology Assessment Programme (£2,257,399)
A randomised, double-blind placebo controlled trial of the effectiveness of low dose oral theophylline as an adjunct to inhaled corticosteroids in preventing exacerbations of COPD. 11/58/15. Sept 2013 – Dec 2017

NIHR Health Technology Assessment Programme (£2,508,343)
A randomised, double-blind placebo controlled trial of the effectiveness of the beta-blocker bisoprolol in preventing exacerbations of COPD. 15/130/20. Feb 2017-Jan 2022

Presentations
Prof Morice's team has contributed to over 100 conferences and meetings (2014-2019), 50 of these at International congresses. In addition, he has chaired and contributed to more than 20 commercial expert panels and trial advisory boards, i.e. GlaxoSmithKline, Merck and AstraZeneca. At the 2019 European Respiratory Society meeting in Madrid (2019), Prof Morice launched the new international guidelines to over 1,200 delegates (**Evidence 2**).

4. Details of the impact
The major impact of our research has been to characterise chronic cough as a disease distinct from asthma and Chronic Obstructive Pulmonary Disease (COPD) and to develop methodology to study it; subsequently, this has allowed drug development in a new therapeutic area. Hence, pharmaceutical companies have novel products in which to invest, and most importantly are able to bring relief to previously undiagnosed and untreatable patients.

2.1 & 2.2 Disease classification and Patient benefit
The simple diagnostic questionnaire, Hull Airway Reflux Questionnaire (HARQ), which the Hull team developed is now validated in 39 different countries and is available in 20 different languages. It is freely available online on ISSC.info; **8,546** UK patients accessed and completed the questionnaire in a single year **(Evidence 1)**. In 2020, the use of these online resources was endorsed in the new International Guidelines **(Evidence 2).** The relief afforded to patients, who are able at last to understand their symptoms as cough hypersensitivity is difficult to understate **(Evidence 3)**.

Patients who were previously dismissed as neurotic because no clear label could be attached, can now be told they have cough hypersensitivity, a disorder of the vagal afferent nerves. Such patients have usually undergone multiple investigation such as endoscopy, CT scan and challenge testing only to be told there is nothing wrong. Inappropriate treatment in the form of anti-asthma, antibiotic, or anti-acid therapy is prescribed, frequently on a long term basis. One patient's account is detailed as an example of the huge impact the Hull team's work has had: "*I have suffered from all the symptoms you describe in your article, to a chronic degree for the last 7 or more years. I have seen so many consultants and specialists they are too numerous to mention. I have undergone all the tests relating to this problem several times over and have taken all the prescribed medications for reflux to no avail and I am still no nearer any sort of a fix. I am depressed and anxious (medicated) due to the worry of the condition of my lungs, airway and throat and the possibility of long term damage or even cancer. ... Your article is the first time in those 7 years that I have seen a diagnosis that entirely matches my symptoms! I am elated ...*" **(Evidence 4).**

The international guidelines provide guidance to clinicians, impact positively on the patient pathway, decrease the chances of costly risks associated with cough management, i.e. CT scan induced breast cancer, and provide effective advice on often unconsidered therapeutic options **(Evidence 2).**

2.3 Developing new drugs for chronic cough
Hull's work, defining at least two different pathways for the pathophysiology of chronic cough, explained why several costly clinical studies blocking the irritant receptors failed in the clinic, as a result of these findings drug development by GSK has now been abandoned. The Clinical Development Director of GlaxoSmithKline stated, *"This study investigated the efficacy and safety of GSK2798745 (a TRPV4 inhibitor) in patients with chronic cough. The results of this study allowed a clear decision to be made regarding termination of development of this compound in this indication. The impact of this work was that there was a cost saving to the project with spending until study completion not required. Because of the specific design of the study, the work also prevented unnecessary recruitment of patients to a study with an ineffective drug."* (**Evidence 5**).

Conversely, Hull's research has led to the substantial investment in the development of a series of effective, novel, therapeutics by various other pharmaceutical companies. Afferent Pharmaceuticals were the first to develop an effective agent blocking vagal afferent hypersensitivity; Gefapixant (AF219/MK7264) was trialled in several phase 2 studies where Prof Morice advised on the study design and conduct. As a result of further studies on Gefapixant,

Afferent Pharmaceuticals was acquired by Merck, a major global pharmaceutical company. The commercial decision was attributed in part due to Hull's research data (**Evidence 6**). The deal involved an immediate payment of $500 million, with a further $750 million payable when the drug was licensed by the US Federal Drugs Agency (application in progress). Prof Morice has continued to work with Merck and indeed was responsible for providing the advice as to the primary endpoint of their pivotal, phase 3, clinical studies (Cough 1 and Cough 2; presented at the ERS Congress September 2020). The Clinical Director of Merck wrote, *"Alyn (Prof Morice) has done a wonderful job of helping educate the overall Merck team on the field of chronic cough and he has provided valuable input on the chronic cough clinical program with regards to appropriate endpoint selection, rigorous patient selection, and expert opinion support during the course of the trial."* **(Evidence 7).**

Finally, first data from Merck's phase III studies of Gefapixant (Cough 1 and Cough 2), studying over 2000 patients with objectively proven chronic cough, clearly showed the effectiveness of using HARQ as a diagnostic tool. The HARQ score at baseline for these patients was 40/70, whereas the upper limit of normal people is 14; demonstrating for the first-time HARQ's global utility **(Evidence 8)**.

In anticipation of a UK licencing application for these new drugs the Hull team have been advising the UK's National Institute for Health and Care Excellence (NICE) as to the correct metrics to use in their assessment of antitussive drugs. Commonly used scores such as Short-form (SF) 35 which measure quality of life (QOL) are inappropriate since patients with chronic cough are rarely physically disabled even if their lives are ruined.

Three other compounds of this new class of drug, exploiting Hull's research that defined a mechanistic pathway, are currently in phase 2 trials. Bayer, Shionogi, and Bellus Health, have all made multi-million investments in these clinical trials; and Prof Morice is supporting the companies by advising as chief or principal investigator, e.g. *"The unique combination of scientific & clinical expertise of Prof. Alyn together with this ability to optimally run and steer clinical studies has informed our research and development programs and allowed us to progress our P2X3 projects to successful demonstrating efficacy in patients with refractory chronic cough(RCC)"* (**Evidence 9**). Preliminary trial results show treatment success in over two thirds of patients and therefore it is highly likely that the first effective drugs for chronic cough in over 40 years will soon be available (**Evidence 10**).

5. Sources to corroborate the impact

Evidence 1. HARQ and ISSC.info usage.
(http://www.issc.info/HullCoughHypersensitivityQuestionnaire.html)

Evidence 2. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Latest modification of the guidelines that revolutionise the management of chronic cough. *European Respiratory Journal* 2020: **55**: 1901136

Evidence 3. YouTube Cough video https://www.youtube.com/watch?v=jtwlv75XuYU&t=19s

Evidence 4. Patient testimonial (Email 31/12/2019).

Evidence 5. Discovery Medicine, GlaxoSmithKline, Clinical Development Director,
Letter of support.

Evidence 6.

- Afferent Pharmaceuticals, Chief Executive Officer, 19 July 2016. Testimonial indicating the key role of Professor Morice in Hull in enabling the commercial impact: by providing expert opinion to inform the investment community, and advising the company on development of their drug using his expertise in conducting cough challenge studies.
- Merck to acquire biotech company Afferent. News item in Wall Street Journal, 9 June 2016. www.wsj.com/articles/merck-to-acquire-biotech-company-afferent-1465509592.
- Merck Announces Presentation of Phase 2 Results for MK-7264, an Investigational, P2X3 Receptor Antagonist, Being Evaluated for the Treatment of Chronic Cough Press release dated 22 May 2017.

Evidence 7. Merck & Co., Inc, Director Clinical Development, Letter of support

Evidence 8. Merck first report on Gefapixant Phase 3 trials.

- McGarvey L, et al. Two Phase 3 Randomized Clinical Trials of Gefapixant, a P2X3 Receptor Antagonist, in Refractory or Unexplained Chronic Cough (COUGH-1 and COUGH-2). Late Breaking Abstract, ERS International Virtual Congress 2020, 7-9 Sept

Evidence 9. Bayer, Director Experimental Medicine Clinician. Letter of support

Evidence 10. Bellus Health, Chief Medical Officer. Letter of support