**Institution: University of Nottingham**

**Unit of Assessment: UoA1**

**Title of case study:** Improving clinical care for lymphangioleiomyomatosis

## 1. Summary of the impact

Research at the University of Nottingham has defined the clinical phenotype and management of lymphangioleiomyomatosis, a rare and often fatal multisystem disease affecting 1 in 200,000 women worldwide. The group has led the development and evaluation of new therapies and diagnostic strategies which are now part of routine clinical care. The research has underpinned the transformation of this previously under recognised and untreatable disease into a condition recognised by respiratory physicians, with international clinical guidelines, patient registries, clinical trials, specific treatments and a UK specialist clinical service.

## 2. Underpinning research

Lymphangioleiomyomatosis (LAM) is a rare disease which almost exclusively affects women. With a prevalence of 1 in 200,000 individuals globally, there are over 200 affected patients in the UK and 17,500 worldwide. Patients with LAM develop lung cysts and recurrent pneumothorax, and have kidney tumours. The disease is progressive and, in the majority of cases, leads to death or lung transplant due to respiratory failure. LAM can occur sporadically or as part of the genetic disease tuberous sclerosis complex (TSC). Increasing recognition of LAM as a clinical problem for adults with TSC has increased our reach to a wider group of patients, with a prevalence of 1 in 6,000; approaching 1 million patients worldwide. Until recently, little research on LAM had been performed, no treatments were available and patients with LAM were told they would die within 5-10 years.

Professor Simon Johnson's work on LAM began in 1995, initially under the guidance of Professor Anne Tattersfield in the Division of Respiratory Medicine, University of Nottingham. They published two clinical papers[1,2] in 1999 and 2000 based around the first comprehensive national cohort to be studied, which helped to redefine understanding of the natural history and clinical phenotype of the disease, showing for the first time the rate of progression of LAM. The first study on the natural history of lung function change in LAM, published in the world's leading respiratory journal, showed that commonly used, anti-oestrogen treatments were ineffective[1]. The second paper showed that early surgical management of pneumothorax could reduce morbidity, and described the risks of pregnancy and pneumothorax in LAM[2]. These papers highlighted the need for a change in management for these patients.

Since appointment to Clinical Senior Lecturer in 2000, Johnson has established a translational research program comprising patients and staff at the National LAM Centre in Nottingham, and a laboratory group within the Division of Respiratory Medicine, University of Nottingham. In 2007, they jointly performed the first clinical trials of mTOR inhibitors in patients with LAM and the related disease TSC[3,4]. These studies showed that mTOR inhibitors could reduce kidney tumour volume in patients with LAM and TSC, and were safe over a sustained period of time for these patients.

After publishing evidence-based European guidelines for the diagnosis and management of LAM[5], the team critically evaluated this evidence-based approach in their National clinical cohort and, in 2012, published a diagnostic strategy to improve diagnostic accuracy using non-invasive means[6]. This study showed that by using the guidelines they had formulated in conjunction with serum biomarkers, a firm diagnosis could be made in most cases using imaging alone. An invasive lung biopsy could be avoided in 70% of patients with suspected LAM[6].

Their laboratory program continues to study new targets for LAM to generate future targets for therapy.

## 3. References to the research


1. **Johnson SR**, **Tattersfield AE**. Decline in lung function in lymphangioleiomyomatosis: relation to menopause and progesterone treatment. *Am J Respir Crit Care Med*. 1999;160:628-633. http://dx.doi.org/10.1164/ajrccm.160.2.9901027

2. **Johnson SR**, **Tattersfield AE**. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000:55:1052-1057 http://dx.doi.org/10.1136/thorax.55.12.1052

3. Davies DM, **Johnson SR, Tattersfield A**, Kingswood JC, Cox JA, McCartney DL, Doyle T, Elmslie F, Saggar A, de Vries P, Sampson JR. Sirolimus therapy in tuberous sclerosis or sporadic lymphangioleiomyomatosis. *New England Journal of Medicine* 2008;358:200-203 http://dx.doi.org/10.1056/NEJMc072500

4. Davies DM, de Vries PJ, **Johnson SR**, McCartney D, Cox JA, Serra AL, Watson P, Howe CJ, Doyle T, Pointon K, Cross J, **Tattersfield AE**, et al. Sirolimus Therapy for Angiomyolipoma in Tuberous Sclerosis and Sporadic Lymphangioleiomyomatosis: A Phase 2 Study. *Clin Cancer Research* 2011;17:4071-4081. http://dx.doi.org/10.1158/1078-0432.CCR-11-0445

5. **Johnson SR**, Cordier JF, Lazor R, Cottin V, Costabel U, Harari S, Reynaud-Gaubert M, Boehler A, Brauner M, Popper H. Bonetti F, Kingswood C, and the Review panel of the ERS LAM Task Force. European Respiratory Society Guidelines for the diagnosis and management of lymphangioleiomyomatosis (LAM). *Eur Resp J* 2010;35:14-26. http://dx.doi.org/10.1183/09031936.00076209

6. Chang WYC, Cane J, Kumaran M, Pointon KS, Blakey J, **Johnson SR**. Application of diagnostic guidelines and putative biomarkers in lymphangioleiomyomatosis. *Respiratory Research* 2012. 13:34. http://dx.doi.org/10.1186/1465-9921-13-34



Grant funding for these studies includes:

- 2005-2006: LAM Foundation ($40,000) to SR Johnson (PI) 'Development of an in vivo model of lymphangioleiomyomatosis'.
- 2005-2007: European Respiratory Society Task Force on Lymphangioleiomyomatosis (€19 300) to SR Johnson and J-F Cordier 'Co-Chair'.
- 2007: British Lung Foundation (£100,000) and LAM Action (£50,000) to SR Johnson (PI) 'A randomised, double blind, placebo controlled trial of doxycycline in LAM'.
- 2009: European Networks of Centres of Expertise for CF, LAM and Lung Transplantation (€999,472). EU, FP7-HEALTH-2007-B. Coordinator Prof T.O.F. Wagner, University of Frankfurt.
- 2001-2013: LAM Action (£250,000) to SR Johnson 'Molecular Pathology of Lymphangioleiomyomatosis'.


## 4. Details of the impact

In the early 1990s, little research on lymphangioleiomyomatosis (LAM) had been performed, no effective treatments were available and patients with LAM were told they would die within 5-10 years. Following on from Professor Johnson's two key papers[1,2], his group's subsequent research papers and widely cited reviews continued to increase the profile of LAM, as shown by an approximately five-fold increase in research papers on LAM from the 1990s to 2010, and by the setting up of a European Respiratory Society Task Force (in 2005) and a European LAM Organisation (in 2009) that has regular research and patient meetings.

The group's work has been instrumental in showing that widely used treatments are ineffective, and in identifying a treatment that does work. This, and their role in establishing a patient support group and the National Centre for LAM, has transformed the outlook for patients with this disease, and vastly improved the patient experience. This program of work at the University of Nottingham has resulted in benefits for patients with LAM, the pharmaceutical industry and, more recently, patients with other cancers for which mTOR inhibitors are being trialled.

**Informing clinical guidelines**

Professor Johnson led a European Task Force, funded by the European Respiratory Society, to form an evidence synthesis which, in 2010, published the first international diagnostic and clinical management guidelines for LAM[a]. These incorporated data from Nottingham's clinical research papers in eight of 112 cited references, including their 2008 study showing effective treatment of LAM with the mTOR inhibitor Sirolimus. Sirolimus was recommended in these guidelines for treatment of patients with progressive lung, kidney and lymphatic disease, and has been funded by National Specialised Commissioning since 2011. Their work has also been cited in US guideline statements for treatment of LAM (American Thoracic Society LAM guidelines group) and TSC (Tuberous Sclerosis Alliance guideline group)[b]. Johnson represents Europe on both of these groups.

The group's findings that commonly used, anti-oestrogen treatments were ineffective in the treatment of LAM have also been picked up by guidelines, such that anti-oestrogen therapy is advised against in the European[a] and North American[b] guidelines.

Following on from their work highlighting that a definite diagnosis can usually be made using imaging alone without need for invasive investigations[6], this strategy is now used at the UK LAM Centre[c] and other units. This, and their finding that early surgical management of pneumothorax can reduce morbidity[2], were adopted in 2011 as quality indicators of patient outcome[c], highlighting their importance in clinical care at the National Centre for LAM.

**Changing clinical practice**

In the 1990s, two-thirds of UK patients were given ineffective hormone therapy which caused frequent side effects including osteoporosis. Johnson and Tattersfield performed the first clinical trials on mTOR inhibitors in patients with LAM and TSC, and, in so doing, the group were instrumental in the development of these drugs as an effective treatment for LAM and TSC. In 2008, mTOR inhibitors were not an option for patients with LAM or TSC. Following publication of the 2010 guidelines, mTOR inhibitors became the standard of care for LAM patients with progressive lung and renal disease in the UK and the USA[a,b]. Now, the majority of patients are considered for mTOR inhibitor therapy, and around 20% of patients with LAM at the UK LAM Centre, and in other developed countries, are now treated with these drugs.

As a result of the group's studies, the use of anti-oestrogens in LAM has fallen from 53% of patients[d] to a small minority of patients, outside of specialist centres.

**Improving patient care**

Professor Johnson's work has led to a number of improvements for patients. Rather than being told they have only 5-10 years to live, LAM patients now have access to an effective treatment. They are also now spared the side effects of an ineffective anti-oestrogen treatment, and a definitive diagnosis can usually be made without invasive investigations. Complications including pneumothorax are now treated earlier[c], thereby reducing patient morbidity. In addition, because the group described the effect of LAM on pregnancy, physicians are now able to advise more women on the true risks of childbirth in LAM where previously all patients were discouraged from pregnancy.

The recognition by the advisory group for National Specialised Commissioning, that LAM is a complex multisystem disease with a variable prognosis and specific treatments, led to the Nottingham group's successful tender to establish a National Clinical Centre[e] to serve the national caseload of patients under National Specialist Commissioning from 2011. This resulted in an initial £1 million of dedicated funding for specialist care for LAM patients. As a result, the service now offers clinical care to all UK patients and sees over half of these patients, and increasingly those with TSC[e]. This has allowed the group to incorporate their research and evidence-based care into treatment of all patients with LAM in the UK. The service also receives referrals of LAM patients from some European countries.

LAM patients also now have the option of participating in clinical trials, and access to a patient

support group (LAM Action), which was established by Tattersfield and Johnson in 1999. LAM Action[f] is a registered National Charity that provides peer support to newly diagnosed patients and is part of the UK Respiratory Alliance, a Pressure group of respiratory organisations lobbying for improved funding for respiratory care and research. LAM Action has raised ~£400,000 since 2008.

LAM research in Nottingham has also extended to patients with TSC-related conditions. As mTOR is overactive in all TSC-related lesions, mTOR inhibitors have widespread application and are being tested across other TSC hamartomas. The group's work has been cited in these publications as part of the rationale for clinical trials of mTOR inhibitors in TSC-related brain tumours, cognitive dysfunction, angiomyolipoma and sporadic renal carcinoma. Acting as a consultant on LAM and TSC biology to Novartis pharmaceuticals on several occasions since 2008, Johnson has been involved in designing and performing these studies.

**A model for rare diseases**

Professor Johnson has led initiatives essential to working in rare diseases; including establishing a database of patients with LAM willing to participate in research, and collecting blood and tissue samples from around half of UK patients. He ran a work-package of the European Network Centres of Expertise (ENCE) programme established in 2009 under FP7, which outlined clinical and research frameworks for the care of rare diseases[g], and Johnson was also responsible for the use of LAM as a model for European rare disease care. This has resulted in discussions with other rare lung disease groups, including alpha-1 anti-trypsin deficiency and hereditary haemorrhagic telangiectasia, both of whom wish to adopt this strategy.

In summary, LAM research at the University of Nottingham has increased awareness of LAM, and significantly changed clinical practice such that the majority of patients now receive multidisciplinary care at a National Specialist Centre. We have improved patient care with better understanding of the disease phenotype and demonstration of the efficacy of mTOR inhibitors, and reduced the use of invasive investigations to make a firm diagnosis. Clinical trials have become the standard of care for patients with progressive disease, with clinical trials running in the USA and Europe, giving most UK patients the opportunity to participate in clinical trials if they wish.

**5. Sources to corroborate the impact**

a) European Respiratory Society LAM Guidelines: http://www.ers-education.org/guidelines.aspx (scroll down to 2010 guidelines – 'European Respiratory Society Guidelines for the diagnosis and management of lymphangioleiomyomatosis (LAM)'. (Alternatively, PDF is available on request). See p20-21 (anti-oestrogens), p21 (pneumothorax), p23 (references).

b) Krueger DA, Northrup H, on behalf of the International Tuberous Sclerosis Complex Consensus Group. Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013;49(255)255-265. http://dx.doi.org/10.1016/j.pediatrneurol.2013.08.002

c) Clinical protocols for diagnostic workup, angiomyolipoma management, pneumothorax and Sirolimus at the National LAM Centre (pdf available on request).

d) The NHLBI Lymphangioleiomyomatosis Registry: Characteristics of 230 Patients at Enrollment (2006) Am J Respir Crit Care Med; 173,105-111 http://dx.doi.org/10.1164/rccm.200409-1298OC

e) The National Centre for Lymphangioleiomyomatosis http://www.specialisedservices.nhs.uk/service/lymphangioleiomyomatosis/search:true

f) LAM Action: http://lamaction.org/

g) European Network of Centres of Expertise (ENCE) http://pneumo-frankfurt.de/297.0.html