BREATHING MATTERS CLINICAL TRIALS TO DATE
INTERSTITIAL LUNG DISEASE

[Updated Jan 2019]

Breathing Matters was established 8 years ago with the aim of finding better treatments for interstitial lung diseases (ILD) and lung infections. Since that time, we have raised money and awareness into these often neglected conditions. Looking back over the 8 years, we have come much further than any of us would have anticipated in the beginning. We have established new theories on the development of ILD or lung fibrosis and the role of the immune system in particular the clotting cascade and neutrophils. We have also better ways of monitoring and diagnosing these conditions and our novel nuclear medicine imaging programme and relatively non-invasive lung biopsy service are the first in the UK. We could not have achieved any of this without the support of our funders and our patients, so thank you all. This review highlights our achievements to date and our future directions in ILD.

Relatively Non-Invasive Lung Cryobiopsy (2014-ongoing):

Objective: To find a less invasive and better diagnostic tool for every patient with ILD

Main benefactors: **Teresa Timberlake and family – equipment purchase**
Lawrence Matz Memorial Fund – Clinical Fellow

Breathing Matters investment: £52,000 salary; £36,000 (total £88,000)

Leveraged funding: £347,000

Outcomes:

1. **Novel cryobiopsy service, first in the UK including training other centres; presentations at European Respiratory Society (2015), British Thoracic Society (2014-6); publications: review 2016; papers in preparation:**
2. **Completed Lung-INHALE study Study (2019) to assess inhaled drug deposition using CLB. This will allow drug companies to develop inhaled therapies for IPF and be sure that they are reaching the part of the lung where they are needed. The use of inhaled therapy will avoid some of the side-effects of anti-fibrotic drugs that are taken as tablets.**

This project was developed in discussion with a family whose mother had had a surgical lung biopsy towards the end of her life. Her experience was such that her family felt that a less invasive alternative must be available. Dr Theresia Mikolasch, the Lawrence Matz Clinical Fellow, took this on for Breathing Matters to find out and about and train in new techniques. Dr Mikolasch then returned to UCLH and established the first and only UK cryoscopic lung biopsy (CLB) service. CLB is a new way of obtaining larger lung biopsies using a flexible bronchoscope passed into the lungs through the mouth. The patient is sedated and surgery is avoided. This is not only better for the patient than a surgical lung biopsy, but also provides a solution to

the lack of biopsy samples available for scientific research. GSK were so excited by the technique that they awarded Dr Mikolasch and Dr Porter a grant of over £300,000 to carry on the service for an additional 3 years.

Novel FDG-PET Imaging to Predict Prognosis and Response to Treatment in ILD (2014-ongoing):

Objective: To find a new test (biomarker) that will enable us to predict prognosis and response to treatment in each individual patient.

Breathing Matters investment: £34,766

Leveraged funding: £173,850

Funding from BLF for clinical trial of FDG-PET in post transplant bronchiolitis £40,000

Outcomes: Novel FDG-PET imaging programme in ILD - first in the UK; presentations at American Nuclear Medicine Society (2015), British Thoracic Society (2015-6); American Thoracic Society (2017)

Publications:

Pulmonary 18F-FDG uptake helps refine current risk stratification in idiopathic pulmonary fibrosis (IPF). Win T, Screaton NJ, Porter JC, Ganeshan B, Maher TM, Fraioli F, Endozo R, Shortman RI, Hurrell L, Holman BF, Thielemans K, Rashidnasab A, Hutton BF, Lukey PT, Flynn A, Ell PJ, Groves AM. Eur J Nucl Med Mol Imaging. 2018 May;45(5):806-815. doi: 10.1007/s00259-017-3917-8. Epub 2018 Jan 16.

Next steps:

1. **FDG-PET will be used as a response biomarker to see if we can detect which patients benefit from anti-fibrotic therapy and which patients do not benefit. We have applied to the NIHR for a £400,000 grant to carry out this study:**
2. **We will use FDG-PET to see if Losmapimod is of benefit in patients with rheumatoid arthritis associated lung fibrosis (RA-ILD) (see below).**
3. **We and others have shown that patients with IPF are more prone to blood clots. We have some very exciting work looking at anticoagulation in IPF. We have completed 2/3rds of the study and will then publish our findings later in 2019 (see below).**

Interstitial lung disease (ILD) consists of a heterogeneous group of diseases with varying amounts of interstitial inflammation and fibrosis. Survival in the most severe form of lung fibrosis, idiopathic pulmonary fibrosis or IPF, is particularly poor; however, there is heterogeneity in outcome. Some patients gradually deteriorate; some undergo stepwise progression, whilst others decline rapidly. Moreover, much of the prognostic data heralds from an era when the criteria for diagnosing IPF were

less well and differently defined than at present. There is a definite need to find prognostic biomarkers to predict outcome in IPF patients

Positron emission tomography (PET) offers the ability to non-invasively investigate cellular metabolism in vivo. PET studies in animals have yielded valuable insights into the biology of IPF and ILD and there is potentially encouraging evidence that PET may aid the development of therapeutic interventions to treat these debilitating conditions. It has been recently demonstrated that 18F-Fluorodeoxyglucose (18F-FDG) PET signal is consistently raised and can be objectively measured in patients with IPF. Moreover, these PET signals are shown to be stable and reproducible. We have shown over several years and imaging hundreds of patients with ILD that the baseline measures of pulmonary 18F-FDG PET signal to predict survival in patients with IPF compared to other more established prognostic data. We have also shown that combing PET data with our clinical scoring system based on gender, age and physiology (GAP) data ("PET modified GAP score") refined the ability to predict mortality.

Future studies are to investigate the role of FDG-PET scanning in other ILDs, such as Rheumatoid arthritis (see below) and systemic sclerosis.

Rheumatoid Arthritis (RA) Associated ILD (2018-ongoing):

Objective: To discover why 1:5 patients with RA will develop lung fibrosis and what novel treatment can prevent disease progression

Breathing Matters investment: £34,766

Leveraged funding: £102,766

Outcomes: Novel biomarker test for neutrophils extracellular traps (NETS) in ILD in discussion with UCL business for further development; presentations at American College of Rheumatology (2014-6); British Thoracic Society (2016); British Rheumatology Society (2014-6); publications: 2 papers in preparation:

Next steps: A trial of the p38 MAPKinase inhibitor Losmapimod in RA-ILD using FDG-PET as a response biomarker

RA is a chronic debilitating disease estimated to afflict 13% of the world population. Around 10% of patients with RA will develop an ILD that is very similar to the lung fibrosis that we see with IPF. Dr Akif Khawaja was funded by Rosetrees and UCL to carry out a PhD into the aetiology of RA-ILD. His work proposed that RA is a disease that starts in the lung. That chronic lung damage caused by smoking, infection and other insults causes the immune response to recognize the lungs and joints as “foreign” and attack them causing chronic damage. His work implicated neutrophils in this process and, in particular, the p38 MAPkinase pathway. Breathing Matters and Rosetrees are now funding Akif to carry out further work to investigate the role of the p38 MAPKinase inhibitor Losmapimod in patients with RA-ILD and this will

combined with our novel PET imaging work. We are also hoping to develop a new test using blood or sputum to detect early activation of neutrophils in the lungs of patients at risk of ILD. This same test may act as a biomarker for prognosis and to detect early response to novel therapies.

This work had led onto the first clinical trial of a treatment in RA-ILD: in particular, we will use an established pharmacological inhibitor of p38 MAPkinase to investigate the role of this pathway in the FDG PET signal seen in the lungs of patients with RA-ILD; in particular, to demonstrate a change in FDG avidity following p38MAPkinase inhibition.

A Trial of Anticoagulation in IPF (2016-2019):

Objective: To assess the potential of anticoagulation as a treatment for IPF

Main benefactors: The Hulme Family - The Mark Hulme Clinical Fellow

Breathing Matters investment: £40,000

Leveraged funding: £100,000 from UCL/H NIHR BRC

Next steps: A trial of anticoagulation with heparin in IPF using FDG-PET as a response biomarker

At present, we do not know the exact cause of idiopathic pulmonary fibrosis (IPF), although research has identified lots of processes that are likely to be involved. Currently, we believe that microscopic injury occurs in patients with IPF and then the body responds to repair this, but does so in a way that leads to more damage and scarring. One of the processes involved in repair pathway is coagulation, which minimises blood loss when tissues are damaged. Patients with IPF are at increased risk of blood clots and this can reduce their already low life expectancy. We also think that these blood clots drive the worsening of their lung disease. Researchers have shown that clotting is over-activated in the lungs of IPF patients and we want to investigate how reducing this might improve the disease. Based on work carried out at UCL, we believe that anticoagulation with heparin is safe and may even prevent disease progression in IPF. Patients will be asked if they would be willing to take the oral anticoagulant dabigitran for 3 weeks, to reduce clotting. We will perform blood tests and FDG-PET scans before and after taking the drug to judge response. If we find that the heparin is safe and the patients report some improvement that we can confirm with questionnaires lung function and FDG-PET scans, then we will progress to leverage funding for a much bigger trial. We have completed 2/3rds of this study and are just recruiting the final patients.

A Trial of a Novel Treatment (Compound X) in IPF (2019-2022):

Objective: To assess the potential of Compound X as a treatment for IPF

Main benefactors: NIHR BRC £100,000

Breathing Matters investment: £40,000

Leveraged funding: Application to British Thoracic Society, Wellcome Trust and NIHE.

Next steps: A trial of Compound X in patients with IPF

Assessing effectiveness of treatments for IPF is difficult as often they do not make patients feel better, despite decelerating disease. Currently, we are guided by regular breathing tests and special imaging of the lungs, which are insensitive to changes and may be unpleasant for patients. We need better tests like a simple blood test to predict the prognosis for individual patients, and their responses to treatment. Causes of IPF are unknown, but we have found that specific white blood cells, called neutrophils, are increased in the lungs of patients with IPF. We also found that the more neutrophils in the lungs, the faster the decline from IPF. This suggests that neutrophils are actively worsening IPF. Neutrophils produce a substance called X that we detect in the bloodstream of patients with IPF. No-one has investigated whether X causes or worsens IPF. We plan to quantify X in the blood and lungs of patients with IPF. By comparing X levels in patients with IPF against healthy individuals, this will establish whether X is increased in patients, whether high levels of X indicate more severe IPF and whether treatment for IPF reduces X levels in patients that respond. These results will ultimately help design future clinical trials testing Compound X that is able to block X as a treatment for IPF.

Understanding Mucin 5 B and Its Role in IPF (2019-2022):

Objective: To assess the role of Muc5B in IPF

Main benefactors: NIHR £100,000

Breathing Matters investment: £40,000

Leveraged funding: Application to Rosetrees

Next steps: Further investigations in patients with IPF of the effects of blocking neutrophil activation

It is unclear what causes IPF, but it is thought to be a response to damage to the lining of the airways (epithelium) following an unidentified injury. This results in the formation of excessive scar tissue which disrupts the delicate architecture of the lung and ultimately death follows from respiratory failure. We have shown from research previously sponsored by The Rosetrees Trust that a certain type of white blood cell which is specialised in fighting infections called neutrophils may play a role

in PF. We have found that neutrophils are increased in the blood and lungs of patients with PF and the more neutrophils you have, the worse the individual's outcome. In addition, it is recognised that you are more likely to develop IPF if you have a commonly occurring genetic mutation that causes increased mucus production by the lung epithelium, and in particular a protein called Mucin or MUC5B that gives sputum its stringy quality. We propose that the overproduction of MUC5B may stress the epithelium, making it more prone to damage and scarring. In addition, the increased MUC5B will attract and activate neutrophils from the blood and these white blood cells can cause further damage. We hope that, by identifying treatments that limit the number of neutrophils moving into the lung, we can protect patients from developing PF or from PF progressing. We will use neutrophils and epithelial samples form patients and healthy volunteers to compare differences and see how the MUC5B affects neutrophil activation in the lung. Lastly, we plan to block neutrophil activation and recruitment with a specific treatment that is already being developed for other indications and has an excellent safety profile. If our results are encouraging, we can take this medication into an early clinical trial for patients with IPF.

If you are a UCLH patient and want to get involved in any of the above studies, please discuss this with your consultant.