Institution: University of Portsmouth

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Inhaled heparin, a novel therapeutic approach with clinical benefits in the treatment of obstructive airways diseases.

1. Summary of the impact

A new intervention has been developed and trialled in patient groups characterised by mucus obstruction of the airways. Outcomes for these patient groups have improved, and health service decisions have been informed by the underpinning research. A spin-out business, Ockham Biotech Ltd., was created and has generated overseas investment.

A novel mucolytic application and inhaled route of administration for heparin has provided a simple and cost-effective therapeutic means of relieving the symptoms of mucus obstruction in diseases including CF and COPD, which cost the NHS ~£600m and £1bn, pa, respectively.

2. Underpinning research

The underpinning research, summarised here, was carried out under the leadership of Professor Janis Shute, who was appointed as Reader in Pharmacology at the University of Portsmouth (UoP) in 2001. Key academic co-investigators involved in the research include Dr Marisa van der Merwe, Senior Lecturer in the School of Pharmacy at UoP (appointed 2004), and Drs Mary Carroll and Peter Hockey, clinical respiratory consultants at Southampton General Hospital (SGH).
In 2002, Prof Shute was appointed to the European Task Force established to explore the use of sputum induction as a means of obtaining a sample from the airway for analysis of inflammatory markers and mediators of inflammation. She contributed to pioneering National and International clinical studies in the use of sputum induction to analyse markers of disease progression and response to mucolytic therapies in children with CF.

While exploring novel anti-inflammatory effects of heparin [reviewed in 1], an anti-coagulant normally used intravenously, Prof Shute noticed a mucolytic effect on CF sputum *in vitro*. The effect was found to be mediated via an interaction of heparin with DNA in the sputum and activation of endogenous DNases, leading to increased delivery of drugs through sputum [2]. These novel observations on the multi-modal pharmacological profile of heparin led to the filing of three patents in 2002. The observations also led to the development of novel dry powder formulations of heparin [3,4].

This research translated into a double-blind placebo-controlled clinical trial of inhaled heparin in patients with CF, conducted in 2002 in collaboration with the Wessex Regional CF centre at SGH [5]. Sputum samples were analysed at the UoP for sputum rheology and inflammatory markers. The research demonstrated that heparin improved the ability of CF patients to expectorate secretions with a positive impact on lung function, exercise capacity and quality of life. Importantly, this study also demonstrated the paradoxical safety of inhaled heparin in patients prone to hemoptysis (bleeding in to the airways).

Prof Shute found that immediately on contact with CF sputum, heparin lost its anti-coagulant activity, which was a critical discovery in the development of inhaled heparin as a treatment. Further work on the rheological characteristics of sputum from patients with COPD [6] demonstrated that inhaled heparin may be equally effective and safe in treating patients with COPD. Extending the reach of the project, in 2011 Prof Shute commenced an on-going collaboration with Professor Mario Cazzola on a clinical trial of inhaled heparin in patients with COPD at the San Raffaele Hospital in Rome.

In parallel, it was recognised that delivering drugs to the airways to achieve therapeutic concentrations in patients in whom viscous sputum restricts airflow, requires a device providing small (between 1 and 5 μm) particle sizes for effective delivery. Dr Marisa van der Merwe investigated particle size distribution and residual volume concentration of heparin solutions

delivered from standard devices (Pari LC Plus® and Pari e-flow Rapid® nebulisers), identified the optimum delivery device, the Pari LC Plus, for the novel inhaled route for heparin in subsequent studies and in the treatment of patients.

3. References to the research

The references to the underpinning research conducted at Portsmouth University include a background review of the context of the research, and five publications in peer-reviewed international journals in the fields of respiratory research and pharmaceutics. Funding for the research was provided by biomedical charities in the UK and Europe, including a multi-national study.

1. **Shute JK**. (2012) Glycosaminoglycans and cytokine/growth factor interactions. In: Lever, R., Mulloy, B. and Page, CP., eds Heparin: A Century of Progress. Handbook of experimental pharmacology (207). Springer-Verlag, Berlin, pp. 307-324. ISBN: 9783642230561

This chapter summarises developments over the past three decades in the field of heparin research that investigates heparin interactions with chemokines and growth factors and novel therapeutic interventions that target this interaction. Available on request.

2. Broughton-Head VJ, Shur J, Carroll MP, Smith JR, **Shute JK**. (2007) Unfractionated heparin reduces the elasticity of sputum from patients with cystic fibrosis. American Journal of Physiology: Lung Cellular Molecular Physiology; 293: L1240-1249. DOI: 10.1152/ajplung.00206.2007

In this study we showed for the first time the unexpected mucolytic properties of heparin relevant to the treatment of patients with CF.

3. Shur J, Nevell TG, **Shute JK**, Smith JR. (2008) The spray drying of unfractionated heparin: optimisation of the operating parameters. Drug Dev Ind Pharm; 34: 559-68. DOI 10.1080/03639040701657552

In this study, heparin was spray-dried to produce spherical micronised particles in the size range 1 – 5 µm, which is suitable for delivery by dry-powder inhalation. Spray drying parameters were optimized using a 2^4 factorial experimental design. Results showed that feed concentration and atomization spray flow rate have the greatest effect on recovery and particle size.

4. Shur J, Ewen RJ, Nevell TG, Smith AJ, **Shute JK**, Smith JR. (2008) Co-spray-dried unfractionated heparin with L-leucine as a dry powder inhaler mucolytic in cystic fibrosis. J Pharm Sci; 97(11): 4857-68. DOI 10.1002/jps.21362

In this study we showed that a combination of heparin with leucine was a stable formulation with good flow properties for delivery to the airways by dry powder inhaler, that also and most importantly, retained mucolytic activity against sputum from patients with cystic fibrosis. The superior physical properties of heparin combined with leucine indicate this is the preferred formulation for development as an inhaled mucolytic, and is the formulation of choice for clinical trials in patients with cystic fibrosis (evidence #9).

5. Serisier D, **Shute JK**, Hockey PM, Higgins B, Conway J, Carroll MP. (2006) Inhaled heparin in cystic fibrosis. Eur Respir J; 27:354-358. DOI 10.1183/09031936.06.00069005

This study was important because it showed that inhaled heparin did not affect blood coagulation parameters nor result in any increase in adverse events in adult patients with cystic fibrosis who are prone to hemoptysis (bleeding in to the airways). Therefore, inhaled heparin was safe and the future evaluation of larger doses over a longer period was warranted.

6. Serisier DJ, Carroll MP**, Shute JK**, Young SA. Macrorheology of cystic fibrosis, chronic obstructive pulmonary disease & normal sputum. Respiratory Research 2009; 10:63 DOI 10.1186/1465-9921-10-63

This paper demonstrated that the macrorheologic properties of whole, mucoid cystic fibrosis sputum are not different from normal. Instead, the high viscoelasticity of the sputum is related to secondary infection, decreases with intravenous antibiotic therapy and correlates with

inflammation. In contrast, COPD sputum demonstrates inherently greater viscoelasticity, providing a novel target for potential therapeutic interventions. This study was important as it identified COPD patients as potential beneficiaries of the new therapeutic approach.

Grants and Funding;
The Cystic Fibrosis Trust. Isolating a heparin-derived sequence to activate DNase I -a novel therapeutic approach to improve airway clearance, reduce infective exacerbations and facilitate delivery of inhaled drugs in cystic fibrosis. £45,000; 2005-2006. PI; Janis Shute, UoP
Italian Cystic Fibrosis Foundation. Identification of agents with multiple favourable activities as potential treatments for cystic fibrosis. Euro 45,000; 2010-2011. PI; A Naggi, University of Milan (a collaborative study between the Universities of Milan, Portsmouth and Liverpool
Charlotte Francis May Foundation. Nebulisation of IV drugs. £3,700; 2009-2011. PI; Marisa Van der Merwe, UoP.

4. Details of the impact

Obstructive airways diseases are of major clinical and economic importance and include chronic obstructive pulmonary disease (COPD) that affects 10% of the world's population and cystic fibrosis (CF), the most common lethal genetically inherited disease affecting Caucasian populations. There is an urgent unmet medical need for drugs to target mucus obstruction of the airways in diseases such as CF and COPD, where mucus obstruction restricts airflow, promotes infection and inflammation, and limits the delivery of other inhaled drugs with potential to cure or treat the underlying airway disease. Additionally, obstruction of the airway that occurs in Intensive Care settings and diseases of muscle weakness, such as motor neurone disease, present similar clinical problems. In these conditions, removal of obstructing secretions is vital to improve the delivery of inhaled drugs to treat the underlying disease.

Prior to 2001, Prof Shute was investigating the anti-inflammatory effects of heparin in sputum from patients with CF. At the time she was working closely with the CF consultants at Southampton General Hospital (SGH), which is the CF Centre for the Wessex region, covering a population of ~2.8m in Hampshire, Dorset, South Wiltshire, Jersey and the Isle of Wight. Her observation that heparin also had mucolytic effects was of immediate significance to the CF (Dr Mary Carroll) and COPD (Dr Peter Hockey) consultants, since it was known that chronic mucus hypersecretion and airway obstruction are significantly associated with an excessive decline in lung function and an increased risk of hospitalization. Further, there was a significant unmet clinical need for new therapies to increase mucus clearance from the airways in both CF and COPD patients. These findings led, in 2002, to the filing of three patents around the use of inhaled heparin (evidence #6), of which one has been granted, and the spin-out of Ockham Biotech Ltd (evidence #1) to facilitate the commercialisation of the IP.

Commercial impact is evidenced by the commercial investment for the projects described. Ockham Biotech Ltd who have invested more than £200,000 in the project to protect the patents (evidence #1) and the Italian pharmaceutical company Zambon S.p.A who have an option agreement with Ockham and invested €70,000 to support the project (evidence #2).
As a result of this research, the CF-specialist Pharmacist at SGH routinely prescribes inhaled heparin for off-label use (evidence #3) and Dr Hockey prescribes it for his COPD patients (evidence #4). Outcomes for these patient groups have improved and no adverse events are reported. The reach of this new approach has extended to Portsmouth Hospitals (evidence #5) where it is used in the intensive care setting, and further afield (evidence #3). Patients report an improvement in their symptoms and improved clearance of congested airways, which is an important outcome for patients, especially those with CF (evidence #8).

Intravenous drugs are generally nebulised for delivery to the airway to increase local concentration and drug efficacy and to reduce systemic side-effects when compared to IV treatment. Laboratory data showed that the anti-coagulant activity of heparin is neutralised by basic proteins in sputum, thus providing a convincing explanation for the surprisingly good safety data seen in the trial. Thus the multiple pharmacological properties of inhaled heparin ensure local mucolytic and anti-

inflammatory effects in the right tissue compartment, with no evidence of systemic side effects. Using the recommended device (see below) ensures effective delivery and decreases wastage of drugs, resulting in significant savings to the NHS.

Our results have shown that heparin is not delivered efficiently, if at all, from the new generation of Pari eFlow Rapid® nebuliser, although it can be delivered successfully from the Pari-LC Plus nebuliser. As a result of our research, IV preparations of heparin are now routinely prescribed for off-licence use by jet nebulisation in patients with CF and COPD in the Wessex region. In addition it is instilled through endotracheal tubes to assist mucus clearance, for example in patients with motor neurone disease in the intensive care unit at SGH.

Dr Shute's pioneering studies helped to overcome the reluctance of respiratory physicians to prescribe inhaled heparin and led to a subsequent far-reaching Phase II clinical trial of inhaled heparin in a dry powder form in CF, which was sponsored by Vectura PLC and conducted in the UK, Ireland, Poland, Australia and Italy in 2008-2010 (evidence #9). Inhaled heparin was reported to be safe and well tolerated, compliance was high, anti-inflammatory activity was demonstrated and sputum was easier to clear from the airways.

Impact Summary: This case study reports impact on health and welfare through the development of a new intervention to improve outcome for patient groups, as well as impact on commerce through creation of a spin-out business that has attracted international investment.

4. Sources to corroborate the impact

1. Letter from the CEO of Ockham Biotech Ltd (www.ockhambiotech.com)

2. Option agreement between Zambon, Milan, (www.zambongroup.com.) and Ockham Biotech Ltd

3. Letter from Adult CF specialist pharmacist at Southampton General Hospital on use of inhaled heparin in CF patients

4. Letter from COPD consultant regarding the use of inhaled heparin in COPD patients

5. Letter and monograph from Intensive care consultant regarding the use of inhaled heparin extended to Portsmouth Hospitals Trust and intensive care.

6. Patents filed in 2002;
   a) PCT/GB0300663 Glycosaminoglycans as a treatment for chronic airflow limitation. Granted in 2009.
   b) PCT/GB0300703 Combination therapy for respiratory disorders
   c) PCT/GB0300668 Glycosaminoglycan-DNase combination therapy

7. Wellcome Trust video (2008) describing Prof Shute's research, as one of five researchers in the UK making an impact of cystic fibrosis research. http://www.port.ac.uk/institute-of-biomedical-and-biomolecular-science/cell-biology-and-pharmacology/janis-shute/

8. See;
http://www.evidence.nhs.uk/search?q=%22What+is+the+evidence+for+the+use+of+nebulised+heparin+in+cystic+fibrosis%22 Prepared by Medicines Q&A pharmacist, Wessex Drug and Medicines Information Centre, Southampton General Hospital.

9. Details of the Phase II clinical trial of inhaled heparin in CF patients, (EudraCT Number 2007-006276-11), sponsored by Vectura PLC, may be found on the EU Clinical Trials Register at www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-006276-11. Results of the trial are reported on the Vectura website at http://www.vectura.com/product-pipeline/licensing-opportunities.aspx. Heparin is identified as VR496 on this page.