Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd | National Institute for Social Care and Health Research

Llywodraeth Cymru
Welsh Government

National Institute for Social Care and Health Research (NISCHR)

Health Fellowship Award 2014

Application form

SECTION A: Applicant details

Please refer to the full application guidance notes when completing this application form.

1. Project details

1a) Title of proposed research

Novel biomarkers and frequency of exacerbations in chronic obstructive pulmonary disease

1b) Lay summary (word limit: 300)

Chronic Obstructive Pulmonary Disease (COPD) is an umbrella term for people with chronic bronchitis, emphysema, or both. It is a preventable and treatable inflammatory lung disease which adversely affects many parts of the human body. COPD will become the third leading cause of deaths worldwide by 2030 where it currently affects up 3.5 million people in the UK with only 1 million diagnosed. In 2010 COPD cost the UK over £800 million per year in direct NHS costs alone and is the second commonest cause of hospital admission. The greatest burden for patients, carers and the whole healthcare system is sudden worsening of the condition of COPD patients (exacerbations). A proportion of COPD patients suffer regular exacerbations whilst others with similar lung function and chronic breathlessness do not. Around half of these exacerbations are triggered by bacterial or viral infection. As many patients do not return to the level of health they were at prior to the exacerbation they are more vulnerable and suffer further exacerbations leading to a rapid decline in health. Identifying early treatment of at risk patients is a high priority but using routine clinical data is not accurate enough. New research is required to identify biomarkers that can predict risk and early onset of exacerbations and there remains a lack of understanding of how bacterial and viral infections relate to the immune system and their role towards frequency and severity of exacerbations. We want to apply new molecular technologies to monitor people with COPD, to identify markers found at a local (lung) and systemic level (blood) that contribute to the risk of exacerbations and ultimately provide targets for both diagnosis and treatment.

2. Applicant details

Name:	Mr. Arwel Wyn Jones
Current job title:	Research Assistant
Institution:	Aberystwyth University and Hywel Dda Health Board
Contact address:	F.25, Carwyn James Building, Penglais Campus, SY23 3FD
Email:	awj7@aber.ac.uk
Telephone:	(01970) 622282

Please state the date on which you received your PhD/MD qualification.

In progress (submitted 9 Dec 2013)

Please state the number of months of post-doctoral research experience you have had since obtaining your PhD/MD qualification

N/A

3. Host Institution Details

Host Institution:	Institute of Human Sciences, Aberystwyth University
Contact address:	Carwyn James Building, Penglais Campus, Aberystwyth, Ceredigion, SY23 3FD
Telephone:	(01970) 621545
Finance Officer:	Emyr Reynolds
Email address:	ehr@aber.ac.uk
Telephone number:	01970 622257

4. Academic Mentor

Academic Mentor:	Chris Bridle
Job title:	Professor
Institution:	Aberystwyth University
Contact address:	F.13, Carwyn James Building, Penglais Campus, SY23 3FD
Email:	chb43@aber.ac.uk
Telephone:	(01970) 621947

Co-Academic Mentors

Academic Mentor:	Luis Mur
Job title:	Professor
Institution:	Aberystwyth University
Contact address	B2.03, Edward Llwyd Building, Penglais Campus SY23 3DA
Email::	lum@aber.ac.uk
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Academic Mentor:	Keir Lewis
Job title:	Associate Professor
Institution:	Swansea University and Hywel Dda Health Board
Contact address:	Respiratory Unit, Prince Philip Hospital, SA14 8QF
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5. Project cost and duration

Please enter the total cost of your project to NISCHR (up to 80% Full Economic Costs):

£257,539.91

Start date:
1/10/2014
End date:
31/09/2017

Please enter the Whole Time Equivalent (WTE) percentage at which you wish to undertake the fellowship:

3 years (100% WTE) ☑
4 years (75% WTE)
5 years (60% WTE)

6. Keywords/UKCRC classification

Keywords:

COPD	Metabolomics	Neutrophil
Immunity	Infection	Microbiome

UKCRC Health Research Classification System
Health category: Respiratory
Research activity code: 2.1, 2.4, 3.4, 4.1, 4.2,

7a. Previous NISCHR/WORD funding

- Direct project funding
- Member of NISCHR/WORD funded group/initiative

(Delete as appropriate)

Please give relevant details: (Word limit: 200)

I (the applicant) have received no previous funding through a NISCHR/Word funded research project or group/initiative.

Please see relevant details of academic mentor in grant sections of attached CV's.

7b. Career development (Word limit: 500)

The Department of Sport and Exercise Science of Aberystwyth University part of the Institute of Human Sciences at Abersytwuth University is a research active department with collaborations with other researchers (internal and external) and organisations. My research interests in neutrophil function and respiratory health as a doctoral research student led to being involved in external research with the Clinical Research Centre (CRC) of Prince Phillip Hospital in an investigation of neutrophil function in COPD patients. I am currently jointly funded as a Research Assistant by Aberystwyth University and Hywel Dda health to develop this research theme. Upon award of a NHS letter for access for research I have been responsible for the handling and analysis of blood and sputa at the Clinical Research Centre (based in Llanelli) as well as liaising with clinical colleagues in the intrepretation of patient data (e.g. medication) in relation to study findings.

In order to facilitate long-term goals of the Clinical Research Centre and the research group, Physical Activity in Ageing, Rehabilitation and Health of the Department of Sport and Exercise Science, activities need to be supported by grant capture. The research groups ('Diet and Health', 'Microbiology') of the Institute of Biological, Rural and Environmental Sciences (IBERS) at Aberystwyth University have an ongoing focus in the use of advanced high-end technology that can discern the role of novel biomarkers or microbes in health and disease (e.g. chemical fingerprints of lung cancer). In addition to assessing the response of innate (neutrophils) and adaptive human immunity (*in vivo* respones to novel antigens) to acute and chronic stress I have recently collaborated with IBERS on a project which showed that changes in bacteria levels in the oral cavity may mediate the incidence of upper respiratory tract infection.

I am keen to integrate the range of biochemistry and analytical techniques used in research in my early career with further development of skills in advanced high-end technology (e.g. metabolomics) to co-ordinate an investigation into COPD which can have immediate impact on disease management and improve future patient care. This award will strengthen the above, existing collaborations by promoting a regional network of COPD researchers in Wales. This is likely to attract interest from researchers and

commercial partners from outside Wales to the work of these organisations. On a personal level, the award will provide an opportunity to be mentored by leading experts in clinical medicine and health research as well as increase my profile as an early career researcher in an area that is held with high priority by the Welsh Government. The award will present further collaborative practices for myself and increase my interdisciplinary working in the NHS and academia beyond my current post as a research assistant with Institute of Human Sciences and Hywel Dda Health Board. By providing such an identity within the health and wealth of a Welsh society the award will allow me to build capacity within health research by developing investigations of the highest quality.

SECTION B: Institution details

8a. Departmental performance rating in most recent Research Assessment Exercise (RAE)

	Unit of Assessment	Staff Submitted (FTE)	By percentage, research activity in the submission judged to reach quality standard				
			4*	3*	2*	1*	UC
RAE 2008[1]	46	8	0%	15%	50%	35%	-
REF 2014[1] (External assessment)	26	10.2	18%	57%	25%	-	-
RAE 2008[2]	16	46.5	10%	35%	50%	5%	-
[1]Primary Host Department; [2]Secondary Host Department							

8b. Supporting information (Word limit: 200)

The Department of Sport and Exercise Science (DSES) was founded in 2002 with an initial investment of over £2,000,000, followed by purpose built laboratories in 2008 at a cost of £500,000. Since its foundation, DSES has invested in high-quality, research-active staff and postgraduate students, and comprises 12 academic staff (including three early career researchers), 13 PhD students and three post-doctoral fellows. Despite its relatively young age and small size, DSES has succeeded in developing a portfolio of high-quality, high-impact research of both national and international importance. This portfolio includes epidemiological studies in chronic conditions, research to guide service provision in rural settings, and clinical trials to inform treatment decision-making. Staff in DSES hold current research grants as PIs in excess of £1,500,000, and are co-applicants on active grants totalling more than £6,000,000. The current portfolio includes research funded by NIHR, RC-UK, EADS, and Wellcome Trust. The current application builds upon, and strengthens, our existing collaborative partnerships with the Institute of Biological, Environmental and Rural Sciences (Professor Mur), and Hywel Dda Health Board (Dr Lewis).

9. Contribution of Academic Mentor (Word limit: 300)

Professor Bridle (DSES) will be responsible for overall academic mentorship, with substantial relevant support from Professor Mur (IBERS) and Dr Lewis (HDHB). Bridle will provide mentorship for overall project management, and has substantial experience of leading large scale, multi-centre projects, including SARAH (8 centres), DAPA (12 centres) and PreFIT (60 centres) (see CV). Bridle is Director of Research at the host institute, and will provide mentorship for the development of an individual research plan that includes a clear pathway for future, linked research, as well as opportunities for engaging in impact activities and wider dissemination, including public health and patient groups.

Professor Luis Mur will provide logistical support and training to Mr. Jones to support post-genomic analyses of key biological events linked to COPD exacerbations. The Mur lab has extensive infrastructure in high resolution Mass Spectrometers to support varied projects focusing on metabolomics- the simultaneous measurement of 1000s of metabolites in a sample. These projects include screens for metabolite biomarkers in sputum linked to lung cancer. The Mur group will also support Mr. Jones experiments on microbiomic changes in in COPD sputa. This will employ the next generation sequencing Ion Torrent platform and will identify most bacterial species in a sample. Full bioinformatic support for data analyses will be provided.

Dr Lewis, is a Clinical Academic with an interest in biomarkers and COPD. He runs a specialist COPD clinic, developed the business case for Pulmonary Rehabilitation and smoking cessation services. As R&D Director in Hywel Dda, he heads the Clinical Research Centre in Prince Philip Hopsital and will identify and help recruit patents and supervise clinical environment, including leading on R&D and ethics permissions.

10. Training and development programme (Word limit: 300)

An individualised training and development programme will be implemented over the period of the fellowship. The precise content of the programme will be determined through two mechanisms: (1) a needs analysis approach, based on project demands, and assessed formally each year, and informally through ongoing mentorship contact, and (2) a career development approach, based on future generic skills. Thus the programme will support development of an independent researcher and will include courses, workshops and conferences relevant to methodology, dissemination, public engagement, knowledge transfer, and both laboratory and clinical based CPD.

Over the last 15 years, Biological Science has development multiple analyses platforms coupled with computational approaches which are allowing unprecedented insights to be gained. This programme will allow Mr Jones to develop and apply two such “post-genomic” approaches to reveal key microbial and biochemical changes which will be linked to COPD exacerbations. This will reveal key biological features which will represent biomarkers which could allow more accurate diagnosis and predict exacerbation events and responsiveness to treatment.

SECTION C: Project Details

11a. Priority policy area(s)

- Prevention and early intervention ☑
- Chronic conditions management ☑ (Delete as appropriate)
- Service organisation and delivery

Please describe how the proposed research addresses one or more of the policy areas indicated above (Word limit: 300):

Hywel Dda Health Board covers an urban and rural population in West Wales of ~ 385,000. Along with the Welsh Assembly, it has highlighted chronic disease (including COPD) as a major health priority. Further research is required into the management of COPD as the current prevalence (3.5 million) and progressive course of the disease has a major societal and economic burden.

Exacerbations of COPD (worsening of symptom severity beyond day to day variation) represent the greatest burden for patients and health care systems and are considered important targets for interventions. It is estimated that 50-60% of exacerbations are due to infection (mostly bacterial and viral). Even when the exacerbations resolve they have a negative impact on overall health and many patients do not achieve their pre-exacerbation health level. It is estimated that 30% of patients who are admitted to hospital can suffer a further exacerbation (or recurrent) within 8 weeks.

Despite optimisation in current pharmacological treatments (e.g. inhaled medications), there remain a large proportion of COPD patients who suffer frequent exacerbations. At present, the largest predictor for the incidence of exacerbations is history of previous exacerbation. In order to provide a greater understanding of the disease and enable the development of more effective treatment options the proposed research will aim to provide novel sensitive measures of disease characterisation and progression. This project (aligned with the Research and Development priority sector of the Welsh Assembly Government: Health and Biosciences) will build capacity within the COPD community by performing a longitudinal observation of frequent exacerbators and infrequent exacerbators of COPD patients. In accordance with Welsh Government (*Service Development and Commissioning Directives for Chronic Respiratory Conditions*) and NHS (*Outcomes strategy for COPD and Asthma*) this project will provide evidence-based care pathways and treatment targets to ensure timely assessment and diagnosis risk of exacerbations in COPD patients.

11b. Priority topic area(s)

Your project should address at least one of the topic areas listed below:

- cancer ☐
- cardio-respiratory/diabetes ☐
- genetics/genomics ☐
- infection, inflammation and immunity ☒
- neuroscience/mental health ☐
- primary care ☐
- public health ☒
- regenerative medicine ☐
- optometry ☐

12. Need and impact (Word limit: 300)

COPD is a major cause of chronic morbidity and mortality, where it is set to become the third leading cause of mortality worldwide by 2030. COPD is a preventable and treatable condition. However, at present the prevalence of COPD in the UK is estimated to be 3.5 million with the number of mortalities from the disease increasing. It is considered to be the second largest cause of emergency admissions in the UK and one of the most costly inpatient conditions treated by the NHS.

The most common reason for hospital admission in COPD is an acute exacerbation where the average cost of hospital stay in the local area (Hywel Dda) is comparable to the UK average of 6 days and costing around £2400 per patient. The total annual cost of COPD to the NHS is estimated to be over £800 million, equating to £1.3 million per 100,000 people. Current diagnosis and staging of COPD does not provide any information on the underlying causes of disease progression and/or acute worsening of symptoms (exacerbations). There is no single parameter that can be used with COPD patients as predictors of important clinical outcomes (e.g. exacerbations). The proposed project will use our expertise in immunology, metabolomics and microbiology and expand on our promising pilot work to identify markers which influence exacerbation frequency.

The outcomes will ultimately promote a ‘personalised medicine’ approach which will result in better use of NHS resources in a climate where there are rising demands in prescriptions and increases in ineffective treatment options (i.e. antimicrobial resistance). Improvement in the prescribing and management of treatments for COPD patients is likely to prevent the onset in deterioration of the disease thereby reducing hospital admissions, GP visits, lost working hours/productivity as a result of the disease and improve the quality of life of patients.

13. Detailed project description (Word limit: 3000)

13.1 Background

On the basis of published systematic reviews (Koutsokera et al., 2012; 2013), there is no single molecule at pulmonary or systemic level which has received wide clinical acceptance to predict incidence of COPD exaerbations. Furthermore, there are no parameters which clearly determine a change in exacerbation frequency (Donaldson et al., 2013). A previous non-interventional, longitudinal prospective three-year study of COPD patients and control participants (ECLIPSE) suggested the strongest predictor of exacerbations was previous history of exacerbations where such patients are considered to be a distinct phenotype (sub-group) known as the frequent exacerbator (Hurst et al., 2010). The parameters investigated in this study were limited to clinical parameters (e.g. lung function) or inflammatory mediators which provide little information towards underlying mechanisms in relation to the major trigger of COPD exacerbations (respiratory infection). Despite the well accepted role that some immune defences (e.g. neutrophils, Sapey and Stockley, 2006) or other markers of infection risk (bacterial colonisation, Wedzicha and Donaldson, 2003) have in the pathogenesis of COPD, there remains a lack of understanding in how these functional measures of the immune system or microbial colonisation differ in COPD patients of a frequent exacerbator phenotype versus an infrequent exacerbator of similar age and lung function. Metabolomics aims to create a 'global metabolic snapshot' of the system under investigation by simultaneously determining as many metabolites as possible without bias towards any particular group. Metabolomics approaches are well-establishing in clinical medicine being used often in biomarker discovery (Monterio et al., 2013). It has been suggested that an integrated approach of high-end technology (metabolomics) with other potential biomarkers will improve understanding of the underlying mechanisms contributing to COPD progression (Kelly et al., 2013).

13.2 Aims and objectives:

The overall objectives of this project goal are to develop the area of COPD research in Wales to generate scientific discoveries on disease mechanisms and phenotypic biomarkers of exacerbation frequency that will lead to improved future prevention and management strategies of disease progression. The project intends to achieve this by:

1. performing metabolomic analysis of sera and sputa that will provide insights into primary metabolism at a local and systemic level which will identify important pathways in inflammation and immunity that mediate frequency of exacerbations
2. validating the findings of pilot work undertaken in our laboratories which presents evidence of different neutrophil responses in sputa and blood of frequent exacerbators and infrequent exacerbators which have implications towards infection and inflammation.

3. undertake microbiome monitoring in sputa to identify bacterial species of that frequent exacerbators and infrequent exacerbators
4. investigating *in vivo* immune responses of frequent and infrequent exacerbators to pathogen challenge (influenza vaccination)

It is via the intended activities that this project will foster innovation and collaboration with other national and international experts in the field. In addition to the outcomes within this 3 year period, this project will initiate the development of a biobank of bodily fluids and tissue samples to improve the understanding of a disease which is set to become the third leading cause of mortality worldwide.

13.2 Design and methodology

13.2.1. Overview

The project will involve a longitudinal, prospective, cohort study. Following written informed consent, all enrolled participants will be asked to attend a nearby hospital to provide a blood and sputum sample at 6 timepoints within an 18 month period (Figure 1). These timepoints will include September 2015 (baseline), December 2015 (3 months), March 2016 (six months), September 2016 (12 months), December 2016 (15 months) and March 2017 (18 months) to provide a closer monitoring of patients than the previous investigations (ECLIPSE cohort). As the aim of this is to determine parameters that are relevant to frequency of exacerbations, the 18 months has been designed to incorporate two winter period where prevalence of excaerbations and repisratory infections are at their greatest (Donaldson and Wedzicha, 2006, Jenkins et al., 2012).

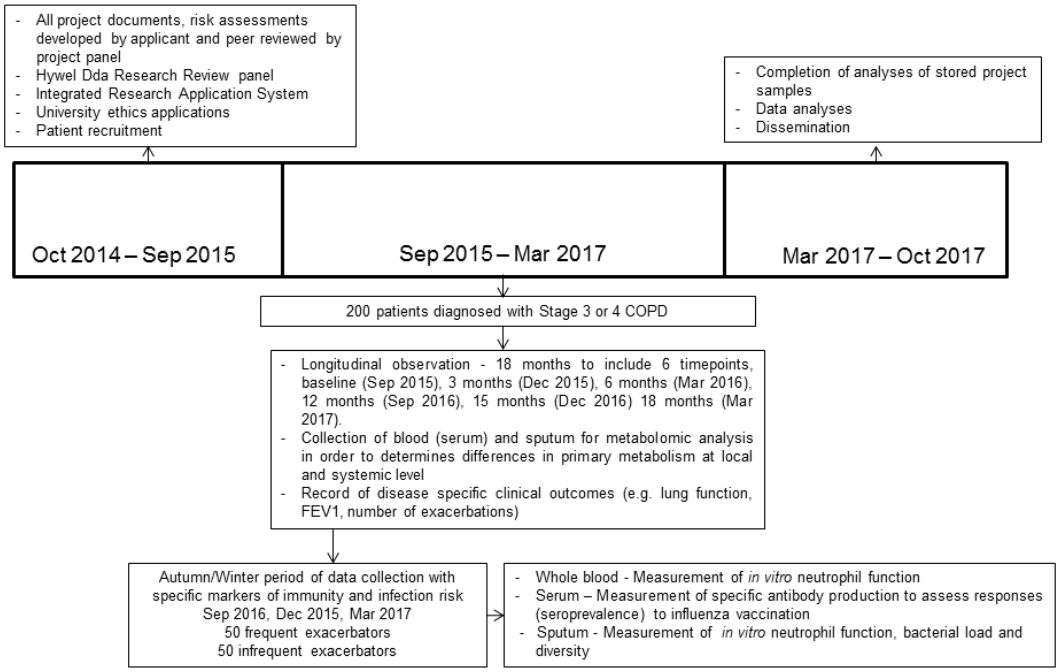

Figure 1) Schematic outline of the 3 year project

13.2.2. Patients

According to Welsh Survey data from of the Public Health Wales Observatory, using Welsh Health Survey data ~ 8% (30005) of patients treated by Hywel Dda have COPD which equates to 14452 alone in the Carmarthenshire region. We will identify potential participants from the relevant databases of the respiratory centre, respiratory outpatient clinics and Clinical Research Centre of Prince Phillip Hospital as well as primary care services and six General Practices (Patient Identification Centres) in the Llanelli area (Adfer x 2, Avenue Villa, Llangenech, Ty Elli x 2). Based on estimates provided by these services we expect at least 2000 of these patients to have been diagnosed with moderate to severe COPD (GOLD stage 3 or 4). Potential participants will be screened using medical notes, pulmonary rehabilitation database, COPD research data base clinic records and/or clinical consultations, for initial eligibility by Dr Keir Lewis, Associate Professor, Swansea University and Honorary Chest Consultant at Prince Phillip Hospital. We will exclude those with mild (stage 1 or 2) COPD, co-existent asthma, bronchiectasis, pulmonary fibrosis, any cancer (except non-melanotic skin cancer), severe renal failure (CKD3 or more), liver failure, anyone taking immunosuppressive medications, known to be HIV positive, Hepatitis BCD E positive, sputum MRSA positive or having treatment for tuberculosis. Potential participants will be contacted by letter (addressed from both the hospital and Institute of Human Sciences) by the applicant to ask to volunteer for the project.

Given the exploratory nature of metabolomics the project will aim to recruit a cohort of 200 patients (costings based on this) which is only 10% of the total number of stage 3 and 4 patients in the Llanelli area. We have planned for a recruitment period of 6 months (Mar 2015 – Sep 2015) following ethical and R&D permissions, giving an overall target of 33.3 patients per month. Patients start date will be reflected by their recruitment date (i.e. patients recruited first, will commence the study at the start of September 2015). Previous evidence suggests that the proportion of stage 3 and 4 COPD patients who are frequent exacerbators is 33% and 47% respectively (Hurst et al., 2010). Therefore we recognised the main cohort of 200 would provide a sufficient number of patients (80 frequent excaerbators and 120 infrequent exacerbators) to meet the power calculations of the measure performed in our pilot study (see below).

As defined elsewhere (Wedzicha et al., 2013), the frequency of exacerbations in the first 12 month period of data collection will form the basis of dividing patients into sub-groups: frequent: ≥ 2 exacerbations per year, infrequent < 2 per year). For a two-tailed test with alpha level (type I error rate) set at 0.05, and power (Type II error rate) set at 0.8, it is estimated that a sample size of 82 and 90 participants (n = 41 or 45 in each group) is required to detect a significant difference (Cohen's *d* effect size: 0.6 and 0.5) between groups in neutrophil responses in blood and sputa respectively. One hundred patients from the main cohort (50 frequent and 50 infrequent in each sub-group) will be involved in the procedures to meet project objectives 2 3 and 4. Please

note that this does not require any additional visits but rather at the timepoints of 12 months, 15 months and 18 months the samples of these 100 patients will be assessed for markers of immunity, inflammation and infection risk (see sections, 13.2.3.2, 13.2.3.3, 13.2.3.4) and thus provide a greater understanding of underlying mechanisms of disease worsening/progression.

13.2.3 Procedures

13.2.3.1 Procedures for project objective 1

Blood (serum) and sputa will be collected at these timepoints and put through the high-throughput/high sensitivity of metabolomics approaches (Fourier Transform Infrared spectroscopy and direct-infusion – electrospray-ionisation – Mass spectroscopy on a Micromass LCT mass-spectrometer) to simultaneously and accurately measure hundreds of metabolites.

13.2.3.2 Procedures for project objective 2

Whole blood will be analysed for *in vitro* stimulated neutrophil oxidative burst response in blood and sputa using a commercially available kit (ABEL, Knight Scientific Ltd, Plymouth, UK) as done previously (Davison, 2011; Davison and Diment, 2010; Jones et al., 2013). Pilot work on the assay carried out by this research team suggests that frequent exacerbators compared to infrequent exacerbators have an enhanced response to bacteria in sputa, lower bacterial-stimulated responses in blood but higher basal (unstimulated) activity in blood. These may suggest that those with a greater frequency of exacerbations have a diminished ability to respond to pathogenic challenge in blood but display greater levels of circulating inflammation at rest and over-exaggerated responses to bacteria in sputum. This project will validate whether this highly sensitive assay can distinguish between frequent exacerbators and infrequent exacerbators.

13.2.3.3 Procedures for project objective 3

This involves the extraction of bacterial DNA from the pellet produced upon centrifugation of a sputum sample, followed by amplification and quantification of a bacterial gene (16S rRNA) by quantitative polymerase chain reaction (measure of total bacteria load). Recent evidence from our laboratories in Aberystwyth University suggests that salivary bacterial load follows a seasonal-pattern (Jones et al., 2013; Cameron et al., unpublished data). One of these studies (Jones et al., 2013) proposed that rather than causing respiratory illness *per se*, an increase in bacterial load is indicative of a compromised innate immune status, and as such is a relevant marker of *in-vivo* (innate) immune status at the site that most pathogens enter the body. It may be that increases in certain species within the total bacterial population are important triggers for exacerbation. Indeed, changes in bacterial colonisation in tissues within the airway have previously been considered to influence frequency of disease exacerbations (Wedzicha and Donaldson, 2003). To investigate this further we will exploit the next-generation sequencing ion torrent platform to describe the microbiome (i.e. bacterial species) of frequent and infrequent exacerbators. Microbiomic approaches

allow the low-cost high-throughput sequencing of every bacterial gene (16S rRNA) based on which the identities of most bacteria in a sample can be established.

13.2.3.4 Procedures for project objective 4

One of the main recommendations for preventative care in COPD patients is a yearly influenza vaccination to reduce the risk of hospitalization, morbidity, and mortality. Sera will be used to determine the response of the body to a model infection (i.e. influenza vaccine, killed or attenuated pathogens). This approach is considered to have high biological relevance, sensitivity and feasibility (Albers et al., 2005). Virus antibody neutralisation assays, which essentially measure the level of antibody in serum against specific strains (seroconversion) contained in the influenza vaccine of that autumn/winter period, will provide an *in vivo* indicator of how the frequent exacerbators and infrequent exacerbators of COPD respond to pathogen challenge within a well-controlled scientific investigation. The main advantages of this approach are that influenza vaccinations are recommended for the study population as part of a national vaccination schedule (at same time of year) and it would allow for *in vivo* adaptive (specific) immune responses to pathogens to be measured without eliciting symptoms of disease that would result from primary infection (Albers et al., 2005). The antigen specific immune responses would provide substantially more information about host defence than measuring circulating protein/inflammatory messengers (i.e. cytokines) that is common within the area of COPD. As the protection provided by a vaccination depends on immunocompetence at time of receiving the dose, this pilot investigation would determine whether differences in frequency of exacerbation may be related to the ability of the host to respond to pathogen challenge.

We propose that the outlined project of monitoring *in vivo* immune function from both an innate (microbiome) and adaptive (vaccination) immune perspective will account for the complex and integrated nature of immune defences that influence susceptibility to exacerbation in the COPD patients.

13.3 Use of resources:

All analyses will use equipment and methodology already developed at the sites of the research team:

- Department of Sport and Exercise Science, Institute of Human Sciences, Aberystwyth University
- Clinical Research Centre; Prince Phillip Hospital, Llanelli
- Institute of Biological Environmental and Rural Sciences, Aberystwyth University

Sputum and blood (venepuncture) will be collected and processed by the applicant according to standard operating procedures already developed by the applicant (at the Clinical Research Centre and Department of Sport and Exercise Science) and published methods (Alexis et al., 2000). All samples will be collected by the applicant at the Clinical Research Centre. The only

analyses that will be performed immediately upon collection of samples is the measurement of *in vitro* neutrophil oxidative burst on site (September 2016 – March 2017) and measurements of neutrophil count (total and differential leukocyte count) obtained by a haematology analyser at the Prince Phillip Hospital.

All other remaining samples (serum, sputum) will be stored at facilities in the Clinical Research Centre of Prince Phillip Hospital until later analyses. Samples (sputa and sera) from the Clinical Research Centre will be transported to the laboratories of Prof. Luis Mur at the Institute of Biological Environmental and Rural Sciences; Aberystwyth University. These samples will be analysed by the applicant under the guidance of Prof. Luis Mur, a leading expert in advanced, high-end biological analysis, for example, currently employing oral/sputum bacterial load and metabolomic approaches to understanding respiratory malignancies such as lung cancer and COPD, and extreme stress as part of one of the scientific teams linked to Sir Ranulph Fiennes "Coldest Journey" expedition (White Mars project) (http://www.thecoldestjourney.org/). Serum will also be transported by the applicant to the Department of Sport and Exercise Science for the assessment of responses to the seasonal vaccination. This analysis (bacteria load, antibodies, metabolomics) will be completed between each timepoint and/or following the last timepoint.

All patients will be reimbursed for their travel to the. Costs of this travel (6 visits each for 200 patients) have been estimated at 40p per mile (by car) within a 15 mile radius of Prince Phillip Hospital as well as additional cover for public transport. Costs for the applicant to travel (same rate per mile) to the Clinical Research Centre are based on his present home in Aberystwyth and close family near Llanelli. For each timepoint, the applicant expects to complete data collection over 20 days (4 weeks) in line with number of patients seen per day in pilot study (10 patients per day). This equates to a total of 24 return (4 weeks at each of the 6 timepoints) journeys. Travel and subsistence costs for attendance of applicant at scientific meetings/conferences (outlined in section 13.6) have also been included in year 3.

13.4 Method of analysis

13.4.1 Method of analysis (project objective 1)

Metabolite data would be analysed using principal components analysis following accepted Metabolomics Standard Initiative procedures (Sansone et al., 2007). Heat-mapping, hierarchical cluster analysis and preliminary univariate statistical analysis would be completed on the metabolomic data using MetaboAnalyst 2.0 (Xia et al., 2012). Multivariate statistics, including principal component analysis and discriminant function analysis would be performed using PyChem software (Jarvis et al., 2006). Following statistical analyses, tentative identification of metabolites of interest would be achieved through interrogation of the Human Metabolome Database (Wishart et al., 2009).

13.4.2 Method of analysis (project objective 2, 3 and 4)

Statistical analysis of all data will be performed via the statistical computer software package SPSS (v21.00 or later version; SPSS Inc., Chicago, IL, USA). Statistical significance would be accepted at $p < 0.05$. Data not normally distributed will be normalized with log or square root transformation before further analysis. Initially, a two factor mixed model ANOVA (group × time) will be carried out on all immunological measures (immune cell counts, oxidative burst, salivary bacterial load, vaccine specific antibody production) to determine if measurements at any point within the study were different between frequent exacerbators and infrequent exacerbators. Any significant main effects identified in the ANOVA, would be further analysed by post-hoc independent or paired t-tests with Holm Bonferoni correction. One way ANOVA on each group would also be performed where there is evidence of group × time interaction (i.e. differences in temporal pattern between groups). In addition to the comparisons between frequent exacerbators and infrequent exacerbators, the above measures (neutrophil function, antibody, bacterial load) will be scrutinised with further analyses via Bland-Altman plots and regression models (e.g. Spearman correlation) to assess for reproducibility and relationships of these potential biomarkers with clinical parameters (e.g FEV1, frequency of exacerbations) respectively.

13.5 Expected outcomes and impact:

The major impact of this project is to provide novel treatment targets in a move towards 'personalised medicine'. The early identification, subsequent better management of COPD will not only lead to longer, healthier working and healthier retired populations but lead to significant lower levels of mortality and morbidity (e.g. exacerbations) that are particularly costly to the health and health care budget in Wales. The specific outcomes and impact of each project objective are provided below.

13.5.1. Outcomes and impact (project objective 1)

Metabolomic analysis at a local and systemic level will provide greater understanding of pathways important in inflammation and infection in COPD patients. It will identify the effectiveness and/or usefulness of pharmacological treatments (e.g. inhaled steroids, antibiotics) in COPD patients of varying stages of disease severity. For example, it may indicate why some COPD patients respond to inhaled corticosteroid treatment and others do not (Crim et al., 2009), including changes in primary metabolism that explain why inhaled corticosteroid treatment induces an increased risk of pneumonia (Janson et al., 2013).

13.5.2 Outcomes and impact (project objective 2)

The comparison of neutrophil responses in sputa and blood of frequent exacerbators and infrequent exacerbators will increase the understanding of infection risk and inflammation. The project will validate neutrophil responses and provide better phenotyping of those most at risk of COPD exacerbations.

Such phenotypes will promote targeted treatments and/or early treatment for patients at high risk of exacerbations (e.g. high risk patients can be prioritised on waiting lists for pulmonary rehabilitation treatment). The measurement of the above neutrophil responses are now available as a quantifiable and reproducible assay that can be performed close to the patient on a portable luminometer (ABEL-Meter). The test has been validated for many years in elite sport to predict or diagnose infection with common pathogens (Knight et al., 2013) but it has yet to be applied to the clinical setting. Despite being based on same principles as the assay proposed in the project, this platform is a means by which to translate the use of this measure from the laboratory into a point of care measure in clinical practice.

13.5.3 Outcomes and impact (project objective 3

Microbiome analysis of sputa will demonstrate the role of bacterial colonisation in COPD and identify which species are most important to determine risk of frequent excaerbations. These microbial markers will promote targeted antibiotics to reduce the risk of antimicrobial resistance. Such targeted treatment will reduce hospital wastage and shorten hospital (i.e. more effective treatment), all of which reduces the economic burden of prescription costs to the NHS.

13.5.4. Outcomes and impact (project objective 4)

Investigation of responses to vaccination will identify any differences in immmunocompetence (*in vivo* immunity) under pathogen challenge between COPD patients. It will indicate whether there is a need to modify vaccinations schedules in order to target those COPD patients at higher risk of morbidity (e.g. frequent exacerbators) in the first wave of vaccines or provide booster vaccinations towards any pandemic or epidemics of infectious diseases.

13.6 Dissemination:

To ensure transparent and efficient reporting of project results, dissemination will be conducted in accordance with recommended guidelines from the EQUATOR network. In addition to any final report required as part of this fellowship to NISCHR, this project is likely to be disseminated by a range of other sources. As the collective aim of this project will be to generate scientific discoveries on mechanisms and phenotypic biomarkers of COPD, one of the major areas of dissemination will be scientific publications in high impact journals**.**

Examples of potential publications from this proposed project include:

- **‘** Metabolic profiling of the frequent exacerbation phenotype of COPD’
- ‘ Evaluation of neutrophil oxidative burst as a biomarker for COPD’
- ‘Association of sputum microbiome markers with COPD exacerbation’

In addition to publications in scientific journals, the applicant will aim to disseminate this work to academic and clinical colleagues at National (Welsh Thoracic Society), European (European Respiratory society) and International (American Thoracic Society) conferences/meetings (during year 3) which occur on a yearly basis.

Given the nature of the proposed work to perform measurements on actual patient-centred outcomes under real world conditions, it is likely that the evidence gathered will be disseminated to health care professionals to make more informed decisions regarding patient management and care pathways. The proposed project on COPD will complement a recent EU award looking at telehealth interventions and self-management of COPD at the Clinical Research centre of Prince Phillip Hospital. Having researchers within the same research centre will allow cross-fertilisation of ideas and future collaborations where biomedical tests to identify those at high risk of exacerbations and hospitalisations could allow most efficient use of limited resources in telehealth monitoring to support and maintain the most vulnerable in their own environment. In addition to health professionals findings will be disseminated to relevant charities including their respective local support groups (e.g. Breathe Easy, British Lung Foundation). The expected outcomes form this project (e.g. vaccination responses in patient sub-groups) has public health and health protection implications. Therefore it will be eessentialthat project results are disseminated to the appropriate agencies (e.g. Public Health Wales, Health Protection Agency) to maintain an effecient service and so that actions are prioritised to combat health inequalities.

14. Timetable and milestones

Please give an indicative timetable for the project including key milestones and outputs (please add more rows if necessary)

Date	Milestones and/or outputs
March 2015	Completion of all ethical approvals
September 2015	Completion of patient recruitment and start of experimental period
September 2016	Commence additional analyses for markers of immunity inflammatory and infection risk
Mar 2017	Completion of all data collection
Mar 2017-October 2017	- Completion of laboratory and data analyses of stored samples - Dissemination (as outlined in section 13.6)

15. Patient and Public Involvement (PPI) (Word limit: 300)

Patient feedback from an existing portfolio study, Medlung (UKCRN 4682) and a pilot study (REC reference number:10/WMW01/30) at the Clinical Research Centre has contributed to the development of the protocol. The Involving People Network has been contacted regarding this research and we will be looking to involve patients with COPD in designing the patient information sheets and consent forms. It is expected that these will involve one frequent exacerbator and one infrequent exacerbator. These will be asked to a project panel along with two clinicians (Dr. Keir Lewis and one other independent clinician) and one staff member from the Hywel Dda Research and Development team and Institute of Human Sciences. This panel will have an annual meeting to discuss issues relevant to the project (ethical considerations, dissemination) at facilities in the clinical research centre. The total involvement (including meeting and reviewing of patient information sheets and consent forms) of the two aforementioned patients will be 5 full days (costs have been included for this involvement at a rate of £150 for a full day as recommended by Involving groups).

All documents within this project will also be reviewed by lay members (part of the ethics committee) to ensure that they are understandable to the patient. This project has been discussed with representatives from the Respiratory department within Hywel Dda Health board to assess whether the number and duration of visits is achievable and has been adjusted according to schedule of data collection (i.e. patients per day) within the pilot study. During the course of the study patient feedback, including any reasons for not taking part will be recorded and monitored. If needed the protocol will be amended in light of this feedback.

16. Ethical considerations and approvals (Word limit: 300)

The project proposes a total of 5 months for completing all documents necessary for ethical approval at NHS and University level. This is deemed achievable following experience of the research team in both type of submissions. Research Ethics Committee Permission (Integrated Research Application System) will be obtained following review by the Hywel Dda Health Board research review panel. Permission will be sought from Hywel Dda Health Board research and development department via the permissions coordinating unit. No research will be undertaken until full research governance approval is provided.

This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice; whichever represents the greater protection of the individual. All patients involved in the study will be provided with an information sheet and have the opportunity to discuss the study with

a member of the research team prior to providing written informed consent.
All samples will be collected and stored in accordance with the study protocol and previously developed standard operating procedures and risk assessments at respective sites. Members of the research team are experienced and trained in research guidelines. Patients will be seen within the hospital in a dedicated research space (i.e. Clinical Research Centre of Prince Phillip Hospital). The investigators are will retain study records for up to 10 years in accordance with standard archiving procedure for the health board.

17. Resources

Please state the level of Full Economic Costs you are seeking: 80% of £321,924.89

NISCHR will pay up to 80% of Full Economic Costs. This table should show the costs of your application *to NISCHR*:

	Resource	Year 1 £	Year 2 £	Year 3 £	Year 4	Year 5	TOTAL £
Directly incurred	Staff						
	Arwel Jones	*31988.08*	*32961.87*	*33965.99*			*98915.94*
	Travel and subsistence	2267.20	6688.80	8011.52			16967.52
	Equipment						
	Consumables	960.00	8011.73	21052.80			30024.53
	Other (PPI involvement)	480.00	240.00	480.00			1200.00
Directly allocated	Staff						
	Chris Bridle	*3417.96*	*3417.96*	*3417.96*			*10253.88*
	Luis Mur	*3417.96*	*3417.96*	*3417.96*			*10253.88*
	Keir Lewis	in-kind	in-kind	in-kind			
	Estate costs	7967.11	7967.11	7967.11			23901.33
	Research facilities/ equipment	839.67	839.67	839.67			2519.01
	Indirect costs	21167.94	21167.94	21167.94			63503.82
	Exceptions						
	VAT (if applicable)						
	TOTAL	72505.92	84713.04	100320.95			257539.91

18. Other applications for funding

Date submitted	Funding body	Title	Value	Date outcome will be known

SECTION D: Declarations

19. Declarations and CVs

a) Applicant

I declare that I have completed the application form in accordance with the guidance notes and confirm that the information provided is accurate to the best of my knowledge.

FULL NAME Arwel Wyn Jones

INSTITUTION Institute of Human Sciences, Aberystwyth University

SIGNATURE *Please see hard copy*

Date

b) Academic Mentor

I declare that I will participate in the project described in this document as an Academic Mentor should the application be successful.

FULL NAME Chris Bridle

INSTITUTION Institute of Human Sciences, Aberystwyth University

SIGNATURE *Please see hard copy*

Date

b) Co-Academic Mentor

I declare that I will participate in the project described in this document as an Academic Mentor should the application be successful.

FULL NAME Luis Mur

INSTITUTION Institute of Biological Environmental and Rural Sciences, Aberystwyth University

SIGNATURE *Please see hard copy*

Date

b) Co-Academic Mentor

I declare that I will participate in the project described in this document as an Academic Mentor should the application be successful.

FULL NAME Keir Lewis

INSTITUTION Swansea University and Hywel Dda Health Board

SIGNATURE

Please see hard copy

Date

Declaration by Institution:

(This application should be submitted through the Applicant's Head of Department and the Administrative Authority who will be responsible for grant administration within the Applicant's institution. Each should sign the following declaration)

I confirm that I have read this application and that, if this application is successful, the work will be accommodated and administered within this body in accordance with the terms and conditions that will form the contractual obligations. All costs are correct and in accordance with the normal practice of this institution.

	Head of Department	Administrative Authority
Name and initials	Bullen K	Reynolds E
Title	Professor	Mr
Institution	Aberystwyth University	Aberystwyth University
Address	P5, Institute of Human Sciences	Research, Business & Innovation, Visualisation centre
Contact number	(01970) 622688	(01970) 622257
Signed	*Please see hard copy*	*Please see hard copy*
Date		

References

Albers, R., Antoine, J. M., Bourdet-Sicard, R., Calder, P. C., Gleeson, M., Lesourd, B., Samartin, S., Sanderson, I. R., Van Loo, J., Vas Dias, F. W. and Watzl, B. (2005). Markers to measure immunomodulation in human nutrition intervention studies. *British Journal of Nutrition*, **94**, 452-81.

Alexis, N., Ghio, A., Soukup, J. and Becker, S. (2000). *Sputum phagocytes from healthy individuals are functional and activated: a flow cytometric comparison with cells in bronchoalveolar lavage and peripheral blood.* Clinical Immunology, **97**, 21-32.

Crim, C., Calverley, P.M.A, Anderson, J. A.,Celli, B., Ferguson, G. T., Jenkins, C., Jones, P. W., Willits, L. R., Yates, J.C. and Vestbo, J.(2009). Pneumonia risk in COPD patient receiving inhaled corticosteroids alone or in combination: TORCH study result. *European Respiratory* Journal, **34**, 641–647.

Davison, G. (2011). Innate immune responses to a single session of sprint interval training. *Applied Physiology Nutrition and Metabolism*, **36**, 395-404.

Davison, G. and Diment, B. C. (2010). Bovine colostrum supplementation attenuates the decrease of salivary lysozyme and enhances the recovery of neutrophil function after prolonged exercise. *British Journal of Nutrition*, **103**, 1425-1432.

Donaldson, G. C., Müllerova, H., Locantore, N., Hurst, J. R., Calverley, P. M., Vestbo, J., Anzueto, A.and Wedzicha, J. A. (2013). Factors associated with change in exacerbation frequency in COPD. *Respiratory Research*, 14, doi: 10.1186/1465-9921-14-79.

Donaldson, G. C. and Wedzicha, J. A. (2006). *COPD exacerbations .1: Epidemiology.* Thorax, **61**, 164-8.

. Hurst, J.R., Vestbo, J. Anzueto, A., Locantore, N., Müllerova, H., Tal-Singer, R., Miller ,B., Lomas, D. A., Agusti, A., Macnee W, Calverley, P., Rennard, S., Wouters, E. F. and Wedzicha, J. A. (2010) Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *New England Journal of Medicine*, **363**, 1128-38.

Janson, C., Larsson, K., Lisspers, K. H., Ställberg, B, Stratelis, G., Goike, H., Jörgensen, L. and Johansson, G. (2013). Pneumonia and pneumonia. related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting beta2 agonist: Observational matched cohort study (PATHOS). *British Medical Journal*, **346**, f3306. f3306. doi: 10.1136/bmj.f3306.

Jarvis, R. M., Broadhurst, D., Johnson, H., O'Boyle, N. M. and Goodacre, R. (2006). PYCHEM: a multivariate analysis package for python. *Bioinformatics*, **22**, 2565-6.

Jenkins, C. R., Celli, B., Anderson, J. A., Ferguson, G. T., Jones, P. W., Vestbo, J., Yates, J. C. and Calverley, P. M. (2012). Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *European Respiratory Journal*, **39**, 38-45.

Jones, A. W., Cameron, S. J. S., Thatcher, R., Beecroft, M. S., Mur. L. A. J. and Davison, G. (2013). Effects of bovine colostrum supplementation on

upper respiratory illness in active males. *Brain Behavior and Immunity*, doi: 10.1016/j.bbi.2013.10.032.

Kelly, E., Owen, C. A., Pinto-Plata, V. and Celli, B. R. (2013). The role of systemic inflammatory biomarkers to predict mortality in chronic obstructive pulmonary disease. *Expert Review in Respiratory Medicine*, **7**, 57-64.

Kim, E. J., Huws, S. A., Lee, M. R. F., Wood, J. D., Muetzel, S. M., Wallace, R. J. and Scollan, N. D. (2008). Fish oil increases the duodenal flow of long chain polyunsaturated fatty acids and trans-11 18 : 1 and decreases 18 : 0 in steers via changes in the rumen bacterial community. *Journal of Nutrition*, **138**, 889-896.

Knight, J., Wakeman, M. and Reeves, J. (2013). International Sports Science + Sports Medicine Conference 2013, Newcastle: UK.

Koutsokera, A., Kostikas, K., Nicod, L. P. and Fitting, J. W. (2013). Pulmonary biomarkers in COPD exacerbations: a systematic review. *Respiratroy Research*, **14**, [Epub ahead of print].

Koutsokera , A. Stolz, D., Loukides, S. and Kostikas, K. (2012). Systemic biomarkers in exacerbations of COPD: the evolving clinical challenge. *Chest*, 141, 396-405.

Monteiro, M. S., Carvalho, M., Bastos, M. L. and Guedes de Pinho, P. (2013). Metabolomics analysis for biomarker discovery: advances and challenges. *Current Medicinal Chemistry*, **20**, 257-71.

Sansone, S. A., Fan, T., Goodacre, R., Griffin, J. L., Hardy, N. W., Kaddurah-Daouk, R., Kristal, B. S., Lindon, J., Mendes, P., Morrison, N., Nikolau, B., Robertson, D., Sumner, L. W., Taylor, C., van der Werf, M., van Ommen, B. and Fiehn, O. (2007). The metabolomics standards initiative. *Nature Biotechnology*, **25**, 846-8.

Sapey, E. and Stockley, R. A. (2006). *COPD exacerbations . 2: aetiology.*Thorax, **61**,250-8.

Wedzicha, J. A. and Donaldson, G. C. (2003). Exacerbations of chronic obstructive pulmonary disease. *Respiratory Care*, **48**, 1204-15.

Wishart,D.S., Knox,C., Guo,A.C., Eisner,R., Young,N., Gautam,B., Hau,D.D., Psychogios,N., Bouatra,S., Mandal,R. et al. (2009) HMDB: a knowledgebase for the human metabolome. Nucleic Acids Res., **37**, 603–610.

Wedzicha, J. A., Rabe, K. F., Martinez, F.J., Bredenbröker, D., Brose, M., Goehring, U. M. and Calverley, P. M. (2013). Efficacy of roflumilast in the COPD frequent exacerbator phenotype. *Chest.*, **143**, 1302-11.

Xia, J., Mandal, R., Sinelnikov, I. V., Broadhurst, D., and Wishart, D. S. (2012). MetaboAnalyst 2.0 – a comprehensive server for metabolomics data analysis. Nucleic Acids Res. **40**,127–133

Applicant CV

Personal details

Title: Mr

Name: Arwel Wyn Jones

Post-doctoral research experience:

Research Assistant (1.0 FTE) September 2013 – present
Institute of Human Sciences (Aberystwyth University) and Hywel Dda Health Board

- Responsible for conducting research and production of manuscripts (e.g. exercise intervention in COPD patients, effects of inhaled corticosteroids on neutrophil function of COPD patients)
- Establish effective working relationships with health professionals, academics and support staff
- Develop grant applications to support the research activities of Aberystwyth University and Hywel Dda Health Board
- Produce report and publications at levels appropriate to the stakeholders

Qualifications:

2010-2013 **Aberystwyth University**
PhD (thesis submitted) – *'Effects of bovine colostrum on immune responses following prolonged exercise and upper respiratory illness*

This project explored the effects of acute and chronic bovine colostrum supplementation on *in vitro* and *in vivo* immune markers, oral microbiome and incidence of upper respiratory tract infection at rest and following prolonged exercise.

Funded by a Knowledge Enterprise Skills Scholarship (KESS). KESS is part-funded by the European Social Fund through the European Union's Convergence Programme (West Wales and the Valleys) and administered by the Welsh Government. This project was supported by an external partner, The Golden Dairy Ltd (supplier for Neovite UK).

2007-2010 **Aberystwyth University**
BSc (Hons) Biology & Sports Science
First class degree classification

Work history: *(please provide relevant dates and description of role/s)*

2010-2013 Teaching assistant and lab demonstrator for undergraduate students
Department of Sport and Exercise Science, Aberystwyth University

Publications:

Jones, A. W., Cameron, S. J. S., Thatcher, R., Beecroft, M. S., Mur. L. A. J. and Davison, G. (2013). Effects of bovine colostrum supplementation on upper respiratory illness in active males. *Brain Behavior and Immunity*, doi: 10.1016/j.bbi.2013.10.032.

Curtis, F., Oliver, E. J., Jones, A. W., Rice, S. and Thatcher. (2013). Health and lifestyle changes associated with ageing in rural communities: the emphasis on current concerns in Wales (Welsh Article). *Gwerddon*, 16, 28-39.

Awards:

- Entrance Scholarship to Aberystwyth University (2007)
- Student Award for the Top Bioscience Undergraduate Student at Aberystwyth University (2010)

Professional Memberships:

- Society of Biology (Associate)
- Physiological Society (Affiliate)
- British Association of Sport and Exercise Sciences
- International Society of Exercise Immunology

Teaching Activity:

Module coordinator for SS32620 Sport and Exercise Nutrition (Third year module on BSc Sport and Exercise Science, Aberystwyth University)

Other Information (Training):

- *Control of substances hazardous to health* (Safety 4 HEd)
- *Conducting a Systematic Review: A practical guide*' (NISCHR CRC, Support Unit for Research Evidence).
- *Good Laboratory Practice* (NISCHR)
- *Introduction to Good Clinical Practice* (NISCHR)
- *Venepuncture* (HealthTrain)

Academic Mentor CV

Personal details

Title: Professor

Name: Chris Bridle

Qualifications:

Social Psychology BSc, Applied Psychology MSc, Health Psychology PhD

Work history: *(please provide relevant dates and description of role/s)*

2012 – Present	Professor of Human Behavioural Science Institute of Human Sciences, Aberystwyth University
2009 – 2012	Associate Professor (Reader) of Health Psychology Clinical Trials Unit, Warwick Medical School
2006 – 2009	Senior Lecturer in Health Psychology Institute of Clinical Education, Warwick Medical School
2003 – 2006	Lecturer in Health Psychology School of Psychology, University of the West of England
2001 – 2003	Research Fellow NIHR Centre for Reviews & Dissemination, University of York

Grants:

Current grant:

- Health Technology Appraisal Review Team (NIHR: £5m): 2010-15
- Prevention of fall-related injuries in community-dwelling older people (NIHR: 2.4M): 2010-15
- Physical activity to slow cognitive decline in people with dementia (HTA: £1.3m): 2011-15

Recent projects:

- Stretching and strengthening exercises for rheumatoid arthritis of the hand (HTA)
- Behaviour change among people with severe mental illness (RfPB)
- Written emotional disclosure for depression in type 2 diabetes (D-UK)
- Behaviour change interventions for socially disadvantaged groups (The King's Fund)
- Computer-based expert system for tailored smoking cessation advice (ESRC)

Selected recent publications:

Bridle C, Spanjers K, Patel S, Atherton N, Lamb S. Exercise for depression among older people: Systematic review and meta-analysis of randomised controlled trials. British Journal of Psychiatry, 2012;201:180-5.

Bridle C, Moss T, Harcourt D, Kainth A, Markham WA. (2008). Methodological issues in health behaviour intervention research: Bridging the research-practice chasm. Annals of Behavioral Medicine, 35(5), 22-32.

Hamilton-West KE, Bridle C. (2008). Effects of written emotional disclosure following residential fire: Randomised controlled trial. Journal of Traumatic Stress, 121(4), 590-602.

Heine P, Williams M, Williamson E, Bridle C. Development and delivery of an exercise intervention for rheumatoid arthritis: Strengthening and stretching for rheumatoid arthritis of the hand (SARAH) trial. Physiotherapy, 2012;98(2):121-30.

Lall R, Mistri D, Bridle C, Lamb S. Telephone interview for follow-up data collection yields valid and reliable data from postal questionnaire non-responders in clinical trials. Journal of Clinical Epidemiology, 2012;65(1):90-9.

Markham WA, Aveyard P, Bridle C. Value-added education and smoking uptake in schools: a cohort study. Addiction, 2008;103(1):3-11.

Markham WA, Lopez ML, Bridle C. Mediated, moderated and direct effects of country of residence, age, and gender on the cognitive and social determinants of adolescent smoking in Spain and the UK. BMC Public Health, 2009;9:173.

Michie S, Jochelson K, Markham WA, Bridle C. Low-income groups and behaviour change interventions: A review of intervention content and effectiveness. Journal of Epidemiology and Community Health, 2009;63(4):250-6.

Sturt J, Ali S, Robertson W, Bridle C. Neurolinguistic programming: Systematic review of effects on health outcomes. British Journal of General Practice, 2012;62:580-7.

Awards:

Chartered Psychologist (British Psychological Society)

Professional Memberships:

- Division of Health Psychology
- British Psychological Society
- UK Society of Behavioural Medicine

Academic Mentor CV

Personal details

Title: Professor

Name: Luis A. J. Mur

Qualifications:

BSc (Hons); PhD

Work history: *(please provide relevant dates and description of role/s)*

1991-1997 BBSRC Research Associate, University of Leicester
1997- 2005 Lecturer. University of Wales, Aberystwyth.
2005- 2013 Senior Lecturer, , University of Wales, Aberystwyth /
2009- Deputy Leader – Biorenewables and Environmental Change Research Division (IBERS)
2013- PERSONAL PROFESSORSHIP

Recent Grants won:

- Welsh Assembly WORD programme (CoI) 2008-10. Early detection of lung cancer: metabolic biomarkers for high risk screening Project No: H07-3-31 E
- BBSRC (CoI): Correlation of metabolic fingerprints with differential growth responses of cold-inhibited salicylate mutants. 1/1/06-31/12/09
- Royal Society: International Project – (PI) The impact of nitric oxide on ethylene signaling. 15/01/08-31/04/10.
- National Science Foundation (CoI) USA: Surveying natural diversity of the model grass *Brachypodium distachyon :* 2009-2013
- Genetic Society 2009 (PI) Developing a *Brachypodium distachyon* germplasm collection.
- BBSRC (CoI) 2011-2014 Exploiting Brachypodium distachyon to elucidate drought tolerance mechanisms : Linking gene expression with changes in cell wall chemistry
- Genetic Society 2011 (PI) Microsatelite analysis of genetic diversity in Brachypodium
- British Society of Plant Pathology (PI) 2011 “Eyes” wide shut - The impact on pathogen-induced stomatal lock-up on Miscanthus.
- BBSRC (PI) Screening for costs of disease resistance caused by stomatal dysfunction: 01/1/11 – 31/12/ 2014
- BBSRC (Co1) Institute Programme Grant; Rumen Systems Biology(2011-2015).

Selected Recent Publications:

Cristescu, S. M., Marchenko, D., Mandon, J., Hebelstrup, K., Griffith, G. W., Mur, L. A. J. and Harren, F. J. M. (2012). Spectroscopic monitoring of NO traces in plants and human breath: applications and perspectives. Applied Physics B, 1-9.

Elwood, P. C., Gallagher, A. M., Duthie, G. G., Mur, L. A. J. and Morgan, G. (2009). Aspirin, salicylates, and cancer. Lancet 373, 1301-1309.

Ghosal, R., Lewis, K., Kloer, P., Bayliss, S., Mur, L. and Lewis, P. (2010). S38 Fourier transform infra-red (FTIR) spectroscopy on sputum from lung cancer patients, healthy controls and a high-risk cohort. Thorax 65, A19-A20.

Gupta, K. J., Brotman, Y., Segu, S., Zeier, T., Zeier, J., Persijn, S. T., Cristescu, S. M., Harren, F. J. M., Bauwe, H., Fernie, A. R. et al. (2013). The form of nitrogen nutrition affects resistance against Pseudomonas syringae pv. phaseolicola in tobacco. Journal of Experimental Botany 64, 553-568.

Jones, A. W., Cameron, S. J., Thatcher, R., Beecroft, M. S., Mur, L. A. and Davison, G. (2013). Effects of bovine colostrum supplementation on upper respiratory illness in active males. Brain Behav Immun.

Kingston-Smith, A. H., Davies, T. E., Rees Stevens, P. and Mur, L. A. (2013). Comparative Metabolite Fingerprinting of the Rumen System during Colonisation of Three Forage Grass (Lolium perenne L.) Varieties. Plos One 8, e82801.

Lewis, P. D., Lewis, K. E., Ghosal, R., Bayliss, S., Lloyd, A. J., Wills, J., Godfrey, R., Kloer, P. and Mur, L. A. (2010). Evaluation of FTIR spectroscopy as a diagnostic tool for lung cancer using sputum. BMC Cancer 10, 640.

Lloyd, A. J., Allwood, J. W., Winder, C. L., Dunn, W. B., Heald, J. K., Cristescu, S. M., Sivakumaran, A., Harren, F. J. M., Mulema, J., Denby, K. et al. (2011). Metabolomic approaches reveal that cell wall modifications play a major role in ethylene-mediated resistance against Botrytis cinerea. Plant Journal 67, 852-868.

Morgan, G., Rothwell, P., Burn, J., Chan, A., Mur, L., Morton, D., Cuzick, J. and McVie, G. (2011). Aspirin, salicylates and cancer:. In ecancer, vol. 5.

Mur, L. A. J. and Ellwood, P. (2012). Salicylates and Cancer: Nova.

Professional Memberships:

- Genetics Society
- Society of Biology
- British Society of Plant Pathology

Teaching Activity:

Biology Degree Scheme co-ordinator

Applicant CV

Personal details

Title: Dr.

Name: Keir Lewis

Qualifications:

Undergraduate

1989-95	United Medical & Dental Schools of Guy's & St Thomas Hospitals
1992	B.Sc. First Class (Hons.) Psychology
1995	MB.BS. (Double Honours)

Postgraduate

1998	M.R.C.P (U.K.)
2004	MD Thesis, University of Wales, Cardiff.
2010	F.R.C.P (U.K)

Work history: *(please provide relevant dates and description of role/s)*

2011 – present	Associate Professor in Respiratory Medicine, University of Wales, Swansea and Honorary; Consultant in Respiratory and General Medicine, Hywel Dda Health Board.
2003 -present	Senior Lecturer in Respiratory Medicine, University of Wales, Swansea and Honorary Consultant in Respiratory and General Medicine, Hywel Dda Health Board.
1998 - 2004	Training in Respiratory & General Medicine - Specialist Registrar –various welsh hospitals
1996 - 1998	Royal Hospitals NHS Trust, London, SHO Training Scheme 1996-1998
1995-1996	Pre-registration, Guys & St Thomas's NHS Trust, London 1995-1996

Professional Memberships:

- Member of the British Thoracic Society
- Member of the Welsh Thoracic Society
- Member of the British Sleep Society
- Fellow Royal College of Physicians
- Member of the British Association of Stop Smoking Practitioners
- Member European Respiratory Society Smoking Policy Unit

Teaching activity:

Graduate Entry Program, (MB BCh) College of Medicine, Swansea University: Clinical lead for learning weeks on 'Bronchial sepsis 120', 'Sleep and Muscle Wall Disease 204'; other lectures on influenza, TB, HIV and chronic lung infections.

Selected publications:

Lewis AT, Jones K, Lewis KE, Jones S, Lewis PD. Detection of Lewis antigen structural change by FTIR spectroscopy. *Carbohydr Polym*. 2013; 92(2):1294-301.

Ghosal R, Lewis KE, Kloer P, Bayliss S, Mur L, Lewis PD. (2010). Fourier Transform InfraRed Spectroscopy on sputum from lung cancer patients, healthy controls and a high risk cohort. *Thorax*; 65: A19

Ghosal R, Lewis KE, Kloer P, Llewellyn-Jones C, Lewis PD. (2007). Fourier transform infrared spectroscopy measuring metabolic markers in sputum in patients with and without lung cancer. *Thorax*, 62: S19

Lewis KE, Ghosal R, Mur L, Bayliss S, Kloer P, Lewis PD (2011). Using Fourier Transform Infrared (FTIR) on sputum to develop a predictive model to differentiate lung cancer from healthy controls. *Proc Am Thoracic Society*. A6098

Mur LAJ, Kloer P, Ghosal R, Lewis KE, Lewis PD. (2008). Fourier transform infrared spectroscopy and metabolic profiling in lung cancer. *Thorax*, 63: S139

Roberts SE, Button LA, Hopkin JM, Goldacre MJ, Lyons RA, Rodgers SE, Akbari A, Lewis KE. Environmental and socio-demographic factors associated with the incidence and outcome of serious asthma: record linkage study. (2012) *Eur Resp J* 2012; 40(3):785-8.

Phillips CO, Syed Y, Parthaláin NM, Zwiggelaar R, Claypole TC, Lewis KE. Machine learning methods on exhaled volatile organic compounds for distinguishing COPD patients from healthy controls. *J Breath Res* 2012 ;6 (3):036003

Lewis PD, Lewis KE, Ghosal R, Bayliss S, Wills J, Godfrey AR, Kloer P, Mur LAJ. Evaluation of Fourier Transform InfraRed Spectroscopy as a diagnostic tool for lung cancer using sputum. *BMC Cancer* 2010; 10: 640-6

Lewis KE, Annandale JA, Warm DM, Hurlin C, Lewis L. (2010). Does home telemonitoring further affect quality of life for patients with COPD who have had pulmonary rehabilitation? A pilot randomised trial. *J Telemed Telecare*, 16: 253-9

Lewis KE, Annandale JA, Warm DM, Blyth H, Syed Y, Hurlin C, Lewis L. (2010). Does home telemonitoring after pulmonary rehabilitation reduce healthcare use in COPD? A pilot randomized trial. *COPD*; 7:44-50

Annandale J, Hurlin C, Lewis KE. Reducing COPD admissions with a specialist chronic disease management team. *Nursing Times* 2009; 105: 25

Sabit R, Griffiths TL, Watkins AJ, Evans K, Bolton CE, Shale DJ, Lewis KE. Predictors of poor attendance at an outpatient pulmonary rehabilitation program. *Respir Med* 2008; 102 (6):819-24.

Selected grants:

- £563,320 United4Health European Integrated Care Technology Policy Support Programme (Call : CIP-ICT-PSP-2012-6): 2012 European Lead for: Telehealth following hospital discharge for COPD.
- £120,000 and £160,000 National Institute for Health and Social Care Research (NISCHR): 2012-15 and 2011-2014 To establish NISCHR Clinical Fellows in Hywel Dda Health Board.
- £287,000 Welcome Trust 2011: 'Prognostic factors and outcomes for medical emergency admissions'. Interrogation of a large NHS database.
-£1.5 Million NISCHR: 2011. To develop a Biomedical Unit in Swansea using haemo-rheology to research pro-thromobotic tendency lead.
- £420,000 NISCHR: 2011. To strengthen research support infrastructure in Hywel Dda.
-£315,000 Welsh Office for Research and Development (NISCHR). 2010. To establish a Welsh Respiratory Research Network.
-£300,000 Welsh Assembly Government (2009) for telemedicine in chronic disease (Clinical Lead and Chief Investigator).
- £104,000 WORD/NISCHR. 2007. For research into metabolic markers for lung cancer.
- £815,000 Informing Health Care Wales: 2007, European eTEN monies grant C046225 researching telemedicine for COPD (UK Chief Investigator).