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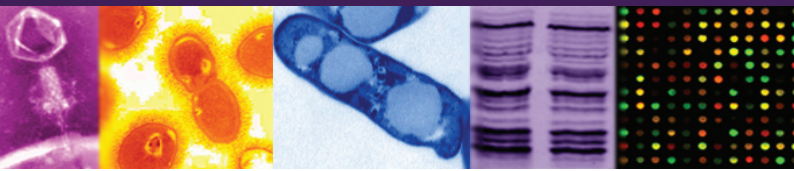

Department of Infection, Immunity & Inflammation

4th Annual Postgraduate Student Conference

16th- 18th April 2012

Programme and Abstracts

Preface

Welcome from the Postgraduate Student Staff Committee (PSSC).

Part of the journey towards becoming a skilled, accomplished and focused scientist involves presenting your research in a professional environment. This Conference provides an ideal opportunity for postgraduate research students to improve these presentation techniques, and also to learn about the diverse range of research topics from other students throughout the Department.

This is the fourth Postgraduate Departmental Conference, and once again has been organised by the student committee members. The aim of this Conference focuses on presentations from first and second year PhD students, allowing them to inform the Department of their progress through their individual projects in a conference-style format. Each presentation falls into a different category, such as Renal Medicine, Immunology, Respiratory Diseases and Infection. Third and fourth year PhD students also play a role in this conference as chairs of the sessions.

To add further interest to the Conference, we are privileged to include keynote speakers in the programme list, including Professor Anne Willis and Prof. Robert B Sim, who have generously agreed to give presentations on a particular area of their interest.

Feedback throughout the sessions for each presentation by the students is greatly appreciated, particularly in the form of constructive criticisms to provide students with insightful help towards development of their research and presentation skills.

Thank you for attending and participating in this Conference, and we hope you enjoy the presentations from both students and invited speakers.

Asel Sarybaeva, Greer Arthur, Nima Abbasian, Nawal Helmis and Sadiyo Siad.
Student Representatives of PSSC 2012

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Abstracts

Day 1, 16th April, MSB LT2

Sherif Gonem

Non-invasive assessment of small airway disease in asthma

Supervisor(s): Prof. Christopher Brightling and Dr. Salman Siddiqui

Small airway dysfunction may account for disease persistence in asthma since topical corticosteroids, the usual mainstay of therapy, may not penetrate to the lung periphery. There is a need for simple non-invasive tests that will sensitively detect the presence of small airway disease. Multiple breath washout (MBW) and the forced oscillation technique (FOT) are promising candidates. We aim to determine the repeatability and accuracy of MBW and FOT biomarkers, as well as to understand the relationship of these parameters to standard pulmonary function tests. We seek to maximise the information that may be gained from MBW and FOT data, including the examination of temporal variability over short time scales. Furthermore, we aim to elucidate the clinical characteristics of patients who manifest small airway disease, and to determine whether small airway tests may be useful as screening tools for early sub-clinical airway disease. Finally, we aim to investigate non-invasive small airway biomarkers within the context of an interventional phase 2 clinical trial. Thus far, we have established that small airway biomarkers are repeatable and discriminate well between health and disease. We have validated our MBW technique using a lung phantom and have derived a number of novel MBW parameters that appear to have significant advantages compared to those in current use. Cluster analysis of our data has revealed a distinct cohort of asthma patients with severe disease expression, fixed airflow obstruction and evidence of small airway dysfunction. This group may benefit from more intensive therapy, including systemic therapy.

Leonarda Di Candia

"RAGE and HMGB1 are expressed by human airway smooth muscle cells and expression levels are changed in asthma"

Supervisor(s):Prof. Christopher Brightling, Prof. John Challiss

The receptor for advanced glycosylation end products (RAGE) is activated by endogenous danger signals, including high mobility group box 1 (HMGB1). RAGE and HMGB1 have been implicated in several diseases, including asthma. RAGE is implicated in lung homeostasis, e.g. in alveolar type I epithelial cell function; however, RAGE expression/function in other airway cell-

types is poorly characterised. Airway smooth muscle (ASM) dysfunction is a feature of asthma. We hypothesised that changes in RAGE and HMGB1 expression may contribute to ASM dysfunction in asthma.

ASM was microdissected from bronchial biopsies and lung resection tissue. Ex-vivo ASM cells were characterised for α-smooth muscle actin and used between P2-P5. Cells were serum deprived prior to experimentation. RAGE and HMGB1 mRNA expression was measured using RT-PCR and qRT-PCR, and protein expression by western blotting, immunofluorescence and flow cytometry.

ASM cells were shown to express full-length and three soluble RAGE transcripts by RT-PCR (n=5), and an HMGB1 transcript by qRT-PCR (n=13). Membrane-localised RAGE expression was increased in ASM cells isolated from asthmatics (ASM-A, 15.5±2.5%, n=9) vs non-asthmatics (ASM-NA, 8.3±2.1%, n=9; $p<0.05$) as assessed by flow cytometry, whereas HMGB1 expression was reduced (mean fluorescence intensity (fold change over isotype control): ASM-A, 2.6±0.2, n=9, vs ASM-NA, 3.6±0.3, n=8, $p<0.05$). RAGE and HMGB1 expression were confirmed by immunofluorescence and western blotting.

In conclusion, ASM cells expressed both RAGE and HMGB1 mRNA and protein. Membrane-localised RAGE expression was significantly increased and HMGB1 expression significantly decreased in ASM-A vs ASM-NA. The contribution of these changes to ASM dysfunction is currently under investigation.

Sally Stinson

Exploring the expression and function of CRTh2 in asthma

Supervisor(s): Professor Chris Brightling and Dr Yassine Amrani

CRTh2 (Chemoattractant Receptor-Homologous molecule expressed on Th2 cells), also called DP2 or GPR44, is a G-protein coupled receptor that has been implicated in the pathogenesis of allergic diseases (Pettipher, Hansel 2008). Its major endogenous ligand prostaglandin D2 (PGD2) is released in large amounts by mast cells during allergic reactions and is found at high levels in the bronchoalveolar lavage fluid of asthmatics (Liu et al. 1990, Crea, Nakhosteen & Lee 1992, Balzar et al. 2011).

Most of the literature for CRTh2 describes its expression and function on peripheral blood derived eosinophils, Th2 cells and basophils (Nagata et al. 1999, Hirai et al. 2001, Schratl et al. 2007, Royer et al. 2008, Shiraishi et al. 2005). Some limited data also demonstrates that CRTh2 is present on epithelial cells (Shirasaki et al. 2009, Chiba et al. 2006, Boehme et al. 2009b). To date there is no literature that describes CRTh2 expression on asthmatic tissue.

This project has been funded by AstraZeneca to investigate the expression and function of human CRTh2 in asthma. The main aim of the first year is to investigate the expression of CRTh2 on

clinically well characterised human asthmatic and normal biopsy tissue via immunohistochemistry. Preliminary data shows that on asthmatic and normal upper airway tissue biopsies CRTh2 is expressed on a sub-set of inflammatory cells within the submucosa and on epithelial cells. Future work aims to further phenotype CRTh2 positive cells and to look at the expression and function of CRTh2 on isolated asthma relevant cell types.

Rebecca Jayne Fowkes
"β 2-Agonist Responses in Human Lung Mast Cells and Airway Smooth Muscle."

Supervisor(s): Prof. Peter Bradding

Asthma is a common, chronic condition typified by variable and reversible airway obstruction and hyperresponsiveness. β 2-adrenoceptor (β2-AR) agonists remain a preferred add on therapy to inhaled corticosteroid (ICS) treatment in asthma due to their powerful bronchodilatory properties. However, β2-agonists are relatively ineffective during acute asthma exacerbations and repeat exposure results in β2-AR desensitisation in mast cells and subsequent tolerance to treatment. Desensitisation may contribute towards clinical observations such as loss of bronchoprotection and deterioration of asthma control. Hence, β2-agonists that do not induce desensitisation may have better potential to control inflammation and smooth muscle dysfunction in asthma.

This research will test the hypothesis that the novel ultra long-acting β2-agonist BI-1744 will be more potent than existing agonists on the market and that exposure to BI-1744 will induce less desensitisation of the β2-receptor.

BI-1744 demonstrated dose-dependent inhibition of HLMC FcεRI -dependent histamine release and had a potency similar to formoterol and greater than salbutamol. BI-1744 and formoterol both failed to inhibit thapsigargin-induced histamine release, indicating that these agonists limit components of the proximal FcεRI-dependent signalling pathway.

Pre-incubation (24h) of cells with salbutamol (10-5 M), formoterol (10-6 M) and BI1744 (10-6 M) results in statistically significant (two-way ANOVA) desensitisation of β2-agonist responses. However no difference was found between the extent of desensitisation induced by BI-1744 and desensitisation induced by other agonists.

A further aim is to examine the mechanism by which airway smooth muscle (ASM) induces mediator release by human lung mast cells (HLMC) when in co-culture, and whether BI-1744 and existing β2-agonists can inhibit this process. Preliminary data from co-culture experiments will be presented.

Osama Eltboli

"Eosinophilic airway inflammation in COPD"

Supervisor(s): Prof. Christopher Brightling

Background: The role of eosinophilic inflammation in COPD is unclear. Macrophages may have altered phagocytosis which could be responsible for sputum eosinophilia.

Methods: The characteristics of 195 COPD subjects from existing cohort were studied and the red hue of macrophages from 100 subjects with the high and low sputum eosinophils was measured. Repeatability of sputum eosinophils was calculated using intraclass correlation coefficient.

Results: The percentage of bacterial infection in eosinophilic subjects is lower than non-eosinophilics. Eosinophilic COPD subjects have low red hue, compared to asthmatics with a similar degree of sputum eosinophilia which might be due to macrophage dysfunction. COPD subjects with sputum eosinophilia had a significant fall of FEV1 and deterioration of VAS dyspnoea during exacerbations in contrast to non-eosinophilics. There was high reproducibility of the eosinophils results.

Conclusions: The prevalence of bacterial infection in eosinophilic COPD subjects is less than non-eosinophilics. Sputum eosinophilia is associated with a greater fall in FEV1 during exacerbation and worsening of VAS dyspnoea. Macrophages may have phagocytic dysfunction which could play a role in the mechanism of sputum eosinophilia in COPD. The eosinophils sputum cell count is highly repeatable in COPD.

Bethan Barker

"Multi-dimensional COPD Phenotyping"

Supervisor(s): Prof Chris Brightling

Background: Current diagnostic criteria do not accurately reflect the heterogeneous pathology and systemic features (e.g. skeletal muscle dysfunction) observed in COPD. Available therapies improve symptoms and reduce exacerbation frequency, but benefits are small and restricted to subgroups of patients. Previous cohorts have focused on pulmonary aspects, despite the fact that targeting skeletal muscle dysfunction can improve exercise performance independent of lung function. There is a need to improve our understanding of the gene-environment interactions that influence disease development, to better stratify and personalise therapies.

Aims: 1) To define multi-dimensional COPD phenotypes by integrating information at different scales of disease i.e. gene-cell, cell-tissue, tissue-organ and organ-whole person, 2) To define underlying pathological processes which will allow new treatment target identification, 3)To use novel phenotypes and biomarkers to drive hypothesis driven mechanistic studies.

Methods and Progress: To date 30 (of a planned 150) patients with COPD (GOLD II-IV) have been recruited into a 3-year observational study. Patients will be reviewed 3 monthly, at exacerbation onset and during exacerbation recovery. At baseline, patients will undergo extensive characterisation which will include assessment of the following; health related quality of life, lung physiology and structure, body composition, skeletal muscle size and function, physical activity and co-morbidities. Matched blood, sputum, urine and muscle samples will be obtained to allow physiological phenotyping from genome to proteome. Physiological and biological sampling will be repeated at exacerbations and at pre-defined time points to monitor disease progression over time. Biostatistical modelling will be used to identify novel phenotypes.

Greer Arthur

"Do mast cell serine proteases activate the airway epithelial Na^+ channel (ENaC)?"

Supervisor(s): Dr Erol Gaillard, Prof. Peter Bradding, Dr Mark Duffy and Dr Mark Leyland

Asthma is a chronic inflammatory disorder of the conducting airways, with characteristic features such as airway obstruction, infiltration of airway epithelium by mast cells (MCs), increased airway mucus production and adherence of mucus to airway surfaces. In particular, mucus adherence and dysfunctional mucociliary clearance (MCC) occur during asthma exacerbations. MCC is an important mechanism of innate immune defence, and conservation of efficient MCC requires precise maintenance of airway surface liquid (ASL) height, which prevents adherence of mucus to ciliated airway surfaces and allows cilia to beat and aid mucus clearance. Studies have shown that the epithelial sodium channel (ENaC) allows apical Na+ entry in absorptive epithelia and consequently controls fluid reabsorption at the air-liquid interface of ciliated epithelia. Overexpression and increased activity of ENaC in animal models has been shown to cause ASL depletion and impede mucus clearance, resulting in mucus obstruction of the airway lumen and chronic airway inflammation. ENaC can be activated by a variety of serine proteases such as trypsin, which has been shown to have similar substrate specificity to the MC-specific serine protease, tryptase. MC proteases such as tryptase are released into the airway epithelium during asthma exacerbations following prolonged MC degranulation. This could indicate a possible role of MC serine proteases in the activation of airway ENaC in asthma exacerbations, resulting in ASL depletion, mucus retention and dysfunction of MCC.

Noor Al-Khathlan

"Lung clearance index (LCI) derived from Multiple-breath Nitrogen Washout Test (MBNW) as a measure of lung progression in children with Cystic Fibrosis (CF)."

Supervisor(s): Dr. Caroline Beardsmore and Dr. Erol Gaillard

Introduction: Early monitoring of CF lung disease is crucial. Recently, LCI, a measure of ventilation inhomogeneity derived from MBNW, has been recognized as a sensitive marker of early CF lung disease. However, there are few data on longitudinal changes in LCI. The overall aim of the project is to collect longitudinal data from children with CF. This abstract will address methodological aspects of MBNW (i) the impact of rate and depth of breathing on LCI; (ii) relating LCI to an index of hyperinflation, residual volume/total lung capacity (RV/TLC).

Methods: (i) We performed MBNW using 3 different breathing patterns (BP). Each subject performed at least 3 washouts with each BP. A visual signal served as a frequency target and an auditory signal used to guide tidal volume (Vt). Repeated measures ANOVA were used to analyze the data. (ii) Children with CF completed MBNW and plethysmography as part of their annual review. Results were examined using Spearman's rank correlation coefficient.

Results: (i) 19 healthy adult volunteers were studied. Two were excluded for technical reasons. There were significant differences in LCI with BP ($p<0.01$). (ii) 37 children with CF completed lung function tests. A significant correlation was found between LCI and RV/TLC ($r=0.516$, $p=0.001$).

Discussion: LCI has become increasingly a measurement of choice in monitoring CF lung disease. Our finding shows that it reduced with increasing Vt and decreasing frequency. So we recommend that both Vt and frequency are controlled. We also showed that LCI correlated with RV/TLC, a measure of air trapping in children with CF.

Jaspreet Sahota

"The characterisation and exploitation of phages in the treatment of *Pseudomonas aeruginosa* infections of Cystic Fibrosis patients."

Supervisor(s): Dr Martha Clokie and Dr Aras Kadioglu

Pseudomonas aeruginosa is a quickly establishing itself as the dominant hospital acquired infection, in particular being the predominant infectious agent of Cystic Fibrosis (CF) sufferers. It is the fourth most commonly-isolated nosocomial pathogen, accounting for 10.1% of all hospital-acquired infections. In the UK the Liverpool Epidemic Strain (LES) is responsible for the majority of the

morbidity and mortality of CF patients with *P. aeruginosa* infections. It is becoming apparent that there is significant phenotypic variation within LES isolates, including multi drug resistance strains in the confines of the CF lung. This emergence of the multi drug resistance phentotypes shows the need to more towards phage therapy. Phages for *P. areuginosa* have been isolated around the world and been incorporated into phage cocktails along with other phages but have not been tested against the UK *P. areuginosa* strains. Single phages isolated from 2 of those mixes, the commercial Pyophage and Intestiphage mixes (Eliava Institute, Georgia) were tested in a number of methods on clinical isolates *of P. aeruginosa* and 40 haplotype variants of the LES derived from CF patients. This was to determine the most effective phage(s) to be used in *ex vivo* and *in vivo* testing, and possible delivery routes such as nebulisation.

Day 2, 17th April, MSB LT2

Jamie Marshall

"Activation of the Complement system by the *Streptococcus pneumoniae* toxin, pneumolysin."

Supervisor(s): Dr Russell Wallis & Prof. Peter Andrew

The common respiratory pathogen *Streptococcus pneumoniae* is a major cause of human disease worldwide. It is a principal agent for bacterial pneumonia, septicaemia, and meningitis, causing >1.2 million infant deaths per year. Pneumolysin (PLY) is a toxin and important virulence factor produced by *Streptococcus pneumonia.* It is a 53 kD protein with four domains, which is produced by virtually all clinical isolates of pneumococcus. In animal studies, isogenic mutant pneumococci lacking pneumolysin are able to be cleared from the lungs of immune-competent mice.

PLY lacks an N-terminal secretion sequence and requires lysis of the pneumococci to be released into the host organism. It has two main effects on the host organism; firstly it is able to oligomerise and insert itself into cholesterol-containing host membranes to form pores; resulting in widespread lysis of host cells and cell death. The second, less well understood function is to activate the host complement system; the current thoughts are that widespread, rapid activation of complement uses up all the available complement proteins, leaving the host without a first-line of defence.

This project aims to understand, at a molecular level, how the pore forming toxin PLY activates the complement system. This is an important question, because complement activation is vital for virulence. For example, *in vivo* studies have shown that mice infected with pneumococci expressing a mutant form of PLY, deficient in complement activation, have less severe pneumonia and bacteraemia compared with mice infected with wild type bacteria. Thus, targeting the complement activation function of PLY could lead to new therapeutics.

Firas Younis

Transcriptional regulation of pneumococcal pyruvate formate lyase

Supervisor(s): Dr Hasan Yesilkaya & Prof. Peter Andrew

Galactose is the main source of sugar in respiratory tract and can be found within the structure of mucin. *S. pneumoniae*, a heterotrophic pathogen that depends on carbohydrates to produce its energy, is able to metabolize galactose to pyruvate.

In homolactic bacteria, lactate dehydrogenase (LDH) plays the main role in conversion of pyruvate to lactate and generating NAD^+. However, in aerobiosis, sugar limitation, or the presence of sugars less preferred than glucose, such as galactose, there is a metabolic shift from lactate production to mixed acid fermentation leading to the production of end products such as ethanol, acetate and formate. Pyruvate formate lyase (PFL) is a key enzyme in galactose metabolism and the mixed acid fermentations take place with the activity of PFL, which transforms pyruvate to acetyl-CoA and formate under microaerobic and anaerobic conditions.

PFL has also been reported as an important determinant of the virulence of *S. pneumoniae* and the mutation of it resulted in reduced pneumococcal virulence, which may be due to a defect in ATP and acetyl-CoA biosynthesis that affect fitness and fatty acid composition, respectively.

PFL is regulated allosterically, posttranslationally by the activity of PFL-activating enzyme, and transcriptionally. Information on how *pfl* is regulated transcriptionally is very limited. Hence, I aim to study the regulation of this gene at genetic level. Through analysis of a strain mutated in *pfl* by microarray, we identified differential regulation of seven transcriptional regulators. We hypothesise that these genes regulate *pfl* transcriptionally. In this study evidence will be sought for direct interaction of these transcriptional regulators with *pfl* regulatory region.

Sumia Mohamed Essid

"The role of C peptide in skeletal muscle metabolism in diabetic nephropathy."

Supervisor(s): Prof Nigel Brunskill and Dr Alan Bevington.

Muscle wasting is defined as loss of muscle protein mass. This loss of lean body mass is an important clinical problem which is associated with morbidity and mortality. This occurs in many diseases such as chronic kidney disease (CKD), uraemia and diabetes. This wasting problem is particularly severe in CKD patients who have diabetic nephropathy. C-peptide is a cleavage product of insulin synthesis and is secreted in equimolar amounts along with insulin and circulates in nanomolar concentration in healthy individuals and is deficient in Type I diabetics. A number of studies have suggested that diabetic complications may occur as a result of decrease in the level of C peptide in blood circulation. It is therefore important to investigate the effects of C-peptide on muscle metabolism, especially the reported strong stimulation of amino acid transport into cultured L6 rat skeletal muscle cells which may have an anabolic effect on muscle protein (Grunberger, et al Diabetologia 44: 1247-57 (2001).

To date, the possible influence of C-peptide on amino acid uptake and intracellular signalling pathways in muscle cells are largely uninvestigated. We hypothesise that the effect of C-peptide on skeletal muscle occurs at least partly by altering active amino acid uptake in vivo and in vitro by acting on the major regulatory amino acid transporter protein SNAT2 (slc38a2).

This is being tested by treating quiescent cultures of the L6 rat skeletal muscle cell line with 3nm rat C-peptide for 1h (conditions which have previously been reported to stimulate SNAT2 (Grunberger at al 2001). The functional effects of C-peptide are being studied by measuring SNAT2 amino acid transporter activity – (assessed from uptake of the specific radio-labelled amino acid analogue ^{14}C-Methylaminoisobutyrate). Intracellular signals involved in these responses are being studied by measuring phospho-activation of Erk by immunoblotting with phospho-specific antibodies.

Initial results have shown no reproducible chronic stimulatory effect of C-peptide on amino acid uptake, but inhibition of the SNAT2 transporter may occur on acute exposure to C-peptide which may be rapidly reversed when the peptide is removed.

James P Hunter

"Randomised controlled trial of the effects of hydrogen sulphide in an experimental model of renal ischaemia-reperfusion injury"

Supervisor(s): Professor M L Nicholson

Aims: Renal ischaemia reperfusion injury (IRI) is a major cause ofacute renal failure and renal transplant dysfunction. The aim of this study was to investigate the efficacy of hydrogen sulphide (H_2S) in protecting against renal IRI.

Methods: Large white, female pigs underwent laparotomy and cross clamping of the left renal pedicle for 60 minutes. Animals were randomly allocated to treatment with an infusion of either H_2S (n=6) or saline control (n=6) 10 minutes prior to clamp release and then underwent a right nephrectomy. Veterinary and surgical staff were blinded to treatment allocation. Animals were recovered for 7 days and serum creatinine was measured as an index of renal function.

Results: Administration of H_2S resulted in a marked reduction in kidney injury with reduced serum creatinine on days 1,3 and 5; reduced area under the curve of creatinine and halving of the time to creatinine <250μmol/L. H_2S also prerserved tubular function demonstrated by urinary protein:creatinine ratio which, compared to baseline, increased at day 1 and 3 in the control group

(3.22 ± 2.86; p=0.01 and 2.585 ± 1.267; p=0.031) but not the treatment group (0.255 ± 0.185; p=0.19 and 1.062 ± 0.4365; p=0.11). TNF-α levels at 6 hours post reperfusion increased in the control animals (57+-15 vs. 109+-51; p = 0.026) but not in the H_2S treated animals (62+-18 vs. 80+-27; p= 0.46).

Conclusions: H_2S offers a promising novel approach to ameliorating renal IRI with potential translation into a number of clinical settings including renal transplantation.

Amandus Ankobil

"The role of complement proteins and microparticles in LPS mediated stimulation of mouse macrophages"

Supervisor(s): Dr. Cordula Stover and Dr. James Burton

Introduction: The role of microparticles as far as proinflammatory or anti-inflammatory responses and disease are concerned have been shown to depend largely on the source from which the MPs are derived. Microparticles thus have the ability to stimulate and suppress immune responses which suggests a complex role in the setting of several diseases. The complement system, an important contributor to acute and chronic disease, is currently being investigated in the development of specific therapeutic targets. Moreover, the regulation of complement proteins (e.g properdin) after LPS stimulation is not yet clearly understood.

Aim: To find out the roles of complement proteins and microparticles in LPS mediated stimulation of mouse macrophages.

Methods: Mouse macrophages(RAW and J774) were stimulated with 100ng/ml LPS in vitro to determine the relative expression of proinflammatory cytokines(TNF-α) as well as complement components(properdin, C3 and factor B) at varying time points. Microparticles were prepared from platelets, monocytes, endothelial cells and mouse thymocytes. Varying amounts of these microparticles were then used to stimulate the mouse macrophages to determine the inflammatory potential of the microparticles from the respective sources.

Results/Conclusion: The results showed an expected rise in TNF-α upon stimulation of macrophages for 4 hours as well as a normal response by complement components properdin, C3 and factor-B. The platelet-derived microparticles produced an anti-inflammatory effect on the macrophages(J774) in contrast to thymocyte microparticles. Further investigation using microparticles produced in a more inflammatory way is strongly recommended.

Asel Sarybaeva

"Characterization of *M.tuberculosis* Rv 3489 as a "player" in nonreplicating persistence.

Supervisor(s): Dr. Galina Mukamolova Prof. Mike Barer

Being accountable for 1.4 million deaths and 8.8 million new cases annually tuberculosis (TB) is yet still a major public health issue. Slow response to chemotherapy with high relapse rates and 2 billion individuals harbouring latent TB infection represent significant obstacle for successful control and eradication of TB. Both latency phenomenon and drug tolerance are associated with dormant subpopulation of *M. tuberculosis.* In experimental dormancy models transition to nonculturable or non-replicating state is followed by upregulation of genes encoding stress proteins and alternative metabolic pathways**.** *Rv 3489* was found to be upregulated in several models of non-replicating persistence (NRP). Location in the same operon with *rv3490(OtsA)* which is responsible for biosynthesis of multifunctional stress protectant- trehalose suggests that Rv3489 might also be involved in trehalose biosynthesis. Along with the function as a simple energy source intrinsic to all carbohydrates unusual chemical structure and stereochemistry of trehalsoe imparts unique properties facilitating to the survival during adverse environmental changes by serving as a compatible osmolyte and stabilizer of membranes, proteins and enzymes. This study aims to investigate physiological role of Rv3489 in mycobacterial growth and dormancy to address the hypothesis of its involvement in NRP through trehalose biosynthesis.

Nino Iakobachvili

"Mycobacterial resuscitation promoting factors: roles and mechanisms in infected macrophages"

Supervisor(s): Galina Mukamolova & Mark Carr

Tuberculosis remains a major global health problem; however, the molecular mechanisms underlying tuberculosis pathogenesis are only slowly starting to emerge. *M. tuberculosis* complex cells produce a large and diverse range of secreted proteins, including members of the ESAT-6/CFP-10 (esx) and resuscitation promoting factor (Rpf) families. It has become apparent that many of these secreted proteins play critical but as yet poorly defined roles in pathogenesis.

Rpfs possess muralytic activity and have been implicated in many processes, including resuscitation of dormant cells, intracellular growth and modulation of the cytokine response of infected macrophages, but their precise roles and mechanisms remain unclear. We have recently identified that *M. tuberculosis* complex RpfA shows over 50% sequence homology to the *Listeria* protein

responsible for actin tail formation, which suggests a specific and key role for RpfA in pathogenesis. The proposed project is aimed to investigate the roles and mechanisms of action of individual *M. marinum* Rpf proteins in infected macrophages, including the potential role of RpfA in bacteria-mediated actin fibre assembly. The work will exploit the potential of confocal microscopy studies of *M. marinum* infected macrophages, which is a proven model for infection by *M. tuberculosis* complex cells.

Abdulwahab Zaid Binjomah

Mycobacterium tuberculosis population heterogeneity in sputum

Supervisor(s): Professor Mike Barer

One in three worldwide is infected with *Mycobacterium tuberculosis* (Mtb) the causative agent for tuberculosis (TB), and nearly 3 million people are killed annually. Tubercle bacilli that coughed up from the margins of the liquefied lesions in the lung have been thought to characteristic of rapid and extensive growth, however, transcriptional and cytological studies on these bacilli provided evidence that the bacilli were in fact growing slowly or in a 'persister'-like state. Therefore, it has been hypothesised that the bacilli in sputum discharged from pulmonary TB patient express unidentified properties necessary for their transmission to the new host. Because transmission is essential for evolutionary endurance, it has been supposed that Mtb experiences powerful selection burdens to maintain and express these unidentified properties. Hence, recognising any phenotype in sputum might provide a clue to identify these properties.

Most pulmonary TB worldwide is diagnosed by examining sputum samples with a stain,Auramine O, that differentiates Mtb from other bacteria on the basis of its acid fastness in these organisms. Acid-fast (AF) staining of Mtb is used as a gold standard for TB diagnosis, despite the current advances in molecular biology. It has been reported that AF staining declines as Mtb cells persist in animal infection and non-replicating cultures. Moreover, there have been some reports of non-AF cells occurring in human infections. Therefore, the presence of non-AF Mtb in sputum is an important consideration.

The aim of this study is to optimise the detection of tubercle bacilli in sputum by fluorescence in-situ hybridisation (FISH) technique using peptide nucleic acid (PNA) probes. An immunofluorescence technique using an anti-Mtb polyclonal antibody raised against a standard protein preparation (PPD) and Guinea pig polyclonal antibody raised to the live Mtb H37Rv infection were also developed. Detection techniques were used in combination with Auramine O AF staining and LipidTox™ Neutral Lipid stain to characterise the various Mtb sub-populations more accurately. In addition to maximising the detection of sputum Mtb, we wish to characterise a

population of non-AF Mtb cells in sputum. FISH-PNA and immunofluorescence methods have been applied in combination with Auramine O and LipidTox labelling to TB sputum samples.

The initial results applying PNA probes reveal sputum consists of different Mtb sub-populations (AF negative PNA positive and the converse). Also, the results show that there are different Mtb lipid-body (LB) sub-populations (LB positive and negative for both PNA and Auramine O positive and negative populations). The immunofluorescence results using both antibodies reveal two apparently mutually exclusive populations (AF positive antibody negative and the converse). In contrast with Mtb from pure culture, a low number of bacilli interacting with the both antibodies were observed, compared with high numbers of Auramine O-positive cells.

This surprising result raises the possibility of relating these newly recognised subpopulations of Mtb in sputum to the clinical status of patients, their response to treatment and their infectiousness.

Day 3, 18th April, MSB LT2

Depesh Pankhania

"Serine/Threonine protein kinases of *Burkholderia pseudomallei*"

Supervisor(s): Dr. E. Galyov and Dr. H. O'Hare

Burkholderia pseudomallei is the causative agent of Melioidosis, a potentially fatal invasive infection in both animals and humans. Despite a substantial research effort since its initial discovery in 1911, relatively little is known about the pathogenicity and metabolism of *B. pseudomallei.*

The *B. pseudomallei* genome sequence has become a vital resource allowing *in silico* analysis to focus experimental studies. The aim of this study is to understand the roles of four genes encoding putative serine/threonine protein kinases (STKs): *BPSL0220*, *BPSL0597*, *BPSL1828*, *BPSS2102*. Phosphorylation by STKs coordinates a vast array of signal pathways in both eukaryotic and prokaryotic organisms.

To date, we have constructed single cross-over insertional mutants in each of the four genes encoding putative STKs and initiated a series of experiments to assess their roles in *B. pseudomallei* virulence and regulation of cellular processes. The growth characteristics of all four putative STK mutants in LB and minimal media were indistinguishable from that of wild type K96243, and so were their ability to form biofilm. However, mutants *BPSL0220*, *BPSL0597* and *BPSL1828* showed a reduced swarming motility when compared to wild type. Furthermore, recombinant STK proteins of BPSL0220 and BPSL1828 have been expressed in *Escherichia coli*, purified and tested for protein kinase activity. This revealed BPSL0220 and BPSL1828 proteins are able to autophosphorylate. In addition, BPSL0220 protein was shown to phosphorylate a general kinase substrate (myelin basic protein) confirming this protein is a protein kinase.

This study should provide valuable information on the role of these putative STKs in *B. pseudomallei* virulence and regulation of cellular processes.

Sadiyo Siad

"The cellular innate immune response against mycobacterial infection."

Supervisor(s): Dr. Cordula Stover and Dr. G. Mukamolova

Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis still claims each year lives of more than 1.7 million people worldwide. This acid fast bacterium resists many types of antibiotic treatment, due to its complex mycolic acid cell wall structure. Further more, its reactivation ability and its infection rate, which occurs at about one per second, makes *M. tuberculosis* particularly difficult to treat.

The cellular innate immune responses play a vital role in the host defence against mycobacterial infection through the activation of cells, the production of chemical mediators and the activation of the complement cascade. Todate, macrophages are known to be the primary target cells which pathogenic mycobacteria initially infect and use to spread, serving as habitat for survival and replication of *Mycobacterium*.

Mast cells are known for their role in allergic and anaphylactic reactions but are important sentinels due to their location in the mucosa. Little is known regarding their role in mycobacterial infection, hence, this presentation will unravel the knowledge gained so far from our infection studies using immature human mast cell line (HMC-1), mature mouse mast cells with *Mycobacterium marinum* (a facultative pathogen, used as a model system) in comparison with macrophages and dendritic cells, as macrophages and dendritic cells are more commonly used in mycobacterial infection research. The roles of complement activations, including complement properdin and low density lipoprotein receptor (LDLR) will also be looked at.

Uzal Umar

"Staphylococcus chromosome cassette mec in Staphylococcus aureus : Impact on phenotype and virulence."

Supervisor(s):Dr. Kumar Rajakumar and Dr. Julie Morrissey

Staphylococcus aureus is a Gram -positive bacterium. It is the second most important cause of hospital-associated infections and the increasing incidence of community –associated infections is of growing concern. The limited number of antibiotics suitable for treatment of infections due to S.aureus contributes to the consequent major public health risk. Acquisition by strains of S. aureus of one of a diverse family of integrated mobile genetic elements the Staphylococcus chromosome cassette mec (SCCmec), which encodes mecA, the central determinant for resistance to meticillin and all other β-lactams, has enhanced the adaptability of this organism and promoted its success as a

pathogen. This project is aimed at assessing the contribution to the bacterial phenotype of SCCmec elements present in clinically-derived strains.

SCCmec-minus derivatives were obtained by introduction of the temperature-sensitive pSR_2 plasmid into parent SCCmec-positive strains to overexpress ccrAB and consequently upregulate spontaneous excision of SCCmec. Excision and deletion of SCCmec was confirmed by PCR analysis for mecA, ccrB and the newly reconstituted intact integration site and determination of susceptibility to oxacillin. Isogenicity of the wild type and SCCmec- minus strain pairs were confirmed by PFGE profiling of SmaI digested DNA.

Preliminary investigation suggested an obvious impact of the SCCmec type II element in BH1 CC on the supernatant protein profile at post- exponential growth of the strain in nutrient rich tryptic soy broth medium. A cell permeability assay based on induction of autolysis on exposure to 0.02 % TritonX-100 showed no significant difference between isogenic strains. Examination of the biofilm-forming phenotype of isogenic strains in CRPMI with or without 10 μM Fe^{2+} ,1% glucose and/or 2.5% NaCl, suggested that the SCCmec type II element has a positive impact on biofilm forming phenotype on BH1 CC grown in CRPMI + Fe^{2+} + 2.5% NaCl . Investigation of the impact of the SCCmec type II in BH1 CC on toxicity suggested that the SCCmec type II in this strain negatively impacts on β–hemolysis as measured by a 6% sheep blood agar assay. Given this finding the ~0.9 kb hlb gene in BH1CC and BH1 CC SCCmec -minus was amplified and sequenced in entirety demonstrating it to be intact and identical in both strains. The function of agr S.aureus global virulence regulon was investigated by phenotypic detection of delta-hemolysin activity on 6% sheep blood agar, BH1 CC was found to be delta hemolysin negative while BH1 CC SCCmec -minus was delta hemolysin positive by this assay, suggesting that these isogenic strains exhibited dysfunctional and functional agr phenotypes, respectively. Work to quantitatively assess agr activity in BH1 CC and BH1 CC SCCmec-minus is ongoing. The virulence of the isogenic strains BH1 CC and BH1 SCCmec- minus was investigated in a time -to -kill experiment in a Galleria caterpillar model, preliminary data suggests a significant difference in virulence between the isogenic strains, with SCCmec- minus derivative being more virulent than its BH1 CC parent. These findings suggest that by some unknown mechanism the SCCmec type II element impairs agr potentially impacting on virulence of the strain.

Future work will be centred on investigating the impact of type II and IV SCCmec elements in diverse clinical S. aureus strains on agr function and the potential consequent effects on time-to-kill , bacterial burden and in- vivo competition in the established Galleria model.

Emma Comber

"Visualising in real-time the assembly of pore-forming proteins in biomembranes"

Supervisor(s):Prof. Peter Andrew, Dr Andrew Hudson and Dr Rana Lonen

Optical tweezing is a technique that allows single particles, of the order of a few nanometres to a few microns (a human hair is 100 microns across), to be trapped in a highly focused laser beam. It can be combined with other methods to monitor changes that a single particle under-goes in various conditions, e.g. during chemical reactions. Recently, it has been applied to biological systems and has allowed many processes to be monitored in real time and in conditions relevant to a real life. Combining optical tweezers with an optical microscope and Raman spectroscopy has allowed us to monitor chemical changes in trapped particles. In this case, I will be exploring how pore-forming toxins interact with cell membranes. Pneumolysin is a pore-forming toxin which is produced by the bacterium streptococcus pneumoniae that causes pneumonia as well as many other infections. It is still unclear how pneumolysin forms pores in cells, but with the use of the above techniques I hope to find out.

Tolis Panayi

"Isolation, characterisation and development of bacteriophages for the treatment of *Clostridium difficile* infections."

Supervisor(s):Martha Clokie

Clostridium difficile is a gram-positive rod anaerobic, spore forming bacterium that colonises the colon of humans and animals, that is recognised as a primarily nosocomial pathogen. *Clostridium difficile* infections (CDIs) include a wide range of clinical manifestations, ranging from asymptomatic carriage, mild and severe diarrhea and pseudomembranous colitis(PCM) an inflammation of the colonic mucosa

In recent years there have been a number of epidemics in the developed world, caused by nosocomial strains of *Clostridium difficile*. In 2010 there were 25000 infections in England and Wales, 4000 of which resulted in death. Its success as a pathogen is mainly derived from the fact that it carries multiple resistances to broad spectrum antibiotics like fluroquinolones. This has created the need for alternative methods for the treatment of *C.difficile*. One such method is the use of bacteriophages.

Bacteriophages are viruses that infect only bacteria. They have several advantages over antibiotics that make them ideal to be used as therapeutic agents in cases where antibiotic resistance is prevalent. However, due to their nature as biological entities, bacteriophages cannot be used without characterisation optimization and testing in various experimental conditions.

In my project I will investigate the potential of exploiting bacteriophages for the treatment of CDIs. At present, there are about 20 bacteriophages that infect a wide range of ribotypes. I will attempt to expand this collection by isolating more bacteriophages, characterise them and the existing ones and optimise them for use as therapeutic agents. These will subsequently be tested in an artificial gut model and in an animal model.

Joe Morley
"Dispersal and potential health effects of bioaerosols emitted from industrial composting sites"

Supervisor(s): Prof. Andrew Wardlaw, Dr. Catherine Pashley

The composting of organic waste is increasingly important. Microbial activity is central to the composting process. Some of the bacteria and fungi involved are known allergens and pathogens. These are released into the air at various stages throughout the composting process and can be carried long distances by the wind. Long term exposure to this high concentration of bioaerosols may have an impact on people's health. People who live near to sites and those who work on the sites may be at risk due to long term exposure to compost bioaerosols. This study aims to look at the dispersal and composition of compost-derived bioaerosols and look at the health of people living/working nearby. Any link between these two will hopefully become apparent.

There is a limited range of antifungal drugs which can be used to treat people with fungal infections, and so the emergence of strains of fungi which are resistant to these drugs is a concern. It has been proposed that this antifungal resistance may develop in the environment, as well as in the clinical setting. This project also aims to see if the diverse and highly dense fungal populations in compost sites may be a source of azole antifungal resistance development in *Aspergillus fumigatus*.

Accurately identifying and quantifying the microbial content of the air being studied is clearly necessary, and so the first step in this project is to run some validation experiments to compare various sampling and sample analysis methods under controlled conditions in a wind tunnel.

Raghad Hassan Sanyi
"Characterisation of mycobacterial proteins essential for replication in macrophages."

Supervisor(s): Dr Bernard Burke and Dr Galina Mukamolova

Macrophages play an important role in *M. tuberculosis* infection because they represent both the host cells and the primary effecter cells which the immune system employs for bacterial killing. The success of this pathogen is mainly due to its ability to overcome the host's immune response and

survive in the hostile environment of the macrophage phagosome. A recent research has identified a transcriptional regulator which was named the *raas* gene (regulator for antimicrobial assisted survival) which may be responsible for the survival of *M. tuberculosis* in non replicating conditions and after infecting macrophages. This transcriptional regulator appears to have a role in the persistence of the mycobacterium in tuberculosis. Initial work will focus on the Rv1279c BCG deletion mutant strain which has already been made in Dr Mukamolova's lab. My project will investigate the difference in growth pattern between the wild type BCG and the mutant (Δ Rv1279c) when infecting macrophages and molecular mechanisms underlying this phenomenon. Current work has focused on infecting macrophages with Wild type BCG and Mutant (Δ Rv1279c) to see if there is a difference in growth pattern between them at different time points. If a difference in growth pattern is observed between the wild type and the mutant, then future work will focus on studying the expression of this gene by quantitative RT-PCR and by application of reporter constructs to determine its role in the survival and replication of the mycobacterium in macrophages.

Nutan P Sapkota
"Phenotypic variation among the Tn*AbaR23* island minus mutants derived from same wild type parent."
Supervisor(s): Dr. Kumar Rajakumar

Acinetobacter baumannii colonization in various healthcare settings and the frequent association of these bacteria with severe hospital associated infections has drawn the attention of researchers and medical professionals over the last few decades. Besides having many antibiotic resistant determinants within the genome, these bacteria can rapidly acquire the resistance determinant genes, plasmids, transposons etc. from the environment. The acquisition of these resistant determinants does provide a survival advantage to the bacteria but this fitness comes with a cost.
Acinetobacter baumannii strain A424 possess 48.3kb resistant island Tn*AbaR23* that harbours 40 - 45 antibiotic resistance and efflux associated genes. The Tn*AbaR23* island was deleted *en bloc* from the wild type by allelic exchange. Two mutants DCO174 and DCOA14 were created in the same way from parent A424WT. The PFGE pattern of both mutants was found similar as expected. However, the antibiotic resistance profile of both mutants clearly showed variation. For the mutant DCO174, MIC of gentamicin, tetracycline and ciprofloxacin was higher compared to the DCOA14. Difference in antibiotic susceptibility profile was supported by variation in the fitness of both mutants in *in vitro* head-to-head competition with their parent A424WT. Both mutants have lost the resistant island but compared to the parent wild type, DCO174 seems less fit than DCOA14. It is hypothesized that the even though the resistant island is lost, the over expression of efflux pumps

other antibiotic resistance genes may have contributed to the observed reduction of fitness in DCO174.

Amin Bakir
"The Effect of Phagocytosis by Neutrophils on Mycobacterial Gene Expression"

Supervisor(s): Dr Bernard Burke

The idea of my research comes from studies on the transcriptome of Mycobacterium tuberculosis and dominance of neutrophils in phagocytosis of Mtb in sputum of TB patients. Their findings indicate that in the sputum where PMN are dominant phagocytes the transcriptome of Mtb is significantly different from transcriptome of Mtb growing in vitro.

Therefore, our aim is to determine if the gene expression profile of M. tuberculosis phagocytosed by PMN in vitro shows strong similarity to profile of Mtb in human sputum.

In this study neutrophils will be infected by BCG and Mtb then the genome of phagocytosed mycobacteria will be analysed for gene expression profile. The ongoing work is on assessing the differences in gene expression between extracellular and intracellular BCG in infected primary human monocytes using RNA extraction and qRT-PCR techniques. Because of the short lifespan of neutrophils we are currently optimising the techniques using monocytes, which have much longer life spans. We are attempting to use amikacin to avoid the interference of extracellular bacteria. We will also attempt the experiment without use of Amikacin, simply comparing the expression of certain key genes using qRT-PCR. Thus a key part of the work plan for the next few months will be to become adept at extraction of RNA from mycobacteria. Our study will then compare the gene expression profile of in vitro grown Mtb with the gene expression profile of phagocytosed Mtb, then search for any gene expression variation in terms of up-regulation or down-regulation

Keynote Speaker Bibliography

Prof. Anne Willis

Professor Anne Willis graduated in 1984 with a degree in Biochemistry from the University of Kent and obtained a PhD in Biochemistry in 1987 from University of London while working in the Imperial Cancer Research Fund laboratories (now CRUK) on DNA repair with Dr Tomas Lindahl. She then moved to Cambridge to work with Professor Richard Perham in the Department of Biochemistry where she also held a Junior Research Fellowship and then a College Lectureship at Churchill College Cambridge. She was appointed to her first independent position in 1992 as a Lecturer in the Biochemistry Department at the University of Leicester, progressing to a Reader in 2002 and a Professor in 2004. In 2004, she moved to Nottingham to take up the position of Director of Cancer Research Nottingham and Chair of Cancer Cell Biology. During this time she built up a large team of researchers working on various aspects of post-transcriptional control of gene expression. In 2009 Professor Willis was awarded a five-year BBSRC Professorial Fellowship to research into post-transcriptional control of gene expression following exposure of cells to agents that cause genotoxic stress. In particular, research initiated by the Willis laboratory has identified a new network that regulates translation following exposure of cells to UVB light. Interestingly, similar pathways are also activated following exposure to chemotoxic agents. In 2010 Professor Willis was appointed as Director of the MRC Toxicology Unit that is based in Leicester.

Prof. Robert B Sim

Animals defend themselves against microorganisms by a range of mechanisms and the first line of immune defence is known as ‘innate immunity’. Proteins of the innate immune system, such as ‘complement’ and ‘collectins’, are found in body fluids and these are capable of directly recognising and binding to microorganisms.

The collectins are proteins which recognise invading microbes and foreign particulate matter by binding to neutral sugars and they then promote interactions with phagocytes which can ingest and neutralise or destroy them – they are particularly important in recognising inhaled particles in the lung. The quaternary structures of these large complex proteins are not yet fully understood and structural studies, as well as collectin-target interactions, form the focus of the work carried out in the group headed by Professor Sim at the MRC Immunochemistry Unit at Oxford University.

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