408. Phagocytes and dendritic cells

P3859 Characterisation of a new Daisy cell line representative of human alveolar macrophage (hAM) 
Yvette Hayman, Simon Hart, Alyn Morice. Academic Cardiovacular and Respiratory Medicine, University of Hull, Castle Hill Hospital, Cottingham, East Yorkshire, United Kingdom

Introduction: Techniques used to obtain primary hAM are invasive, often providing low yields which cannot be expanded in vitro. No human cell line exists as an alternative. We characterised a new human cell line capable of expansion and spontaneous differentiation.

Methods: Cells were cultured in RPMI640 with 10% foetal bovine serum and penicillin/streptomycin (100U/ml,1mg/ml) in a humidified 5% CO2 atmosphere, passed every 2 days. Light and transmission electron microscopy comparing Daisy cells with THP-1 cells stimulated with phorbol myristate acetate (PMA,50ng/ml,24h) and flow cytometric immunophenotyping studies were performed analysing CD11b, 14, 16, 23, 24, 32, 36, 64, 163 and 206 expression. Results were compared with both THP-1 cells and primary hAM obtained by bronchoalveolar lavage. Phagocytic capability by zymosan uptake (mg/ml,1h), mycoplasma screening by fluorescence microscopy and opsonised antigen binding by flow cytometry were also assessed.

Results: Morphology showed Daisy cells to be similar in size, shape and granularity to PMA stimulated THP-1 cells with a higher proportion of heterochromatin, pseudopodia and vesicular inclusions. Daisy cells were shown to express lower levels of CD11b, 14 and 32 compared with PMA stimulated THP-1 cells yet higher levels of CD36, 80, 163 and 206. CD marker expression of Daisy cells were more closely resembled that of primary hAM. Zymosan was readily phagocytosed, mycoplasma was not detected and high levels of opsonised antigen binding were seen in Daisy but not THP-1 cells.

Conclusions: The new Daisy cell line shows characteristics of mature hAM yet can be maintained and cultured providing a useful tool in respiratory research.

P3860 Sirtuins, the anti-ageing molecules, regulate anti-oxidant capacity via FoxO3 activity in monocyctic cell line
Laura Nunez Navaira, Nicolas Mercado, Kazuhiro Ito. Airway Disease, National Heart and Lung Institute (NHLI), Imperial College, London, United Kingdom

Chronic Obstructive Pulmonary Disease (COPD) is characterised by high levels of oxidative stress due to reduced anti-oxidative stress capacity, leading to an increase of endogenous oxidative stress. Sirtuins, type III histone deacetylases, and FoxO3 are reported to participate of the oxidative stress defence and also the levels of SIRT1 and 6 are reduced in COPD samples (Nakamura Y, FASEB J, 2009).

Aims: To evaluate the effects of sirtuin inhibition and oxidative stress on the expression of several FoxO3-responsive genes, such as catalase, superoxide dismutase (MnSOD) and thioredoxin (TXN) and also on FoxO3 binding activity.

Methods: THP-1 monocytic cells were treated with a sirtuin inhibitor (sirtinol) and hydrogen peroxide (H2O2) as oxidative stress reagent. SIRT1, 2 and 6 were knocked down using RNA interference. The mRNA levels of catalase, MnSOD and TXN were measured by RT-PCR and normalized against GNB2L1. FoxO3 binding capacity was measured by ELISA.

Results: FoxO3 nuclear localization was not affected by H2O2 or sirtinol, but the activity binding was increased with oxidative stress. This activation was abrogated with a pretreatment of sirtinol. H2O2 increased mRNA levels of MnSOD (25%) and TXN (70%), and again sirtinol pretreatment led to the abrogation of this activation. SIRT1, 2 and 6 were knocked down by 50% at protein level. TXN activation by H2O2 was blocked in every sirtuin knock down.

Discussion: Defect of sirtuin expression may cause a reduction of the anti-oxidative stress capacity by regulating mRNA levels of TXN through FoxO3 as COPD. These results highlight the important role of sirtuins and its possible use as therapeutic target for treating COPD.

P3861 YKL-40: Novel marker for pro-inflammatory M1 macrophages
Lisa Kunz, Emily van’t Wout, Annemarie van Schadewijk, Pieter Hiemstra. Pulmonology, Leiden University Medical Center, Leiden, Netherlands

Macrophages play a major role in the pathogenesis of COPD and comprise a heterogeneous cell population with pro- (M1) and anti-inflammatory (M2) cells. CD163 has been identified as a M2 marker, however, many M1 markers are not suitable for analysis. Cells positive for YKL-40, a chitinase-like-protein, are elevated in the lungs of smoking than non-smoking COPD patients. YKL-40 strongly reduces YKL-40 expression in peripheral blood mononuclear cells in vitro, suggesting that inhalated steroids in COPD may decrease YKL-40 expression. We evaluated YKL-40 expression in cultured M1 and M2, and the effect of dexamethasone on its expression.

Monocytes were cultured in vitro for 7 days with GM-CSF or M-CSF (for M1 and M2, respectively) and stimulated for 24h with LPS, TNFα, oncostatin M or IL-6. Dexamethasone was added in various concentrations. IL-12 and IL-10 ELISA were used to check differentiation into M1 and M2, respectively. YKL-40 ELISA was performed on supernatants; quantitative PCR (qPCR) was used to analyse YKL-40 mRNA. Differences between conditions were calculated with Wilcoxon signed rank tests.

M1 cells secreted more YKL-40 than M2, independent of stimulation (261±mg/ml vs 65ng/ml, p<0.03). Compared to medium, LPS, TNFα, oncostatin M or IL-6 stimulation did not affect YKL-40 release in M1 and M2 (p>0.05). qPCR confirmed these results. Dexamethasone dose-dependently and strongly inhibited YKL-40 in both M1 and M2 (p<0.05).

In conclusion, M1 have a higher expression of YKL-40 than M2, which is unchanged by pro-inflammatory stimuli. In addition, YKL-40 release is strongly inhibited by dexamethasone in both M1 and M2. These results indicate that YKL-40 expression can be used as a marker for M1 macrophages in vivo, and possibly in vitro.

P3862 Lipid laden alveolar macrophages arise from airway reflux and aspiration
Yvette Hayman, Simon Hart, Alyn Morice. Academic Cardiovacular and Respiratory Medicine, University of Hull, Castle Hill Hospital, Cottingham, East Yorkshire, United Kingdom

Introduction: Lipid laden macrophages have previously been reported to be present in the diseased human airway, secondary to gastro-oesophageal reflux. We investigated the possibility that the lipid index (LI) system of scoring cellular lipid content by oil red o (ORO) staining could correlate with disease status and the Hull Airway Reflux Questionnaire (HARQ). We also investigated the hypothesis that lipid could be ingested directly from gastric contents by alveolar macrophages.

Methods: Primary alveolar macrophages were obtained from bronchoalveolar lavage (BAL) fluid of patients undergoing diagnostic bronchoscopy. Patients were asked to fill in the HARQ prior to treatment. Lavage fluid was filtered and centrifuged (350g;10min.) and cells transferred to glass slides using cytospin equipment. Cells were stained with ORO, counterstained with haematoxylin and the LI system of scoring cellular lipid content performed on supernatants; quantitative PCR (qPCR) was used to analyse YKL-40 mRNA.

Results: 18 patients with a range of respiratory diseases had LI scores ranging from 4 to 309. LI scores correlated with the HARQ but not to a particular disease group. PMA stimulated THP-1 cells showed maximal lipid accumulation by ORO staining with 10% v/v high fat liquid meal for 24h. No lipid accumulation was seen with the control feed.

Conclusions: Macrophages were shown to be capable of lipid uptake directly from liquid meal and airway reflux correlates with the presence of lipid laden macrophages in the airway.
P3863
Reprogramming of alveolar macrophages – Prospect of successful treatment in COPD
Svetlana Lyamina1, Igor Maev2, Georgy Yurenev2, Igor Malyshev1.

Objective: To testify that serum concentration change with TGF-β expression level of cell markers CD80, CD25 (M1), CD206, CD163 (M2) and CXCL8 release in cell culture promotes reprogramming of morphological and functional phenotype of alveolar macrophages, which can be used for reaching Th1/Th2 balance and regulation of lung immunity in COPD patients.

Results: Serum concentration from 5% to 15% led to increasing of serum concentration from 5% to 15% led to increasing of obtained data decreasing of serum concentration from 15 to 5% led to M1 phenotype reprogramming. In view of obtained data decreasing of serum concentration from 15 to 5% led to M1 phenotype reprogramming.

Conclusions: Changes in serum concentration in cell culture promotes reprogramming of morphological and functional phenotype of alveolar macrophages, which can be used for reaching Th1/Th2 balance and regulation of lung immunity in COPD patients.

P3864
Lipid laden macrophages in patients with chronic cough

Methods: Twenty five patients with chronic cough that could not be attributed to other causes were included. Blood samples were obtained from all patients and after overnight fasting. Preparation of platelet poor plasma (PPP) was done with a plateletpheresis machine. Phagocytic activity of mononuclear cells obtained from PPP were stained with MitoTracker (M7515, Invitrogen) and counted. Statistical analysis was performed with the Chi-squared test and Student t-test for continuous variables and p<0.05 was considered statistically significant.

Results: We observed that percentage of phagocyting blood monocytes was significantly increased in SA as compared to healthy controls, we found significantly increased expression of CD14+CD16+CD35- and decreased expression of CD35 and CR3 (CD11b) receptors.

Conclusions: The presence of LLM in sputum could represent worse pulmonary radiological findings (mild lesions) in 60% of them and they had less FEV1 240 mL. The LLM in sputum can appear in these patients as a marker of aspiration. This finding may be a marker of aspiration. This finding may be related to aspirated food bolus that cause more severe lesion and worse inflammation.

P3865
Effects of Bu-Zhong-Yi-Qi-Tang (Hocheukito; TJ-41) on the inflammatory responses in alveolar macrophages of hyperglycemic mice

Methods: The presence of LLM in sputum can appear in these patients as a marker of aspiration. This finding may be related to aspirated food bolus that cause more severe lesion and worse inflammation.

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present in the blood and lung during respiratory diseases including bacterial pneumonia and ARDS. However, the precise pathogenic role of immune complexes in these conditions is unclear.

Binding of immune complexes to the uniquely human stimulatory IgG receptor FcγRIIA is constitutively suppressed on neutrophils and macrophages. Elucidating the mechanism behind this suppression will help us understand how the body regulates its response to immune complexes.

The erythroleukaemia cell line K562 that expresses the FcγRIIA inherently and exhibits FcγRIIA suppression was used as a model. The effects of microbial neuraminidases on DC activity were determined by binding the FcγRIIA were tested by flow cytometry. We also investigated whether there is a protein in close proximity to FcγRIIA that could potentially block its IgG binding site by protein cross-linking.

Lastly, the stimulatory character of the receptor was explored by calcium signalling. Although the receptor exhibits suppressed immune complex binding, microbial neuraminidases can significantly augment the ability of the FcγRIIA to bind immune complexes. The cross-linking experiments reveal that there is a protein in close proximity with FcγRIIA that could be blocking its IgG binding site under basal conditions. Finally, while FcγRIIA exhibits limited binding of immune complexes in its native state, the stimulatory signals produced by the receptor on contact with immune complexes are significantly strong.

Understanding how the body regulates immune complexes could lead to identification of novel methods for both activating and inhibiting the progression of immune complex mediated inflammation.

### P3869

**Anti-inflammatory activity of macrolides in peripheral blood mononuclear cells and the identification of potential biomarkers of azithromycin administration**

Simon Hall, Stuart Farrrow. **Refractory Respiratory Inflammation DPU, GlassSmithKline, Stevenage, United Kingdom**

Many studies in the recent past have determined that macrolide antibiotics have anti-inflammatory and immunomodulatory activity in addition to their efficacy in treating bacterial infection. Macrolides have been successfully used in the treatment of diverse chronic inflammatory respiratory disorders, including diffuse panbronchiolitis (DPB), cystic fibrosis (CF) and bronchiolitis obliterans (BOO).

We investigated the ability of azithromycin to attenuate the effects of a lymphocyte directed pro-inflammatory stimulus in PBMCs from healthy volunteers. Our results demonstrate that azithromycin significantly inhibited the induction of proliferation and the release of IL17 in these cells. Treatment with azithromycin in the absence of a pro-inflammatory stimulus in PBMCs induced the release of IL10 in a dose dependent manner 24 h after challenge. In the same model, azithromycin caused a dose dependent increase in GMCSF 24 h after treatment. In contrast, azithromycin exhibits significant anti-inflammatory and immunomodulatory properties and IL10 and GMCSF may prove to be useful biomarkers following macrolide therapy in respiratory disorders.

### P3870

**A novel macrodil fluoride/fluoroketolide, solithromycin (CEM-101), reverses corticosteroid insensitivity via activation of protein phosphatase PP2A**

Yoshiki Kobayashi, Rossos Christos, Peter Barnes, Kazunori Ishii. **Airway Disease, NHLL, Imperial College, London, United Kingdom**

**Introduction:** Activation of PI3K kinase causes oxidative stress-induced corticosteroid (CS) resistance via HDAC2 reduction. We have recently demonstrated that a novel macrodil fluoride/fluoroketolide, solithromycin (Soli, CEM-101) restores CS sensitivity via HDAC2 reduction. We have recently demonstrated that a novel macrolide/fluoroketolide, solithromycin (Soli, CEM-101) restores CS sensitivity via HDAC up-regulation due to PI3K signaling inhibition (ATS2010).

**Aims:** To investigate the role of a serine/threonine phosphatase PP2A on regulation of the PI3K pathway as the target of Soli. We have recently demonstrated that a novel macrodil fluoride/fluoroketolide, solithromycin (Soli, CEM-101) restores CS sensitivity via HDAC up-regulation due to PI3K signaling inhibition (ATS2010).

**Methods:** Patients with asthma were treated with suboptimal doses of classical pro-inflammatory stimuli were boosted by the action of OM-85, opening new venues for further investigation.

**Conclusions:** NOD1 and NOD2 receptors in a significant, dose-response manner.

OM-85 (Broncho-Vaxom®, Broncho-Munal®, Ommunal®) has proven efficacy in the prevention of recurrent infections of the airways and acute exacerbations in COPD. OM-85 is a lyophilized bacterial extract comprising fractions of 21 different inactivated bacterial strains. Previous work has shown that OM-85 acts as an immunostimulant, and that it may act on human dendritic cells (hDC). However, the molecular mechanisms through which OM-85 activates hDC remained largely unknown.

**Aims:** Investigate the impact of OM-85 stimulation on hDC and identify the immune receptors implicated in OM-85 response.

**Methods:** Primary and in vitro derived hDC were used to determine the precise OM-85 effects on DC biology. Stably transfected cell lines expressing human receptors were used to characterize OM-85 receptor-dependent activity.

**Results:** In hDC, OM-85 induced the secretion of IL-6 and of several chemokines (CCL2, CCL3, CXCL8, CXCL6, CCL20, CCL22) with a potency comparable to the prototypical activating stimulus LPS. OM-85 potentiated the effect of IFNγ in terms of IL-6, IL-12 and IL-10 release. The induction of selected chemokines by suboptimal doses of classical pro-inflammatory stimuli were boosted by the presence of OM-85. In addition, it was identified that OM-85 activates TLR2, TLR4, NOD1 and NOD2 receptors in a significant, dose-response manner.

**Conclusions:** OM-85 induces a mild and weak shaped iDC activation through selected pattern recognition receptors. This activation may contribute to the generation of a “pre-alarm state” resulting in an early protection towards incoming infection. These results provide new insights in the understanding of the mode of action of OM-85, opening new venues for further investigation.

### P3871

**Exposure to cigarette smoke affects the response of dendritic cells to pneumococcus**

Olivier Le Rouzic1,1, Gaille Remy1, Cyrille Jardin2, Isabelle Tillie-Leblond2, Muriel Pichavant1, Philippe Gossel1, 1Center for Infection and Immunity of Lille, Institut Pasteur de Lille, Lille, France; 2Service de Pneumologie et d’Immunologie, Hôpital A Calmette, CHRU de Lille, Lille, France

Development of chronic obstructive pulmonary disease (COPD) is linked to tabagism. Acute exacerbation potentially related to infection by streptococcus pneumoniae is responsible for the progression of the disease. Innate immunity associated with dendritic cells (DC) mobilization is involved in the pathophysiology of the disease. We hypothesize that cigarette smoke impairs the response of DC to pathogens, a mechanism that may be involved in COPD progression.

Monocyte-derived DC of healthy donors were exposed to cigarette smoke extract (CSE) and next to pneumococcus (serotype 1). First, endotoxicity and bactericidity of S. pneumoniae was analyzed. DC phenotype (costimulatory molecules and en- doctysis receptors) and production of immunoregulatory cytokines were measured as well as the capacity of DC to activate naive T cells. Our data showed that CSE exposure inhibited the pneumoccus-dependent expression of CD40, CD80 and CD86 costimulatory molecules. Similarly, preflam- matory cytokine production (IL-12 and TNF-a) was inhibited by CSE exposure. In DC/T coculture, this was associated with a decrease secretion of IL-17 and IFNγ by T cells. Unexpectedly, this exposure to CSE increased the endocytosis of pneumococcus, whereas CD206 and CD16 expression was affected in an opposite manner. The effect of CSE was mostly related to oxidative stress since it was inhibited by addition of N-acetyl cysteine.

In summary, CSE exposure impairs the capacity of DC to activate antigen-specific T cells against pneumococcus, although it does not alter their endocytosis. These data will be confirmed by the ex vivo analysis of DC phenotype in COPD patients with exacerbation.

### P3872

**OM-85 shapes dendritic cell activation into a “pre-alarm” phenotype**

Daniela Bossi1,1, Nacha Nowak1, Xena Vaira1, Patricia Jeande1, Gabriella Sabatini2, Silvano Sozzani1,1, 1Dipartimento di Scienze Biomediche e Biotecnologie, Università degli Studi di Brescia, Brescia, Italy; 2Preclinical Development, OM Pharma, Myerin/Geneva, Switzerland; 3Department Immunology and Inflammation, IRCCS Clinical Institute Humanitas, Milan, Italy

**Background:** OM-85 (Broncho-Vaxom®, Broncho-Munal®, Ommunal®) has proven efficacy in the prevention of recurrent infections of the airways and acute exacerbations in COPD. OM-85 is a lyophilized bacterial extract comprising fractions of 21 different inactivated bacterial strains. Previous work has shown that OM-85 acts as an immunostimulant, and that it may act on human dendritic cells (hDC). However, the molecular mechanisms through which OM-85 activates hDC remained largely unknown.

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**Conclusions:** OM-85 induces a mild and weak shaped iDC activation through selected pattern recognition receptors. This activation may contribute to the generation of a “pre-alarm state” resulting in an early protection towards incoming infection. These results provide new insights in the understanding of the mode of action of OM-85, opening new venues for further investigation.

### P3873

**Altered phenotype of blood dendritic cells in patients with acute pneumonia**

Katharina Dreschler, Kai Bratke, Sebastian Petermann, Petra Thamm, Michael Kuepper, J. Christian Virchow, Marek Lommatzsch. **Pneumology, University of Rostock, Rostock, Germany**

**Background:** Dendritic cells (DCs) play a key role in the host defense against inherited pathogens. However, the phenotype of blood DCs in patients with acute infections is unknown.

**Objective:** To investigate the number and the expression of function-associated molecules of blood DCs in patients with acute infections.

**Methods:** Sixteen patients with an acute pneumonia and 19 controls without pneumonia were included in the study. The number as well as the expression of function-associated molecules of myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) were analysed in peripheral blood using four-colour flow cytometry.

**Results:** Elevated concentrations of procalcitonin (median: 0.55 ng/ml) and the
rapid response to antibiotic treatment suggested a bacterial origin of the pneumonia in the patients. Total mDC (median: 27% of the controls) and pDC counts (median: 53% of the controls) were markedly reduced in patients with pneumonia, as compared to controls. Percentages of blood mDCs, but not pDCs, were negatively correlated with serum concentrations of c-reactive protein (CRP). Patients with pneumonia were characterised by a significantly increased expression of Fe gamma receptors (CD32 and CD64) on mDCs and the Toll-like receptor 9 (TLR9) in pDCs.

Conclusions: Circulating DCs are markedly reduced in patients with pneumonia, and characterised by an upregulation of molecules recognising pathogen-associated molecular patterns (PAMPs) and opsonised antigens.

P3874
Humanized S.typhi flagellin (FliC) transfected non-small cell lung cancer (NSCLC) cells induce local inflammatory and necrotic changes in an experimental model

Marek Jankowski1, Janusz Kowalewski2, Tomasz Wandike1, Robert Lenartowski1, Piotr Kopinski1, Maciej Danczewicz2, Tomasz Trykowski1, 1Dept of Gene Therapy, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; 2Dept of Thorax and Tumor Surgery, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; 3Dept of Clinical Pathobiotechnology, Nicolaus Copernicus University, Bydgoszcz, Poland; 4Dept of Clinical Pathobiotechnology and Chemistry, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

Background: Tumors, including NSCLC, develop numerous local mechanisms which impair maturation of dendritic cells (DCs). The delivery of stimulatory signals to DCs in cancer microenvironment is believed to be an effective means to break tumor-induced tolerance.

Aim: Evaluation of immunostimulatory properties ofTLR5 ligand, FliC, cell membrane-displayed in experimental model of Lewis Lung Cancer (LLC) transfected with a novel plasmid vector system.

Methods: Cell membrane-expressed humanized FliC transgene was inserted to the pCDNA3.1Zeo(+) plasmid-based construct. Tumor specific two-step transcriptional activation system was additionally used. A549 cells, the model of NSCLC, transfected with FliC-coding plasmid, induced the maturation of human monocyte-derived DCs in co-cultures. Two groups of C57BL6 mice bearing a subcutaneous LLC tumor were injected intratumorally with in-vivo-JetPEI and FliC plasmids or in vivo-JetPEI and phosphate-buffered saline as a control. Four administrations were performed within 1 week. Tumor volumes and animal survival were monitored for 6 weeks.

Results: Plasmid injections delayed the growth of implanted LLC tumors and significantly improved animal survival rates. Histological examination of specific plasmid-injected tumors revealed lymphocyte infiltrates and remarkable necrosis.

P3875
LSC 2011 Abstract: Thymic stromal lymphopoietin is a central regulator of anti-viral CD8+ T cell response

Koshika Yadava1,2, Sichelstiel Anke1,2, Aurelien Trompette1,2, Nicola Harris3, Benjamin Marsland1,2, 1 Service de Pneumologie, CHUV (Centre Hospitalier Universitaire Vaudois), Lausanne, Vaud, CH; 2 Faculty of Biology and Medicine, University of Lausanne, University of Lausanne, Vaud, CH; 3 Global Health Institute, EPFL (École Polytechnique Fédérale de Lausanne), Lausanne, Vaud, CH

TSLP is an IL-7 like cytokine that is primarily produced by epithelial cells at mucosal surfaces. It has been widely studied in Th2-driven inflammatory disorders such as atopic dermatitis and asthma. Although both viral nucleic acid analogues and pro-inflammatory cytokines associated with active viral infections are potent stimulators of TSLP expression in vitro, its role in antiviral immunity is unknown. To elucidate the role of TSLP in viral infections, we investigated the immune response against influenza A in mice deficient in TSLPR. We found that TSLPR-deficient mice exhibited impaired clearance of the virus at late time points post infection, indicative of a defect in the adaptive immune response. Although priming in the lymph node was unaffected, the virus-specific CD8+ T cell response in the lung was compromised in the absence of TSLPR. This defect was characterized by the reduced frequency of virus-specific CD8+ T cells as well as reduced effector functions such as granzyme B expression and interferon-γ production. Using mixed bone marrow chimeras and adoptive transfer studies, our data suggests that TSLP affects influenza-specific responses by modulating the function of recruited inflammatory dendritic cells (DCs). Pulmonary DCs isolated from infected lungs of TSLPR deficient mice were defective in inducing proliferation of antigen specific naïve T cells in vitro. Furthermore in the absence of TSLPR the production and trans presentation of IL-15 by CD11b+ inflammatory DC was impaired. We propose that TSLP regulates activation of antigen specific cytotoxic T cells at the site of infection by modulation of DC function and suggest a crucial link between TSLP and IL-15 production during infection.