LMG
LEUKOCYTE
MIGRATION
GROUP

Second BSI Leukocyte Migration Group Meeting

"Leukocyte Migration in Health and Disease"

Birmingham 10-11th February 2015

Programme

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Welcome to Birmingham

We are delighted to welcome you to Birmingham for the second meeting of the BSI Leukocyte Migration Affinity Group (LMG).

The LMG aims to facilitate discussion, networking and the dissemination of knowledge for all those interested in the migration of immune cells. Leukocyte migration influences every aspect of immunology from immune homeostasis to inflammation and disease. It is a topic of interest to a broad spectrum of immunology researchers in UK and worldwide. Those in the UK studying leukocyte migration come from a range of related disciplines including chemokine biology, lymphoid organ development, inflammation and infection. We aim to bring together these related disciplines and highlight the latest developments in this most exciting of fields.

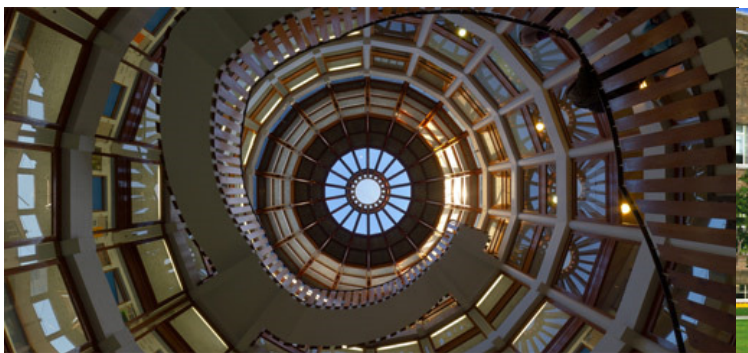
For our second meeting, we have representatives from across the UK and abroad.

The meeting has five themes:
- Dendritic cell migration
- Crossing Blood Vessel Endothelium
- Regulation of Recruitment
- T Cell Migration
- Migration in Cancer and Infection

Each theme features one of our keynote speakers, accompanied by talks from students and early career researchers.

The Leukocyte Migration Group Committee

Chris Hansell
Megan MacLeod
Clive McKimmie
Helen McGettrick
Graeme O'Boyle
Rob Nibbs



DAY 1 10th FEBRUARY 2015

13.00 – 14:00	Registration & coffee.
14:00 – 14:10	Welcome and Introduction by host, Helen McGettrick (LMG)
14:10 – 15:00	**Nancy Hogg (London):** How adhesion guides the migration of leukocytes

SESSION 1: Dendritic Cell Migration
Chair: Helen McGettrick (LMG)

15:00 – 15:20	**Menna Clatworthy (Cambridge):** IgG immune complexes stimulate CCR7-dependent dendritic cell migration
15:20 – 15:40	**Steven Bryce (Glasgow):** The atypical chemokine receptor ACKR4 facilitates dendritic cell migration during inflammation by scavenging CCL19
15:40 – 16:00	**Louise Johnson (Oxford):** A key role for the lymphatic vessel endothelial receptor LYVE-1 in hyaluronan-mediated dendritic cell trafficking
16:00 – 16:30	Coffee/Tea. Put up Posters

SESSION 2: Crossing Blood Vessel Endothelium
Chair: Clive McKimmie (LMG)

16:30 – 16:50	**Myriam Chimen (Birmingham)**: Monocyte subsets differentially modulate the inflammatory responses of endothelial cells
16:50 – 17:10	**Jasmeet Reyat (Birmingham):** Endothelial cell ADAM10 promotes lymphocyte transmigration *in vitro*
17:10 – 17:50	**Sussan Nourshargh (London):** Neutrophil transmigration *in vivo*: Mechanisms and pathogenesis
18:00 – 19:00	Wine, Nibbles and Posters
19:00	**Social Event:** The Green Man, Harborne (http://www.emberinns.co.uk/the-green-man-harborne/)

DAY 2 11th FEBRUARY 2015

SESSION 3: Regulation of Recruitment
Chair: Graeme O'Boyle (LMG)

09:00 – 09:10	Welcome and short introduction, Graeme O'Boyle (LMG)
09:10 – 09:50	**David Adams (Birmingham):** Enzymatic control of leukocyte recruitment to the liver
09:50 – 10:10	**Lydia Edey (London):** Ly-6C^{high} monocyte trafficking to the myometrium in late gestation
10:10 – 10:30	**Vicky Morrison (Glasgow):** Beta2 integrins in dendritic cells
10:30 – 11:00	Coffee/Tea. Poster Viewing

SESSION 4: T Cell Migration
Chair: Chris Hansell (LMG)

11:00 – 11:20	**Jessica Borger (Edinburgh):** Caveolin-1 is involved in integrin-mediated CD8 T cell adhesion and homing to lymphoid tissues.
11:20 – 11:40	**Helen Baldwin (London)**: CCR6^{+} T cells from Psoriatic Arthritis patients are resistant to suppression of migration by Treg towards CCL20
11:40 – 12:00	**Kave Shams (Glasgow):** The atypical chemokine scavenging receptor ACKR2 prevents psoriasiform pathology by defining the boundaries of T cell localisation within the skin
12:00 – 12:40	**Bernhard Moser (Cardiff):** Control of T cell localization during immune surveillance of peripheral tissues
12:40 – 13:40	Lunch. Poster Viewing

SESSION 5: Migration in Cancer and Infection
Chair: Megan Macleod (LMG)

13:40 – 14:20	**Bin-Zhi Qian (Edinburgh):** Characterisation and functional study of metastasis-associated macrophages
14:20 – 15:00	**Philippe Bousso (Paris):** Decoding T cell responses to cancer and infections using *in vivo* imaging (Supported by the Abercrombie Fund)
15:00 – 15:10	Closing Remarks by Megan MacLeod (LMG)
15:10	Departure

Nancy Hogg

Emeritus Group Leader, London Research Institute, UK

Nancy Hogg has had long and distinguished career, culminating in her role as head of the Leukocyte Adhesion laboratory at the London Research Institute. Although she has made many contributions to the field she is particularly well known for her work that has highlighted how leukocytes use integrins to enter and exit tissues. She is perhaps best known for her work that investigated interactions between ICAM-1 and the integrin LFA-1(aLβ2;CD11a/CD18), which mediates many adhesive interactions necessary for the function of leukocytes. Integrins on leukocytes are normally in an inactive state, preventing random interactions, and are activated via triggering through other receptors. Her work has shown how signalling activates LFA-1 as well as the signals generated by LFA-1 itself upon ICAM-1 binding, using both in vitro and in vivo model systems. More recently she has focused on kindlin-3, which is mutated in LAD-III patients. Recent publications have also highlighted a crucial role for S100A9 in the regulation of neutrophil recruitment in models of cancer and infection.

http://www.london-research-institute.org.uk/research/past-researchers/nancy-hogg

Sussan Nourshargh

Head of Centre for Microvascular Research & Professor of Microvascular Pharmacology, Barts and The London, Queen Mary's School of Medicine and Dentistry, London, UK.

Sussan Nourshargh investigates the mode, dynamics and mechanisms of leukocyte transmigration, the final stage in the leukocyte adhesion cascade that describes the movement of leukocytes from the vascular lumen into inflamed and/or injured tissues. To achieve this goal she has investigated the interactions of leukocytes with different components of microvessel walls (endothelial cells, pericytes and the vascular basement membrane) using both physiologically relevant as well as pathological inflammatory models. A key component of her work is a research programme that investigates how pathological inflammatory insults impact the dynamics of neutrophil-vessel wall interactions and the implications of disrupted modes of neutrophil transmigration (eg neutrophil reverse transmigration) on inflammatory disease development and dissemination. Collectively through the application of advanced imaging platforms such as confocal intravital microscopy to analyse leukocyte-vessel wall interactions *in vivo*, her work aims to unravel previously unexplored cellular and molecular physiological concepts and identify disease-specific phenomena.

Sussan is a pharmacologist who studied at University College London (BSc) and King's College London (PhD) and became Professor of Immunopharmacology at Imperial College London in 2006. In 2007 she joined Barts and The London Medical School to establish and head a new Centre focusing on Microvascular Research. In 2012 was awarded status as a Wellcome Trust Senior Investigator Award and a Fellow of the Academy of Medical Sciences.

http://www.whri.qmul.ac.uk/staff-all/staff-research/161-nourshargh-sussan-fmedsci

Barts and The London
School of Medicine and Dentistry

David Adams

Professor of Hepatology and Dean of Medicine, University of Birmingham, UK

David Adam's research interests are focused on mechanisms of immune-mediated liver disease. His clinical interests are transplant hepatology and autoimmune liver disease. After initial training in hepatology in Birmingham he continued his immunology training with Dr Stephen Shaw at the Experimental Immunology Branch of the National Cancer Institute, Bethesda, USA before being appointed to the Chair of hepatology in Birmingham in 1997. He is currently an associate editor of Liver Transplantation and the American Journal of Physiology and special section editor for the Journal of hepatology. He served on the scientific committee and governing board of the European Association for Study of the Liver between 2004-2007 and currently sits on its Ethics committee. He was a councillor for the European Society for Organ Transplantation between 2004-2008. He was made a Fellow of the Academy of Medical Sciences in 2000.

He has a long-standing interest in understanding how leukocyte-endothelial interactions regulate the recruitment of effector cells in chronic liver disease and his group have defined molecular mechanisms used by hepatic endothelium to control the entry of leukocytes from the blood. They have recently begun to use this information to develop cell therapy for liver disease by targeting pathways involved in the recruitment of damaging effector cells or by promoting the recruitment of therapeutic cells including dendritic cells, stem cells and regulatory T cells that may be used to manipulate immune responses in patients.

http://www.birmingham.ac.uk/staff/profiles/iandi/adams-david.aspx

UNIVERSITY OF BIRMINGHAM

Bin-Zhi Qian

Academic Research Fellow, Edinburgh Cancer Research UK Centre, UK.

Bin-Zhi Qian received his bachelor degree in biochemistry from Fudan University at Shanghai, China. He then joined Chinese Human Genome Centre at Shanghai (CHGCS) as a research fellow working on gene expression profiling of gastric cancer and hepatocellular carcinoma using patient samples (PNAS 2001, World J Gastroenterol. 2004). In 2002, Bin-Zhi moved to New York to join the Ph.D. program at Albert Einstein College of Medicine under the mentorship of Professor Jeffrey Pollard's. His research was focusing on the role of macrophages in breast cancer distal metastasis (PLoS One 2009, Cell 2010, Nature 2011). He received his PhD in biomedical sciences in 2009 and stayed for a short postdoctoral training with a prestigious 'Susan G. Komen for the Cure' Postdoctoral Fellowship. He then joined Dr. Charles Sawyers' group at Memorial Sloan Kettering Cancer Center in New York to continue his training to investigate the role of tumour microenvironment in prostate cancer metastasis and drug resistance.

In 2014, he was awarded a Cancer Research UK Career Development Fellowship and University of Edinburgh Chancellor's Fellowship to establish his independent research group with a joint appointment at Edinburgh Cancer Research UK Centre & MRC University of Edinburgh Centre for Reproductive Health at University of Edinburgh. His long-term research goal is to understand the mechanism of cancer metastasis and develop effective therapeutic approaches by focusing on the interactions among metastatic tumour cells and associated host cell types.

http://www.ecrc.ed.ac.uk/Research/item/Dr-Bin-Zhi-Qian.html

Philippe Bousso

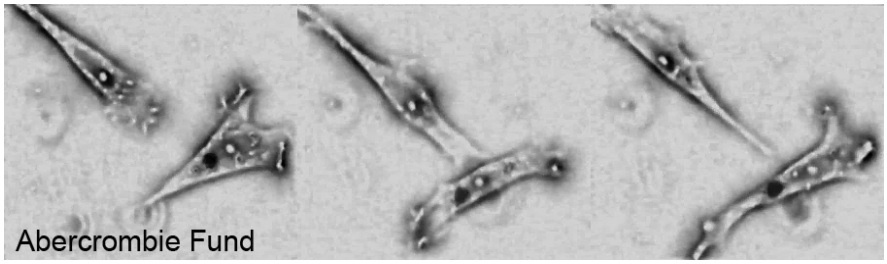
Group Leader, Dynamics of Immune Responses Unit, Institut Pasteur Paris, France

Philippe Bousso is an internationally leading immunologist heading the Dynamics of Immune Responses Unit at the Pasteur Institute who has diverse research interests in infectious disease, transplant biology and cancer. With the help of innovative functional imaging approaches, his research aims at understanding and manipulating immune responses in the context of disease pathogenesis. In recent years, his lab helped redefine the process by which T cells are activated *in vivo*. His work in the field of infectious diseases offered the first real demonstration that effector cytokines were acting over extended distances within infected tissues to control infections with intracellular pathogens. His lab has also characterized a novel cellular pathway responsible for graft rejection. Finally, in the context of tumor immunity, his group identified distinct roles of T cells and NK cells in tumor cell killing and uncovered the mode of action of anti-CD20 therapy, the most common immunotherapy used to treat B cell lymphomas.

http://www.pasteur.fr/recherche/unites/dri/

Institut Pasteur

Philippe Bousso travel was supported by the:



SESSION 1: Dendritic Cell Migration

IgG Immune Complexes Stimulate CCR7-dependent Dendritic Cell Migration to Lymph Nodes
Menna Clatworthy, Caren Aronin, Rebeccah Mathews, Ronald Germain

Antibodies are critical for defense against a variety of microbes but may also be pathogenic in some autoimmune diseases. Many effector functions of antibody are mediated by Fc_γ receptors ($Fc_\gamma Rs$), which are found on most immune cells, including dendritic cells (DCs). DCs are important antigen presenting cells and play a central role in inducing antigen-specific tolerance of immunity. Following antigen acquisition in peripheral tissues, DCs migrate to draining lymph nodes via lymphatics to present antigen to T cells. In this study we demonstrate that $Fc_\gamma R$ engagement by IgG immune complexes (IC) stimulates DC migration from peripheral tissues to the paracortex of draining lymph nodes. *In vitro*, IC-stimulated murine and human DCs embedded in a 3D collagen matrix showed enhanced directional migration in a CCL19 gradient and increased CCR7 expression. Using intravital two-photon microscopy, we observed that local administration of IC resulted in dermal DC mobilisation in CD11c EYFP mice. We confirmed that dermal DC migration to lymph nodes was CCR7-dependent and increased In the absence of the Inhibitory Fc receptor, $Fc_\gamma RIIb$. These observations have relevant to autoimmunity, because autoantibody-containing serum from mice and humans with systemic lupus erythematous also increased dermal DC migration to lymph nodes *in vivo*, suggesting that this process may occur in lupus, potentially driving the inappropriate localisation of autoantigen-bearing DCs.

The atypical chemokine receptor ACKR4 facilitates dendritic cell migration during inflammation by scavenging CCL19
Steven Bryce, Darren L Asquith, Shannon Bromley, Andrew Luster, Gerard Graham, Robert Nibbs

The migration of dendritic cells from tissues to draining lymph nodes is a critical step in the induction of peripheral tolerance and the initiation of adaptive immune responses. This is dependent on CCR7 expression by dendritic cells. In response to the chemokine CCL21, CCR7 directs dendritic cells into lymphatic vessels in the tissue, and permits their transit from the subcapsular sinus into the lymph node parenchyma. The CCR7 ligands CCL19 and CCL21 also bind ACKR4, an atypical chemokine receptor expressed by keratinocytes in the skin and lymphatic endothelial cells lining the subcapsular sinus. In mice, ACKR4 controls interfollicular CCL21 gradients, and enhances dendritic cell entry into the lymph node parenchyma from the subcapsular sinus. Here we report that Ackr4 deficiency disrupts CCR7-dependent dendritic cell arrival at skin-draining lymph nodes during cutaneous inflammation. We show that this, at least in part, is due to the defective departure of dendritic cells from inflamed skin, and is accompanied by dysregulation of bioavailable CCL19 and CCL21 in the skin. Strikingly, genetic deletion of CCL19 completely rescues the defective inflammationdriven trafficking of dendritic cells caused by Ackr4 deficiency. Thus, by regulating CCL19, ACKR4 helps maintain CCR7-dependent dendritic cell departure from inflamed tissues.

A Key Role for the Lymphatic Vessel Endothelial Receptor LYVE-1 in Hyaluronan-mediated Dendritic Cell Trafficking
Louise Johnson, Suneale Banerji, David Jackson

The lymphatic system provides an essential conduit for antigen presenting cells such as mature dendritic cells (DCs) to migration from the periphery to draining lymph nodes, to elicit immune responses. Diapedesis across the lymphatic endothelium is a critical step in this process and previous work from our own and other laboratories has shown that this is tightly regulated by adhesion molecules and chemokines. The lymphatic endothelial hyaluronan receptors LYVE-1 is highly expressed in the lymphatic endothelium of initial lymphatic capillaries associated with DC transit. Here, we show that lymph-borne trafficking of DC from inflamed skin to draining lymph nodes is impaired in LYVE-$1^{-/-}$ mice and in wild-type mice administered with LYVE-1 mAbs that block hyaluronan binding. Furthermore, we demonstrated that LYVE-1 mediated adhesion and transmigration of DC to primary lymphatic endothelium *in vitro* through transient interactions with hyaluronan expressed on the DC surface as a pericellular matrix. Critical to these events is the formation of a lymphatic endothelial transmigratory cup lined with LYVE-1 that surrounds transiting DCs and promotes their engagement with hyaluronan. These findings reveal a previously unrecognised role for hyaluronan in lymphatic trafficking and identify for the first time the physiological function of a widely used lymphatic marker.

SESSION 2: Crossing Blood Vessel Endothelium

Monocyte Subsets Differentially Modulate the Inflammatory Responses of Endothelial Cells
Myriam Chimen, Clara Yates, Gerard Nash, Ed Rainger

Monocytes contribute to the cycle of inflammation which occurs during the initiation of atherosclerosis. We have shown in a monocyte-endothelial cell (EC) coculture, that monocytes stimulate EC so they recruit flowing neutrophils. Here we investigated the contributions of $CD14^+CD16^-$ ($CD16^-$) and $CD14^+CD16^+$ ($CD16^+$) monocyte subsets to this process. $CD16^-$ and $CD16^+$ monocytes were cocultured with EC for 24 hours, and recruitment of flowing neutrophils was tested. Expression of EC E-selectin was measured using flow cytometry and qPCR and cytokine were measured by luminex. Both $CD16^-$ and $CD16^+$ monocytes stimulated EC to support adhesion of flowing neutrophils, with an increase in the presence of $CD16^+$ monocytes. TNF-α levels were higher in cocultures of EC/$CD16^+$, and blockade of TNF-α reduced neutrophil recruitment. $CD16^-$ cocultures contained high concentrations of IL-6. Interestingly, addition of IL-6-rich $CD16^-$ coculture supernatant to $CD16^+$ co-cultures reduced neutrophil recruitment, and blockade of IL-6 in $CD16^-$ cocultures increased recruitment of neutrophils. The adhesion molecule E-selectin was up-regulated in $CD16^+$ cocultures, contributing to the observed increase in neutrophil adhesion. Differences in the ability to modulate the inflammatory responses of EC exist between monocyte subsets. IL-6 plays a central role in this process and may mediate crosstalk between $CD16^-$ and $CD16^+$ monocytes.

Endothelial cell ADAM10 promotes lymphocyte transmigration *in vitro*
Jasmeet Reyat, Ed Rainger, Michael Tomlinson
The endothelial cells lining all blood vessels play an important role in immunity by regulating the transmigration of leukocytes from the blood into sites of inflammation within tissues. The transmembrane metalloprotease ADAM10 on endothelial cells is required for normal vascular permeability and T cell transmigration. ADAM10 appears to achieve this by cleaving the extracellular regions from one or more of its endothelial cell substrates, the cell-cell adhesion molecule VE-cadherin and the transmembrane chemokines CXCL16 and CX3CL1. The aim of the current study was to establish whether endothelial cell ADAM10 is necessary for leukocyte adhesion, rolling and/or transmigration, using a flow-based system and video microscopy. Pharmacological inhibition of ADAM10 activity was found to substantially reduce lymphocyte transmigration. Knockdown of ADAM10 expression with siRNA similarly reduced lymphocyte transmigration. However, neutrophil transmigration was not affected by ADAM10 inhibition or knockdown. Future studies will aim to determine which endothelial TspanC8s promote ADAM10 regulation of lymphocyte transmigration, and which ADAM10 substrates are important in this process. This work is important because targeting a particular TspanC8-ADAM10 complex is a potential treatment for inflammatory diseases such as atherosclerosis, without the toxic side effects that would result from global ADAM10 inhibition.

SESSION 3: Regulation of Recruitment Crossing Blood Vessel Endothelium

Ly-6Chigh monocyte trafficking to the myometrium in late gestation
Lydia Edey, Kieran O'Dea, Masao Takata, Mark Johnson

Late gestation and labour is associated with inflammatory changes both in the myometrium and systemically that include an increase in leukocyte numbers. In early gestation in mice it has been shown that the Ly-$6C^{high}$ 'inflammatory' subset of monocytes infiltrate the myometrium in a CCR2-dependent fashion and serve as macrophage precursors. Myometrial macrophages are considered to be integral in the process of transforming the myometrium from a quiescent to a contractile tissue. However, the trafficking and role of Ly-$6C^{high}$ monocytes in the late gestation and labour has not been described. In this study we used flow cytometry to assess whether Ly-$6C^{high}$ monocyte trafficking dynamics to the myometrium are altered by hormonal intervention. We found that progesterone supplementation and the resultant delay in labour onset was associated with reduced Ly-$6C^{high}$ monocyte trafficking to the myometrium. Administration of RU486, a progesterone and glucocorticoid receptor antagonist that induces preterm labour, significantly increased Ly-$6C^{high}$ monocyte numbers within the myometrium. This increase was inhibited by systemic treatment with a CCR2 antagonist (RS504393). Further investigation into monocyte subset trafficking to the myometrium may be critical in identifying novel targets for the prevention of preterm birth.

Beta2 integrins in dendritic cells
Vicky Morrison, Martyn James, Katarzyna Grzes, Peter Cook, David G Glass, Terhi Savinko, Hwee San Lek, Christian Gawden-Bone, Colin Watts, Owain Millington, Andrew MacDonald, Susanna Fagerholm

Dendritic cells (DCs) express high levels of the beta2 integrin family of adhesion molecules and yet the contribution of these receptors to DC functions under physiological conditions *in vivo* remains poorly defined. In this study, we used a novel beta2 integrin knock-in mouse model, which lacks the beta2 integrin-kindlin-3 interaction (TTT/AAA-beta2-integrin knock-in mice) and thus has non-functioning beta2 integrins, to investigate beta2 integrin function in DCs. Interestingly, we found that beta2 integrin knock-in bone marrow-derived DCs had a mature migratory phenotype. In addition, beta2 integrin knock-in mice had elevated numbers of DCs in secondary lymphoid tissues under homeostatic conditions, with a specific increase in numbers of migratory DC populations. Furthermore, following administration of fluorescent OVA antigen into the skin, we found increased numbers of OVA+ DCs in the draining lymph nodes 24 h later in beta2 integrin knock-in mice. Adhesion-deficient beta2-integrin knock-in DCs had an elevated activation phenotype in terms of cytokine production and MHC class II and co-stimulatory molecule expression, and primed increased Th1 responses *in vivo*. Thus, beta2 integrins restrict DC migration and maturation under homeostatic conditions *in vivo*.

SESSION 4: T Cell Migration

Caveolin-1 is involved in integrin-mediated CD8 T cell adhesion and homing to lymphoid tissues
Jessica Borger, Vicky Morrison, Rose Zamoyska

Caveolin-1 (Cav1), a transmembrane protein involved in signaling and polarity in nonlymphoid cells, was recently identified in T cells to be required for TCR-mediated membrane polarity and effector functions. Cav1 is known to associate with β1 integrins and to influence the regulation of integrin signaling in fibroblasts, however the role of Cav1 in integrin signaling in primary lymphocytes has not been previously described. We found that in Cav1-deficient CD8 T cells, signaling through the TCR was impaired with reduced upregulation of activation markers, cytokine production and proliferation. Cav1-deficient CD8 T cells bound normally to the β2 integrin ligand ICAM-1 under shear flow following stimulation with the chemokine CXCL12 (SDF-1a). In contrast, Cav1-deficient CD8 T cells stimulated through the TCR were significantly less adherent to ICAM-1 under shear flow conditions. *In vivo* homing to lymphoid organs was also impaired in Cav1-deficient CD8 T cells after adoptive transfer into wild-type recipient mice. These results identify Cav-1 as being involved in the regulation of LFA-1-mediated cell adhesion and lymphocyte trafficking *in vivo*, in a TCR-dependent, but chemokine-independent pathway.

CCR6$^+$ T cells from Psoriatic Arthritis patients are resistant to suppression of migration by Treg towards CCL20
Helen Baldwin, Amara Ezeonyeji, Michael Ehrenstein

Regulation of Th17 cell migration via CCR6 to inflammatory sites of patients with psoriatic arthritis (PsA) is likely to be a crucial factor in perpetuating inflammation. We hypothesise that Th17 migration is normally controlled by Treg but this process is dysfunctional in patients with PsA. CD4 T cells from PsA patients produced significantly more IL-17 than healthy controls (HC) after 3 days anti-CD3 and anti-CD28 stimulation. However, the percentage of CCR6$^+$ CD4 cells was, paradoxically, significantly lower in the blood of PsA patients compared to HC, suggesting migration to sites of inflammation. Co-culturing HC or PsA Treg in a transwell with HC CCR6$^+$ T cells, in the presence of the CCR6 ligand CCL20, showed that both HC and PsA Treg could inhibit migration of HC CCR6$^+$ T cells. However, HC or PsA Treg could not inhibit migration of PsA CCR6$^+$ T cells under the same conditions. These data suggest that, HC and PsA Treg are able to suppress T cell migration, but PsA CCR6$^+$ T cells are resistant to Treg suppression. We hypothesise that an inability of Treg to suppress Th17 migration leads to an accumulation of Th17 cells at the site of inflammation and exacerbation of inflammatory disease.

The atypical chemokine scavenging receptor ACKR2 prevents psoriasiform pathology by defining the boundaries of T-cell localisation within the skin
Kave Shams, Michelle Le Brocq, Mariola Kurowska-Stolarska, Clive McKimmie, David Burden and Gerry Graham

Chemokines are the principal regulators of leukocyte migration and play a pivotal role in inflammatory skin disease. The atypical chemokine-scavenging receptor ACKR2 lacks the ability to signal, instead scavenging and internalizing inflammatory CC-chemokines and thereby plays a key role in regulating inflammation. We have previously shown that ACKR2 expression was significantly elevated in unaffected psoriatic skin whilst ACKR2 expression in lesional skin was reduced in comparison. Using a novel *in vitro* 3D model of human T-cell migration we show that high ACKR2 expression in primary keratinocytes prevents chemokine-mediated T-cell migration towards a chemotactic stimulus. To study the functional effects of ACKR2 *in vivo*, we used the well-established imiquimod mouse model of psoriasis. Following application of imiquimod to the skin, a significantly higher proportion of CD3+ T-cells localised to the epidermis of ACKR2$^{-/-}$ mice, as compared to wild type mice, which comparatively had few epidermal T-cells. Epidermal T-cell accumulation in ACKR2$^{-/-}$ mice was associated with a more severe psoriasiform skin inflammation, with enhanced epidermal thickening and hyperproliferation, as compared to wild-type mice. Together this suggests that keratinocyte-expressed ACKR2 prevents the development of psoriasiform skin pathology by inhibiting the recruitment of inflammatory T-cells to the epidermis. To determine if we could modulate ACKR2 expression, and thereby prevent psoriasiform inflammation, we identified endogenous regulators of ACKR2 expression. We show that soluble T-cell cytokines rapidly upregulated ACKR2 by over 100-fold in human primary keratinocytes, and that this was partly, but not entirely, mediated by IFNγ. Similarly, injection of IFNγ into mice significantly upregulated cutaneous ACKR2 expression and critically protected them from developing psoriasiform pathology in response imiquimod application. Thus, ACKR2 expression *in vivo* protects against psoriasiform inflammation and its targeted upregulation, by IFNγ, protects mice from psoriasiform inflammation. We conclude that novel modulators of chemokine systems constitute an exciting target for new therapies and/or biomarkers in psoriasis.

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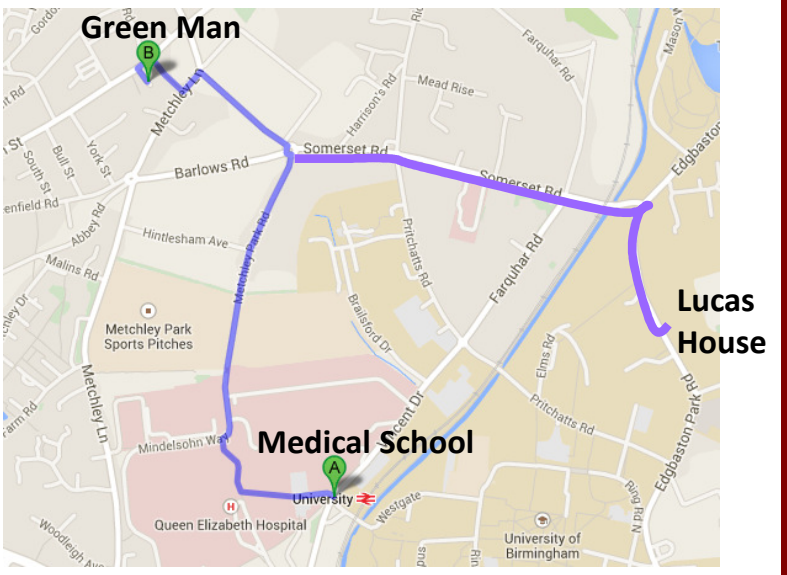
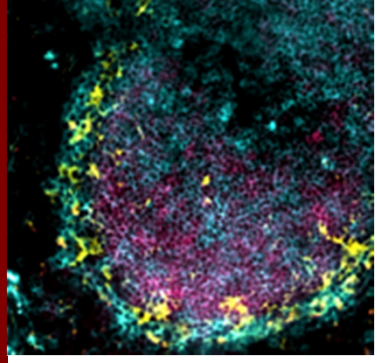
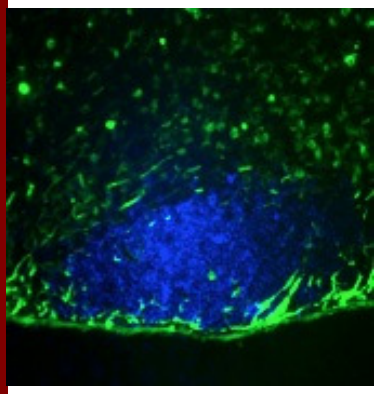
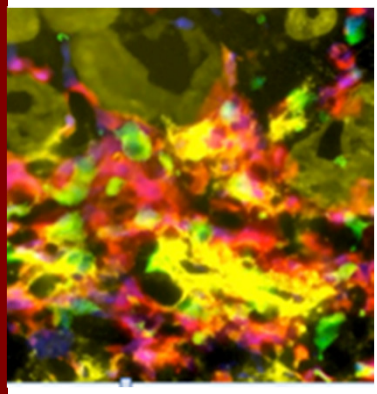
The Leukocyte Migration Group Committee cordially invite all participants to join us at The Green Man on Harborne Road after the first day of the meeting (a 15 minute walk from the lecture theatre, map below). For you information we have listed below the post codes for these venues. We very much look forward to seeing you all there.

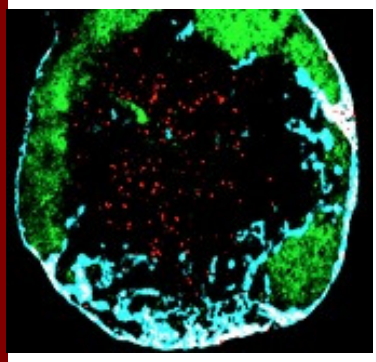


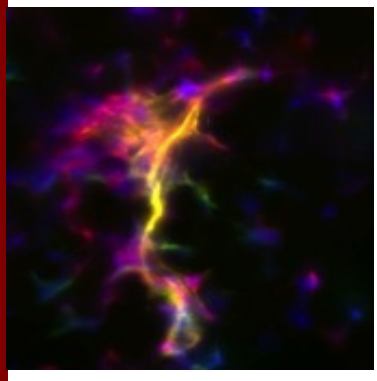
Medical School	B15 2SG
Lucas House	B15 2RA
Green Man	B17 9NE

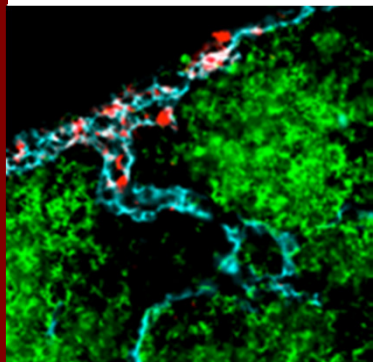












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3rd Meeting
Tyne and Wear
Autumn 2016