Professor Ann Ager

Nationality: British

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Education:

1974 B.Sc. (Hons) Biochemistry, Class I, University of London

1980 Ph.D., University of Cambridge

Present Appointment

2018- Professor of Cellular Immunity and Immunotherapy, Cardiff University

Previous appointments

2007 - 2018 Reader, Infection and Immunity, School of Medicine, Cardiff University
1992 - 2007 Senior Scientist, MRC National Institute for Medical Research, London
2003 - 2008 Honorary Reader, Immunology & Molecular Pathology, UCL, London
1989 - 1994 Honorary Lecturer in Immunology, Department of Cell & Structural Biology, University of Manchester
1987 - 1992 MRC Senior Fellow, Immunology Department, University of Manchester
1983 - 1987 MRC Post-doctoral Fellow, Immunology Department, University of Manchester
1980 - 1983 Post-doctoral Fellow, Department of Cell Biology, Babraham Institute
1979 - 1980 Visiting Scientist, Childrens' Hosptial, Harvard Medical School, USA
1978 - 1979 Visiting Scientist, Ciba-Geigy Laboratories, Horsham, Surrey
1976 - 1979 SERC-CASE Research Student, University of Cambridge, working at Babraham Institute

Contributions to Research

The focus of my research is how T lymphocytes move around the body in order to protect against infection, fight cancer and contribute to dementia, such as in Alzheimer's disease. This has resulted in a body of work based on a tractable *in vitro* model of lymphocyte-blood endothelial cell recognition and studies of lymphocyte trafficking and immune responses in genetically modified mice developed in the Ager lab. A major focus has been the regulation of L-selectin expression by proteolysis and its impact on physiological and pathological T cell trafficking via specialised high endothelial venules (HEV) blood vessels. Using mouse models of virus infection we have revealed a novel role for L-selectin in the recruitment of killer T cells from the blood into flu-infected lungs, which is essential to clear virus (http://www.bbc.co.uk/news/uk-wales-south-east-wales-35373730). Studies using mouse models of cancer immunotherapy indicate that L-selectin is also required for killer T cells to restrict the growth of solid cancers. Future studies will explore pharmacological and genetic approaches to prevent loss of L-selectin from the surface of human T cells to boost immunotherapies for solid cancers and use L-selectin to help killer T cells find and destroy other viruses or cancer cells in patients. We also want to characterise the addressins on blood vessels in virus infected and cancerous tissues that allows killer T cells to home using L-selectin. New studies using cell based models of blood flow, have shown that a gene associated with Alzheimer's disease acts on blood vessels in the brain to increase the recruitment of inflammatory cells. Future work will determine how changes in inflammatory cell recruitment in the brain are regulated and what impact these changes to vascular health have on Alzheimer's disease.

Science Citizenship:

Invited Speaker:

'Altered Immune Surveillance and Hereditary Cancer Risk', Collaborative Group of the Americas (CGA) on Inherited Gastrointestinal Cancers, Salt Lake City, Utah, USA, 2019.
'Tracking L-selectin enhanced T cells in cancer immunotherapy using PET/CT', British Society for Immunology Annual Congress, Brighton, UK, 2018.
'Directing the Traffic of Effector Lymphocytes: Breaking Down Dogma', Sun-Yat Sen University, Guangzhou, China, 2017.
'Directing the traffic of T lymphocytes for effective cancer immunotherapy', Applied Tumour Biology Department, University Hospital of Heidelberg, Germany, 2017.
'Cancer Immunotherapies', Cancer Council New South Wales, Sydney, Australia, 2017.
'Regulating L-selectin expression during T cell homing: Getting to the right place at the right time', Haematology Department, Monash University, Melbourne, Australia, 2017.
'Mapping Changes to Vascular Health in Alzheimer's Disease: The Role of EPHA1 Risk Alleles', Alzheimer's Association International Conference, Toronto, 2016.
'T lymphocyte homing in adoptive cell therapies for solid cancers', Chimeric Antigen Receptor therapy in Haematology and Oncology: current Successes and Challenges, London, 2015.
'ADAMs and ectodomain proteolytic shedding in leucocyte migration', 16th Signal Transduction Society Meeting on Receptors, Mediators and Genes, Weimar, Germany, 2012.

Chair:

UK Cell Adhesion Society (2015-2018).
British Society for Immunology Forum (2019-2023).
Genetics: Alternative Phenotypes for Genetic Studies, Alzheimer's Association International Conference, Toronto (2016).
Inflammation theme lead, Systems Immunity Research Institute, Cardiff University (2018-).

Executive Committees:

Nominations Committee, British Society for Immunology (2019-2023).
Inflammation theme lead, Systems Immunity Research Institute, Cardiff University (2018-).
Honorary Degrees and Fellowship Committee, Cardiff University (2019-).
Cardiff Institute for Tissue Engineering and Repair (2016-18).

Expert Panels and Consultancies:

Scientific Board, Leukaemia Research Fund (now Bloodwise), UK.
Expert Witness, European Patent Attourney.
Consultant and Advisor on HEV, T cell trafficking and ADAMs for biotech companies and academic-industry partnering agencies (Protagonist, Obsidian, Immunocore, Celyad, Pharos, Guidepoint, Linknovate and Biowebspin).
Wellcome Trust Institutional Strategic Support Fund Early Career Researcher Panel, Cardiff University.

Society Membership:

British Society for Immunology (1987-).
UK Cell Adhesion Society (1996-).

Grant Reviews:

MRC; BBSRC; Cancer Research-UK; Wellcome Trust; Versus Arthritis UK; Breast Cancer Care; British Heart Foundation; Brain Research Trust; Hadwen Trust; Leverhulme Trust; Barts Charity; Bloodwise; Multiple Sclerosis Society; Worldwide Cancer Research; NASA; European Space Agency; Swiss International Science Foundation; Netherlands Organisation for Scientific Research.

Journal reviews:

Nature group journals; Science Immunology; Journal of Experimental Medicine; Blood; Circulation Research; Journal of Immunology; Journal of Leucocyte Biology; Frontiers in Immunology; European Journal of Immunology; Immunology; Immunity; Inflammation and Disease; Journal of Cell Science; Experimental Cell Research; Parasite Immunology; FEBS Letters; International Journal of Cell Biology; Cancer Immunology and Immunotherapy; British Journal of Pharmacology; Trends in Molecular Medicine; Marine Drugs.

Teaching

External Examiner

MSc in Immunology and Immunogenetics, Manchester University (2012-2016)
PhD theses for Kings College London, Imperial College London, Birmingham, Dundee, Cardiff; Toronto, Adelaide and Canberra.

Student Supervision

Postgraduates: Lead supervisor18 PhD students and 7 Masters students.
Undergraduates: Final year laboratory based projects for Bioscience, Pharmacology, Medical and Erasmus students at the Universities of Manchester, London and Cardiff.

Teaching:

Director of Postgraduate Studies, MRC National Institute for Medical Research, London
Graduate Education Executive Sub-committee, UCL, London.
British Society for Immunology Summer and Winter Schools.
PhD progress monitoring, Infection and Immunity, Cardiff University
Lectures, seminars and tutorials on Lymphocyte trafficking at the Universities of Manchester, Glasgow, Nottingham and Westminster, Pasteur Institute and the John Humphrey Advanced Programme in Immunology in Russia.

Administrative Experience

Chair: Expert Advisory Group on pre-clinical PET refurbishment, Cardiff University.

Executive member.

Board of Trustees, British Society for Immunology (2019-2013).
Harmonisation Project Operations Group for C21:Developing Tomorrow's Doctors.
Joint Biological Services Users Group, Cardiff University.

Outreach:

Cardiff's Science in Health Programme for 16-18 year old science students; Cancer Research UK open day; Alzheimer's Research-UK Open Day; Cardiff Radio; BBC press release; Women's Institute; Soapbox Science;Cardiff. Pint of Science; Tackling Cancer Together in Wales.

Mentorship

Academic Mentor, School of Medicine, Cardiff University
ECR Mentor for BSI and Cardiff Futures programme

GRANT INCOME SINCE 2012

1. BBSRC (2019-2022) "The regulation of protective immunity to viruses by L-selectin", £556,000.

2. Cancer Research-UK (2017-2020) "Unravelling the relationship between T cell trafficking and cancer immunotherapy", £270,915.

3. MRC (2014- 2018) "Dissecting the impact of L-selectin on T lymphocyte dependent tumour immunity", £529,291.

4. GE-Healthcare (2015-2016) "Longitudinal monitoring of T lymphocyte migration in vivo", £21,571.

5. CR-UK Cardiff Centre Development Fund (2015-2016) "Longitudinal monitoring of T lymphocyte migration in vivo using Positron Emission Tomography-Computed tomography (PET-CT)", £6,926.

6. Neuroscience and Mental Health Institute PhD studentship, Cardiff University (2015-2018). "Mapping changes to vascular health in Alzheimer's disease", Co-PI, £ 85,498.

7. Wellcome Trust Grant (2015-2017) "Regulation of T cell functions by enzymatic proteolysis of L-selectin", £68,092.

8. MRC/Cardiff University School of Medicine PhD Studentship (2013- 2017) “The Regulation of L-selectin Activity by Proteolysis”, £80,000.

9. Wellcome Trust Project Grant (2011-2017) “Manipulating T lymphocyte homing and activation for cancer immunotherapy”, £313,321.

10. Wales Cancer Research Centre (2015- 2018) “Preclinical models for novel immunotherapies using MHC restricted and non-restricted T cells”, Co-PI, Lead Professor Matthias Eberl, £85,000.

11. School of Medicine PhD studentship (2017-2020) “Engineering homing properties of cancer-specfic T lymphocytes in adoptive cell therapy”**,** £80,000.

12. MRC/Cardiff University School of Medicine PhD Studentship (2011- 2014) “Improving Adoptive T cell Immunotherapy through Manipulation of T cell Activation”, £90,000.

13. Lilly UK Project Grant (2013- 2014) “The impact of Alzheimer’s susceptibility variants on immune function; a dissection of the biological link to Alzheimer’s disease development”, Co-PI, Lead Professor Julie Williams; £350,000.

14. Wellcome Trust ISSF and SREF Equipment Grants (2012) “A thermoelectrically cooled CCD camera for the IVIS 200; a state-of the art, non-invasive, *in vivo* imaging system”. Co-PI. £49,000

PUBLICATIONS: H-index 32 (68 papers, 3660 citations):
Papers since 2007

1. Seth, S., Ager, A., Arends, M.J. and Frayling, I.M. (2018) Lynch syndrome – cancer pathways, heterogeneity and immune escape *Journal of Pathology* DOI: 10.1002/path.5139

2. Jones, E., Gallimore, A. and Ager, A. (2019) Defining High Endothelial Venules and Tertiary Lymphoid Structures in Cancer. *Methods in Molecular Biology*. 1845:99-118; DOI: 10.1007/978-1-4939-8709-2_7

3. Miles, J,, Tan, M. P., Dolton, G., Edwards, E., Galloway, S., Laugel, B., Clement, M., Makinde, J., Ladell, K., Matthews, K.K., Watkins, T.S., Tungatt, K.,Wong, Y., Lee, H.S., Clark, R.J., Pentier, J.M., Attaf, M., Lissina, A., Ager, A., Gallimore, A., Rizkallah, P.J., Gras, S., Rossjohn, J., Burrows, S.R., Cole, D.K., Price, D.A. and Sewell, A.K. (2018) Peptide Mimic for Influenza Vaccination Using Non-natural Combinatorial Chemistry. *Journal of Clinical Investigation* DOI: 10.1172/JCI91512

4. Gaweł-Bęben, K., Nazim, A., Ellis, V., Velasco, G., Poghosyan, Z., Ager, A .and Knäuper, V. (2017) TMEFF2 shedding is regulated by oxidative stress and mediated by ADAMs and transmembrane serine proteases implicated in prostate cancer. *Cell Biology International.* DOI: 10.1002/cbin.10832

5. Colbeck, E. J., Jones,E., Hindley, J. P., Smart, K., Schulz, R., Browne, M., Cutting, S., Williams, A., Parry, L., Godkin, A., Ware, C. F., Ager, A. and Gallimore, A. (2017) Treg Depletion Licenses T Cell Driven HEV Neogenesis and Promotes Tumor Destruction. *Cancer Immunology Research* 5 (11): 1005-1015. DOI:10.1158/2326-6066.

6. Colbeck, E.J., Ager, A., Gallimore, A. and Jones, G.W. (2017) Tertiary Lymphoid Structures in Cancer: Drivers of Antitumor immunity, immunosuppression, or Bystander Sentinels in Disease? *Frontiers in Immunol*ogy DOI:10.3389/fimmu.2017.01830

7. Ager, A. (2017) High Endothelial Venules and Other Blood Vessels: Critical Regulators of Lymphoid Organ Development and Function. *Frontiers in Immunology* 8:45. DOI:10.3389/fimmu.2017.00045

8. Caucheteux, S. M., Hu-Li, J., Mohammed, R., Ager, A. and Paul, W. E. (2017) Cytokine Regulation of Lung Th17 Response to Airway Immunization using LPS Adjuvant. *Mucosal Immunology* DOI:10.1038/mi.2016.54

9. Watson, H. A., Dolton, G., Ohme, J., Ladell, K., Vigar, M., Wehenkel, S., Hindley, J., Mohammed, R. N., Miners, K., Luckwell, R. A., Price, D. A., Matthews, R. J. and Ager, A. (2016) Purity of transferred CD8+ T cells is crucial for safety and efficacy of combinatorial tumor immunotherapy in the absence of SHP-1. *Immunology and Cell Biology.* 94, 802–808; DOI:10.1038/icb.2016.45

10. Ager, A., Watson, H. A., Wehenkel, S. C., Mohammed, R. N. (2016) Homing to solid cancers: a vascular checkpoint in adoptive cell therapy using CAR T-cells. *Biochemical Society Transactions* 44 377-385; DOI: 10.1042/BST20150254

11. Watson, H. A., Wehenkel, S., Matthews, J., and Ager, A. (2016) SHP-1: the next checkpoint target for cancer immunotherapy? *Biochemical. Society. Transactions*. 44, 356–362; doi:10.1042/BST201502

12. Mohammed, R. N., Watson, H. A., Vigar, M., Ohme, J., Thomson, A., Humphreys, I. R. and Ager, A. (2016) L-selectin is essential to deliver activated CD8+ T cells to virus-infected organs for protective immunity. *Cell Reports* 14, 760–771; .doi.org/10.1016/j.celrep.2015.12.090

13. Ager, A. and May, M.J. (2015) Understanding high endothelial venules: lessons for cancer immunology. *Oncoimmunology.* 4:6, e1008791, DOI:10.1080/2162402X.2015.1008791

14. Bento, D.C., Jones, E., Junaid, S., Tull, J., Williams, G., Godkin, A., Ager, A. and Gallimore, A. (2015) High endothelial venules are rare in colorectal cancers but accumulate in extra-tumoral areas with disease progression. *Oncoimmunology* 4:3, e974374, DOI: 10.4161/2162402X.2014.974374

15. Ondondo, B., Colbeck, E., Jones, E., Smart, K., Lauder, S.N., Hindley, J., Godkin, A., Moser, B., Ager, A. and Gallimore, A. (2015) A Distinct Chemokine Axis Does not Account for Enrichment of Foxp3(+) CD4(+) T cells in Carcinogen-Induced Fibrosarcomas. *Immunology* 145:94-104 DOI: 10.1111/imm.12430.

16. Ondondo, B., Jones, E., Hindley, J., Cutting, S., Smart, K., Bridgeman, H., Matthews, K.K., Ladell, K., Price, D.A., Jackson, D.G., Godkin, A,. Ager, A. and Gallimore, A. (2014) Progression of carcinogen-induced fibrosarcomas is associated with the accumulation of naïve CD4+ T cells via blood vessels and lymphatics. *International Journal of Cancer.*134:2156-2167 DOI: 10.1002/ijc.28556

17. Spary, L.K., Al-Taei, S., Salimu, J., Cook, A.D., Ager, A., Watson, H.A., Clayton, A., Staffurth, J., Mason, M.D. and Tabi, Z. (2014) Enhancement of T cell responses as a result of synergy between lower doses of radiation and T cell stimulation. *Journal of Immunology.* 192(7):3101-10*.*

18. *G*allimore A., Godkin A. and Ager A. (2012) High endothelial venules: Help or hindrance in the quest for antitumor immunity? *Oncoimmunology 2:* e24272

19. Hindley, J. P., Jones, E., Smart, K., Bridgeman, H., Lauder, S. N., Ondondo, B., Cutting, S., Ladell, K., Wynn, K. K., Withers, D., Price, D. A,, Ager, A., Godkin, A. J. and Gallimore, A. M. (2012) T-cell trafficking facilitated by high endothelial venules is required for tumor control after regulatory T-cell depletion. *Cancer research*, 72: 5473-82

20. Humphreys, I. R., Clement, M., Marsden, M., Ladell, K., McLaren, J. E., Smart, K., Hindley, J. P., Bridgeman, H. M., van den Berg, H. A., Price, D. A., Ager, A., Wooldridge, L., Godkin, A. and Gallimore, A. M. (2012) Avidity of influenza-specific memory CD8(+) T-cell populations decays over time compromising antiviral immunity. *European Journal of Immunology* 10.1002/eji.201242575

21. Ager, A. (2012) ADAMs and ectododomain proteolytic shedding in leucocyte migration: Focus on L-selectin and ADAM17. *Current Immunology Reviews* 8:103-117

22. McGinn, O., English, W. R., Roberts, S., Ager, A., Newham,.P. and Murphy, G. (2011) Modulation of α4β1 integrin by ADAM28 promotes lymphocyte adhesion and transendothelial migration. *Cell Biology International* 35:1043-1053

23. Klinger A., Gebert A., Bieber, K., Kalies, K., Ager, A., Bell, E. B. and Westermann J. (2009) Cyclical expression of L-selectin (CD62L) by re-circulating T cells. *International Immunology* 21: 443-455

24. Sinclair, L. V., Finlay, D., Feijoo, C., Cornish, G. H., Gray, A., Ager, A., Okkenhaug, K., Haagenbeek, T. J., Spits, H. and Cantrell, D. A. (2008) Phosphatidylinositol-3-OH kinase and nutrient-sensing mTOR pathways control T lymphocyte trafficking. *Nature. Immunology* 9: 513-521

25. Anderson, B. E., Taylor, P. A., McNiff, J. M., Jain, D., Demetrius, A. J., Panoskaltsis-Mortari, A., Ager, A., Blazar, B. R., Shlomchik, W. D. and Shlomchik, M. J. (2008) Effects of donor T cell trafficking and priming site on GVHD induction by naive and memory phenotype CD4 T cells. *Blood* 111: 5242-5241

26. Richards, H., Longhi, M. P., Wright, K., Gallimore, A. and Ager, A. (2008) CD62L downregulation does not affect memory T cell distribution but failure to shed compromises anti-viral immunity. *Journal of Immunology* 180: 198-206

27. Galkina, E., Florey, O., Zarbock, A., Smith, B.R.E., Preece, G., Lawrence, M.B., Haskard, D. O. and Ager, A. (2007) T lymphocyte rolling and recruitment into peripheral lymph nodes is regulated by a saturable density of L-selectin (CD62L). *European Journal of Immunology* 37: 1243-1253.