University of Birmingham

Professor Benjamin Willcox BA, DPhil

Professor of Molecular Immunology

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School of Cancer Sciences

About

Ben Willcox is Professor of Molecular Immunology based at the Cancer Research UK Cancer Centre in the School of Cancer Sciences.

Ben leads an active research group in the field of cancer immunology and immunotherapy, with a focus on understanding immune receptor recognition. His recent work focuses on novel tumour antigens and unconventional T cell function, particularly in immunosurveillance of cellular stress. He has received major grants from Cancer Research UK, the Medical Research Council, the Biotechnology and Biological Sciences Research Council, and most recently the Wellcome Trust.

In addition, Ben is director of the University's Cancer Immunology and Immunotherapy Centre, a collaborative grouping of over 30 academic and clinical groups focussed on understanding fundamental aspects of tumour immunology and applying these to the development of novel cancer immunotherapy strategies. Ben is also scientific director of the CMDS Protein Expression Facility, a component of the College Technology Hub that supports a diverse range of biomedical research across CMDS by providing high quality protein expression services. He is also a member of the Birmingham Structural Biology Consortium, a cross-college grouping of structural biology research teams.

Qualifications

- DPhil Immunology 1999 (University of Oxford)
- BA (Hons) Biochemistry 1995 (University of Oxford)

Biography

Throughout his career Ben has been involved in research into the molecular basis of immune receptor recognition, a theme his research group at the University of Birmingham is focussed on.

Initial PhD studies at the University of Oxford centred on understanding protein-protein interactions critical to conventional T-cell antigen recognition. Subsequent Wellcome Trust-funded postdoctoral work in Professor Pamela Bjorkman's US-based laboratory focussed on the Leukocyte Immunoglobulin-like Receptors (LILRs), a novel immune receptor family expressed predominantly on myeloid lineages, which play important roles in immune tolerance. Ben then returned to the UK in 2002 to establish his own independent research group at the University of Birmingham, supported by an MRC Career Development Award from 2004. He was appointed as Senior Research Fellow in 2005, and as Reader in Molecular Immunology in 2010.

Ben's research team combines molecular, structural and cellular expertise to understand clinically important immune receptor recognition events, including those underpinning the graft-versus leukaemia effect, unconventional T cell immunosurveillance of tumours, and receptors regulating myeloid cells.

Teaching

- Intercalated BmedSc in Clinical Sciences
  Lecture on "Protein 3D structure determination by X-ray crystallography"
- MSc in Clinical Oncology
  Lecture in Module 1 on "Introduction to Cellular Immunology"
- MBChB 2nd year course "Cancer Causes to Cures"
- Small group teaching on "Primary and Secondary Cancer Prevention"
- Lead organiser, MRes Laboratory Practical Week 4: Experimental approaches; Structural Biology component (2011-) Lecture: "Protein analysis and biophysics"
- Lead organiser, 2011-2012 MRes Cancer Module

Postgraduate supervision

Ben is interested in supervising doctoral research students in the following areas:

- The role of gamma delta T cells in tumour immunity
- Immune presentation and recognition of phosphopeptide antigens

If you are interesting in studying any of these subject areas please contact Ben on the contact details above, or for any general doctoral research enquiries, please email: **dr@contacts.bham.ac.uk (mailto:dr@contacts.bham.ac.uk)** or call +44 (0)121 414 5005.

Research

Research Themes

Tumour Immunology and Immune/Gene Therapy, Structural Biology and Biomarkers, Cancer Cell Biology

Research Activity

My group has two active and related research areas, focussing on antigen recognition by conventional and unconventional T cells, respectively.

Understanding T-cell recognition of novel tumour-associated antigens
Conventional T-cells make key contributions to anti-tumour immunity, by using their T-cell receptors (TCRs) to recognise tumour peptides presented in the context of MHC molecules on the tumour cell surface. Their huge potential in cancer immunotherapy is evident during stem cell transplantation treatment of haematological malignancies, where they underly the potent “graft versus leukaemia” (GvL) effect that is frequently curative. Understanding the critical receptor-ligand recognition events involved is vital if we are to effectively exploit them in cancer immunotherapy. Our approach employs both cellular techniques and molecular ones such as surface plasmon resonance and x-ray crystallography to examine the properties of key TCR/MHC interactions. Our previous studies focussed on novel tumour associated antigens (TAAs), including minor histocompatibility antigens and allo-MHC-restricted TAAs that circumvent conventional tolerance mechanisms. More recently, a key focus of interest is in immune presentation of post-translationally modified antigens, in particular phosphorylated peptides, which may provide an immunological signature of “transformed self” on tumours. Our phosophopeptide immunology research involves interactions with Dr Mark Cobbold, and various international collaborators. Collectively these studies will help us understand and exploit key clinically relevant immunotherapeutic targets and approaches.

Immunosurveillance and tumour targeting by unconventional T-cells
Compelling evidence also suggests unconventional lymphocytes including gamma delta T-cells play important roles in innate immunity to cancer by sensing and reacting to cellular stress. In mice, gamma delta T-cells mediate immune protection from cutaneous malignancy. In humans, numerous studies highlight killing of cancer cells by human gamma delta T-cells, and expansions in this T-cell subset correlate with lower rates of post-transplant malignancies. In addition, several clinical trials designed to elicit gamma delta T-cell anti-tumour immunity have achieved objective clinical responses in patients with either haematological (eg multiple myeloma) or solid (eg metastatic prostate cancer) maligancies. Moreover, a common and effective treatment for bladder cancer is vaccination with BCG, a mycobacterium known to stimulate both gamma delta and CD1-restricted T-cells. These findings strongly suggest the natural capacity of unconventional lymphocytes such as gamma delta T-cells to provide immunosurveillance and targeting of transformed cells may be effectively exploited in the clinic.

Our research is primarily focussed on characterising the molecular basis of gamma delta T-cell recognition. Despite overwhelming evidence for gamma delta T-cell recognition of tumours, the ligands recognised directly by gamma delta TCRs on tumour cells have remained largely unidentified. With national and international collaborators, we are identifying novel gamma delta TCR ligands and using molecular and structural techniques to characterise key receptor ligand interactions. A second area has focussed on understanding CD1-restricted responses to mycobacterial lipid antigens. Collectively, these studies will shed new light on immune recognition by unconventional lymphocytes, and in doing so facilitate design of improved cancer immunotherapy approaches.

Therapeutic application of immune receptors in cancer immunotherapy
A final aim is to extend our basic immunology studies in order to apply our molecular insights to improved targeting strategies for cancer treatment. In this area, we have several ongoing collaborations both within the CRUK Centre and with other UK or international groups to understand and explore both targeting of novel TAAs, and tumour targeting by unconventional lymphocytes.

Other activities

Outreach charity work for Cancer Research UK, including at local fundraising events, local media events, and laboratory tours.

Publications

Willcox-BE, Thomas-LM and Bjorkman-PJ (2003). Crystal structure of HLA-A2 Bound to LIR-1, a Host and Viral MHC Receptor. Nature Immunology 4(9): 913-9

Antrobus-RD, Khan-N, Hislop-AD, Montamat-Sicotte-D, Garner-LI, Rickinson-AB, Moss-PA and Willcox-BE. (2005). Virus-specific cytotoxic T lymphocytes differentially express cell-surface leukocyte immunoglobulin-like receptor-1, an inhibitory receptor for class I major histocompatibility complex molecules. Journal of Infectious Diseases 191 (11): 1842-53

Willcox-BE, Willcox-CR, Dover-LG and Besra-G. (2007). “Structures and functions of microbial lipid antigens presented by CD1”., In: Moody, D.B. (ed). T cell activation by CD1 and Lipid Antigens. Springer. Curr Topp Microbiol Immunol: 314: pp73-110

Hart-DP, Xue-SA, Thomas-S, Cesco-Gaspere-M, Tranter-A, Willcox-BE, Lee-SP, Steven-N, Morris-EC and Stauss-HJ. (2008). Retroviral transfer of a dominant TCR prevents surface expression of a large proportion of the endogenous TCR repertoire in human T cells. Gene Ther.; 15(8):625-31.

Mohammed-F, Cobbold-M, Zarling-AL, Salim-M, Barret-Wilt-GA, Shabanowitz-J, Hunt-DF, Engelhard-VH and Willcox-BE. (2008). Phosphorylation-dependent interaction between antigenic peptides and MHC class I: a molecular basis for the presentation of transformed self. Nature Immunology 9(11): 1236-43

Nicholls-S, Piper-KP, Mohammed-F, Dafforn-TR, Salim-M, Tenzer-S, van Endert-P, Schild-H, Cobbold-M, Engelhard-VH, Moss-PAH and Willcox-BE. (2009). Secondary anchor polymorphism in the HA-1 minor histocompatibility antigen critically affects MHC stability and TCR recognition. Proc Natl Acad Sci 106(10):3889-94.

Montamat-Sicotte-DJ, Millington-KA, Willcox-CR, Hingley-Wilson-S, Hackforth-S, Innes-J, Kon-OM, Minnikin-DE, Besra-GS, Willcox-BE* and Lalvani-A*. (2011). Mycolic acid-specific T-cells in human tuberculosis are dynamically related to antigen load and exhibit memory expansion after cure. Journal of Clinical Investigation doi:10.1172/JIC46216

Cheng-H, Mohammed-F, Nam-G, Chen-C, Qi-J, Garner-LI, Allen-RL, Yan-J, Willcox-BE and Gao-GF. (2011). Crystal structure of Leukocyte Immunoglobulin-like Receptor LILRB4: a myeloid inhibitory receptor involved in immune tolerance. Journal of Biological Chemistry 286(20): 18013-25

Simpson-AA*, Mohammed-F*, Salim-M, Tranter-A, Rickinson-AB, Stauss-HJ, Moss-PAH, Steven-NM and Willcox-BE. (2011). Structural and energetic evidence for highly peptide-specific tumor antigen targeting *via* Allo-MHC-restriction. Proc Natl Acad Sci 108(52):21176-81

Willcox-CR*, Pitard-V*, Netzer-S, Couzi-L, Salim-M, Silberzahn-T, Moreau-JF, Hayday-AC, Willcox-BE*, Dechanet-Merville-J*. (2012). Cytomegalovirus and tumor stress surveillance by binding of a human gamma delta T cell antigen receptor to endothelial protein C receptor. Nat Immunol 13(9): 872-9

*These authors contributed equally