# Professor Eric Jenkinson

Director of the MRC Centre for Immune Regulation
Professor of Experimental Medicine

School of Immunity and Infection

## Contact details

**Telephone** +44 (0)121 414 6825 (tel:+44 121 414 6825)

**Fax** +44 (0)121 414 3599

**Email** e.j.jenkinson@bham.ac.uk (mailto:e.j.jenkinson@bham.ac.uk)

MRC Centre for Immune Regulation
Institute for Biomedical Research
College of Medical and Dental Sciences
University of Birmingham
Edgbaston
Birmingham
B15 2TT
UK

## About

Eric Jenkinson is known internationally for his work on the thymus and T cell development and for the development of novel assays which are widely used for studies in this area.

In particular his work is focused on the developmental regulation of key stromal cell populations that make up the thymus and on the thymocyte/stromal cell interactions that determine the role of the thymus in regulating the development and selection T-cell lymphocytes to provide immune protection without autoreactivity.

Pioneering experiments using single cell cloning in thymus organ cultures have shown that a diverse T-cell antigen recognition repertoire can be generated from a single thymus colonising lymphoid progenitor, identified apoptosis as the mediator of negative selection in the thymus, demonstrated that cortical and medullary thymic epithelium derive from a common precursor, and defined the different roles of bone marrow-derived APC, epithelial cells and mesenchymal cells in thymocyte differentiation and selection.

## Qualifications

- Elected Fellow of the Academy of Medical Science
- PhD University College of North Wales, Bangor
- BSc (Hons) Zoology II, University of Bristol

## Biography

Eric qualified with a BSc in Zoology from Bristol University and went on to complete a PhD at University College of North Wales, Bangor. He undertook two postdoctoral research posts before joining the University of Birmingham Lecturer in the Department of Anatomy In 1992. He was appointed Professor of Experimental Immunology, then Head of Immunity and Infection in (2000-2011) and Director of MRC Centre for Immune Regulation (2004 to present).

## Teaching

- MBChB – year 1 embryology
- BDS – year 1 embryology

## Postgraduate supervision

If you are interesting in studying any of subject areas listed please contact Eric at 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.

For a full list of available Doctoral Research opportunities, please visit our Doctoral Research programme listings

## Research

Eric's research over the past 30 years has focused on the biology and function of the thymus in supporting the development of T lymphocytes – cells which play a central role in both immunological protection and, in some circumstances, the development of auto-immune disease.

Eric's research over the past 30 years has focused on the biology and function of the thymus in supporting the development of T lymphocytes – cells which play a central role in both immunological protection and, in some circumstances, the development of auto-immune disease. During this period, considerable advances have been made in our understanding of the factors that determine how the T cell antigen recognition repertoire is able to discriminate self from non-self, a key requirement for protective versus harmful immune responses. Much of this understanding has been based on the elucidation of cellular interactions between thymic stromal cells and developing lymphoid progenitors, an area where Eric's work has made a significant contribution.

Interactions between developing thymocytes and different stromal elements constituting the thymic microenvironment provide the developmental signals and growth factors that support thymocytes through successive phases of proliferation, antigen receptor gene rearrangement and T lineage specification. In addition, these interactions play a crucial role in selecting cells with useful antigen receptor specificities for future survival and export and in eliminating potentially auto reactive cells which may generate autoimmune disease. Arising from Eric's previous interests in histocompatibilty antigen expression at the feto-maternal interface (Nature 1975), his early studies on the thymus were amongst the first to demonstrate that, unlike the majority of other epithelial cells, epithelial cells of the thymus constitutively express MHC class II as well as

MHC class I antigens (Nature 1980; J Exp Med, 1981). These observations opened the way to an appreciation of the role of thymic epithelial cells in the selection of the T cell receptor repertoire and to much subsequent experimental work in his own and other laboratories to define the function of the different stromal components of the thymus in T cell development and selection.

Building on these observations, Eric's laboratory provided the first functional evidence that the induction of T cell tolerance to self antigens is more effectively mediated by interaction with antigen presented on bone marrow derived antigen presenting cells rather than cortical thymic epithelial cells, even though both cell types express the full range of MHC antigens (Nature, 1984). These observations aroused wide interest and were the basis for a substantial body of work from various laboratories investigating selection of the T cell receptor repertoire. Many of these studies exploited the use of foetal thymus organ culture systems as an accessible model to investigate thymocyte/stromal cell interactions within a three dimensional environment replicating that in vivo. With advances in assays for T cell function, Eric's laboratory were able to demonstrate that this system faithfully replicates the development of functional and phenotypic subsets of T lymphocytes seen in vivo. These findings were fundamental in establishing a technology that later enabled one of the major advances in modern immunology – the definition of MHC restricted peptide presentation for TCR recognition in repertoire selection.

Eric's discovery that deoxyguanosine (dGuo), added to foetal thymus organ cultures, is selectively toxic to thymocytes and bone marrow derived antigen presenting cells whilst sparing thymic epithelial cells (Eur J Immunol, 1982) proved to be a major advance in the development of methods to dissect the influence of thymocyte/stromal cell interactions on T cell development. By enabling the removal of bone marrow cells to provide "empty" thymus lobes for in vitro recolonisation or in vivo engraftment, this discovery has formed the basis for a considerable body of experimental work and has become a standard methodology in the study of T cell development. Subsequently, Eric developed new methodologies to manipulate the cellular composition of the thymus using reaggregate thymus organ cultures (RTOC). This technology allows individual stromal and lymphoid components in the thymus to be separated, purified and reassociated in defined combinations in 3D structures capable of supporting ongoing T cell development (J Ex Med, 1992) both in vitro in organ culture systems and following in vivo transplantation. RTOC have been widely adopted in many laboratories and have made an important contribution to the study of T cell development. Currently, RTOC are proving to be a powerful tool to investigate the molecular regulation of intra thymic events by combining stromal and lymphoid components carrying defined mutations to produce 'chimeric' thymus lobes with combinations of tissue specific defects in defined signaling pathways - a rapid alternative to the extensive cross breeding programmes required to establish mouse strains carrying combinations of mutations with tissue restricted expression.

Establishment of these novel experimental approaches opened the way to a range of experimental studies that have enabled Eric's laboratory to make a sustained and substantial contribution to our understanding of T cell developmental processes. Notably, he provided the first definitive evidence that the CD4 and CD8 T cell lineages arise from a common intra thymic precursor (Nature, 1985) using a novel clonal assay for individual T cell progenitors based on colonising alymphoid dGuo treated lobes with a single micromanipulated cell. Using the same approach his laboratory also showed unequivocally, and for the first time, that the T cell receptor repertoire is generated by gene rearrangement within the thymus rather than by recruitment of precursors with pre existing gene rearrangements (Nature, 1986), confirming the central role of the thymus in the development of immunocompetence.

Exploitation of their novel methodologies also allowed them to carry out fundamental studies demonstrating that triggering of the T cell receptor on immature cortical thymocytes within the physiological environment of the thymus can lead to the induction of programmed cell death (apoptosis) rather than the activation response seen in mature lymphocytes (Nature, 1989). This study was the first to demonstrate a mechanism to explain the process of clonal deletion, long considered a key element in shaping the T cell receptor repertoire through the elimination of auto reactive cells. Again, this finding stimulated wide interest in programmed cell death as an important factor in lymphocyte selection and led to a range of studies investigating the cellular and molecular mechanisms involved, both from our own group and many others.

In subsequent work to dissect the role of individual stromal elements in supporting T cell development, Eric was able to provide the first demonstration of a requirement for both mesenchymal and epithelial cells to support the earliest stages of T cell development (Nature, 1993, J Exp Med, 2000), identifying a previously undiscovered role for mesenchyme in this context. His work in this area also established the concept that thymic epithelial cells are uniquely efficient in their ability to provide signals for the crucial process of positive selection that allows cortical thymocytes to mature into functional T cells (J Exp Med, 1994). Using similar approaches, his laboratory were also able to demonstrate that these cells are the key player in the expression of chemokines recruiting lymphoid progenitors to the thymus, an area that has subsequently seen much development. More recently they have developed novel methods for the isolation of epithelial and mesenchymal compartments during the earliest stages of thymus formation. This enabled them to show that Notch ligands are expressed by thymic epithelial cells, indicating that one of the key molecular functions of thymic epithelium in supporting T cell development is to provide Notch ligands regulating the Notch signalling pathway, now known to be a crucial factor in T cell development. In this context, their ability to isolate developing lymphoid cells for molecular analysis from these early thymic compartments during initial colonisation led them to develop the hypothesis, contrary to prevailing dogma, that T/B cell lineage choice occurs prior to Notch signalling within the thymus during development even though this is subsequently required for intrathymic developmental progression (Blood, 2005; Nature Reviews Immunology, 2006).

Complementary to Eric's studies on early T cell development, he has a longstanding interest in the developmental processes controlling the formation of the thymic stromal microenvironment itself. Significant achievements from his laboratory in this area include the demonstration that interaction with thymic mesenchyme is a crucial requirement for the development of epithelial progenitors that give rise to later thymic epithelial populations, through mechanisms mediated by fibroblast growth factors (FGFs) (J Exp Med, 2003). A novel application of embryo fusion chimaeras between wild type and thymus deficient nude mice has also enabled Eric's laboratory to titrate the number of available thymic epithelial progenitors in an in vivo system and thereby examine the influence of the epithelial progenitor pool size on thymus growth and size (J. Immunol, 2008). These observations are improving their understanding of the regulation of thymus growth and the factors determining the availability of intrathymic niches which in turn determine the number of T cells that are produced (Blood, 2007). They are also providing a basis for new studies on changes in epithelial progenitor populations in relation to age related loss of thymic function.

A major breakthrough in Eric's understanding of the origin of functionally specialised thymic epithelial subsets mediating different aspects of thymocyte selection, was provided by his development of a novel clonal assay for thymic epithelial progenitors involving the micro-injection of genetically marked single cells into carrier fetal thymic lobes subsequently grafted in vivo (Nature, 2006) This allowed him to resolve a longstanding issue regarding the developmental origin of thymic epithelial populations and to provide definitive evidence that the two specialised epithelial lineages in the thymus (cortex mediating positive selection and medulla involved in negative selection) arise from a common epithelial progenitor type. This is an important insight for the development of thymus replacement therapy where the co-ordinated renewal of both epithelial compartments is likely to be essential to restore T cell immunocompetence without the development of autoreactivity.

Their recent observations have also opened up a new concept in relation to the development of central self tolerance by demonstrating a novel role for interactions involving cells of the innate immune system in RANK mediated signaling regulating the maturation and promiscuous expression of AIRE dependent self antigens by medullary epithelial cells (J Exp Med, 2007). Currently they are also making progress in defining lineage restricted epithelial progentitors for the cortical and medullary epithelial compartments of the developing thymus (J Immunol 2009) These are an important foundation for our future studies which will focus on the identification of epithelial progenitor populations in the adult thymus, the molecular signals controlling their activation and differentiation and consequently their potential for the reversal of age or ablation related thymic involution.
Arising from Eric's previous interests in histocompatibilty antigen expression at the feto-maternal interface (ref 1, Nature 1975), his early studies on the thymus were amongst the first to demonstrate that, unlike the majority of other epithelial cells, epithelial cells of the thymus constitutively express MHC class II as well as MHC class I antigens (ref 2, Nature 1980; ref 3, J Exp Med, 1981).

These observations opened the way to an appreciation of the role of thymic epithelial cells in the selection of the T cell receptor repertoire and to much subsequent experimental work in his own and other laboratories to define the function of the different stromal components of the thymus in T cell development and selection.

Building on these observations, Eric's laboratory provided the first functional evidence that the induction of T cell tolerance to self antigens is more effectively mediated by interaction with antigen presented on bone marrow derived antigen presenting cells rather than cortical thymic epithelial cells, even though both cell types express the full range of MHC antigens (ref 5, Nature, 1984).

These observations aroused wide interest and were the basis for a substantial body of work from various laboratories investigating selection of the T cell receptor repertoire. Many of these studies exploited the use of foetal thymus organ culture systems as an accessible model to investigate thymocyte/stromal cell interactions within a three dimensional environment replicating that in vivo.

With advances in assays for T cell function, Eric's laboratory were able to demonstrate that this system faithfully replicates the development of functional and phenotypic subsets of T lymphocytes seen in vivo. These findings were fundamental in establishing a technology that later enabled one of the major advances in modern immunology – the definition of MHC restricted peptide presentation for TCR recognition in repertoire selection.

Eric's discovery that deoxyguanosine (dGuo), added to foetal thymus organ cultures, is selectively toxic to thymocytes and bone marrow derived antigen presenting cells whilst sparing thymic epithelial cells (ref 4, Eur J Immunol, 1982) proved to be a major advance in the development of methods to dissect the influence of thymocyte/stromal cell interactions on T cell development.

By enabling the removal of bone marrow cells to provide "empty" thymus lobes for in vitro recolonisation or in vivo engraftment, this discovery has formed the basis for a considerable body of experimental work and has become a standard methodology in the study of T cell development. Subsequently, Eric developed new methodologies to manipulate the cellular composition of the thymus using reaggregate thymus organ cultures (RTOC).

This technology allows individual stromal and lymphoid components in the thymus to be separated, purified and reassociated in defined combinations in 3D structures capable of supporting ongoing T cell development (ref 9, J Ex Med, 1992) both in vitro in organ culture systems and following in vivo transplantation. RTOC have been widely adopted in many laboratories and have made an important contribution to the study of T cell development.

Currently, RTOC are proving to be a powerful tool to investigate the molecular regulation of intra thymic events by combining stromal and lymphoid components carrying defined mutations to produce 'chimeric' thymus lobes with combinations of tissue specific defects in defined signaling pathways - a rapid alternative to the extensive cross breeding programmes required to establish mouse strains carrying combinations of mutations with tissue restricted expression.

Establishment of these novel experimental approaches opened the way to a range of experimental studies that have enabled Eric's laboratory to make a sustained and substantial contribution to our understanding of T cell developmental processes. Notably, he provided the first definitive evidence that the CD4 and CD8 T cell lineages arise from a common intra thymic precursor (ref 6, Nature, 1985) using a novel clonal assay for individual T cell progenitors based on colonising alymphoid dGuo treated lobes with a single micromanipulated cell.

Using the same approach his laboratory also showed unequivocally, and for the first time, that the T cell receptor repertoire is generated by gene rearrangement within the thymus rather than by recruitment of precursors with pre existing gene rearrangements (ref 7, Nature, 1986), confirming the central role of the thymus in the development of immunocompetence.

Exploitation of their novel methodologies also allowed them to carry out fundamental studies demonstrating that triggering of the T cell receptor on immature cortical thymocytes within the physiological environment of the thymus can lead to the induction of programmed cell death (apoptosis) rather than the activation response seen in mature lymphocytes (ref 8, Nature, 1989).

This study was the first to demonstrate a mechanism to explain the process of clonal deletion, long considered a key element in shaping the T cell receptor repertoire through the elimination of auto reactive cells. Again, this finding stimulated wide interest in programmed cell death as an important factor in lymphocyte selection and led to a range of studies investigating the cellular and molecular mechanisms involved, both from our own group and many others.

In subsequent work to dissect the role of individual stromal elements in supporting T cell development, Eric was able to provide the first demonstration of a requirement for both mesenchymal and epithelial cells to support the earliest stages of T cell development (ref 10, Nature, 1993, ref 12, J Exp Med, 2000), identifying a previously undiscovered role for mesenchyme in this context.

His work in this area also established the concept that thymic epithelial cells are uniquely efficient in their ability to provide signals for the crucial process of positive selection that allows cortical thymocytes to mature into functional T cells (ref 11, J Exp Med, 1994). Using similar approaches, his laboratory were also able to demonstrate that these cells are the key player in the expression of chemokines recruiting lymphoid progenitors to the thymus, an area that has subsequently seen much development. More recently they have developed novel methods for the isolation of epithelial and mesenchymal compartments during the earliest stages of thymus formation.

This enabled them to show that Notch ligands are expressed by thymic epithelial cells, indicating that one of the key molecular functions of thymic epithelium in supporting T cell development is to provide Notch ligands regulating the Notch signalling pathway, now known to be a crucial factor in T cell development. In this context, their ability to isolate developing lymphoid cells for molecular analysis from these early thymic compartments during initial colonisation led them to develop the hypothesis, contrary to prevailing dogma, that T/B cell lineage choice occurs prior to Notch signalling within the thymus during development even though this is subsequently required for intrathymic developmental progression (ref 14, Blood, 2005; ref 16, Nature Reviews Immunology, 2006).

Complementary to Eric's studies on early T cell development, he has a longstanding interest in the developmental processes controlling the formation of the thymic stromal microenvironment itself. Significant achievements from his laboratory in this area include the demonstration that interaction with thymic mesenchyme is a crucial requirement for the development of epithelial progenitors that give rise to later thymic epithelial populations, through mechanisms mediated by fibroblast growth factors (FGFs) (ref 13, J Exp Med, 2003).

A novel application of embryo fusion chimaeras between wild type and thymus deficient nude mice has also enabled Eric's laboratory to titrate the number of available thymic epithelial progenitors in an in vivo system and thereby examine the influence of the epithelial progenitor pool size on thymus growth and size (ref 19, J. Immunol, 2008). These observations are improving their understanding of the regulation of thymus growth and the factors determining the availability of intrathymic niches which in turn determine the number of T cells that are produced (ref 17, Blood, 2007). They are also providing a basis for new studies on changes in epithelial progenitor populations in relation to age related loss of thymic function.

A major breakthrough in Eric's understanding of the origin of functionally specialised thymic epithelial subsets mediating different aspects of thymocyte selection, was provided by his development of a novel clonal assay for thymic epithelial progenitors involving the micro-injection of genetically marked single cells into carrier fetal thymic lobes subsequently grafted in vivo (ref 15, Nature, 2006) This allowed him to resolve a longstanding issue regarding the developmental origin of thymic epithelial populations and to provide definitive evidence that the two specialised epithelial lineages in the thymus (cortex mediating positive selection and medulla involved in negative selection) arise from a common epithelial progenitor type.

This is an important insight for the development of thymus replacement therapy where the co-ordinated renewal of both epithelial compartments is likely to be essential to restore T cell immunocompetence without the development of autoreactivity.

Their recent observations have also opened up a new concept in relation to the development of central self tolerance by demonstrating a novel role for interactions involving cells of the innate immune system in RANK mediated signaling regulating the maturation and promiscuous expression of AIRE dependent self antigens by medullary epithelial cells (ref 18, J Exp Med, 2007). Currently they are also making progress in defining lineage restricted epithelial progentitors for the cortical and medullary epithelial compartments of the developing thymus (ref 20, J Immunol 2009)

These are an important foundation for our future studies which will focus on the identification of epithelial progenitor populations in the adult thymus, the molecular signals controlling their activation and differentiation and consequently their potential for the reversal of age or ablation related thymic involution.

## Other activities

- Member of MRC Infections and Immunity Board from January 2004 – 2010
- Appointed to sub panel 3 for RAE 2008, Member MRC IIB Strategy Portfolio Overview Group [SPOG] 2007
- Member MRC IIB/MRCT – Pilot Industry Collaboration Award Scheme Panel 2007
- Arthritis Research UK, Scientific Strategy Committee, 2009 to present
- Arthritis Research UK Programme Grant committee, 2010 to present

## Publications

Hou TZ, Mustafa MZ, Flavell SJ, Barrington F, Jenkinson EJ, Anderson G, Lane PJ, Withers DR, Buckley CD. (2010). Splenic stromal cells mediate IL-7 independent adult lymphoid tissue inducer cell survival. Eur J Immunol. 40: 359-65.

Kvell K, Varecza Z, Bartis D, Hesse S, Parnell S, Anderson G, Jenkinson EJ, Pongracz JE. (2010). Wnt4 and LAP2alpha as pacemakers of thymic epithelial senescence. PLoS One. May 18; 5 (5): e10701.

White AJ, Nakamura K, Jenkinson WE, Saini M, Sinclair C, Seddon B, Narendran P, Pfeffer K, Nitta T, Takahama Y, Caamano JH, Lane PJ, Jenkinson EJ, Anderson G. (2010 Oct) Lymphotoxin signals from positively selected thymocytes regulate the terminal differentiation of medullary thymic epithelial cells. J Immunol. 15;185(8):4769-76. Epub 2010 Sep 22

Varecza Z, Kvell K, Talabér G, Miskei G, Csongei V, Bartis D, Anderson G, Jenkinson EJ, Pongracz JE. (2011 Apr 27) Multiple suppression pathways of canonical Wnt signalling control thymic epithelial senescence. Mechanisms of Ageing and Development [Epub ahead of print]

Talaber G, Kvell K, Varecza Z, Boldizsar F, Parnell SM, Jenkinson EJ, Anderson G, Berki T, Pongracz JE. (2011 Mar 31) Wnt-4 Protects Thymic Epithelial Cells Against Dexamethasone-Induced Senescence. Rejuvenation Research [Epub ahead of print]

Desanti GE, Jenkinson WE, Parnell SM, Boudil A, Gautreau-Rolland L, Eksteen B, Ezine S, Lane PJ, Jenkinson EJ, Anderson G. Clonal (2011 May) Analysis Reveals Uniformity in the Molecular Profile and Lineage Potential of CCR9+ and CCR9- Thymus-Settling Progenitors. Journal of Immunology. 1;186(9):5227-35. Epub 2011 Mar 18

Roberts NA, White AJ, Jenkinson WE, Turchinovich G, Nakamura K, Withers DR, McConnell FM, Desanti GE, Benezech C, Parnell SM, Cunningham AF, Paolino M, Penninger JM, Simon AK, Nitta T, Ohigashi I, Takahama Y, Caamano JH, Hayday AC, Lane PJ, Jenkinson EJ, Anderson G. (2012 Mar) Rank Signaling Links the Development of Invariant γδ T Cell Progenitors and Aire(+) Medullary Epithelium. Immunity. 23;36(3):427-37. Epub 2012 Mar 15. PubMed [in process]

Gibson VB, Benson RA, Bryson KJ, McInnes IB, Rush CM, Grassia G, Maffia P, Jenkinson EJ, White AJ, Anderson G, Brewer JM, Garside P. (2012 Mar) A novel method to allow noninvasive, longitudinal imaging of the murine immune system in vivo. Blood. 15;119(11):2545-51. Epub 2012 Jan 23. PubMed [in process]