

Professor Peter Cockerill BSc, PhD

Chair of Cytokine Gene Regulation

School of Immunity and Infection

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About

Peter is a professor within the School of Immunity and Infection and has spent his career engaged in research in the field of molecular immunology. Peter recently moved the University of Birmingham from the University of Leeds.

Peter has published over 50 research papers in scientific journals as well as reviews and book chapters in the fields of molecular immunology and chromatin structure. He has received major grants from Leukaemia and Lymphoma Research, the BBSRC, the AICR and YCR.

His research aims at defining mechanisms that control the development and activation of the immune system. These studies use the combined approaches of investigating chromatin structure in parallel with analyses of the DNA elements that control gene expression. This has allowed the group to develop a comprehensive picture of the detailed mechanisms that allow cytokine genes to become activated in a tissue-specific manner in response to immune stimuli.

Qualifications

- PhD Biochemistry 1983
- BSc (Hons) Microbiology and Biochemistry 1976

Biography

Peter Cockerill qualified with a BSc (Hons) in Microbiology and Biochemistry from the University of Melbourne in 1976. He went on to study for a PhD in Biochemistry at the Institute for Cancer Research in London.

Peter took up a post-doctoral position at the University of Texas in Dallas in 1983 where he defined a new class of genetic elements termed MARs which anchor DNA to the nuclear matrix. Peter continued this research at the Walter and Eliza Hall Institute in Melbourne before moving to the Hanson centre for Cancer Research in Adelaide in 1990.

At the Hanson Centre Peter commenced his studies of cytokine gene regulation and chromatin structure. This led in 1993 to the discovery of an inducible enhancer upstream of the human GM-CSF gene which is also the target for immunosuppressant Cyclosporin A.

Peter was appointed as a professor at the Leeds Institute of Molecular Medicine after moving to Leeds in 2001, where he identified all the additional elements required for the correct regulation of the human IL 3/GM-CSF locus. These studies also defined the pattern of developmental regulation of the locus during haematopoietic development and T cell maturation. This led to the discovery of a significant new class of regulatory elements that function to maintain epigenetic imprints within genes that exist in a primed state in memory T cells.

Peter moved to Birmingham in 2011 where he runs a joint program of research together with Constanze Bonifer. He has major funding from the BBSRC to study the epigenetic basis of memory T cells, and is a joint holder of a Leukaemia and Lymphoma Research program grant investigating the molecular basis of leukaemia.

Teaching

Teaching Programmes

Professor Cockerill has only recently moved to the University of Birmingham and has not yet taken up teaching responsibilities.

Postgraduate supervision

Peter currently has one PhD student and is interested in supervising doctoral research students in the following areas:

- Cytokine gene regulation in the immune system
- Epigenetics of memory T cells

Mechanisms responsible for myeloid leukaemia

Research

RESEARCH THEMES

Gene Regulation, Chromatin Structure, Cytokine Genes, Molecular basis of Leukaemia

RESEARCH ACTIVITY

RESEARCH

Overview

Peter Cockerill has worked in the field of molecular immunology for nearly 30 years. Research in the Cockerill lab combines studies of gene regulation with studies of chromosomal structure so as to understand how genes function at the level of the nucleus. The main focus of these studies has been to understand how genes become turned on by signals that activate the immune system, and how tissue-specific patterns of gene expression become established during the development of the immune system. The model system they use is a locus which has the genes for IL-3 and GM-CSF, which are cytokines that help to coordinate inflammatory responses within the immune system. This program of research has elevated the human IL-3/GM-CSF locus to a level where it is now one of the best characterised models for the study of inducible gene regulation and chromatin remodelling. These studies have identified all of the regulatory elements within this locus, determined which elements are sufficient for correct *in vivo* function, and defined their molecular mechanisms of action. They revealed that this locus contains inducible enhancers that recruit the transcription factor NFAT, which in T cells is induced by activation of the TCR, and functions to initiate chromatin remodelling. This process converts the enhancers to accessible regions of chromatin that exist as DNase I Hypersensitive Sites (DHSs), thereby enabling the binding of additional transcription factors required for enhancer function. These enhancers were also found to be targets for the immunosuppressant Cyclosporin A which inhibits NFAT.

ONGOING STUDIES

Regulation of the IL-3/GM-CSF locus during T cell development and in memory T cells

This group discovered that the IL-3/GM-CSF locus is transcriptionally and epigenetically silent in immature T cells in the thymus, and is progressively activated during T cell development and differentiation. They made the significant observation that this locus still remains in an inactive chromatin state in mature naive resting T cells, but undergoes extensive chromatin remodelling when T cells are first exposed to immune stimuli that initiate proliferation. Once T cells have been through a cycle of activation, they acquire a greatly increased ability to express IL-3 and GM-CSF upon re-stimulation. They found that the IL-3/GM-CSF locus could be maintained indefinitely in an active chromatin structure by a novel specific class of epigenetically modified DHSs that remained modified by histone H3 K4 methylation. Because this same primed state also exists in memory T cells, they propose that this class of DNA elements underlies the epigenetic basis of T cell memory. They now have a BBSRC grant to identify and characterise these DHSs, termed "memory modules", in genome-wide studies.

Mirabella F, Baxter E, Boissinot M, James SR and Cockerill PN. (2010) The human IL-3/GM-CSF locus is epigenetically silent in immature thymocytes and is progressively activated during T cell development. **J. Immunol.** 184, 3043-3054.

Activation of the GM-CSF locus in Acute Myeloid Leukaemia (AML)

The GM-CSF gene is often inappropriately expressed in AML, where it can support uncontrolled proliferation of AML cells. This lab found that the GM-CSF locus often exists in an abnormal epigenetically activated state in cases of AML where the normally inducible GM-CSF enhancer undergoes aberrant chromatin remodelling to form a constitutive DHS in the absence of specific inducing agents. In collaboration with Conny Bonifer, this group is currently performing genome-wide studies to map locations of aberrantly activated DHSs in AML patients, using this as a tool to identify the transcription factors and DNA elements responsible for reprogramming gene expression in AML.

PUBLISHED RESEARCH OUTPUT

Mechanisms of action of the transcription factor NFAT

This group found that the transcription factor NFAT plays a pivotal role in mediating the effects of the signals that activate inducible genes with immune system. They demonstrated that NFAT cooperates with other factors at the level of chromatin remodelling, thereby creating accessible regions of chromatin that exist as DHSs. They also revealed that activation of an NFAT-dependent enhancer led to extensive rearrangement of nucleosomes within the surrounding chromatin. By cooperating with different classes of transcription factor, NFAT was also found to be able to direct different patterns of tissue-specific gene expression.

Cockerill PN, Shannon MF, Bert AG, Ryan GR and Vadas MA. (1993) The GM-CSF/IL3 locus is regulated by an inducible cyclosporin A sensitive enhancer. **Proc.Natl.Acad.Sci. USA** 90, 2466-2470.

Bert AG, Burrows J, Hawwari A, Vadas MA and Cockerill PN. (2000) Reconstitution of T cell-specific transcription directed by composite NFAT/Oct elements. **J. Immunol.** 165, 5646-5655.

Johnson BV, Bert AG, Ryan GR, Condina A, and Cockerill PN. (2004) GM-CSF enhancer activation requires cooperation between NFAT and AP-1 elements and is associated with extensive nucleosome reorganisation. **Mol. Cell. Biol.** 24, 7914-7930.

Alternate modes of enhancer function

By studying distinct lineages of blood cells, this group found that the DHS within the GM-CSF enhancer adopted a very different structure in myeloid cells that expressed GATA factors compared to T cells which express NFAT. GATA factors bound to a region of the enhancer just upstream of the previously defined NFAT-dependent DHS. They found that GATA factors evict a specific nucleosome and create a distinct DHS to prime the locus for high level expression. Upon stimulation the GATA elements were able to cooperate with the nearby AP-1 elements even in the absence of NFAT. Hence, the enhancer adopted different nucleosome positions and utilised distinct sets of chromatin-remodelling transcription factors in T cells and myeloid cells.

Bert AG, Johnson BV, Baxter EW and Cockerill PN. (2007) A modular enhancer is differentially regulated by GATA and NFAT elements that direct different tissue-specific patterns of nucleosome positioning and inducible chromatin remodeling. **Mol. Cell. Biol.** 27, 2870-2885.

Transgenic models for studying the intact IL-3/GM-CSF locus

The IL-3 and GM-CSF genes lie just 10 kb apart and are co-expressed in T cells. However, this group showed that these two genes are in fact independently regulated. They found (i) that GM-CSF transgenes are correctly regulated by just the GM-CSF enhancer and promoter, (ii) that the independent regulation of these two genes is enabled by the existence of a transcriptional insulator located between these genes, which recruits CTCF and Cohesin, and (iii) that the IL-3 gene is regulated by a separate upstream enhancer.

Cockerill PN, Bert AG, Roberts D and Vadas MA. (1999) The human granulocyte-macrophage colony-stimulating factor gene is autonomously regulated *in vivo* by an inducible tissue-specific enhancer. **Proc.Natl.Acad.Sci. USA** 26, 15097-15102.

Bowers SR, Mirabella F, Calero-Nieto FJ, Valeaux S, Hadjurs, Baxter EW, Merckenschlager M and Cockerill PN. (2009) A conserved insulator that recruits CTCF and cohesin exists between the closely related but divergently regulated IL-3 and GM-CSF genes. **Mol. Cell. Biol.** 29, 1682-1693. 29, 1682-1693.

Publications

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Calero-Nieto FJ, Bert AG and Cockerill PN. (2010) Transcription-dependent silencing of inducible convergent transgenes in transgenic mice. **Epigenetics & Chromatin** 3:3.

Mirabella F, Baxter E, Boissinot M, James SR and Cockerill PN. (2010) The human IL-3/GM-CSF locus is epigenetically silent in immature thymocytes and is progressively activated during T cell development. **J. Immunol.** 184, 3043-3054.

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Cockerill PN. (2011) Structure and function of active chromatin and DNase I hypersensitive sites. **FEBS J.** 278, 2182-2210.

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Baxter EW, Mirabella F, Bowers SR, James SR, Bonavita AM, Bertrand E, Strogantsev R, Hawwari A, Bert AG, Gonzalez de Arce A, West AG, Bonifer C, and Cockerill PN. (2012) The inducible tissue-specific expression of the human IL-3/GM-CSF locus is controlled by a complex array of developmentally regulated enhancers. **J. Immunol.** 189, 4459-4469.

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