Name	PETER RATCLIFFE
Position	Senior Group Leader Director of Clinical Research (50% FTE)
Year joined *(Crick or founder institute)*	2016

Career History

CONCURRENT CURRENT APPOINTMENT (50% FTE)
2016- present: Director, Target Discovery Institute and Distinguished Scholar, Ludwig Institute for Cancer Research, University of Oxford

PREVIOUS APPOINTMENTS
1978 – 1979 House Officer, St Bartholomew's Hospital and Hackney Hospital, London
1979– 1981 Senior House Officer, Hammersmith Hospital, London Chest Hospital, the Brompton Hospital at the National Hospital, Queen's Square, London
1981– 1983 Registrar in Renal and General Medicine, Renal Unit, Nuffield Department of Medicine and Department of Geriatric Medicine, Oxford.
1983– 1987 Research Fellow, Nuffield Department of Medicine, Oxford.
1987 - 1990 Clinical Lecturer in Clinical Medicine, Nuffield Department of Medicine, Oxford.
1990- 1992: Wellcome Senior Fellow in Clinical Science, Nuffield Department of Medicine, Oxford.
1992- 1996: University Lecturer in Clinical Medicine (Nephrology), Nuffield Department of Medicine, Oxford.
1996- 2003: Professor of Renal Medicine and Senior Research Fellow, Jesus College, University of Oxford
2004- 2016: Nuffield Professor and Head of Nuffield Department of Medicine, University of Oxford

Major Awards, Honours and Prizes

POSTGRADUATE AWARDS & PRIZES
1998: Mary Evelyn Lucking Prize for Research in Nephrology (Royal College of Physicians)
1991: Milne-Muerke Foundation Award for Clinical Nephrology (Renal Association)
1998: Graham Bull Prize in Clinical Science (Royal College of Physicians)
2002: International Society for Blood Purification Award - Contributions to understanding of anaemia and oxygen homeostasis
2009: Louis-Jeantet Prize for Medicine - Work on mechanisms in cellular oxygen sensing
2010: Canada Gairdner International Award - *for identification of molecular mechanisms of oxygen sensing in the cell*
2011: 24th Annual Robert J. and Claire Pasarow Foundation Award in Cardiovascular Research
2011: Baly Medal, the Royal College of Physicians
2012: Scientific Grand Prix of the Foundation Lefoulon-Delalande, Institute of France
2013: Jakob Herz Preis, Friedrich Alexander Universität Erlangen-Nürnberg, Germany
2014: KBE for Services to Clinical Medicine, January
2014: Wiley Prize for Biomedical Science
2016: Albert Lasker Basic Medical Research Award
2017: *Doctor honoris causa,* University of Zurich

2017: Buchanan Medal, The Royal Society
2018: Massry Prize
2019: Nobel Prize for Physiology or Medicine
2020: *Doctor honoris causa,* University of Oulu
2020: Homer W. Smith Award
2021: Capo D'Orlando Award

ELECTIONS TO THE FELLOWSHIP OF LEARNED SOCIETIES
1996: Fellow, The Royal College of Physicians (London)
2002: Fellow, The Academy of Medical Sciences (London)
2005: Fellow, The Royal Society (London), 2002; Elected Member of Council
2006: Member, EMBO
2007: Foreign Honorary Member, American Academy of Arts and Sciences
2020: Fellow, AACR Academy
2020: Member, German National Academy of Sciences Leopoldina

Membership of external committees, editorial boards, review panels, SABs etc

- SAB, Weatherall Institute of Molecular Medicine, University of Oxford
- Editorial Boards: Embo Journal, Embo Reports, Hypoxic Signaling
- Reviewing Editor, eLife
- Trustee, The Wolfson Foundation

Lab Name	***Hypoxia Biology Laboratory***

Research programme and achievements

The laboratory's principal achievement prior to the quinquennium was the discovery and elucidation of oxygen sensing mechanisms that underpin adaptive responses to low oxygen (hypoxia) in human and animal cells. The process, oxygenase-catalysed post-translational hydroxylation of specific amino acid residues in the hypoxia inducible transcription factor HIF, was unprecedented as a signalling mechanism. Our work has since revealed (i) that oxygenase-catalysed post-translation oxidations, of different types, are not (as had previously been supposed) rare on human intracellular proteins and (ii) that in addition to the HIF system, at least one of these modifications (N-Cysteine di-oxygenation) has a signalling role in oxygen homeostasis alongside the HIF hydroxylase system.

In addition to defining the source(s) of oxygen sensitive signals, we have extensively studied the downstream pathways delivering the physiological outputs of the HIF system. This work includes pan-genomic assays of the direct HIF transcriptional response using chromatin immunoprecipitation and related assays, and characterisation of integrated physiological responses to hypoxic stress in transgenic or recombinant mice. It also includes the testing of the therapeutic potential of pharmacological modulators, both *in vitro*, and *in vivo*.

Future Research
Ongoing and planned research builds on this work in two interrelated ways.

Novel sensors and pathways for oxygen homeostasis
Based on the absolute requirement to maintain oxygen homeostasis over different time-scales, and in tissues operating over widely different ranges of oxygen tensions, we hypothesise that there must be multiple systems in addition to the HIF hydroxylase pathway operating in a co-ordinated fashion to deliver the precision implicit in physiological oxygen homeostasis. We aim to identify novel oxygen-sensitive enzyme-substrate couples and explore their physiological signalling output and therapeutic tractability.

In outline, we are operating two strategies in parallel:
(i) a candidate enzyme-led strategy, focusing on oxygenases that have high candidacy as oxygen sensors, aiming to define their kinetics and substrate repertoire(s) accurately.
(ii) a phenotype-led strategy, exploring pan-genomic and pan-proteomic technologies to display candidate oxidative modifications of proteins and nucleic acids at massive scale. Our intention is to use this output as a "sieve" to define those modifications which are highly sensitive to oxygen levels.

The overall aim is to link the enzyme-led and phenotype-led approach to define key oxygen sensing enzyme-substrate couples.

Since hypoxia can be applied in a quasi-physiological graded manner across different *in vitro*, in *cellulo* and intact organismal systems we also hope to gain insights into a number of conceptual problems in signalling including range-finding, intracellular localisation of signals, and the problems of reconciling interaction with accuracy.

Implications of the oncogenic switching of massive interconnected hypoxia signalling pathway in cancer
Hypoxia signalling pathways are often pathologically activated in cancer, either genetically or by micro-environmental hypoxia. Based on known physiology, and genetic evidence, we have proposed that activation of such pathways entrains multiple anti-tumorigenic as well as pro-tumorigenic actions and that it is the balance of these effects that constrains tumour development.

Under such a model we propose that cancer cells are under selective pressure to modulate or extinguish the anti-tumorigenic properties of hypoxia pathway activation and that this process of "accommodation" drives cancer phenotypes, including those associated with resistance to therapy.

To study these processes it is necessary to track cancer cells accurately from the point of initiating oncogenic mutation. Unfortunately this is not possible in human tumours where history must be inferred from existing cells. Therefore, we have constructed a mouse in which a molecular marker is activated as an obligate consequence of tumour suppressor inactivation. Unlike lineage marking technology, this employs a single allele so that marker gene inactivation can be exactly linked to tumour suppressor inactivation and followed in real-time. We are applying this system to the study of tissue-specific tumour formation, for instance following activation of hypoxia signalling pathways following inactivation of the von Hippel-Lindau tumour suppressor (VHL). We aim to compare and contrast all the events that follow VHL inactivation, in order to better understand how selective pressures are accommodated in cancer-prone as opposed to cancer-resistant tissues. We anticipate that the work should have general relevance to other oncogenic pathways whose "switching" in cancer may likewise alter extensive interconnected pathways, with both anti-tumorigenic as well as pro-tumorigenic potential.

Research outputs

Masson N, Keeley TP, Giuntoli B, White MD, Puerta ML, Perata P, Flashman E, Licausi F, Ratcliffe PJ. (2019) *Conserved N-terminal cysteine dioxygenases transduce responses to hypoxia in animals and plants.* Science 365, 65-69. DOI: 10.1126/science.aaw011
The work identifies cysteamine (2-aminoethanethiol) dioxygenase (ADO) as a high K_mO_2 N-terminal cysteine dioxygenase that transduces cellular response to hypoxia in animals and humans, including the regulation of G-protein signalling by the N-degron pathway. ADO catalyses an identical post-translational modification to the plant cysteine oxidases, defining a mechanism of oxygen sensing that is conserved across multicellular eukaryotes.

Yamamoto A, Hester J, Macklin PS, Kawai K, Uchiyama M, Biggs D, Bishop T, Bull, K, Cheng X, Cawthorne E, Crockford TL, Davies B, Dow LE, Goldin R, Coleman ML, Kranc K, Kudo H, Lawson H, McAuliffe J, Milward K, Scudamore CL, Soilleux E, Issa F, Ratcliffe PJ, Pugh CW. (2019) *Systemic silencing of PHD2 causes reversible immune regulatory dysfunction*. J Clin Invest 130, pii. 124099. DOI: 10.1172/JCI124099.
The work describes a binary tetracyclin inducible shRNA transgenic system for genetic intervention on the “oxygen sensing” HIF-prolyl hydroxylase enzymes. It demonstrates that systemic silencing of these enzymes has the potential to create an aggressive lymphoproliferative disorder due to abnormal T-cell regulatory function. The work complements cell-specific genetic interventions in the immune system in demonstrating an interface between hypoxia signalling and immune regulation, and highlights the importance of considering this as human therapeutics are developed.

Cockman ME, Lippl K, Tian YM, Pegg HB, Figg WD, Abboud MI, Heilig R, Fischer R, Myllyharju J, Schofield CJ, Ratcliffe PJ. (2019) *Lack of activity of recombinant HIF prolyl hydroxylases (PHDs) on reported non-HIF substrates*. eLife 8:e46490. DOI: 10.7554/eLife.46490
One of the most important current uncertainties in the field of hypoxia biology is whether the “oxygen sensing” prolyl hydroxylases have targets beyond the established Hypoxia Inducible Factor (HIF) system. This paper describes a series of assays using mass spectrometry and radio-chemical detection of hydroxyproline which challenge an accruing body of high-profile literature purporting to describe non-HIF targets of these enzymes. It lays out standards for the assignment of enzyme dependent protein oxidations.

Schmid V, Lafleur VN, Lombardi O, Li R, Salama R, Colli L, Choudhry H, Chanock S, Ratcliffe PJ, Mole DR. (2019) *Co-incidence of RCC-susceptibility polymorphisms with HIF cis-acting sequences supports a pathway tuning model of cancer*. Sci Rep 9, 18768. DOI: 10.1038/s41598-019-55098-7
The work describes highly significant co-incidence of GWAS associated human susceptibility polymorphisms for renal cancer and pan-genomic assays of regulatory elements that transduce the HIF transcriptional cascade. It argues strongly for a new model of cancer development whereby major switches in oncogenic pathways are initially restrained by the extent and complexity of the downstream pathways and require accommodating modulation to occur for progression to cancer.

Cheng X, Prange-Barczynska M, Fielding JW, Zhang M, Burrell AL, Lima JD, Eckardt L, Argles I, Pugh CW, Buckler KJ, Robbins PA, Hodson EJ, Bruick RK, Collinson LM, Rastinejad F, Bishop T, Ratcliffe PJ. (2020) *Marked and rapid effects of pharmacological HIF-2α antagonism on hypoxic ventilatory control*. J Clin Invest 130(5):2237-2251. DOI: 10.1172/JCI133194.

The paper establishes isoform specificity of the action of Hypoxia Inducible Factors in specific physiological control mechanisms; specifically, the non-redundant role of HIF2 in ventilatory acclimatisation to sustained hypoxia. It also establishes that pharmaceutical antagonism of HIF2 using agents which are undergoing trials in clinical renal cancer have the ability to disrupt normal human ventilatory control.