Name	PAUL NURSE	
Position	Senior Group Leader Director of The Francis Crick Institute	
Year joined *(Crick or founder institute)*	1984-1987; 1993 - present	

Career History

1967-1970: University of Birmingham – BSc (First Class Honours) in Biological Sciences
1970-1973: University of East Anglia - PhD in Cell Biology/Biochemistry
1974-1980: Department of Zoology, University of Edinburgh; SERC Research Fellow
1980-1984: School of Biology, University of Sussex; MRC Senior Research Fellow
1984-1987: Imperial Cancer Research Fund, London; Head of Cell Cycle Control Laboratory
1987-1993: University of Oxford, Head of Microbiology Department, Royal Society Research Professor
1993-2002: Imperial Cancer Research Fund; Director of Research: Director General
2002-2003: Cancer Research UK, Director-General (Science), Chief Executive
2003-2011: The Rockefeller University, New York, USA, President
2010-2015: The Royal Society, London, President
2010-present: Francis Crick Institute. Director and Head of Cell Cycle Control Laboratory

Major Awards, Honours and Prizes

Major International Award Lectures and Medals:
Louis Jeantet Prize for Medicine in Europe (Switzerland) (1992); Gairdner Foundation International Award (Canada) (1992); Pezcoller Award for Oncology Research (Italy) (1995); Royal Society Royal Medal (UK) (1995); Dr H P Heineken Prize for Biochemistry & Biophysics (The Netherlands) (1996); General Motors Cancer Research Foundation Alfred P Sloan Jr Prize & Medal (USA) (1997); Albert Lasker award (USA) (1998); The Nobel Prize for Physiology or Medicine (Sweden) (2001); The Royal Society of Edinburgh Royal Medal (UK) (2003); The Royal Society Copley Medal (UK) (2005); Albert Einstein World Award of Science (International) (2013); Genetics Society Centenary Medal (UK) 2019.

Election to Academies and Organisations:
Member of the European Molecular Biology Organisation (EMBO) (1997); Fellow of the Royal Society (1989); Member of Academia Europea (1992); Foreign Associate of the US National Academy of Sciences (1995); Founder Member of the Academy of Medical Sciences (1998); Chinese Academy of Sciences (2015); Royal Irish Academy Dublin (2016); President of the UK Genetical Society (1990-1994); Lasker Jury Member (1999-2020); Member of the Council for Science and Technology advising the Prime Minister and Cabinet on Science (2000-2015).

Other Awards:
Knighthood for services to Cell Biology and Cancer Research (1999); Legion d'Honneur, France (2002); Order of the Rising Sun, Gold and Silver Star, Japan (2018).

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

Chair/Member of Scientific Board/Councils of EMBL; Institut Curie; Institut Pasteur; VIB; Basel Biozentrum; Sanger Institute; Memorial Sloan Kettering (mostly 2015-2021). Chancellor of University of Bristol (2017-2021), Secretary General EMBO (2015-2021), Trustee British Museum (2015-2020), Trustee QEII prize for Engineering (2015-2021), Trustee Kirkhouse Trust (founded by Ed Southern for crop improvement in Africa (2015-2021), Member of STS Council Japan (2015-2021), Member of Lasker Jury (2015-2020), Chief Science Advisor, European Commission (2017-2021).

Lab Name	***Cell Cycle Laboratory***

Research programme and achievements

The objective of the Cell Cycle Laboratory is to better understand the global controls regulating the eukaryotic cell cycle. The organism used for this work is the fission yeast which has many powerful methodologies and resources available for its study, including a 99% genome wide gene deletion collection constructed by a consortium led by the Laboratory.

The main achievements of the Laboratory since 2015 are as follows:

1. Screening of the gene deletion collection which identified 538 cell cycle genes. Diploid haploinsufficiency and haploid mitotic advancement screens of the gene deletions identified 32 genes potentially encoding rate limiting components for cell cycle control and CDK regulation.
2. Establishing that the meiotic and mitotic cell cycles can be driven by a single cyclin-CDK complex, supporting a model proposed by the Laboratory that quantitative increase in total cellular CDK activity is a major principle underlying cell cycle progression.
3. Describing the cell cycle patterns of CDK substrate phosphorylation and identifying substrates phosphorylated early, middle, and late in the cell cycle. Developing an *in vivo* protein kinase assay and using this to reveal that total cellular CDK activity has a wide dynamic range during the cell cycle, rising 50-fold. This results in early substrates involved in S-phase being more easily phosphorylated than late mitotic substrates. Determining the average CDK phosphosite turnover half-life as 2-3 mins and showing it is the same at different cell cycle stages.
4. Demonstrating that CDK and other cell cycle protein kinases at both the microlevel (within mitosis) and macrolevel (throughout the cell cycle) act like rheostats. These can form the basis for maintaining temporal order during the cell cycle. The high CDK phosphosite turnover could create futile cycles to help to ensure there are sharp rises in substrate phosphorylation at cell cycle transitions.
5. Showing that cell size homeostasis at the G2/mitosis transition is maintained in cells that cannot phosphorylate Cdc2Y15, indicating that regulators of Y15 phosphorylation are unlikely to have roles in the primary cell size sensing mechanism as has been proposed, although could co-operate with such a primary mechanism to make it more accurate.
6. Identifying a centrosomal Spindle Pole Body (SPB) targeting motif in the B-type cyclin Cdc13, and showing that this motif is required for cells to enter mitosis. This motif is conserved in human cells targeting cyclin B1 to the centrosome. In the absence of the

motif, weak CDK substrates located at the SPB are not efficiently phosphorylated. This result suggests that CDK localisation at the SPB extends the CDK activity dynamic range allowing weak mitotic CDK substrates to become phosphorylated at mitosis.

7. Demonstrating there is a nuclear size homeostasis mechanism ensuring that nuclei with an altered size are returned to a normal nuclear/cytoplasmic ratio within one cell cycle, and identification of genes potentially involved in that mechanism. Showing that the nuclear envelope protein Lem2 may act as a 'valve' between membrane bounded organelles, and that membrane flow between these organelles may play a role in nuclear size homeostasis.
8. Developing improved single DNA molecule combing methods to determine the organisation of origin firing throughout S-phase. Early in S-phase origins are shown to fire stochastically, and later in S-phase to fire in clusters. Molecules 2-5Mb in length can be combed, allowing analysis of entire fission yeast chromosomes. In human cells 8-12Mb DNA molecules can be analysed using the same methods similar stochastic firing and cluster formation were observed.

Future work of the Laboratory will focus on the roles CDK and CDK regulators play in ensuring orderly progression through the cell cycle. This will include investigation of: (1) cell size and ploidy controls acting at the onset of mitosis, (2) How differential CDK substrate sensitivity is brought about, (3) How transitions into cell cycle events such as mitosis are brought about in a sharp 'digital' manner in response to less rapid 'analogue' increases in CDK activity, (4) CDK family differences between different organisms and their implications for the evolution of cell cycle control. In addition, two subsidiary projects will be pursued: (1) Nuclear size control and (2) TOR pathway phosphorylation and its effects on protein and RNA synthesis.

Research outputs

Gutiérrez-Escribano P, and Nurse P. (2015) *A single cyclin-cdk complex is sufficient for both mitotic and meiotic progression in fission yeast*. Nat Commun. 6:6871-93. DOI: 10.1038/ncomms7871
The requirements of the six CDKs expressed during meiosis have been analysed. All six cyclins have been deleted and can be replaced by a single Cdc13-cdc2 fusion protein. We conclude that the meiotic and mitotic cell cycles can be driven by a single CDK complex.

Swaffer MP, Jones AW, Flynn HR, Snijders AP, Nurse P. (2016) *CDK Substrate Phosphorylation and Ordering the Cell Cycle*. Cell. 167(7):1750-1761. DOI: 10.1016/j.cell.2016.11.034
A phosphoproteomics analysis of CDK substrates has shown that the correct cell cycle temporal order of CDK substrate phosphorylation can be established by a single CDK. It is shown that there is a 50-fold increase of *in vivo* CDK activity during the cell cycle. Temporal order is achieved by a combination of this rise with differential sensitivity of substrates to CDK activity. Phosphosite turnover is very rapid which helps ensure sharp cell cycle transitions.

Swaffer MP, Jones AW, Flynn HR, Snijders AP, Nurse P. (2018) *Quantitative Phosphoproteomics Reveals the Signaling Dynamics of Cell-Cycle Kinases in the Fission Yeast Schizosaccharomyces pombe*. Cell Rep. 24(2):503-514. DOI: 10.1016/j.celrep.2018.06.036

A phosphoproteomics analysis of cell cycle protein kinases indicates that different mitotic kinases (CDK, NIMA related, Polo-like and Aurora) are activated sequentially during mitosis. The timing of these waves of activation is determined by the differential sensitivities of the mitotic kinases to the rising level of upstream CDK activity.

Kume K, Cantwell H, Burrell A and Nurse P. (2019) *Nuclear membrane protein Lem2 regulates nuclear size through membrane flow*. Nat Commun. 10(1):1871. DOI: 10.1038/s41467-019-09623-x
Deletion of *lem2* the nuclear membrane protein Lem2 alters the size of the nucleus. Fatty acid synthesis inhibition reduces lipid availability for membranes, and membrane flows rapidly out of the nucleus in cells deleted for *lem2*. It is proposed that membrane flow between organelles is part of the mechanism maintaining nuclear size homeostasis.

Basu S, Roberts EL, Jones AW, Swaffer MP, Snijders AP, Nurse P. (2020) *The Hydrophobic Patch Directs Cyclin B to Centrosomes to Promote Global CDK Phosphorylation at Mitosis*. Curr Biol. 30(5):883-892. DOI: 10.1016/j.cub.2019.12.053
Disruption of a hydrophobic patch in the Cdc13 B-cyclin prevents localisation of CDK at the centrosomal spindle pole body, blocks mitosis, and compromises phosphorylation of the weakest CDK substrates. We propose this mechanism contributes to CDK substrate regulation.