Name	PETER J J PARKER
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	1990

Career History

1976- 1979: Post-graduate student Professor sir Philip Randle, Clinical Biochemistry University of Oxford, UK.
1979- 1982: Post-Doc; Professor sir Philip Cohen, University of Dundee, UK *MRC Fellowship Award*
1982- 1985: Post-Doc; Professor Mike Waterfield, ICRF London, UK *ICRF Post-Doc Fellowship*
1985- 1986: ICRF, London, UK, *Head of Signal Transduction Laboratory (Tenure track position)*
1986- 1990: Middlesex Hospital, Ludwig Institute for Cancer Research, London, UK *Head of Cell Regulation Laboratory*
1990- 2015: ICRF/London Research Institute, CRUK, London, UK, *Principal Scientist*
2006- current: King's College London, London, UK *Professor of Cancer Cell Biology, Director CRUK Cancer Centre (2015-)*
2015- current: Francis Crick Institute, London, UK *Senior Group Leader*

Major Awards, Honours and Prizes

1997: Elected to the European Molecular Biology Organisation
2000: Elected to the Academy of Medical Sciences
2002: First non-US Council member of the American Society for Biochemistry and Molecular Biology
2004: Awarded the Biochemical Society Morton Lecture
2006: Elected to the Fellowship of the Royal Society
2011: Elected a Fellow of the European Academy of Cancer Sciences

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

2010-2019 MATWIN *Advisory Board*
2011-Current Medical Research Council *Translational Research Group*
2012-2019 Sixth Element *Advisory Board member*
2012-Current Max F Perutz Laboratory, Vienna *Scientific Advisory Board*
2014-Current Cancer Research Technology *Chair of the TBAB Advisory Group*
2014-Current FASTBASE Solutions (cofounder) *Chair Scientific Advisory Board*
2015-Current Babraham Institute *Science Advisory Committee*
2016-2019 Novintum *Advisory Board*
2016-2019 CRUK Expert Review Panel, *Committee member*
2019-Current Beatson Institute Drug Development Unit *Advisory Board*
2020-Current Varian Bio *Chair of the Scientific Advisory Board*
2020-Current Medical Research Council Strategic Review, *Panel member*
2020-Current Samsara, *Consultant*

Lab Name	*Protein Phosphorylation Laboratory*

Research programme and achievements

Work in my laboratory focuses on a class of proteins that are pivotal in controlling biological processes, the protein kinases. Their study will aid our understanding of fundamental mechanisms of (patho)physiology and as druggable targets, they provide opportunities for therapeutic intervention in a number of diseases, including cancer.

Within this family we have worked extensively on the protein kinase C (PKC) subfamily, with a sightline to dysregulation/emergent properties in cancer, a core biomedical theme within the Crick. Alongside the specific and sometimes surprising PKC-associated mechanisms, the output in fundamental kinase knowledge (e.g. conformation dependence, substrate switching, *in vivo* substrate screening) offer unexpected insights/opportunities in what some might consider a mature field. Evidently there is much to unravel and the laboratory seeks to deliver the depth of knowledge required for a comprehensive understanding of kinase (patho)biology.

The laboratory has been focused on four areas:
(i) the role of aPKCi in polarity and proliferation, in particular its contribution towards Ras oncogenic output, alongside an aPKC drug discovery and development programme
(ii) the emergent role of PKCe in controlling a genome protective 'failsafe' pathway associated with a subset of transformed cells
(iii) the requirements of PKN in mammalian development and (patho)physiology
(iv) extracting generic lessons from the PKC family germane to the wider kinase field and of value to our understanding of cancer-associated mechanisms

In pursuing these goals we have worked with key collaborators inside and outside the Institute, brought a spectrum of disciplines to bear on our work, developed, adopted and imported novel technologies, and established excellent commercial interactions.

Highlights include:

• Defining a role for PKCe in controlling the metaphase/anaphase transition in G2 arrest defective cells
• Identifying regulators of the Topo2A dependent G2 arrest, defects in which trigger engagement of the PKCe dependency programme
• Discovering an aPKCi substrate docking domain required to support polarity that is rarely but repeatedly mutated in cancer
• Demonstrating that the PKN2 gene is required for murine development, associated with a defective mesenchyme and failure in neural crest migration
• Demonstrating that PKCe switches AuroraB substrate recognition to facilitate exit from the abscission checkpoint
• Elaborating on our conformational observations for PKC by demonstrating that nucleotide pocket occupancy of the pseudokinase HER3 is essential for its signalling (most recently, identifying the HER3 pocket-binding inhibitor AC3573)

Future laboratory plans (for completion within 18 months):

• Determine the validity of PKCe as a target for inhibition in the context of p53$^-$ and hTERT
• Characterise the translational control exerted by PKCe in mitosis

• Define PKN3 requirement in a prostate cancer model *in vivo*.
• Ascertain the liability associated with PKN2 loss of function in mice and specifically the effects on cardiac development and cardiac function in adults
• Assess the loss/gain of function roles of PKCa and PKCb associated with penetrant point mutations in two rare cancers: chordoid glioma and ATLL respectively.

Translational activities will include (5-year period):

• Promoting the implementation of the aPKC inhibitor programme in clinical testing through Varian Bio who have licenced this opportunity.
• Progressing the portfolio of oncology biomarkers implemented by FASTBASE Solutions (cofounder) exploiting the technology licenced from the Crick and building upon it within the company.
• Triggering a drug development programme directed at PKCe, dependent upon completion of validation studies

Research outputs

Kelly, J. R., S. Martini, N. Brownlow, D. Joshi, S. Federico, S. Jamshidi, S. Kjaer, N. Lockwood, K. M. Rahmen, F. Fraternali, P. J. Parker* and T. N. Soliman* (2020). *The Aurora B specificity switch is required to protect from non-disjunction at the metaphase/anaphase transition*. Nat Commun 11(1): 1396. DOI: 10.1038/s41467-020-15163-6
The paper unravels the cell cycle dependent input to PKCe engagement and its proximal action through AuroraB. The non-apoptotic M-Phase role of caspase7 in cleaving a chromatin-associated pool of PKCe, alongside the site switching mechanism that plays out in the control of Topo2A by AuroraB are unusual and distinctive features of this cell cycle programme. The mechanistic insights into this transformation-associated pathway provide a specific steer to intervention opportunities in cancer.

Deiss, K., N. Lockwood, M. Howell, H. A. Segeren, R. E. Saunders, P. Chakravarty, T. N. Soliman, S. Martini, N. Rocha, R. Semple, L. P. Zalmas and P. J. Parker (2019). *A genome-wide RNAi screen identifies the SMC5/6 complex as a non-redundant regulator of a Topo2a-dependent G2 arrest*. Nucleic Acids Res 47(6): 2906-2921. DOI: 10.1093/nar/gky1295
The paper reports a genome wide screen identifying the non-redundant genes required for the normal operation of the G2 arrest defective in many tumour cells. This identified the SMC5/6 complex as a critical mediator of arrest operating through a novel Topo2a sumoylation mechanism effected by the NSE2 subunit. A germline mutation in NSE2 in a patient, corroborated this requirement. The mechanisms elaborated provide clear genetic evidence for the distinction between this topological stress pathway and that engaged by DNA damage.

Claus, J., G. Patel, F. Autore, A. Colomba, G. Weitsman, T. N. Soliman, S. Roberts, L. C. Zanetti-Domingues, M. Hirsch, F. Collu, R. George, E. Ortiz-Zapater, P. R. Barber, B. Vojnovic, Y. Yarden, M. L. Martin-Fernandez, A. Cameron, F. Fraternali, T. Ng and P. J. Parker (2018). *Inhibitor-induced HER2-HER3 heterodimerisation promotes proliferation through a novel dimer interface*. Elife 7. DOI: 10.7554/eLife.32271
The paper was a broad collaboration with a team from one of our Partner Institutions and others, and illustrates how our learning from insights in the PKC field, here concerning kinase nucleotide pocket occupation, can impact our understanding of the broader

kinome. Specifically, the work demonstrates that the pseudokinase HER3 which is upregulated in cancer and drug resistance settings, undergoes essential nucleotide pocket occupation dependent changes in conformation to drive HER2 partner dependent signalling. Of importance clinically, the paper offers a route to small molecule-based intervention and also raises questions of inhibitor liability associated with HER3.

Quetier, I., J. J. Marshall, B. Spencer-Dene, S. Lachmann, A. Casamassima, C. Franco, S. Escuin, J. T. Worrall, P. Baskaran, V. Rajeeve, M. Howell, A. J. Copp, G. Stamp, I. Rosewell, P. Cutillas, H. Gerhardt, P. J. Parker* and A. J. Cameron* (2016). ***Knockout of the PKN Family of Rho Effector Kinases Reveals a Non-redundant Role for PKN2 in Developmental Mesoderm Expansion*****. Cell Rep 14(3): 440-448. DOI: 10.1016/j.celrep.2015.12.049**
The paper reports on a long-term study that has led to the knock-out of all three PKN family proteins in the mouse. The work defines the essential nature of PKN2 wherein systemic knockout of this gene at E7 leads to loss of mesoderm. Mesoderm derived cells from PKN2 knockouts display proliferative and migratory dysfunction *ex vivo*, reflecting the loss of proliferation and defective neural crest migration *in vivo*.

Pike, T., N. Brownlow, S. Kjaer, J. Carlton and P. J. Parker (2016). ***PKCepsilon switches Aurora B specificity to exit the abscission checkpoint*****. Nat Commun 7: 13853. DOI: 10.1038/ncomms13853**
The paper defines the critical mechanisms engaged by PKCe to control the Aurora B abscission checkpoint. In so doing the study defines a novel kinase control mechanism of broad importance to the field and shows how this switches a downstream output to afford a change in behaviour of this patho-biological control.