Name	JULIAN DOWNWARD
Position	Senior Group Leader Associate Research Director
Year joined *(Crick or founder institute)*	1989

Career History

1979 –1982: Undergraduate at Cambridge University, U.K.
1982: B.A. hons (first class) in Natural Sciences (Biochemistry).
1982 – 1986: Graduate Student at Imperial Cancer Research Fund (ICRF), London, UK, in laboratory of Dr Michael Waterfield.
1986: Ph.D. from Imperial College, University of London, for work at ICRF.
1986 – 1989: Post-doctoral research fellow at Whitehead Institute, Massachusetts Institute of Technology, Cambridge, MA, USA, in laboratory of Dr Robert Weinberg.
1989 – 1993: Junior Group Leader at Imperial Cancer Research Fund, London, UK.
1993 – 2015: Senior Group Leader at Imperial Cancer Research Fund (renamed Cancer Research UK London Research Institute in February 2002).
2005 – 2015: Associate Director, Cancer Research UK London Research Institute.
2011 – 2019: Senior Group Leader at the Institute of Cancer Research, Fulham Road, London (part time secondment, 20%).
2015 – present: Senior Group Leader at Francis Crick Institute, Oncogene Biology Laboratory
2015 – present: Associate Research Director, Francis Crick Institute. Oversight of Science Technology Platforms and Biological Research Facility.

Major Awards, Honours and Prizes

1979: Open scholarship, Clare College, Cambridge University.
1981: Foundation scholarship, Clare College, Cambridge University.
1986-8: Imperial Cancer Research Fund travel fellowship.
1992: Science journal "Rising Star of European Biology": named as one of the fifty most promising European research biologists under age 42.
1993: I.S.I. "Citation Classic" status for publication J.Downward et al. (1984) Nature 307, 521. "Close similarity of epidermal growth factor receptor and v-erb B oncogene protein sequences."
1995: Elected a Member of the European Molecular Biology Organisation (EMBO).
1999: 14th in I.S.I analysis of most cited UK life scientists, 1989-1998 (Times Higher Education supplement).
2004: European Association for Cancer Research Mike Price Memorial Lecture.
2005: Elected a Fellow of the Royal Society (FRS), the UK's national academy of sciences.
2009: Elected a Fellow of the Academy of Medical Sciences (FMedSci), the UK's national academy of medical science.
2009: 20th in I.S.I analysis of most cited European cell biologists, 1999-2008 (Lab Times magazine).
2009: Cambridge University Biochemistry Department Alkis Seraphim Memorial Lecture.

2010: Elected a Fellow of the European Academy of Cancer Sciences.
2012: Elected an Honorary Fellow of the Royal College of Physicians.
2018: Michel Clavel Memorial Lecture of the European Organisation for Research and Treatment of Cancer / National Cancer Institute / American Association for Cancer Research.
2019: Understanding Animal Research Openness Award for Media Engagement for BBC Radio 5 broadcast live from the Crick's animal facility.

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

1994 - present Associate Editor, Cell.
2001 - 2015 Board of Reviewing Editors, Science.
2004 - present Associate Editor, Molecular Cell.
2007 - present Editorial Board, Molecular Cancer Research.
2008 - present Editorial Board, Cell Cycle.
2009 - present Editorial Board, BBA Reviews on Cancer.
2010 - present Editorial Board, Cell Research.
2012 - present Editorial Board, PLOS Biology.
2016 - present Editorial Board, Cell Discovery.
2015 – 2016 Chair, Cancer Research UK Small Molecule Expert Review Panel.
2015 – present Executive Chair, British Association for Cancer Research.
2004 – present Scientific Advisory Board, FIRC Institute of Molecular Oncology, Milan (IFOM).
2015 – present Scientific Advisory Board, CRUK Lung Cancer Centre of Excellence, Manchester and University College London.
2016 – present Advisory Council, European Association for Cancer Research (EACR).
2020 – present International Scientific Advisory Board, Cyprus Institute for Cancer Research, Nicosia.
2020 – present Scientific Advisory Board, Jubilant Therapeutics, Inc., New Jersey
2020 – present Scientific Advisory Board, Karolinska Comprehensive Cancer Centre, Stockholm.

Lab Name	***Oncogene Biology Laboratory***

Research programme and achievements

The Oncogene Biology Laboratory focuses on characterisation of molecular mechanisms involved in tumorigenesis by RAS and related oncogenes with a view to identifying novel therapeutic strategies for RAS and RAC mutant cancers.

Principal achievements in the past quinquennium have been:
1. Exploration of combinatorial approaches to targeting RAS mutant cancers. This was started before the advent of direct KRAS inhibitors and attempted to find the optimal approach to blocking the actions of mutant RAS through inhibition of druggable signalling nodes both downstream and upstream of RAS. We have now included the use of G12C mutant specific KRAS inhibitors and sought to find ways of potentiating the activity of these agents by interfering with signalling network adaptation to their actions.
2. We have investigated the role in cancer of RAS signalling through one specific effector enzyme, PI 3-kinase p110α. We have shown this link to be essential in KRAS driven lung

tumour maintenance. In addition, we find that wild type RAS signalling to p110α is critical in mutant EGFR driven lung cancer.
3. Our investigation of the interaction of RAS proteins with other isoforms of PI 3-kinase has led us to the conclusion that, unlike p110 α, γ, and δ, the ubiquitously expressed p110β is regulated not by RAS proteins but by related small GTPases from the RAC family. We have further studied the function of an activated oncogenic mutant form of RAC1, P29S, establishing the mechanistic basis for its impact in BRAF mutant melanoma. P29S RAC1 acts through several effectors, in particular the transcriptional regulator SRF/MRTF, to promote in melanoma cells a mesenchymal differentiation state that is resistant to BRAF inhibitors.
4. Due to awareness of the limitations in advanced cancers of even the most effective treatments targeting growth signalling pathways, as evidenced by the common development of resistance to agents targeting mutant BRAF and EGFR oncogenic drivers, we have investigated how RAS oncogenic signalling might be contributing to control of the tumour immune microenvironment. We asked whether there are specific mechanisms by which RAS might promote the ability of tumours to evade the immune system that might provide a rational basis for combining inhibitors of the RAS signalling network with modulators of the immune system. We have shown that in lung cancer cells, RAS, acting principally via the MEK pathway, controls the expression of the immune checkpoint regulatory ligand PD-L1 by modulating the stability of its mRNA through control of the 3' AU rich element binding protein Tristetraprolin.

Future plans for the Oncogene Biology Laboratory will focus on the interplay between the signalling networks in the cancer cells driven by RAS oncoproteins and the patient's immune system, and whether this offers unique therapeutic opportunities. We have developed a number of mouse models of lung cancer that aim to better replicate the high tumour mutational burden found in the clinic, this being achieved for example by overexpressing genes such as the cytidine deaminase APOBEC3B or deleting genes such as 0'6 methylguanine methyltransferase, resulting in accumulation of clinically relevant mutations. These models are then used to study the response of tumours to therapies targeting RAS signalling, including G12C KRAS inhibitors, focusing on the effects of the interaction between the tumour and the host immune system. We have optimised protocols in imaging mass cytometry and single cell sequencing that allow us to determine the impact of RAS on the tumour immune microenvironment and indicate the optimal approaches to combining RAS pathway targeted therapy with immunotherapy to achieve ultimate complete eradication of tumours.

In addition, we will investigate mechanisms of metastatic spread of RAS mutant cancer cells, in particular the roles of proteins identified as essential for metastasis in a recent functional genomic screen in the lab, including the palmitoyl transferase ZDHHC20. We will also further explore RAF1 signalling downstream of RAS in lung cancer mouse models and investigate the possibility of blocking RAS interaction with effectors in a KRAS isoform selective manner. This latter is the subject of translational drug discovery projects in collaboration with commercial partners such as AstraZeneca.

Research outputs

M.A. Coelho, S. de Carné Trécesson, S. Rana, D. Zecchin, C. Moore, P. East, B. Spencer-Dene, E. Nye, K. Barnouin, A.P. Snijders, W.S. Lai, P.J. Blackshear, J. Downward. (2017) *Oncogenic RAS signalling promotes tumour immunoresistance by stabilising PD-L1 mRNA*. Immunity 47, 1083-1099 DOI: 10.1016/j.immuni.2017.11.016

This work establishes for the first time a link between oncogenic RAS signalling and increased immuno-suppressive expression of the immune checkpoint protein PD-L1. RAS signalling results in phosphorylation and inactivation of TTP, a factor involved in degrading PD-L1 mRNA transcripts. As TTP inactivation causes accumulation of PD-L1 mRNA, interfering with the RAS pathway increases TTP binding to AU-rich elements of the transcripts, decreases PD-L1 protein production, and leads to enhanced antitumor immunity.

M.M. Murillo, S. Rana, B. Spencer-Dene, E. Nye, G. Stamp, J. Downward. (2018) ***Disruption of the interaction of RAS with PI 3-kinase induces regression of mutant EGFR-driven lung cancer*****. Cell Reports 25, 3545-3553. DOI:** **10.1016/j.celrep.2018.12.003**
We have investigated the role in cancer of RAS signalling through one specific effector enzyme, PI 3-kinase p110α, creating an inducible mouse model in which we can assess the need for the RAS binding domain (RBD) of p110α in the maintenance of RAS driven lung tumours. As well the interaction of RAS with p110α being required for the maintenance of established KRAS driven lung tumours, we further show here that interaction of endogenous wild type RAS with p110α is also required for lung cancer formation and maintenance driven by upstream signalling components such as mutant EGFR.

D.A. Lionarons, D.C. Hancock, S. Rana, P. East, C. Moore, M.M. Murillo, J. Carvalho, B. Spencer-Dene, E. Herbert, G. Stamp, D. Damry, D.P. Calado, I. Rosewell, R. Fritsch, R.R. Neubig, M. Molina-Arcas, J. Downward. (2019) ***RAC1P29S Induces a Mesenchymal Phenotypic Switch via Serum Response Factor to Promote Melanoma Development and Therapy Resistance*****. Cancer Cell 36, 68-83. DOI:** **10.1016/j.ccell.2019.05.015**
Metastatic melanoma is a lethal disease, in part because of rapid acquisition of resistance to therapy. Using genetically engineered mouse models, we demonstrate that the activating RAC1 P29S mutation, present in up to 5% of melanoma patients, cooperates with BRAF as a driver of melanoma initiation and promotes BRAF inhibitor resistance. The critical RAC1 effector pathway in melanoma is shown to be the transcription factor complex SRF/MRTF, which initiates a switch to a mesenchymal-like state characterized by therapy resistance. Therapeutic targeting of SRF/MRTF may have potential to reverse BRAF inhibitor resistance in melanoma patients bearing the oncogenic RAC1 P29S mutation.

M. Molina-Arcas, C. Moore, S. Rana, F. van Maldegem, E. Mugarza, P. Romero-Clavijo, E. Herbert, S. Horswell, L.S. Li, M.R. Janes, D.C. Hancock, J. Downward. (2019) ***Development of combination therapies to maximize the impact of G12C KRAS inhibitors in lung cancer*****. Science Translational Medicine 11:eaaw7999. DOI:** **10.1126/scitranslmed.aaw7999**
KRAS is the most commonly mutated oncogene in human lung cancer, but direct targeting of RAS proteins has proved difficult. A recently developed inhibitor of G12C mutant KRAS protein inhibits lung cancer progression in mouse models but does not provide durable regressions. By studying signalling pathways required for survival of KRAS mutant cells, we demonstrate a strong and selective potentiation of the effects of G12C KRAS inhibitors when mTOR and/or IGF1R are also inhibited. Using mutant specific G12C KRAS inhibitors rather than MEK inhibitors in these combinations is associated with greater specificity and lower toxicity. We propose that adding IGF1R and mTOR inhibitors will increase the impact of G12C KRAS inhibitors in clinical trials.

D. Zecchin, C. Moore, F. Michailidis, S. Horswell, S. Rana, M. Howell, J. Downward (2020). ***Combined targeting of G-protein-coupled receptor and EGF receptor signalling overcomes resistance to PI3K pathway inhibitors in PTEN-null triple negative breast cancer*****. EMBO Molecular Medicine e11987 DOI: 10.15252/emmm.202011987**

As a consequence of loss of PTEN tumor suppressor function, triple-negative breast cancers (TNBCs) show aberrant PI3K pathway activation. However, clinical efficacy of PI3K inhibitory drugs has so far been modest in this setting. We identify here a molecular network that impairs response to PI3K inhibitors in PTEN-null TNBCs. Both the G protein-coupled receptor PAR1 and EGFR were discovered to signal to PI3Kβ in these tumors. Simultaneous inhibition of PI3Kβ and EGFR efficiently blunted the activation of the pathway and produced anti-tumor activity both in vitro and in vivo in different PTEN-null TNBC models.