Name	KAREN VOUSDEN
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	2017

Career History

1981-1985 Post-doctoral Fellow with Prof Chris Marshall, ICR, London, UK
1985-1987 Visiting Fellow with Dr Doug Lowy, NCI, USA
1987-1992 Assistant Member, Ludwig Institute for Cancer Research, London, UK
1992-1995 Associate Member, Ludwig Institute for Cancer Research, London, UK
1995-1998 Laboratory Director, ABL Basic Research Program, USA
1998-1999 Interim Director, ABL Basic Research Program, USA
1999-2002 Laboratory Chief, NCI-FCRDC, USA
2002-2016 Professor, University of Glasgow, UK
2002-2016 Director, Cancer Research-UK Beatson Institute, Glasgow, UK

Major Awards, Honours and Prizes

2019
The Clifford Prize for Cancer Research, Australia
Sergio Lombroso Award, Weizmann Institute, Israel
President, BACR
Honorary Fellow of the Association of Cancer Physicians (UK)
2018
Mike Price Gold Medal
Foreign Associate of the National Academy of Sciences
STS Honorary Medal
The 2018 CDD Award
2017
Fellow of the AACR Academy
Honorary DSc, Queen Mary University, London
2016
Fellow of the American Academy of Arts and Sciences
Honorary Fellow of the Royal College of Physicians and Surgeons (Gla)
Outstanding Woman of Scotland
Alkis Seraphim Medal Lecture, Cambridge
Mühlbock Lecture, EACR, Manchester
Dean’s Distinguished Lecture, Weill Cornell Medicine, New York
Vallee Visitng Professor, New York
2015
CCR Eminent Lecture, NCI, Bethesda, Maryland
Academia Europaea
Lola and John Grace Lecture, ISREC
2014
Fellow of American Association for the Advancement of Science

EMBO Council
Norman Heatley Lecture, Oxford
Inaugural Lecture, Women of Distinction, Queen Mary, London
2012
Board of Directors, AACR
ECDO Lifetime Achievement Award
Marguerite Vogt Lecture, SALK
2010
Commander of the British Empire (Services to Clinical Science)
Almoth-Wright Lecture, London
2009
Fellow of the European Academy of Cancer Sciences
Royal Society of Edinburgh Gold Medal
Scottish Woman of the Year (Wisdom)
2008
Honorary DSc, University of Strathclyde
Sir Frederick Gowland Hopkins Medal
The Mike Price Lecture
2006
Fellow of the Academy of Medical Sciences
Honorary DSc, University of London
2004
Member of EMBO
Fellow of the Royal Society of Edinburgh
2003
Fellow of the Royal Society
Tom Connors Award Lecture, BACR
Wellcome trust Lecture, BSCB
2001 NIH Merit Award (Major Contributions to Research)
1998 Tenovus Gold Medal

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

2020-present Volastra Therapeutics Science Advisory Board
2019-present Vallee Foundation Vallee Scholars Committee
2019-present Founder, Faeth Therapeutics
2018-present Board of Directors, Bristol Meyers Squibb
2018-present Frankfurt Cancer Centre Science Advisory Board
2018 Emerson Collective Funding Panel
2017-present Science Committee, Cancer Research UK
2017-present AAAR Nomination Committee
2017-2020 Royal Society Sectional Committee 6
2017-2020 Oncode Institute, Netherlands Science Advisory Board
2017-present The Gurdon Institute, Management Committee
2016-2017 Vallee Foundation Vallee Scholars Committee
2016-2019 Grail Science Advisory Board
2015-2016 SU2C Review Committee
2015-present ISREC Science Advisory Board
2015-present RAZE Therapeutics Science Advisory Board
2015-present EMBO Council
2014-2017 Expert Review Group, Wellcome Trust
2014-present Ludwig Cancer Research Science Advisory Committee

2014-2016 ERC Consolidator Grant review panel LS3
2014-present PMV Science Advisory Board
2012-2016 Abramson Cancer Center (Philadelphia) SAB
2012-2016 MCR-Protein Phosphorylation Unit (Dundee) SAB
2006-2016 IRB (Barcelona) Advisory Board
2004-2017 CNIO (Madrid) Advisory Board

Lab Name	***P53 and metabolism laboratory***

Research programme and achievements

Over the past five years we have continued to develop our understanding of the regulation and function of p53, a tumour suppressor that is lost or mutated in most cancers. We have made a significant contribution to the understanding of how p53 is regulated and the responses that are driven by p53. These studies led us to investigate the role of metabolism in the control of tumorigenesis, focusing on serine metabolism and the regulation of oxidative stress.

As the principal E3 ligase that targets p53 for degradation, MDM2 is essential for survival. Our structural analysis showing how the RING domain of MDM2 interacts with the E2/ubiquitin complex allowed us to identify MDM2 mutants that cannot target p53 for degradation but retain the ability to control p53 function. Using these mutants, we are validating a new approach to MDM2 inhibition for cancer therapy, based on the selective targeting of MDM2's E3 function.

Our early studies focused on understanding functions of p53 – like the induction of cell death - that drive the elimination of nascent cancer cells. However, more recently we have pursued the unexpected observation that p53 can also function to allow survival and adaptation to non-genotoxic signals such as metabolic stress. Loss of p53 in cancer cells results in an inability to survive serine or glutamine starvation (3), an observation that we developed to show a therapeutic efficacy of dietary serine and glycine depletion in various mouse models (4). We also found that these survival functions can be retained by cancer derived mutant p53s, suggesting that the selective retention of this wild type p53 activity is beneficial during cancer progression. This work led us to examine more generally the role of serine and one carbon metabolism in cancer development, where we showed the importance of *de novo* ATP synthesis in supporting the methionine cycle and DNA methylation (5). At least some of the survival functions of p53 are associated with the ability of p53 to assist in antioxidant defence, mediated through the transcriptional activation of a number of target genes including p21, MDM2 and TIGAR. Regulation of oxidative stress can have opposing effects during tumour development, with evidence for tumour promoting functions of both pro- and antioxidant signals. We found that cancer cells placed into detached conditions undergo metabolic remodelling to remove damaged mitochondria and limit increased ROS (2). While this response allows cancer cell survival during loss of attachment to the extracellular matrix, we also showed that defects in antioxidant defence during pancreas tumour development can enhance metastasis (1). Taken together our work indicates that temporal, dynamic control of ROS underpins full malignant progression and helps to rationalise conflicting reports of pro- and anti-tumor effects of antioxidant treatment.
Finally, we showed that loss of p53 in cancer cells modulates the tumor-immune landscape to circumvent immune destruction. This response to loss of p53 reflected both

an increase in myeloid and Treg recruitment and an attenuation of the CD4+ and CD8+ T-cell response *in vivo*. Interestingly, we were able to show that two key drivers of tumorigenesis, activation of KRAS and deletion of p53, cooperate to promote immune tolerance.

Moving forward we are focusing of a few key areas. We continue to assess the potential of dietary manipulation of amino acid availability to complement cancer treatment, expanding our work to examine the role of amino acids beyond serine and glycine. We have established a small company (Faeth Therapetics) with colleagues from the UK and US to take the idea of precision nutrition into clinical trials. We are testing potential new targets in mitochondrial one carbon metabolism that could affect the balance of metabolite production and antioxidant defence and so provide therapeutic efficacy. Most importantly, we will continue to assess the consequences of modulating nutrient availability on the immune response to cancer. It is clear that the tumour microenvironment is critical in providing support for cancer cells and we are determining the role of adipocytes in this context. The interaction between tumour cells can also impact oncogenic progression and we are investigating how differences in p53 status affect the way cancer cells interact with each other. Finally, we have developed a mouse model to test the therapeutic response to inhibition of the ability of MDM2 to ubiquitinate p53, and in collaboration with Astra Zeneca we will explore the potential of this approach in cancer treatment.

Research outputs

Cheung EC, DeNicola GM, Nixon C, Blyth K, Labuschagne CF, Tuveson DA, Vousden KH. (2020) *Dynamic ROS control by TIGAR regulates the initiation and progression of pancreatic cancer*. Cancer Cell 37:168-182. DOI: 10.1016/j.ccell.2019.12.012
We show that during the development of pancreatic cancer, regulation of reactive oxygen species can both promote or restrain tumorigenesis, depending on the stage of malignant progression. This work highlights the complexity of the response to targeting ROS regulation in cancer therapy.

Labuschagne CF, Cheung EC, Blagih J, Domart M-C, Vousden KH. (2019) *Cell clustering promotes a metabolic switch that supports metastatic colonisation*. Cell Metabolism 30:720-734. DOI: 10.1016/j.cmet.2019.07.014
We show that the clustering of cancer cells following detachment from ECM results in hypoxia, which activates mitophagy to remove damaged mitochondria and reductive metabolism to support glycolysis. These responses limit mitochondrial ROS production, allowing cell survival and metastasis.

Tajan M, Hock AK, Blagih J, Robertson NA, Labuschagne CF, Kruiswijk F, Humpton T, Adams PD and Vousden KH*. (2018) *A role for p53 in the adaptation to glutamine starvation through the expression of SLC1A3*. Cell Metabolism 28:721-736. DOI: 10.1016/j.cmet.2018.07.005
In this paper we show that the ability of cells to survive glutamine depletion depends on aspartate metabolism, which is supported by the aspartate/glutamate transporter SLC1A3. The tumor suppressor p53 is shown to induce the expression of SLC1A3, explaining in part how p53 can help cancer cells survive under glutamine starvation.

Maddocks ODK, Athineos D, Cheung EC, Lee P, Zhang T, van den Broek NJF, MacKay GM, Labuschagne CF, Gay D, Kruiswijk F, Blagih J, Vincent DF, Campbell KJ, Ceteci

F, Sansom OJ, Blyth K and Vousden KH. (2017) *Modulating the therapeutic response of tumours to serine and glycine starvation*. Nature 544, 372-376. DOI: 10.1038/nature22056
This paper expands on our previous work to show the therapeutic benefits of dietary serine and glycine starvation in several genetically engineered mouse models. We find that activation of KRAS makes tumours less responsive to this approach, reflecting an ability of activated KRAS to increase expression of serine synthesis pathway (SSP) enzymes and *de novo* serine synthesis.

Tajan M, Hennequart M, Cheung E, Zani F, Hock AK, Legrave N, Maddocks ODK, Ridgway RA, Athineos D, Suárez-Bonnet A, Ludwig RL, Novellasdemunt L, Angelis N, Li VSW, Vlachogiannis G, Valeri N, Mainolfi N, Suri V, Friedman F, Manfredi M, Blyth K, Sansom OJ and Vousden KH (2021) *Serine synthesis pathway inhibition cooperates with dietary serine and glycine limitation for cancer therapy*. Nature Communications 12, 366. DOI: 10.1038/s41467-020-20223-y
Targeting the nutritional requirements of cancers through selective dietary intervention is an emerging therapeutic approach. Dietary limitation of the non-essential amino acids serine and glycine can limit the growth of some, but not all, cancers. This study extends this approach by showing combined treatment with an inhibitor of the intrinsic serine synthesis pathway with a serine/glycine free diet improves the therapeutic response and inhibits the growth of cancers that are not responsive to the diet alone. Extension of this work to human studies may offer an important new avenue for the treatment of a broad range of cancers.