Name	AXEL BEHRENS
Position	Former Senior Group Leader, now Visiting Scientist
Year joined *(Crick or founder institute)*	2001

Career History

1995 – 1998 - PhD thesis at IMP Vienna with Prof. Dr. Erwin Wagner
1999 – 2001 - Postdoc at Univ. Zurich (Switzerland) with Prof. Dr. Adriano Aguzzi, Institute of Neuropathology
2001 – 2005 - Tenure Track Group Leader, ICRF/Cancer Research UK, London
2006 – 2015 - Senior Scientist, Cancer Research UK, London (UK)
2013 – 2020 - Principal Fellow, King's College, London (UK)
2015 – 2020 - Senior Group Leader, The Francis Crick Institute, London (UK)

Major Awards, Honours and Prizes

2012 - EMBO member
2015 - Member of Academia Europaea
2018 - Honorary Full Professor, Sun Yat-Sen University, Shenzhen, China

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

Review panel DFG SFB 2017 (Munich, Germany
Review panel EPH facility at the CRI (Cambridge) 2018
Review panel French government "Laboratoires d'excellence" initiative (Paris, France). 2018
Review panel Deutsche Krebshilfe Initiative 'Mildred-Scheel-Nachwuchszentren' (Bonn, Germany) 2018

Lab Name	***Adult Stem Cell Laboratory***

Research programme and achievements

It has become clear that tumours are organised in a cellular hierarchy, with the so-called cancer stem cells (CSC), also called Tumour initiating cells (TICs), being at the apex. It is believed that CSCs mediate tumour growth, precipitate tumour relapse after treatment, and are responsible for metastasis formation. Therefore, understanding the molecular mechanisms underlying CSC function may lead to novel therapeutic approaches. During the last quinquennium my laboratory has focussed on identifying and characterising CSC populations, with the long-term view to uncover molecular vulnerabilities.

In the last years we have made significant contributions to the stem cell biology of cancer. We identified a CSC population for luminal breast cancer marked by Lgr6 (Blaas et al., Nature Cell Biology, 2016). Remarkably, Lgr6-posititve CSCs are required to maintain the cellular heterogeneity and malignancy of luminal breast cancer, suggesting that the cellular diversity of luminal breast cancer is generated by CSC, conceptually similar to the function of stem cells in normal organs. In addition, we gained novel insights into the cellular biology of pancreatic cancer. We showed that pancreatic adenocarcinoma (PDAC) can arise from both pancreatic ductal cells and pancreatic acinar cells, with

implications for PDAC stratification (Ferreira et al. Cell Reports, 2017). In addition, we characterised the molecular mechanism underlying the early stages of PDAC development (Gruber et al., Gastroenterology, 2016). Recently, we characterised a CSC population in PDAC marked by the tetraspanin surface molecule CD9. We showed that CD9Hi CSCs are required for the epithelial and mesenchymal cellular heterogeneity seen in PDAC (Wang et al., Nature Cell Biology, 2019). We found that CD9 assembles a cell surface protein complex involved in regulating PDAC metabolism. *CD9* depletion dramatically inhibited PDAC growth, identifying CD9 as a therapeutic PDAC target.

To better understand tumour development and morphology, we developed a 3D imaging technology termed FLASH that provides unprecedented capabilities to visualise large tissues at single cell resolution (Messal et al., Nature Protocols, 2020). FLASH opened a novel field of experimental 3D tumour imaging. We used FLASH to study the early stages of PDAC development, and found that PDAC has 2 fundamental tumour growth modes. In an interdisciplinary collaboration with the Salbreux lab, we found that the basic physical properties of the cellular structure from which the tumour originates, in this case the pancreatic ductal system, determines the subsequent tumour morphology. (Messal et al., Nature, 2019).

Research outputs

Hendrik A. Messal, Silvanus Alt, Rute M.M. Ferreira, Corina Cotoi, Guillaume Salbreux, and Axel Behrens. (2019) *Tissue curvature and apico-basal mechanical tension imbalance instruct cancer morphogenesis*. Nature 566(7742):126-130. DOI: 10.1038/s41586-019-0891-2.
This study introduces a new technique, FLASH, which enables immunostaining of whole organs for imaging and opens up the possibility of analysing a plethora of antigens and tissues that were previously impossible to study in 3D. By achieving this feat, we were able to study epithelial deformation from the moment of transformation, within the intact pancreas. Collaborating with the Salbreux lab, we used FLASH to identify 2 fundamental modes of epithelial tumour growth.

Victoria M.-Y. Wang, Rute M. M. Ferreira, Jorge Almagro, Theodore Evan, Nathalie Legrave, May Zaw Thin, David Frith, Joana Carvalho, David J. Barry, Ambrosius P. Snijders, Eleanor Herbert, Emma L. Nye, James I. MacRae, and Axel Behrens. (2019) *CD9 identifies pancreatic cancer stem cells and modulates glutamine metabolism to fuel tumour growth*. Nature Cell Biology 21, 1425-1435. DOI: 10.1038/s41556-019-0407-1.
This work identifies a cancer stem cell (CSC) population in pancreatic cancer marked by the tetrapsanin CD9. We showed that CD9Hi CSCs are required for the epithelial and mesenchymal cellular heterogeneity seen in PDAC. We found that CD9 assembles a protein complex involved in regulating PDAC metabolism on the cell surface. *CD9* depletion dramatically inhibited PDAC growth, identifying CD9 as a therapeutic PDAC target. These findings suggest that the cellular composition of pancreatic cancer is controlled by a CSC population.

E. Josue Ruiz, Markus E. Diefenbacher, Rocio Sancho, Fabio Pucci, Atanu Chakraborty, Paula Moreno, Alessandro Annibaldi, Gianmaria Liccardi, Vesela Encheva-Yokoya, Richard Mitter, Ambrosius P. Snijders, Pascal Meier, Marco A. Calzado, and Axel Behrens. (2019) *LUBAC determines chemotherapy resistance in squamous cell lung cancer*. J Exp Med 216(2):450-465. DOI: 10.1084/jem.20180742
Lung squamous cell carcinoma (LSCC) and adenocarcinoma (LADC) are the most common lung cancer subtypes. Molecular targeted treatments have improved LADC patient survival but are largely ineffective in LSCC. We decibed anovel mouse model of LSCC generated by combining oncogenic KRasG12D activation with inactivation of the Fbxw7 tumour supressor (KF model). KF LSCC tumors recapitulated human LSCC resistance to cisplatin-based

chemotherapy, and we identified LUBAC-mediated NF-κB signaling as a determinant of chemotherapy resistance in human and mouse LSCC. Inhibition of NF-κB activation using TAK1 or LUBAC inhibitors resensitized LSCC tumors to cisplatin, suggesting a future avenue for LSCC patient treatment.

Leander Blaas, Fabio Pucci, Hendrik Messal, Agneta Andersson, E. Josue Ruiz, Marco Gerling, Iyadh Douagi, Bradley Spencer-Dene, Alexandra Musch, Richard Mitter, Leena Bhaw, Richard Stone, Dorothee Bornhorst, Abdul K. Sesay, Jos Jonkers, Gordon Stamp, Ilaria Malanchi, Rune Toftgård and Axel Behrens. (2016) ***Lgr6 labels a rare population of mammary gland progenitor cells that are able to originate luminal mammary tumours*****. Nature Cell Biology 18(12):1346-1356. DOI: 10.1038/ncb3434**
In this study we characterise the role of Lgr6+ stem cells in the healthy mammary gland and in breast cancer. In physiology, Lgr6+ stem cells mediate breast tissue expansion during pregnancy. In cancer, Lgr6+ stem cells function as tumour-initiating and cancer stem cells of luminal breast cancer. Remarkably, Lgr6-posititve CSCs are required to maintain cancer cellular heterogeneity and malignancy, suggesting that the cellular diversity of luminal breast cancer is generated by CSC, conceptually similar to the function of stem cells in normal organs.

Ralph Gruber, Richard Panayiotou, Emma Nye, Bradley Spencer-Dene, Gordon Stamp, and Axel Behrens. (2016) ***YAP1/TAZ controls pancreatic cancer initiation by direct upregulation of JAK/STAT3*****. Gastroentrology 151(3): 526-39. DOI: 10.1053/j.gastro.2016.05.006**
This study demonstrated an important reason why KRas mutations are so ubiquitous in pancreatic ductal adenocarcinoma (PDAC) and proposed a molecular mechanism for how KRas-mutated cells become sensitized to inflammation in the pancreas. We showed that the JAK/STAT and the YAP/TAZ (Hippo) signalling pathways are crucial in pancreatic cell reprogramming which occurs at PDAC tumour initiation.