11th International Conference on

CANCER STEM CELLS AND ONCOLOGY RESEARCH

June 11-13, 2018 | Dublin, Ireland

DAY 1

Keynote Forum

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Philippe Juin, J Med Oncl Ther 2018, Volume 3

Philippe Juin

[1]Institute de Recherche en Santé de l'Université de Nantes, France
[2]Institute de Cancérologie de l'Ouest, Saint Herblain, France

Biography

Philippe Juin obtained his PhD degree in 1995 for his work on mitochondrial assembly. During his post-doc in the UK, he defined the mitochondrial apoptotic pathway as one major intrinsic tumor suppressor mechanism triggered by oncogene deregulation. As an Associate Researcher at INSERM, he led increasingly ambitious investigations of the regulation of the mitochondrial apoptotic pathway by Bcl-2 family members in human cancer cells and he created in 2012 an INSERM team that specifically focusses on the role of this pathway in stress adaptation and tumor escape. This team gained international recognition for its fundamental and translational research on the regulation of therapeutic response and tumor progression by BCL-2 family members (Nature Rev. Cancer 2013, Cell Rep. 2016, EMBO Rep. 2018 in press). This team contributed to establish that changes in mitochondrial apoptotic priming are at the core of breast cancer cells response to cytotoxic stress and treatments, being influenced by oncogene signaling, tumor suppressor pathways, therapy and tumor context. This team recently established a new function of BCL-2 members, that contributes contributing to the self renewal of breast cancer initiating cells, and defined the molecular events involved (Nature Comm., 2017).

philippe.juin@univ-nantes.fr

BCL-XL DIRECTLY MODULATES RAS SIGNALLING TO FAVOUR CANCER CELL STEMNESS

In tumours, accumulation of chemoresistant cells that express high levels of anti-apoptotic proteins such as BCL-XL is thought to result from the counter selection of sensitive, low expresser clones during progression and/or initial treatment. We herein show that BCL-XL expression is selectively advantageous to cancer cell populations even in the absence of pro-apoptotic pressure. In transformed human mammary epithelial cells BCL-XL favours full activation of signalling downstream of constitutively active RAS with which it interacts in a BH4 dependent manner. Comparative proteomic analysis and functional assays indicate that this is critical for RAS-induced expression of stemness regulators and maintenance of a cancer initiating cell (CIC) phenotype. Resistant cancer cells thus arise from a positive selection driven by BCL-XL modulation of RAS-induced self-renewal, and during which apoptotic resistance is not necessarily the directly selected trait.

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Dean G Tang

Roswell Park Cancer Institute, USA

Biography

Dean G Tang, PhD, currently Professor and Chairman of Department of Pharmacology & Therapeutics at the Roswell Park Comprehensive Cancer Center (RPCCC) in Buffalo, NY, USA, was trained as an Oncological Pathologist and received his PhD at Wayne State University (Detroit, MI, USA) in 1994 Tang pursued a Burroughs-Wellcome senior post-doctoral fellowship with Dr. Martin Raff (MRC LMCB, UCL, London, UK) studying stem/progenitor cell development. Tang joined the University of Texas M.D Anderson Cancer Center (MDACC) as a faculty in 2000 In June of 2016, he moved to RPCCC to head the Department of Pharmacology & Therapeutics. Tang has made many contributions to cancer research, among which the most important is his pioneering work on identifying, characterizing, and targeting the prostate cancer stem cells (PCSCs). His laboratory, since 2002, has been applying normal stem cell biology knowledge to elucidate the fundamental biological principles that govern the generation of tumor cell heterogeneity via CSCs and epigenetic mechanisms. By focusing on prostate cancer (PCa), Tang and his colleagues have demonstrated the presence and revealed many unique biological, molecular, and tumorigenic properties of PCSCs. One line of Tang's laboratory studies is now undergoing a phase Ib/II clinical trial. Tang has published 170 papers with many in top-tier journals and a current h-index of 65 Tang has won many awards and is an elected fellow of AAAS. Tang is a passionate educator and has mentored about 20 graduate students and 40 postdoc fellows and junior faculty.

dean.tang@roswellpark.org

CANCER STEM CELLS: ENGINE OF THERAPY RESISTANCE & SEEDS OF TUMOR RECURRENCE

Our lab has been studying basic principles governing generation of tumor cell heterogeneity via cancer stem cells (CSCs). By employing prostate cancer (PCa) as a model, we have demonstrated that PCa cells are not all equal with respect to their tumorigenic and metastatic potential. Rather, there exist stem cell-like PCa cells that are mostly undifferentiated (i.e., PSA-/lo), relatively quiescent, and resistant to clinical therapies including castration. These prostate CSCs (PCSCs) preferentially express stem cell genes and epigenetic landmarks, can undergo asymmetric cell division and regenerate differentiated (PSA+) cells, and become greatly enriched in treatment-failed tumors (Cell Stem Cell, 2012; Oncotarget, 2015, 2016; Clin Cancer Res, 2016). Several tumor-suppressive miRNAs, including miR-34a, miR-141, and miR-128, potently suppress the PCSC properties and PCa metastasis (Nat Med, 2011; Cancer Res, 2014; Nat Commun, 2017). Both PSA- normal human prostate basal/stem cells (Nat Commun, 2016) and PSA-/lo PCSCs express an intrinsic neurogenesis program that causally regulates their stem/progenitor cell activities. Of clinical relevance, PCa cell heterogeneity, in particular, AR heterogeneity, has a great impact on PCa response to current clinical therapeutics (Nat Commun, In revision). While we are uncovering novel therapeutics using organoids-based high throughput screening that can specifically target undifferentiated CSCs, we are already translating some of our laboratory findings to clinical trials.

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Chann Lagadec, J Med Oncl Ther 2018, Volume 3

Chann Lagadec

INSERM, France

Biography

Chann Lagadec has spent five years as a Post-doctoral fellowship in Dr. Pajonk'lab, a pioneer in CSC research field. Within the time at UCLA in the Radiation Oncology Department, he got trained in CSC and was the first to demonstrate the phenotype plasticity of CSC induced by radiation treatment. Since 2012, he set up his own team in the INSERM U908 lab in Lille, France, where he studies the molecular mechanisms involved in the reprogramming process. He develops molecular tools and an animal model to track and characterize CSC and iCSC. His domain of interest enlarges recently to understand the potential role of reprogramming in tumor dormancy and metastasis development.

chann.lagadec@inserm.fr

Note:

INFLAMMATORY CYTOKINES, INDUCED BY IONIZING RADIATION, REPROGRAM NON-TUMORIGENIC CANCER CELLS INTO CANCER STEM CELLS IN BREAST CANCER

Identification of cancer stem cells (CSC) in solid tumours – with self-renewal, multipotency, tumorigenesis, and therapy resistance capacities – has opened path to new targeting therapeutic approaches. However, CSC targeting alone might not be sufficient to eradicate a tumour. Indeed, recent studies showed that cancer cells are plastic, and conventional therapies, such as radiotherapy, can lead to cancer cells (non-CSC) reprogramming into iCSC (induced-CSC). The goal of our work is to identify the molecular mechanisms responsible for treatment-induced CSC emergence. First, we have shown that conditioned media from irradiated non-CSC is sufficient to induce iCSC reprogramming. These results suggest that cell plasticity might be actively regulated by diffusible factors secreted by irradiated cells. By using proteins arrays and ELISA, we demonstrated that the secretion of a specific cocktail of chemokines is induced by ionizing radiation, such as CXCL1 and CCL5. Interestingly, recombinant CXCL1 and CCL5 treatments increase the sphere forming capacity (SFC) of isolated non-CSC treated population. Concomitantly, treatment with neutralizing antibodies targeting CXCL1 and CCL5 leads to a decreased CSC number (ALDH+ cells). Most importantly, treatment with neutralising antibodies through radiation treatment of xenograft in SCID mice double the survival time of the mice. Preclinical study show predictive value of CXCL1 and CCL5 expression. We also studied the expression of the corresponding chemokines receptors, by flow cytometry. First, we saw that reprogrammable ALDH- cells are enriched for CXCL1 and CCL5 receptors expressing cells compare to unsorted population or ALDH+ population (CSC). We analysed the reprogramming potential of isolated ALDH-/receptor-positive cells versus ALDH-/receptor-negative cells. The ALDH-/receptor-positive-derived cell population is more able to form spheres and overcomes the receptor-negative-derived population when the two populations are mixed and tested for their sphere forming capacity. The use of pharmacological inhibitors against the receptors induce a slight decrease of CSC. Taken together, our results indicate the involvement of chemokines, in particular CXCL1 and CCL5, in the reprogramming mechanism.

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Ralf Huss

Definiens, Germany

Biography

Ralf Huss joined Definiens in 2013 and has more than 20 years of training and experience in histopathology and cancer research. He also co-founded the biotech company APCETH. He has published more than 100 papers, and has worked with the Nobel Laureates Rolf Zinkernagel and E. Donnell Thomas.

rhuss@definiens.com

IDENTIFICATION OF CANCER STEM CELL (CSC) IN ITS SPATIAL CONTEXT AND IMMUNE ENVIRONMENT THROUGH THE APPLICATION OF COGNITIVE AND MACHINE LEARNING

The identification of Cancer Stem Cells (CSC) or better cancer initiating cells (CIC) as therapeutic targets is of pivotal importance to limit the progression, recurrence and metastasis of cancer. This requires the understanding of the residence of CSC/CIC in their tissue environment with contextual information on their spatial connectivity with many different surrounding structures. Advanced tissue diagnostic including multiplexing immunohistochemistry and the integration of all available data has become key to predict the response to treatment and can be used to target CSC/CIC . With the ability to combine cognitive learning technologies with sophisticated analytics assessing the tumor-forming cells, its environment and immune cells including its spatial relationship, image analysis can identify complex and meaningful signatures that incorporate new knowledge into existing (empirical) wisdom to better predict patient response. Artificial intelligence and machine learning applied to image analysis offer an automated solution using quantitative measurements of unique cellular features to objectively and accurately assess a patient's tumor composition. The improved and increased use of immunotherapies (alone or in combination) to target CSC/CIC will be a result of the automation of contextual cell identification, cell counting and algorithm application to deal with n-dimensional complexity of different stem cell compartments.

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Wei Qiang Gao, J Med Oncl Ther 2018, Volume 3

Wei Qiang Gao

Shanghai Jiao Tong University, China

Biography

Wei Qiang Gao received his PhD from Columbia University in 1989 and did his post-doctoral research at Columbia University and Rockefeller University. From 1993-2010, he was a Scientist and Senior Scientist at Genentech, Inc.. He then relocated to China to initiate his endowed chair professorship in Shanghai. He has made important contributions to the fields of neuroscience, stem cells and tumorigenesis. More recently, his group focuses on "cancer research and cancer stem cells". Dr. Gao has published more than 80 papers as either corresponding or the first author, including Nature, Cell, Science, Neuron, Nature Neuroscience, Nature Communications, Gastroenterology, PNAS, J. Neurosci., Stem Cell Reports, etc. and has been granted 48 US patents. He is a scholar of national "Thousand-Talents Program", the Chief Scientist of 2 program projects from the Ministry of Science and Technology of China and 2 key grants from the National Natural Science Foundation of China. He has served as a reviewer for grant proposals of Wellcome Trust in UK, NIH in US, and NSFC and 36 journals including Nature, Nature Medicine, Nature Cell Biology, Nature

gao.weiqiang@sjtu.edu.cn

KEY REGULATORS OF SYMMETRICAL AND ASYMMETRICAL DIVISION OF EPITHELIAL CELLS IN PROSTATE DEVELOPMENT AND TUMORIGENESIS

Although symmetrical and asymmetrical divisions of stem cells are extensively studied in invertebrate and mammalian neural epithelia, their role remains largely unknown in mammalian non-neural epithelial development, regeneration and tumorigenesis. Using basal and luminal cell-specific markers and cell lineage tracing transgenic mice, we report that in developing prostatic epithelia, basal and luminal cells exhibit distinct division modes. While basal cells display both symmetric and asymmetric divisions leading to different cell fates, luminal cells only exhibit symmetrical divisions, producing two luminal cells. Examination of cell division modes in prostate-specific Pten mull mice indicates that while transformed luminal cells can independently produce tumors composed of exclusive luminal cells via symmetrical divisions, transformed basal cells appear to generate cancer through the daughter luminal cells derived from asymmetrical divisions. Cell polarity and correct mitotic spindle positioning are essential for the proper prostate epithelial cell division mode, and disruption of the two biological features occurs at early stages in prostate tumorigenesis. However, whether and how these two epithelial attributes are coordinated *in vivo* is largely unknown. We report that conditional genetic deletion of E-cadherin, a key component of adherens junctions, in a mouse model results in loss of prostate luminal cell polarity and randomization of spindle orientations. Critically, E-cadherin ablation causes prostatic hyperplasia which progresses to invasive adenocarcinoma. Mechanistically, E-cadherin forms a complex with the cell polarity protein SCRIB and the spindle positioning determinant LGN to link cell polarity and cell division orientation. Collectively, these findings provide direct evidence for the existence of a hierarchy of epithelial cell lineages during prostate development and tumorigenesis and a novel mechanism by which E-cadherin acts an anchor to maintain prostate epithelial division orientation and to prevent tumorigenesis *in vivo*.

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Yong Li

[1]St George Hospital, Australia
[2]University of New South Wales, Australia

Biography

Yong Li obtained his PhD degree at University of New South Wales (UNSW), Australia in 2000. He became Cancer Research Group leader in 2006, and is an established cancer researcher, with expertise in cancer biomarker discovery, radiation biology, target cancer therapy and cancer metastasis. Currently, he is Principal Scientific Officer and Head of Cancer Research Program at Cancer Care Centre, St George Hospital, and Associate Professor at St George and Sutherland Clinical School, UNSW Australia. He has published more than 100 papers and book chapters in peer-reviewed journals in cancer research area. His current research program is aimed at: To investigate novel biomarkers from human body fluids and tissues, cancer cell lines and animal models for cancer diagnosis and developing personalized medicine; to investigate mechanisms of cancer metastasis and chemo-/radio-resistance and role of tumor microenvironment, cancer stem cells and epithelial-mesenchymal transition in cancer progression; to use targeted cancer therapy and combination therapy to control metastatic and therapeutic resistant cancers.

y.li@unsw.edu.au

EPITHELIAL CELL ADHESION MOLECULE (EpCAM) AS A CSC MARKER IN PROSTATE CANCER CHEMO-/RADIO-RESISTANCE

Prostate cancer (CaP) is the most common cancer in males in Australia which caused more than 3000 deaths in 2015. EpCAM is a transmembrane protein that is expressed at low levels in a variety of human epithelial tissues, but overexpressed in most solid tumors. Our previous study indicated that EpCAM was strongly expressed in metastatic CaP cell lines, primary human CaP tissues and lymph node metastasis and is a biomarker involved in CaP progression, and chemo-/radio-resistance. However, the role of EpCAM in CaP progression and therapeutic resistance is still uncertain. The aim of this study was to investigate the role of EpCAM in CaP progression and chemo-/radio-resistance as well as underlying mechanisms using *in vitro* CaP cell lines and *in vivo* mouse models for a potential therapeutic target.