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SEMINAR ANNOUNCEMENT

Andreas Trumpp

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Stem Cell Dormancy and Drug Resistance in Pancreatic Cancer

Date: Wednesday, 13 January 2016
Time: 2pm – 3pm
Venue: CeLS Auditorium, Centre for Life Sciences (28 Medical Drive, Singapore 117456)
Host: Prof. Toshio Suda

Abstract:

Despite the recognition of significant heterogeneity, pancreatic ductal adenocarcinoma (PDAC) is clinically still treated as a single disease. Here, we present patient-derived models representing the full spectrum of previously identified quasi-mesenchymal (QM-PDA), classical and exocrine-like PDAC subtypes, and identify two markers—HNF1A and KRT81—that enable stratification of tumors into different subtypes by immunohistochemistry. Individuals bearing tumors of these subtypes show significant differences in overall survival and their tumors differ in drug sensitivity, with the exocrine-like subtype being resistant to tyrosine kinase inhibitors and paclitaxel. Cytochrome P450 3A5 (CYP3A5) metabolizes these compounds in tumors of the exocrine-like subtype, and pharmacological or shRNA-mediated CYP3A5 inhibition sensitizes tumor cells to these drugs. Whereas hepatocyte nuclear factor 4 alpha (HNF4A) controls basal expression of CYP3A5, drug-induced CYP3A5 upregulation is mediated by the xenobiotic receptor NR1I2. CYP3A5 also contributes to acquired drug resistance in QM-PDA and classical PDAC, and is highly expressed in several additional malignancies. These findings designate CYP3A5 as predictor of therapy response and as a tumor cell-autonomous detoxification mechanism that must be overcome to prevent drug resistance.

Biography:

Andreas Trumpp is full professor and head of the Department for Stem Cells and Cancer at the German Cancer Research Center (DKFZ) in Heidelberg (Germany) and also the founding director of the Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM) gGmbH. He studied biology at the University of Freiburg (Germany) and received his PhD from the European Molecular Biology Laboratories in Heidelberg (Germany). In 1994, he moved to the USA where he did postdoctoral research in the laboratories of Dr. J. Michael Bishop and Dr. Gail R. Martin at the University of California at San Francisco. In 2000 he became head of the Genetics and Stem Cell Laboratory at the Swiss Institute for Experimental Cancer Research (ISREC) in Epalinges/Lausanne and subsequently professor of molecular oncology and stem cell biology at the École Polytechnique Fédérale de Lausanne (EPFL) before moving to Heidelberg in 2008. Over the last 15 years the Trumpp team has contributed to a better understanding of the molecular and cellular basis of normal and malignant stem cell self-renewal and differentiation. For example, they have shown that the most potent hematopoietic stem cells (HSC) are in a state of deep dormancy during homeostasis and that stress signals (chemotherapy) or bacterial/viral infections cannot only activate these HSCs to produce new stem cells and progenitors, but make them also exquisitely sensitive to chemotherapy induced killing (Nature 2001, GenesDev. 2004, Cell 2008; Nature 2009; Nature Reviews Immunology 2010; J. Exp. Med. 2013, Cell Stem Cell 2014; Nature 2015). In addition to a MDS and leukemic stem cell program (Cell Stem Cell 2014), the team has also identified circulating metastasis stem cells in the blood of breast cancer patients, which offer novel possibilities for the design of better diagnostic and therapeutic tools for metastatic breast cancer (Nature Biotechnology 2013, Oncotarget 2014). Dr. Trumpp is also scientific editor at the “Journal of Experimental Medicine”, founding member and 2013/2014 President of the “German Stem Cell Network” (GCSN) as well as member of numerous international scientific advisory and review boards.