Award Winners 2020

1) David T. W. Jones, PhD (Date of birth 22/04/1983)

Hopp Children's Cancer Center Heidelberg (KiTZ) & German Cancer Research Center (DKFZ)
Group Leader "Pediatric Glioma Research Group"

Short CV:

Since 2016	**Group Leader** 'Pediatric Glioma Research', German Cancer Research Center (DKFZ), Heidelberg, Germany
2012 – 2016	**Senior Post-Doctoral Scientist,** Division of Pediatric Neurooncology, DKFZ, Germany
2010 – 2012	**Post-Doctoral Scientist**, Division of Pediatric Neurooncology, DKFZ, Germany
2009 – 2010	**Post-Doctoral Research Fellow,** Dept. of Pathology, University of Cambridge
2005 – 2009	**PhD,** Department of Pathology and Clare College, University of Cambridge, UK
2004 – 2005	**Research Assistant,** Dept. of Pathology, University of Cambridge
2001 – 2004	**B.A. (Hons) in Natural Sciences,** Clare College, University of Cambridge, UK

Project title: **Identifying novel therapeutic targets for childhood brain tumors using CRISPR in vivo screens in orthotopic mouse models**

Summary:

Pediatric high grade glioma (pHGG) is an aggressive tumor entity with poor prognosis that urgently requires novel treatment options. The proposed project aims to identify these by an unbiased search for tumor vulnerabilities followed by an in vivo validation and subsequent preclinical studies. To this end, multiple mouse models for pHGGs will be characterized regarding their utility for CRISPR screening approaches by using a non-targeting barcode library. Suitable models will then be screened with model-specific, custom gRNA libraries to identify gRNA targets that lead to tumor regression upon knockout. The use of complementary immunocompetent allograft- and human xenograft-models will provide an unparalleled amount of in vivo CRISPR screening data across a spectrum of molecularly-defined subtypes of this tumor entity. A detailed bioinformatic analysis will unravel multiple insights into tumor biology and model-specific traits. Identified genes representing potential new therapy targets will undergo separate validation by inducing expression of the respective single-gene gRNA during tumor growth in vivo. Residual tumors will be analyzed by single cell RNA sequencing to investigate tumor adaptation after gRNA expression (i.e. possible resistance mechanisms), and to logically plan combination therapies. Ultimately, these combination treatments will be evaluated in a preclinical setting. A close, well-established collaboration with the Heidelberg University Hospital and pediatric early-phase clinical trial networks provides a clear path to allow the direct translation of promising findings into clinical application.

2) Ana S. Guerreiro Stücklin, MD PhD (Date of birth 22/07/1980)

Department of Oncology and Children's Research Center, University Children's Hospital Zurich

Short CV:

Since 2018	**Staff Oncologist and Junior PI,** University Children's Hospital, Zurich, Switzerland
2015 - 2018	**Research Postdoctoral Fellow,** Program in Developmental and Stem Cell Biology, Brain Tumor Research Center, the Hospital for Sick Children, Toronto, Canada
2013 - 2018	**Clinical and Research Fellow,** Division of Hematology/Oncology, the Hospital for Sick Children, Toronto, Canada
2008 - 2013	**Resident in Pediatrics,** University Children's Hospital Zurich and Stadtspital Triemli Zurich, Switzerland
2005 - 2008	**MD PhD Student,** University Children's Hospital Zurich, Switzerland
2004 - 2005	**Research Student,** University Children's Hospital Zurich, Switzerland
2004	**MD,** University of Porto, Portugal

Project title: Targeting the kinome in oncofusion-driven pediatric gliomas

Summary:

Background. Brain tumors account for the majority of morbidity and mortality in pediatric cancer patients. While studying congenital brain tumors, we recently described a distinct group of pediatric gliomas harboring key targetable rearrangements in a cluster of highly homologous receptor tyrosine kinases (RTK). The role of these ALK/ROS1/NTRK/MET oncofusions in gliomagenesis remains largely unknown but their detection has immediate clinical implications. While eagerly anticipating encouraging responses to targeted agents, concerns for development of drug resistance under selective therapeutic pressure are mounting. Further advances in patient care will rely on studies that decipher the mechanisms driving tumor formation and response / resistance of RTK-rearranged gliomas to targeted therapies.

Overall goal and specific aim. The overall goal of this project is to deliver detailed molecular insights into a group of pediatric brain tumors to inform the next generation of clinical trials. We aim to: (1) investigate the mechanisms underlying glial transformation by RTK oncofusions; (2) understand the kinome-wide impact of targeted therapies; and (3) harness combination treatments to enhance antitumor activity and prevent drug resistance in RTK-rearranged gliomas.

Approach and Expected Results. At a first level – oncofusion functional characterization – we develop and deploy models that mimic the human disease, to characterize cellular functions regulated by fusion proteins. At a second level – pathway elucidation – we use technological advances (kinase microarrays) to profile the kinome and elucidate the downstream pathway activity, both at baseline and upon treatment with current RTK inhibitors. We further seek clinical translation and determine the expression of pathway components associated with drug resistance in patient tumor samples (nanoString 3D). Lastly, at a third level – therapy optimization – combining these results, we design and validate new combination strategies with enhanced anti-tumor activity and preventing drug resistance.

Significance. This project clarifies the molecular basis of RTK oncofusion-driven pediatric gliomas and evaluates strategies to prophylactically prevent resistance in the setting of targeted treatments. Successful completion provides the preclinical bases for future clinical studies aimed at improving survival and increasing the quality of life for survivors.