Medical University of Graz

Molecular Mechanisms of Transformations in Cancer

Summary

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Supervisor:	Prof. Dr. Philipp Jost
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between March 24, 2021 00:00 and May 05, 2021 23:59 (Europe/Zurich)

Description

Background:

Despite the advances in therapeutic targeting strategies, such as the development of immune check point inhibitors, cancer is still the second leading cause of morbidity worldwide (Bray et at., 2018). The most common subtype is lung adenocarcinoma (LUAD), which is associated with considerable rates of morbidity and mortality. Approximately 25% of LUAD patients carry activating mutations in *KRAS* (Cancer Genome Atlas Research Network, 2014), which remain difficult to target in the clinical setting. Loss of the tumor suppressor *TP53* is another common event in cancer and it has been observed in 46% of lung cancer patients. Using an inducible mouse model of Kras-driven lung cancer, we dissect the contribution of critical tumor-promoting as well as tumor-suppressive genes/proteins in cancer (Munkhbataar et at., Nature Comm. 2020). Based on these findings, the PhD project will study the role of genes located on the amplicon on chromosome 1q21 in lung cancer development, in proliferation and their effect on p53 on lung cancer progression.

Hypothesis and Objectives:

Evasion of programmed cell death represents a critical form of oncogene addiction in cancer cells. Understanding the molecular mechanisms underpinning cancer cell survival despite the oncogenic stress could provide a molecular basis for potential therapeutic interventions. This PhD project explores the role of pro-survival genes located on chromosome 1q21 in lung cancer cell integrity during clonal evolution. Based on our finding that gains of MCL-1 occur both clonally and subclonally at high frequency in lung cancer (Munkhbataar et at., Nature Comm, 2020), the project will study gene co-amplified together with MCL-1 on chromosome 1q21. Relevant genes from this 1q21 amplicon will be functionally tested for their relevance using a state-of-the-art mouse model system to study tumor progression as well as pharmacologic or genetic inhibition. These data will reveal the relevance of tumor-promoting genes on 1q21 and potentially help in the identification of novel therapeutic targets.

Methodology:

Apart from all standard molecular and cellular biological techniques and infrastructure, the project offers the use of our specifically generated *in vivo* CRISPR-gene editing mouse model system. Specifically, fox-STOP-lox-KrasG12D (Isl-KrasG12D) (Jackson et al., 2001), Cas9 (Platt et al., 2014b), p53 (Jacks et at., 1994) mice have been crossed to generate triple gene-targeted mice for the induction of lung cancer *in vivo.* At 6-8 weeks of age Kras;Tp53 and Kras;Tp53; Cas9 mice will be infected with 5x10E6 plaque forming units (PFU) of Adeno-Cre (AdCre) (Anton and Graham, 1995) by intranasal instillations (Jackson, 2001). These mice will be used to study *in vivo* CRISPR-gene edited lung cancer using deletions or overexpression (CRISPRa mice) of individual genes on 1q21. The host laboratory has ample experience in using gene targeted mouse models for cancer research.

References:

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