Gene fusions of tyrosine kinases and non-coding RNAs as novel pathogenic drivers of tumor metabolism and escaping immune surveillance

Summary

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Supervisor:	Prof. Dr. Martin Pichler
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 04, 2019 00:00 and March 31, 2019 23:59 (Europe/Zurich)

Description

Background:

In recent years, gene fusions – meaning the combination of different parts of two different genes – including the fibroblast growth factor receptor (FGFR) family and the tropomyosin receptor kinase family (NTKR) have been identified as oncogenic drivers in several human cancers. Several clinical trials with chemical inhibitors are currently evaluated, but despite the relatively late stage of clinical development, there is a lack of fully understanding the biological background between gene fusions. In addition, no optimal cellular model systems mimicking the true nature of such gene fusions are available for the most types of gene fusions and cancer. The molecular basis and model systems for these genomic alterations are, however, of paramount interest to understand resistance mechanisms and develop new approaches for combined and sequential treatment approaches.

Hypothesis and Objectives:

The central hypothesis of this PhD thesis is to determine biological role of gene fusions between FGFR/NTKR tyrosine kinase proteins with other protein as well as non-coding RNA gene fusion partners. Based on the biological function, altered signaling pathways, changes in tumor metabolism and immunological factors we will seek for novel combined treatment strategies and determine the factors of treatment resistance against FGFR/NTKR tyrosine kinase inhibitors in human cancer.

Methodology:

Based on already existing FGFR/NTKR gene fusion harboring cancer cell lines, we will further characterize the influence of these novel genomic alterations on several hallmarks of cancer including tumor metabolism and immune surveillance. In addition, we will create novel cellular models harboring gene fusions between these receptors and non-coding RNAs using CRISPR/Cas9 including murine cell lines and characterize the biological function as well as the efficacy of kinase inhibitors by high-throughput drug screening strategies. Last but not least, we will test in international collaborative efforts with leading US cancer centers RNA-therapeutics in combination with small molecule tyrosine kinase inhibitors increase the efficacy and overcome mechanisms of resistance.

References:

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