Medical University of Graz

Analysis of circulating tumor DNA to enhance precision oncology

Summary

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Supervisor:	Prof. Dr. Ellen Heitzer
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 14, 2020 00:00 and October 10, 2020 23:59 (Europe/Zurich)

Description

Background:

Precision oncology hypothesizes that anticancer therapy should be matched to each patient in accordance with the molecular profile of a tumor(1). In contrast to molecular profiling of primary tumors, the analysis of circulating tumor DNA (ctDNA) from plasma representsanon-invasive,cost-effective alternative and is increasingimplemented in oncologyasthese biopsies are associated with significant risk, when tumor tissue is insufficient or inaccessible, and/or serial assessment of tumor molecular abnormalities is needed to optimize treatment(2-4).Numerous studies indicate the association of ctDNA with tumor burdenandthe utiltyof ctDNA analysis forMRDdetection. Moreover,ctDNA analysis enablesa betterunderstanding of mechanisms of resistance to treatmentand adynamicguidingof therapy. Longitudinal ctDNA analysis will improveour knowledge of the tumor evolution, will accelerate drug development, and will contribute to the implementation of precision medicine to improve clinical outcomes(2, 3).ctDNA is thought to reflect tumor-derived fragmentsfrom all sites of disease and originates mostlyfrom apoptotic tumor cells, which is why ctDNA is highly fragmented and representsnucleosome–protected DNA(5).Our group has extensive expertise in the analysis of plasma DNA which is reflected in numerous publicationsin high-raking journaland we have established a variety of ctDNA analysis approaches ranging from high-resolutionsingle single targetassaysto comprehensive wohle genome analyses(6-12). Moreover, we recently demonstratedthat plasma DNA analyses has more to offer than the detection of mutationsand copy numberalterationsand developed new machine learning approaches, which relateto nucleosome positionsand enablethe assessment of theactivationstatus of a gene or theactivity of transcriptionfactors from DNA sequencing data(9, 13).Therefore,we think acombination of geneticprofilingand nucleosome positioning patterns mightcontribute to an improved understanding tumor biology and tretamentresponse.

Hypothesis and Objectives:

The main aim of this project is to leverage non-invasive means to select appropriate treatment strategies and to better understand treatment outcome of advanced cancer patients. In particular, we aim to correlate genetic as well as epigenetic data to functional analyses based on nucleosome occupancy to identify aberrant cancer pathways, which can be targeted by selective drugs. Moreover, since most available liquid profiling approaches focus on mutations,we intend to identify and characterize cancer driver genes in high-level focal amplifications, since the stability/consistency of gene expression patterns in focal amplifications is yet unknown and has not been followed over time.

Methodology:

- The student employs and further develops a broad range of *next generation sequencing* aproaches.
- These analyses include *high resolution ssays, gene panels, whole genome sequencing or bisulfite sequencing* on clinical samplesin order to investigate the activity of cancer driver genes and pathways over time and possibly identify actionable targets or mechanisms of resistance against targeted therapies
- Moreover, the candidate will make use of bioinformatics approaches such as variant/copy number calling and interpretation, read depth analysis, pathwayanalysis, or machinelearning technologies. Therefore, *knowledge of Linux and programming skills* are beneficial, but not mandatory

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