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Elucidating the biology of ctDNA release in in colorectal cancer

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 03, 2022 00:00 and September 20, 2022 23:59 (Europe/Zurich)

Description

Background:

Colorectal cancer (CRC) stage at diagnosis plays a key role in determining the outcome of disease treatment and overall survival. On average, the five-year survival for CRC is about 60%, but this varies greatly, from 90% for stage I patients to 10% for those diagnosed with metastatic disease, which make up to 20% of the diagnoses. Incidence is rising due to increasing population age and life. The Doctoral Network ColoMARK aims to find immediate solutions to better prevent, treat, and manage CRC.

The analysis of ctDNA (cell-free circulating tumour DNA) is a very promising tool and is thought to revolutionize cancer care with respect to early detection, identification of minimal residual disease, assessment of treatment response, and monitoring tumour evolution (summarized in [1-5]). However, a major challenge for ctDNA applications is the differentiation of circulating DNA derived from the tumour from non-tumour circulating DNA (cfDNA). In principle, attempts to use cfDNA/ctDNA as a cancer biomarker focus on two classes of alterations, i.e. quantitative and qualitative abnormalities. These approaches appeared powerful and achieved a good sensitivity, however prior knowledge about the tumour-associated alterations is necessary. Even though the detection of cancer-specific mutations offers a genotypic means to distinguish tumoral from non-tumoral plasma DNA, a major problem is that every cancer has a unique fingerprint and therefore there is no universal marker that can be used for cancer screening. Exact knowledge about the biology of cfDNA/ctDNA might reveal other useful parameters, which can be used in the early detection setting and might dramatically increase sensitivity/specificity for detecting early-stage disease.

Objective:

Compared to the number of studies addressing the clinical applicability of ctDNA, data regarding the actual origin, the kinetics, and the mechanisms of release and clearance are limited and often contradictory. The aim of the proposed thesis is to close this gap. Although the ability to detect mutations or other cancer-specific alterations in plasma cell-free DNA (cfDNA) is thought to correlate with the tumour burden[6-8], the exact size and the degree of vascularization for DNA release into the circulation have not yet been tested. The doctoral candidate will address this question using novel cutting-edge technologies for tumour profiling and ctDNA detection.

Hypothesis:

We hypothesize that the rate of shedding of ctDNA into the circulation is dependent upon the location, size, and vascularity of the tumour and therefore leads to a high variability in levels across patients. A sharper picture of the biology and kinetics of ctDNA release and turnover should expand the utility of circulating nucleic acids as tumour markers.

Methodology:

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We will comprehensively analyse primary tumours from localized CRC patients at various omics-levels, whose tumours will be resected with curative intent. Genetic alterations at the genome-level will be tracked to in plasma. Tumours will be classified as ctDNA shedders and non-shedders and using bioinformatics and statistical methods such as PCA, correlation and regression analysis, we will search for genetic, histological, or phenotypic features that are associated with ctDNA release.

Competences required for the position:

The student will employ and further develop a broad range of next generation sequencing (NGS) approaches, which is why *experience with NGS* is desirable.

Moreover, the candidate will make use of a variety of bioinformatic approaches. Therefore, *knowledge of Linux and programming skills are beneficia*l, but not mandatory.

References:

1 Heitzer, E., Ulz, P. & Geigl, J. B. Circulating tumor DNA as a liquid biopsy for cancer. *Clin Chem* **61**, 112-123, doi:10.1373/clinchem.2014.222679 (2015).

2 Siravegna, G. & Bardelli, A. Blood circulating tumor DNA for non-invasive genotyping of colon cancer patients. *Molecular oncology* **10**, 475-480, doi:10.1016/j.molonc.2015.12.005 (2016).

3 Diaz, L. A., Jr. & Bardelli, A. Liquid biopsies: genotyping circulating tumor DNA. *J Clin Oncol* **32**, 579-586, doi:10.1200/JCO.2012.45.2011 (2014).

4 Crowley, E., Di Nicolantonio, F., Loupakis, F. & Bardelli, A. Liquid biopsy: monitoring cancer-genetics in the blood. *Nat Rev Clin Oncol* **10**, 472-484, doi:10.1038/nrclinonc.2013.110 (2013).

5 Heitzer, E., Haque, I. S., Roberts, C. E. S. & Speicher, M. R. Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat Rev Genet* **20**, 71-88, doi:10.1038/s41576-018-0071-5 (2019).

6 Newman, A. M. *et al.* An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat Med* **20**, 548-554, doi:10.1038/nm.3519 (2014).

7 Abbosh, C. *et al.* Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature* **545**, 446-451, doi:10.1038/nature22364 (2017).

8 Parkinson, C. A. *et al.* Exploratory Analysis of TP53 Mutations in Circulating Tumour DNA as Biomarkers of Treatment Response for Patients with Relapsed High-Grade Serous Ovarian Carcinoma: A Retrospective Study. *PLoS Med* **13**, e1002198, doi:10.1371/journal.pmed.1002198 (2016).

This project is embedded in the MSCA Doctoral Network 2021 ColoMARK. Specific selection criteria apply!

1) ColoMARK:

The ColoMARK network integrates 17 teams with multidisciplinary expertise (omics, epidemiology, microbiome, circulating tumour DNA, bioinformatics, assay development, circulating RNAs, circulating tumour cells, tumour profiling, clinics) aiming at the identification and development of novel colorectal cancer (CRC) biomarkers via state-of-the-art liquid biopsy approaches. ColoMARK will provide cross- and interdisciplinary innovative training with special emphasis on transversal competences to 10 young researchers that will constitute the next generation of effective, multi-skilled and proactive future professionals that comply with the tenets of the Principles for Innovative Doctoral Training, and that achieve enhanced intersectoral employability.

2) Eligibility criteria:

The candidates MUST not have resided or carried out their main activity (work, studies, etc.) in the country of the recruiting beneficiary (Austria) for more than 12 months in the 36 months immediately before the recruitment date (unless as part of a compulsory national service or a procedure for obtaining refugee status under the Geneva Convention).

3) Working conditions:

PhD students receive a fully funded working contract (30 hours/week, annual gross salary 40.860,00) for three years (1 initial year + 2 years extension) including health insurance and social benefits. If a fourth year is needed, beneficiaries will inspect alternatives for employment funding for the doctoral candidate until PhD completion.

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4) Requirements and obligations:

- The doctoral candidate will be *enrolled in the PhD-program Molecular Medicine* at the Medical University Graz, Austria, which will contribute greatly to providing specialized education on both core scientific topics, as well as transversal skills.
- In addition, the doctoral candidate will participate in *training activities provided by the ColoMARK* including network-wide training, clinical rotations, workshops, summer/winter schools, or e-training. This reinforces the doctoral candidates´s exposure to a varied choice of training activities outside of the host lab, and will be focused on enhancing the personal, team-wide and network-wide capabilities of the DCs.
- One of the strongholds of MSCA Doctoral Network actions is the flexibility of DC work amongst the different teams, and this mobility enhances and improves the participant interrelations. Therefore, all ColoMARK doctoral candidates will perform *a minimum 5 months of secondments*, including at least 3 weeks in the non-academic sector (e.g. IARC, QIAGEN, GeomeScan, DESTINA) according to internal regulations that restrict interactions with for-profit organisations.

5) Recruitment process and evaluation:

DC recruitment will take into account gender equality policies, and where two candidates are tied with regards to merits, we will choose the one from the underrepresented sex.

On stage 1, candidates will be evaluated according to their CV (eligibility, academic and professional qualifications, prior research experience, publications, teaching activities, level of independence, knowledge transfer and dissemination output, mobility experience, transdisciplinary work - amongst others), letter of motivation describing their purpose and goal in participating in ColoMARK, recommendation letters and English fluency. Career breaks or variations in the order of CVs will not be penalised. The top candidates or those attaining a minimum score will then proceed to stage 2, where they will have a face-to-face interview (potentially videoconference) with the Selection Committee. In stage 3 top candidates are invited to the hearing of the PhD-Faculty MolMed, at the Medical University of Graz.

To get more information or to apply online, visit https://mug.glowbase.com/positions/262 or scan the the code on the left with your smartphone.