Open PhD student position

H2020-MSCA-ITN-2016
Early Stage Researcher (ESR2/PhD)

TRANSMIT - TRANSlating the role of Mitochondria in Tumorigenesis

The consolidation of the knowledge that cancer is not only a genetic, but also a metabolic disease, has led scientists to investigate the intricate metabolic plasticity that transformed cells must undergo to survive the adverse tumor microenvironment conditions, and the contribution of oncogenes and tumor suppressors in shaping metabolism. In this scenario, genetic, biochemical and clinical evidences place mitochondria as key actors in cancer metabolic restructuring, not only because these organelles have a crucial role in the energy and biosynthetic intermediates production but also because occurrence of mutations in metabolic enzymes encoded by both nuclear and mitochondrial DNA has been associated to different types of cancer. TRANSMIT aims to dissect the metabolic remodeling in human cancers, placing the focus on the role of mitochondria and bridging basic research to the improvement/development of therapeutic strategies. Further, TRANSMIT fosters the communication of this emerging field to the patients and their families. To these aims, TRANSMIT will create a network of seven different countries, among which world-leading basic science and clinical centers of excellence, several industrial partners with up-to-date omics technologies, as well as non-profit foundations and associations who care for cancer patients. By creating the critical mass of scientific excellence, TRANSMIT will allow to transfer the current knowledge into the wide field of cancer research, translating scientific and technical advances into the education and training of eleven Early Stage Researchers. TRANSMIT will implement training-through-research dedicated to unravel the metabolic features of cancer, as well as to provide a full portfolio of complementary skills through the creation of a network of basic, translational and industrial laboratories, devoted to a multidisciplinary/multisectorial education of young scientists.

Project Description

1) Job summary

The researcher will be involved in the development, evaluation and application of new respiratory substrate-uncoupler-inhibitor-titration (SUIT) protocols designed to assess the role of mitochondrial NAD-linked malic enzyme in mitochondrial and cellular energetics of cancerous and benign cells. In addition, ERS2 will help improving the extension of high-resolution respirometry to MultiSensor analysis enabling the simultaneously measurement of several mitochondrial functions (e.g. mitochondrial membrane potential and reactive oxygen species levels and proton production rates as an estimate of glycolytic activity). These measurements will contribute to the identification of mitochondrial metabolic biomarkers for characterizing the transformation from benign to cancer cells and this will subsequently be extended using proteomics and metabolite tracing.

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2) Job description

Cell ergometry and mitochondrial metabolic biomarkers in cancer

After a brief period of re-emergence of the Warburg effect in oncological research, the underlying concept has been shown to be ineffective for elucidating causal relationships between mitochondrial dysfunction and tumor progression. During metabolic re-programming in many cancers and actively dividing cells mitochondrial respiratory competence is retained with a shift towards biosynthetic functions (Tan AS et al. *Cell Metab* 21:81-94, 2015). Mitochondrial NADH-linked malic enzyme (ME2) does not only play a key role in glutaminolysis, but its enforced expression suppresses senescence, whereas downregulation of ME2 modulates the outcome of p53 activation, leading to strong induction of senescence but not apoptosis (Jiang P, et al. *Nature* 493:689-93, 2013). Development, evaluation and application of new respiratory substrate-uncoupler-inhibitor-titration (SUIT) protocols are required to assess the role of ME2, which is allosterically controlled by fumarate, succinate and ATP, in mitochondrial respiratory control in cancer versus benign cells. SUIT protocols are a hallmark of the success of high-resolution respirometry and cell ergometry (Gnaiger E. *4th ed. Mitochondr Physiol Network 19.12,* 2014; Pesta, D, Gnaiger E. *Methods Mol Biol,* 810:25-58, 2012). ESR2 will improve the extension of high-resolution respirometry to MultiSensor analysis for simultaneous evaluation of several mitochondrial functions (e.g. mitochondrial membrane potential, reactive oxygen species production, proton flux in comparison to aerobic lactate production). This approach will contribute to the identification of mitochondrial metabolic biomarkers for characterizing the transformation from benign to cancer cells. ESR2 will therefore develop and test such novel biomarker protocols initially on prostate cancer cells, in comparison with metabolic remodeling of non-cancer epithelial cells. One secondment will extend the study with proteomics and metabolite tracing. Another secondment will aim at a detailed analysis of the respiratory complexes in prostate cancer cells versus non-cancer epithelial cells.

3) Host University that will provide the PhD degree:

Medical University of Innsbruck, www.i-med.ac.at

4) Subject area of PhD program in which the ESR will be enrolled over the three-year PhD program duration:

Molecular Cell Biology / Molecular Oncology

5) PhD program starting date

2017-10-01

Required Educational Level

Degree: Master of Science

Degree field: Natural Sciences

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Skills: team-player, self-organized, goal-oriented working style,

Languages: English, additional languages, e.g. German, of benefit
(Applicant should be fluent in written and spoken English)

Applications, in English, should include CV, detailed academic transcripts, a copy of the thesis, a motivation letter and a reference letter, which are all to be submitted by email to verena.laner@oroboros.at

*Eligibility: The applicants must be in possession of a Master's degree at the date of recruitment - an 'early stage researcher' (i.e. in the first four years of his/her research career and not have a doctoral degree).

The applicant may be a national of a Member State, of an Associated Country or of any other Third Country. The applicants must not have resided in the country where the research training activities take place for more than 12 months in the 3 years immediately prior to the recruitment date and not have carried out their main activity (work, studies, etc.) in that country.

Benefits

- Enrollment in a PhD school in a specific area;
- 3-year employment contract (2.534 EUR gross/month, 14x per year incl. mobility allowance)
- A highly multidisciplinary, cross-cultural and competitive training program in the field of metabolism in cancer (or molecular oncology)
- Secondments and a specific training program
- Vacation days/year: 25

Selection criteria

First selection step: Curriculum evaluation. Numerical scores will be awarded for grading criteria such as study marks, duration of study, scientific publications in peer reviewed journals, presentations at conferences, participation in training workshops, reference letters. Only the admitted candidates will be contacted by e-mail for the second selection step.
Second selection step: Skype or face-to-face interview in which candidates will give a short presentation of their master thesis and of a scientific paper that they will receive two to three weeks before the interview.

Deadline for application: **15. May 2017**
Evaluation period: **45 days**
Website: wiki.oroboros.at/index.php/TRANSMIT