Call for applications: Scholarships for doctoral MD students in the RTG 2158 (Promotionsstipendien für Medizin-Studierende)

The Research Training Group (RTG) 2158 *"Natural products and natural product analogs against therapy-resistant tumors and microorganisms: new lead structures and modes of action"* is looking for two MD students for doctoral research projects with the topic **"Anticancer efficacy and adverse effects of natural compounds/histone deacetylase inhibitors and conventional anticancer therapeutics"** in the working groups of Prof. Dr. G. Fritz, Toxicology, and Prof. Dr. M. Kassack, Pharmacy.

Scholarships for doctoral MD students are available in October 2022. Monthly stipends (861 €) can cover up to 9 months. At least one research semesters and the respective semester breaks are obligatory for conducting the practical research work and preparing the written thesis. During this time, the MD students will have the opportunity to participate in the official training program (i.e. lectures, seminars) provided by the RTG 2158. Detailed descriptions of the currently available projects can be found on our website.

Requirements:

- Completion of 6th semester and completed midterm exam (1. Abschnitt der ärztlichen Prüfung)
- Enrollment at the University Düsseldorf (HHU)
- High motivation, interest and dedication for experimental research in the field of the RTG.
- 1 research semester

We offer:

- Close supervision by the principle investigator (PI)
- Detailed training of lab methods and daily guidance by staff members
- Scholarship (861,- € / month) for up to 9 month
- Participation in the RTG-related education program

Application documents:

- Cover letter / Motivation letter (max. 1 page)
- Curriculum vitae
- Transcript of records to prove the above-mentioned requirements (including the M1 exam certificate)
- School report / certificate (Abiturzeugnis)

If you are interested in a research project for your doctoral thesis, please send your application with the required documents in **one PDF** document to grad2158@uni-duesseldorf.de. Please feel free to contact the coordinator with any inquiries about the projects, application procedure or the RTG. On our website (www.grk2158.hhu.de) you can find information about the individual research projects, project leaders and our curriculum! Application deadline is **30.04.2022**.

Personal data will be reviewed for the application process, shared with the people involved in the procedure and stored for the duration of the application process. Please only submit your application if you agree to these terms.

Project description

"Anticancer efficacy and adverse effects of natural compounds/histone deacetylase inhibitors and conventional anticancer therapeutics"

Background: Apart from causing tumor cell death, (conventional) anticancer therapeutics (cAT) frequently evoke substantial adverse effects to normal tissue that are life-threatening or severely impact the quality of life of tumor patients. In previous studies, we have identified a number of novel natural compounds (NC) and histone deacetylase inhibitors (HDACi) that are cytotoxic to malignant cells. The cytotoxicity of the pre-selected NC/HDACi towards platin-resistant malignant cells and their adverse effects to non-malignant (normal) cells if used in mono- or combination-treatment with cAT is largely unknown. Yet, detailed knowledge about their anticipated therapeutic window is a prerequisite for subsequent meaningful *in vivo* studies.

Aim: Here, we will investigate stress response of malignant (i.e. ovarian carcinoma cells and head and neck tumor cells) as well as non-malignant human induced pluripotent stem cells (hiPSC) following treatment with selected NC/HDACi and platinating cAT *in vitro*. The aim of our study is to identify NC/HDACi that reveal synergistic toxicity with cAT and, at the same time, are well-tolerated by hiPSC if used in mono- or co-treatment with cAT.

Experimental approach and methods: In order to support the 3R concept aiming to Reduce, Refine and Replace animal experiments, parental and platin-resistant human ovarian and/or head-and-neck carcinoma cells as well as non-malignant human induced-pluripotent stem cells (hiPSC) will be used as timely *in vitro* models. These cells will be treated with the most promising NC/HDACi (as concluded from the results of our previous studies) plus/minus selected cAT (e.g. cisplatin) and the toxic stress responses of the cells will be recorded systematically. To this end, cell viability (Alamar Blue Assay (determination of IC_{50})), proliferation activity (EdU incorporation), cell cycle progression and cell death (caspase activation, apoptosis, flow cytometry), DNA damage induction (formation of DNA double-strand breaks) and gene expression (qRT-PCR) will be investigated in dose- and time kinetic analyses. Thereby, we aim to identify the NC/HDACi with the most favorable toxicity profile (i.e. broadest therapeutic window) and, hence, the most promising candidate compound for forthcoming *in vivo* studies.