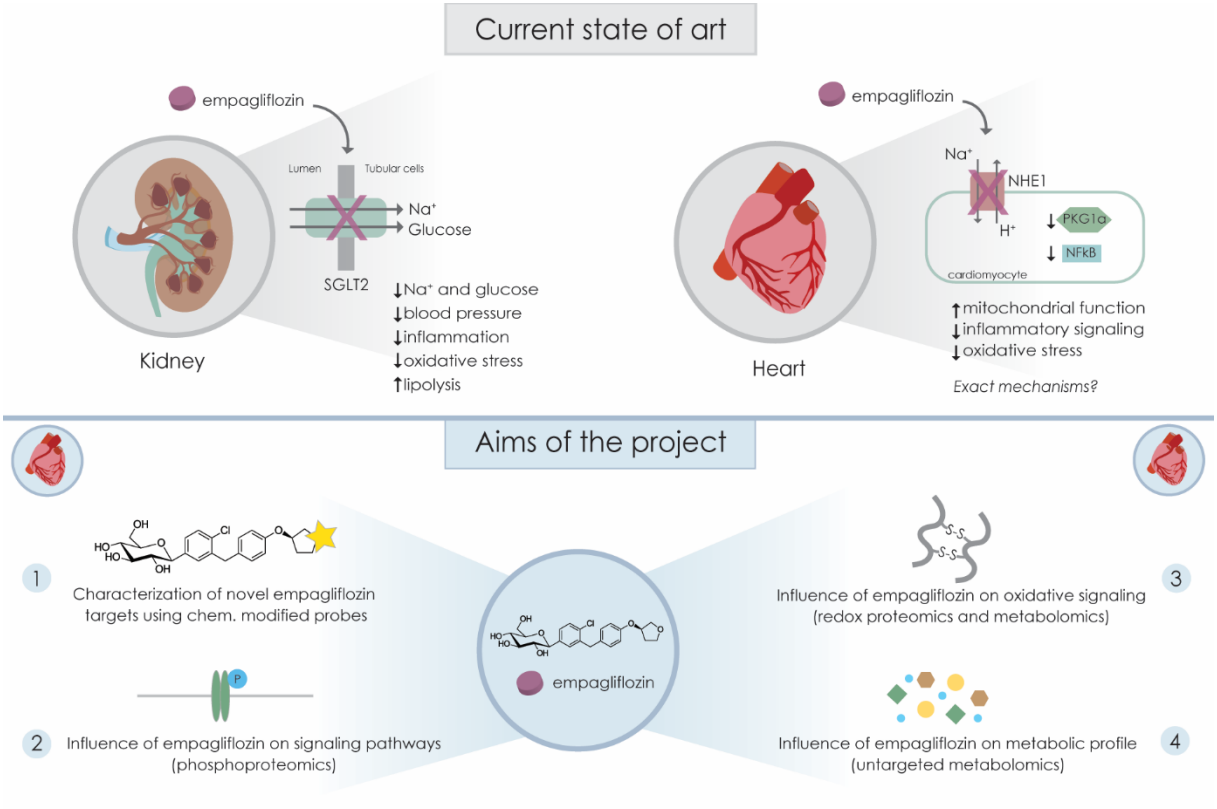
P23: FUNCTIONAL PROTEOMICS OF GLIFLOZIN DRUG (OFF) TARGETS



Supervisory Team[1]

Primary Supervisor: *Ruth Birner-Gruenberger, Bioanalytics Research Group, Instrumental Analytics and Imaging Research Unit, Institute of Chemical Technologies and Analytics, TU-Wien*

Co-supervisors: *Matthias Schittmayer, Bioanalytics Research Group, Instrumental Analytics and Imaging Research Unit, Institute of Chemical Technologies and Analytics, TU-Wien*

Tamara Tomin, Bioanalytics Research Group, Instrumental Analytics and Imaging Research Unit, Institute of Chemical Technologies and Analytics, TU-Wien

TU Wien project partner: *Hannes Mikula, Molecular Chemistry & Chemical Biology Research Group, Organic and Biological Chemistry Research Unit, Institute of Applied Synthetic Chemistry, TU-Wien*

External academic partner: *Bernd Wollscheid, Department of Health Sciences and Technologies, ETH Zürich*

[1] The Early Stage Researchers (ESRs) will be accompanied during their thesis by an individual "Thesis Advisory Committee" (TAC), which will guide the ESR through the graduate studies. The TAC will consist of the thesis primary supervisor, and two additional members of the Supervisory Team selected by the ESR.

Project Description

This PhD project focuses on the design and application of functional proteomic approaches to study molecular and cellular drug (off) target effects of gliflozins. Gliflozins are sodium-glucose cotransporter 2 (SGLT2) inhibitors used to treat diabetic conditions (1). SGLT2 is responsible for glucose reabsorption in the kidney. From clinical trials and animal studies, next to lowering blood glucose, many beneficial metabolic and cardioprotective effects of SGLT2 inhibition have been proposed including a reduction in oxidative and mitochondrial stress and cardiovascular disease risk (2). Thus, the use of gliflozins is now being studied in the treatment of heart failure, even in patients without diabetes. The mechanism(s) of the direct cardioprotective effects of gliflozins, however, are still not understood.

Key Goals and Tasks

The primary aim of this PhD thesis is to elucidate the cellular effects and molecular mechanism of gliflozins on cardiomyocytes. To this end, the ESR will use cardiomyocyte cell models and perform functional phenotyping after drug treatment. Employing proteomics, phosphoproteomics and redoxproteomics (3) the ESR will investigate protein expression changes and altered phospho- and redox-signaling. To study the impact of the drug on metabolism, the ESR will use metabolomics, redoxmetabolomics and lipidomics. In order to identify direct drug (off) targets the ESR will design an affinity probe by chemically modifying gliflozins to introduce a bioorthogonal linker and a photoreactive group. The gliflozin probe will then be applied by the ESR to pull down specific binders, similar to our published activity-based proteomics workflow (4). Drug (off) targets will be validated by gene silencing or knock out.

References:

(1) Zelniker TA, Braunwald E, 2020, JACC 75:422, doi:10.1016/j.jacc.2019.11.031
(2) Kolijn D et al, 2021, Cardiovasc Res 117:495, doi:10.1093/cvr/cvaa123
(3) Tomin T et al, 2021, Int J Mol Sci 22:1787, doi:10.3390/ijms22041787
(4) Schittmayer M et al, 2020, Mol Cell Proteomics 19:2104, doi: 10.1074/mcp.RA120.002171

Project-specific Requirements

- Completed master studies in chemistry, biochemistry or eqivalent
- Knowledge on cell biology, biochemistry, bioanalytics (especially proteomics, metabolomics), bioinformatics and organic chemistry
- Experience and skills in biochemistry, bioanalytics and organic chemistry
- Interest in working with human cells and clinical samples
- Enthusiasm for mass spectrometry-based omics technologies
- Affinity for organic and biological chemistry
- Willingness to travel to project meetings and scientific conferences
- Excellent English language skills
- Independence, ability to work in a team, communication, problem-solving skills