Ulrich STELZL (ORCID: 0000-0003-2500-3585):

Deep mutational scanning of functional protein interaction determinants in the activation of cellular lipolysis and of kinase cancer drivers.

Research interest and scientific background: Current DNA sequencing approaches and mass spectrometry based proteomics technologies allow the simultaneous measurements of gene/protein variants for series of cell types, conditions or disease states. As most of the variation alone is not causal with respect to the observed phenotype, the question arises how to systematically analyze the large number of molecular variation and how to assess the importance of combined changes for cellular function, disease development and drug action (1)? In our work we focus on the systematic analyses of the functional impact of genetic variation and post-translational protein modification on protein-protein interaction, which as universal protein function underlies cellular phenotypes. We will use our high resolution interaction approach (2) to perturb protein kinase A-dependent activation mechanisms of cellular lipolysis and determine other selected protein kinase dependencies in cancers.

Approach and methods: The group is focusing on the analysis of molecular interaction networks with the aim to understand the dynamics of molecular networks underlying cellular processes related to human disease. Experimental functional genomics techniques, such as Y2H-seq screening and mass spectrometry (3,4), are utilized in combination with biochemical, cell biological and computational methods. In deep scanning mutagenesis approaches (2) we bridge the knowledge gap between nucleotide resolution genomics and protein resolution proteomics.

Accepted students will interact with other research groups of the doc.fund Molecular Metabolism, in the tri-university framework of BioTechMed-Graz and the research and training network of the University Graz.

Affiliation: The student will work at the Institute of Pharmaceutical Sciences at the University of Graz. The projects are directly connected to the doc.fund Molecular Metabolism.

References:

(1) Woodsmith J, Stelzl U; Understanding Disease Variants through the Lens of Protein Interactions; *Cell Syst* 5(6): 544-46 (2017); doi: 10.1016/j.cels.2017.12.009

(2) Woodsmith J, Apelt L, Casado-Medrano V, Özkan Z, Timmermann B, Stelzl U; Protein interaction perturbation profiling at amino acid resolution; *Nat Methods* 14(12): 1213-21 (2017); doi: 10.1038/nmeth.4464

(3) Weimann M, Grossmann A, Woodsmith J, Özkan Z, Birth P, Meierhofer D, Benlasfer N, Valovka T, Timmermann B, Wanker EE, Sauer S, Stelzl U; A Y2H-seq approach defines the human protein methyltransferase interactome; *Nat Methods* 10(4): 339–42 (2013); doi: 10.1038/nmeth.2397

(4) Corwin T, Woodsmith J, Apelt F, Fontaine JF, Meierhofer D, Helmuth J, Grossmann A, Andrade-Navarro MA, Ballif BA, Stelzl U; Defining Human Tyrosine Kinase Phosphorylation Networks Using Yeast as an In Vivo Model Substrate; *Cell Syst* 5(2): 128–39 (2017); doi: 10.1016/j.cels.2017.08.001