SL-5 **Genotypic Variability and the Quantitative Proteotype**

Ruedi AEBERSOLD
ETH Zurich / University of Zurich

The question how genetic variability is translated into phenotypes is fundamental in biology and medicine. Powerful genomic technologies now determine genetic variability at a genomic level and at unprecedented speed, accuracy and (low) cost. Concurrently, life style monitoring devices and improved clinical diagnostic procedures generate an even larger amount of phenotypic information. To date, the effects of genomic variability on the expressed information of the cell, and thus on the phenotype, have been mainly studied by transcript profiling. Yet, most biochemical activities are catalysed by proteins.

We are therefore aiming at the systematic determination of the effects of genomic variability on the proteotype (the acute state of the proteome of a cell). This is becoming feasible due to the development of new mass spectrometric methods, exemplified by SWATH-MS, that generate highly reproducible proteome maps from samples of (large) cohorts (1).

In this presentation we will discuss the current state of the computational and quantitative aspects of SWATH-MS. We will additionally talk about selected applications of the technology using genetic reference strain and cell line compendia, to determine the effect of genetic variability on the quantitative proteome, thus functionally connecting the genome, the proteome, and complex phenotypes (2,3,4).

1. Gillet LC, Navarro P, Tate S, Roest H, Selevsek N, Reiter L, Bonner R, Aebersold R. (2012) Targeted data extraction of the MS/MS spectra generated by data independent acquisition: a new concept for consistent and accurate proteome analysis (2012). *Mol Cell Proteomics* 11:O111.016717.
2. Picotti P, Clément-Ziza M, Lam H, Campbell DS, Schmidt A, Deutsch EW, Röst H, Sun Z, Rinner O, Reiter L, Shen Q, Michaelson JJ, Frei A, Alberti S, Kusebauch U, Wollscheid B, Moritz RL, Beyer A, Aebersold R. (2013) A complete mass-spectrometric map of the yeast proteome applied to quantitative analysis. *Nature. 494(7436):266-70.*
3. Multilayered genetic and omics dissection of mitochondrial activity in a mouse reference population (2014). Wu Y, Williams EG, Dubuis S, Mottis A, Jovaisaite V, Houten SM, Argmann CA, Faridi P, Wolski W, Kutalik Z, Zamboni N, Auwerx J, Aebersold R. *Cell.* 158(6):1415-30. doi: 10.1016/j.cell.2014.07.039.
4. Williams EG, Wu Y, Jha P, Dubuis S, Blattmann P, Argmann CA, Houten SM, Amariuta T, Wolski W, Zamboni N, Aebersold R, Auwerx J.(2016) Systems proteomics of liver mitochondria function. *Science* 10;352(6291):aad0189.