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## Phosphoproteomic-based systems pharmacology for drug discovery

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A major challenge for bringing safe and effective new treatment to patients is the deep understanding of a disease. Here, we describe the integration of multi-omics data with systems biology algorithms for tackling three milestones in the drug development process: Construction of pathways and comparison between normal or diseased cells; Identification of drug mode of action (MoA) and Prediction of drug toxicity and efficacy. On the experimental front, we develop custom multiplex proteomic and phosphoproteomic assays based on the Luminex technology. To guarantee the quality of the assays we quantify the cross-reactivity profile of antibodies and we have developed optimization algorithms to select the optimal pairs. Currently, a ~40x phosphoprotein panel and a ~80x cytokine panel have been developed. On the computational front, signaling cascades are modeled with a Boolean or fuzzy logic framework and signaling pathways are optimized in order to fit the phosphoproteomic data at hand. Then, knowing the cells topology, we monitor drug-induced topology alterations in order to reveal drug mode of action. Subsequently, supervised machine learning algorithms were able to select MoAs with reduced toxicity and increased efficacy. So far we have applied our approach in several diseases including liver cancer, osteoarthritis and multiple sclerosis.

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## Proteome-wide prediction of protein solubility

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I will discuss the extent to which the solubility of proteins can be predicted from the physico-chemical properties of their amino acid sequences. By exploiting the recent availability of proteome-wide mass spectrometry measurements of protein abundance levels, I will then illustrate how these protein solubility predictions can provide insights into the mechanisms of protein homeostasis. An important principle that has emerged from these studies is the 'life on the edge hypothesis', according to which in living systems proteins are expressed at levels close to their solubility limits. This finding implies that the concentrations of proteins are often close to their critical values and thus that these molecules are constantly in danger of aggregation. Investigation of the consequences of this idea has recently resulted in the discovery that the native states of proteins are kinetically but not thermodynamically stable under many conditions, thus modifying very significantly one of the major principles on which protein science is based that is the native states of proteins are global minima on their free energy landscapes under physiological conditions. This result has profound implications in molecular biology and medicine as the fact that proteins are only marginally soluble in the cell makes them vulnerable to aggregation under stress conditions or as a consequence of other changes such as those associated with ageing.

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