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## Novel drug targets and novel drugs using proteomics technology

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Proteomics technologies are revolutionizing the speed and depth of novel drug discovery. I will describe 2 examples: Example 1: A chemi-proteomics platform was used to capture and identify proteins that bind to small molecule hits from a cell-based genetic screen. This screen was geared to identify molecules that are selectively lethal to cells with aberrantly active RAS-signaling pathway. This approach resulted in identification of several novel cancer targets and paved the way for creation of a novel small molecule currently in clinical Proof-of-concept (Phase 2a) studies in cancer patients. Example 2: Huntington's disease (HD) is a fatal neurodegenerative condition caused by expansion of the polyglutamine tract in the Huntingtin (Htt) protein. Neuronal toxicity in HD is thought to be a consequence of protein interactions involving mutant Htt. We therefore hypothesized that genetic modifiers of HD neurodegeneration should be enriched among Htt protein interactors. To test this idea, we identified a comprehensive set of Htt interactors using two complementary approaches: High-throughput yeast two-hybrid screening and affinity pull down followed by mass spectrometry. This effort led to the identification of 234 high-confidence Htt-associated proteins, 104 of which were found with the yeast method and 130 with the pull downs. We then tested an arbitrary set of 60 genes encoding interacting proteins for their ability to behave as genetic modifiers of neurodegeneration in a *Drosophila* model of HD. This presentation will outline the identification and validation of novel drug targets for HD.

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## Unveiling interactions between proteolytic enzymes, their inhibitors and protein ligands/substrates by MS-functional proteomics

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Presently, there is a tendency towards an integrated view of proteolytic enzymes (proteases) and partners *in vivo*, particularly in the genomics-proteomics-interactomics context. This is also valid for one of their frequent variants like metalloproteases and within them for metallo-carboxypeptidases (MCPs or CPs). The strong growth in the number of MCPs in the last decade has not been paralleled with the understanding of how they act simultaneously or specifically on natural substrates neither on their ligands and inhibitors. The fact that such binders-effectors frequently are of proteic nature, adds further degrees of sophistication to these interactions as well as to the modulation of activities and specificities that they promote. Nowadays we could estimate around 30 the number of variants of such MCPs classified among the M14A, B and C forms and the recently emerged cytosolic forms (CCPs) for the M14D subfamily. Since all of them seem to keep the "canonic" domain of metallo-carboxypeptidases and equivalent recognition sites, it is a real challenge in understanding of their complex relationships, their discriminative interactions with natural substrates (peptidic or proteic, since they are proteases) and with the environmental protein inhibitors. The same happens in the design of drugs through the generation of specific ligands that could control such proteases. MCPs like other proteases share another characteristic interactomics property: They act transiently over protein substrates promoting cleavages which strongly affect conformations and functionalities. How to detect such interactions usually is not an easy task although feasible. Also, the occurrence and role that play in nature numerous protein inhibitors of them usually is poorly known. The talk will focus on cases of recently discovery of such inhibitors and/or ligands-substrates and about strategies of proteomics, interactomics and others followed for its identification and characterization.

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