UCSD Center for Computational Mass Spectrometry for 1. Multi-modal data informatics.

Targeting somatically modified peptides in cancer via receptor internalization

Proteogenomic approaches have been highly successful in the discovery of somatically mutated peptides in cancer. However, the targeting of these peptides for development of therapeutics is still challenging, and represents that next frontier. In a new class of drugs being developed, targeting is used to deliver cytotoxic agents directly to the tumor cell. In these ligand-targeted therapeutics, a generic cytotoxic drug is conjugated with a ligand that binds specifically to a receptor expressed predominantly on tumor cells. CCMS has begun to systematically mine all available tumor proteomics data (e.g., TCGA/CPTAC) using advanced proteogenomic and spectral networks based techniques to search for (a) peptides that are mutated or modified; (b) mutations that are highly recurrent in tumor samples vs normal; (c) membrane bound proteins with the mutation in the extracellular domain. Filtering and development of a small number of such protein targets will be pursued in collaboration with other P41 centers with experiments that test if antibody ligands can be developed to bind to these proteins, if these proteins can be endocytosed (internalized) via ligand binding, and if the ligand can be conjugated with a cytotoxic agent. Preliminary results on CPTAC colorectal cancer identified ~20 examples of prevalent somatically mutated peptides on extracellular domains of cell surface proteins which are being developing further in collaboration with partners.