Affinity-Mass Spectrometry to Determine Target Proteins of Reactive Small Molecules

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Platinum-based anticancer agents are successful therapeutic small molecules that alkylate DNA and interfere with replication. Together with arsenic trioxide they are frequently administered in cancer chemotherapies. In contrast, next-generation metal-based drug candidates are being discovered that may engage with protein targets, but their identification and validation proved to be a challenging task, partly due to the preconception that such reactive metal-based therapeutics would be highly unspecific. At the Department of Analytical Chemistry, we investigate the unique features of next-generation metal-based anticancer agents beyond the benefits of pure cytotoxic activity. We established two-dimensional proteomics approaches by combining affinity purification and response profiling to generate testable hypotheses about novel drug targets and modes of action. We found that an organometallic ruthenium drug candidate selectively targets plectin, a scaffold protein and cytolinker. The organometallic compound seems to affect the protein-protein interaction between plectin and non-mitotic tubulins with considerable effects on cell shape and migration [1,2].

References:

[1] Samuel M. Meier and Christopher Gerner et al., *Angewandte Chemie Int. Ed.* **56** (2017), 8267.

[2] Samuel M. Meier-Menches and Christopher Gerner et al., *Metallomics* **11** (2019), 118.