# Activity-based proteomics – target and ligand discovery on a global scale

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Advances in DNA sequencing have radically accelerated our understanding of the genetic basis of human disease. However, many of human genes encode proteins that remain uncharacterized and lack selective small-molecule probes. The functional annotation of these proteins should enrich our knowledge of the biochemical pathways that support human physiology and disease, as well as lead to the discovery of new therapeutic targets. To address these problems, we have introduced chemical proteomic technologies that globally profile the functional state of proteins in native biological systems. Prominent among these methods is activity-based protein profiling (ABPP), which utilizes chemical probes to map the activity state of large numbers of proteins in parallel. In this lecture, I will describe the application of ABPP to discover and functionally annotate proteins that contribute to human diseases, such as cancer and autoimmunity. I will also discuss the generation and implementation of advanced ABPP platforms for proteome-wide ligand discovery and how the integration of these global 'ligandability' maps with emergent human genetic information and phenotypic screening can expand the druggable fraction of the human proteome for basic and translational research objectives.