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Advances in DNA sequencing have radically accelerated our understanding of the genetic basis of humana(hum)-5.9 (humi)2.7 (s)-2 (eas)-2 (e.)-6.6 (H)2.6 (ow)13.5 (ev)8.9 (er)-5.9 (,)-6.6 (remain uncharacterized and lack selective small-molecule probes. The functional annotation of these proteins should enrich our knowledge of the biochemical pathways that support5humana(hu6 (phy)8.9 (s)-2.1 (i)2.7 (ol)2.6 (og)-11.3 (y)8.9 (and di)2.6 (s)-2 (eas)-2 (e,)4.3 (a therapeutic targets. To address these problems, we have introduced chemical proteomic technologies that enable 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 number parallel. In this lecture, I will describe the application of ABPP to discov functionally annotate proteins that contribute to human diseases, such a autoimmunity. I will also discuss the generation and implementation of a platfms for p roteome-wide ligand discovery and how the integration o 'ligandability' maps with emergent human genetic infmation and phenot can expand the druggable fraction of the human proteome f basic huma research objectives.