Abstract: Nature regulates many biological processes through post-translational modifications that modify protein activity and relay signals through protein networks. Interpretation of how nature uses these modifications will provide new insights to biological regulation, and open new frontiers in the design of therapeutic modalities that mimic nature to treat human disease. We combine probe development and protein engineering with chemical proteomics to address key challenges in reading and rewriting post-translational modifications, with a focus on the nutrient sensor O-linked N-acetyl glucosamine (O-GlcNAc) and the C-terminal cyclic imide marker of protein damage. In parallel, we investigate chemical ligands that modify protein function to probe for natural regulatory events in biological systems. Here, I will describe chemical and biological approaches to redirect chemical signals on substrates in cells that in combination with molecular mechanistic studies have led to the discovery of new regulatory processes through protein modifications in our cells.