Within our control? Leveraging precision electrophile signaling toward drug discovery

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Precisely timed and spatially regulated electrophilic chemical signals are slowly being implicated as bona fide signaling events in numerous cells. However, modeling these low-stoichiometry signaling events and defining the precise biological impacts of localized signals under physiologic conditions has proven to be highly challenging. This lecture presents a unique set of proximity-directed chemical biology tools that enables interrogation into functional consequences of specific redox-linked events. This toolkit includes T-REX™ precision electrophile delivery and G-REX™ profiling in living systems. With these in vivo-validated technologies, we identify bona fide "*first responders*" that interact with native signaling electrophiles under close to endogenous redox signaling conditions (i.e., "k_{cat}/K_m"-like). Our data show that these first responders lie at nexuses between electrophile- and canonical-signaling pathways. Thus, these proteins translate information encoded by electrophile to phosphate or ubiquitin to reroute signaling pathway flux, even at the organismal level. With the growing importance of covalent drugs in the treatment of various human disorders, our new ability to discover and functionally decipher precision electrophile signaling mechanisms opens new avenues toward targeted therapeutics and novel target discovery.