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Chemoproteomic characterization of covalent kinase inhibitors

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The therapeutic value of targeting protein kinases is demonstrated by the small molecule inhibitors receiving regulatory approval primarily for cancer therapy. Despite these successes, only a handful of truly selective inhibitors have been developed for the nearly 600 human kinases. Hence, a large fraction of the druggable genome remains unexplored. Pharmacologic validation of new disease-associated kinases is further hampered by our inability to interrogate the full range of proteins targeted by small molecule probes. The recent approval of cysteine-directed covalent inhibitors of BTK and EGFR has reignited interest in covalent drugs which target kinases or other protein families. One advantage of covalent drugs is their ability to potently and permanently disable protein function often with only transient drug exposure. We are focused on probes which covalently modify members of the cys-kinome, the subset of approximately 200 kinases which harbor a targetable cysteine residue in proximity to the ATP-binding site. We have developed quantitative mass spectrometry approaches which enable site-level interrogation of proteins targeted by irreversible inhibitors on a proteome-wide scale. For individual probes which target kinases such as EGFR, JNK, BMX, FGFR, CDK7 or BTK, we typically identify several hundred intracellular protein targets. We developed a companion, competition-format assay to discriminate between protein targets which exhibit selective, concentration-dependent probe binding and those that bind non-specifically. Importantly we successfully differentiate the repertoire of binding targets for probes which comprise structurally similar analogs, suggesting an efficient mechanism to optimize medicinal chemistry campaigns. Finally, our quantitative approach provides important clues for development of probes targeting obscure kinases. The combination of structure-guided medicinal chemistry informed by chemoproteomic target and site identification provides a scalable platform that delivers well-annotated first-in-class covalent chemical probes that are well-suited for pharmacological validation studies and may serve as useful starting points for future development of small molecule therapeutics.

Biography

Jarrod A Marto is internationally recognized for his expertise in the development and use of state-of-the-art mass spectrometry and other bio-analytical techniques to characterize cellular communication pathways that underlie normal physiology and human disease. His lab pursues technology development with the primary objective of using quantitative mass spectrometry for analysis of primary human tissues and other high-fidelity model systems. He has published widely in the areas of basic chemistry, analytical science, advanced instrumentation, mass-/bio-informatics and cancer biology. In addition he holds intellectual property in mass spectrometry and the use of endogenous peptides as novel cancer therapeutics.

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