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CITe-Id as a novel chemoproteomic platform to characterize covalent kinase inhibitors

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. The recent approval of cysteine-directed covalent inhibitors of BTK and EGFR has reignited interest in covalent kinase therapeutics. 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 kinase 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 called 'CITe-Id' which discriminates non-specific versus selective, concentration-dependent inhibitor binding to protein targets. Importantly we successfully differentiate the repertoire of binding targets for probes which comprise structurally similar analogs, suggesting an efficient mechanism for medicinal chemistry optimization of second-generation inhibitors. Finally, our quantitative approach provides important clues for development of inhibitors targeting obscure kinases. The combination of structure-guided synthesis informed by CITe-Id chemoformic target and site identification provides a scalable platform that delivers first-in-class covalent chemical probes that may serve as useful starting points for future 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 bioanalytical techniques to characterize cellular communication pathways that underlie normal physiology and human diseases. His lab pursues technology development in mass spectrometry for quantitative analysis of primary human tissues or high-fidelity model systems. He has published widely in the areas of basic chemistry, analytical science, advanced instrumentation, mass/bio-informatics and cancer biology.

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