Overcoming Resistance to the THZ Series of Covalent Transcriptional CDK Inhibitors

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ABSTRACT: Irreversible inhibition of transcriptional cyclin-dependent kinases (CDKs) provides a therapeutic strategy for cancers that rely on aberrant transcription; however, lack of understanding of resistance echanisms to these agents will likely impede their clinical evolution. Here, we demonstrate upregulation of multidrug transporters ABCB1 and ABCG2 as a major mode of resistance to THZ1, a covalent inhibitor of CDKs 7, 12, and 13 in neuroblastoma and lung cancer. To counter this obstacle, we developed a CDK inhibitor, E9, that is not a substrate for ABC transporters, and by selecting for resistance, determined that it exerts its cytotoxic effects through covalent modification of cysteine 1039 of CDK12. These results highlight the importance of considering this common mode of resistance in the development of clinical analogs of THZ1, identify a covalent CDK12 inhibitor that is not susceptible to ABC transporter-mediated drug efflux, and demonstrate that target deconvolution can be accomplished through selection for resistance.