TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER™

Graduate School *of* Biomedical Sciences

Dissertation Defense

Narciclasine Impairs c-MYC Activity by Inhibiting DNA-PKcs-Mediated Phosphorylation of OCT4 in Small Cell Lung Cancer

Presented by:

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Translational Neuroscience and Pharmacology

Friday, April 2nd, 2021

Zoom Link: https://ttuhscgsbs.zoom.us/j/91315425720

10:00 am – 11:00 am

ABSTRACT: Small cell lung cancer (SCLC), accounts for 15% of all lung cancer cases. Initially, most patients respond to first-line chemotherapy, but relapse occurs in nearly all patients and is fatal. Overexpression of the *MYC* family of oncogenes occurs in a subset of chemoresistant SCLC. While *MYC* amplification accounts for some of these phenotypes, c-MYC overexpression is frequently seen, suggesting that c-MYC transcriptional activation drives aggressive disease. We identified a novel pathway of c-MYC activation via DNA-PKcs-mediated phosphorylation of OCT4 at Ser93. We present a novel cell-based screening assay to identify inhibitors of the OCT4-DNA-PKcs interaction. We screened ~80,000 compounds and identified 56 “hits” inhibiting kinase-substrate binding. We validated narciclasine as a potent inhibitor of DNA-PKcs-mediated phosphorylation of OCT4 at Ser93. Narciclasine impairs c-MYC expression and induces apoptosis in high c-MYC-expressing SCLC and augments the activity of ABT-199, a BH3-mimetic, *in vitro* and *in vivo* in high c-MYC-expressing SCLC models.

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