# Pharmacological inhibition of TRIP13 induced DNA damage, cell cycle arrest and apoptosis in bladder cancer cell

***Surya P. Singh****, Krishnendu Goswami, Adam S Asch,*

 *Chinthalapally V. Rao, Venkateshwar Madka*

*Center for Cancer Prevention and Drug Development, Stephenson Cancer Center,*

*Hem-Onc Section, Department of Medicine, University of Oklahoma HSC, Oklahoma City, OK*

Urinary bladder cancer (BCa) is the second most prevalent malignancy of the genitourinary tract worldwide. Major obstacles to the management of this disease include a high recurrence rates, progression to muscle-invasive BCa, and poor prognosis of metastatic disease. The lack of effective therapeutic options for advanced-stage BCa necessitates the development of new agents to treat this disease. Thyroid receptor-interacting protein 13 (TRIP13), a member of the AAA-ATPase family, controls several biological processes such as DNA repair, spindle assembly checkpoint, and drug resistance. Numerous studies have recently revealed that TRIP13 overexpression contributes to the development of various cancer types, including BCa. However, the role of TRIP13 in BCa and its potential as a therapeutic target remain elusive. Data from the TCGA and our studies indicate over expression of TRIP13 in human BCa tissue and cell lines with the expression correlating with disease stage and mortality. BCa cells growth was markedly decreased by the pharmacological suppression of TRIP13 using the potent inhibitor DCZ0415. Additionally, DCZ0415 treatment caused cell cycle arrest and apoptosis in BCa cells. We also observed an increase in the levels of cleaved caspase-3 and PARP. Furthermore, the treatment with DCZ0415 reduced the migration and invasion abilities of BCa cells by decreasing the expression of MMP7 and MMP9. Moreover, DCZ0415 treatment significantly reduced the growth of the 3D BCa models. We also observed modulation of the cGAS–STING signaling pathway in BCa cells after treatment with DCZ0415 suggesting potential for a combination and increased response to cGAS-STING targeted therapy. Overall, these findings suggest that TRIP13 could be a promising target for treating bladder cancer and requires further validation in in vivo models. (Funding supported by P30CA225520 and ACS-IRG grant).