Repurposing drugs that target the interaction between HPV and TBX3 to treat cervical cancer

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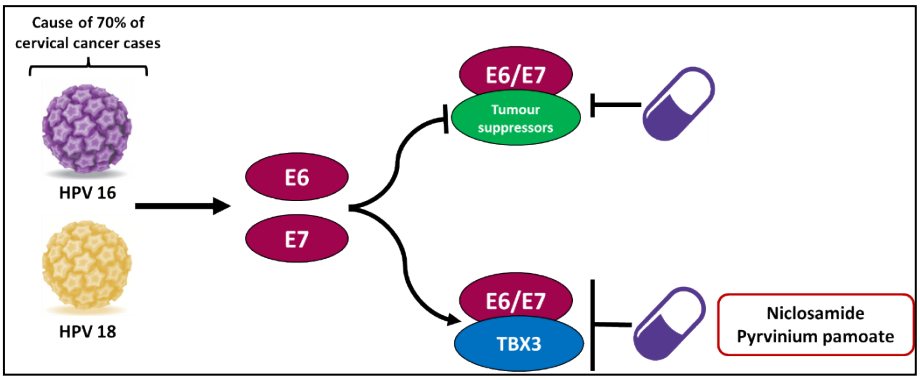

Repurposing drugs that target the molecular mechanism(s) underpinning cervical cancer progression

INTRODUCTION: Cervical cancer (CC) is the leading cause of cancer related deaths in South African women. Human Papillomavirus (HPV) is the causative agent of CC and its oncoproteins, E6/E7, degrade host tumour suppressors and cooperate withhost oncoproteins to induce and maintain CC. A potential approach to facilitate rapid and cost-effective drug development is to identify and target these host oncoproteins with commercially available non-cancer drugs. TBX3 is a key driver of several cancers, but little is known about its status and role(s) in CC [1,2]. Furthermore, we have identifiedthe commercially available drugs, niclosamide and pyrvinium pamoate (hit drugs) that target TBX3 and exhibit anti- cancer activity in melanoma and rhabdomyosarcoma. We hypothesize that TBX3 may be an important oncoprotein in CC and that these hit drugs may also target TBX3 and display potent anti-cervical cancer activity.

METHODOLOGY: TBX3 status was determined in HPV+ CC patient tissues using immunohistochemistry. TBX3 was depleted by siRNA in HPV+ (HeLa and CaSki) and HPV- (C33A) CC cells and the impact on proliferation (growth curves) and migration (scratch assay) assessed. CC cells were treated with hit drugs and the impact on TBX3 levels (western blotting), cell survival (MTT and clonogenic assays), migration (scratch assay), cell cycle profile (FACS), senescence and spheroid formation were investigated.

RESULTS: This study reveals that (1) TBX3 is upregulated and maintained in advanced stages of HPV+ CC; (2) TBX3 promotes HPV+ CC, but not HPV-, proliferation and migration; (3) niclosamide and pyrvinium pamoate reduced TBX3 levels, induced CC cell cycle arrests and senescence and inhibited CC cell survival, migration and 3D spheroid formation andinvasion.

DISCUSSION AND CONCLUSION: Results from this study suggests that TBX3 cooperates with E6/E7 to promote HPV+ CC proliferation and migration and reveal two cheap and effective drugs that have the potential to be used to treat the poorest women in the world suffering from this disease.

REFERENCES:

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2. Khan, S. F. S. F. *et al.* The roles and regulation of TBX3 in development and disease. *Gene* **726**, 144223 (2020).

KEYWORDS: TBX3, HPV E6/7, drug repurposing, migration, targeted therapy