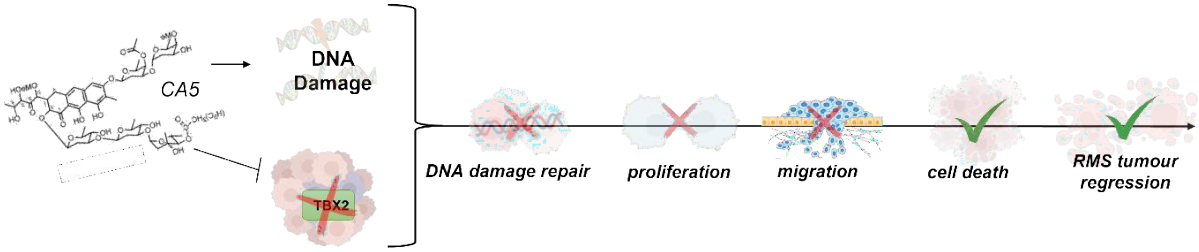
**Marine-derived chromomycin A5: A novel strategy to treat TBX2-driven rhabdomyosarcoma**

**M. Mlaza**[1], B. Del Bianco Sahm[2], P. Rezende Teixeira[2], L. Costa-Lotufo[2], and S. Prince[1,2]

[1]Faculty of Health Sciences, Department of Human Biology, University of Cape Town, Observatory, CapeTown, South Africa

[2] Department of Pharmacology, Institute of Biomedical Sciences, University of São Paulo, Brazil

*E-mail: Mlzmih001@myuct.ac.za




**CA5 inhibits RMS tumour progression:** CA5 induces DNA damage, depletes TBX2 protein levels and induces cancer cell death in RMS.

**Introduction:** Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of the paediatric cancers. To date, localized RMS can be cured with multi-modal therapy, however, overall survival for patients with metastatic or recurring RMS has not improved over the last five decades[2]. This highlightsthe need for developing novel and targeted therapies to treat RMS[2,3]. TBX2, a T-box transcription factoris overexpressed in RMS and is required to drive oncogenic phenotypes such as promoting proliferationand bypassing cellular senescence. Importantly, the depletion of TBX2 inhibits these oncogenic phenotypes[5] which suggest that targeting TBX2 may be a promising anti-RMS strategy. Recently, we and others have reported that chromomycin A5 (CA5), the marine derived compound and anti-tumour antibiotic, interacts with TBX2[1] and exerts cytotoxicity against a panel of murine and human cancer celllines[4]. This study investigates and describes the anti-cancer activity of CA5 in RMS.

**Methodology:** Alveolar (RH30) and embryonal (RD) RMS cells were treated with CA5 and an array ofmolecular and cell biology techniques were employed such as MTT cell viability, clonogenic and scratch motility assays, western blotting, immunocytochemistry, and qRT-PCR.

**Results:** We show that at 48 hr treatment of RMS cells and non-malignant FG0 fibroblasts, CA5 has IC50 values of <5 nM in RMS cells and ~10 in FG0 fibroblasts. CA5 therefore displayed selective cytotoxicity towards RMS cells with a selectivity index of ≥2. Furthermore, we show that in RMS cells, CA5 depletes TBX2 protein levels, induces DNA damage, exhibits long-term cytotoxicity, and induces cell death via mitotic catastrophe and the apoptotic pathway.

**Discussion and Conclusion:** Taken together, our data show CA5 to have great promise for the targeted treatment of TBX2-driven RMS.

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**Keywords:** Rhabdomyosarcoma, targeted therapy, TBX2, chromomycin A5.