Receptor Tyrosine Kinase ROR2 as a Candidate for Antibody-Drug Conjugates in Androgen Receptor-Independent Prostate Cancer

Nakisa Tabrizian[1,2], Shaghayegh Nuoruzi[1,2], Cassandra Jingjing Cui[1,2], Aaron Matthew Lebeau[3], Amina Zoubeidi[1,2]

1. Department of Urologic Sciences, The University of British Columbia, Vancouver, BC V5Z 1M9, Canada; Vancouver Prostate Centre, Vancouver, BC V6H 3Z6, Canada.
2. Vancouver Prostate Centre, Vancouver, BC V6H 3Z6, Canada.
3. Department of Pathology & Lab Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI 53705-2281.

Background: The widespread clinical application of androgen receptor (AR) pathway inhibitors in prostate cancer has led to the emergence of tumors that relapse with diminished AR signaling, transitioning from a luminal to an alternate lineage state. Various genomic and epigenomic aberrations correlate with this lineage reprogramming. Although receptor tyrosine kinases (RTKs) have been shown to rewire the transcriptome, facilitating survival and growth, the specific RTKs contributing to lineage plasticity and de-differentiation following AR pathway inhibition remain poorly defined.

Methods: RNA sequencing (RNA-seq) and functional assays, including gene knockdown and overexpression studies, were conducted to assess the effects on neuronal differentiation and tumor growth. Additionally, in vitro and in vivo models were used to evaluate the role of ROR2 in promoting lineage plasticity. To explore the therapeutic potential of targeting ROR2, we utilized Variable New Antigen Receptors (VNARs) from shark immune systems, known for their small size and unique binding capabilities. Sharks were immunized with peptides representing distinct extracellular domains of ROR2, and B cell mRNA was isolated to construct a VNAR library.

Results: We conducted a survey of RTKs and identified ROR2 as the most upregulated RTK following AR pathway inhibition, which promotes stem cell-like and neuronal networks, contributing to lineage plasticity and de-differentiation. Our studies demonstrated that ROR2 activation leads to MAPK/ERK/CREB signaling pathway engagement, facilitating the expression of ASCL1, a lineage commitment transcription factor, thereby supporting lineage plasticity and treatment resistance. From the VNAR library, we identified four VNARs with high specificity and affinity for ROR2. These VNARs are currently being evaluated for their potential in developing ROR2 VNAR-drug conjugates.

Conclusion: The pronounced upregulation of ROR2 in response to AR pathway inhibition and in AR-independent prostate tumors underscores its significant potential as a therapeutic target. The VNARs derived from shark immune systems offer a novel approach to developing ROR2-targeted agents, which could significantly impact the management of AR-independent resistance in prostate cancer. This research paves the way for the development of innovative antibody therapies targeting RTKs implicated in cancer lineage plasticity.

Funding Acknowledgements: This research was supported by funding from the Terry Fox Research Institute New Frontiers Program (F22-00589; to A.Z.) and the Canadian Institutes of Health Research (169173; to A.Z.).

Conflicts of Interest Disclosure Statement: The authors declare no competing interests.