Targeting the lncRNAs SChLAP1 and MALAT1 in aggressive prostate cancer

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Background: Treatment of advanced prostate cancer (PCa) is hampered by the inability to identify indolent versus aggressive cancers and the surprisingly few effective therapies available for aggressive forms. The recently unveiled predictive power of SChLAP1 (second chromosome locus associated with prostate-1) long noncoding RNA (lncRNA) in prostate cancer aggressiveness gives credence to the hypothesis that lncRNAs, rather than proteins, may be the most active drivers of human prostate cancer. Silencing of SChLAP1 revealed its prominent role in invasion and metastasis, likely by abrogating the tumor suppressive activity of the SWI/SNF chromatin-modifying complex. The minimal expression of SChLAP1 in other tissues confirms the availability of a therapeutic window, and recent noninvasive methods to measure SChLAP1 as a biomarker are expected to allow personalized therapy. Furthermore, the recent identification of the critical RNA element needed for the invasive phenotype will permit direct therapeutic targeting.

Similarly, the overexpression of lncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) was found to be predictive of several clinical features associated with castration-resistant PCa, including high PSA-levels and advanced tumor stage. Intratumoral delivery of MALAT1-targeting siRNAs in prostate cancer xenografts has been shown to slow tumor growth and reduce metastasis. Recent studies of a an evolutionarily conserved triple helix element at the 3'-end of MALAT1 suggest that this structure has a pivotal role in enabling MALAT1 accumulation, thereby posing this region as an attractive target for small molecule-based disruption.

These functional insights allow a unique opportunity for the in-depth examination of the "druggability" of lncRNAs such as SChLAP1 and MALAT1. Our long-term goal is to realize the therapeutic potential of targeting SChLAP1 and MALAT1 lncRNA with first-in-class multivalent small molecule ligands and to translate these findings into clinical trials that directly benefit patients diagnosed with aggressive and metastatic prostate cancer.

Methods: We are approaching this goal through fundamental investigations, including: 1) Structural probing of lncRNA to identify target "hot spots;" 2) Development of a diverse RNA-targeted small molecule library for rapid screening and subsequent optimization of specific RNA ligands and; 3) Optimization of these ligands for inhibition of lncRNA-dependent invasion and metastasis, which will identify lead compounds for future lncRNA-targeted drug development.

Results: To date, we have used computational analysis to identify chemical space preferred by biologically active RNA ligands and developed synthetic routes to diversify RNA binding scaffolds to yield derivatives within this privileged RNA space. Specifically, we have conducted extensive literature analysis to identify biologically active RNA-targeted ligands and have identified, physicochemical, structural and spatial elements that privilege molecules for RNA targeting in a biological system. Our current synthetic library includes more than 100 novel molecules that are combined with a commercial RNA-targeted library to give more than 900 RNA-specific ligands. We have identified the first small molecule ligands for lncRNA MALAT1 and confirmed both high affinity and specificity. Investigations of the structure and binding of SChLAP1 are underway.

Conclusions: Specific targeting of lncRNA is expected to lead to entirely novel paradigms in prostate cancer biology and treatment that directly benefit patients with advanced prostate cancer. Furthermore, similar correlations between specific lncRNAs and aggressiveness have been identified in liver, bladder, and several other cancers, suggesting that these technologies have the potential to open new horizons both in lncRNA cancer biology and a broad range of therapeutics avenues in cancer.

Conflict of Interest: None

Funding acknowledgement: Prostate Cancer Foundation Young Investigator Award; Duke University; National Institute of General Medicine.