

Targeting the lncRNA SChLAP1 in aggressive prostate cancer by the assembly of multivalent small molecule inhibitors

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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. These functional insights allow a unique opportunity for the in-depth examination of the “druggability” of lncRNAs such as SChLAP1. Our long-term goal is to realize the therapeutic potential of targeting SChLAP1 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 SChLAP1 to identify target “hot spots;” 2) Development of a diverse RNA-targeted small molecule array for rapid screening and subsequent assembly of specific, multivalent RNA ligands and; 3) Optimization of these ligands for inhibition of SChLAP1-dependent invasion and metastasis, which will identify lead compounds for future SChLAP1-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 four RNA binding scaffolds to yield derivatives within this privileged RNA space. Our current synthetic library includes more than 60 novel molecules that are combined with a commercial RNA-targeted library to give more than 120 RNA-specific ligands. Our proof-of-concept efforts against smaller RNAs have yielded specific ligands with greater than 100x-increased potency over the parent lead molecule and have demonstrated our ability to visualize RNA binding via microarray. Investigations of the structure and binding of SChLAP1 are underway.

Conclusions: Specific targeting of SChLAP1 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.

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