Phosphatase deregulation in prostate cancer progression

Shane Comiskey[1], Lakshmi Kadkol[1], **Renée de Leeuw**[1,2]

1University of Illinois at Chicago, Department of Pathology, Chicago, IL
2University of Illinois Cancer Center, Chicago, IL

Background
There is currently no durable cure for prostate cancer (PCa) once it metastasizes. To discover new targets for more successful, patient-tailored therapeutic strategies for advanced PCa, it is critical to understand how the cancer progresses. While targetable kinase signaling cascades are intensely investigated in PCa, the phosphatases that regulate kinases and other proteins are vastly understudied, with the exception of PTEN, one of the most highly deregulated tumor suppressors in PCa. The overarching goal of this project is to discover new biomarkers and therapeutic targets to improve outcomes for advanced, lethal PCa.

Methods
We performed an inquiry of 255 phosphatases in the TCGA primary PCa database, which revealed that PPP2CB is more frequently deregulated than PTEN, comprising ~30% of all cases. The majority display either decreased mRNA expression or deep deletion, also commonly observed in other patient datasets. These events do not significantly co-occur with PTEN and the gene resides on a different chromosome (8p12 versus 12q23), precluding a bystander effect of PTEN loss. Further analyses in independent PCa patient data revealed that PPP2CB loss is associated with poor survival and metastasis. Therefore, we hypothesize that PPP2CB loss can drive PCa aggressiveness and/or castration resistance. We are in the process of generating new CRISPR knockout models of PPP2CB in PCa cancer cells to characterize the effects on PCa aggressiveness. To this end, we will evaluate impact of PPP2CB loss on proliferation, migration and invasion and metastatic potential, and castration resistance in vitro and in vivo.

Results
Two new PPP2CB-KO models of 22RV1 and C4-2B cells have been successfully generated and validated, and other cell models are under development. Preliminary data show that PPP2CB loss enhanced proliferation in 22RV1 cells. Further characterization of these models is currently underway.

Conclusion
PPP2CB loss or downregulation is associated with poor PCa outcomes and may contribute to PCa aggressiveness, which will be the focus of future investigation. Anticipated discoveries will determine the clinical relevance of a common yet novel uncharacterized phosphatase aberration in PCa aggressiveness and aim to unravel the underlying biology by which altered phosphatase signaling can promote progression to lethality.

Conflict of Interest
The authors declare no conflicts of interest.