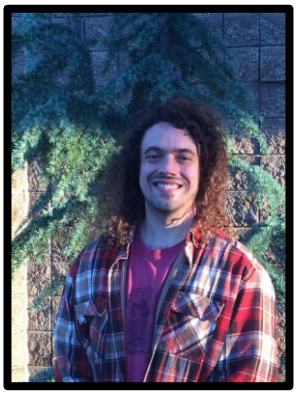
THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Joshua Moses Corbin

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
Department of Pathology



Friday, May 3, 2019 | 8:30 am
Biomedical Science Building
Hensley Library, Room 433

Functional Analyses of TMEFF2 in Prostate Regeneration and Cancer Lead to the Identification of a Prognostic Gene Signature and Potential Therapeutic Strategy for Prostate Cancer

COMMITTEE IN CHARGE: Maria Ruiz-Echevarria, PhD, Doris Benbrook, PhD, Wei-Qun Ding, PhD, Yuechueng Liu, PhD, Joe Zhao, PhD

ABSTRACT: The lack of adequate markers for patient stratification and the development of resistance to androgen deprivation therapy are the major causes of reduced livelihood and survival of prostate cancer (PCa) patients. In addition, the heterogeneity of PCa presents a major hurdle in overcoming these clinical challenges. The TMEFF2 gene has been implicated in development and cancer, and exhibits highly variable expression in PCa. As reported in this dissertation, investigating the function of TMEFF2 in prostate regeneration and cancer in vivo, not only provided new information about the complex role of TMEFF2 in these processes, but also contributed to hypothesis generation that led to the identification of a prognostic gene signature and potential therapeutic strategy for PCa.

Using a transgenic mouse model developed in our lab, we discovered a novel role of TMEFF2 as a promoter of prostate branching morphogenesis during androgen induced prostate regeneration. In addition, we showed that TMEFF2 overexpression inhibited tumor growth in TRAMP-C2 allografts, and also discovered a novel role for TMEFF2 as a promoter of NEPC incidence in TRAMP mice.

The studies mentioned above led us to investigating a potential role for TMEFF2 in androgen signaling in human PCa cell lines. We identified an androgen responsive cell cycle related gene signature (TMCC11) associated with low TMEFF2 expression that is prognostic of PCa recurrence, and provided data suggesting that TMCC11 performs well when compared to other published prognostic gene signatures. Additionally, using TMEFF2 targeted shRNA in PCa cell lines, we identified a potential RNAi-based therapeutic strategy that promotes PCa cell death through the depletion of numerous essential and androgen signaling regulatory genes.

These studies point to a significant and complex role of TMEFF2 in PCa, and provide the rationale for continued investigation of TMCC11 as predictive marker in PCa and TMEFF2-RNAi as a therapy in preclinical mouse PCa models, as we seek to overcome the prevalent clinical challenges and improve the outcome for men diagnosed with this common malignancy.