Patient Derived Models Reveal Impact of the Tumor Microenvironment on Therapeutic Response

Ayesha A. Shafi[1], Matthew J. Schiewer[1], Renée de Leeuw[1], Emanuela Dylgjeri[1], Peter A. McCue[1], Neelima Shah[3], Leonard G. Gomella[1,2], Costas D. Lallas[1,2], Edouard J. Trabulsi[1,2], Margaret M. Centenera[4,5], Theresa E. Hickey[4], Lisa M. Butler[4,5], Ganesh Raj[6], Wayne D. Tilley[4], Edna Cukierman[3], and Karen E. Knudsen[1,2,7]

[1]Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, Pennsylvania. [2]Department of Urology, Sidney Kimmel Cancer Center Thomas Jefferson University, Philadelphia, Pennsylvania. [3]Fox Chase Cancer Center, Cancer Biology, Temple Health, 333 Cottman Ave, Philadelphia, Pennsylvania. [4]Dame Roma Mitchell Cancer Research Laboratories, Adelaide Prostate Cancer Research Centre and Freemason's Foundation Centre for Men's Health, School of Medicine, University of Adelaide, Adelaide, Australia. [5]South Australian Health and Medician Research Institute, Adelaide, Australia. [6]University of Texas Southwestern Medical Center, Dallas, Texas. [7]Departments of Cancer Biology and Medical Oncology at Thomas Jefferson University, Philadelphia, Pennsylvania.

Prostate cancer (PCa) is the most common non-cutanenous cancer and the third leading cause of cancer-related death in American men. Androgen receptor (AR) is a hormone-activated transcription factor that plays an important role in both the development and progression of PCa. Androgen deprivation therapy is a common first-line therapy for disseminated disease. However, virtually all tumors become resistant to such therapy and the tumor recurs and is termed castration resistant prostate cancer (CRPC). There is no durable cure for CRPC; thus, there is a vital need for the development of novel, more effective drugs. One major hurdle in this aspect is the lack of adequate preclinical models. Current models do not effectively recapitulate the heterogeneity and the microenvironment of human PCa tumors, significantly hindering the ability to accurately predict therapeutic response. Our collaborative group has utilized and characterized a method to culture patient tumors *ex vivo*, termed Patient Derived Explant (PDE). This approach maintains the integrity of the native tumor microenvironment (TME), tumor tissue morphology, and endogenous molecular signaling. Importantly, our PDE model can be manipulated both chemically (drugs/compounds) and genetically (shRNA) in order to determine specific reactions and mechanisms of response on individual tumor growth. Furthermore, with this model we can quantitatively assess drug efficacy on numerous parameters (i.e. AR levels, Ki67 staining, apoptosis screening, and desmoplasmic indices). Data to be discussed will assess the variances in response to AR-directed therapeutics and underlying mechanisms of action, while also utilizing TME characteristics as a means to predict response to therapy. In addition, we can identify potentially clinically relevant subpopulations of patients and molecularly profile their cultured tissue to uncover new pathways for therapeutic intervention. Thus, the PDE model allows for a comprehensive evaluation of individual tumors in their native TME to ultimately develop more effective therapies. Discernment of novel stromal markers may provide a basis for applying precision medicine in treating advanced PCa, which would have a transformative effect on patient outcomes. Thus, this study will have great clinical impact discerning novel metrics for the inclusion of precision medicine for advanced PCa.

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