Understanding heterogeneity and drug resistance in 3D cultures of patient prostate cancer bone metastases and primagrafts

Mendoza, T[1,2], Muldong, MT[1,2], Gallegos, A[3], Wu, CN[1,2,4], Edsall, LE[3], Park, JS[6], Liss, MA[5], Raheem, O[1], Park, SC[7], Zhu, W[1,2], Godebu, E[1], Woo, JR[1], Burner, D[1,2], Strasner, A[1,2], Miakicheva, O[1,2], Cacalano, NA[8], Jamieson, CHM[4], Kane, CJ[1,2], Kulidjian, AA[2,9], Gaasterland, T[3] and C.A.M. Jamieson*[1,2]

[1]Dept. of Urology, Dept. of Surgery, [2]Moores Cancer Center, University of California, San Diego (UCSD), [3]Scripps Genome Center, Institute for Genomic Medicine, UCSD, [4]Dept. of Medicine, UCSD, [5]Dept. of Urology, University of Texas Health Sciences Center, San Antonio, TX, [6]Dept of Urology, Eulji University School of Medicine, Seo-gu, Daejeon, South Korea, [7]Dept of Urology, Wongkwak University, Jeonbuk, South Korea, , [8]Dept. of Radiation Oncology, University of California, Los Angeles (UCLA), [9]Dept. of Orthopaedic Surgery, UCSD.

Background: One in six men will be diagnosed with prostate cancer (PCa), making it one of the leading health problems affecting men in today's society. Patients diagnosed during the earlier stages are surviving longer due to improved therapies and the prevalence of prostate-specific antigen (PSA) testing. However, over 80% of advanced PCa patients develop bone metastatic prostate cancer for which there is no cure. Cell lines, widely used for the development of new drug treatments and therapies, fail to accurately recapitulate the heterogeneity of prostate cancer. Thus, it is important to establish new patient-derived cell culture models for bone metastatic prostate cancer which could better recapitulate the physiological processes that occur *in vivo*.

Methods: Surgical prostate cancer bone metastasis samples were collected at the time of orthopaedic repair surgery and used to establish four novel patient-derived xenograft (PDX) models for advanced prostate cancer in the bone: PCSD1, PCSD4, PCSD5 and PCSD13. These PDX models closely reproduced bone metastatic disease in prostate cancer patients. In order to understand the changes that occur which may lead to progressive therapy resistance of the prostate cancer bone metastases we investigated and compared the genomic and transcriptomic variation in the longitudinal series of surgical bone metastasis prostate cancer patient samples and the xenografts derived from them. Through the incorporation of previously established methods into our own culturing methods, we optimized three-dimensional cell culture conditions which keep our patient-derived xenograft tumor cells viable *in vitro*.

Results and Conclusions: Currently, we have established *in vitro* cultures for our patient-derived xenograft (PDX) and primary patient prostate cancer bone metastasis tumor cells which remain viable for more than 6 weeks without passaging. Furthermore, preliminary experiments showed that our three-dimensional cultures consist of heterogeneous cell populations that exhibit differential responses to hormone and drug treatments. In future experiments, we hope to further optimize our culturing conditions to improve the robustness and reproducibility of our three-dimensional cell cultures for patient-derived xenograft and primary prostate cancer tumor cells.

Funding: The Leo and Anne Albert Charitable Trust