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A novel patient-derived intra-femoral xenograft model of bone metastatic prostate cancer that recapitulates mixed osteolytic and osteoblastic lesions.

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a) Introduction and Objective: Prostate cancer metastasizes to bone in the majority of patients with advanced disease leading to painfully debilitating fractures, spinal compression and rapid decline. Prostate cancer bone metastases often become resistant to therapies including androgen deprivation, radiation and chemotherapy. There are currently few models to elucidate mechanisms of interaction between the bone microenvironment and prostate cancer. It is, thus, essential to develop new patient-derived, orthotopic models. Here we report the development of PCSD1 (Prostate Cancer San Diego 1), a novel patient-derived intra-femoral xenograft model of prostate bone metastatic cancer that recapitulates mixed osteolytic and osteoblastic lesions.

b) Methods: A femoral bone metastasis of prostate cancer was removed during hemiarthroplasty and transplanted into Rag2-/-;ᔓc-/- mice either intra-femorally or sub-cutaneously. Xenograft tumors were analyzed for prostate cancer biomarker expression using RT-PCR and immunohistochemistry. Osteoblastic, osteolytic and mixed lesion formation was measured using micro-computed tomography (OCT).

c) Results: PCSD1 cells isolated directly from the patient formed tumors in all mice that were transplanted into Rag2-/c-/-mice. Xenograft tumors expressed human prostate specific antigen (PSA) in RT-PCR and immunohistochemical analyses. PCSD1 tumors also expressed AR, NKX3.1, Keratins 8 and 18, and AMACR. Histologic and microCT analyses revealed that intra-femoral PCSD1 xenograft tumors formed mixed osteolytic and osteoblastic lesions. PCSD1 tumors have been serially passaged in mice as xenografts intra-femorally or sub-cutaneously as well as grown in culture. Prostasphere growth was characterized in 3D co-culture model of the bone niche with human bone marrow derived stromal cells. PCSD1 tumors grew in mice treated with the anti-androgen, bicalutamide, thus, demonstrating castrate resistance with standard of care therapy.

d) Conclusions: PCSD1 xenografts tumors were characterized as advanced, luminal epithelial prostate cancer from a bone metastasis. PCSD1 intra-femoral xenografts formed mixed osteoblastic/osteolytic lesions that closely resembled the bone lesions in the patient. Castration-resistant growth in the bone niche was evaluated in young and aged mice as well as in the presence and absence of novel bone signaling pathway inhibitors. PCSD1 is a new primary prostate cancer bone metastasis-derived xenograft model to study castrate-resistant metastatic disease in the bone and to develop novel therapies for inhibiting prostate cancer growth in the bone- niche.

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