**Temporal Dynamics of Macrophage Plasticity in Bone Metastatic Prostate Cancer**

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Prostate cancer primarily metastasizes to the skeleton and promotes extensive bone remodeling. These incurable lesions lead to disease complications and poor patient morbidity. Understanding how metastatic prostate cancer (mPC) manipulates the bone microenvironment (BME) is crucial for therapy development. Macrophage (M0) plasticity has well described roles in pro-/anti-tumor progression, and separately in normal bone turnover. However, temporal dynamics of M0 infiltration and plasticity is unexplored to date in bone mPC. We hypothesize that M0 polarization affects cancer-bone interaction and ultimately the pathophysiology of bone mPC. We will integrate mathematical ordinary differential equation (ODE)-based models and biological experimentation to simulate multicellular interactions across time and test our hypothesis. We first parameterized the model with what is empirically known about M0 in normal bone repair. Inflammation follows bone injury, marked by inflammatory monocytes recruitment, which readily polarize to M1 status when exposed to factors like nitric oxide. Once M1 clear the stroma debris, osteoblast (OBL) precursors expand and secrete osteoclastogenesis factors including receptor activator of nuclear kappa B ligand (RANKL). Osteoclasts resorb bone, releasing growth factors like transforming growth factorβ (TGFβ). TGFβ drives M2 polarization to suppress inflammation and facilitate OBL-driven bone formation. The M2 recedes, returning the bone to homeostasis. Our ODE model uses *in* and *ex vivo* testing and empirical data, and captures temporal changes in M0 plasticity during normal bone remodeling. We are currently using the model to interrogate and identify how mPC progression perturbs M0 plasticity in the BME and the result bone stroma behavior. These *in silico* outputs will then be verified with *in vivo* models of the disease. This integrated approach will reveal how M0 contribute to the bone growth mPC over time and will identify key circuits that can be therapeutically targeted to treat the disease.