An integrated computational model of the bone microenvironment in bone-metastatic prostate cancer

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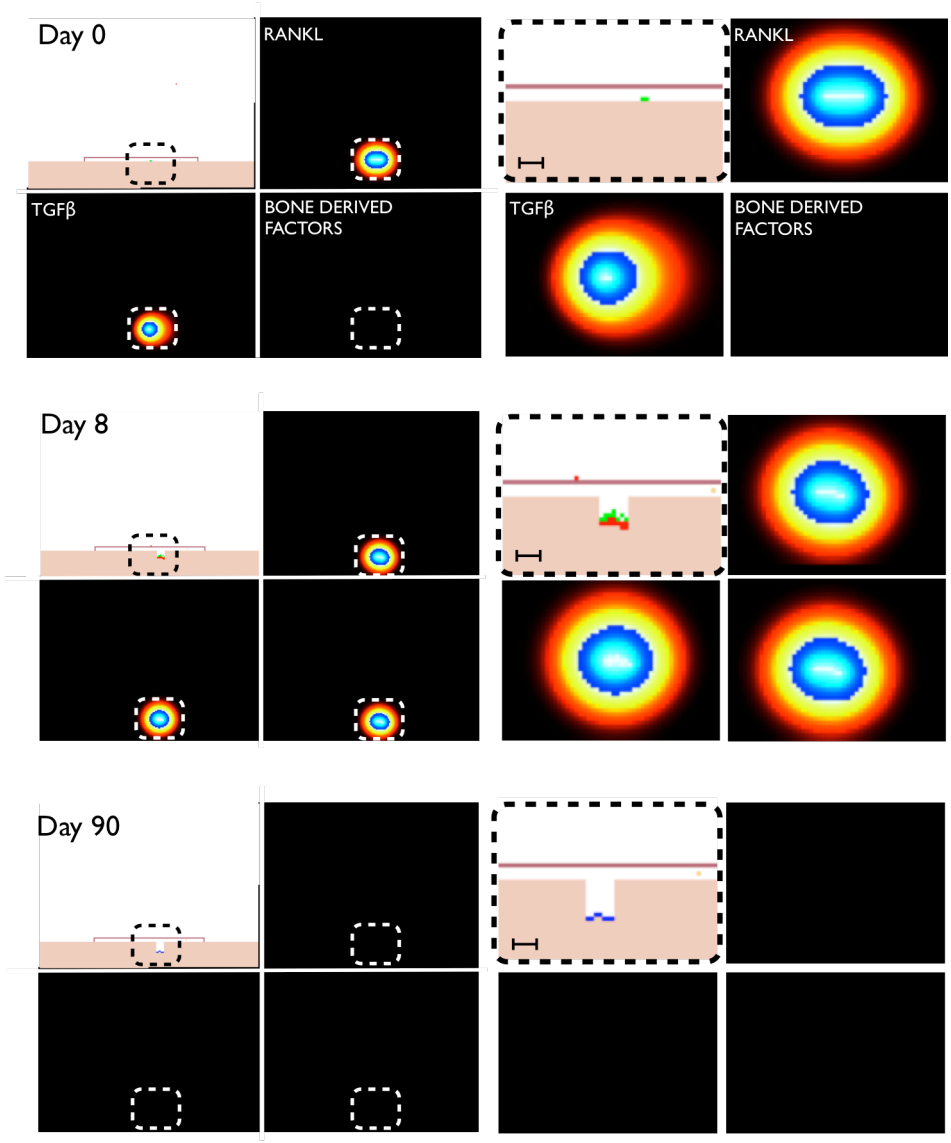
Supplemental Methods

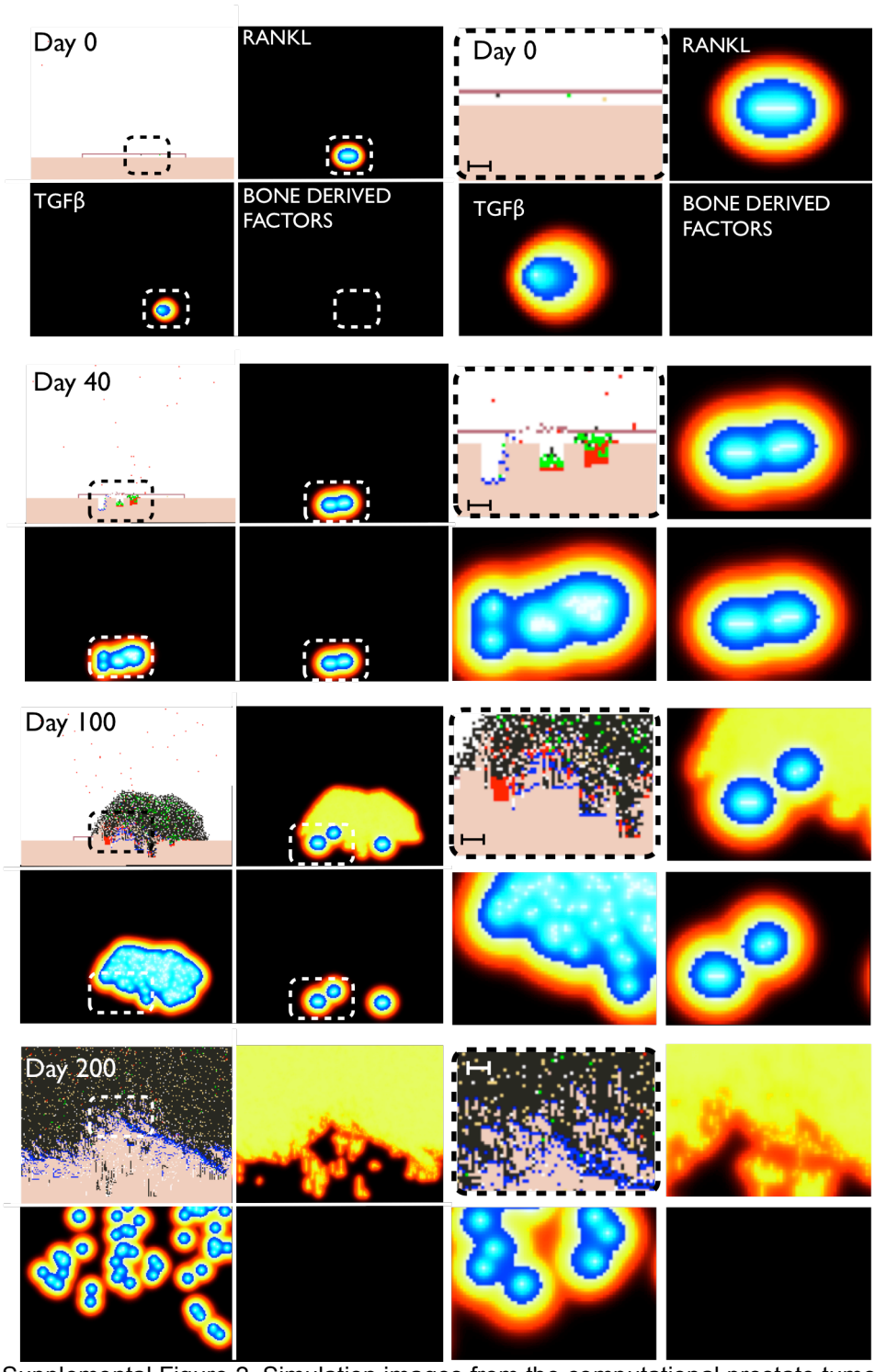
Cell Culture. PAIII rat prostate adenocarcinoma cells were cultured in a mixture of Dulbecco's modified Eagle's medium (DMEM;Invitrogen) with ribonucleosides, deoxyribonucleosides, 2 mM L-glutamine and 1 mM sodium pyruvate supplemented with: 10% fetal bovine serum (FBS) and 1% penicillin/streptavadin (Pen/Strep;GIBCO) (32). Mouse MSCs were isolated as previously described and were cultured in low-glucose DMEM supplemented with 10% FBS, 1% Pen/Strep, and 10µg/ml platelet-derived growth factor (PDGF) to maintain the pluripotent phenotype (33). Mouse osteoblast precursor cells, MC3T3-E1, were commercially purchased (ATCC) and were cultured in Alpha Minimum Essential Medium with ribonucleosides, deoxyribonucleosides, 2 mM L-glutamine and 1 mM sodium pyruvate supplemented with 10% FBS and 1% Pen/Strep.

Statistical Analysis. Statistical analysis was performed using the analysis of variance (ANOVA) with the appropriate post multiple comparison analysis.

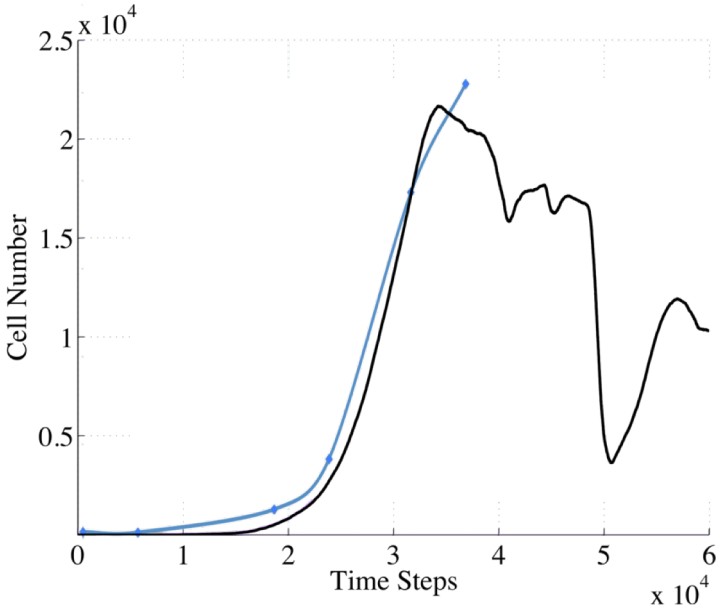
Supplemental Figures



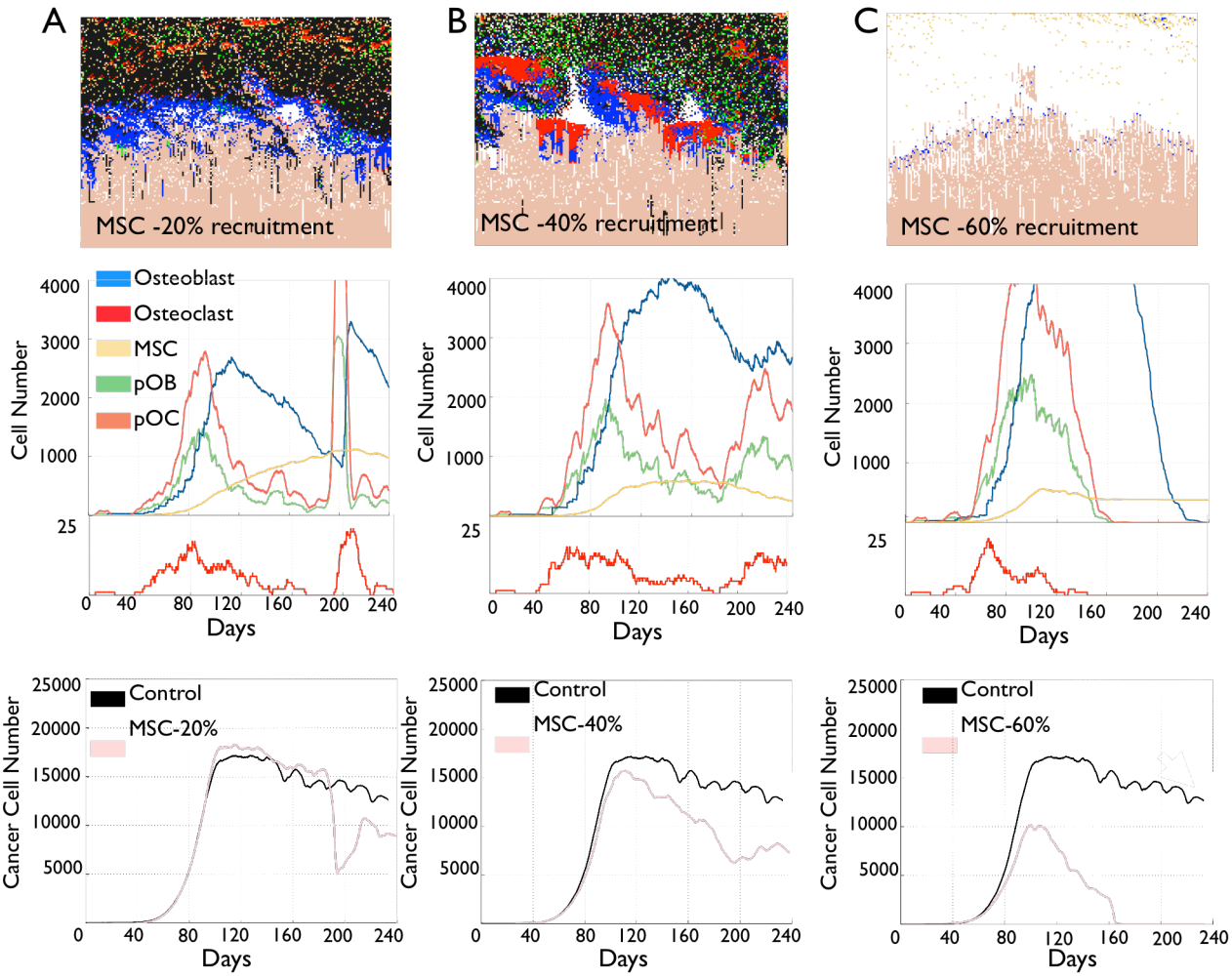
Supplemental Figure 1 and Movie 1. Simulation images from the computational homeostatic basic multicellular unit (BMU) including parallel images of RANKL, TGFβ and bone derived factors including insulin like growth factor of the course of bone resorption and apposition. Dashed box is magnified in right hand side panels. Scale bar represents 100μm. Movie 1 illustrates the dynamic nature of the BMU over the course of 90 days.



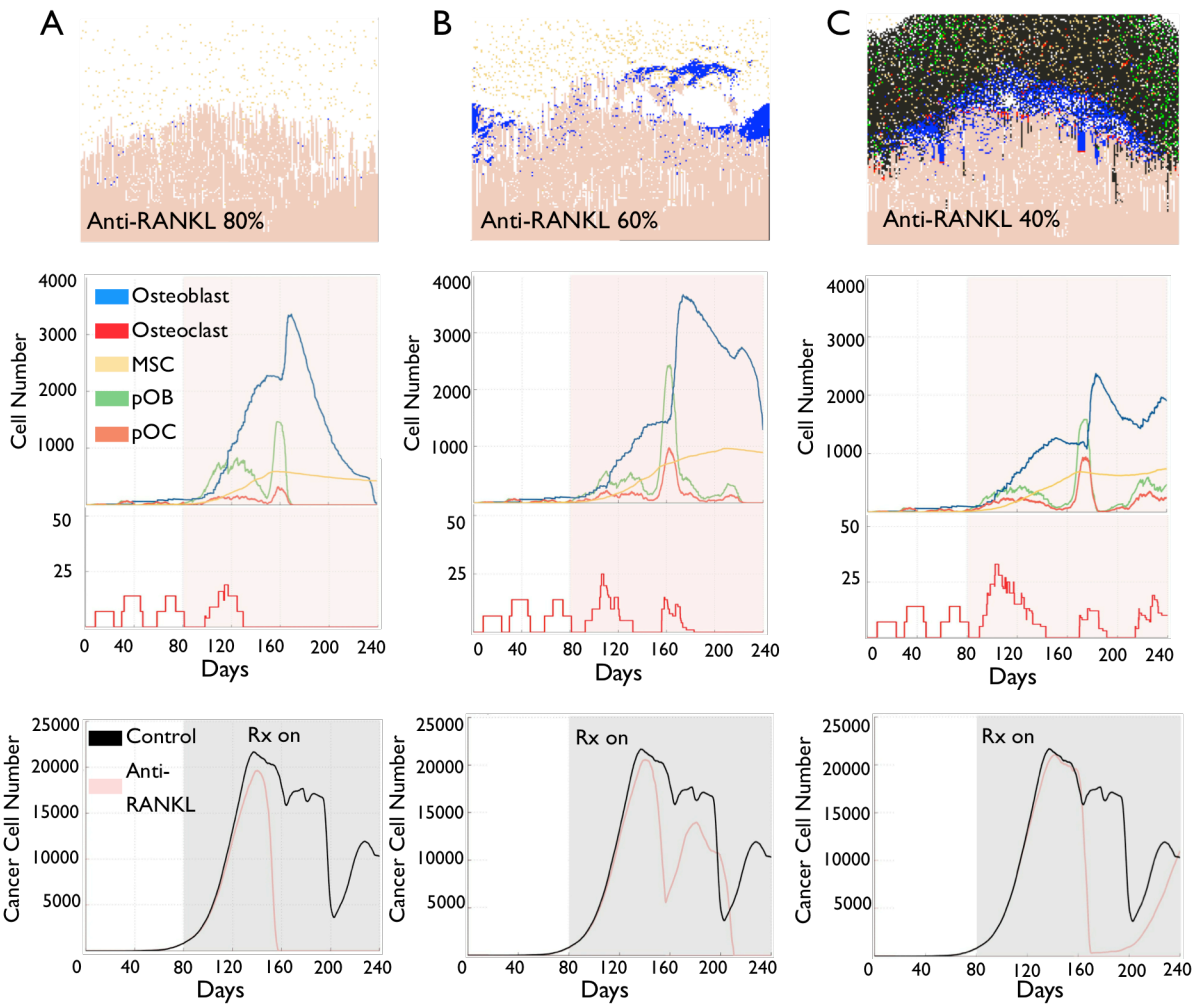
Supplemental Figure 2. Simulation images from the computational prostate tumor-bone microenvironment model including parallel images of RANKL, TGFβ and bone derived factors of the course of 200 days. Dashed box is magnified in right hand side panels. Scale bar represents 100 μm at days 0-40 and 200μm from Day 100-200. Movie 2 illustrates the dynamic nature of the BMU over the course of 200 days.



Supplemental Figure. 3. Plot shows that the behavior of the biological model (blue line) and computational model (black line) produce comparable outputs and show similar trends.



Supplemental Figure 4. Determining the importance of MSC recruitment in the computational model. **A-C** Reducing the probability of MSC recruitment by 20% (A), 40% (B) and 60% (C). Representative images of the computational prostate tumor-bone microenvironment are illustrated at day 240.



Supplemental Figure 5. Analysis of dosing efficacy in the computational model. **A-C** Applying the anti-RANKL inhibitor at 80% (A), 60% (B) and 40% (C) dosing efficacies. Representative images of the computational prostate tumor-bone microenvironment are illustrated at day 200. Rx indicates the time at which the bisphosphonate or Anti-RANKL therapies were applied.