Credibility in multiscale modeling of bone environment response to metastatic cancer

Basanta D & Lynch CC

Tumor Biology and Integrative Mathematical Oncology Depts., H. Lee Moffitt Cancer Center, 12902 USF Magnolia Drive, Tampa, FL

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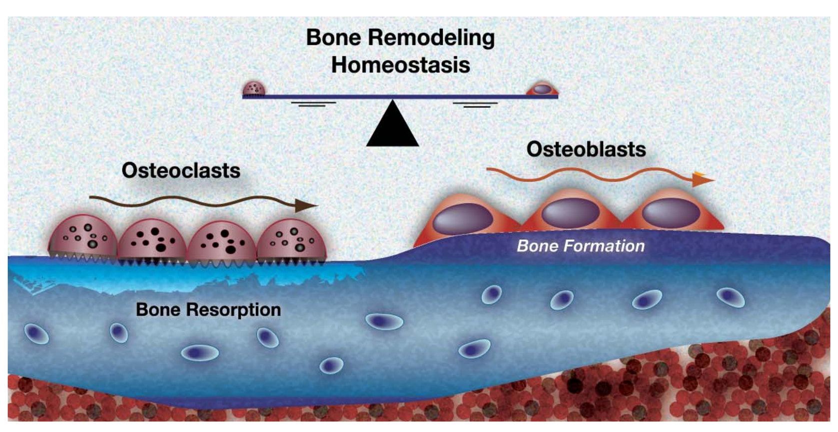
Integrated Mathematical Oncology

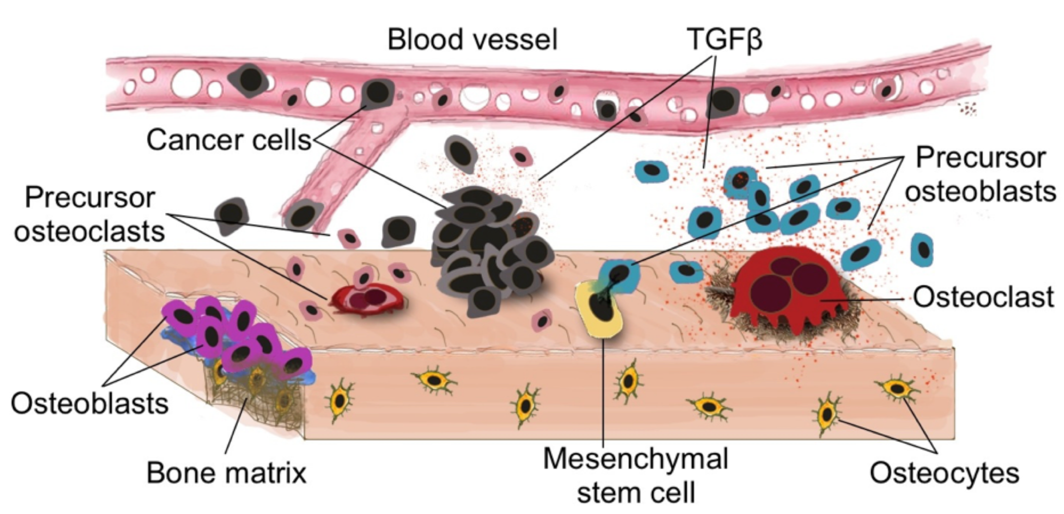
1. Context: Bone Malignancies and The Vicious Cycle

- Various metastatic malignancies are osteophilic, including prostate, lung and breast cancer
- Most cancers are incurable at bone-metastatic stages and cause vicious cycle by disrupting osteolysis and osteogenesis, resulting in poorly-vascularized brittle bone with painful lesions susceptible to fractures
- Microenvironment-targeted therapies have enjoyed success in some primary solid malignancies but their application in bone metastatic diseases are unknown
- Here we take an interdisciplinary multiscale *in silico*/*in vivo* approach to understand the largely unexplored role of the bone environment and ecosystem in bone metastatic cancer.

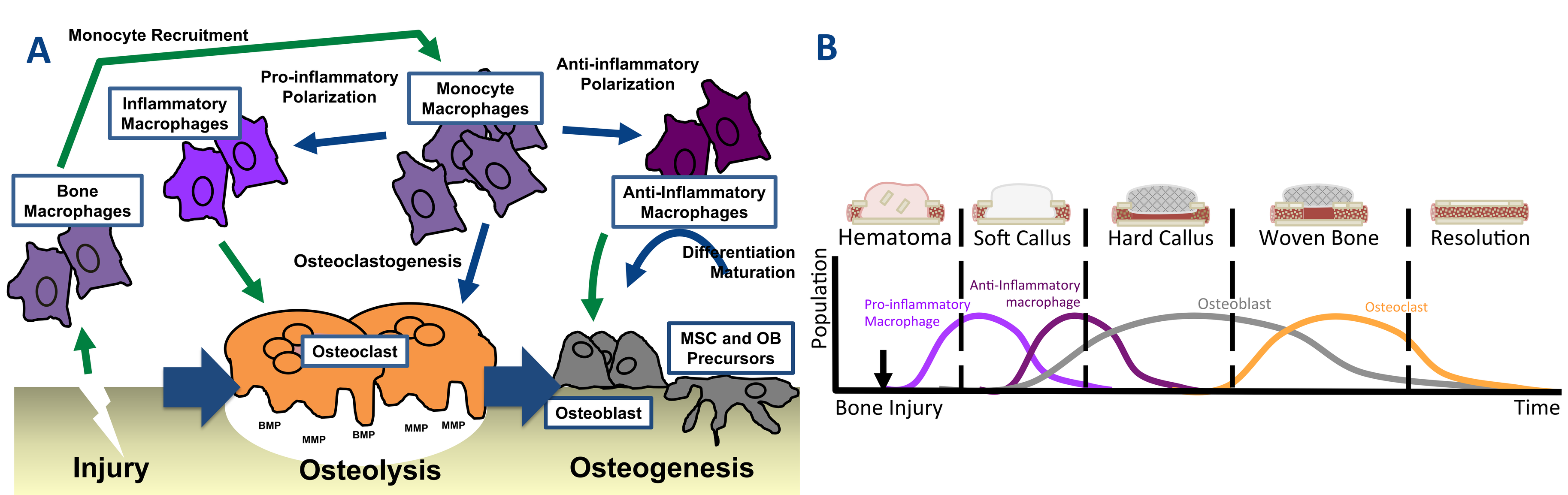


Bone is a highly dynamic organ where the amount and quality depend on the interactions between various cell types, mainly bone-depositing osteoblasts and bone resorpting osteoclasts.

The cancer ecosystem is made of many different cell types and environmental factors that can play a role in a number of skeletal diseases including metastatic cancer.

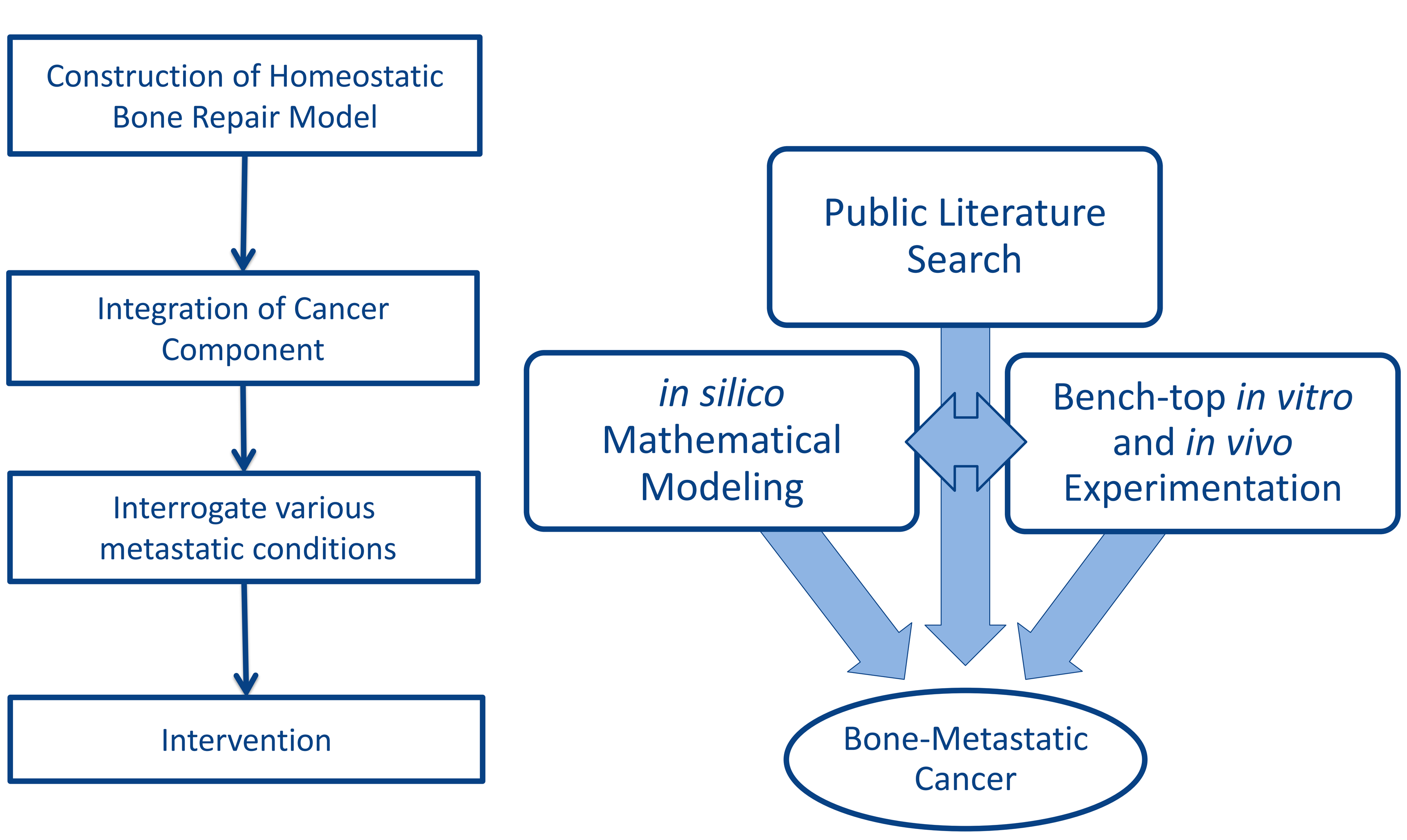


2. Vignette: Macrophages in Bone Remodeling/Repair



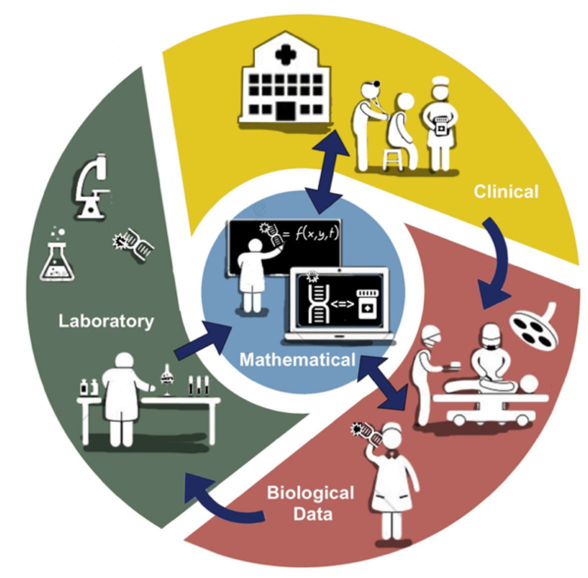
A. Macrophage behavior in bone remodeling (Raggatt et al. 25285719, Schindeler et al. 18692584 Horwood 26498771). Arrows indicate **differentiation process** or **agonistic interaction**. **B**. Temporally-regulated polarized pro- and anti-inflammatory macrophages emerge to trigger clearance and repair responses bye osteoblasts and osteoclasts to restore the bone microenvironment.

3. Integrating Bench Top Experiments and Math Modeling



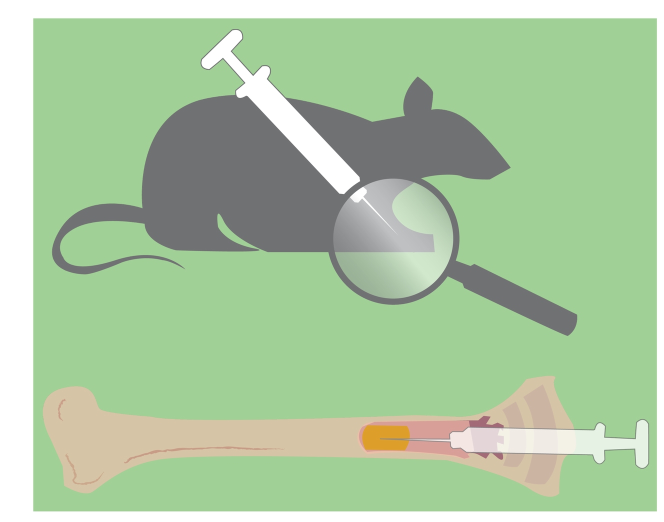
Math modeling facilitates the simultaneous observation of multiple cell populations and their interactions over time within a complex microenvironmental system. Math models powered by empirical and published parameters allow researchers to identify key components within networks of interactions, and make *in silico* predictions that can be validated biologically. **A**. The math model was initially parameterized to reflect cellular interactions underlying normal bone healing processes prior to the integration of metastatic prostate cancer cells. **B**. Building *in silico* models require a blend of empirical and published data to appropriately parameterize the model.

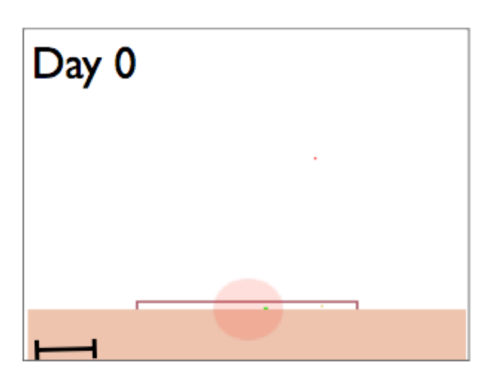
4. Combining multidisciplinary expertise

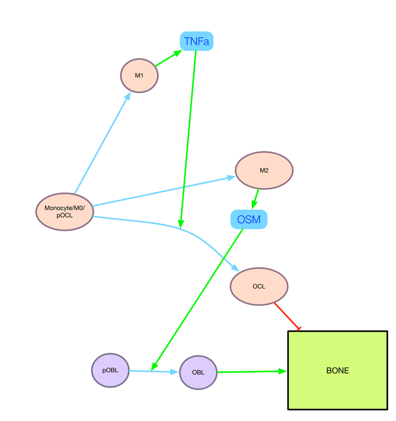


By integrating modeling expertise at different levels (agent-based, ODE, etc) as well as experimental models and clinical data and expertise we ensure that all aspects of our approach are thoroughly discussed.

Key *in vivo* experiments are performed with the mathematical model in mind. Experimental data at one scale either parameterizes the mathematical model or provides support for the emergent outputs and hypothesis generated by the equations. This way, key mathematical assumptions are grounded in experimental generated specifically for the project.







$$\begin{pmatrix} & OB & OC & T & T_R \\ OB & & \alpha & \delta & \delta \\ OC & \beta & & & \\ T & & \gamma & \epsilon & \epsilon \\ T_R & & \gamma - r & \epsilon & \epsilon \end{pmatrix}$$

Our group has developed expertise in a variety of mathematical and computational approaches. As a consequence, many of the insights and assumptions governing our description of bone remodeling, injury repair and homeostasis have been tested using spatial and non spatial models, agent-based and ODE models as well as game theoretical ones. The degree of agreement between the outputs generated by all these models allow us to trust tht the fundamental biology is recapitulated.

5. Multiprogram credibility

IMAG

As part of Moffitt's Integrated Mathematical Oncology department. The PIs and investigators of this of this grant have access to Moffitt-based researchers and expertise in initiatives that are synergistic with IMAG MSM such as the NCI's CSBC and PSON. Seminars, retreats and departmental meetings allow us to get feedback with regards to our MSM-funded research.

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8. Conclusions and Future Directions

- Model credibility can be ensured by the combination of multidisciplinarity and multi-modeling expertise.
- Access to expertise from synergistic programs allow us to obtain feedback that has been used to increase the credibility of our modeling approaches.
- Future work includes inviting IMAG members to check code and experimental data.

OK to share

8. Acknowledgments

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