Model credibility plan

The PIs of this proposal are building on their experience developing mechanistic predictive models of prostate cancer to bone metastases that integrate a variety of experimental and clinical data obtained at different scales. Our aim is to continue on this line of work and thus have a computational framework that can bridge the gap between basic sciences and the clinic. With that aim in mind, we are building credibility into our project through a number of approaches:

1. Mechanistic modeling. We will be building on known and documented mechanisms describing bone homeostasis. The model already recapitulates key aspects of bone remodeling and we will test those results with every new molecular or cellular element added to the model.
2. Robust model parameterization. We have used and continue to use existing literature to parameterize the different elements that constitute the Basic Multicellular Unit (BMU) that maintains bone homeostasis. We are using both existing data as well as our own in order to characterize the prostate cancer phenotypes that are then seeded into the model. We will be using both cell lines (for consistency) and patient-derive cancer cells (for realism).
3. Stability analysis. While most parameters of the model have been abundantly documented in literature, some of them remain obscure. A stability analysis centered on those parameters will allow us to assess whether model-derived hypotheses are sensitive to the parameterization employed.
4. Validation of the model (*in vivo*). As we have done before, the most promising and reliable model predictions can be tested *in vivo* once a clear observable has been identified. In the past we have used metrics like tumor size with or without treatment as well as pathological bone to compare the rich dynamics that the model can yield with *in vivo* features that could be experimentally measured.
5. Validation of the model (clinical retrospective data). The PIs of this proposal as well as the clinical co-investigators have been participating in a Moffitt-funded project to gather biosamples from prostate cancer patients with bone metastases. We will be able to use that data to further validate how treatments impact a heterogeneous metastasis.

The order in which these approaches are listed provides a time line in which they will be applied with 1) and 2) being applied from the start. 3) will be applied only after the model has been sufficiently enriched after the first two years of the proposal. 4) will be used in years 3 and 4 and 5) in the last year of the project. While 5) requires patient data that will need to remain at Moffitt, steps 1-4 can easily be made accessible to a 3rd party from the MSM consortium.