Moffitt PSOC Title: Cheating dynamics in prostate cancer

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Project Description: When prostate cancer initially presents as a clinical tumor, the vast majority of cancer cells are dependent upon exogenous androgen (testosterone) for survival and growth. As a result, androgen deprivation therapy (ADT) is initially very effective in reducing tumor size. However, after 1 to 2 years nearly all prostate cancers become resistant to therapy and the men progress to a metastatic Castrate-Resistant Prostate Cancer stage. A common mechanism of resistance to ADT is increased expression of CYP17A1, a key enzyme for androgen synthesis. This generates an autocrine loop that replenishes intratumoral testosterone concentrations. Abiraterone acetate, a CYP17A1 inhibitor, reduces PSA, and improves overall survival. In subjects who initially respond to abiraterone, median time to PSA progression ranges from 5.8 to 11.1 months.

The Moffitt PSOC has developed an evolution-informed method (adaptive therapy) of administering abiraterone that greatly increases the time to progression and permits reduced dosing. In developing the mathematical models for therapy, we see an unexpected evolutionary dynamic – termed "cheating." CYP17A1 expressing cells produce testosterone (TP cells) that leaks into the tumor intercellular space. As a result, it becomes a "public good" that can support the testosterone dependent (T+) cells despite the absence of systemic testosterone. The T+ cells, in this context, are evolutionary "cheaters" that use testosterone but do not incur the cost of producing it. Our current clinical trial shows evidence for cheating in histological sections and in the response to therapy that is often more rapid than expected for just treatment of the TP cells. In this project, we will apply the evolutionary models of cheating dynamics to the ecology of metastatic castrate resistant prostate cancers and explore its potential role in sensitivity and resistance to abiraterone. This will integrate game-theoretic concepts of producer-scrounger games with tumor heterogeneity and possible therapeutic strategies with broad applicability to this and other tumor cell-cell interactions.

Relevant literature:

- Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer. Zhang J, Cunningham JJ, Brown JS, Gatenby RA. Nat Commun. 2017 Nov 28;8(1):1816. doi: 10.1038/s41467-017-01968-5. PMID: 29180633
- Spatial vs. non-spatial eco-evolutionary dynamics in a tumor growth model. You L, Brown JS, Thuijsman F, Cunningham JJ, Gatenby RA, Zhang J, Staňková K. J Theor Biol. 2017 Dec 21;435:78-97. doi: 10.1016/j.jtbi.2017.08.022. Epub 2017 Sep 21. PMID: 28870617
- Evolutionary dynamics in cancer therapy. Cunningham JJ, Gatenby RA, Brown JS. Mol Pharm. 2011 Dec 5;8(6):2094-100. doi: 10.1021/mp2002279. Epub 2011 Aug 23. PMID: 21815657
- Cancer treatment as a game: integrating evolutionary game theory into the optimal control of chemotherapy. Orlando PA, Gatenby RA, Brown JS. Phys Biol. 2012 Dec;9(6):065007. doi: 10.1088/1478-3975/9/6/065007. Epub 2012 Nov 29. PMID: 23197192