**Systematically understanding immunity leading to CRPC progression**

Zhiwei Ji1, Weiling Zhao1, Hui-Kuan Lin2, Xiaobo Zhou1,\*

1Center for Bioinformatics & Systems Biology, Department of Radiology, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA.

2Prostate Cancer Center of Excellence, Department of Cancer Biology, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA.

Presenter: Zhiwei Ji

Grant No. 4 U01 CA166886 05

It is well known that prostate cancer (PC) growth is dependent on androgens. Androgen blockade therapy (ABT) now has become a standard strategy for treating prostate cancer. Most patients initially respond well to ABT leading to disease regression. Unfortunately, PC will ultimately become unresponsive and recur within 3 years after ABT as a castration-resistant prostate cancer (CRPC). Extensive clinical experience has demonstrated that AR (androgen receptor) signaling reactivation is an important reason for PC developing to CRPC after ABT. Recent clinical studies suggested TAM (tumor-associated macrophages) exert a negative impact on treatment response. TAMs expressed elevated levels of the *PD-L1*, *IL10*, and *EGF*, which can promote treatment resistance by enhancing immune suppression and tumor proliferation, respectively. Our experiments show that CTL-derived *IL2* induced Treg differentiation and the expression of *WNT5A* by Tregs, which also potentially results in resistance to ABT. Hence, we hypothesized that combing ABT with inhibition of TAM and Treg expansion will potentially improve the efficacy and durability of ABT for prostate cancer. Therefore, we proposed a 3D **H**ybrid **M**ulti-scale **A**gent-based **M**odel of **C**RPC (HMAMC) which includes immune cell components and prostate cancer cells and predicted the effects of combined treatment. The HMAMC combines an ODE system and Agent-based model. The ODEs was used for modeling the dynamic changes of intracellular signaling transductions and ABM for modeling cell-cell interactions between prostate tumor cell (PC) and immune components (TAM, CTL, and Treg). Our predicted results show that *blockade of TAMs* and *prevention of Tregs* or *blockade of PD-1 along with castration* can be effective in preventing tumor recurrence after ABT. The proposed model may serve as a novel computational platform for understanding the immunity leading to CRPC progression and provides a potential therapeutic strategy in effectively improving the therapeutic response of ABT for prostate cancer.