KEYNOTE TALK

Tuesday, October 15, 2019 at 1:30pm
(Emerald Bay 123)

Converting Cancer Revelations into Effective Treatments with the Aid of Multiscale Modeling

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Abstract: Increased understanding of the molecular drivers of tumor initiation and progression has led to targeted manipulation of intracellular signaling pathways for patient-specific therapeutic benefit. In this talk, we outline a multiscale modeling strategy for linking intracellular signaling pathways critical to cell proliferation and apoptosis; receptor-ligand binding on the cell surface that triggers these intracellular signaling cascades; and population-level tumor growth dynamics and response to treatments targeting these pathways. Integration of these tiers of information is precisely the level of detail required to uncover possible hidden mechanisms that mediate both expected and potentially counterintuitive therapeutic effects of novel, targeted therapeutics on the multiple cell types responsible for tumor progression. We demonstrate the predictive therapeutic power of our multiscale computational approach with two specific examples. The first considers treatments targeting VEGF and its receptors. In this case, it is difficult to tease out the differential anti-angiogenic and anti-tumor effects of drug combinations experimentally due to the dynamic crosstalk between tumor cells and vascular endothelial cells, which impacts critical aspects of tumorigenesis, independent of angiogenesis. Our model predicts that certain therapeutic combinations result in antagonism in vivo, but not in vitro. In the second example, our computational approach is used to study the therapeutic impact of Tocilizumab, a competitive IL-6R inhibitor, on tumor growth and cancer stem cell fraction, alone and in combination with the traditional chemotherapeutic agent, Cisplatin. Targeting critical regulators of the cancer stem cell phenotype to overcome their acute influence on tumor growth is a promising new strategy for cancer treatment. Our results suggest that nonintuitive dose scheduling strategies will optimize the synergy of combination therapy. Both examples show that this predictive modeling framework can serve to evaluate strategies for signaling pathway modulation rapidly and can provide a basis for proposing optimized dose scheduling for combination treatments involving targeted therapeutics.

Speaker Bio-Sketch: Trachette L. Jackson earned her Ph.D. in Applied Mathematics from the University of Washington. She conducted postdoctoral research at the Institute for Mathematics and its Applications (IMA) and Duke University and is currently a Professor of Mathematics at the University of Michigan. Dr. Jackson specializes in Computational Cancer Research or Mathematical Oncology. Motivated by addressing critical challenges associated with cancer therapeutics, developing multiscale mathematical models is the aim of much of Dr. Jackson's research. These models are designed to optimize the use of anticancer agents that specifically target active molecular pathways that cancer cells use to promote their growth and survival. Dr. Jackson is an award-winning educator and scholar who has received honors for

her accomplishments in both areas. In 2003, she became the second African American woman to receive the prestigious Alfred P. Sloan Research Award in Mathematics; in 2005 she received the James S. McDonnell 21st Century Scientist Award; in 2008 Diverse Magazine honored her as one of the year's Emerging Scholars. In 2010 she received the Blackwell-Tapia Prize, which biannually recognizes a mathematician for both their research achievements and for their contributions to addressing diversity in mathematics. Dr. Jackson has built her career on collaborative research and educational activities that cut across traditional disciplinary boundaries and envisions that this type of team science will eventually change the face of cancer research.