JMNMF 2013 RSA Photo & Summary
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Pictured Left to Right Rear: Greg Safko, JMNMF President; Jose R. Conejo-Garcia, MD, PhD, Tumor Microenvironment and Metastasis Program Leader, Director of Graduate Studies; Dario Altieri, Director, The Wistar Institute Cancer Center, EVP & Chief Scientific Officer; Front: Ashani Weeraratna, PhD, Assistant Professor, Molecular and Cellular Oncogenesis Program; Esther Hoffberg, JMNMF Board Member; Aman Kaur, JMNMF RSA Recipient; and, Regina S. Bodnar, RN, JMNMF Chair.

Role of Wnt Receptor Signaling in Resistance to BRAF Inhibitors

Melanoma is the most aggressive form of skin cancer, and metastatic melanoma is largely incurable. Recent discoveries identifying some of the key drivers of melanoma, such as the oncogene BRAF, have led to the development of targeted therapy. However, while these therapies have met with astounding early success, patients often relapse within a few months. Understanding the mechanisms that govern this resistance to BRAF inhibitors is of critical importance.

Our laboratory has identified a signaling pathway, the Wnt signaling pathway, which guides the transition of melanoma cells to a highly invasive state. The proteins that initiate the set of changes leading to the increased invasion of melanoma do so by binding to additional proteins known as receptors, which act as a conduit for messages relayed into the cell. These messages may tell a cell how to grow, when to stop growing, when to die, or when to move. We have recently found that two of these receptors ROR1 and ROR2 play opposing roles in melanoma. If the receptor ROR1 is present on a melanoma cell, this predicts for a less invasive melanoma, while ROR2 predicts for a highly invasive melanoma. Importantly, we are finding that the mechanisms that guide invasion, may also direct therapy resistance. Thus, we find that ROR2, in addition to predicting for a highly invasive melanoma cell, also drives resistance in these same cells.

Our goal in the current proposal is to understand how ROR1 and ROR2 communicate with each other, and to determine whether shifting the balance of ROR2 to ROR1 in the cell will sensitize melanoma cells to therapy. To achieve this, we will build artificial skin in the lab, in which the levels of these receptors are manipulated using genetic approaches. We will then test the ability of the current inhibitors to stall the growth of these tumors, and cause them to regress. We expect that shifting the balance from ROR2 to ROR1 will increase the sensitivity of the melanoma cells to the inhibitors. This work will allow us to explore ways to overcome resistance to the available inhibitors, and may also identify alternate targets for therapy.