

## **2011 JMNMF RSA SUMMARY**

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**Metastatic melanoma is a particularly devastating disease because of the lack of effective therapies.** While some therapies have initially shown great promise, most patients develop resistance over short periods of time. Model systems have suggested that patient resistance to therapies may be overcome by simultaneously targeting several pathways in the cell. The goal of our work is to identify and understand these synergies and exploit them for better therapies. Our collaborators in the UVA Cancer Center have conducted high-throughput drug combination screens on 20 melanoma cell lines and identified several synergistic drug pairs. Our lab is developing several tools to measure cell signaling on the molecular level with high-throughput assays. We plan to use the data from these tools to build data-driven models of the signaling network. Our hypothesis is that these diverse measurements will reveal specific mechanisms of drug synergy and tumor mutation that could not be anticipated by the direct targets of the drug inhibition or mutation.

Towards this end, I am developing a high-throughput assay to profile kinase activity in melanoma lines. A vast amount of information flow in cells is catalyzed by kinases and their regulation is often disrupted in cancer, and many of our current drugs are kinase inhibitors. Over the past 15 years, work toward therapeutic targeting of protein kinases has revealed two challenges: 1) targeted drugs do not usually work when used singly, or do not work for long and 2) oncogenes that appear to perturb the same kinase pathways do not have the same effects when inhibited pharmacologically. Major hurdles to addressing these challenges are our inability to study kinase activity dynamically, at the network level, and under the diverse conditions of genetics, physiology, and microenvironment. Existing kinase-activity assays measure kinase function individually or indirectly. Our design utilizes Luminex technology, where kinase substrates are attached to 5.6 $\mu$ m beads and can be separated and measured by fluorescence. Our generalizable assay format allows panels of six kinases to be measured simultaneously from one sample at high sensitivity. This assay design allows us to track network activation patterns in situations where sample amounts are limited, such as high-throughput screens and clinical biopsies. We will use our kinase activity assay, in combination with other assays developed in our lab, to interrogate network activation patterns in melanoma cell lines treated with synergistic drug pairs identified by our drug screens. This data will help us to understand drug synergies and resistance to identify more effective therapies for melanoma patients.