Dr. Kevin Kalinsky

Abstract:
The goal of this project is to determine whether the combination of metformin plus atorvastatin has significant anti-proliferative activity in patients with operable breast cancer. Breast cancer cells require energy homeostasis shifts with enhanced anabolism to enable rapid growth and continued proliferation. The main energy regulatory system in eukaryotes and breast cancer cells is the AMP-activated kinase (AMPK) pathway. AMPK is triggered by changes in the AMP/ATP ratio, thus impacting energy reserves and requirements. AMPK pathway closely interacts with the PI3K/AKT signaling pathway, affecting downstream function of the master regulator mTOR. In cell lines, dual therapy with both metformin (i.e. an AMPK activator) and with statins alone (i.e. HMG CoA reductase inhibitors) has demonstrated synergistic activity, with the anticipation that combination therapy may have a greater anti-cancer impact than single agent treatments. Pre-surgical "window of opportunity" studies with single agent metformin have demonstrated mixed results, while pre-surgical studies with statins reporting a reduction of proliferation and increase in apoptosis in women with early stage operable breast cancer. Utilizing a pre-surgical model, we plan to conduct a pilot study of 40 women with newly diagnosed invasive breast cancer will receive oral metformin and atorvastatin daily for at least two weeks, in the interval between diagnostic breast biopsy and definitive breast surgery. In this pre-surgical trial, patients will receive metformin (1500mg per day: divided 500mg in the morning and 1000mg in the evening) and atorvastatin 80mg once a day at bedtime. Specific Aim #1 is to assess whether pre-surgical treatment with the combination metformin and atorvastatin for at least 2 weeks will alter tumor proliferation, as measured by decrease in the natural log expression of ki-67 of breast tumor cells, in patients with newly diagnosed breast cancer. Specific Aim #2 is to evaluate changes in AMPK/mTOR and insulin growth factor pathways signaling and in apoptosis by reverse phase protein microarray (RPPA) as well as in blood-based biomarkers. The results of this trial will be directly compared to a recently completed pre-surgical trial of single-agent metformin at our institution, serving as a control. We hypothesize that treatment with metformin in combination with a statin will have a greater reduction in cellular proliferation as manifested by ki-67 expression. . We also anticipate modulation of the AMPK/mTOR pathway, increase in apoptosis, and reduction in IGF pathway markers. Results from this pre-surgical trial will aid in the development of future clinical trials utilizing metformin and statin in the treatment of women with breast cancer.