Preclinical evidence suggests stress accelerates breast cancer progression via sympathetic nervous system (SNS)/β-adrenergic receptor (β-AR) signaling. These studies have linked this stress/SNS/β-AR signaling axis to several tumor-promoting pathways, suggesting a pleiotropic central mediator may govern stress/cancer interactions. In recent years, exosomes, nanometer scale extracellular vesicles containing tunable protein cargo, have been mechanistically linked to cancer pathogenesis. As such, we hypothesized that stress would regulate tumor progression in association with modified exosome content. To model human disease progression, we employed MMTV-PyMT mice, a spontaneous model of hormone receptor-positive metastatic breast cancer. Stressed mice were exposed to a novel stressor combining chronic social isolation throughout malignant transformation overlaid with acute restraint. Non-stressed controls consisted of mice that remained group-housed throughout the experimental period with no exposure to restraint.

Overall, key findings of this thesis are: 1) the presence of mammary tumors dysregulates SNS outflow, 2) β-AR signaling restrains tumor progression, a novel breast cancer inhibitory mechanism that runs counter to the prevailing view that SNS activation promotes cancer progression, and 3) exosomes represent novel intermediaries for stress-induced alterations in tumor progression. These findings demonstrate the presence of novel bidirectional interactions between the SNS and tumors, provide proof-of-concept for the use of exosomes as biomarkers in the study of stress/cancer interactions, and implies that therapeutic outcomes can be optimized by exploiting nervous system regulation of cancer in a patient-specific manner.