Abstract: "*Dietary- and Fasting-based Interventions as Novel Approaches to Improve the Efficacy of Cancer Treatment*"

Short-term starvation (STS or fasting) protects normal cells, mice and potentially humans from the harmful side-effects of chemotherapeutic drugs. In this dissertation I demonstrate that fasting-like cell culture conditions reduce cancer cell survival and sensitize human and murine cancer cell lines to chemotherapy. *In vivo*, cycles of STS were as effective as chemotherapeutics in delaying the progression of specific tumors and increased the effectiveness of these drugs and radiotherapy against melanoma, glioma, and breast cancer cells. In mouse models of neuroblastoma, STS cycles in combination with chemotherapy, but not either treatment alone, resulted in long-term cancer-free survival. In 4T1 breast cancer cells, STS led to increased phosphorylation of the stress-sensitizing AKT and S6 kinases, increased oxidative stress, caspase-3 activation, DNA damage, apoptosis, and reduced expression of the stress resistance transcription factor NFkB; all changes were not observed in normal tissues. Several of these effects are linked to the activity of the stress-responsive enzyme heme oxygenase-1, whose modulation was central in regulating chemotherapy-dependent cell death in breast cancer cells. These studies suggest that multiple cycles of STS promote differential stress sensitization in a wide range of tumors and could potentially replace or augment the efficacy of some toxic chemotherapy drugs in the treatment of various cancers.

In addition, we evaluated the contribution of calorie restricted (CR) diets and defined macronutrient (carbohydrate, protein, fat) ratios for their effects on stress sensitization markers and protection in mice treated with high-dose chemotherapy. Short-term 50% CR, combined with either severe protein-deficient or ketogenic diets, improved chemotoxicity resistance similarly to the standard 50% CR, but did not result in the high protection caused by STS. Notably, a high protein diet reversed the beneficial effects of short-term CR. In a subcutaneous mouse model of glioma, feeding a low protein (4% calories from protein *vs.* 18% in the control) diet for more than 20 days did not delay tumor progression once the tumor became palpable. Also, cycles of short-term (3 days) 50% CR did not augment the chemotherapy efficacy of cisplatin in a murine breast cancer model. These results indicate that the protection from chemotoxicity and retardation of tumor progression achieved with fasting could not be obtained with short-term calorie and/or macronutrient restriction.