THE EFFECTS OF THE SELECTIVE ESTROGEN RECEPTOR MODULATORS MPP AND RALOXIFENE IN NORMAL AND CANCEROUS HUMAN AND MURINE UTERINE TISSUE

Angela Marie Davis

Dr. Cheryl S. Rosenfeld and Dr. R. Michael Roberts, Thesis Co-Supervisors

ABSTRACT

The goal of this research was to determine the *in vitro* and *in vivo* effects of the Selective Estrogen Receptor Modulators (SERMs), methyl-piperidino-pyrazole (MPP), raloxifene, ICI 182,780 and 17β-estradiol on endometrial carcinoma cells in culture and on murine uterine tissue. These SERMs have been developed to target and understand the role of estrogen receptor action in estrogen-responsive organs. Based on their antagonistic actions, SERMs have both real and potential value in treating estrogen-responsive cancers, including endometrial cancer. The studies described herein verify that the SERMs MPP and raloxifene demonstrate partial agonistic effects in ovariectomized wild-type and ER-β knockout (ERβKO) mice but also induce apoptosis and proliferation *in vitro* in cultured endometrial cell lines, Ishikawa and RL-95. Thus, MPP and raloxifene exert apparently contrasting *in vitro* and *in vivo* effects due to their mixed agonist/antagonist action on murine uterine estrogen receptor *in vivo*. In addition to these data, I report gene expression changes in the uterus of mice treated individually or with the combination of 17β-estradiol and the SERMs, MPP, raloxifene, ICI 182,780 are reported herein. A greater number of genes showed up- or down regulation when the

mice were co-treated with estrogen and one of the SERMs than when dosed with one of the compounds alone. A combination of a SERM and 17β-estradiol resulted in a combinatorial or synergistic effect. These data may be explained by the fact that dual administration of a SERM with β-estradiol allows the compounds to bind combinatorially to heterodimers as well as homdimers of the two receptors ERα and ERβ. These studies provide a framework of how 17β-estradiol and various SERMs act in the uterus and might result in future therapies for gynecological maladies, including endometrial cancer.