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Our research focuses on two main projects: (1) breast cancer and (2) gynecological malignancies. The common thread between these two projects is the role of hormones and growth factors in malignant initiation and progression.

Epidemiological evidence implicate the steroid hormone estrogen in the pathogenesis of breast cancer. Published evidence, including ours, suggest that estrogen production in breast tissue, and not only ovarian-produced estrogen, plays an important role in breast carcinogenesis. Our initial studies suggest that estrogen produced in the breast alters the expression of growth factors implicated in carcinogenesis such as the epidermal growth factor (EGF) and transforming growth factor beta (TGF β). Additional alterations include genes involved in apoptosis (i.e., programmed cell death) and angiogenesis (i.e., formation of new blood vessels), two very relevant processes in carcinogenesis. We have also shown



by using animal models of breast cancer that estrogen may be protective against growth factor driven breast cancer. Published evidence suggest that the timing of estrogen exposure during the life cycle may have opposing effects on the risk of breast cancer development. We are currently, examining the hypothesis that alterations in estrogenic exposure during puberty may affect breast cancer development later in life. Because food we consume contain nutrients and compounds (due to food processing or pesticide contamination) that may have estrogenic properties or inhibit

estrogen production, part of our focus is to examine how these factors may affect estrogen availability during puberty and consequently influence breast cancer risk.

Our interest in gynecological malignancies focuses on cervical and endometrial cancers, both of which are sensitive to estrogenic stimulation. We are focusing on the role of TGF β in these malignancies. We have shown that TGF β stimulates the expression of the macrophage colony stimulating factor (m-CSF) receptor and the platelet derived growth factor receptor, suggesting that TGF β enhances cellular signaling associated with these factors, which have been implicated in disease progression in cervical and endometrial cancers. Molecular analysis of the promoter regions of the m-CSF receptor, encoded by the *c-fms* gene, suggested that TGF β induces the macrophage specific promoter, one of two promoters driving the expression of *c-fms*. The TGF β receptor 1 and the mitogen activated protein kinase p38, a downstream signaling molecule of TGF β , may mediate this induction. TGF β also induced invasiveness of primary endometrial cells, a process important to malignant progression and metastasis. We are currently addressing whether drugs that antagonize specific aspects of TGF β signaling are effective in the treatment of cervical and endometrial cancers. This is supported by our preliminary data showing that antagonists of TGF β receptor 1 and p38 inhibit *c-fms* induction and TGF β -induced invasion.

