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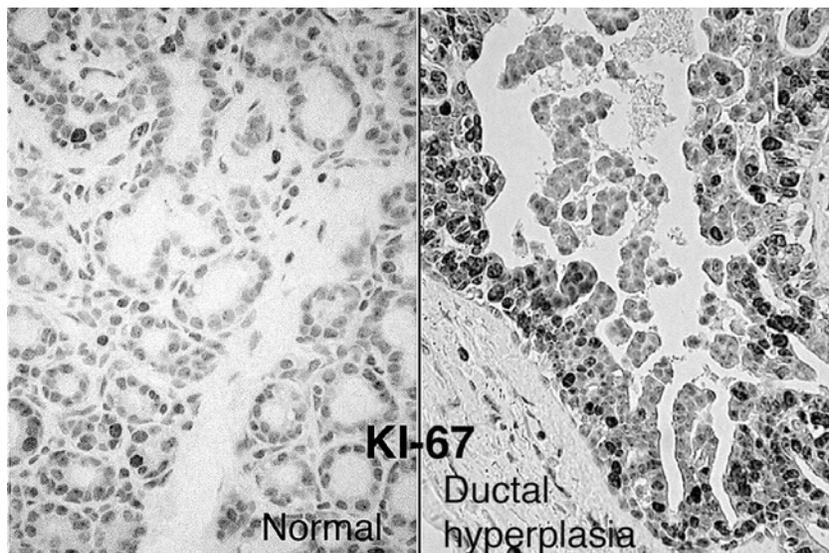
Associate Professor

Pathology/Comparative Medicine

My work focuses on the effects of hormones and hormonal modulators on the development of cancer of the breast and cancers of the female and male reproductive systems. Much of this work is performed using a non-human primate model, in collaboration with other investigators in the Section on Comparative Medicine. Treatments evaluated for their effects on cancer risk include estrogens, progestins, androgens, and selective estrogen response modifiers (SERMs) such as the drug raloxifene. Endpoints evaluated in my laboratory include histology, histomorphometry, cell proliferation, expression of sex steroid receptors (ER, PR, AR), p53, and GST; through collaboration with Dr. Tom Register (Comparative Medicine), we also assess ER beta and telomerase expression. Some of the most exciting results to come out of this work relate to the effects of soy phytoestrogens on cancer risk in animal models. It appears that consumption of a soy diet prevents estrogen-induced proliferation in the breast and uterus of monkeys. Complementary studies using rodent models have shown that this anti-estrogenic effect is dependent on both the dose of soy phytoestrogens and on the presence of other estrogens. Further work on estrogen-phytoestrogen interactions is the subject of my current primary grant support from the NIH Center for Complementary and Alternative Medicine.

Other cancer-related projects include:

1. Collaboration with Drs. Thomas Clarkson, Jay Kaplan, and Michael Adams on a large program project grant to evaluate the long-term health effects of dietary and pharmaceutical effects of soy phytoestrogens on the breast, uterus, and prostate of monkeys.
2. A molecular study of the cancer-preventive effects of progestin-containing oral contraceptives on the human and monkey ovary and endometrium, in collaboration with investigators at the National Cancer Institute, Duke University, and the University of Chicago.
3. Ongoing collaborations with colleagues at the Karolinska Institute in Stockholm regarding regulation of the breast by hormonal therapies.
4. Evaluation of the cancer-promoting effects of moderate alcohol consumption in the breast and uterus of monkeys, in collaboration with Dr. Carol Shively (Comparative Medicine).
5. Evaluation of prostatic changes induced by dietary soy supplementation in men at high risk of prostate cancer, in collaboration with Drs. Electra Paskett and Robert Lee.
6. Provision of histopathology and immunohistochemistry support for various investigators using



Immunohistochemical stain for the proliferation marker Ki67 in monkey breast tissue.

rodent tumor models, most recently Drs. Mark Miller and Suzy Torti (Cancer Biology), and Dr. Kenneth Wheeler (Radiology).

7. Operation of a primate resource to facilitate cancer-related work in primates; this effort has benefited several investigators in the Cancer Center (i.e., preclinical testing of a novel anti-leukemic fusion toxin developed by Dr. Arthur Frankel, Hematology-Oncology). The latest project in this effort is the development of a tissue bank from primates chronically consuming different dietary fats (monounsaturated, polyunsaturated, and saturated).

Publications

Cline JM, Soderqvist G, Skoog L, von Schoultz B. Effects of conjugated estrogens, edroxyprogesterone acetate, and tamoxifen on the mammary glands of macaques. *Breast Cancer Research and Treatment* 8:221-229; 1998.

Cline JM, Hughes CL. Phytochemicals for the prevention of breast and endometrial cancer. In: Muss H, Foon K, eds. *Biological and Hormonal Therapies of Cancer*. Kluwer: Boston; 1998.

Gressani KM, Rollins LA, Leone-Kabler S, Cline JM, Miller MS. Induction of mutations in Ki-ras and INK4a in liver tumors of mice exposed in utero to 3-methylcholanthrene. *Carcinogenesis* 6:1045-52; 1998.

Obasanjo I, Cline JM, Schmotzer S, Weaver DS. Nandrolone decanoate causes pathologic changes in the uterus of surgically postmenopausal female cynomolgus macaques. *Menopause* 5:163-168; 1998.

Foth D, Cline JM. Effects of mammalian and plant estrogens on mammary glands and uteri of macaques. *Am J Clin Nutr* 68(suppl):1413S-7; 1998.

Rodriguez SGC, Walmer D, Lessey B, Cline M, Krigman H, Hughes CL. The effect of contraceptive progestins on the ovarian epithelium: cancer prevention through apoptosis. *Journal of the Society for Gynecologic Investigation* 5:271-276; 1998.

Hotchkiss CE, Hall, PD, Cline JM, Willingham MC, Kreitman RJ, Gardin J, Latimer A, Ramage J, Feely T, DeLatte S, Tagge EP, and AE Frankel. Toxicology and pharmacokinetics of DTGM, a fusion toxin consisting of a truncated diphtheria toxin (DT388) linked to human granulocyte-macrophage colony-stimulating factor, in cynomolgus monkeys. *Toxicology and Applied Pharmacology* 158:152-60; 1999.

Isaksson E, Cline JM, Skoog L, Söderqvist G, Wilking N, von Schoultz E, von Schoultz B. p53 expression in breast and endometrium during estrogen and tamoxifen treatment of surgically postmenopausal cynomolgus monkeys. *Breast Cancer Res Treat* 53:61-67; 1999.

Anderson JJB, Anthony MS, Cline JM, Washburn SA, Garner SA. Health potential of soy isoflavones for postmenopausal women. *Public Health Nutrition* 1:489-504; 1999.

Foth D, Cline JM, Romer T. Effect of isoflavones on mammary gland and endometrium of postmenopausal macaques (*Macaca fascicularis*) [German] *Zentralblatt fur Gynakologie* 122(2): 96-102; 2000.

Wheeler KT, Wang LM, Wallen CA, Childers SR, Cline JM, Keng PC, Mach RH. Sigma-2 receptors as a biomarker of proliferation in solid tumors. *Brit J Cancer* 82:1223-1232; 2000.

Cline JM, Gunnar Söderqvist, Thomas C. Register, J. Koudy Williams, Michael A. Adams, Bo Von Schoultz. Assessment of hormonally-active agents in the reproductive tract of female nonhuman primates. *Toxicologic Pathology* 29:84-90; 2001

Wagner JD, Anthony MA, Cline JM. Soy Phytoestrogens: Research on benefits and risks. *Clinical Obstetrics and Gynecology* 44:843-852; 2001