

Current Types of Activities and Services

The Stiles Program in Integrative Oncology is primarily oriented toward advancement of the science of integrative medicine through laboratory research and development of clinical trials to assess the antitumor efficacy and safety of treatment modalities. Further, advancement of the field of integrative medicine through training and education is another important aim of the Program.

Education

More than 80% of Americans with cancer use some form of complementary medical therapy. Overall, US healthcare consumers spend more than \$30 billion each year on complementary and alternative medical treatments. This high interest in unconventional therapies led the US Congress to establish the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health in 1992. In order to facilitate scientific research and public education in this area in Southern California, the Program in Integrative Oncology was established at UCLA.



The Stiles Program provides education and information on the efficacy and safety of complementary medicine to patients, physicians and medical students in the community. Resources from the Stiles Program, NCCAM and other international programs and institutions are provided to patients and to doctors. This website, "Cancer Alternatives" (www.canceralternatives@mednet.ucla.edu), helps to disseminate collected data and provide a resource guide. Information on clinical trials for specific interventions and guidelines for cancer prevention are provided. Public lectures for lay

people and healthcare providers (see

http://cancerresources.mednet.ucla.edu/5_info/5i_video/2007/Pietras.htm) also offer up-to-date information and data. In these forums, we try to reverse the "don't ask, don't tell" policy that currently exists in the cancer clinic; wherein physicians "don't ask" what complementary therapies patients may be using, and patients "don't tell" their doctors. This situation can have catastrophic consequences for healthcare due to dangerous drug interactions. Patients are also educated on the importance of determining the purity and efficacy of a given treatment.

A course in "Integrative Cancer Medicine" is offered for advanced medical students to broaden their professional perspectives on available healthcare practices. It is important for doctors to learn, at an early stage in their careers, to treat patients in a more wholistic fashion, rather than as 'machines with broken parts'.

In view of the diverse ethnic groups represented in the greater Los Angeles area, we plan to undertake field and survey investigations on the ethnomedical use of herbs and other alternative anticancer treatments in our community. This information will be very useful for physicians involved in patient care and for drug and treatment discovery.

Clinical-Translational Research

The Stiles Program is directing efforts toward scientific evidence-based evaluation of complementary medicine in the clinic. It is important to probe the clinical efficacy of all proposed patient therapies and to evaluate the benefit or potential harm of healthcare practices. Without good clinical trials, physicians cannot accurately advise patients about complementary treatments. The Stiles Program is directed toward study of :

1) *Effects of complementary therapies on cancer progression*: Clinical research studies focus, for example, on the role of squalamine, a natural substance originally isolated from shark tissues and used in folk medicine as an anticancer agent, on blockade of the formation of new tumor-associated blood vessels (angiogenesis) in cancers, thus leading to specific starvation and death of tumor cells. Synthetic forms of squalamine were developed in the laboratory for clinical use and show significant efficacy in treatment of patients with advanced and treatment-refractory forms of ovarian and lung cancer.

2) *Effects of complementary therapies on pain, quality of life and palliative care in cancer patients* : Research efforts are also devoted to use of mind-body, alternative medical systems, such as traditional Chinese medicine, manipulative and body-based systems for control of debilitating symptoms during or after cancer treatment and for palliative care in patients who have failed conventional therapy; reduction of symptoms that impact the lives of children with cancer; assessment of cognitive deficits associated with adjuvant cancer therapy and investigation of therapies to manage these problems.

3) *Effects of complementary therapies on cancer prevention* : Research studies are assessing the efficacy of vitamins and naturally-occurring phytohormones on cancer incidence or recurrence in patients at high risk for cancer, such as individuals with a history of breast cancer, ductal carcinoma *in situ* of the breast or gene mutations.

4) *Initiate state-of-the-art laboratory-based technologies for selecting new botanicals and natural products targeted for specific cancer therapy or prevention*: Many patients use herbs, vitamins, minerals and antioxidant supplements for cancer remedies. In fact, more than 2/3rds of anticancer drugs in current use were originally derived from natural sources, and new ones, such as paclitaxel (Taxol), are being discovered. Most patients are unaware that botanicals are actually dilute natural drugs containing many different chemicals, a majority of which are undocumented. New approaches for efficient screening and evaluation of such compounds for efficacy and safety are needed.

The Stiles Program has established a new drug discovery effort for selecting novel botanicals and natural products and for development of related congeners targeted for specific cancer therapy. Since it is estimated that less than 5% of all natural product sources on the surface of the Earth and in the oceans have been investigated to date for development of therapeutics, this undertaking will be a major challenge and is urgently needed. These statistics suggest that a wealth of new therapeutics from our environment are simply waiting to be discovered. We are undertaking molecular assessments of biologic agents for human therapy using human tumor microarrays and advanced proteomic technology. Further, we are developing new models for testing drug efficacy and safety for potential human therapy.



Finally, the Stiles Program is part of UCLA's Jonsson Cancer Center, identified by *US News & World Report* as one of the leading comprehensive cancer centers in the US. This affiliation offers access to excellence in many areas of biomedicine and traditional practices, including the Oncology Center, Revlon Breast Cancer Center, the Collaborative Centers for Integrative Medicine (CCIM), Simms/Mann Integrative Oncology Center, Pediatric Pain Center, Center for East-West Medicine and the Molecular Biology Institute. Basic scientists and clinicians from medical, botanical, nursing and public health fields have been invited to join in a true multidisciplinary effort.

Clinical Service

Dr. Pietras provides consultations in the general area of medical oncology and supervises medical students, residents and fellows in rotations on the Hematology-Oncology Consult and Ward Services and in the Medical Oncology Clinic.

Selected Program Accomplishments

Education

1) The internet site, "Cancer Alternatives" (www.canceralternatives.mednet.ucla.edu), provides a resource guide on complementary medical approaches in patients with cancer.

2) Educational information is provided in public lectures for lay people, doctors in training and healthcare workers at UCLA and in the Los Angeles community (see Fig. 1).



Fig. 1. A lecture offered by Dr. Pietras is available for your viewing online as a webcast at http://cancerresources.mednet.ucla.edu/5_info/5i_video/2007/Pietras.htm. In addition, you may view slides from the lecture on this website in the section "Tips & Info". The lecture, "Herbal and Natural Products for Cancer Prevention and Therapy", is available, with information for you about the efficacy and safety of numerous natural products, clinical trials in progress and tips on how to maintain your health and wellness and reduce the risk of cancer in your lifetime.

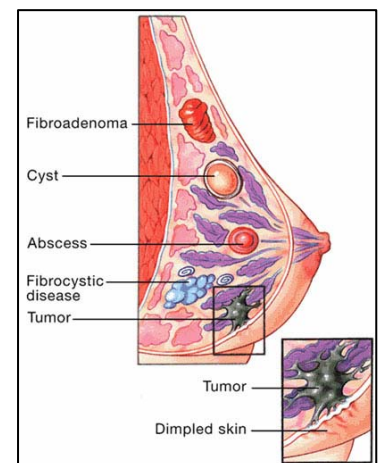
As Director of the Stiles Program, Dr. Pietras has participated in public education programming projects for local and national media services and lectures to community groups under sponsorship of the Jonsson Cancer Center, the Simms/Mann Center, the Wellness Community and the American Cancer Society. Dr. Pietras has also served as an advocate for cancer research on the Contact Congress Committee of the American Association for Cancer Research.

3) The course in "Integrative Cancer Medicine" is offered in the School of Medicine for physicians-in-training to broaden their professional perspectives on available healthcare practices. It is important for doctors to learn, at an early stage in their careers, to treat patients in a more holistic way, rather than as 'machines with broken parts'. It is notable that this course has attracted students from national and international medical schools, including Harvard, Yale, UCSF, UCSD, Stanford, Johns Hopkins, Georgetown, Chicago, Australia, India and Pakistan.

Clinical-Translational Research (Bench-to-Bedside)

▪ The Stiles Program has directed efforts to scientific evidence-based evaluation of complementary and biologic-based medicines. As Director of the Stiles Program, Dr. Pietras is an active co-investigator in several clinical trials, including those assessing effects of biologic therapies, such as monoclonal antibodies targeted to tumor cell proteins or growth factors in patients with advanced breast cancer, the efficacy of kinase inhibitors and hormonal therapies in patients with lung tumors, the potential role of the natural substance, squalamine, in patients with advanced ovarian and lung malignancies, and effects of chemotherapy on endocrine and cognitive function in patients in the clinic.

Fig. 2. Schematic drawing (left) showing varying human breast pathology, including benign conditions, such as a fibroadenoma, cyst, abscess and fibrocystic disease, and malignant conditions, such as the cancerous lesion (tumor) in the lower breast quadrant.



Dr. Pietras also leads a phase II clinical trial assessing antitumor efficacy of a pure antiestrogen (fulvestrant) and Herceptin targeted therapy as a tandem treatment in patients with advanced breast cancers expressing both HER-2 and estrogen receptors (see Fig. 2). This innovative clinical-translational work may yield significant clinical benefit for affected breast cancer patients in the near future.

- Anti-angiogenic steroids, such as squalamine, occur in nature and appear to have significant efficacy in the blockade of tumor blood vessel growth. Studies on the nature of these angiostatic factors and their interaction with angiogenesis signaling pathways, such as the vascular endothelial growth factor (VEGF) cascade, are ongoing (see Fig. 3).

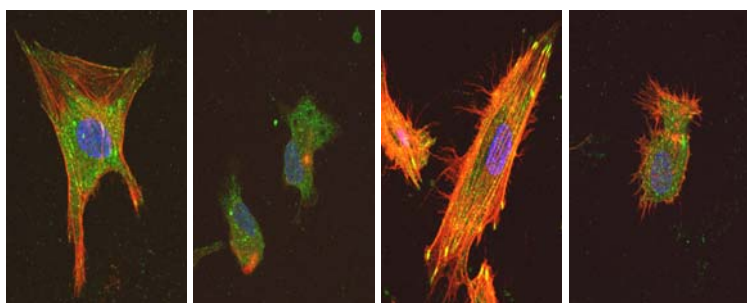


Fig. 3. Squalamine (SQ) blocks the reorganization and growth of tumor-associated vascular cells stimulated by vascular endothelial growth factor (VEGF), thereby starving the tumor mass of vital nutrients and oxygen. This leads to killing of the tumor.

Control SQ VEGF VEGF + SQ

Promising clinical trials of squalamine have been conducted, and as a result of this work the FDA has designated squalamine as an orphan drug candidate for treatment of ovarian cancer. The Congressionally-Directed Ovarian Cancer Research Program selected this work as a “Research Highlight” on their online site and in postings at national meetings.

- New laboratory studies of molecular signaling pathways in tumor cells are providing a convenient, more efficient way to screen natural compounds for antitumor efficacy. For example, in breast cancer, estrogens stimulate activation of mitogen-activated protein kinase (MAPK), a cytoplasmic enzyme that can migrate to the cell nucleus and promote changes in tumor cell DNA leading to cell division and tumor growth. The anticancer activity of medicinal herb extracts from traditional Chinese medicine were evaluated in the laboratory by using cultures of human breast tumor cells. Estrogen-induced activation of MAPK was tested by using immunofluorescent microscopy. Results of these surveys show that extracts of the Chinese herb, *Scutellaria*, block the expected MAPK activation by estrogens (see results in Fig. 4).

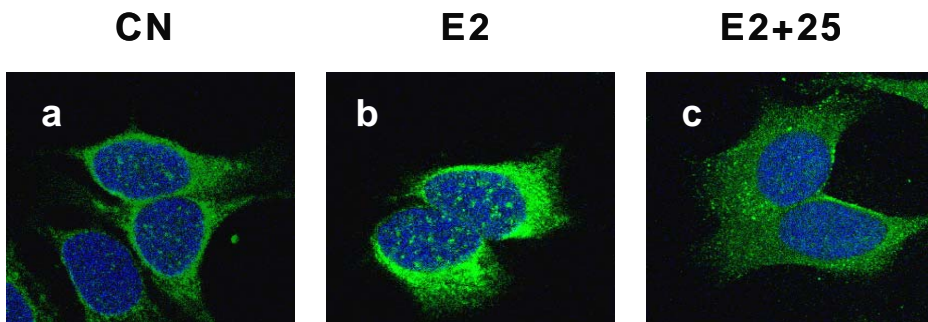
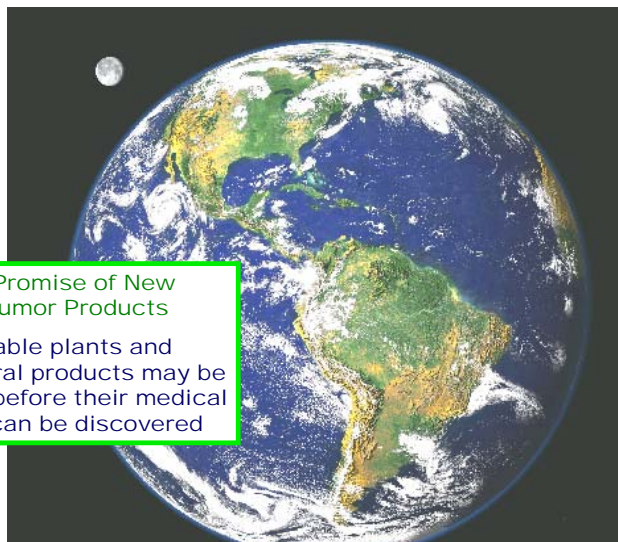


Fig. 4. *Scutellaria* extracts blocks estrogen-induced activation of MAPK in human breast cancer cells. Specific immunofluorescent staining of MAPK (green color) shows little activity and no nuclear localization of MAPK in cells not exposed to estrogen (a, control=CN). In contrast,

estrogen increases MAPK activity and markedly promotes its accumulation in the tumor cell nucleus (see green dots in central nucleus) (b, E2=estrogen). This estrogen-induced effect is blocked by the herbal extract (c, E2+25=estrogen + herbal extract). Hoechst dye was used to color the nuclei blue for improved imaging.

Using confocal microscopy and specific immunofluorescence methods to image MAPK, estrogen treatment stimulates activation and increased nuclear localization of MAPK in human breast cells, and



The Promise of New Antitumor Products
Valuable plants and natural products may be lost before their medical use can be discovered

these estrogen-induced effects are disrupted by crude extracts of *Scutellaria* (Fig. 4). In follow-up studies, it was confirmed that the herbal extract was also a potent inhibitor of tumor cell growth, thus validating the initial screening data. This approach may prove valuable in future investigation and screening of the anticancer effects of many other natural substances. Since it is estimated that less than 5% of all natural products on the surface of the Earth and in the oceans have been investigated to date for development of therapeutics, this undertaking will be a major challenge and is urgently needed. These statistics suggest that a wealth of new antitumor agents from our environment are simply waiting to be discovered. It

is important to undertake this task before we lose any more of these valuable resources from our forests and oceans due to unabated urban development and overpopulation.

- Lung cancer is now the leading cause of mortality from malignancy in both men and women in the US. In fact, more women now die from lung cancer each year than from breast, ovarian and uterine cancers combined (refer to data presented in Fig. 5).

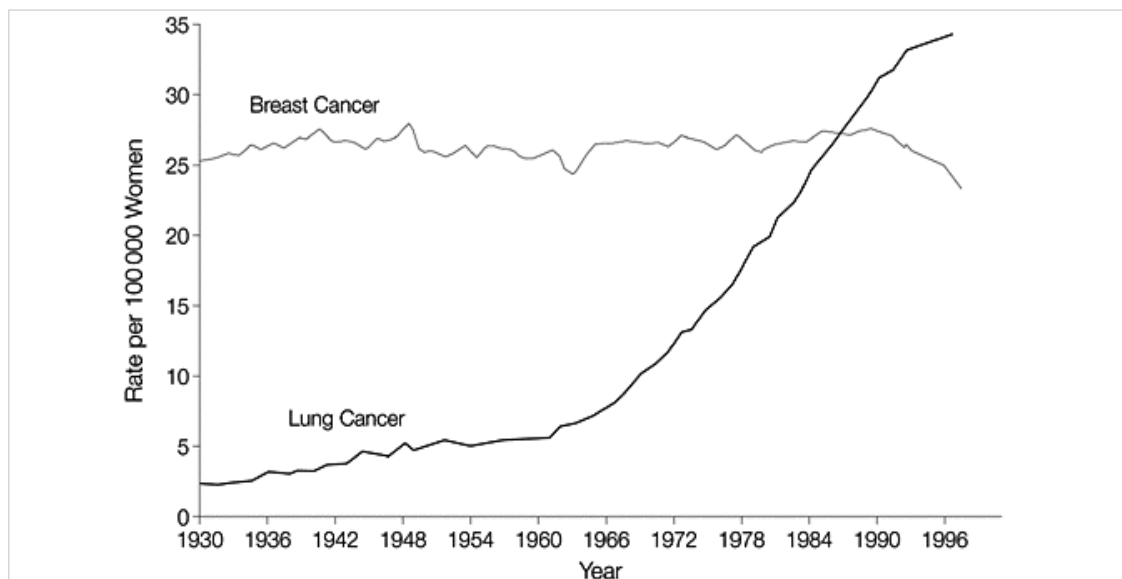


Fig. 5. Age-adjusted death rates for lung cancer and breast cancer among US women from 1930-1997. Data from 2001 Surgeon General's report [Patel et al. (2004)].

New findings from our research group indicate that human non-small cell lung tumors bear estrogen receptors and respond to therapy with antiestrogens. Moreover, aromatase, an enzyme that converts androgens to estrogens in tissues, occurs in lung tumor specimens from the clinic. Laboratory studies suggest that antiestrogens and aromatase inhibitors suppress the progression of lung cancers, and a new clinical trial to assess this hypothesis is underway at UCLA. This research is also supported by the National Cancer Institute Lung Cancer SPORE (Specialized Projects of Research Excellence) Program.

- Alternative models to animal research. The Stiles Program recently participated in a special workshop sponsored by UCLA (January, 2008) to find new methods to replace the use of laboratory animals in experiments, reduce the number of animals tested and refine necessary tests to eliminate pain and distress. Dr. Pietras's research group presented new experimental data suggesting that introduction

of novel molecular and biologic-based assay systems in the laboratory may prove useful in the future replacement of animals in oncology research.

Dr. Pietras has been honored with many invitations to present his findings in platform sessions at national and international meetings, including the American Association for Cancer Research (AACR), the San Antonio Breast Cancer Research Symposium, the Federal Breast Cancer Research Program Meeting, the Susan G. Komen Breast Cancer Meeting, the International Symposium on Translational Research in Oncology, the Breast Cancer Summit held in Switzerland and the International Lung Cancer Congress in Japan. Dr. Pietras is also active in the Federation of American Societies for Experimental Biology (FASEB), and was elected as Chairman for a FASEB Research Conference.

These bench-to-bedside efforts have yielded important new findings that are detailed in selected current literature references that follow:

Pietras R (2006). Biologic basis of sequential and combination therapies for hormone-responsive breast cancer. *Oncologist* 11 : 704.

Levin E, Pietras R (2006). Extranuclear actions of estrogen in breast cancer. In: *Hormone Receptors in Cancer* (S. Fuqua, editor), Springer, New York.

Pio BS, Park CK, Pietras R et al. (2006). Usefulness of 3-deoxy-3-[18F]fluorothymidine with positron emission tomography in predicting breast cancer response to therapy. *Molecular Imaging and Biology* 8: 36.

Sartippour M, Pietras R, Marquez-Garban D, Chen H et al. (2006). The combination of green tea and tamoxifen is effective against breast cancer. *Carcinogenesis* 27: 2424.

Pietras R, Marquez-Garban D (2007). Membrane-associated estrogen receptor signaling pathways in human cancers. *Clin Cancer Res* 13: 4672.

Mah, V, D Seligson, A Li et al. (2007). Aromatase expression predicts survival in women with early stage lung cancer. *Cancer Research* (in press).

Davidson, S, Pietras, R, Chap, L et al. (2008). A Phase IIA trial of continuous 5-day infusions of MSI-1256F (squalamine lactate) plus carboplatin for therapy of persistent or recurrent advanced ovarian cancer. (in preparation).