



IN THIS ISSUE:

The March—Coming Together to Conquer Cancer p. 2

Leaders of CALGB met with representatives from virtually all cancer research constituencies in mid-July at a Summit on Clinical Trials in prelude to this important grass-roots event coming to Washington D.C. this fall. *Report by CALGB Chair Richard L. Schilsky, M.D.*

Summer Group Meeting Reports

An 8-page section devoted to some of the noteworthy presentations at CALGB's Group Meeting, held June 26-28 in Ft. Lauderdale.

Plenary Scientific Symposium Abstracts p. 3

Alternative Medicines and Treatments for Cancer p. 6

Tackling Accrual Problems p. 10

New CALGB-Janssen Clinical Research Award p. 11

The CALGB Foundation requests applications for research grants for novel studies in signal transduction.

Data Management p. 12

The CALGB is tightening its guidelines for data submission to revise definitions for delinquent data. *Report by CALGB Quality Assurance Coordinator Sherry Breaux, M.P.H.*

Cancer Cachexia p. 13

Progressive cachexia is one of the major causes of mortality in advanced cancer patients. Malnourishment and/or metabolic abnormalities resulting from the cancer or its treatment frequently bring about this debilitating condition. *Report by Brenda Werner, R.N., CALGB Research Nurse at the University of Iowa Hospital and Clinics*

New NCI Program Announcements p. 14

Grant programs announced for:

- Cancer Pharmacology and Treatment in Older Patients
- Clinical Correlative Studies Using Specimens from Multi-Institutional Therapeutic Trials

Protocol News

Update on 9270, Colorectal Adenoma Prevention Study p. 16

CALGB 9344 Abstract. The May, 1998 ASCO meeting featured a special press briefing to discuss CALGB 9344, a Breast Committee protocol. Preliminary results show that the addition of Taxol to standard adjuvant chemotherapy regimen of doxorubicin plus cyclophosphamide increases survival rate over 25% in node-positive breast cancer patients. *Full text of abstract p. 17*

Protocol Update: Nine new protocols opened in the last 4 months, 13 studies closed to accrual. p. 18

Innovation and Progress at CALGB Summer Group Meeting in Fort Lauderdale

Several innovative programs and changes debuted at the CALGB Summer Group Meeting in Fort Lauderdale June 26-28, prompting many members to call it one of the best CALGB meetings yet.

Meeting highlights included:

- A special scientific symposium of the Plenary Session was dedicated to emerging therapeutic options in solid tumor therapy. Attendees heard three significant presentations focusing on signal transduction (see reprints of abstracts beginning on page 3).
- In-depth examination of p53 gene was the sole focus of the Solid Tumor Correlative Sciences Committee meeting (more details to come in the Fall *CalGab*).
- Presentations on alternative medicines and treatments for cancer, and ongoing scientific efforts to document their effectiveness, at the CRA/Oncology Nurses CE workshop (see article on page 6).
- The Surgery Committee presented details of its efforts to improve study accrual (see article on page 10).
- New committee chairs were introduced in the Pathology, Lymphoma, Pharmacy, and Thoracic Surgery Committees (Carolyn Compton, Dan Longo, Christine Berard and Malcolm DeCamp, respectively); and the new Melanoma Working Group convened for the first time, with co-chairs Frank Haluska and Alan Houghton.
- First-time ever (or first in a long time) workshops were held on preparing for institutional audits and patient advocate training.
- Attendees were greeted with a new computerized registration desk, and a new look for the Agenda Book. The new binder had index tabs, pockets, and removable sections.

A special section on the CALGB Summer Group Meeting starts on page 3.

Cancer and Leukemia Group B

Central Office of the Chair
208 S. LaSalle St., Suite 2000, Chicago, IL 60604-1104
(773) 702-9171 www-calgb.uchicago.edu

PLEASE Note:

While we make every effort to provide accurate dosing information in the *CalGab*, you should always check the appropriate drug dosages before prescribing and/or administering any medication.

Message from the Group Chair...

As many of you know, *The March—Coming Together To Conquer Cancer* will be held in Washington D.C. on September 25 and 26, 1998. The March is a national grass-roots effort supported by virtually all cancer survivor groups, cancer research organizations and cancer professional societies in the country. The mission of The March is threefold:

- To call on all Americans to make the cure and prevention of cancer the Nation's top research priority;
- To demand greater government investment in the public and private sectors for all cancer research, treatment, education and prevention;
- To ensure access to clinical trials and quality care for everyone.

As a prelude to The March, leading cancer research organizations and professional societies sponsored a Summit on Clinical Trials in mid-July. Stephen George (CALGB Group Statistician) and I had the opportunity to participate in this extraordinary meeting that included representatives from virtually all constituencies involved in the fight against cancer: patients, physicians, investigators, cooperative groups, cancer centers, government agencies, pharmaceutical firms, the insurance industry and others. The Summit was sponsored by the Cancer Leadership Council, the Cancer Research Foundation of America, the Coalition of National Cancer Cooperative Groups, and the Oncology Nursing Society.

The Summit's goal was to spur open and frank discussions of strategies to implement clinical trials in a more efficient, cost-effective, patient-friendly, and less cumbersome way than the current system allows.

The meeting began with presentations on patient participation in clinical trials, the role of the cooperative groups, the current status of the National Cancer Clinical Trials Program and the role of industry in cancer drug development. Breakout sessions, each led by a physician and a patient representative, featured free-wheeling discussions on *tabula rasa*, high quality studies, rapid results, broadest patient base, and accrual issues. The groups reconvened to share insights; and the meeting concluded with a panel discussion and town hall meeting attempting to reach consensus on a quality clinical trials system.

Participants agreed that the National Cancer Clinical Trials Program is grossly under-funded and that a major infusion of resources is necessary to sustain and improve the program. Increased congressional funding is a major objective of The March. At the same time other sources of support should be considered, including the pharmaceutical and health insurance industries.

Second, a clear consensus was reached that patients must be included at every phase in the clinical trials process and that we must make a concerted effort to market more effectively the importance of cancer clinical trials to the American people. There is no doubt that clinical trials will be completed more quickly if patients demand participation in research studies.

Attendees also agreed that all those involved in cancer clinical trials need to come together in a better coordinated effort to develop and complete high quality studies. We have remarkable resources in this country that are not optimally deployed in the fight against cancer. Cooperative groups, physician networks and drug companies all conduct clinical trials, often in competition with each other. Regulatory agencies have imposed barriers to closer cooperation among these groups that must be removed to facilitate collaboration.

The investigator community must take responsibility for developing studies that address truly important questions and for simplifying the clinical trials process by eliminating unnecessary eligibility criteria, testing and data collection.

Finally, all participants recognized that the Summit on Clinical Trials could only begin a dialogue that must continue on a regular basis. The Coalition of National Cooperative Groups will consider sponsoring additional summit meetings in the years ahead. More important, however, is the need to create a national strategic plan for conquering cancer. *The March—Coming Together To Conquer Cancer* is only the beginning, but we hope it is the beginning of the end of cancer. I urge all CALGB members to participate in The March either by traveling to Washington D.C. or by participating in events in your local community.

More information about The March can be obtained by calling 1-877-THE MARCH or by visiting their web site at www.themarch.org. CALGB is committed to the mission of The March and to achieving the goals of the Summit on Clinical Trials. We will continue to do all that we can to contribute to and enhance the National Cancer Clinical Trials Program.

Richard L. Schilsky, M.D.



Richard L. Schilsky, M.D.

SUMMER GROUP MEETING REPORTS

Summer Meeting Recap...

Attendance

There were 617 registrations for this Summer Group Meeting, slightly less than the typical average of over 700, according to CALGB Meetings Manager Helen Pollard.

New Agenda Book Format

The familiar soft-cover CALGB Agenda Book was replaced by a redesigned binder with index tabs and removable sections at this meeting. CALGB goals were to try out a more flexible and accessible format that also represented a significant cost savings.

Attendees surveyed about their preferences afterwards were very positive. Rating the new versus the old format on a 1-to-5 scale, the new format scored 1.16 overall (n=57).

The new Agenda Binders included three removable quick-reference booklets: a Meeting & Agenda information booklet; 1998 CALGB Directory; and a Study Summary booklet.

Based on the positive feedback and cost savings, CALGB will continue the new binder format at future meetings, while incorporating many of the attendees' suggestions for improvement.

There are a limited number of Agenda Binders still available for sale. See the order form on page 19.

Plenary Session brought to you by Janssen

Janssen Pharmaceutica provided an unrestricted educational grant to support the scientific section of the plenary session, and offered extensive assistance with pre-meeting promotion, on-site signage, and plenary session folders and literature. The CALGB-Janssen Clinical Research Award was also announced at the meeting. (see article on page 11)



Recognition for CRAs and Oncology Nurses

The CALGB expressed appreciation to CRAs and Oncology Nurses with 5 or more years of service in the group. At the plenary session, CALGB Chair Richard Schilsky praised their efforts and emphasized their valuable role in CALGB's cancer research. The names of 46 CRAs and 97 Oncology Nurses were printed on a Service Recognition list on the back cover of the CALGB Meeting Agenda Booklet, and those attending the Group Meeting had special service ribbons affixed to their name badges. The Service Recognition list is available on the CALGB Web Site: www-calg.uchicago.edu.

Plenary Abstracts

The theme of the scientific portion of the Plenary Session was "Emerging Therapeutic Options in Solid Tumor Therapy: Focus on Signal Transduction."

Proto-oncogenes, Oncogenes, and Oncoproteins

Neal Rosen, M.D., Ph.D.

Oncogenes are mutated versions of their functionally normal, protooncogenic counterparts. When activated, oncogenes are capable of producing oncoproteins. Overexpression of an oncogene results in the synthesis of oncoproteins that migrate to the nucleus, signaling the cell to grow continuously and converting the cell from a normal to an abnormal state of growth. At least 20 oncogenes have been identified in human tumors. A majority of them produce intracellular signals through activation of phospholipase C, which activates the protein kinases that regulate the cell cycle. Examples of oncogenes are *myc*, *ras*, *HER-2/neu*, and *abl*.

Oncoproteins are proteins that have lost the normal regulatory constraints on cell growth, proliferation, and differentiation and no longer respond appropriately to transduction signals or the usual controls necessary to maintain normal cell growth.

The pivotal role that protein phosphorylation plays in signal transduction is exemplified by the observation that oncoproteins often form protein kinases. Protein kinase activity and phosphorylation-dephosphorylation reactions are involved in signaling pathways and appear to function as receptor sites for a variety of growth factors, including epidermal growth factor, platelet derived growth factor, insulin, and macrophage colony-stimulating factor.

One of the ways researchers probe signal transduction pathways is by studying the protein phosphorylation that follows stimulation by a growth factor. Some oncogenes, such as *v-src*, can phosphorylate many protein substrates. It is theorized that phosphorylated proteins modify the activity of cellular enzymes involved in intracellular signaling within the cell membrane and in the nucleus. For example, studies suggest that the proto-oncogene *c-raf* stimulates tyrosine kinase to produce phosphotyrosine-containing proteins that transmit signals from the cell membrane to the cytoplasm and the nucleus. It is now known that mutations of the proto-oncogene *ras* occur in about 30% of human cancers. Ras is a protein essential to the normal division of cells, but, when transformed into an oncoprotein, it loses the ability to switch cell division off, resulting in unchecked growth.

Recently, some progress has been made in stopping unchecked growth through mediating signal transduction pathways. Two examples that have met with some success are interrupting the action of the cyclin-dependent kinase pathway and interrupting the Ras pathway.

continued on next page

PLENARY ABSTRACTS *continued from page 3*

Suggested Reading

Heimbrook DC, Oliff A, Gibbs JB. Essentials of signal transduction. In: DeVita VT Jr., Hellman S, Rosenberg SA (eds.) *Cancer: Principles and Practice of Oncology*. 5th ed. Philadelphia: Lippincott-Raven; 1998;35-46.

Perkins AS, Stern DF. Molecular biology of cancer: oncogenes. In: DeVita VT Jr., Hellman S, Rosenberg SA (eds.) *Cancer: Principles and Practice of Oncology*. 5th ed. Philadelphia: Lippincott-Raven; 1998;79-102.

Clinical Development of Cyclin-Dependent Kinase Inhibitors

Adrian M. Senderowicz, MD

Abnormalities in the cell cycle are responsible for the majority of human neoplasias. The key regulators of the cell cycle are the cyclin-dependent kinases (CDKs), enzymes that periodically form complexes with proteins known as cyclins. Cyclin expression varies during the cell cycle, and when they bind with CDKs, the complex becomes activated. Different CDKs operate during different phases of the cell cycle. For example, CDK4 and CDK6, coupled with their respective cyclin D partners, are responsible for progression through the G1 phase, and CDK2 in combination with cyclin E is responsible for normal progress from G1 into S phase. CDK2 in combination with cyclin A is required for progression through S phase, and CDK1 combined with cyclin B is necessary for mitosis to occur. These complexes are in turn regulated by a stoichiometric combination with small proteins. These proteins, called cyclin-dependent kinase inhibitors (CKIs), include p16, p15, p21, and p27. Mutations and/or deletions in some cell cycle proteins can result in the inactivation of the retinoblastoma (*RB*) gene product. Such mutations are responsible for the development of human neoplasia. Therefore, a pharmacologic CKI would be of great theoretical interest as a treatment strategy for many neoplasms.

Flavopiridol (NSC 649890, HMR 1275) is a novel flavonoid with potent (~100 nM) CDK inhibitory activity.¹ In preclinical models of lymphoid and head and neck cancers, flavopiridol induced apoptosis irrespective of the presence of *BCL-2* or *p53* function (A. Senderowicz, unpublished data).² It is unclear whether the apoptosis observed in these models is dependent on CDK modulation. Phase I trials with flavopiridol have been completed.³ In these trials, the main side effects noted with flavopiridol were secretory diarrhea and reversible hypotension. Antitumor activity was observed in patients with non-Hodgkin's lymphoma and renal, colon, and prostate cancers. Concentrations between 300 and 500 nM—necessary to inhibit CDK and achieve an antiproliferative effect—were achieved safely. Phase 2 trials in several tumor types and phase 1 trials with different schedules have been initiated. The recommended dose for phase 2 trials is 50 mg/m²/day by continuous infusion over 72 hours.

Another protein kinase inhibitor, UCN-01 (7-hydroxystaurosporine; NSC 638850), has also begun clinical trials (A. Senderowicz et al, unpublished data). UCN-01 can inhibit

CDK activity at concentrations 10 times higher than those required to inhibit protein kinase C; moreover, UCN-01 can modulate CDK activity at much lower concentrations by affecting the phosphorylations that regulate such activity.⁴ UCN-01 showed potent apoptotic and cell cycle effects in different in vitro models.^{4,5} Moreover, UCN-01 abrogates the G2 arrest induced by DNA-damaging agents in cells lacking normal *p53* function due to modulation of CDK1 activity.⁶ These results suggest a novel strategy to combine UCN-01 with DNA-damaging agents. In the initial clinical trial, in which UCN-01 was administered by continuous infusion for 72 hours, a prolonged half-life of about 600 hours (roughly 100 times longer than the half-life seen in preclinical models) was observed.⁷ The most prevalent side effects observed to date are headache, muscle cramps, hypotension, and hyperglycemia (A. Senderowicz, unpublished data). In current trials, the maximum tolerated dose has not yet been defined, but at doses of 53 mg/m²/day, we have observed significant reversible elevation of glucose in 50% of patients. Stabilization of disease has been observed in some patients with non-small cell lung cancer and non-Hodgkin's lymphoma.

In summary, the first two CDK modulators have shown encouraging results in early clinical trials. We are currently examining whether the presumed mechanism of antitumor effect—the modulation of CDKs—can be observed in samples from patients treated in these two trials.

References

- Carlson BA, Dubay MM, Sausville EA, Brizuela L, Worland PJ. Flavopiridol induces G₂ arrest with inhibition of cyclin-dependent kinase (CDK) 2 and CDK4 in human breast carcinoma cells. *Cancer Res*. 1996;56:2973-2978.
- Parker BW, Kaur G, Nieves-Neira W, et al. Early induction of apoptosis in hematopoietic cell lines after exposure to flavopiridol. *Blood*. 1998;15:458-465.
- Senderowicz AM, et al. A phase I trial of continuous infusion labeled flavopiridol: a novel cyclindependent kinase inhibitor in patients with refractory neoplasms. *J Clin Oncol*. In press.
- Wang Q, Worland PJ, Clark JL, Carlson BA, Sausville EA. Apoptosis in 7-hydroxystaurosporine-treated T-lymphoblasts correlates with activation of cyclin dependent kinases 1 and 2. *Cell Growth Differ*. 1995;6:927-936.
- Seynaeve CM, Kazanietz MG, Blumberg PM, Sausville EA, Worland PJ. Differential inhibition of protein kinase C isozymes by UCN-01, a staurosporine analogue. *Mol Pharmacol*. 1994;45:1207-1214.
- Wang Q, Fan S, Eastman A, Worland PJ, Sausville EA, O'Connor PM. UCN-01: a potent abrogator of G₂ checkpoint function in cancer cells with disrupted p53. *J Natl Cancer Inst*. 1996;88:956-965.
- Sausville E, et al. *Cancer Chemotherapy Pharmacol*. In press.

p21 Ras: A New Target for Therapeutic Intervention

Ivan D. Horak, MD

Over the past decade, the molecular function of cancer cells has continued to be revealed. One area of intense interest has been signal transduction. Various therapeutic strategies based on signal transduction pathways have been implemented in the laboratory and the clinic. One area of long-standing interest in the laboratory is G protein signaling, especially that mediated by *ras*.

The Ras proteins are 21-kd guanine nucleotide-binding proteins that control a multitude of cell-signaling events. Situated at the inner surface of the plasma membrane, Ras proteins normally respond to growth stimuli, such as epidermal growth factors and platelet-derived growth factors, by exchanging guanosine triphosphate (GTP) for constitutively bound guanosine diphosphate (GDP), which triggers cell division.¹ The signal is terminated when the Ras protein hydrolyzes its bound GTP to GDP in a reaction stimulated by guanosine triphosphatase (GTPase)-activating protein (GAP).¹

Advances in the understanding of Ras oncoprotein function suggest novel points for antitumor intervention. Ras is synthesized as a cytosolic precursor that ultimately localizes to the cytoplasmic face of the plasma membrane after a series of post-translational modifications.² The first and necessary step in this series is the addition of a farnesyl moiety to the cysteine residue of the COOH-terminal CAAX motif (C, cysteine; A, usually an aliphatic residue; X, any other amino acid) in a reaction catalyzed by farnesyl protein transferase (FPTase).² This modification is essential for Ras function. FPTase appears to be an appropriate biochemical target for the development of agents that inhibit the post-translational processing of Ras to prevent Ras-mediated cellular transformation.² One route to developing inhibitors of the CAAX farnesyltransferase is through the tetrapeptide binding site. Many tetrapeptides that conform to the CAAX consensus act as alternative substrates in vitro, thereby competitively inhibiting the farnesylation of Ras proteins.

Tetrapeptides such as Cys-Val-Phe-Met (CVFM), which contain an aromatic residue in the third position of the CAAX sequence, inhibit farnesyltransferase without becoming farnesylated themselves.¹ The resistance of these tetrapeptides to farnesylation depends not only on the aromatic residue but also on the presence of a charged NH₂-terminus. Unfortunately, such tetrapeptides are ineffective when added to intact cells, either because they are taken up inefficiently, because they are rapidly degraded, or both.³

Peptidomimetic analogs were therefore created to inhibit the enzyme in vivo as well as in vitro.³ Several studies have suggested that benzodiazepine peptidomimetics can reverse the phenotype of Ras-transformed cells at concentrations that permit the long-term growth of normal cells.⁴ This raises the possibility that partial inhibition of farnesyltransferase may allow cells to synthesize sufficient farnesy-

lated laminins and other proteins to allow growth while blocking the action of mutant oncogenic Ras proteins. Further, it is also possible that GTPase-defective Ras proteins act as dominant negative regulators of cell growth when rendered cytosolic by the inhibition of farnesyltransferase.

References

1. Gibbs JB, Oliff A. The potential of farnesyltransferase inhibitors as cancer chemotherapeutics. *Annu Rev Pharmacol Toxicol.* 1997;37:143-166.
2. Kohl NE, Mosser SD, deSolms SJ, et al. Selective inhibition of ras-dependent transformation by a farnesyltransferase inhibitor. *Science.* 1993;260:1934-1937.
3. Sepp-Lorenzino L, Ma Z, Rands E, et al. A peptidomimetic inhibitor of farnesyl: protein transferase blocks the anchorage-dependent and -independent growth of human tumor cell lines. *Cancer Res.* 1995;55:5302-5309.
4. James GL, Goldstein JL, Brown MS, et al. Benzodiazepine peptidomimetics: potent inhibitors of Ras farnesylation in animal cells. *Science.* 1993;260:1937-1942.

Suggested Reading

Clinical experience with R115777, an FPTase inhibitor:

End D, Skrzat S, Devine A, et al. R115777, a novel imidazole farnesyl protein transferase inhibitor (FTI): biochemical and cellular effects in H-ras and K-ras dominant systems. *Proc Am Assoc Cancer Res.* 1998. Abstract 1847.

Skrzat S, Angibaud P, Venet M, Sanz G, Bowden C, End D. R115777, a novel imidazole farnesyl. protein transferase inhibitor (FTI) with potent oral antitumor activity. *Proc Am Assoc Cancer Res.* 1998. Abstract 2169.

Zujewski J, Horak ID, Woestenborghs R, et al. Phase I trial of farnesyl-transferase inhibitor, R115777, in advanced cancer. *Proc Am Assoc Cancer Res.* 1998. Abstract 1848.

Methodological issues in the design of clinical trials of FPTase inhibitors:

Geller NL. Design of phase I and II clinical trials in cancer: a statistician's view. *Cancer Invest.* 1984

Discovering the Science Behind Alternative Medicine

The old definition of alternative medicine as therapies not reimbursed by insurance, not taught in medical school, and not evaluated for efficacy is now obsolete.

*Mary Ann Richardson, Dr.PH., Assistant Professor,
University of Texas-Houston School of Public Health,
Center for Health Promotion Research and Development &
The Center for Alternative Medicine Research in Cancer*

Up to 50% of cancer patients in the United States use complementary and alternative medicine (AM), most in conjunction with conventional treatment and at costs upwards of \$25 billion annually, despite limited evidence of efficacy and safety. In 1997, an estimated 1.4 million Americans were diagnosed with cancer, another 7.4 million Americans had a history of cancer, and one of every four deaths were attributed to cancer. Cancer will surpass heart disease as the leading cause of death by the year 2000, despite the expected decline in age-adjusted mortality rates due to smoking cessation. As cancer incidence rises and mortality rates decline modestly, more and more individuals will live longer and be at greater risk of developing cancer. Use of AM is expected to increase with these demographic trends, making systematic evaluations of efficacy and safety more critical.

AM has been recently defined in Clinical Oncology as "...diagnosis, treatment, and/or prevention that complements mainstream medicine by contributing to a common whole by satisfying a demand not met by orthodoxy or by diversifying the conceptual framework of medicine." Interest in complementary/alternative medicine is also an international phenomenon with significant numbers of Germans, French, Australians and UK residents using these therapies. The continued rise in public interest suggests that previously overlooked practices are experiencing a renaissance and newer therapies are emerging. In the U.S., AM was recently ranked the third most important topic for 1998 by the American Medical Association. Approximately 34 of the 125 U.S. medical schools now offer training in AM; residency training programs in "Integrated Medicine" are being developed; insurance coverage is expanding to embrace the modalities; and research efforts are increasing globally. Thus, the traditional definition of AM as therapies not reimbursed by insurance, not taught in medical school, and not evaluated for efficacy is now obsolete.

AM Use by Cancer Patients

Individuals who face the challenge of a cancer diagnosis may seek expanded choices for less toxic and more supportive treatments, whether they refuse conventional care, fail conventional care, or simply wish to complement conventional care. Interestingly, 80% of cancer patients who use AM continue conventional care, and only 5% abandon conventional for alternative treatments. In the U.S., users tend to be more educated with higher incomes, Caucasian, 30 to 50 years of age, living in the West or Northeast, and suffering from prolonged illnesses such as cancer of the

central nervous system, ovarian cancer, leukemia, and lymphoma.

Despite the widespread use and availability of alternative therapies, information on efficacy and toxicity remains largely anecdotal, and efforts to facilitate research are underway internationally. The National Cancer Institute of Canada recently launched a research program to evaluate AM therapies for breast cancer. Evaluations continue in England, Switzerland, and Germany. The U.S. National Institutes of Health (NIH) allocated \$44 million across the Institutes in 1996 to evaluate AM therapies. Congressional funding for the Office of Complementary and Alternative Medicine (OCAM) at NIH established 10 exploratory research centers, including The University of Texas Center for Alternative Medicine Research (UT-CAM), a collaboration between the UT School of Public Health and the MD Anderson Cancer Center.

One of the research initiatives at UT-CAM is a survey of use and attitudes of AM among cancer patients at MD Anderson Cancer Center. A pilot study of outpatients found that 73% were using AM in addition to conventional treatment. The most frequently used therapies were prayer (62%), imagery (31%), vitamins (29%), herbs (25%), and massage (23%). The primary reason for using AM was to feel more hopeful (59%). Most patients (59%) disclosed use of AM with their physicians and reported the following responses: physicians encouraged them to continue (43%), were neutral (39%), encouraged them to stop (4%), or warned them of dangers (4%).

73% of outpatients used alternative treatments to augment conventional therapy.

The most commonly cited reason (59%) for using alternative medicines and treatments was to feel more hopeful.

A qualitative study of oncologists and general practitioners in Toronto showed that physicians were more open to AM therapies if the patient's prognosis on standard treatment was poor, or if the alternative treatment was non-invasive. Many physicians perceived themselves to be unfamiliar with available alternative cancer therapies and indicated that their main sources of information were their patients and the lay press. Although most of the physicians viewed the efficacy of such therapies as scientifically unproven, they would respect their patients' decision to use them and encourage them to continue with standard treatment. They reported the most apprehension about AM therapies that were perceived to be harmful or where AM was used when a patient's prognosis under standard treatment was good. (See figure 1).

UT-CAM's initial efforts included comprehensive surveys of current AM treatments, and analysis of published literature and studies. Six major modalities of AM treatment

Impact of Alternative Treatment Use on Provider/Patient Relationship (fig. 1)

<i>If patient rejects conventional treatment in favor of alternative treatment ...</i>	PHYSICIAN IS:	RELATIONSHIP IS:
...and patient has poor prognosis.	Tolerant	More Intimate
...and patient has good prognosis.	Upset	Conflictual
<i>If patient continues conventional treatment augmented by alternative treatment ...</i>	PHYSICIAN IS:	RELATIONSHIP IS:
...and the alternative treatment is non-invasive .	Supportive	Collaborative
...and the alternative treatment is invasive .	Cautious	Tense

CONCLUSION:
Physician attitudes towards alternative treatments are more shaped by the **prognosis** under conventional treatment and the **nature** of the alternative treatment than by the efficacy of the alternative treatment.

FIGURE 1. Bourgeault IL, *Can Med Assoc J*, 1996, 155(12):1679

were identified and profiled (see sidebar). Rigorous scientific criteria for further study of AM therapies were established, based on models of controlled clinical studies. Research projects currently underway (see accompanying article) at UT-CAM include:

- Five AM agents researched with Phase I/II or *in vitro* studies
- Melatonin with CHOP examined in a Phase III clinical trial
- Epidemiological studies of four other AM therapies

These studies at UT-CAM are designed to investigate alternative/ complementary cancer therapies with established, conventional oncologists and researchers who will apply rigorous, scientific methodology. When completed, the studies will provide valuable data on efficacy and safety of these agents. Should the results be promising, the preliminary data and experience will be the foundation for more definitive trials of these agents with the final goal of advancing knowledge and impacting the clinical treatment of cancer.

For a list of references cited in this article or for further information please visit the UT-CAM Web site at www.sph.uth.tmc.edu/utcam/ or contact:

UT-School of Public Health, P.O. Box 20186; Houston, Texas 77225.

Center for Alternative Medicine Web Site Wins Award

The UT-CAM Web Site received the OncoLink Editor's Choice award in June for outstanding presentation of oncology and cancer information. More detailed information on AM agents and research activities at UT-CAM is available at www.sph.uth.tmc.edu/utcam/

Six Predominant Treatment Modalities of Alternative Medicine

1. Nutrition and Lifestyle/Behavioral Change

An estimated 35% of all cancer mortality can be attributed to a high-fat, low-fiber dietary intake. International studies show correlations between dietary fat and cancer: higher incidence of breast cancer as well as higher risk of colorectal cancer. Epidemiological studies show a protective effect with fiber, particularly for colorectal adenomas. Dairy products and other fats are considered to be a source of accumulated toxins that contribute to disease onset. Thus, AM approaches often include *detoxification* to restore healing mechanisms (e.g., limited consumption of animal products and increased intake of whole grains, fresh vegetables, and fruits). *Gerson therapy* encourages potassium supplementation and sodium restriction to arrest tumor formation and increase oxidative enzyme levels for tumor necrosis. The *macrobiotic diet* emphasizes high-complex carbohydrates and low fat intake; the *Kelley regimen* includes nutritional supplements and pancreatic enzymes that act directly and indirectly on cancer progression.

Smoking cessation, exercise, and limited dietary fat intake may not be considered alternative, but most AM therapies include lifestyle change interventions as part of their multidisciplinary treatment approach.

2. Mind/Body Control

With bi-directional communication between the nervous and immune systems established, researchers have attempted to link cancer development and progression with immune response and psychosocial factors (eg, coping, stress, and emotional well-being). Possibly the most widely used AM approach is *imagery*, which involves cognitive processes that alter awareness and physical and psychological processes (i.e., increased survival time and reduced anxiety, nausea, and pain).

Social support interventions have reportedly improved quality of life, coping skills, and in some cases, survival. *Psychosocial adjustment* has been associated with reduced depression, anxiety, and pain. In a structured psychiatric intervention for patients with malignant melanoma, five-year survival was improved and recurrence rates reduced with the multi-component psychosocial intervention.

3. Structural Manipulation, Energetic

According to energy therapies, vital energy exists as a physical entity (e.g., *chi, prana*) that flows along channels or meridians throughout the body and as the animating force in living organisms that connects them to the external environment. By integrating and realigning this internal energy, individuals can access internal resources and restore health. Nursing professionals describe techniques for directing and modulating energy and propose theories of electromagnetic fields. Controlled research, predominately in the nursing community, has demonstrated the modulation of subtle energy flow and energy fields and voltage signals with *deep tissue therapy, rolfing, and therapeutic massage*. *Therapeutic touch* has been shown to reduce

continued on next page

AM Treatment Modalities (continued from page 7)

anxiety levels in hospitalized patients, increase hemoglobin levels, reduce postoperative pain, and enhance emotional support. A single-blind study showed that therapeutic touch decreased the patient's need for analgesic medication but did not reduce postoperative pain.

4. Massage/Acupressure

Few controlled studies have evaluated the efficacy of massage and none have evaluated the physiological, psychological, and therapeutic effects. *Massage* has been shown to reduce pain perception and anxiety and enhance relaxation among cancer patients. A nursing study found a significant, short-term reduction in pain after massage for men, but not women. *Acupressure* combines massage with deep pressure on points along the hypothesized energy meridians of the body. Patients who receive acupressure post-operative have less nausea and vomiting than patients who received either drugs only or no treatment. Patients in hospice care who received acupressure from wrist bands had reduced nausea.

5. Bioelectromagnetic/Electroacupuncture

Pulsed or direct current to solid tumors has augmented the impact of chemotherapeutic agents in-vivo with fibrosarcomas. By inserting anodes and cathodes into the base of tumors, tumor-free long-term survival resulted, which is significant since fibrosarcoma is difficult to cure despite radiation, chemotherapy, and surgical approaches. *Electrochemical treatment* (ECT) inhibits cell proliferation and DNA synthesis in vitro, and morphological results are consistent with the cell culture observations. Clinical studies report beneficial local effects for squamous cell carcinomas of the head and neck, solitary neoplasms of the lung, and other soft tissue tumors. Although electrical stimulation may reduce local tumors, potentiate the effects of chemotherapeutic agents, and possibly stimulate an antitumor immune response, the method has been restricted to local treatment of tumors that are unsuitable for surgery or radiation treatment. Rigorous engineering and biological studies are needed to provide a solid foundation for this therapeutic approach for treatment of localized tumors.

In contrast to traditional acupuncture, *electroacupuncture*

Alternative Medicine Research Projects Now Underway AT UT-CAM

Co-administration of Coenzyme Q10 (Vitamin CoQ10) with standard anticancer drugs

In vitro experiments are underway to co-administer the vitamin CoQ10 (i.e., ubiquinone) with standard anticancer drugs, including Adriamycin, Paclitaxel, Cisplatin, and Taxol, to determine the relative toxicity and growth-inhibitory properties of CoQ10 with these standard chemotherapeutic agents as well as with the new anticancer drugs, proteasome inhibitors. Tightly regulated proteins in the cell are degraded through addition of branched chain ubiquinone molecules which in turn signals their obligate destruction through the proteasome complex. Proteasome inhibitors appear to be very promising as potential anticancer agents in that many of the critical cells regulating cell growth and cycling are controlled by the ubiquinone-proteasome pathway. Initially, the studies will be conducted in a human breast cancer cell line (MCF7). If activity is indicated from the *in vitro* results, *in vivo* models will be considered to test the potential interactions of CoQ10 with standard chemotherapeutic compounds.

Antioxidant Properties of Green Tea

In vitro experiments were designed to test green tea extract as a possible antioxidant to reduce the number of chromatid breaks by adding green tea to the mutagen-exposed cell from four human cell lines. The analysis of the antioxidant properties of green tea suggests that green tea may prevent spontaneous chromatid breaks after controlling for the effect of the mutagen and the interaction of the mutagen and green tea. More carefully defined studies are being designed and the first Phase I trial of

Green Tea extract in the U.S. is currently underway at MD Anderson Cancer Center.

Impact of Ginseng Saponins on Abberant Crypts *In-Vivo*

The purpose of the studies was to test the effect of Korean Red ginseng saponins on colon cancer in cell lines of an animal model. After a dose-finding study, two protocols were designed to determine if Korean Red Ginseng saponins can 1) modulate carcinogenic metabolism and 2) impact the progression of established and developing precancerous lesions in the rat colon. In Protocol 1, ginseng significantly modulated aberrant crypt foci in the low-dose group (0.1 g/kg), amounting to a 25% suppression compared with carcinogen-only controls; however, we did not find suppression at the higher dose (1g/kg). Results of Protocol 2 suggest no protective effect of ginseng on developing lesions. Plans are underway to replicate the findings of Protocol 1.

Multi-center Phase I/II study of Shark Cartilage Extract for Prostate Patients

Angiogenesis is responsible for the progression and the exacerbation of so-called angiogenesis-dependent diseases, including cancer of the prostate. Cartilage is an avascular tissue highly resistant to invasion by blood vessels when compared to other tissues. The avascular property of cartilage has prompted several laboratories to study the biological potential of this tissue to inhibit blood vessel formation. The rather small amounts of cartilage in living organisms is a factor that has limited the analysis and use of this tissue and its development in

continued on next page

ture stimulates peripheral nerves to activate opioid centers in the brain. Small, sub-sensory pulsed currents across the head produce mild analgesia and a relaxation effect. Locally applied small currents stimulate bone regeneration in chronically disunited fractures and wound healing of soft tissue with resultant reduced scar tissue formation. Reported therapeutic effects include analgesia for chronic pain management, anti-emetic effects, and immune enhancement. Low-current stimulation may be beneficial after surgery or radiation. Although the impact of low-intensity electric fields on cells remains controversial with no evidence of beneficial effects, the approach has been promoted and gained popular attention.

6. Herbal/Biopharmacologic

An estimated 80% of the world's population use herbal therapies. In the U.S., herbal products represent a major growth industry with sales increasing 2% each year and totaling over \$3 billion annually. Some 8,000 to 10,000 practitioners are licensed in the U.S. to practice *Chinese medicine*, and most (70-80%) prescribe herbal medications.

Although Chinese and herbal medicines are usually purchased in health food stores, conventional oncology uses chemotherapeutic drugs derived from botanicals, including etoposide from the mayapple plant, vinblastine and vincristine from the rosy periwinkle plant, and taxol from the Pacific yew tree.

Biopharmacologic approaches include biochemical agents, vaccines, blood products, or synthetic chemicals that are used alone or in combination with diet, detoxification, and other health practices. In contrast to conventional drug models, these alternative medicines are touted as containing unique, largely non-toxic mixtures to control or combat cancer indirectly by enhancing recuperative powers within individuals. Despite widespread use and preliminary evidence of therapeutic promise elsewhere, these approaches lack rigorous scientific evaluation for efficacy and safety in the U.S. Biopharmacologic therapies are controversial among healthcare professionals and without supporting evidence, are regarded negatively.

UT-CAM Research Projects Underway (continued from page 8)

clinical oncology. Cartilage accounts for approximately 0.5% of the body weight in bovine species but 6% in shark species. Therefore, shark is a privileged source of anti-angiogenic factors derived from cartilage.

In Phase I of this study, optimal dose of cartilage extract after tumor inoculation will be determined by observing the impact on PSA and growth kinetics of the tumor. Phase II, which will accrue a total of 15 patients, includes an 8-week treatment of cartilage intervention. Study objectives are measuring the impact on 1) survival; 2) PSA and vascular endothelial growth factor (VEGF secretion is important because of the correlation with angiogenesis); and 3) microvascular density of the tumor volume at 3, 6, 12, and 24 weeks and 9 months post-treatment.

Pilot Study Evaluating Mistletoe Extract in Patients with Advanced Esophageal Solid Tumors

This feasibility study examines recruitment, administration of the therapy, safety data, and measures of efficacy of an aqueous fresh plant extract of mistletoe (*Viscum album L*).

Using a single arm, prospective design, patients (n=10) who have advanced, unresectable, or recurrent (Stage IIB, III, IV) esophagus cancer and are candidates for palliative treatment (i.e., stent tube) will receive a 3-month treatment.

Randomized Phase III Study of Melatonin with CHOP for Patients with Lymphoma

The study's objectives are to determine 1) the impact of 20 mg of melatonin in a continuous schedule on hematopoietic recovery post chemotherapy (i.e., CHOP) and 2) the response rate, failure-free survival, and survival of patients with large-cell lymphoma treated with the standard regimen CHOP plus melatonin.

Pattern of Use Survey of Flor•Essence herbal mixture

The epidemiological study will document cancer patients' reasons for using this herbal product (e.g., to treat a condition, relieve symptoms associated with a condition, or promote health), and the perceived benefits associated with the therapy.

Retrospective Comparison of Outcomes for Patients treated with Coley Toxins versus SEER

The survival experience of patients with breast, ovarian, kidney, sarcoma who received the Coley toxins has been compared with patient records of the Surveillance Endpoint Epidemiologic Results (SEER). The Cox Proportional Hazard model with time-dependent covariates controls for the lapse time from diagnosis to treatment with the Coley toxins and tests for the significance of covariates to assess the survival experience. This analysis extends the previous analysis that compared the survival distributions of the Coley and SEER.

Historical Cohort Studies of Hoxsey and Livingston Cancer Therapies

The Hoxsey and the Livingston-Wheeler therapies are multiple-approach treatment regimens incorporating biopharmacologic or herbal agents with diet and/or psychosocial interventions. Two historical cohort studies with external controls taken from the SEER database will compare the survival experience of patients treated with Hoxsey and Livingston regimens during 1992 at two established alternative/complementary clinics with that of conventional care.

Surgery Committee Tackles Accrual Issues

The Surgery Committee has initiated a program to study accrual problems and develop strategies to improve accrual response. In this article, Todd Demmy discusses the Surgery Committee's efforts to date. The *CalGab* invites comments and response from other committees about their approaches to accrual issues, as well as feedback on the Surgery Committee initiatives.

*By Todd Demmy, M.D.
University of Missouri*

Many clinical trials of the CALGB and other cooperative groups designed to answer important questions suffer because of slow patient accrual. This major problem adversely affects the statistical power and hence the science of studies which do not come close to reaching their subject enrollment goals. Study designs are often very detailed in statistical planning and other scientific aspects. Less attention is given, however, to accrual strategies, i.e., how to market the study to maximize accrual, and how to manage accrual failures. There are reliable systems to track patient accrual within the cooperative group setting, but few mechanisms to record and measure non-accrual and its causes. Lack of information about the problem therefore leads to difficulties in managing it.

The Surgery Committee of the CALGB has recently sponsored an initiative to study the problem of poor accrual in an organized fashion. One goal is to develop and test tools to gather and analyze information from physicians and other health care professionals who refer patients for clinical trials. Another objective is to monitor the concerns and responses of patients referred for group trials who refuse participation or randomization. We want to determine if effective utilization of this information about non-accrual and physician non-referral can better regulate study design, study closure, and lead to improved strategies to increase study accrual.

One systematic survey of reasons for non-accrual was conducted at the Ellis Fischel Cancer Center several years ago. Anecdotally, we know that some CRAs keep records of patients screened to document accrual problems and to show the considerable work done by them that does not pay off in an enrollment. Nonetheless, accrual problems have not yet been studied at the cooperative group level, according to our literature search. Some authors have, however, noted the need to document provisions for corrective action when enrollment goals are not met.

Accrual as a marketing project

This challenge is in essence a marketing project. The product is the clinical trial; the target audience is eligible patients; and the distribution channel is physicians and health care professionals. Questions appropriate to this marketing plan include: "How do we make physicians bet-

ter salesmen of the study?" "How do we reward busy physicians to present this study to colleagues and patients?" "Who are the initial contact health care workers?" "What will be the major concern(s) of the patients?" "How will the information be presented to patients?" "How will the information be presented to physicians?" "Which media will educate most effectively and minimize patient and physician confusion?" and "What will be the feedback mechanism to determine why study accrual is failing?"

Most problems in patient accrual fall into one of the three categories: failure to disperse the information to the key parties, failure to convince referring physicians of study merit, and failure to convince patients. To learn from these failures, we need to first develop effective mechanisms to gather information and document where and why accrual problems occurred.

Lack of information about the causes of slow accrual logically leads to difficulties in managing the problem

Failure to disperse information

This can be tracked by contacting key investigators at main member institutions to determine where, when and how the study scheme was presented. Typical venues are Grand Rounds and informal meetings used by the local investigator to disperse the information. Problems of project initiation such as IRB concerns can be documented as well. This information is relatively easy to obtain.

Failure to convince physicians

An institution or investigator can be rewarded for compiling comments from local physicians likely to be main contributors to the proposed clinical trial. Physicians would be asked to fill out a short questionnaire about the trial with standardized questions and ratings scales (ranging from "strongly agree" to "strongly disagree"). If incentives are offered for data about non-accrual, institutions and investigators will be more likely to present the clinical trial to referring physicians. The study designers, in turn, will receive valuable outside feedback and can determine the likelihood of patients being referred to that trial institution.

Anonymous survey data can also be used to assess the merits of a protocol during the early design phase. Attendees at group meetings represent a large pool of clinical insight that otherwise goes untapped. Many valid criticisms are probably not brought to the attention of the potential study chair because of the time constraints and the reluctance of participants to dissent. Such a feedback survey, similar to rating lecturers at CME meetings, can measure the support of a study from committee members as the protocol goes through the review process. The Thoracic Surgery Committee has already developed a sim-

continued on next page

Accrual Issues *(continued from page 10)*

ple survey form for its members to assess problems with various thoracic surgical protocols.

Failure to convince patients

Patients are often reluctant to sign up for randomized clinical trials, especially studies with non-treatment control arms. Accrual failures occur when patients have trouble understanding or accepting the merits of the research. Accurate feedback is an essential part of the process of learning from these failures. Again, institutions can be given incentives to document the reasons for patient non-accrual. Analyzing patient concerns can lead to development of more effective presentation materials. A form to simplify reporting of these concerns has also been developed by the Thoracic Surgery Committee.

Testing effectiveness

When these new feedback systems are utilized, and "marketing" strategies are rolled out to address identified accrual problems, success can be measured by comparing accrual rates at institutions which implemented the corrective steps. Such pilot data may be useful in developing a comprehensive accrual management system that could be tested prospectively.

As these tools are refined and put into practice we will be better able to determine why studies are not achieving their accrual goals. This will limit supposition by study designers and other committee members. It will lead to balanced explanations because reasons for accrual failure at one institution could be quite different from others. Unsuccessful attempts at accrual, often time intensive, would be documented and rewarded appropriately.

Significant cost savings in medical and human resources can be realized as well. Timely feedback on accrual problems could identify fatal study flaws: these studies can be terminated early, freeing personnel and resources for other projects.

Ultimately, our goal is to study non-accrual in a much more organized fashion to develop a more rapid response. These responses will improve patient and investigator education and incentives. For example, a video or multi-media presentation could be produced to explain complex and confusing randomized trials.

A larger goal would be to integrate the marketing concepts developed from this process into basic study design. Projects that may have difficulty with accrual can be targeted for similar data collection and rapid assistance.

Finally, ethical aspects of these efforts must be considered. Programs designed to more aggressively convince doctors and patients to participate in clinical trials need to ensure a balanced and careful presentation of the information in order to prevent bias or coercion.

CALGB-Janssen Clinical Research Award

The CALGB Foundation, with support from Janssen Pharmaceutica, is offering a \$25,000 research grant for novel clinical or translational studies by oncology fellows in the area of signal transduction.

"This program is an exciting step for us," said CALGB Chair Richard L. Schilsky. "We want to help develop the next generation of cancer researchers. By leveraging industry support and collaboration, we can boost promising research by young oncologists."

Janssen's funding for this award stems from its commitment to research and development of new anti-cancer agents. Research grant applications should focus on elucidating the importance of signal transduction pathways in the biology of human cancer, on assessing prognosis, or on determining response to therapy. Clinical trials of novel signal transduction inhibitors are also appropriate.

Applicants must have at least one year of training remaining after June, 1999, when the award recipient will be announced. Physicians at CALGB main member or affiliate institutions who have completed at least one year of clinical oncology training but do not have a faculty appointment are eligible. Clinical or translational studies supported by this grant should ideally be conducted within CALGB.

The one-time, one-year funding, to begin by July 1, 1999, can be augmented by up to \$2,500 to the recipient's institution for overhead expenses.

Applications must be submitted by January 15, 1999. Send an original plus 6 copies to:

Mary Sherrell, M.A., Treasurer
CALGB Foundation
208 S. LaSalle St., Suite 2080
Chicago, IL 60604

Application Checklist

Applications must include the following:

Research Proposal (10 pages or less, plus references)

- Specific objectives
- Background and rationale
- Preliminary data
- Research methods
- Statistical considerations
- Description of patient population (if appropriate)
- References
- Appendix: Draft of clinical trial protocol (if a therapeutic clinical trial is proposed)

Additional documentation:

- Applicant CV
- Summary of other research support
- Letters of support from department chair and research mentor
- Budget with justifications

For further information, please contact Mary Sherrell at the address above. Phone: 773-702-9856, e-mail: msherrel@midway.uchicago.edu.

DATA MANAGEMENT

New Standards for Data Submission in CALGB

By Sherry Breaux, CALGB Quality Assurance Coordinator

The CALGB is tightening its guidelines for required data submission. The definition of delinquent data has been changed to reflect the following standards: survival and clinical data must be submitted to the CALGB Data Management Center (DMC) at least every 6 months for the first 2 years after a patient is registered to a CALGB treatment study, and at least annually thereafter, for as long as follow-up is required by the protocol. These guidelines, which replace the previous 15-month standard allowed for data submission, will be phased in over the next year and will be reflected in Institutional Performance Evaluation Committee (IPEC) reports for the first time in November 1999.

Monthly Lists to Institutions of Cases with Delinquent Data

Beginning in the Fall of 1998, the survival request lists and requests for data sent monthly to institutions from the DMC will be replaced by more specific monthly lists of patients considered delinquent according to the new standards of data submission. The new lists will closely resemble the reports of delinquent patients which have been sent to institutions in the past as part of the IPEC review process. The following items will be indicated for each delinquent case: patient name and CALGB patient ID number, CALGB study number, institution number and short name, study entry date, survival date and status, clinical date and clinical data requirement, and delinquency status.

These lists will serve as periodic reminders to institutions of the cases that the DMC has been unable to update adequately in the database. In some instances, the DMC will have received no recent data from the institution. In others, data may have been received which were incomplete with respect to protocol requirements and therefore were insufficient to allow for assessment of survival or clinical status. The lists should prompt data management personnel at institutions to send the DMC any data which have not yet been submitted, or to contact the DMC with questions if submissions have already occurred.

It is anticipated that, for the first few months, the lists incorporating the more stringent delinquency standards will be lengthy. Institutions should take advantage of the phase-in period from Fall 1998 to Fall 1999 to reduce these lists by submitting the required data. In September 1999, the monthly list will flag those cases which will appear as delinquent on the Fall IPEC report if sufficient data are not received by the deadline indicated.

Cases Considered Delinquent by IPEC

IPEC reviews institutional performance semi-annually. The delinquency of data submission by institutions is one aspect of that review. The DMC generates reports which summarize for each main member network the status of survival data submission and submission of complete case report forms for patients entered on CALGB-coordinated

treatment studies in each of the 4 calendar years prior to the last full calendar year. The last calendar year is deleted because of insufficient follow-up potential.

Currently, preliminary lists of cases with delinquent data are sent to main member institutions one month before final IPEC reports are run and provide the institutions with an opportunity to submit missing data just before the IPEC report deadline. These preliminary lists will be replaced by the new monthly lists from the DMC, described above, which will provide the main member institutions with an on-going record of patients with missing data and encourage more timely submission of delinquent materials.

The Fall 1998 and Summer 1999 IPEC report cycles will continue to use the old definition of delinquency, in which a patient is considered delinquent if they were alive at last contact and have more than 15 months since the last reported contact. This concurrent use of the old definition in IPEC reports and new definition in monthly reminder lists will end in Fall 1999.

CALGB Long-Term Follow-up Policy and the New Delinquency Definition

The CALGB long-term follow-up (LTFUP) policy states that data should be submitted per protocol until one year after the end of treatment and every 6 months thereafter. The new delinquency definition states that data are delinquent if they are not submitted at least every 6 months for the first two years after study entry and annually thereafter. Although these two policies are not completely concordant, they are not inconsistent. Most treatment protocols require data submission at least every 6 months for the first two years and virtually all require at least annual data submission thereafter. The LTFUP policy requests data submission every 6 months in the long-term, but the IPEC delinquency standard will not penalize an institution until the data are delinquent for more than one year.

Nevertheless, it is possible that when the new standards are first incorporated into the monthly and semi-annual reports, unanticipated errors will occur that will result in cases being falsely identified as delinquent. It will be important for institutions to communicate as soon as possible to the DMC and Quality Assurance Coordinator any errors found in these reports, as well as any suggestions for enhancement of the format. Input from data management personnel at CALGB institutions will be vital to the rapid implementation of the new data submission policy and improvement of the new reporting mechanisms.

A Few Other Policy Changes

Future delinquency reports will reflect a few other recent changes in CALGB policy. First, institutions will no longer be required to submit survival information for patients who have never received treatment (cancelled patients). Second, a main member which accepts an affiliate from another main member, or which accepts another main member network, will become responsible for the follow-up and data submission for patients from all associated active and inactive affiliates.

ONCOLOGY NURSING

Cachexia

By Brenda Werner, R.N., CALGB Research Nurse, University of Iowa Hospital and Clinics

Nutritional complications are a common problem of cancer or its treatment. Malnourished individuals are more prone to infection and are less likely to tolerate or receive optimal benefits from therapy. Malnutrition also is an important issue in the quality of life of individuals with cancer.

Protein-calorie malnutrition occurs when the protein-calorie composition of the diet does not meet the individual's physiologic requirements. When dietary calories and protein are insufficient, adipose reserves and muscle are catabolized for energy. Therefore one of the first signs of malnutrition may be a reduction in fat stores and loss of muscle mass. Demands for nutrients are tremendous because of the effects of cancer. Regardless of quantity, dietary intake of protein and calories may be insufficient to meet the demands of the tumor. Body stores of fat and protein are used. This process leads to loss of muscle protein, which results in weakness and debilitation; loss of subcutaneous fat, predisposing the individual to skin breakdown; impaired cellular and humoral immunity, increasing the individual's risk of infection; poor wound healing; apathy and depression.

The most severe consequence of malnutrition in cancer is cancer cachexia which is a group of signs and symptoms that includes inanition, anorexia, weakness, tissue wasting, and organ dysfunction. One half to two thirds of all individuals with cancer experience cachexia. Progressive cachexia is one of the major causes of mortality in individuals with advanced cancer. The relation of cachexia to tumor burden, stage of disease, and tumor histology is inconsistent, and no single theory explains the cachectic state. The cause of cachexia is primarily due to alterations

in protein, carbohydrate and lipid metabolism caused by inflammatory cytokines released by the tumor.

Currently there is an active CALGB trial (CALGB 9473) for the management of cancer cachexia. This study involves research as to whether taking omega-3 fatty acids, which come from fish oil, as capsules will improve the weight loss in patients with cancer associated cachexia. This study will also attempt to determine if omega-3 fatty acids will result in an objective anti-tumor response in patients with advanced cancer and associated weight loss. CALGB 9473 is a phase I/II trial. Phase I, which was a limited access study, was to determine the maximal tolerated dose of omega-3 fatty acids, is now complete. Phase II of 9473 is now open group wide. The dosage for patients enrolled will be 0.3g/kg/day. Doses of omega-3 fatty acids will be given in two divided doses during the day. Omega-3 fatty acids are stored by the University of Iowa Pharmacy and will be distributed to CALGB institutions when needed for a patient. When a patient is accrued, a supply will be sent by overnight or regular mail. Capsules should be refrigerated upon arrival and by the patients at home. To request capsules, institutions should call 319-356-3944 or 319-356-1616 and ask for pager 3569 or 4142.

References

1. Daly JM and Torosian MH. "Nutritional Support." *Cancer Principles and Practice of Oncology* 4th edition. DeVita, VT, Hellman, S, and Rosenberg, SA (eds). pp2480-2481, JB Lippincott Company, Philadelphia, 1993.
2. Woodruff R. *Symptom Control in Advanced Cancer*, pp106-107, Australian Print Group, Victoria, 1997.
3. Groenwald SL, Frogge MH, Goodman M, et.al. *Cancer Nursing: Principles and Practice*, 2nd edition, p 496, Boston: Jones and Bartlett publishers, 1992.

Causes of Cachexia

- Metabolic abnormalities due to presence of tumor malnutrition
- Malnutrition due to:
 - Poor intake due to anorexia
 - Functional blockage: mouth, esophagus, stomach mal-absorption
 - Vomiting, diarrhea, fistulas
 - Protein loss: ulceration, hemorrhage, repeated paracenteses
 - General effects of surgery, radiotherapy, chemotherapy
- Tumor metabolism

Clinical Features of Cachexia

- Weight loss
- Pallor
- Anemia
- Lethargy
- Edema (hypoalbuminemia)
- Muscle wasting, asthenia
- Poor wound healing
- Loss of body fat
- Pressure sores

Treatment of Cachexia

- Correct or palliate cause of malnutrition, anorexia
- Treat tumor, where feasible
- Drug treatment of cachexia
- Dietary measures:
 - General measures
 - Dietary supplements
 - Enteral nutrition
 - Parental nutrition
- Management of the psychosocial consequences

Program Announcements from NCI

PA-98-069: Cancer pharmacology and treatment in older patients.

Purpose

The National Institute on Aging (NIA) and the National Cancer Institute (NCI) invite research grant applications to expand the understanding of the pharmacology of anti-neoplastic agents in older patients. This research initiative specifically addresses the disposition, efficacy, and effectiveness of anti-cancer agents in older cancer patients. The increased risk of the major cancers with advancing age and their prominence in older-aged persons are well known. The information developed in the past three or more decades in cancer pharmacology and geriatric pharmacology should be integrated to provide extensive application of the combined expertise to devise appropriate therapeutic strategies for cancer patients 65 years and older.

Experts in aging and cancer can benefit from interdisciplinary studies provided by the combined perspectives of the pharmacology of aging and cancer pharmacology, comparing knowledge and experience, and developing studies on unique aspects of aging on pharmacokinetics (time course of absorption, distribution, metabolism, and excretion of drugs from the body) and pharmacodynamics (response of the human host to the drug). In treating elderly cancer patients, special consideration also must be given to the pathophysiological changes that occur with aging, particularly the decline of organ systems and their decrease in functional capacity. Age-associated loss of efficiency is an acknowledged issue.

The goal of this program announcement is to stimulate research to improve treatment and care of older persons affected with cancer with explicit attention to aging and old age and their effects on anti-cancer therapy pharmacokinetics and pharmacodynamics.

Background

Cancer is a disease primarily associated with aging. More than 60% of all cancers diagnosed and 69% of all deaths due to cancer are in persons 65 years and older. For leukemia and cancers of the lung, pancreas, rectum, stomach, and urinary bladder, the median age range is 66-74 years for both men and women. The median age for prostate cancer is 71 years. Breast and ovarian cancers, often regarded as diseases of young women, have median ages of 64 and 63 years, respectively.

The age group 65 years and older makes up approximately 13% of the total U.S. population. This percentage is expected to increase to more than 20% by 2030. Older persons bear the brunt of the cancer problem and the number of aged individuals at high risk for a malignancy will increase. But data on evaluation and management of cancer in the elderly, on the impact of age-associated changes and intercurrent diseases, are sparse.

Numerous studies in gerontology and geriatric medicine

indicate that the prevalence of chronic diseases (e.g., arthritis, heart disease, cerebrovascular disease, diabetes, hypertension) increase with advancing age. Some elderly cancer-diagnosed individuals have multiple concurrent pathologies and associated debilitation; while others experience minimal age-associated changes. Moreover, the health status of older persons is often affected by physiologic alterations (i.e., "geriatric conditions") that produce vulnerabilities such as renal insufficiency, chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease, urinary incontinence, falls, decreased immune response to infections, hearing impairment, poor nutrition, and disability. Clinicians need to know how the drugs perform in older persons with far less than ideal health and those with good to excellent health.

The medical oncology literature is sparse on how elderly cancer patients tolerate chemotherapy or how oncologists treat older cancer patients. Patients in the large multi-center cancer treatment trials that provide the fundamental data for medical practice tend to be younger than 65 years (with the exception of prostate cancer patients). Thus, research questions addressed in the multi-center clinical trials efforts are not generalizable to older patients with concomitant diseases and poor physiological functioning. These age-associated problems have precluded their entry into such studies. We face the dilemma that cancer treatment interventions are not targeted for the age group enduring the most cancer.

As new therapies such as biologics and anti-angiogenic agents are developed that are not cross resistant to standard chemotherapy and involve less toxicity, the pharmacodynamics of these agents and potential efficacy must be addressed in an elderly population. Definitive answers to the many questions that arise about the impact of aging on cancer therapy are urgently needed.

Research Goals and Scope

The PA emphasizes research to improve the care and treatment of older-aged patients through evaluation of tolerance and response to standard, experimental, newly-designed anti-cancer agent regimens independent of, and in conjunction with, multimodality interventions in the context of geriatric pharmacology. It encourages the extramural research communities in cancer and geriatric pharmacology to combine expertise and apply the knowledge bases of both disciplines to research initiatives relevant to older cancer patients.

Clinical studies relevant to this pharmacology initiative promote two major areas of investigation:

1. Studies to assess the age-dependent differences that influence drug efficacy and adverse drug effects used to treat the tumors that disproportionately affect the elderly. This includes the parameters of drug absorption, distribution, metabolism, and excretion as well as age-host and drug interactions. Alterations in immune function and cell cycle kinetics may also affect the pharmacodynamics of the therapeutic drugs. What influence does

age have on these physiologic factors and the proposed therapeutic intervention?

2. Cancer site-specific studies that confront and deal with the multiple health problems inherent in older persons diagnosed with a malignancy. How are these conditions and their multiple pharmacy needs managed in the context of cancer treatment planning?

To address the goal of advancing optimum therapy for older cancer patients, selected areas for studies are listed. Grant applications are not limited to these specific areas. The list is neither all-inclusive nor exclusive, nor is it in order of priority interests. Additional research aims that maximize the potential for positive therapeutic effects and minimize toxicity in elderly patients will be considered.

- Studies on how anti-cancer agent effects are modified by aging processes with attention to dosage, adverse reactions, drug-drug interaction, drug-age interaction, changes in body composition, organ, and immune function, and the older person's own use of medications (prescribed and over the counter).
- Prospective studies that emphasize the entry of older-aged patients into cancer treatment protocols that will evaluate the independent effects of age-related factors. These studies may involve chemotherapy, biologic therapy, surgery, radiation therapy, and multimodality treatment interventions.
- Pharmacokinetics and pharmacodynamics modeling of selected anti-cancer agents and patient response applied to chemotherapy and biologic therapy questions pertinent to elderly patients.
- Age-associated toxicity effects—Mucositis, cardiotoxicity, nephrotoxicity, myelotoxicity, and neurotoxicity.
- Age-associated pharmacodynamic effects—Mechanisms of antitumor drug resistance and repair; markers of angiogenesis and related events; immune responsiveness.
- Explore differences in the pharmacokinetics and pharmacodynamics of chemotherapeutic and biologic antitumor agents between older and younger patients and the potential mechanisms for these differences.
- Studies that characterize the inadmissible elderly patients to research protocols (e.g., physical incapacity from other medical conditions; family/patient decisions; memory loss; depression; cognitive function; lack of social support or transportation) that include data on treatment administered in the clinical setting outside the protocol involvement.
- Development of methods to evaluate performance status of older patients regarding preexisting diseases or conditions (renal problems, cardiac history, severity of hypertension, immune suppression, etc.) as prognostic indicators for drug sensitivity and dose intensity.

Mechanism of support

Support of this program announcement is through the National Institutes of Health (NIH) traditional investigator-initiated research project grant (R01) mechanism and the

exploratory/developmental grant (R21) mechanism. The R21 program is used for pilot projects or feasibility studies to support creative and novel research that may produce innovative advances in science. R21 awards are limited to \$100,000 direct costs per year (up to two years). Continuation of projects developed under the R21 mechanism is through the R01 mechanism.

Clinical Correlative Studies Using Specimens from Multi-institutional Therapeutic Trials (New PA)

Objective of Project:

The objectives of this PA are to foster collaborations and interactions between basic researchers, private industry, and clinical investigators to advance therapeutic clinical research and conduct correlative studies on potential prognostic factors utilizing specimens from the NCI Clinical Trial Cooperative Groups (NCI Groups) or from other large multi-institutional clinical studies. Basic investigators will be expected to contact the NCI Groups to forge new collaborations and obtain access to patient specimens and NCI supported tumor banks for laboratory analysis under this program announcement. NCI program staff will be able to provide assistance in identifying NCI Groups that would be interested in collaborating with basic science investigators on laboratory and clinical studies of new markers. The NCI Tissue Expeditor will be available to assist investigators in determining the appropriate tissue resource for their research project. The PA will include an Internet address for a web page that will provide information on available resources and the contacts for each NCI Group. As additional resources become available from Intergroup trials and other tissue banks, the Internet site will be updated and expanded with links to other relevant internet sites.

Description of Project:

The correlative studies for new markers should be based on strong and testable hypotheses. A clear rationale should be given for the experimental design and technical methodologies selected. Preliminary data supporting the hypotheses must be provided. The hypotheses tested must relate to potential clinical applications such as patient monitoring for therapeutic response, development of new treatment strategies or identification of patient subsets for specific treatment approaches.

For more information or application instructions see the NCI web site at <http://www.nih.gov/grants/guide> or contact: Ms. Diane Bronzert

*Division of Cancer Treatment and Diagnosis
National Cancer Institute
6130 Executive Boulevard, Suite 734,
MSC 7432*

Bethesda, MD 20892-7432

Telephone: (301) 496-8866 FAX: (301) 480-4663

Email: Bronzertd@ctep.nci.nih.gov

PROTOCOL NEWS

Update on CALGB 9270: Colorectal Adenoma Prevention Study Using Aspirin (CAPS)

Sponsoring Committee: Cancer Control

Study Chair: Robert Sandler, M.D., UNC Medical Center

Opened: 5/15/93; Accrual to date: 593

CAPS is a randomized, placebo-controlled, double-blind Phase III study testing whether 325 mg daily aspirin use can prevent large bowel neoplasms (adenomas) — precursors to most colorectal cancers.

Colon cancer patients with early stage disease can be enrolled immediately, and those with advanced disease become eligible if they have been recurrence-free after resection for the last five years. A colonoscopy for detection and removal of all adenomas is performed within 4 months of entry to ensure that patients all start with a clean slate. Evidence of adenoma growth during the 3-year duration of the trial is assessed with an exit colonoscopy. The three-year interval coincides with current best practices for follow-up colonoscopies; however, the CAPS protocol permits follow-up examinations at one year, as long as a second follow-up is done two years later. Colonoscopies may also be done at other intervals if clinically indicated by symptoms such as gastrointestinal bleeding or abdominal pain.

Aspirin and other nonsteroidal anti-inflammatory agents show great promise as chemopreventive agents for cancer. The CAPS trial has the potential to provide important information on the risks and benefits of aspirin.

CAPS is a high-priority intergroup study. Slow accrual has been an issue since 1995, and numerous efforts have been taken to generate enrollment. CALGB distributed a survey in fall 1995 to assess reasons for slow accrual. Special CAPS Study Workshops were held in 1995 and 1996, as well as at Group Meetings. A newsletter, the CAPSTONE, began publishing in January 1996 for distribution to physicians, CRAs and oncology nurses in GI areas. A patient information brochure, recruitment poster, and informative slide sets have also been produced. Denise Pearsall, CAPS Study data coordinator, recently made site visits to the eight top-accruing institutions to encourage enrollment.

Supplemental funding for 9270 is available: the NCI Division of Cancer Prevention will grant \$500 per patient accrued to the enrolling institution.

Study chair Robert Sandler discussed the status of 9270 recently.

“There are about 136,000 colon cancer cases in the US each year. Since half of colon cancer patients don't die, there are up to 60,000 patients each year to draw from. There is clearly a large pool of colon cancer survivors who are eligible for the study who receive treatment at CALGB institutions. We have many of the major medical centers in the country and lots of their affiliates, yet in five years we have enrolled fewer than 600 patients.

“This study can yield some very significant results, but the accrual status is getting critical. A couple institutions are accruing well, but most CALGB institutions are not. Successful institutions have people who care about the study and take interest and initiative. In my experience, if someone is championing the study, accruals can come easily.

“If that doesn't happen, we run the risk of not completing the study. And as other interesting new treatments come on line, it would be a blow to our science if we have no useful results from this aspirin study for comparison.

“Now is the best time to start focused efforts to enroll patients to 9270. There is a large body of scientific evidence that suggests that aspirin might be effective. In fact, there are no cancer preventive drugs that appear more promising. In order to determine the appropriate dose and duration, we must conduct randomized trials like CAPS.”

Publicity about the benefits of aspirin use, both in lay press and the NEJM, has made accrual more difficult. Some IRBs decline participation because they believe that aspirin benefits are already documented; and many patients are unwilling to be randomized to placebos. Dr. Sandler responds that “Lots of people are taking aspirin to prevent heart disease even though authoritative organizations like the U.S. Preventive Services task force recommend aspirin only for those with special risks: i.e. previous heart attack, peripheral vascular disease, or transient ischemic attacks. They do not recommend aspirin for average risk people who are appropriate for the CAPS study.”

Denise Pearsall of the CALGB Data Management Center is available to visit interested institutions and assist in accrual development programs for 9270. To receive more information, recruitment posters, patient brochures, or the CAPSTONE newsletter, contact Pearsall at 919-286-0045, ext. 246.

ACKNOWLEDGMENTS

The following organizations have generously supported CALGB research, educational programs, publications, and data resources during 1998:

Alza Pharmaceuticals
Amgen, Inc.

Arrow International
Berlex Laboratories
Breast Cancer Research
Foundation
Bristol-Myers Squibb Oncology
Cellcor, Inc.
Chiron Therapeutics
Genetics Institute
Glaxo Wellcome Oncology
Immunex Corporation

Impact Communications
Janssen Pharmaceutica
Research Foundation
Lederle International / Wyeth
Ayerst Laboratories
Lilly Oncology
Nexstar Pharmaceuticals
Novartis Oncology
Ortho Biotech Inc.
Pfizer Inc.

Pharmacia & Upjohn Co.
Rhône-Poulenc Rorer
Pharmaceuticals, Inc.
Schering Corporation
SEQUUS Pharmaceuticals, Inc.
SmithKline Beecham
T.J. Martell Foundation for
Leukemia, Cancer and AIDS
Research
Vysis, Inc.

CALGB 9344 Presented at ASCO

The following abstract for CALGB 9344: Doxorubicin dose escalation, with or without Taxol, as part of the CA adjuvant chemo regimen for node-positive breast cancer: A Phase III Intergroup Study, was presented at the American Society of Clinical Oncology, May 18, 1998. (Proc ASCO 17:390a, 1998)

Improved disease-free and overall survival from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients with node-positive primary breast cancer.

I.C. Henderson, D. Berry, G. Demetri, C. Cirincione, L. Goldstein, S. Martino, J.N. Ingle, M.R. Cooper, G. Canellos, E. Borden, G. Fleming, J.F. Holland, S. Graziano, J. Carpenter, H. Muss, L. Norton., For CALGB, ECOG, SWOG, and NCCTG.

No previous randomized trial has found an adjuvant chemotherapy more active than doxorubicin plus cyclophosphamide (C). To test if dose escalation of doxorubicin, or the sequential use of paclitaxel (as suggested by modelling) could improve results, 3170 patients were randomized between May 1, 1994 and April 15, 1997 in a 3 x 2 factorial trial design to cyclophosphamide, 600 mg/m² plus doxorubicin 60, 75, or 90 mg/m² (+ G-CSF) q 3 wks x 4 followed either by no paclitaxel (AC) or by paclitaxel 175 mg/m² q 3 wks x 4 (AC→T). Tamoxifen 20 mg po daily for 5 years was then offered to patients with estrogen receptor positive tumors (ER+). An independent board provided group sequential monitoring. The arms were balanced in entry characteristics: 62% were premenopausal and 58% were ER+; 46% had 1-3 involved axillary nodes, 42% had 4 to 9, and 12% had 10 or more. At the first pre-planned interim analysis (450 events), no differences in disease-free survival or overall survival related to doxorubicin dose were seen, but use of paclitaxel reduced the recurrence rate by 22% and the death rate by 26% by multivariate analysis.

Kaplan-Meier estimates at 18 months

(p unadjusted for interim analysis):

	AC	AC →T	p =
Disease-Free	86% ± 1.2%	90% ± 1.0%	0.0077
Overall Survival	95% ± 0.7%	97% ± 0.6%	0.0390

No unusual toxicities of doxorubicin plus cyclophosphamide were seen. Common toxicities (grade ≥ 3) in patients given paclitaxel were: transient myelosuppression 21%, neuropathy 5%, pain 5%, and hyperglycemia 5%. Post-chemotherapy cardiotoxicity occurred in 6% of patients but was not significantly associated with the dose levels of doxorubicin or the use of paclitaxel. Hence, evidence to date indicates that the sequential addition of paclitaxel to doxorubicin plus cyclophosphamide as post-operative adjuvant therapy of node-positive primary breast cancer is well tolerated and significantly improves disease-free survival and overall survival.

CALGB Study Funding

Support is available to qualifying institutions for participation in these studies. Payments are made through the main member institution. For more information, consult the "Study Funding List" on the CALGB website ("members only" Financial section). You may also contact Mary A. Sherrell, Financial Officer at (773) 702-9856.

- 9170 Hospital vs Early Discharge Therapy of Low-Risk Patients with Fever and Neutropenia. Multi-Center Phase III Study.
- 9270 Colorectal Adenoma Chemoprevention Trial Using Aspirin. Phase III Study.
- 9334 Sclerosis of Pleural Effusion by Talc Thoracoscopy vs. Talc Slurry. Phase III Study.
- 9335 Video-assisted Wedge Resection + Radiotherapy for High Risk T1 NSCLC. Phase II Study.
- 9371 Weight Loss Program of Women with Breast Cancer. Pilot Feasibility Study.
- 9380 Thoracoscopic Staging for Esophageal Cancer. Phase II Study.
- 9431 Sequential and Concomitant Chemoradiotherapy with New Agents in Combination with Cisplatin for Inoperable Stage IIIA and IIIB NSCLC. Randomized Phase II Study.
- 9473 Omega-3 Fatty Acids for Cancer Cachexia. Phase I/II Trial.
- 9480 Suramin Dose Comparison Administered with a Fixed Dosing Schedule in Patients with Advanced Prostate Cancer. Phase III Study.
- 9481 Hepatic Artery Floxuridine, Leucovorin, and Dexamethasone vs Systemic 5-FU and Leucovorin as Treatment for Hepatic Metastases from Colorectal Cancer. Phase III Study.
- 9484 Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data. Specialized Registry.
- 9490 Does an Oral Analgesic Protocol Improve Pain Control for Patients with Cancer? (ECOG E4293)
- 9499 Chemoprevention Trial to Prevent Second Primary Tumors with Low-Dose 13-CIS Retinoic Acid in Head and Neck Cancer. (MDACC DM90-094)
- 9581 Adjuvant Immunotherapy with Monoclonal Antibody 17-1A after Resection for Stage B2 Colon Adenocarcinoma. Phase III Randomized Study.
- 9594 Intermittent Androgen Deprivation in Patients with Stage D2 Prostate Cancer. Phase III Study. (SWOG 9346)
- 9596 Vincristine, Doxorubicin, and Dexamethasone with or w/o PSC-833 in Patients with Relapsing or Refractory Multiple Myeloma. Phase III Study. (ECOG E1A95)
- 9670 Barriers to Participation of Older Women with Breast Cancer in Clinical Trials. Pilot Study.
- 9682 Prognostic Significance of Endorectal MRI in Predicting Outcome After Combined Radiation and Androgen Suppression for Prostate Cancer. Prospective Phase II Study.
- 9730 Taxol vs. Taxol + carboplatin for advanced NSCLC. Randomized Phase III Study.
- 9770 High-Dose vs Conventional Dose Octreotide Acetate vs Loperamide in the Treatment of Chemotherapy-related Diarrhea in Patients with Colorectal Cancer. Randomized Trial. (ECOG E1295)

Protocol Update

NEW STUDIES:

4/15/98

9732- A randomized phase III study comparing etoposide and cisplatin with etoposide, cisplatin, and paclitaxel in patients with extensive small cell lung cancer.

Study Chair: Harvey B. Niell, M.D.

5/15/98

9734- A phase III study of surgical resection and chemotherapy (paclitaxel and carboplatin) with or without adjuvant radiotherapy for resected stage IIIA non-small cell lung cancer.

Study Chair: Leslie Kohman, M.D.

9782- A phase II trial of potency-sparing hormonal therapy in patients with elevated serum PSA after radiation therapy or radical prostatectomy for prostate cancer.

Study Chair: Joel Picus, M.D.

9791/GOG 164- A randomized, controlled intergroup trial of salvage therapy with paclitaxel and carboplatin versus salvage therapy with stem cell supported high-dose carboplatin, mitoxantrone and cyclophosphamide in patients with persistent low volume ovarian cancer and response to primary therapy.

Study Chair: Kenneth Zamkoff, M.D.

6/15/98

9863- Phase I study of irinotecan (CPT-11) in patients with abnormal liver or renal function or with prior pelvic radiation therapy.

Study Chair: Alan Venook, M.D.

7/15/98

39801- Concurrent carboplatin, paclitaxel, and radiation therapy versus induction carboplatin and paclitaxel followed by concurrent carboplatin, paclitaxel and radiation therapy for patients with unresectable stage III non-small cell lung cancer: a phase III trial.

Study Chair: Everett Vokes, M.D.

9790/SWOG 9628-Phase II study of dexamethasone/alpha interferon in AL amyloidosis.

Study Chair: Richard A. Larson, M.D.

9840- A phase III study of paclitaxel via weekly 1 hour infusion versus standard 3 hour infusion every 3 weeks in the treatment of patients with metastatic breast cancer.

Study Chair: Andrew D. Seidman, M.D.

9870- Quality of life and cost analysis of prospective randomized phase III trial comparing trimodality therapy to surgery alone for esophageal cancer. (Companion to CALGB 9781)

Study Chairs: Marcy List, Ph.D. and David Pfister, M.D.

CLOSED PROTOCOLS:

1/5/98

9466- Correlative science studies in non-small cell lung cancer: intergroup E4592. (Companion to E3590/9393)

Study Chair: Leslie Kohman, M.D.

4/15/98

9731- Weekly paclitaxel for advanced non-small cell lung cancer: A phase II limited access trial.

Study Chair: Wallace Akerley, M.D.

4/30/98

9683- A phase II study of oral GW776 (NSC #687296), 5-fluo-

rouracil (5-FU) (NSC # 19893), and leucovorin (LV) in patients with advanced colorectal carcinoma.

Study Chair: Neal Meropol, M.D.

5/27/98

8892/ECOG 8892- Phase III trial of orchiectomy/LHRH analog + flutamide + suramin + hydrocortisone vs orchiectomy/LHRH analog + flutamide in patients with metastatic prostate cancer.

Study Chair: Nancy Dawson, M.D.

5/29/98

9082- A randomized, comparative study of high dose CPA/CDDP/BCNU and ABMS versus standard dose CPA/CDDP/BCNU as consolidation to adjuvant CAF for patients with operable stage II or stage III breast cancer involving > 10 axillary lymph nodes.

Study Chair: William P. Peters, M.D., Ph.D.

6/15/98

9371- A weight loss program of women with breast cancer: a pilot feasibility study.

Study Chair: Consuelo Skosey, R.N.

6/30/98

9431-Sequential and concomitant chemoradiotherapy with new agents in combination with cisplatin for inoperable stage IIIA and IIIB non-small cell lung cancer: a randomized phase II study.

Study Chair: Everett E. Vokes, M.D.

7/1/98

8891/SWOG 8710- Trial of cystectomy alone versus neoadjuvant M-VAC + cystectomy in patients with locally advanced bladder cancer.

Study Chair: Nicholas Vogelzang, M.D.

7/15/98

9238- Pulmonary exercise testing as a tool for operative selection in patients with lung cancer.

Study Chair: Gregory Loewen, D.O.

9480- A phase III study of three different doses of suramin (NSC #34936) administered with a fixed dosing schedule in patients with advanced prostate cancer.

Study Chair: Eric Small, M.D.

9195/SWOG 9008- Trial of adjuvant chemoradiation after gastric resection for adenocarcinoma: Phase III.

Study Chair: J. Milburn Jessup, M.D.

9565- Phase I study of gemcitabine in patients with organ dysfunction.

Study Chair: Alan P. Venook, M.D.

7/24/98

9281- A phase II trial of induction chemotherapy followed by radiation therapy plus concurrent chemotherapy for poor prognosis, locally advanced previously untreated carcinomas of the anal canal.

Study Chair: Neal Meropol, M.D.

8/3/98

9496/ECOG 2190- A phase III study of conventional adjuvant chemotherapy versus high dose chemotherapy and autologous bone marrow transplantation or stem cell transplantation as adjuvant intensification therapy following conventional adjuvant chemotherapy in patient with stage II and III breast cancer at high risk of recurrence.

Study Chair: William Vaughan, M.D.

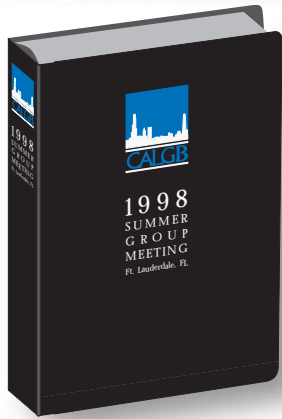


CALGB 40th Anniversary Book

CALGB is proud to present our 40th Anniversary Book, available to interested members. This two-volume commemorative edition features selected published studies from the Breast, Lymphoma, Respiratory, GI, Prostate and Leukemia Committees.

The compiled articles offer a retrospective view of the Group's accomplishments and invaluable contributions to cancer research since 1956.

CALGB will reprint a limited number of both volumes for the exclusive use of CALGB members. The Anniversary Books will be shipped to members who have pre-ordered by September 1. We request a suggested donation of \$45 each to cover the costs of printing and mailing. Please fill out the form below to reserve your copies now.



CALGB Summer 98 Agenda Book

A limited number of the new Agenda Books distributed at the Summer Group Meeting in Fort Lauderdale are now available for \$30.

The new Agenda Book is a black 3-ring binder with pockets and tabs. Inside are three removable reference booklets, and loose-leaf statistical reports from CALGB open protocols, (320 pages, separated by index tabs and organized by Committee).

The removable sections are:

- Agenda and meeting information booklet—16 pages
- CALGB Directory—12 page booklet with complete committee rosters, leadership, contact information for CALGB staff.
- Study Summary—24 page booklet with accrual data, protocol status by committee, protocol index and study bibliography.



Update your *Cal•Gab* Subscription

The *Cal•Gab* is CALGB's quarterly newsletter. Copies are mailed free of charge to CALGB members. Interested non-members may also request complementary subscriptions.

Please use the form below to update or correct your mailing address, add a new subscription for yourself or a colleague, or cancel your subscription.

Please send me:

 ___ 40th Anniversary Book(s) (\$45 each)

 ___ CALGB Summer 98 Agenda Book(s) (\$30 each)

NAME _____ PHONE # _____

INSTITUTION _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

My check enclosed, payable to **CALGB Foundation**, in the amount of \$_____.

Please charge my credit card. MasterCard Visa

CARD NUMBER _____ EXP. DATE _____

CARDHOLDER'S SIGNATURE _____

Mail to: CALGB Foundation
Mary A. Sherrell, M.A., Treasurer
208 S. LaSalle St., Suite 2080
Chicago, IL 60604-1104

FAX to: (312) 345-0117

Start
Please Update my *Cal•Gab* Subscription.
 Cancel

CALGB CALENDAR

Fall '98 Group Meeting	Nov. 20–22, 1998	New Orleans, Louisiana (Hilton New Orleans Riverside Hotel)
Summer '99 Group Meeting	June 25–27, 1999	Toronto, Ontario, Canada (Sheraton Centre)

ABSTRACT DEADLINES

Abstracts reporting on CALGB studies must be submitted to the Central Office for review at least two weeks prior to the submission deadline.

	ABSTRACTS DUE AT CENTRAL OFFICE	SUBMISSION DEADLINE	MEETING DATE	LOCATION
ASH American Society of Hematology	Aug. 16	Sept. 1	Dec. 4–8, 1998	Miami, FL
AACR American Association for Cancer Research	Oct. 23	Nov. 6	April 10–14, 1999	Philadelphia, PA
ASCO American Society of Clinical Oncology	Nov. 19	Dec. 3	May 15, 1999	Atlanta, GA



Cancer and Leukemia Group B
Central Office of the Chair
208 S. LaSalle St., Suite 2000
Chicago, IL 60604-1104