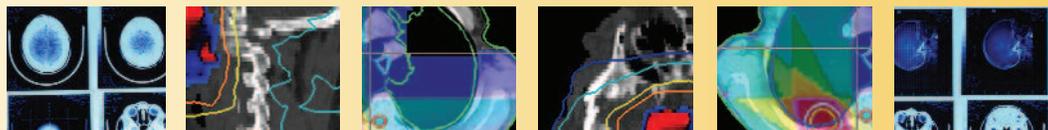


SUMMER 2012



Group Chairman Welcome

We have made significant progress in forging our new relationships with GOG and NSABP under the auspices of NRG Oncology. NCI is expected to release the “Funding Opportunity Announcements (FOAs)” for proposals to fund group administration grants, biostatistical and data management centers, academic centers of excellence, translational research centers, and quality assurance centers for imaging and radiation oncology sometime this summer. We have worked in an extremely collaborative manner with our partners in GOG and NSABP in preparation for these FOAs and will be well prepared to submit very competitive applications this fall. We expect that there will be seven cancer disease site committees within the NRG Oncology application (Brain Tumor, Head and Neck Cancer, Lung Cancer, Breast Cancer, Gastrointestinal Cancer, Gynecologic Cancer, and Genitourinary Cancer), as well as an appropriate number of scientific resource committees. The American College of Radiology also plans to submit a proposal with several partners to serve as a resource for both radiation oncology and imaging quality assurance for all groups. To describe the atmosphere surrounding these changes as dynamic would be an understatement.



Walter J. Curran, Jr. MD

Please take advantage of the tremendous educational opportunities present here at our RTOG Semiannual Meeting. Our Friday Symposium on tissue biobanking promises to be extremely relevant to many activities within RTOG and NRG Oncology, as does NSABP Chair Dr. Wolmark’s keynote address on Saturday.

RTOG Semiannual Meeting Highlights

The June 14–17 Semiannual Meeting is packed with opportunities to learn more about RTOG’s science, programs and future initiatives. Following are just a few of the meeting’s highlights.

Thursday, June 14

The full-day Research Associates Education Session will feature in-depth presentations about the Medidata RAVE electronic data capture system; information about purpose, design, and administration of neurological assessments; and a lineup of relevant topics for the afternoon session.

Friday, June 15

- ▶ The RTOG Internet Café & Medidata RAVE Demonstration opens at 8:00 AM and will be open until 6:00 PM on Friday and 2:00 PM on Saturday. Stop by to see what the RAVE is all about!
- ▶ Interested in RTOG 1115 participation? Join the trial kick-off breakfast (7:00 to 9:30 AM)—advance registration is required.
- ▶ The RTOG Symposium (*Molecular Analyses on Biospecimens: Doing More with Less*) (8:00 to 11:00 AM) brings together pathology and biomarker experts from around the country to discuss strategies for maximizing the use of limited tissue resources in an environment of increasing demand.
- ▶ The Translational Research Program (TRP) Immunomodulation Subcommittee holds its inaugural meeting (11:00 AM to 12:00 PM) with the introduction of the recently appointed subcommittee liaison James Hodge, MD, MBA.

Saturday, June 16

- ▶ The TRP session (10:00 AM to 12:00 PM) offers presentations from investigators advancing cancer treatment that involves the interplay of chemotherapy, radiation therapy, and immunology as the program begins to actively integrate immunomodulation into its research planning.
- ▶ You will not want to miss the Publications Scientific Session (1:00 to 2:00 PM) that features the RTOG oral abstracts recently presented at ASCO 2012.
- ▶ During the meeting’s Plenary Session and Keynote Address (2:00 to 3:00 PM), RTOG Chair Walter Curran, MD will provide updates on RTOG research activities and plans underway for NRG Oncology. RTOG welcomes Norman Wolmark, MD, National Surgical Adjuvant Breast & Bowel Project (NSABP) Group Chair, to deliver the keynote address about NSABP research.

Visit www.RTOG.org for the latest group news

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RADIATION THERAPY
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RTOG Presentations at ASCO 2012 Focus on Biomarker-Driven Science

RTOG-sponsored research was significantly represented at the American Society of Clinical Oncology (ASCO) 2012 Annual Meeting, held from June 1–5 in Chicago. RTOG investigators participated in 3 oral abstract presentations (highlighted below), one of which reported long-term findings related to the primary aims of a phase III brain cancer trial, as well as in 4 poster presentations and 1 poster discussion session.

Oligodendroglioma: Long-Term Results Show Chromosomal Abnormality is a Strong Indicator for Determining Treatment and Outcome

RTOG 9402 was undertaken to evaluate whether the addition of chemotherapy (CT) to radiation therapy (RT) would prolong overall survival (OS) for patients with relatively rare malignant oligodendroglioma brain tumors that were co-deleted for chromosomes 1p and 19q. The phase III trial randomized 291 patients with oligodendrogliomas to treatment with PCV (procarbazine, CCNU [lomustine], and vincristine) chemotherapy and RT or to treatment with RT alone. After a median follow-up of 11.3 years, the current analysis demonstrated that for the 126 patients with 1p and 19q co-deletion, those in the PCV + RT arm had a much longer median survival time (MST) than those in the RT-alone arm (14.7 years versus 7.3 years).

J. Gregory Cairncross, MD, the trial principal investigator (PI) and professor and head of the Department of Clinical Neurosciences at the University of Calgary in Alberta, Canada, says, “We now have evidence that the chromosomal structure of 1p and 19q co-deletion can be used as a marker to determine which patients will benefit from combined chemotherapy and radiation therapy.”

Biomarker Profiles Added to Glioblastoma Analysis Model May Allow Identification of More Relevant Prognostic Classes

RTOG 0525, a phase III trial comparing RT plus conventional adjuvant temozolomide (TMZ) with RT plus dose-intensive TMZ in patients with newly diagnosed glioblastoma, included a sub-study related to molecular analysis of tumor tissue. Additional molecular variables specifically related to glioblastoma treated with TMZ were identified in order to update the former recursive partitioning analysis (RPA) model that relied on clinical variables in order to classify this tumor type into relevant prognostic categories. Profiling of key signaling molecules in tissues collected from 162 trial participants demonstrated a significant association of pAKT, c-met, and MGMT protein with adverse outcome on multivariate analysis.

By combining these molecular biomarkers with the clinical variables (eg, age, performance status, and extent of resection) used in the former RPA model, study investigators were able to generate a more discriminatory RTOG RPA model with better separation of prognostic groups (41.7% explained variation for molecular versus 14.9% for clinical). They concluded that, although further validation is indicated, the classification model holds promise for patients with glioblastoma who are treated with RT and TMZ.

“Much has been learned about the molecular makeup of malignant gliomas. With this trial, we’ve taken a step toward updating the classification system to include molecular factors,” says Arnab Chakravarti, MD, Radiation Oncology Department Chair at Ohio State University’s Comprehensive Cancer Center/Arthur G. James Cancer Hospital, and an RTOG 0525 co-chair. “These data will be useful in prognostic classification of glioblastoma tumors, which could be used to direct patients to clinical trials aiming to develop targeted treatments based upon a tumor’s molecular profile.”

The Role of Radiation Therapy in “Good-Risk” DCIS Featured in the “Best of ASCO” Meetings

The increasingly more common diagnosis of noninvasive ductal carcinoma in situ (DCIS) has heightened interest in optimizing treatment strategies for this earliest and most curable form of breast cancer. Building upon the experience of previous retrospective studies suggesting that small DCIS lesions with a low-grade pathology classification (“good risk”) can be effectively treated with RT or with observation, RTOG 9804 investigators sought to evaluate the efficacy of observation alone in such a subset of DCIS patients. From December 1999 to July 2006, 636 women with mammographically detected DCIS with low or intermediate nuclear grade, tumor size <2.5 cm, and surgical margins ≥3 mm were randomized to receive RT (50 Gy) or undergo observation.

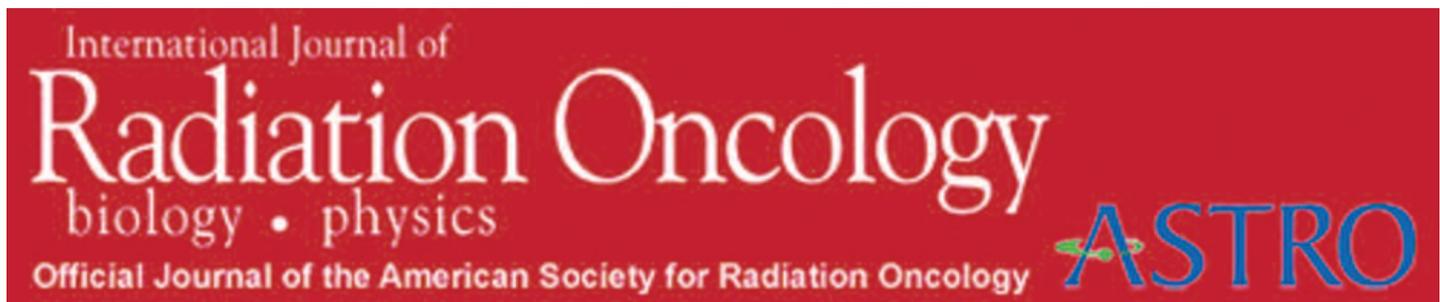
Initial data analysis from this phase III trial demonstrated reduced rates of local failure associated with whole-breast radiation versus observation alone. Although the overall number of women experiencing a breast cancer recurrence (invasive or in situ) was small, the addition of RT showed a statistically significant reduction in such recurrence—0.4% for the RT arm and 3.2% for the observation arm—at 5 years.

The rates of disease-free survival and overall survival were considered excellent. The rate of grade 1–2 toxicities was 76% in the RT arm versus 30% in the observation arm; however, higher grade toxicities occurred at similar rates (4%) in both arms. “The low number of study participants who had a recurrence of their breast cancer strongly suggests that we have successfully identified criteria that distinguish good-risk DCIS patients, which is important for evaluating treatment options for this patient population,” says RTOG PI Beryl McCormick, MD, chief of External Beam Radiotherapy Service at Memorial Sloan-Kettering Cancer Center. RTOG plans continued follow-up with the patients on this trial to assess long-term outcomes.

The RTOG 9804 ASCO abstract presentation was hand selected to be included in 3 domestic and 15 international “Best of ASCO” meetings, which are held shortly after the ASCO Annual Meeting. This educational initiative condenses Annual Meeting highlights into a 2-day program for the purpose of increasing global access to cutting-edge science. Selected abstracts reflect research that is relevant and significant in oncology today.

Recent Journal Publications

RTOG investigators continue the strong pace of research results dissemination. Through the first half of this year, 26 articles and one editorial have been published in peer-reviewed journals, with 15 of the published papers appearing in the *International Journal of Radiation Oncology*Biography*Physics*. Through June 5, researchers have given 24 abstract presentations at a wide range of scientific venues, including eight presentations at the 2012 ASCO Annual Meeting.



RTOG 0229 Trial Establishes the Safety and Efficacy of Chemotherapy Plus Radiotherapy Prior to Surgery for Stage III Non-Small-Cell Lung Cancer

Survival of patients with stage III non-small-cell lung cancer is improved when full-dose radiotherapy is added concurrently to chemotherapy, followed by surgery, according to results of a Radiation Therapy Oncology Group (RTOG) trial recently published online in the *International Journal of Radiation Oncology*Biography*Physics*. In this first multicenter study of its kind, RTOG 0229 investigators reported that 27 of the 43 (63%)

“An important trial goal was to show that full-dose radiation therapy with chemotherapy prior to surgery can eradicate cancer of the mediastinal lymph nodes, which results in improved patient outcomes. In this study, we found a survival rate of 75% at 2 years for patients whose lymph nodes were clear of cancer after treatment.”

Mohan Suntharalingam, MD
RTOG 0229 Principal Investigator

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study participants whose regional (mediastinal) lymph nodes were available for posttreatment pathologic review had no evidence of lymph node disease, which was the strongest predictor of participants' long-term survival.

The trial principal investigator, Mohan Suntharalingam, MD, professor of radiation oncology at the University of Maryland School of Medicine in Baltimore, explains, “An

Eighteen RTOG institutions, including 3 Community Clinical Oncology Program (CCOP) members, enrolled a total of 60 study participants in RTOG 0229. “These results provide us with prospective data demonstrating that in the right patient population you can safely deliver full-dose radiation and chemotherapy prior to surgery,” says Walter J. Curran, Jr., MD, RTOG Group Chair and Executive Director of the Winship Cancer Institute of Emory University in Atlanta. “An important study conclusion was a new standard for future research, specifically, the RTOG 0839 trial that is currently evaluating concurrent presurgical chemotherapy and radiation therapy with or without the EGFR [epidermal growth factor receptor] inhibitor panitumumab.”

The study was supported by the RTOG U10 CA21661 and CCOP U10 CA37422 grants from the National Cancer Institute.

[RTOG 0229 Publication Link](#)

Redesigning Radiotherapy Quality Assurance Workshop Publication

The National Cancer Institute sponsored a 2-day workshop in 2010 to examine challenges and opportunities for optimizing radiotherapy quality assurance (QA) in clinical trial design. Recommendations of the invited thought leaders are published in the July 1, 2012 issue of the *International Journal of Radiation Oncology*Biography*Physics*. [View the abstract](#). A link is also available on the [RTOG Web site](#). A login and password are required to access the full-text article.

People in the News

The RTOG Translational Research Program Committee Welcomes Two New Investigators.

Dr. Peter Houghton Joins the RTOG Translational Research Program



The Radiation Therapy Oncology Group (RTOG) recently announced Peter Houghton, PhD, director of the Center for Childhood Cancer at Nationwide Children's Hospital of the Ohio State University, as the new liaison to the Translational Research Program's Sarcoma Subcommittee. Houghton is a well-established scientist whose work has focused on understanding the biology of childhood solid tumors, especially sarcomas. His

research has led to the development of xenograft models of childhood cancers, as well as of drugs such as topotecan and irinotecan, which are now standard in many pediatric clinical protocols; this work prompted the formation of the Pediatric Preclinical Testing Program (PPTP) that he directs. RTOG's Vice Chair for Translational Research, Adam Dicker, MD, PhD, chair of the radiation oncology department at Thomas Jefferson University in Philadelphia, comments, "I have known Dr. Houghton for over 20 years and highly regard his work that has led to laboratory processes to systematically evaluate new agents against molecularly characterized solid tumor models, resulting in the expedited translation of new treatments into clinical care."

Houghton has established collaborations with the adult sarcoma surgical oncology program at OSU to also develop new models of adult sarcomas through genomic profiling and expression. The goal of these collaborations is to develop comprehensive models of several adult sarcomas to enable the development of novel therapeutics and allow for identification of biomarkers that can be tested prospectively in clinical trials. "I look forward to contributing my knowledge of drug mechanisms and childhood sarcomas to support the development of clinical trials for adults with sarcomas," says Houghton.

In his new role, Houghton will work closely with RTOG's Sarcoma Working Group, chaired by Dian Wang, MD, PhD, an associate professor of radiation oncology at the Medical College of Wisconsin. "Dr. Houghton has an impressive track record of laboratory discovery, and we are thrilled to gain his expertise," says Wang.

RTOG Group Chair Walter Curran, MD, executive director of the Winship Cancer Institute of Emory University, also enthusiastically welcomes Houghton. "As RTOG continues to expand its biomarker-driven research," states Curran, "Dr. Houghton's success in translating laboratory findings into a clinical care setting will be a tremendous asset."

The Radiation Therapy Oncology Group Names Dr. James Hodge to Guide Immunomodulation Research

Launch of the Translational Research Program (TRP) Committee's new

Immunomodulation Subcommittee at its June Semiannual Meeting is extremely timely, according to James Hodge, PhD, MBA, the newly appointed subcommittee liaison. "Developments in the past several years employing both

radiation therapy and immunotherapy to treat cancer have created an explosion of interest and activity," explains Hodge, "and the timing is perfect to begin to focus our efforts on rigorous research strategies that combine these modalities." Hodge, an investigator and director of the Recombinant Vaccine Group in the Laboratory of Tumor Immunology and Biology of the National Cancer Institute, has been active in the area of tumor immunity for nearly 20 years and has made significant contributions to the design and development of novel recombinant vaccines and vaccine strategies for cancer immunotherapy. The concepts and therapeutics developed within the Recombinant Vaccine Group have been translated into over 30 clinical trials.



Adam Dicker, MD, PhD, RTOG's Vice Chair for Translational Research and chair of the radiation oncology department at Thomas Jefferson University, echoes Hodge's enthusiasm. "Use of immune modulatory strategies in cancer treatment is now being demonstrated in the clinic. Patients are experiencing durable tumor remissions in the setting of metastatic cancer. Significant advances generated from basic and translational research have energized the field of immunotherapeutics. The recent approvals of ipilimumab and sipuleucel-T, provide proof of its clinical applicability and benefit."

Hodge says of his RTOG research interest, "RTOG has enormous intellectual resources and offers the opportunity for thought leaders to come together and agree on future research practices; for example, the best immune parameters to observe or the best thing to stain for in the very limited biopsy material ... how we can move beyond anecdotal observation with a common purpose and process." In the near term, Hodge views standards development in areas such as analyzing patient samples and immunomonitoring techniques as a key success factor for research activities. Intending also to tackle the top handful of questions that need to be clarified to move forward prospectively, Hodge notes, "Across trials we will need to

Program Highlights

RTOG 1115 Trial Goes Live With New Electronic Data Capture System

As one of the first cancer cooperative groups to activate Medidata RAVE, RTOG expects the electronic data capture system to offer research personnel significant efficiencies in managing clinical trial data.

RTOG announced that the recently activated RTOG 1115 study* marks the cooperative group's first trial to employ Medidata RAVE, a user-friendly electronic data capture (EDC) system. The application offers many helpful features to make the data entry and submission experience more streamlined for end users. It is particularly advantageous that RAVE, as a National Cancer Institute (NCI)-sponsored initiative, will be available for use by all NCI cooperative groups in future studies. When RAVE is fully implemented, research associates and investigators will need to learn only one EDC software program, instead of the multiple (some paper-based) systems currently in use. New features that RAVE end users can look forward to include:

- Instantaneous feedback on submitted data and any resulting action items (eg, responding to data queries)
- Data queries resolved electronically on the same data entry screen
- Trial-specific task lists itemizing all data issues for review (eg, data queries, past due forms, study notifications)
- Real-time submission of reports that previously had to be mailed (eg, pathology reports) via uploading of scanned documents directly into the RAVE database.

To get started, new RAVE users will need to create an iMedidata account. Helpful information about the entire RAVE process, including a Medidata RAVE start-up tutorial for RTOG 1115 research personnel and Medidata RAVE account activation instructions, is found on the [RTOG Web site](#).



Please note that the NCI Cancer Trials Support Unit (CTSU) Help Desk will provide support for RAVE and iMedidata navigation, and all RAVE functionality questions, as well as offer assistance with eLearning and account access. The contact information for this Help Desk is 1-888-823-5923 or [contact the CTSU](#). Support is provided from 9:00 AM to 8:30 PM eastern time.

To learn more, [click here](#).

*More information about RTOG 1115 (*Phase III Trial of Dose Escalated Radiation Therapy and Standard Androgen Deprivation Therapy (ADT) with a GnRH Agonist vs. Dose Escalated Radiation Therapy and Enhanced ADT with a GnRH Agonist and TAK-700 for Men with High Risk Prostate Cancer*), activated on May 1, 2012, is available on the RTOG Web site. Also see the "Recently Activated RTOG Clinical Trials" section of this issue of the *RTOG Newsletter*.

NCI Updates Proton Radiation Therapy Guidelines

In response to rapidly evolving proton radiation therapy (PRT) technology, NCI announced on April 12, 2012 new guidelines for the use of PRT in NCI-sponsored cooperative group trials. These guidelines, which update those established in 2010 to address PRT-related credentialing and quality assurance procedures, are available on the [RTOG Web site](#).

RTOG Trials Meet Target Accrual Goals

RTOG is pleased to recognize that the following three trials have recently met study participant accrual goals:

- ▶ RTOG 0831, an RTOG CCOP trial, exceeded its target accrual goal of 218 study participants. The goal of the double-blinded, randomized phase III trial is to determine whether tadalafil is effective in preventing erectile dysfunction in patients treated with radiotherapy for prostate cancer.
- ▶ RTOG 0232 accrued 586 study participants and met its accrual goal in February 2012. The phase III trial compared the efficacy of combined external beam radiation and transperineal interstitial permanent brachytherapy with brachytherapy alone in patients with intermediate-risk prostate cancer.
- ▶ RTOG 0837 closed in May 2012 after accruing 261 study participants onto the phase II trial to test the efficacy of conventional chemoradiation and adjuvant temozolomide plus cediranib for treating patients with newly diagnosed glioblastoma.

Our congratulations to the research teams working on these trials for successfully completing accrual!

Trial Spotlight RTOG 0524: We're Almost There!

RTOG is pleased to report that participant accrual for the RTOG 0524 trial is approaching completion. Activated in July 2005, the phase I/II trial is assessing the safety and efficacy of the weekly co-administration of paclitaxel and trastuzumab in combination with daily radiation therapy in patients with muscle-invasive bladder cancer who are not candidates for surgical removal of their bladder. The trial also is assessing whether overexpression of the human epidermal growth factor receptor-2 (or HER-2/neu) protein by a tumor can predict a patient's response to therapy. Trastuzumab is a monoclonal antibody against HER-2/neu.

According to the trial's principal investigator, M. Dror Michaelson, MD, clinical director of the Genitourinary Cancer Center at Massachusetts General Hospital, "We are excited about completing this trial in the near future; it brings us closer to establishing an effective treatment option for patients with bladder cancer who cannot undergo bladder removal surgery for one reason or another. We appreciate the work that sites have done thus far in accruing participants to the trial and, with just a little more time, we will complete accrual for the trial."

"...this trial...brings us closer to establishing an effective treatment option for patients with bladder cancer who cannot undergo bladder removal surgery for one reason or another."

M. Dror Michaelson, MD
RTOG 0524 Principal Investigator

General Hospital trial site comments, "Our site has had much success in accruing participants based on close collaboration of the research team. I commend everyone's effort and have every confidence that, with the combined effort of all sites, we will meet the accrual goal soon."

As of June 4 of this year, 72 of the study's target 88 participants had been enrolled. William Shipley, MD, RTOG Genitourinary Committee Co-Chair, professor of radiation oncology at Harvard Medical School, and chair of the Genitourinary Oncology Unit at Massachusetts

Thank you to all the investigators who have enrolled patients onto the RTOG 0524 trial. Institutions that have enrolled 3 or more participants as of June 4, 2012 are acknowledged below.

Accrual Category Institutions	Principal Investigator Contact Research Associate Contact
8 STUDY PARTICIPANTS	
Massachusetts General Hospital Boston, MA	William Shipley, MD Shannon Himber
4 STUDY PARTICIPANTS	
Virginia Mason CCOP Seattle, WA	Huong Pham, MD Beth Edelheit
Penrose Cancer Center Colorado Springs, CO	Anuj Peddada, MD Jodi Harr
McGill University Montreal, Canada	Luis Souhami, MD Marianna Perna
Nevada Cancer Research Foundation CCOP Las Vegas, NV	Raul Meoz, MD Karen Sartell
3 STUDY PARTICIPANTS	
Utah Cancer Specialists Salt Lake City, UT	R. Jeffery Lee, MD Lisa Olsen
Christiana Care Health Services, Inc. CCOP Newark, DE	Adam Raben, MD Karen Sites
Parkview Comprehensive Cancer Center Fort Wayne, IN	Brian Chang, MD Breck Hunnicutt
Cleveland Clinic Foundation Cleveland, OH	John Suh, MD Rhonda Towns
University of Kansas Cancer Center Kansas City, KS	Thank you University of Kansas Cancer Center for enrolling 3 study participants through the Cancer Trials Support Unit (CTSU)!

Target Accrual: 88

Current Accrual: 92

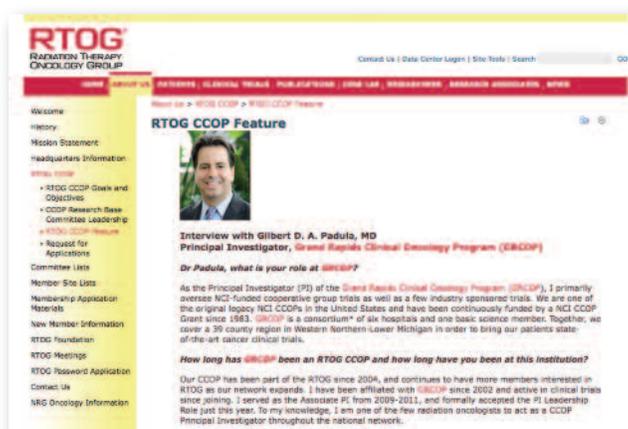
CCOP News

Web Site Feature Highlights Researchers from CCOP Sites

The Radiation Therapy Oncology Group (RTOG) Community Clinical Oncology Program (CCOP) coordinates research focused on alleviating symptoms associated with radiation therapy and combination therapy in patients undergoing such treatments for cancer. The RTOG looks to recognize the work of principal investigators (PIs) at RTOG CCOP sites on its *RTOG CCOP Featured Researcher* Web site page.

The feature consists of a short interview with a PI detailing his or her RTOG CCOP work, personal research interests, and projects planned for the future. This highlight serves as a glimpse into the CCOP world for the greater RTOG community, introducing CCOP investigators and keeping RTOG abreast of the research currently being pursued by CCOP sites.

Gilbert D. A. Padula, MD, the PI at Grand Rapids Clinical Oncology Program in Grand Rapids, MI, is the first CCOP researcher to be featured. **Check out** the Padula interview and those of other CCOP investigators throughout the year.



CCOP Pilot Grant Award Recipients

In order to promote a pipeline of symptom management research, the RTOG CCOP offers a pilot study grant program focusing on research with a strong potential to lead to a phase II or phase III symptom management intervention trial. Through this program, as funding becomes available, requests for applications are announced that invite investigators to submit a study proposal, and those chosen are funded by the RTOG CCOP for 1 year.

Award recipients present their study concepts at the first RTOG semiannual meeting following award receipt, and results are presented the following year. As of June 2012, awards for this year have been granted to four investigators. Congratulations to the award recipients acknowledged below.

Award Recipient	Research Project Title
Daniel Bernard, MSc, MPhil, MD McGill University	Pilot Study on the Effects of Radiation on Memory Processing and Hippocampal Neurogenesis in Adults with Benign Disease
Ronald Chen MD, MPH University of North Carolina, Chapel Hill	A Study to Evaluate Cardiovascular Risk Factors and Receipt of Primary and Preventive Care in Prostate Cancer Patients who Receive Definitive Radiation Therapy and Androgen Deprivation Therapy
Bridget F. Koontz, MD Duke University	The Effect of Aerobic Exercise Training on Radiation-Induced Erectile Dysfunction in a Rodent Model of Prostate Radiotherapy
Tian Liu, PhD Emory University School of Medicine	Ultrasound Imaging and Ultrasonic Tissue Characterization for Measurement of Radiation-Induced Vaginal Toxicity

RTOG Continues Its Robust Record of Trial Activations

Recently Activated RTOG Clinical Trials

RTOG 1115: Phase III Trial Evaluating TAK-700 for Increasing Patient Survivorship and Quality of Life of Patients With High-Risk Prostate Cancer

This phase III trial, with a target accrual of 900 study participants, was activated on May 1, 2012 with the goal of determining the effects of adding TAK-700 (Orteronel) to standard treatment of prostate cancer patients who are at high risk for cancer recurrence. Current standard treatment involves androgen deprivation therapy (ADT) paired with radiation treatment. Previous single-center trials have shown the addition of Orteronel to this treatment regimen to be effective at further reducing serum testosterone in patients, which has led researchers to test the drug's ability to amplify the reduction in serum testosterone of traditional treatment in a multicenter clinical trial setting.

“Orteronel appears to stop *all* testosterone production in the body, including production in the adrenal glands and in the cancer itself,” says M. Dror Michaelson, MD, PhD, of Massachusetts General Hospital in Boston and the trial's principal investigator (PI), of the addition of Orteronel to treatment. Current ADT eradicates only testicular testosterone production, which leaves trace amounts of testosterone in the body—high-risk prostate cancer is particularly susceptible to these trace amounts.

Orteronel's effects on patient quality of life will also be monitored closely during the trial. Says Deborah Bruner RN, PhD, FAAN of Nell Hodgson Woodruff School of Nursing at Emory University in Atlanta, and Outcome Co-Chair of the trial, “We aren't only

interested in whether this treatment incrementally improves survival, but we're also interested in whether this treatment will decrease quality of life, and if it does, then by what increment. We have to balance our improvement in survival with decreases in quality of life; survival is always

“We have to balance our improvement in survival with decreases in quality of life; survival is always our number one concern, but we are equally concerned with the *quality* of that survival.”

Deborah Bruner, RN, PhD, FAAN
RTOG 1115 Outcome Co-Chair

our number one concern, but we are equally concerned with the *quality* of that survival.” The results of this trial could mean an alteration in treatment options for patients with high-risk prostate cancer, offering them increased levels of survivorship.

RTOG 1012: Phase II Trial Tests Whether Chemoradiation Therapy-Induced Esophagitis-Related Pain Can Be Reduced Using Prophylactic Manuka Honey

RTOG 1012 opened to accrual on April 23, 2012 to study the effects of manuka honey on therapy-induced esophagitis (inflammation of the esophagus) pain in patients undergoing

combination chemotherapy and radiation therapy. Honey has been used for centuries for its medicinal properties, and it has been shown in recent research to be an antiviral agent, an effective wound dressing, and to be strongly bacteriostatic. These qualities, partnered with results from three small clinical trials, make honey (specifically manuka honey, considered the standard medicinal honey) a prime candidate for testing as a mucosal healing agent.

Patients undergoing combination chemotherapy and radiation therapy for lung cancer are at an increased risk for developing esophagitis when compared with patients undergoing radiation therapy alone; however, they also have a higher survival rate. Says the trial's PI, Lawrence Berk, MD, PhD, associate professor of radiation oncology at Moffitt Cancer Center in Tampa, “With the administration of manuka honey, we are looking to reduce the symptoms associated with combined chemotherapy and radiation therapy for lung cancer in order to afford patients the most effective and tolerable treatment.” Should trial results show patients with lung cancer experience significant relief from painful esophagitis, this could provide the needed data to support a phase III trial to definitively determine if this natural remedy with no side effects could play a larger role helping patients tolerate the most effective treatment strategies.

“Reducing the symptoms of severe treatment-induced esophagitis would result in less esophageal pain, less difficulty swallowing, and improved patient appetite,” says Ethan Basch, MD, a medical oncologist at Memorial Sloan-Kettering Cancer Center in New York and the trial's quality of life co-chair. Basch is overseeing the evaluation of the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) tool intended to improve understanding of the patient experience of adverse events. As Basch explains, “As part of an NCI-funded initiative, this trial provides an excellent opportunity to assess the feasibility of incorporating the PRO-CTCAE tool into a cooperative group trial to include providing sites computer hardware, training research personnel, and evaluating patients' willingness and capacity to complete PRO-CTCAE forms via Web interface at clinic visits.”

RTOG 1102: Phase I Trial Tests Ganitumab Therapy for Locally Advanced Pancreatic Cancer

High-dose chemotherapy followed by chemoradiation is the current standard approach to treating locally advanced pancreatic cancer; this standard protocol generally results in patient survival of less than 12 months. Activated in September 2011, this trial aims to increase survival time of patients with locally advanced disease by increasing the effectiveness of standard treatment with the introduction of the monoclonal antibody ganitumab. Ganitumab is an agonist of the insulin-like growth factor-1 receptor (IGF-1R);

Recently Activated RTOG Clinical Trials *(Continued from page 8)*

IGF-1R plays a significant role in both tumor cell growth and tumor cell resistance to chemotherapy and radiation treatment.

“Ganitumab...has shown promising results in early-phase trials for patients with metastatic pancreatic cancer,” says Christopher Crane, MD, professor of radiation oncology at MD Anderson Cancer Center in Houston and PI for the RTOG 1102 trial. “Collecting information about the best drug dose and safety of administering [it] is critical to further evaluating the efficiency of this treatment regimen,” Crane further elaborates.

Participants in the trial will receive 2 months of induction chemotherapy with gemcitabine and ganitumab. Study participants will then receive ganitumab in increasing dosage (if tolerated) alongside standard chemoradiation treatment. Following the completion of treatment, participants will receive maintenance doses of gemcitabine and ganitumab until tumor progression.

Amgen is currently conducting a trial of ganitumab in metastatic pancreatic cancer. Thus, the results of RTOG 1102 are of high importance, as they “will expedite further evaluation of this targeted therapy,” says Walter Curran, MD, RTOG Group Chair and Executive Director of the Winship Cancer Institute of Emory University in Atlanta.

RTOG 1106/ACRIN 6697: Evaluating Radiotherapy With FDG-PET/CT for Patients With Non-Small-Cell Lung Cancer

The first positron emission tomography (PET)-based adaptive radiotherapy (RT) treatment trial to be carried out in a multicenter setting activated in February. It is evaluating the potential benefits of altering RT dosage in patients with inoperable stage III non-

small-cell lung cancer (NSCLC) by using information gained from fluorodeoxyglucose (FDG)-PET/computed tomography (CT) scans over the course of treatment. This serves as an alternative to the current standard, in which RT dosage does not vary throughout the course of treatment.

“The trial’s adaptive approach is intended to benefit those patients with locally advanced disease who cannot receive curative local treatment. We will individualize treatment to every patient’s cancer, including the primary lung tumor and any involved lymph nodes. We hope to achieve a 20% increase in local tumor control as well as an improvement in survival,” says the study PI Feng-Ming (Spring) Kong, MD, PhD, clinical associate professor of radiation oncology at the University of Michigan, the institution whose single-center assessment of the concept is being tested in this study.

Participants randomized to the control arm will receive a uniform RT dose (60 Gy). All participants will undergo a baseline FDG-PET/CT scan as part of their treatment planning. Participants in both arms will receive RT once a day 5 days a week for 6 weeks. After 4 weeks of treatment, participants in both arms will undergo a second FDG-PET/CT scan. Participants in the experimental arm will have the RT planning modified to provide as high a dose as possible to the residual active tumor while keeping doses to normal lung tissue constant (mean lung dose of 20 Gy) and doses to other adjacent organs within safe limits. Participants in the control arm will complete treatment as initially planned.

As Kong emphasizes, “The trial will also compare the rates of severe radiation-induced lung toxicity and other adverse events in both arms.”

Metamorphosis of an Idea into a Clinical Trial**RTOG 1106/ACRIN 6697, the first multicenter trial using functional image to guide personalized adaptive radiation in locally advanced non-small-cell lung cancer**

An idea has the potential to become a multicenter trial that provides a new promise, as seen in the case of the recently activated RTOG 1106/ACRIN 6697 trial. The trial began with a young doctor’s idea: Feng-Ming Kong, MD, PhD had been interested in the application of PET imaging in radiation treatment of lung cancer since she was a resident in radiation oncology at Washington University in St. Louis. Guided by Jeffery Bradley, MD, then director of the resident program and current chair of RTOG’s Lung Cancer Committee, Kong and her colleagues initiated a study using PET imaging to improve tumor targeting for radiation therapy (RT) treatment of lung cancer.¹

In 2003, Kong joined the University of Michigan, where she developed the idea of using during-treatment PET imaging to predict and guide radiation treatment. Taking during-radiation PET images was considered to be a radical idea at the time because radiation was believed to induce inflammation that could confound the PET image. Kong’s academic mentor, Theodore Lawrence, MD, PhD, professor and chairman of the university’s radiation oncology department, provided her with full support. With Lawrence’s recommendation, Kong attended ASCO’s Methods in Clinical Cancer Research workshop, during which she gained important insight about clinical trial design, collaboration with other researchers, and data analysis. She subsequently received an ASCO Young Investigator Award and a seed grant from the Radiological Society of North America (RSNA) to initiate a pilot study investigating PET imaging biomarkers.

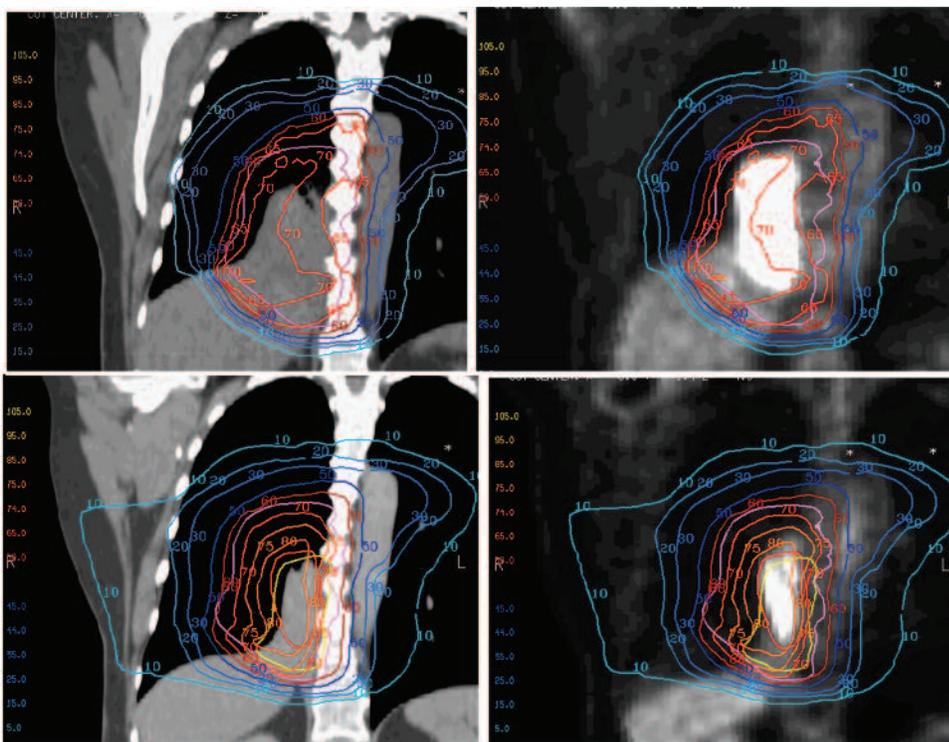
Energized by the workshop to focus her career on radiation oncology research, Kong enrolled in a Clinical Trial Design Master of Public Health graduate program funded by the National Institute of Health’s K30 program at the recommendation of Dean Brenner, MD, a senior

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medical oncology professor at the University of Michigan. This mentored program provided Kong with more extensive knowledge about conducting clinical trials and shaped her initial ideas into a series of research projects and clinical trials.

The result of the first pilot study of 15 study participants suggested a significant correlation between during-radiation therapy FDG-PET scan results and post therapy tumor response,² as well as the finding that during-treatment PET could be used for adaptive treatment to boost radiation to the most resistant tumor.³⁻⁶ An additional 100 participants were enrolled and results further demonstrated that tumor shrinkage was significantly more apparent on the PET scan images than on the CT scan images after 40–50 Gy during RT. Supported by many collaborators, including Randall Ten Haken, PhD, a chief medical physicist, and Gregory Kalemkerian, MD, co-director of thoracic oncology at the University of Michigan, Kong then initiated a prospective trial (UMCC 2007123) incorporating a mid-treatment PET scan for adapting RT with escalated dose to resistant active tumor while keeping doses to normal organs at safe levels in patients treated with concurrent chemotherapy. The trial completed enrollment of 42 participants and showed very promising preliminary tumor control and survival results. “I am very fortunate to have had excellent mentors and team collaborators; the support of the physicists, radiologists, pulmonologists, and medical oncologists has been especially valuable for this study,” says Kong of her research experience. “I am also very grateful to have received funding support to carry out this work.” The Lance Armstrong Foundation (through the ASCO Career Development Award), Pardee Foundation, and National Cancer Institute (through R21, R01, and P01 awards) all partially supported Kong’s work.



This is a 60-year-old woman with stage IIIB T4N2M0 unresectable non-small-cell lung cancer treated with concurrent chemoradiation. Using pretreatment guided conventional planning, she would have received 65 Gy to the PET-identified active tumor (the top panel). With the use of during-RT PET-based adaptive planning, the patient received 80 Gy to the active tumor on during-RT PET-CT (bottom panel) without exceeding the safe limits to normal structures. She is doing well now without evidence of disease progression at 28 months from treatment. RTOG 1106/ACRIN 6697 is to test the effect of local control with the adaptive plan.

Kong’s research interest led her to become active in RTOG’s research program, in which she has served on the Lung Cancer Committee and as a member of the Translational Research Program Committee. Encouraged by RTOG Deputy Chair Mitchell Machtay, MD, Kong presented the results of the UMCC 2007123 adaptive trial to the RTOG Lung Cancer Committee and proposed conducting a randomized, multicenter trial to validate that altering radiation therapy based upon during-treatment FDG-PET scans would result in more effective lung cancer treatment. With support and encouragement from RTOG leadership, ACRIN leaders, trial co-chairs, the RTOG Lung Cancer Committee—in particular, the investigators who participated in the trial’s “dry run” exercise—and many, many others along the way, Kong’s efforts resulted in a full-fledged RTOG clinical trial. The protocol was activated on February 22, 2012.

Citations

1. Biehl KJ, Kong FM, Dehdashti F, Jin JY, Mutic S, El Naqa I, Siegel BA, Bradley JD. 18F-FDG PET definition of gross tumor volume for radiotherapy of non-small cell lung cancer: Is a single standardized uptake value threshold approach appropriate? *J Nucl Med*. 2006;47(11):1808-1812. PubMed PMID: 17079814.
2. Kong FM, Frey KA, Quint LE, Ten Haken RK, Hayman JA, Kessler M, Chetty IJ, Normolle D, Eisbruch A, Lawrence TS. A pilot study of [18F]fluorodeoxyglucose positron emission tomography scans during and after radiation-based therapy in patients with non small-cell lung cancer. *J Clin Oncol*. 2007;25(21):3116-3123. PubMed PMID: 17634490.
3. Chetty IJ, Fernando S, Kessler ML, McShan DL, Brooks C, Ten Haken RK, Kong FM. Monte Carlo-based lung cancer treatment planning incorporating PET-defined target volumes. *J Appl Clin Med Phys*. 2005;6(4):65-76. Epub 2005 Nov 21. PubMed PMID: 16421501.
4. Feng M, Kong FM, Gross M, Fernando S, Hayman JA, Ten Haken RK. Using fluorodeoxyglucose positron emission tomography to assess tumor volume during radiotherapy for non-small-cell lung cancer and its potential impact on adaptive dose escalation and normal tissue sparing. *Int J Radiat Oncol Biol Phys*. 2009;73(4):1228-1234. PubMed PMID: 19251094.
5. Kong FM, Mahasittiwat P, Yuan S, Xie C, Ritter T, Shen Z, Daniel T, Hayman J, Cao Y, Ten Haken RK. Define tumor volume during radiotherapy to individualize adaptive radiation dose escalation in non-small cell lung cancer. Imaging for Treatment Assessment in Radiation Therapy (ITART) 2010, Abstract 14327.
6. Kong FM, Ten Haken RK, Hayman JA, Cease K, Ramnath N, Arenberg D, Curtis J, Orringer M, Kalemkerian GP, Lawrence TS. Can We Deliver High Dose Radiation in 6 Weeks with Concurrent Chemotherapy in Stage III Non-small Cell Lung Cancer? *Int J Radiat Oncol Biol Phys*. 2010;78(suppl 3):S35.

Looking Ahead

Grant Submitted to Fund PROMIS: An Ancillary Study Assessing Patient Reported Outcomes for Women with Advanced Gynecologic Cancers

The RTOG 1203 trial in development—*A Randomized Phase III Study of Standard vs. IMRT Pelvic Radiation for Post-operative Treatment of Endometrial and Cervical Cancer*—offers the opportunity to collaborate with Gynecologic Oncology Group (GOG) investigators to embed an ancillary study assessing the impact of pelvic intensity-modulated radiation therapy (IMRT) on patients' quality of life (QOL).

The study, led by GOG investigator Lari Wenzel, PhD, a professor of medicine and public health at the University of California, Irvine and the QOL Chair for the RTOG 1203 trial, intends to assess the validity and responsiveness to change of Patient Reported Outcomes Measurement Information System (PROMIS) domains central to women with advanced gynecologic cancers undergoing primary cancer treatment. Specifically, the PROMIS short forms containing items from the domains of fatigue, pain interference, physical function, interest in sexual activity, and vaginal discomfort will be administered before IMRT, at the end of IMRT, and 4–6 weeks after IMRT. GOG investigator David Cella, PhD, professor and chair of the Department of Medical Social Sciences at Northwestern University Feinberg School of Medicine in Chicago, will oversee the data analysis. The PROMIS tool was developed at Northwestern University.

Validation of the PROMIS measures would provide the scientific justification for future use across clinical trials and care settings, thereby promoting improved health outcomes for women with ovarian, endometrial, or cervical cancer. A grant application has been submitted to the National Institutes of Health to fund the study.

RTOG Submits NCI Brain Tumor SPORE Proposal

Years in the development, the brain tumor SPORE proposal includes 20 unique projects focused on translational research for glioblastoma multiforme (GBM) tumors.

Under the leadership of Arnab Chakravarti, MD, Radiation Oncology Department Chair at Ohio State University's Comprehensive Cancer Center and Arthur G. James Cancer Hospital, RTOG submitted a brain tumor Specialized Program of Research Excellence (SPORE) proposal to the National Cancer Institute (NCI) in early June. As Chakravarti, who serves as Brain Tumor Subcommittee Liaison to RTOG's Translational Research Program and Co-Chair of the RTOG Brain Tumor Committee, explains, "The proposed scope of work continues RTOG's effort to improve the molecular classification of GBM tumors as exemplified by the RTOG 0525 trial that prospectively validated MGMT protein as a categorical prognostic molecular marker in GBM. It also addresses the tremendous amount of work to be done to identify mechanisms of resistance to current therapies for patients with GBM, not only for the purposes of identifying which patients are likely to benefit from these therapies, but also to devise effective strategies for overcoming such resistance mechanisms."

The SPORE initiative is a cornerstone of NCI's efforts to promote collaborative, interdisciplinary translational cancer research. Each SPORE, carried out over a 5-year funding period, is focused on a specific organ site and involves both basic and clinical investigators working on new and diverse approaches to reduce cancer incidence and mortality, and to improve survival and quality of life for cancer patients. The RTOG brain tumor SPORE proposal, if funded, would represent the first time a cancer cooperative group is designated as a SPORE.

The RTOG brain tumor SPORE proposal includes four main translational research projects developed by RTOG investigators related to glioblastoma tumors:

- *Project 1*, led by Arnab Chakravarti, MD (Ohio State University), proposes to investigate signal transduction in biomarkers and therapeutic targets in glioblastoma
- *Project 2*, led by Mark R. Gilbert, MD (MD Anderson Cancer Center), intends to investigate toxicity profiling and the creation of novel paradigms to personalize cancer treatment
- *Project 3*, led by Kenneth D. Aldape, MD (MD Anderson Cancer Center), focuses on predictive markers of response to target new agents for populations of patients in whom standard treatment fails
- *Project 4*, led by Erwin G. Van Meir, PhD (Emory University School of Medicine), explores novel small molecule therapeutics for malignant brain tumors, focusing on evaluating their efficacy in cell culture and animal glioma models

People in the News *(Continued from page 4)*

address such targets as treatment sequencing, standard dosing, and use of different RT modalities. Deciding what to focus on as a group will help us to provide guidance as different trial opportunities arise within RTOG.” Another interest area of Hodge’s is the development of a mechanism to capture anecdotal observations of patients who have had encouraging responses with experimental therapies plus RT to investigate patterns of success.

“Dr. Hodge brings a unique skill set and experience that will greatly enhance our clinical trial strategies that use immunotherapeutic approaches in combination with radiation and chemotherapy,” says Dicker. “The RTOG is constantly reaching out to talented investigators who will enhance our mission to improve the lives of our patients.”

“I am very excited about the addition to the TRP Committee of this promising area of research that is now ready for multicenter clinical trial validation,” says RTOG Group Chair Walter Curran, MD, executive director of the Winship Cancer Institute of Emory University, “and am confident of Dr. Hodge’s ability to establish a strong foundation as we incorporate immunotherapy into RTOG and, in the future, NRG Oncology clinical trials.”

About the RTOG Translational Research Program Committee

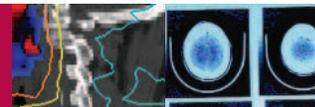
The RTOG Translational Research Program (TRP) promotes communication of scientific ideas from the research laboratory into RTOG clinical trials by informing the basic science committees and working groups about important emerging research in tumor biology, chemical and biological modifiers, and pathology. To that end, specimens derived from RTOG clinical trials are viewed as the Group’s most valuable and precious resource, limited and nonrenewable. It is the TRP Committee’s highest priority to encourage, optimize, and prudently prioritize the use of this resource.

[Click here](#) for more about the RTOG Translational Research Program.

RTOG Submits NCI Brain Tumor SPORE Proposal *(Continued from page 11)*

The establishment of four core resources—administrative, biostatistical, tissue, and animal—is envisioned to provide the necessary infrastructure to support carrying out the proposed research projects. Additionally, the brain tumor SPORE intends to create a developmental research program to fund several smaller projects each year that have the potential to develop into major SPORE initiatives and a career development program that will support at least two investigators each year in this field.

“RTOG’s research experience and the expertise of its investigators uniquely position the group to provide a comprehensive investigation of brain malignancies and their underlying mechanisms to guide future therapeutic decision making and improve patient outcomes,” says Walter J. Curran, Jr., MD, RTOG Group Chair and Executive Director of the Winship Cancer Institute of Emory University in Atlanta. The SPORE grant submission represents several years of data collection to complete the groundwork for the SPORE projects, as well as hundreds of hours of investigator collaboration and RTOG staff support. “I extend a sincere thank you to RTOG Headquarters staff, led by Sharon Hartson Stine, and everyone who played a role in developing this exciting initiative,” concludes Chakravarti.

RADIATION THERAPY ONCOLOGY GROUP newsletter

The *RTOG Newsletter* is published by the Radiation Therapy Oncology Group and is distributed to current members and others interested in the work of the Group. RTOG is supported by National Cancer Institute Grants U10CA21661, U10CA37422, and U24CA114734.

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RTOG is administered by the American College of Radiology (ACR) and is located in the ACR Clinical Research Center.