

UT SOUTHWESTERN
THE TARGET

News from the Department of Radiation Oncology

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Fat loss, inflammation and cancer



Assistant Professor Puneeth Iyengar was one of two recipients of this year's Distinguished Research Award, presented by UT Southwestern's President's Research Council. His research into cachexia—the massive loss of fat and muscle found in many disease states, including cancer—shows an intriguing link between cancer-induced anorexia, inflammation and disease.

Puneeth Iyengar, M.D., Ph.D.

Story continues on page 2

What's Inside

1-2 FAT LOSS, INFLAMMATION, CANCER
3 DEPARTMENT NEWS

4-5 CPRIT GRANTS
6 VERO: THE CLINICAL EXPERIENCE
7 CLINICAL TRIAL LISTINGS

Inflammation—as induced by both external factors (tobacco use) and internal factors (cachexia)—has long been thought to help promote lung cancer initiation or progression. As importantly, there may be a distinct possibility that the development of therapeutic resistance is also driven by inflammatory changes in the body.

Similar to a viral infection, in which the body's own immune system creates the high fever, runny nose and other inflammatory response symptoms of a cold, we believe that in the process of lung cancer development, the body is in a constant state of inflammation that may drive tumor formation and inadvertently promote tumor resistance to radiation.

Cachexia accounts for 20-30 percent of all deaths in patients with cancer.

Part of the mechanism for such events may occur by the release of inflammatory proteins into our bloodstreams—cytokines—that act on cancers and signal them to avoid being killed by radiation. Therefore, after treatment, a collection of cells in tumors may be left that are resistant to treatment and more aggressive in surviving and spreading.

The first focus of our current research is to characterize the inflammatory states in lung cancer patients that may trigger tumor development and resistance to radiation therapy. Our research is also attempting to

identify the mechanisms by which cytokines (and other, yet unknown proteins) induce resistance in lung cancer cells. Blocking the action of these proteins in the future may increase the effectiveness of radiation, thereby promoting longer survival in patients.

A clue with cachexia

Cachexia (Greek for 'bad condition') is triggered in a number of illnesses—cancer, AIDS, infection, rheumatoid arthritis, congestive heart failure (CHF), tuberculosis, Crohn's disease, etc. It is characterized by systemic metabolic dysregulation driven by the two main features of the syndrome: loss of both adipose tissue and muscle mass, leading to undesired weight loss.

If one examines each of the diseases associated with cachexia, a common theme is demonstrated—that of a heightened inflammatory state.

One of the main clinical outcomes of cachexia is reduced patient performance status. Numerous retrospective evaluations have demonstrated the importance of performance status to overall survival in cancer. In fact, performance status, as driven by cachexia, usually is the most important predictor of survival outcomes in lung cancer. Cachexia itself accounts for 20-30 percent of all deaths in patients with cancer and is seen in up to 50 percent of all cancer patients at some point in their disease course.

Part of the failure in treating many solid tumors resides in the inability of patients to receive combined modality therapy—surgery, radiation, and systemic agents – as components of the standard of care due to poor performance status. In general, patients with cancer cachexia have limited therapeutic options, with no randomized data suggesting a practice-changing beneficial pharmacologic intervention.

Most recently, however, a randomized trial established that early, non-pharmacologic palliative care for newly diagnosed patients with metastatic non-small cell lung cancer (NSCLC) and eventual poor performance status/cancer cachexia improved quality of life and overall survival compared to those without the early intervention. Therefore, it seems that from every vantage point understanding the pathophysiology of cachexia and attempting to reverse its effects would be advantageous from a symptom perspective and tumor treatment outcome perspective.

Diabetes drugs show promise

The second focus of our research has been to better understand the biology of cancer cachexia as a means of bringing to clinic new pharmacologic inhibitors of this detrimental process.

In multiple pre-clinical lung and colon carcinoma models of cachexia, we have shown that certain drugs used for diabetes double overall survival, reduce tumor burden, and promote adipose tissue health or limit adipose atrophy.

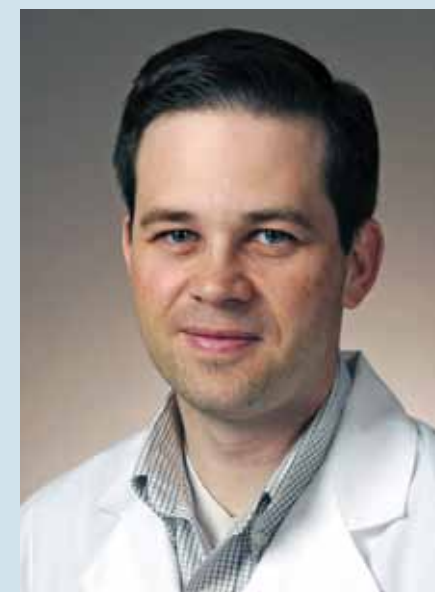
Our original purpose in using these compounds was to gain some insight into mechanisms governing cachexia development. Based on our initial pre-clinical observations with pioglitazone (a member of the thiazolidinedione class), we propose further testing to decipher how classes of anti-diabetic drugs may reverse cachexia and help patients by: 1.) improving performance status through a reversal of cachectic inflammatory states; 2.) allowing patients with improved performance status to be capable of receiving multimodality therapy; and 3.) reversing tumor progression by limiting inflammatory "fuel" that could potentially promote radiation resistance. ☺

- By Puneeth Iyengar, M.D., Ph.D.

News

Westover joins clinical faculty, establishes lab

Ken Westover, M.D., Ph.D., recently joined the 16-member physician team of the Department of Radiation Oncology.



Ken Westover, M.D., Ph.D.

Dr. Westover earned both his medical degree and his Ph.D. in biophysics from Stanford University. Following an internship in internal medicine at Brigham and Women's Hospital in Boston, he completed residency training in the Harvard Radiation Oncology Program and received additional training through Harvard's Intensive Translational Research Program.

As a physician scientist, Dr. Westover has established a research lab at UT Southwestern to concentrate on structure-based drug design, chemical biology, and developing new combined modality therapies for cancer. In the clinic, he will focus on the treatment of lung cancer patients.

Dr. Westover's work has been published in both clinical and basic science journals. He has also authored several book chapters relating to radiation therapy. His graduate work was cited in the 2006 Nobel Prize in Chemistry awarded to Roger Kornberg.

"My primary objective is to improve cancer care through innovation, particularly through efforts to understand and manipulate fundamental aspects of biology," says Dr. Westover. "I believe this approach will be critical to achieve the delivery of personalized medicine to our patients." ☺

First Ph.D.s awarded in biology program

A milestone was reached this spring when the university awarded its first doctoral degrees to students in the Department of Radiation Oncology's Division of Molecular Radiation Biology.

Brian McEllin, Ph.D., and Cristel Camacho, Ph.D., have been working in Sandeep Burma, Ph.D.'s lab since 2007 as part of the Cancer Biology track in UT Southwestern's Graduate School of Biomedical Sciences. Radiation biology faculty also mentor students in the Cell Regulation and the Genetics & Development programs. Dr. Camacho's dissertation was titled "Genetic Events Underlying Radiation-Induced Gliomagenesis." Dr. McEllin's was titled "Dissecting Molecular Mechanisms of Radioresistance Using Genetically Defined in vitro and in vivo Brain Tumor Model Systems."

The university's Cancer Biology program has been ranked #10 in the nation (as Molecular Biology and Cell Biology) by U.S. News & World Report. ☺



Brian McEllin, Ph.D., and Cristel Camacho, Ph.D.

Department spearheads \$4.1m CPRIT grant

With seed money from UT Southwestern's Department of Radiation Oncology and the Simmons Cancer Center, radiation oncology researchers have already shown that a compound developed here (bavituximab) will not only inhibit the development of blood vessels supplying a tumor, but



Robert Timmerman, M.D.

will attack the tumor directly following treatment with stereotactic body radiation therapy (SBRT) – a more potent form of radiation delivery.

Now a \$4.1 million grant from the Cancer Prevention & Research Institute of Texas (CPRIT) to lead investigator Robert Timmerman, M.D., Professor of Radiation Oncology and Neurosurgery, will further investigate the mechanisms behind that effect.

The grant includes a core of nearly

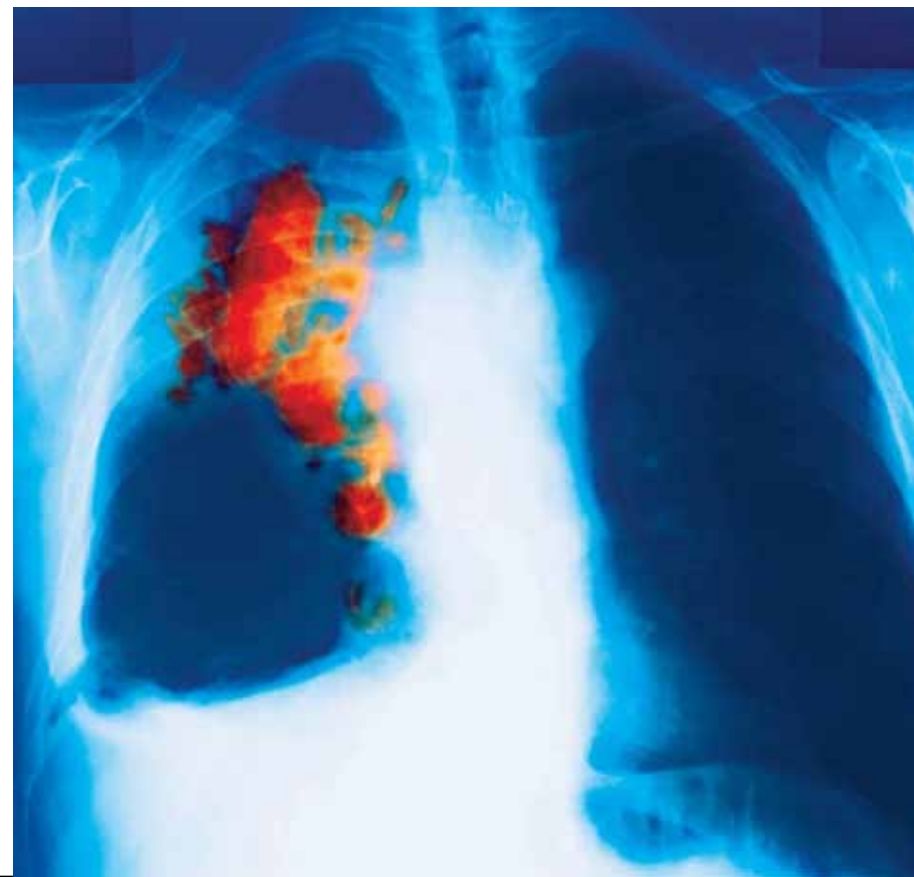
\$1 million for small animal targeting led by Timothy Solberg, Ph.D., a physicist in the Department of Radiation Oncology, which will integrate with two larger CPRIT-sponsored projects: "Radiation-Guided Vascular Targeting of Lung Cancer," a \$1.3 million grant led by Philip Thorpe, Ph.D., Professor of Pharmacology; and "Effects of Hypoxia," a \$1.2 million grant led by Ralph Mason, Ph.D., Professor of Radiology.

Hypoxia, or the lacking of an adequate oxygen supply, has an effect on solid tumor response to therapy, with tumor aggressiveness—including growth, development and metastasis—being enhanced in the absence of oxygen.

"Solid tumor cancer cells that are hypoxic are harder to destroy than the cells of well-oxygenated tumors,

particularly by radiation therapy," Dr. Mason says. "A major long-term goal of our research has been to identify tumors that are hypoxic and likely to resist therapy. Moreover, we try to exploit the hypoxia or develop robust methods of altering hypoxia. This new grant will allow us to extend our studies to lung cancer, one of the most lethal and prevalent cancers, which is also particularly challenging to evaluate."

Dr. Mason plans to use his latest CPRIT funds to focus on imaging tumor hypoxia, specifically looking at how to identify patients whose tumors will benefit most from a particular type of therapy (such as SBRT, pioneered by Dr. Timmerman), with the potential addition of bavituximab to enhance response. Hypoxic tumor cells are unusually resistant to radiotherapy,



Dr. Mason says, but they can be made more sensitive when the amount of oxygen in the cells is increased.

CPRIT funds are also helping members of the Simmons Cancer Center reveal new insight into why the most common, deadly kind of brain tumor in adults – glioblastoma multiforme (GBM) – usually recurs.

Researchers aim to identify a potential target for future therapies for this devastating form of brain cancer, which is currently considered incurable. The current treatment for these tumors – surgical removal when possible followed by radiation and chemotherapy – is ineffective at blocking eventual tumor regrowth.

"We have identified a subset of brain tumor cells that are slower growing or remain at rest, and appear to be the source of cancer recurrence after standard therapy," said Luis Parada, Ph.D., Chairman of Developmental Biology and a member of the Simmons Cancer Center. "After thoroughly understanding the mechanisms by which this form of cancer can be arrested, we plan to focus our current CPRIT funding on a few of the most promising [treatment] compounds."

Using a genetically engineered mouse model of GBM, the researchers have already found that the resting tumor cells act more like stem cells – the non-cancerous cells the body uses to repair and replenish itself – which exist in a resting state until needed, he said. ☺

CPRIT grant to study head and neck cancer



Michael Story, Ph.D.

Michael Story, Ph.D., Associate Professor of Radiation Oncology, is the recipient of an \$851,490 grant from the Cancer Prevention and Research Institute of Texas to identify predictive biomarkers for tumor response in head and neck squamous cell carcinomas (HNSCC).

The project, titled "Enhancing the Identification of Markers and Potential Therapeutic Targets for Improving Tumor Response via miRNA and DNA Methylation Analysis," is led by Dr. Story with co-investigators Lianghao Ding, Ph.D., and John Yordy, M.D., Ph.D., of UT Southwestern in a collaborative effort with Kian Ang, M.D., Ph.D., of MD Anderson Cancer Center. The project will assess miRNA expression, DNA methylation status, and identify oncogenic fusion genes.

The initial search for biomarkers and potential therapeutic targets will be conducted using approximately 180 archival HNSCC specimens, as well as promising candidates from the literature and from the investigators' preliminary data. These leads will be validated using annotated tumor specimens from patients enrolled into large phase III trials and treated using uniform protocols.

The research is intended to complement an NCI-funded project co-led by Dr. Story and J. Heymach, M.D., Ph.D., of MD Anderson Cancer Center, which focuses on genomic-proteomic assays conducted on the same specimens as this project. "This will enable us to interrogate molecular alterations contributing to clinical resistance in HNSCC in an integrated manner," says Dr. Story.

"The importance of this research is that it will contribute to streamlining cancer therapy by facilitating selection of specific therapy strategies for patients with certain defined tumor features," Dr. Story continues. "Individualization of therapy has become a priority for improving overall outcome, reducing toxicity, and reducing the financial burden to patients and society." ☺

Vero: the clinical experience

The first Vero radiation therapy system in North America was installed last year at UT Southwestern, allowing our physicians and physicists to be among the first to evaluate its clinical usage.

A joint venture between two industry leaders, Mitsubishi Heavy Industries in

mechanical stability. The ring is capable of rotating plus or minus 60 degrees about the vertical axis to facilitate non-coplanar beam arrangements that optimize the avoidance of healthy structures while providing very compact dose distributions.

calculations in heterogeneous media.

The Vero treatment planning computer utilizes a Monte Carlo dose calculation algorithm, the most advanced dose calculation algorithm available. Treatment planning calculations demonstrated excellent agreement with dosimetry measurements in specialized lung phantoms, while calculations performed using conventional algorithms were incorrect by 20 percent or more.

Dosimetric commissioning was further verified through the use of the Radiological Physics Center thorax phantom, and as a result, the Vero is now credentialed for use in National Cancer Institute-sponsored radiotherapy trials for lung cancer.

Patient treatments on the UT Southwestern Vero began in October 2011. Many are treated using an approach called stereotactic body radiation therapy, or SBRT, a procedure that delivers radiation in a concentrated, precise manner while reducing treatment sessions to between one and five fractions. UT Southwestern physicians have pioneered the SBRT approach, which has been shown to be highly effective in the treatment of early stage lung cancer, metastatic tumors of the lung, liver and spine, and other disease sites.

Later in 2012, the Vero will be upgraded to allow the treatment beam to track moving targets in real time. This will further improve the treatment accuracy for lung tumors, which can move as a patient breathes. ☺

- By Timothy Solberg, Ph.D.

Before initiating clinical service, the Vero system was thoroughly tested and commissioned by UT Southwestern faculty physicists. An evaluation of the accuracy and precision of the gantry and ring rotations yielded a maximum deviation from isocenter of 0.12 mm and 0.02 mm respectively. End-to-end studies were performed in specialized head and body phantoms. Tissue density targets imbedded in artificial lung allowed direct verification of dosimetric



Vero radiation therapy system

Japan and BrainLAB in Germany, Vero integrates several state-of-the-art radiation therapy capabilities designed to locate tumors and direct radiation with precision.

Vero consists of a small 6 MV linear accelerator and two orthogonal diagnostic imaging subsystems (two X-ray sources plus two digital detectors) mounted in a ring gantry for maximum

Clinical Trials Listing

BRAIN

042011-075 Interstitial radioactive iodine implants for the treatment of pan-invasive pituitary macroadenomas

042011-050 Phase II trial of hippocampal-avoiding whole brain irradiation with simultaneous integrated boost for treatment of brain metastases

E3F05 Phase III study of radiation therapy with or without temozolomide for symptomatic or progressive low-grade gliomas

BREAST

072010-015 A phase I study of CyberKnife® partial breast irradiation (PBI) for early stage breast cancer

RTOG 1014 A phase II study of repeat breast preserving surgery and 3D-conformal partial breast re-irradiation (PBRI) for local recurrence of breast carcinoma

RTOG 1005 A phase III trial of accelerated whole breast irradiation with hypofractionation plus concurrent boost versus standard whole breast irradiation plus sequential boost for early-stage breast cancer

GASTROINTESTINAL

072010-093 Dose escalating study of single fraction stereotactic body radiation therapy (SBRT) for patients with hepatic metastases

RTOG 1010 A phase III trial evaluating the addition of trastuzumab to trimodality treatment of Her2-overexpressing esophageal adenocarcinoma

GYNECOLOGIC

GOG 0249 A phase III trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin in patients with high-risk, early stage endometrial cancer

GOG 0238 A randomized trial of pelvic irradiation with or without concurrent weekly cisplatin in patients with pelvic-only recurrence of carcinoma of the uterine corpus

GOG 0258 A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma

GOG 0724 Phase III randomized study of concurrent chemotherapy and pelvic radiation therapy with or without adjuvant chemotherapy in high-risk patients with early-stage cervical carcinoma following radical hysterectomy

HEAD AND NECK

ALD518 A phase 2, multi-center, randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of ALD518 in the reduction of oral mucositis in subjects with head and neck cancer receiving concomitant chemotherapy and radiotherapy

072010-48 A phase II multi-center study of concomitant cetuximab and cisplatin with re-irradiation using intensity-modulated radiotherapy (IMRT) in patients with recurrent squamous cell carcinoma of the head and neck

072010-046 A phase I/II study of nab-paclitaxel, cisplatin and cetuximab with concurrent radiation therapy for local-regionally advanced head-and-neck squamous cell carcinoma

RTOG 0920 A phase III study of postoperative radiation therapy (IMRT) +/- cetuximab for locally-advanced resected head and neck cancer

RTOG 1008 A randomized phase II study of adjuvant concurrent radiation and chemotherapy versus radiation alone in resected high-risk malignant salivary gland tumors

LUNG (THORACIC)

Small Cell Lung Cancer

CALGB 30610/RTOG 0538 A phase III comparison of thoracic radiotherapy regimens with cisplatin and etoposide in limited small cell lung cancer

RTOG 0937 Randomized phase II study comparing prophylactic cranial irradiation alone to prophylactic cranial irradiation and consolidative extracranial irradiation for extensive disease small cell lung cancer (ED-SCLC)

Non-Small Cell Lung Cancer

—Stage 1

RTOG 1021 A randomized phase III study of sublobar resection (+/- brachytherapy) versus stereotactic body radiation therapy in high risk patients with stage I NSCLC

—Locally Advanced (Stage 3) or Inoperable (Stage 1 or Stage 2)

RTOG 0813 Seamless phase I/II study of stereotactic body radiotherapy (SBRT) for early stage, centrally located non-small cell lung cancer (NSCLC) in medically inoperable patients

RTOG 839 Randomized phase II study of preoperative chemoradiotherapy +/- panitumumab followed by consolidation chemotherapy in potentially operable locally advanced (stage IIIA, N2+) non-small cell lung cancer

072010-050 Phase I study of accelerated hypofractionated image-guided radiation therapy (IGRT) in patients with stage II-IV non-small cell lung cancer and poor performance status

—Metastatic (2 or more sites)

072010-061 A phase II trial of erlotinib (Tarceva®) in combination with stereotactic body radiation therapy (SBRT) for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)

— Non-therapeutic (non-small cell lung cancer)

042011-034 Investigating the feasibility of using rapid cine-MRI for monitoring moving and deforming tumors.

PROSTATE AND BLADDER

RTOG 0815 A phase III prospective randomized trial of dose-escalated radiotherapy with or without short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer

RTOG 0534 A phase III trial of short term androgen deprivation with pelvic lymph node or prostate bed only radiotherapy (SPPORT) in prostate cancer patients with a rising PSA after radical prostatectomy

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

SPINE

072010-134 A phase II study of stereotactic body radiation therapy and vertebroplasty for localized spine metastasis

RTOG 0631 A phase II/III study of image-guided radiosurgery/SBRT for localized spine metastasis

For more information, please contact Clinical Research Manager Jean Wu at 214-633-1753 or jean.wu@utsouthwestern.edu

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