Will the frontiers of space exploration impact cancer therapy?

UT Southwestern researchers gain $7.5 million NASA grant to find the answer.

Cancer is probably not the first thing that comes to mind when most people think about astronauts traveling in outer space. Yet cancer-causing, high mass and energy (HZE) particles like iron or silicon found in galactic cosmic rays currently pose a significant barrier to long-term manned space missions—a challenge that has opened promising new lines of investigation for cancer researchers.

Understanding and minimizing the health risks of space radiation is the primary goal behind a recent $7.5 million NASA Specialized Center of Research (NSCOR) grant awarded to UT Southwestern researchers in the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research and the Department of Radiation Oncology. It follows on the heels of a $9.8 million grant that first established UT Southwestern as a NASA research center in 2005.
Understanding radiation’s impact on the molecular and cellular level may lead to better assessment of the risk for cancer, as well as impacting other aspects of space exploration, from materials and design of aircraft to the creation of habitats for long-term missions.

The five-year grant “Risk Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation” is led by Dr. John Minna, director of the W.A. “Tex” and Deborah Moncrief Jr. Center for Cancer Genetics and the Nancy B. and Jake W. Hamon Center for Therapeutic Oncology Research. Other principals include Dr. David Chen, professor of radiation oncology and head of the molecular radiation biology division; Dr. Jerry Shy, professor of cell biology; Dr. Michael Story, associate professor of radiation oncology and director of the Simmons Cancer Center Genomics Core Facility; Dr. Yang Xie, assistant professor of clinical sciences; and Dr. Adi Gazdar, professor of pathology.

The grant is just one of several NASA grants in which the Department of Radiation Oncology participates through its Division of Molecular Radiation Biology [see box]. Currently, NASA astronauts are limited to radiation exposure equal to a 3 percent life risk for a fatal cancer. For deep space missions that might be as little as a single mission, given the current margins of error in cancer risk estimation.

“That’s a problem,” pointed out Dr. Michael Story. “You can’t spend millions of dollars to train someone to go into space one time.” Understanding radiation’s impact on the molecular and cellular level, he said, may lead to better assessment of the risk for cancer, as well as impacting other aspects of space exploration, from materials and design of aircraft to the creation of habitats for long-term missions.

Dr. Story’s portion of the NSCOR grants aims to determine how the combination of mass and energy of various particles affects the response of normal lung cells at the molecular and cellular level, including the rate of cellular transformation—one of the first steps in the oncogenic process. From there, using cell lines from Dr. John Minna’s laboratory, the goal is to determine the variability in response to radiation between individual human lung cell lines, which may help NASA more precisely assign individual risk for cancer.

Another line of investigation is the examination of DNA damage and repair. Dr. David Chen, whose laboratory was the first to identify a key process (phosphorylation of DNA-PK) in DNA double-strand break repair, is examining DNA damage and repair in differentiated cell cultures that closely model cells of the lung. Dr. Jerry Shy is using mouse models to examine the role that chronic inflammation from very low dose rate radiation exposures may play in the onset of cancer.

Finally, Drs. Minna, Xie, and Gazdar are using an extensive tissue bank collected by Dr. Gazdar and colleagues from non-smokers with lung cancer to develop biomarkers for lung cancer in non-smokers. Drs. Minna and Xie will collaborate with all projects to build a similar set of biomarkers denoting the post-irradiation response, and compare and contrast those with Dr. Gazdar’s biomarkers.

“By doing that, we essentially provide a toolkit for NASA for predicting lung cancer risk, possibly even before someone goes into space, just by assessing them genetically and looking at particular biomarkers,” said Dr. Story. “Or we could enable them to assess these individuals throughout their careers to see if certain biomarkers appear.”

From the viewpoint of radiation oncology, there is another important benefit to this program. Heavy particles are now being used for therapy—carbon in particular—but the mechanisms by which they generate a clinical response are not yet well understood. Carbon therapy is being used in Europe and Asia, particularly in Japan and China. Currently there is no heavy particle treatment facility in North America. Dr. Michael Story’s portion of the NSCOR grants includes Dr. David Chen; “Mechanisms of the Repair of HZE Induced DNA Double-Strand Breaks in Human Cells” ($1,248,986; September 7, 2007–2011)

Dr. Shy’s work includes Dr. Sandeep Burma; “Radiation and Glomageneus: A Sensitizer Mechanism System to Evaluated the Tumorigenic Potential of HZE Particles” ($1,948,172; January 2010–2013)

Dr. Gazdar’s portion of the NSCOR grants includes Dr. Adi Gazdar; “Risk Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation” ($7,500,000; 2011–16)

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**Individual Grants**

**Shared NSCOR Grants**

- **John Minna, Michael Story**, Jerry Shy, David Chen; Yang Xie, Adi Gazdar; “Risk Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation” ($7,500,000; 2011–16)

- **Michael Story**; “Generic Analysis” ($1,042,907, part of NASA Specialized Center of Research on Radiation Carcinogenesis; 1 July 2009–31 May 2014)

**Oncology NASA research**

**Department of Radiation Oncology NASA research**

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  - **John Minna, Michael Story**, Jerry Shy, David Chen; Yang Xie, Adi Gazdar; “Risk Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation” ($7,500,000; 2011–16)

- **Individual Grants**
  - **Sandeep Burma**; “Radiation and Glomageneus: A Sensitizer Mechanism System to Evaluated the Tumorigenic Potential of HZE Particles” ($1,948,172; January 2010–2013)
  - **David Chen**; “Mechanisms of the Repair of HZE Induced DNA Double-Strand Breaks in Human Cells” ($1,248,986; September 7, 2007–2011)
  - **Benjamin Choe**; “Impact of HZE Particles on Adult Neural Stem Cells and Neurogenesis” ($1,357,800; August 2007–2011)

Aspirin may enhance prostate cancer survival

Aspirin was recently linked to a reduced risk of prostate cancer death in a study of 5,295 men led by UT Southwestern physician and researcher Kevin Choe, MD, PhD.

Participants in the study had localized adenocarcinomas of the prostate treated either with radical prostatectomy (3,525 subjects) or radiotherapy (1,772 subjects). Thirty-seven percent of the total group were taking an antiplatelet (primarily aspirin), at enrollment or during follow-up.

After a median follow-up of 59 months, deaths attributable to prostate cancer were significantly reduced in the aspirin-taking group. The reduction in mortality was most prominent in patients with high-risk disease: at seven years only 2 percent of the high-risk patients who took aspirin had succumbed to prostate cancer versus 8 percent of the non-aspirin takers.

At 10 years the difference was even more striking: 4 percent mortality in the aspirin-taking group versus 22 percent of the non-aspirin takers. The benefit in prostate cancer mortality was not as significant in those taking other anticoagulants besides aspirin.

Further studies are necessary to elucidate the underlying mechanism for this effect, but it may be that aspirin operates by suppressing metastasis,” said Dr. Choe.

The findings were highlighted at the most recent annual meeting of the American Society for Radiation Oncology. @

**News**

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**SPRING 2011 The Target 3**
In the Clinic

Technology makes more women candidates for breast-sparing radiation treatment

Multilumen catheters for accelerated partial breast irradiation —by Ann Spangler, MD

High dose rate intravacuolar brachytherapy for early stage breast cancer has been in use for approximately five years. In this procedure, a balloon catheter delivers a high dose of radiation therapy (usually with iodine-192) to the breast tissue immediately surrounding the partial mastectomy tumor bed.

The advantage of this form of radiation is its ability to spare the remaining normal breast tissue from high doses of radiation, and to deliver treatment over a short time period, usually five days.

Initially, treatment was delivered using a Mammotome® single lumen catheter. The radiopaque material was located in a single catheter in the center of the balloon, and delivered the radiation dose in a spherical distribution. By using several positions within the single lumen, a more elongated radiation distribution could be obtained, but the radiation dose was the same to all of the tissue at the same distance from the center of the catheter.

This generally provided an acceptable dose distribution, but in some patients with a smaller distance from the balloon to the skin or chest wall, those tissues would have received a higher dose than desired, and this treatment could not be offered.

Newer catheters now in use by the Department of Radiation Oncology at UT Southwestern have multiple lumens, permitting the iodine-192 source to be positioned either in the central catheter, as it would have been with the original single lumen catheter, or in one or more additional catheters offset from the central catheter. This permits differential shaping of the radiation dose to provide increased or decreased radiation dose depending on the shape of the cavity, or the normal tissues next to the balloon, specifically the skin and chest wall.

Several multilumen catheters are available, including Contura® and Mammotome®. By using the multilumen balloon catheter, the improved dose distribution permits consideration of this treatment modality in more women than with the single lumen catheter dose distribution.

Women who previously were not candidates for partial breast irradiation because their tumors were located close to the skin or chest wall may now be considered for this treatment as a result of the ability to spare the dose away from these structures with the newer catheters.

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UT Southwestern one of top sites nationwide for lung cancer clinical trials

The Department of Radiation Oncology at UT Southwestern Medical Center is the 2nd highest-enrolling facility in the U.S. for lung cancer clinical trials initiated by the Radiation Therapy Oncology Group (RTOG), the leading multicenter research organization for radiation therapy trials.

According to the group’s recent data, UT Southwestern has accrued more patients to lung cancer studies since joining the RTOG in 2005 than any other radiation facility except Cleveland Clinic Hospitals in Ohio.

“This ranking shows our commitment to research and to making leading-edge treatments available to our patients,” says Dr. Robert Timmerman, professor of radiation oncology and neurosurgery, and director of clinical research in the Department of Radiation Oncology.

Currently the department has 23 total studies open to accrual, including 12 RTOG studies and 11 investigator-initiated studies. Last year, 104 UT Southwestern and Parkland patients were enrolled in therapeutic studies. An additional 229 patients were enrolled in non-therapeutic studies, most of them to create a tissue bank to help researchers explore the individual genetic response to radiation.

A further 23 patients were enrolled last year by study substes at University of Minnesota, University of Colorado, Medical College of Wisconsin, MD Anderson Orlando, Case Western Reserve University, and Baylor Medical Center, all of which participate in the department’s investigator initiated studies. This year, Stanford University joins the group by participating in the UT Southwestern study “Hypofractionated image-guided radiation therapy (HIRT) in lung cancer patients with poor performance status.”

Breast specialists in the Department of Radiation Oncology: (l to r) Dr. Dan Garwood, Dr. Asal Shoushtari Rahimi (arriving July 2011) and Dr. Ann Spangler.
Spring 2011 The Target 7

CASE STUDY

John Bacon of Irving, Texas, age 63, didn’t think he had much to worry about when he was told the lump in his right forearm didn’t warrant immediate treatment. Lipomas, or masses of fatty tissue, are fairly common and benign. “I let it go for about a year,” recalled Mr. Bacon. “I assumed it was benign. But it was so big—about the size of a small egg—that it bothered me. I finally scheduled a surgery to have it removed.”

When he did, lab analysis of the tumor revealed that it actually contained a 5 cm soft tissue sarcoma, a rare but aggressive cancer. Mr. Bacon came to UT Southwestern for his definitive treatment, which included a re-excision of the tumor bed to remove all positive margins, followed by radiation therapy. Radiation oncologist Thomas Boise, MD, felt that a customized brachytherapy treatment, in which catheters are placed into the wound at the time of surgery, would deliver the most tightly controlled radiation dose to the tumor bed while sparing healthy tissue. “In this case, the goal was to preserve the skin and elbow joint, which closely abutted the tumor bed.”

Mr. Bacon’s personal circumstances were also a consideration. “Typically a six-week course of radiation therapy could be offered,” Dr. Boise explained. “But Mr. Bacon works full-time to support his family and it would have been difficult to take time off for six weeks. With brachytherapy, we can deliver the same dose in a more focused manner, in just five days.”

With the multidisciplinary team of medical, surgical, and radiation oncologists specializing in treating sarcoma proud to have the option of high dose rate brachytherapy to offer our patients,” he added. “Our emphasis is interdisciplinary care.”

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Department of Radiation Oncology at UT Southwestern

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Medical Records: 214-648-2498
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UT Southwestern Patient Services
Ambassadors: 214-648-7001

Physicians who would like to make a referral may call the department's main clinic number or UT Southwestern's physician referral line at 214-645-5455 (toll free 866-645-5455) for adult patients or 800-5379 for pediatric patients.

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