Space Radiation Newsletter

Vol. 6 No. 1 - August 2006 | Executive Editor: Dr. Francis Cucinotta | Contributing Editor: Kay Nute

4th International Workshop and 17th Annual NASA Space Radiation Investigators' Workshop

The 4th International Workshop on Space Radiation Research and 17th Annual NASA Space Radiation Investigators' Workshop was the first such workshop that featured a dual-city venue. Researchers initially convened at the Russian Academy of Sciences in Moscow on June 5, 2006 for three intense days of scientific talks, posters, and cultural events. Then, workshop participants boarded the night train from Moscow bound for the All-Russian Center of Emergency and Radiation Medicine in St. Petersburg and two more days of scientific talks, posters, and cultural events.

Sponsoring agencies included the Russian Academy of Sciences, Federal Space Agency, Ministry of Education and Science of Russian Federation, Ministry of Emergency Situations of Russian Federation, Russian Federation for Basic Research, Scientific Council of RAS on Radiobiological Problems, State Scientific Center of RF - Institute for Biomedical Problems of RAS, Joint Institute for Nuclear Research, All-Russian Center of Emergency and Radiation Medicine, the National Aeronautics and Space Administration, and the European Space Agency.

Dr. Eric J. Hall, Director of the Columbia University College of Physicians and Surgeons' Center for Radiological Research, presented the Basil Worgul Memorial Lecture honoring the late biologist and Columbia University professor, Dr. Basil V. Worgul, who studied radiation's harmful effects on the eye, and in particular, the potential for cataracts to form in the eyes of astronauts who are exposed to cosmic rays.

View the Scientific Program that included 61 oral talks and 65 posters

Image left: Dr. Viktor Petrov (right) joins the chorus with Russian folk singers during a motorboat tour down the Neva River in St. Petersburg.

Image right: Singers play traditional instruments and sing Russian folk songs during a motorboat tour down the Neva River in St. Petersburg.

IOM Report

In response to a request by NASA, the Institute of Medicine and National Research Council of the National Academies conducted a comprehensive assessment of its Bioastronautics Roadmap to identify the challenges for accomplishing the Roadmap's goals. An ad hoc committee examined the content of the Roadmap, the process used in developing and updating it, and the context in which the Roadmap was developed and will be used.

That report entitled Review of NASA's Bioastronautics Critical Path Roadmap (BCPR) has been published and may now be purchased or read online.

NASA Space Radiation Summer School

The NASA Space Radiation Summer School has completed its third successful run at the Brookhaven National Laboratory (BNL) on Long Island. The goal of the summer school program is to help train a "pipeline" of researchers to perform experiments at the NASA Space Radiation Laboratory and to motivate them to consider a career in radiobiology. There were 11 students in the 2004 class, 15 students in 2005, and 15 students plus 4 programmatic participants in the 2006 summer school.

BNL personnel and university and NASA space radiation researchers presented lectures that introduced the students to physics, radiobiology, radiation carcinogenesis, radiation chemistry, tissue responses to radiation, the space radiation environment and shielding, and the risk assessment model used in the NASA Space Radiation program. The students then used their newly gained knowledge to perform experiments using the NSRL facility.

2005 summer school student Dr. Jarah Meador described her experiences, "The course provided a comprehensive overview of radiation biophysics and the latest research in the field by researchers who actively use the NSRL facility and who are each prominent in their respective fields. It was a unique opportunity to learn from these experts in a relaxed environment in which we were able to ask as many questions as were necessary to fully understand the research topics."

Image right: 2006 NSRSS students with instructor Marcelo Vazquez in front of the NSRL. Courtesy of Brookhaven National Laboratory

Dr. Rachael Casey, a researcher for USRA at the NASA Johnson Space Center and a student in the 2006 summer school echoed those sentiments. She added, "The course highlighted crucial differences between the types of radiation found on Earth and the cosmic rays found in space. I also valued the opportunity to interact with the summer school instructors, who are today's top researchers in radiation biology. Learning from their experience has given me a much better insight into the field of radiobiology, as well as providing practical advice on how to utilize the NSRL facility to pursue my own research projects."

The course is designed for graduate students, postdoctoral fellows, and faculty with an interest in radiation biology. Applications have been posted on USRA DSLS NASA Space Radiation Summer School and have been nominally due by the end of February for the course held in the summer. Sixty-eight applications were received for the 2006 course.

Both foreign nationals and U.S. citizens have been eligible to apply for the program. All students must satisfy Brookhaven National Laboratory safety and security requirements in order to be admitted. Expenses for travel within the U.S. and for room and board have been covered for those selected for the program. Successful applicants from outside the U.S. have been required to provide for their travel to and from the U.S.

Course sponsors are the NASA Space Radiation Health Project, Brookhaven National Laboratory, Loma Linda University, and the Universities Space Research Association. Course directors are Gregory Nelson, Ph.D. (Loma Linda University) and Marcelo Vazquez, M.D., Ph.D. (BNL).

Additional course information is available at BNL's NASA Space Radiation Summer School.

View Summer School Images

Special Issue of Radiation Research: The 3rd International Workshop on Space Radiation Research

Papers from the Third International Workshop on Space Radiation Research have been published in the October 2005 issue (Volume 164, Number 4, Part 2) of Radiation Research, the Official Journal of the Radiation Research Society. The Workshop was held May 16-2004 in Port Jefferson, New York.

Papers published include an introduction, two reviews, two articles on biomarkers and biodosimetry, two articles on tissue responses, eight articles on cell biology, six articles on degenerative tissue effects, and five articles on biophysics. Abstracts are available online, but a subscription to Radiation Research is required to retrieve the full text of articles.

16th Annual Space Radiation Investigators Meeting

The 16th Annual Space Radiation Investigators meeting was held at Pt. Jefferson on Long Island, NY near BNL from May 15-18, 2005. View abstracts of the oral talks and posters presented by 80 NASA Space Radiation

investigators, as well as a list of participants. An album of photos and additional information about the Workshop may be found here.

Many of the studies discussed at the Workshop were performed at the NASA Space Radiation Laboratory, a NASA-dedicated facility housed at the Brookhaven National Laboratory that uses beams that simulate the harmful rays of space radiation.

Image right: Dr. Walter Schimmerling, Program Scientist for NASA's Space Radiation Program, acknowledged the good wishes of the audience, as he reflected on his approaching retirement.

A special tribute to Bill Holley who passed away on November 19, 2004 was also presented at the Workshop.

Walter Schimmerling announced his retirement as the NASA Program Scientist for the Radiation Health Program after a long and distinguished career in the field. He was honored by his many colleagues with gifts, good words, and general bonhomie.

Spotlight on Charles Limoli

As a boy in front of his TV set in San Diego, California, Charles Limoli watched men land on the moon and dreamed of the day he would be able to help NASA make a difference.

More than 30 years later, and with several research grants from NASA's Space Radiation Health Program, he studies how ionizing radiation affects the function of neural precursor cells - with the hopes of illuminating the mechanisms underlying cancer development as well as limiting the potentially adverse impact of irradiation on the cognitive performance of astronauts on exploration missions.

Image right: Charles Limoli poses in his laboratory at the University of California San Francisco.

The route from dreaming about the space program to becoming a part of it took him from California to the East coast, where he received a degree in Chemistry from the Massachusetts Institute of Technology. He then returned to California and the University of California San Diego where he joined the Radiobiology Lab of John Ward and ultimately received his Ph.D. in Biomedical Sciences. From there a postdoctoral fellowship in radiobiology took him north to Bill Morgan's Lab at the University of California San Francisco, where he has since progressed to Associate Professor of Radiation Oncology. In February, 2006 he joined the University of California Irvine where he was recruited for a tenure-tracked position as Associate Professor in the Department of Radiation Oncology.

The genesis for his interest in understanding and solving the health problems associated with exposure to radiation began in graduate school, where along with his mentor John Ward, he developed a new method for producing clustered damage in cells using a photochemical technique. The ability to produce high yields of DNA double-strand breaks (DSBs) into cellular DNA in the relative absence of other competing lesions prompted a number of related studies by them and others aimed at dissecting the intricacies of DNA damage and repair.

Eventually, he moved north to the University of California San Francisco and enjoyed a productive postdoctoral position with Bill Morgan, where they made strides in determining how specific types of DNA and cellular damage impacted the onset and perpetuation of chromosomal rearrangements that define genomic instability.

Continued work to identify the mechanisms underlying genomic instability led him to find that replication stress promoted genomic instability by a mechanism involving the formation of DNA DSBs at sites of stalled replication forks. In related work, he identified that oxidative stress was both associated with

genomic instability and could induce a range of abnormal phenotypes. His work has since supported the idea that chronic oxidative stress and mitochondrial alterations disrupt the genomic integrity of cells by perturbing a range of redox sensitive biochemical pathways.

Image left: (From left) Erich Giedzinski, Charles Limoli, and Jennifer Baure are pictured in the target room of the NASA Space Radiation Laboratory, Brookhaven, New York.

That work set the stage for many of his currently funded NASA projects investigating how oxidative stress alters redox state to impact the function and radioresponse neural precursors cells. Microenvironmental and intracellular changes in redox state have been shown to impact the behavior of neural precursors both in vitro and in vivo. His lab has shown that exposure of these cells to y- or x-rays, as well as to the protons and heavy ions that characterize the space radiation environment, leads to acute and chronic increases in the level of reactive oxygen species (ROS). Elevated ROS are associated with an apoptotic depletion of neural precursor cells, mitochondrial dysfunction, lipid peroxidation, and DNA damage.

Dr. Limoli along with his collaborator Dr. John Fike, has also shown that oxidative stress that persists months after irradiation temporally coincides with the onset of neuroinflammation, two factors that are likely to inhibit neurogenesis and possibly contribute to cognitive dysfunction. Work is currently underway to determine if/how antioxidant and/or anti-inflammatory interventions might ameliorate certain radiation-induced sequelae in the CNS. Recent studies have also shown that oxidative stress is radiomodifying, and can further sensitize cells to the effects of irradiation. This work will help elucidate how redox changes regulate the phenotypic fate of multipotent precursor cells, and whether such changes exacerbate the acquisition of genetic alterations conducive to brain cancer.

Selected peer-reviewed publications (since 2000 from a total of 50).

1. **Limoli, C.L.**, Ponnaiya, B., Corcoran, J.J., Giedzinski, E., Kaplan, M.I., Hartmann, A. and Morgan, W.F. Genomic instability induced by high and low LET ionizing radiation. Adv. Space Res. 25:2107-2117 (2000).

2. **Limoli, C.L.**, Giedzinski, E., Morgan, W.F. and Cleaver, J.E. Polymerase n deficiency in the xeroderma pigmentosum variant uncovers an overlap between the S phase checkpoint and double-strand break repair. Proc. Natl. Acad. Sci. USA 97:7939-7946 (2000).

3. **Limoli, C.L.**, Ponnaiya, B., Corcoran, J.J., Giedzinski, E. and Morgan, W.F. Chromosomal instability induced by heavy ion irradiation. Int. J. Radiat. Biol. 76:1599-1606 (2000).

4. **Limoli, C.L.**, Corcoran, J.J., Jordan, R., Morgan, W.F. and Schwartz, J. A role for chromosomal instability in the development of and selection for radioresistant cell variants. Br. J. Cancer 84:489-492 (2001).

5. Milligan, J.R., Aguilera, J.A., Paglinawan, R.A., Ward, J.F. and **Limoli, C.L.** DNA strand break yields after post-high-LET-irradiation incubation with endonuclease III provide evidence for hydroxyl radical clustering. Int. J. Radiat. Biol. 77:155-164 (2001).

6. Cleaver, J.E., Karplus, K., Kashani-Sabet, M. and **Limoli, C.L.** Nucleotide excision repair “A legacy of creativity” Mutat. Res. 485:23-36 (2001).

7. Cleaver, J.E., Crowley, E., Kashani-Sabet, M., and **Limoli, C.L.** DNA replication arrest and p53-dependent and p53-independent cell death pathways in xeroderma pigmentosum variant cells. Scientific World Journal, 1:60 (2001).

8. **Limoli, C.L.**, Kaplan, M.I., Giedzinski, E. and Morgan, W.F. Attenuation of radiation-induced genomic instability by free radical scavengers and cellular proliferation. Free Radic. Biol. Med. 31:10-19 (2001).

9. Thakur, M., Wernick, M., Collins, C., **Limoli, C.L.**, Crowley, E. and Cleaver, J.E. DNA polymerase ? undergoes alternative splicing, protects against UV sensitivity and apoptosis, and suppresses Mre11-dependent recombination. Genes, Chrom. Cancer 32:222-235 (2001).

10. **Limoli, C.L.**, Giedzinski, E., Bonner, W.M. and Cleaver, J.E. UV-induced replication arrest in the xeroderma pigmentosum variant leads to DNA double-strand breaks, ?-H2AX formation, and Mre11 relocalization. Proc. Natl. Acad. Sci. USA, 99:233-238 (2002).

11. Cleaver, J.E., Bartholomew, J., Char, D., Crowley, E., Feeney, L. and **Limoli, C.L.** Polymerase ? and p53 jointly regulate cell survival, apoptosis and Mre11 recombination during S phase checkpoint arrest after UV irradiation.

DNA Repair 1:41-57 (2002).

12. Morgan, W.F., Hartmann, A., **Limoli, C.L.**, Nagar, S. and Ponnaiya, B. Bystander effects in radiation-induced genomic instability. Mutat. Res. 504:91-100 (2002).

13. **Limoli, C.L.**, Laposa, R. and Cleaver, J.E. DNA replication arrest in XP Variant cells after UV exposure is diverted into an Mre11-dependent recombination pathway by the kinase inhibitor wortmannin. Mutat. Res. 510:121-129 (2002).

14. **Limoli, C.L.**, Giedzinski, E., Morgan, W.F., Swarts, S.G., Jones, G.D.D. and Hyun, W. Persistent oxidative stress in chromosomally unstable cells. Cancer Res. 63:3107-3111 (2003).

15. Cleaver, J.E., Laposa, R.R. and **Limoli, C.L.** DNA replication in the face of (in)surmountable odds. Cell Cycle, 2:310-315 (2003).

16. **Limoli, C.L.** and Giedzinski, E. Induction of chromosomal instability by chronic oxidative stress. Neoplasia, 5:339-346 (2003).

17. **Limoli, C.L.**, Giedzinski, E, Radoslaw Rola, Shinji Otsuka, Palmer, T.D. and Fike, J.R. Radiation response of neural precursor cells: linking cellular sensitivity to cell cycle checkpoints, apoptosis and oxidative stress. Radiat. Res. 161:17-27 (2004).

18. Rola, R., Otsuka, S., Obenaus, A., Nelson, G.A., **Limoli, C.L.**, Vandenberg, S.R. and Fike J.R. Indicators of hippocampal neurogenesis are altered by 56Fe irradiation in a dose dependent manner. Radiat. Res. 162:442-446 (2004).

19. **Limoli, C.L.**, Rola, R., Giedzinski, E., Mantha, S., Huang, T-T. and Fike J.R. Cell-density-dependent regulation of neural precursor cell function. Proc Natl Acad Sci USA 101:16052-116057 (2004).

20. **Limoli, C.L.**, Giedzinski, E. and Cleaver J.E. Alternative recombination pathways in UV-irradiated XP Variant cells. Oncogene 24:3708-3714 (2005).

21. Rola, R., Sarkissian, V., Obenaus, A., Nelson, G.A., Otsuka, S., **Limoli, C.L.** and Fike J.R. High LET irradiation induced inflammation and persistent changes in markers of hippocampal neurogenesis. In press, Radiat. Res. (2005).

22. Giedzinski, E., Rola R., Fike J. and **Limoli, C.L.** Efficient production of reactive oxygen species in neural precursor cells following exposure to 250 MeV Protons. In Press, Radiat. Res. (2005).