National Aeronautics and Space Administration

NASA Presentation to the Brookhaven National Laboratory Community Advisory Council

Victor Schneider, M.D.
Francis Cucinotta, Ph.D.

May 13, 2010

Brookhaven National Laboratory
Community Advisory Council Questions for NASA

- What is the background – why is NASA interested in these types of radiation effects for deep space mission? What is NASA's projected strategy and plan for deep space travel? What specifically are the potential concerns for astronaut safety? How have those concerns surfaced? How serious are these issues in NASA's assessment?

- What's the compelling argument that there will be benefits from this research? What are the specific research objectives of this program (the key questions to be answered)? How critical to the Space Program and to astronaut safety are the answers to these questions? When are the answers to the posed research questions needed and why?

- What are the realistic expectations of this research in terms of benefit and cost? What is the likelihood that the research objectives will be met through this program? What is the expected total cost for the program? How does this cost compare to other research initiatives at NASA?

- What are the programmatic consequences to NASA and the deep space program if this research is not conducted? Will programs/activities be cancelled? Will funding be lost?

- To what extent could the research objectives be met using non-animal alternatives research methods? What is the state of technology for non-animal research? Which specific research objectives could be met this way and which ones could not? How would using non-animal research alternatives affect the budget and schedule for the research?

- Are there dual-purpose benefits to conducting this research – benefits to society, science or NASA beyond the specific research objectives?

Introduction

- NASA is directed by the President and Congress to address challenges to human space exploration
  - Space radiation and its health effects is one of the critical areas that needs to be addressed to enable long-term missions beyond low-Earth orbit, including missions to Mars
- NASA's Space Radiation Research Program is charged with addressing the human health risks associated with exposure to space radiation
  - All space radiation research studies are solicited Nationally based on recommendations from the National Academy of Sciences and National Council on Radiation Protection and Measurements and are selected using a rigorous, independent peer review process
- Astronaut health is a critical priority at NASA, and this research study "Long term effects of space radiation in non-human primates" will focus on one of the most important unknowns: the effect of space radiation on the central nervous system
  - There are currently no existing data sources that can provide the needed information and there are no other research methods that can provide this information
  - It would be unethical to send people on long-duration spaceflights beyond low-Earth orbit without first defining radiation exposure limits
- NASA is concerned for both human and animal welfare, and the Agency is committed to the humane and ethical, treatment and care of all animals associated with the U.S. space program

The Space Radiation Environment

Solar particle events (SPE) (generally associated with Coronal Mass Ejections from the Sun):

- medium to high energy protons
- largest doses occur during maximum solar activity
- not currently predictable
- MAIN PROBLEM: develop realistic forecasting and warning strategies

Trapped Radiation:

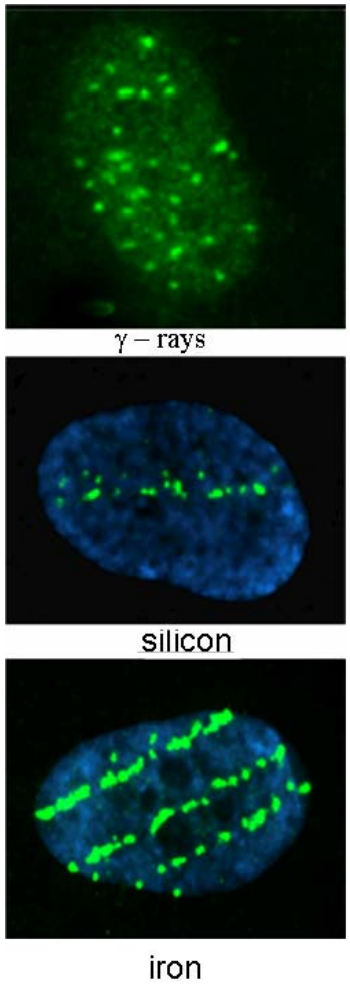
- medium energy protons and electrons
- effectively mitigated by shielding
- mainly relevant to ISS
- MAIN PROBLEM: develop accurate dynamic model

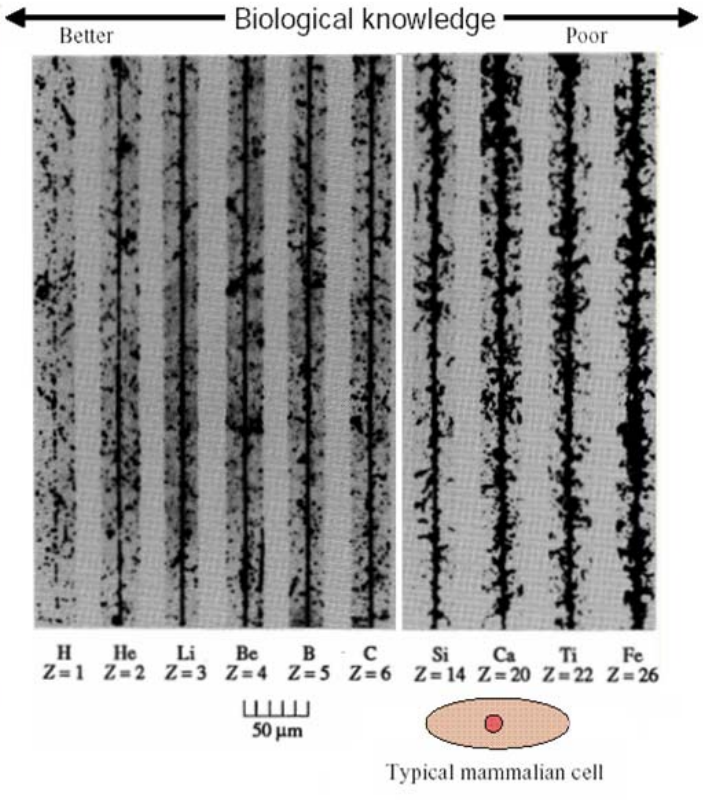
Galactic Cosmic Rays (GCR)

- high energy protons
- highly charged, energetic atomic nuclei (HZE particles)
- not effectively shielded (break up into lighter, more penetrating pieces)
- abundances and energies quite well known
- MAIN PROBLEM: biological effects poorly understood but known to be most significant space radiation hazard

The Space Radiation Problem

- Space radiation is comprised of high-energy protons and heavy ions (HZE's) and secondary protons, neutrons, and heavy ions produced in shielding
- Unique damage to biomolecules, cells, and tissues occurs from HZE ions that is qualitatively distinct from X-rays and gamma-rays on Earth
- No human data to estimate risk from heavy ions
- Animal models must be applied or developed to estimate cancer, CNS risks, and other risks
- Solar particle events (SPEs) can not be predicted with sufficient warning at this time
- Shielding has excessive costs and will not eliminate galactic cosmic rays (GCR)

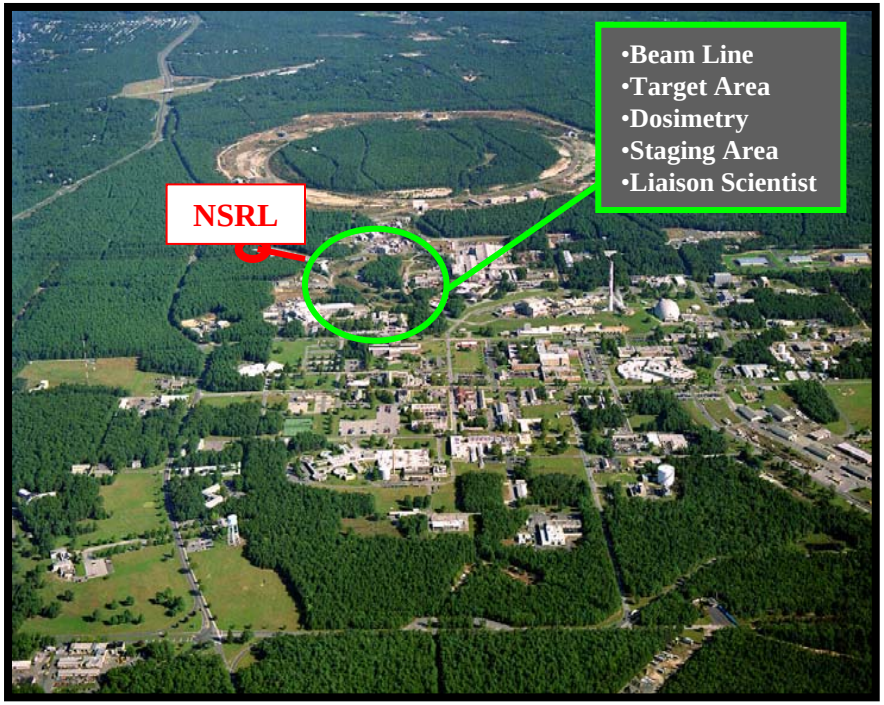




Cucinotta and Durante, Lancet Oncology (2006)

NASA Space Radiation Laboratory at the Brookhaven National Laboratory

- Within a year of creation of NASA in 1958, it was realized that cosmic rays are substantial threat to human space missions and a need for particle accelerator simulation was identified
- The NASA Space Radiation Laboratory (NSRL) at BNL is critical to enabling deep space missions
  - It is one of the few places in the world that can simulate the harsh cosmic and solar radiation environment found in space.
- Currently a Mars mission is projected to exceed NASA safety guidelines for astronauts by a large margin



1958	1963	1968	1973	1978	1983	1988	1993	1998	2003	2008	2013	2018	2023	2028
NASA notifies Congress of Accelerator need		*Light flashes observed by Apollo Astronauts*		*NASA piggy-backs on LBL Program*			*LBL Program ends / AGS Program Starts*	*BAF conceptual design report*	*NSRL Opens*			*Return to the Moon*		*Mars Mission*
NASA Created	*Mercury Flight*	*SREL opens in Newport news*	*NAS Report recmds HI Collider*			*First Booster interest by NASA*		*BAF const. start*	*ISS start*			*ISS End*		

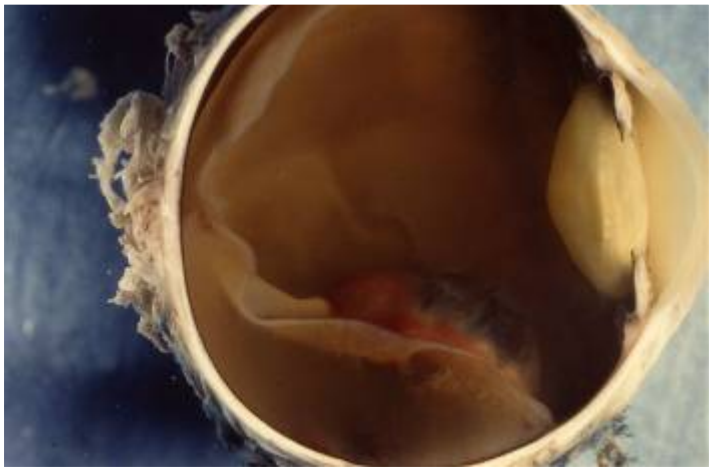
Categories of Space Radiation Risks

Four categories of risk of concern to NASA:

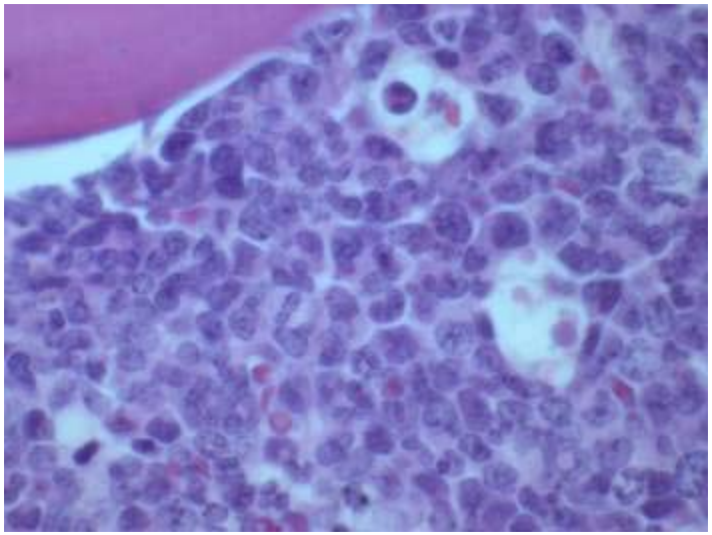
- ***Carcinogenesis (morbidity and mortality risk)***
- ***Acute and Late Central Nervous System (CNS) risks***
  - ✓ immediate or late functional changes
- ***Chronic & Degenerative Tissue Risks***
  - ✓ cataracts, heart-disease, etc.
- ***Acute Radiation Risks*** – sickness or death

Differences in biological damage of heavy nuclei in space compared to x-rays, limits Earth-based radiation data on health effects for space applications

- **New knowledge on risks must be obtained**



Lens changes in cataracts



First experiments for leukemia induction with GCR

2007 National Council for Radiation Protection, Report No. 153

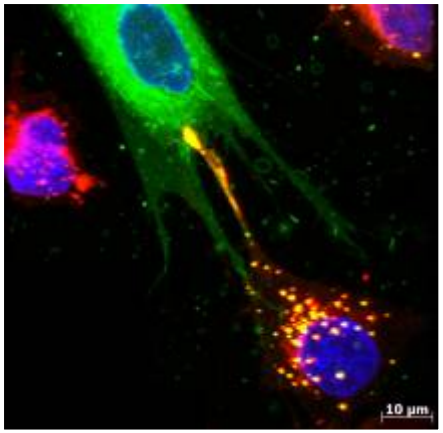
- Information Needed To Make Radiation Protection Recommendations For Space Missions Beyond Low-Earth Orbit
  - The accumulated evidence from the reported studies on DNA damage, loss of neurons, altered behavior, and motor function requires a careful assessment of the total risk to the CNS from exposure to high atomic number and energy (HZE) particles
  - While no reliable estimate of risk of important damage to the CNS from heavier charged particles can yet be given, there are enough data to indicate much more must be known before risk estimates of the effects of exposures in deep space can be made with any confidence
  - There are not sufficient data on the threshold doses for effects on the functions of the CNS despite a considerable number of relevant studies especially with regard to late radiation damage and its relationship to aging. An important unanswered question is whether neurons traversed by HZE particles and which survive, will develop changes as a late consequence of the damage they incurred
  - Behavioral effects mediated by the CNS, such as learning, that involve the dopaminergic nervous system are disrupted by exposure to iron ions, while exposure to equal or higher doses of other types of radiation (e.g., gamma rays or neutrons) do not show a similar effect. These adverse behavioral and neuronal effects are similar to those seen in aged animals, and the cognitive deficits are dependent on the individual dose response or age at exposure, and are unique to radiations found in space
  - It is recommended that experiments be conducted to: determine the effects of protracted exposures to low dose rates of protons, HZE particles, and neutrons of relevant energies on the CNS

Recent External Reviews of Space Radiation

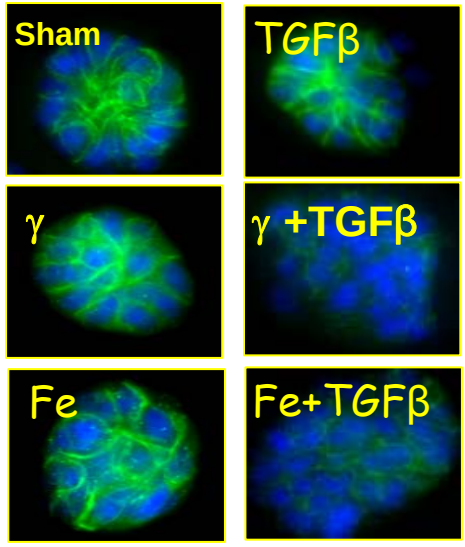
- National Academy of Sciences, NAS. National Academy of Sciences Space Science Board, *Report of the Task Group on the Biological Effects of Space Radiation. Radiation Hazards to Crews on Interplanetary Mission National Academy of Sciences*. National Academies Press, Washington, D.C., 1996.
- National Research Council, NRC, Space Science Board. *Review of NASA's Biomedical Research Program*. National Academies Press, Washington D.C., 2000.
- National Council on Radiation Protection and Measurements, NCRP. *Radiation protection guidance for activities in low-earth orbit*. Bethesda, MD; NCRP Rep. 132, 2000.
- National Academy of Sciences, Institute of Medicine, IOM. *Safe Passage: Astronaut Care for Exploration Missions. Institute of Medicine*. Washington, DC: National Academies Press, Washington D.C., 2001.
- NCRP, *Information Needed To Make Radiation Protection Recommendations for Space Missions Beyond Low-Earth Orbit.* Bethesda MD; NCRP Report No. 153, 2006.
- NAS, Institute of Medicine, IOM. *Bioastronautics Roadmap: A Risk Reduction Strategy for Human Exploration of Space*. National Academies Press, Washington D.C., 2006.
- NAS, Institute of Medicine, IOM. *Review of the HRP/Life Science Evidence Book: 2008*.
- NRC, Aeronautics and Engineering Board. *Managing Space Radiation Risk in the New Era of Space Exploration*. National Academies Press, Washington D.C., 2008.
- Review of US Human Spaceflight, *Seeking a Human Spaceflight Program Worthy of a Great Nation*. Washington D.C, 2009.
- NCRP, *Impact of individual genetic susceptibility and previous radiation exposure on radiation risk for astronauts*. Bethesda MD; NCRP Report No. (In press), 2010.

Space Safety Requirements

- Congress has chartered the National Council on Radiation Protection (NCRP) to guide Federal agencies on radiation limits and procedures
  - NCRP guides NASA on astronaut dose limits
- Crew safety
  - limit of 3% fatal cancer risk
  - prevent radiation sickness during mission
  - new exploration requirements limit brain and heart disease risks from space radiation
- Mission and Vehicle Requirements
  - shielding, dosimetry, and countermeasures
- NASA programs must follow the ALARA (as low as reasonably achievable) principle to ensure astronauts do not approach dose limits



Cell fusion caused by radiation



Space Radiation in breast cancer formation

NASA Requirements for this Research

- The need for non-human primate subjects was determined after reviewing current and previous recommendations from the National Academy of Sciences and the National Council on Radiation Protection and Measurements as well as other NASA advisory groups

- Preliminary studies evaluating the effects of high-energy radiation equivalent to a human mission to Mars have been completed on cells and animals (mice and rats) and published in the peer-reviewed literature

  – These studies have raised concerns not only for a Mars mission but for shorter missions to the moon or International Space Station on adverse health effects of space radiation

- Data on high-energy cosmic ray radiation effects on central nervous system (CNS) does not yet exist

  – Therefore, no established data that could be “data mined” or evaluated

- Any mathematical models of the consequences of the effect of high-energy cosmic ray radiation that do exist are only based on assumptions which have not been verified

NASA Research Proposal Process

- NASA research proposal process has the following steps:
  - National competitive solicitation based on research areas recommended by the National Academy of Sciences and National Council on Radiation Protection and Measurements
  - Review for relevance to the solicitation
  - Merit-based peer review using external experts
  - Institutional Animal Care and Use Committee (IACUC) verification
  - Ethics assessment
  - Tentative selection and negotiation with research institution
  - Award of research grant

- The proposal titled “Long term effects of space radiation in non-human primates” was submitted in response to a competitive NASA research announcement (NRA) soliciting radiobiology research in the following areas:
  - to reduce the uncertainties in risk predictions for cancer/radiation risks;
  - provide the necessary data/knowledge to develop risk projection models for central nervous system (CNS) and other degenerative tissue risks;
  - and advance the understanding of the mechanisms of biological damage that underlies radiation health risks for astronauts

- Scientific Review
  - Initial Step-1 proposal was deemed to meet the objectives and requirements of the NRA and the Principal Investigator (PI) was invited to submit a full Step-2 proposal
  - Independent peer review contractor confirmed that the investigator had complied with all required NRA elements
  - Proposal underwent scientific merit based peer review using external experts

- Comprehensive scientific merit review conducted by external experts deemed this proposal scientifically sound and meritorious
  - The panel had no concerns or issues with the experimental protocol

NASA Research Proposal Process

- IACUC Requirements
  - Each IACUC is required to follow a number of laws, policies and guidelines during its review and must consider a variety of factors to assure the appropriate use and welfare of the animal
  - When reviewing a protocol, questions that must be addressed include:
    - does the research justify the use of animals;
    - is the use of animals required or are there suitable alternatives;
    - has the appropriate animal model been selected;
    - is the appropriate numbers of animals requested;
    - are the living conditions for the animals appropriate for the species and do they contribute to their health and comfort;
    - is the investigator adequately trained to use animals in research;
    - are all policies and laws being followed?
  - During a review, an IACUC may request changes be made to a protocol to assure clarity, conformity with local procedures and policies, and animal welfare

- IACUC Reviews for the proposal “Long term effects of space radiation in non-human primates”
  - Both the Principle Investigator and the institutions involved (McLean Hospital and BNL) have long records of productive research with non-human primates and are highly experienced in providing the husbandry and oversight needed for this research
  - Both facilities are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC), and are regularly inspected and comply fully with institutional and federal guidelines
  - IACUC’s from both institutions have approved the respective research protocols in advance of any research being conducted, and have certified that they comply with the Animal Welfare Act, the NRC Guide for the Care and Use of Research animals, and all other regulations governing the use of animals in research

NASA Research Proposal Process

- Ethical Review Criteria
  - NASA adheres to the animal welfare principles articulated in the NASA policy directive “NASA Principles for the Ethical Care and Use of Animals”
  - These principles, which are modeled after those created for the use of humans in research, were created in 1996 by a panel of bioethicists and animal welfare experts, as well as representatives from the American Society for the Prevention of Cruelty to Animals and the Humane Society of the United States
  - NASA Principles for the Ethical Care and Use of Animals include: Respect for Life, Societal benefit and Nonmaleficence
    - These were developed to guide careful and considered discussion of the ethical challenges that arise in the course of animal research, a necessary activity that must balance risks, burdens and benefits
    - These principles are not meant to eliminate the use of animals in research, limit the use of any species in NASA’s research, nor prescribe definite procedures for resolving conflicts, but rather to provide a framework within which challenges can be addressed in a rational manner
  - In the case of this research study, reviews by external biomedical ethicists have concluded that the study is compliant with the NASA guidelines
  - NASA is also adhering to the National Institutes of Health guidelines for care and use of vertebrate animals in research

NASA Research Proposal Process

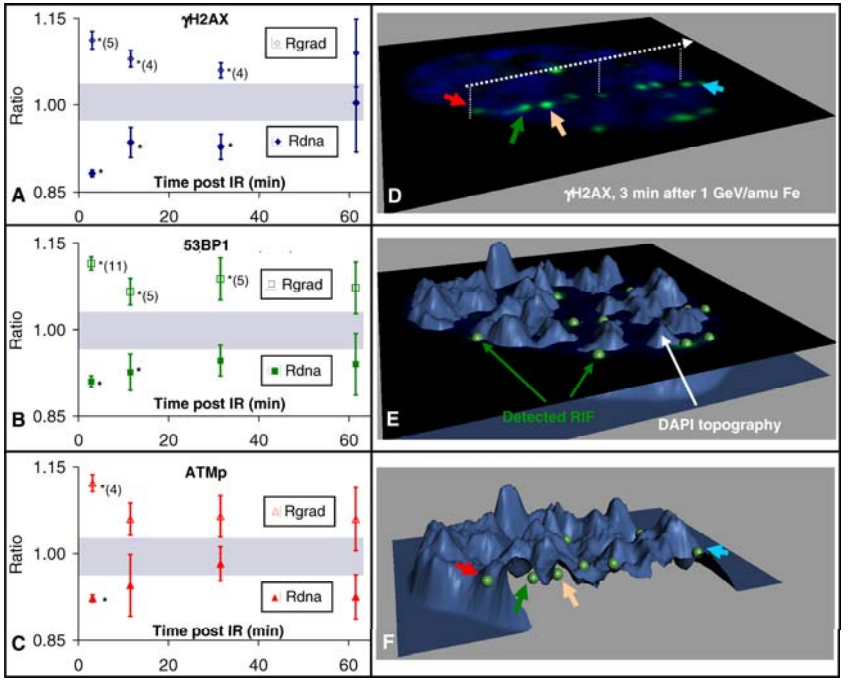
- Following the successful peer review of the proposal in question, NASA reviewed the proposal to confirm:

  1) It fulfilled the requirements of the solicitation
  2) The proposed research would provide critical data needed to protect human lives in deep space, and
  3) The IACUC at the Principle Investigator's (PI) home institution had approved the protocol within the required timeframe (initial approval obtained August 12, 2009, and updated approval obtained January 13th, 2010)
  4) NASA was satisfied with the ethics of this particular proposal

- NASA then selected this research proposal in order to begin negotiations with the PI and his institution, and to initiate the process for use of the NASA Space Radiation Laboratory at the Brookhaven National Laboratory.

Major Findings from NSRL

- First experiments at NSRL were started in October 2003 and there are now over 400 publications. Findings to date include the following:
  - A low relative biological effectiveness (RBE) for leukemia from iron due to high efficiency of apoptosis and evidence that RBE concept holds (scaling to gamma-ray effects)
  - A high RBE for solid cancer is emerging and also evidence that RBE concept fails
  - Major differences in signaling pathways between high and low linear energy transfer (LET) and high and low dose
  - Evidence that CNS effects will occur at doses <0.5 Gy, however morbidity in humans still undefined



Fundamental understanding of DNA repair mechanisms: DNA damage movement to low chromatin density regions suggests the existence of repair centers in the nucleus (Costes et al, 2007)

Potential Benefits for US Citizens

- New knowledge will be obtained on risk assessment for astronauts that will benefit others exposed to radiation: hospital workers, nuclear power plant workers, and patients diagnosed or treated with radiation
  - As proton beam therapy of brain and other cancers in adults and children is expanded in the U.S. (Mass. General Hospital, MD Anderson, U. Penn, etc), new data of importance in understanding proton treatment side-effects will be obtained

- Research should help with early detection of CNS cognitive dysfunction including Alzheimer's disease which impacts up to 50% of the population
  - Benefit to our understanding of the aging process
  - New approaches for prevention and therapy of cognitive disorders may be developed

Summary

- NSRL is a critical facility that enables NASA's mission
- The research being performed at NSRL is of the highest priority for NASA as recommended by the National Academy of Science and National Council for Radiation Protection
- The Agency has been, and remains, committed to the humane and ethical, treatment and care of all animals associated with the U.S. space program