NASA Space Radiation Program Element: Research Overview

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20th Radiation Health Working Group Meeting

RERF

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Overview

- NASA Human Research Program (HRP) & Space Radiation Program Element (SRPE)
- Space Radiation Overview
- Research Updates:
  - Part I – Radiation Carcinogenesis
  - Part II – Central Nervous System and Cardiovascular/Degenerative Risks

Human Research Program-
Crew Health Risks in Space

- **Reduced Gravity**
  - *Bone Loss, Muscle Atrophy, Reduced Immune Function*
- **Isolation / Confinement / Altered Light-Dark**
  - *Sleep Issues, Psychological Stress*
- **Hostile / Closed Environment**
  - *Atmosphere, Microbes, Dust, Habitability*
- **Distance from Earth**
  - *Autonomy, Food Systems/Nutrition, Clinical Medicine*
- **Increased Radiation**
  - *Cancer, CNS, Degenerative Changes, Acute Risks*

HRP Goal is to provide human health and performance countermeasures, knowledge, technologies & tools to enable safe, reliable, and productive human space exploration

Integrated Radiation Protection Strategy Enables Human Mars Exploration

Long-Term Commitment across Research and Technology Required…

National Aeronautics and Space Administration

NASA

Mission and Architecture Systems Analysis


Near Earth Asteroid Systems

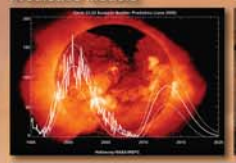

Mars NTV


In-situ Resource Utilization


Active Shielding Concepts

Environmental Modeling, Monitoring, and Prediction

Predictive Models



Precursor Data — MSL RAD


On-board Dosimetry– ISS TEPC

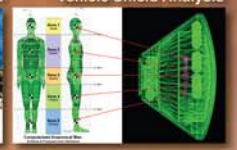
Crew Selection and Operations


Human Digital Twin

Integrated Radiation Protection System Design and Analysis

Design and Optimization Tools

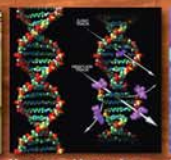
Crew Exploration Vehicle Shield Analysis

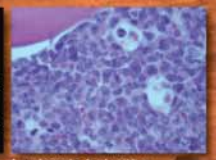


High Energy Nuclear Physics and Transport

Radiobiology and Biological Countermeasures


NASA Space Radiation Lab at Brookhaven National Laboratory


X-ray vs. Heavy Ion Track Damage to DNA

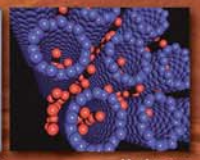

Leukemia induction with GCR — Mouse Model

Innovative Multi-Purpose Shield Solutions


Heavy Ion Testing of Inflatable Shield Prototype


Water Filled Composite Shield Sections


Reconfigurable Personal Shielding

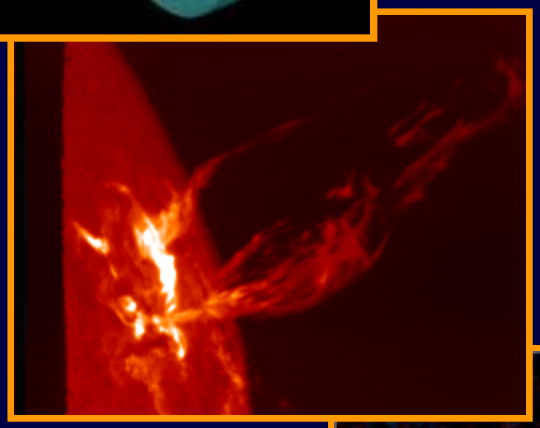

Hydrogen Storage BNNT

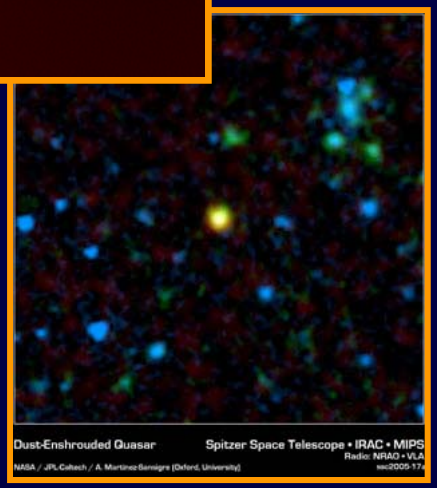
Advances benefit homeland security, cancer therapy, Earth observing and communication satellites, and commercial air safety

www.nasa.gov

Space Radiation

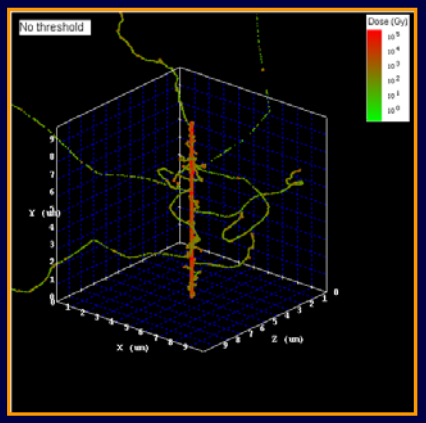
- Trapped Radiation
- Solar Particle Events
- Galactic Cosmic Radiation



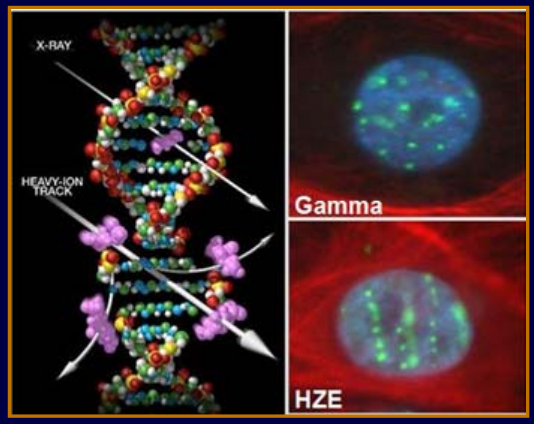


Heavy ions are Qualitatively Different from X-rays or Gamma-rays

- **High linear energy transfer (LET)**
  - Densely ionizing along particle track
  - Cause unique damage to biomolecules, cells, and tissues
  - Distinct patterns of DNA damage and profile of oxidative damage
- **Distinct biological effects and health risks?**
- **Shielding not effective**
- **No human data to estimate risk**
  - Use animal and cellular models with simulated space radiation



1 GeV/nucleon ^{56}Fe ion (LET~150 keV/μm) Qualitative differences due to track "core" and correlated tissue damage along a particle path. (RITRACKs –Plante & Cucinotta, 2011)



HZE complex DNA damage: γH2AX foci mark double strand breaks in nuclei of human epithelial cells (Cucinotta & Saganti, Patel & Huff)

Space Radiation Risks

Risk of Radiation Carcinogenesis

- Morbidity and mortality risks

Risk of Acute & Late Central Nervous System Effects

- In flight changes in motor function, cognition, behavior
- Late neurodegenerative disease

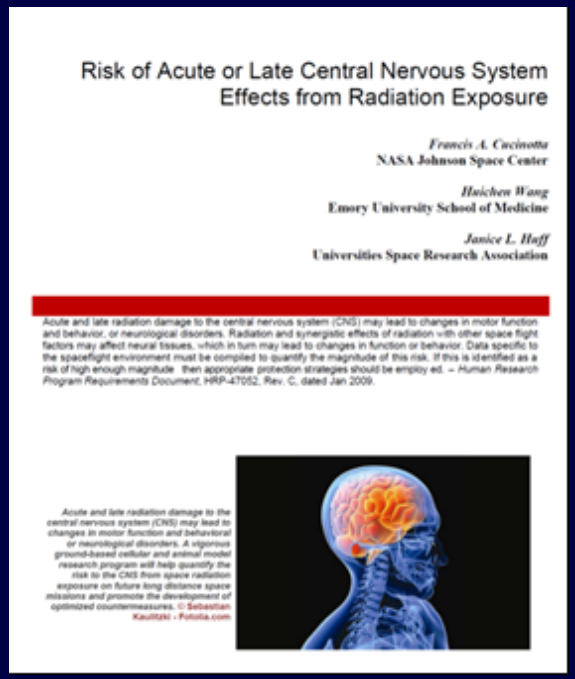
Risk of Cardiovascular Disease and other Degenerative Health Effects

- Cardiovascular diseases and stroke
- Cataracts and diseases related to aging, including digestive, respiratory, endocrine, and immune system dysfunction

Risk of Acute Radiation Syndromes due to SPEs

- Prodromal effects (nausea, vomiting, anorexia, and fatigue), skin injury, and depletion of the blood-forming organs

Risks documented in HRP Evidence Books


Risk of Acute or Late Central Nervous System Effects from Radiation Exposure

Francis A. Cucinotta
NASA Johnson Space Center

Huichen Wang
Emory University School of Medicine

Janice L. Huff
Universities Space Research Association

Acute and late radiation damage to the central nervous system (CNS) may lead to changes in motor function and behavior, or neurological disorders. Radiation and synergistic effects of radiation with other space flight factors may affect neural tissues, which in turn may lead to changes in function or behavior. Data specific to the spaceflight environment must be compiled to quantify the magnitude of this risk. If this is identified as a risk of high enough magnitude then appropriate protection strategies should be employ ed. – *Human Research Program Requirements Document*; HRP-47052, Rev. C, dated Jan 2009.

Acute and late radiation damage to the central nervous system (CNS) may lead to changes in motor function and behavioral or neurological disorders. A vigorous ground-based cellular and animal model research program will help quantify the risk to the CNS from space radiation exposure on future long distance space missions and promote the development of optimized countermeasures. © Sebastian Kaulitzki - Fotolia.com

http://humanresearchroadmap.nasa.gov/

Foundation of SRPE Research Plan

- External review by National Council on Radiation Protection (NCRP), National Academy of Sciences (NAS), and HRP Standing Review Panels
- Seven NASA Specialized Centers of Research (NSCOR's)
- Funded research at over 40 US Universities including collaboration with US Department of Energy (DoE)
- Space radiation simulated at the NASA Space Radiation Laboratory (NSRL)
- Partnership with NASA's Space Radiation Analysis Group (SRAG) on development of tools for risk assessment
- Collaborate with NASA's Science Missions on advanced SPE alert & Mars robotic missions
- Partnership with National Space Biomedical Research Institute (NSBRI) on acute and cardiovascular risks

NASA Space Radiation Laboratory (NSRL) at Brookhaven National Lab

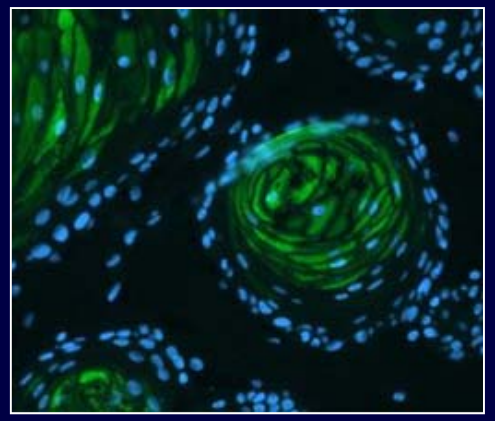
- Simulates the space radiation environment- high energy ion beams (H^+, Fe, Si, C, O, Cl, Ti, etc.)
- Beam line, target area, dosimetry, biology labs, animal care, scientific, logistic and administrative support
- 3 experimental campaigns per year

NSRL Beam Line

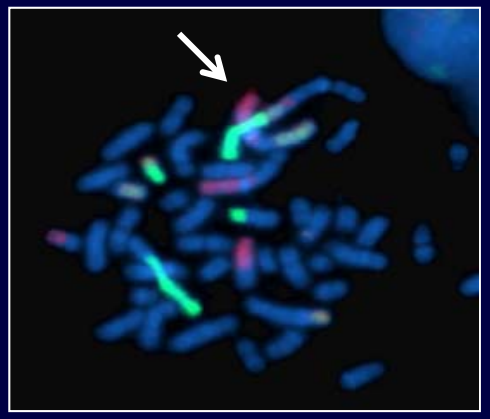
Radiation Carcinogenesis

Risk Summary & Research Strategy

- Morbidity/mortality risks for a wide range of cancers
  - Lung, breast, colon, stomach, esophagus, blood system (leukemias), liver, bladder, skin, and brain
- Major driver of Space Radiation Permissible Exposure Levels (PELs)
- Cancer incidence in Life Span Study cohort forms basis for risk modeling
  - Major research emphasis of SRPE
- Research approach is designed to feed the development of an integrated risk model
  - Acceptable uncertainty for exploration missions
  - Long-term goal to improve knowledge in support of accurate individual risk assessments and development of countermeasures



Cell invasion in 3-D organotypic cell model (Patel and Huff)

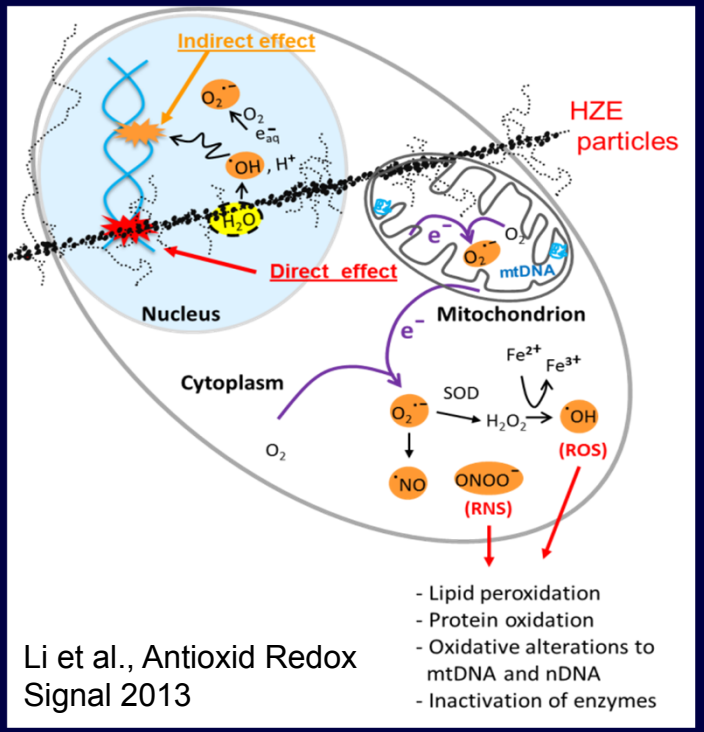


Complex chromosome damage following SR exposure (Hada)

Major Findings on Cancer Risk from NSRL

New research further characterizes GCR solid cancer risk

- A low RBE for HZE-induced Leukemia
- Evidence for increased aggression of HZE tumors
- Persistent oxidative stress and inflammatory pathway activation
- Distinct gene expression changes between high and low LET, and between specific ions
- Evidence for non-linear response at low dose due to non-targeted effects, which may confound conventional paradigms and RBE estimates



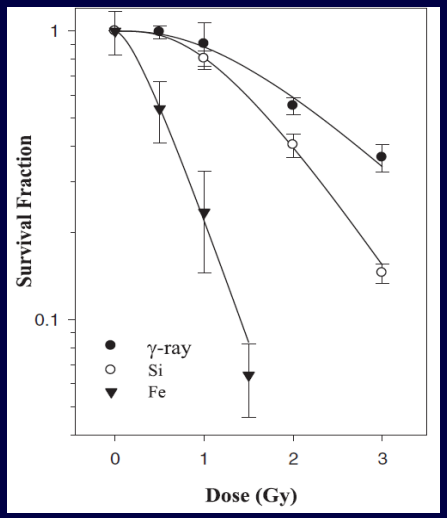
Li et al., Antioxid Redox Signal 2013

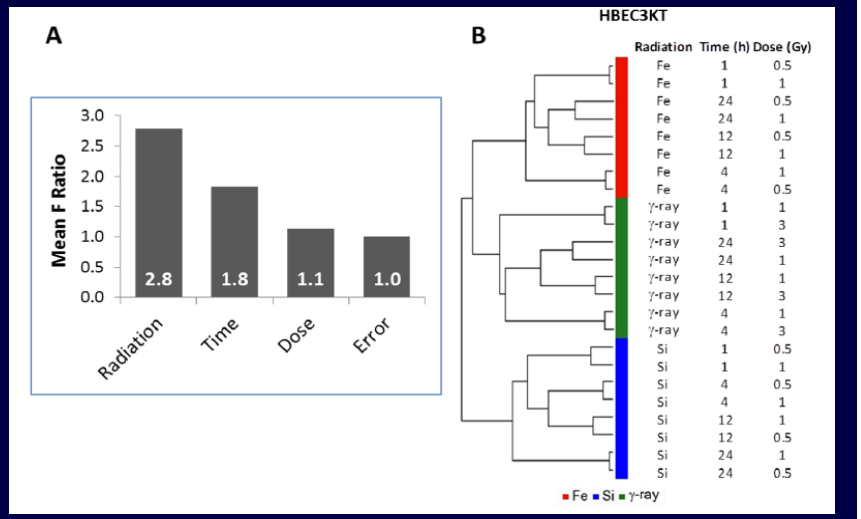
Distinct transcriptome profiles exposure to γ-rays and heavy ions in bronchial epithelial cells

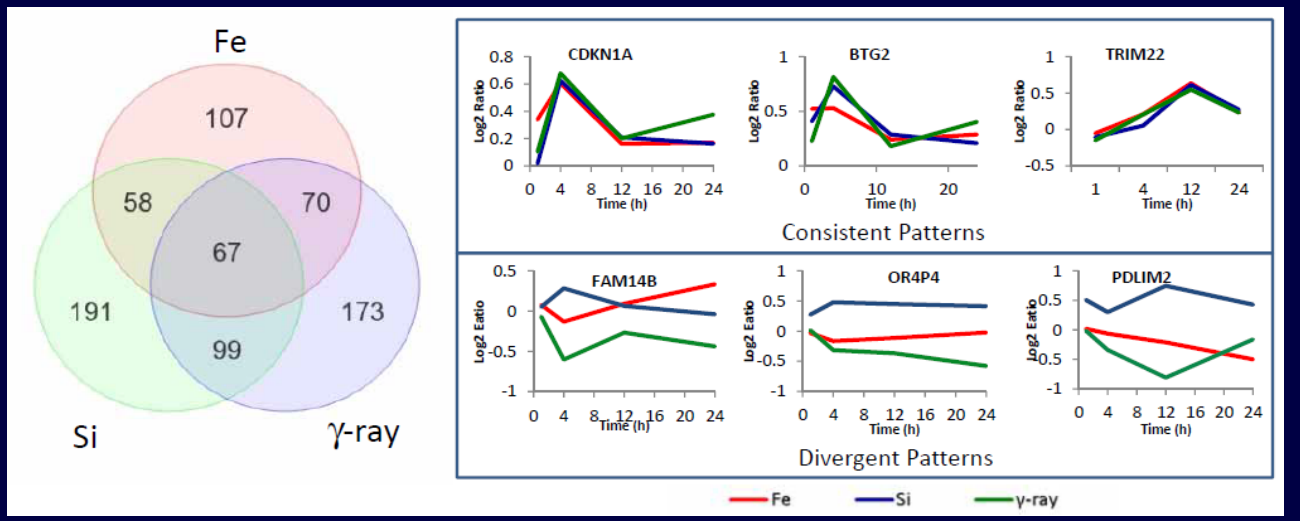
Ding L-H et al., *BMC Genomics* 2013

Purpose: Determine Radiation Quality-dependent transcriptome profiles of HBECs following γ-rays and HZE ions (^{28}Si and ^{56}Fe)

- Radiation quality most influential factor driving differential gene expression
- 73 gene signature predicts radiation type
- The pro-inflammatory Acute Phase Response Signaling was specifically induced after HZE particle irradiation
- This may explain the more severe biological effect induced by HZE particles



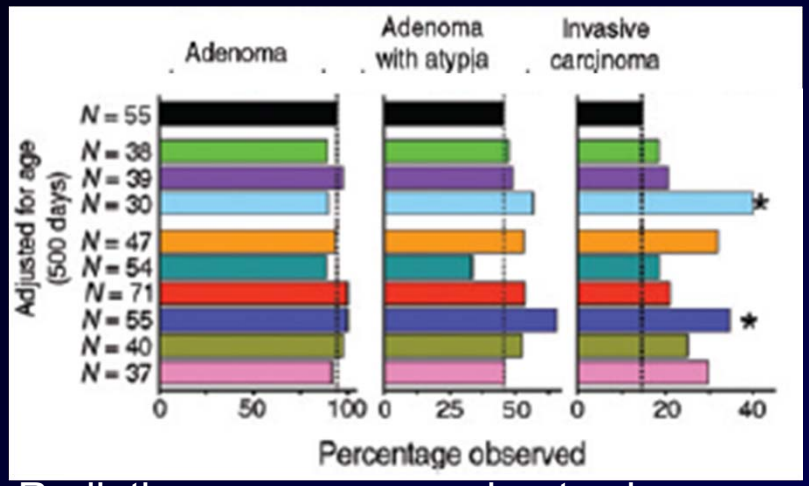




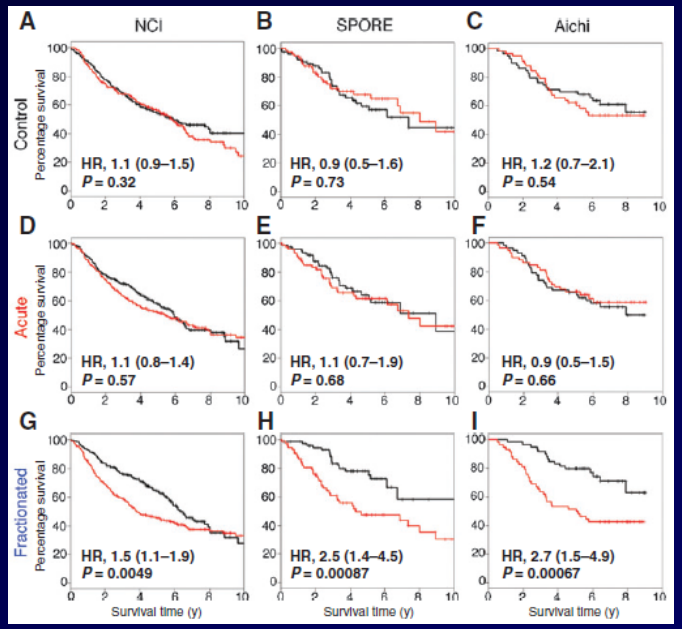
Radiation-Enhanced Lung Cancer Progression in a Transgenic Mouse Model of Lung Cancer Is Predictive of Outcomes in Human Lung and Breast Cancer

Delgado et al. Clinical Cancer Research 2014

Purpose: Determine the impact of radiation exposure on lung cancer progression *in vivo* and assess the relevance of this knowledge to human carcinogenesis



Radiation exposure accelerates lung cancer progression in the K-ras^{LA1} lung cancer mouse model; dose fractionation is more permissive for cancer progression



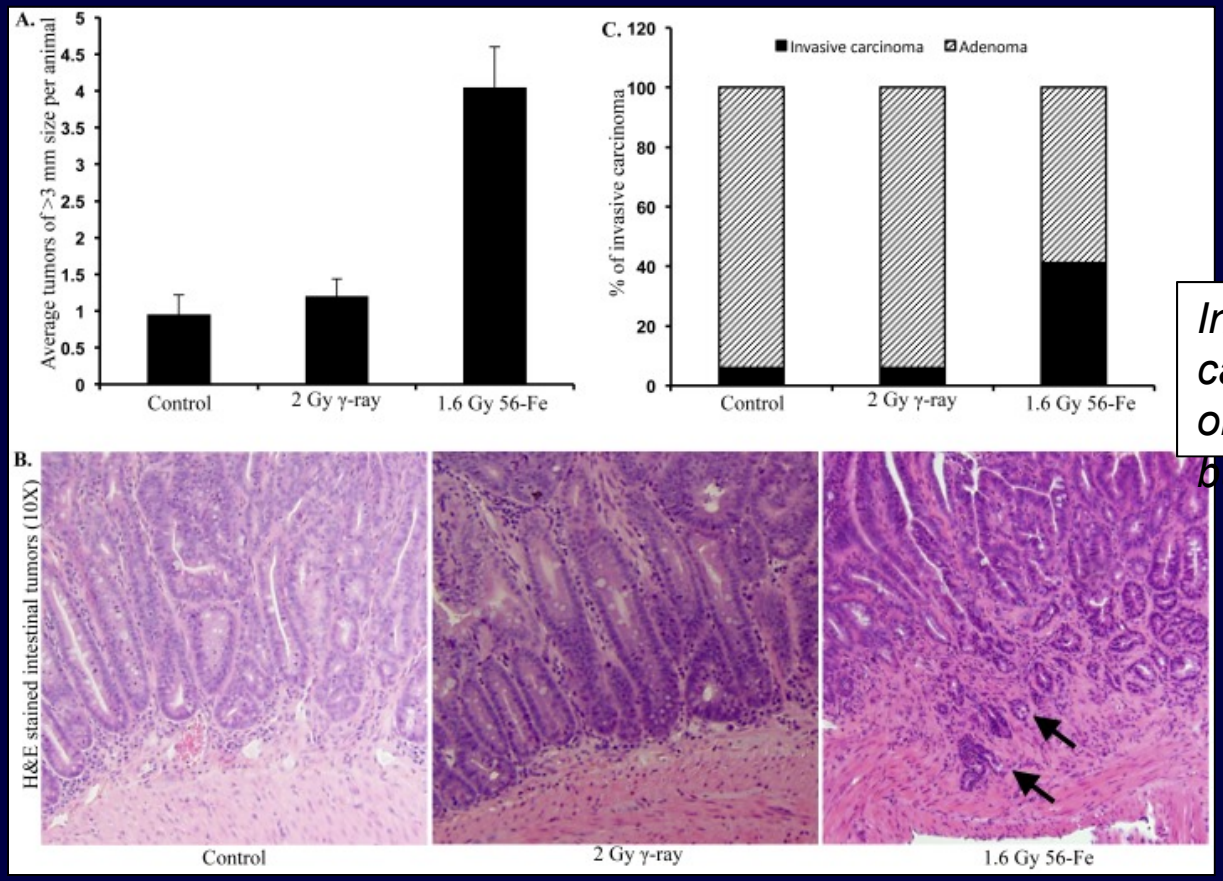
"Fractionated" classifier capable of predicting lung cancer patient survival across multiple data-sets. Red lines denote high-risk patients and black lines denote low-risk patients.

- The protracted HZE non-random mRNA signature, but not the single dose mRNA signature when found in human tumor specimens, is predictive of both human lung (and breast cancer) overall survival.
- Radiation exposure can cooperate with benign lesions in a transgenic model of cancer by affecting inflammatory pathways which are permissive for tumor progression

Higher Intestinal Tumor Frequency in APCMin/+ Mice

Datta K et al., *PLoS One* 2013

Purpose: Comparison of tumor frequency and grade in APC$^{Min/+}$ mice following γ-ray and ^{56} Fe exposure



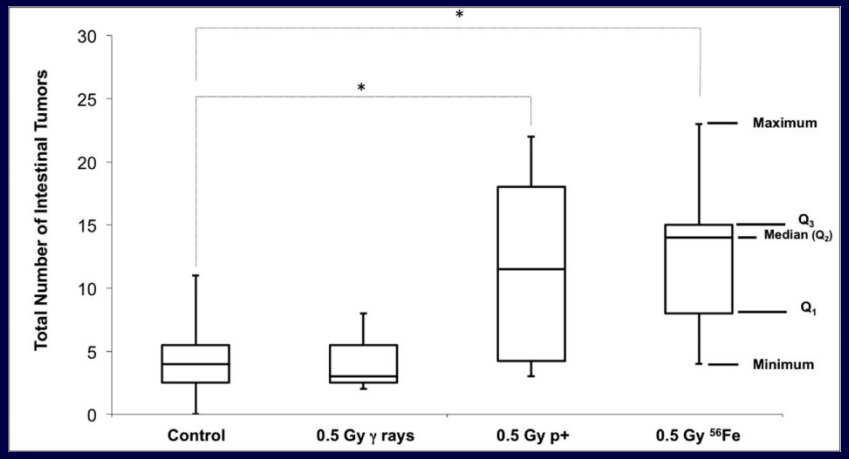
Invasive carcinomas observed after ^{56}Fe but not γ-rays

- Relative to controls and γ-ray, ^{56}Fe radiation-induced larger and higher-grade intestinal tumors.
- Tumors in control and γ-irradiated mice were mostly adenomas.
- Tumor incidence per unit of radiation (per cGy) was also higher after ^{56}Fe radiation relative to γ radiation

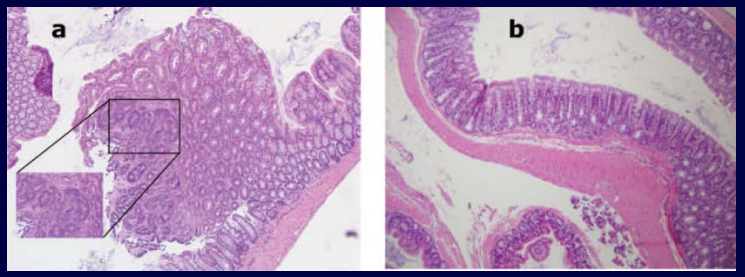
High-Energy Particle-Induced Tumorigenesis Throughout the Gastrointestinal Tract

Trani et al., *Radiat Res.* 2014

Purpose: Analyze Intestinal Tumor induced in Apc1638N/+ mice that develop small numbers of spontaneous lesions



a significant difference was observed in total intestinal tumor burden of proton and ^{56}Fe irradiated animals compared to controls



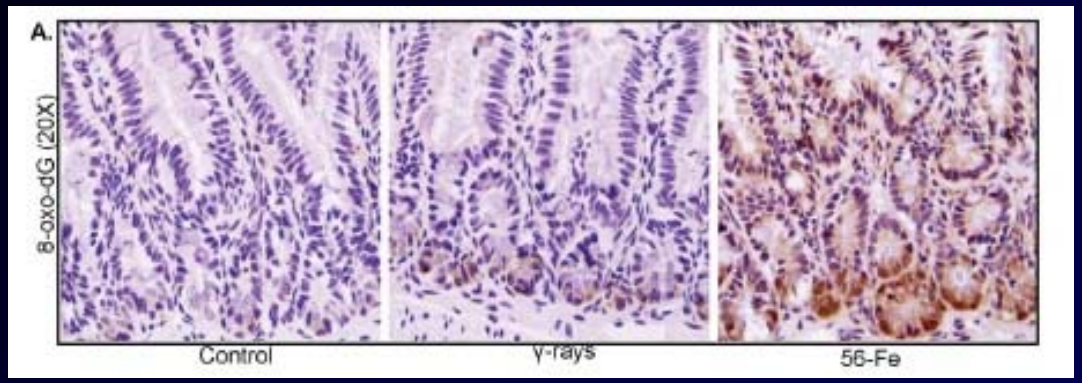
Colon carcinomas were observed only in 56Fe-ion-irradiated animals (a), but not in gender-matched gamma- and proton-irradiated mice (b)

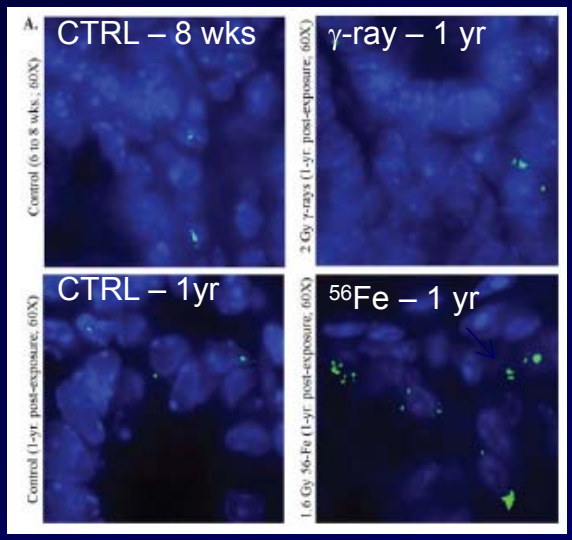
- Particle radiation increases tumor frequency and grade in the whole intestinal tract including stomach
- A single dose of 0.5 Gy of gamma rays did not induce significant change in total intestinal tumor burden compared to age- and gender-matched controls.
- Conversely, a significant difference was observed in total intestinal tumor burden of 0.5 Gy of protons and 56Fe ions irradiated animals compared to controls
- Radiation-Induced intestinal tumorigenesis is gender dependent only for gamma rays, but not for particle radiation

Persistent Oxidative Damage in Intestine

Datta *et al*. (PLoS One 2012)

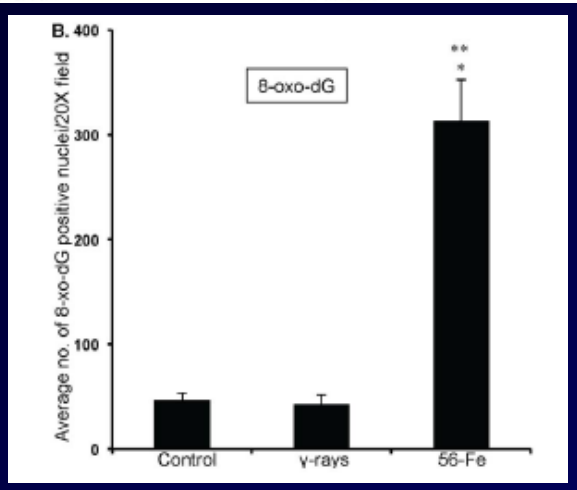
Purpose: Analyze oxidative damage in C57BL/6J intestinal cells 1 yr following ^{56}Fe exposure

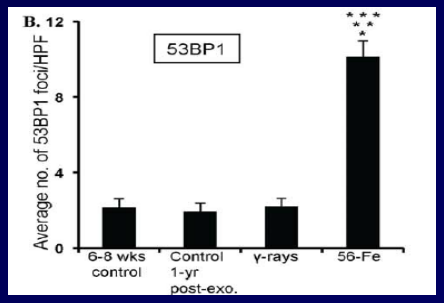


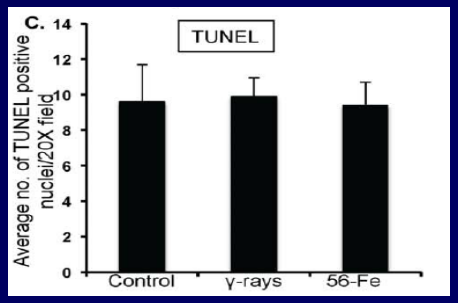


Persistent DDR foci after ^{56}Fe exposure

Higher 8-oxo-dG after ^{56}Fe exposure





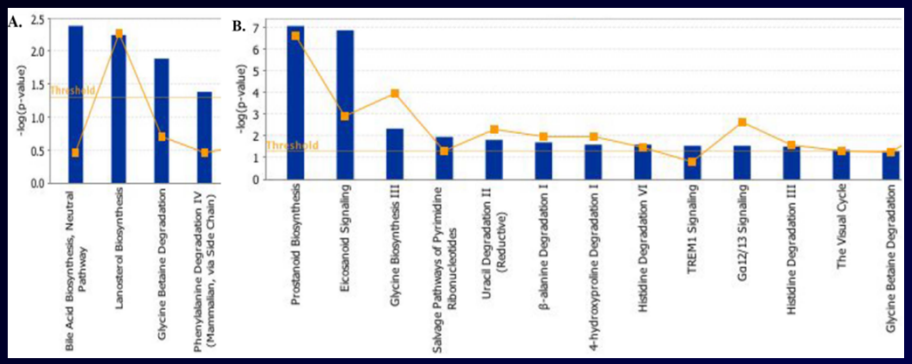


- Radiation quality affected the level of persistent oxidative stress with higher elevation of intracellular ROS, mitochondrial superoxide and oxidative DNA damage in ^{56}Fe compared to controls and γ radiation.
- Correlates with long-term functional dysregulation of mitochondria and increased NADPH oxidase activity

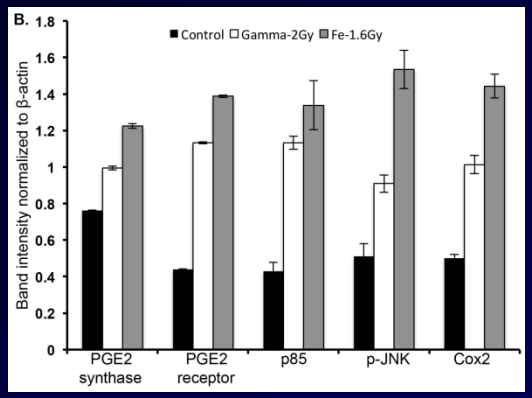
Long-Term Differential Changes in Mouse Intestinal Metabolomics

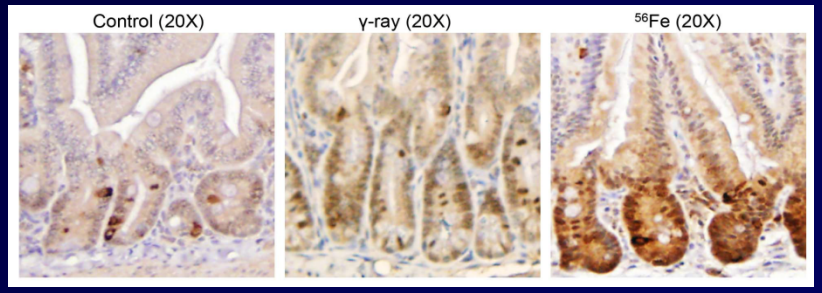
Cheema AK et al.,*Plos ONE*, 2014

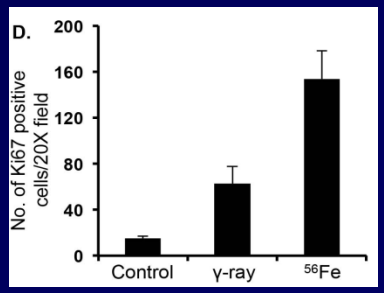
Purpose: Analyze long-term metabolomic markers of radiation injury and perturbation of signaling pathways in mice after heavy ion or gamma radiation exposure



Metabolites from gamma-and ^{56}Fe-irradiated groups were associated with distinctly different canonical pathways identified by Ingenuity Pathway Analysis.







Greater activation of PGE2 dependent signaling pathways and increased proliferation in intestinal epithelial cell after 56Fe radiation

- Intestinal tissues (C57BL/6J) analyzed using UPLC-QToFMS two months after 2 Gy gamma ray and equitoxic ^{56}Fe (1.6 Gy) exposures
- Metabolites from gamma and ^{56}Fe-irradiated groups were associated with distinctly different canonical pathways
- ^{56}Fe radiation caused upregulation of ‘prostanoid biosynthesis’ and ‘eicosanoid signaling’, which are interlinked events related to cellular inflammation and activation of cell proliferation

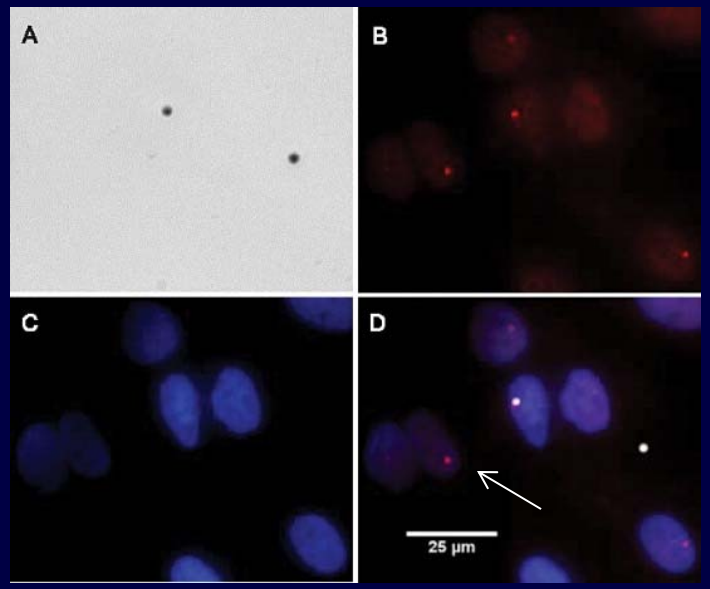
Non-Targeted Effects of Heavy Ions

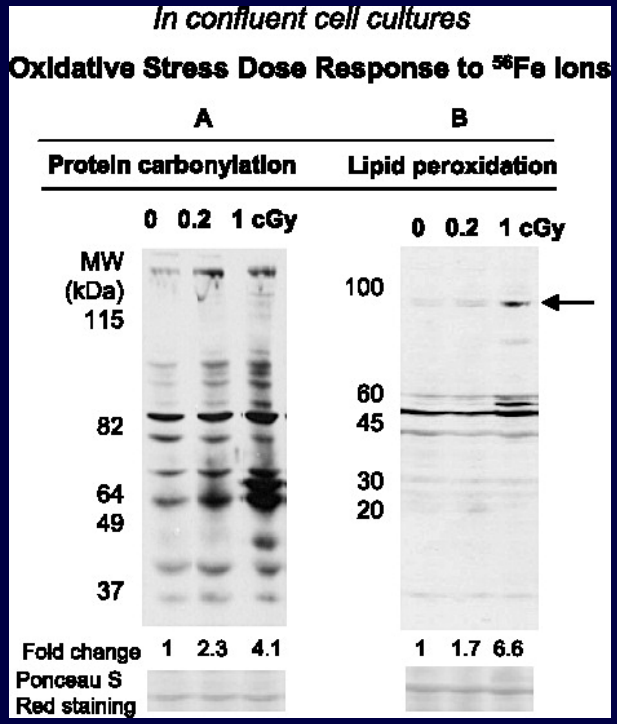
Azzam *et al*. (Radiat Res 2013)

Non-Targeted Effects of Heavy Ion Exposure on Markers of Oxidative Stress

Non-targeted DNA damage detected with CR-39-nuclear track detector

DNA damage foci in cells not directly hit by HZE particle





Oxidative stress markers higher than expected at low particle fluence

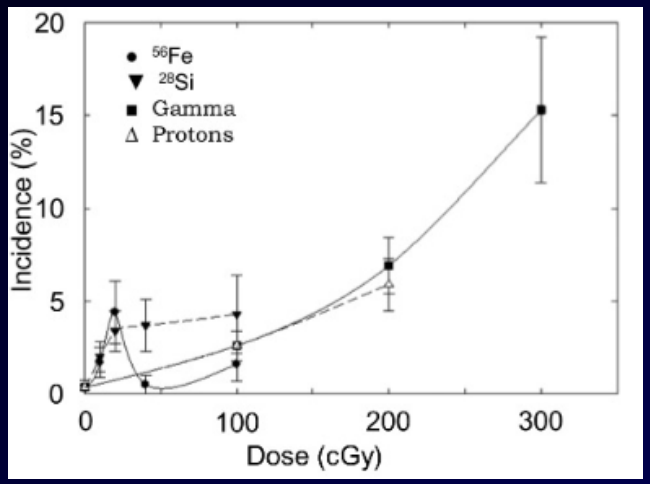
- Further evidence for amplification of stressful effects after exposure to doses as low as 0.2 cGy of HZE ions where only 1–3% of nuclei are traversed by a primary particle track and radial dose from delta rays is limited
- Previous work shows propagation of stressful effects in the progeny of bystander cells is LET-dependent

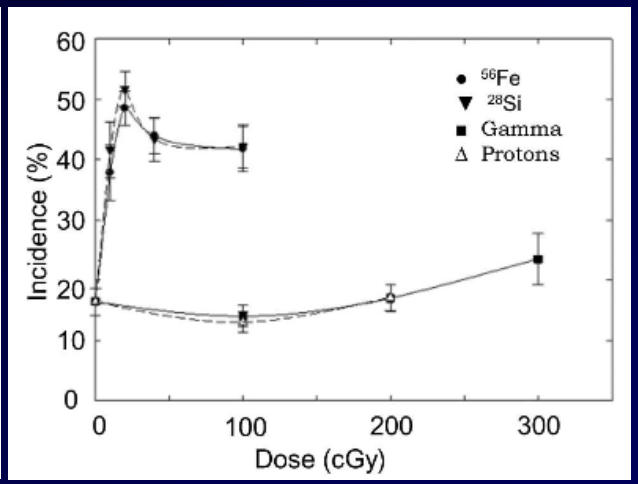
Effects of ^{28}Si Ions, ^{56}Fe Ions, and Protons on the Induction of Murine Acute Myeloid Leukemia and Hepatocellular Carcinoma

Weil MM, Ray FA, Genik PC, Yu Y, McCarthy M, Fallgren CM, Ullrich RL.

PLoS ONE. 2014

Purpose: Evaluate carcinogenic effects of ^{28}Si or ^{56}Fe ions in a mouse model of radiation-induced acute myeloid leukemia (AML) and hepatocellular carcinoma (HCC)





Incidence of AML (left) and HCC (right) following exposure to 300 MeV/n ^{28}Si, 600 MeV/n ^{56}Fe; ^{137}Cs gamma rays, or 1972 SPE protons

- ^{28}Si or ^{56}Fe ions were not more effective than gamma rays in the induction of AML
- However, these ions caused a higher incidence of HCC than gamma rays or protons
- frequency of lung metastases were significantly higher in both the ^{28}Si and ^{56}Fe ion but not between spontaneous tumors, gamma ray and proton irradiated mice
- demonstrate potentially different mechanisms of tumorigenesis between leukemia and solid tumors

Cancer References

High-Energy Particle-Induced Tumorigenesis Throughout the Gastrointestinal Tract. Trani D, Nelson SA, Moon BH, Swedlow JJ, Williams EM, Strawn SJ, Appleton PL, Kallakury B, Nathke I, Fornace AJ. *Radiat Res.* 2014

Heavy Ion Radiation Exposure Triggered Higher Intestinal Tumor Frequency and Greater b-Catenin Activation than Gamma Radiation in APCMin/+ Mice Datta K, Suman S, Kallkury B, Fornace AJ. *PLoS One* 2013

Radiation-Enhanced Lung Cancer Progression in a Transgenic Mouse Model of Lung Cancer Is Predictive of Outcomes in Human Lung and Breast Cancer Delgado et al. Clinical Cancer Research 2014

Distinct transcriptome profiles identified in normal human bronchial epithelial cells after exposure to γ-rays and different elemental particles of high Z and energy Ding L-H, Park S, Peyton M, Girard L, Xie Y, Minna JD, Story MD. *BMC Genomics* 2013

Long-Term Differential Changes in Mouse Intestinal Metabolomics after Gamma and Heavy Ion Radiation Exposure Cheema AK, Suman S, Kaur P, Singh R, Fornace AJ, Katta K. *Plos ONE*, 2014

Persistent Oxidative Damage in Intestine Datta *et al*. (PLoS One 2012)

Non-Targeted Effects of Heavy Ions Azzam *et al*. (Radiat Res 2013)

Effects of ^{28}Si Ions, ^{56}Fe Ions, and Protons on the Induction of Murine Acute Myeloid Leukemia and Hepatocellular Carcinoma Weil MM, Ray FA, Genik PC, Yu Y, McCarthy M, Fallgren CM, Ullrich RL. *PLoS ONE.* 2014

Risk of Acute and Late CNS Effects from Space Radiation Exposure- Background

The concern for CNS risks originated with the prediction of the light flash phenomenon from single HZE nuclei traversals of the retina; this phenomenon was confirmed by the Apollo astronauts

At therapeutic doses progressive deficits in short-term memory, spatial relations, visual motor processing, quantitative skills, and attention are reported months to years after radiation exposure

- Doses are well above those expected in space even for a large SPE
- Very little data is available from low LET studies of human populations at low to moderate doses (<2 Gy) in adults
- Lack of human epidemiology data to form the basis for risk assessment for CNS effects
- Evidence relies on studies in cell and animal models using simulated GCR at NSRL

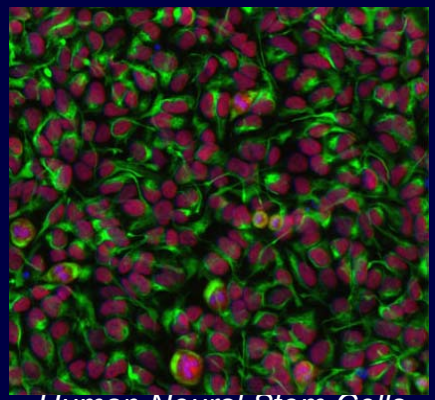
– *Research to date has been focused on understanding whether there are significant risks to the CNS from space radiation exposure*

The ALFMED device as worn during light flashes investigation (Apollo light flash moving emulsion detector) image credit: NASA

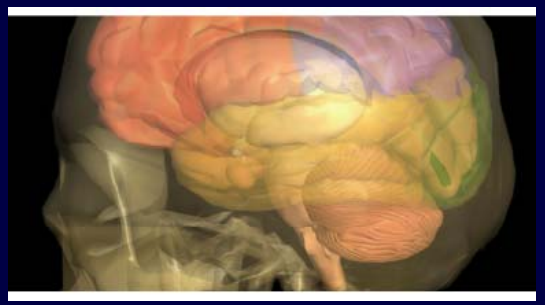
Acute CNS Risk Summary

Acute CNS risks - altered cognitive function including short-term memory, reduced motor function, and behavioral changes, which may affect performance and human health

- NASA studies reveal effects in hippocampus, neostratum, and pre-frontal cortex
- Low doses of GCR alter the creation of new neurons in rodents, disrupting “new memory” and cognition
- Changes in cognitive performance are associated with neuronal degeneration, oxidative stress, apoptosis, inflammation, and changes in dopamine function
- Interdependency of multiple neural cell types for normal function (supporting glia and vasculature)
- *Decrements dependent on radiation dose and quality as well as on age of animal at time of exposure.*
- *Effects not seen with similar doses of low-LET radiation*



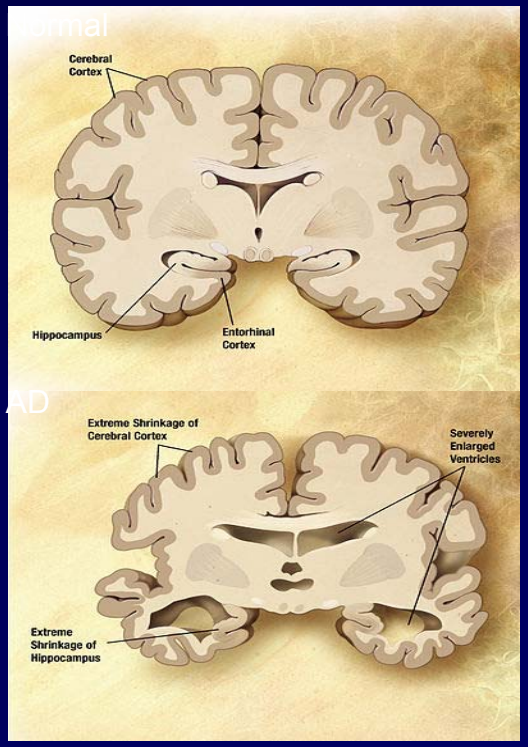
Human Neural Stem Cells
C.Limoli UC Irvine



Late CNS Risk Summary

Late CNS risks are possible neurological disorders such as Alzheimer's disease (AD), dementia, cerebrovascular disease or premature aging

- NASA animal studies have quantified rate of neuronal degeneration, oxidative stress, inflammation
- Plaque formation similar to Alzheimer's Disease observed in mouse models
  - *AD is fatal, with mean time from early stages to death approx. 8 yrs*
  - *Inclusion in overall acceptable REID probability for space missions if AD risk is established*

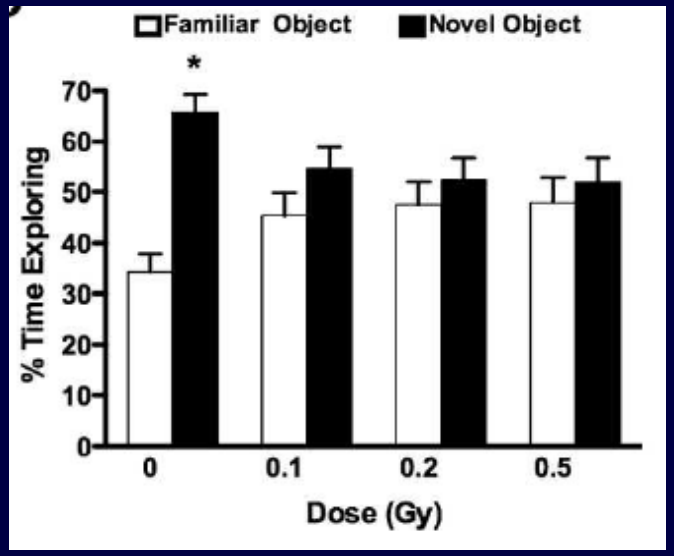


en.wikipedia.org/wiki/Alzheimer's_disease

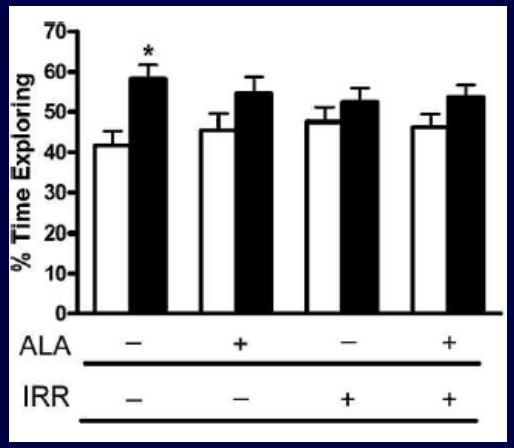
Hippocampal Dependent Memory/Cognition

Haley et al. (Radiat Res 2013)

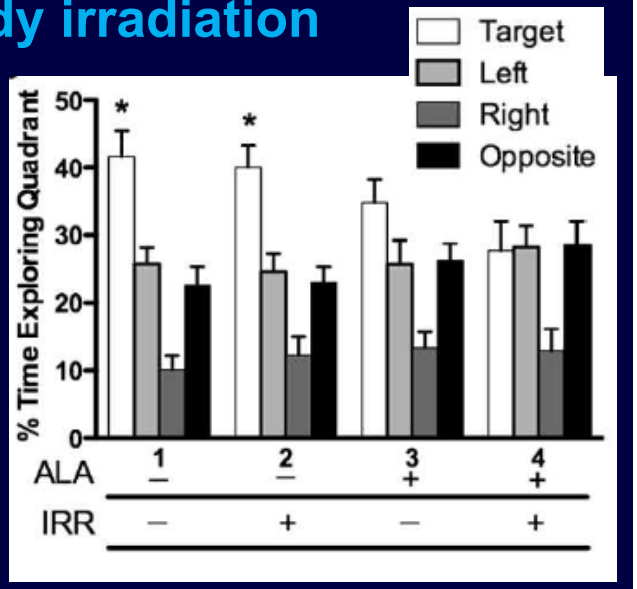
Assessment of effects of ^{56}Fe irradiation on hippocampal function in C57BL/6J mice starting 2 weeks after whole-body irradiation



HZE impairs novel object recognition ^{56}Fe (600 MeV, 0.1 Gy).



ALA did not prevent radiation induced impairment in NOR, but did impair NOR in sham-irradiated mice



No effect of HZE on spatial learning
ALA impaired spatial learning in first trial

→ Loss of memory/cognition (novel object recognition) at low doses of HZE particle irradiation at early time points (as early as 2 weeks after radiation) independent of ROS

- Novel object recognition test is particularly sensitive to detect early cognitive effects of ^{56}Fe irradiation (no effects observed on contextual fear conditioning or spatial memory retention)
- ALA impaired spatial memory retention of sham-irradiated and irradiated mice - may be related to the dual role of ROS in the brain, having both positive and negative effects on cognition

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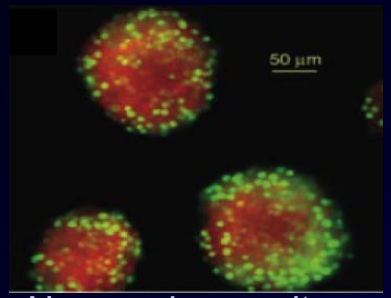
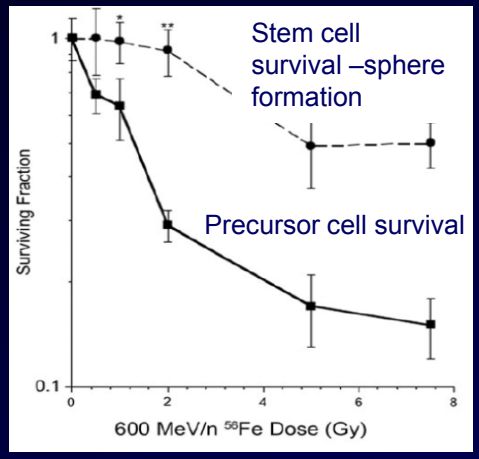
Oxidative stress in neural stem and precursor cells

Tseng et al. (Antioxid Redox Signal 2013)

Investigation of low dose charged particle irradiation elicited oxidative stress in neural stem and precursor cells and correlation with cognitive impairment

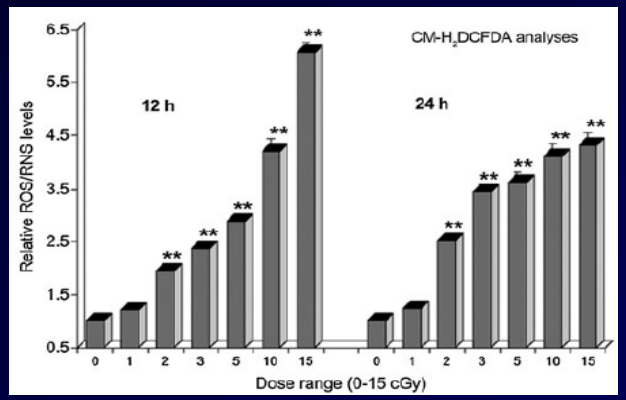


Neurosphere culture

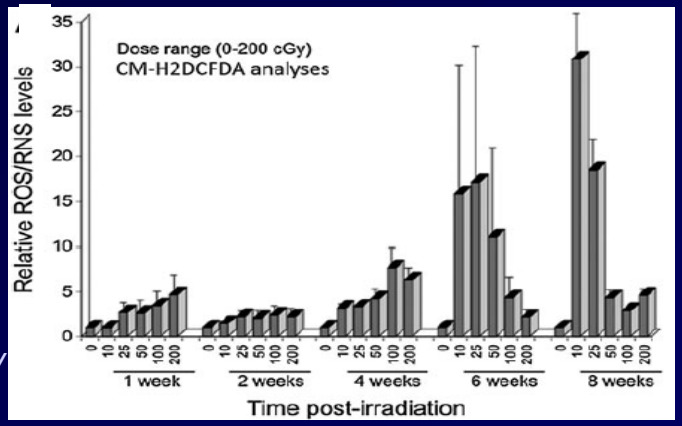


Neural stem cells exibited higher radioresistance compared to progeny

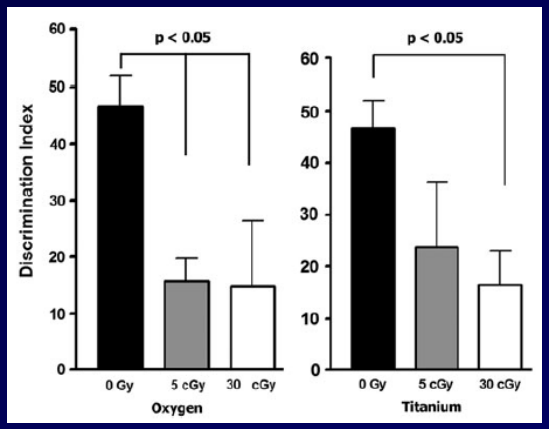
Early dose-dependent rise in ROS/RNS following ^{56}Fe exposure of neurospheres



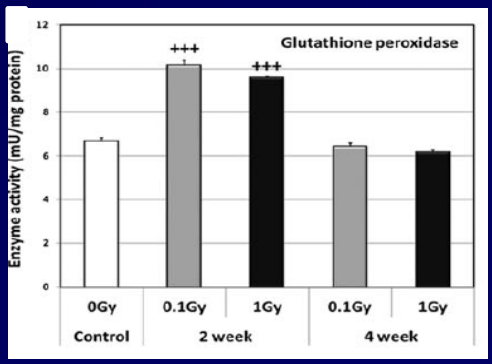
Persistent late ROS/RNS following ^{56}Fe exposure in neurosphere cultures



low dose exposure to charged particles leads to impaired NOR performance over extended postirradiation times.



Transient increase in brain tissue antioxidant capacity (2 wks)



→ ***Acute exposure of neural stem cells and the CNS to very low doses of charged particles can elicit a persisting oxidative stress lasting weeks to months that is associated with impaired cognition***

Effects of HZE on Executive Function

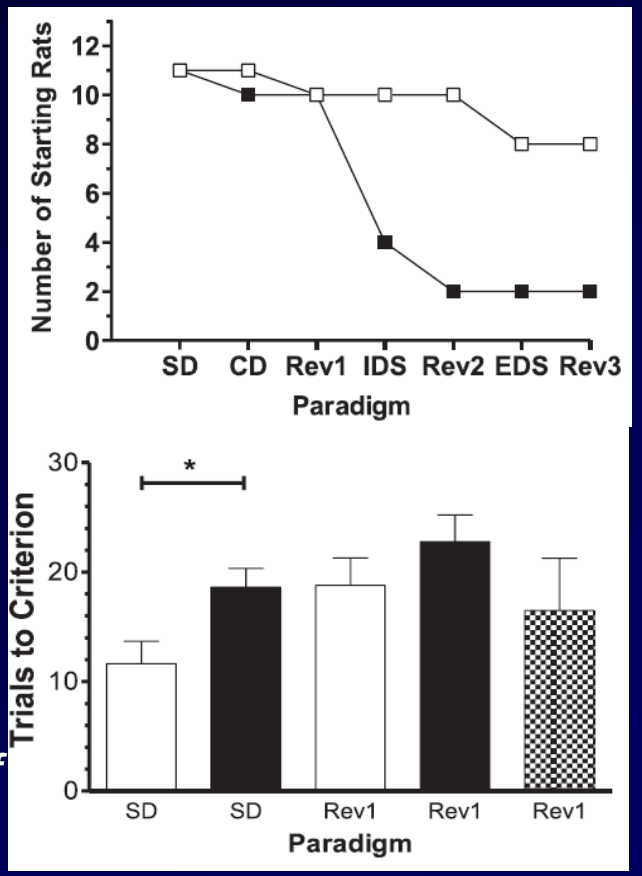
Lonart *et al*. (Radiat. Res.2013)

Effects of 20 cGy doses of 1 GeV/n ^{56}Fe particles on executive function (prefrontal cortex) in Wistar rats tested 3 months after radiation for their ability to perform attentional set shifting

TABLE 1
Order of Discrimination Tasks and Exemplars Used

Task	Correct (food reward)	Incorrect (no food)
Simple discrimination	Rum	Rum
	Corn cob	Rocks
Complex discrimination	Rum/Cherry	Rum/Cherry
	Corn Cob	Rocks
Reversal 1	Rum/Cherry	Rum/Cherry
	Rocks	Corn cob
Intra-dimensional shift	Mint/Orange	Mint/Orange
	Epp. Tube Bott.	Epp. Tube Top
Reversal 2	Mint/Orange	Mint/Orange
	Epp. Tube Top	Epp. Tube Bott.
Extra-dimensional shift	**Coconut**	Cinnamon
	Vase filler/Beads	Vase filler/Beads
Reversal 3	**Cinnamon**	Coconut
	Vase filler/Beads	Vase filler/Beads

Odor and digging medium combinations



Only 2/11 irradiated rats completed all the paradigms; while 8/11 controls completed all paradigms

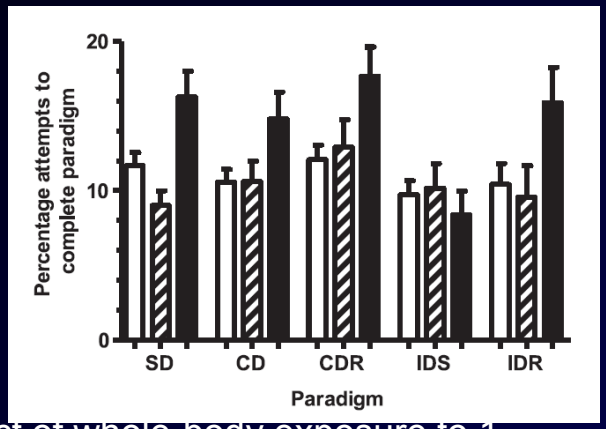
Irradiated rats: more trial attempts to complete the simple discrimination stage

- *Animals required to discriminate amongst several perceptual features (e.g., odor and texture) of complex stimuli to solve a series of problems to gain a food reward*
- *Requires rat to locate food reward and learn which "clue" (e.g., tactile information of digging medium, odor) is associated with reward. Once the rat learns which clue is associated with food, the clue is changed*

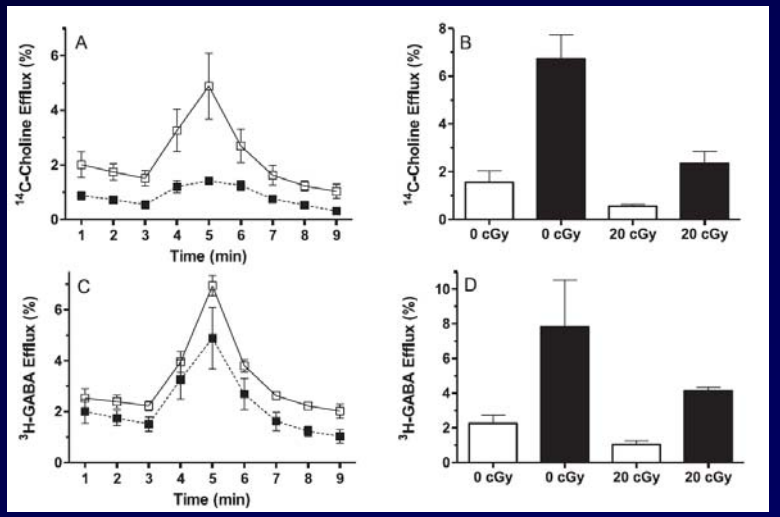
→ ***Executive function in rats is impaired by low (20 cGy) doses of ^{56}Fe particles***

→ ***Interindividual variation evident in that some irradiated rats performed as well as controls***

Exposure to Mission Relevant Doses of 1 GeV/Nucleon 56Fe Particles Leads to Impairment of Attentional Set-Shifting Performance in Socially Mature Rats
Britten et al., Rad Res 2014



Effect of whole-body exposure to 1 GeV/nucleon 56Fe particles on the paradigm-specific performance of retired breeder rats. sham-irradiated (open bar) and whole-body exposure to 15 cGy (hatched bar) or 20 cGy (solid bar) 1 GeV/nucleon 56Fe



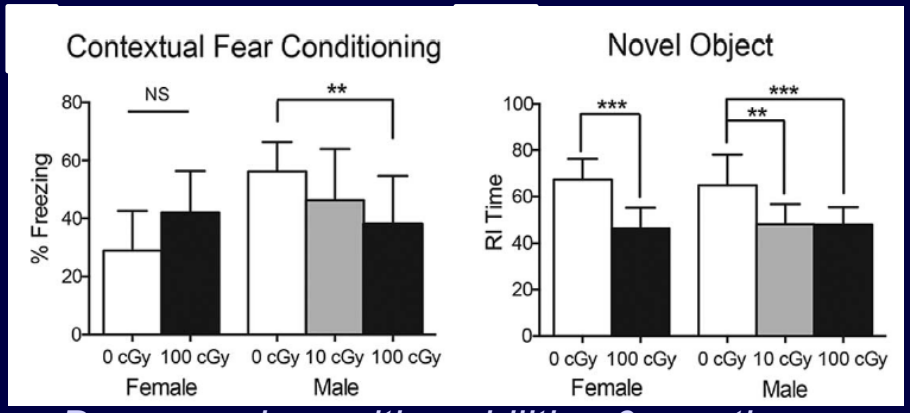
At 90 days postirradiation, there was a significant reduction in the cholinergic RRP in synaptosomal preparations from the basal forebrain of HZE-irradiated rats

- whole-body exposures to 15 and 20 (but not 10) cGy of 1 GeV/nucleon 56Fe-particles radiation results in attentional set shifting (ATSET) impairments in both juvenile and socially mature rats.
- behavioral decrements are associated with a reduction in the cholinergic RRP within basal forebrain, which has been shown to play a major role in regulating the activity of the Prefrontal cortex

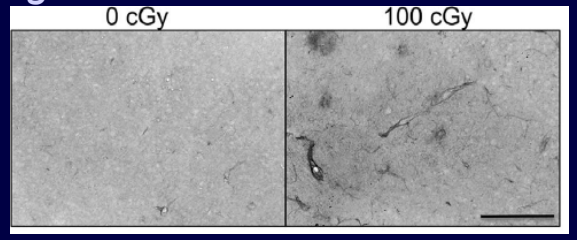
Late CNS Risks

Evidence Updates: Cherry et al. (PLOS One 2013)

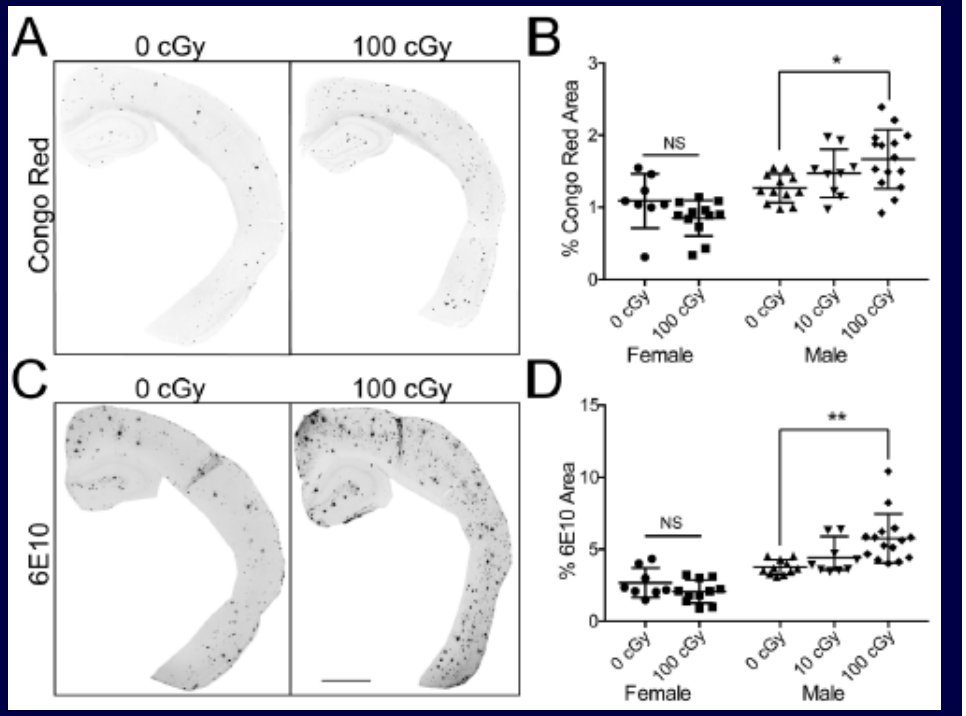
Effects of ^{56}Fe particle irradiation in an APP/PS1 mouse model of AD



Decreased cognitive abilities 6 months following ^{56}Fe ion irradiation



- *Elevated ICAM-1 expression following HZE exposure (marker of endothelial activation)*
- *No indication of microglial activation*



Acceleration of Aβ plaque pathology at 6 months post exposure to ^{56}Fe ions

→ ***First report of increased appearance of markers of AD at HZE doses as low as 10 cGy***

- Associated with cognitive impairment
- Increased markers of endothelial activation

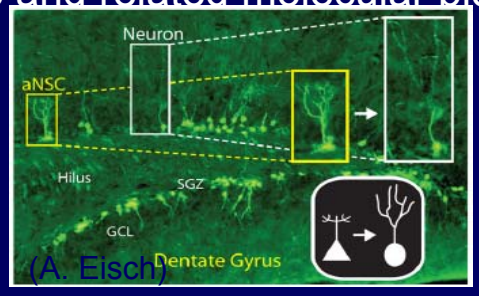
CNS Risks
Research Summary

Key Research Results:

Research with animal models shows important changes to the CNS occur at HZE exposure levels in range of concern to NASA. However, the significance of these results on the morbidity to astronauts has not been elucidated

- Exposure to HZE nuclei at low doses (< 50 cGy) induces neurocognitive deficits (learning, behavioral, memory, operant response, executive function) in rodents; same effects not seen ≤2 Gy of low-LET radiation (γ- rays or X-rays)
  - Alterations depend on physical properties of the ions (LET), and age of animal at exposure
  - Neurocognitive deficits in the dopaminergic system are similar to aging and may be unique to HZE
- HZE exposure disrupts hippocampal neurogenesis in mice at low dose (<1 Gy)
- Elevated reactive oxygen species (ROS) are observed in neuronal precursor cells following exposure to HZE nuclei and protons at low dose and persist for several months
- Neuroinflammation observed following exposure to HZE nuclei and protons
- Studies using transgenic mice prone to develop pathologies reflective of Alzheimer's disease show low dose of GCR accelerates time of appearance and related molecular biomarkers


(B. Rabin)



(A. Eisch)

CNS Risks
Research Summary

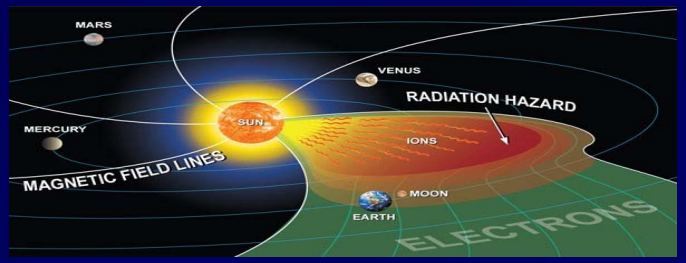
Limitations:

- Studies are limited by the number of GCR particles, doses, dose-rates considered, # animals
- Accurate characterization of radiation quality and dose response relationships requires analysis of large numbers of particles (>6) with a sufficient number of low to moderate doses (at least 5 doses below 0.5 Gy); also larger sample size required for lower dose threshold studies
- Limitation in using rodent models
- The use of primate models more representative of humans has not been considered, but may be required because of the large differences between the brains of primates and rodents

→ ***Radiation safety standards will protect against clinically significant CNS risks in-flight, and would limit late CNS effects to an acceptable risk level.***

- Need to understand exposure levels were violation of safety standards would occur

→ ***Further biological research is required to establish risk levels in space, to establish risk projection models, and, if risks are found to be significant, to design countermeasures.***



CNS References

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2. Tseng BP, Giedzinski E, Izadi A, Suarez T, Lan ML, Tran KK, Acharya MM, Nelson GA, Raber J, Parihar VK, Limoli CL. Functional consequences of radiation-induced oxidative stress in cultured neural stem cells and the brain exposed to charged particle irradiation. Antioxid Redox Signal. 2014 Mar 20;20(9):1410-22. doi: 10.1089/ars.2012.5134. Epub 2013 Aug 12. PubMed PMID: 23802883; PubMed Central PMCID: PMC3936501.

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5. Grabham P, Sharma P, Bigelow A, Geard C. Two distinct types of the inhibition of vasculogenesis by different species of charged particles. Vasc Cell. 2013 Sep 17;5(1):16. doi: 10.1186/2045-824X-5-16. PubMed PMID: 24044765; PubMed Central PMCID: PMC3856512.

Degenerative Risks

Risk Summary

Risk of Degenerative Tissue Effects:

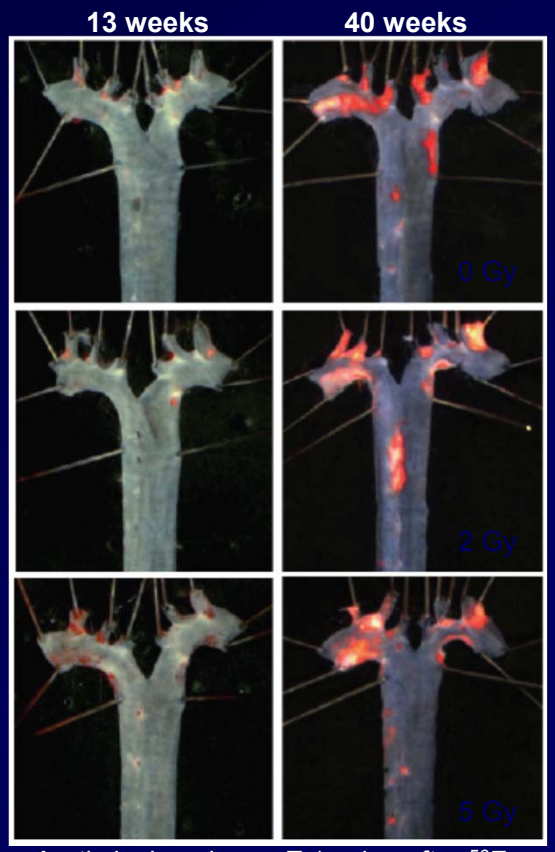
- Cardiovascular and circulatory changes
- Cataract formation

Other Health Effects:

- Diseases related to aging, including digestive, respiratory disease, premature senescence, endocrine, and immune system dysfunction

Driving Evidence:

- Astronaut data (cataracts)
- Radiotherapy, environmental disasters, atomic bomb survivor data, radiation workers
  - Data is confounded by life-style factors to larger extent than cancer
- Most prior experimental work focused on high dose effects, high fat diets or other protocols that are atypical for astronauts



Aortic lesions in apoE-/- mice after ^{56}Fe irradiation (Kucik et al., Rad Res 2011)

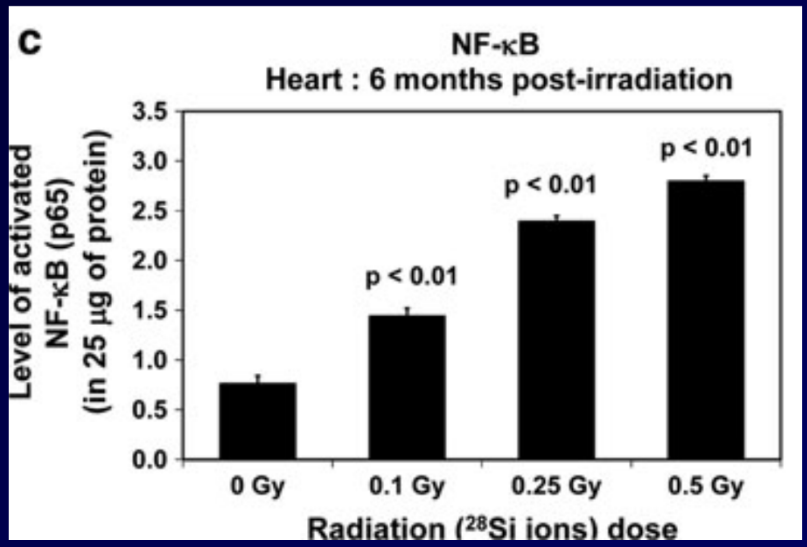
Risk Projections:

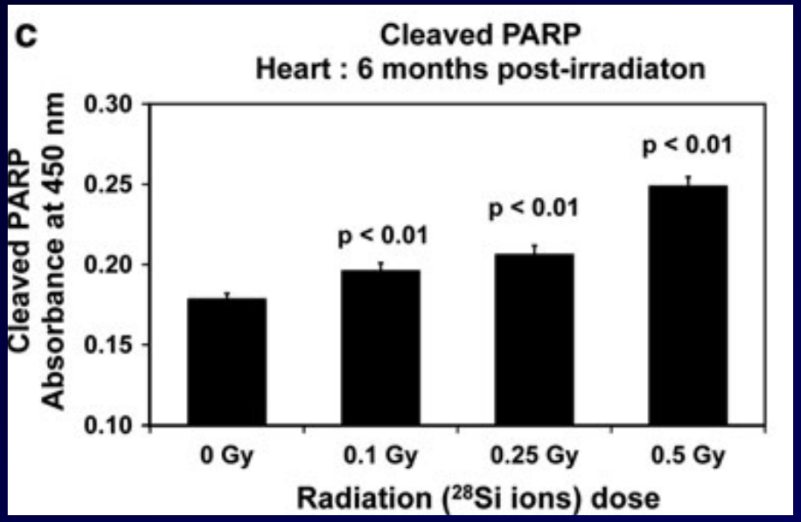
- Preliminary risk assessment models being formulated
- Current exposure limits set as dose thresholds; recent studies suggest there may be low dose and dose-rate effects

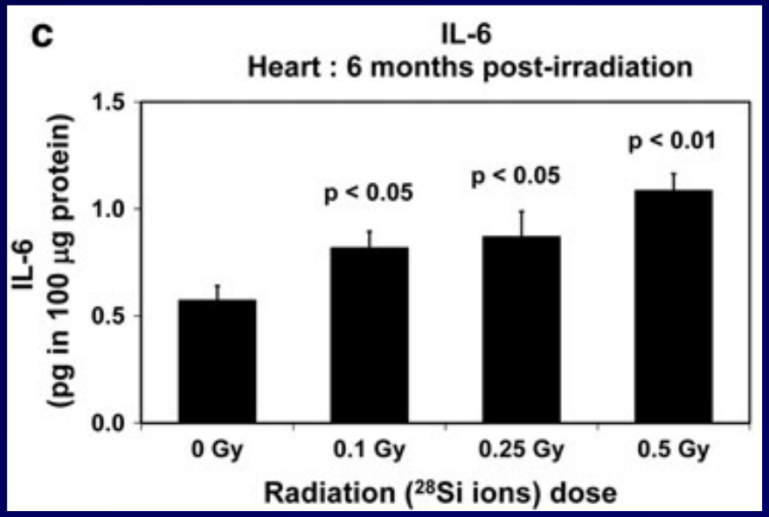
Degenerative Risks

Rithidech et al. (Radiat Environ Biophys 2013)

- Heart tissue harvested from irradiated male mice (^{28}Si with 2 fractionated exposures)
- Sustained cell apoptosis (cleaved PARP) at 6 months
- Persistent increased levels of NF-κB and associated inflammatory cytokines (IL-6, IL-1β, TNF-α)





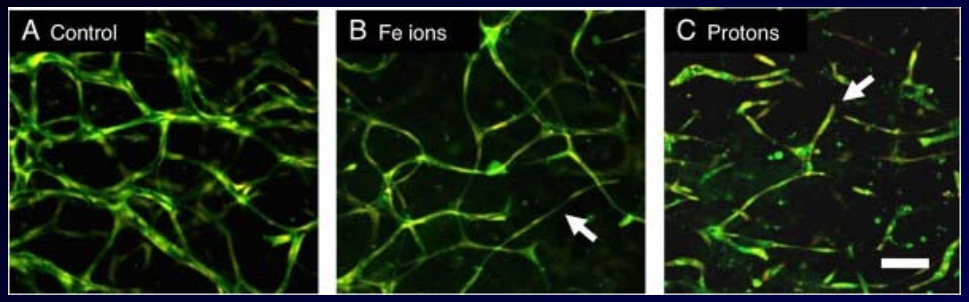


→ **Low dose effects for HZE irradiation, including apoptosis and sustained inflammation, seen in heart tissue at time points up to 6 months**

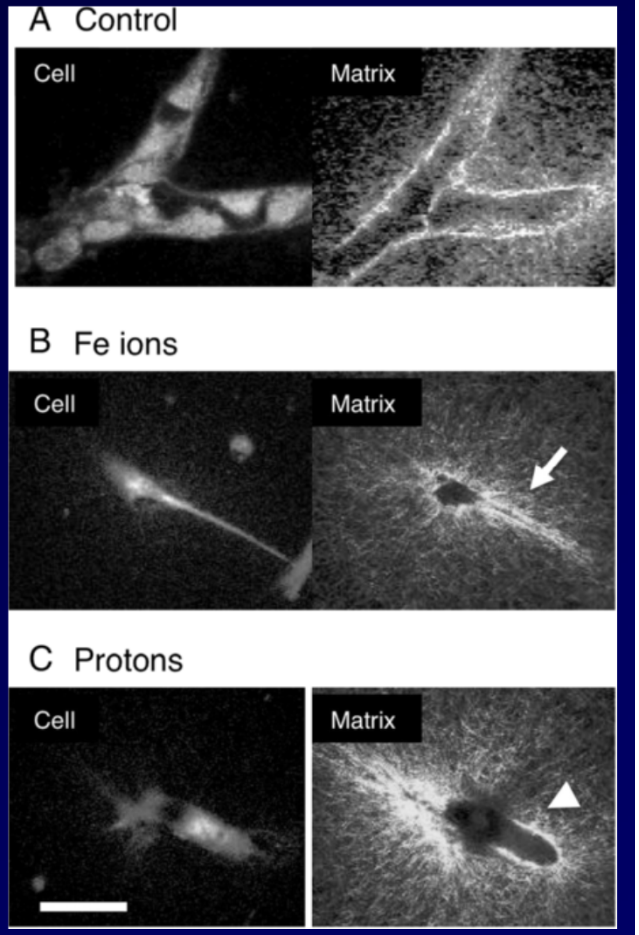
CNS + Degenerative Effects

Grabham et al. (Vascular Cell 2013)

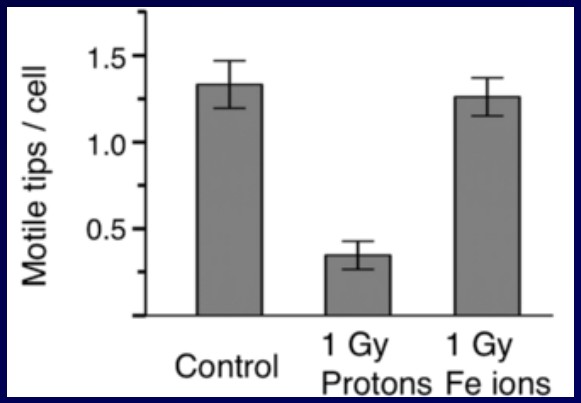
Assess angiogenesis using endothelial cells in 3-D culture exposed to low-LET protons and high-LET ^{56}Fe ions



- Exposure to protons and Fe ions results in distinct morphologies of mature 3-Dimensional vessel models



- Protons inhibited early steps of vasculogenesis (no mobility at protuding tips of endothelial cells but formed lumen)
- Iron inhibited later steps of vasculogenesis (extended cellular processes but no central lumen formation)



→ Evidence for impact of radiation quality on mechanisms of inhibition of vasculogenesis following radiation exposure

Degenerative Risks

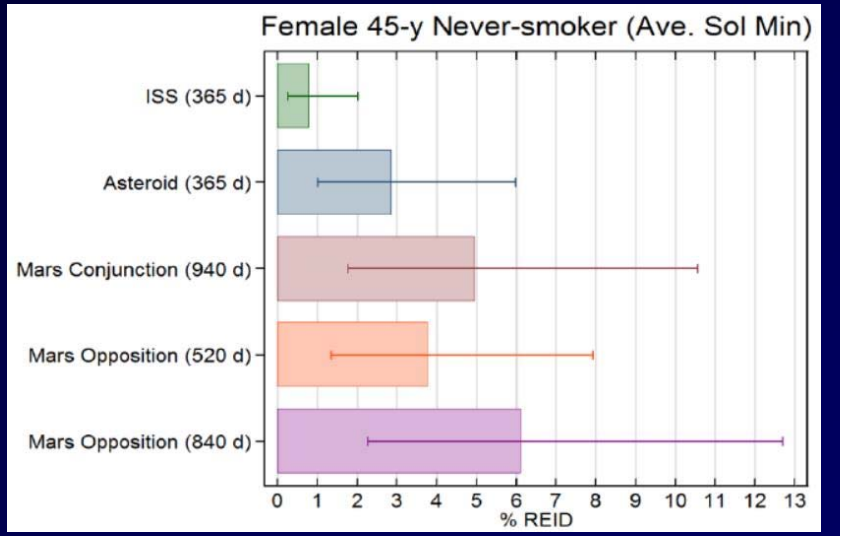
Cucinotta et al. (PLOS One 2013)

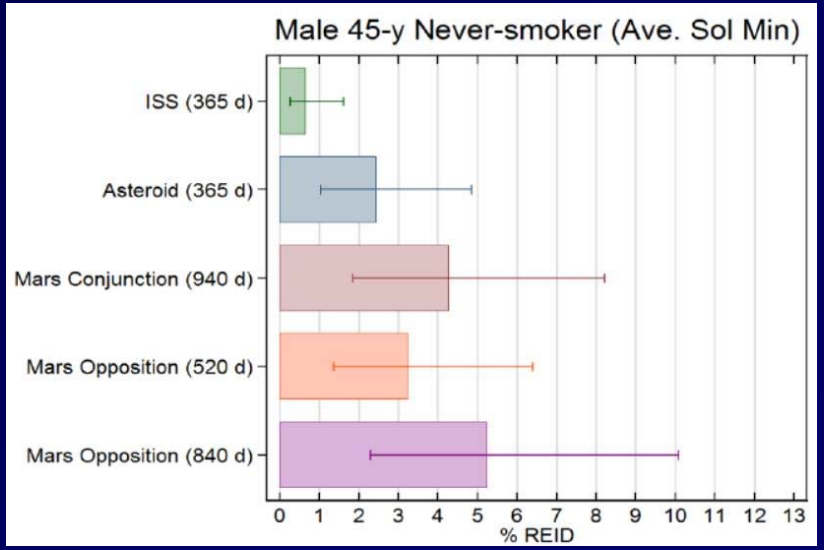
- Radiation risks and uncertainties for Mars and other exploratory missions evaluated using the new NASA Space Cancer Risk (NSCR) model
- Combined risk estimates ~40% higher than for cancer alone
- Discussion of avenues for risk mitigation that include considerations for solar cycle timing, individual sensitivities, and biological countermeasures

	%REID, Cancer	*%REID,Circulatory*	*% REID, Combined*
U.S. Average	5.32 [0.95, 14.3]	1.48 [0.57, 3.05]	6.57 [1.38, 14.8]
Never-Smokers	3.56 [0.51, 8.87]	1.55 [0.58, 3.20]	4.98 [1.77, 10.6]
U.S. Average	3.52 [0.66, 8.23]	1.53 [0.64, 3.05]	4.94 [1.91, 9.78]
Never-Smokers	2.75 [0.63, 6.52]	1.62 [0.68, 3.21]	4.28 [1.86, 8.22]

Lifetime risks for 940d Mars conjunction mission for average solar minimum.

→ **Mars mission radiation risk estimates are higher than expected if calculated as combined risk for cancer and circulatory diseases**





Degenerative Risks Summary

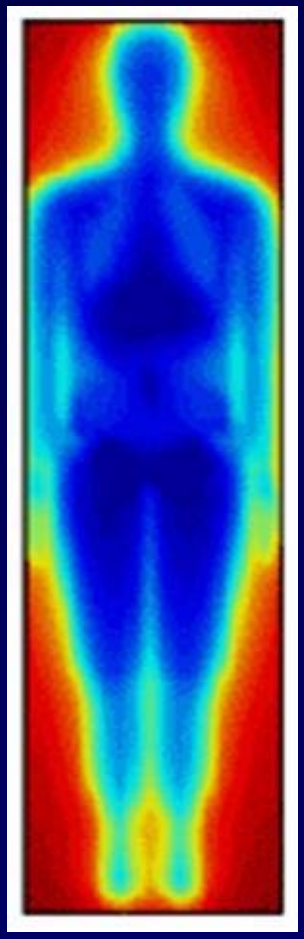
Cardiac and Circulatory Disease Risk

- Radiation effects at low doses resulting in chronic oxidative stress – this is correlated to atherosclerosis in human studies (**Rithidech et al., Radiat Environ Biophys 2013**)
- Radiation quality effects observed on mechanisms related to vasculogenesis (**Grabham et al., Vascular Cell 2013**)
- Epidemiology data establishing the risk at lower doses than previously estimated; incorporated with NASA cancer risk estimates (**Cucinotta et al., PLOS One 2013**)

Qualitative differences between GCR and gamma-rays are a major concern

Dose threshold is possible making risk unlikely for ISS Missions(<0.2 Sv) ; however a concern for Mars or lunar missions due to higher GCR and SPE dose

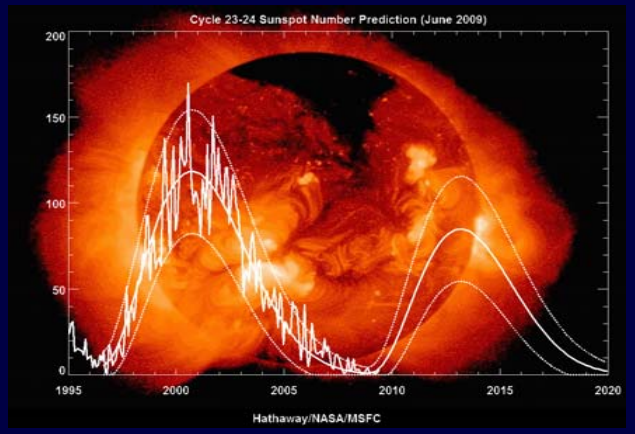
Recently established NSBRI Center for Space Radiation Research will focus on Cardiovascular Risk Research



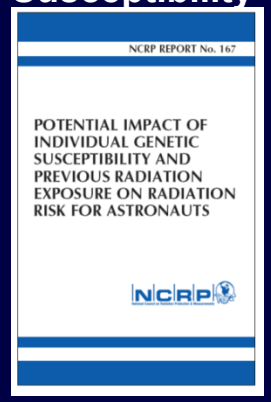
Mitigation Approaches

- **Time in the Solar Cycle**
- **Radiation Shielding**
  - Amounts and material types
  - Design Optimization
- **Accurate Risk Quantification / Uncertainty reduction**
- **Crew Selection**
  - Age, gender, lifestyle factors, etc,
  - Individual Sensitivity (genetic factors)
- **Biological Countermeasures (BCMs)**
  - Radioprotectors / Mitigators
- **Biomarkers predictive of radiation induced diseases**
  - Future individualized risk assessment
  - Early detection and prognostic monitoring

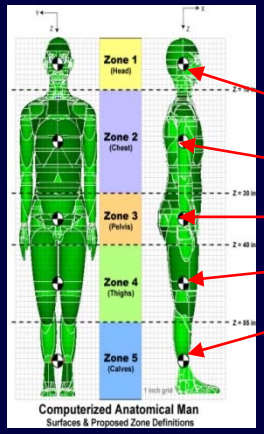
Variation of Solar Activity

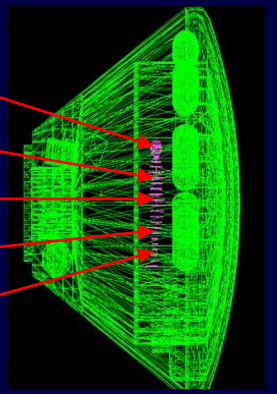


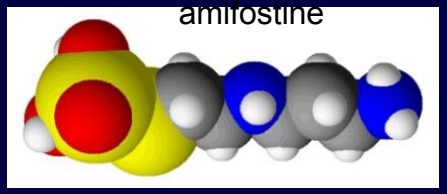
Individual Susceptibility



Shield Design and Optimization





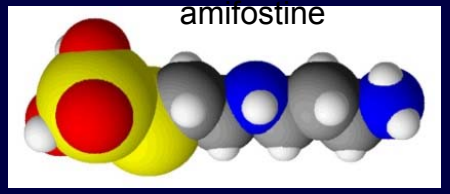


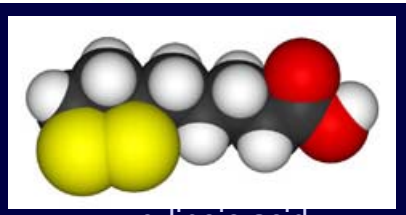
BCM: Pharmaceuticals

NCRP 2011

Biological Countermeasures

Attributes of an Ideal Biological Countermeasure (BCM):


amifostine


α-lipoic acid

- Tolerated by humans at levels needed for protection
  - Chronic intake up to 3 years for Mars missions
  - Level of side effects none or as dependent on risk level
- Mechanism of action well known (extrapolation to humans)
  - Reflects new cancer, CNS, etc biology understanding
- Effective against high and low LET ionizing radiation (radiation quality and dose rate)
  - Reduces the yield of mutants/instable cells by more than it increases survival
  - Effectiveness in microgravity understood
- Protective against many risks (e.g. Solid cancers, Leukemia, CNS, cataract, heart)
- Age and gender dependent effectiveness
- Other CMs developed for other risks are not antagonistic with ours
- Uncertainty in projection of effectiveness not overcome by uncertainties in risk projection models

Summary

Space radiation is a major challenge to exploration:

- Risks are high limiting mission length or crew selection
- Large mission cost to protect against risks and uncertainties
- New findings may change current assumptions

NASA approach to solve these problems:

- Probabilistic risk assessment framework for ISS and Exploration Trade Studies
- Ground-based research focused on uncertainty reduction at NASA Space Radiation Laboratory (NSRL)
- Collaborative research with other HRP Elements on cognitive and combined spaceflight risks
- Ongoing external reviews by authoritative bodies

NASA Space Radiation Program - Windows Internet Explorer

http://spaceradiation.usra.edu/

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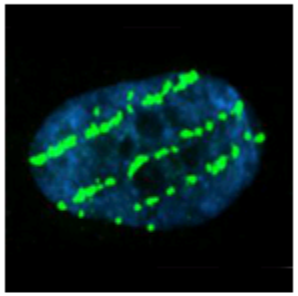
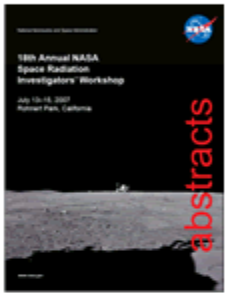
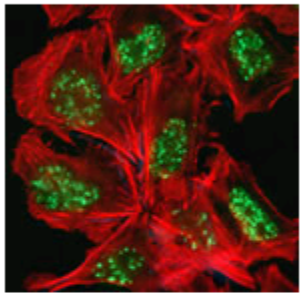


About Space Radiation



Calendar of Events, Workshops and Conferences



Space Radiation Research

NASA Space Radiation Laboratory

The Health Risks of Extraterrestrial Environments Encyclopedia

NASA Space Radiation Summer School

http://spaceradiation.usra.edu/

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John Uri-Element Manager

M51: The Whirlpool Galaxy in Dust and Stars
Image Credit: N. Scoville (Caltech), T. Rector (U. Alaska, NOAO) et al., Hubble Heritage Team, NASA

Back-up Slides

Acute and Late CNS Risks

Risk Summary – CNS PELs

Current NASA Permissible Exposure Limits for the CNS:

ICRP Pub-60

Organ	*30 day limit*	*1 Year Limit*	*Career*
CNS	**500 mGy-Eq**	**1000 mGy-Eq**	**1500 mGy-Eq**
CNS (Z≥10)	**-**	**100 mGy**	**250 mGy**

- The unit mGy-Eq is used but the RBE for CNS effects is largely unknown; therefore, the use of the quality factor function for cancer risk estimates is advocated
- For particles with charge Z>10, an additional PEL requirement limits the physical dose (mGy) for 1 year and career to 100 mGy and 250 mGy, respectively
- CNS PELs correspond to doses at the hippocampus
- NASA uses computerized anatomical geometry models to estimate the body self-shielding at the hippocampus

→ ***For exploration mission planning preliminary dose limits for the CNS risks are based largely on experimental results with animal models.***

→ ***Further research is needed to validate and quantify these risks, and to refine values for dose limits.***

CNS Gaps

CNS - 1: Is there a significant probability that space radiation would lead to immediate or acute functional changes in the CNS during a long-term space mission and if so what are the mechanisms of change? Are there threshold doses for these effects?

CNS - 2: Is there a significant probability that space radiation exposures would lead to long-term or late degenerative CNS risks if so what are the mechanisms of change?

CNS - 3: How does individual susceptibility including hereditary pre-disposition (Alzheimer's, Parkinson's, apoE) and prior CNS injury (concussion or other) alter significant CNS risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?

CNS - 4: What are the most effective biomedical or dietary countermeasures to mitigate CNS risks? By what mechanisms are the countermeasures likely to work?

CNS - 5: How can new knowledge and data from molecular, cellular, tissue and animal models of acute CNS risks or clinical human data, including altered motor and cognitive function and behavioral changes be used to estimate acute CNS risks to astronauts from GCR and SPE?

CNS - 6: How can new knowledge and data from molecular, cellular, tissue and animal models of late CNS risks or clinical human date be used to estimate late CNS risks to astronauts from GCR and SPE?

CNS - 7: What are the best shielding approaches to protect against CNS risks, and are shielding approaches for CNS and cancer risks synergistic?

CNS - 8: Are there significant CNS risks from combined space radiation and other physiological or space flight factors (e.g., sleep deprivation, psychological, microgravity, immune-endocrine systems or other)?