Considerations of Space Radiation Exposure Health Effects Including Microbiome Risk and Possible Mitigation Strategies for Exploration Class Spaceflight

Radiation Risks from a Flight Surgeon's Perspective
TRISH- Red Risk School
April 29, 2020

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Disclosure

No conflicts of interest to disclose

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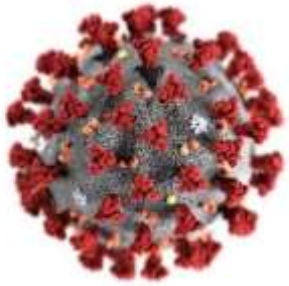
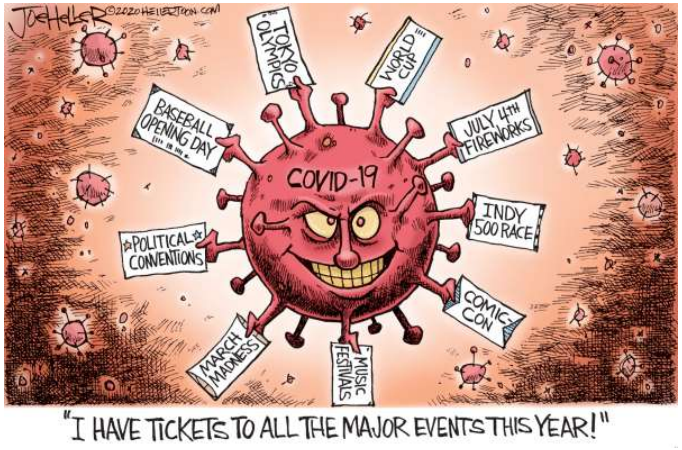
If anyone has a COI to offer- will be happy to consider

No COVID 19 scamming, will not mention:

“Stimulus Check" or "Stimulus Payment”

What we did during the COVID 19 Pandemic

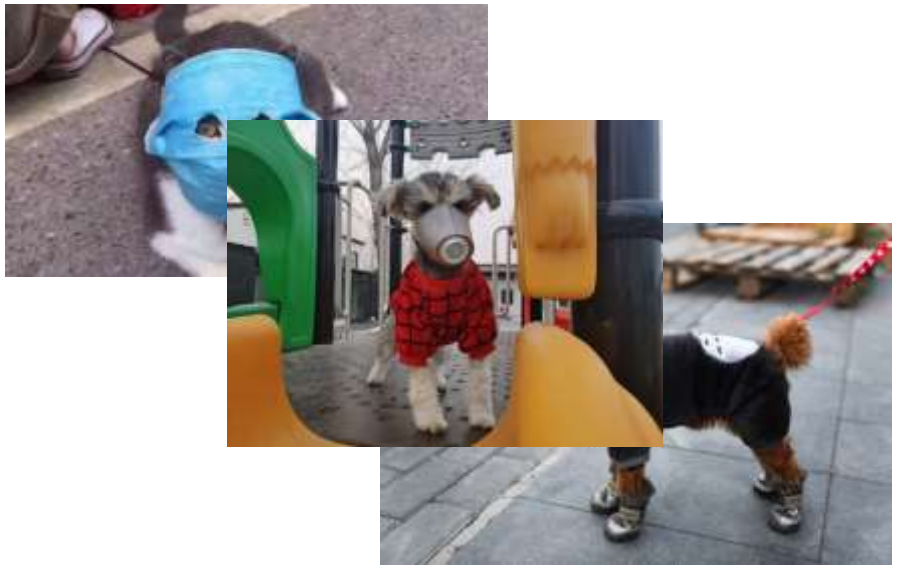




COVID 19 has brought out- Human Ingenuity at its finest:

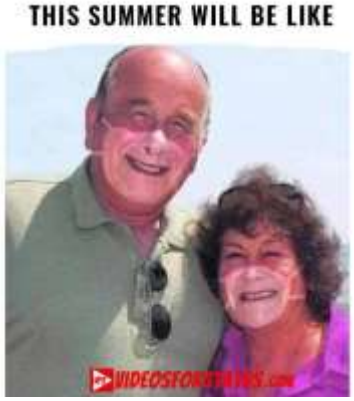
Mask and Face Shield Protection

Protect our Pets



When we run out of Masks


Coronavirus mask in Russia



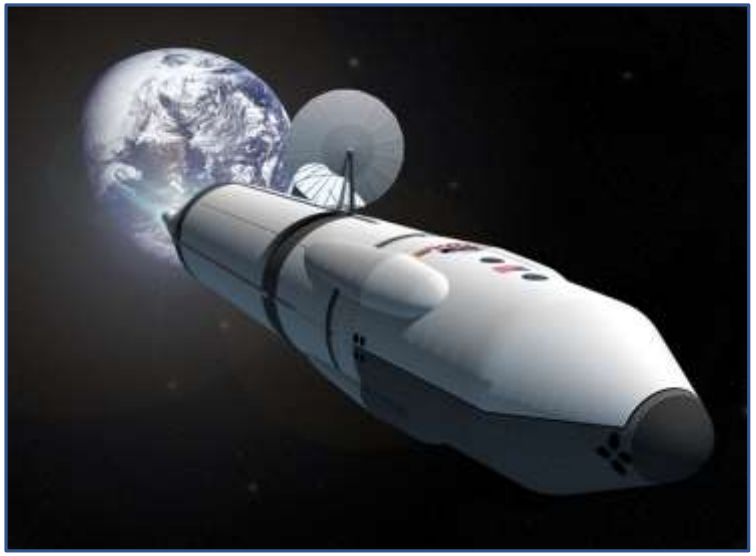
Introduction

- The future of human spaceflight is expected to consist of long duration missions to the Moon, Mars, or a near Earth asteroid

- The space environment is characterized by four key parameters:
  - Neutral gas density (near vacuum)
  - Microgravity
  - Extreme temperature variations
  - Charged particles

- The space environment beyond the geomagnetosphere is characterized by continuous exposure to ionizing radiation

- Space radiation is considered to be one of the major obstacles to long duration human spaceflight

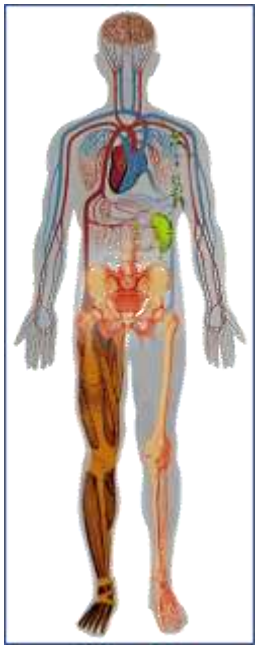


Introduction: Space Medical Issues- Past & Present

- Physiological Issues in Microgravity-possible **synergistic** health effects with space radiation

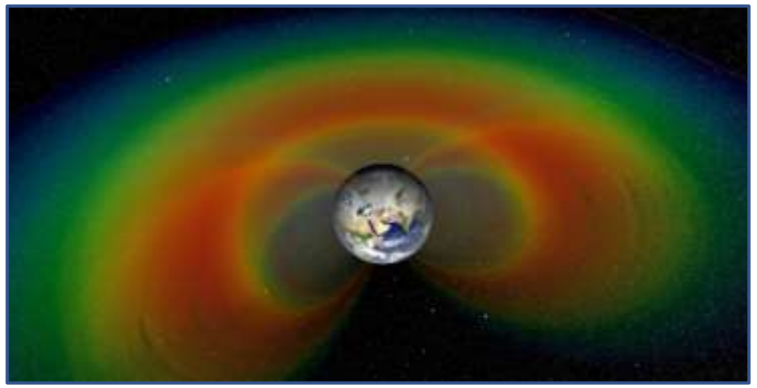
  Adaptation to lack of gravity vector and space environment -problem when return back to 1-g constant vector

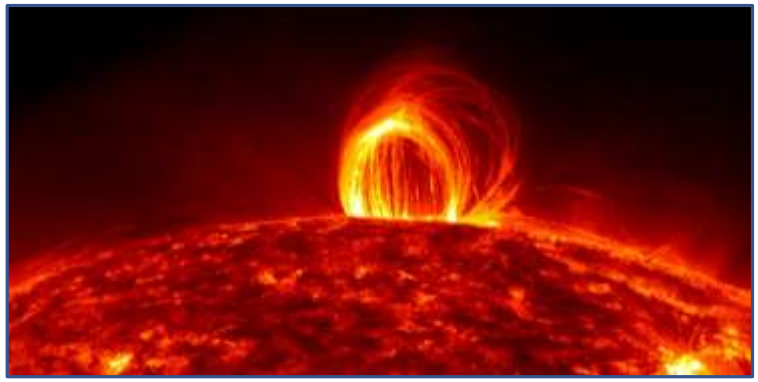
  - Cardiovascular
  - Space Motion Sickness (SMS)
  - Neurovestibular
  - Musculoskeletal
  - Immune/Hematologic
  - Psychiatric/Psychological
    - Behavioral Health & Performance

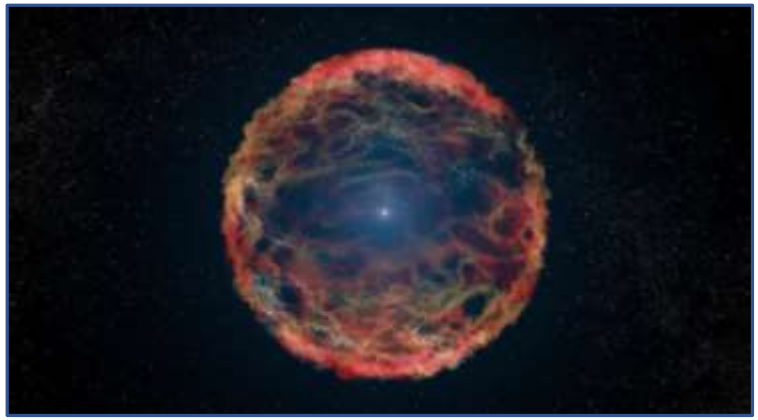


Sources of Space Radiation

- Three principal sources of space radiation
  - Geomagnetically trapped radiation
  - Solar radiation
    - Solar wind
    - Solar particle events
  - Cosmic radiation
    - Distant supernovae, quasars

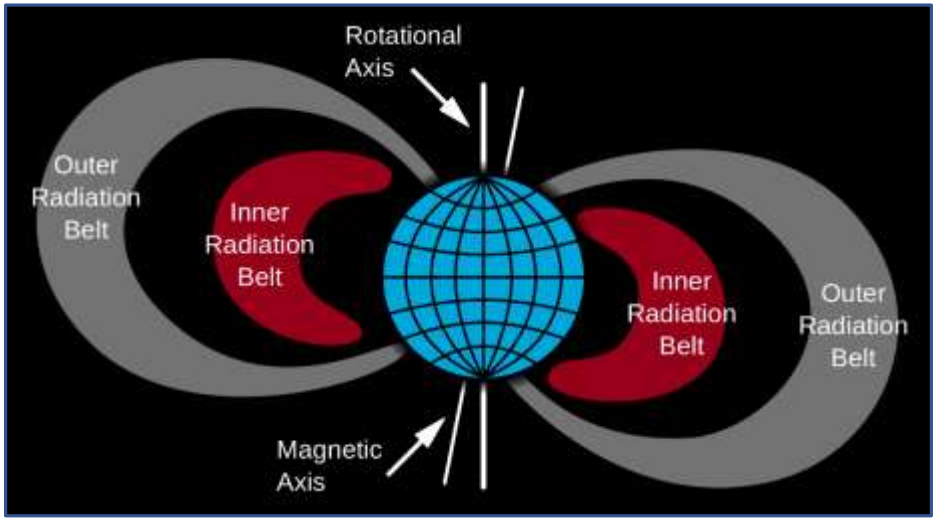


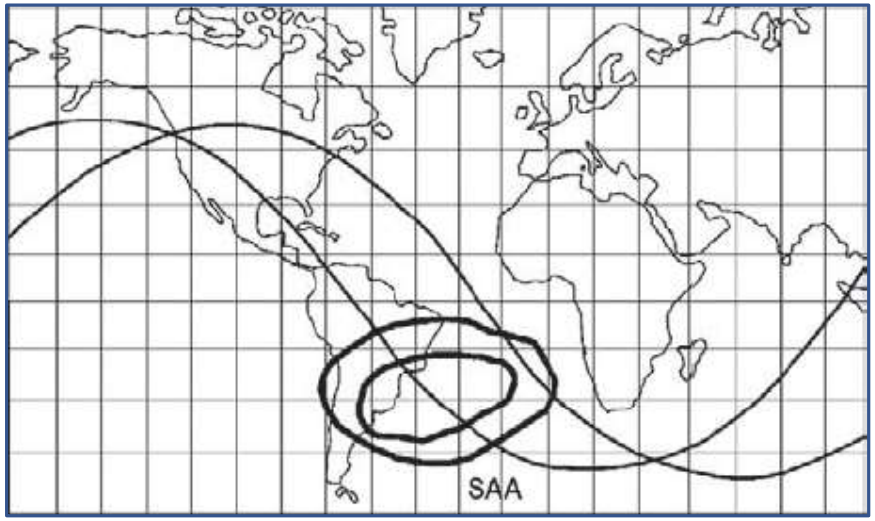




Sources of Space Radiation

- Geomagnetically Trapped Radiation (Van Allen Belts)
  - Major components: electrons, protons
  - Typical energy range: MeV
  - Source: trapped solar radiation
  - Inner belt: 1000 - 6000 km altitude
    - South Atlantic Anomaly: ↓ to 200 km → significant radiation source in LEO
  - Outer belt: 13,000 – 60,000 km

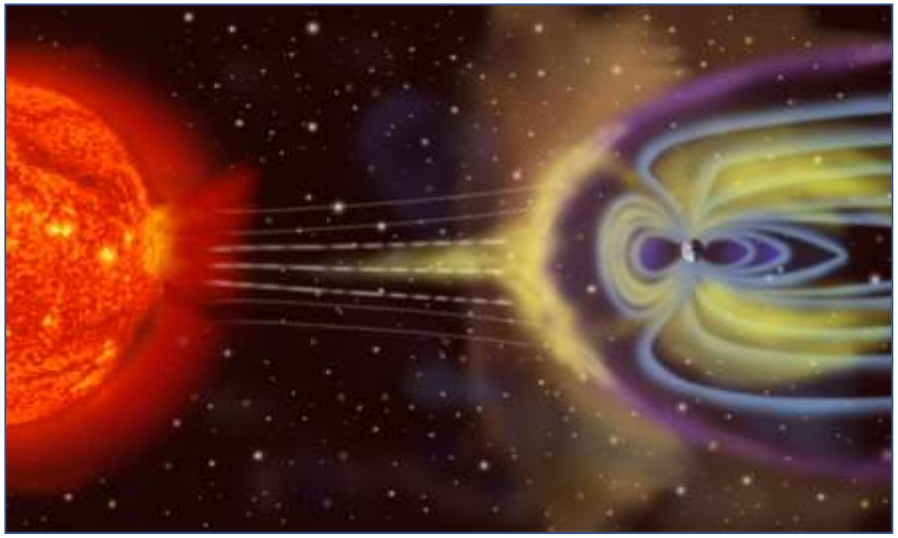




Source of Space Radiation and Space Weather
& Space Weather has major impacts on Earth Weather

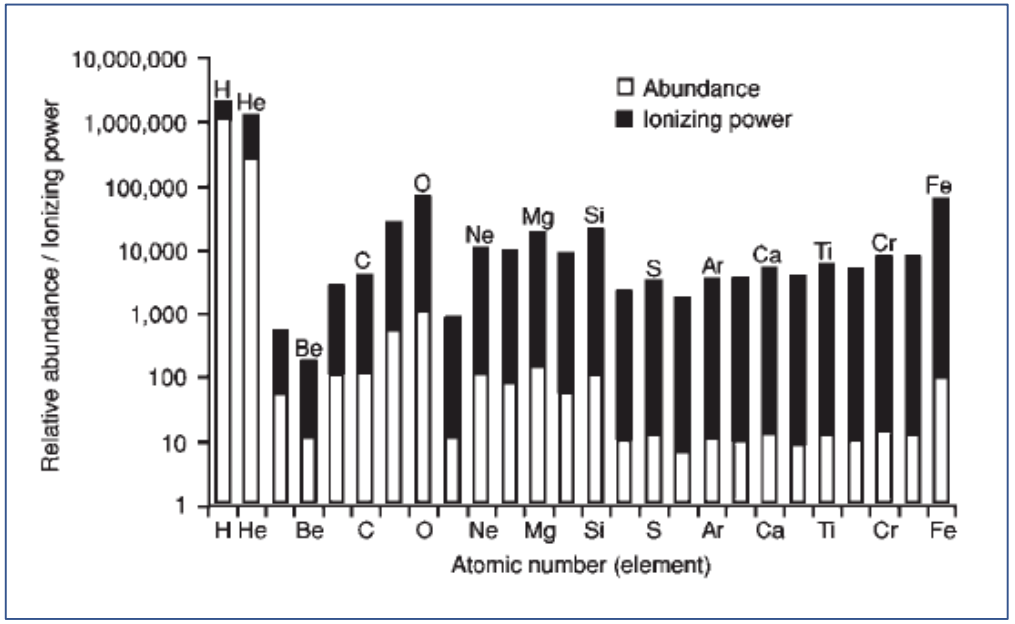
- Solar wind
  - Major components: protons, electrons, alpha particles
  - Typical energy range: keV
  - Solar cycle: 11 years
  - Influences GCR dose (lower at solar maximum)

- Solar Particle Events (SPEs)
  - Major components: protons
  - Typical energy range: keV to MeV, ***high flux***
  - Source: solar-flare, coronal mass ejections
  - Most likely source of an acute exposure event



Types of Space Radiation

- Galactic Cosmic Rays (GCR)
  - Components: protons (85%), helium (13%), ***HZE ions (1%)***
  - Typical energy range: MeV to GeV **High LET**- Lineal Energy Transfer
  - Sources: distant supernovae, quasars
    - Isotropic, variations with solar cycle
  - Main source of chronic exposure beyond low-earth orbit
    - Principal source of biologic uncertainty



Space Environmental Threat Summary

Putting Exposures into Context

- Radiation Exposures
  - **Earth** (Houston - sea-level): 1 mSv/yr
    (Denver - 1524 m): 2 mSv/yr
  - **CXR:** 0.1 mSv/exposure
  - **ISS**: 160 - 200 mSv/yr
  - **Moon**: 110 - 380 mSv/yr
    (solar max to solar min)
  - **Interplanetary space**: 1.8 (1.5-3.0) mSv/d
    552 – 794 mSv/yr
  - Mars Surface: 0.8 (0.6-1.3) mSv/d

- Radiation Limits (Stochastic)
  - **General public**: 5 mSv/yr
  - **Radiation workers**: 50 mSv/yr
  - **Astronauts**: 500 mSv/yr
    1 Sv/career

Mission to Mars: 6 months outbound & return, variable surface stay

Expected mission exposure: ***~0.7-1.0 Sv***

Space Radiation Permissible Exposure Limits (PEL) for non-cancer effects

NASA PEL *Short- and Long-term Dose Limits for Non-cancer Effects (Deterministic)*

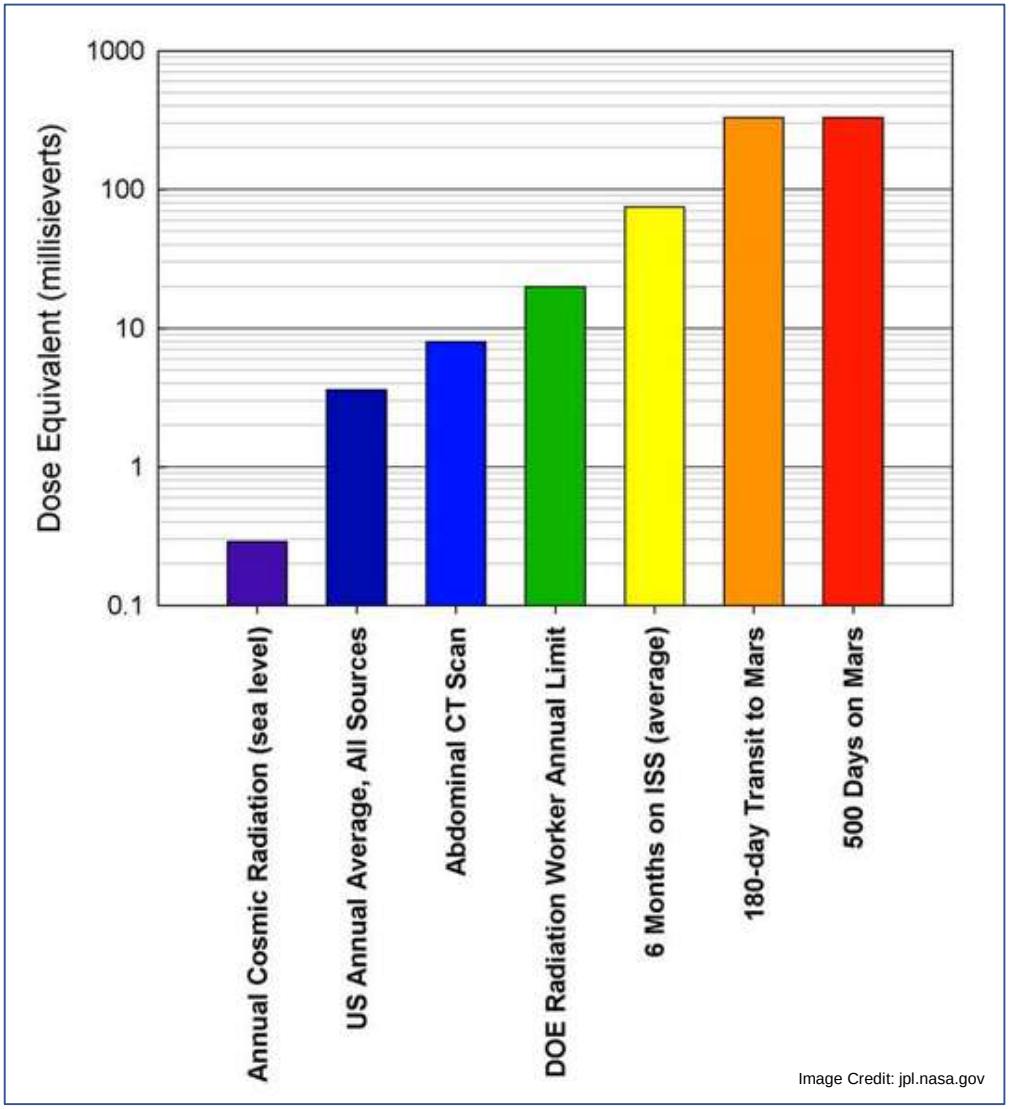
Organ	30-day limit	1-year Limit	Career
Lens*	1,000 mGy-Eq	2,000 mGy-Eq	4,000 mGy-Eq
Skin	1,500 mGy-Eq	3,000 mGy-Eq	4,000 mGy-Eq
BFO	250 mGy-Eq	500 mGy-Eq	Not applicable
Heart**	250 mGy-Eq	500 mGy-Eq	1,000 mGy-Eq
CNS***	500 mGy-Eq	1,000 mGy-Eq	1,500 mGy-Eq
CNS***(Z≥10)	–	100 mGy	250 mGy
BFO Cancer	25 rem (250 mSv)	50 rem (500 mSv)	? 1-1.5 Sv

*Lens limits are intended to prevent early (<5 years) severe cataracts (e.g., from an SPE). An additional cataract risk – sub-clinical cataracts – exists at lower doses from cosmic rays, which may progress to severe types after long latency (>5 years). Although thesecataract risks are not preventable by existing mitigation measures, they are deemed an acceptable risk to the program. BFO 30-d limit to prevent affects on testicular fertility (reversible at the limit)

**Heart doses calculated as average over heart muscle and adjacent arteries.

***CNS limits should be calculated at the hippocampus.

Putting Exposures into Context

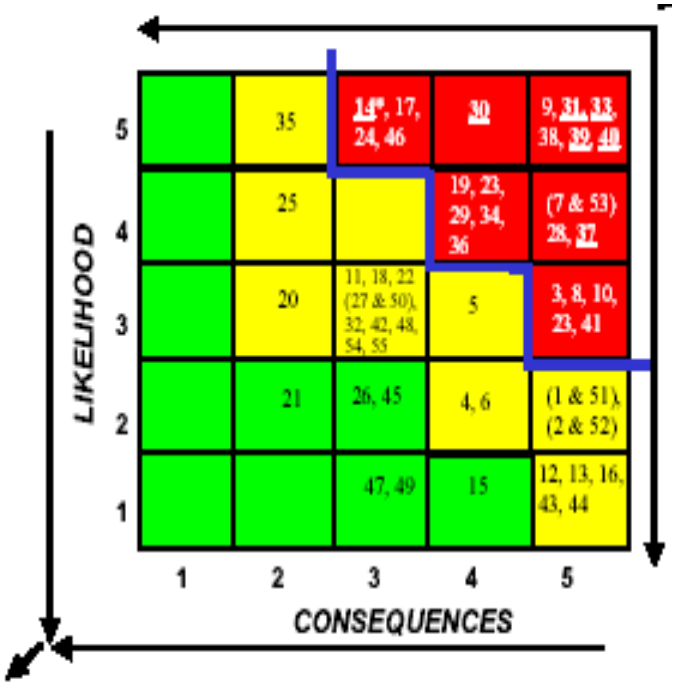


- Radiation Assessment Detector (RAD) measurements
  - Mars Curiosity Rover mission transit vehicle
  - Interplanetary space and Martian surface measurements

Importance of radiation exposure as a risk to astronaut health

- Risks to personnel in space from naturally occurring **radiations** are one of the most serious limitations to human space missions

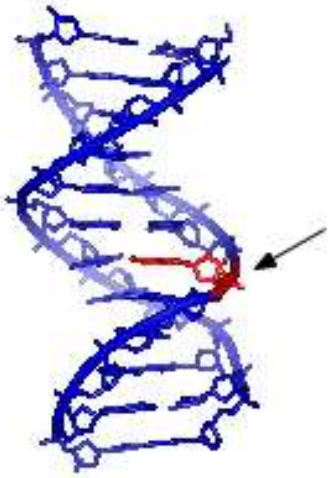
- The major risk from radiation exposure is later **cancer development**, but can have neuro-degeneration, vascular fibrosis, etc.



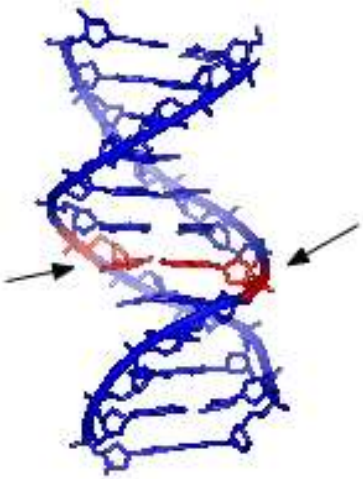
- BEIR V (1990); BEIR VII (1998), National Research Council, Washington, DC
- Williams et al. (1999). Mutation Res, 430, 255-269.
- Safe Passage: Astronaut Care for Exploration Missions. (2001) Eds. J.R. Ball, C.H. Evans, Jr.. National Academy Press

Mechanisms: Degree of DNA Injury

- Single-strand DNA breaks
  - Excision repair mechanisms: nuclear, base, mismatch
  - If all else fails → apoptosis
  - When apoptosis fails → oncogenesis

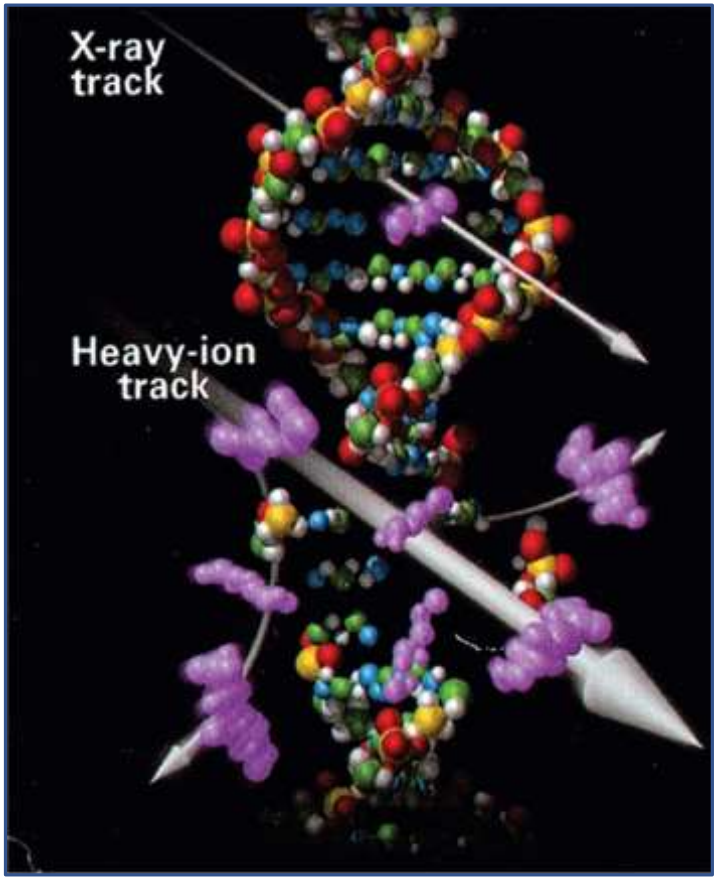


- Double-strand DNA breaks
  - Repair relies on more complex mechanisms
    - Fidelity of repair is less likely
  - More likely to lead to cell death, if widespread
  - More common with exposure to high-LET radiation (HZE, SPE)

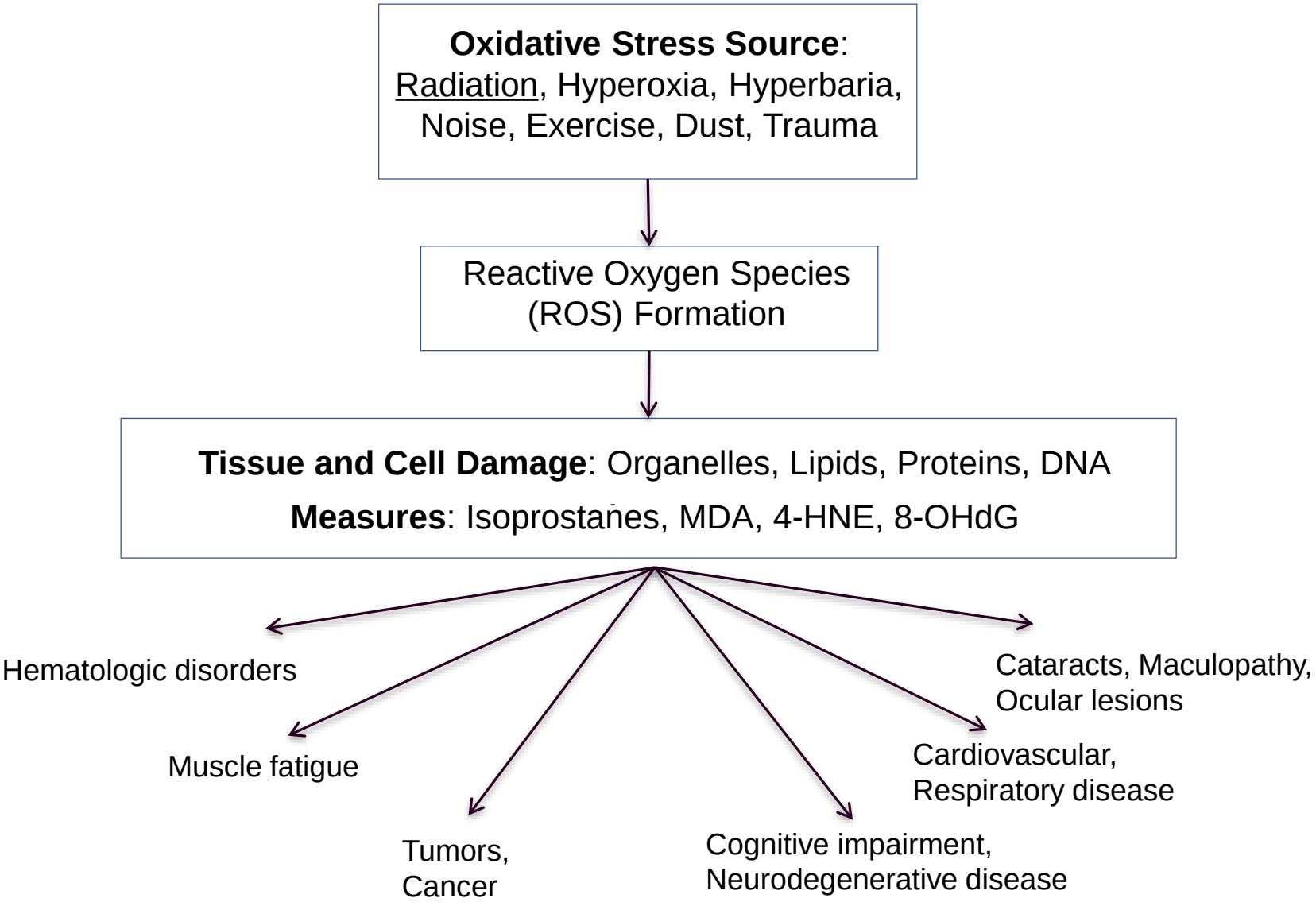


Mechanisms of Radiation Injury

- The nature of the damage depends on the type of radiation
  - Low-LET radiation (X-rays)
    - 2/3 of damage via indirect action
    - Amenable to radioprotectors
  - High-LET radiation (HZE, SPE)
    - Direct DNA damage more common
    - Difficult to protect against
    - Cell death vs. genomic instability

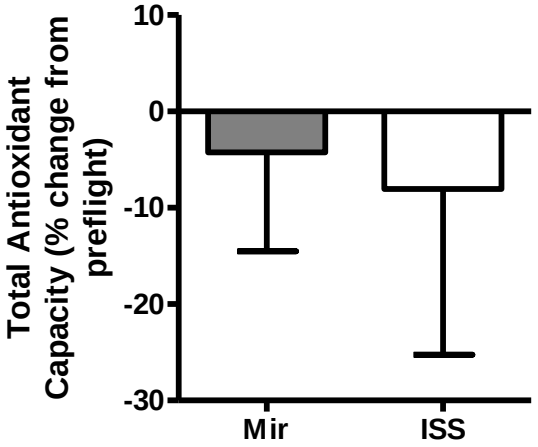


Mechanisms: Oxidative Stress

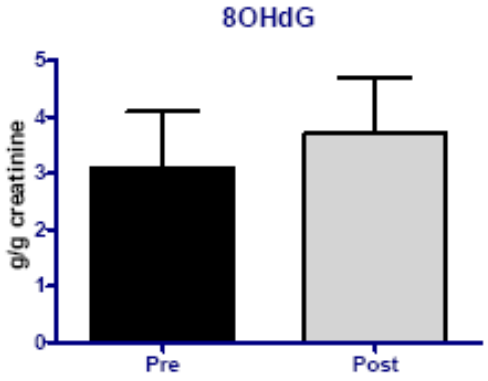


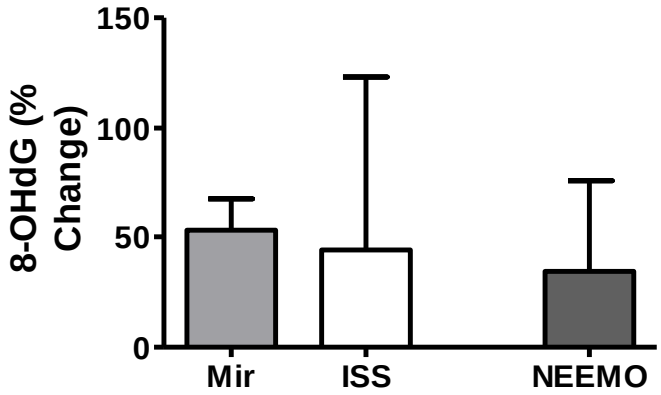
Evidence for Oxidative Stress during Spaceflight

Compound analyzed	Example Pre-flight value	Example Post-flight value	Normal ranges observed in-flight	Maximal changes observed post-flight (percentage change from pre-flight)
Total Antioxidant Capacity	1.54	1.47	1.29-1.83	Decreased up to 30%
SOD	1,318	1,172	1,092-1,817	Decreased 10-30%
Glutathione Peroxidase	51.5	50.8	27.5-73.6	Decreased 5-15%
Malondialdehyde	0.8	0.6	0-2.00	Increased 100-200%
4-OH-alkenal	0.45	0.45	0-2.00	Increased 50-150%
Urinary 8OHDG	3.2	3.7	0.49-7.29	Increased 40-200%



Total antioxidant capacity after space flight for Mir (n = 2) and ISS (n = 11). (Smith et al., 2001 and 2005).



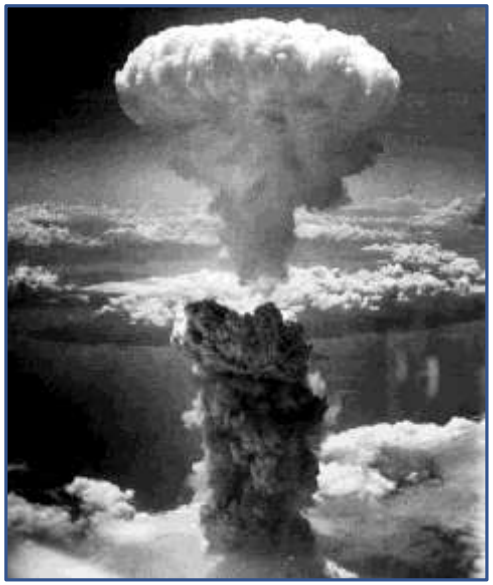
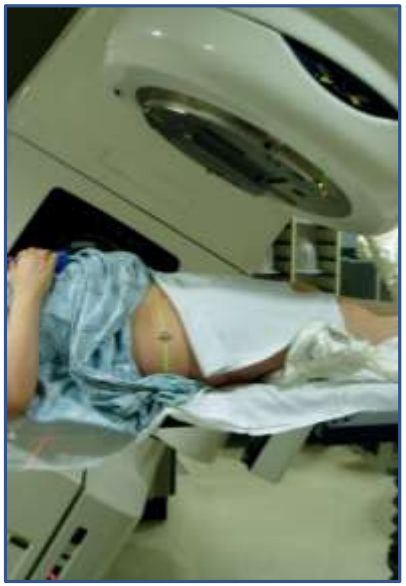


Urinary 8-OHdG pre- and post- flight and The percent change of 8-hydroxy 2'deoxyguanosine (8-OHdG) from pre flight values for Mir (n = 2), ISS (n = 11) (Smith et al. 2005), and the ground based analog NEEMO (n = 6) (Smith et al. 2004).

Radiobiology: Knowledge Base

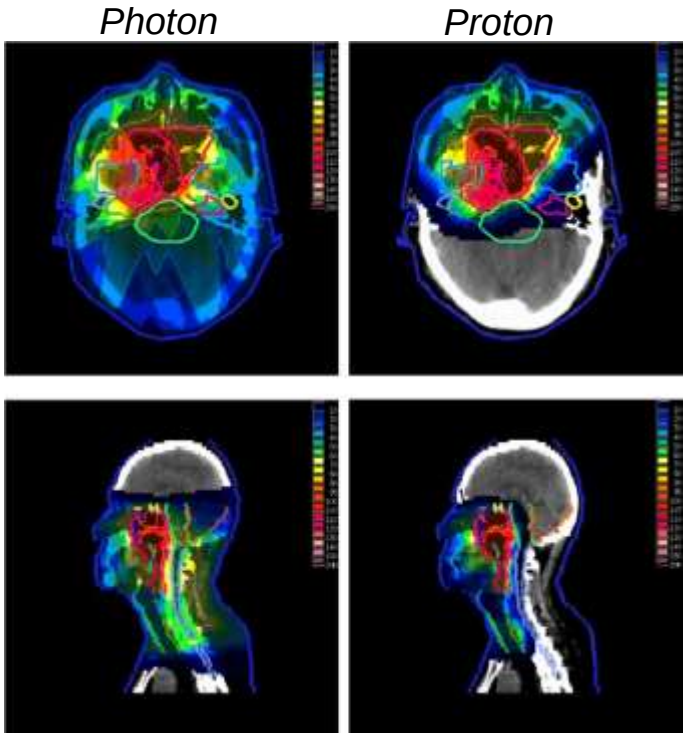
- Four main data sources
  - Occupational exposures
  - Nuclear weapons
  - Medical treatment
  - Animal experiments
  - Cell cultures

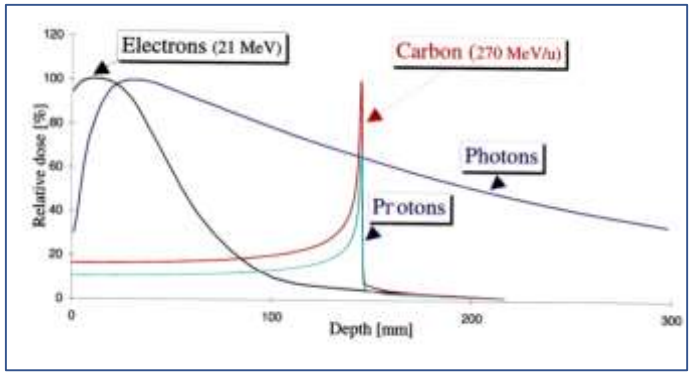
Generally photon based (x-rays, γ-rays)
Some particle radiation data from ISS


Radiobiology: Knowledge Base

- Human data for proton and HZE particle radiation is very limited
- Extrapolation from photon radiation or animal models is difficult
  - Dose distribution between radiation types is inherently different
  - Dose gradients very difficult to re-create in different sized animals
  - Additional factors to consider: dosing, time, animal life cycle, intrinsic biological differences and/or responses to injury





Radiation Effects: Acute

- Symptoms of acute radiation exposure are predictable and dose-dependent

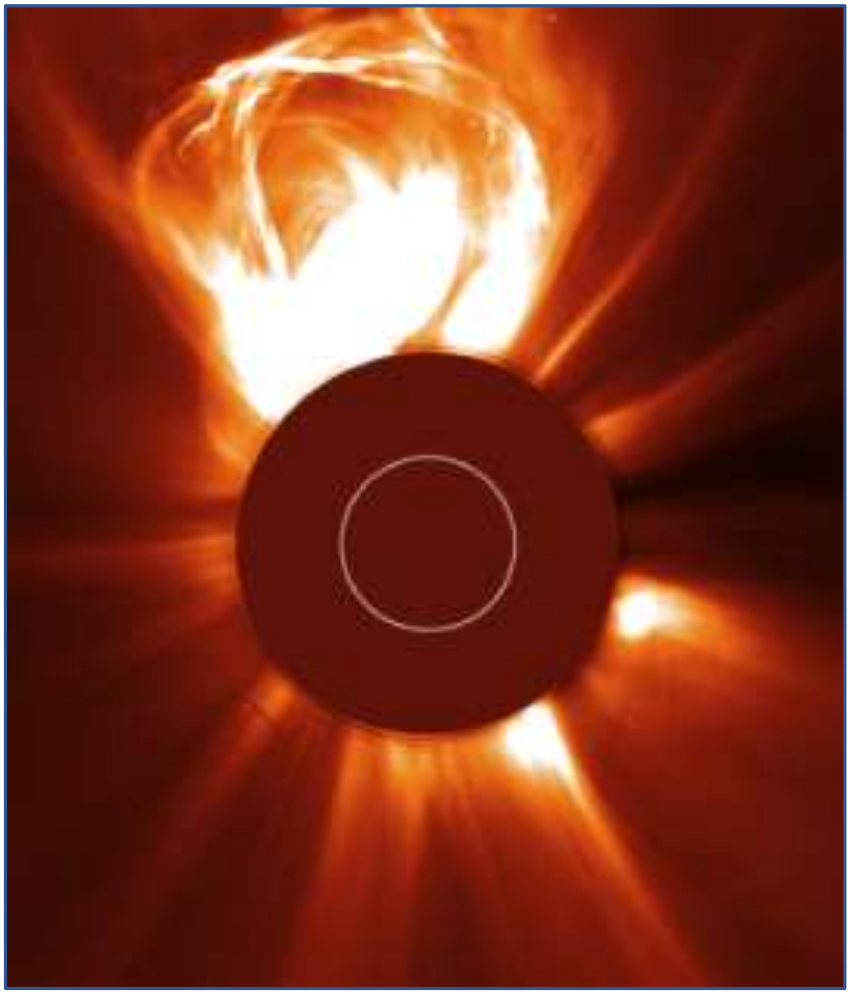
TABLE 23.10. Selected features of acute radiation syndromes after whole-body exposure.

Principal cause of death (latency period)	Lethal dose range, Gy	Underlying cellular event	Characteristic signs and symptoms prodromal phase	Principal phase
Hematopoietic (2–3 weeks)	2.5–10	Necrosis of bone marrow cells	Anorexia, nausea, vomiting	Petechia and purpura, bleeding from mucous membranes, infection
Gastrointestinal (3–7 days)	10–50	Necrosis and mitotic arrest of mucosal stem cells	Anorexia, nausea, vomiting	Fever, bloody diarrhea, loss of fluids and electrolytes
Acute incapacitation (15 min–3 h)	50+	Unknown; perhaps direct injury of endothelial cells, death of neurons and vasculitis at very high doses	Anorexia, nausea, vomiting, confusion, ataxia, anxiety	Apathy, lethargy. somnolence, tremors, convulsions, coma

Source: From Fajardo et al.[61].

Radiation Effects: Acute

- SPEs are the main potential source of acute exposure
  - **Example:** August 1972 SPE
    - Occurred between Apollo 16 and 17 missions
    - Average exposure behind 2 g/cm^2 aluminum shielding: **1.5 Sv/hour**
      - Apollo CM shielding: 7-8 g/cm^2
      - EVA Suit shielding: 0.25 g/cm^2
  - Highlights need for storm shelter
    - Needs to be **10-20 g/cm^2** aluminum equivalent
    - Hydrogen rich



Radiation Effects: Chronic

- Generally, we are concerned with three categories of chronic effects secondary to radiation exposure
  - Malignancy
  - Central nervous system (CNS) effects
  - Degenerative effects
- The majority of human data comes from exposures to photon based radiation

Chronic Radiation Effects: Malignancy

Chronic Radiation Effects

Malignancy

CNS Effects

Degenerative Changes

Malignancy: Particle Radiation Study Highlight - 1

PLoS One. 2014 Aug 15;9(7):e104819. doi: 10.1371/journal.pone.0104819. eCollection 2014.

Effects of 28Si ions, 56Fe ions, and protons on the induction of murine acute myeloid leukemia and hepatocellular carcinoma.

Weil MM[1], Ray FA[1], Genik PC[1], Yu Y[2], McCarthy M[2], Fallgren CM[1], Ullrich RL[2].

- Study design:
  - Groups of mice irradiated with 4 different types of radiation at varying doses
  - Followed until moribund or 800 days old

	Radiation Quality	Dose in cGy (Initial Animal Numbers)
	None	0 (300)
1	300 MeV/n ^{28}Si	10 (300)
		20 (300)
		40 (200)
		100 (200)
2	600 MeV/n ^{56}Fe	10 (300)
		20 (300)
		40 (200)
		100 (200)
3	^{137}Cs Gamma Rays	100 (400)
		200 (300)
		300 (100)
4	1972SPE Protons	100 (400)
		200 (300)

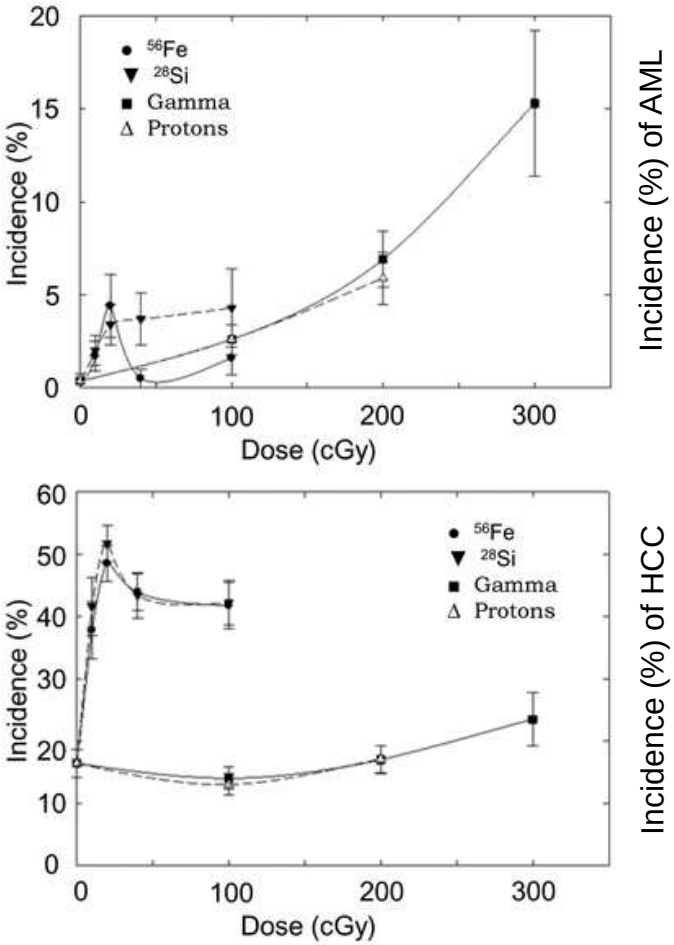
Malignancy: Particle Radiation Study Highlight - 1

PLoS One. 2014 Aug 15;9(7):e104819. doi: 10.1371/journal.pone.0104819. eCollection 2014.

Effects of 28Si ions, 56Fe ions, and protons on the induction of murine acute myeloid leukemia and hepatocellular carcinoma.

Weil MM[1], Ray FA[1], Genik PC[1], Yu Y[2], McCarthy M[2], Fallgren CM[1], Ullrich RL[2].

- Results:
  - ***No difference*** in overall ***AML*** incidence between radiation types
  - ***Increased*** incidence of ***HCC*** with ^{28}Si and ^{56}Fe ions
  - ***Increased*** rate of ***metastatic HCC*** with ^{28}Si and ^{56}Fe ions
- Conclusions:
  - HZE radiation appears to have a higher rate of ***solid tumor*** induction



Malignancy: Particle Radiation Study Highlight - 2

Radiat Res. 2015 Feb;183(2):233-9. doi: 10.1667/RR13884.1. Epub 2015 Jan 30.

Relative effectiveness at 1 gy after acute and fractionated exposures of heavy ions with different linear energy transfer for lung tumorigenesis.

Wang X[1], Farris Iii AB, Wang P, Zhang X, Wang H, Wang Y.

- Study design:
  - Wild type mice irradiated with x-rays, 600 MeV ^{16}O, 300 MeV ^{28}Si or 600 MeV ^{56}Fe
  - Randomized to 1 Gy acute or fractionated (0.2 Gy x 5) for each radiation type
- Outcomes:
  - Overall survival 18 months post irradiation event
  - Lung tumorigenesis 18 months post irradiation event

Malignancy: Particle Radiation Study Highlight - 2

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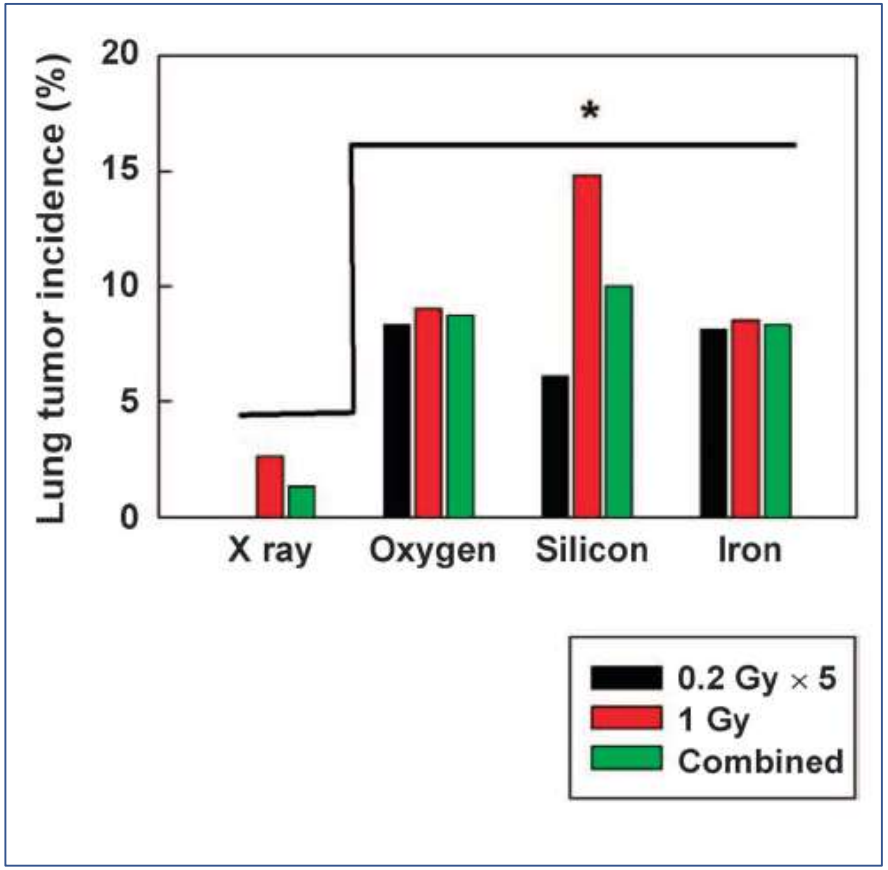
Relative effectiveness at 1 gy after acute and fractionated exposures of heavy ions with different linear energy transfer for lung tumorigenesis.

Wang X[1], Farris Iii AB, Wang P, Zhang X, Wang H, Wang Y.

- Results:
  - ***Increased*** incidence of lung tumorigenesis with HZE particles as compared to x-rays
    - Relative HZE effectiveness at 1 Gy ***>6***
  - Tumours induced by ^{28}Si radiation appear to be ***more aggressive***
  - Overall mortality was ***higher*** in mice exposed to ^{28}Si radiation
- Conclusions:
  - HZE radiation appears to have a ***higher incidence*** of tumor induction
  - Tumor aggressiveness may be influenced by both particle ***energy*** and ***type***



Chronic Radiation Effects: Central Nervous System

Chronic Radiation Effects

Malignancy

CNS Effects

Degenerative Changes

CNS Effects: Proton Radiation Study Highlight

Radiat Res. 2014 Mar;181(3):258-71. doi: 10.1667/RR13359.1. Epub 2014 Mar 10.

Individual differences in attentional deficits and dopaminergic protein levels following exposure to proton radiation.

Davis CM[1], DeCicco-Skinner KL, Roma PG, Hienz RD.

- Recent animal studies with proton radiation have revealed significant changes in behavioral effects and neuronal function[8-11]
- Study design:
  - Rats were trained in a rodent version of the psychomotor vigilance test (rPVT) +/- visual line orientation discrimination (LD) task
  - Irradiated with 150 MeV protons at 25, 50, 100, 200 cGy
- Outcomes examined:
  - Deficits in rPVT and LD performance
  - Levels of dopamine transporter (DAT) and D2 receptor post radiation

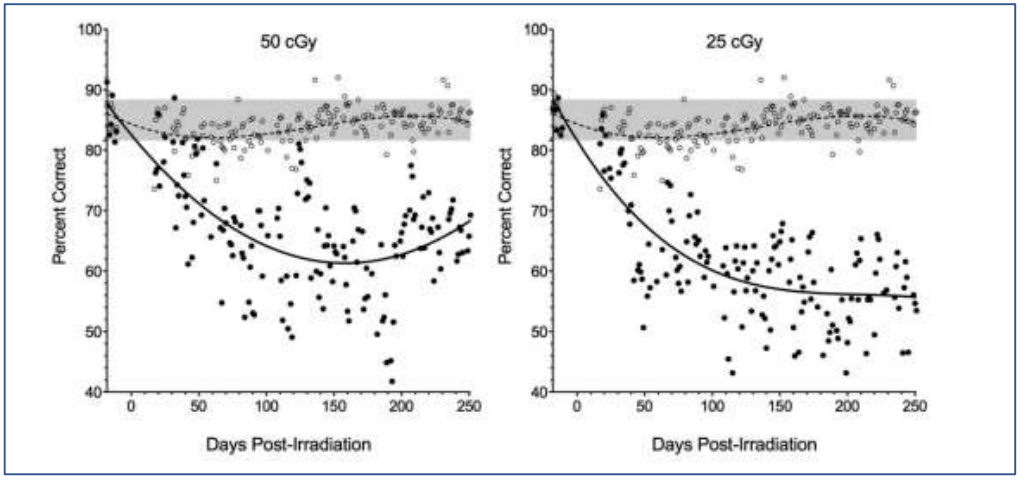
CNS Effects: Proton Radiation Study Highlight

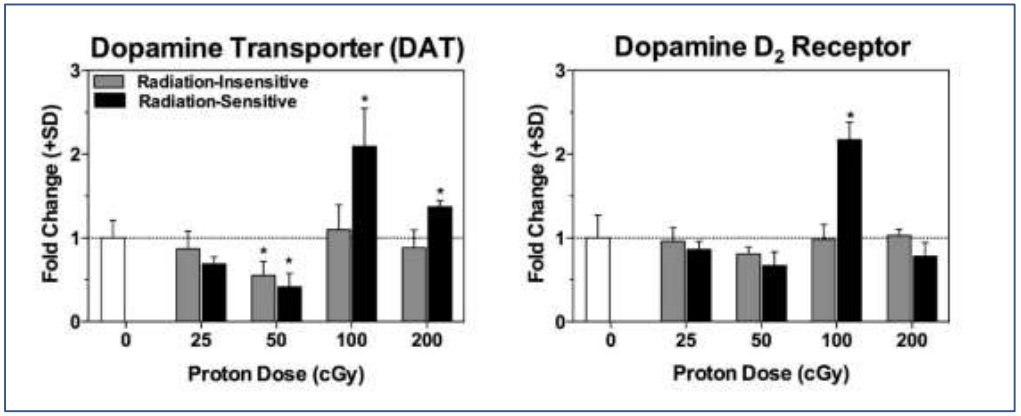
Radiat Res. 2014 Mar;181(3):258-71. doi: 10.1667/RR13359.1. Epub 2014 Mar 10.

Individual differences in attentional deficits and dopaminergic protein levels following exposure to proton radiation.

Davis CM[1], DeCicco-Skinner KL, Roma PG, Hienz RD.

- Results
  - ***Decreased*** rPVT performance in irradiated rats
    - ***No difference*** across doses
  - ***No decrease*** in LD performance
  - ***Decreased*** DAT and D2 receptor levels in radiation sensitive mice
    - Possible mechanism to explain behavioral findings





CNS Effects: HZE Radiation Study Highlight

Radiat Res. 2014 Sep;182(3):292-8. doi: 10.1667/RR3766.1. Epub 2014 Jul 16.

Exposure to mission relevant doses of 1 GeV/Nucleon (56)Fe particles leads to impairment of attentional set-shifting performance in socially mature rats.

Britten RA[1], Davis LK, Jewell JS, Miller VD, Hadley MM, Sanford LD, Machida M, Lonart G.

- Study design:
  - Groups of rats were randomized to sham vs. whole body irradiation
  - Irradiated with 1 GeV ^{56}Fe particles at 10, 15 and 20 cGy
- Outcomes examined:
  - Attentional set shifting testing (ATSET) performance
  - Cholinergic and GABAnergic readily releasable pools (RRP) in basal forebrain

CNS Effects: HZE Radiation Study Highlight

Radiat Res. 2014 Sep;182(3):292-8. doi: 10.1667/RR3766.1. Epub 2014 Jul 16.

Exposure to mission relevant doses of 1 GeV/Nucleon (56)Fe particles leads to impairment of attentional set-shifting performance in socially mature rats.

Britten RA[1], Davis LK, Jewell JS, Miller VD, Hadley MM, Sanford LD, Machida M, Lonart G.

- Results
  - ATSET component performance ***decreased*** at doses of 15 and 20 cGy but ***not*** at 10 cGY
  - ***Decreased*** cholinergic RRP at a dose of 20 cGy → implications for regulation of prefrontal cortex

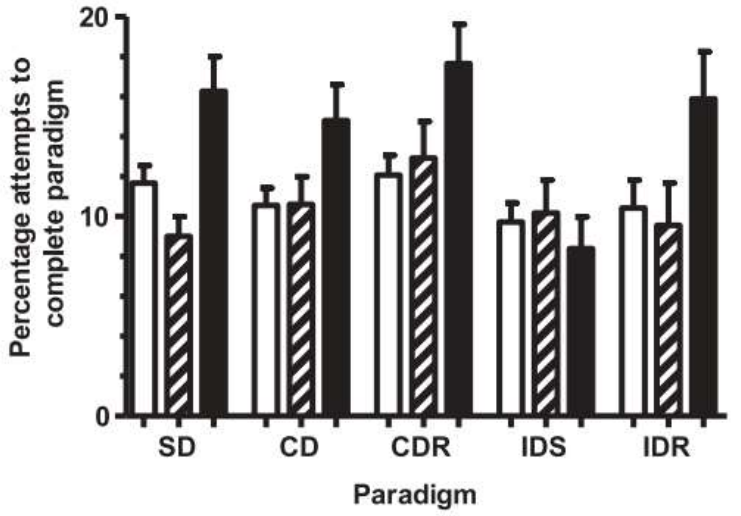


FIG. 5. Effect of whole-body exposure to 1 GeV/nucleon ^{56}Fe particles on the paradigm-specific performance of retired breeder rats: number of attempts required to reach criterion in sham-irradiated (open bar) and whole-body exposure to 15 cGy (hatched bar) or 20 cGy (solid bar) 1 GeV/nucleon ^{56}Fe. Graphs show means ± SEM. HAB: habituation; SD: simple discrimination; CD: compound discrimination; CDR: compound discrimination reversal; IDS: intra-dimensional shifting; IDR: intra-dimensional shifting reversal; EDS: extra-dimensional shifting; EDR: extra-dimensional shifting reversal.

Chronic Radiation Effects: Degenerative

Chronic Radiation Effects

Malignancy

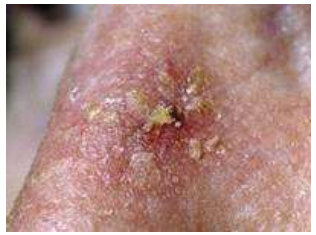
CNS Effects

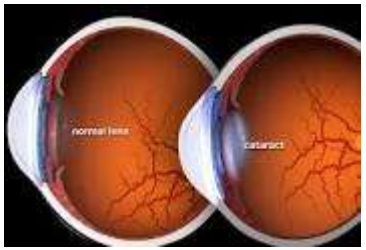
Degenerative Changes

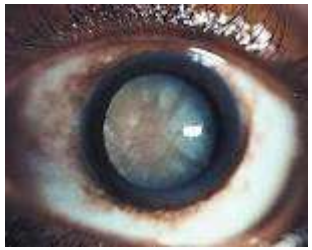
Degenerative Effects

- Cataracts
- Keratosis
- Cardiovasculopathies
  - Accelerated atherosclerosis
  - Cardiomyopathy
- Reduced joint fluid production- arthritic effects
- Diminished endocrine and exocrine glandular production, via cellular senescence (failure to maintain telomeres), reduced flow
- Diminished immunity
  - Microbiome shifts

Fibrosis-common path

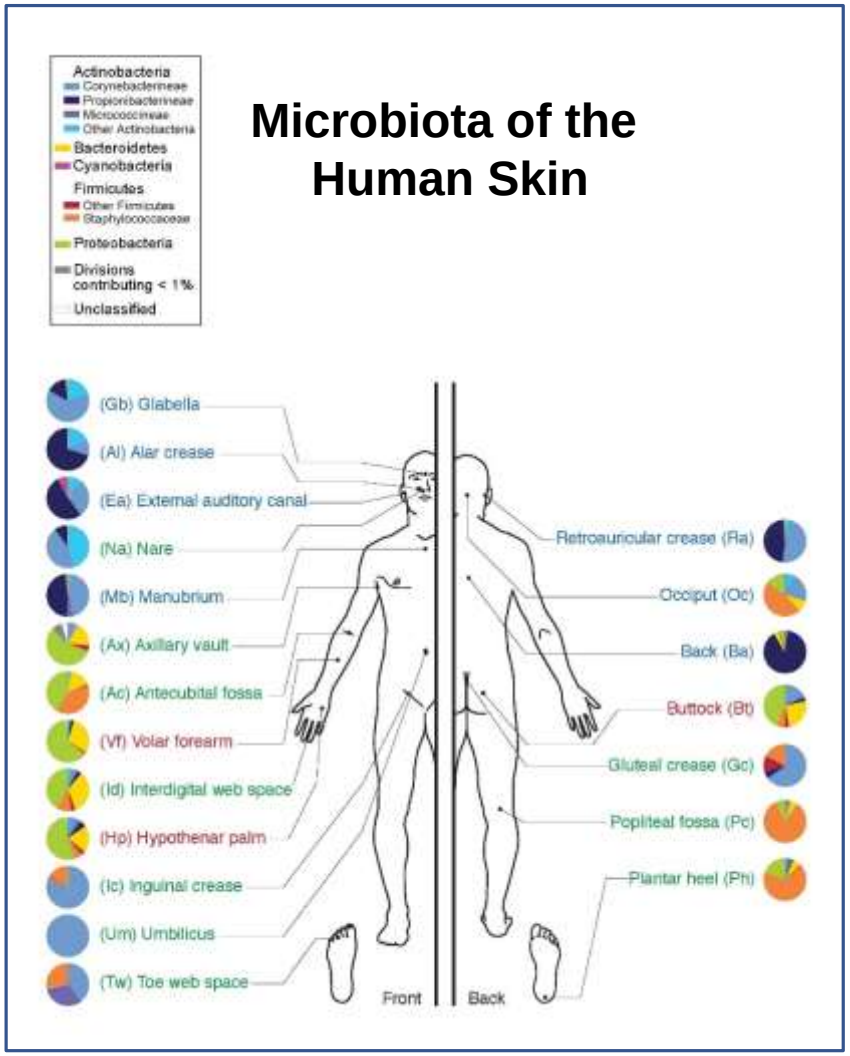






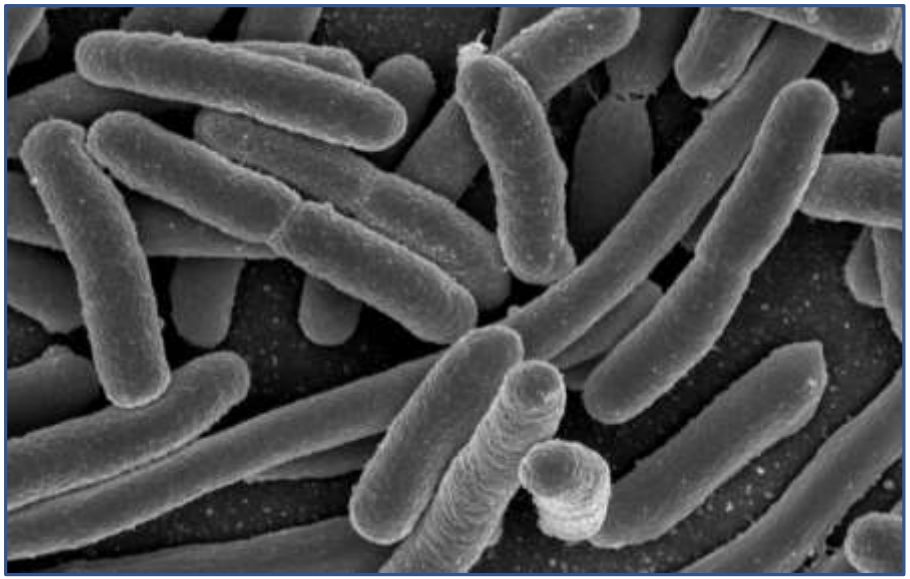
The Human Microbiome

- Definitions
  - **Microbiota:** the ecological community of microorganisms that share an environmental niche
  - **Microbiome:** the collective genome of the microbiota
- Generally refers to organisms that, under normal conditions, exist in symbiotic harmony with their hosts



The Human Microbiome: Anatomy

- There are a number of major anatomical sites where commensal organisms have a well defined presence
  - Skin Surface
  - Nasopharyngeal Cavity
  - Otic Cavity
  - Gastro-intestinal Tract
  - Respiratory Tract
  - Genitourinary Tract



- Each site contains a distinct population of micro-organisms that can be further sub-divided

The Gastrointestinal Microbiome

- Characteristics
  - 10^{14} microorganisms (~10^{12}/mL)
    - Approximately 10 times more than # of human cells in body
  - Collective genome (microbiome): 4 x 10^{6} genes
    - Approximately 150 times larger than human genome
  - Between 300 – 1000 unique species
    - Mostly bacteria, but also fungi, protozoa and archaea

- "The forgotten organ"
  - Important metabolic activities
    - eg. Fermentation, vitamin synthesis, bile acid breakdown
  - Emerging evidence of key role in host immune function

The Gastrointestinal Microbiome: Role in Health and Disease

- Metabolism
  - Fermentation, Vitamin synthesis
- Suppression of pathogenic microbes
  - eg. *Clostridium difficile* managed by competitive exclusion
- Host Immune Function
  - Key to development and function of mucosal immune system
  - Expression of host toll-like receptors (TLRs)
    - Important for host repair of injury induced damage (e.g. ***radiation***)
  - Modulation of immune system during development to prevent allergies
- Emerging evidence of complex role in disease states:
  - Tumor formation, IBD, Colitis, Obesity, Mood/cognitive disorders; **gut-brain axis** (GI-brain signaling)

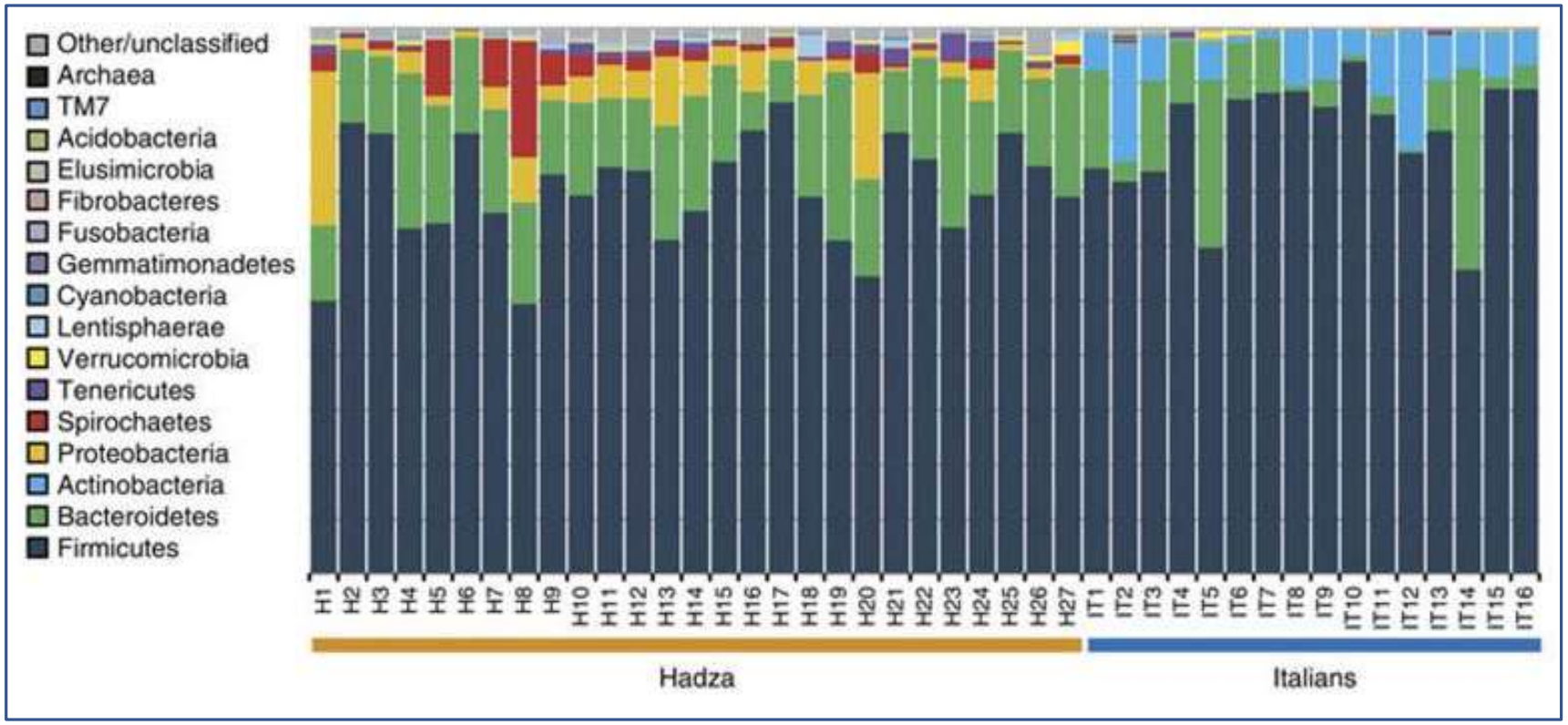
The Gastrointestinal Microbiome: Human Variablity

Nat Commun. 2014 Apr 15;5:3654. doi: 10.1038/ncomms4654.

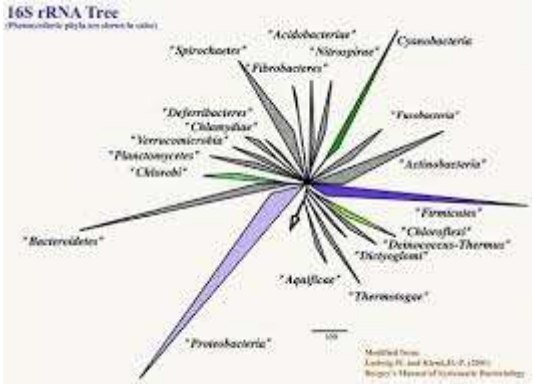
Gut microbiome of the Hadza hunter-gatherers.

Schnorr SL[1], Candela M[2], Rampelli S[3], Centanni M[3], Consolandi C[4], Basaglia G[3], Turroni S[3], Biagi E[3], Peano C[4], Severgnini M[4], Fiori J[3], Gotti R[3], De Bellis G[4], Luiselli D[5], Brigidi P[3], Mabulla A[6], Marlowe F[7], Henry AG[8], Crittenden AN[9].

- A survey of fecal samples among 43 subjects reveals notable differences in microbiome composition between hunter-gatherer and urban humans



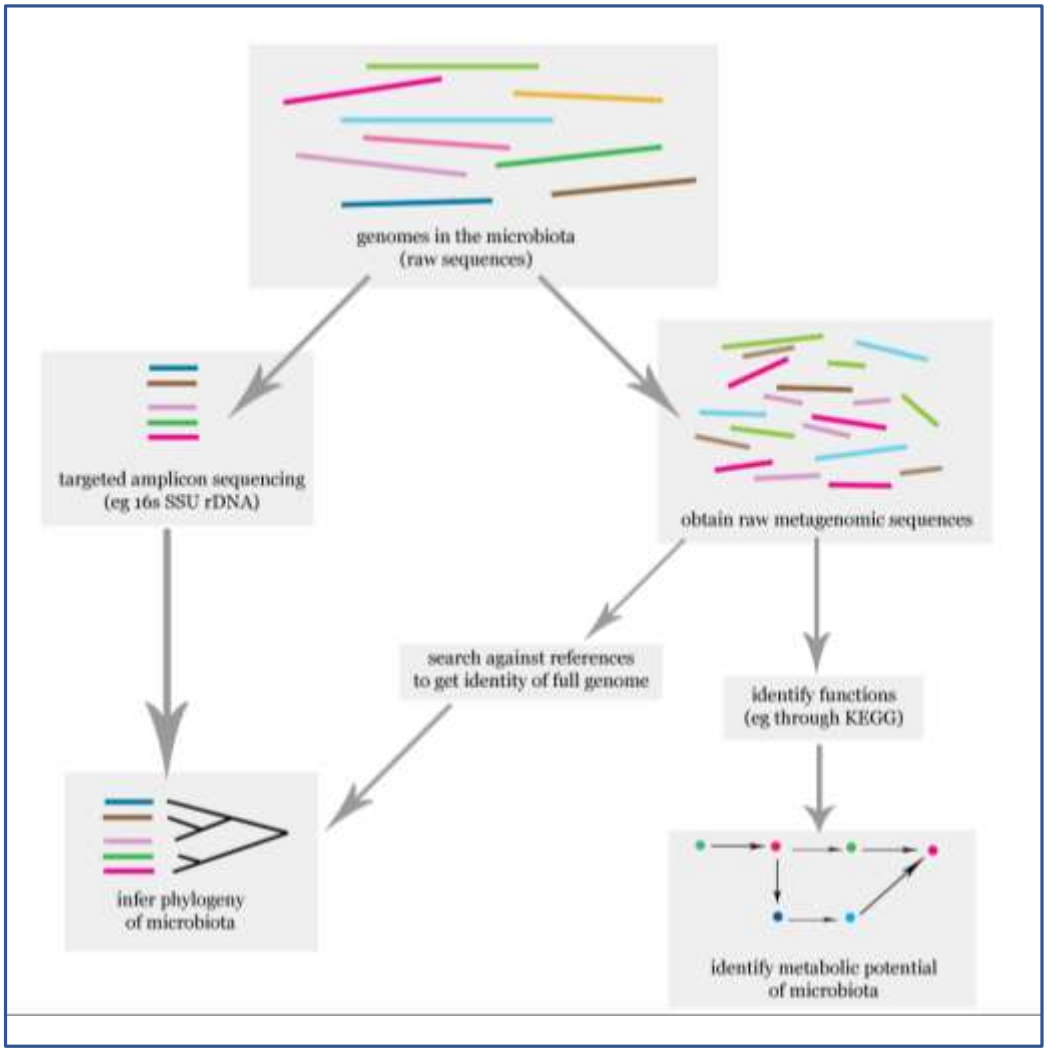
The Gastrointestinal Microbiome



- Four dominant phyla in the human gut
  - Firmicutes (64%)
  - Bacteroidetes (23%)
  - Proteobacteria (8%)
  - Actinobacteria (3%)
- Human gut microbiomes can be classified into three **enterotypes** based on dominant genus
  - *Prevotella* (Bacteroidetes)
  - *Bacteroides* (Bacteroidetes)
  - *Ruminococcus* (Firmicutes)
- Enterotypes are independent of age, gender, weight, nationality
  - However, species variation within enterotypes can be affected by multiple factors and have important functional consequences

How We Study the Microbiome

- Main tool is high throughput DNA sequencing technology
  - Avoids the pitfalls of earlier culture-based methods
- Sequences are amplified, identified and then cross-referenced to infer taxonomy and/or function



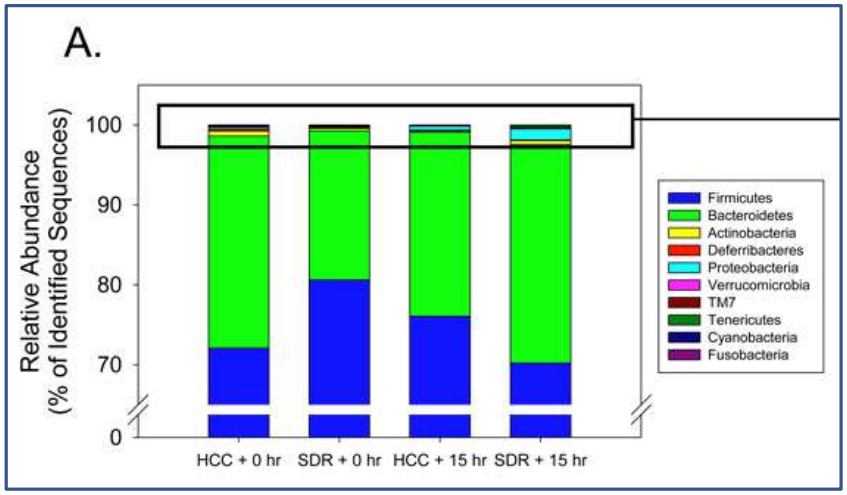
The Gastrointestinal Microbiome: Alteration in Response to Stressors

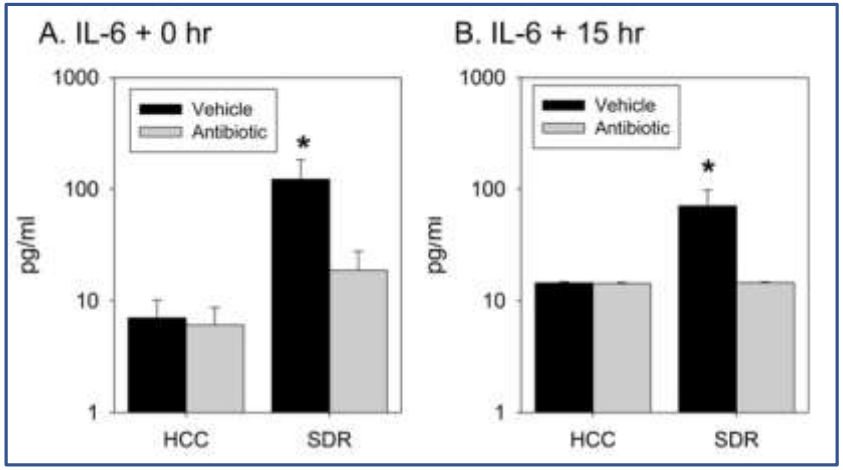
Brain Behav Immun. 2011 Mar;25(3):397-407. doi: 10.1016/j.bbi.2010.10.023. Epub 2010 Oct 30.

Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation.

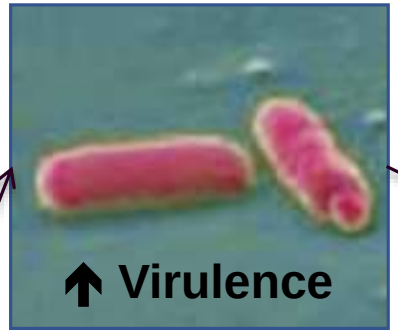
Bailey MT[1], Dowd SE, Galley JD, Hufnagle AR, Allen RG, Lyte M.

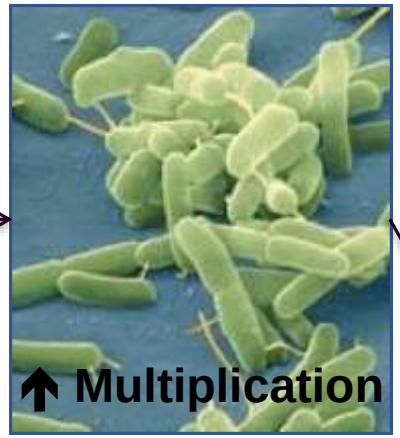
- Mice exposed to a social stressor (SDR) exhibited altered cecal microbiota
  - ↓ relative *Bacteroides* abundance
  - ↑ relative *Clostridium* abundance
- Circulating levels of IL-6 and MCP-1 inversely associated with stressor induced changes in three bacterial genera
- SDR failed to increase circulating levels of IL-6 and MCP-1 in antibiotic treated mice
  - Microbiota may be ***required*** for proper stressor response

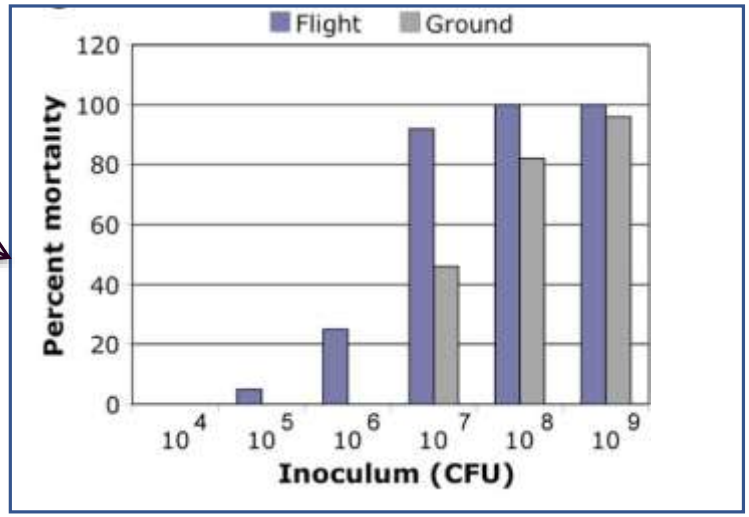




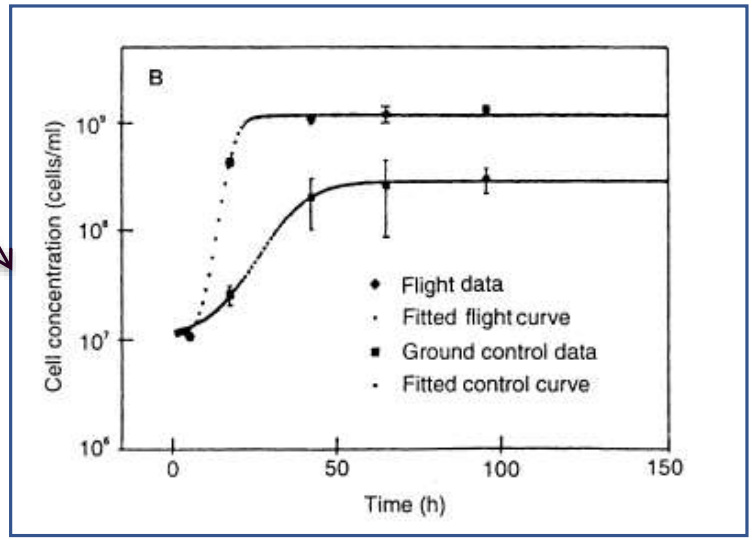
Microbial Behavior in Space







Wilson JW, 2007. Proc Natl Acad Sci USA 104:16299-16304.



Kacena et al., Appl.Microbiol Biotechnol (1999) 51:229-234

Microbial Behavior in Simulated Microgravity and Space

- Bacterial growth kinetics are generally promoted
- Increase of virulence of pathogenic bacteria
- Increased formation and mass of biofilm
  - Novel architecture of biofilm in *P. aeruginosa*
- Increased bacterial resistance to stresses and antibiotics
  - Increased frequency of bacterial mutations
- No universally negative effect on secondary metabolites

Microbes and the Immune System in the Space Environment

Int Rev Immunol. 2015 Aug 19:1-16. [Epub ahead of print]

Dysbiosis and Immune Dysregulation in Outer Space.

Cervantes JL[1], Hong BY.

- In the healthy state, gut microbes exist in a balanced balanced state with the local immune system
- Exposure to microgravity and the space environment affects the function of multiple cell types in the host immune system
  - Microgravity, stress, isolation, containment, radiation, microbial contamination, sleep disruption, and insufficient nutrition may all contribute to immune system dysfunction

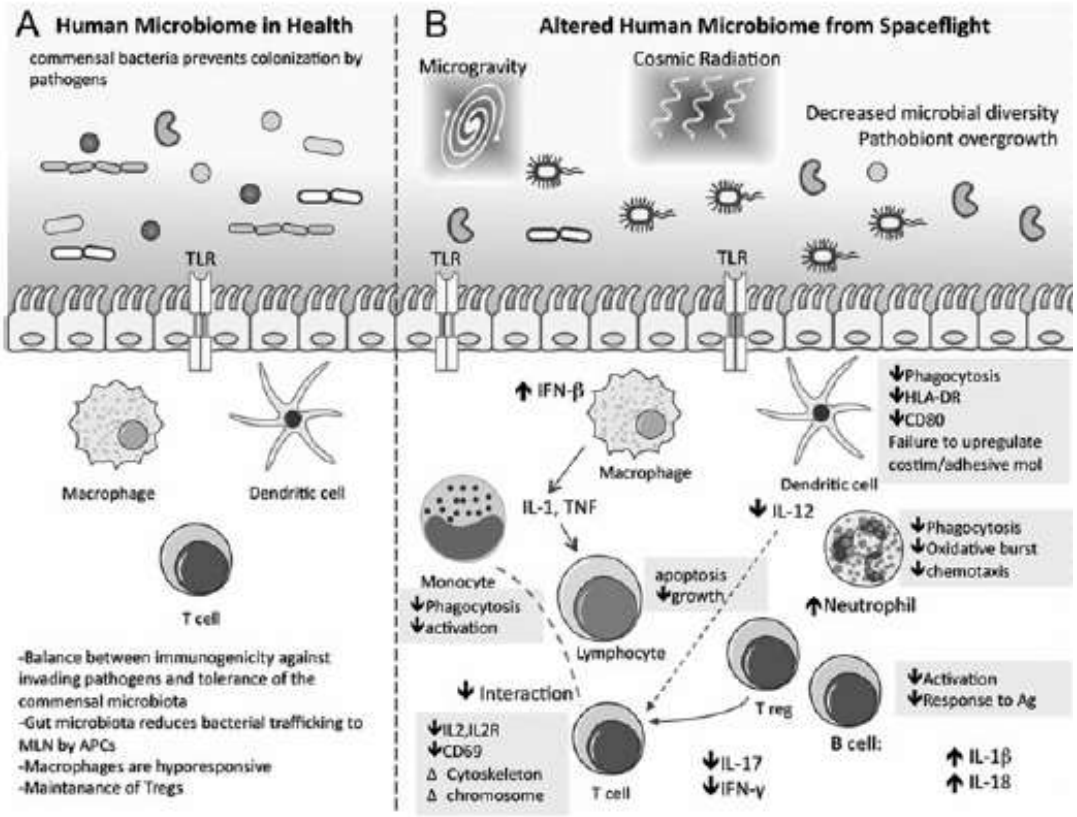


FIGURE 1. Dysbiosis and Immune Dysregulation in Outer Space.

Study Highlight: Impact of Whole Body Radiation on Intestinal Microbiome

- Fecal sample OTUs ***increased*** post-radiation

Taxa ID	Phylum	Class	Order	Family	Fold Change (Post/Pre)	T-Test
280	Firmicutes	*Bacilli*	*Turicibacterales*	*Turicibacteraceae*	21.8	0.048
644	Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteriaceae*	20.5	0.005
267	Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteriaceae*	8.5	0.007
952	Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteriaceae*	6.7	0.004
476	Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteriaceae (Genus: Escherichia)*	6.5	0.010
787	Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteriaceae*	6.3	0.012
477	Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteriaceae*	6.2	0.017
1022	Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteriaceae*	6.1	0.022
946	Firmicutes	*Clostridia*	*Clostridiales*	*unclassified*	5.9	<0.001
567	Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteriaceae*	5.3	0.044
956	Proteobacteria	*Gammaproteobacteria*	*unclassified*	*unclassified*	4.3	0.018
633	Proteobacteria	*Alphaproteobacteria*	*unclassified*	*unclassified*	4.2	0.010
435	Proteobacteria	*Gammaproteobacteria*	*unclassified*	*unclassified*	4.1	0.033
1018	Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteriaceae*	3.5	0.027
286	Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteriaceae*	2.8	0.041
765	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	2.5	0.009
1061	Tenericutes	*Mollicutes*	*RF39*	*unclassified*	2.2	0.009
1042	Bacteroidetes	*Bacteroidia*	*Bacteroidales*	*unclassified*	2.1	0.030
534	Bacteroidetes	*Bacteroidia*	*Bacteroidales*	*RikenellaceaeII*	1.9	0.021
960	Proteobacteria	*Alphaproteobacteria*	*Rhodospirillales*	*Rhodospirillaceae*	1.8	0.004
834	Firmicutes	*Clostridia*	*Clostridiales*	*Ruminococcaceae*	1.8	0.032
775	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.7	0.009
297	Bacteroidetes	*Bacteroidia*	*Bacteroidales*	*RikenellaceaeII*	1.6	0.022
1024	Proteobacteria	*Alphaproteobacteria*	*Rhizobiales*	*Bradyrhizobiaceae (species:Bradyrhizobium_elkanii)*	1.6	0.018
275	Firmicutes	*Bacilli*	*Lactobacillales*	*Lactobacillaceae (genus:lactobacillus)*	1.6	0.009
465	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.7	0.007
599	Firmicutes	*Bacilli*	*Lactobacillales*	*Lactobacillaceae (Enterococcus)*	1.6	0.007
171	Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteriaceae*	1.6	0.031
798	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.5	0.028
47	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.5	0.013

Study Highlight: Impact of Whole Body Radiation on Intestinal Microbiome

- Fecal sample OTUs ***decreased*** post-radiation

Taxa ID	Phylum	Class	Order	Family	Fold Change (Post/Pre)	T-Test
909	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	9.0	<0.001
856	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	4.6	0.007
1	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	3.3	<0.001
914	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	2.6	0.012
872	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	2.5	0.007
818	Firmicutes	*Clostridia*	*Clostridiales*	*Ruminococcaceae*	2.5	0.033
374	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	2.5	0.049
501	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	2.4	0.016
330	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	2.3	0.025
257	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	2.1	0.001
430	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae (genus:Clostridium)*	2.1	0.001
794	Proteobacteria	*Alphaproteobacteria*	*Sphingomonadales*	*Sphingomonadaceae*	2.1	0.036
878	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	2.0	0.027
913	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	2.0	0.034
890	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.9	<0.001
928	Bacteroidetes	*Bacteroidia*	*Bacteroidales*	*Prevotellaceae (genus:Prevotella)*	1.7	0.001
990	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.7	0.048
727	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.7	0.026
754	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.7	0.029
623	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.6	0.011
804	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.6	0.007
93	Cyanobacteria	*Chloroplast*	*Streptophyta*	*unclassified*	1.6	0.047
408	Proteobacteria	*unclassified*	*unclassified*	*unclassified*	1.6	0.001
910	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.6	0.004
572	Proteobacteria	*Alphaproteobacteria*	*Rhodospirillales*	*Rhodospirillaceae*	1.6	0.041
846	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.6	0.016
315	Chloroflexi	*Anaerolineae*	*Anaerolineales*	*Anaerolineaceae (A4b)*	1.6	0.021
988	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.6	0.010
124	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.5	0.005
970	Firmicutes	*Clostridia*	*Clostridiales*	*Lachnospiraceae*	1.5	0.015

Study Highlight: Impact of Whole Body Radiation on Intestinal Microbiome

- OTUs with largest ***increase***:
  - *Turicibacteraceae* (Bacilli) and *Enterobacteriaceae* (Gammaproteobacteria) families
- OTUs most represented:
  - *Lachnospiraceae* (Clostridia) and *Enterobacteriaceae* with 17% and 37% of total OTUs present

- OTUs with largest ***decrease***:
  - *Lachnospiraceae* and *Ruminococcaceae* families
- OTUs most represented:
  - *Lachnospiraceae* (Clostridia) with 77% of total OTUs present

Study Highlight: Impact of Whole Body Radiation on Intestinal Microbiome

- Fecal shift ***towards*** potential pathogens
  - *Lactococcus garvieae*
    - Zoonotic pathogen that causes hyperacute and haemorrhagic septicemia
    - Recently associated with endocarditis, septicaemia, spondylodiscitis, and acute acalculous cholecystitis in humans
  - *Allobaculum sp*.
    - Key variable element in formation of precancerous lesions in rat models
  - *E.coli*
    - Enteric/diarrhogenic infections in human, UTIs, sepsis
  - *Bradyrhizobium elkanii*
    - Type III and IV secretion systems which are known to be essential for the virulence of many pathogenic bacteria.
  - *Lactobacillus* species
    - Associated with cholecystitis, sepsis, endocarditis, pneumonia, pyelonephritis, meningitis, endovascular infection, and bacteremia
    - Vast majority of the cases associated with immunocompromised patients.
  - *Enterococcus* species
    - Most prevalent multidrug resistant in-hospital pathogens worldwide
    - Capable of causing a variety of infections including endocarditis, sepsis, surgical wound infections, and UTIs

Study Highlight: Impact of Whole Body Radiation on Intestinal Microbiome

- Fecal shift inducing ***loss*** of potentially important species, which may protect GI tract and/or immune
  - *Clostridium* groups
    - Exert a strong influence on the host immune system by induction of T cell receptors, intraepithelial lymphocytes, antibody IgA cells, and regulatory T cells.
  - *Prevotella* species
    - Important physiological functions in the human large intestine because of the ability to degrade polysaccharides and for biosynthesis of vitamin B1
    - Central role in maintaining the community structure and diversity of the human gut microbiome
  - *Anaerolineaceae* species (*A4b*)
    - Unknown role

The Gastrointestinal Microbiome: Effects of Particle Radiation

Radiat Res. 2014 Jan;181(1):45-53. doi: 10.1667/RR13352.1. Epub 2014 Jan 7.

Intestinal microbiota reduces genotoxic endpoints induced by high-energy protons.

Maier I[1], Berry DM, Schiestl RH.

- Experimental Protocol
  - Subjects: C57/BL6J Mice with Conventional (CM) and Restricted (RM) intestinal microbiota
  - Intervention: total body ***particle*** radiation at 100 cGy delivered over several minutes vs. sham
    - ^{28}Si ions at 850 MeV, ^{56}Fe ions at 1 GeV and protons at 2.5 GeV
- Outcomes
  - Differences in microbiota composition between CM and RM
  - Radiation induced DNA damage and oxidative stress between CM and RM groups

The Gastrointestinal Microbiome: Effects of Particle Radiation

Radiat Res. 2014 Jan;181(1):45-53. doi: 10.1667/RR13352.1. Epub 2014 Jan 7.

Intestinal microbiota reduces genotoxic endpoints induced by high-energy protons.

Maier I[1], Berry DM, Schiestl RH.

- RM and CM have ***distinct*** fecal microbiota
  - RM mice had lower phylotype richness
- RM mice sustained ***greater*** amounts of double-strand breaks in T-lymphocytes (Fig 3)
  - Quantified by immunostaining of γ-H2AX histone protein
- RM mice exhibited ***increased*** oxidative stress in response to radiation (Fig 4)

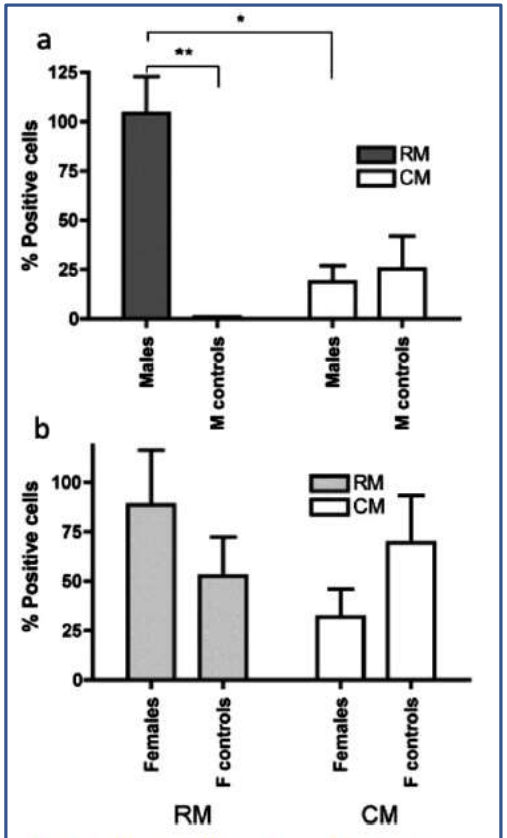


FIG. 3. High-energy protons initiate persistent DNA double-strand breaks (DSBs) in male RM mice ($P < 0.01$). γ-H2AX foci for irradiated and nonirradiated (panel a) male RM and CM mice and (panel b) female RM and CM mice measured in T-lymphocytes 4 weeks after whole-body exposure to ^{1}H, 2.5 GeV/n, 1 Gy. n = 4 for all groups of male (M) mice, n = 5 for irradiated females, and n = 4 for nonirradiated female (F) control mice. The analysis was performed in duplicate and 100 cells were counted for each blood preparation.

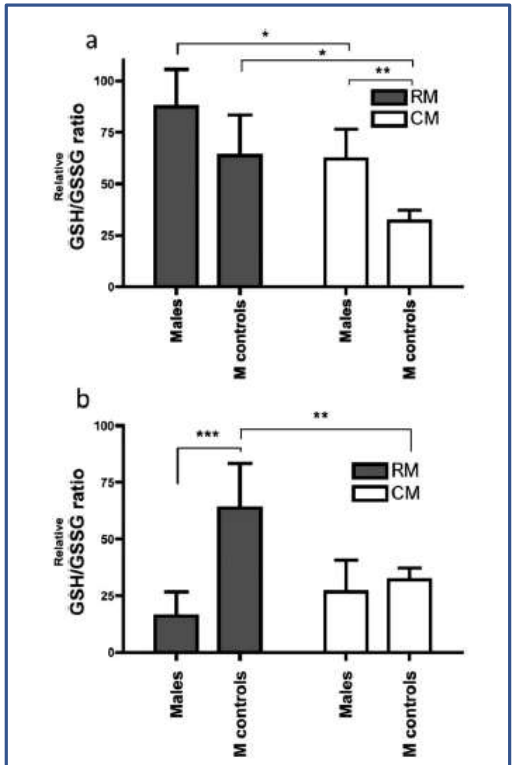


FIG. 4. Antioxidant levels for RM and CM mice irradiated with ^{1}H. GSH/GSSG ratio for RM and CM male mice irradiated with a single-whole-body exposure of protons (2.5 GeV/n, 1 Gy) and nonirradiated controls. Panel a: Three weeks after exposure: $P < 0.05$ for all irradiated and nonirradiated male mice (RM vs. CM); $P < 0.01$ for irradiated vs. nonirradiated CM mice; n = 6 mice/group for irradiated RM and CM; and n = 4 for nonirradiated RM and CM control mice. Panel b: Five to six weeks after exposure: $P < 0.001$ for irradiated vs. nonirradiated RM mice; $P < 0.01$ for nonirradiated CM vs. RM mice; n = 5 mice/group irradiated; and n = 4 for nonirradiated. Mean values of three measurements were compared by two-way ANOVA.

Future Directions: Human Research

- Research recently completed on the International Space Station
  - "Study of the Impact of Long-Term Space Travel on the Astronauts' Microbiome"
  - Sponsoring space agency: NASA
  - ISS Expeditions assigned: 35 – 48
  - Duration: March 2013 – September 2016, included 6 month and 12 month missions
  - Focus: characterizing the microbiota composition in the skin, nasopharynx, gut and bloodstream and its correlation with mission duration and physiologic/health parameters
- https://www.nature.com/articles/s41598-019-46303-8

Study of the impact of long-duration space missions at the International Space Station on the astronaut microbiome

- Alexander A. Voorhies, C. Mark Ott, Satish Mehta, Duane L. Pierson, Brian E. Crucian, Alan Feiveson, Cherie M. Oubre, Manolito Torralba, Kelvin Moncera, Yun Zhang, Eduardo Zurek & Hernan A. Lorenzi

- We present evidence showing that the microbial communities of the gastrointestinal tract, skin, nose and tongue **change** during the space mission. The composition of the intestinal microbiota became more similar across astronauts in space, mostly due to a **drop in the abundance of a few bacterial taxa,** some of which were also correlated with changes in the **cytokine profile** of crewmembers. Alterations in the skin microbiome that might contribute to the **high frequency of skin rashes/hypersensitivity episodes** experienced by astronauts in space were also observed. The results from this study demonstrate that the composition of the astronauts' microbiome is altered during space travel. The impact of those changes on crew health warrants further investigation before humans embark on long-duration voyages into outer space.

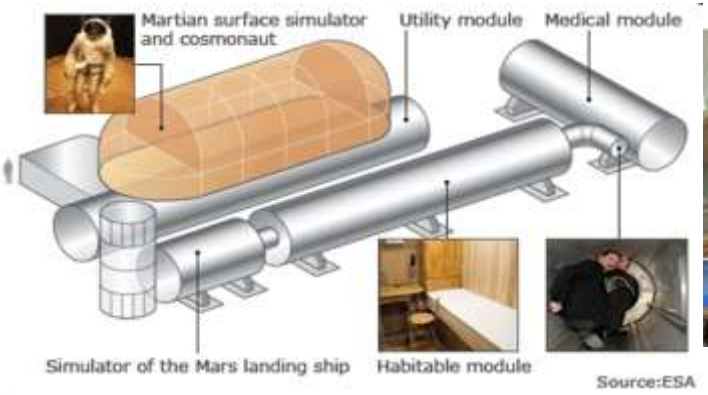
Dysbiosis Countermeasures

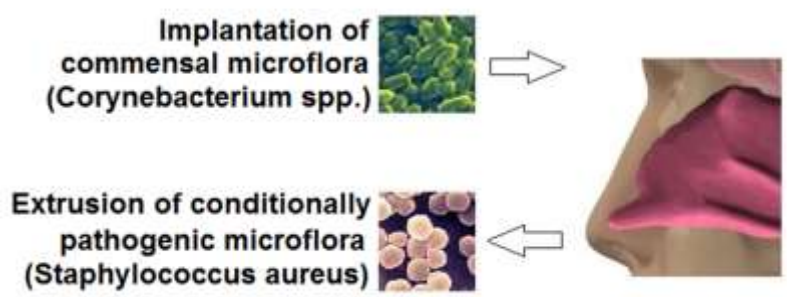
- Probiotics – microorganisms that provide health benefits when consumed
  - GI system: Lactic (acetic)acid producing bacteria (Lactobacillus and Bifidobacter genus are the best studied to date (e.g *L. caseii*, acidophilus; *B. longum, lactis* and *infantis)*
    - Lactose fermentation products: Acetic (SCFA) > Lactic acid inhibit molds and pathogenic yeasts
    - Immune stimulation, energy metabolism (succinic and formic acid), vitamin and other co-factor production; **gut-brain axis**- Truly synergistic species with human gut
    - Other important species: *Saccharomyces boulardii*
  - Various evidence to suggest that consumption of probiotics may:
    - Increase mucosal IgA response
    - Enhance response to live oral vaccines
    - Activate leukocytes and stimulate release of inflammatory cytokines TNF-a, IFN-g, IL-12 and regulatory cytokines IL-4 and IL-10
    - Down-regulate proinflammatory cytokine IL-8
  - Mucous Membranes: *Corynebacter pseudodiptheriticum*
  - Storage considerations for long-duration space flight
    - Temperature control, radiation shielding, sporulation
- Dietary and pharmacologic interventions
  - Nutritional nucleotides/**prebiotics**, anti-oxidant supplements, radiation countermeasures
- Engineering of the microbiota (possibly selective or genetic)
  - Combination of sequential depletion and inoculation of microbiota to achieve a desired effect; possible gen-modification of probiotic species to enhance radio-resistance

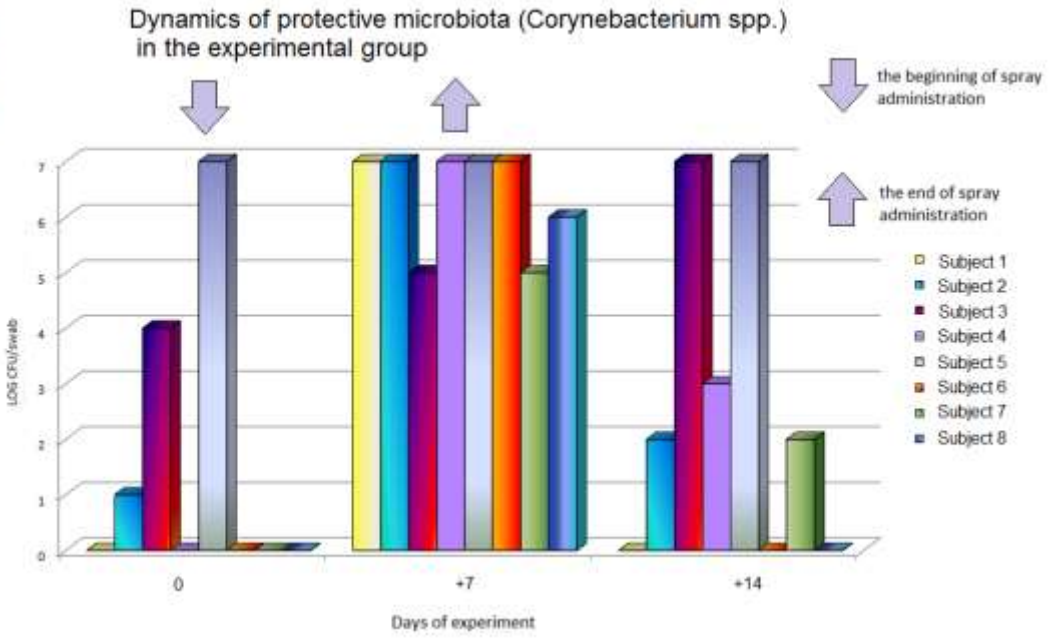
Ilyin V.K., Skedina M.A., Kiryukhina N.V., Soloviova Z.O.

Results and discussion – microbiota investigation

Both subjects with Corynebacterium countermeasure swabs and strips, never exhibited dysbiotic shifts due to *S. aureus* contamination in the nasal or pharyngeal mucosa seen in test participants







General Radiation Countermeasures

- Exposure minimization
  - Travel time (faster propulsion), trajectory optimization, monitoring for SPE
- Shielding
  - Effective for low-LET radiation
    - Hydrogen rich shields → principal composition of storm shelter aboard an exploration-class spacecraft
  - For HZE: mass required for effective shielding is a major obstacle
    - Beware secondary radiation, neutron shower
  - Theoretical potential for magnetic fields generated by on-board nuclear reactor
    - Unclear feasibility or biological implications
- Biologic/Pharmacologic agents

Biologic / Pharmacologic Countermeasures

- Three mechanisms of biological protection
  - **Radiomodulators**: act to elevate ***baseline*** resistance of organism to radiation insult and oxidative stress
  - **Radioprotectors**: act at the ***cellular*** level to neutralize reactive oxygen species
  - **Radiomitigators**: act at the ***systemic*** level to accelerate post-radiation recovery, prevent complications
- A given agent may act via multiple pathways and be employed for more than one purpose

Radiomodulators

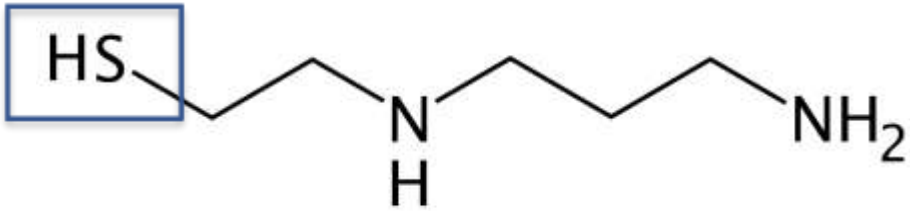
- Agents that act to increase the baseline resistance of an organism to radiation exposure
  - Indication: ***prophylactic*** administration
  - Many different compound functions
    - Bio-antimutagens (eg. *Vanillin*)
    - Desmutagens (eg. *Polyphenols*)
    - Antioxidants (eg. *NAC*)
    - Arachidnoic acid metabolism modulators (eg. *ASA*)
    - Anti-proliferatives (eg. *Flavanoids*)
    - Oncogene activity modulators (eg. *Quercitin*)
    - Immune function modulators (eg. *Selenium*)
    - DNA methylation modulators (eg. *Folic acid*)
    - Intracellular communication stimulators (eg. *Retinoids*)
  - Many radiomodulator compounds can be incorporated into the diet

TABLE 23.14. Natural sources of chemical radioprotective agents in plants.

Compounds	Sources
Allium and N-acetyl cysteine [diallyl sulfide]	Onions, garlic, chives, scallions
Sulphoranes, indoles, and isothio cyanates [dithiolthiones, indole-3-carbinol]	Cruciferous vegetables (e.g., broccoli, cauliflower, kale, cabbage)
Isoflavones and phytoestrogens	Soybeans (e.g., tofu, soy milk)
Terpenes and ascorbic acid [perillyl alcohol, limonene]	Citrus fruits (esp. lemon peels), cherries, tomatoes
Curcumins	Tumeric
Carotinoids, lycopene, lutein, antioxidants	Yellow vegetables, fruits (e.g., carrots, tomatoes, squash)
Polyphenols and flavonoids [epigallocatechin gallate, thearubigens, theaflavins]	Green and black teas, fruits, wine
[Phenolic acids- ellagic acid, ferulic acid]	Whole grains, nuts, tomatoes, carrots, citrus fruits

Radioprotectors

- Agents that act directly to protect cellular components and oppose the action of radiation induced free radicals and reactive oxygen species, e.g. Super Oxide Dismutase
  - Indication: administration shortly ***before*** an exposure event
    - Short-term duration of protective effect
  - Example: Thiols

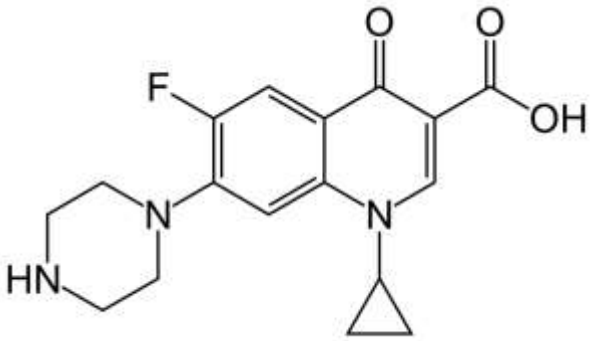


WR-1065 is the active metabolite of amifostine

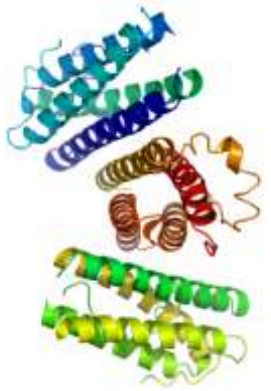
- ***Amifostine***: the only FDA approved medication for radiation exposure
  - Approved for prevention of radiation mucositits

Radiomitigators

- Agents that act at a systemic level to accelerate post-radiation recovery, prevent complications
  - Indication: administration ***before*** and ***after*** an exposure event to reduce clinical sequelae of the exposure
  - Examples: steroids, growth factors, immuno-adjuvants, antibiotics, autologous stem cells/blood forming elements (heterologous pluripotential stem cells rejected in first 10 days)
  - Soviet medical administered to Chernobyl victims: analgesics, antihistamines, alcohol + whole blood



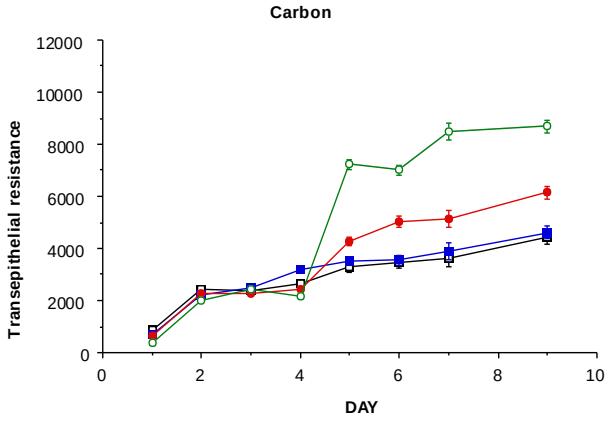
Molecular structure of Ciprofloxacin

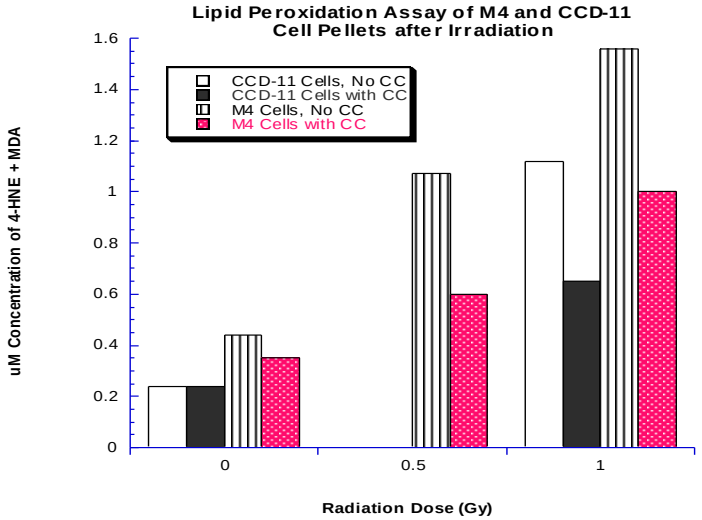


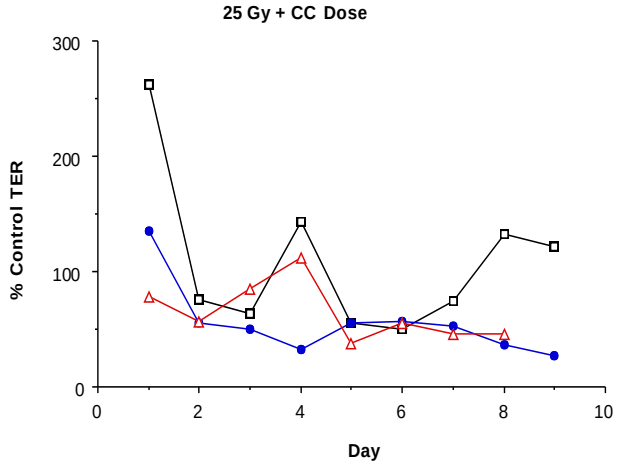
Crystal structure of G-CSF

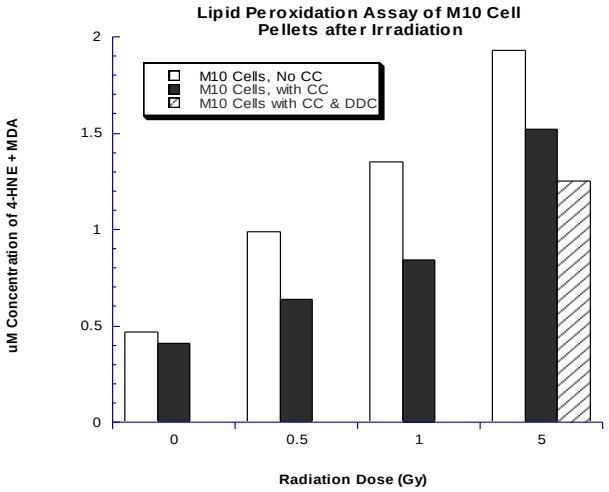
Mammary Epithelial and Pneumocyte cellular experiments w HZE Particulate Exposure +/- CC

Transmembrane resistance decrease and lipid peroxidation decrease with radiation exposure partial mitigation by chemoprevention cocktail









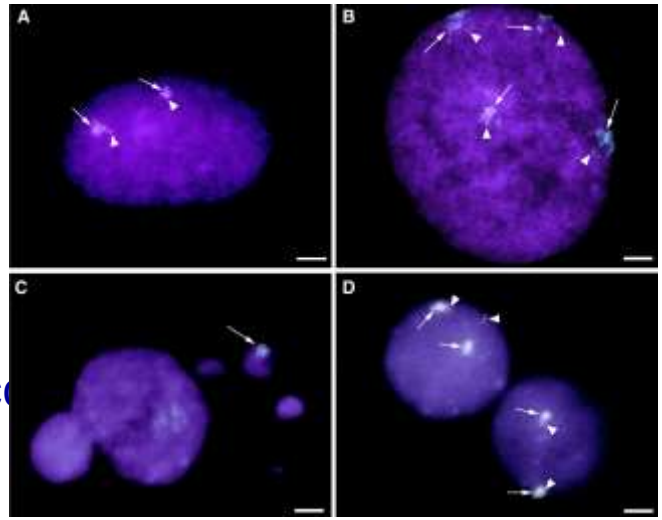
Hydrolysis of Sphingomyelin;
lipid peroxidation, tight junction dysfunction

Results Summary of FISH analysis comparing placebo vs chemoprevention cocktail (CC)

- Comparison of number of chromosomal aberrations seen in cells with(+) irradiation(ir) or without(-) irradiation,
- HZE C-Carbon ions, Ne- Neon ions;

Breaks: C-C classic region, C-A alphoid satellite

- Cells with (+) or without (-) chemoprotective cocktail(c



Exp Cond	# scored	% with aberr	% w C-C Brk	% w C-A Brk	% Monoso	% Tripl	% Tetrapl	% HypTetraploid
-irrad, - cc	44	6.8	2.3	0.0	0.0	2.3	2.3	0.0
-irrad, + cc	251	4.4	0.4	0.0	0.8	2.0	1.2	0.0
+C irr, - cc	494	23.6	17.1	1.3	1.8	8.3	7.5	1.8
+C irr, +cc	234	13.7	2.9	0.0	1.7	6.0	3.4	0.0
+Ne ir, - cc	52	32.7	9.6	0.0	3.8	7.7	9.6	5.8
+Ne ir, +cc	125	17.6	1.8	0.0	0.8	8.0	5.6	0.8

Ground Radiation Studies II - Tumor & Oxidative Stress at NASA / ARC Proteomics (S. Bhattacharya + K. Prasad & G Haase)

upd = os

DOME

hop

marelle = STAT92E

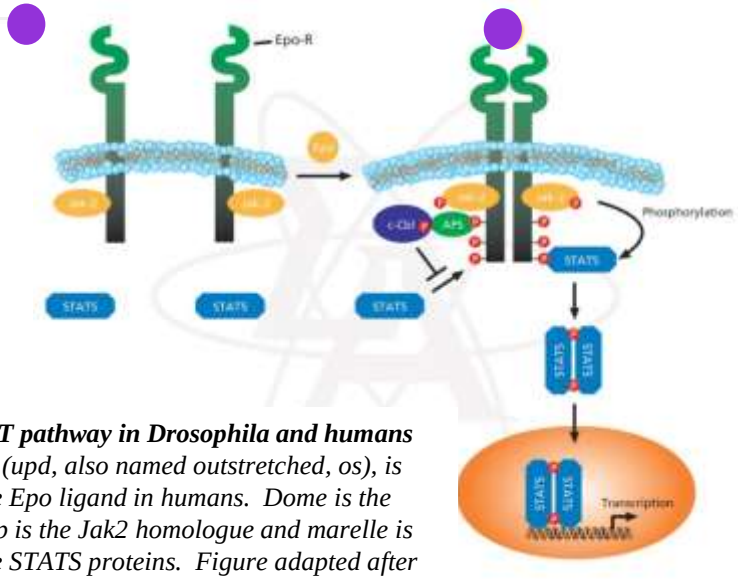
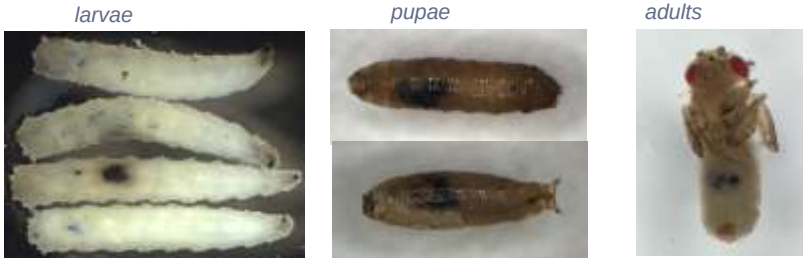
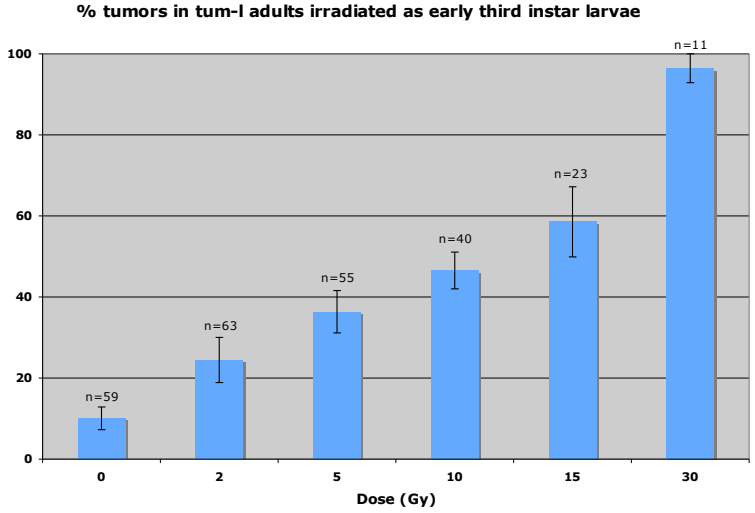


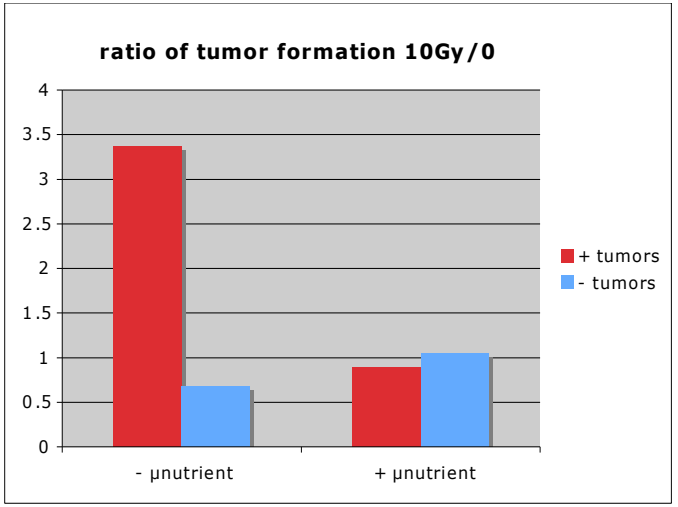
Fig.1. The Jak-STAT pathway in Drosophila and humans *The unpaired ligand (upd, also named outstretched, os), is the homologue of the Epo ligand in humans. Dome is the fruit fly receptor, hop is the Jak2 homologue and marelle is the homologue of the STATS proteins. Figure adapted after Sigma-Aldrich.*



Melanotic tumors induced by radiation



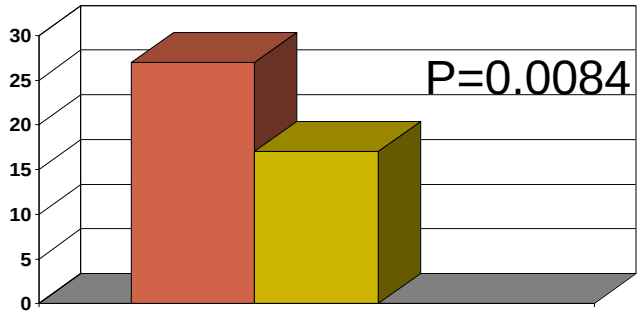
Tumor formation is radiation dose-dependent



Tumor frequency reduced by antioxidant pretreatment -- indicates involvement of oxidative stress

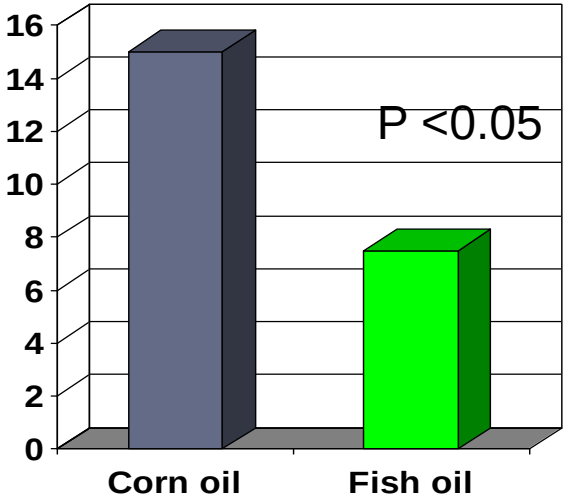
Radiation increased the number of high multiplicity aberrant crypts while fish oil-based formula reduces oxidative stress and tumor formation in the face of radiation (J. Lupton, TxAM U.)

of aberrant crypts

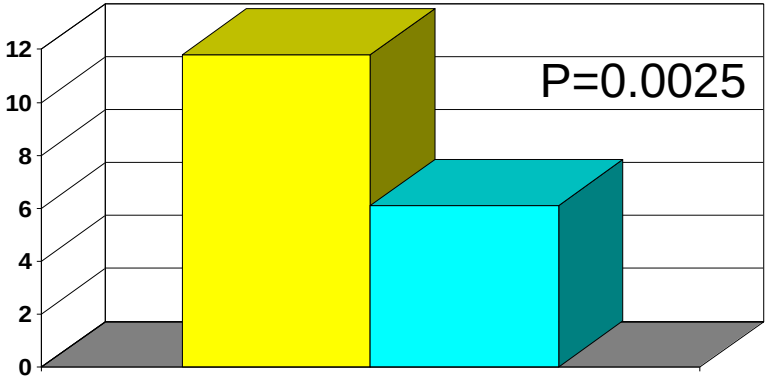


+radiation -radiation

Oxidative DNA damage as measured by 8-OH deoxyguanosine staining

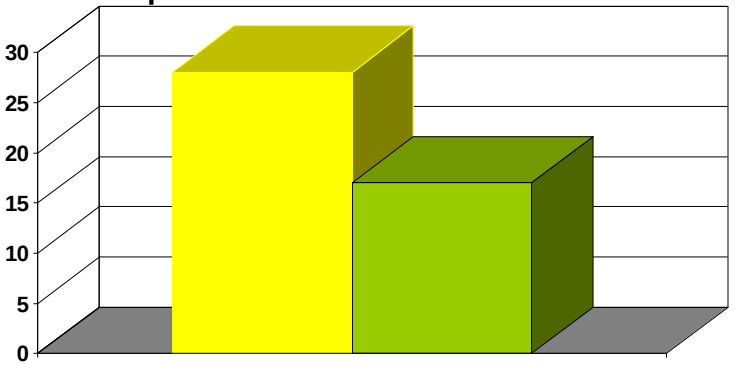


# of aberrant crypts



Corn oil Fish oil

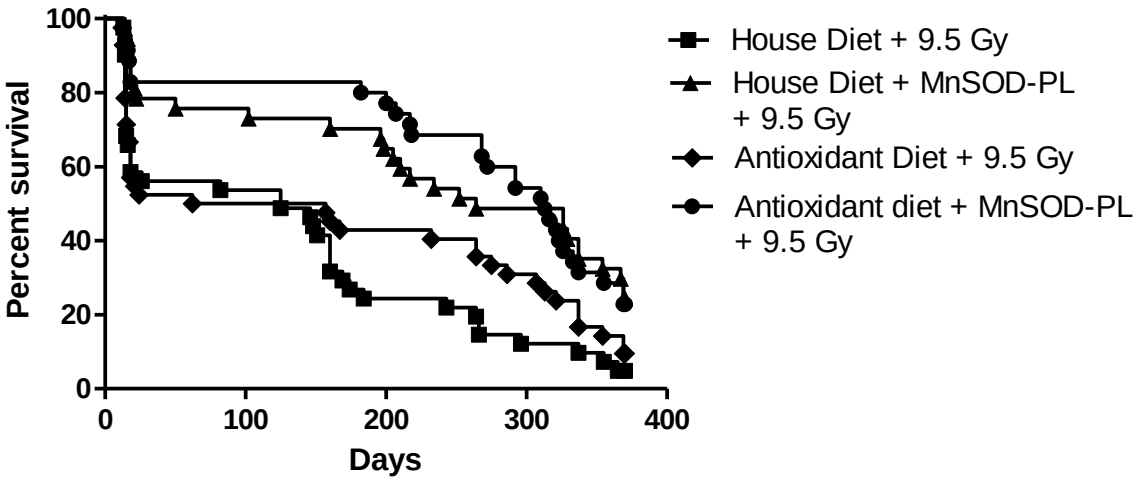
Proportion of rats with tumors



Corn Oil Fish Oil

Antioxidant Diet + SOD Effect on Lethal γ-Radiation Mortality Exposure

- Study design:
  - 160 female mice irradiated with 9.5 Gy TBI
  - Four subgroups:
    - Regular Diet (RD) +/- MnSOD-PL
    - Antioxidant Diet (AD) +/- MnSOD-PL
- Results:
  - MnSOD-PL alone ***increased*** survival
  - AD + MnSOD-PL ***increased*** survival over RD + MnSOD-PL



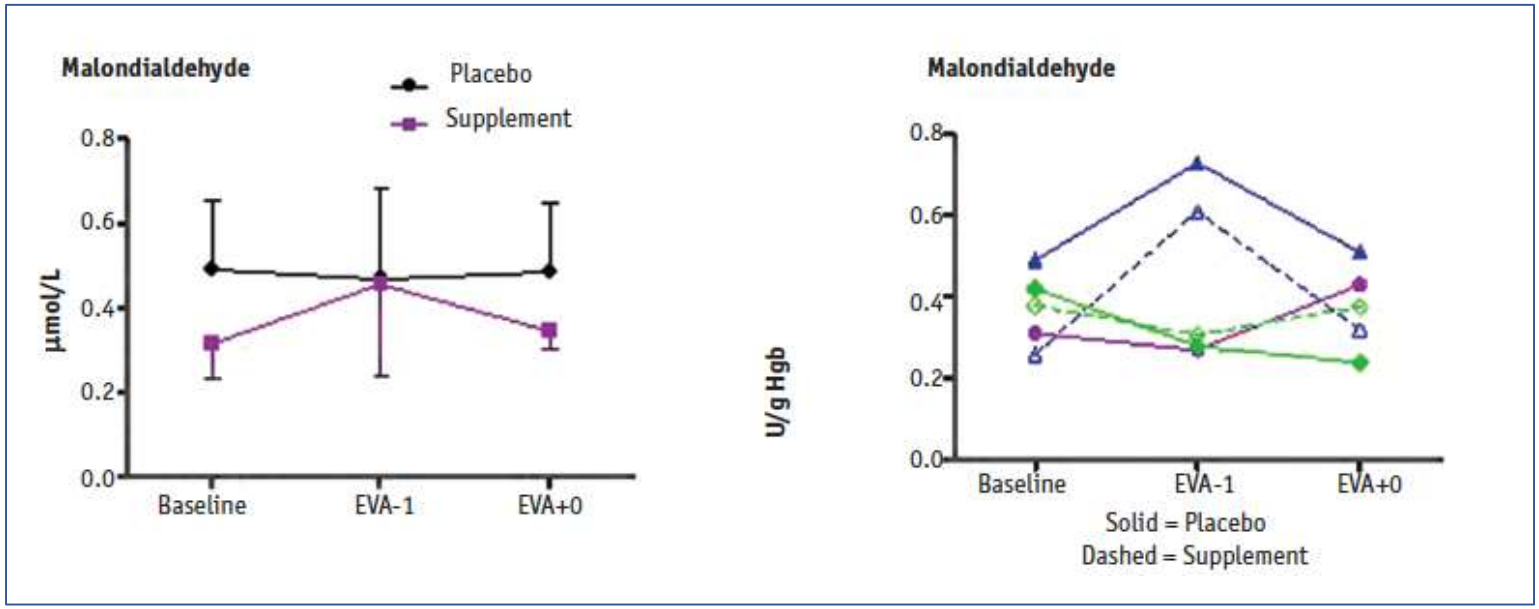
- Rodent survival after 9.5 Gy gamma ray exposure, with 80% of rodents surviving 20 days that received the proposed NASA diet supplement, vs. <20% survival for alternative diet.

Highlight: Chemoprevention Formula Effect on Human Oxidative Stress

- Study design:
  - Astronauts performed 6-8 hours of EVA training activities at the NBL
  - Hyperoxic environment
  - Served as their own controls
    - EVA 1: No countermeasures
    - EVA 2: Antioxidant diet started 1 week prior to activity
- Outcomes:
  - Markers of lipid peroxidation
  - Forearm fatigue

Highlight: Chemoprevention Formula Effect on Human Oxidative Stress

- Results:
  - ***Less*** lipid peroxidation was observed with antioxidant diet
  - ***Improved*** hand-grip endurance with antioxidant formula
- Follow-up:
  - Four crewmembers subsequently took formula on Shuttle and ISS missions
  - Well tolerated in-flight



Highlight: Chemoprevention Formula Effect on Human Oxidative Stress

- 6 month human safety study has been conducted and has shown good tolerability with maintenance of normal lab parameters and wellness indicators
- Chemoprevention formula utilized by 2 Shuttle crews and one long duration ISS crewmember Proposal in work to study "–omic" profile indicators of oxidative stress

A) Multivitamins/Trace Minerals (as tablet)		
Vitamin A	2500	IU
(as 70% beta-carotene and 30% vitamin A palmitate)		
Vitamin C (as ascorbic acid)	250	mg
Vitamin D (as cholecalciferol)	1200	IU
Vitamin E	200	IU
(as natural d-alpha tocopheryl succinate and mixed tocopherols)		
Vitamin K (as phytonadione)	80	mcg
Thiamine (vitamin B1) (as thiamine mononitrate)	2.25	mg
Riboflavin (vitamin B2)	2.55	mg
Niacin (as inositol hexanicotinate)	30	mg
Vitamin B6 (as pyridoxine hydrochloride)	3	mg
Folate (as folic acid)	600	mcg
Vitamin B12 (as cyanocobalamin)	9	mcg
Biotin	450	mcg
Pantothenic acid (as d-calcium pantothenate)	15	mg
Calcium	500	mg
(as calcium carbonate, dicalcium phosphate)		
Iodine (from kelp)	30	mcg
Magnesium	200	mg
(as magnesium oxide and chelate)		
Zinc (as zinc chelate [monomethionine or glycinate])	15	mg
Selenium (as L-selenomethionine)	100	mcg
Copper (as copper amino acid chelate)	0.18	mg
Manganese (as manganese amino acid chelate)	2	mg
Chromium (as chromium picolinate)	200	mcg
Molybdenum (as molybdenum amino acid chelate)	56	mcg
Potassium (as potassium citrate) (7.5 mEq)	290	mg

B) Antioxidant/Chemoprevention agents (as capsule)		
Quercetin [Source quercetin dihydrate and/or citrus peel)]	800	mg
Rutin/Hesperidin Source citrus peel]	25/5	mg
Green Tea Polyphenols [Source: Green Tea Extract (leaf)]	225	mg
Epigallocatechin Gallate (EGCG)	125	mg
Alpha Lipoic Acid	100	mg
N-Acetyl-L-Cysteine(NAC) synthetic	600	mg
Lycopene [Source: Source: Tomato Extract 5%]	5	mg
Astaxanthin [Source: Haematococcus Algae Extract 2%] Lutein Source [Source: Marygold Extract 5%]	1 10	mg mg
Phytosterols [Source: Soy and Avocado]	250	mg
Isoflavones [Source: Soy and/or Avocado Extracts]	350	mg
Allicin [Source: High-Potency Garlic Extract (bulb)]	7.5/275	mg
Glucosinolates [Source: Cruciferous Vegetable Extract (Brassica spp.) (plant)]	4/100	mg
High ORAC Fruit Extract [Source: strawberry, escobillo, blueberry, blackberry, cranberry, grape, pomegranate]	100	mg
Coenzyme Q-10	100	mg
Resveratrol [Source: phytoalexin from grape juice/seed extract (incl: flavonoids, polyphenols, proanthrocyanins)]	150	mg
Lipid Supplement (from omega-3 fatty acids alpha-linolenic, as gel capsule)		
DHA (docasahexaenoic acid- from algal oil) EPA (eicosapentanoic acid- from fish oil)	750 250	mg mg

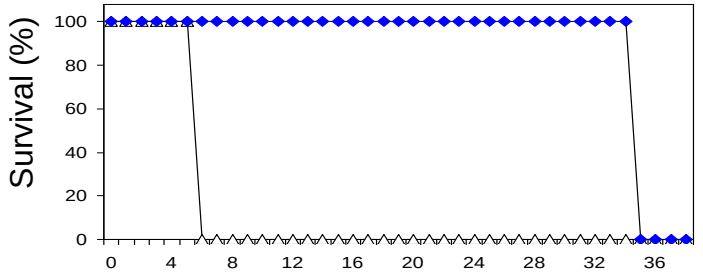
Hyperimmune Serum and Radiation Vaccine Development

- Serum and Vaccine creation:
  - Specific radiation determinant (SRD) toxins have previously been identified and found to be glycoproteins with high enzymatic activity
  - SRDs appear to be breakdown products of radiation necrosis
  - SRDs were isolated from central lymph of irradiated animals and used to derive hyperimmune serum and a vaccine
- Study design:
  - **Animals**: mice, rats, rabbits, sheep, pigs, dogs, cattle
  - **Intervention**: animals received either placebo, vaccine or hyperimmune serum prior to lethal irradiation

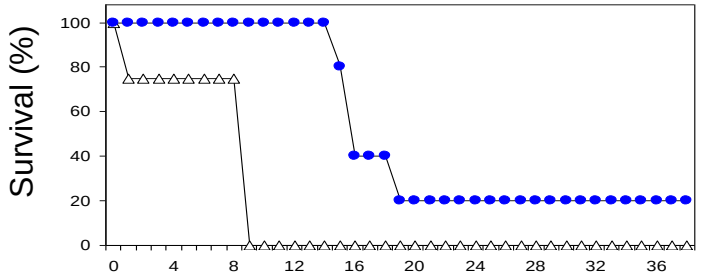
Highlight: Radiation Vaccine

- Results:
  - Administration of SRD produced clinical effects of radiation toxicity
  - SRD Vaccine ***increased*** survival in all species

Sheep



Rabbit



Days after irradiation

Summary of the effect of high dose radiation (expressed in Gy) on various animal species and the impact of a radiation vaccine countermeasure [113]

Species	Radiation (Gy)	SDR vaccine (mg/kg)	Number of animals	Survival rate (%) 30 days	60 days	180 days	360 days
Dogs	6.5	0	17	0	0	0	0
		15	93	88	79	65	65
Pigs	7.5	0	30	0	0	0	0
		15	68	65	61	54	54
Sheep	6.5	0	23	0	0	0	0
		20	112	90	84	78	78
Horses	6.5	0	5	0	0	0	0
		20	19	14	13	13	13
Cattle	9.2	0	10	0	0	0	0
		20	60	59	57	54	51
Rats	8.5	0	250	0	0	0	0
		10	3696	3326	3142	---	---
Mice	7.0	0	300	0	0	0	0
		10	2170	1628	1628	---	---

Baylor College of Medicine

Conclusions

- Interplanetary radiation exposure presents a significant biologic hazard for future exploration-class space missions
- Much of the radiation hazard from low-LET radiation is associated with reactive oxygen species and single-strand DNA breaks
- HZE particles produce a much higher rate of double-strand breaks
  - Other mechanisms are not well characterized and warrant further investigation
- The development of pharmacologic countermeasures represents promising approach towards the mitigation of space radiation
  - Acute exposure → radioprotectors and radiomitigators
  - Continuous exposure → radiomodulators
- There is promise in the development of vaccines and hyperimmune serum against the products of radiation necrosis

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Questions to Pontificate:

1. Space Radiation is not a potential show-stopper for exploration-class space missions outside LEO
    a. True
    b. False
    c. Not enough information to determine
    d. Who cares?

2. What are the 3 principle types of radiation that astronauts may be exposed to that may affect their health:
    1. Solar Wind Radiation, Geomagnetically Trapped Particles, Galactic Cosmopolitan Rays
    2. Geomagnetically Trapped Particles, Solar Particle Inversions, Galactic Cosmic Rays
    3. Stochastically Trapped Particles, Solar Particle Inversions, Cosmically Charged Radiation
    4. Galactic Cosmic Radiation, Solar Particle Events, Geomagnetically Trapped Particles

3. Name 3 possible means to protect the crew from space-derived radiation:
    1. Lead shielding, rapid interplanetary transit, pharmacologic agents
    2. Pharmacologic agents, Venus swing-by transit, high – H composition shielding
    3. Rapid interplanetary transit, pharmacologic agents, high-H composition shielding
    4. Conventional propulsion transit, lead shielding, OTC agents

4. Three types of biologic radiation countermeasures:
    1. Chemopreventives, Telomitigators, Radiomodulators
    2. Radiomitigators, Radiomodulators, Radioprotectors
    3. Radiomodulators, Radiomitigators, Teloprotectors
    4. Teleprotectors, Radiomodulators, Telomitigators

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Questions?

Some people aren't shaking hands because of the Coronavirus. I'm not shaking hands because everyone is out of toilet paper.