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Cardiovascular Effects at Low Doses of Radiation: Perspectives for Space Exploration

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SPACEFLIGHT HAZARDS

Space Radiation

Acute In-flight effects

Cancer

CNS Pathologies

Cardiovascular Disease

Altered Gravity Fields

Balance Disorders

Fluid Shifts

Cardiovascular Deconditioning

Muscle Atrophy & Bone Loss

Isolation & Confinement

Behavioral Impacts

Sleep Disorders

Team Dynamics

Hostile & Closed Environments

Vehicle Design

Environmental- CO_2 Levels, Toxic Exposures, Water, Food

Decreased Immune Function

Distance from Earth

Requirement for "Autonomous" Medical Care Capacity

Communication Delays

CVD - A HUMAN SYSTEM RISK

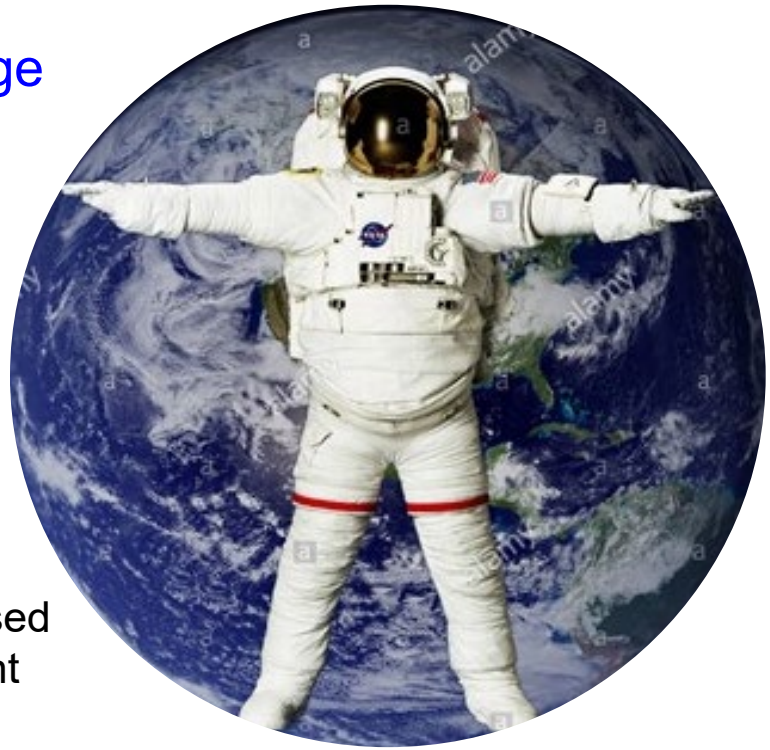
Genetics

Sex

Age

Lifestyle

Radiation



Altered gravity

Hostile/closed environment

Isolation/Confinement/ Circadian shifts

Distance from Earth

Atherosclerosis

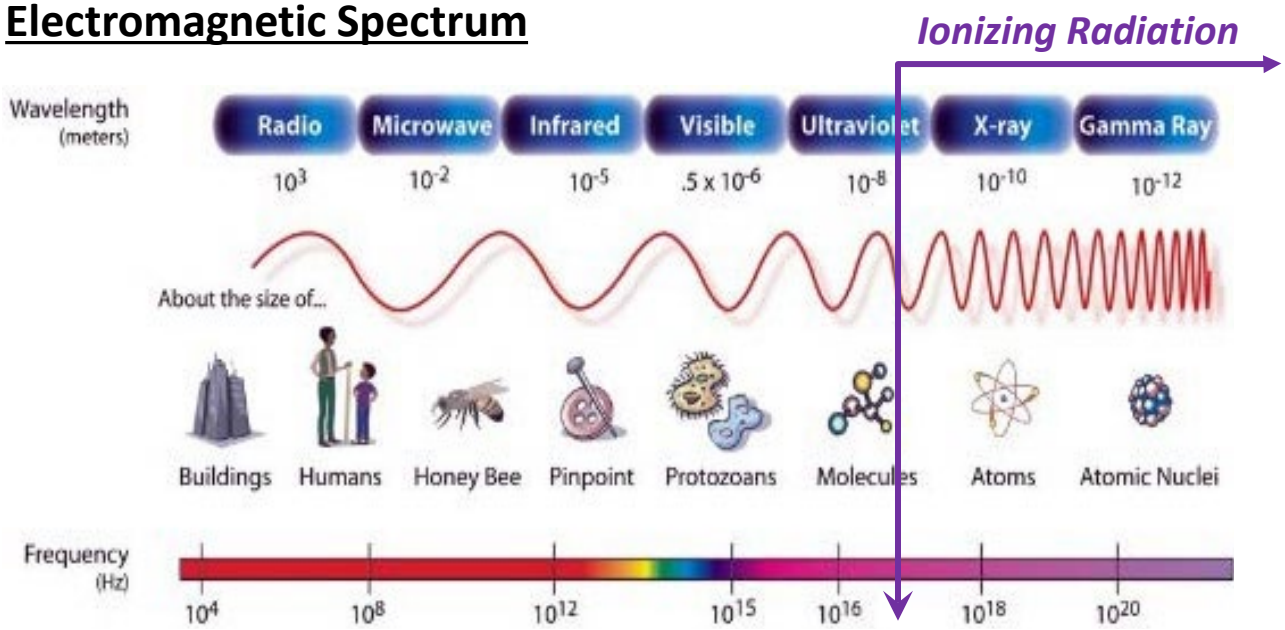
Myocardial Infarction

Stroke

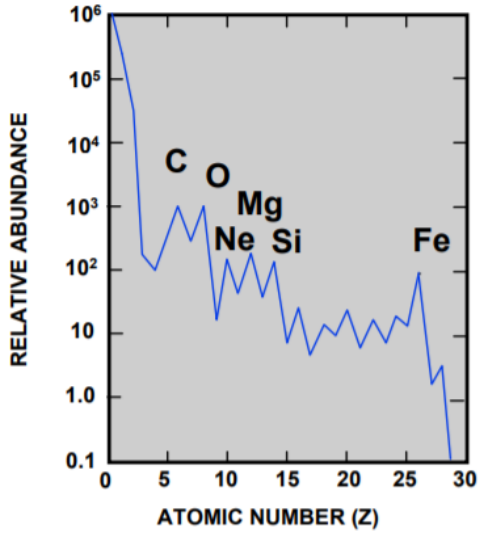
CARDIOVASCULAR DISEASE

IONIZING RADIATION

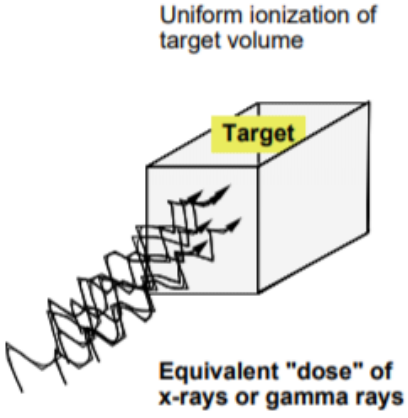
Electromagnetic Spectrum

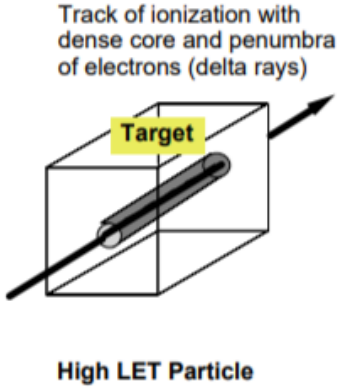


Galactic Cosmic Rays



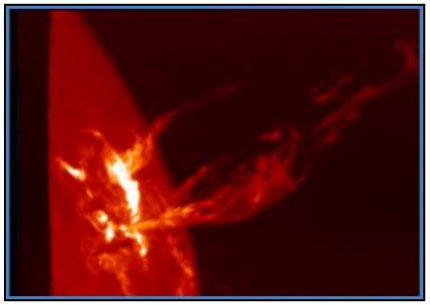
→ **Energy deposition happens differently between x-rays/gamma-rays and GCR.**





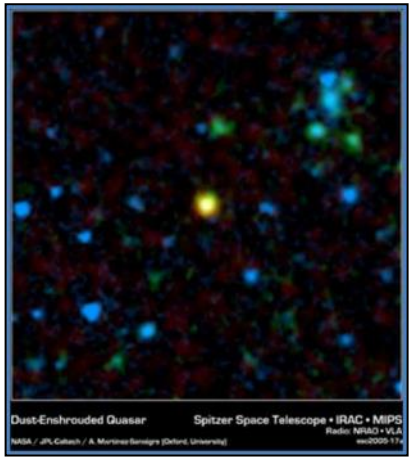
SPACE RADIATION ENVIRONMENT

Solar Particle Events (SPE)



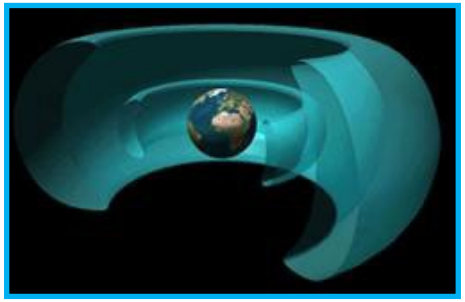
- Medium to high energy protons from intermittent coronal mass ejections, with peak activity during solar max
- While effectively shielded against to prevent risk of ARS, exposure contributes to inflight and late CNS, Cancer, and Degenerative risks
- **Main challenge**: Optimized storm shelter mass, active dosimetry, operational constraints/forecasting

Galactic Cosmic Rays (GCR)



- Highly charged, energetic atomic nuclei (HZE particles) and protons
- Major GCR particle types: H, He, C, O, Ne, Si, Ca, and Fe with broad energy spectra of interest - primarily from ~10 MeV/n to 10,000 MeV/n
- Low dose-rate, chronic exposures from continuous flux of particles, varies with solar cycle
- Not effectively shielded (fragment into lighter, penetrating species)
- **Main challenge**: Uncertainty about biological effects limits ability to accurately evaluate risks and countermeasures

Trapped Radiation (Van Allen Belts)



- Low to medium energy protons and electrons
- Effectively mitigated by shielding
- Mainly relevant to ISS and contributes ~40% of dose eq.
- **Main challenge**: Develop accurate dynamic model

ISS Low Earth Orbit

- Magnetosphere offers protection against SPEs (except high energy tail) and low energy GCR
- Exposure from trapped radiation and high energy GCR
- Total dose-rate similar to Mars surface
- 6-12 mo. missions

Deep Space

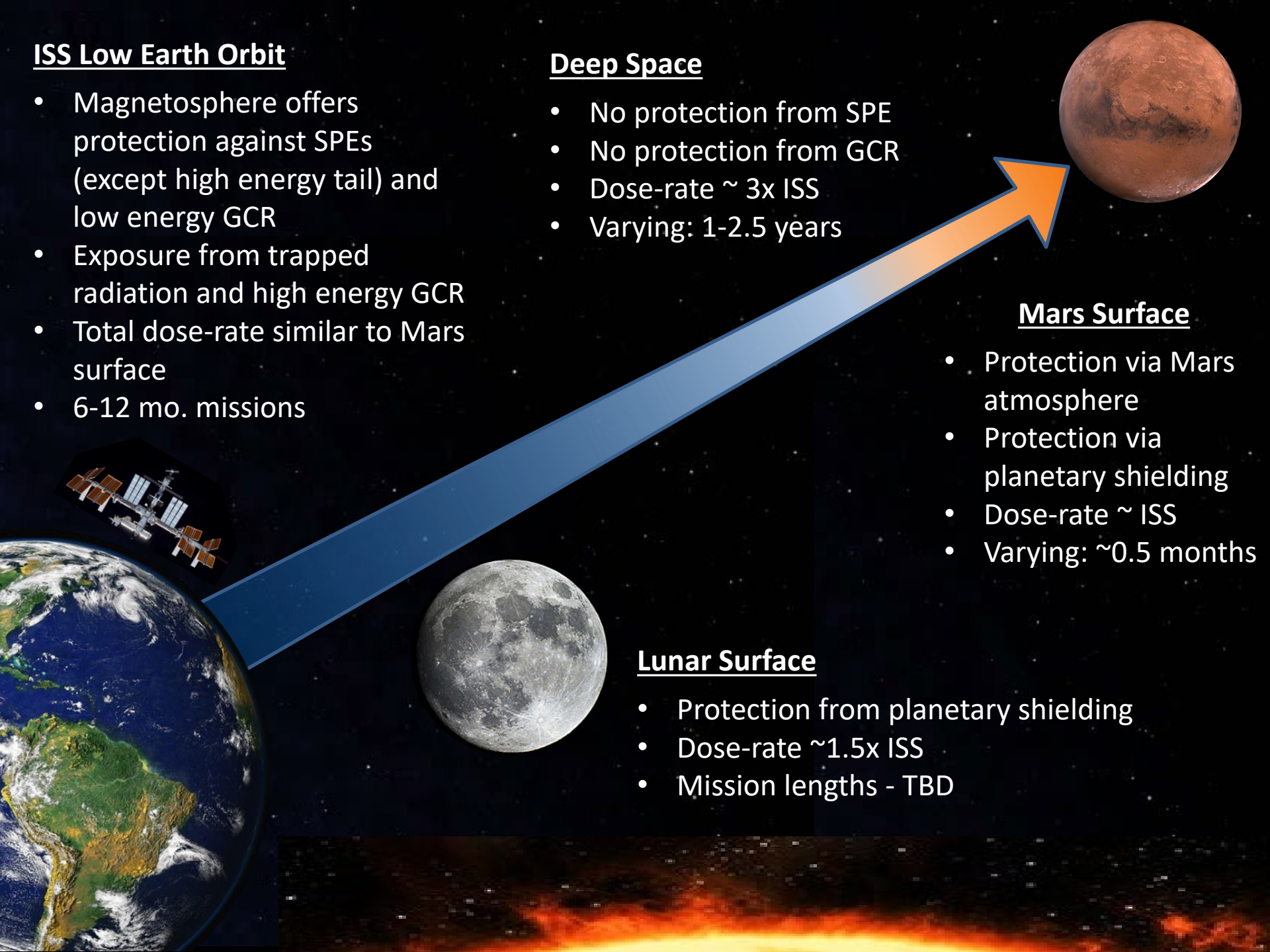
- No protection from SPE
- No protection from GCR
- Dose-rate ~ 3x ISS
- Varying: 1-2.5 years

Mars Surface

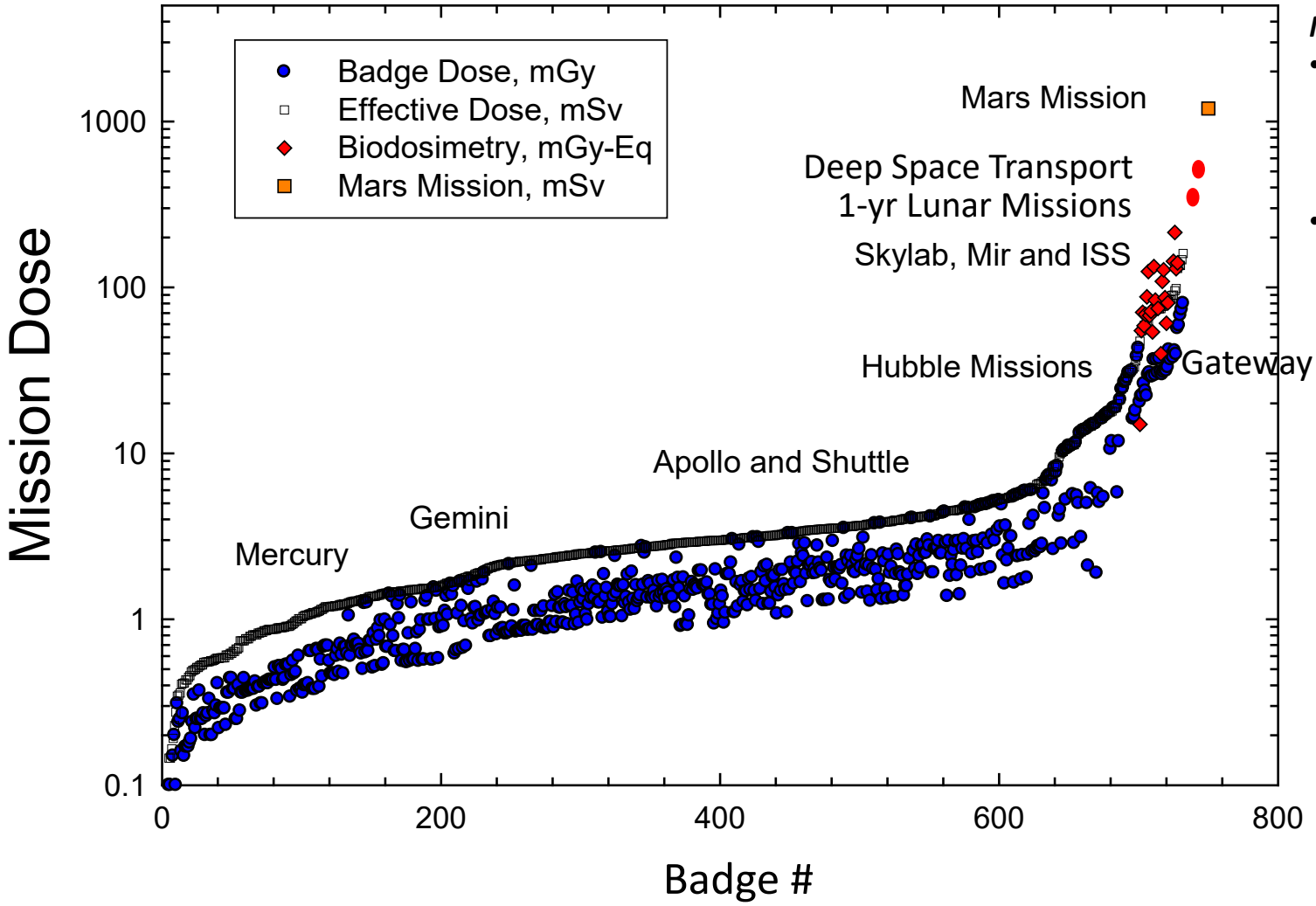
- Protection via Mars atmosphere
- Protection via planetary shielding
- Dose-rate ~ ISS
- Varying: ~0.5 months

Lunar Surface

- Protection from planetary shielding
- Dose-rate ~1.5x ISS
- Mission lengths - TBD



NASA CREW MISSION DOSES



***NASA Experience**:*

- *Single ISS mission approximately 1/10 of Mars mission exposure*
- *Many crew with multiple missions have accumulated 1/3 of Mars exposure risk*

Update from Cucinotta et al. Radiat Res (2008)

DRIVING EVIDENCE

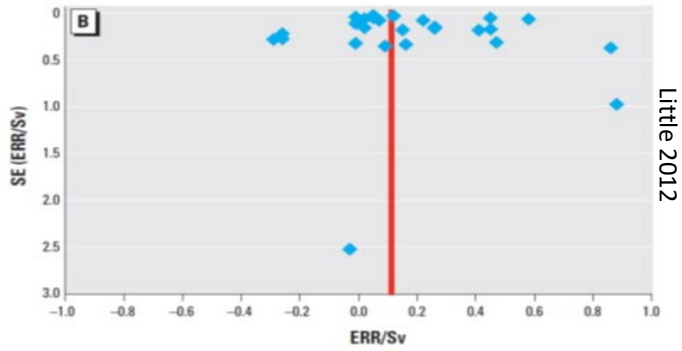
Space Relevant Doses

Exploration Mission	Dose (mGy)
ISS in LEO	30–60
ISS in LEO	60–120
Sortie to Gateway (free space)	20
Lunar Surface Mission (2 weeks on surface)	25
Sustained Lunar Operations	100–120
Deep-Space Habitat	175–220
Mars Mission	300–450

Simonsen et al. 2020. "NASA's First Ground-Based Galactic Cosmic Ray Simulator."

< 0.5 Gy

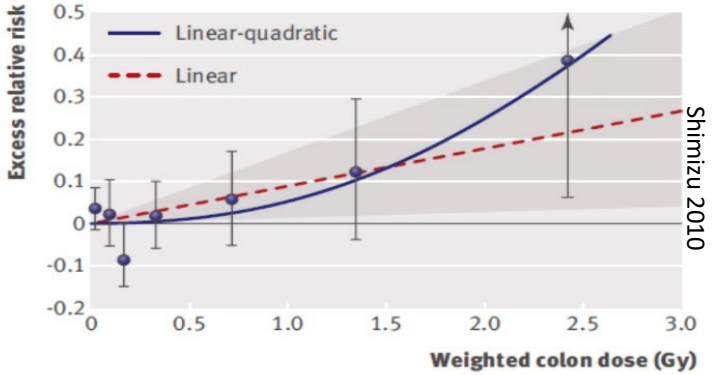
- Systemic effects?
- Non-targeted effects, kidney dysfunction, monocyte killing?



Little 2012

0.5 - 5 Gy

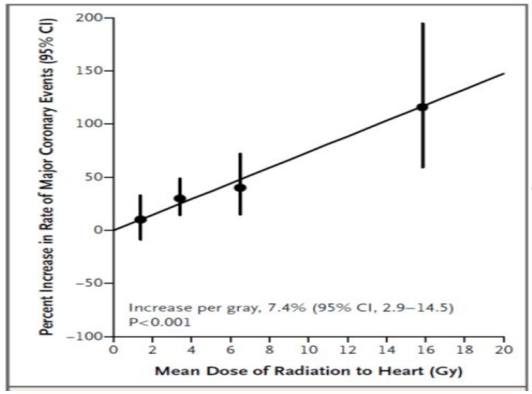
- Atherosclerosis; micro and microvasculature damage
- Endothelial dysfunction; inflammation and oxidative stress



Shimizu 2010

> 5 Gy

- Cell killing and inactivation
- Tissue damage and functional impairment



Darby 2013

CVD / LATE CNS RESEARCH STRATEGY

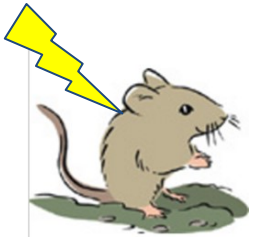
CVD → **COMMON PATHWAYS** (e.g. vascular dysfunction, inflammation, oxidative stress, metabolic dysfunction, accelerated aging) ← **Late CNS**

Traditional Risk Factors (e.g. Framingham factors, apoE, etc.)

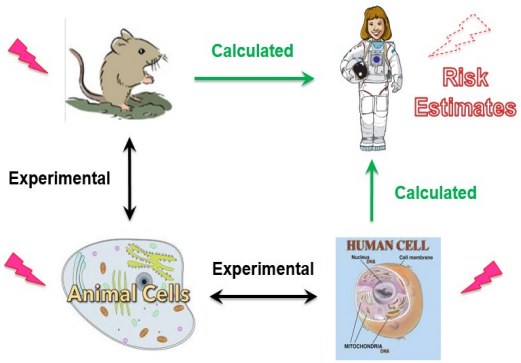
Radiation-Sensitive Disease Biomarkers (e.g. troponin, CRP, growth factors, imaging data, CAC, amyloid, cognitive tests, metabolomics/proteomics)

Clinical Standard-of-Care Practices (e.g. diet, exercise, aspirin, statins)

Human research (top-down) approach



Validation in Animals with HZE



DELIVERABLES

Recommendations for clinical guidelines with CMs, PELs, Combined Risk Model with Cancer

TRANSLATION: EARTH TO SPACE

Baseline disease rates

US Mortality, Incidence, Lifespan

Future generations & medical advances

Excess risk (relative or absolute)

TERRESTRIAL EXPOSURES

Excess risk (relative or absolute)

EXTRATERRESTRIAL EXPOSURES

NSRL GCR Simulator

Radiation Quality

Dose Rate

US Million Worker Study

Japanese Atomic Bomb Survivors

LATE CNS

Radiotherapy,
Million worker data

CVD

Radiotherapy, A-bomb,
nuclear workers

CANCER

Radiotherapy, A-bomb, nuclear workers, INWORKS

Acute Radiation Syndromes

A-bomb, accidental exposures

Levels of Evidence

ASTRONAUT COHORT DATA

TODAY'S ASTRONAUTS

- Average age is 35-55 years old with first space mission at ~ 47 years old for ISS crews
- Current corps is approximately 30% female
- Most astronauts are lifetime never-smokers.
- Healthy lifestyle factors (never-smokers, normal weight, diet)

ASTRONAUT CVD-RELATED HEALTH

Cancer incidence and mortality in the USA Astronaut Corps, 1959–2017 — 2021

Mortality of US astronauts: comparisons with professional athletes — 2019

Radiation Exposure and Mortality from Cardiovascular Disease and Cancer in Early NASA Astronauts — 2018

The Mortality of Space Explorers — 2018

The effect of competing risks on astronaut and cosmonaut mortality — 2018

Incidence Rate of Cardiovascular Disease End Points in the National Aeronautics and Space Administration Astronaut Corps — 2017

TRANSLATION: EARTH TO SPACE

Baseline disease rates

US Mortality, Incidence, Lifespan

Future generations & medical advances

Excess risk (relative or absolute)

TERRESTRIAL EXPOSURES

Excess risk (relative or absolute)

EXTRATERRESTRIAL EXPOSURES

US Million Worker Study

Japanese Atomic Bomb Survivors

Levels of Evidence

GROUND ANALOGS

NASA Space Radiation Laboratory (NSRL)

- Simulates the space radiation environment- high energy ion beams 3 “runs” per year
- Beam line, target area, dosimetry, biology labs, animal care, logistic and administrative support
- Liaison Scientists

Medical Building:

- Gamma-ray source
- Long-term labs and animal facilities
- Liaison scientists and administrative support

Example of NSRL Energy Beams and Characteristics

Beam*	Energy, MeV/u	LET, keV/µm	Range in Water, cm
protons	50-2500	1.2 - 0.21	2 to >100
^{4}He	50- 1200	5 – 0.8	2 to > 100
^{16}O	50- 1000	80 – 14	0.5 – 80
^{20}Ne	50-1000	125 – 22	0.45 – 64
^{28}Si	75-1000	179 – 44	0.66 – 46
^{37}Cl	100-1000	212 – 64	0.9 – 39
^{48}Ti	100-1000	354 – 107	0.8 – 32
^{56}Fe	100-1000	495 – 150	0.66 – 27
Solar particle event simulator	50-2000	NA	NA

NSRL Beam Line

Before final award of selected proposals, the Space Radiation Element will further review the choices of beams and doses to be used in funded research plans.

https://www.bnl.gov/nsrl/

EXPERIMENTAL DATA

Animal Data – CV Functional Outcomes

Table 1. Continued.

Reference	Models and methods	Key findings/conclusions	Radiation details
Animal/functional physiology			
Seawright et al[125]	C57BL6/J, male, TTE evaluation, 3, 5, 7, and 9 months after irradiation	^{16}O -Mild changes in cardiac function as determined by TTE ^{1}H or ^{1}H followed by ^{16}O- cardiac function did not change	^{16}O, 600 MeV/n 0, 0.05, 0.1, 0.25, or 1 Gy) ^{1}H (150 MeV, 0, 0.5, or 1 Gy), ^{1}H (150 MeV, 0.5 Gy) followed by ^{16}O (0.1 Gy).
Yan et al[130]	C57Bl/6NT mice, male, 8-10 mos. age, with/without MI, TTE evaluation	**Healthy mice** ^{1}H- Initial improvement in cardiac function @ 1 M that declines by 10 M post-irradiation. ^{56}Fe- significant decline in cardiac function @1 M and 3 M but recovery by 10 M. **MI-mice** ^{1}H prior to MI improved cardiac function restoration and enhanced cardiac remodeling. ^{56}Fe prior to MI led to poorer cardiac function and more adverse remodeling	^{1}H 0.5 Gy, 1 GeV ^{56}Fe 0.15 Gy, 1 GeV ^{1}H
Yu et al[131]	male apoE-/- mice	^{56}Fe accelerated development of atherosclerosis in irradiated portions of the aorta. Larger necrotic cores associated with greater numbers of apoptotic macrophages and reduced lesional collagen. Intima media thickening of the carotid arteries was exacerbated.	2 to 5 Gy ^{56} Fe, targeted to specific arterial sites, comparisons made to sham-irradiated mice
Sasi et al[129]	(8–9 months old) male C57BL/6NT. Subgroup underwent MI surgery 28 days post radiation Cardiac structure and function were assessed in all animals at days 7, 14 and 28 after MI surgery was performed	Healthy: No negative effect on cardiac function or structure MI: no negative effect post MI/post rad No negative effect on cardiac function or structure After MI: 24% increase in mortality, significant decrease in LV function, and 35% in infarct size Healthy: depressed LV functions at 1 month with concomitant enhancement in cardiac fibrosis and induction of cardiac hypertrophy signaling at 3 months MI: no negative effect post MI/post rad	3-fractionated doses of 17 cGy ^{1}H every other day (^{1}Hx3) 3-fractionated doses of 17 cGy ^{1}H every other day followed by 15 cGy ^{56} Fe two days after the final ^{1}H dose (^{1}Hx3 + ^{56}Fe) single low dose of 15 cGy ^{56}Fe followed (after 2 days) by three fractionated doses of 17 cGy ^{1}H every other day

Davis et al. 2021. “Consequences of space radiation on the brain and cardiovascular system.”

Table 1. Continued.

Reference	Models and methods	Key findings/conclusions	Radiation details
Sridharan et al[127]	Male Long Evans rats, ultrasonography and blood flow pulsed wave Doppler at 3, 5, 9, and 12 months post rad	No significant change in cardiac function with ^{1}H or ^{16}O (decrease in LV posterior wall thickness at 3-5 months, but no change in echocardiographic measures). Mild changes in aortic vascular function following ^{16}O.	exposed to whole-body ^{1}H (250 MeV, 0.5 Gy) or ^{16}O, 600 MeV/n, 0.5 Gy
Soucy et al[126]	Rats, pulse wave velocity, aortic ring assays	Rats exposed to 1 Gy ^{56}Fe exhibited significantly increased aortic stiffness, impaired endothelial- dependent relaxation consistent with endothelial dysfunction.	Whole body of ^{56}Fe 0, 0.5, or 1 Gy
Amino et al[132]	Rabbit, MI model, In-vivo epicardial potential mapping on the free wall	In the context of the MI model, Carbon ion a. Improved conduction b. decreases the spatial heterogeneity of repolarization c. Reversed vulnerability to ventricular arrhythmias	Carbon (5–15 Gy) targeted to heart 2 weeks after MI
Amino et al[128]	Rabbit, New Zealand White Longitudinal echocardiography (UCG) and electrocardiography (ECG) before, 2 wk., and 3, 6, and 12 mo. after 15 Gy Carbon. In vivo electrophysiological study (EPS) was performed 1 yr. after Carbon.	No significant changes in cardiac function 1 year post 15 Gy Carbon.	Targeted heavy ion radiation (5–15 Gy), carbon ions 290 MeV/u

Davis et al. 2021. “Consequences of space radiation on the brain and cardiovascular system.”

Molecular Biology Outcomes (Tissues or Cells Isolated from Irradiated Animals)

Table 1. Continued.

Reference	Models and methods	Key findings/conclusions	Radiation details
Miousse et al[140]	Male C57BL/6 J mice, heart, LV, cardiac methylome and one-carbon metabolism	Dynamic changes in cardiac epigenome and metabolome were seen as long as 90 days post ^{16}O exposure. At 14 days, 0.25 and 1 Gy ^{16}O elicited global DNA hypo- methylation in the 5′-UTR of LINE-1. At 90 days, specific LINE-1 elements were hypermethylated. Gene expression showed first a decrease followed by an increase in transcript abundance. Metabolomics analysis homocysteine remethylation, were unaffected by radiation, but the transsulfuration pathway was impacted after 90 days	0.1, 0.25, or 1 Gy of ^{16}O (600 MeV/n).
Amino et al[128]	Rabbit	Cx43 protein and mRNA significantly upregulated in the ventricular myocardium from 2 wk. up to 1 yr. All regions of the LV, RV, and septum were similarly affected in terms of Cx43 upregulation. Cx43 was present in intercalated disk region, lateral surface of ventricular myocytes, and sarcolemma.	THIR (5–15 Gy), Carbon
Amino et al[132]	New Zealand White Rabbits, MI model	THIR was associated with an increase of Cx43mRNA and protein levels in the LV in control as well as in MI rabbits. THIR also increased lateralization ofCx43, which was no longer colocalized with cadherins. In MI hearts, immunoreactive Cx43 signals were reduced in the peri-infarct zone, and the reduction was reversed byTHIR.	THIR (5–15 Gy) targeted to heart 2 weeks after MI
Seawright et al[125]	C57BL6/J, male, cardiac tissue was collected to assess apoptosis, tissue remodeling, and markers of immune cells immune cell infiltration, histology	Evidence of mild apoptosis was seen with each radiation type as well as histological evidence of cardiac tissue remodeling. Increased evidence of immune cell infiltration was seen in heart. ^{16}O was more damaging than ^{1}H and ^{1}H followed by ^{16}O was least damaging.	^{16}O, 600 MeV/n 0, 0.05, 0.1, 0.25, or 1 Gy) ^{1}H (150 MeV, 0, 0.5, or 1 Gy), ^{1}H (150 MeV, 0.5 Gy) followed by ^{16}O (0.1 Gy). ^{1}H (0.1 Gy) ^{56}Fe (0.5 Gy)
Koturbash et al[141]	C57BL/6J male mice	Cardiac DNA methylation associated with repetitive elements detected. Modest hypomethylation of retrotransposon LINE-1 was observed at day 7 after irradiation with either ^{1}H or ^{56}Fe. LINE-1, and other retrotransposons, ERV2 and SINE B1, other major satellite DNA was hypermethylated at day 90 post ^{56}Fe. Alterations in the expression of DNA methylation machinery that involve the one-carbon metabolism pathway. substantial accumulation of mRNA transcripts, associated with major satellites seen at day 90	

Davis et al. 2021. “Consequences of space radiation on the brain and cardiovascular system.”

Table 1. Continued.

Reference	Models and methods	Key findings/conclusions	Radiation details
		from 2 wk. up to 1 yr. All regions of the LV, RV, and septum were similarly affected in terms of Cx43 upregulation. Cx43 was present in intercalated disk region, lateral surface of ventricular myocytes, and sarcolemma.	
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Seawright et al[125]	C57BL6/J, male, cardiac tissue was collected to assess apoptosis, tissue remodeling, and markers of immune cells immune cell infiltration, histology	Evidence of mild apoptosis was seen with each radiation type as well as histological evidence of cardiac tissue remodeling. Increased evidence of immune cell infiltration was seen in heart. ^{16}O was more damaging than ^{1}H and ^{1}H followed by ^{16}O was least damaging.	^{16}O, 600 MeV/n 0, 0.05, 0.1, 0.25, or 1 Gy) ^{1}H (150 MeV, 0, 0.5, or 1 Gy), ^{1}H (150 MeV, 0.5 Gy) followed by ^{16}O (0.1 Gy). ^{1}H (0.1 Gy) ^{56}Fe (0.5 Gy)
Koturbash et al[141]	C57BL/6J male mice	Cardiac DNA methylation associated with repetitive elements detected. Modest hypomethylation of retrotransposon LINE-1 was observed at day 7 after irradiation with either ^{1}H or ^{56}Fe. LINE-1, and other retrotransposons, ERV2 and SINE B1, other major satellite DNA was hypermethylated at day 90 post ^{56}Fe. Alterations in the expression of DNA methylation machinery that involve the one-carbon metabolism pathway. substantial accumulation of mRNA transcripts, associated with major satellites seen at day 90	
Ramadan et al[138]	Male C57BL/6 mice at 10 weeks of age, examined selected proteins	^{56}Fe caused an increase in expression of α-smooth muscle cell actin, collagen type III, the inflammatory cell markers mast cell tryptase, CD2 and CD68, the endothelial glycoprotein thrombomodulin, and cleaved caspase 3. ^{1}H induced a small increase only in cleaved caspase 3 levels. Exposure to ^{1}H 24 hours before ^{56}Fe prevented all of the responses to ^{56}Fe. low dose of ^{1}H may prime the heart to respond differently to a subsequent challenge dose of heavy ions	Sham-irradiation, 0.1 Gy of ^{1}H (150 MeV), 0.5 Gy of ^{56}Fe (600 MeV/n), or 0.1 Gy of ^{1}H 24 hours prior to 0.5 Gy of ^{56}Fe.

Davis et al. 2021. “Consequences of space radiation on the brain and cardiovascular system.”

Table 1. Continued.

Reference	Models and methods	Key findings/conclusions	Radiation details
Beheshti et al[142]	Cardiomyocytes from male C57BL/6 mice followed-up for 28 days human endothelial cells (HUVECs) cultured for 7 days on the International Space Station (ISS). Bioinformatics comparison of mouse cells on ground versus cells in space Re-analysis of Coleman et al[158]	Common molecular pathways (FYN being central driver/hub) between simulated space radiation and HUVECs flown on the ISS were found. Known oxidative stress induced immediately following radiation would only be transient and would upregulate FYN, which in turn would reduce reactive oxygen species (ROS) levels, protecting the cardiovascular system. The transcriptomic signature of exposure to ^{1}H was closer to the spaceflight signature than ^{56}Fe signature.	900 mGy of 1 GeV ^{1}H 150 mGy of 1 GeV/n ^{56}Fe
Tungjai et al[139]	Male CBA/CaJ mice measured selected proteins in heart and bone marrow: cleaved poly (ADP-ribose) polymerase (cleaved PARP, activated nuclear factor-kappa B (NF-KB) and selected NF-KB-regulated cytokines	Up to 6 months post-radiation, cell death and inflammatory responses in tissues from the heart and BM from exposed mice were statistically higher than those in sham controls. Overall suggestive of chronic apoptotic cell death and inflammation	Whole body exposure. 0, 0.1, 0.25, or 0.5 Gy of 300 MeV/nucleon ^{28}Si (two exposures, 15 days apart
Sridharan et al[127]	Tissues from male Long Evans rats	No significant changes in histopathology or histological quantification of total collagens in heart or aorta. an increase in a 75 kDa peptide of collagen type III in LV of exposed to ^{1}H and ^{16}O ^{16}O caused increases in left ventricular protein levels of immune cell markers CD2, CD4, CD8, and CD68.	exposed to whole-body ^{1}H (250 MeV, 0.5 Gy) or ^{16}O, 600 MeV/n, 0.5 Gy or ^{16}O (600 MeV/n and 1 GeV/n)
Coleman et al[158]	Cardiomyocytes from mice exposed to radiation. Re-analyzed in Beheshti et al[142]	Molecular responses and gene expression to ^{56} Fe are unique and long lasting. ^{56}Fe showing the greatest level of gene modulation. ^{1}H little differential transcript modulation. Major networks affected cell cycle, oxidative responses, and transcriptional regulation functional groups. Key nodes regulating expression. ^{56} Fe regulates ERK1/2, p38 MAPK, NFATc4, GATA4, STAT3, and NF-KB	90 cGy, 1 GeV ^{1}H 15 cGy, 1 GeV/^{56} Fe 28 days after exposure.
Yan et al[130]	C57Bl/6NT male, with/without MI Western blot for proteins in key pathways	^{1}H- increased pro-survival factors in cardiac tissues long term ^{56}Fe decreased angiogenesis and pro-survival factors in cardiac tissues long term	^{1}H 0.5 Gy, 1 GeV ^{56}Fe 0.15 Gy, 1 GeV

Davis et al. 2021. “Consequences of space radiation on the brain and cardiovascular system.”

Cell Culture Data

Table 1. Continued.

Reference	Models and methods	Key findings/conclusions	Radiation details
Cultured cells			
Heselich et al[134]	Avian cardiomyocyte cultures, electrophysiology	Capacity to repair induced DNA damage within 24 h up to 7 Gy complete recovery in proliferative behavior. no significant effects on apoptosis beat rate remained more or less unaffected	Ti, ^{56}Fe, C up to 7 Gy
Beck et al[136]	Human endothelial cell line (EA.hy926) DNA damage 2 and 24 h following irradiation by γ-H2AX foci. gene expression changes (microarrays at 8 and 24 h post-radiation)	Persistent DNA damage response up to 24 h after treatment. downregulation of genes involved in cell cycle regulation Upregulation of genes involved in cell cycle checkpoint, DNA damage response, oxidative stress, apoptosis and cell-cell signaling(cytokines) E2F and NFκB may be involved	(Ni) (LET, 183 keV/ μm) 0.5, 2 and 5 Gy.
Baselet et al[135]	ECs (human coronary artery) transduced with retroviruses bearing the est2 gene proteomics transcriptomics cytokine analysis evaluated 1 and 7 days post rad	Cell cycle, cell adhesion, and caveolar mediated endocytosis signaling affected in time and radiation type dependent manner. Transcriptome and proteome was more pronounced and longer lasting for ^{56}Fe ions than for X-rays ^{56}Fe and X-Ray decreased the expression of genes involved in cell-cell adhesion and enhanced the expression of proteins involved in caveolar mediated endocytosis signaling.	2 Gy of X-ray ^{56}Fe ions (1 GeV/u, 155 keV/μm)
Grabham et al[137]	3D human vessel model created with human endothelial cells in a gel matrix	^{56}Fe more damaging than ^{1}H. ^{56}Fe- significant reduction in the length of intact vessels in both developing and mature vessels ^{1}H-no effect on mature vessels but inhibited vessel formation Inhibition of vessel development or deterioration of mature vessels was not due to apoptosis	low-LET ^{1}H and high-LET ^{56}Fe

Davis et al. 2021. “Consequences of space radiation on the brain and cardiovascular system.”

Long-Term Effects of Very Low Dose Particle Radiation on Gene Expression in the Heart: Degenerative Disease Risks

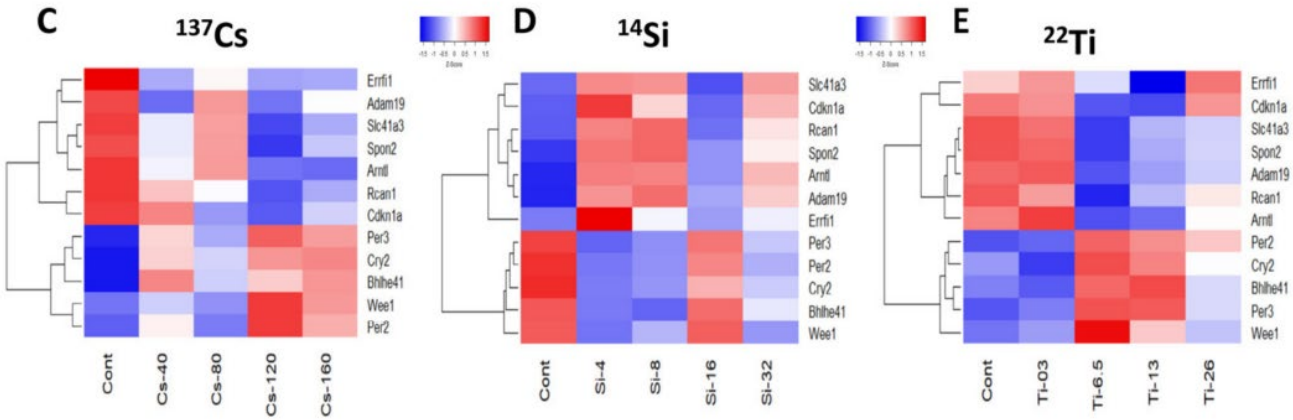
Venkata Naga Srikanth Garikipati [1], Arsen Arakelyan [2,3], Eleanor A. Blakely [4], Polly Y. Chang [5], May M. Truongcao [6], Maria Cimini [6], Vandana Malaredy [6], Anamika Bajpai [6], Sankar Addya [7], Malik Bisserier [8], Agnieszka Brojakowska [8], Abrisham Eskandari [8], Mary K. Khlgatian [8], Lahouaria Hadri [8], Kenneth M. Fish [8], Raj Kishore [6] and David A. Goukassian [8,*]

Tissue Sharing:

- 3-4 months old
- CB6F1/Hsdmice
- Female
- T= 16-months post-exposure
- Hearts harvested and archived

Table 1. Ionizing radiation types. Beam energies, doses, and LET used in this study.

Ion	Dose (cGy)	Energy (MeV/n)	Entrance LET (keV/μ)
^{137}Cs	0 40 80 120 160	0.662	0.8
^{14}Si	0 4 8 16 32	260	70
^{22}Ti	0 3 6.5 13 26	1000	100



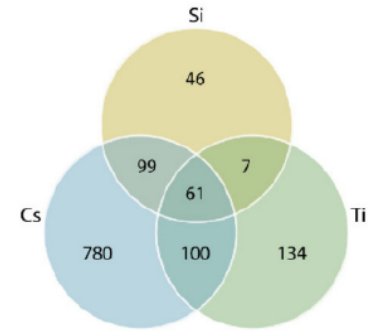
Garikipati et al. 2021. "Long-Term Effects of Very Low Dose Particle Radiation on Gene Expression in the Heart: Degenerative Disease Risks."

Results:

Table 5. Intracellular pathways involvement of 12 overlapping differentially expressed genes.

	Spon2	Adam19	Arntl	Cdkn1a	Cry2	Per2	Per3	Wee1	Rcan1	Slc41a3	Errfi1	Bhlhe41
Circadian rhythm			+		+	+	+					+
ErbB signaling pathway				+								
HIF-1 signaling pathway				+								
FoxO signaling pathway				+								
Cell cycle, circadian regulated				+				+				
p53 signaling pathway				+								
PI3K-Akt signaling pathway				+								
Cellular senescence				+								
JAK-STAT signaling pathway				+								
Oxytocin signaling pathway				+					+			
Transcriptional misregulation in cancer				+		+						
Circadian entrainment						+	+					
Acute myeloid leukemia						+						
Human Immuno-deficiency virus 1 infection								+				
Thyroid hormone signaling pathway									+			

A



B

N	Term
1	Abnormal circadian rhythm
2	Colon cancer DOID-219 mouse GSE63032 sample 662
3	Hutchinson-Gilford progeria syndrome UMLS CUI-C0033300 mouse GSE32609
4	acute myocardial infarction DOID-9408 mouse GSE775 sample 1003
5	Type 1 diabetes mellitus C0011854 mouse GSE1623 sample 53
6	Mouse liver 6 months vs 26 months GSE20426 aging:374
7	Mouse liver 6 months vs 26 months GSE20425 aging:366
8	Mouse peripheral adipocyte 6 months vs 14 months GSE25905 aging:297
9	Mouse bone marrow adipocyte 14 months vs 18 months GSE25905 aging:296
10	Mouse liver 6 months vs 26 months GSE20425 aging:372
11	Mouse cardiacventricle 4 months vs 25 months GSE12480 aging:149
12	Mouse hippocampus 3 months vs 18 months GSE29075 aging:274
13	Interleukin-1; human fibroblast GDS4539 ligand:208
14	17 beta-estradiol mouse uterus GDS1058 ligand:31
15	Circadian clock system Homo sapiens P00015
16	Meprobamate BOSS
17	Exercise-induced Circadian Regulation WP544
18	Circadian rhythm

→ Lower doses of HZE ions do cause differential gene expression

→ Still, no clear dose threshold detected in this analyses

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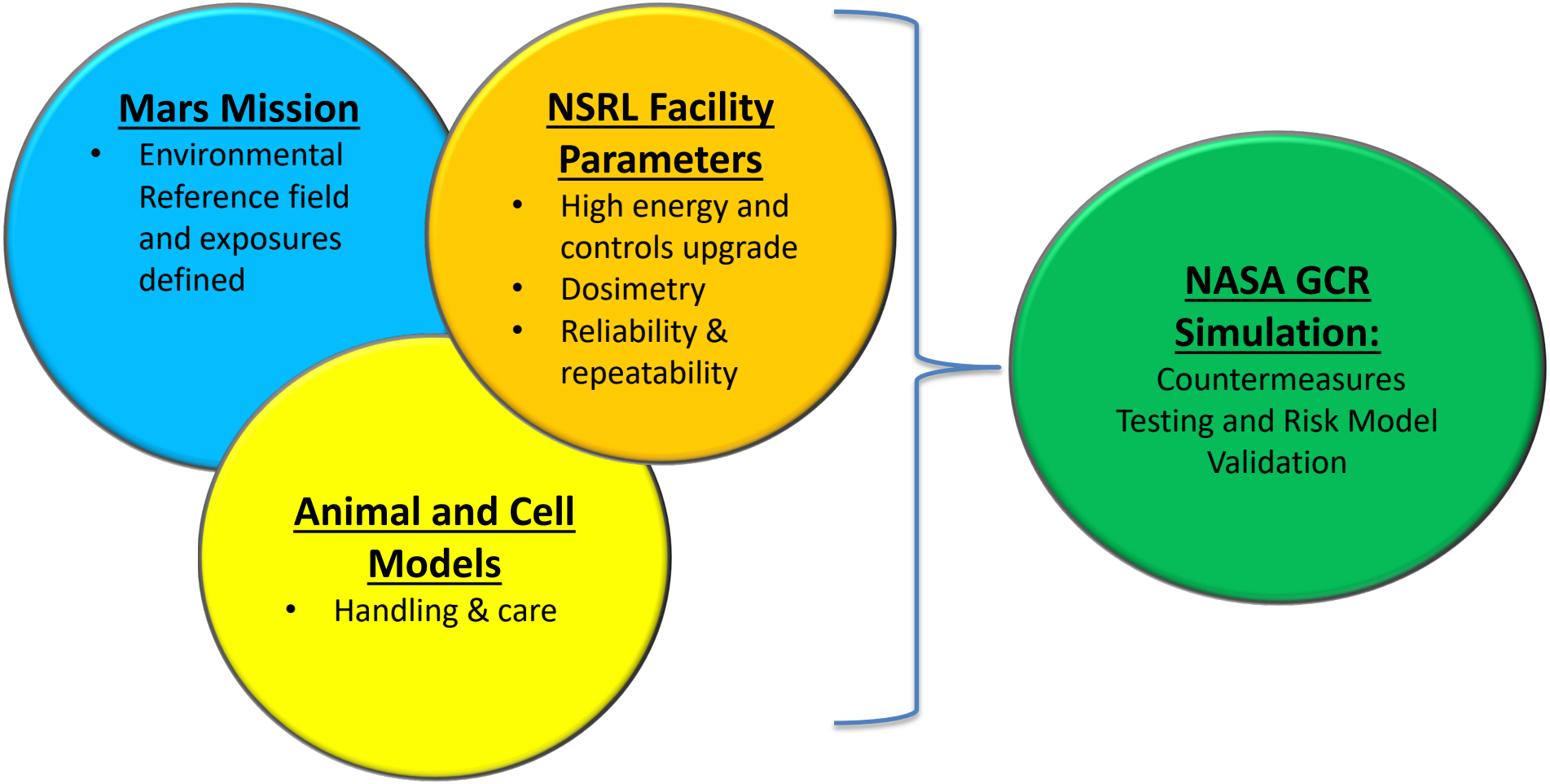
EXPLORATION MISSIONS - GCR SIMULATION

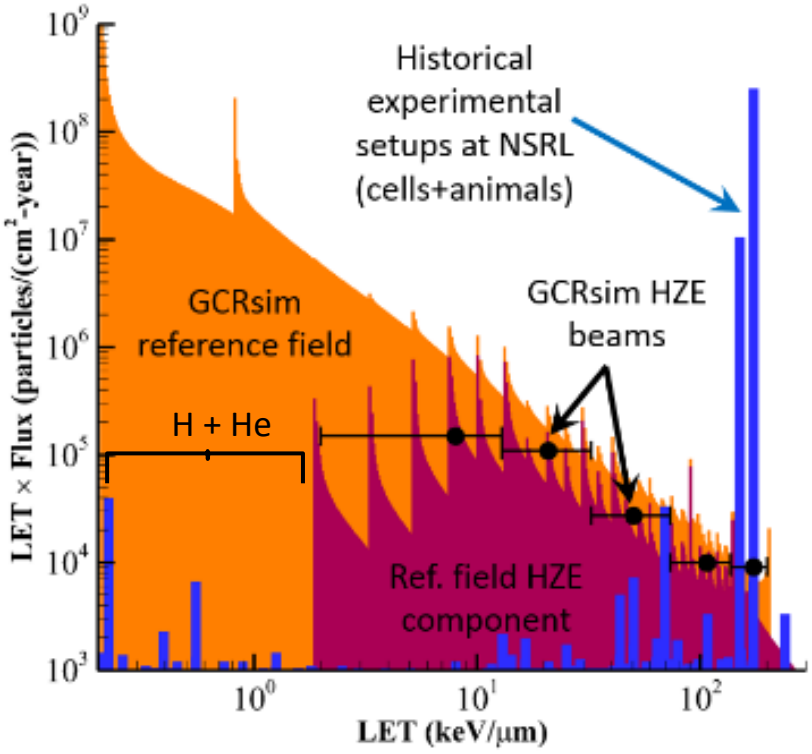
NSRL Deep Space Radiation Simulation Challenges

- Delivery of Mixed Ion Species to approximate environmental data
- Dose-Rate and Duration to better simulate deep space environment
- Translation to Humans – Appropriate Animal or Cell Models to address health risks

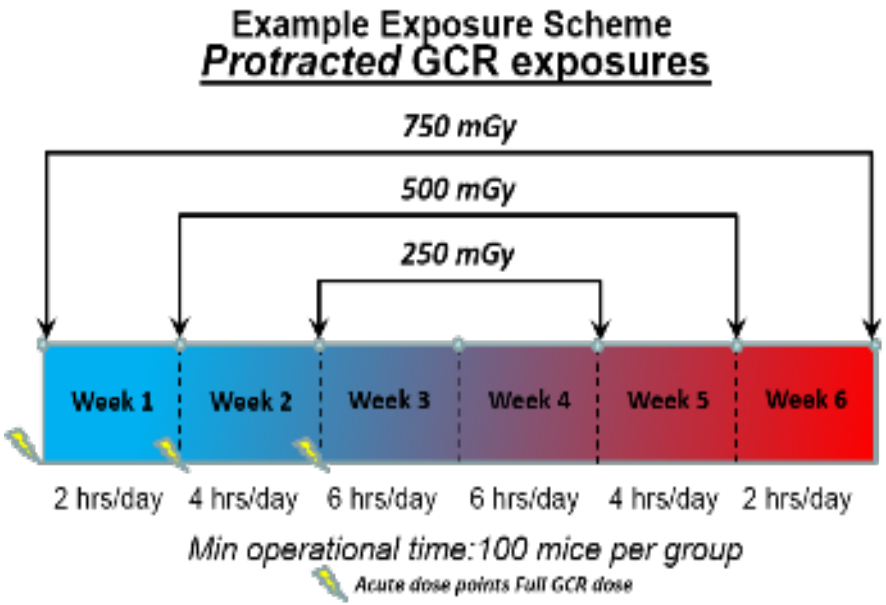


NASA GCR SIMULATOR

Standardized GCR Simulation at NSRL



Systematic Approach to Testing Dose-Rate Effects



GCR Simulation Beam consists of:

- 5 proton energies plus degrader
- 5 helium energies plus degrader
- 5 Heavy ions: C, O, Si, Ti, Fe

Chronic exposure over 2-6 weeks:

- Full GCRsim ~30 ion beams delivered daily
- Beam delivered 6 days per week to allow for contingencies
- Protons, Alpha, HZE – repeat

NASA GCR SIMULATOR

Table 3. "NSRL GCR Simulation" beam definition normalized to 500 mGy.

Primary ion-energy beam combinations in GCR simulator				Dose (mGy)	Fractionated dose- 24 exposures (mGy/day)
Ion	E (MeV/n)	LET (keV/ μm)	Range (cm)		
^{1}H	20–100	Polyethylene degrader to lower energies		140.6	5.86
^{1}H	150	0.54	15.9	35	1.46
^{1}H	250	0.39	38.1	68.9	2.87
^{1}H	1,000	0.22	326.6	123.6	5.15
^{4}He	20–100	Polyethylene degrader to lower energies		39.6	1.65
^{4}He	150	2.17	16	7.5	0.31
^{4}He	250	1.56	38.3	16.4	0.68
^{4}He	1,000	0.88	327.8	24.9	1.04
^{12}C	1,000	7.95	110.13	11.7	0.49
^{16}O	350	20.8	16.95	15.4	0.64
^{28}Si	600	50.2	22.73	8.1	0.34
^{48}Ti	1,000	109.5	32.53	4.5	0.19
^{56}Fe	600	175.1	13.09	4.1	0.17
			Total	500	20.8

Table 6. Simplified 5-ion mixed field normalized to 500 mGy. **20-25 mins.**

Ion species	Energy (MeV/n)	LET (keV/ μm)	Range (cm)	Dose (mGy)	Percent contribution to total dose (%)	delivery order	Fractionated dose- 24 exposures (mGy/day)
^{1}H	1,000	0.2	326.6	174.1	35	1	7.3
^{28}Si	600	50.4	22.7	5.7	1	2	0.2
^{4}He	250	1.6	38.3	90.2	18	3	3.8
^{16}O	350	20.9	16.9	29.1	6	4	1.2
^{56}Fe	600	173.8	13.1	5.1	1	5	0.2
^{1}H	250	0.4	38.1	195.9	39	6	8.2
			total	500.0			20.8

Abbreviations: LET, linear energy transfer

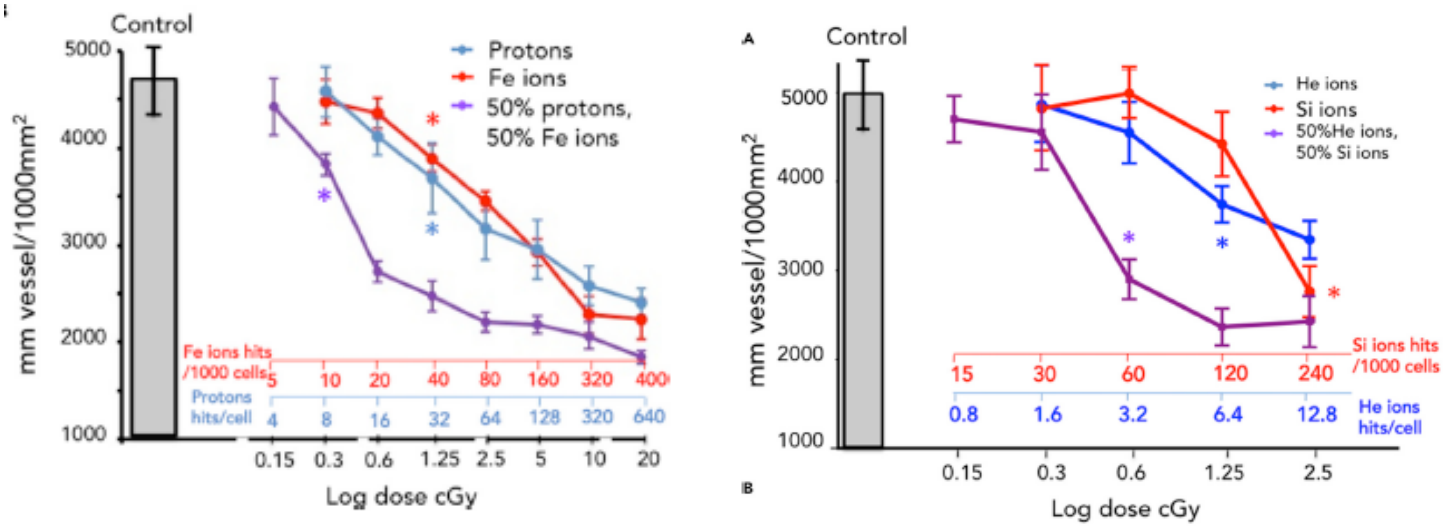
"simGCRsim"

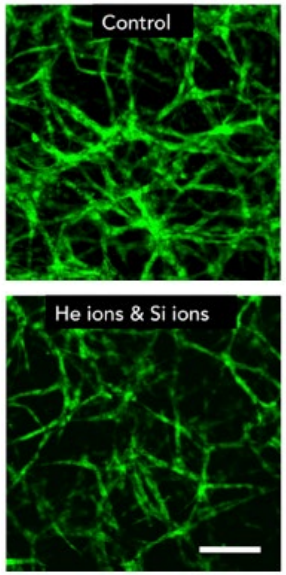
Simonsen et al. (2020), "NASA's First Ground-Based Galactic Cosmic Ray Simulator."

LET-Dependent Low Dose and Synergistic Inhibition of Human Angiogenesis by Charged Particles: Validation of miRNAs that Drive Inhibition

Yen-Ruh Wuu,[1] Burong Hu,[2] Hazeem Okunola,[3] Amber M. Paul,[4,5] Elizabeth A. Blaber,[5,6] Margareth Cheng-Campbell,[5,6] Afshin Beheshti,[7,*] and Peter Grabham[3,8,*]

In Vitro **Cell Culture Experiment Results**:



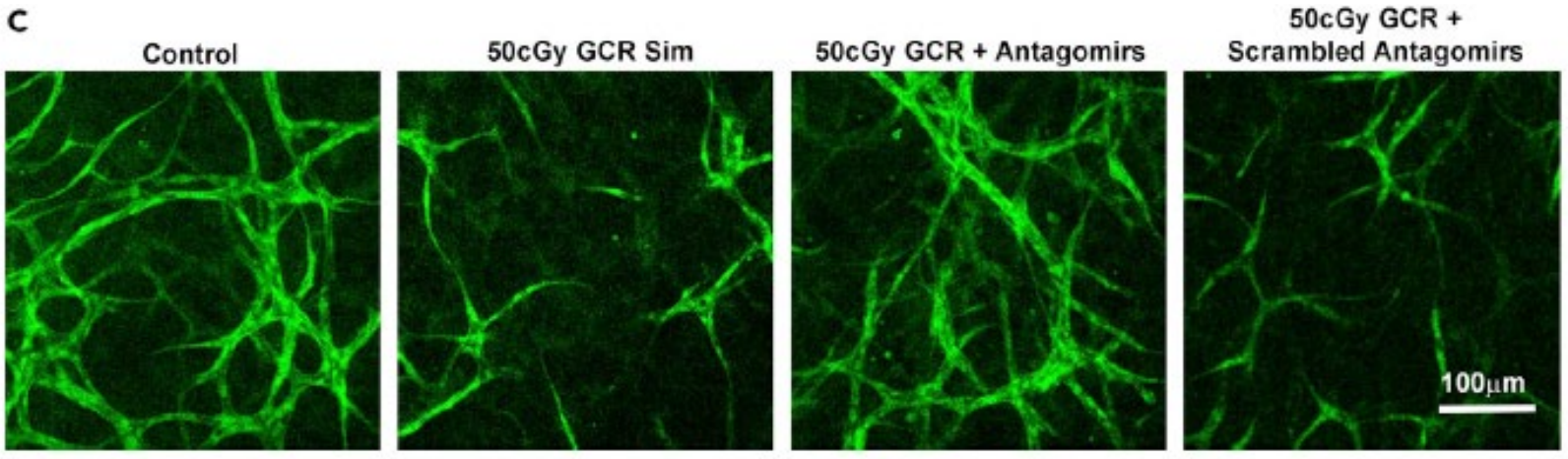


→ Angiogenesis inhibited in vitro with mixed beams of HZE ions

Wuu et al. 2020. "LET-Dependent Low Dose and Synergistic Inhibition of Human Angiogenesis by Charged Particles: Validation of miRNAs that Drive Inhibition."

In Vivo Experiment Results:

Experimental Models: Organisms/Strains		
C57Bl/6J Wt female mice	Jackson Laboratories	000664
Simplified 5-ion GCR Siulation	Protons at 1000 MeV, ^{28}Si at 600 MeV/n, ^{4}He at 250 MeV/n, ^{16}O at 350 MeV/n, ^{56}Fe at 600 MeV/n, and protons at 250 MeV	n/a

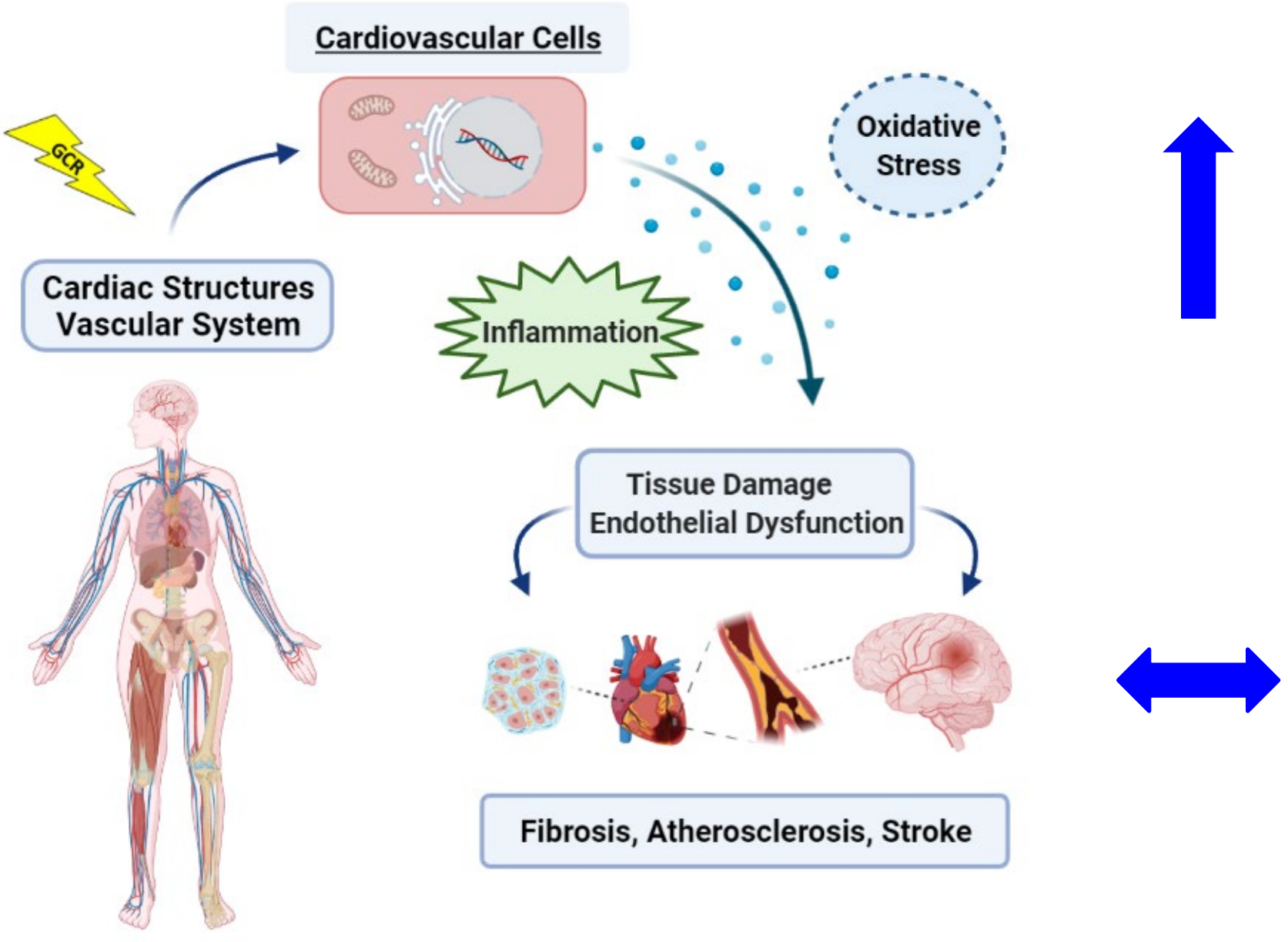


→ Angiogenesis pathways (miRNA) are disrupted / inhibited in vivo after simGCRsim irradiation

→ This may be reversed with miRNA inhibitors

Wuu et al. 2020. "LET-Dependent Low Dose and Synergistic Inhibition of Human Angiogenesis by Charged Particles: Validation of miRNAs that Drive Inhibition."

SR CVD RESEARCH SUMMARY

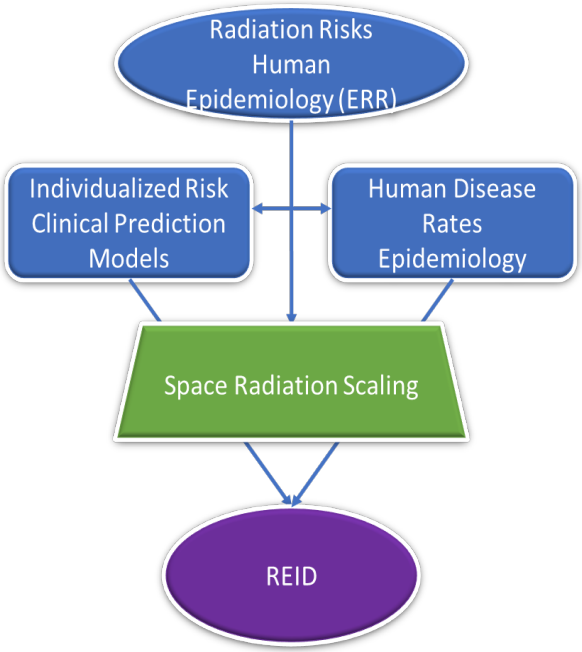


SR-CVD: FOCUS AREAS FOR RESEARCH

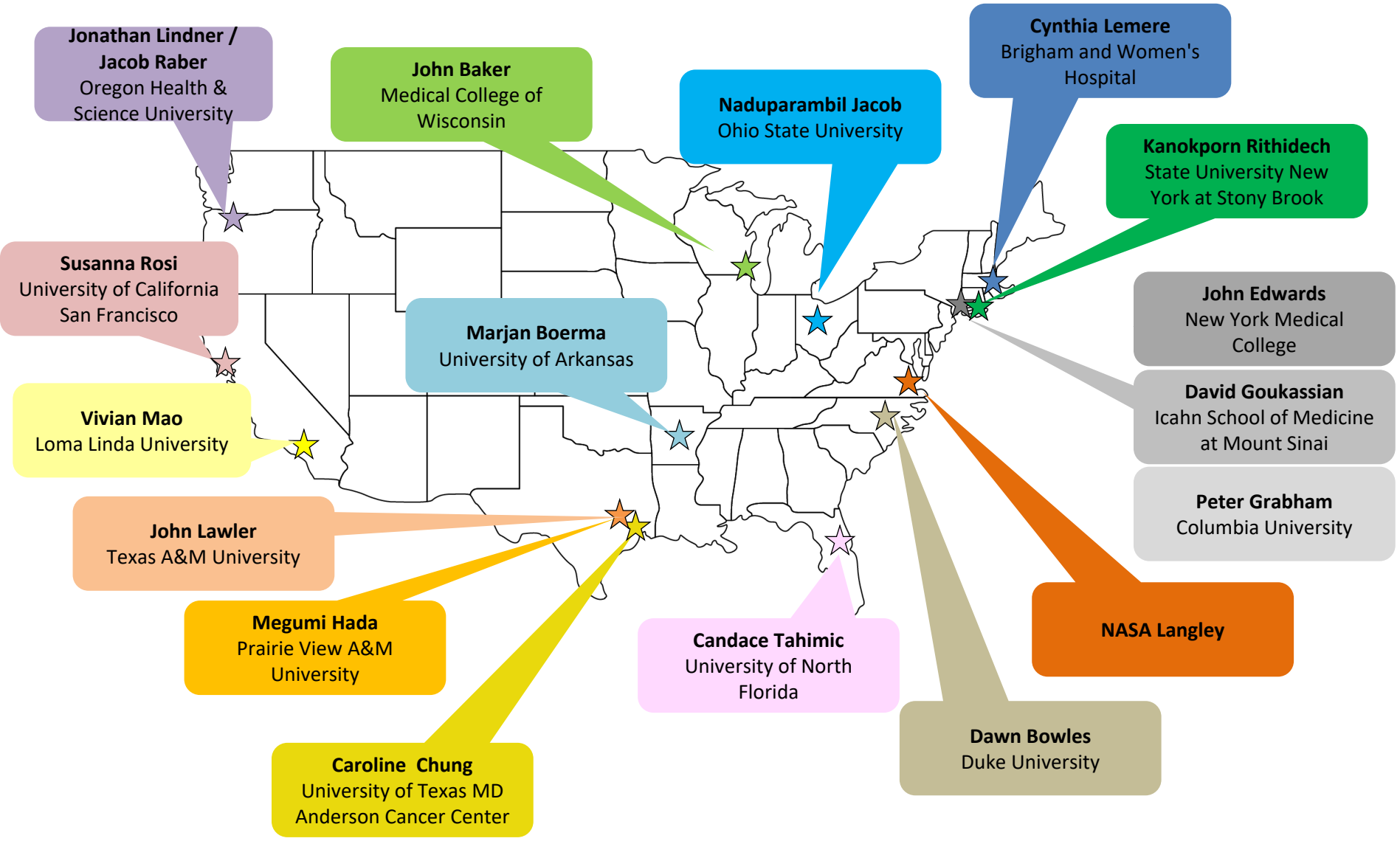
→ Overall, there is still a paucity of experimental data related to space radiation-induced CVD at low-to-moderate doses:

- Identify **disease spectrum and latency** for low dose heavy ions
- Establish **dose thresholds** for heavy ions and mixed fields
- Evaluate **qualitative differences** between GCR and gamma-rays to establish RBEs
- Evaluate effect of **dose-rate**
- Identify and validate **surrogate biomarkers** for radiation-induced disease endpoints
- Evaluate **medical countermeasures** for risk mitigation
- Address impact of **individual sensitivity**, **gender**, and **other spaceflight stressors** on risk levels

Astronaut Risk Assessment & Modeling

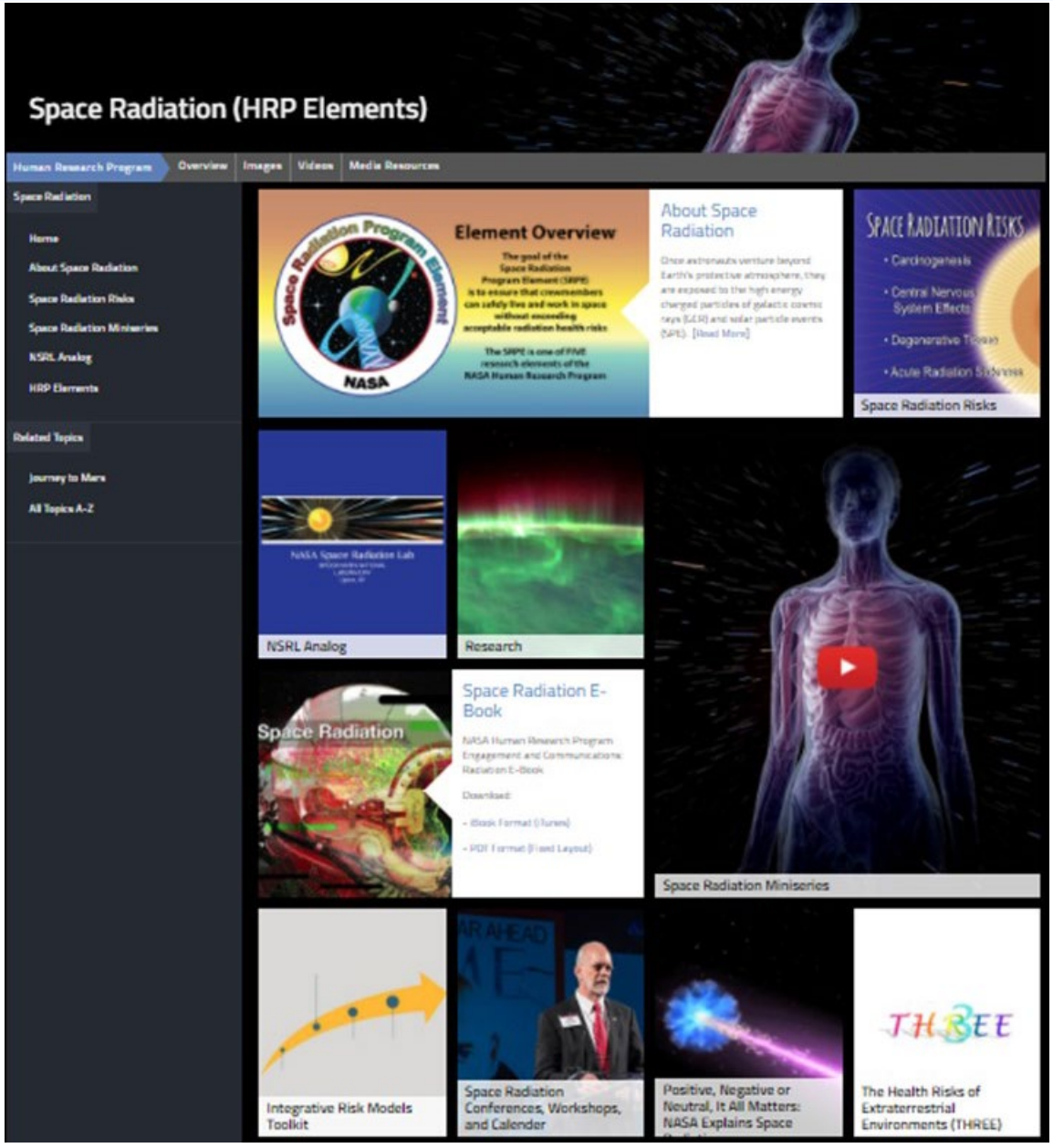


SR CVD INVESTIGATORS



RESOURCES

https://www.nasa.gov/hrp/elements/radiation



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A cluster of massive stars NGC 3603 seen with the Hubble Space Telescope.
Credits: NASA/U. Virginia/INAF, Bologna, Italy/USRA/Ames/STScI/AURA