Space Radiation Countermeasure Research Plan

National Aeronautics and Space Administration

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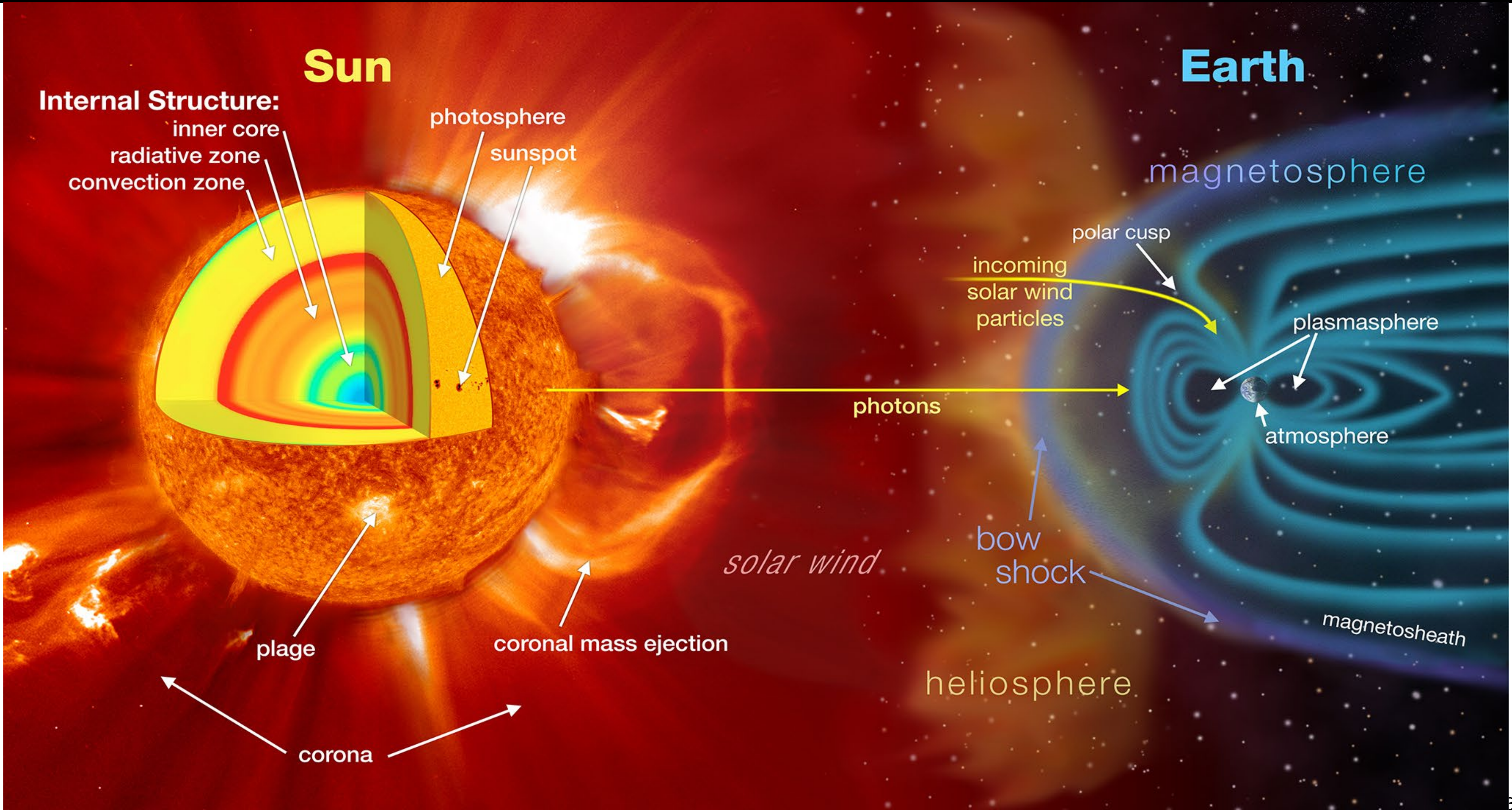
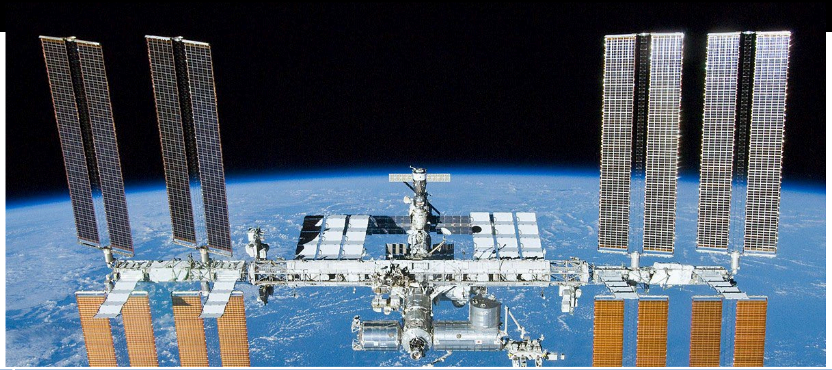
Overview

1. **Space radiation background overview**
2. Current Evidence of Space Radiation-induced Effects
    a) Cancer
    b) Cardiovascular (CV)
    c) Central Nervous System (CNS)
    d) Past Drug Experiments
3. Overall Research Strategy
    A. Research Emphases
        a) Research, Techniques, and Tools
        b) Sequence of Tasks
    B. Deliverables & Risk Buy Down
4. Collaborations, Stakeholders and Customers Integration

Low Earth Orbit Environment

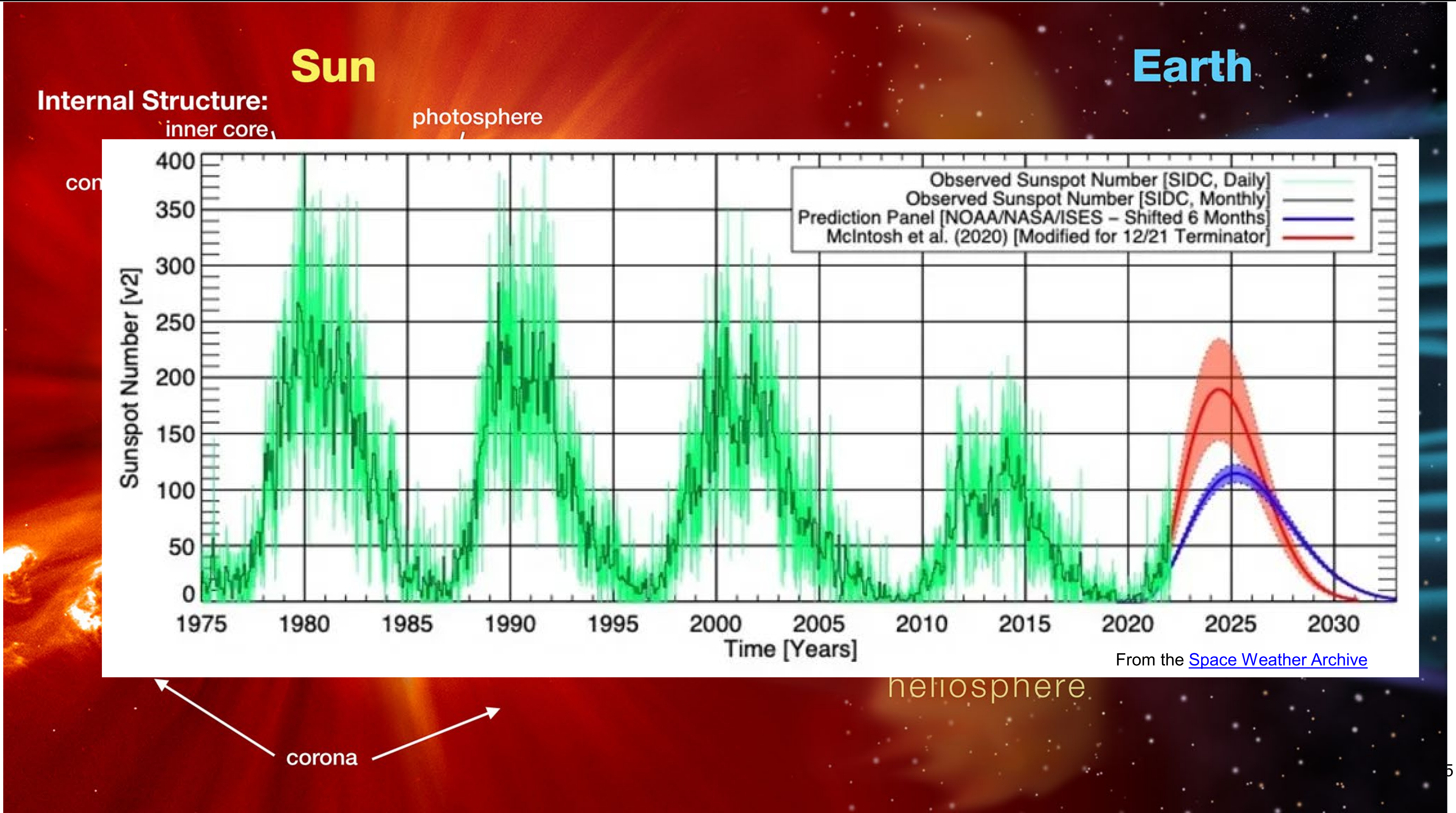


What's out there? The Space Radiation Environment



Exposure Type	ISS (51.6° inclination)	Beyond Low Earth Orbit (LEO)
Galactic Cosmic Rays (GCR)	• **Limited to polar regions** • Fractionated low dose-rate • ~ 87% protons, 12% Helium, 1% High charge and Energy (HZE)	• **Continuous** • Chronic low dose-rate • ~ 87% protons, 12% Helium, 1% HZE
Trapped Radiation	• **South Atlantic Anomaly (SAA)** • Fractionated low dose-rate • Protons	• **Transit through Van Allen Belts** • Quasi-acute • Protons
Solar Particle Events (SPEs)	• **Limited to polar regions** • Fractionated low dose-rate • Protons	• **Full Event** • Quasi-acute • Protons
Neutrons, Secondary Radiation	• Shielding affects Secondary Radiation • Chronic low dose-rate	• Shielding affects Secondary Radiation • **Planetary (albedo)** • Chronic low dose-rate

Space Weather



From the Space Weather Archive

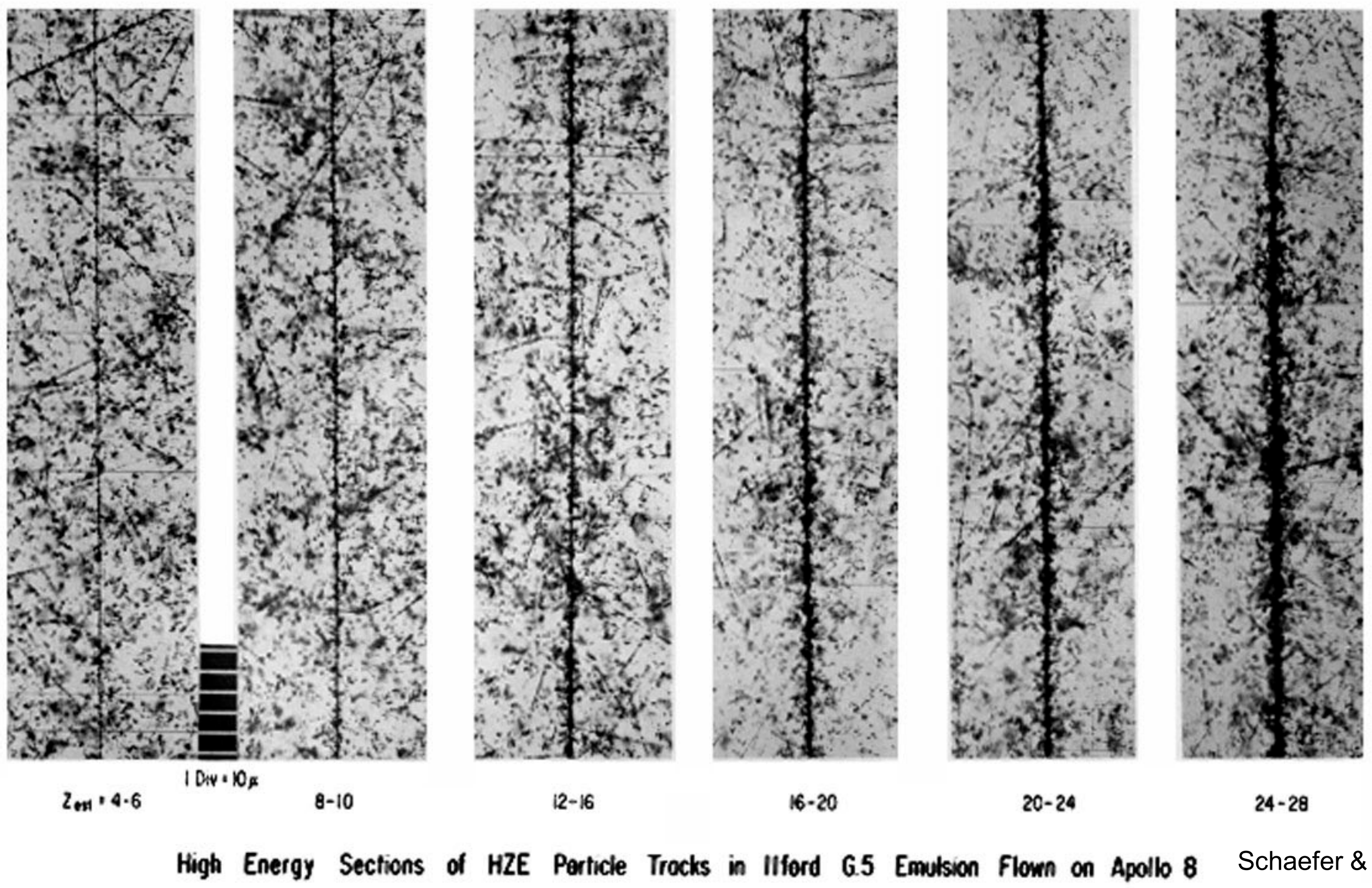
Beyond Low Earth Orbit (BLEO) Exposure

Space radiation is complex and unlike terrestrial radiation

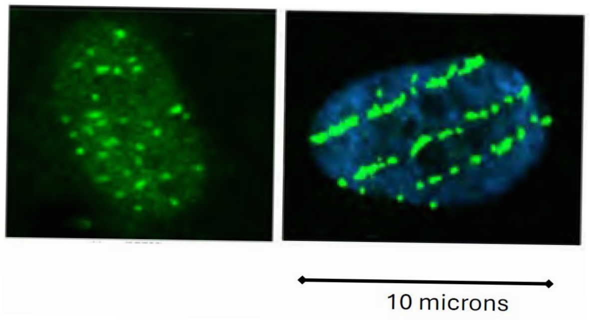
- High energy, fully ionized particles
  - ✓ Deposit energy along tracks quantified by linear energy transfer (LET)
  - ✓ Ionization density depends on LET and charge (Z)

GCR composition

- 87% protons
- 12% helium
- 1% High charge & energy (HZE) ions Z > 2

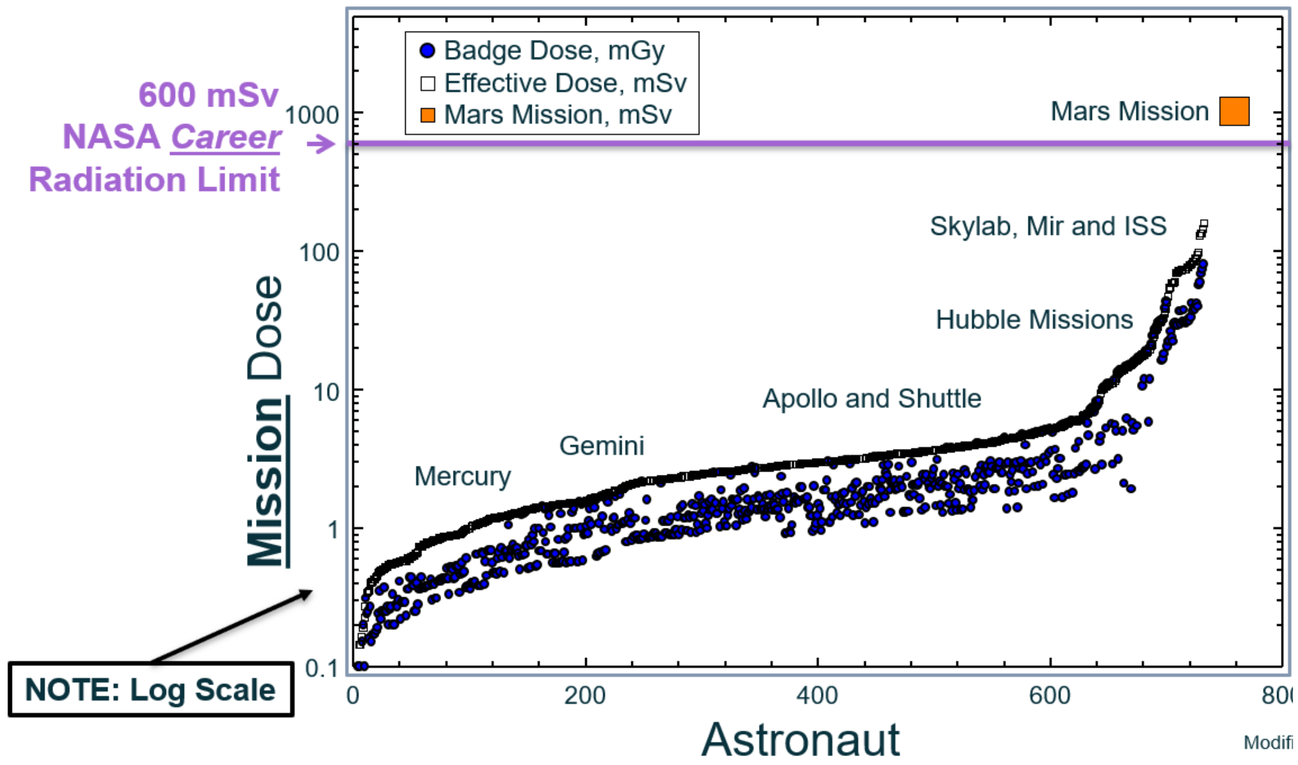


Schaefer & Sullivan, 1976

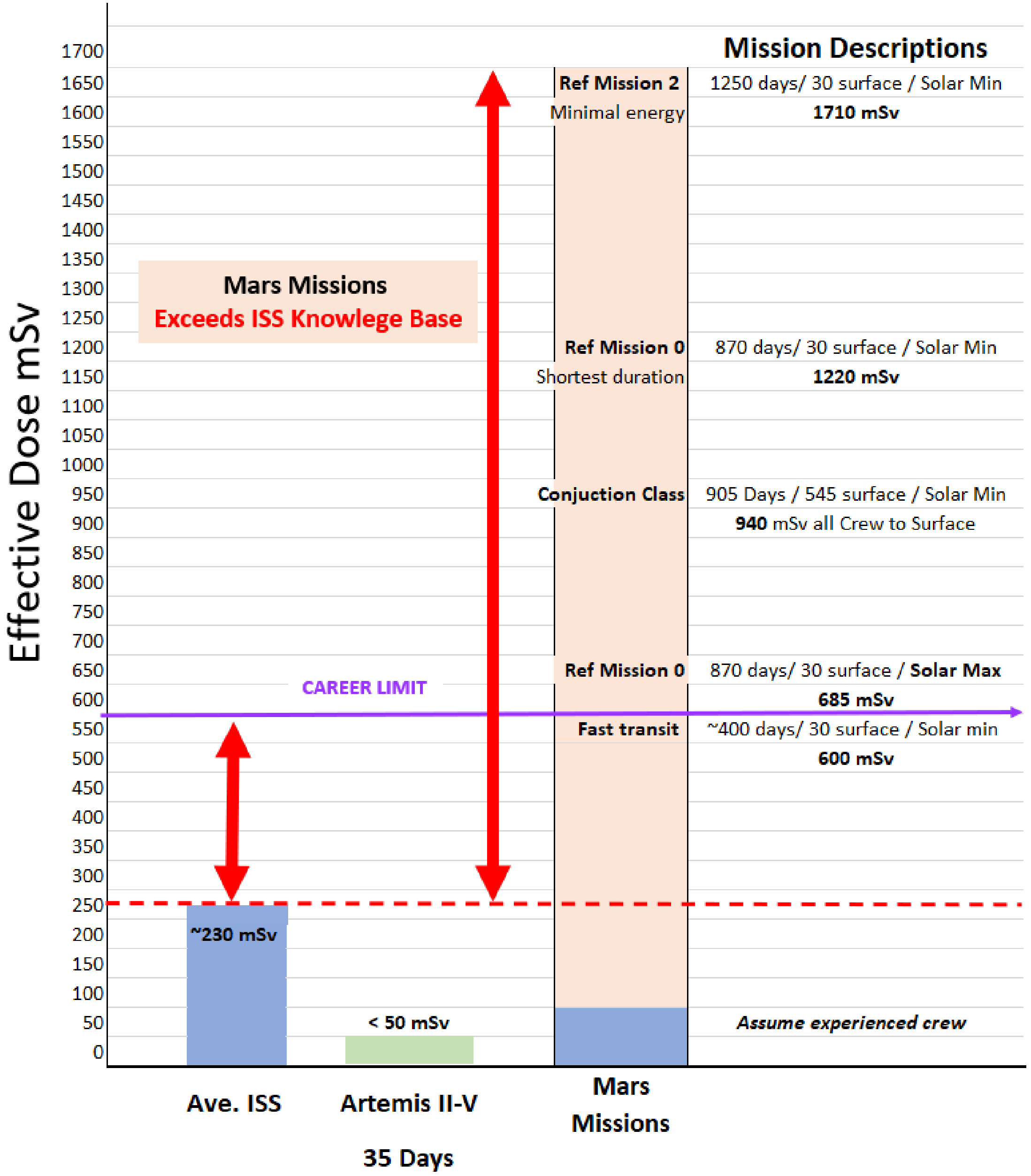


Cucinotta and Durante, *Lancet Oncology*, 1976

Historical and Future NASA Crew Mission Doses



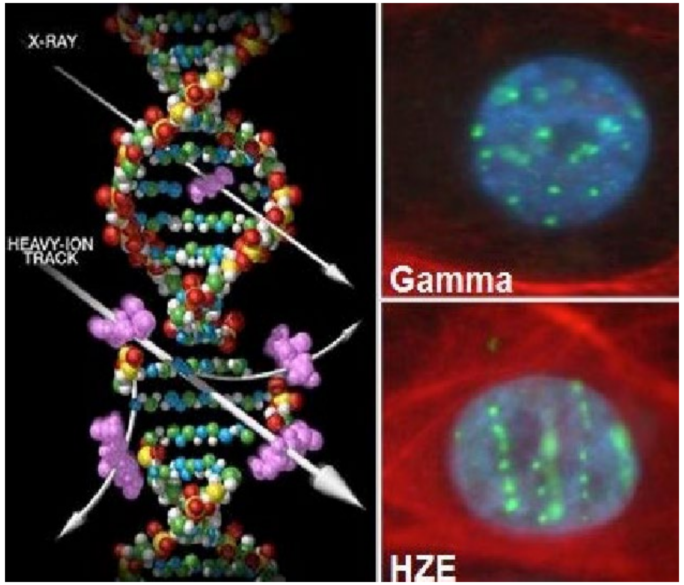
Mission	Exposure mSv
Earth Rad Worker / lifetime	20
ISS Experience	230
Artemis II-V	50
Long Duration Increments /Cislunar	500
Mars Demo Mission	1650



Space Radiation Health Risks

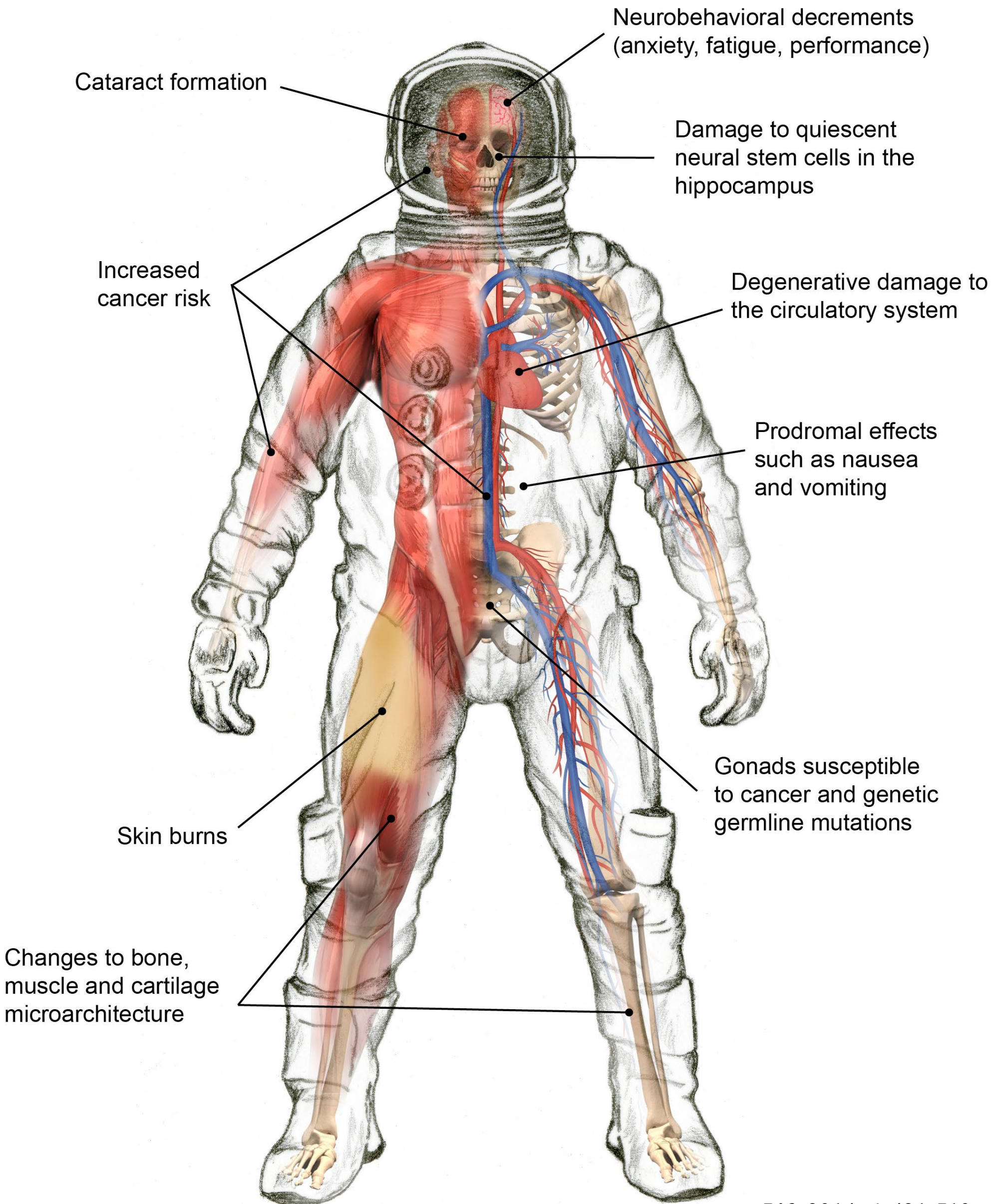
Major Risks:

- **Radiation Carcinogenesis** (long-term health)
- **Central Nervous System Effects** – in-flight and post mission
- **Degenerative Diseases** – cardiac and vascular (Long-term health), ~~cataracts~~
- ~~Acute Radiation Syndrome~~



DNA Damage in Cells: Space radiation (HZE) dense ionizing particle track

GCR composition
- 87% protons
- 12% helium
- 1% High charge & energy (HZE) ions Z>2



Life 2014, *4*, 491-510

The Space Radiation Protection Challenge

Traditional terrestrial protection strategies fall short in space:

- Time
  - At some point you will always reach a limit
- Distance
  - There is no point source to move away from
- Shielding
  - Energetic particles are penetrating
  - Secondary particles

NASA is exploring other protection strategies:

- Individualized risk characterization
- Health surveillance including early disease detection
- Compound-based countermeasures
  - Biomarkers

- **Each crew member is badged**
- **Active radiation area monitoring**

Background and Justification – NASA Requirements Document

NASA STD 3001 Vol. I

4.8.1 As Low as Reasonably Achievable (ALARA) Principle

All crewmember radiation exposures shall be minimized using the ALARA principle.

4.8.2 Career Space Permissible Exposure Limit for Spaceflight Radiation

An individual crewmember's total career effective radiation dose due to spaceflight radiation exposure shall be less than **600 mSv**. This limit is universal for all ages and sexes

Radiation Countermeasures Gap – ESDMD #0308

- 0308-02: Radiation risk models for crew health and performance
- **0308-03: Biomedical countermeasures to mitigate health effects from exposure to space radiation**
- **0308-04: Galactic Cosmic Radiation (GCR) effects mitigation**

GOAL: Utilize countermeasures (CM) to mitigate the radiation health risk to crew and potentially increase the permissible mission duration.

Gap ID	Gap Title	Priority
ESDMD #0308	Radiation Countermeasures	

Gap Description

Solar Particle Event (SPE) radiation shielding is relatively well understood and passive shielding can be applied to small volumes of habitat. Galactic Cosmic Radiation (GCR) is very difficult to mitigate. Passive shielding is mass-prohibitive, while active methods are very low maturity and utilize substantial vehicle mass and power. New shielding techniques as well as other potential mass-efficient countermeasures are needed to reduce the risk of adverse medical impacts on crew. GCR shielding will also help shield for SPE radiation.

Architecture-Driven Child Gaps

- 0308-01: Solar Particle Event (SPE) radiation effects mitigation and shielding
- 0308-02: Radiation risk models for crew health and performance
- 0308-03: Biomedical countermeasures to mitigate health effects from exposure to space radiation
- 0308-04: Galactic Cosmic Radiation (GCR) effects mitigation

Architecture Impact and Benefits

With gap closure, the benefits are reduction in crew lifetime radiation dose and reduction of detrimental crew health effects from radiation exposure during long-duration exploration missions. Using lunar proving ground to prove out Mars.

Architecture Traceability

UC/Fs

- UC-H-102 M -- FN-H-106 M
- UC-H-103 M -- FN-H-110 M
- UC-X-105 M
- UC-X-106 M
- UC-X-109 M

Key Decision

- Mars Architecture Loss of Crew Risk Posture
- Acceptable Crew Radiation Exposure Limit
- Total Crew Mission Duration Lower and Upper Bounds
- In-Space Radiation Mitigation

Metrics

Current State of the Art

Operational and physical mitigation strategies are used to reduce crew doses on ISS. No medical radiation countermeasures have been identified/validated to protect against long-term health effects. Countermeasures exist to protect against acute, high-dose terrestrial exposures and are most likely suitable for protection against an unanticipated exposure to a large SPE.

Performance Target

Develop long-duration, mass-efficient exploration mission-compatible countermeasures performing adequately to reduce adverse crew health outcomes, including a combination of 1) passive shielding 2) active shielding 3) other countermeasures in alignment with NASA-STD-3001 V1 4030 & 4031.

Sub-Architecture(s)

Campaign Segment(s)

Sustained Lunar Evolution

Humans to Mars

Higher Priority

!

NASA Responsibility - Operational Exception to Health Standards

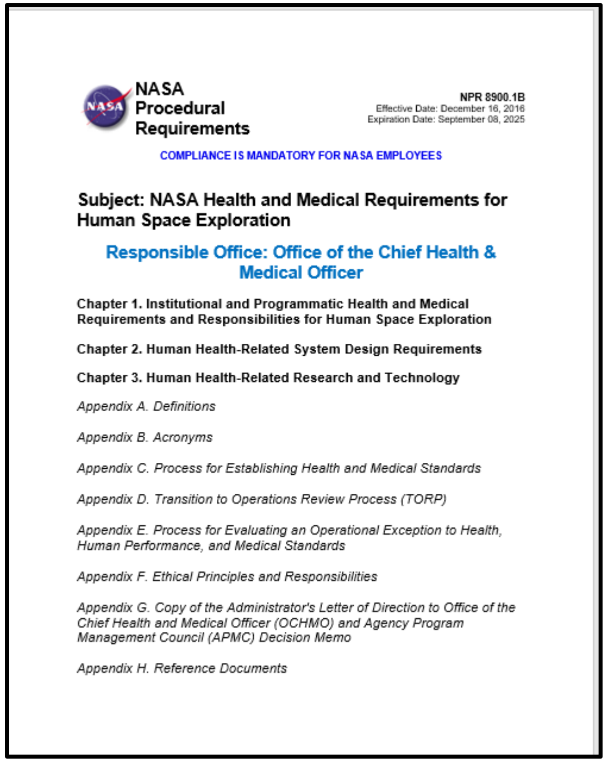
Procedures in place to consider exception to standards following an ethics-based framework – for missions or individuals (NPR-8900-1B)

Ethics Principles:

- Avoid Harm
- Beneficence
- Favorable Risk-Benefit Balance
- Respect for Autonomy
- Fairness
- Fidelity

Responsibilities:

- **Fully inform astronauts**
- **Continuous updating knowledge base**
- **Ensure transparency**



NASA Procedural Requirements

NPR 8900.1B
Effective Date: December 16, 2016
Expiration Date: September 08, 2025

COMPLIANCE IS MANDATORY FOR NASA EMPLOYEES

Subject: NASA Health and Medical Requirements for Human Space Exploration

Responsible Office: Office of the Chief Health & Medical Officer

Chapter 1. Institutional and Programmatic Health and Medical Requirements and Responsibilities for Human Space Exploration

Chapter 2. Human Health-Related System Design Requirements

Chapter 3. Human Health-Related Research and Technology

Appendix A. Definitions

Appendix B. Acronyms

Appendix C. Process for Establishing Health and Medical Standards

Appendix D. Transition to Operations Review Process (TORP)

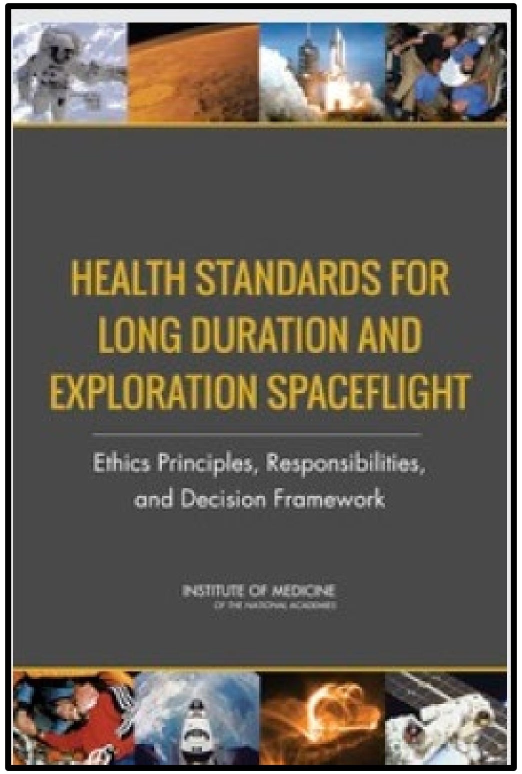
Appendix E. Process for Evaluating an Operational Exception to Health, Human Performance, and Medical Standards

Appendix F. Ethical Principles and Responsibilities

Appendix G. Copy of the Administrator's Letter of Direction to Office of the Chief Health and Medical Officer (OCHMO) and Agency Program Management Council (APMC) Decision Memo

Appendix H. Reference Documents

NASA Procedural Requirements 8900



Institutes of Medicine, 2014

OCHMO provides determination of risk and mitigation

NASA Administrator has final decisional authority

Cancer Risk Approach Plan

HRR Knowledge Gap	Risk Characterization	Countermeasure (CM) Development, Evaluation, Validation, and Integration
	Cancer-103: Determine the effects of **radiation quality** on cancer initiation, promotion, progression. **Cancer-104:** Determine the effects of radiation **dose and dose-rate** on cancer initiation, promotion, progression. (Brookhaven National Laboratory, ISS) **1** **NSCR update with Qnew development (2025)**	**Cancer-403:** Identify and/or develop potential **biomarkers** to support health surveillance and countermeasure implementation. **Cancer-504:** Identify and validate **safe and effective countermeasures** to reduce radiation carcinogenesis. **Cancer-604:** **Operationalize validated pharmaceutical countermeasures and surveillance technologies** for spaceflight. (Brookhaven National Laboratory, ISS, Artemis)
	Cancer-202: Evaluate the contribution of **genetic background/ diversity** on carcinogenesis risk. **Cancer-203:** Evaluate the **tissue-specific risks** of space radiation exposure on cancer outcomes. **Cancer-204:** Evaluate the **sex-specific risks** of space radiation exposure on cancer outcomes. (Brookhaven National Laboratory, ISS) **2** **NPR 8900 Baseline (PEL evaluation) (2025)** **3** **NPR 8900.1B Acceptance – Characterization Data (2030)**	**4, 8** **Clinical Practice Guideline (CPG) Recommendations (2030, 2038)** **5** **Countermeasure Identification (2036)** **6** **8900 Acceptance - Mitigation Data (2038)** **7** **Integrated CM Toolkit (2038)** **9** **Fitness for Duty Standard Recommendations (2040)**

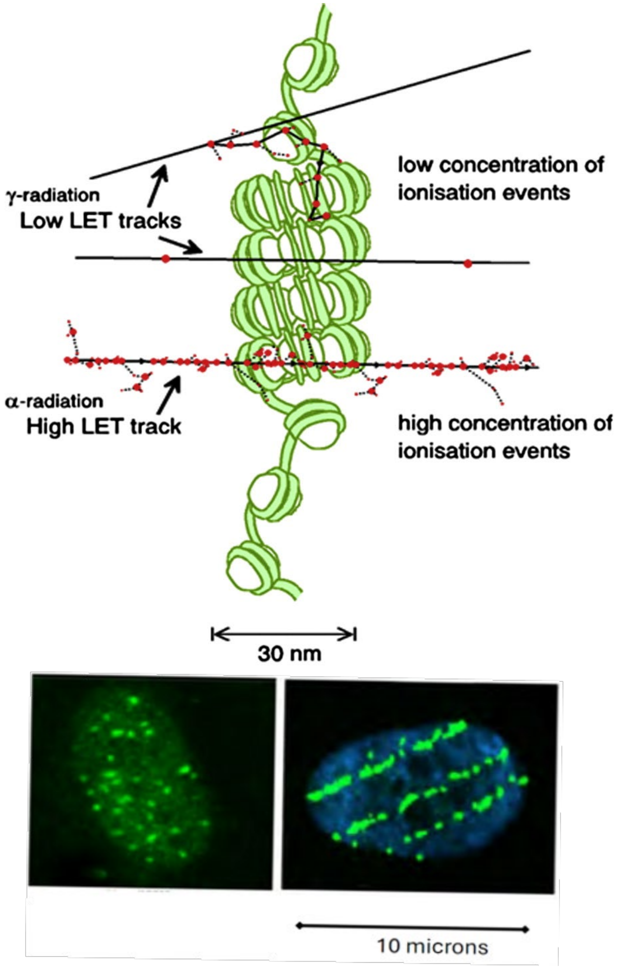
Legend: M2M Deliverable; Lunar Deliverable; ISS; Brookhaven National Laboratory; Artemis

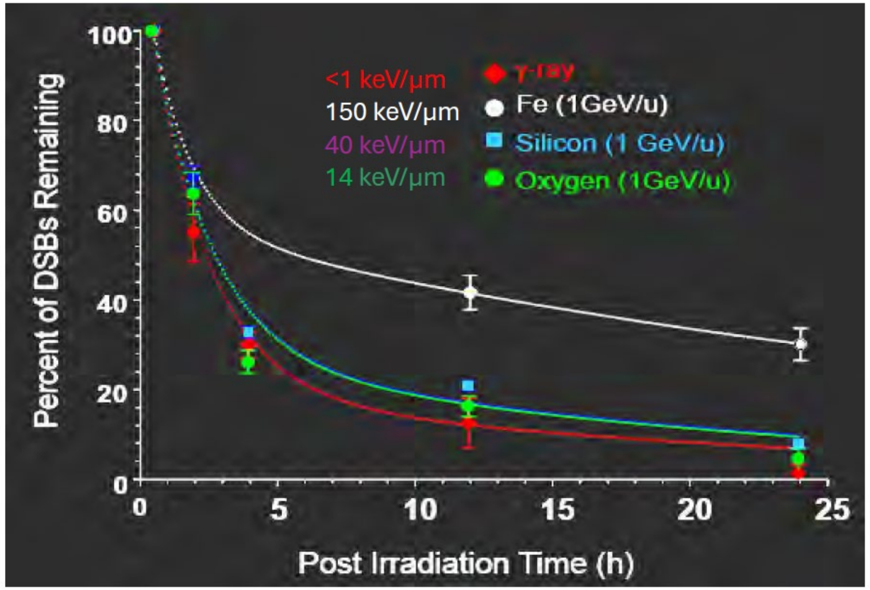
Timeline

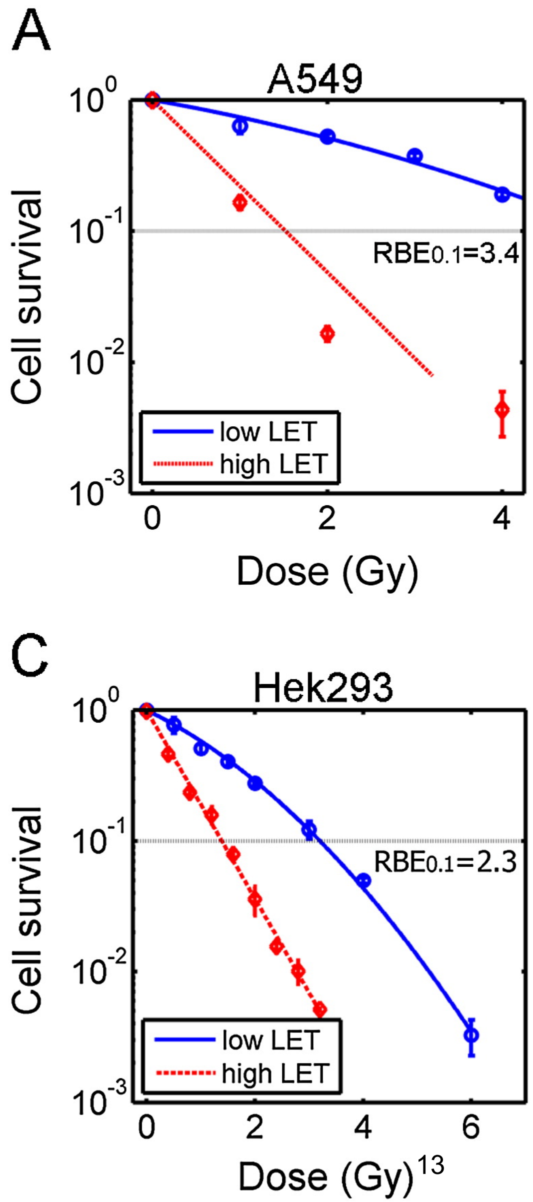
1, 2	3, 4	5	6, 7, 8	9
2025	2030		2038	2040

Risk Maps to ESDMD Gap ID # 0308

DNA Damage Complexity Increases with Increasing LET







Less effective DNA repair

Higher rate of residual lesions

Genomic instability

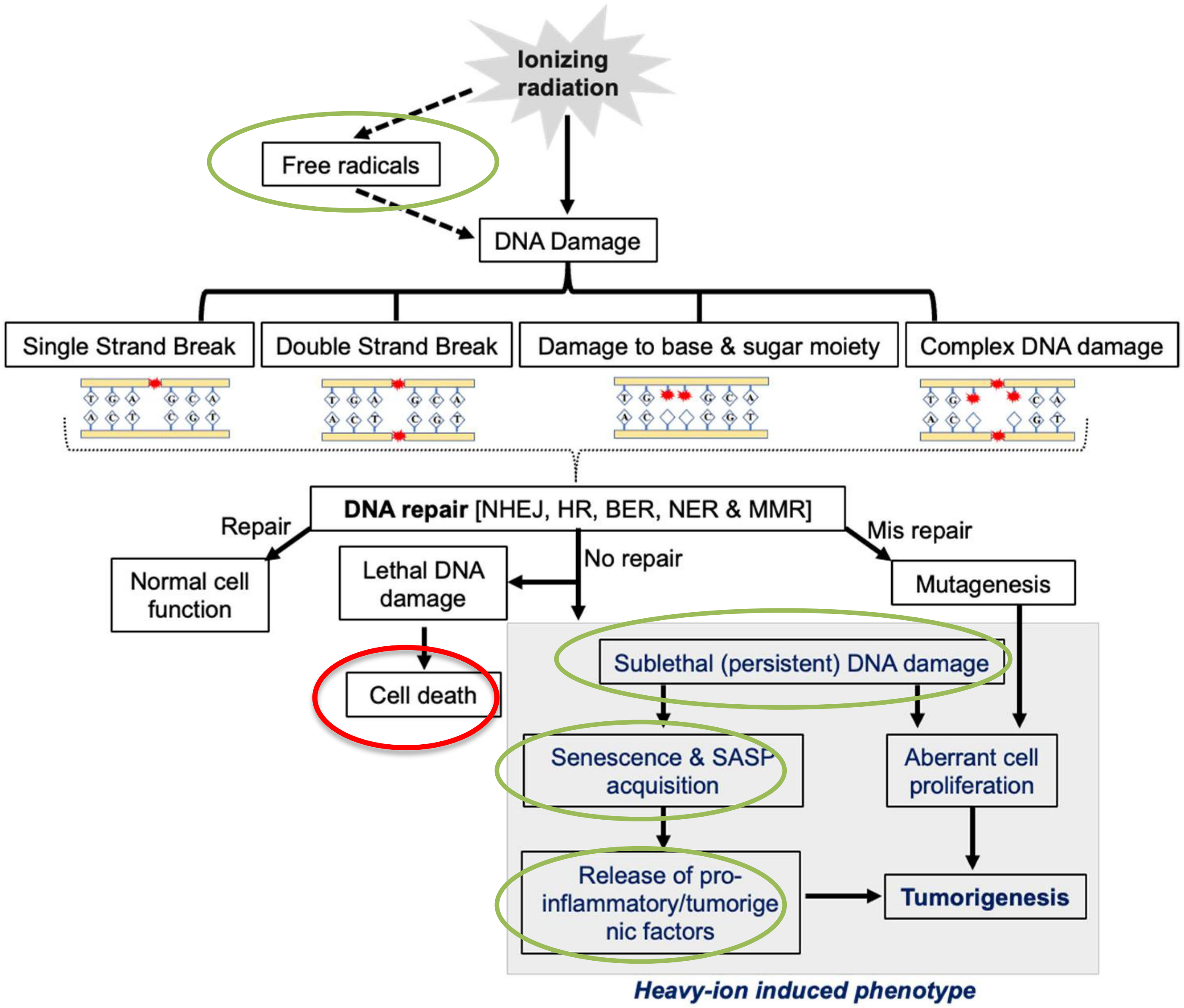
Enhanced cell killing

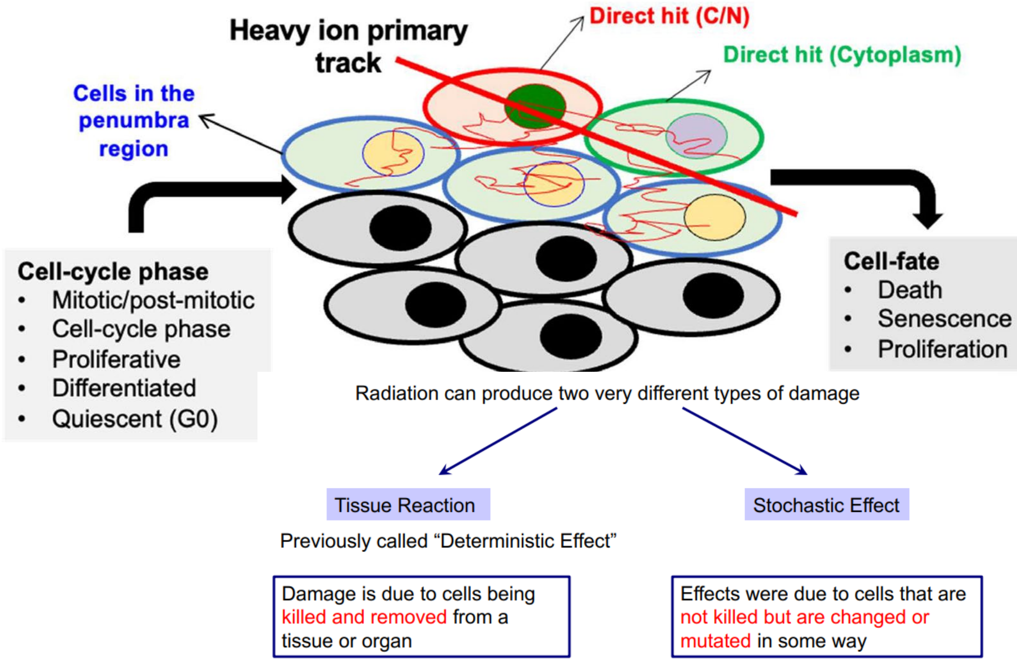
Complex Chromosome Aberrations

Lomax et al. Clinical Oncology. Clinical Oncology 25 (2013) 578e585

Int J Radiation Oncol Biol Phys, Vol. 83, No. 4, pp. 1291e1297, 2012

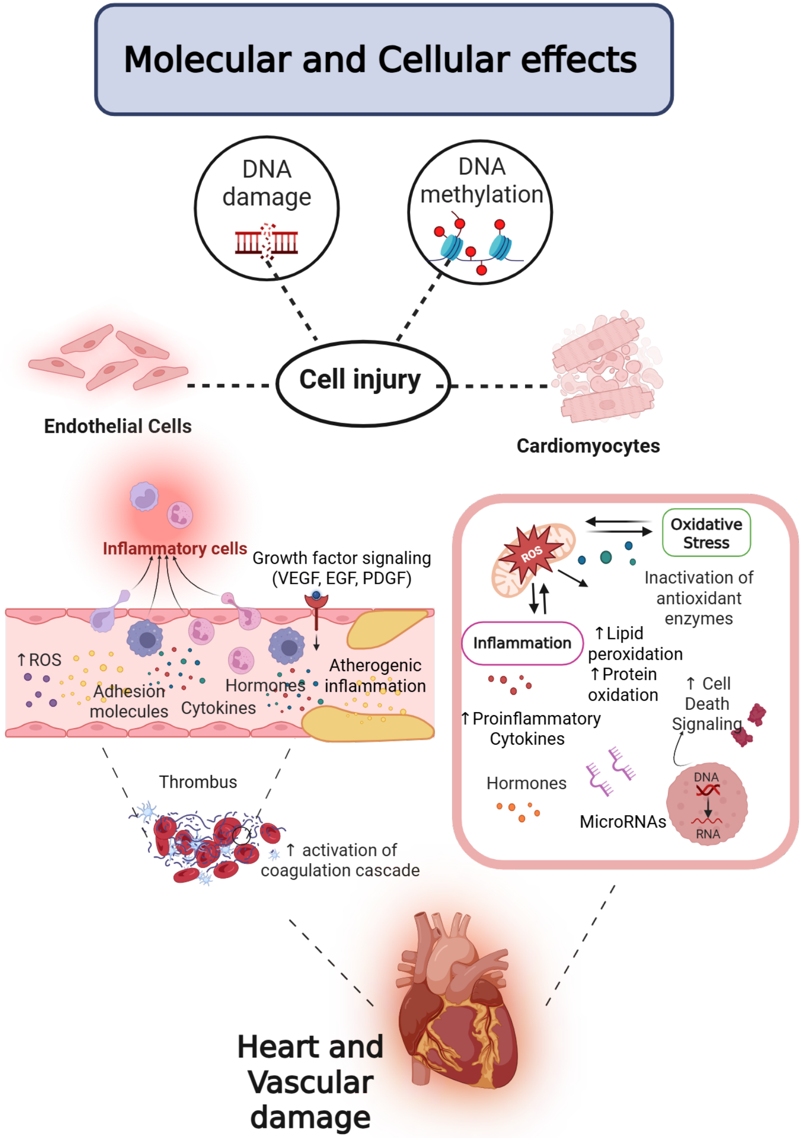
Types of DNA Damage and Repair Pathways

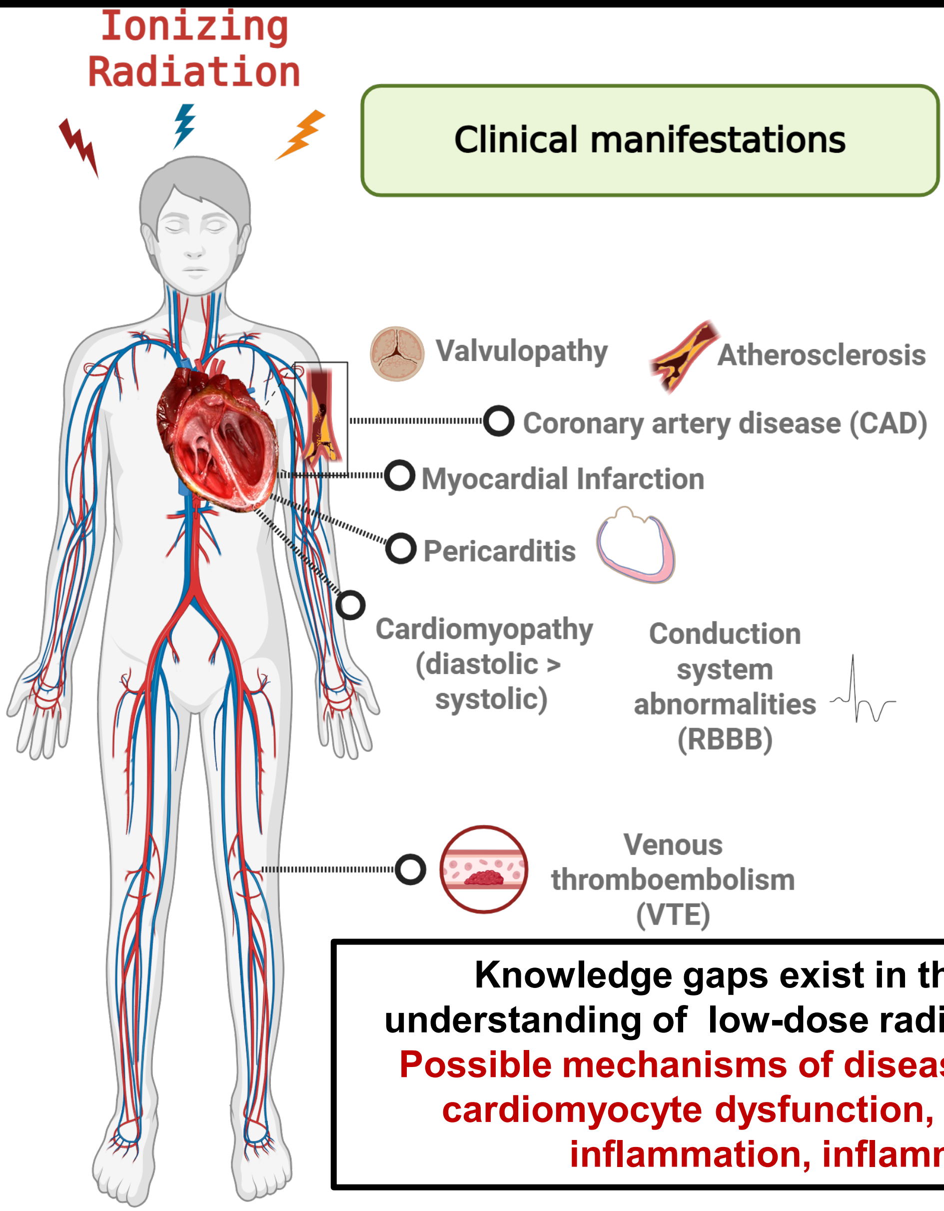




Curr. Oncol. **2023**, *30*(6), 5497-5514; https://doi.org/10.3390/curroncol30060416

Putative Mechanisms of Radiation-induced CVD

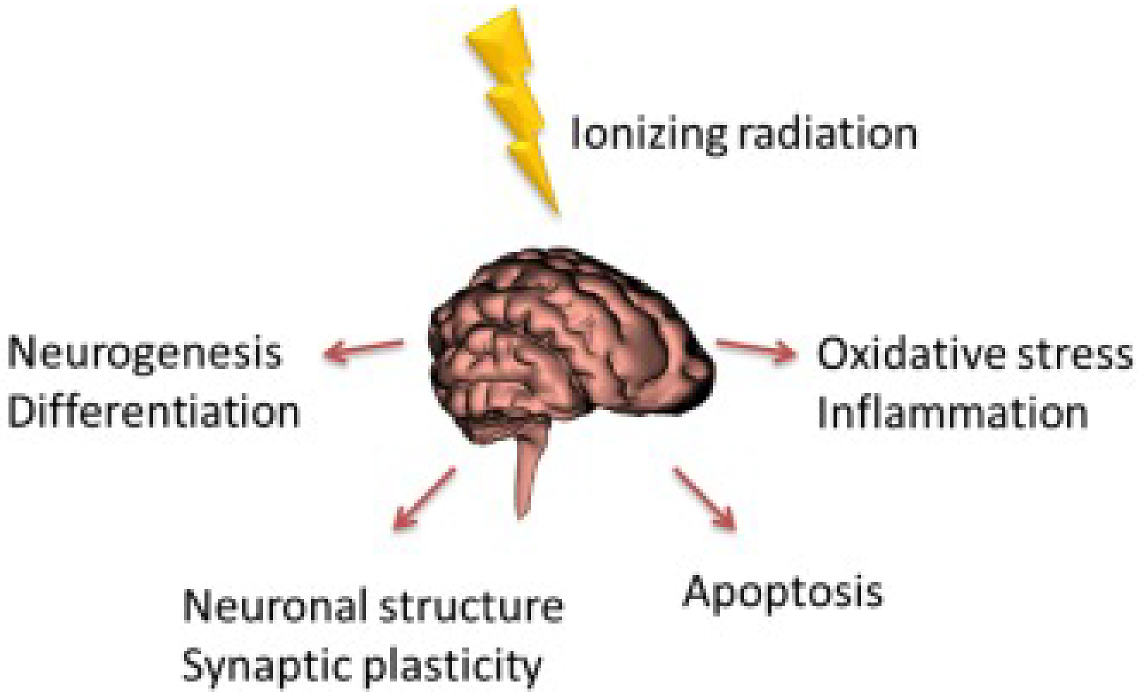




Knowledge gaps exist in the mechanistic understanding of low-dose radiation-induced CVD.
Possible mechanisms of disease: endothelial and cardiomyocyte dysfunction, atherosclerosis, inflammation, inflammasomes

Cruz-Topete D, and Nelson G.A. et al. Unpublished 2025

Central Nervous System Changes after Space-Like Radiation Exposure



- **Changes in neurochemicals, synaptic and neuroinflammatory proteins**
- **Increased activation of microglia (signaling neuroinflammation)**
- **Deficits in neurocognitive performance for several mouse and rat behavioral paradigms**
- **High-LET nuclei at low doses (<10 cGy) significantly reduced production of new neurons in brain** (data not shown)
- **Reduction in neuron arborization and synapse number (dendritic spines)**
  - Persistent reductions for > 1 year after doses of high Linear Energy Transfer (LET) nuclei below 5 cGy (data not shown)

<u>Performance deficits following exposure to high-LET nuclei depends on</u>

- Physical particle characteristics, strain, sex, age at exposure, evaluation time after exposure and measure used
- Male mice appear to be more radiosensitive than female mice

Overview of SR-Funded Cancer Countermeasures

Past SRE F		
PI Last Name	PI Institution	Risk
Edwards	New York Medical College	CVD
ahng	Stanford University	CVD
Lawler	Texas A&M University	CVD
Baulch	University of California Irvine	Degen
Beheshti	KBR/NASA Ames Research Center	Degen
Vunjak-Novakovic	Columbia University	Degen
Bateman	University of North Carolina at Chapel Hill	Degen
Schreurs	NASA Ames Research Center	Degen

PI Last Name	PI Institution	Risk					
Chatterjee	University of Colorado at Boulder	CNS					
Kiffer	Children's Hospital of Philadelphia	CNS					
Maletic-Savatic	Baylor College of Medicine	CNS					
Suman	Georgetown University	CNS					
Suman	Georgetown University	CNS					
Rosi	UCSF	CNS		whole body helium irradiation (^{4}He, 0,15,50, 1000cGy)	impairments	irradiation	not PLX5622
Limoli	UCSD	CNS	PLX5622	Male C57Bl/6 fed dietary inhibitor PLX5622 starting 2 weeks after whole body helium irradiation (^{4}He, 30 cGy, 400 MeV/n)	Yes – Reduction in brain inflammation and improved cognition	5-7 weeks post-irradiation	PLX3397 is Approved but not PLX5622

Past SRE Funded Cancer Countermeasure Testing

PI Last Name	PI Institution	Risk	Countermeasure Name	Model	Significant Improvement (Y/N)	Time point measured	FDA Approved
Emmett	The University of Texas Medical Branch	Cancer	No Countermeasure tested. However, one FDA approved, one clinical trial drug and 4 approved dietary supplements are proposed for future.	Mouse	Yes-Two novel computational algorithms developed. Two lipid biomarkers identified.	N/A (ongoing study)	N/A
Fornace	Georgetown University	Cancer	Aspirin 75, 150, 300 mg/day (human equivalent); Metformin 1000ppm, equal to 200mg/kg conc i.p. or chow (0.1% W/W); CDDO	Mouse and Human colon and lung cells, human 3D colonocytes	Yes- significant increase in survival and reduction in GI, colon and lung tumoriganesis	Radioprotection (radiation pre administration) and tumor observation 150 days post IR	Yes
Shay	University of Texas Southwestern Medical Center	Cancer	Metformin 200mg/kg in vivo	Mouse. 75cGy GCR exposed lung cancer susceptible K-rasLA-1 mice.	Pretreatment reduced micronuclei, increased DNA damage repair enzyme, reduced apoptosis in colon and lung tissue after GCR exposure, decreased plasma lipid peroxidation, the number and area of pre-malignant lesions in lung tissue in	Pre-treatment in dietary form, for 3 consecutive days prior to exposure of 7.5 Gy of X-rays and sacrifice at 24hr post IR	Yes
Story	University of Texas, Southwestern Medical Center	cancer	GC4419 (Avasopasem manganese) i.p. dose of 24 mg/kg of dose	Mouse	Yes- Mitigated radiation-induced lung fibrosis, reduces radiogenic lung cancers in low LET or high LET radiations simulating the space environment. Survival of the 1.5 Gy 137Cs-irradiated cohort treated with avasopasem is higher than the cohort not treated with avasopasem (study still going on hence, statistical significance is inconclusive).	**Radioprotection:** administered 30-60 minutes pre-irradiation. **Radiomitigation:** administered daily starting at least 24 hours post-irradiation for increasing durations up to 24 weeks.	No
Weil	Colorado State University	Cancer	MitoTEMPO 5 µM (Mitochondria-targeted antioxidant)	humans in vitro models	Yes-MT treated cells exhibited attenuation in radiation-induced DNA damage, cytokine release and oxidative stress.	5 days post IR	No

Past Funded Countermeasure Testing (Misc. Risk/Organs)

PI Last Name	PI Institution	Risk	Countermeasure Name	Model	Significant Improvement (Y/N)	Time point measured	FDA Approved
Kennedy	University of Pennsylvania	Other	Enrofloxacin	C3H/HeNCr MTV-mice with bacterial challenge (Pseudomonas) exposed to 2 Gy of gamma or proton radiation.	YES- Enhanced bacterial clearance and reduced morbidity and bacterial load in challenged mice.	10 days post irradiation	Y- for dogs & cats
Kennedy	University of Pennsylvania	Other	Neulasta (Granulocyte colony stimulating factor)	C3H/HeNCr MTV-mice with bacterial challenge (Pseudomonas) exposed to 2 Gy of gamma or proton radiation.	YES- Enhanced bacterial clearance and reduced morbidity and bacterial load in challenged mice.	10 days post irradiation	Y
Miguad	University of South Alabama	Other	Nicotinamide riboside (ox-NAD(P) reducer)	2D & 3D HepG3 cells (proposed)	No CM results yet	N/A	N
Nickerson	Arizona State University	Other	EC-18 (synthetic monoacetyldiacylglyceride)	3D biomimetic intestinal tissue models (consisting of HT-29 epithelial cells & PMA-differentiated U937 macrophages) exposed to 0.1 or 0.5 Gy 320 kV X-ray (0.1 Gy/min).	No CM results yet	N/A	N

Past Research

- ~23 studies using drugs
- In vitro and rodent models used to assess efficacy
- 91% of studies had significant results
- 43% of drugs were FDA approved
- Aspirin, Metformin, Avasopasem Manganese, MitoTEMPO, Enrofloxacin, Neutasta, Nicotinamide Riboside, EC-18 (synthetic monoacetyldiacylglyceride), Antidiabetic, Serotonin Receptors Antagonists, Fish Oil, Pectin, Genistein, Simvastatin, Non-Protein Thiol, Amifostine , Antagonists to the miRNAsignatures (miR-16-5p,mir-12b-5p, and let-7a-5p, pegfilgrastim, Osteoprotegerin (OPG), Zoledronate, Bisphosphonates, Parathyroid Hormone, Macrophage-Colony Stimulating Factor, Diet Supplement Dried Plum, SB_NI_112 Targeting NF-kB and NLRP3, CDDO-EA, Ligands to Tailless Receptor, NSI-189, P20187 Apoptosis Inducer, Fisetin, PLX5622.

Overview of SR-Funded Cancer Countermeasures

Drug	FDA status	Model	Radiation	Cancer
Aspirin	Approved	APC1638N/+ male mice	**28Si-ions** (10, and 50 cGy)	GI-intestinal, colonic
Metformin	Approved	APC1638N/+ mice, WT 129/Sv mice	**28Si-ions** (10 cGy), **X-ray** (10 Gy), **33-ion GCRsim** (75 cGy)	GI-colon, Lung,
CDDO	Approved	CDX2PApcflox/+ mice, WT 129/Sv mice; LA-1 mice, CPC;APC mice	**Proton** (2 Gy), **Fe-ions** (1 Gy: 0.2 Gy x 5), **X-ray** (10 Gy), **33-ion GCRsim** (75 cGy)	Lung, Colon

Suman et al.,2021 Life Sci. Space Res.; Suman & Fornace, 2022 Life Sci. Space Res.; Siteni S et al., 2024 PLoS ONE

Overview of SR-Funded Cancer Countermeasures

Drug	FDA status	Model	Radiation	Cancer	Outcome
Aspirin	Approved	APC1638N/+ male mice	**28Si-ions** (10, and 50 cGy)	GI-intestinal, colonic	↓ radiation-induced genomic instability ↓ PGE2 **Does not protect against space radiation-associated tumorigenesis**
Metformin	Approved	APC1638N/+ mice, WT 129/Sv mice	**28Si-ions** (10 cGy), **X-ray** (10 Gy), **33-ion GCRsim** (75 cGy)	GI-colon, Lung,	↓ x-rays, protons, and GCR ions-induced genomic instability, inflammation ↓ **heavy ions-induced GI tumorigenesis**
CDDO	Approved	CDX2PApcflox/+ mice, WT 129/Sv mice; LA-1 mice, CPC;APC mice	**Proton** (2 Gy), **Fe-ions** (1 Gy: 0.2 Gy x 5), **X-ray** (10 Gy), **33-ion GCRsim** (75 cGy)	Lung, Colon	↓ x-rays, protons, and GCR ions-induced DNA damage, inflammation and potential anti-senescence ↓ **proton-induced colon tumorigenesis, reduced invasive carcinomas in both lung and colon models** **Prevents GCR** **cognitive changes in GCR irradiated female mice**

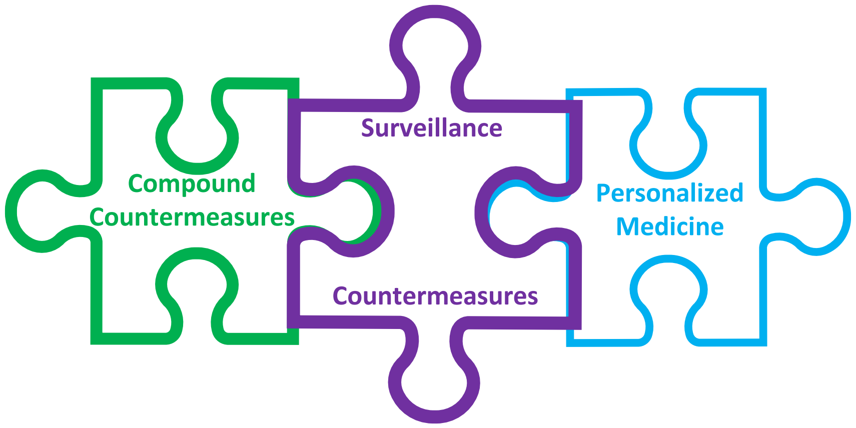
Future directions •Post-exposure testing •Testing with full GCR • Dose response studies

Implications: Metformin and CDDO as potential radioprotectant, particularly in astronauts, cancer patients undergoing radiotherapy, or populations affected by nuclear accidents

Suman et al.,2021 Life Sci. Space Res.; Suman & Fornace, 2022 Life Sci. Space Res.; Siteni S et al., 2024 PLoS ONE

Space Radiation Countermeasure Research Plan

TWO-PRONGED STRATEGY approach to reduce the risk of space radiation induced carcinogenesis and other organ/tissue effects.



Compound Countermeasures

Focus on off label use of already FDA approved drugs and/or Investigational New Drugs that have well known safety profiles.

- Accelerates discovery
- Reduced budget
- Known terrestrial toxicity profiles

Surveillance Countermeasure (FDA Approved):

Imaging

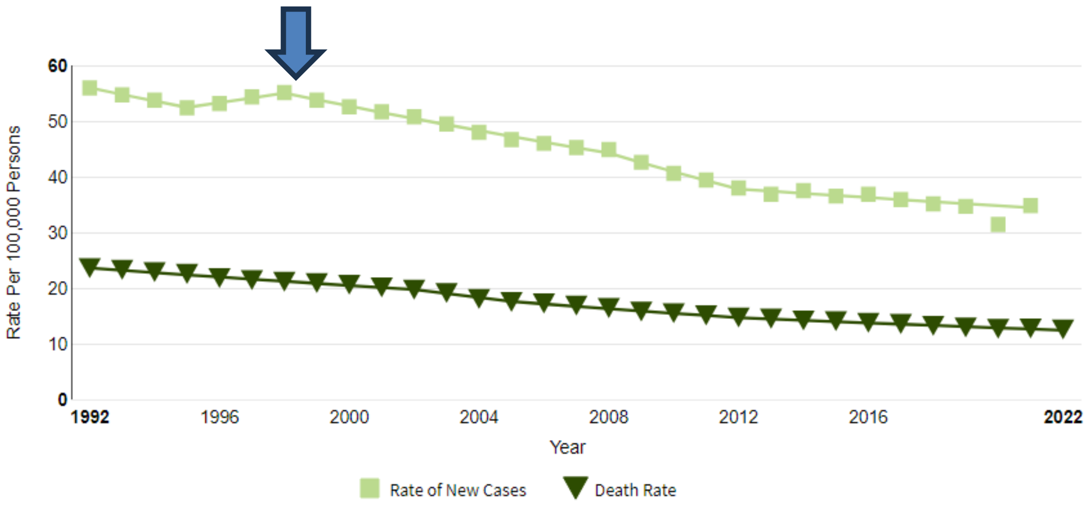
Colonoscopy
Mammography
PET

Blood test

PSA
cfDNA
- Methylation
- mRNA

Cells/biopsy

Pap smear
Tissue
Fecal sample
- Hemoglobin
- Methylated DNA



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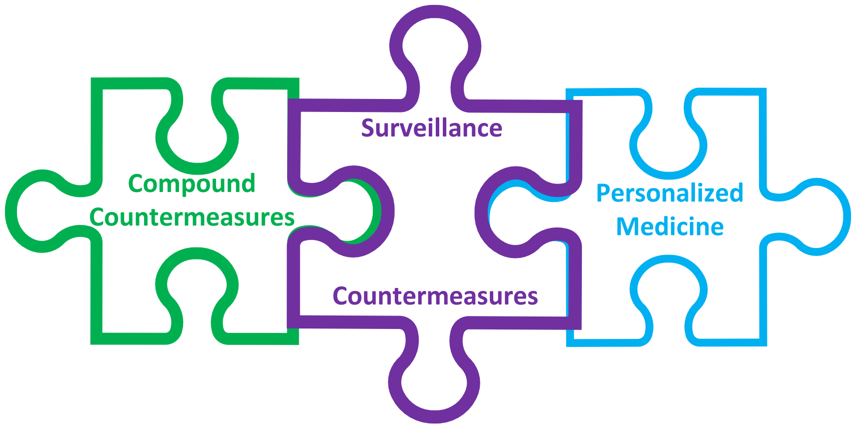

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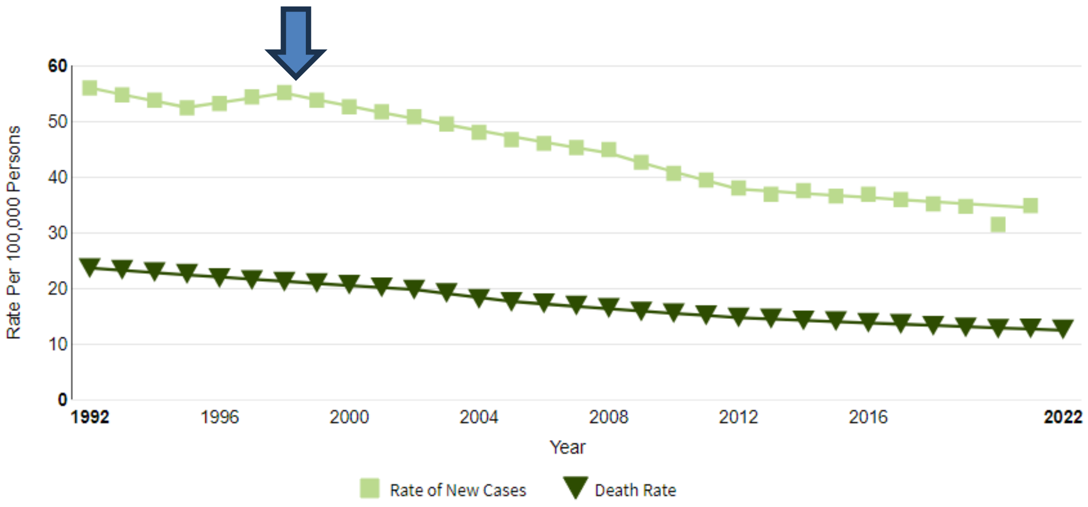
Surveillance Countermeasure (FDA Approved):

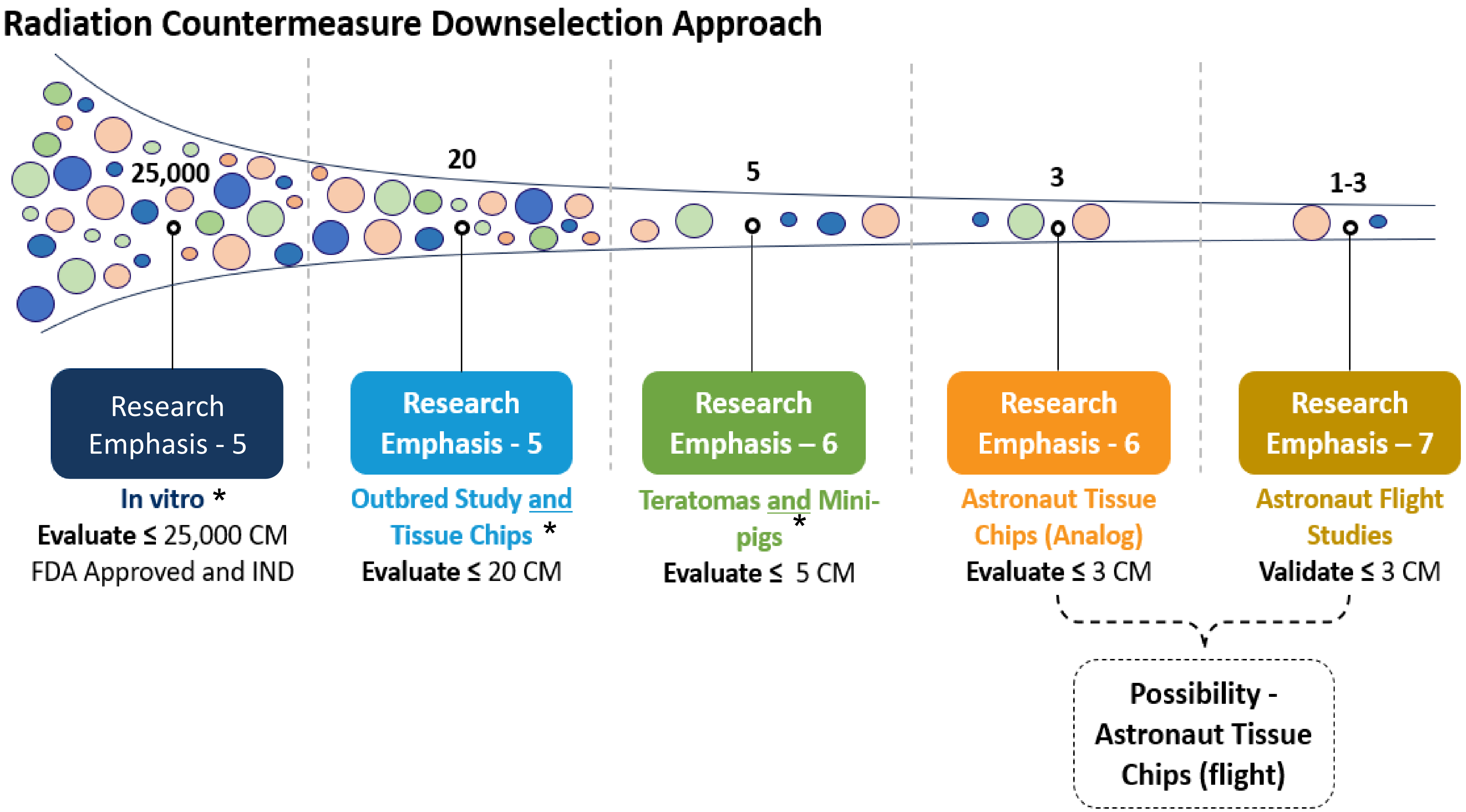
Imaging
- Colonoscopy
- Mammography
- PET

Blood test
- PSA
- cfDNA
  - Methylation
  - mRNA

Cells/biopsy
- Pap smear
- Tissue
- Fecal sample
  - Hemoglobin
  - Methylated DNA

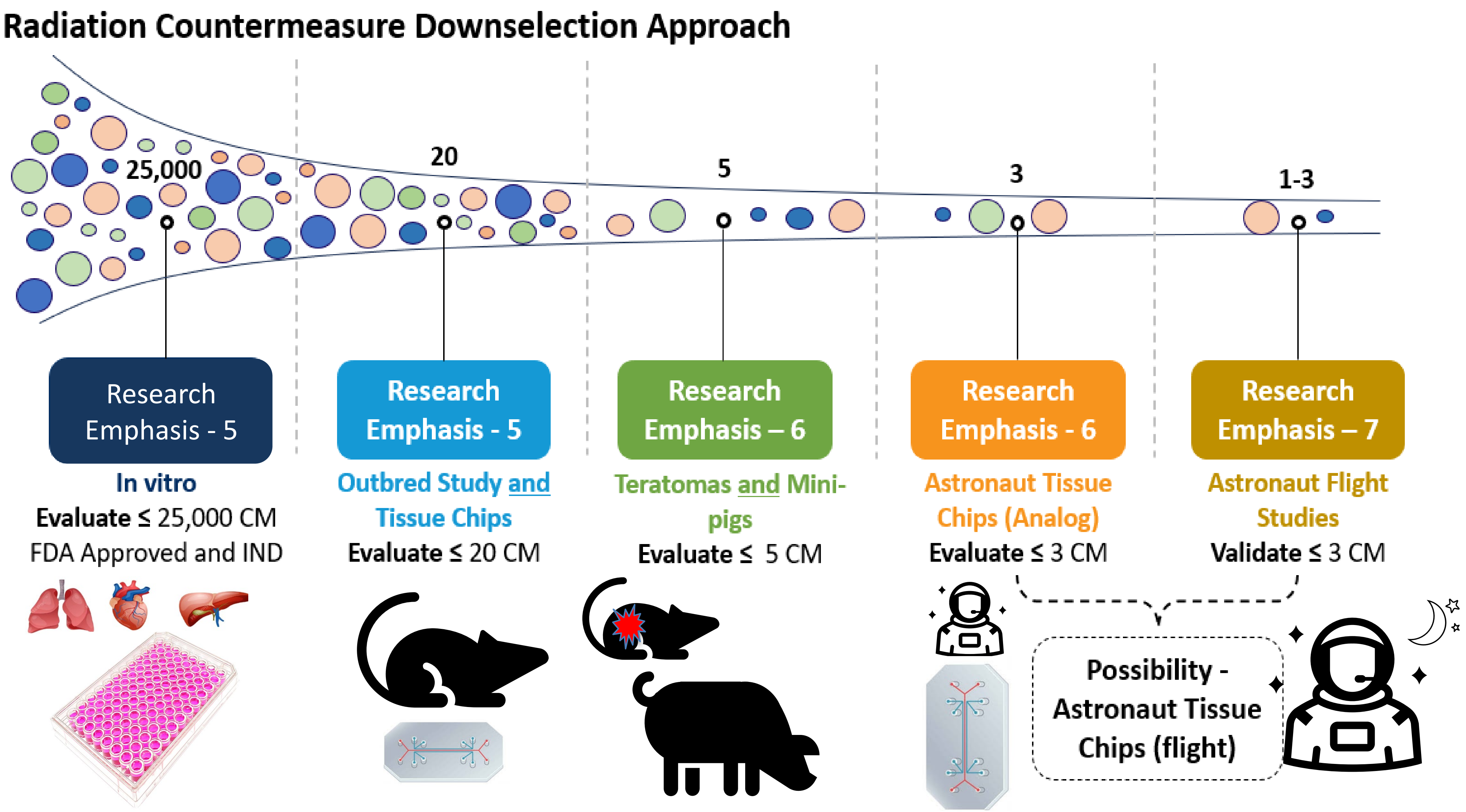


Pharmaceutical Down Selection Approach



* Drug down selection will be a concerted and informed effort with stakeholders and customers (OCHMO, SMOD, ESDMD)

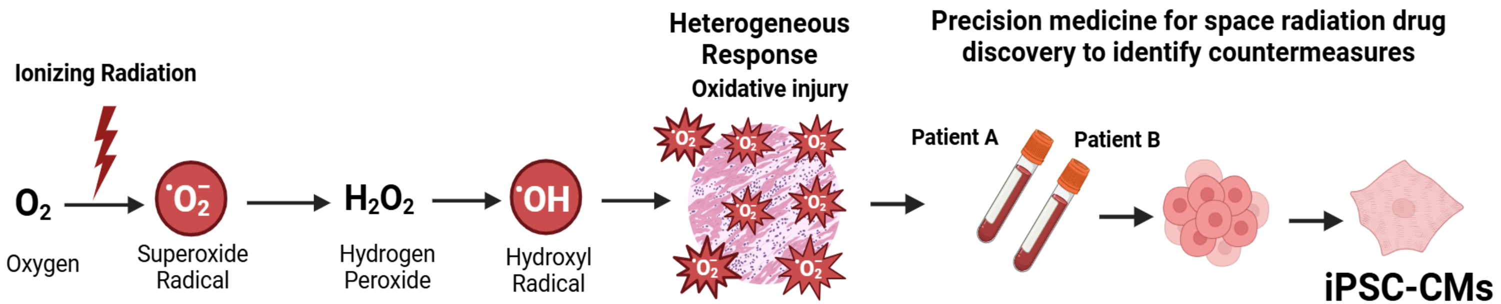
Pharmaceutical Down Selection Approach

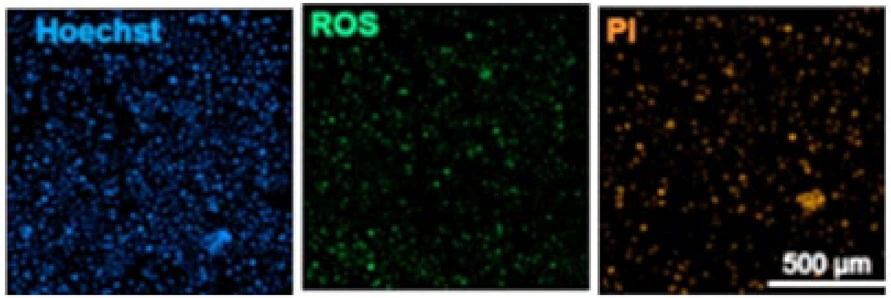


In vitro down selects of FDA-approved drugs – Planned work for cancer countermeasure and Greenstone Biosciences Directed Task

Aim 1:

- hiPSCs-derived cardiomyocytes (**iPSC-CMs**) were used to study X-ray-induced damage and screen for protective drugs.
- **Screening process:**
- ✓ 10 Gy radiation dose was used. 2,320 compounds were screened (post 4 hrs of exposure) .
- ✓ 1st screening → 44 drug candidates.
- ✓ 2nd screening (2 and 10 μM concentration) → 23 drug candidates
- ✓ Final selection (low dose) → **10 reproducible and effective drug candidates.**





Ideal drug candidate

↑ cell count (↑ Hoechst)

↓ ROS (↓ CellRox)

↑ cell viability (↓ PI)

		ROS 2μM	ROS 10μM	Cell death 2μM	Cell death 10μM	Pathway	Target	Information
A2149	Bosutinib (SKI-606)	3.68	3.94	3.18	14.55	TGF-β / Smad Signaling	Bcr-Abl	Potent Abl/Src kinases
A4219	Birinapant (TL32711)	24.57	2.46	5.49	11.96	Apoptosis	IAP	Potent XIAP/cIAP1 antagonist
A4377	Evacetrapib (LY2484595)	26.84	3.27	4.37	12.24	Metabolism	CETP	CETP inhibitor,potent and selective
A5133	Irinotecan	38.80	3.09	2.78	29.31	DNA Damage/DNA Repair	Topoisomerase	Topoisomerase I inhibitor
A8307	Crenolanib (CP-868596)	16.40	3.67	5.07	28.42	Tyrosine Kinase	PDGFR	PDGFR-β inhibitor, potent and selective
A8406	Dextrose (D-glucose)	1.97	3.35	2.90	17.62	Others	Others	Simple sugar (monosaccharide)
A8434	Flurbiprofen	24.67	3.37	29.33	16.54	Immunology/Inflammation	PGE synthase	Cyclooxygenase inhibitors
A8436	Gabapentin	25.28	4.27	4.69	16.21	Neuroscience	GABA Receptor	GABA enhancer
A8639	Deferasirox	36.53	1.61	4.95	19.91	Cell Cycle/Checkpoint	Cyclin-Dependent Kinases	Oral iron chelator
B2300	Tolvaptan	43.68	6.48	6.59	21.44	GPCR/G protein	Vasopressin Receptor	AVP V2-receptor antagonist
		45.13	11.06	10.53	40.61			

Average of ctrl. Group after IR treatment

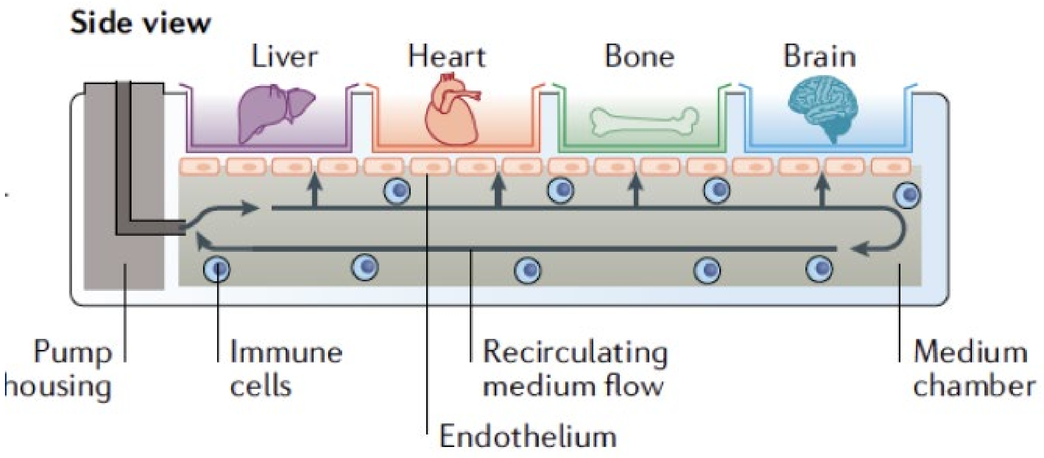
Future studies will utilize Fibroblasts, DSB Measurements, and simGCR exposure

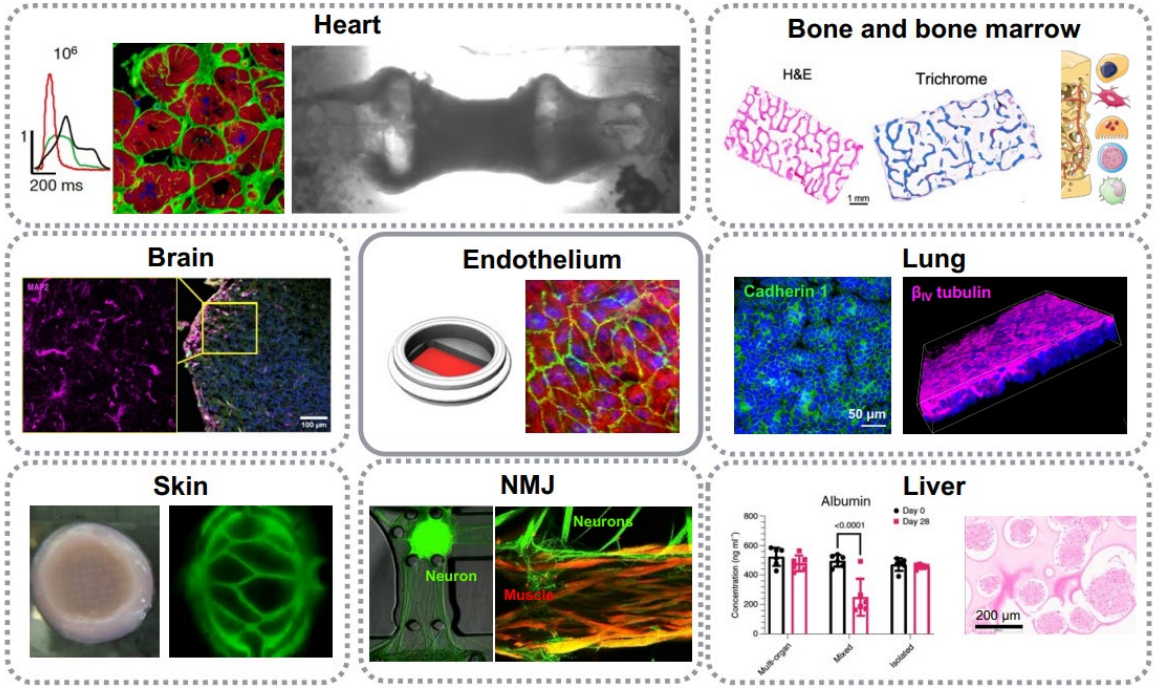
Greenstone Screening Downselects

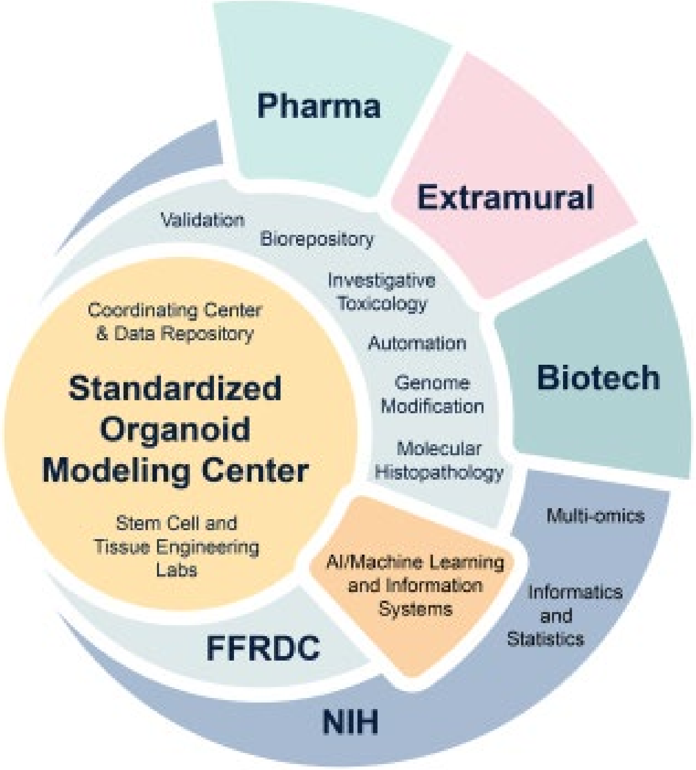
Compound	Company	Pathway	Target	Advantages & Disadvantages
Atovaquone	GlaxoSmithKline	• Mitochondrial electron transport chain inhibitor • Potential effects on metabolism	Binds ubiquinone binding site on cytochrome bc1	✓ Extensive characterization in parasitic diseases. Good tolerance and safety in humans ✓ Long half-life × Its effects on mitochondria maybe deleterious for cells like cardiomyocytes that are high-energy demanding × Too suppressive of ROS signaling × GI irritation, possible hepatotoxicity
Evacetrapib	Eli Lilly	• Lipid Metabolism/cardio vascular	Inhibits cholesterylester transfer protein (CETP)	✓ Oral bioavailability ✓ Improves lipid profiles × Failed in phase III for CV outcomes (ACCELERATE trial) × ↑ aldosterone and ↑blood pressure
Flurbiprofen	Generic	• Nonsteroidal anti-inflammatory drugs (NSAIDs)	COX-1 and COX-2	✓ Oral bioavailability and anti-inflammatory ✓ Reduces ROS × GI irritation, ↑ risk for heart attack or stroke in chronic use, kidney damage
Deferasirox	Generic	• Iron homeostasis/oxidative stress	Iron chelation	✓ Oral bioavailability ✓ Reduces free iron × GI irritation, ↑ risk for kidney and liver toxicity with long-term treatment
Methylcobalamin (vitamin B12)	Generic	• One-carbon metabolism, DNA-methylation, nucleotide synthesis	Coenzyme for methionine synthase. Converts homocysteine to methionine	✓ Excellent safety profile, few adverse effects ✓ Vitamin ✓ Maintain DNA methylation, DNA repair, antioxidant ✓ Low cost ✓ Neuroprotective effects
Geniposide	Natural Product	• GLP-1R receptor activator or sensitizer	GLP-1R activator (not fully established. Involved in AMPK, Nrf2, PI3K/Akt, and NF-kB signaling	✓ Positive effects in cardiomyocytes ✓ Protects in myocardial infarction and prevents fibrosis ✓ Bioactive natural compound × Liver and kidney toxicity × Clinical studies are limited × No FDA approved
Irsogladine		• PDE inhibitor	Increased intracellular cAMP	✓ Antioxidant, anti-inflammatory, cytoprotective, antiapoptotic effects × No evidence of cardioprotection × No FDA approved

Advance biological systems/tissue chip radiation dose response

Drs. Sharon Gerecht and Gordana Vunjak-Novakovik - TRISH Funded

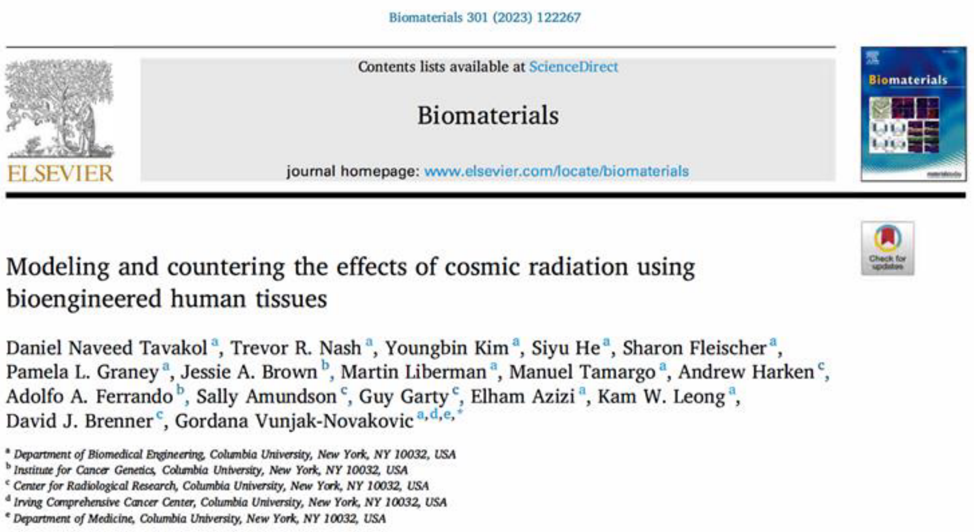






The SOM Center connects resources across the NIH with other federal agencies and industry partners to foster collaboration and accelerate NAMs technologies for the greater scientific community.

Advance biological systems/tissue chip radiation dose response


Biomaterials 301 (2023) 122267

Contents lists available at ScienceDirect

Biomaterials

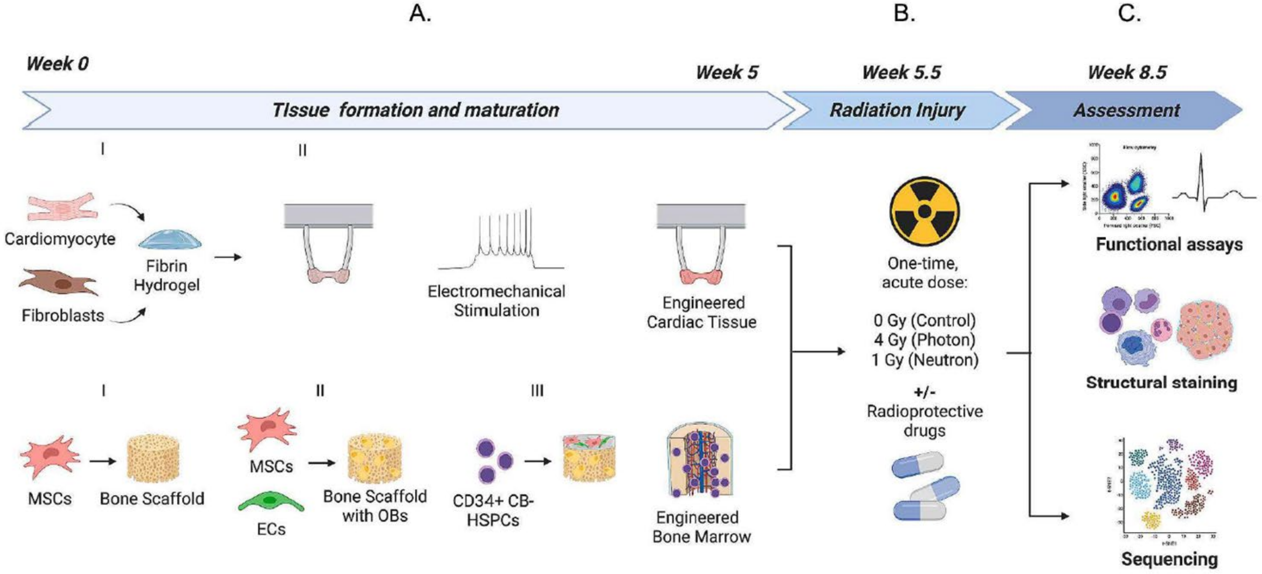
journal homepage: www.elsevier.com/locate/biomaterials

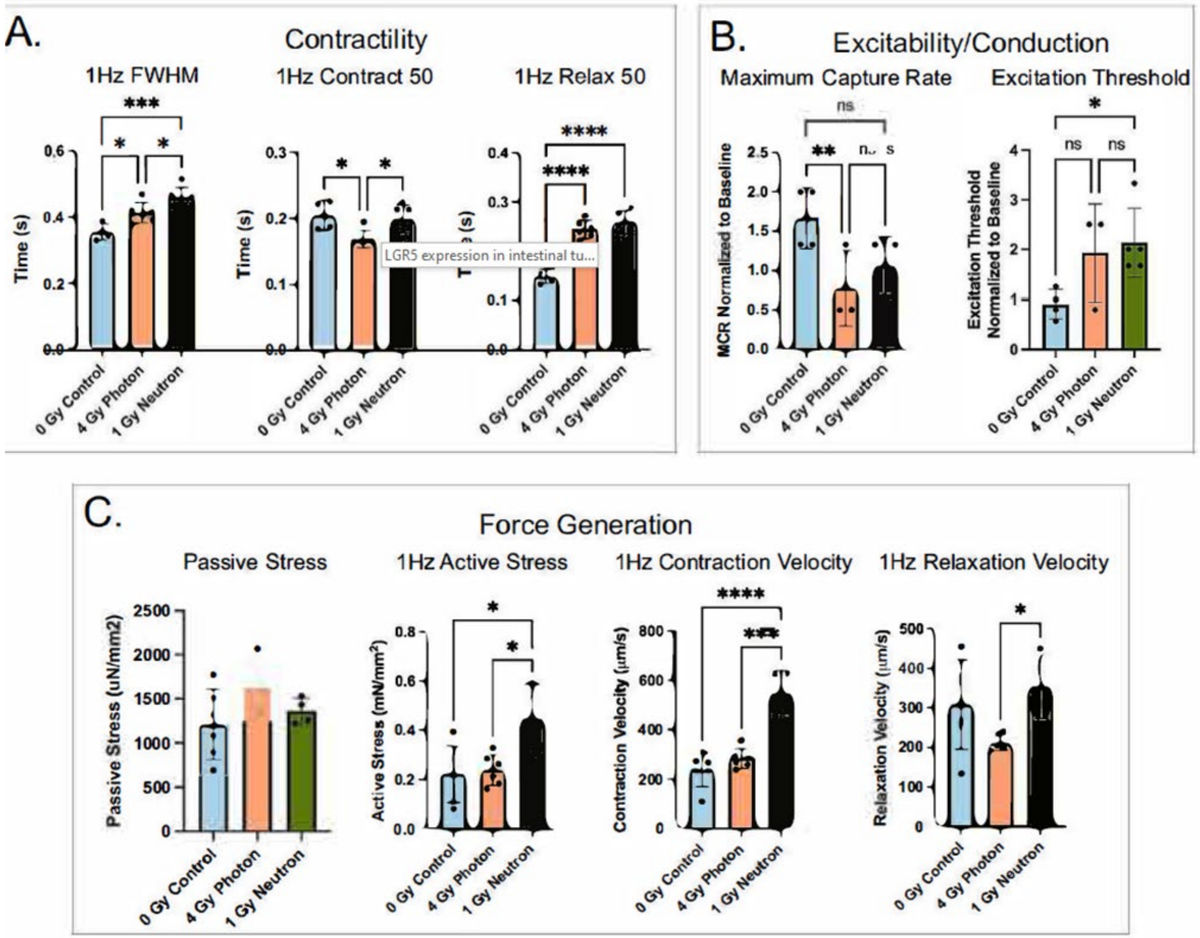
ELSEVIER

Modeling and countering the effects of cosmic radiation using bioengineered human tissues

Daniel Naveed Tavakol[a], Trevor R. Nash[a], Youngbin Kim[a], Siyu He[a], Sharon Fleischer[a], Pamela L. Graney[a], Jessie A. Brown[b], Martin Liberman[a], Manuel Tamargo[a], Andrew Harken[c], Adolfo A. Ferrando[b], Sally Amundson[c], Guy Garty[c], Elham Azizi[a], Kam W. Leong[a], David J. Brenner[c], Gordana Vunjak-Novakovic[a,d,e,*]

[a] Department of Biomedical Engineering, Columbia University, New York, NY 10032, USA
[b] Institute for Cancer Genetics, Columbia University, New York, NY 10032, USA
[c] Center for Radiological Research, Columbia University, New York, NY 10032, USA
[d] Irving Comprehensive Cancer Center, Columbia University, New York, NY 10032, USA
[e] Department of Medicine, Columbia University, New York, NY 10032, USA



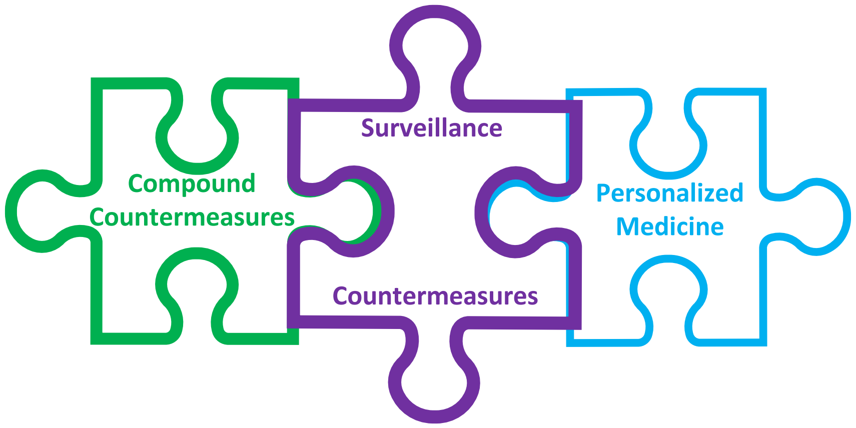


Functional analysis was performed for all eCT tissues before radiation and after 3 weeks post-irradiation, using a combination of bright field and fluorescent calcium imaging (based on the endogenous GCaMP reporter) to reveal tissue contractility, excitability, and force generation by measuring muscle movement and pillar displacement.

Simplified GCRsim dose curve in Spring 2027

Space Radiation Countermeasure Research Plan

TWO-PRONGED STRATEGY approach to reduce the risk of space radiation induced carcinogenesis and other organ/tissue effects.



Compound Countermeasures

Focus on off label use of already FDA approved drugs and/or Investigational New Drugs that have well known safety profiles.

- **Accelerates discovery**
- **Reduced budget**
- **Known terrestrial toxicity profiles**

Surveillance Countermeasure (FDA Approved):

Imaging

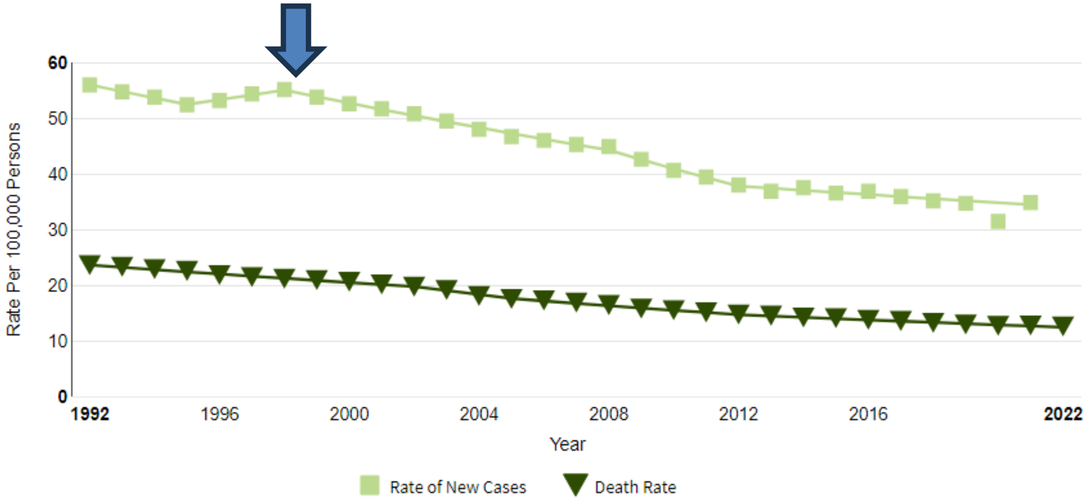
Colonoscopy
Mammography
PET

Blood test

PSA
cfDNA
Methylation
mRNA

Cells/biopsy

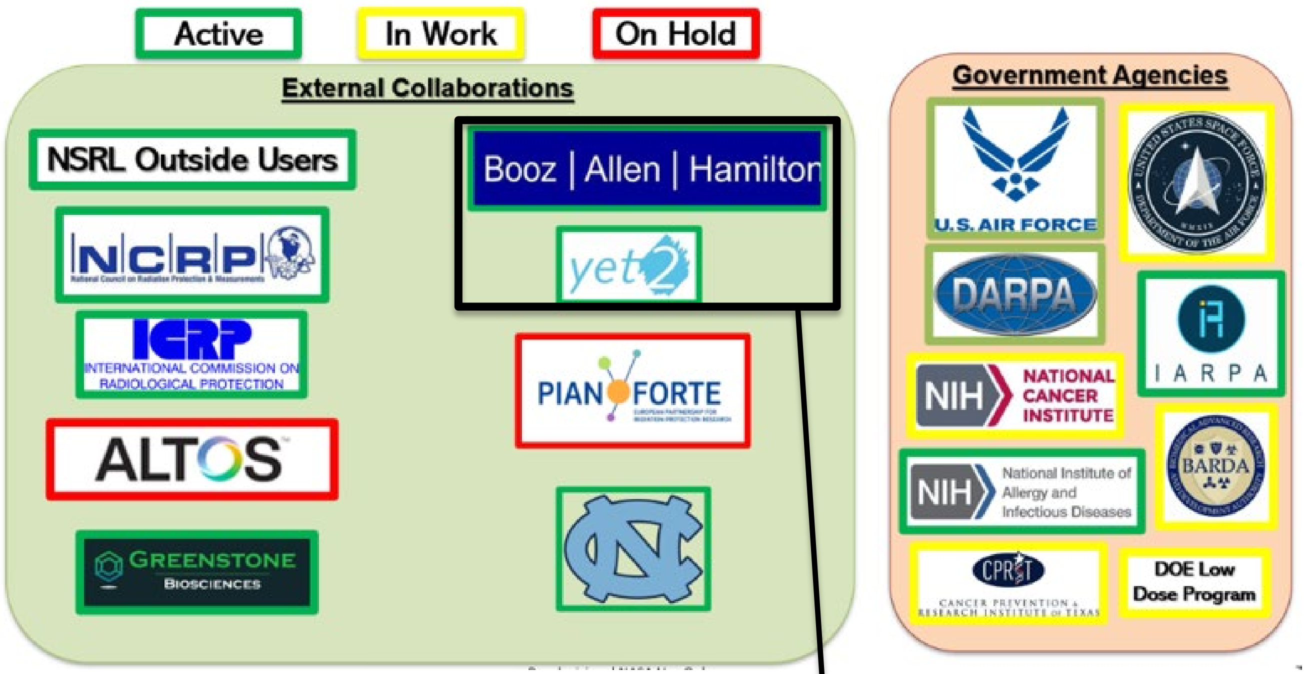
Pap smear
Tissue
Fecal sample
Hemoglobin
Methylated DNA



Screening and Surveillance Research Strategy

Surveillance/Screening Multi-prong Strategy:

1. Collaborations



2. Tech/Lit. Searches

Yet2 (Results in Research Emphasis 2)

3. Meetings

1. NASEM Workshop I: Enabling 21st Century Applications for Cancer Surveillance through Enhanced Registries and Beyond. July 29 & 30, 2024.
2. NASEM Workshop II: Opportunities and Challenges for the Development and Adoption of Multi-cancer Detection Tests: Oct 28 & 29, 2024
3. Occupational Flight Exposure and Cancer Risk Symposium (March 2025, Annual), Houston, TX.
4. Early Detection of Cancer Conference (Annual), Portland, OR.
5. American Association for Cancer Research (annual meeting in April 2026).
6. Precision Medicine World Conference (March 4-6, 2026)

Identify early surrogate biomarkers that correlate with cancer, pre-malignancy, or the hallmarks of cancer

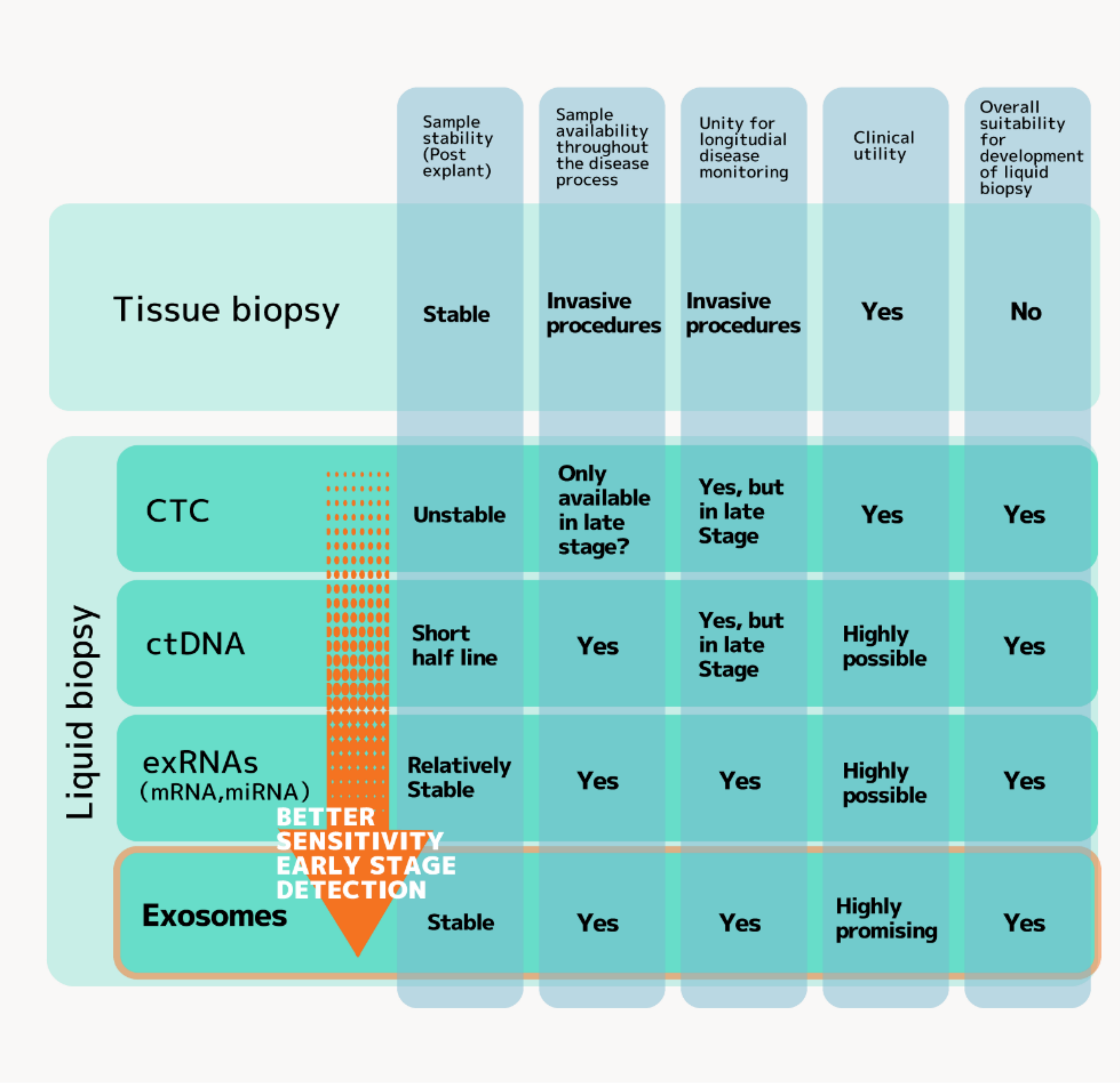
Task 2: Landscaping of Cancer Advances (Multi-Cancer Early Detection [MCED], Biomarker etc.)

POP: 2021, 2026, 2031, 2035

Aim 1: Technology watch(es) will be used to assess current and upcoming technologies with high technology readiness levels, and techniques to help identify and develop actionable cancer, CVD, and CNS biomarkers

Deliverables:

- Valid, actionable, and robust biomarkers of cancer, CVD, and/or CNS decrements
- Recommendations and incorporation of MCED into SRE-initiated clinical studies on long-term health
- Recommendations to clinical practice guidelines



		Sample stability (Post explant)	Sample availability throughout the disease process	Unity for longitudinal disease monitoring	Clinical utility	Overall suitability for development of liquid biopsy
Tissue biopsy		Stable	Invasive procedures	Invasive procedures	Yes	No
Liquid biopsy	CTC	Unstable	Only available in late stage?	Yes, but in late Stage	Yes	Yes
Liquid biopsy	ctDNA	Short half line	Yes	Yes, but in late Stage	Highly possible	Yes
Liquid biopsy	exRNAs (mRNA,miRNA)	Relatively Stable	Yes	Yes	Highly possible	Yes
Liquid biopsy	Exosomes	Stable	Yes	Yes	Highly promising	Yes

Research Emphasis 2, Task 2:
YET2 Insights and Observations

Yet-2: SolutionScape - 2021

Liquid Biopsy

- **Blood**
  - Thrive
  - GRAIL
  - Datar Cancer Genetics
  - StageZero Life Sciences
  - Nanostics
  - Freenome
  - Lucence
  - Bluestar Genomics
  - BioFluidica
  - Micronoma
  - Singlera Genomics
  - Hummingbird Diagnostics
  - Mercy Bioanalytics
  - Delfi Diagnostics
  - Guardant Health
  - Harbinger MSK
- **Saliva**
  - Summit Biolabs
- **Urine**
  - Entopsis
  - Hirotsu Bio Science
  - NIB Biotech
- **Breath**
  - Canary Health Technologies
- **Imaging**
  - Ezra
  - Ultrasonic Med. Mapping
  - Skin Vision
  - DermaVision
- **Multiple Sample Types**
  - Owlstone Medical
  - Ceres Nanosciences
  - Nucliex
  - Elypta
  - NuView Life Sciences
- **Other**
  - Cyrcadia Health
  - Skin DNA

New	Highly Interesting “A”
Interesting “B”	On Hold/ Rejected “C”

yet2

Research Emphasis 4, Task 1:
Identify and/or develop monitoring tools to support spaceflight research, long-term health surveillance, and countermeasure implementation

Multi-Cancer Early Detection – GRAIL Galleri Test

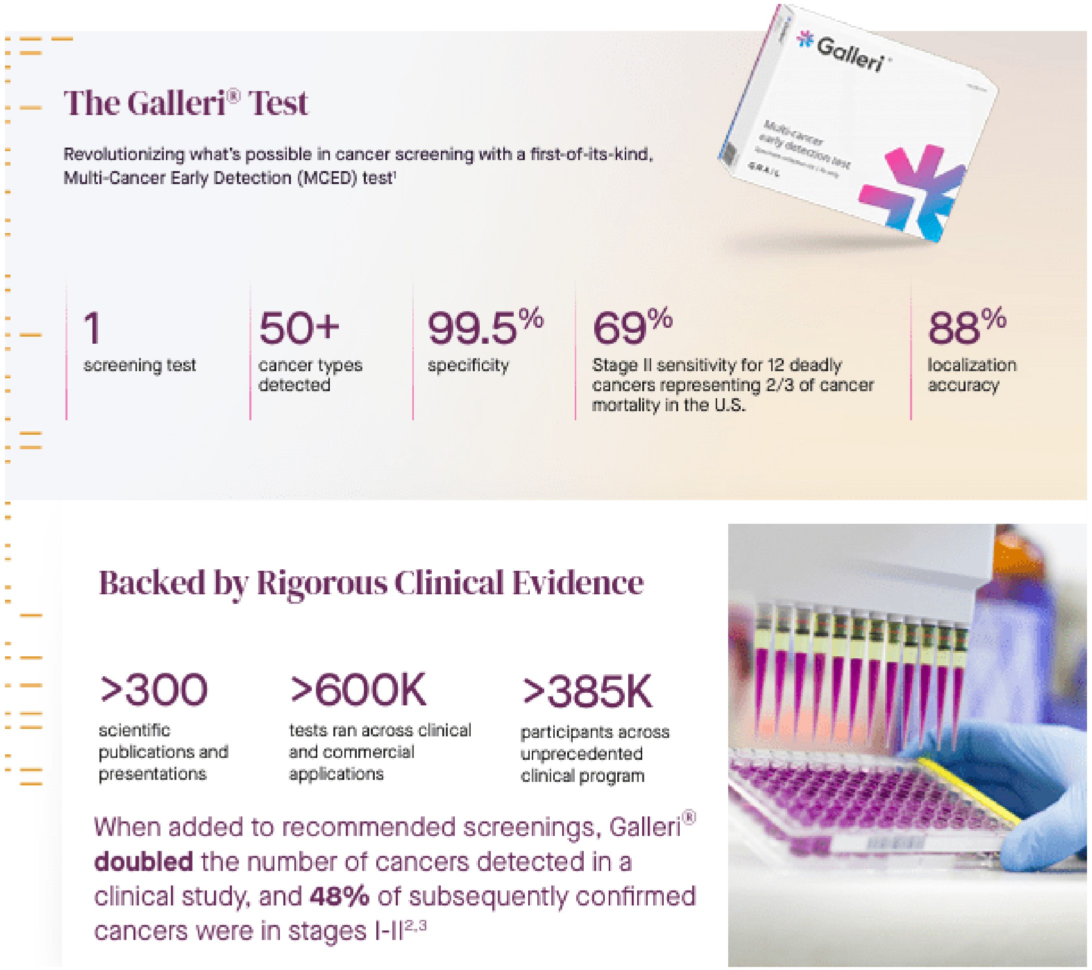
Consistent Results Across Studies

Clinical Validation Study (CCGA3)		
0.5% False positive rate	**44%** Positive predictive value	**89%** Localization accuracy

Confirmatory Intended Use Population Study (PATHFINDER)*		
0.5% False positive rate	**43%** Positive predictive value	**88%** Localization accuracy**

Refined test used commercially; **1st or 2nd location prediction

Klein EA, et al. Ann Oncol. 32:1167, 2021
Schrag et al. Lancet 402:1251, 2023



Purpose of Study:

- Captures measures of anxiety, acceptance/satisfaction with test
- Process testbed for incorporation into the astronaut corps
- Socialize test

Chen et al., Clin Cancer Res 27:4221, 2021

Research Emphasis 2, Task 3:
CHIP in Astronauts

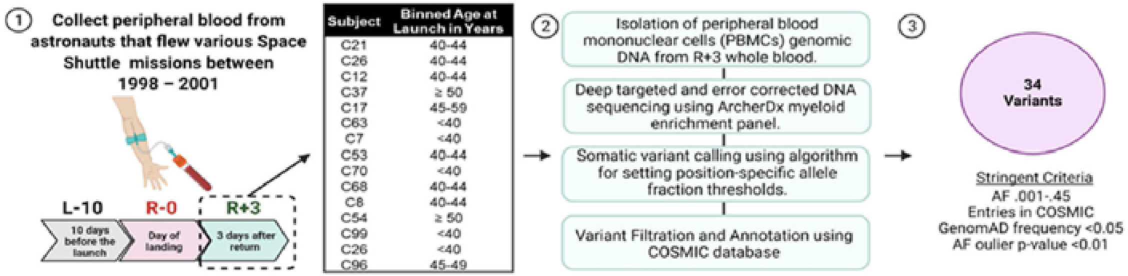
communications
biology

ARTICLE

https://doi.org/10.1038/s42003-022-03777-z OPEN

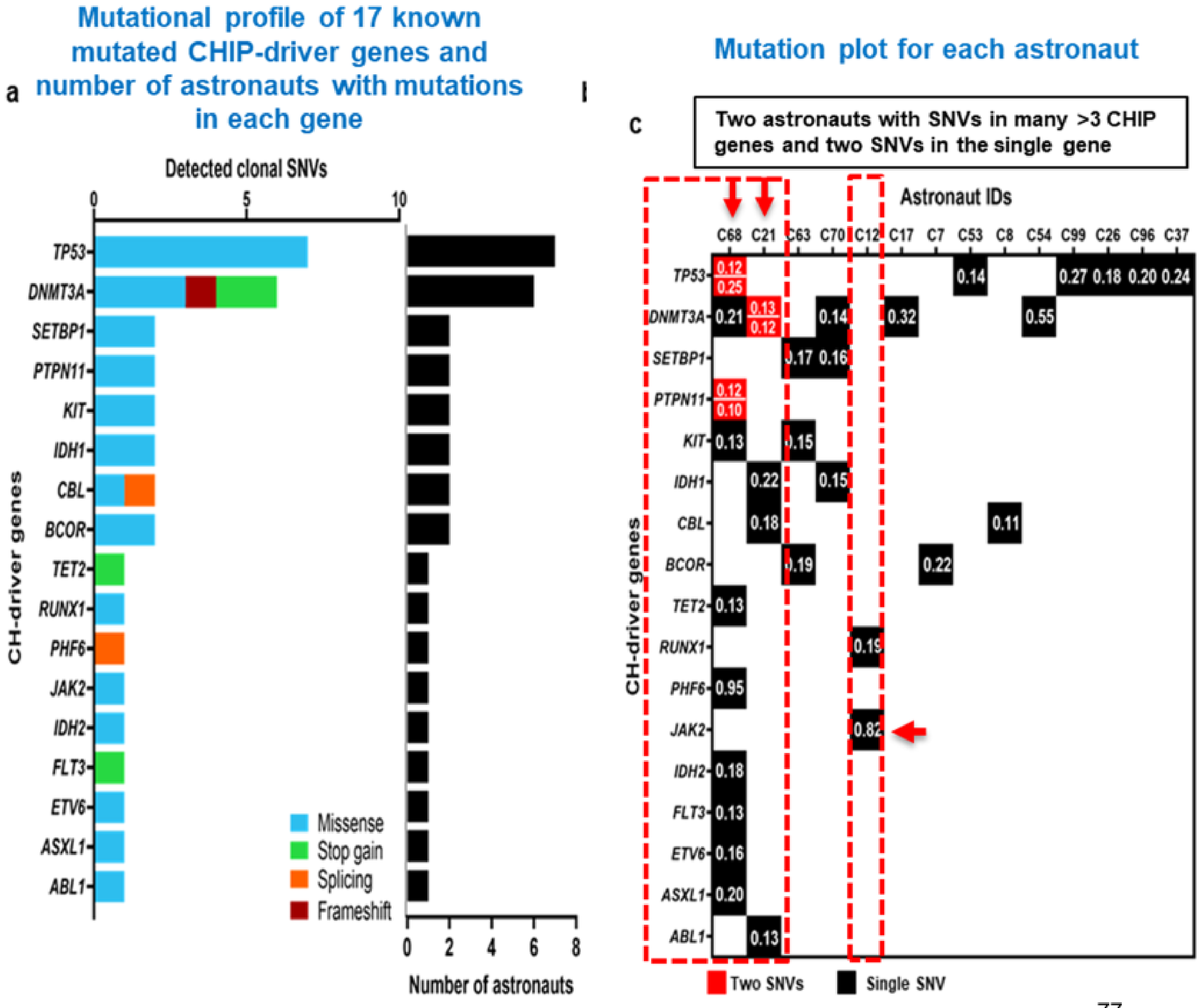
Retrospective analysis of somatic mutations and clonal hematopoiesis in astronauts

Agnieszka Brojakowska[1,5], Anupreet Kour[2,5], Mark Charles Thel[2], Eunbee Park[2], Malik Bisserier[1], Venkata Naga Srikanth Garikipati[3], Lahouaria Hadri[1], Paul J. Mills[4], Kenneth Walsh[2] & David A. Goukassian[1]✉



Subject	Binned Age at Launch in Years
C21	40-44
C26	40-44
C12	40-44
C37	≥ 50
C17	45-59
C63	<40
C7	<40
C53	40-44
C70	<40
C68	40-44
C8	40-44
C54	≥ 50
C99	<40
C26	<40
C96	45-49

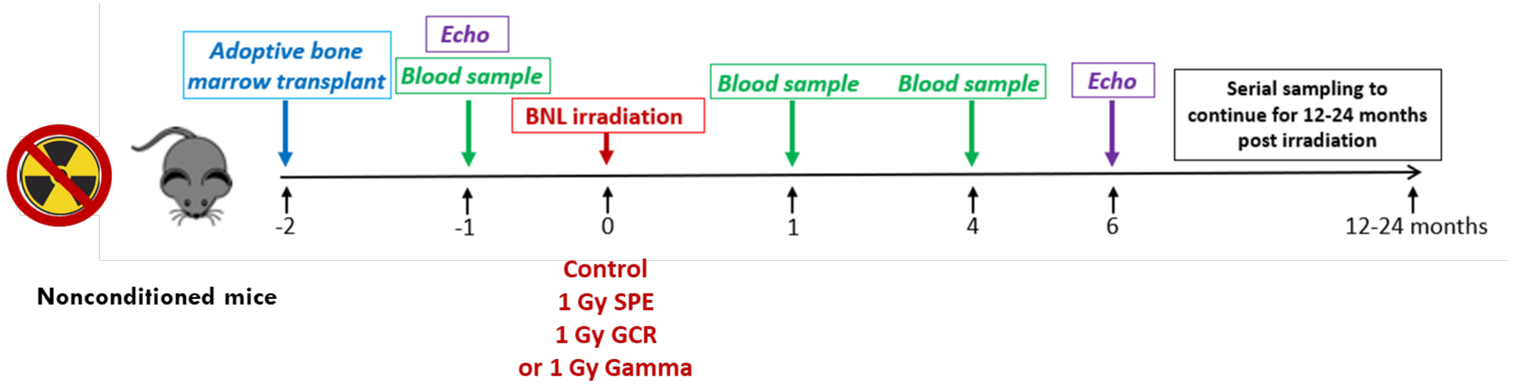
- Identified 34 nonsynonymous SNVs in 17 known CH-driver genes, of which TP53 and DNMT3A were the most frequent.
- 5/14 astronauts harbored mutations in at least two CH-driver genes, and subject C68 had variants in the four mutated genes.
- Clone size did not achieve the technical threshold of CHIP.
- The DDR gene TP53 was the most frequently mutated in this astronaut cohort (median age 44 years, range 37–67).



Research Emphasis 2, Task 3:
Understanding the sex-specific consequences of ionizing radiation on clonal hematopoiesis.
PI: Kenneth Walsh, IWS Student Augmentation: Megan Evans

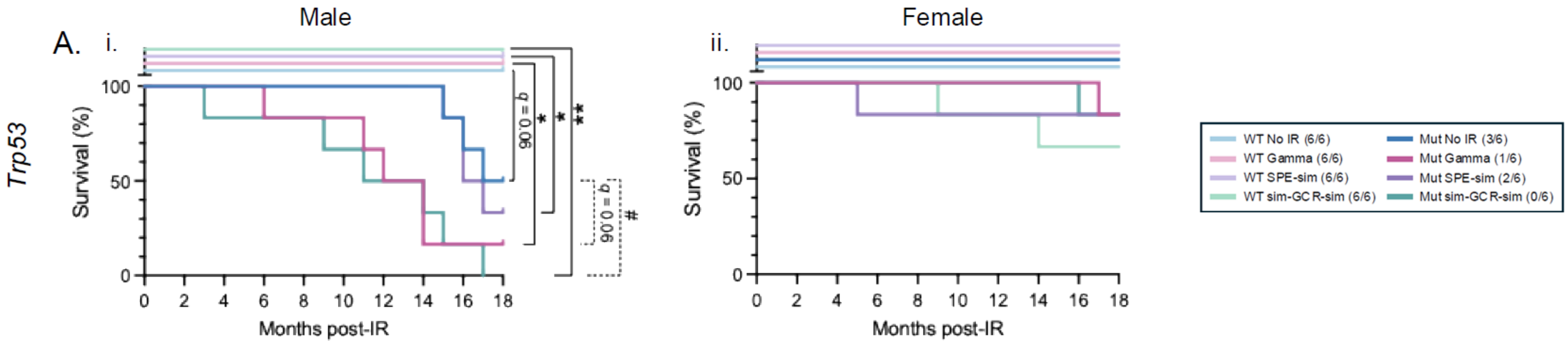
Relevance:

- Studying the effect of radiation on driving clonal hematopoiesis (CHIP), specifically TP53, PPM1D, TET2, and DNMT3A driver genes due to their association with CVD and cancer.
- **Easily measurable and could inform risk estimates but also post-mission surveillance for both cancer and cardiac.**



Observations:

- Some forms of clonal hematopoiesis are promoted by space radiation, with striking effects on morbidly and mortality (e.g. TP53)



Research Emphasis 2, Task 4:
Mosaic Loss of Y (mLOY)

The New York Times

As Y Chromosomes Vanish With Age, Heart Risks May Grow

A study of mice might explain why.

Share full article

A scanning electron micrograph of human X and Y suggests loss of the Y chromosome could explain m
Associates/Science Source

Popular Latest Newsletters *The Atlantic* Sign In

SCIENCE

The Disappearing Y Chromosome

It's surprisingly common for men to start losing entire chromosomes from blood cells as they age.

By Sarah Zhang

BBC Sign in Home News Sport Business Innovation

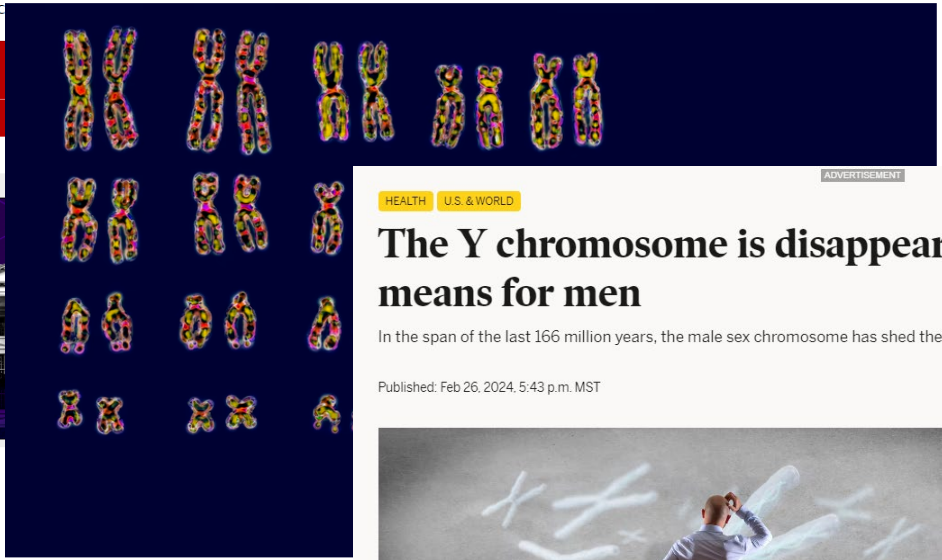
NEWS

Home | Israel-Gaza war | War in Ukraine | Climate | Video | World | US & Canada | UK | Business | Tech

Health

Y chromosome linked to cancer and death risk in men

22 October 2014



uman chromosomes, with a pair of XY and XX chro

HEALTH U.S. & WORLD

The Y chromosome is disappearing. Here's what it means for men

In the span of the last 166 million years, the male sex chromosome has shed the majority of its 1,600 genes

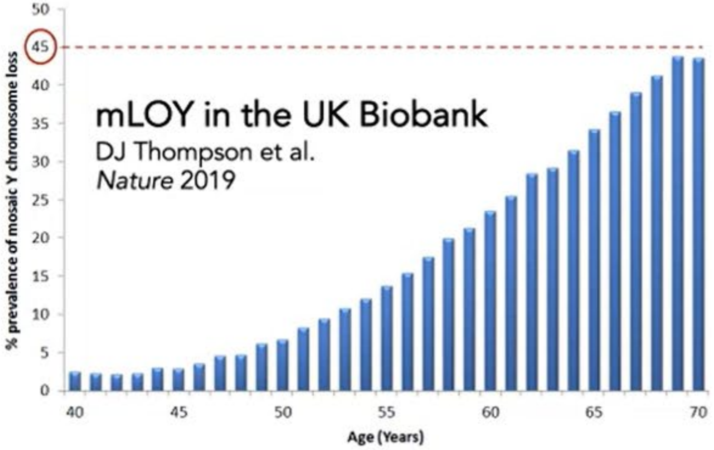
Published: Feb 26, 2024, 5:43 p.m. MST

VIEW COMMENTS SHARE

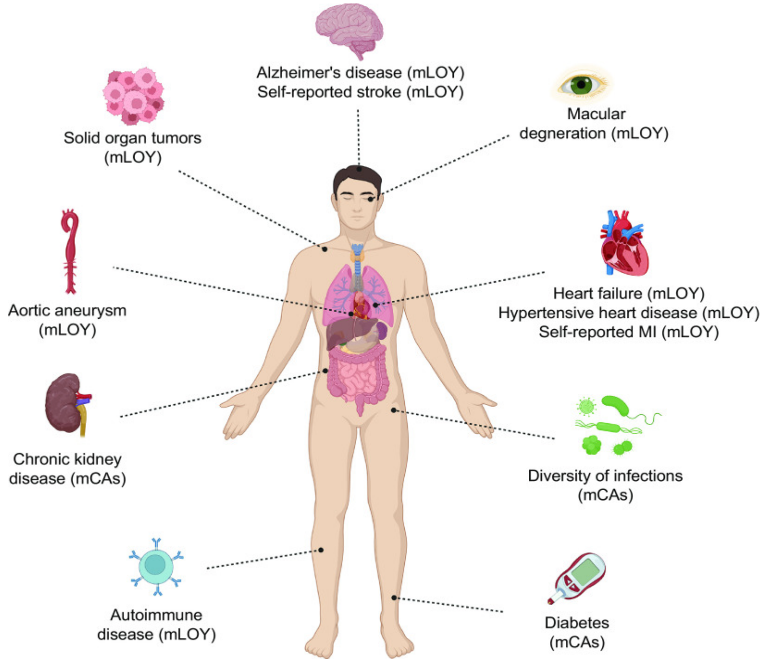
Scientists are monitoring the degradation of the Y chromosome in humans, and explaining what it means for the human race. | Adobe.com

By Alyssa Bradford
Alyssa is a trending desk writer for the Deseret News. She covers health and travel.

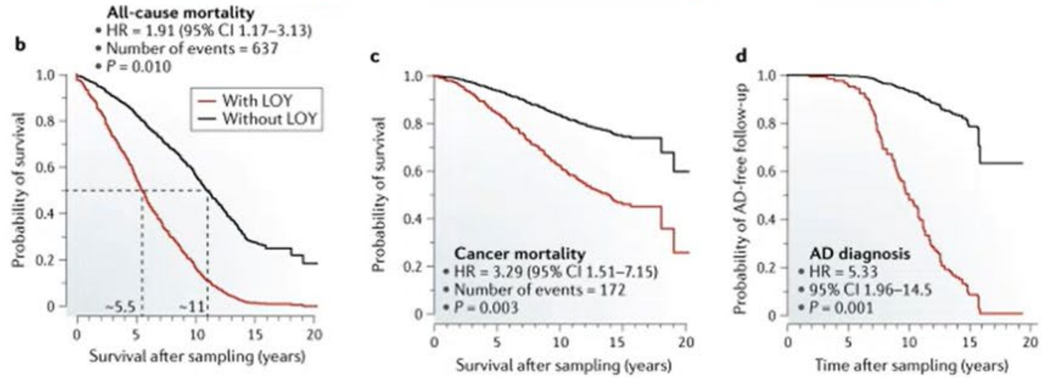
Research Emphasis 2, Task 4: Mosaic Loss of Y (mLOY)



~45% mLOY by age 70 in males



All-cause mortality | Cancer mortality | AD diagnosis



From Jobling and Tyler-Smith *Nat Rev Genet* 2017; 18:485-497

"I'm quite certain that the loss of the Y chromosome with age explains a very large proportion of the increased mortality in men, compared to women."

Lars Forsberg, Uppsala Univ.
New York Times, 2018

79 years | 73 years

M. A. Evans and K. Walsh Physiological Reviews 103:649-716 (2023)

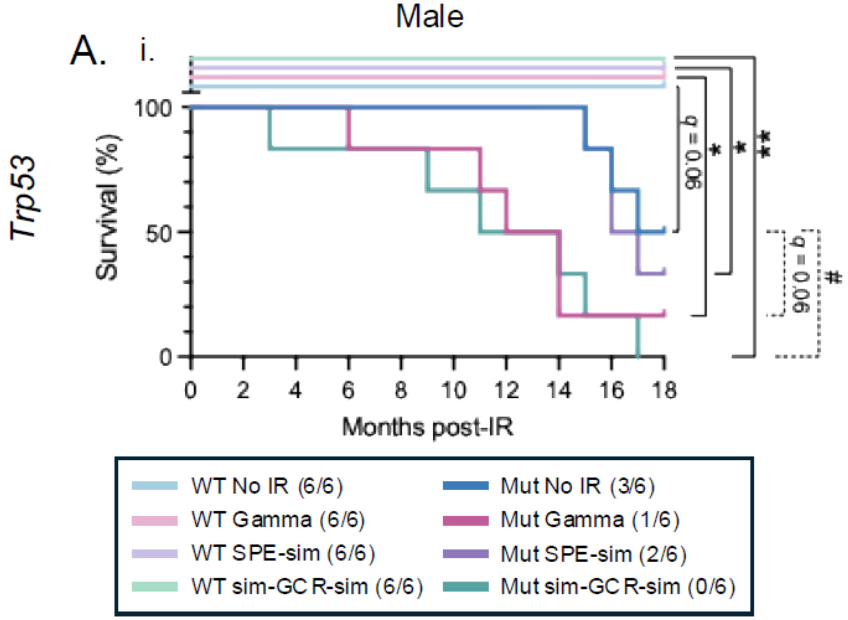
Research Emphasis 2, Task 4:
Understanding the sex-specific consequences of ionizing radiation on clonal hematopoiesis.
PI: Kenneth Walsh, IWS Student Augmentation: Megan Evans

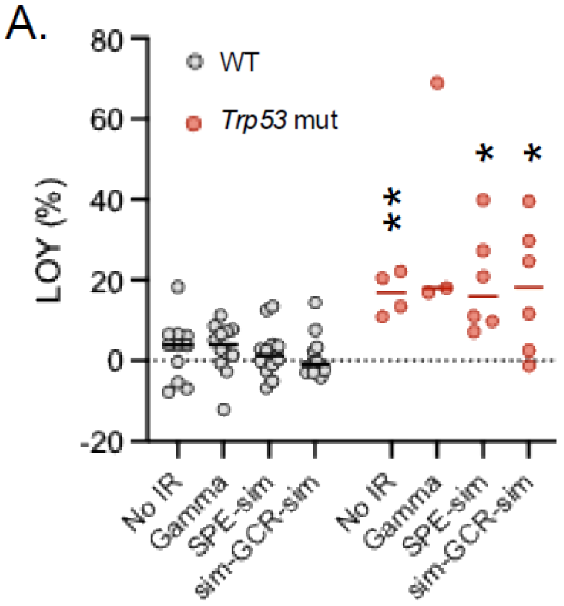
Relevance:

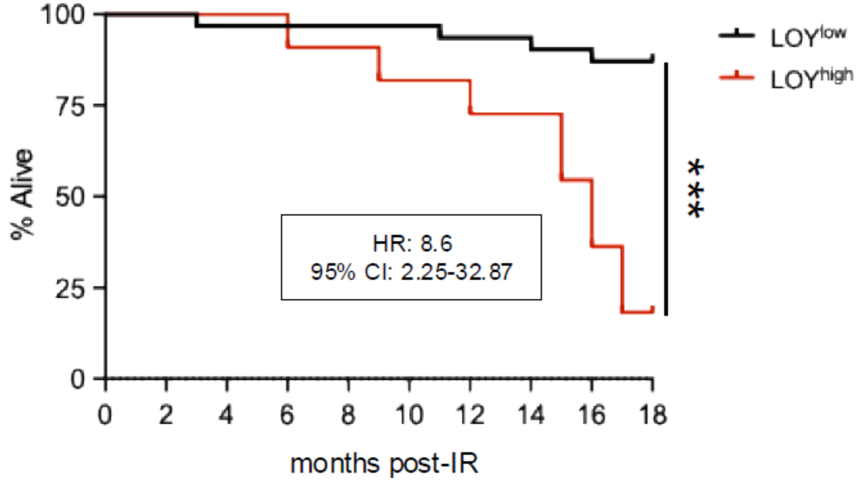
- Studying the effect of radiation on driving clonal hematopoiesis (CHIP), specifically TP53, PPM1D, TET2, and DNMT3A driver genes due to their association with CVD and cancer.
- Studying how the loss of the Y chromosome (LOY), only in male animals, may affect mortality in combination with CHIP and radiation.
- **Easily measurable and could inform risk estimates but also post-mission surveillance for both cancer and cardiac.**

Observations:

- Some forms of clonal hematopoiesis are promoted by space radiation, with striking effects on morbidly and mortality (e.g. TP53)
- Strong male-dependence of space radiation on survival in the TP53 condition may be partly explained by the tumorigenic effects of LOY.

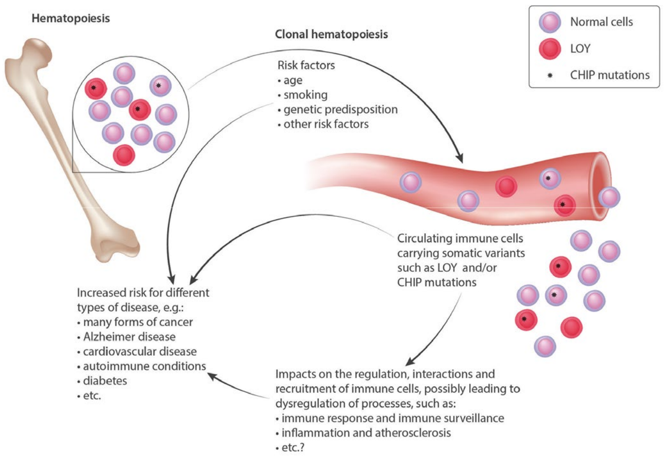






Research Emphasis 4, Task 2:
Long-Term Health Standard Measures Baseline

CHIP and mLOY



MCED

GRAIL

Galleri®

Disease Surveillance

Parkinson's Disease detection assays:

- Mito DNA_{DX}
- α-Synuclein

Timeline for LTH measures

Pre-flight Baseline/ASCAN | **One-Year Post Mission** | **Every 5 Years** | **End of Active Career** | **Post Retirement – Dependent on Crew Participation**

David P. Steensma et al. Blood 2015;126:9-16

Panagiotis Baliakas Lars A. Forsberg. Haematologica Vol. 106 No. 2 (2021): February, 2021

Cancer Risk Approach Plan

HRR Knowledge Gap	Risk Characterization	Countermeasure (CM) Development, Evaluation, Validation, and Integration
	Cancer-103: Determine the effects of **radiation quality** on cancer initiation, promotion, progression. **Cancer-104:** Determine the effects of radiation **dose and dose-rate** on cancer initiation, promotion, progression. (Brookhaven National Laboratory; ISS) 1 **NSCR update with Qnew development (2025)**	**Cancer-403:** Identify and/or develop potential **biomarkers** to support health surveillance and countermeasure implementation. **Cancer-504:** Identify and validate **safe and effective countermeasures** to reduce radiation carcinogenesis. **Cancer-604:** **Operationalize validated pharmaceutical countermeasures and surveillance technologies** for spaceflight. (Brookhaven National Laboratory; ISS; Artemis)
	Cancer-202: Evaluate the contribution of **genetic background/ diversity** on carcinogenesis risk. **Cancer-203:** Evaluate the **tissue-specific risks** of space radiation exposure on cancer outcomes. **Cancer-204:** Evaluate the **sex-specific risks** of space radiation exposure on cancer outcomes. (Brookhaven National Laboratory; ISS) 2 **NPR 8900 Baseline (PEL evaluation) (2025)** 3 **NPR 8900.1B Acceptance – Characterization Data (2030)**	4, 8 **Clinical Practice Guideline (CPG) Recommendations (2030, 2038)** 5 **Countermeasure Identification (2036)** 6 **8900 Acceptance - Mitigation Data (2038)** 7 **Integrated CM Toolkit (2038)** 9 **Fitness for Duty Standard Recommendations (2040)**

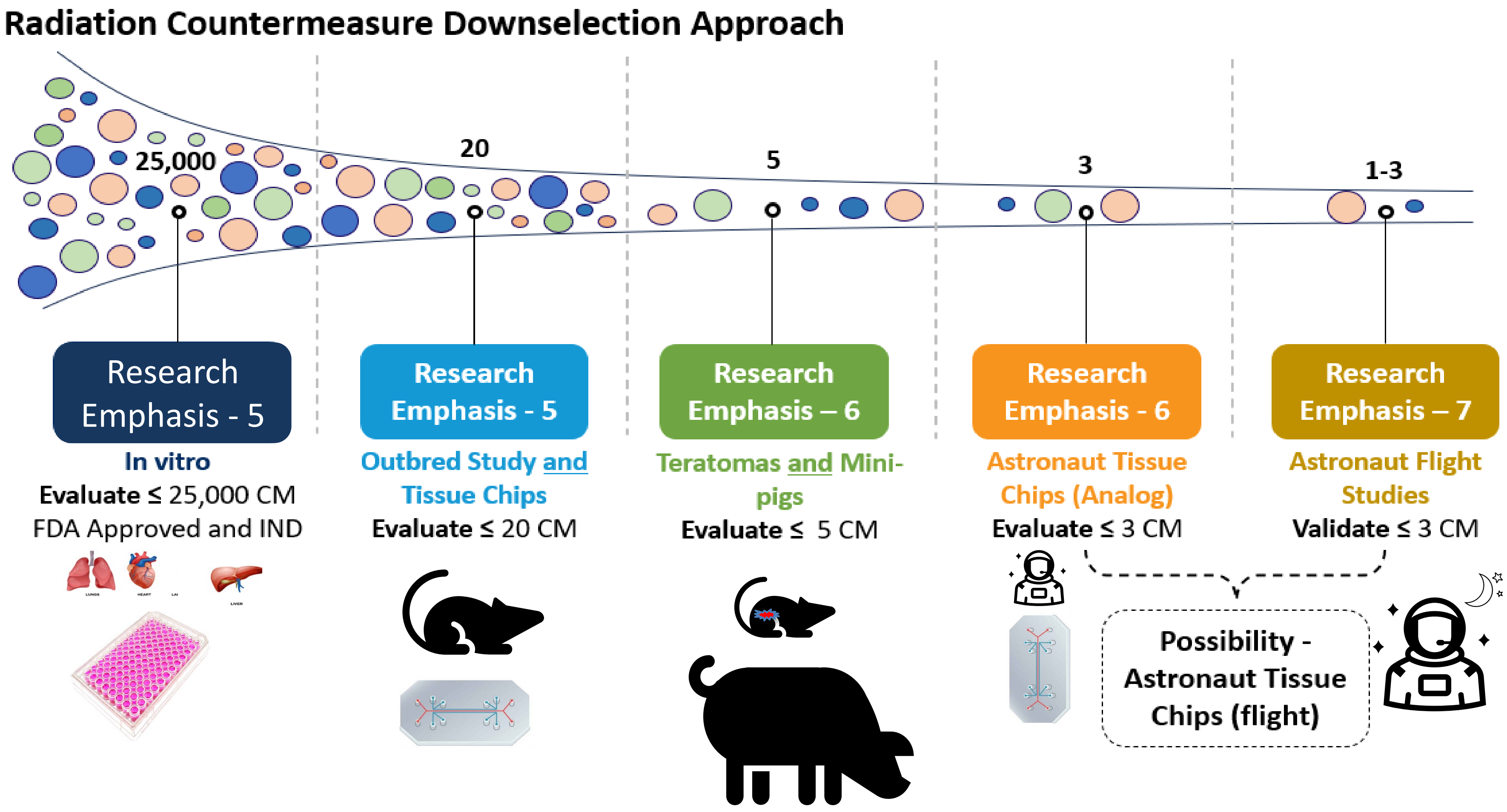
Legend: M2M Deliverable; Lunar Deliverable; ISS; Brookhaven National Laboratory; Artemis

Timeline

1, 2	3, 4	5	6, 7, 8	9
2025	2030		2038	2040

Risk Maps to ESDMD Gap ID # 0308

Pharmaceutical Down Selection Approach



BIOMARKERS

- Assessment of drug efficacy in tissue chips, animals and/or in astronauts
- Threshold of damage for delivery of the drug
- Personalized medicine approaches, determination of who is administered the drugs

Research Emphasis 4, Task 3:
Identification of Transcriptomic and Proteomic Biomarkers in Plasma and Urine Samples of Astronauts in CardioOx Study

PI: David Goukassian / Icahn School of Medicine at Mount Sinai

Experimental Design

Utilizing CardioOx Study samples

PRE-FLIGHT		IN-FLIGHT			POST-FLIGHT
180 days	45 days	15 days	60 days	160 days	5 days

Pre-flight: Baseline detection expression - Determination of interpersonal variability

In-flight: In-flight space hazard-associated alterations in biomarkers and the kinetics of changes over time – Novel biomarker identification and the assessment of validity with published plasma biomarkers and clinical data in this cohort of astronauts

Post-flight: Recovery or progression

n = 8 subjects

PLASMA

Cell Free Mitochondrial DNA (cf-mtDNA)
Cell Free DNA (cf-DNA
Cell Free RNA (cf-RNA)

PLASMA and URINE

In small extracellular vesicles (sEV)
RNA and Protein Biomarkers:
Messenger – mRNA
Small non-coding – miRNA, snRNA, snoRNA, tRNA
Long non-coding – lncRNA
Proteins

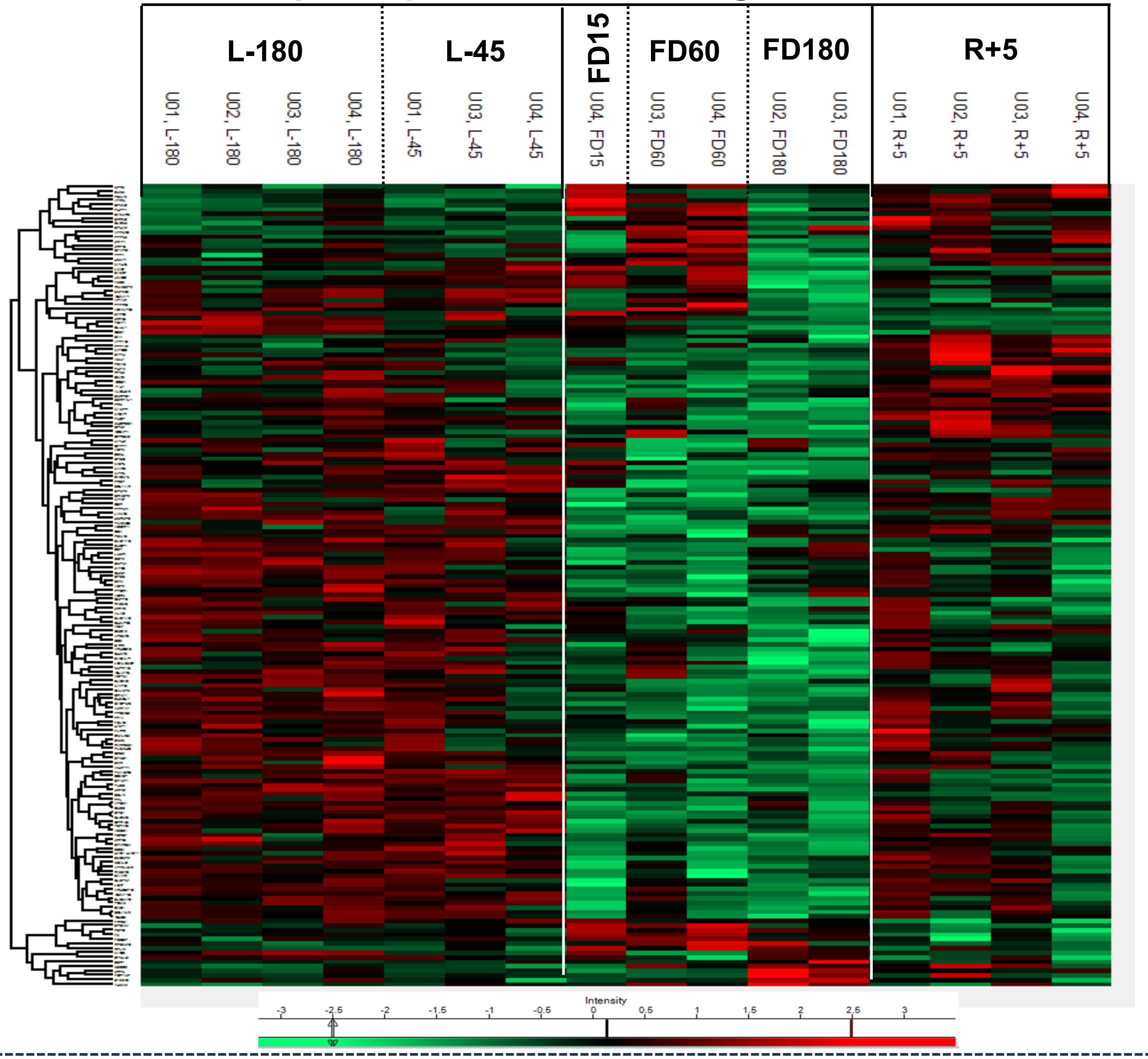
Research Emphasis 4, Task 3:
Identification of Transcriptomic and Proteomic Biomarkers in Plasma and Urine Samples of Astronauts in CardioOx Study

Top 3 upregulated proteins in URINE L-180 vs. Fs and R

FD15	FD60	FD180	R+5
ARTN 263-fold	IQGAP1 167	AHNAK 174	PSMA1 100
PSMA1 256	RPL7A 34	RPL7A 9	IQGAP1 85
NPR3 36	PTPRO 15	PEPD 3	MFGE8 28

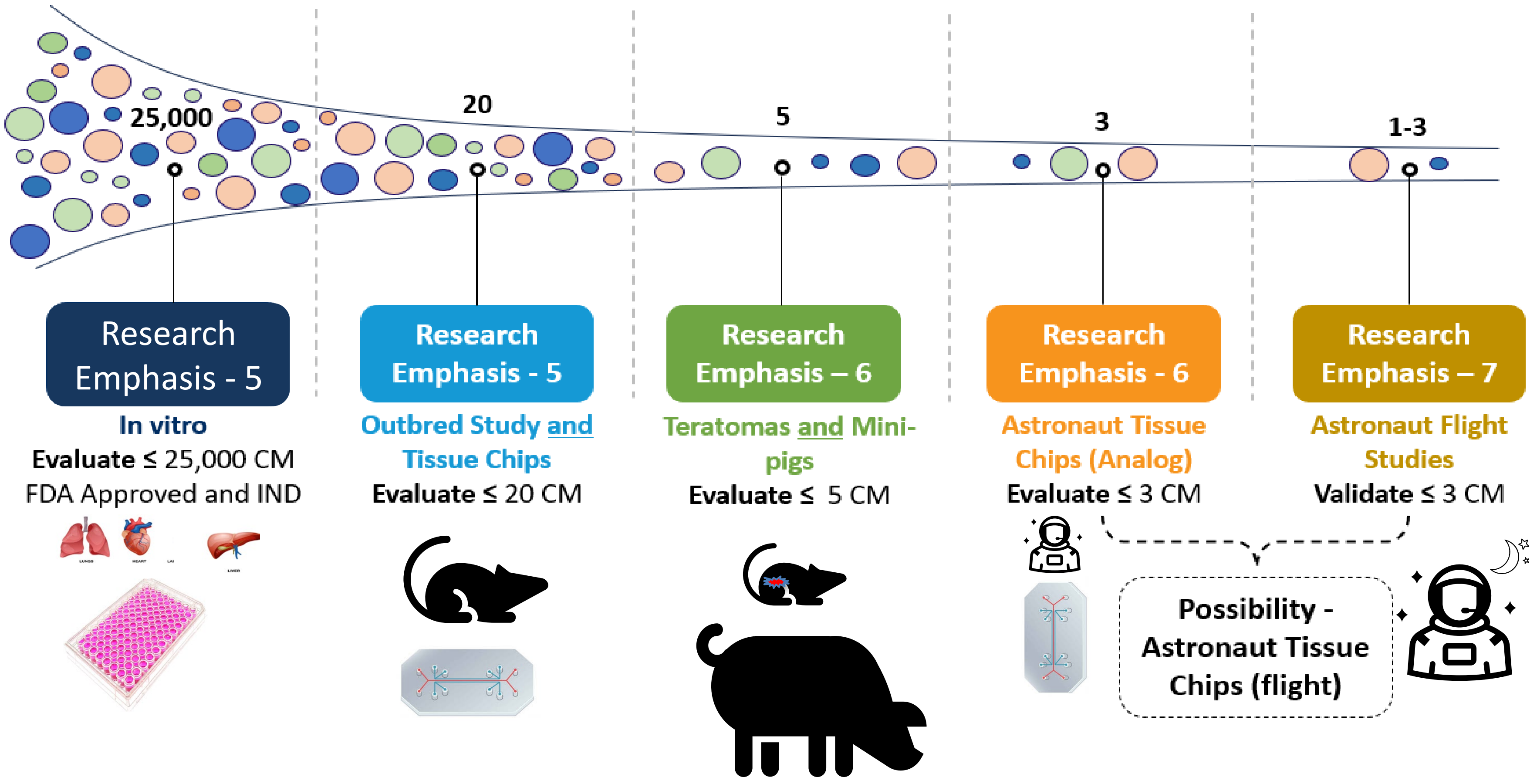
The **PSMA1** is a critical component of the 20S proteasome, a multi-protein complex responsible for degrading unneeded or damaged proteins inside a cell. **Gastric cancer:** High **PSMA1** expression is linked to poor prognosis, promotes the proliferation, migration, and invasion of cancer cells. **Lung cancer:** Overexpression of **PSMA1** is associated with poor prognosis and increased tumor growth in lung squamous cell carcinoma. **Triple-negative breast cancer (TNBC):** a circular RNA derived from **PSMA1** (circPSMA1) promotes tumorigenesis, metastasis, and migration. **Colon cancer:** High expression of **PSMA1** may be a biomarker for early-stage colon cancer. **RPL7A -** encodes ribosomal protein L7a, a component of the large 60S ribosomal subunit essential for protein synthesis. **Clinical Relevance** - up-regulation by ethanol in breast cancer, may influence translational regulation and contribute to tumor progression and metastasis.

Heatmap – Supervised Clustering URINE Proteins



Pharmaceutical Down Selection Approach

Radiation Countermeasure Downselection Approach

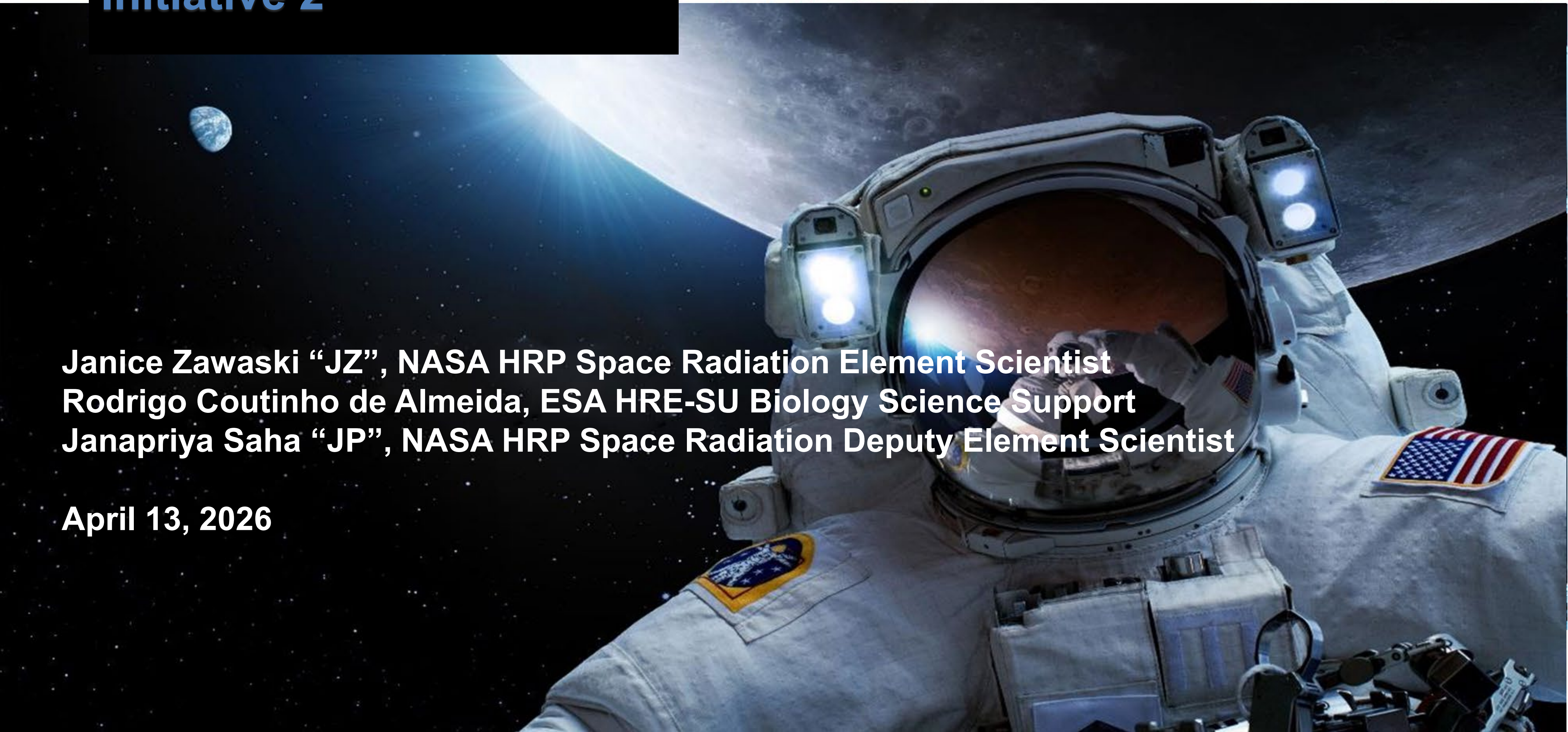


BIOMARKERS

- Assessment of drug efficacy in tissue chips, animals and/or in astronauts
- Threshold of damage for delivery of the drug
- Personalized medicine approaches, determination of who is administered the drugs

Radiation Working Group
Initiative 2

National Aeronautics and Space Administration



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Janapriya Saha “JP”, NASA HRP Space Radiation Deputy Element Scientist

April 13, 2026

- **Objectives:**
- Identify spaceflight-relevant gaps in radiation and omics research domains.
- Recognize opportunities for collaborations between agencies where these research gaps may be more efficiently addressed through international cooperation.
- Identify strategic (e.g. research roadmaps/strategy) and/or tactical (e.g. individual studies) level opportunities.
- Determine whether and where it may make sense for agencies to standardize research methodology and data standards.

Length:

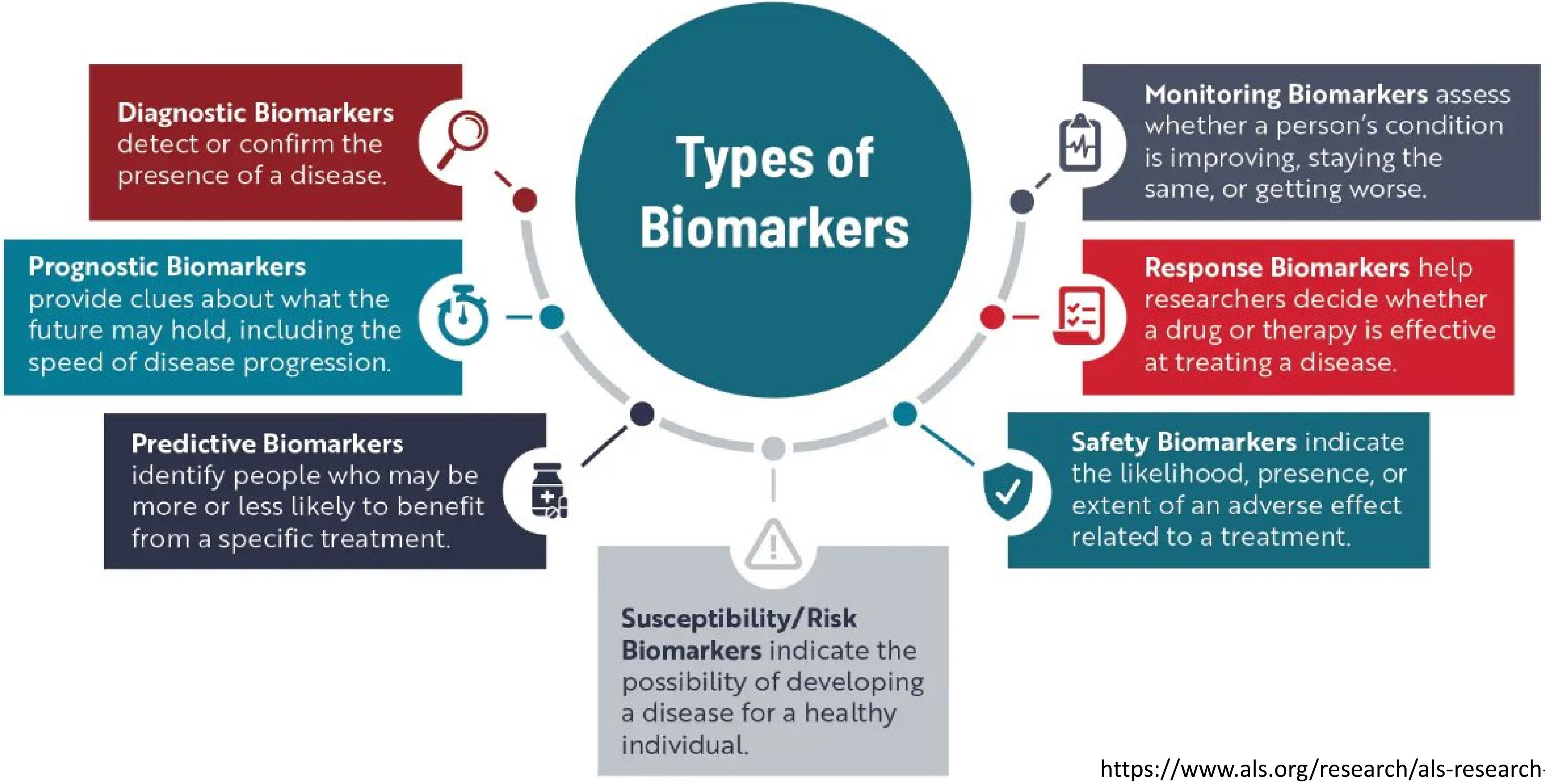
- Initially 8 Agencies represented but afterwards only ESA, NASA, CSA, ASI and JAXA were actively participating.

LESSONS LEARNED

- Focused objective
- Appropriate meeting cadence with time commitment from POC
- Appropriate POC (knowledgeable/doers)
- Inclusion of agencies with active work
- Semiannual reporting out

BIOMARKERS

Definition: Biomarkers (biological markers) are objectively measured, quantifiable characteristics—such as proteins, genes, or imaging findings—that indicate normal or abnormal biological processes, disease states, or pharmacological responses to treatment. They function as biological clues **to diagnose diseases early, predict risks, or determine if a therapy is working.**



https://www.als.org/research/als-research-topics/biomarkers

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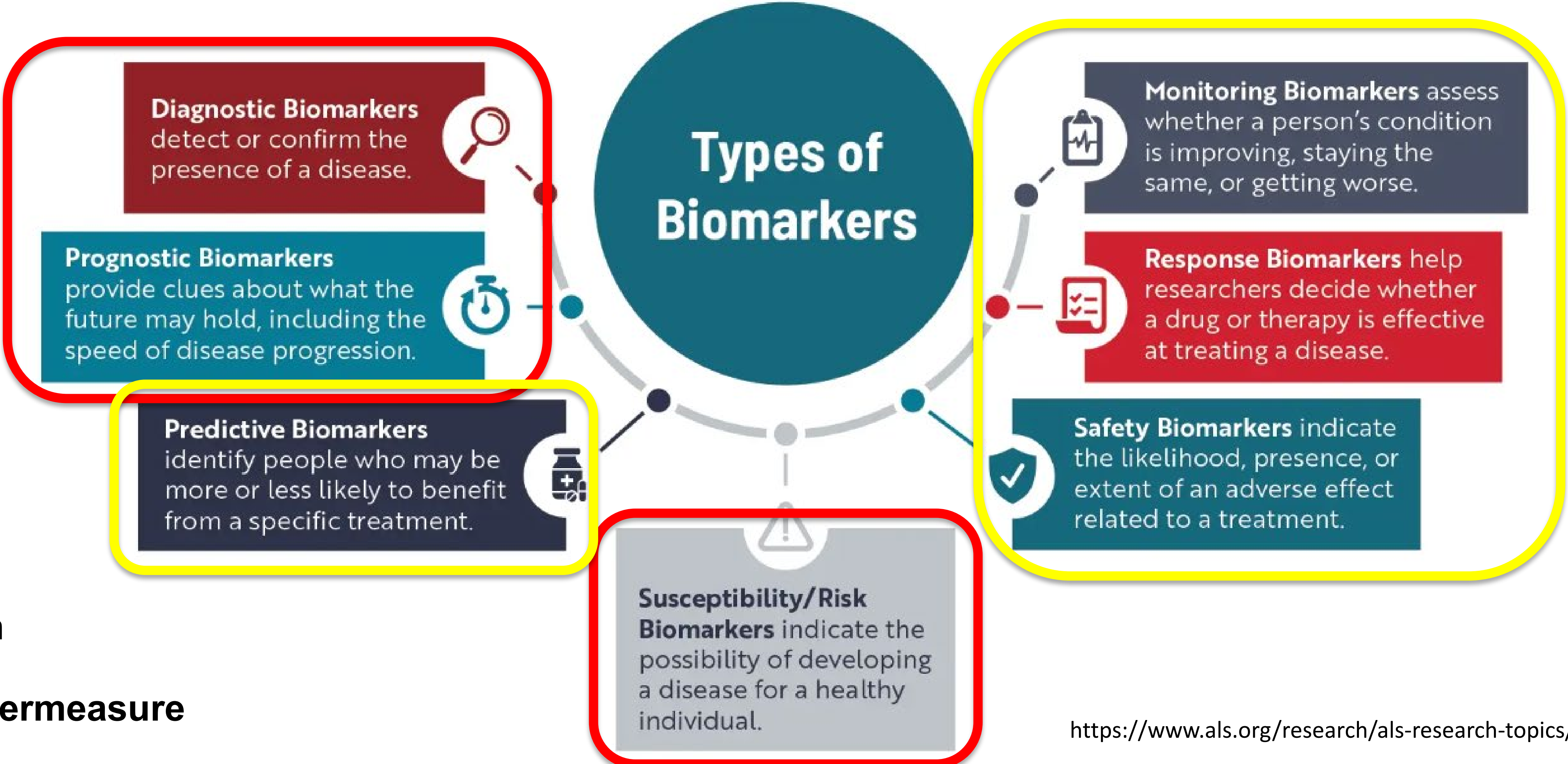


Health

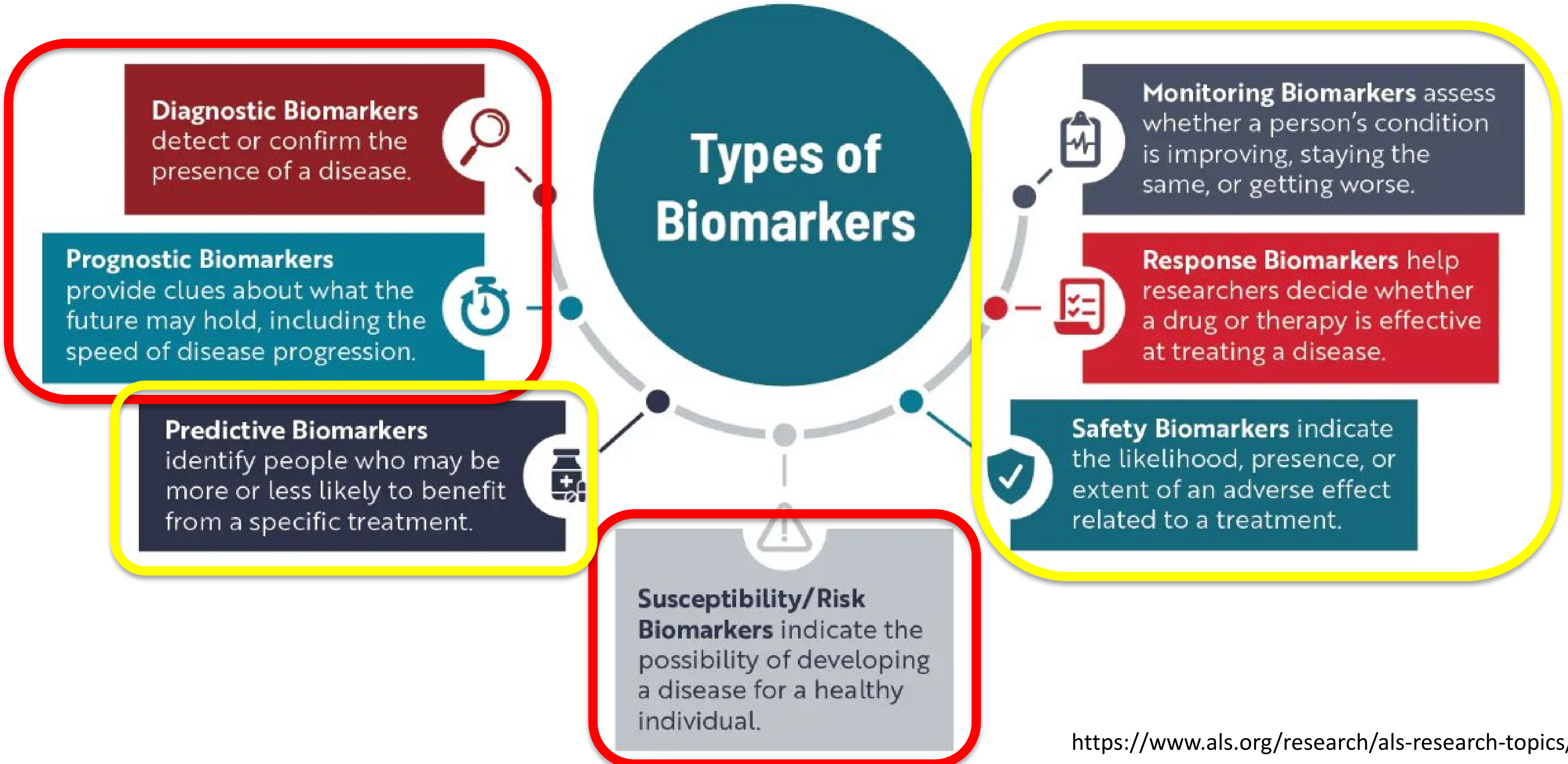
Countermeasure

https://www.als.org/research/als-research-topics/biomarkers

BIOMARKERS

Health (Cancer, CVD, CNS, Accelerated Aging)

Informs Countermeasure Administration



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SCHEDULE AND AGENCY INCLUSION

Meetings schedule: Monthly for the first 6 months and then we will reevaluate

Inclusion: Agencies with active biomarker work or techniques to identify potential biomarkers

- Knowledgeable in biomarker area
- Time availability
- Well connected with others

REPORTING

- **Meetings will be recorded**
  - For awareness videos can be dispersed regardless of inclusion of a POC
- **Actions documented**
- **Results will be presented semi annually**
  - ISLSWG

Thank you for your attention!

Questions?