Mitigation Strategies for Space Radiation Health Risks

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Introduction

Astronauts embarking on missions beyond low Earth orbit (LEO) will be exposed to a radiation field that may increase the risks of developing cancer, cardiovascular diseases, central nervous system disorders, and immune decrements. Operational parameters will be the primary determinants of crew radiation exposure. NASA uses integrated design tools and risk models to optimize these parameters to minimize radiation exposure. NASA is also considering medical countermeasures (MCMs) to reduce radiation-associated health risks.

MCMs for potential use in space-based applications can be developed from a variety of sources, including:

a) population-based chemoprevention trials against targeted diseases

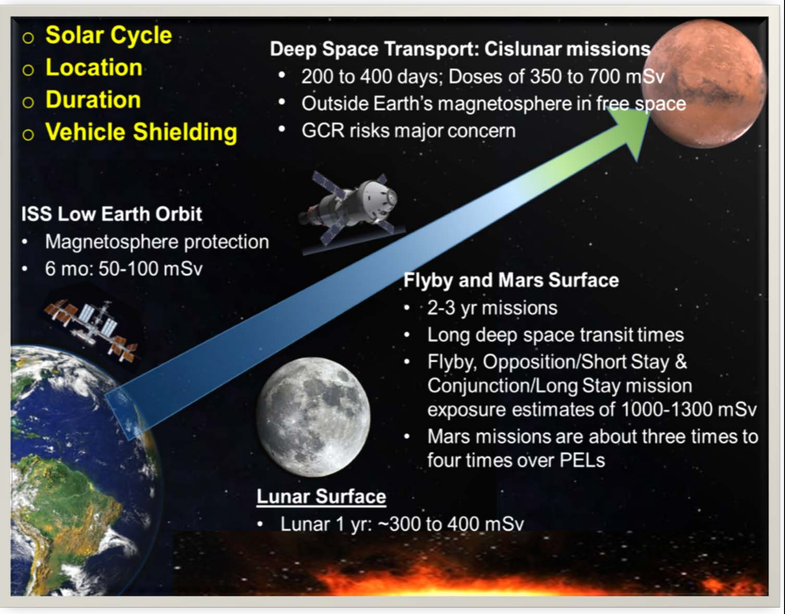
b) drug development efforts focused on treating acute effects from accidental radiation exposures

c) drug development to mitigate side effects of radiotherapy

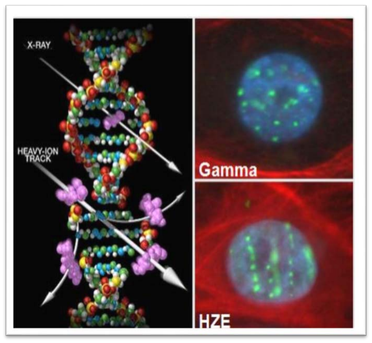
d) mechanistic studies of distinct damage caused by high charge (Z) and energy (HZE) radiation

Use of agents developed for other applications, or repurposed, is advantageous because long-term safety in humans is already established.

Mission Specific Radiation Dose Estimates



Space Radiation Health Risks



Unique Challenges

- *Radiation Quality Effects*
- *Low Dose-Rates in Space*
- *Understanding Individual Susceptibility/Sensitivity*
- *Quantifying Combined Stressors – "Spaceflight Exposome"*

DNA Damage in Cells: Space radiation (HZE) produces densely ionizing particle tracks associated with complex DNA damage and unique biological responses.

[Cucinotta & Saganti (left), Patel & Huff (right), NASA]

Risk Reduction Strategies

Pre - Mission

- Space Rad Environmental Models and **Mission Design** (ALARA)
- **Ensemble Models of Risk Projection** - Increase safe days in space - Understand impact of medical advances on mortality projections
- **Crew Selection**: age, sex, healthy worker effects
- Pre-screening for **Individual Susceptibility** and early disease indicators* (Genetic, Biomarkers)

In - Mission

- **Mission Location & Duration**
- **Solar Conditions** - Min vs. Max
- Optimized GCR **Shielding** with Storm Shelter
- **Operational** Planning: Monitoring/Dosimetry
- **Medical Countermeasures** Radioprotectants & Mitigators (Pharmaceutical, Nutritional, Exercise)
- **Biomarkers/Inflight detection** genomic health/personal risk indicators

Post - Mission

- Occupational **Health Care** for Astronauts
- **Advances in Terrestrial Treatments** – Precision Medicine*
- **Biomarkers:** health monitoring for early disease detection, and targeted treatments
- **Medical Countermeasures**

**long-term development*

- Enables longer mission durations
- Allows for larger portion of crew office to qualify for flight

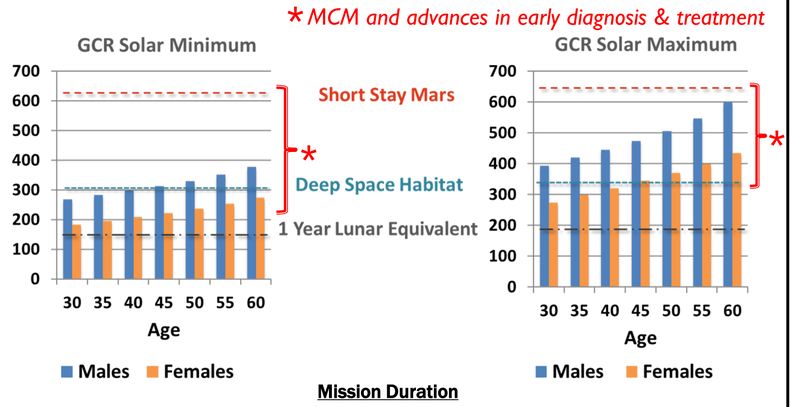
Reduction in Total Risk Posture

- Increased quality of life & outcomes

Reducing Exploration Mission Radiation Risks

"Safe Days" in Space: Current State of Knowledge

* *MCM and advances in early diagnosis & treatment*



Mission Duration

Short Stay Mars: 621 Days

Deep Space Habitat: 364 Days

1 Year Lunar Stay: ~230 equivalent days in free space needed

Required number of "Safe Days", delineated by age and sex, for a given mission to be within agency Permissible Exposure Limits (Not to Exceed 3% Cancer Risk of Exposure Induced Death)

Note: Measurements with 20g/cm² Aluminum shielding; NSCR 2012_V2 never smokers: updated per T. Slaba calculations June 2018

Space Radiation Countermeasures – Agent Selection Criteria

Requirements Driven by Mission Operations

- FDA approved, FDA Off-label, FDA IND Status drugs - "repurposing" clinically ready agents, chemopreventive agents, dietary supplements, nutraceuticals, probiotics, anti-aging drugs
- Minimal side effects in humans with proven long-term use
- Chronic administration (potentially during and after mission)
- Mechanism of action well known
- Easily self administered (e.g. oral, inhaled)
- No contraindications with other drugs
- Long shelf-life

Challenges

- Potential side effects of therapeutic treatments in otherwise healthy individuals
- Long timelines for disease development
- Potential need for long term use
- Lack of validated predictive biomarkers to serve as intermediate endpoints

Potential Preventive Strategies – Enhance DNA repair, scavenge electrophiles and ROS, decrease inflammation, suppress proliferation, enhance differentiation, enhance immunity, target aging-related pathways

Summary

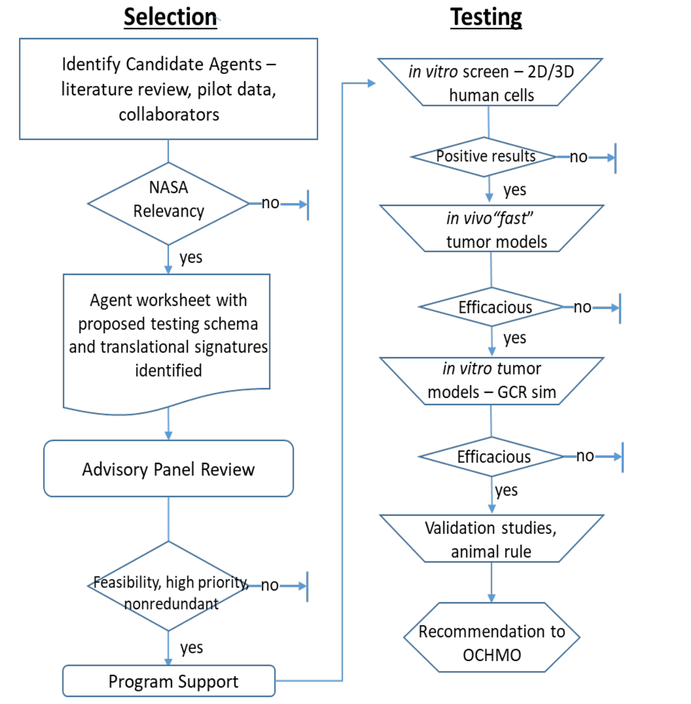
Radiation environment in space is associated with significant health risks to crew with development of late cancers as a key driver limiting safe days in space.

In addition to optimizing mission parameters and shielding to reduce space radiation exposure, development of effective medical countermeasures as a mitigation strategy, although challenging, is warranted.

One approach is to use a streamlined decision-gate agent selection and testing process for agent evaluation modeled after process developed by the National Cancer Institute's Division of Cancer Prevention.

- **Leverage external body of evidence to screen drugs with known safety profiles – Repurposing**
- Oversight by advisory panel to include flight surgeons, external experts, key NASA personnel
- Focus on chemoprevention - natural, synthetic, or biologic agents, able to delay, reverse, or inhibit tumor development
- Focus on highest at risk tissues where early detection options are not robust, such as breast & lung, as well as cancers with short latency that have potential to manifest in-mission (leukemias)
- Leverage scientific knowledge and recent advances in understanding of premalignant biology
- Target agents with potential cross-risk efficacy
- Tech watch for advances in immunoprevention strategies, senolytic drugs, and precision medical approaches applicable to astronauts
- FDA animal rule approach will be used for agent validation, as required
- Partner with external agencies with common interests
- Develop risk assessment strategies incorporating MCM

Decision-Gate Agent Selection & Testing



Decision-gate process for selection and testing of MCM for space radiation health risks.

- *Increase likelihood of success by implementing defined criteria and protocols*
- *Candidate agent selection – must meet mission criteria, safety profiles, with supporting literature*
- *Testing protocol has a clearly established translational path*
- Modeled after process developed by the National Cancer Institute

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NIH NATIONAL CANCER INSTITUTE Division of Cancer Prevention

Generalized Drug Repurposing Pipeline for Space Radiation MCMs

	Testing Capacity	Platform	Endpoint/Goal
in vitro screen-human cell based		2D - high throughput (ex. ROS scavenging, DNA repair, proliferation) 3D organoid –premalignant biology (ex. inflammatory signatures, genomic instability)	Functional *in vitro* activity modification of diseases processes – includes primary & secondary prevention
in vivo screen – animal models		"Fast" tumor models – (GEMMs, imaging for early tumor detection)	Functional *in vivo* modification of disease processes, intermediate endpoints-translational signatures
in vivo GCR sim – animal models		Tumor models - GCR sim	Functional *in vivo* modification of disease incidence, overall burden or time to occurrence
in vivo validation		Tumor models – GCR sim, Alternate models, diversity outbred pop	FDA animal rule, dosing, etc.
Precision medicine		Astronaut avatar models / Digital twins	Individual susceptibility, tailored treatment options

Criteria

In vitro screens:

- Endpoints must be predictive of benefiit in human disease - follow a translational path
- Sufficient capacity to screen multiple compounds

In vivo screens:

- Utilize intermediate endpoints - reasonably likely surrogate endpoints
- For cancer chemoprevention, focus on premalignant biology
- Utilize non-invasive imaging

Tumor models:

- Capture early events in cancer initiation, as well as progression
- Exhibit histological & biological features in common with human disease
- Dysregulation in related molecular pathways

Exposure Scenarios Defined:

- Screening - single mixed field dose, gamma controls, minimal drug dosages, males only, unless sex-specific tumor
- Validation - requires GCR simulator and FDA animal rule