



Mitigating Space Radiation Health Risks: Challenges and Opportunities

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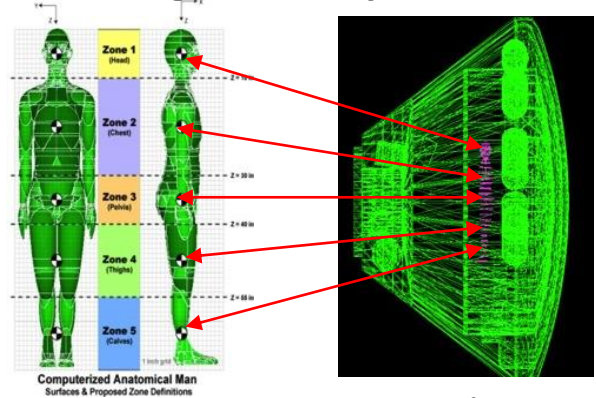
NCRP 2021 Annual Meeting
April 20, 2021

Protection and Mitigation Approaches



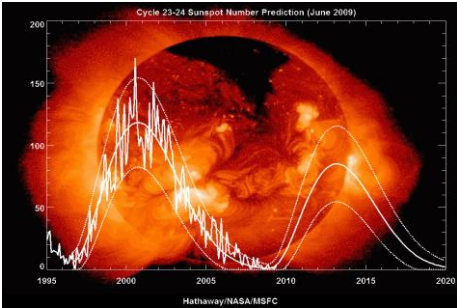
- Mission Design
- Shielding / Storm Shelter
- Operations
- Ensemble Models of Risk Projection
- Crew Assignment
- Individual Susceptibility
- Biomarkers
- Occupational Health Care for Astronauts
- Advances in Terrestrial Medicine
- Countermeasures

Shield Design and Optimization



courtesy of OLTARIS.nasa.gov

Solar Activity

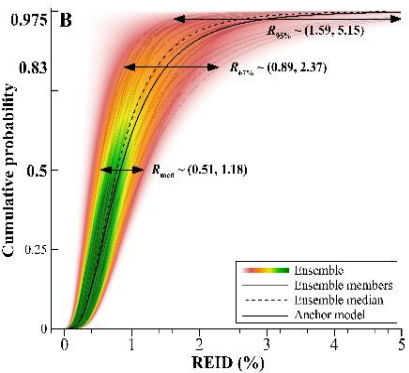


Exercise & Diet

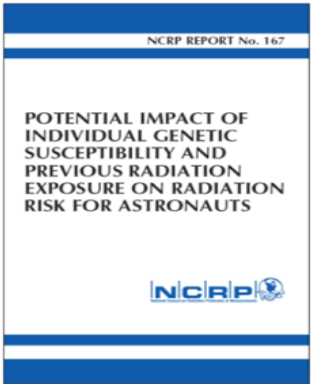


Image courtesy of NASA

Accurate Risk Assessment



Individual Susceptibility



(NCRP 2011)

Medical Countermeasures



Spaceflight Hazards

Radiation

Altered Gravity

Hostile, Closed Environment

Isolation, Confinement

Distance from Earth

HUMAN RISKS

Sex

Lifestyle

Personal History

Age

Individual Factors

Microbiome

Genetics, Epigenetics



SR Countermeasures – Agent Selection Considerations

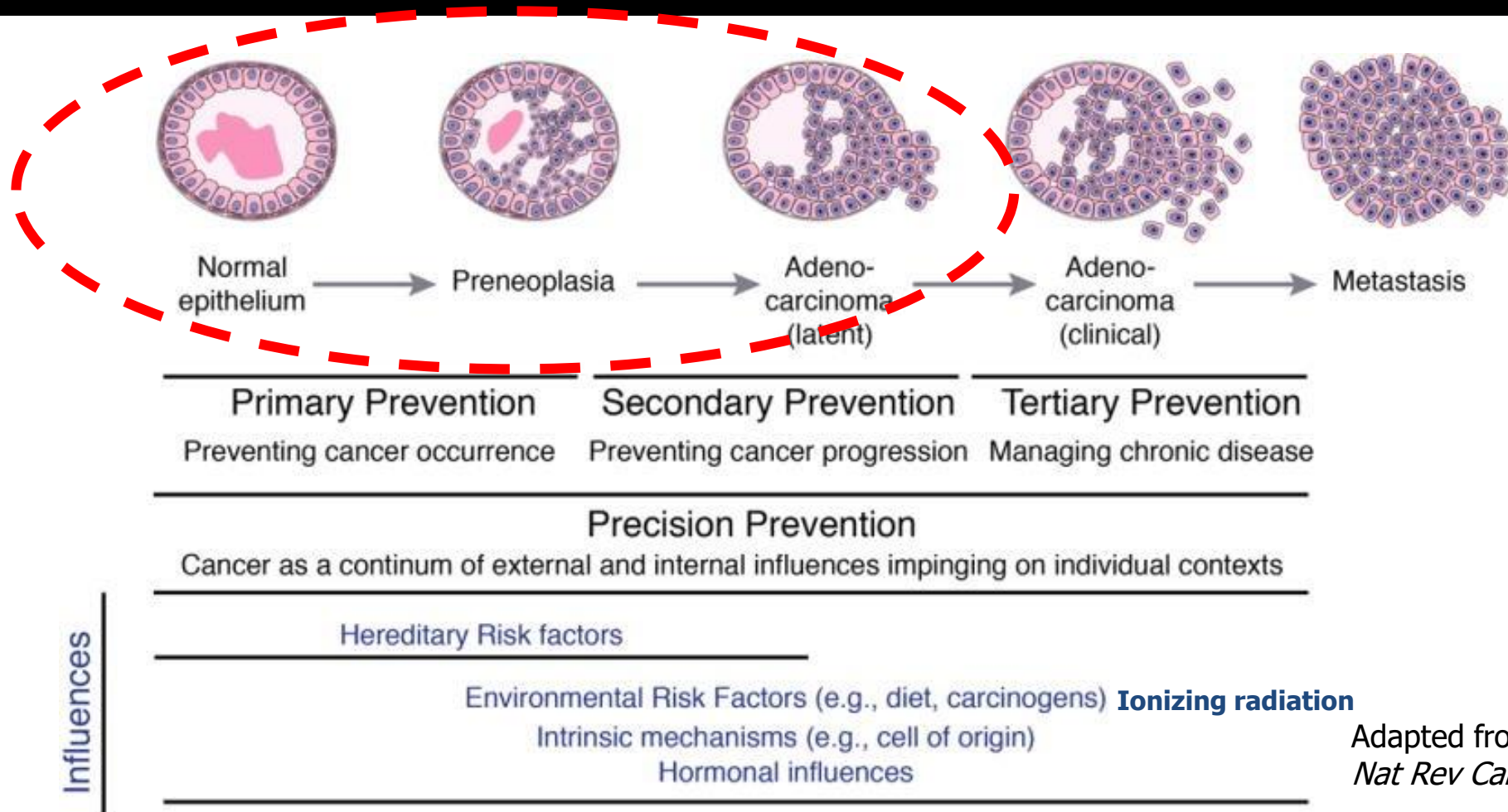


Attributes/requirements driven by mission operations:

- FDA approved, FDA off-label, FDA IND Status drugs (timeline and budget)
- Mechanism of action well known
- Minimal side effects in humans with proven long-term use
- Chronic administration (potentially pre- in- and post-mission)
- Easily self-administered (e.g., oral, inhaled)
- Long shelf-life
- Works in spaceflight realistic environment – GCRSim, Microgravity
- No contraindications with other drugs
- Cross-risk, targeting common disease pathways (ideal)



Stages of Cancer Development and Points of Intervention



Adapted from Le Magnen C et al.
Nat Rev Cancer 2016

➤ *Preventive approaches target premalignant biology by blocking initiation or intercepting cancer development*

Cancer chemoprevention (cancer prevention) involves the chronic administration of a synthetic, natural or biological agent to reduce or delay the occurrence of malignancy.



"I'll have an ounce of prevention."

Challenges with Prevention Studies



■ Home ■ News ■ Travel ■ Money ■ Sports ■ Life ■ Tech ■ V

News » Health & Behavior ■ Medical Resources ■ Health Information ■ Your Health: Kim Painte

Vitamins get 'F' in cancer prevention

Updated 1d 22h ago | Comments 66 | Recommend 14

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[Enlarge](#)

By Tim Dillon, USA TODAY

Vitamin E capsules.

By Liz Szabo, USA TODAY

A flotilla of recent studies — including two papers published today — has sunk the notion that individual vitamin supplements prevent cancer.

With so many earlier studies suggesting that people can eat their way to longer lives, experts acknowledge that their latest findings may leave people confused and even frustrated.

Q&A: Which studies should we listen to?

BETTER LIFE: More on supplements and alternative medicine

"A lot of people are looking at this and asking, 'What happened?'" says Lori Minasian, whose study in today's *Journal of the American Medical Association* found that taking vitamin E or selenium does not ward off cancer.



Other ways to share:



What's this?

➤ *Trials have not demonstrated health benefits, and some have shown harm*

- Potential side effects of therapeutic treatments in otherwise healthy individuals
- Long timelines for disease process makes it difficult to know if intervention is helpful
- Timing of intervention and potential need for long term use
- Lack of validated predictive biomarkers to serve as intermediate endpoints

Challenges: Targets for Intervention

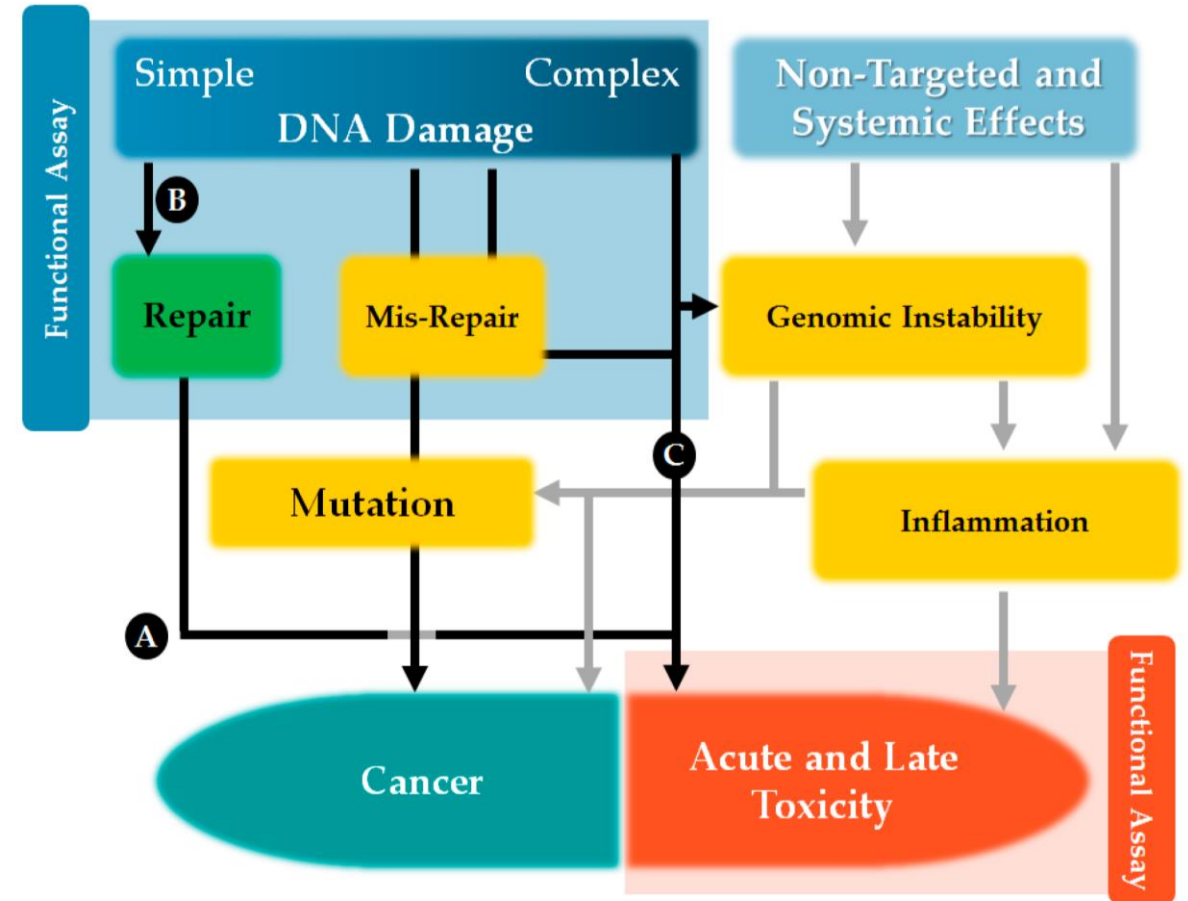


Potential preventive strategies:

- Scavenge electrophiles and ROS
- Enhance DNA repair
- Decrease inflammation
- Suppress proliferation
- Enhance differentiation
- Enhance immunity

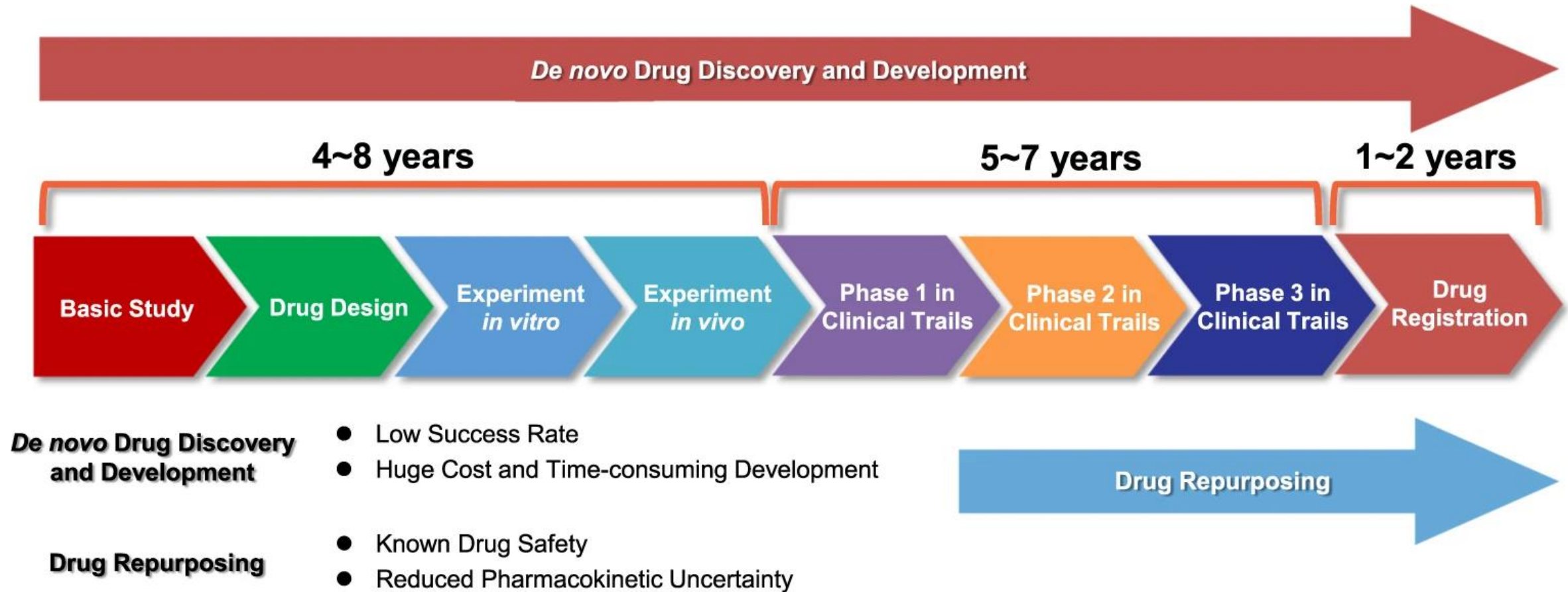
Potential sources of agents:

- Chemoprevention
- FDA repurposing
- Radiation Nuclear Countermeasures
- Radiotherapy Drugs
- Drugs targeting distinct damage caused by HZE radiation



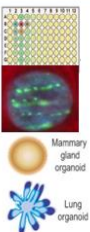
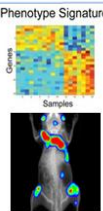
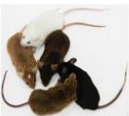
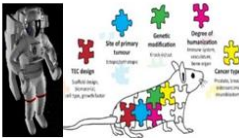
Habash M *Cancers* 2017

General Challenges with Drug Development



Space Radiation MCM Repurposing Pipeline – Example



Testing Capacity	Platform	Endpoint/Goal
<i>in vitro</i> screen- human cell based	2D - high throughput (ex. ROS scavenging, DNA repair, proliferation) 3D organoid –premalignant biology (ex. inflammatory signatures, genomic instability) 	Functional <i>in vitro</i> activity modification of diseases processes – includes primary & secondary prevention
<i>in vivo</i> screen- animal model	<i>in vivo</i> animal– (GEMMs, other species, imaging for early disease detection) 	Functional <i>in vivo</i> modification of disease processes, intermediate endpoints-translational signatures
<i>in vivo</i> GCR sim – animal models	Tumor models - GCR sim 	Functional <i>in vivo</i> modification of disease incidence, overall burden or time to occurrence
<i>in vivo</i> 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

In vitro screens:

- Endpoints chosen are predictive for beneficial effects in human disease - follow a defined translational path
- Sufficient capacity to screen multiple compounds; >1 assays

In vivo screens:

- Intermediate endpoints - reasonably likely surrogate endpoint
- non-invasive imaging

Tumor models:

- Capture early events in cancer initiation as well as progression
- Histological & biological features in common with human disease
- Related molecular pathways that are dysregulated
- Defined efficacy requirements – decreased incidence, overall burden or time to occurrence

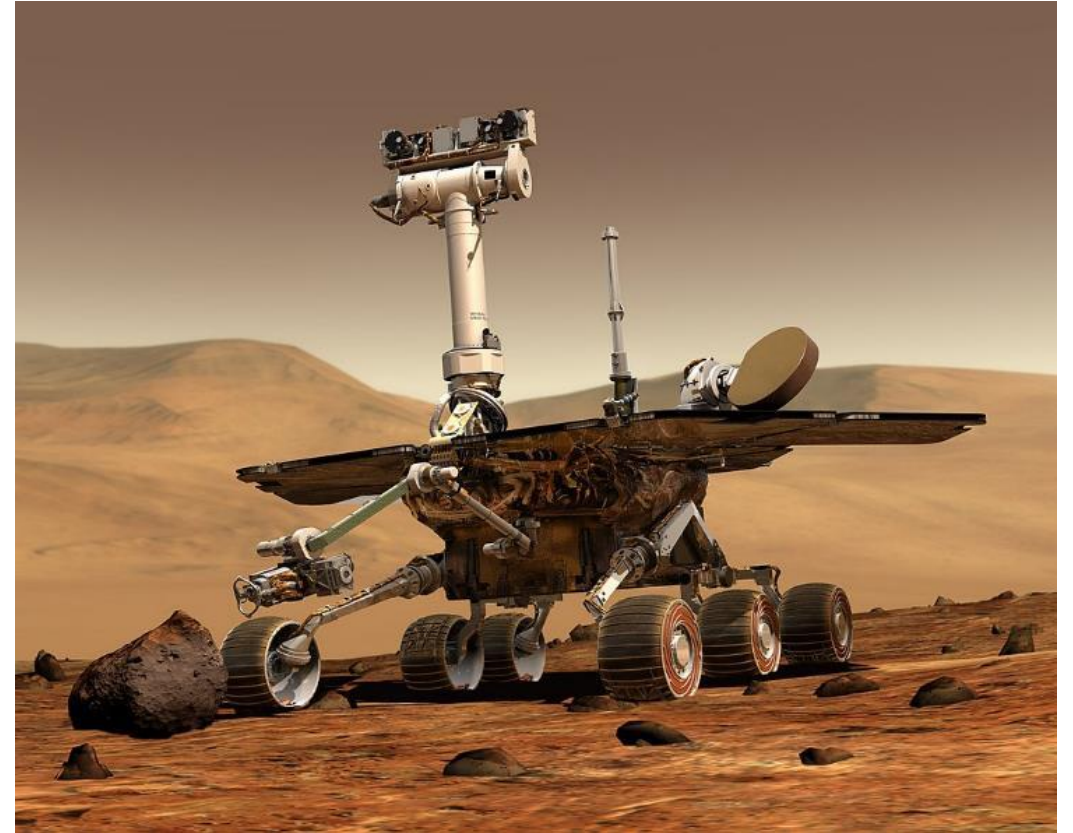
Exposure Scenarios Defined:

- *Screening parameters - single mixed field dose, gamma controls, minimal drug dosages, both sex?*
- *Validation - requires GCR simulator*

Opportunities to Explore - Examples



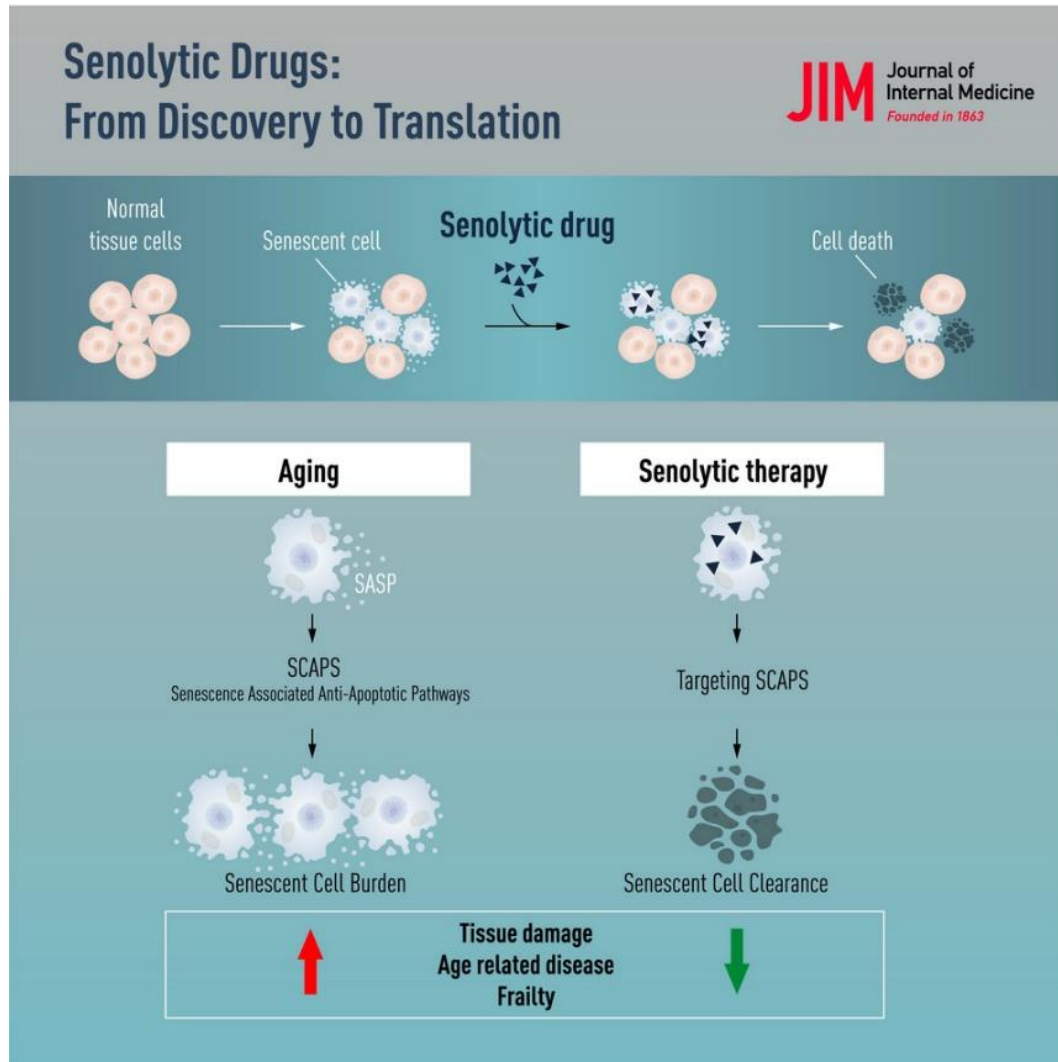
- Anti-aging drugs/Senolytics
- Microbiome
- Risk stratification – the case of CHIP
- Precancer Atlas
- Immunoprevention



Artist's notion of a NASA Mars Exploration Rover "**Opportunity**", operational on Mars for over 14 years

Image Credit: NASA/JPL/Cornell University

Opportunities: Anti-Aging/Senolytic Drugs

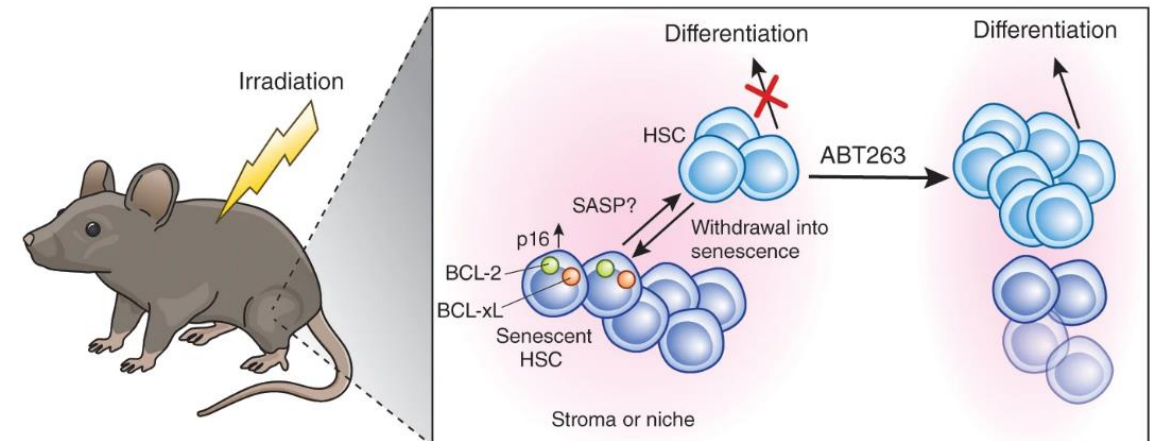


Kirkland JL, Tchkonian T *JIM* 2020



Selective removal of senescent cells

Adapted from Baker et al. *Nature* 2016

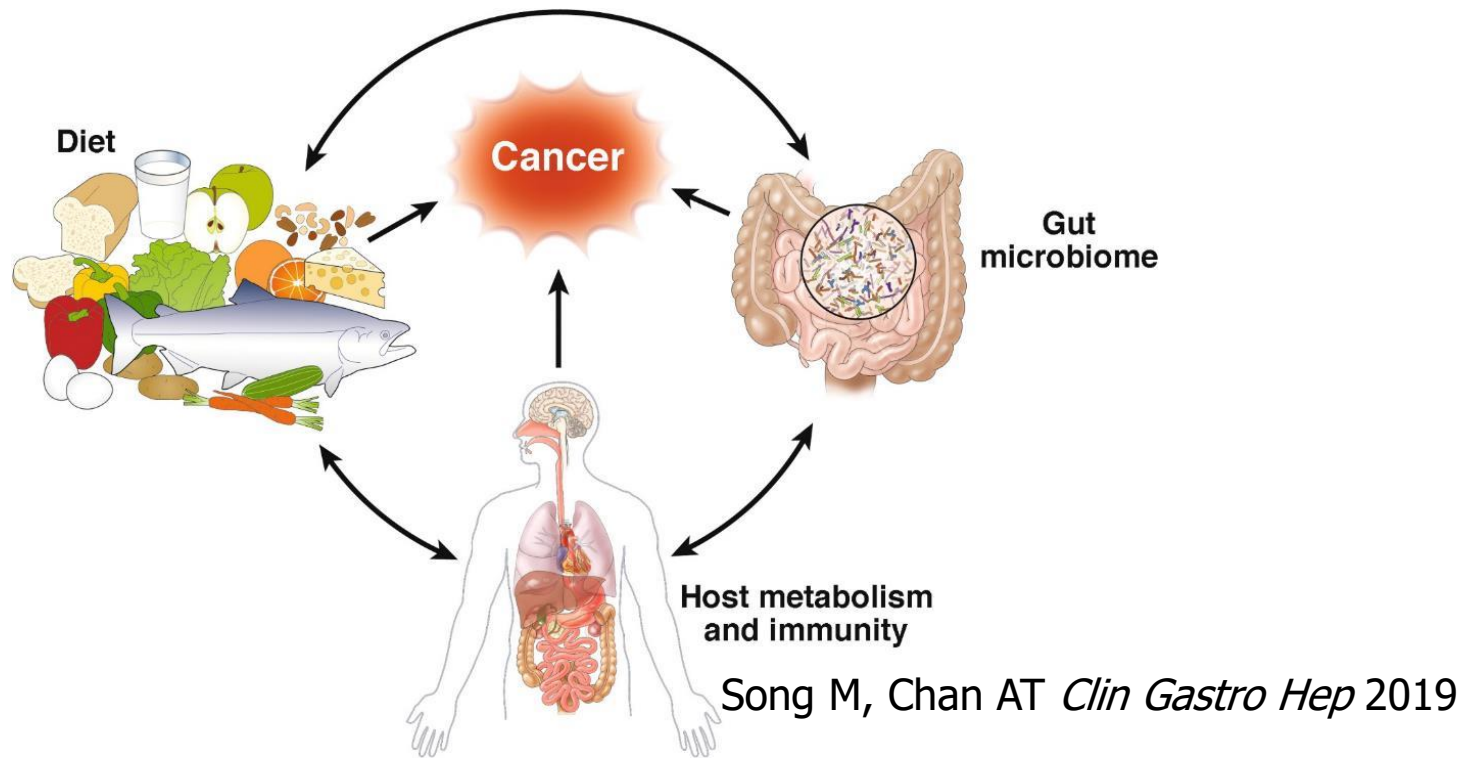


Geiger H *Nat Med.* 2016

Potential Advantages:

- Intermittent administration
- Cross-Risk

Opportunities: The Microbiome



Microbiome Influences Include:

- Barrier Functions, mucosal immunity
- Host Immunity – innate, adaptive and immune modulation
- Metabolism
- Cancer therapeutic response

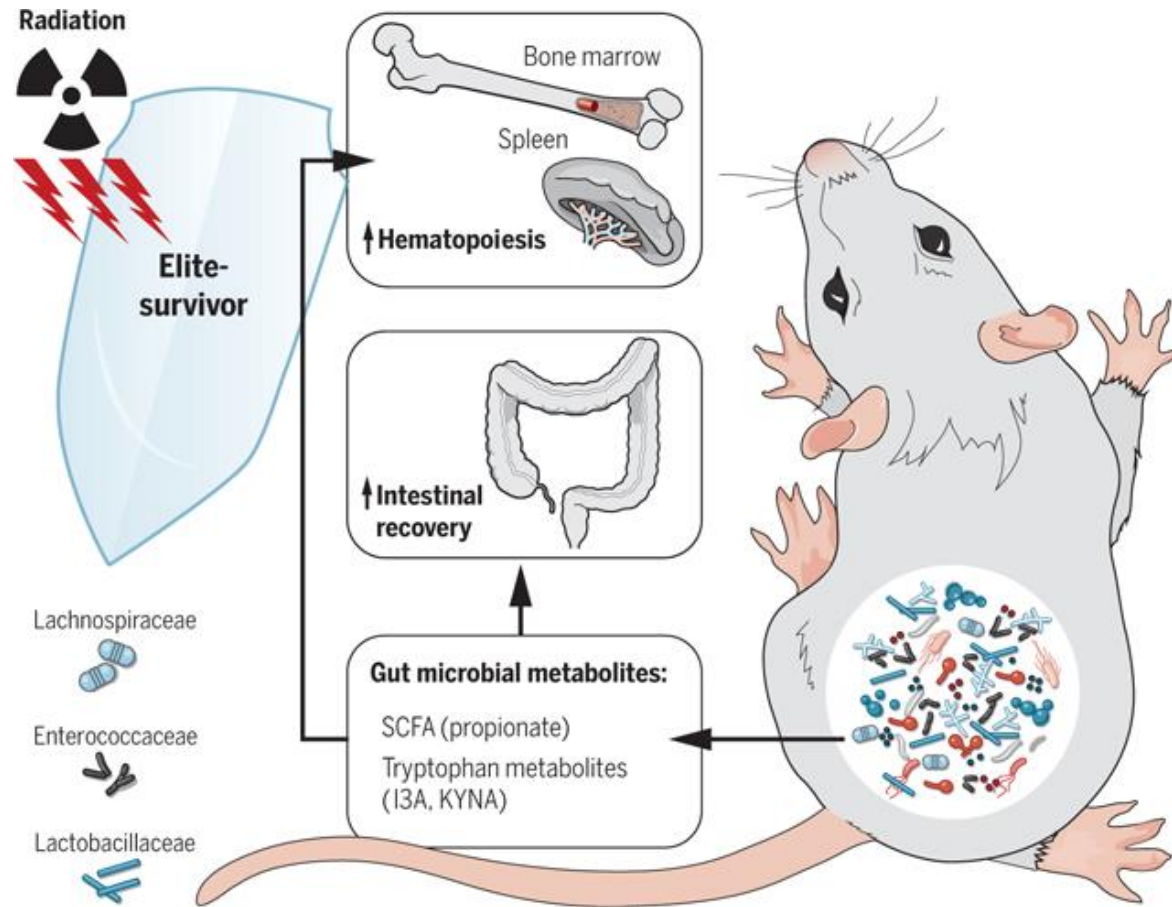


NIH Human Microbiome Project

The Microbiome and Radiation Protection



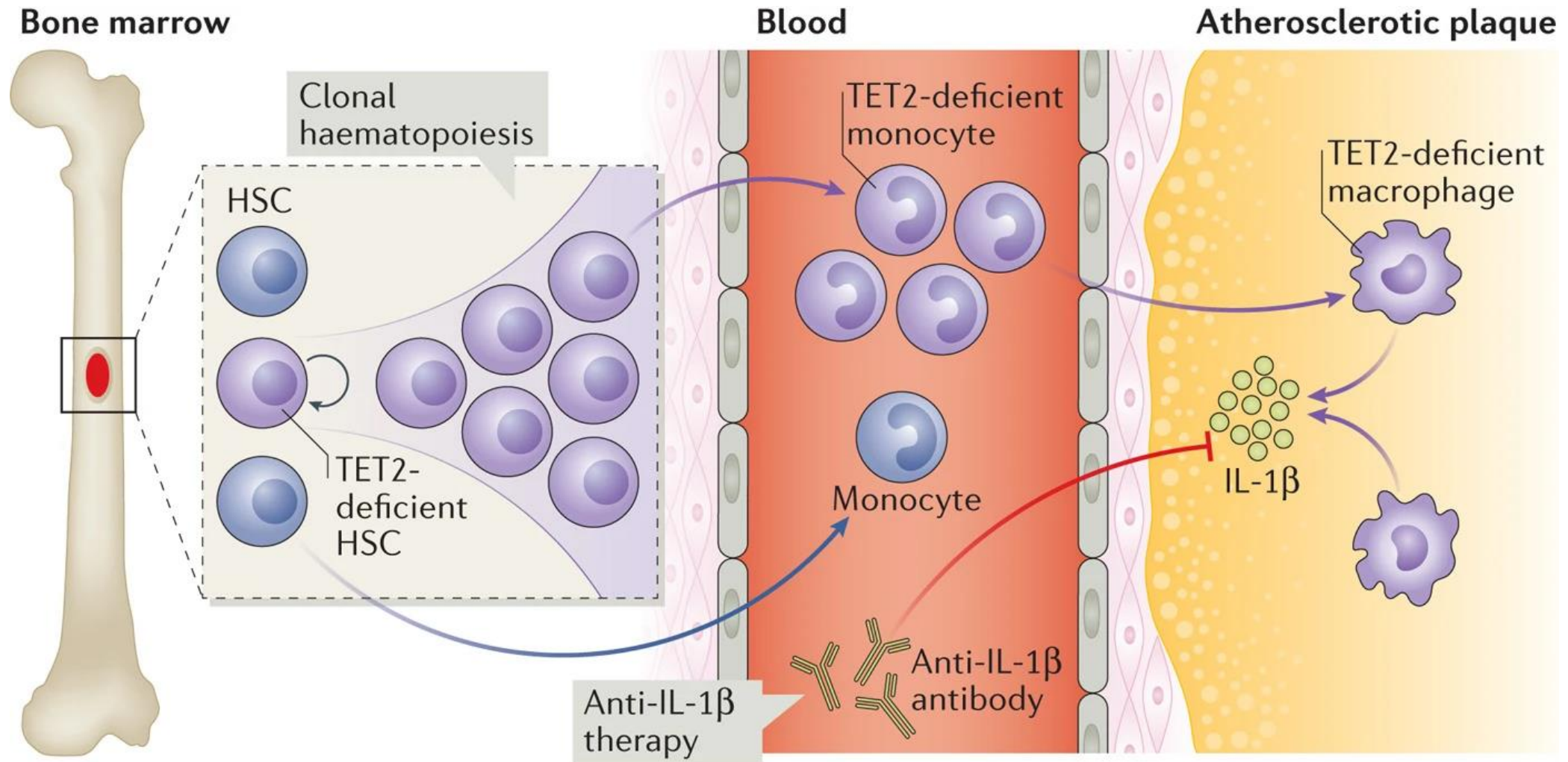
Gut microbiota—and associated metabolites—play a central role in protecting against high dose radiation



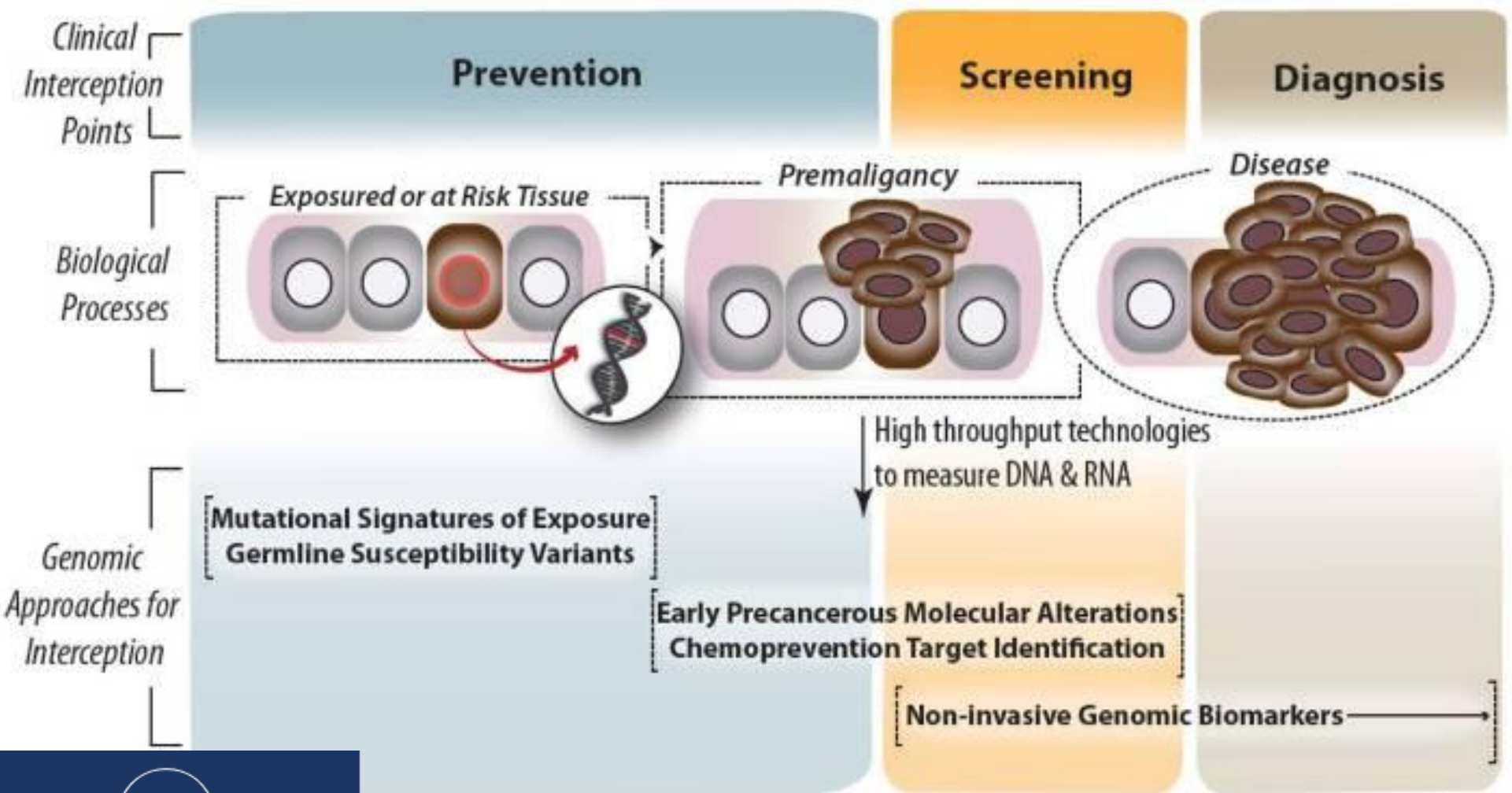
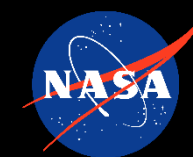
Guo H *Science* 2020

➤ Opportunities to modify microbiome for space radiation protection?

Opportunities: Personalized Risk Stratification- Example CHIP



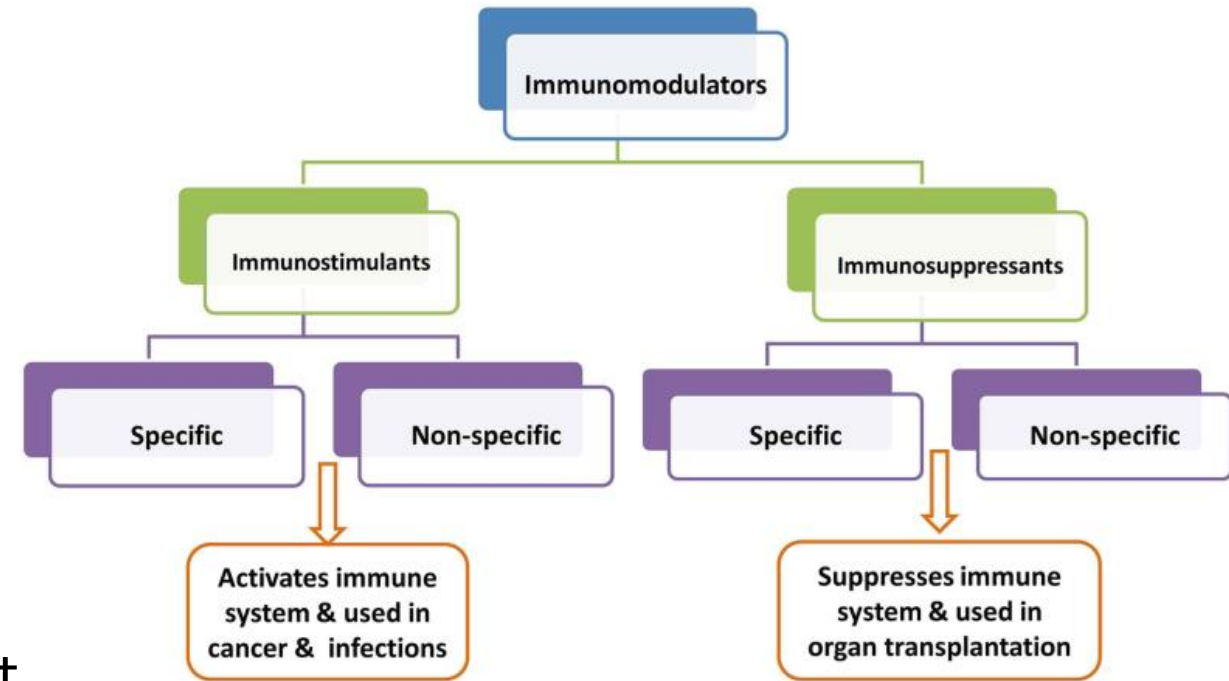
Opportunities: The Precancer Atlas



Opportunities: Immunoprevention Strategies



- Vaccines: HPV, HepB
- Broad Anti-inflammatory agents: i.e., aspirin, celecoxib, naproxen (cross-risk potential)
- Immunomodulators: bolstering natural immunoediting to eliminate precancerous cells
- Neoantigen vaccines – personalized approach
- Improved **understanding** of preneoplastic host immunity and tissue **microenvironment in radiogenic cancers**



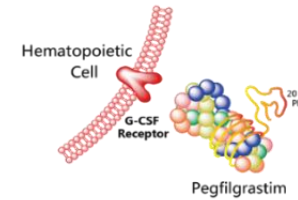
Mandlik DS, Namdeo AG *Springer* 2021

MCMs for Acute Radiation Syndromes due to Solar Particle Events

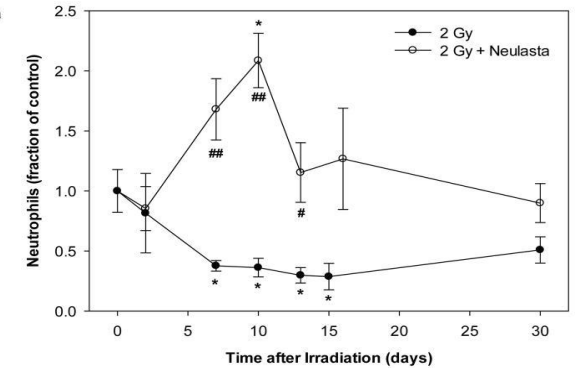
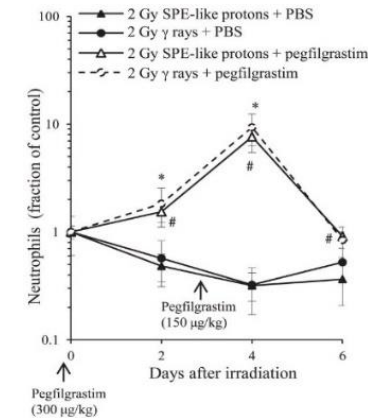


Challenges:

- Possibility of variable dose distribution in the body
- Combined skin injury
- Impact of microgravity & other spaceflight stressors

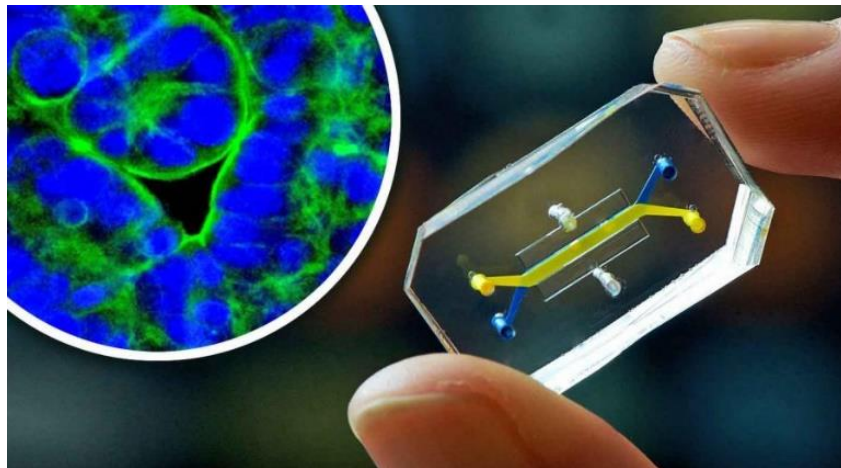


Neulasta increased neutrophil counts in mice and minipigs exposed to either gamma ray or SPE-like protons



Romero-Weaver AL et al. *Radiat Res.* 2013

Sanzari J et al. *Life Sci Space Res.* 2015



Human Organ Chips – "Gut-on-a-Chip"
(Credit: Wyss Institute at Harvard University)

Further Info:

Kennedy AR *Life Sci Space Res.* 2014

Carnell LS *Int J Radiat Biol.* 2020

- Focusing on primary prevention and early interception provide the greatest benefit
- Repurposing strategies using FDA approved drugs offer reduced timelines and reduced overall costs, but limits the pool of potential targets
- Leverage on scientific knowledge and recent advances in understanding of premalignant biology and prevention strategies developed by external biomedical community – many opportunities
- Identifying individuals with higher risk profiles provides opportunities for tailored interventions

The Translational Research Institute for Space Health (TRISH)

How TRISH is Currently Addressing the Radiation Risk

We invest in:

- **Countermeasures**
 - Gene editing
 - Nucleic acid therapeutics
 - Materials/biomaterials
- **Biodosimetry**
 - Biomarkers
 - Physiological readouts
 - Personalized
- **Human tissue models**
 - Stem cells
 - Humanized animal models
- **Analogs**
 - GCR
 - Human tissue models

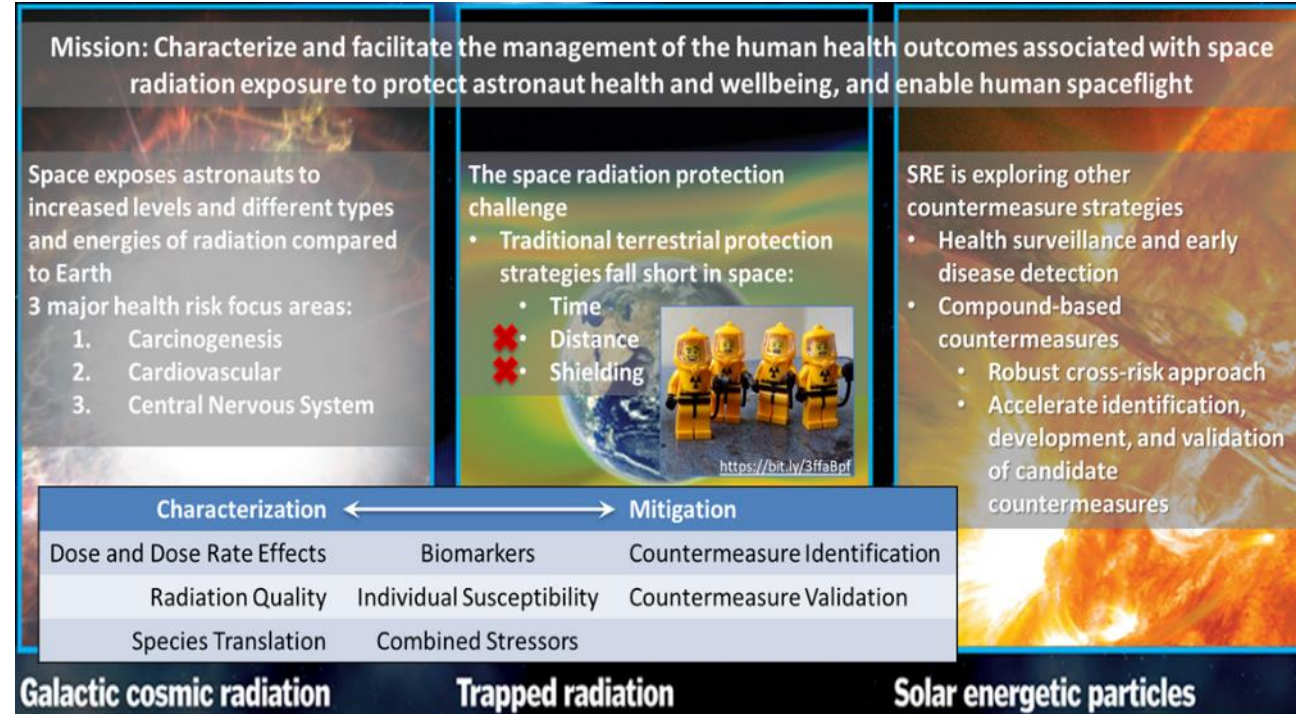
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- trish.force.com
- SpaceHealth-Info@bcm.edu
- **TRISH Website:**
<https://www.bcm.edu/academic-centers/space-medicine/translational-research-institute>

TRISH IS A **PARTNERSHIP** between Baylor College of Medicine/Caltech/MIT and the NASA Human Research Program Focused on translating disruptive approaches to reduce spaceflight hazards - we take risks, we challenge the boundaries SpaceHealth-Info@bcm.edu



NASA Human Research Program: Space Radiation Element



Contact:

isc-hrp-space-radiation-element@mail.nasa.gov

A deep-field astronomical image showing a vast number of galaxies in various colors (blue, orange, white) against a black background. The galaxies are of various shapes and sizes, some appearing as bright, distinct objects and others as faint, distant specks. The text "Thank You" is centered in a bold, yellow, italicized font.

Thank You

Hubble Ultra Deep Field 2014

Image Credit: NASA, ESA, H.Teplitz and M.Rafelski (IPAC/Caltech)