

# A mechanistic framework to assess the efficacy of aspirin and other radioprotectors to reduce carcinogenesis by space radiations

Micaela Cunha  
David Brenner, Igor Shuryak

Center for Radiological Research  
Columbia University Irving Medical Center

April 26<sup>th</sup> 2018



COLUMBIA UNIVERSITY  
MEDICAL CENTER

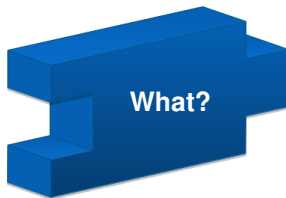


TRANSLATIONAL  
RESEARCH INSTITUTE FOR  
SPACE HEALTH

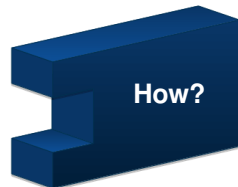
**Goal:** to provide a general methodology to assess any radiation countermeasure under consideration for use in space



Space radiation risks to human health



Need for effective biomedical radiation countermeasures



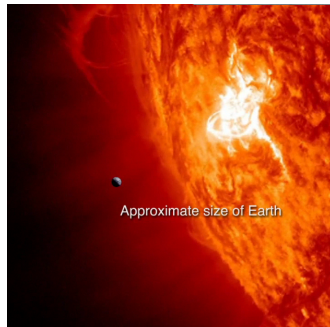
Extend our model of radiation cancer risk

## Origin of ionizing radiation

- Solar particle events (SPE)
- Galactic cosmic rays (GCR)
  - densely-ionizing radiation

## Possible effects

- Cancer
- Damage to central nervous system
- Cataracts
- Acute radiation sickness
- Hereditary effects



Credit: NASA



- NASA is planning multi-year interplanetary manned missions, including Mars landing
- Current spacecraft shielding methods do not provide protection against GCR
- Exposure to space radiation is estimated to lead to unacceptably high cancer risks



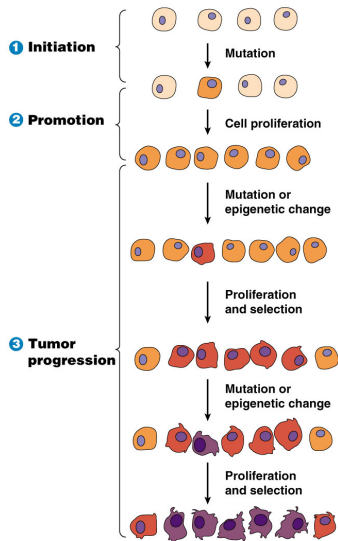
Need for safe and effective biomedical countermeasures against radiation effects

## State-of-the-art

- Carcinogenesis stages can be modulated by some drugs
  - a plethora of substances studied
  - if promising results, must undergo FDA approval process
    - **prohibitively long**



What about off-label use of already FDA-approved drugs?



© 2012 Pearson Education, Inc.



## Aspirin

- The most widely studied pharmacological agent for the prevention of colorectal cancer (CRC)
  - 3<sup>rd</sup> most common cancer among those affecting men and women
  - 2<sup>nd</sup> in leading cause of cancer-related deaths
- Overall 20%–25% decrease in cancer incidence and mortality (long-term use)
- Particularly effective against gastrointestinal (GI) tumors
  - 30%–50% for esophageal adenocarcinoma
  - 25%–35% for colorectal cancer
  - 25%–40% for stomach cancer
- Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are thought to inhibit cyclooxygenase-2 (COX-2), which plays a critical role in CRC initiation and promotion



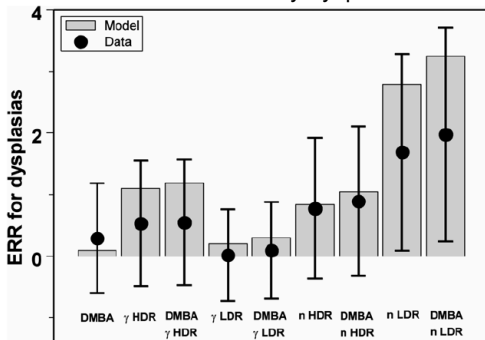
## Our mechanistic model of radiation carcinogenesis

Shuryak *et al.* 2011

- analysis of data on mice mammary dysplasia and tumors
- effect of the interactions between:
  - DMBA, a carcinogen (modifies the number of pre-malignant clones)
  - low-LET and with high-LET radiation (neutrons)  
at both high and low dose rates

**Results:** Good description of low-dose data on mouse mammary dysplasias and tumors

Excess relative risk (ERR)  
for mouse mammary dysplasias



Shuryak *et al.* 2011

## Interactions with DMBA

- low-LET: additive
- high-LET: synergistic

DMBA (2.5 mcg)  
 $\gamma$ : gamma rays (25 cGy)  
n: neutrons (2.5 cGy)

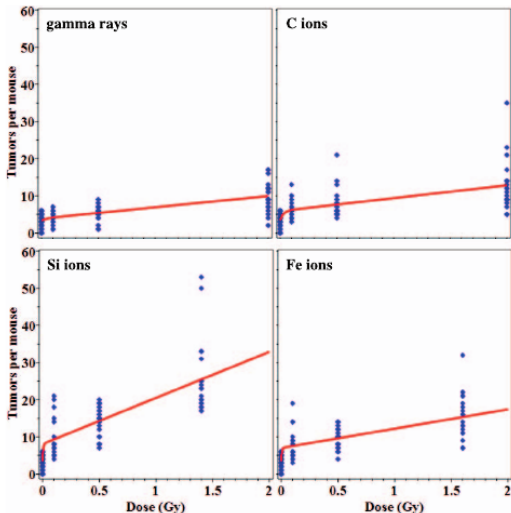
# Radiation carcinogenesis formalism

Previous results



TRANSLATIONAL  
RESEARCH INSTITUTE FOR  
SPACE HEALTH

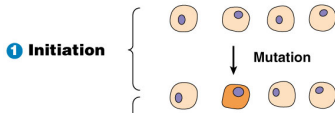
**Results:** Good description of the experimental data on intestinal tumors in mice for both low- and high-LET radiation



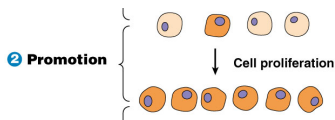
Shuryak *et al.* 2017

## Earlier conclusions

- Sparsely ionizing radiation mainly causes cell **initiation**



- Densely ionizing radiation mainly acts by **promotion** of the growth of pre-existing pre-malignant cells
  - probably mediated by a non-targeted bystander effect



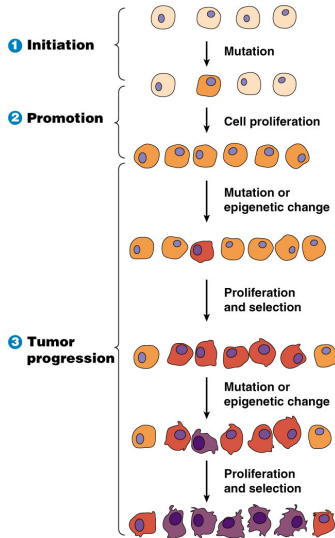


## Hypothesis

Unlike X rays, GCR induce cancer through promotion of pre-malignant cells



Drugs that reduce background cancer risks (e.g. aspirin) may also reduce GCR-induced cancer



© 2012 Pearson Education, Inc.



**Specific aim 1:** Extend our mechanistic model of radiation carcinogenesis by including

- the effects of different types of radiation (e.g. protons, HZE ions)
- the effects of the radiation countermeasure (e.g. aspirin)

**Specific aim 2:** Test and calibrate the model using animal data for the effects of aspirin on high-LET radiation induced carcinogenesis

## Strategy

- Start by analyzing data on aspirin and GI cancers
- Use other data sets to test the robustness of the mechanistic framework



## Currently at Specific Aim 1

- Reimplementing and testing our mechanistic model of radiation carcinogenesis
  - learning R (steep learning curve)
  
- Next step is using animal data currently being produced by the Georgetown NSCOR (PI: Dr. Fornace)
  - APC1638N/+ male mice irradiated at the NASA NSRL facility
  - effects of aspirin treatment on intestinal tumorigenesis induced by low doses of  $^{28}\text{Si}$ -induced
    - 50 and 10 cGy of 300 MeV/n  $^{28}\text{Si}$  ions
    - Human equivalent daily doses of 75, 150, or 300 mg aspirin tablets starting 1 month before irradiation until the end of the study
    - Mice euthanized 150 d after radiation
    - Intestinal and colonic tumors counted



## Postdoc Career Panel Series

- Communication and Outreach Career Panel ✓
- Careers in Academia/Universities ✓
- Careers in Pharmaceutical/Biotech Companies ✓
- Careers in Administration: Government, Academic and Non-Profit (5/10)
- Careers in Consulting Firms (5/24)

## Other events

- Evidence-Based Teaching in Science and Engineering
- The Humble PhD and Postdoc: How to Overcome Common Career Challenges
- Presenting Your Expertise
- Navigating the Research Enterprise Part II: Focus on Publishing



## Planned

- *Postdoc Academic Application Bootcamp* (May to July 2018)
  - Teaching Statement (May)
  - Research Statement (June)
  - Academic CV/Cover Letter (July)
  
- *Postdoc Research Symposium* (Fall 2018)
  
- *Funding and Grantsmanship Course* (Spring 2019)
  
- *Responsible Conduct of Research* (auditing, Spring 2019)



### **Current project**

- Transition from physical to biological modeling
- Work with new tools and concepts
  - R steep learning curve

### **Research level**

- Keep up with literature in the field
- Time management

### **Career level**

- Job availability constrains career choices
- Development of soft skills/networking
- Strategy for social media presence and visibility

### **Personal level**

- Distance from home country and family