# NSBRI Radiation Effects Team Strategic Plan

## 11.0 Radiation Effects

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## 11.1 INTRODUCTION

The risks to human health inherent in space exploration are enumerated in the NASA Critical Path Roadmap, which lists radiation as one of the four Severe Type I Risks, the most critical type. It follows that the principal aims of the NSBRI Radiation Program are to improve the predictions of risks to human health from space radiations and to provide effective countermeasures that will significantly reduce these risks. The radiation risk areas, in terms of long-term missions, both low-Earth orbit or extra planetary, and their relation to the overall space program are shown in the following figure adapted from NASA's Critical Path Roadmap. As shown, generally, radiation is one of several initiating events of a multistep process that can take years or decades before a clinically relevant consequence manifests itself. The overarching concern is to minimize the radiation exposure to as low as reasonably possible. Because the outcome of exposure is dependent upon multiple initiating agents, as well as, factors in the promotion and progression stages of the diseases, there are multiple risk factors that can alter the outcome. The major consequences are shown graphically in Figure 11.1 and are delineated in the next section.

## 11.2 RISKS

The following risks in the Radiation Effects Discipline Area of the Critical Path Roadmap have been identified (risk number in parentheses):

- Carcinogenesis Caused by Radiation (38)
- Damage to Central Nervous System from Radiation Exposure (39)
- Synergistic Effects from Exposure to Radiation, Microgravity and other Spacecraft Environmental Factors (40)
- Early or Acute Effects from Radiation Exposure (41)
- Radiation Effects on Fertility, Sterility, and Heredity (42)

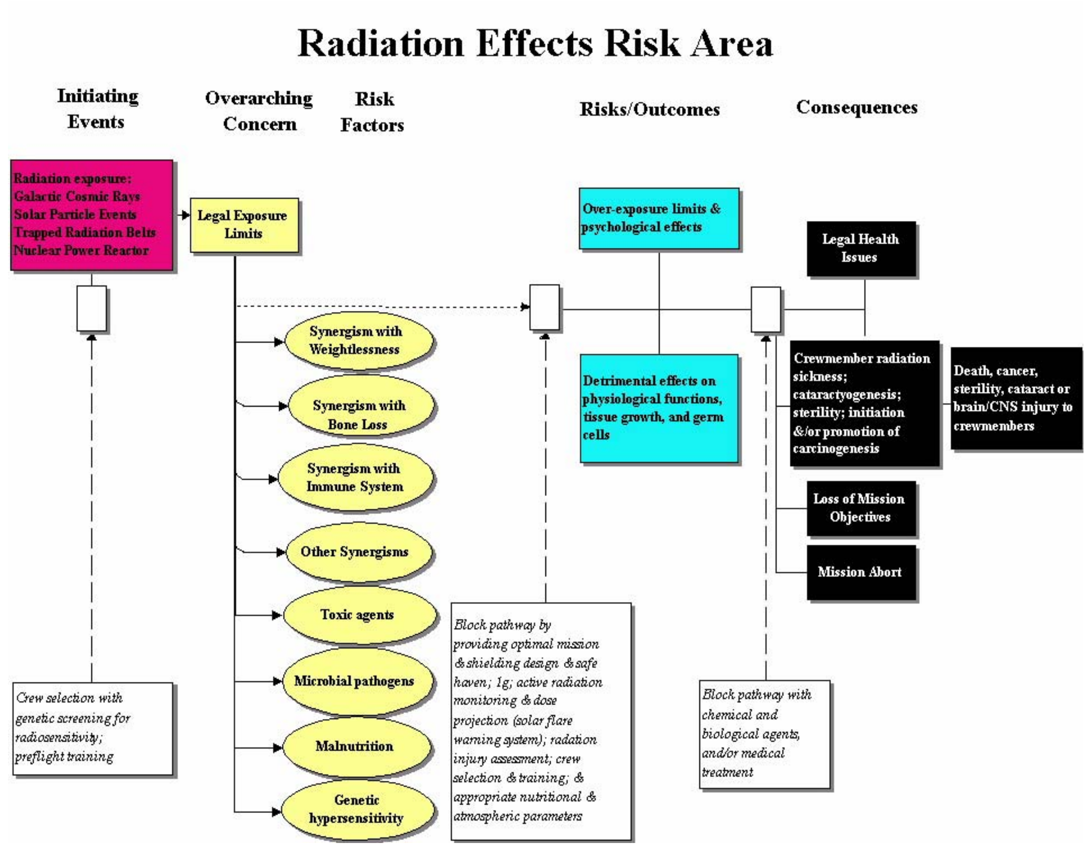



Figure 11.1. Radiation effects risks.

## 11.3 GOALS

The Radiation Effects Team has the following goals for its program:

**<u>Risk-Based Goals</u>**

**Goal 1**: *Reduce risk of carcinogenesis caused by radiation (38)*

**Goal 2**: *Reduce risk of damage to central nervous system from radiation exposure (39)*

**Goal 3**: *Reduce risk of synergistic effects from exposure to radiations, microgravity and other spacecraft environmental factors (40)*

**Goal 4:** *Reduce risk of early or acute effects from radiation exposure (41)*

**Goal 5:** *Reduce risk of radiation effects on fertility, sterility, and heredity (42)*

**Non Risk-Based Goals**

**Goal 6:** *Develop methods for assessing level of health risk, prevention of diseases, & appropriate medical care*

**Goal 7:** *Develop Earth-based applications*

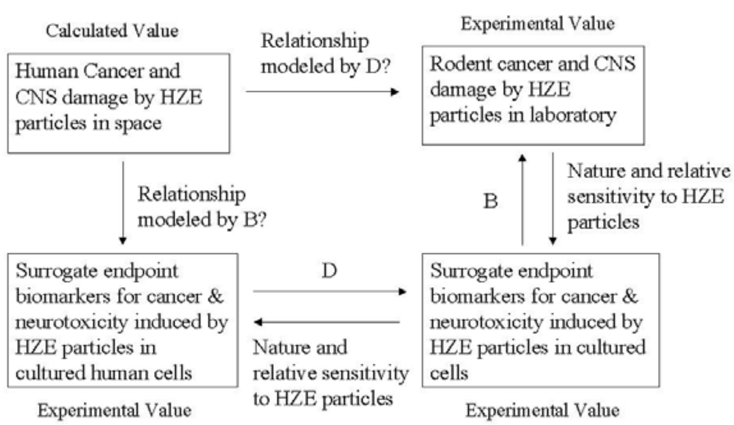
**Goal 8:** *Integrate research and analysis*

Although all of these goals are part of the Radiation Team and/or NASA's long-term goals, not all are being addressed at this time, as shown in Table 11.3. As part of NASA's mission, it is appropriate, however, that they be enumerated in the design plan to define future directions and areas of new emphasis.

## 11.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

The underlying philosophy of the program's approach is modeled after that proposed in the NASA report on Modeling Human Risk (1997): experimentally determined risks for carcinogenesis and CNS damage in appropriate animal models with corresponding in vitro measurements can be used to validate theoretical relations between animal results and human response. These theoretical relations, then, can be used to extrapolate known responses of humans to acute exposures of low-LET radiations to expected responses to protracted exposures to protons and HZE particles. When such relations have been established, then this same process and these same animal and cell models can be used to determine the potential of pharmaceutical agents, including both chemopreventive drugs and dietary supplements, for reducing risks. This concept is illustrated schematically in the following figure (Fig. 11.2) which is a revision of that proposed in the NASA report on modeling human risk (1997).

**Figure 11.2. Philosophy of radiation effects program.**




Adapted from Modeling Human Risk: Cell & Molecular Biology in Context, 1997

**Description of Current Projects and Progress Towards Risk-Based Goals**

Currently, the Radiation Effects Team has six principal projects. In Table 11.1, these projects are summarized, including those risks that are currently being addressed, the experimental system, the countermeasure target, and whether a project is part of the strategic steps of Phase 1, 2 or 3 Activities. A brief description follows of each project and the countermeasures being studied:

**PROJECT I: In vivo Studies of Mammary Carcinomas**
**John F. Dicello, PhD, *Johns Hopkins University***

> **Critical Path Risk(s):** Carcinogenesis caused by radiation (38:1, 3, 5, 6, 7, (8), 9, 10, 11), Addresses Goal 1, Countermeasure Readiness Level: 4
> **Specific Aim:** Determine risk of carcinogenesis in a relevant animal model and supply exposed animals for chemopreventive studies.
> **Countermeasure:** Chemoprevention of cancers by use of pharmaceuticals administered after high-level exposure to radiations. Improved risk factors can be used to optimize spacecraft design for optimal shielding

**PROJECT II: Chemoprevention and Radiation-Induced Neoplasms**
**David L. Huso, DVM, PhD**, *Johns Hopkins University*

> **Critical Path Risk(s):** Carcinogenesis caused by radiation (38:1, 3, 5, 6, 7, (8), 9, 10, 11), Addresses Goal 1, Countermeasure Readiness Level: 5
> **Specific Aims:** Studies of the pathology of cancer induced by HZE particles and pharmaceutical intervention.
> **Countermeasure:** Tamoxifen as a model for pharmaceutical intervention in the promotion and progression stages of carcinogenesis to reduce risk after exposure

**PROJECT III: Countermeasures for Space Radiation Biological Effects**
**Ann R. Kennedy, PhD,** *University of Pennsylvania*

> **Critical Path Risk(s):** Carcinogenesis caused by radiation (38:1, 3, 9, 10), Early or acute effects from radiation exposure (41:1,3,5,10,11), Addresses Goals 1 and 4, Countermeasure Readiness Level: 4
> **Specific Aims:**
> (1) Determine the ability of various dietary supplements to reduce radiation-induced oxidative stress in cultured cells
> (2) For the combinations of agents demonstrating efficacy as antioxidants *in vitro*, determine the ability of these agents to decrease radiation induced oxidative stress in Sprague Dawley rats.
> **Countermeasure:** Dietary supplements prior to and after exposure to radiation to reduce the cancer incidence.

**PROJECT IV: Risk Assessment and Chemoprevention of HZE Induced CNS Damage**
**Marcelo E. Vazquez, MD, PhD,** *Brookhaven National Laboratory*

**Critical Path Risk(s):** Damage to CNS system from radiation exposure (39:1, 3, 7, 10, 11), Early or acute effects from radiation exposure (41:1, 3, 5, 10, 11), Addresses Goals 2 and 4, Countermeasure Readiness Level: 3-4
**Specific Aims:**
(1) Examine cell death in cycling and non-cycling neural cells
(2) To characterize the putative cell signaling cascades induced by high-LET radiation in the apoptotic pathways (ceramide- and p53-dependent).
**Countermeasure:** Modulate signaling pathways by pharmacological manipulation (trophic factors, free-radical scavengers, p53 modulators)

**PROJECT V: CNS Damage and Countermeasures (In vivo Studies)**
**Marcelo E. Vazquez, MD, PhD,** *Brookhaven National Laboratory*

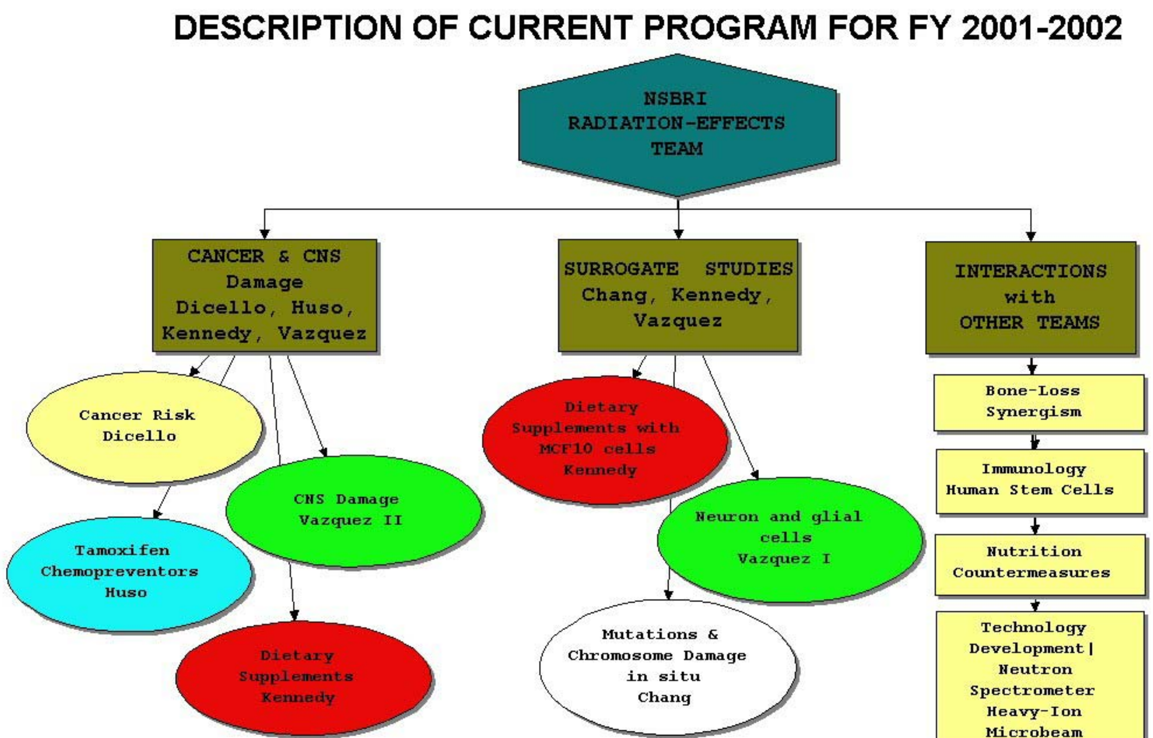
**Critical Path Risk(s):** Damage to CNS system from radiation exposure (39:1, 3, 7, 10, 11), Early or acute effects from radiation exposure (41:1, 3, 5, 10, 11), Addresses Goals 2 and 4, Countermeasure Readiness Level: 3-4
**Specific Aims:**
(1) Characterize the behavioral, neurochemical and structural changes induced by heavy ions and protons.
**Countermeasure:** To protect neural cell populations in vivo using pharmaceuticals, such as neuroprotectants (gangliosides), antioxidants (melatonin) and signal pathways modulators (p53 modulators)

**PROJECT VI: Charged Particle Radiation-Induced Genetic Damage in Transgenic Mice**
**Polly Yee Chang, PhD,** *SRI International*

**Critical Path Risk(s):** Carcinogenesis caused by radiation (38), Damage to central nervous system from radiation exposure (39), Early or acute effects from radiation exposure (41: (3), 5, 10), Addresses Goals 1, 2, and 4, Countermeasure Readiness Level: 2
**Specific Aims:**
(1) Examine both the dose and temporal-dependence of particle radiation-induced mutation in vivo using the LacZ transgenic mice model system. In particular, acute and long-term tissue specific mutagenic responses of CNS and rapidly renewing organ systems will be determined after exposure to protons and HZE particles.
(2) Examine the impact of genetic backgrounds, e.g. p53 on radiation sensitivity using the p53/lac Z double transgenics.
**Potential Countermeasures:** Determine if known radioprotective pharmaceuticals (e.g. tamoxifen, anti-oxidants) or cytokines ( e.g., interleukins) reduce tissue-specific mutation frequencies or genetic damage *in vivo*. Such alterations in the genome may be precursors of cancer.

A summary diagram, Figure 11.3, describes the current program.

**Figure 11.3 Current radiation effects program.**




The major themes of this program are the understanding of risks and the development of effective countermeasures for the radiation-induced biological effects identified to be of major concern: radiation-induced cancer and CNS damage. It is also possible that because of the complexity of the space environment, unanticipated effects may occur in organ systems other than the CNS. Thus the major aims will cover five categories:

1. Develop countermeasures for mitigating effects of radiation exposure.
2. Develop markers for determining risks and monitoring the efficacy of countermeasures.
3. Determine carcinogenic and CNS effects for space radiation.
4. Determine acute and long-term pathological responses of rapidly renewing organ systems at risk.
5. Characterize differences in cell and molecular mechanisms for pathological effects for high- versus low-LET radiation in defined model systems.

**Progress Towards Non Risk-Based Goals**

Figure 11.1 refers to Goal 6, Develop methods for assessing level of health risk, prevention of diseases, & appropriate medical care. At present, this goal is not being explicitly expressed; however, progress towards this goal has been made. We have determined for the first time the risks of carcinogenesis in tissues relevant to humans from protons and HZE particles. We have further shown that relatively non-toxic pharmaceuticals can be used to reduce those risks in animal models in the promotion and progression stages after radiation. In order to extrapolate these risks to humans, we have to examine the interspecies variation in carcinogenesis as a function of particle type. As mentioned previously, it is imperative that the radiation studies of this program be mechanistically based in order to be able to extrapolate results to human models. Developing such appropriate theoretical, human models, that we presently do not have and that are not currently funded as part of this program, should be a major future goal (see elaboration under Goal 8, "integration using modeling"). Input for such models requires not only carcinogenesis studies but also the appropriate genetic, epigenetic, and cytogenetic data to define the mechanisms leading to carcinogenesis. The present results suggest that we could begin formulating ground-based and space-based clinical studies. In this respect we are already looking for less toxic combinations of pharmaceuticals and/or dietary supplements.

Several activities support the early development of Earth-based applications (Goal 7). We currently have an NIH grant (Joseph Lombardo, P.I.) at Johns Hopkins for medical telecommunications that resulted from the NSBRI collaborations. Another NIH program grant (Jerry Williams, P.I.) at JHU to develop novel treatment protocols in radiation therapy is a spin-off from a previous project of our team headed by Dr. Jerry Williams.

Table 11.2 at the end of this document illustrates in tabular form activities that are ongoing in achieving the Team's integration goal, Goal 8. A brief summary of these activities in provided here as well. To aid team integration, the Team holds weekly meetings at Johns Hopkins University School of Medicine and monthly teleconferences integrating experimental development. In terms of overall strategy, four of the team projects described are collaborating on investigating carcinogenesis (3) and CNS damage (1) *in vivo,* and three projects are addressing corresponding cellular effects. Collaborations among team members involve a great deal of integrated experiment development. The team as a group, under the direction of Drs. John Dicello and Marcelo Vazquez, is one of the strongest participants at the NASA biomedical facility of AGS acceleration at Brookhaven National Laboratory (BNL). This participation requires a series of proposals not only to NSBRI but also to each of the home institutions and to BNL for separate reviews and the necessary but not always automatic approval. Similarly, animal research and research involving human cells requires proposals to separate Institutional Review Boards at the home institutions and at the BNL, again requiring approval. The Team also does extensive sample sharing. For instance, Dr. Dicello provides animals and animal tissues for Dr. David Huso's tamoxifen studies. He is also irradiating animals for Dr. Jerry Williams' earlier cytogenetic studies.

We also have been collaborating with researchers on other NSBRI teams, where team goals overlap. There is a strong need for synergistic collaborations within and with other teams, some of which may address achievement of Goal 3. Preliminary experiments to show feasibility have been carried out by Dr. Dicello's group looking at 1) synergies between different types of radiations; 2) synergies arising between radiation and the immune system (with Immunology Team); and 3) synergistic interactions between radiation and bone (with Bone Team). In all cases significant synergistic effects have been observed, although uncertainties associated with the data have been large. However, currently, no additional funding has been available either for feasibility studies or for further research. We have also been collaborating with the team leader for the Education and Outreach since its inception. The Radiation program has included numerous undergraduate, graduate and postdoctoral students and has attracted additional external funding from NASA and the Johns Hopkins University Bloomberg School of Public Health among other sources, as well as, travel grants for the students to scientific meetings.

As a means of integrating their research with the scientific community beyond the NSBRI, Dr. Dicello's group has also had a long collaboration preceding the establishment of the NSBRI with scientists at the Johnson Space Center and Headquarters that has resulted in a continuous productivity of peer-reviewed publications and invited talks. Dr. Francis Cucinotta, JSC, spent his sabbatical leave at Johns Hopkins working with Dr. Dicello. Currently, there is no support within or outside of NSBRI for integration and analyses since it was eliminated as a line item from the NSBRI awards. A theoretically-based research approach is the only practical method by which the cell and animal data can be extrapolated to humans (except for identical responses), so it is an indispensable part of the strategic plan for the Radiation Program and should be supported.

Dr. Dicello's project was also successful in generating new and unique theoretical models to describe genetic and cytogenetic pathways and in vivo carcinogenesis, which contributes to the development of a computer model of integrated human function. Future strategic activities associated with this modeling project and a timeline for these activities are provided in Table 11.3H. Funding for this extensive modeling project is still needed.

**Gaps and Weaknesses of the Program**

Remaining gaps and weaknesses in the Radiation Effects Team plan have been identified:

1. In vivo data for synergistic effects of mixed fields.
2. Animal studies for protracted exposures.
3. A need for a more comprehensive analysis of human responses to low-dose, protracted exposures.
4. Improved methods for extrapolating animal data to humans too imprecise.
5. Inadequate research on early or acute consequences from radiation exposures (Goal 4).
6. No present research on effects on fertility, sterility, or heredity (Goal 5).

## 11.5 OBJECTIVES AND STRATEGIC ACTIVITIES

Presented here are the objectives underlying each goal and the strategic activities that we plan to use to achieve the goals and objectives of our program. The timelines for achievement of the activities underlying each goal are presented in Table 11.3.

**Goal 1:** *Reduce risk of carcinogenesis caused by radiation*

Objective 1A: Assess risk and target level of acceptable risk

- In vivo measurements of carcinogenesis

Objective 1B: Determine mechanisms

- Cellular and Subcellular endpoints as surrogate biomarkers leading to carcinogenesis

Objective 1C: Develop countermeasures

- In vitro testing followed by in vivo studies of pharmaceuticals and dietary supplements

**Goal 2:** *Reduce risk of damage to central nervous system from radiation exposure*

Objective 2A: Assess risk and target level of acceptable risk

- In vivo measurements of CNS damage

Objective 2B: Determine mechanisms

- Cellular and Subcellular endpoints as surrogate biomarkers leading to CNS damage

Objective 2C: Develop countermeasures

- In vitro testing followed by in vivo studies of pharmaceuticals and dietary supplements

**Goal 3:** *Reduce risk of synergistic effects from exposure to radiation, microgravity and other spacecraft environmental factors*

Objective 3A: Assess risk and target level of acceptable risk

- In vivo measurements of combined hazards

Objective 3B: Determine mechanisms

- Cellular and Subcellular endpoints for combined hazards in comparison with responses to individual hazards

Objective 3C: Develop countermeasures

- Exercise, dietary supplements, and pharmaceutical intervention

**Goal 4:** *Reduce risk of early or acute effects from radiation exposure*

Objective 4A: Assess risk and target level of acceptable risk

- Observe acute responses for in vivo measurements of combined hazards

Objective 4B: Determine mechanisms

- Theoretical modeling compared with measurements

Objective 4C:Develop countermeasures

- Minimize dose with shielding and spacecraft design and choice of travel interval

**Goal 5:** *Reduce risk of radiation effects on fertility, sterility, and heredity*

Objective 5A: Assess risk and target level of acceptable risk

- Use existing epidemiological data for photon exposures

Objective 5B: Determine mechanisms

- Theoretical modeling of existing data base

Objective 5C: Develop countermeasures

- Minimize doses through spacecraft design and choice of travel interval

**Goal 6:** *Develop methods for assessment of level of health risk, prevention of diseases, and appropriate medical care*

Objective 6A: Develop markers for determining risks and monitoring the efficacy of countermeasures from previous experiment.

**Goal 7:** *Develop Earth-based applications*

Objective 7A: Translational research to move new discoveries into medical and industrial arena with the Industrial Forum.

**Goal 8:** *Integrate experimental research with theoretical analysis to be used to extrapolate data to risk and countermeasures in humans.*

Objective 8A: Integrate research within the radiation effects team

- All team projects focused on a major programmatic goal
- Samples and experimental design shared

Objective 8B: Integrate research with other teams, using modeling as well as other approaches.

- Foster collaborations with Bone and Immunology Teams
- Obtain funding for theoretical modeling

Objective 8C: Integrate research with scientists within NASA and outside of NSBRI

- Foster collaborations at JSC

## 11.6 SUMMARY

The risks to human health inherent in space exploration are enumerated in the NASA Critical Path Roadmap, which lists radiation as one of the four Severe Type I Risks, the most critical type. Most recently, radiation is being categorized as the most serious of these hazards in space. It follows that the principal aims of the NSBRI Radiation Program are to improve the predictions of risks to human health from space radiations and to provide effective countermeasures that will significantly reduce these risks. The major radiation risk area in terms of long-term missions, both low-Earth orbit or extra planetary, is carcinogenesis. Damage to the central nervous system and synergisms of different types of radiation or synergisms of radiation with other hazards including bone loss and reduced immunological response are all areas of concern as well. The current Radiation Effects Team projects are making significant progress towards assessing these risks and potential pharmacological, nutritional, and shielding countermeasures.

The underlying philosophy of the program's approach to experimentally determine risks for carcinogenesis and CNS damage in appropriate animal models with corresponding *in vitro* measurements can be used to validate theoretical relations between animal results and human response. These theoretical relations, then, can be used to extrapolate known responses of humans to acute exposures of low-LET radiations to expected responses to protracted exposures to protons and HZE particles. When such relations have been established, then this same process and these same animal and cell models can be used to determine the effectiveness of potential countermeasures, such as pharmaceutical agents, including both chemopreventive drugs and dietary supplements, for reducing risks.

## Table 11.1. Project Research Activities

| PI/Project | Risk(s) Addressed | Countermeasure Target | Experimental System | Phase 1 Activities: Focused Mechanistic Research | Phase 2 Activities: Preliminary Countermeasure Development Research | Phase 3 Activities: Mature Countermeasure Development Research |
|---|---|---|---|---|---|---|
| CHANG/Charged Particle Radiation-Induced Genetic Damage in Transgenic Mice | •Carcinogenesis caused by radiation<br>•Damage to CNS from radiation exposure<br>•Early or acute effects from radiation exposure | •Pharmaceuticals (e.g. tamoxifen, anti-oxidants)<br>•Cytokines ( e.g., interleukins) | Transgenic mice | •Examine both the dose and temporal-dependence of particle radiation-induced mutation *in vivo* using the LacZ transgenic mice model system<br>•Examine the impact of genetic backgrounds, e.g., p53, on radiation sensitivity using the p53/LacZ double transgenics | Determine if known radioprotective pharmaceuticals (e.g. tamoxifen, anti-oxidants) or cytokines ( e.g., interleukins) reduce tissue-specific mutation frequencies or genetic damage *in vivo*. Such alterations in the genome may be precursors of cancer. Examine potential drugs *in vitro*. | Examine potential potential drugs *in vivo* |
| DICELLO/In vivo Studies of Mammary Carcinomas | Carcinogenesis caused by radiation | •Chemoprevention of cancers by use of pharmaceuticals administered after exposure to radiations.<br>•Shielding | Sprague Dawley rats | Determine risk of carcinogenesis in a relevant animal model and supply exposed animals for chemopreventive studies | •Obtain improved risk factors which can be used to optimize spacecraft design for optimal shielding and to select clinical trials<br>•Chemoprevention of cancers by use of pharmaceuticals administered after exposure to radiations. | Clinical trials and flight experiments |

| | | | | | | |
|---|---|---|---|---|---|---|
| HUSO/Chemoprevention and Radiation-Induced Neoplasms | Carcinogenesis caused by radiation | Pharmaceuticals (Tamoxifen) | Sprague Dawley rats | Studies of the pathology of cancer induced by HZE particles and use of Tamoxifen as a model for pharmaceutical intervention in the promotion and progression stages of carcinogenesis to reduce risk after exposure | Obtain improved risk factors to select appropriate clinical trials | Clinical trials and flight experiments |
| KENNEDY/Countermeasures for Space Radiation Biological Effects | •Carcinogenesis caused by radiation<br>•Early or acute effects from radiation exposure | Dietary supplements | •Cultured cells<br>•Sprague Dawley rats | Determine the ability of various dietary supplements to reduce radiation-induced oxidative stress in cultured cells | •Dietary supplements prior to and after exposure to radiation to reduce cancer incidence<br>•For the combinations of agents demonstrating efficacy as antioxidants *in vitro*, determine the ability of these agents to decrease radiation-induced oxidative stress in Sprague Dawley rats | Clinical trials and flight experiments |
| VAZQUEZ/Risk Assessment and Chemoprevention of HZE Induced CNS Damage | •Damage to CNS from radiation exposure<br>•Early or acute effects from radiation exposure | Pharmacological manipulation | Cells obtained from rats | •Examine cell death in cycling and non-cycling neural cells<br>•Characterize the putative cell signaling cascades induced by high LET radiation in the apoptotic pathways (ceramide- and p-53 dependent) | Modulate signaling pathways by pharmacological manipulation; test use of trophic factors, free-radical scavengers, p53 modulators in modulating signaling pathways | Bases for *in vivo* experiments |
| VAZQUEZ/CNS Damage and Countermeasures (*In vivo* Studies) | •Damage to CNS from radiation exposure<br>•Early or acute effects from radiation exposure | Pharmacological agents | C57 black mice | Characterize the behavioral, neurochemical, and structural changes induced by heavy ions and protons | Test protective efficacy of pharmaceuticals such as neuroprotectants (gangliosides), antioxidants (melatonin), and signal pathways modulators (p53 modulators) on neural cell populations | Clinical trials and flight experiments |

**Table 11.2. Integration Activities – See discussion under section 11.4, Goal 8**

| Activities common to all projects unless specified | | | | |
|---|---|---|---|---|
| **Internal Communication** | Weekly NSBRI staff meetings | Monthly teleconference of principal investigators | Scheduled NSBRI meetings of investigators at national and international meetings. | |
| **Integrated Experiment Development** | Monthly NSBRI luncheon meeting | Collaborations between PIs in Radiation with Technology Team on two projects | Members of several NASA, NCRP, and NAS/NRC committees | |
| **Sample Sharing** | Sprague-Dawley rats shared with Tamoxifen project (Huso and Dicello) | Tissue samples shared between Carcinogenesis project and Tamoxifen project | Animals irradiated at Loma Linda used for Gridley's immunology study (Dicello) | Carcinogenesis and Tamoxifen projects agreed to provide animals and tissues for several proposals submitted to NSBRI and NASA |
| **Synergistic Studies of Opportunity** | Dicello funded immunological studies at Loma Linda University (Daila Gridley) | Dr. Dicello is collaborating with Dr. Jay Shapiro on the combined effects of radiation and microgravity on bone loss. | Sequential studies at BNL (HZEs) and LLUMC (protons) | |
| **Development of Computer Model of Integrated Human Function** | Dicello and, previously, F. Cucinotta at JSC had been carrying out theoretical studies. | | | |

## Table 11.3a. Achieving Goal 1: Reduce Risk of Carcinogenesis Caused by Radiation (38)

| Countermeasure Development Phases | Pre 2001 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase 0: Observational & Phenomenological Research**<br>Five of the seven principal investigators had extensive research experience with regard to the carcinogenic effects from radiation. The sixth was a senior biologist working on DNA damage, a major pathway to cancer from radiation, and the seventh is an animal pathologist and veterinarian, a unique resource for these studies | | | | | | | | | | | | | |
| **Phase 1: Focused Mechanistic Research** | | | | | | | | | | | | | |
| • Preliminary data and proposal to measure risk of carcinogenesis in a relevant animal model and tissue for protons and HZEs | | | | | | | | | | | | | |
| • Preliminary data and proposal for chemopreventive drugs in promotion/progression stage of cancer | | | | | | | | | | | | | |
| • Preliminary data and proposal for dietary supplements to reduce risk of cancer | | | | | | | | | | | | | |
| • Preliminary data and proposal to study cytogenetic aberrations to understand the process leading to cancer at low doses, to determine biomarkers of risk for cancer, and to determine chemical pathways that will reduce risk.. | | | | | | | | | | | | | |
| • Preliminary data and proposal to study DNA damage to understand the process leading to cancer at low doses and to determine biomarkers of risk for cancer. | | | | | | | | | | | | | |
| • Preliminary data and proposal to study a transgenic mouse to characterize mutation changes in different tissue types. | | | | | | | | | | | | | |
| **Phase 2: Preliminary Countermeasure Development Research** | | | | | | | | | | | | | |
| • Initial studies to measure risk of carcinogenesis in a relevant animal model and tissue for protons and HZEs for pharmaceutical studies and spacecraft design | | | | | | | | | | | | | |
| • Initial studies of chemopreventive drugs in promotion/progression stage of cancer | | | | | | | | | | | | | |
| • Initial studies of dietary supplements to reduce risk of cancer | | | | | | | | | | | | | |
| • Initial studies of cytogenetic aberrations to understand the process leading to cancer at low doses, to determine biomarkers of risk for cancer, and to determine chemical pathways that will reduce risk.. | | | | | | | | | | | | | |
| • Initial studies of DNA damage to understand the process leading to cancer at low doses and to determine biomarkers of risk for cancer. | | | | | | | | | | | | | |
| • Initial studies of a transgenic mouse to characterize mutation changes in different tissue types leading to drug studies | | | | | | | | | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase 3: Mature Countermeasure Development Research** | | | | | | | | | | | | | |
| • Determine risk of carcinogenesis in a relevant animal model and tissue for protons and HZEs | | | | | | | | | | | | | |
| • Determine efficacy of a chemopreventive drug in promotion/progression stage of cancer | | | | | | | | | | | | | |
| • Determine specific dietary supplements to reduce risk of cancer | | | | | | | | | | | | | |
| • Determine cytogenetic aberrations to understand the process leading to cancer at low doses, to determine biomarkers of risk for cancer, and to determine chemical pathways that will reduce risk. | | | | | | | | | | | | | |
| • Initial studies of DNA damage to understand the process leading to cancer at low doses and to determine biomarkers of risk for cancer. | | | | | | | | | | | | | |
| • Determine mutations in different tissues in a transgenic mouse leading to carcinogenesis. | | | | | | | | | | | | | |
| • Develop pharmacological countermeasure and test with human subjects | | | | | | | | | | | | | |
| • Determine whether there are synergistic or antagonistic interactions between radiation and other major risks such as bone loss or reduced immunology. | | | | | | | | | | | | | |
| **Phase 4: Countermeasure Evaluation & Validation** | | | | | | | | | | | | | |
| • Testing in space environment | | | | | | | | | | | | | |
| **Phase 5: Operational Implementation of Countermeasure Strategy** | | | | | | | | | | | | | |

## Table 11.3b. Achieving Goal 2: Reduce Risk of Damage to Central Nervous System from Radiation Exposure (39)

| Countermeasure Development Phases | Pre 2001 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase 0: Observational & Phenomenological Research** | | | | | | | | | | | | | |
| **Phase 1: Focused Mechanistic Research** | | | | | | | | | | | | | |
| • Preliminary data and proposal to measure effects of radiation on CNS cells *in vitro* for protons and HZEs | | | | | | | | | | | | | |
| • Preliminary data and proposal to measure effects of radiation on CNS *in vivo* for protons and HZEs | | | | | | | | | | | | | |
| **Phase 2: Preliminary Countermeasure Development Research** | | | | | | | | | | | | | |
| • Initial studies to measure effects of radiation on CNS cells *in vitro* for protons and HZEs leading to drug studies in-vitro | | | | | | | | | | | | | |
| • Initial studies to measure effects of radiation on CNS *in vivo* for protons and HZEs leading to in-vivo drug studies | | | | | | | | | | | | | |
| **Phase 3: Mature Countermeasure Development Research** | | | | | | | | | | | | | |
| • Develop integrated exercise, nutritional, and pharmacological countermeasure and test in humans | | | | | | | | | | | | | |
| • Determine whether artificial gravity, in conjunction with the exercise, nutritional, and pharmacological countermeasure above, further reduces muscle atrophy in humans | | | | | | | | | | | | | |
| **Phase 4: Countermeasure Evaluation & Validation** | | | | | | | | | | | | | |
| • Testing in a space environment | | | | | | | | | | | | | |
| **Phase 5: Operational Implementation of Countermeasure Strategy** | | | | | | | | | | | | | |

# National Space Biomedical Research Institute

## RADIATION EFFECTS

**Table 11.3c. Achieving Goal 3: Reduce Risk of Synergistic Effects from Exposure to Radiations, Microgravity, and Other Spacecraft Environmental Factors (40)**

| Countermeasure Development Phases | Pre 2001 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase 0: Observational & Phenomenological Research** | | | | | | | | | | | | | |
| **Phase 1: Focused Mechanistic Research** | | | | | | | | | | | | | |
| • Experimental observation of antagonistic effects of protons and iron ions for carcinogenesis *in vivo* | | | | | | | | | | | | | |
| • Demonstrated dietary restriction reduced cancer and extended life of our rats | | | | | | | | | | | | | |
| • Experimental observation of abscopal effects *in vivo* | | | | | | | | | | | | | |
| • Experimental observation of apparent adaptive response *in vitro* and *in vivo* | | | | | | | | | | | | | |
| • Funded preliminary study of potential synergistic effects of radiation and immunology.. | | | | | | | | | | | | | |
| **Phase 2: Preliminary Countermeasure Development Research** | | | | | | | | | | | | | |
| • Effect of dietary supplements on oxidative stress | | | | | | | | | | | | | |
| • Proposal submitted to NASA for Bone/Radiation collaboration | | | | | | | | | | | | | |
| • Studies initiated in Nutrition and Immunology Teams. Based upon initial data obtained by Dicello's project. | | | | | | | | | | | | | |
| **Phase 3: Mature Countermeasure Development Research** | | | | | | | | | | | | | |
| • Clinical trial of dietary supplements | | | | | | | | | | | | | |
| • Determine whether microgravity affects chemo-effectiveness of drugs or dietary supplements. | | | | | | | | | | | | | |
| **Phase 4: Countermeasure Evaluation & Validation** | | | | | | | | | | | | | |
| • Testing of drugs in Space | | | | | | | | | | | | | |
| **Phase 5: Operational Implementation of Countermeasure Strategy** | | | | | | | | | | | | | |

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Table 11.3d. Achieving Goal 4: Reduce Risk of Early or Acute Effects from Radiation Exposure (41)

| Countermeasure Development Phases | Pre 2001 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase 0: Observational & Phenomenological Research** | | | | | | | | | | | | | |
| **These effects are considered Type II, rank 4 risks in NASA's Strategic Plan and are not being explicitly examined at the present time with resources available. Our research on carcinogenesis and CNS damage, however, will provide some data to further assess problems in these three areas.** | | | | | | | | | | | | | |
| **Phase 1: Focused Mechanistic Research** | | | | | | | | | | | | | |
| **Phase 2: Preliminary Countermeasure Development Research** | | | | | | | | | | | | | |
| **Phase 3: Mature Countermeasure Development Research** | | | | | | | | | | | | | |
| **Phase 4: Countermeasure Evaluation & Validation** | | | | | | | | | | | | | |
| **Phase 5: Operational Implementation of Countermeasure Strategy** | | | | | | | | | | | | | |

**Table 11.3e. Achieving Goal 5: Reduce Risk of Radiation Effects on Fertility, Sterility, and Heredity (42)**

| Countermeasure Development Phases | Pre 2001 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase 0: Observational & Phenomenological Research** | | | | | | | | | | | | | |
| **These effects are considered Type III risks in NASA's Strategic Plan and are not being explicitly examined at the present time with resources available. Our research on genetics and biomarkers, however, will provide some data to further assess problems in these three areas.** | | | | | | | | | | | | | |
| **Phase 1: Focused Mechanistic Research** | | | | | | | | | | | | | |
| **Phase 2: Preliminary Countermeasure Development Research** | | | | | | | | | | | | | |
| **Phase 3: Mature Countermeasure Development Research** | | | | | | | | | | | | | |
| **Phase 4: Countermeasure Evaluation & Validation** | | | | | | | | | | | | | |
| **Phase 5: Operational Implementation of Countermeasure Strategy** | | | | | | | | | | | | | |

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### Table 11.3f. Achieving Goal 6: Methods for Assessing Level of Health Risk, Prevention of Diseases, & Appropriate Medical Care

| Countermeasure Development Phases | Pre 2001 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase 0: Observational & Phenomenological Research** | | | | | | | | | | | | | |
| **This strategy being pursued presently to achieve this goal is to reduce the level of radiation exposure, to determine and measure appropriate biomarkers, and to find drugs, diet, and environmental factors that can be used to reduce risk.** | | | | | | | | | | | | | |
| **Phase 1: Focused Mechanistic Research** | | | | | | | | | | | | | |
| • Propose chemopreventive drugs in promotion/progression stage of cancer | | | | | | | | | | | | | |
| • Propose chemopreventive dietary supplements to reduce risk of cancer | | | | | | | | | | | | | |
| • Propose chemopreventive drugs to reduce risk of CNS damage | | | | | | | | | | | | | |
| **Phase 2: Preliminary Countermeasure Development Research** | | | | | | | | | | | | | |
| • Begin *in vivo* studies of Tamoxifen as a chemopreventive drug in the promotion/progression stages. | | | | | | | | | | | | | |
| • Propose chemopreventive dietary supplements to reduce risk of cancer | | | | | | | | | | | | | |
| • Propose chemopreventive drugs to reduce risk of CNS damage | | | | | | | | | | | | | |
| **Phase 3: Mature Countermeasure Development Research** | | | | | | | | | | | | | |
| • *In vivo* studies of Tamoxifen as a chemopreventive drug in the promotion/progression stages. | | | | | | | | | | | | | |
| • Cell/animal studies of dietary supplements to reduce risk of cancer | | | | | | | | | | | | | |
| • Cell/animal chemopreventive drugs to reduce risk of CNS damage | | | | | | | | | | | | | |
| **Phase 4: Countermeasure Evaluation & Validation** | | | | | | | | | | | | | |
| **Phase 5: Operational Implementation of Countermeasure Strategy** | | | | | | | | | | | | | |

**Table 11.3G. Achieving Goal 7: Potential Earth-Based Applications**

| Countermeasure Development Phases | Pre 2001 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase 0: Observational & Phenomenological Research** | | | | | | | | | | | | | |
| **Phase 1: Feasibility Research** | | | | | | | | | | | | | |
| • Propose broad-band neutron detector for Tech Team | | | | | | | | | | | | | |
| • Propose network-based remote treatment planning for radiotherapy to NIH | | | | | | | | | | | | | |
| • Propose chemopreventive drugs in promotion/progression stage of cancer | | | | | | | | | | | | | |
| • Propose microbeam of energetic heavy ions for Tech Team | | | | | | | | | | | | | |
| • Propose chemopreventive dietary supplements to reduce risk of cancer | | | | | | | | | | | | | |
| • Propose chemopreventive drugs to reduce risk of CNS damage | | | | | | | | | | | | | |
| **Phase 2: Development Research** | | | | | | | | | | | | | |
| • Initiate broad-band neutron detector in Tech Team leading to design changes in spacecraft and selection of drug categories needed | | | | | | | | | | | | | |
| • NIH funds network-based remote treatment planning | | | | | | | | | | | | | |
| • Begin *in vivo* studies of Tamoxifen as a chemopreventive drug in the promotion/progression stages. | | | | | | | | | | | | | |
| • Initiate design of microbeam of energetic heavy ions in Tech Team | | | | | | | | | | | | | |
| • Propose chemopreventive dietary supplements to reduce risk of cancer | | | | | | | | | | | | | |
| • Propose chemopreventive drugs to reduce risk of CNS damage | | | | | | | | | | | | | |
| **Phase 3: Mature Research and Development** | | | | | | | | | | | | | |
| • Tech Team flies broad-band neutron detector in planes and balloons | | | | | | | | | | | | | |
| • NIH clinical trials of remote treatment planning for radiotherapy | | | | | | | | | | | | | |
| • *In vivo* studies of Tamoxifen as a chemopreventive drug. | | | | | | | | | | | | | |
| • Prototype of microbeam of energetic heavy ions in Tech Team | | | | | | | | | | | | | |
| • Cell/animal studies of dietary supplements to reduce risk of cancer | | | | | | | | | | | | | |
| • Cell/animal chemopreventive drugs to reduce risk of CNS damage | | | | | | | | | | | | | |
| **Phase 4: Evaluation & Validation** | | | | | | | | | | | | | |
| **Phase 5: Operational Implementation Strategy** | | | | | | | | | | | | | |

**Table 11.3H. Achieving Goal 8: Integrate Experimental Research with Theoretical Analysis to be Used to Extrapolate Data to Risk and Countermeasures for Humans.**

| Countermeasure Development Phases | Pre 2001 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase 0: Observational & Phenomenological Research** | | | | | | | | | | | | | |
| **Phase 1: Focused Mechanistic Research** | | | | | | | | | | | | | |
| • Integrate Research in the Radiation Team | | | | | | | | | | | | | |
| • Request proposals on this topic, review, and fund | | | | | | | | | | | | | |
| • Develop theoretical model to relate cell biomarkers (genetic, cytogenetic, epigenetic, and abscopal) in animals to carcinogenesis in animals | | | | | | | | | | | | | |
| • Develop theoretical model to relate animal carcinogenesis to human carcinogenesis | | | | | | | | | | | | | |
| • Develop theoretical model to relate cell biomarkers (genetic, cytogenetic, epigenetic, and abscopal) in animals to CNS damage in animals | | | | | | | | | | | | | |
| • Develop theoretical model to relate animal CNS to human CNS | | | | | | | | | | | | | |
| **Phase 2: Preliminary Countermeasure Development Research** | | | | | | | | | | | | | |
| • Apply model with new data to obtain improved risk assessments and models to evaluate effect of drugs in humans | | | | | | | | | | | | | |
| • Request proposals on this topic, review, and fund | | | | | | | | | | | | | |
| • Apply model with new data to obtain improved risk assessments | | | | | | | | | | | | | |
| **Phase 3: Mature Countermeasure Development Research** | | | | | | | | | | | | | |
| • Initiate shielding designs based upon model calculations of risk | | | | | | | | | | | | | |
| • Develop pharmaceutical strategy based upon model predictions | | | | | | | | | | | | | |
| **Phase 4: Countermeasure Evaluation & Validation** | | | | | | | | | | | | | |
| • Modify existing spacecraft and design new vehicles according to new criteria | | | | | | | | | | | | | |
| • Initiate ground-based clinical trials of chemopreventives and dietary supplements. | | | | | | | | | | | | | |
| **Phase 5: Operational Implementation of Countermeasure Strategy** | | | | | | | | | | | | | |