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Radioprotectors and Mitigators for Improving Radiotheapy

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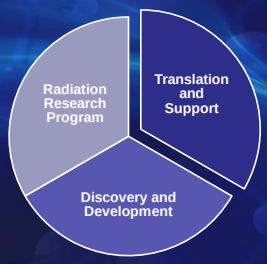

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Outline

- Objectives
- Significance
- Radiation-Induced Lung Injury
- Funding Approach to Discovery, Development, and Translation of Radiomodifiers

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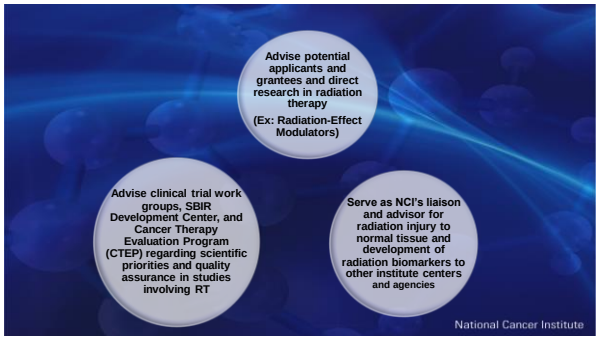

Sites	Estimated New Cases	Estimated Deaths
All sites	**1,658,370**	**589,430**
Oral Cavity and Pharynx	45,780	8,650
Digestive System	291,150	149,300
Respiratory System	240,390	162,460
Brain and Nervous System	22,850	15,320
Breast	234,190	40,730
Prostate	220,800	27,540
Lymphoma	80,900	20,940

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Projected Worldwide Data

- Radiation therapy for some cancer types is already a curative modality and for many others it is transitioning from palliative to curative
- Implementing familiar technology will increase curability

	2012	2030
New Cases	14.1 M	24.6 M
Number of cases treated with RT	7 M	12 M

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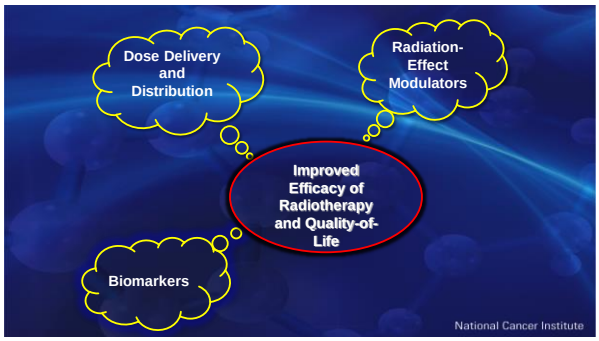
Dose Delivery and Distribution
Radiation-Effect Modulators
Improved Efficacy of Radiotherapy and Quality-of-Life
Biomarkers
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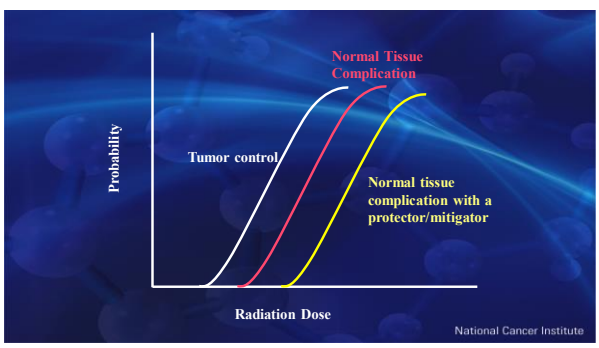
Normal Tissue Complication
Probability
Tumor control
Normal tissue complication with a protector/mitigator
Radiation Dose
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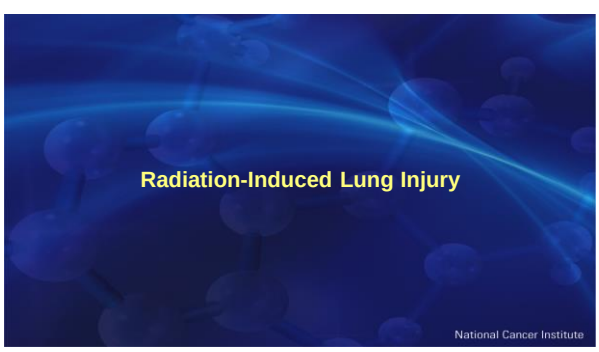
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Challenges in Treatment Planning for the Upper Thoracic Region

- Precise definition of tumor's anatomical location
- Avoidance of critical organs
- Motion-associated movement of tumor during and between treatment
- How to decrease dose to normal tissue?

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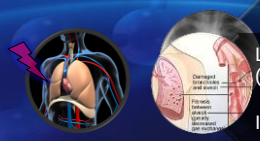
Radiation-Induced Lung Injury



Pneumonitis

Asymptomatic

Opaque chest X-ray

Late response (months to years)

Irreversible

Fibrosis

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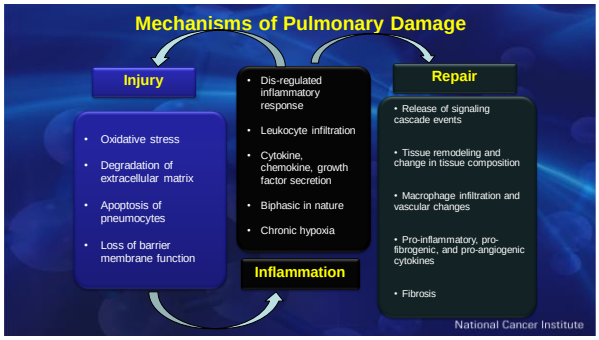
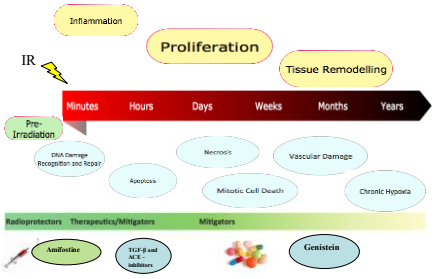
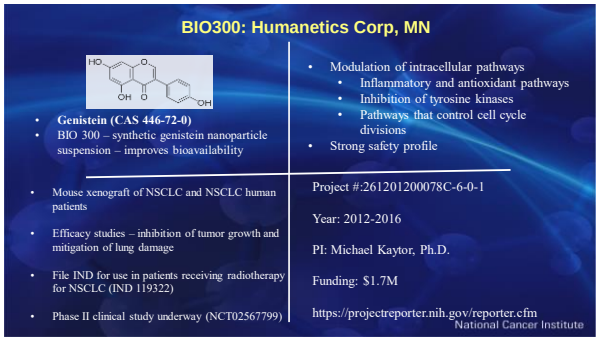


Possible Approaches to Protect and Mitigate Lung Injury





Funding Approach to Discovery, Development and Translation of Radiomodifiers

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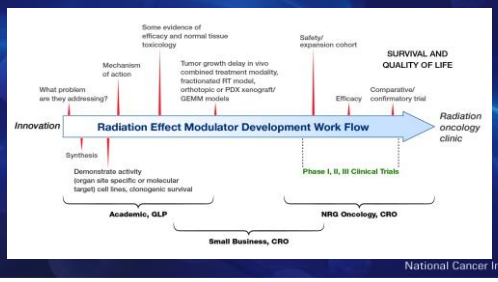
A Generalized Workflow Model for the Translation of Radiation-Effect Modulators



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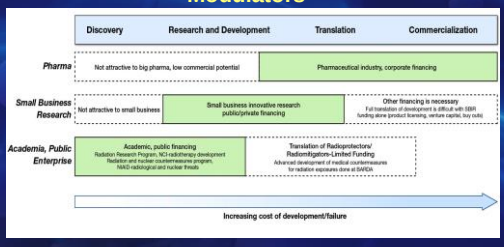
Synergy in the Development of Radiation-Effect Modulators



Prasanna *et al*., Radiat. Res. 2015

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Summary

- Radiation therapy is transitioning from palliative therapy to a potentially curative modality. Implementing familiar technology will increase curability.
- Decreasing the dose to the normal tissue and minimizing the collateral damage is the greatest challenge in treatment planning for the upper thoracic region
- Radiation-induced fibrosis involves vascular damage and collagen deposition
- Treatments that modify cellular damage and death processes, inflammation, tissue regeneration and remodeling will help mitigate intermediate to long-term radiation-induced lung injury

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Other Organs and Mitigators

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Radiation-Induced Mucositis

Drug (Company)	Award Type	Year Started	Current Status	Model	Aims
CBLB502 (TLR-5 agonist); Buffalo Biolabs, Buffalo, NY)	Phase I	2012	Complete	Mouse model of head and neck cancer	• Protective effect to skin and oral mucosa after single- and fractionated multiple radiation dose regimens
RLIP76 (proteoliposome) Terapio Inc., Austin, TX	Phase I	2013	Complete	Hamster Cheek	• Develop RLIP as a topical mouthwash • Test efficacy, systemic absorption and demonstrate no tumor protection.
JVRSOD (gene therapeutic); Colby Pharmaceuticals, Menlo Park, CA	Fast Track	2013	Ongoing	Mouse model and patients with head and neck cancer	• Perform dose- and schedule optimization • Identify and qualify a GMP manufacturing site • Submit IND application • Safety and efficacy clinical trials

Note: All information provided here and in the text is publicly accessible at http://projectreporter.nih.gov/reporter.cfm.

Extracted from Prasanna et al 2015

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Radiation-Induced Brain Injury

Drug (Company)	Award Type	Year Started	Current Status	Model	Aims
TP508 (Biotherapeutic, 23-amino acid peptide) [Chrysalis Biotherapeutics Galveston, TX]	Phase I	2011	Complete	Cell lines and Mouse xenograft orthotopic model	• Dose- and schedule- optimization for vascular protection • Demonstrate protection to brain tissue from radiotherapy damage • Determine whether the protection is selective normal tissue without altering radiation cell-killing of cancer cells
	Phase II	2013	Ongoing	Mouse orthotopic Xenograft	• Determine whether the drug: i) protects also cancer stem cells or whether its protective effects are specific for neuroprogenitor cells, ii) reduces radiotherapy induced neuronal atrophy and cognitive impairment, and iii) determine how the drug affects neuroprogenitor cells and generation of new neurons
Fullerene-based radioprotectors [Luna Innovations, Roanoke, VA]	Phase I	2014	Ongoing	Cell lines and animals	• Preclinical studies to demonstrate safety • Preclinical studies to demonstrate effectiveness and improvement in therapeutic ratio

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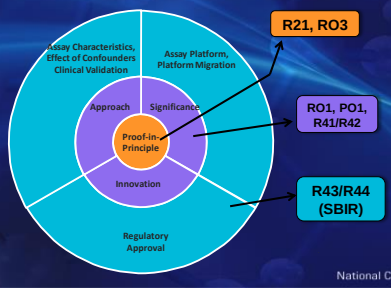
Funding Mechanisms



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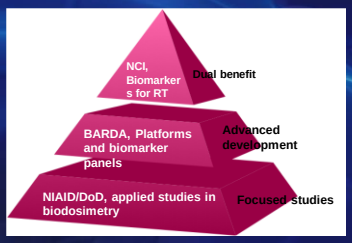
Leveraging Development Across Programs for Clinical Use



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Important Adverse Effects after Conventional Radiotherapy of GBM and H&NC

Cancer Type	Standard of Care	Mortality (Yr)	Median Survival (Mo)	Late Adverse Effects
Glioblastoma	Temozolomide	73.5% (2)	14.6	Cognitive
Head and Neck (Unresectable)	Cetuximab	45% (3)	49	
Head and Neck (Resected)	Cisplatin	Not available	48	

Prasanna et al. 2012

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Radiation-Induced Brain Damage

Days → **Weeks** → **Months** → **Years**

Acute
- Edema
- Headache
- Drowsiness
- Rare under current treatment conditions

Early Delayed
- Transient demyelination, resolves
- Somnolence
- Attention deficits
- Short-term memory loss
- Severity is not predictive of late effects

Late
- Occurs at high doses (>60 Gy)
- Intellectual deterioration can occur even at lower doses
- Vascular abnormalities
- Demyelination
- White matter necrosis
- Memory loss
- Cognitive impairment occurs in up to 50% of patients undergoing RT
- Includes hippocampus

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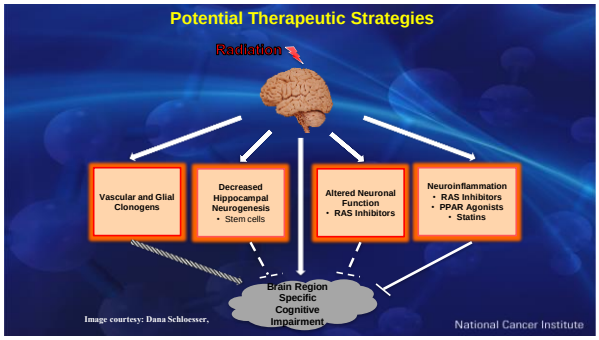
Potential Therapeutic Strategies
Radiation
Vascular and Glial Clonogens
Decreased Hippocampal Neurogenesis
• Stem cells
Altered Neuronal Function
• RAS Inhibitors
Neuroinflammation
• RAS Inhibitors
• PPAR Agonists
• Statins
Brain Region Specific Cognitive Impairment
Image courtesy: Dana Schloesser,
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Dose Delivery and Distribution
tissue sparing
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