Radioprotectors and Mitigators for Improving Radiotherapy

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• No financial conflict of interest
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Outline

• Objectives
• Significance
• Radiation-Induced Lung Injury
• Funding Approach to Discovery, Development, and Translation of Radiomodifiers
Advise potential applicants and grantees and direct research in radiation therapy (Ex: Radiation Effect Modulators)

Serve as NCI’s liaison and advisor for radiation injury to normal tissue and development of radiation biomarkers to other institute centers and agencies

Advise clinical trial work groups, SBIR Development Center, and Cancer Therapy Evaluation Program (CTEP) regarding scientific priorities and quality assurance in studies involving RT

Estimated Number of New Cancer Cases and Deaths, US 2015 (ACS Data)

<table>
<thead>
<tr>
<th>Sites</th>
<th>Estimated New Cases</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>1,658,370</td>
<td>589,430</td>
</tr>
<tr>
<td>Oral Cavity and Pharynx</td>
<td>45,780</td>
<td>8,650</td>
</tr>
<tr>
<td>Digestive System</td>
<td>291,150</td>
<td>149,300</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>240,390</td>
<td>162,460</td>
</tr>
<tr>
<td>Brain and Nervous System</td>
<td>22,850</td>
<td>15,320</td>
</tr>
<tr>
<td>Breast</td>
<td>234,190</td>
<td>40,730</td>
</tr>
<tr>
<td>Prostate</td>
<td>200,800</td>
<td>27,540</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>80,900</td>
<td>20,940</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>New Cases</th>
<th>2012</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.1 M</td>
<td></td>
<td>24.6 M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of cases treated with RT</th>
<th>7 M</th>
<th>12 M</th>
</tr>
</thead>
</table>
Radiation - Effect Modulators
Dose Delivery and Distribution
Biomarkers

Improved Efficacy of Radiotherapy and Quality-of-Life

Radiation-Induced Lung Injury

Normal Tissue Complication
Tumor control
Normal tissue complication with a protector/mitigator

Probability
Radiation Dose
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?

Radiation-Induced Lung Injury

- Pneumonitis
- Asymptomatic
- Opaque chest X-ray
- Late response (months to years)
- Irreversible
- IL-6 appear to

- Fibrosis
Mechanisms of Pulmonary Damage

**Injury**
- Oxidative stress
- Degradation of extracellular matrix
- Apoptosis of pneumocytes
- Loss of barrier maintenance function

**Inflammation**
- Oxidative stress
- Degradation of extracellular matrix
- Apoptosis of pneumocytes
- Loss of barrier maintenance function

**Repair**
- Release of signaling cascade events
- Tissue remodeling and change in tissue composition
- Macrophage infiltration and vascular changes
- Proinflammatory, proangiogenic, and pro-fibrogenic cytokines
- Fibrosis

Possible Approaches to Protect and Mitigate Lung Injury

**Amifostine**
- TGF-β and ACE-inhibitors

**Genistein**
- BIO 300: Humanetics Corp, MN
  - Genistein (CAS 446-72-0)
  - BIO 300: synthetic genistein nanoparticle suspension - improved bioavailability
  - Modulation of intracellular pathways
  - Inflammatory and antioxidant pathways
  - Inhibition of tyrosine kinases
  - Pathways that control cell cycle divisions
  - Strong safety profile
  - Mice xenograft of NSCLC and NSCLC human patients
  - Efficacy studies - inhibition of tumor growth and mitigation of lung damage
  - FDA IND for use in patients receiving radiotherapy for NSCLC (IND 119322)
  - Phase II clinical study underway (NCT02567799)

Project #: 261201200078C
Year: 2012-2016
PI: Michael Kaytor, Ph.D.
Funding: $1.7M
https://projectreporter.nih.gov/reporter.cfm
Funding Approach to Discovery, Development and Translation of Radiomodifiers

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

Synergy in the Development of Radiation-Effect Modulators
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.

Other Organs and Mitigators

Radiation-Induced Mucositis

<table>
<thead>
<tr>
<th>Drug (Company)</th>
<th>Award</th>
<th>Type</th>
<th>Year Started</th>
<th>Current Status</th>
<th>Model</th>
<th>Aims</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBLB502 (TLR5 agonist); Buffalo Biolabs, Buffalo, NY</td>
<td>RLIP76 (proteoliposome); Terapio Inc., Austin, TX</td>
<td>Phase I</td>
<td>2012</td>
<td>Complete</td>
<td>Mouse model of head and neck cancer</td>
<td>Protective effect to skin and oral mucosa after single- and fractionated multiple-radiation dose regimens. Develop RLIP as a topical mouthwash. Test efficacy, systemic absorption and demonstrate no tumor protection.</td>
</tr>
<tr>
<td>JVRSOD (gene therapeutic); Colby Pharmaceutical, Menlo Park, CA</td>
<td>Fast Track</td>
<td>2013</td>
<td>Ongoing</td>
<td>Mouse model and patients with head and neck cancer</td>
<td>Perform dose- and schedule optimization. Identify and qualify a GMP manufacturing site. Submit IND application. Safety and efficacy clinical trials.</td>
<td></td>
</tr>
</tbody>
</table>
Radiation-Induced Brain Injury

<table>
<thead>
<tr>
<th>Drug (Name)</th>
<th>Award Type</th>
<th>Year Started</th>
<th>Current Status</th>
<th>Model</th>
<th>Aims</th>
</tr>
</thead>
</table>
| TP508 (Biotherapeutic, 23-amino acid peptide) | Phase I | 2011 | Complete | Cell lines and Mouse orthotopic xenograft | • Dose and toxicity optimization for vascular protection
• Demonstrate protection in vivo from radiation damage
• 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. |

| Fullerene-based radioprotectors | Phase I | 2014 | Ongoing | Cell lines and animals | • Preclinical studies to demonstrate safety
• Preclinical studies to demonstrate effectiveness and improvement in therapeutic ratio |

Note: All information provided here and on the site is publicly accessible at [http://projectreporter.nih.gov/reporter.cfm](http://projectreporter.nih.gov/reporter.cfm), Extracted from Prasanna et al 2015

Funding Mechanisms

- R21, R03
- RO1, PO1, R41/R42
- R43/R44 (SBIR)
Leveraging Development Across Programs for Clinical Use

- NCI Biomarker strategy
- BARDA, Platforms and biomarker panels
- NIAID/DoD, applied studies in biodosimetry

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

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Standard of Care</th>
<th>Mortality (%)</th>
<th>Median Survival (Mo)</th>
<th>Late Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma</td>
<td>Temozolomide</td>
<td>73.9% (2)</td>
<td>14.6</td>
<td>Cognitive</td>
</tr>
<tr>
<td>Head and Neck (Unresectable)</td>
<td>Cetuximab</td>
<td>45% (3)</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Head and Neck (Resected)</td>
<td>Cisplatin</td>
<td>Not available</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

Radiation-induced Brain Damage

- 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
Potential Therapeutic Strategies

- Vascular and Glial Clonogens
- Decreased Progenitor Proliferation
- Altered Neuronal Function
- Decreased Hippocampal Neurogenesis
- Decreased Neurogenesis
- Statins
- PPAR Agonists
- RAS Inhibitors
- Neuroprotection
- Stem Cells
- Specific Cognitive Impairment

Image courtesy: Dana Schloesser.

Brain Tumor Therapies

- Conventional Radiotherapy
  - LINAC
  - Improved normal tissue sparing
- Proton Therapy
  - Precise dose delivery
- Brachytherapy
  - Continuous irradiation and low integral dose

Dose Delivery and Distribution

Image courtesy: National Cancer Institute.