Nanoparticles in cancer medicine – a physician’s perspective

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Disclosure Information
Sunil Krishnan

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I WILL NOT include discussion of investigational or off-label use of a product in my presentation.

Physical dose enhancement

The underlying physics

• Ejection of orbital electron & emission of x-ray fluorescence photon (or characteristic x-ray)

Courtesy: Nivedh Manohar, PhD

Physical dose enhancement


Physical dose enhancement

Internalization


Enhancing physical dose enhancement

Passive targeting

Active targeting

Conjugated gold nanorod

on the order of 10 μm
**Apoptotic markers**

<table>
<thead>
<tr>
<th>Caspase-mediated apoptotic markers</th>
<th>Mitochondrial-mediated apoptotic markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaspase 3</td>
<td>Procaspase 3</td>
</tr>
<tr>
<td>Procaspase 8</td>
<td>Procaspase 8</td>
</tr>
<tr>
<td>Procaspase 9</td>
<td>Procaspase 9</td>
</tr>
<tr>
<td>Actin</td>
<td>Actin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rad (4 Gy)</th>
<th>PGNR + Rad</th>
<th>cGNR + Rad</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hr</td>
<td>1 hr</td>
<td>1 hr</td>
</tr>
<tr>
<td>24 hr</td>
<td>24 hr</td>
<td>24 hr</td>
</tr>
</tbody>
</table>

**Total oxidative stress**

<table>
<thead>
<tr>
<th>Time after 4 Gy radiation</th>
<th>Rad</th>
<th>PGNR</th>
<th>cGNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 hrs</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Tissue effects**

<table>
<thead>
<tr>
<th>Post irradiation time</th>
<th>Rad (4 Gy)</th>
<th>PGNR + Rad</th>
<th>cGNR + Rad</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 hrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 days</td>
<td></td>
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</tr>
</tbody>
</table>
Tissue effects

Post irradiation period
Average microvessel density per field of view with 10X objective
Radiation (10 Gy)
GNR + Rad (10 Gy)
C225-GNR + Rad (10 Gy)

Intracellular distribution
Time

The underlying physics

- Ejection of orbital electron & emission of x-ray fluorescence photon (or characteristic x-ray)

Summary

- Targeted payload delivery feasible with smaller nanoparticles bioconjugated to peptides/antibodies
- Tumor accumulation does not increase much, BUT distribution is altered at the cellular level
- Both the intracellular localization and the perivascular sequestration result in greater radiosensitization at a biological level, mediated primarily by:
  - Increased DNA damage and downstream signaling
  - Increased oxidative stress
  - Increased vascular disruption
Another approach

Thermosensitive liposome

Focused ultrasound
Deep penetration of tumors
Summary

• Triggered release from thermosensitive liposomes enhances deep penetration of nanoparticles
• Deep penetration improves radiosensitization independent of the effect of hyperthermic radiosensitization
• In principle, this could be a class solution for a variety of tumor types

Photoacoustic imaging

Xray fluorescence imaging

Progressive intracellular accumulation
Inc’d oxidative stress
Inc’d DNA damage

XRT

Deep penetration of nanoparticles

~120nm Thermo-sensitive liposome with gold

PEG-AuNp Aqueous core Phospholipid bilayer Hydrophobic region

120-130 nm

Control HT TSLAuNp Rad TSLAuNp + Rad TSLAuNp + HT + Rad

Days

Normalized tumor volume

Summary

- Larger particles for vascular-targeted applications (thermoablation, hyperthermia, vascular imaging)
- Smaller particles for parenchymal applications (imaging, targeted payload delivery)
- Combinations of above
- Unresolved issues related to clinical translation
Patients receiving radiation therapy for cancer

~60% of all patients receive radiation therapy

Often, standard doses of radiation therapy are unable to cure the tumor but higher doses cannot be given due to high risk of side effects from overdosing adjacent normal organs

Can one give the same (standard) dose of radiation to the tumor but make it behave like a higher dose of radiation?

The target population

We need new approaches

A new radiosensitization strategy
What nanoparticles work best?

Bland?

Spicy?

What nanoparticles work best?

Where do we stand today?


Courtesy: Gabriel Sawakuchi

Courtesy: Jan Schuemann
Roadmap to the clinic

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