Gold nanoparticles as radiosensitizers – what does it take to go from the bench to the bedside

Sunil Krishnan, MD
Director, Center for Radiation Oncology Research
John E. and Dorothy J. Harris Professor, Radiation Oncology
MD Anderson Cancer Center, Houston, TX

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Sunil Krishnan

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I WILL include discussion of investigational or off-label use of a product in my presentation.

Hyperthermia

Chatterjee DK, Krishnan S. Cancer Nanotechnology. Elsevier 2013
Nanoparticles for hyperthermia


Gold nanoparticles

• Dielectric silica core
• Thin gold coating
• Light absorbed by the free electrons on the gold is converted to heat
• Core-shell ratio determines the optical characteristics

Gold nanoshells
Real time MRTI

(0.6 W/cm² for 20 min at 808-nm)

Normalized tumor volume

Mechanisms

Early effects

Late effects

Anti-hypoxic effect

Vascular disrupting effect?
Scanning Electron Microscopy


Stem cell sensitization

<table>
<thead>
<tr>
<th>Treatment (Tumor T7)</th>
<th>10000</th>
<th>1000</th>
<th>105</th>
<th>30</th>
<th>Tumor Initiation Cell Frequency (7x10^5 CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mkt</td>
<td>6/6</td>
<td>1/6</td>
<td>0/6</td>
<td>1.02 (1.78-8.16)</td>
<td></td>
</tr>
<tr>
<td>0 Gy</td>
<td>6/6</td>
<td>2/6</td>
<td>1/6</td>
<td>1.03 (0.49-0.95)</td>
<td></td>
</tr>
<tr>
<td>0 Gy + 42C</td>
<td>0/6</td>
<td>3/6</td>
<td>0/6</td>
<td>1.02 (0.37-0.95)</td>
<td></td>
</tr>
</tbody>
</table>


Thermal dosimetry

Gold nanoshells

- Consistency of formulation under GLP conditions
- No endotoxin contamination
- No pyrogenicity - US Pharmacopeia [USP] method, rabbit
- No genotoxicity – Ames bacterial mutagenicity, CHO cell chromosomal aberration assay, in vivo mouse micronucleus
- No in vitro hemolysis
- No intracutaneous reactivity in the rabbit
- No sensitization - maximization assay in the guinea pig
- No acute systemic toxicity in the mouse – single, multiple injections
- No late toxicity in Beagle dogs - up to 404 days

Magnetic fluid hyperthermia

Magnetic fluid hyperthermia

Magforce phase II study in recurrent glioblastoma
59 patients – direct injection of ~5ml of 12nm Fe₃O₄ particles coated with aminosilane, twice weekly AMF 100kHz, in conjunction with 30Gy at 2Gy/fraction

Median OS from diagnosis of recurrence was 13.4 months

Toxicity – sweating, fever, tachycardia, convulsions

Regulatory approvals

http://www.nanospectra.com
http://www.magforce.de

Nanoparticle hyperthermia caveats

Location
- Accumulate passively in tumors via leaky vasculature
- Perivascular sequestration (larger particles) or a gradient away from the vessel (smaller particles)
- Significant accumulation in liver and spleen (unless they are <5nm)
- Can accumulate preferentially in tumor if decorated with peptides/antibodies (active targeting)

Heterogeneity of temperature within tumor
- Inside-out hyperthermia
- Vascular-focused hyperthermia
  - Preferential sensitization of stem cell niche?

Theranostics
- Dual imaging and therapy potential
- May facilitate thermal dosimetric modeling

Combination strategies
- Drug delivery? Radiation dose enhancement?
Nanoparticle hyperthermia challenges

Biocompatibility
- Possibly less of a concern with gold and iron-oxide
- Some concerns with carbon nanotubes, gold nanorods

Variability
- Physicochemical consistency
- Batch-to-batch uniformity
- Scale-up challenges

Extrinsic energy transduction efficiency
- Low for magnetic nanoparticles – need high concentrations of NPs in tumor, not achievable with i.v. administration

Focusing energy on just the tumor
- Technically challenging for AMF

Heating deep-seated tumors
- Challenging with light as the activator - limited to superficial tumors (IBC, melanoma, head and neck, GI luminal?) or the operative bed
- But high transduction efficiency – i.v. administration sufficient

Next-generation nanoparticles


Untreated animals, black
GNP-C225 + laser alone, orange
Doxi-C225 + radiation, blue
Doxi-C225, GNP-C225, laser and radiation, red

Enhancing physical dose enhancement

Passive targeting
- nanoparticles

Active targeting
- nanoparticles + peptides
  - on the order of 10 µm

Cho et al. Med Phys 2010

Tumor cell targeting

250 kVp

6 MV

Biodistribution


DNA damage
**Theranostic Gd nanoparticle**


**Direct injection**


**Summary**

- Radiosensitization possible with
  - Unconjugated gold NPs – but need large quantities
  - Conjugated gold NPs – but need to optimize construct
    - Vascular endothelial
    - Cancer cell
  - Trojan-horse delivery of gold NPs – need to optimize construct
  - Theranostic nanoparticle (AGuIX)
  - Direct injection of NPs (hafnium)
NP dose enhancement challenges

Biocompatibility
- Less of a concern with gold and iron oxide, some concerns with rods
- All probably need entire battery of tests for safety/tolerability (NCL)

Variability
- Physicochemical consistency, batch-to-batch uniformity
- Scale-up challenges

Biodistribution = size, charge, functionality dependent
- Liver and spleen uptake with i.v. administration
- Renal clearance only if <5.5 nm

Combination with chemotherapy
- Limited data

Device or drug
- Need IND if decorated with peptides or antibodies

Ideal clinical scenario for testing
- Benefit from dose escalation, good differential uptake (tumor vs. critical adjacent organ), retained in tumor for long, does not interfere with concurrent chemo, imageable

Quantifying gold nanoparticles in tumor

Imaging gold nanoparticles in tumors


Photoacoustic imaging

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