AAPM 2014 innovation
56th Annual Meeting & Exhibition • July 20–24, 2014 • Austin, TX

Gold nanoparticles as vascular-disrupting agents during clinical radiation therapy

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Disclosures

No conflicts of interest to disclose

Funding
- BWH Biomedical Research Institute
- NIH/NCI R03CA164645
- JCRT Foundation

Introduction

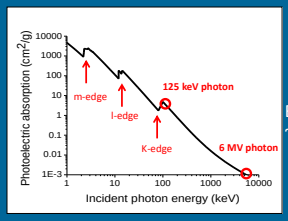
Physics – covered by Jan Schuemann

Biology – covered by Devika Chithrani

Clinical applications….

Clinical translation

Problem #1: Effect is highly dependent on incident photon energy



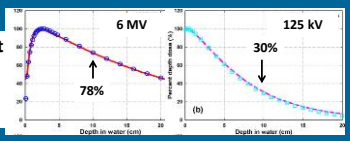
But we don't treat with ~100 kV photons, do we?

Photoelectric mass attenuation coefficient $\propto \frac{Z^3}{E^3}$

Clinical translation

Problem #2: Most effective energies are the least penetrating

Percent Depth Dose (PDD)

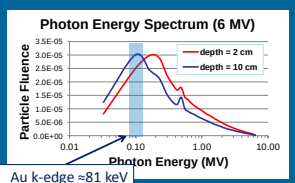


@ 10 cm depth
PDD (6 MV) ≈ 78%
PDD (125 kVp) ≈ 30%

→ MV is standard of care
→ How can we use GNP with MV beams?

Clinical translation

"6 MV" beam is actually composed of an energy spectrum
and
Scatter increases the low energy spectrum of MV beams



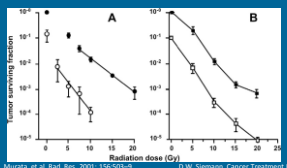
Au k-edge ≈81 keV

Beam "softening" will occur due to scatter

GNP as vascular disrupting agents

Our idea: target specific structures → tumor blood vessels

Synergistic effect of vascular disrupting drugs with radiation (*in vivo*)



Murata, et al. Rad. Res. 2001; 156:503–9.

(closed symbols) radiation alone
(open symbols) radiation plus VDA

(VDA administered 1-3 hrs after RT)

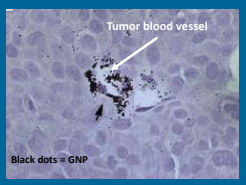
D.W. Siemann Cancer Treatment Reviews 37 (2011) 63–74

(A) ASA404 and
(B) OXi4503 in the murine KHT sarcoma model

Rationale

Our Solution is based upon 3 observations…

1. **Gold nanoparticles tend to trap in the tumor vasculature**



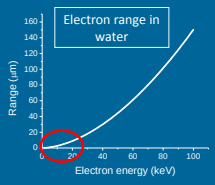
Perrault et al. 2009

Untargeted GNP are seen congregating near the vascular wall
8 hours post-injection

Rationale

Our Solution is based upon 3 observations…

1. Gold nanoparticles tend to trap in the tumor vasculature
2. **The photoelectric dose enhancement is localized within a short distance**

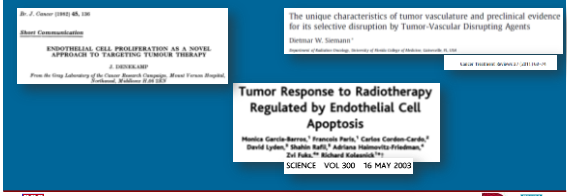


Cole et al. (1969)

Rationale

Our Solution is based upon 3 observations…

1. Gold nanoparticles tend to trap in the tumor vasculature
2. The photoelectric dose enhancement is localized within a short distance
3. **The tumor endothelium is a potent therapy target**


ENDOTHELIAL CELL PROLIFERATION AS A NOVEL APPROACH TO TARGETING TUMOUR THERAPY

The unique characteristics of tumor vasculature and preclinical evidence for its selective disruption by Tumor-Vascular Disrupting Agents

Tumor Response to Radiotherapy Regulated by Endothelial Cell Apoptosis

SCIENCE VOL 300 16 MAY 2003

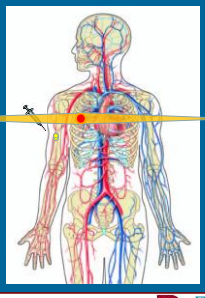
Rationale

Minimize toxicity → maximize translational potential

Double targeted therapy

1. GNP are targeted to the tumor vasculature
2. Radiation is targeted to the tumor

→Imperfect targeting of GNP is benign



Theory

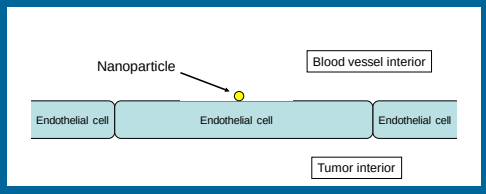
Clinically, MV beams would be preferable, but
Monte Carlo results indicate little MV dose enhancement

- Cho *et al.* (2005):
  - 0.7% enhancement for 6 MV beam @ 6.5 cm depth (7 mg/g AuNP)
- Work by Roeske *et al.* (2007), Jones *et al.* (2010), Leung *et al.* (2011), Lechtman *et al.* (2011), etc. all came to the same conclusion…

"GNP radiosensitization using a 6 MV photon source is not clinically feasible"
(Lechtman *et al.*)

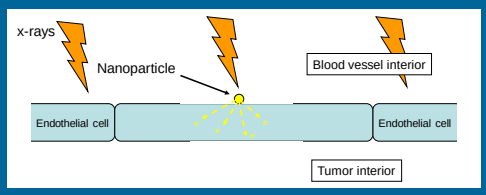
Theory

Analytical calculation using Monte Carlo photon energy spectra



Theory

Analytical calculation using Monte Carlo photon energy spectra



Theory

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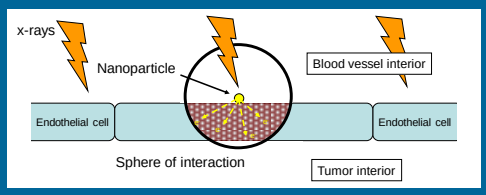
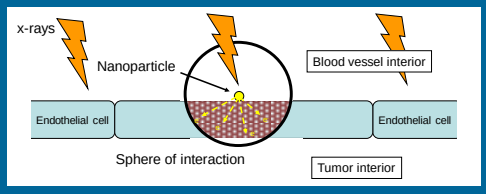


Theory

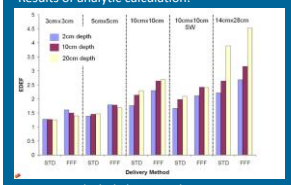
Analytical calculation using Monte Carlo photon energy spectra



$$E_{endothelial} = \int_{R_n}^{R_n+Dt} \frac{shell_{hemisphere} - shell_{\text{spherical cap beyond the endothelial cell}}}{shell_{\text{entire sphere}}} \times \frac{dE}{dr} dt.$$

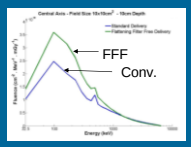
Theory

Results of analytic calculation:



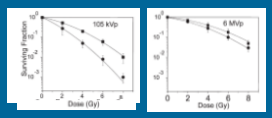
EDEF = Endothelial Dose Enhancement Factor

Monte Carlo energy spectrum @ 10 cm depth



Key results: GNP enhancement increases with field size, depth, FFF

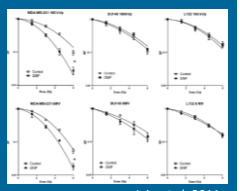
Experiment – in vitro



DEF (105 kVp) = 1.66
DEF (6 MV) = 1.17

Chithrani et al. 2010

DEF (6 MV) = 1.08-1.29
→ depends on cell type

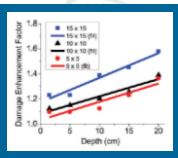


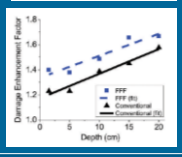
Jain et al. 2011

Key results: GNP dose enhancement is not negligible for 6 MV photons

Experiment – in vitro

In vitro experiments at DFCI
-6 MV clinical linac
- HeLa cells
- γH2AX
- Depth in phantom
- Field size
- Flattening filter free



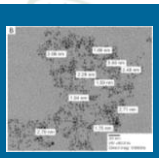


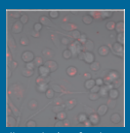

DNA Damage Enhancement from Gold Nanoparticles for Clinical MV Photon Beams

Key results: GNP enhancement increases with field size, depth, FFF

Experiment – GNP characterization

Necessary Characteristics
- Long circulation (PEG)
- Renal clearance (< 10 nm)
  - consistent sizing
- Selective targeting (RGD)
- Imaging (AF647)
- Cell uptake
- Stable (> 6 months)


<10 nm after PEGylation (TEM imaging)

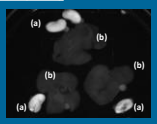

Robust cell uptake (confocal imaging)


Third generation gold nanoplatform optimized for radiation therapy

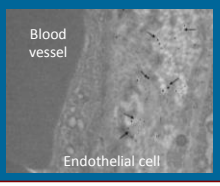
Experiment – imaging

Ex vivo @ 24 hrs (n=3)

(a) Tumors
(b) Pancreas
(c) Spleen



(a) Kidneys
(b) Livers



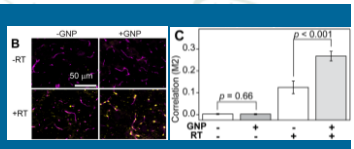
1) Preferential tumor uptake
2) Renal clearance
3) Tumor endothelial cell uptake

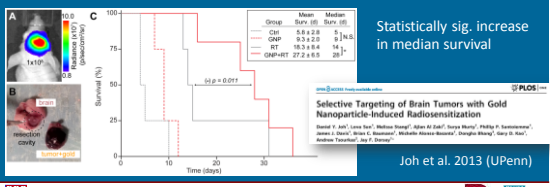
Kumar et al., *manuscript in preparation*

Experiment – in vivo

Mouse brain, 20 Gy (175 kVp)

Co-localization of γH2AX and CD31 images





Statistically sig. increase in median survival

Selective Targeting of Brain Tumors with Gold Nanoparticle-Induced Radiosensitization

Joh et al. 2013 (UPenn)

Summary

- Theoretical predictions indicate a clinically significant dose enhancement is possible in clinical MV beams
- *In vitro* experiments confirm that dose enhancement is not negligible and will increase in clinical beams for deeper targets and for flattening filter free (FFF) delivery
- Preferential GNP uptake in tumor has been shown *in vivo*
- Co-localization of tumor endothelial cell and DNA damage with injected GNP has been shown *in vivo*
- Therapeutic efficacy has been demonstrated *in vivo*

Conclusions

- Exciting time for gold nanoparticles in radiation therapy
- Preliminary results indicate that targeted GNP can damage tumor endothelial cells after irradiation
- Strong justification for continued investigation
- Therapeutic efficacy will depend on
  - GNP formulation (uptake, size, targeting, biodistribution, etc.)
  - Cancer model
- Always keep in mind: clinical translation

Acknowledgements

BWH/DFCI

- Houari Korideck, MD
- Wilfred Ngwa, PhD
- Matt Luchette
- Alex Detappe
- Sijumon Kunjachan, PhD
- Panos Tsiamas, PhD
- Mike Makrigiorgos, PhD
- Piotr Zygmanski, PhD
- Alec Kimmelman, MD, PhD
- Brendan Price, PhD
- Jerry Maddox, MS
- Cliff Miner

Northeastern University

- Sri Sridhar, PhD
- Rajiv Kumar, PhD

Ross I. Berbeco, Ph.D. – Gold nanoparticles as vascular disrupting agents – July 24, 2014