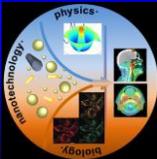


## Gold nanoparticles as radiosensitizers – what does it take to go from the bench to the bedside

**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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## Disclosure Information Sunil Krishnan

I have the following financial relationships to disclose:

Grant or research support from:  
Genentech, Merck, Malaysian Palm Oil Board, Hitachi, Shell, FUS Foundation.

Honoraria from:  
Carestream Molecular Imaging

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

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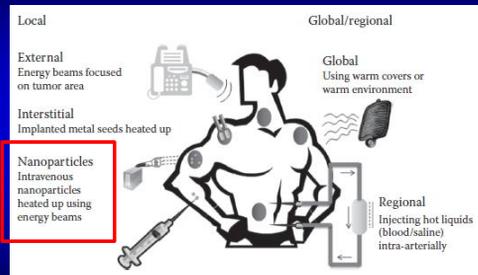
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## Hyperthermia



Chatterjee DK, Krishnan S. Cancer Nanotechnology. Elsevier 2013

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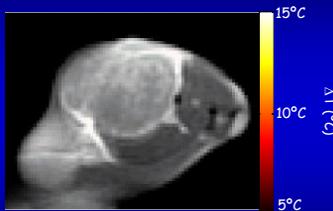
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### Real time MRTI



(0.6 W/cm<sup>2</sup> for 20 min at 808-nm)

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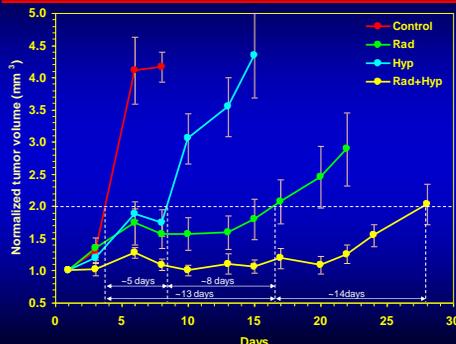
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### Normalized tumor volume



Diagaradjane et al. *Nano Lett.* 2008 8(5):1492-500

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### Mechanisms

Early effects

Late effects

Anti-hypoxic effect

Vascular disrupting effect?

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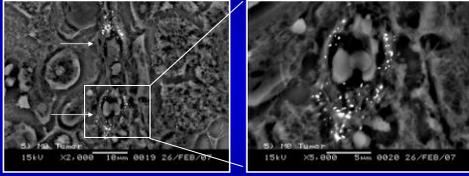
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## Scanning Electron Microscopy




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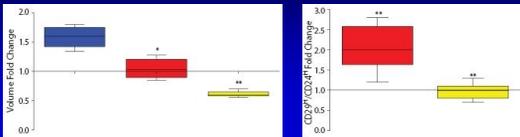
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## Stem cell sensitization



| Treatment (Tumor T7) | 10000 | 1000 | 100 | 10  | Tumor Initiation Cell Frequency (TIC) 95% CI |
|----------------------|-------|------|-----|-----|--|
| Mock                 | 6/6   | 6/6  | 1/6 | 0/6 | 1/323 (128-814)                              |
| 6 GY                 | 6/6   | 6/6  | 2/6 | 1/6 | 1/175 (61-498)                               |
| 6 GY + 42°C          | 6/6   | 3/6  | 0/6 | 0/6 | 1/1626 (575-4602)*                           |

Atkinson RA, et al. Sci Translat Med, 2010; 2(55):55ra79

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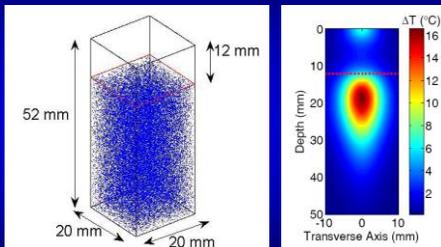
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## Thermal dosimetry



Cheong S-K et al. Med Phys 36(10):4664-71, 2009

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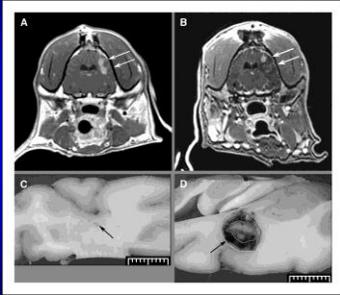
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## Gold nanoshells



Schwartz JA, et al. Cancer Res 2009

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## Gold nanoshells

### Toxicity evaluation

- 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

Gad SC, et al. Int J Toxicol. 2012

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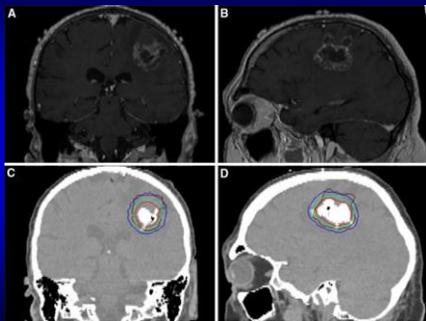
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## Magnetic fluid hyperthermia



Maier-Hauff K, et al. J Neurooncol. 2011

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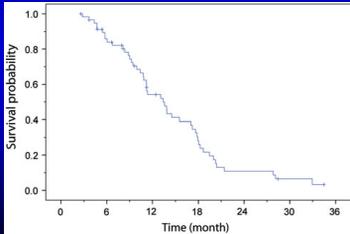
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## Magnetic fluid hyperthermia

Magforce phase II study in recurrent glioblastoma  
59 patients – direct injection of ~5ml of 12nm Fe<sub>3</sub>O<sub>4</sub> 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

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## Regulatory approvals

<http://www.nanospectra.com>

<http://www.magforce.de>

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## 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?

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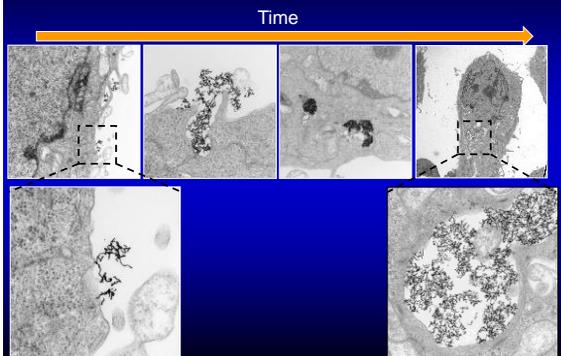
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### Intracellular distribution



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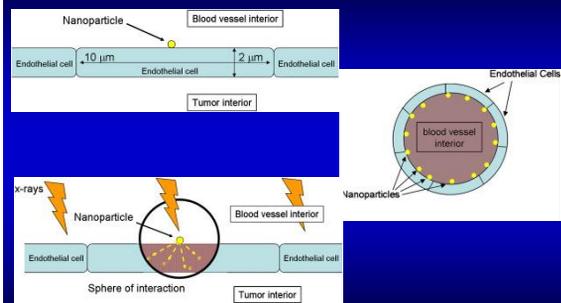
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### Vascular-targeting



Berbeco RI et al. Int J Rad Oncol Biol Phys 2011

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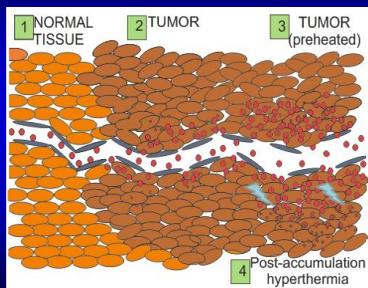
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### Trojan horse approach



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## 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

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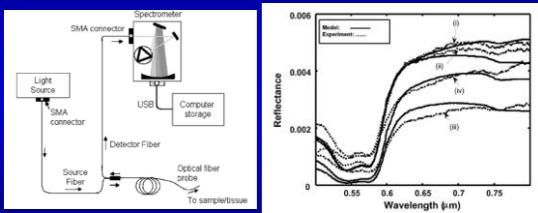
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## Quantifying gold nanoparticles in tumor



Zaman et al IEEE J Sel Top Quant Elec 13(6):1715-20, 2007.

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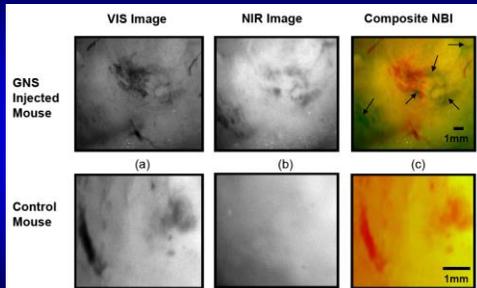
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## Imaging gold nanoparticles in tumors



Puvanakrishnan P et al. J Biomed Optics 14(2):024044, 2009.

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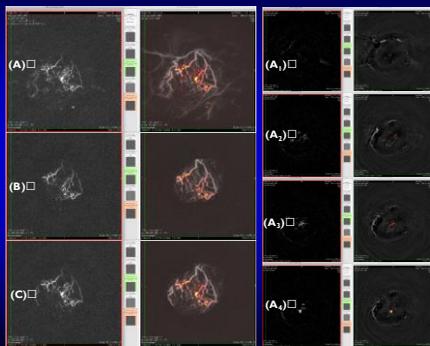
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Photoacoustic imaging




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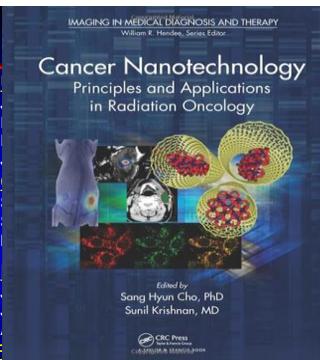
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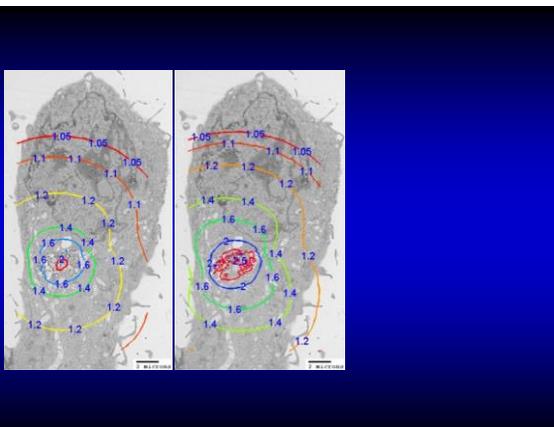
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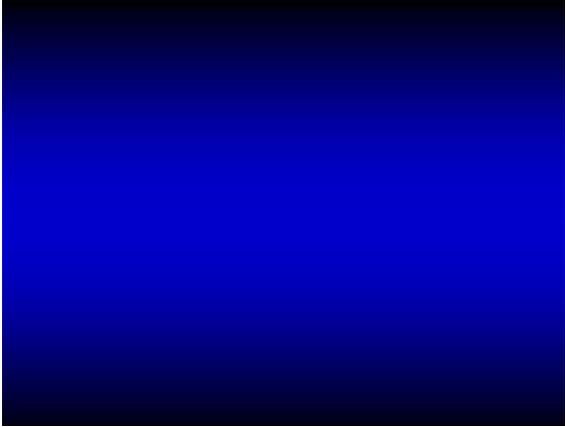
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