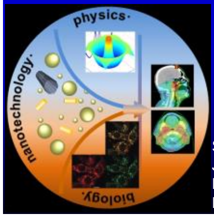
Nanoparticles in cancer medicine – a physician's perspective



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

Disclosure Information
Sunil Krishnan

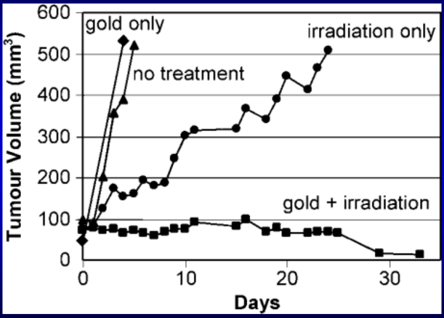
I have the following financial relationships to disclose:

Grant or research support from:
NIH, DoD, CPRIT, Alliance for Nanohealth, Shell, Hitachi, FUSF, Dunn Foundation, MDACC

Royalties
Taylor and Francis (book sales)

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

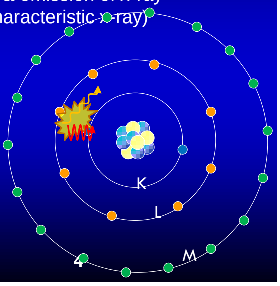
Physical dose enhancement



Hainfeld et al. Phys Med Biol 2004; 49: N309-15

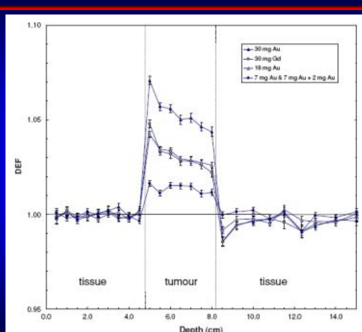
The underlying physics

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



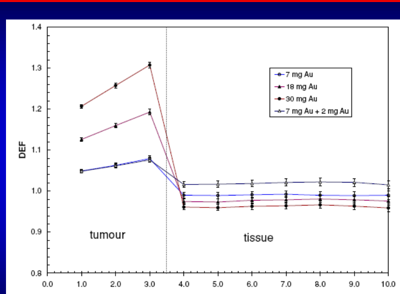
Courtesy: Nivedh Manohar, PhD

Physical dose enhancement



Cho et al. Phys Med Biol 2009

Physical dose enhancement



Cho et al. Phys Med Biol 2009

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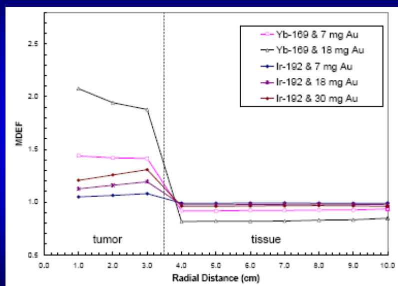
Physical dose enhancement



Cho et al. Phys Med Biol 2009, 54(16):4889-905.

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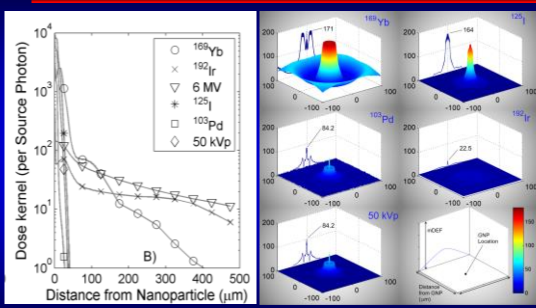
Physical dose enhancement



Cho, Krishnan Med Phys 2010

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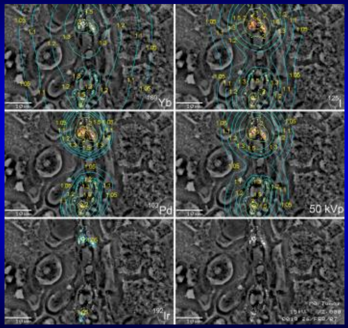
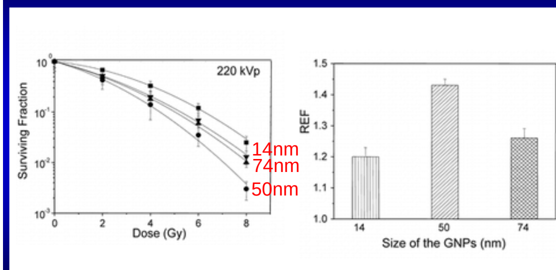
Physical dose enhancement

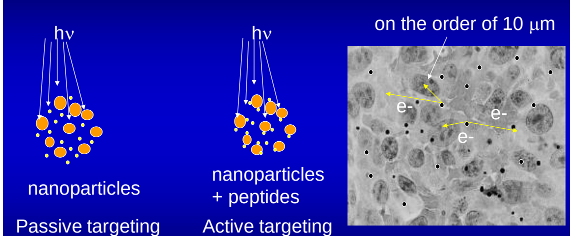


Internalization

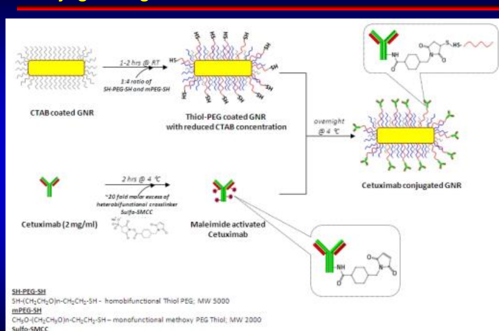


Chithrani DB, et al. Rad Res 2010 173(6):719-728.

Enhancing physical dose enhancement



Conjugated gold nanorod



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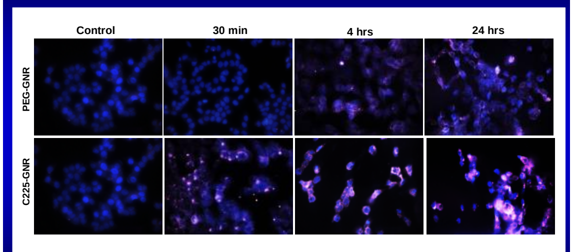
Gold nanorod



Krishnan lab, unpublished data

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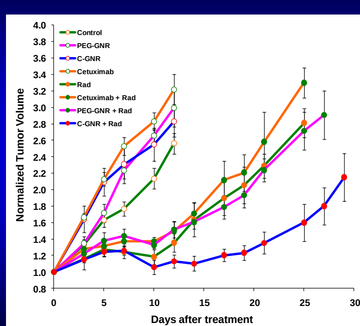
Tumor regrowth delay



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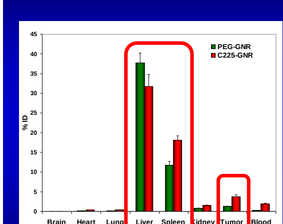
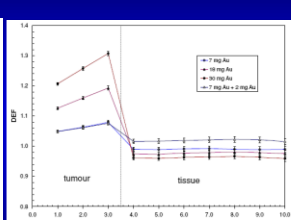
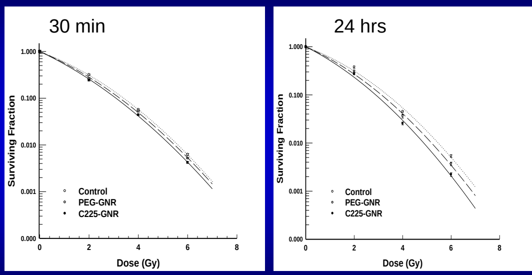
Biodistribution





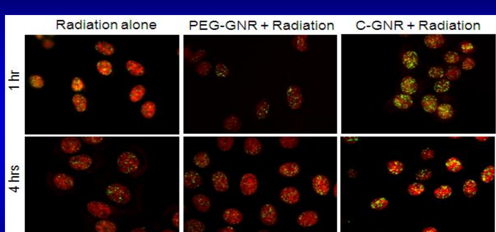
Cho SH. Phys Med Biol 2005; 50: N163-73

Clonogenic survival

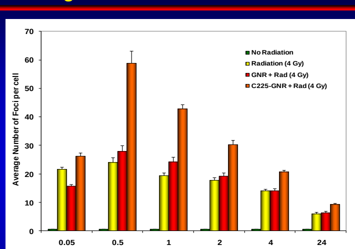


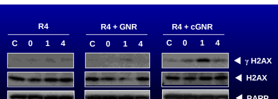
DEF 10% DEF 15%

DNA damage

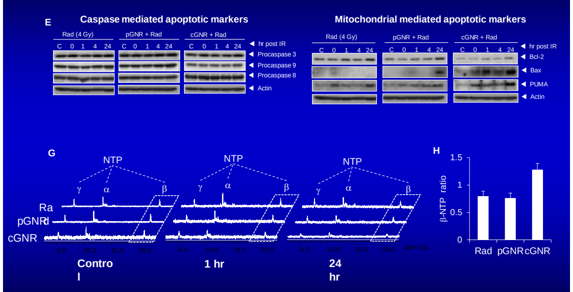


DNA damage

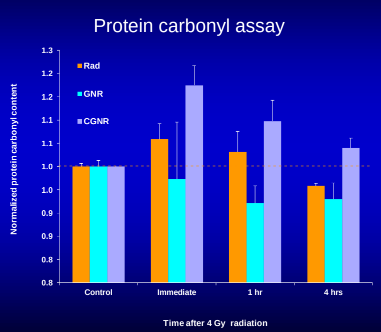




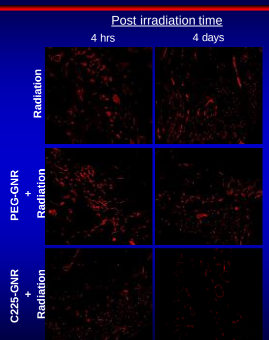
Apoptotic markers



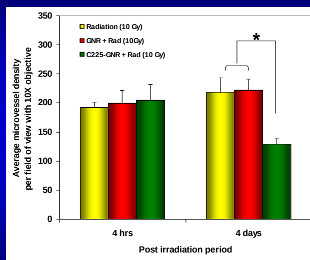
Total oxidative stress



Tissue effects

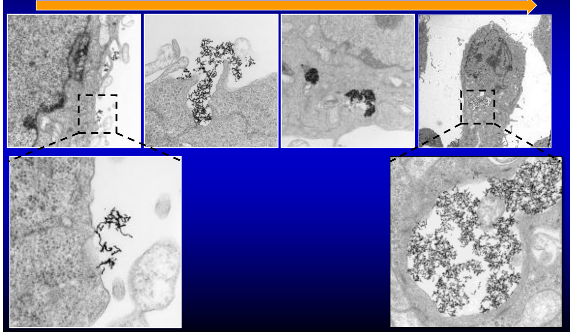


Tissue effects

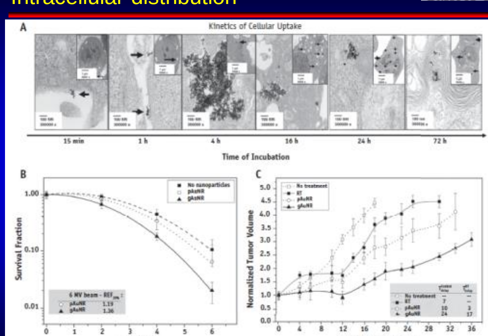


Intracellular distribution

Time



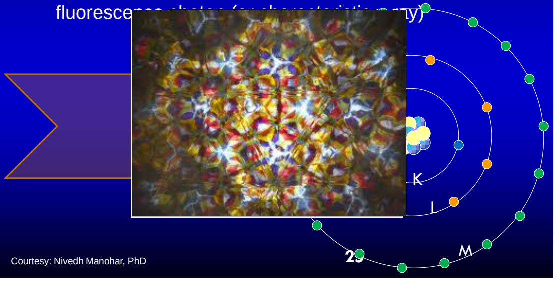
Intracellular distribution



Wolfe T, et al. Nanomedicine 2015;11:1277-1283

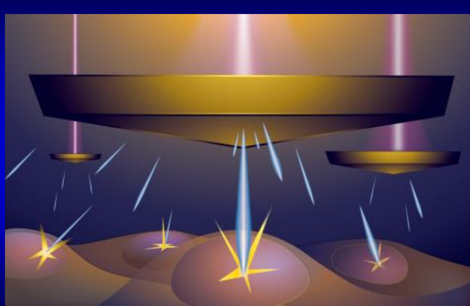
The underlying physics

- Ejection of orbital electron & emission of x-ray fluoresce[illegible]ay)



Courtesy: Nivedh Manohar, PhD

Summary

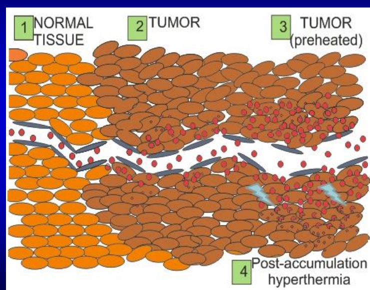


Bhattarai SR, et al. Nanoscale. 2017 Apr 20;9(16):5085-5093.

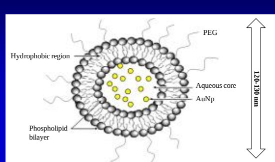
Summary

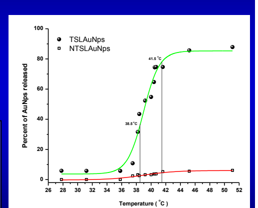
- Targeted payload delivery feasible with smaller nanoparticles bioconjugated to peptides/antibodies
- Tumor accumulation does not increase much, BUT distribution is altered at the cellular level
- Both the intracellular localization and the perivascular sequestration result in greater radiosensitization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

Another approach

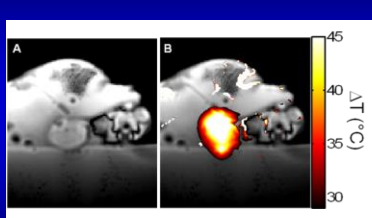


Thermosensitive liposome





Focused ultrasound



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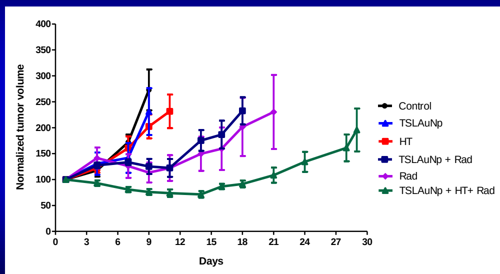
Radiosensitization



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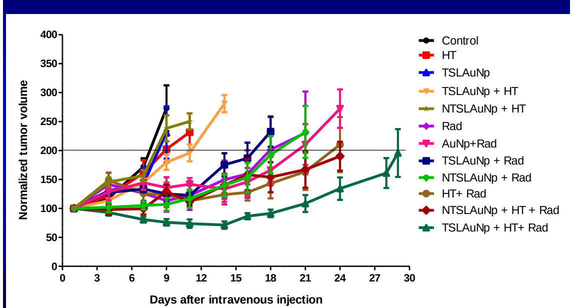
Radiosensitization



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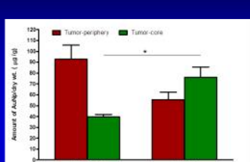
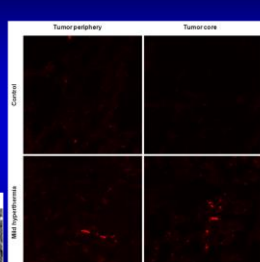
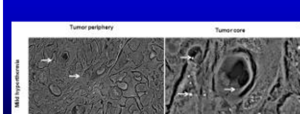
Deep penetration of tumors



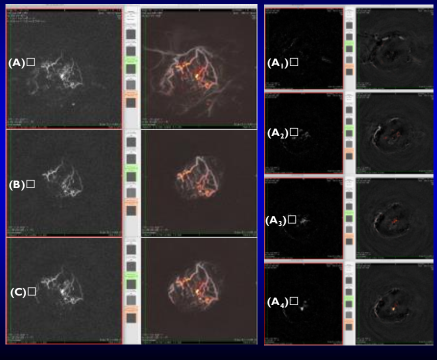




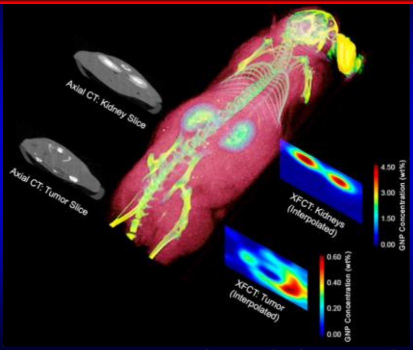
Summary

- 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

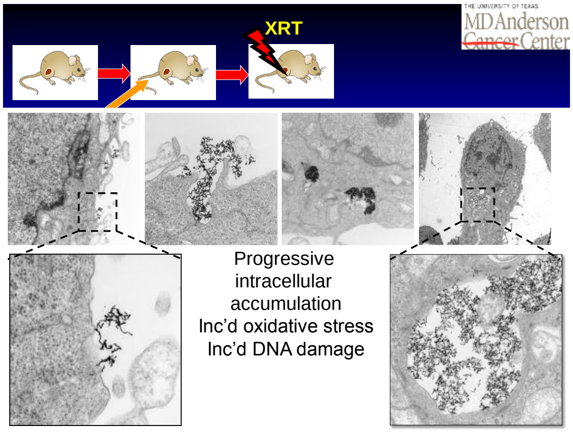
Photoacoustic imaging

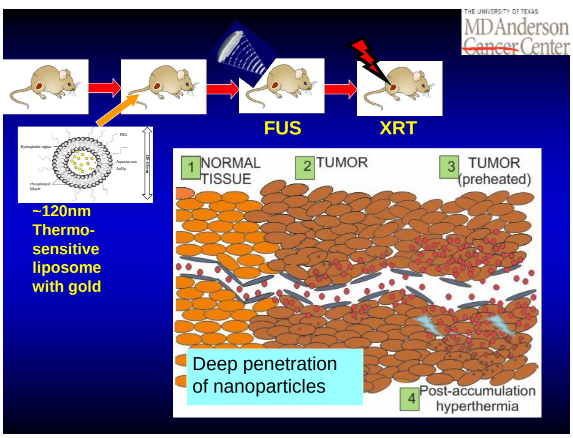


Xray fluorescence imaging



Manohar N, et al. Sci Rep. 2016 Feb 25;6:22079.





Summary

- Larger particles for vascular-targeted applications (thermo-ablation, hyperthermia, vascular imaging)
- Smaller particles for parenchymal applications (imaging, targeted payload delivery)
- Combinations of above
- Unresolved issues related to clinical translation

The target population

Patients receiving radiation therapy for cancer

~60% of all patients receive radiation therapy

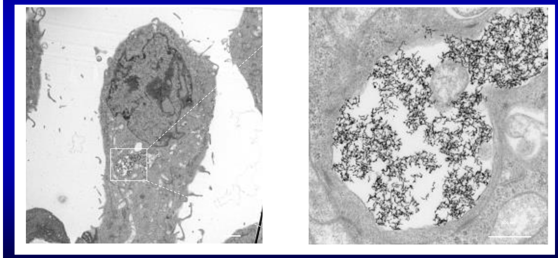
Often, standard doses of radiation therapy are unable to cure the tumor but higher doses cannot be given due to high risk of side effects from overdosing adjacent normal organs

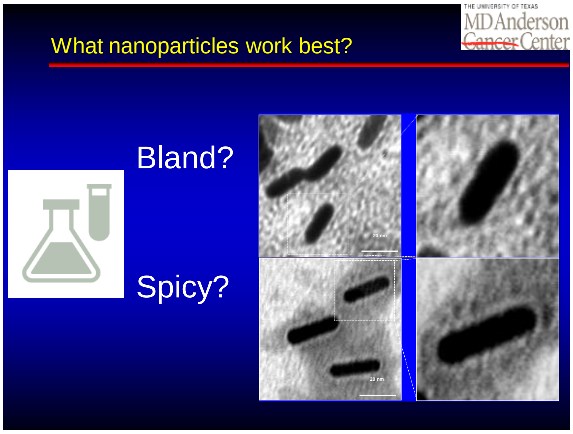
Can one give the same (standard) dose of radiation to the tumor but make it behave like a higher dose of radiation?

We need new approaches

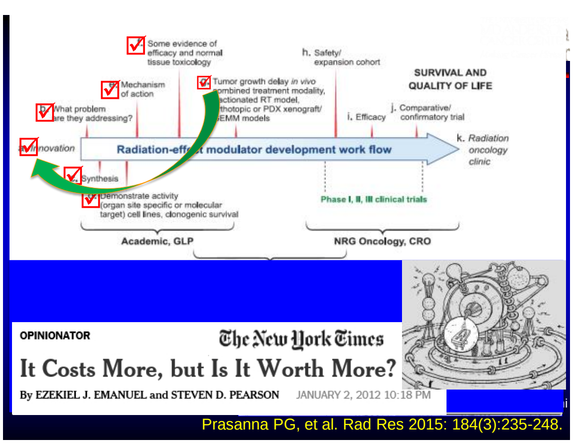
Pipeline Breakdown According to Number of Drugs
Marketed# 93
Registered# 1
Pre-registration# 5
Phase III# 47
Phase II# 103
Phase I# 62
Preclinical# 73
No Data# 5
Suspended# 7
Ceased# 150

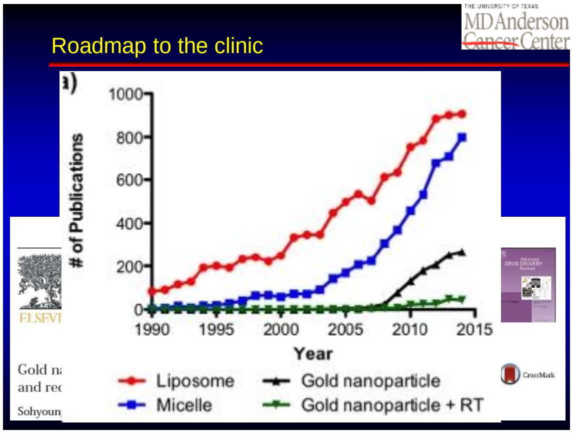
A new radiosensitization strategy

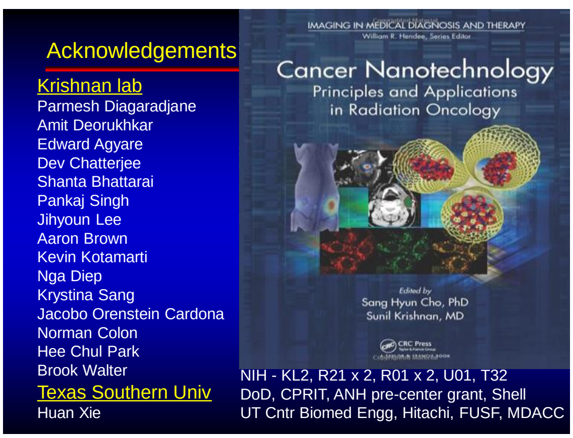



What nanoparticles work best?
MD Anderson Cancer Center
Bland?
Spicy?


What nanoparticles work best?
MD Anderson Cancer Center


Some evidence of efficacy and normal tissue toxicology
h. Safety/ expansion cohort
SURVIVAL AND QUALITY OF LIFE
Mechanism of action
Tumor growth delay in vivo
What problem are they addressing?
i. Efficacy
j. Comparative/ confirmatory trial
Radiation-effect modulator development work flow
k. Radiation oncology clinic
Synthesis
Demonstrate activity (organ site specific or molecular target) cell lines, clonogenic survival
Phase I, II, III clinical trials
Academic, GLP
NRG Oncology, CRO
OPINIONATOR
The New York Times
It Costs More, but Is It Worth More?
By EZEKIEL J. EMANUEL and STEVEN D. PEARSON
JANUARY 2, 2012 10:18 PM
Prasanna PG, et al. Rad Res 2015: 184(3):235-248.


Roadmap to the clinic
MDAnderson Cancer Center
# of Publications
1000
800
600
400
200
0
1990
1995
2000
2005
2010
2015
Year
Liposome
Micelle
Gold nanoparticle
Gold nanoparticle + RT


Acknowledgements
Krishnan lab
Parmesh Diagaradjane
Amit Deorukhkar
Edward Agyare
Dev Chatterjee
Shanta Bhattarai
Pankaj Singh
Jihyoun Lee
Aaron Brown
Kevin Kotamarti
Nga Diep
Krystina Sang
Jacobo Orenstein Cardona
Norman Colon
Hee Chul Park
Brook Walter
Texas Southern Univ
Huan Xie
IMAGING IN MEDICAL DIAGNOSIS AND THERAPY
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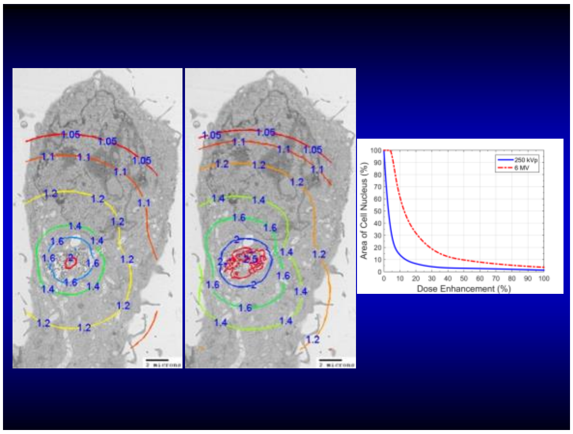
Principles and Applications in Radiation Oncology
Edited by
Sang Hyun Cho, PhD
Sunil Krishnan, MD
CRC Press
NIH - KL2, R21 x 2, R01 x 2, U01, T32
DoD, CPRIT, ANH pre-center grant, Shell
UT Cntr Biomed Engg, Hitachi, FUSF, MDACC


250 kVp
6 MV
Area of Cell Nucleus (%)
Dose Enhancement (%)