Warren Sinclair Memorial Symposium: Physics Application for New Radiobiology

"This session has been designated, among the President's choices, for exemplary science consistent with the theme of ***Reinvigorating Scientific Excellence*** *in the Medical Physics Enterprise. As described in the meeting program, that theme is meant to recognize the importance of scientific research to the AAPM mission and to the future of medical physics"*

- AAPM

AAPM2015
REINVIGORATING SCIENTIFIC EXCELLENCE
57th Annual Meeting & Exhibition • July 12–16 • Anaheim, CA

Warren Sinclair Memorial Symposium: Physics Application for New Radiobiology

Beyond Radiation Induced Double Strand Breaks – a New Horizon for Radiation Therapy Research

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THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

NC STATE UNIVERSITY

Disclosure:

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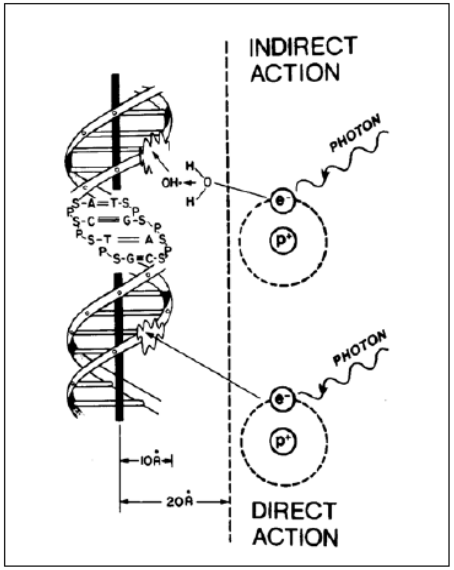
- NIH Cancer nanotechnology Center of Excellence grant
- NIH Grand Opportunity Grant
- North Carolina NCTraCS large pilot grant

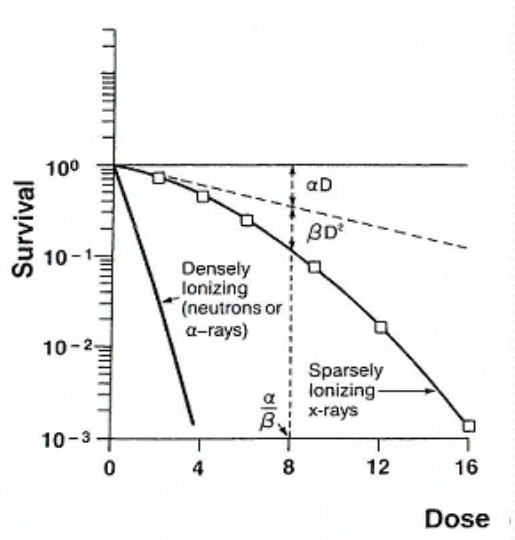
I am the co-inventor of 3 patents relevant to the technologies presented.

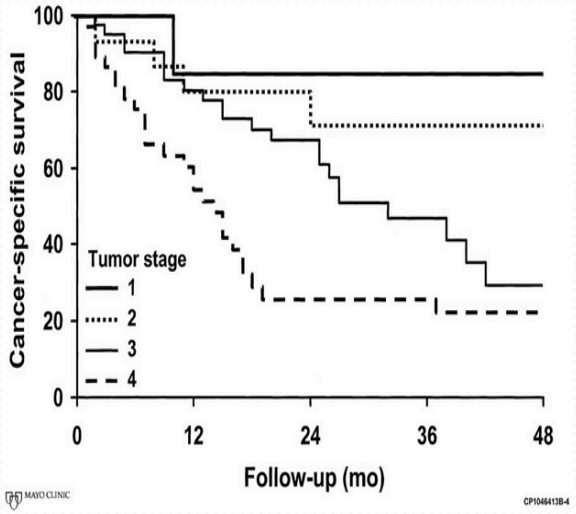
Mechanism of cancer radiation therapy

- Textbook radiobiology:

  radiation causes DNA dsbs→ cell death →tumor control/tissue toxicity→ patient survival

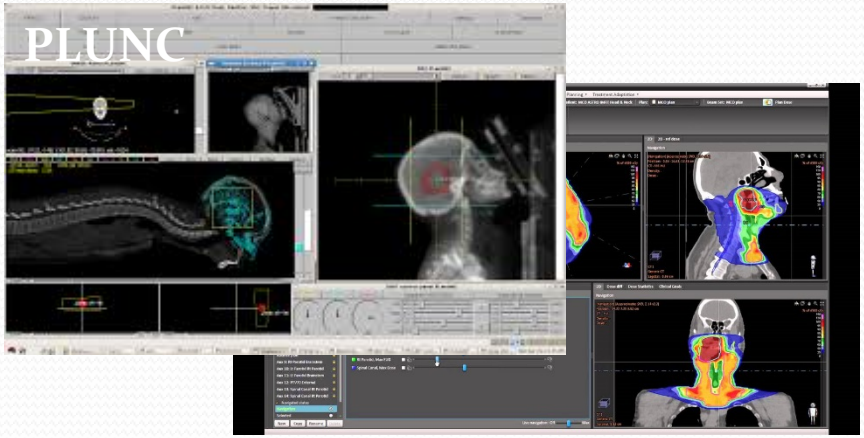


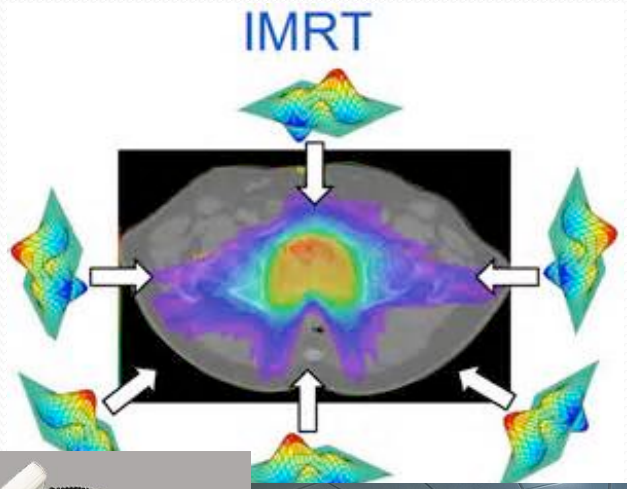




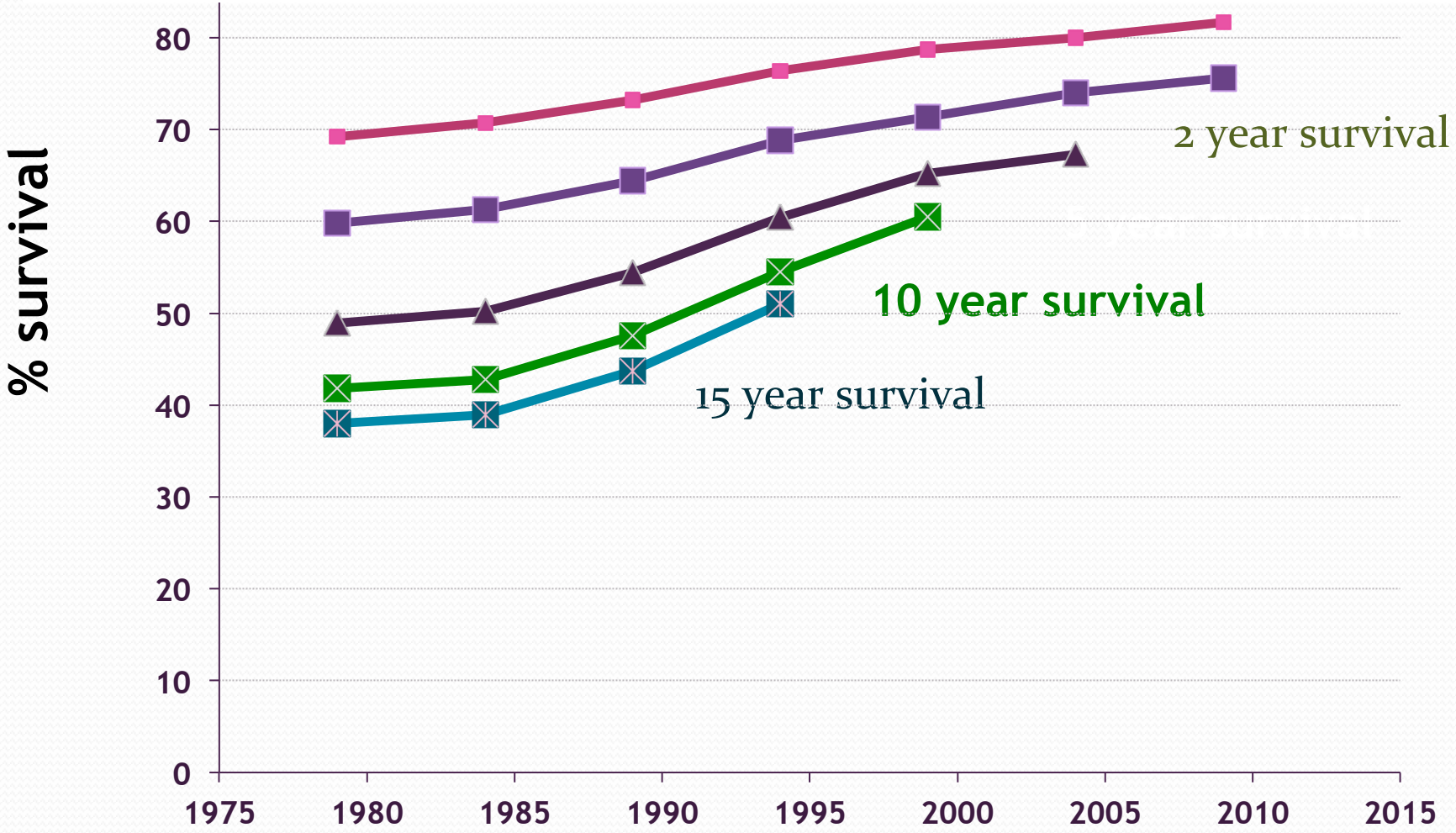
RT→DNA dsbs →cell death → tumor control/toxicity

the fundamental belief behind the RT technological revolution in the last 2 decades





Radiation therapy technological revolution have not led to a significant change in survival.

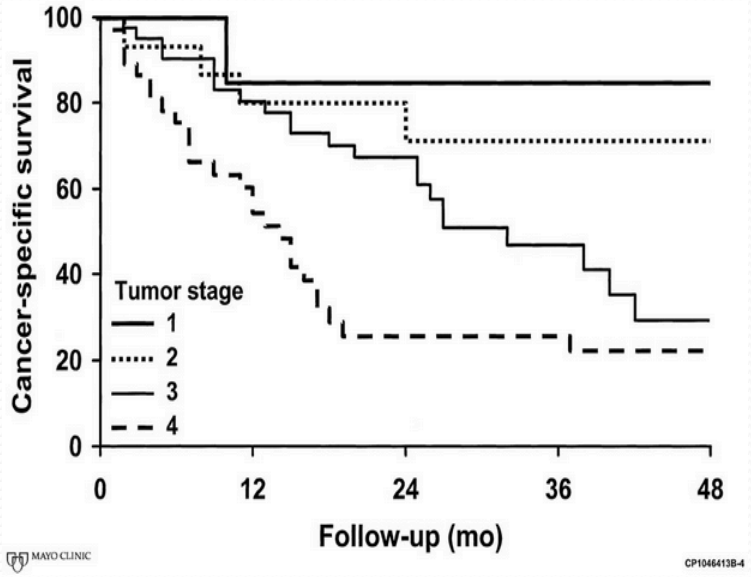


SEER database USA Survival figures after cancer

Question to Radiation Oncologists:

- "If I can give you the *delivered* patient dosimetry that is precisely what you asked for, would the survival data be any different?"
- Answer:

"It won't be better"



"What does it take to significantly improve clinical outcome?"

"What does it take to significantly improve clinical outcome?"

- We cannot intercalate/extrapolate from existing knowledge to a breakthrough.
- We need to ask new questions and challenge the established.
- We need to open up new horizons to explore the unexplored.

We need to reinvigorate scientific and multidisciplinary research.

*"What **physics** can do toward significantly improving clinical outcome?"*

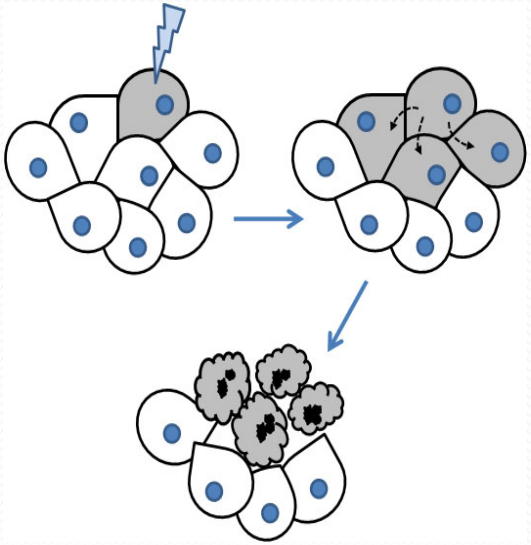
Clinical outcome

Radiobiology

Better understand the converter between physics and clinical impact.

Some phenomena cannot be explained by the RT kills by DNA double strand break theory:

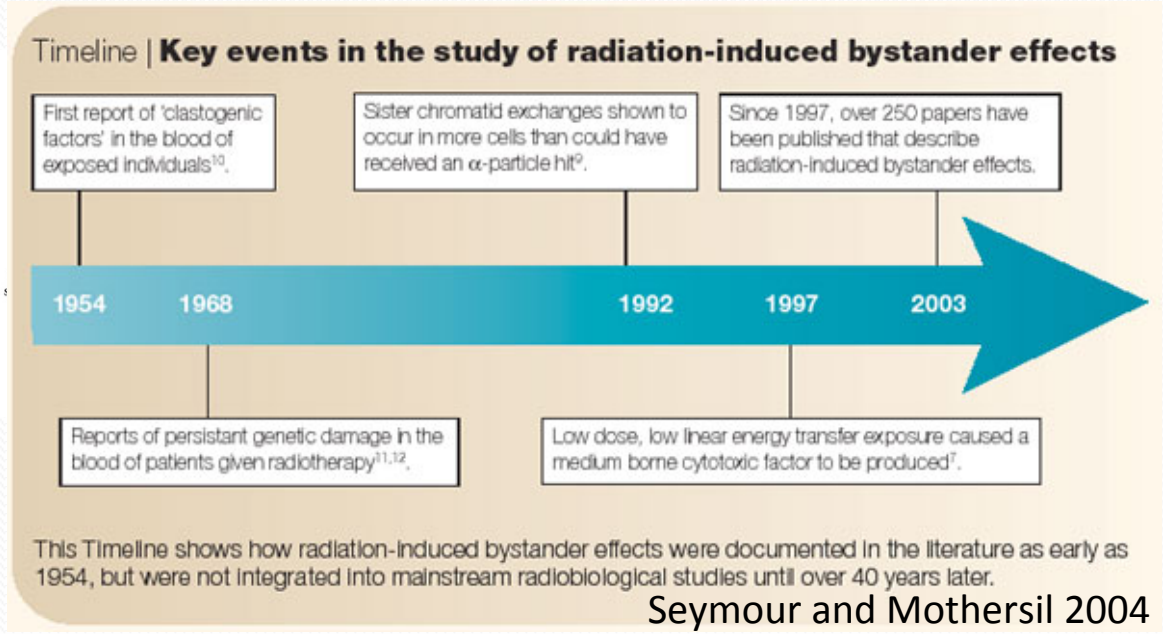
Bystander effect



(Nagasawa and Little 1992)

Abscopal effect

Migration effect

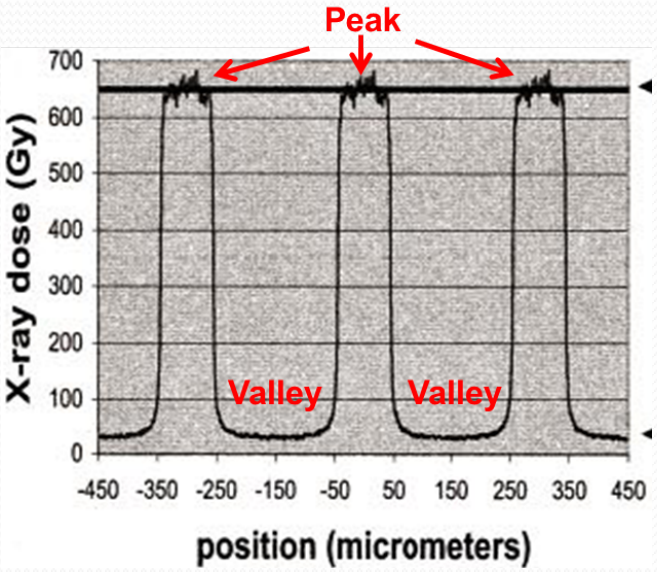


Seymour and Mothersil 2004

(Postow et al 2012)

Microbeam Radiation Therapy (MRT)

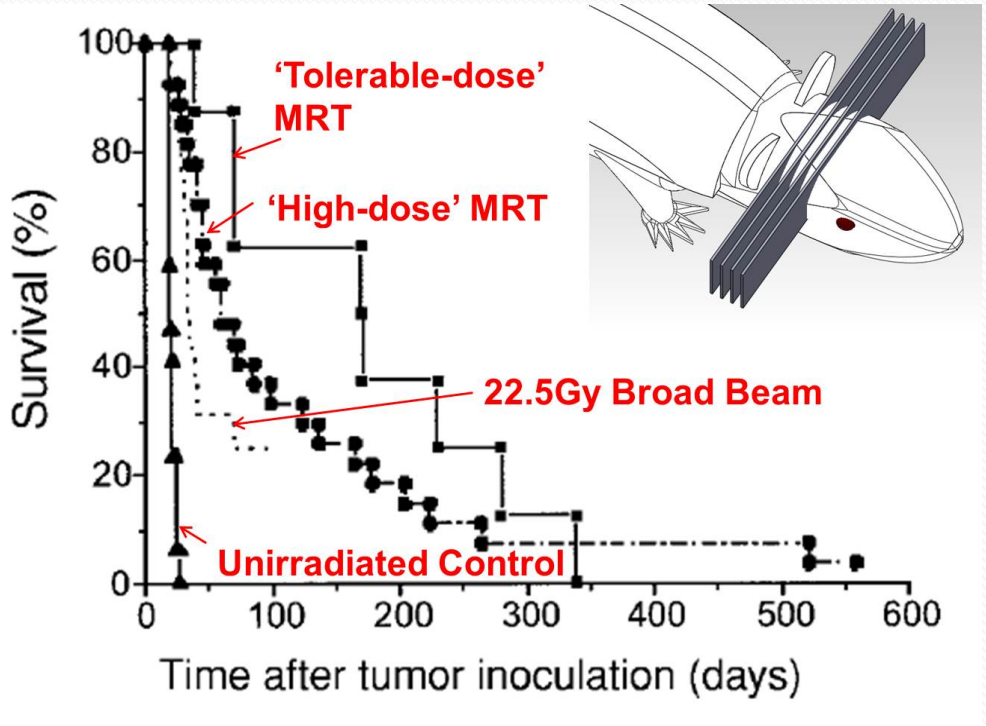
MRT(1960s) is a form of Spatially-Fractionated Radiation Therapy (SFRT)



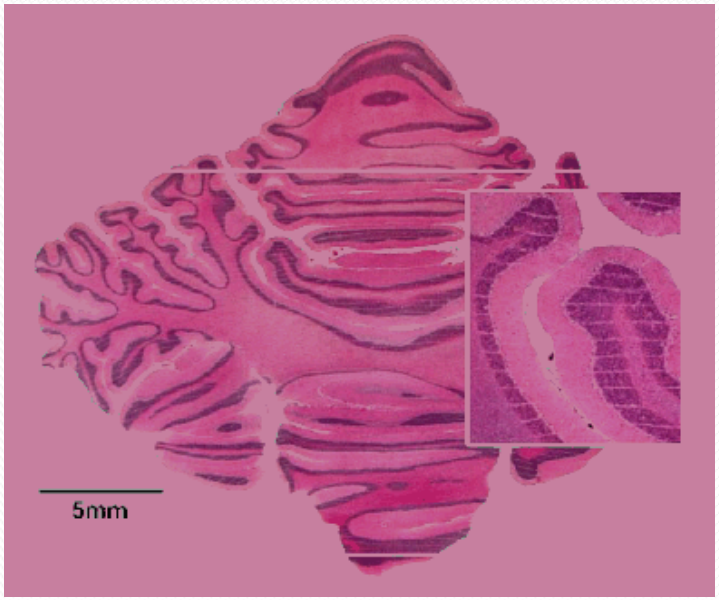
- Oscillating sub-regions of high and low doses (peaks and valleys) in the treatment field
- Beam width small (50 – 500 μm)
- Single-fraction treatment
- High peak dose (100s Gy)

MRT eradicates tumor and spares normal tissue

Most work done in synchrotron facilities in BNL, ESRF



Dilmanian, F.A., et al., *Response of rat intracranial 9L gliosarcoma to microbeam radiation therapy.* Neuro. Oncol., 2002. **4**(1): p. 26-38.

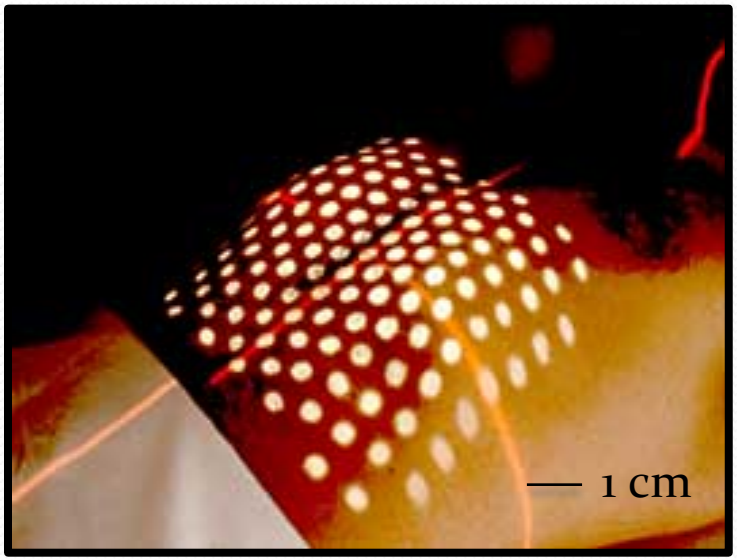


Horizontal section of the cerebellum of a piglet of 15 months after irradiation with a skin entrance dose of **300 Gy** [Laissue et al 2001]

MRT Preclinical studies

	MRT, and MBRT (MRT w/ thicker beams, or minibeam RT)
Beamwidth	20 - 100, or 270 - 300, or 600 - 700 μm
Beam c-t-c distance	100 – 500, or 1120 - 4000 μm
Peak dose	40 - 2000 Gy
PVDR	5 - 56
Irradiation geometry	1). Co-planar; 2). Cross-planar; 3). Interlacing.
Animal/tumor models	Rats with 9L gliosarcoma, C8 glioma, F98 glioma; Mice with EMT-6 carcinoma, SCCVII murine carcinoma, U251 glioma;
Biological effects	1). Significant tumor suppression and lifespan extension (up to factor of 8) [12-14]; 2). Observed complete tumor ablation and long term survivors (over a year) [12, 17]; 3). No or little normal brain tissue necrosis with up to 625 Gy [16]; 4). Transient cerebral edema resolved within 2 weeks after 1000 Gy [33]; 5). Remyelination within 3 months with 750 Gy in spinal cord [43]; 6). No apparent neurological or behavior disorder with up to 750 Gy [51]; 7). More effective tumor control with cross-planar and interlaced-MRT [14]; 8). Thicker beams are well tolerated by both normal brain tissue and spinal cord at high doses [25];
Key references	Slatkin et al. [16]; Laissue et al. [17, 39]; Dilmanian et al. [12,13, 25, 42, 43]; Serduc et al. [32, 33, 51, 56]; Prezado et al. [14]

GRID therapy: a large-scale SFRT generated by linac



Univ. of Kentucky, Arkansas, Maryland
Dr. Mohiuddin, M.

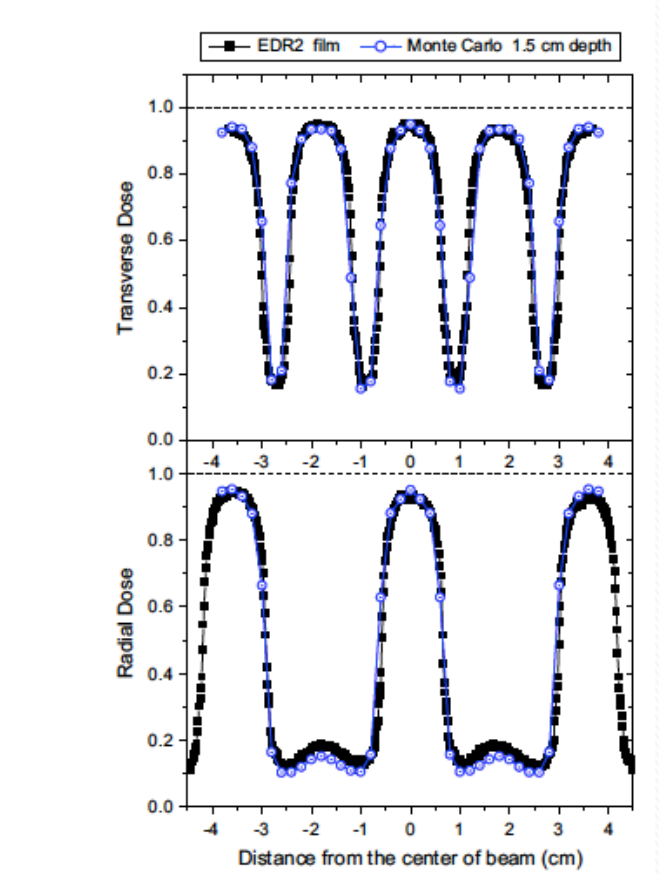
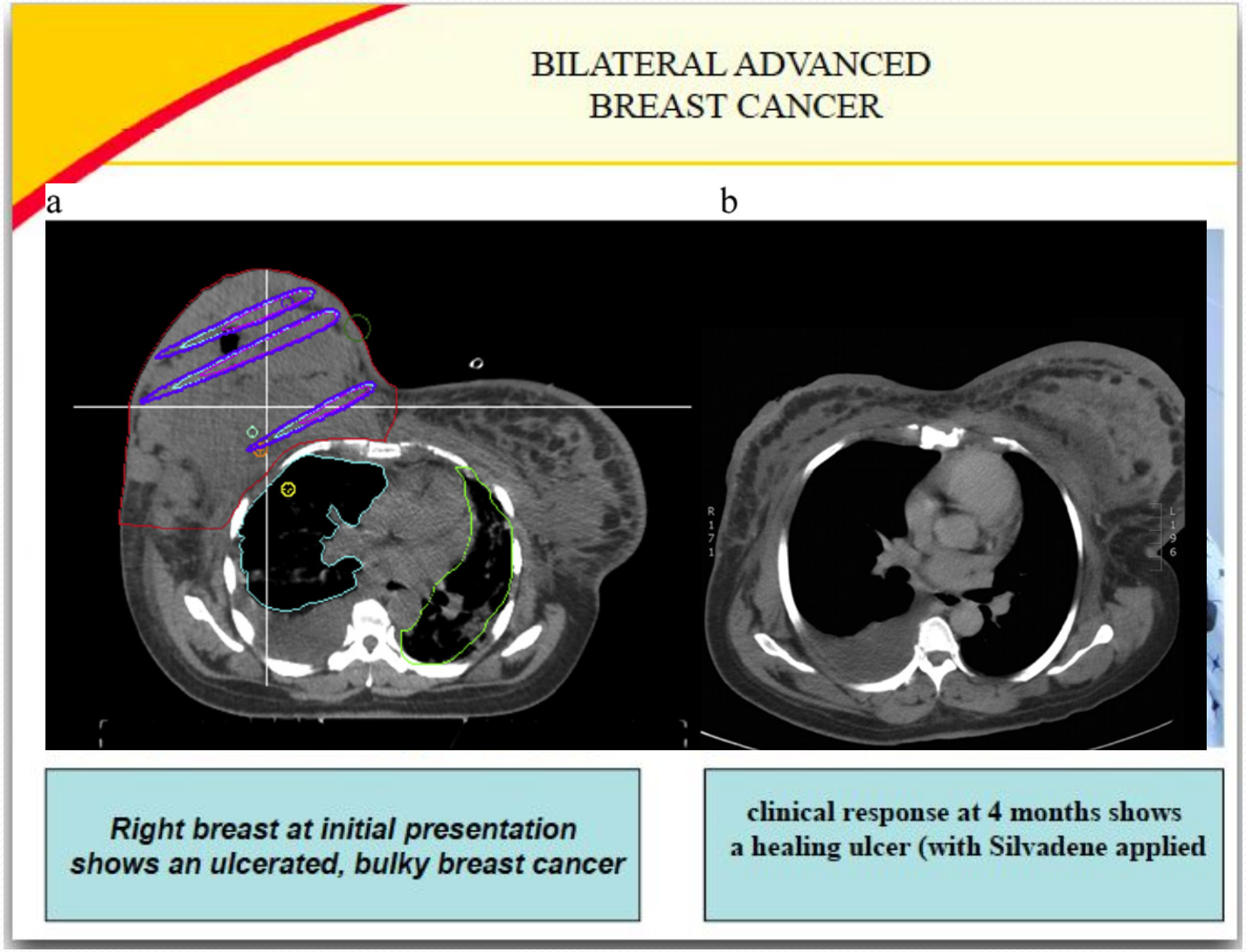


Fig. 3. Radial and transverse dose profiles of grid therapy in a were normalized to a 10 × 10 cm open field at 1.5-cm depth, EDR2 = extended dose range.

Zhang et al 2008

GRID therapy case studies

(Neuner et al 2012)

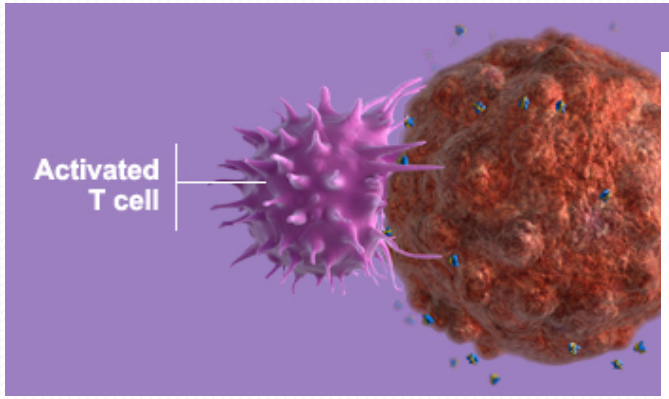


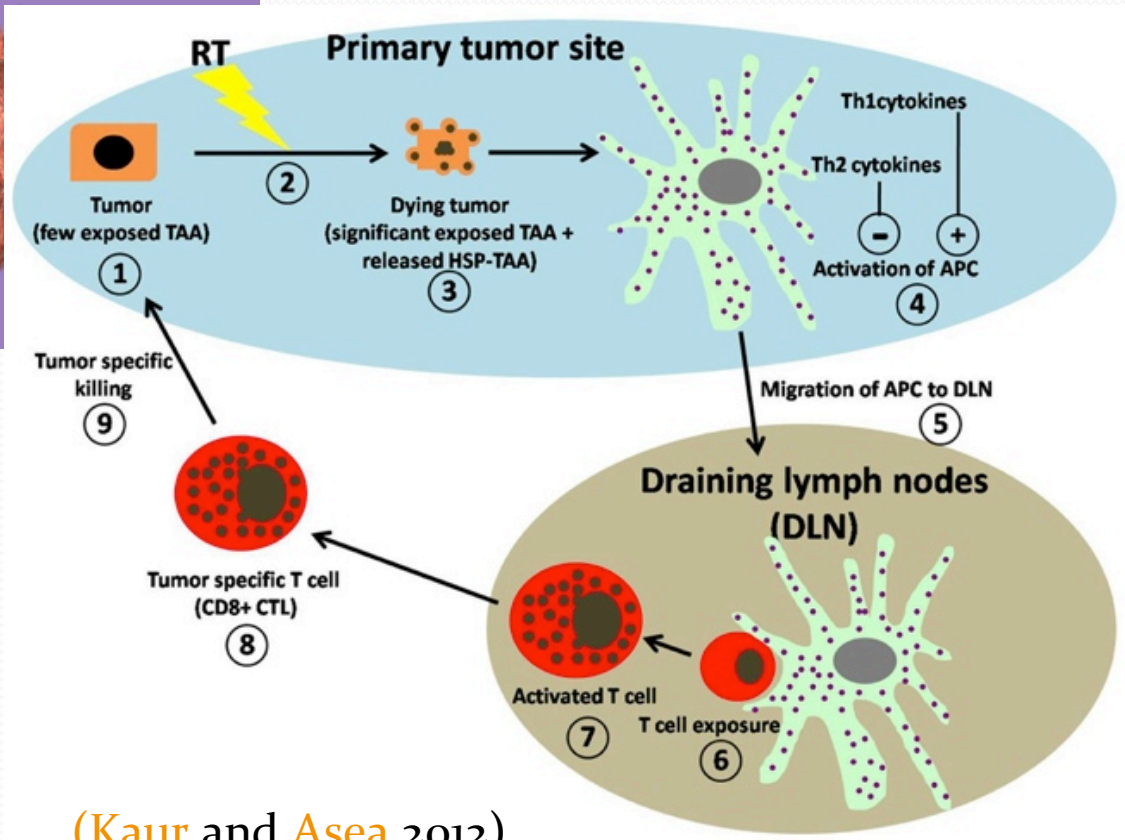
"If these radiation effects are real, why I haven't seen it, and why we are not all using them?"

- Underlying mechanism of SFRT not well understood
  - Hypotheses
    - Cellular bystander effect
    - Tumor microvasculature diff. than that of normal tissue
    - **RT-induced Immune response** (Dr. M Ahmed's talk)
- Clinical radiation delivery technology for MRT is not available (ESRF and UNC)
- Need more research- multidisciplinary research to explore the unknown.

Immune system - the perfect targeted cancer therapy!

(Dr. Jeraj talk)





(Dr. Ahmed talk)

(Kaur and Asea 2012)

"Is it radiobiologists' problem?"

- Carrying out physician's treatment directive is what we do for patient care today.
- Understanding of radiobiology allows us to better convert physics effort and ingenuity to improve patient care tomorrow.

Physicists in medicine can have unique contributions to radiobiology research

- Technological ingenuity
  - Small animal imaging and irradiation technology development (Stanford, Toronto, John Hopkins, UNC, etc)
  - Microbeam radiation technology (synchrotron, nanotechnology, proton)
  - Etc
- **Brilliant open minds**
  - Critical thinking
  - Quantitative analysis
  - Understand clinical application
  - Asking good questions

2015 AAPM abs

- 17 on "drug"
- 11 on "GRID or MRT"
- 6 on "Bystander effect"
- 43 on IGRT
- ~200 on proton therapy

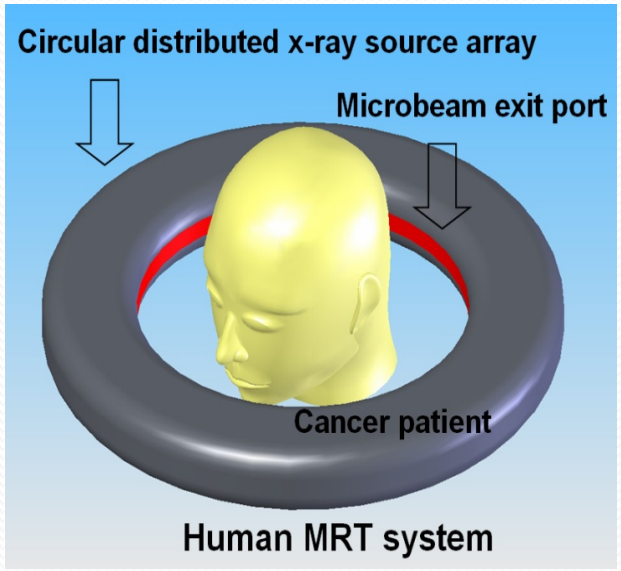
"How can I do radiobiology research?"

- There are many ways
  - Create one (PI of a grant)
  - Participate in one (co-investigator)
  - Consult for one (consultant)
  - Volunteer for one (find a research group of your interest and offer to help)
- You HAVE to love it
  - Willing to take risk and sacrifices

Examples of Physics application in radiobiology and pharmacology

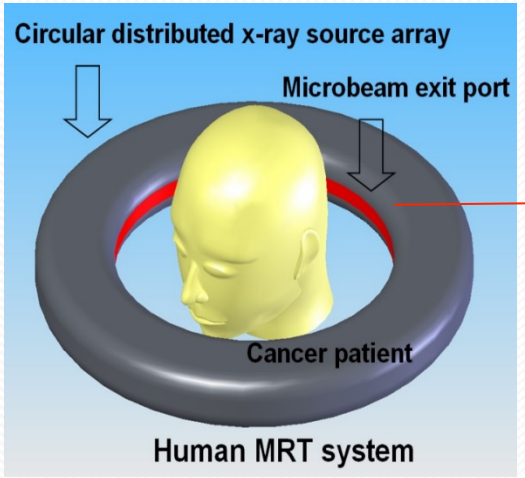
A bold proposal: Compact MRT using carbon nanotube field emission x-ray technology

Synchrotron facility that has been used to generate MRT radiation.

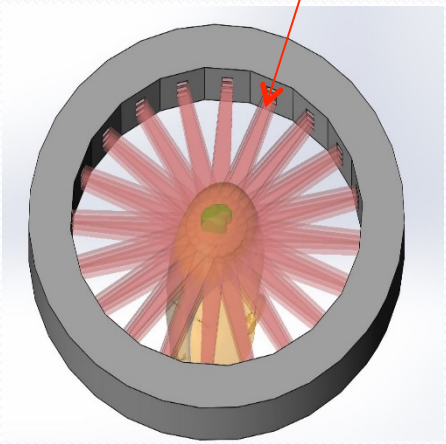


This innovative work has been supported by 3 grants from NIH and university.

Ring-design structure compact MRT system

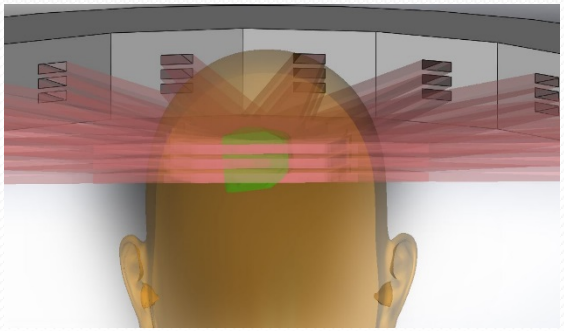


N individually controlled
MRT source arrays



Top view

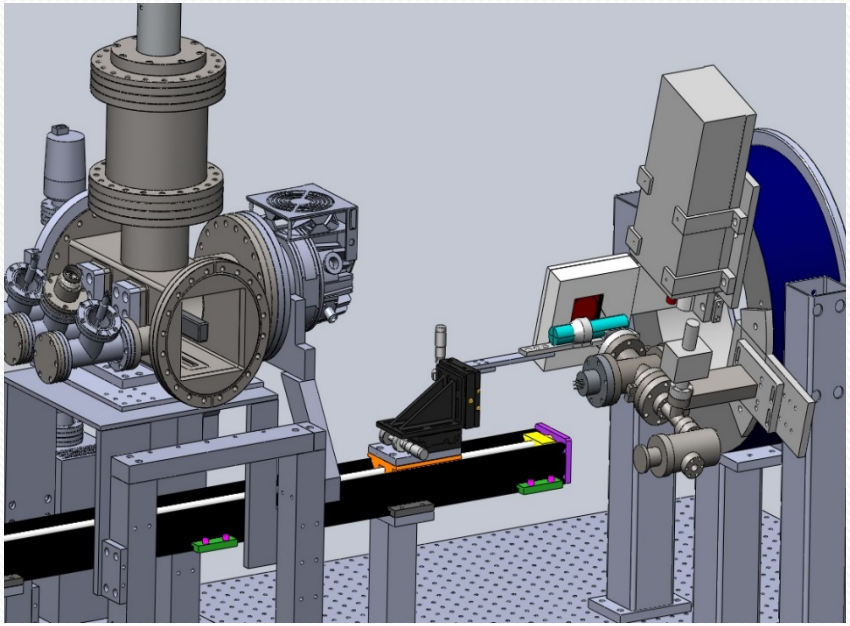
Each source array produces a microplanar beam

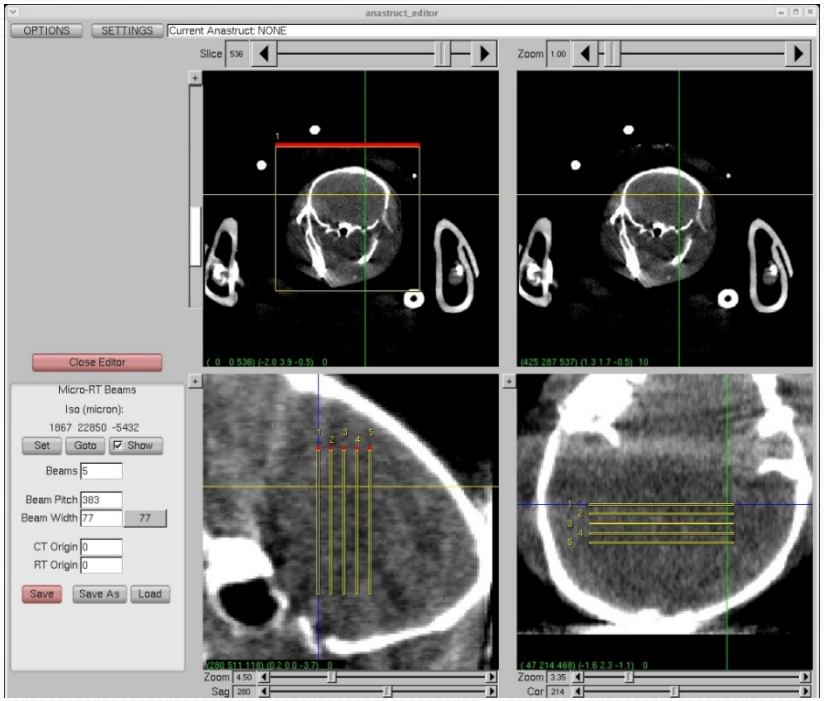


Back view

O. Zhou and S. Chang, US patent 8,600,003B2 (2013)

Micro-CT guided MRT





A MRT treatment image-guidance software (micro-PLUNC) based on the clinically used PLUNC TPS from UNC. Shown in the figure is a screen shot showing 5 beams as yellow boxes or bars in tri-orthogonal view

Radiobiological study of compact MRT

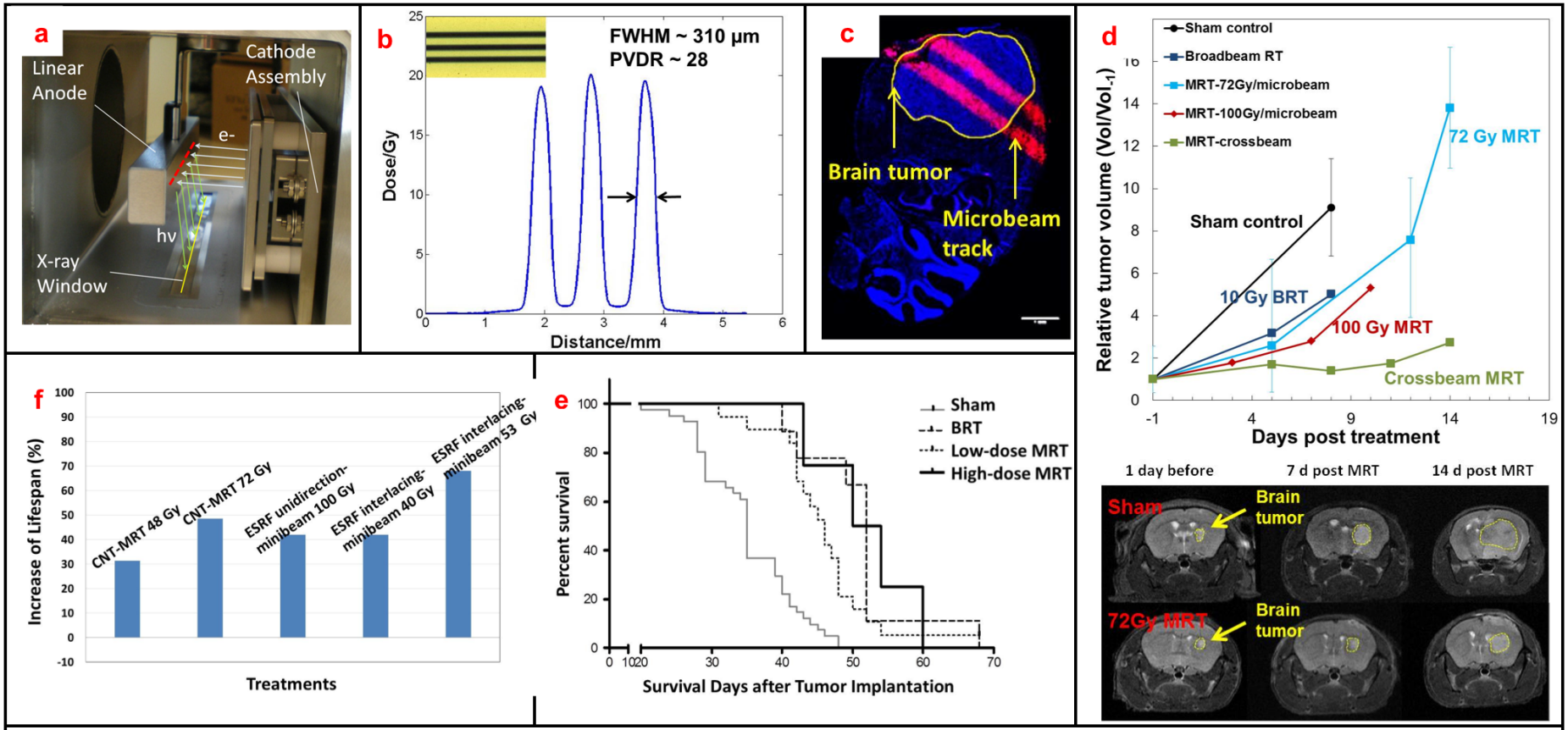
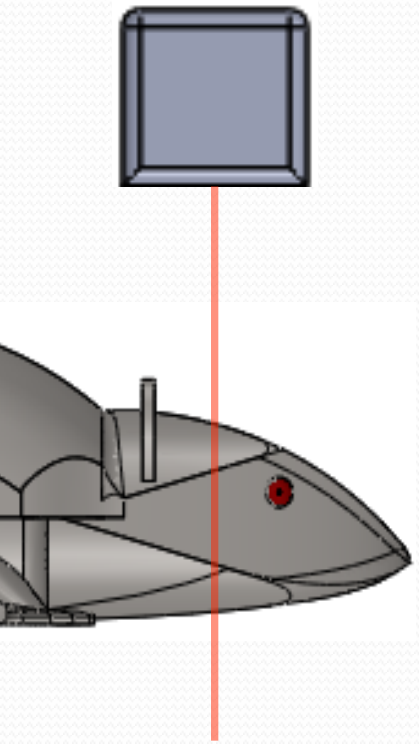
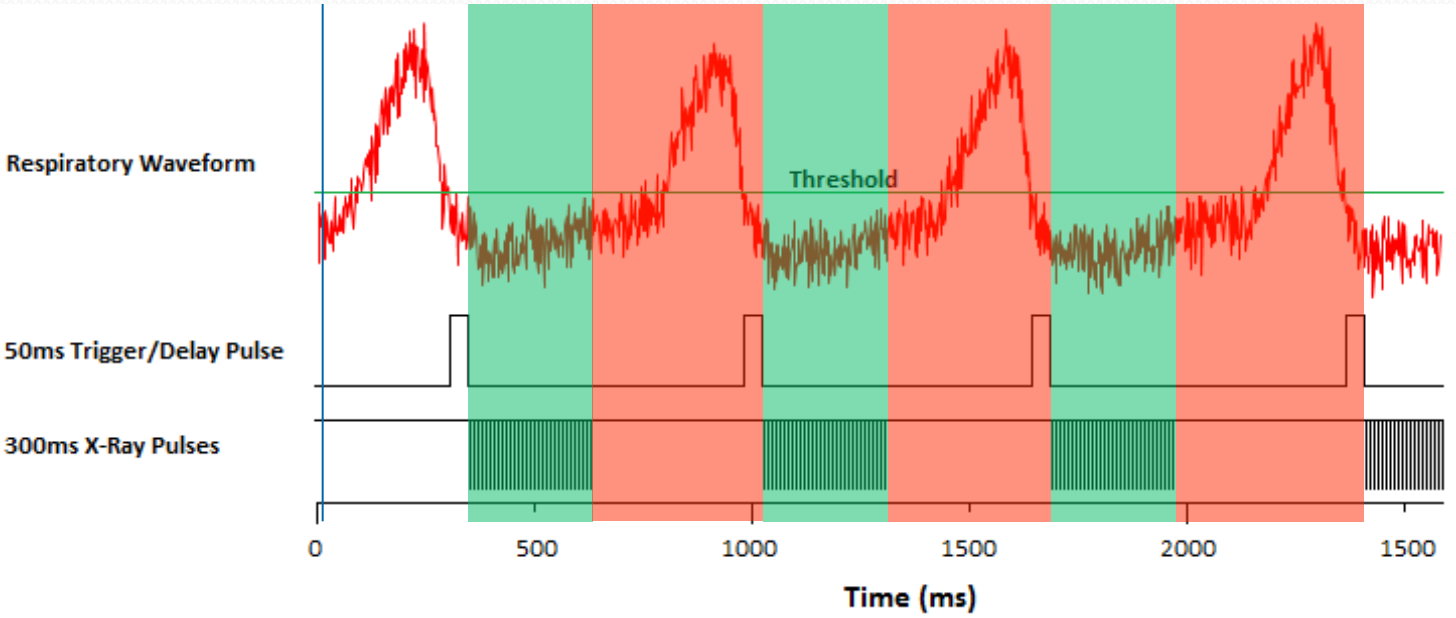


Figure 1: Clockwise: (a) Cross sectional view of the CNT MRT irradiator [66]. (b) Microbeam profile obtained at the mouse skin entrance in our Gen-1 system: 310 μm width with a PVDR of 28 at 900μm pitch (film inserted). (c) γ-H2Ax stained mouse brain tissue showing microbeams delivered to the tumor with the pink tracks indicating radiation-induced DNA damage along the beam path [85]. Result was achieved using MRI/X-ray image-guided MRT protocol. (d) Relative tumor volume changes after different treatments monitored by MRI (brain tumor in yellow contour). The crossbeam MRT group showed a significantly lower tumor growth rate compared to sham and the broadbeam group. (e) Survival curve of U87 mice treated with GEN-1 CNT-MRT system, compared to sham control and broad-beam radiated group. (f) Comparison of relative increases of lifespan of tumor bearing small animals achieved using CNT-MRT system and synchrotron mini-beams (640 μm beam width at 1120 μm pitch) [14].

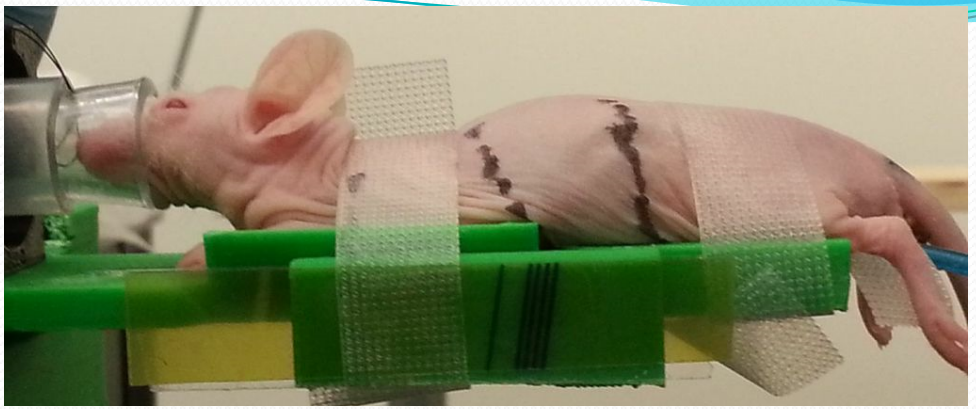
Physiological motion gated CNT-MRT

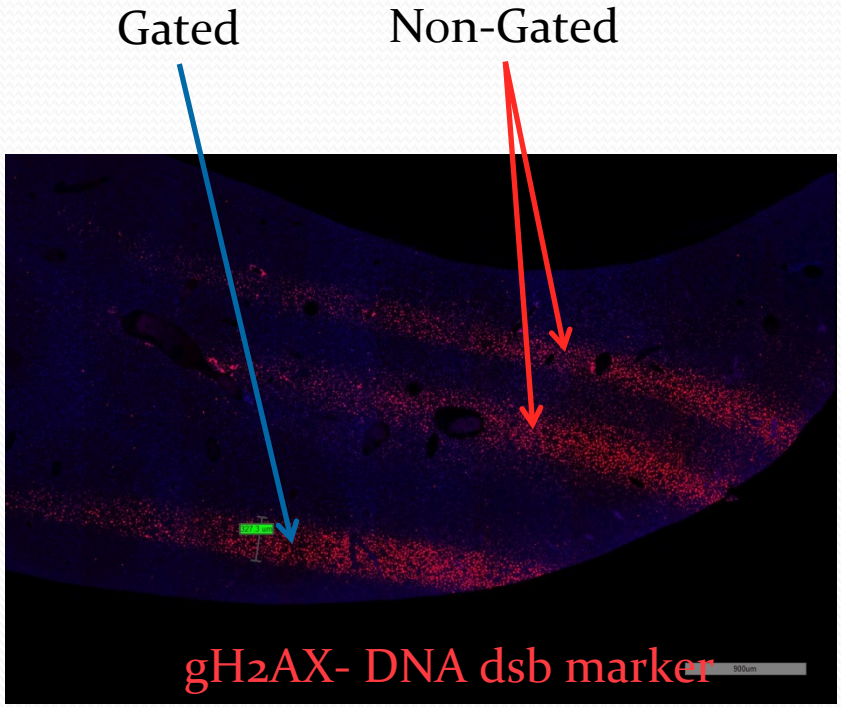


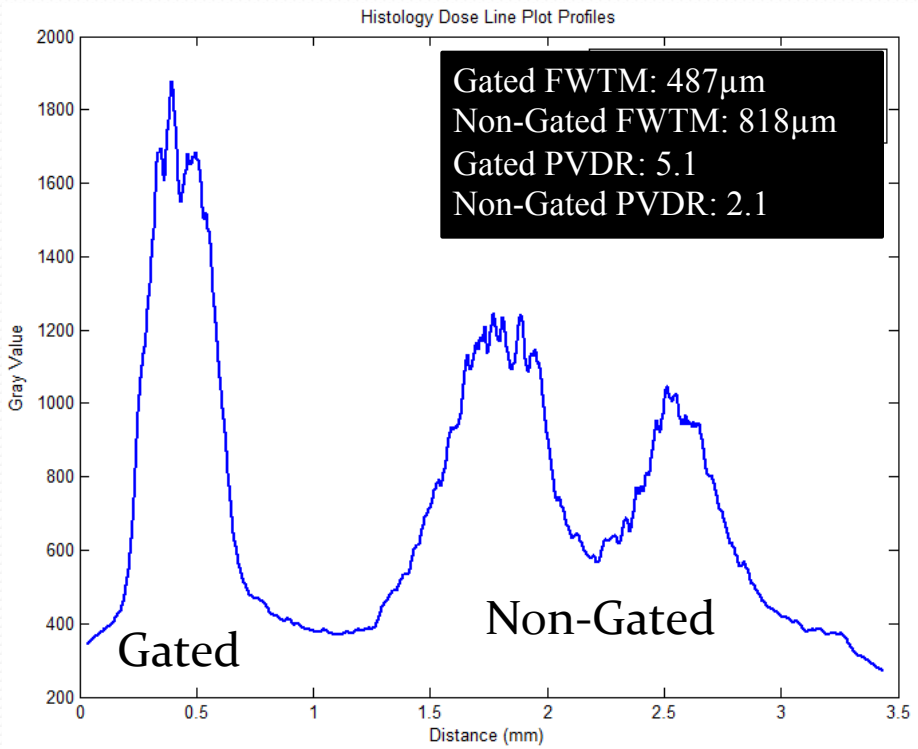
CNT field emission x-rays are intrinsically gated.



Gated Liver irradiation

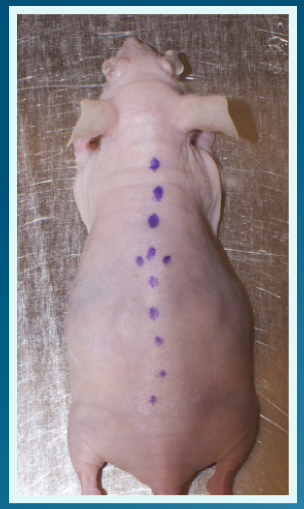


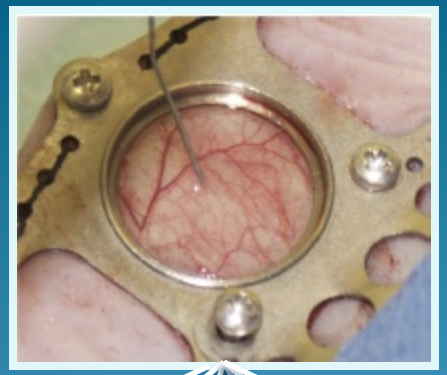




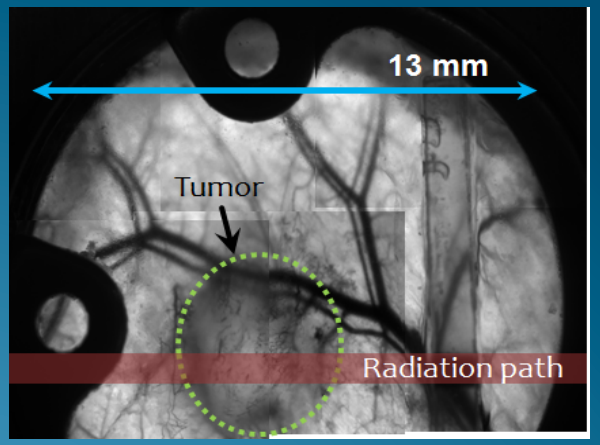
Histology of the gated MRT irradiated mouse liver (Pavel 2014)

Tumor microvasculature study (collaboration with Dewhirst)

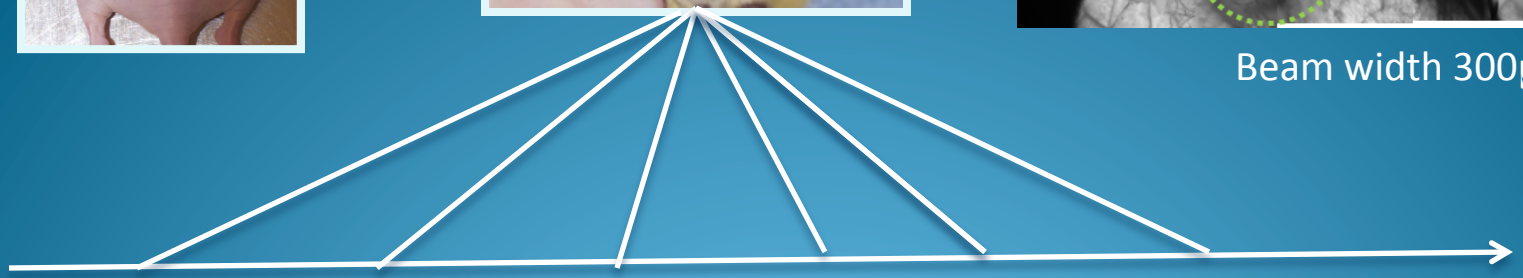




(Dewhirst, Duke)



Beam width 300μm



Optical imaging

Before RT

After RT

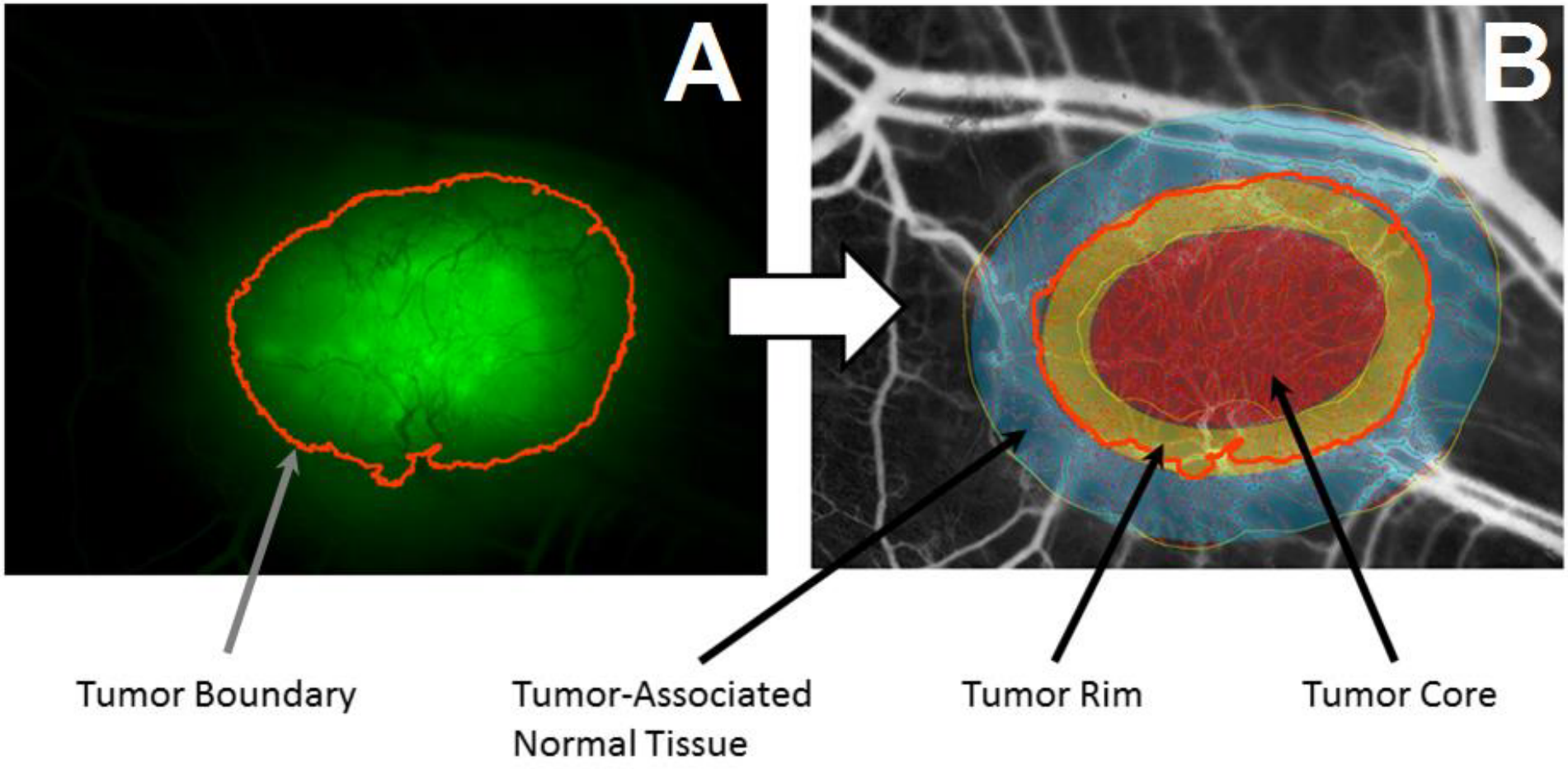
1 day

3 day

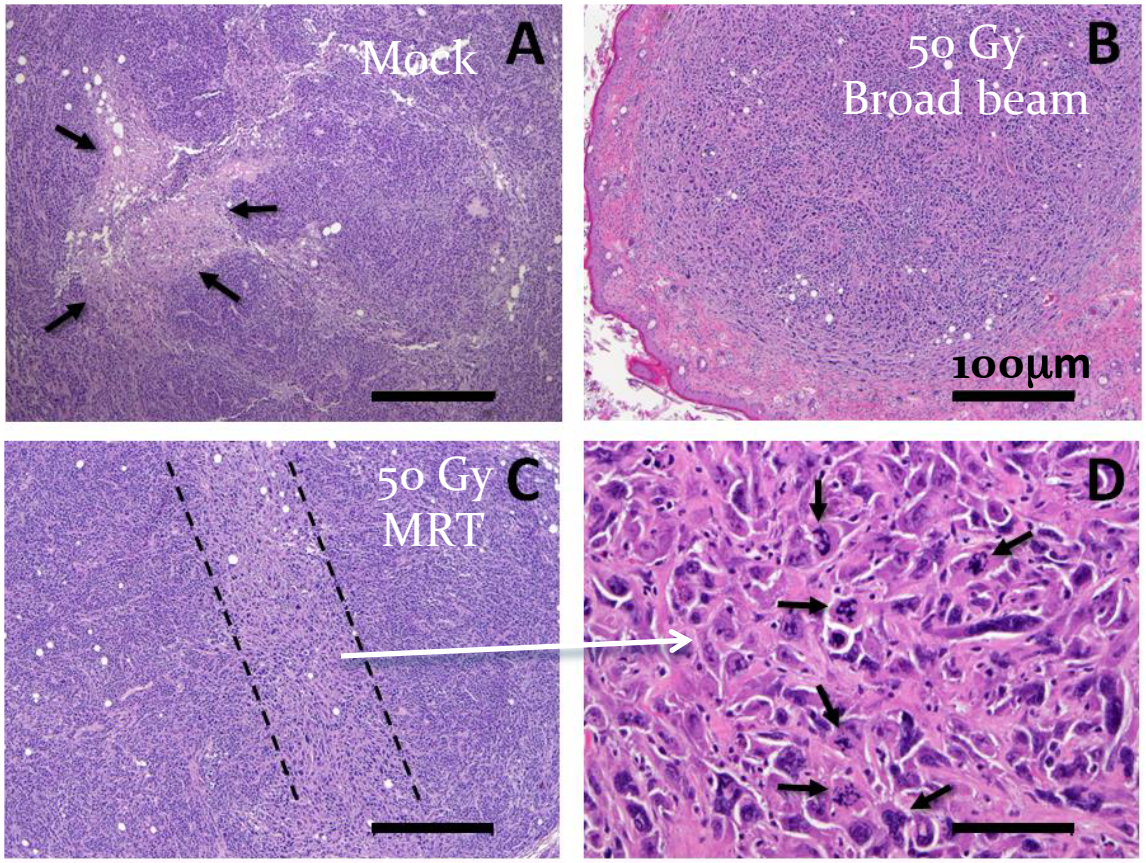
5 day

7 day

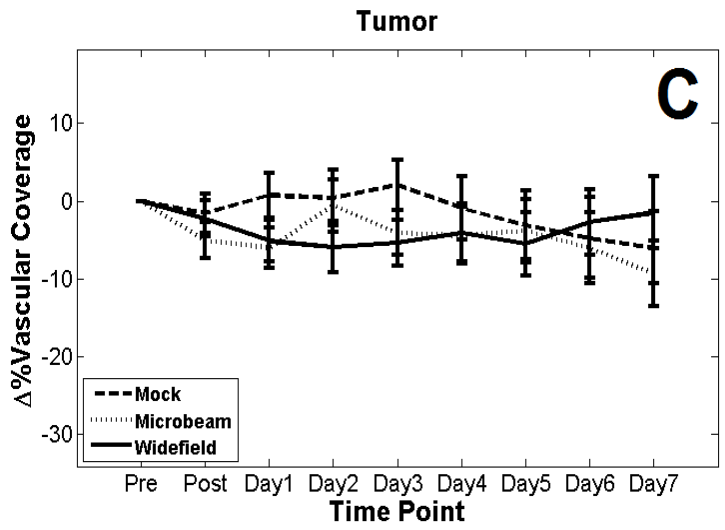
Window chamber tumor model structure

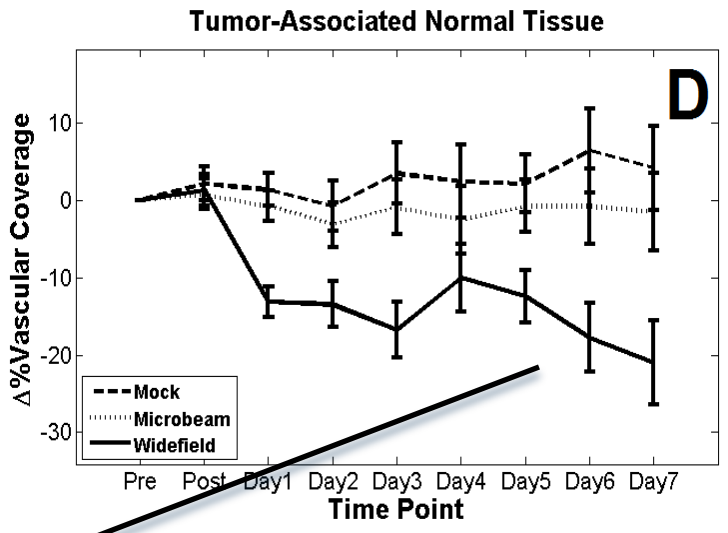


- Cells within the MRT beam are similar to that irradiated by the broad beam (widespread cell death).
- Cells outside the MRT beam are similar to that of the mock group



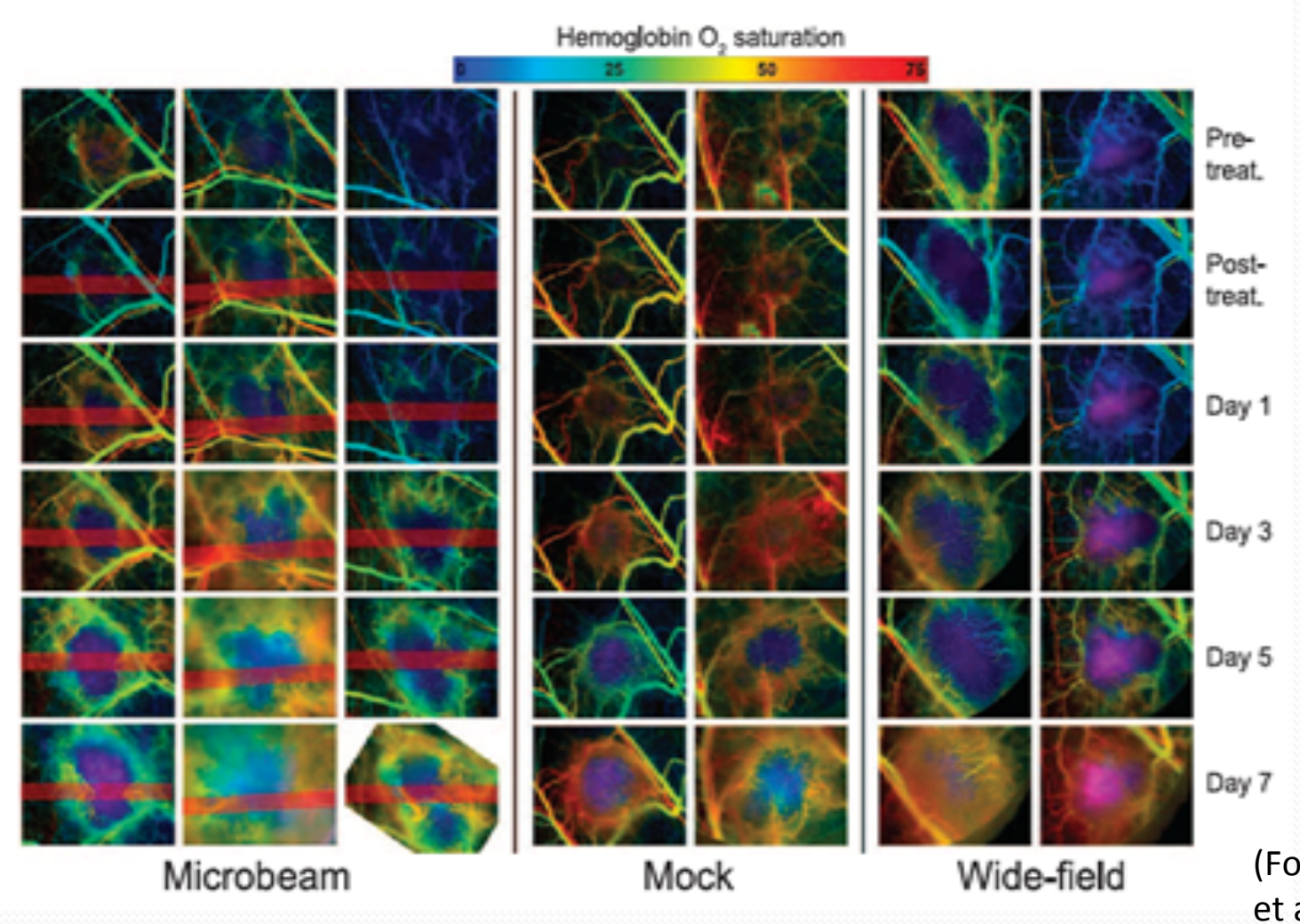
No RT-induced microvasculature damage in tumor





Broad beam radiation damaged vasculature in tumor-associated normal tissue.

MRT radiation induces profound angiogenesis in tumor in rodent tumor model



(Fontanella et al 2015)

HYPOTHESIS

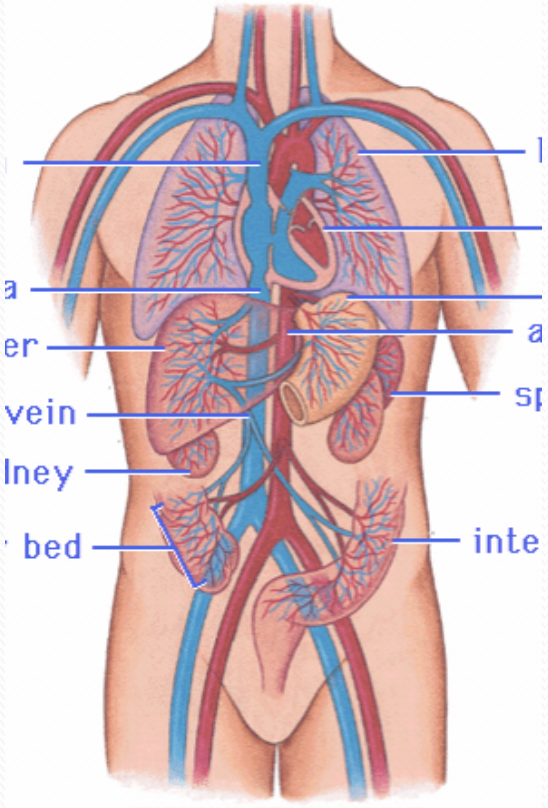
Microbeam radiation therapy (MRT) can significantly and safely enhance nanoparticle drug delivery to tumor through tumor microvasculature modulation.

WE-EF-BRA-9 1:45 PM - 3:45 PM Ballroom A

"Microbeam Radiation Therapy Enhances Tumor Drug Uptake of PEGylated Liposomal Doxorubicin (PLD) in a Triple Negative Breast Cancer GEM Model"

Anti-cancer drugs

- Many cytotoxic chemotherapy drugs effective in killing cancer cells have significant toxicity

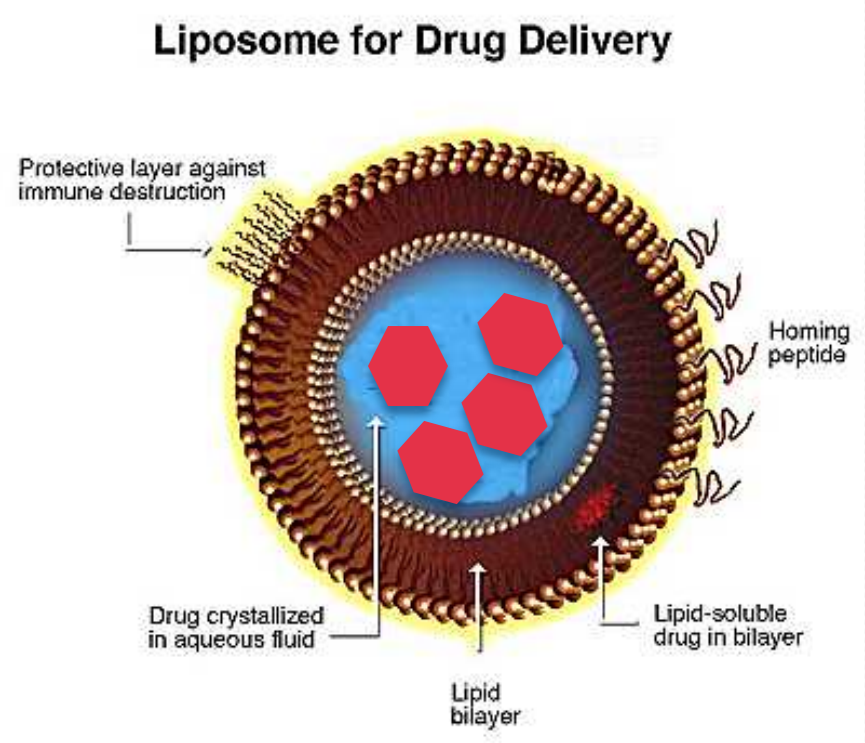


Side effects:

- *Heart damage*
- Myelosuppression (fever, infections, septic shock, etc)
- 2nd leukemia
- liver
- skin

Anti-cancer drug tumor delivery

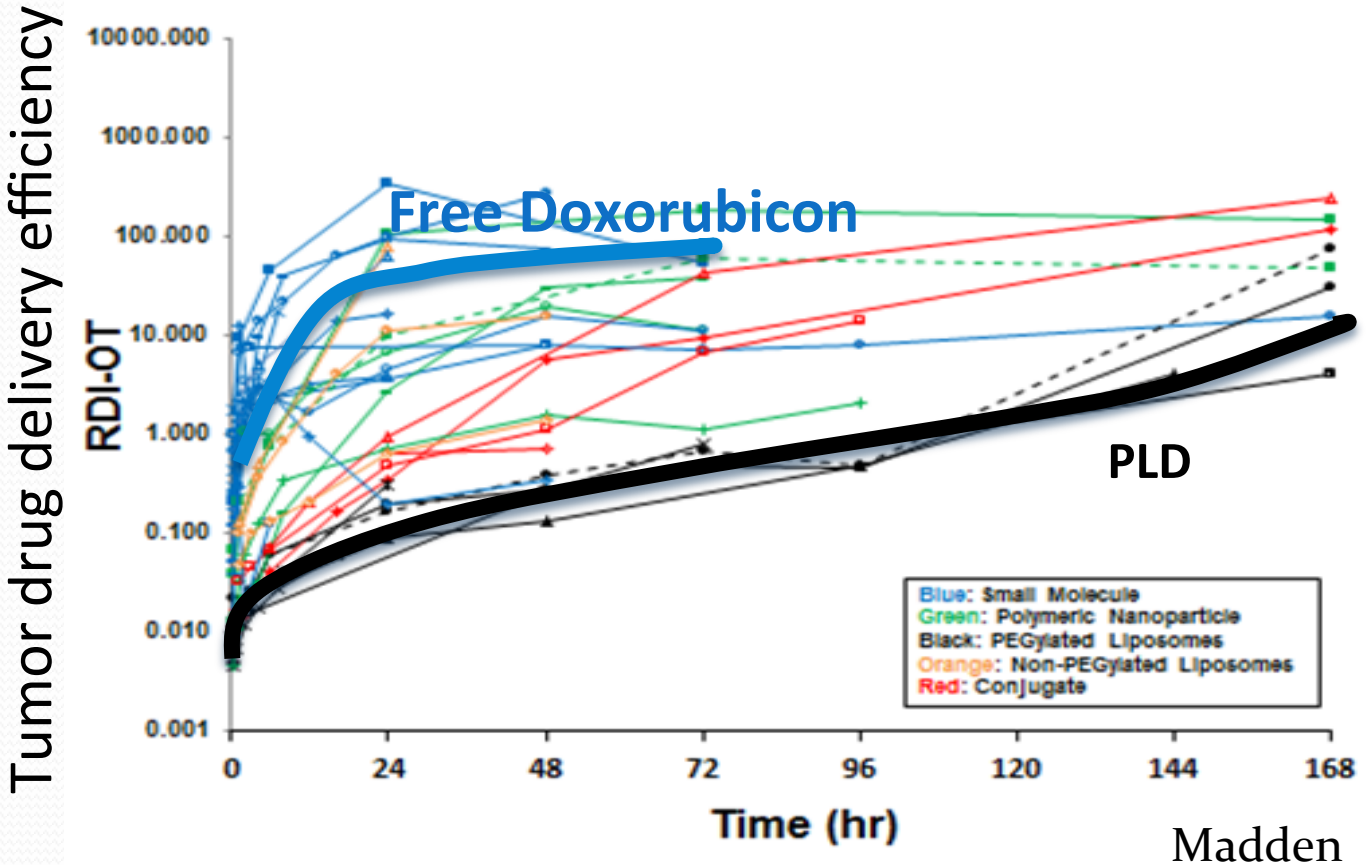
- Carrier-mediated agents (CMAs): nanoparticles (NPs) and liposomes



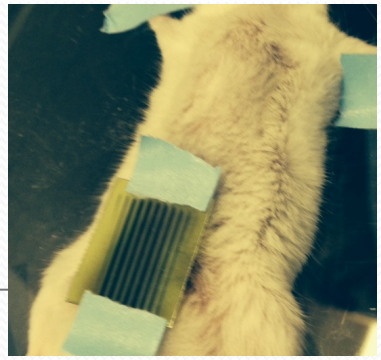
Promises:

- *Biodegradable* carrier
- Encapsulated drug is non-toxic (*safe*)
- Long circulation and exposure to tumor
- Selective delivery to tumor
- High therapeutic Index

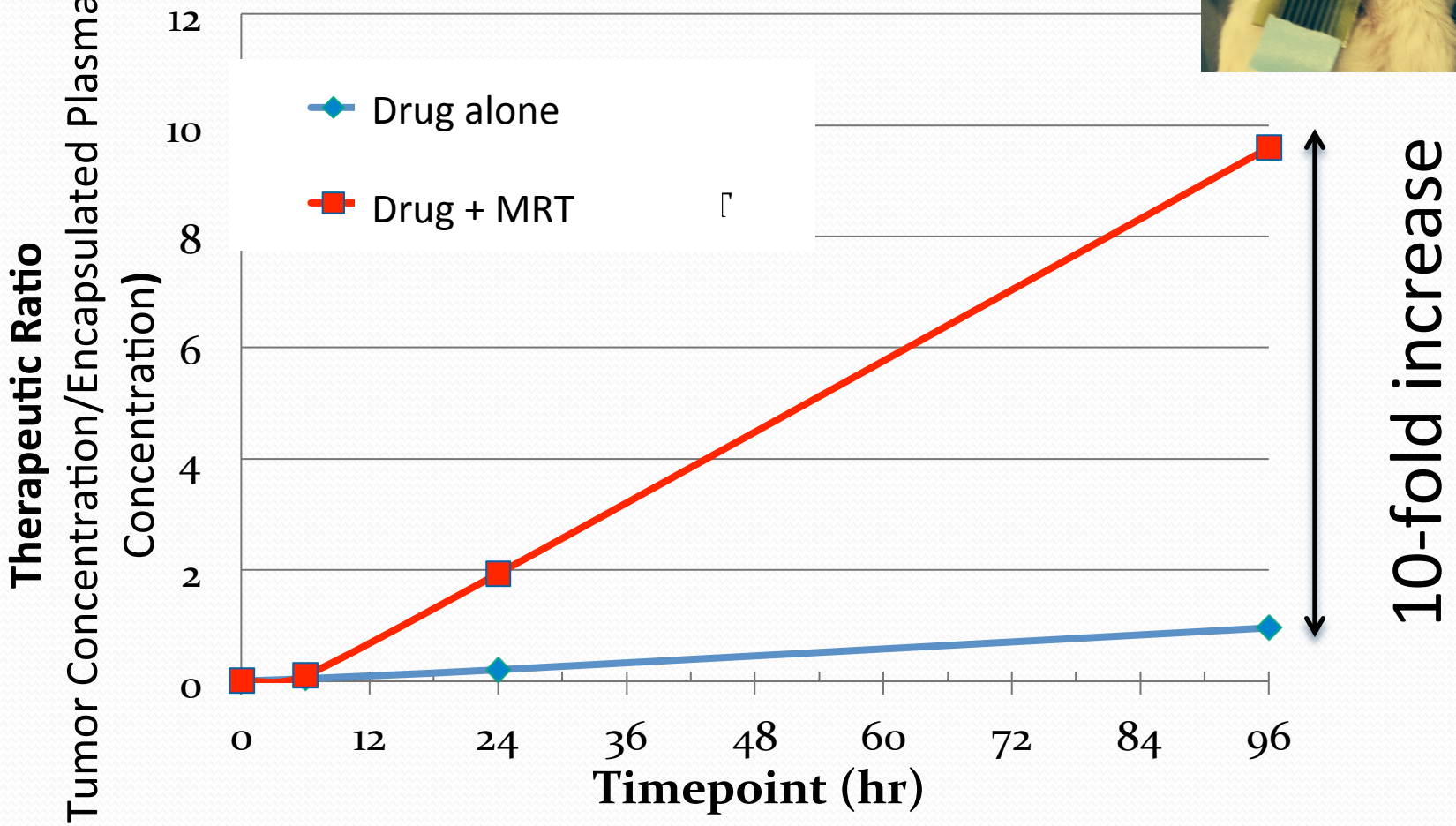
CMA anti-cancer drug delivery is hampered by a low tumor uptake



Madden et al, 2014)



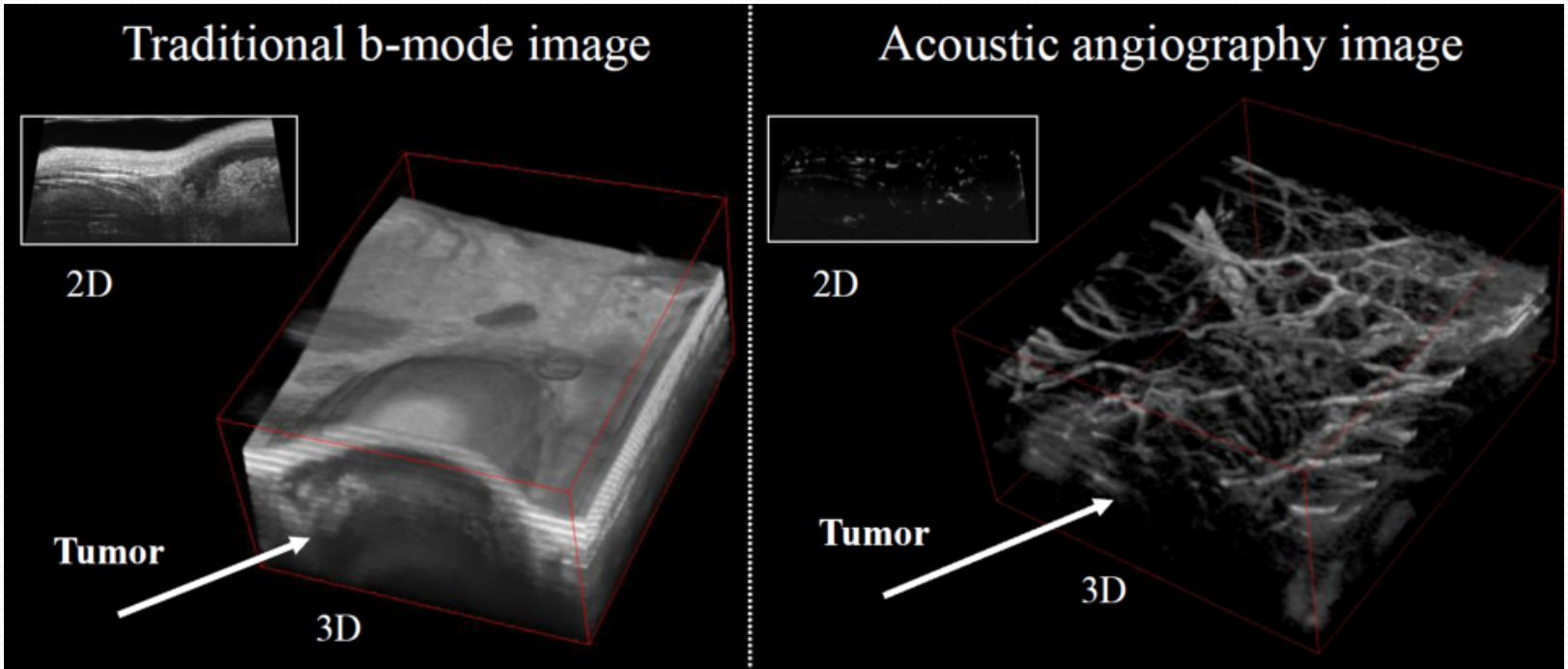
Drug-in-tumor/drug-in-Plasma



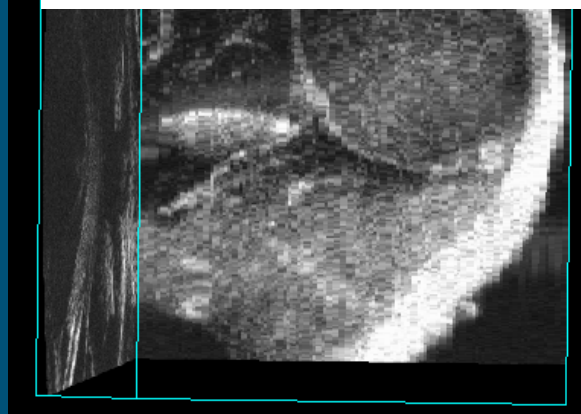
Acoustic angiography: seeing microvasculature using US probe

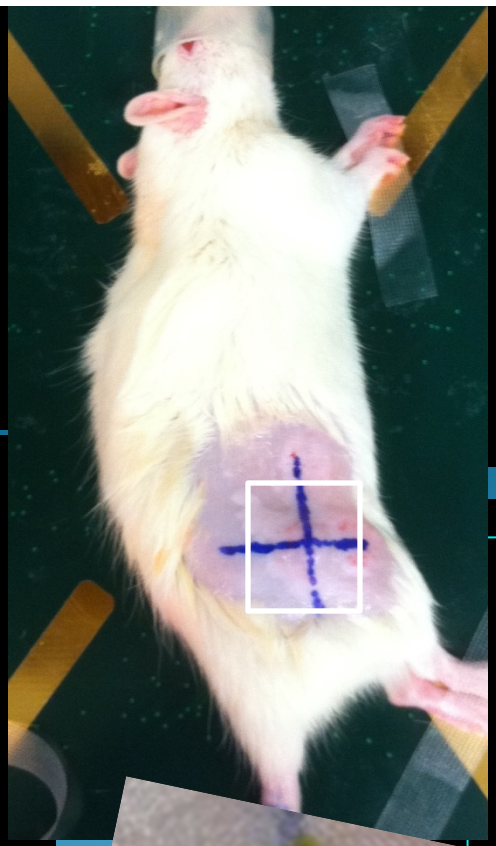
- Microbubble contrast enhanced imaging for microvascular imaging

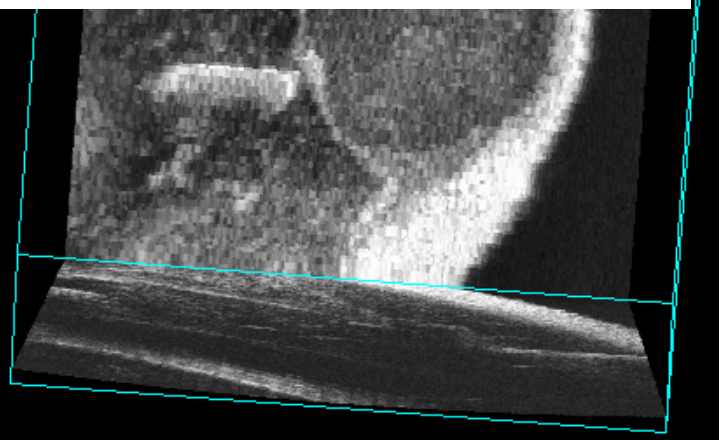
Same tissue volume



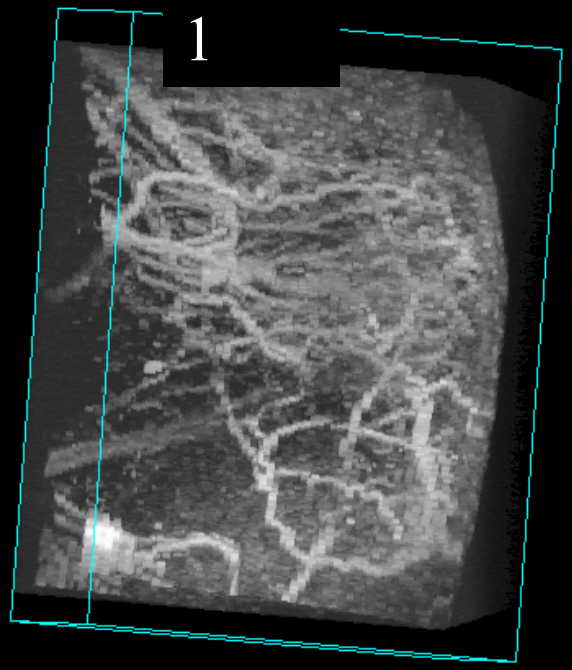
Noninvasive, low cost, low toxicity tool to study radiation induced microvasculature modulation.



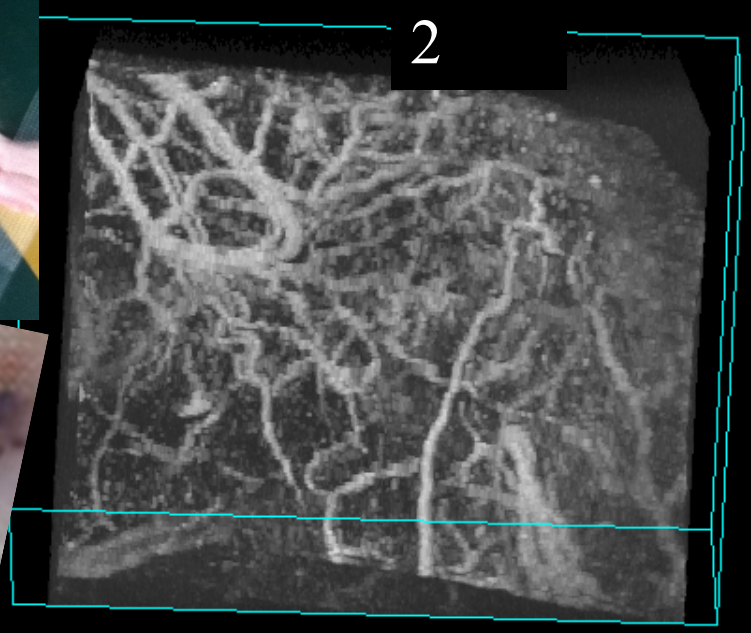




Scan 1

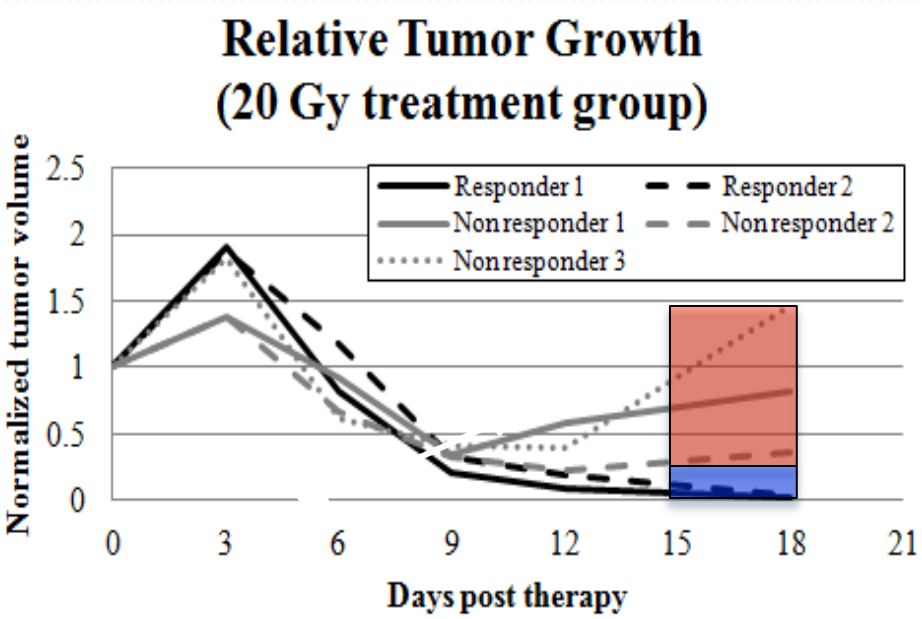


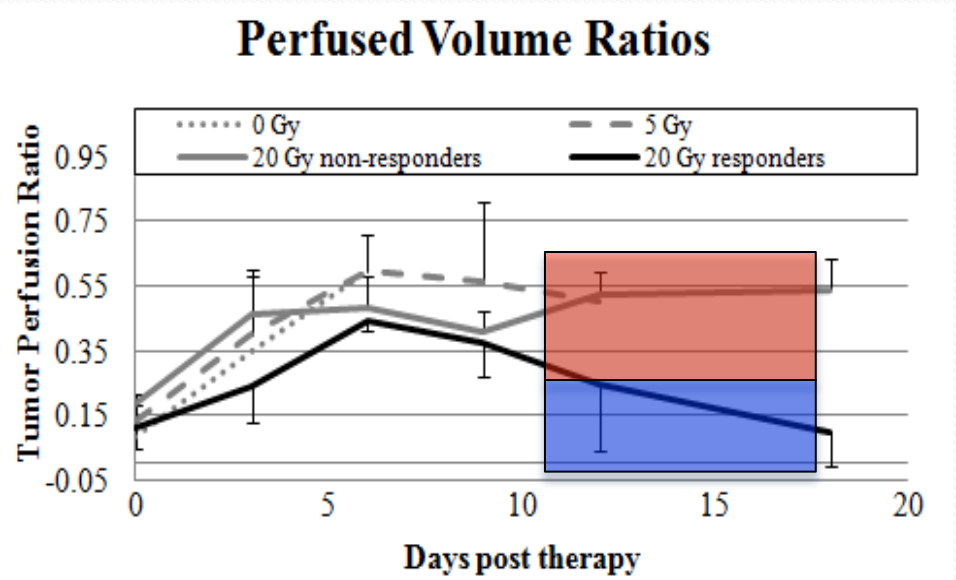
Scan 2



Preliminary Results

Microvasculature change by acoustic angiography may be used as an early detection of RT treatment response.





SUMMARY

- RT does more than cellular DNA double strand break, the impact of radiation is beyond the site of dose deposition.
- The underlying mechanisms of these non-cytotoxic effects of RT are under intense investigation.
- Understanding the full spectrum of radiation induced radiobiological effect will open up new horizons for radiation research and application

SUMMARY

- Physicists in medicine should expand our research horizon beyond the traditional boundary and be part of the exciting multidisciplinary research endeavor to advance cancer research for better patient care tomorrow.
- Ask new questions and focus on clinical impact
- Radiobiology is  from physics effort to clinical impact.

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