Memorial Sloan Kettering Cancer Center

Recoil-based short lived alpha-emitting devices: a new brachytherapy approach?

April, 2019

Antonio Damato, PhD, DABR

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- No conflict of interest regarding DaRT
- Some of the material in this presentation was kindly provided by Lior Arazi (Ben Gurion University), who has a stake in Alpha Tau
- The devices described in this talk are not FDA approved for standard use and are not commercially available in the US

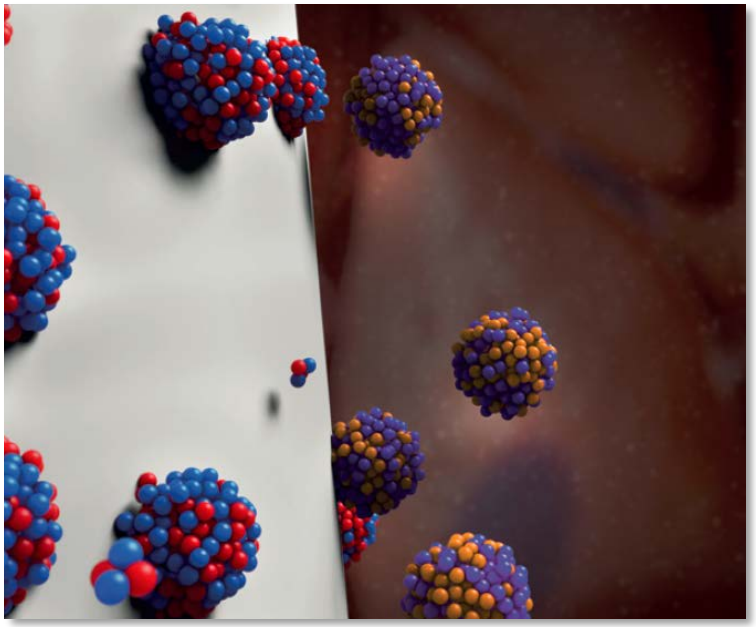
Alpha radiation?

- High LET radiation:
  - Double-strand break
  - Effective against hypoxic tumors

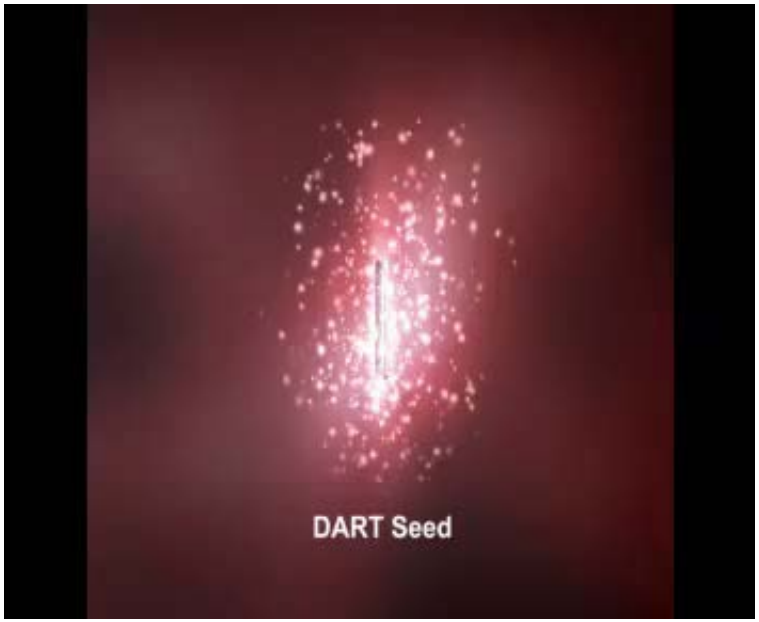
- Short range (~50μm)
  - Need a delivery method to the tumor cells
  - Range doesn't permit direct implantation of alpha emitting "seeds" into bulky tumors
  - Targeted alpha particle therapy typically a nuclear medicine approach

Courtesy: Lior Arazi

Alpha DaRT: Overcoming the short range of alpha particles

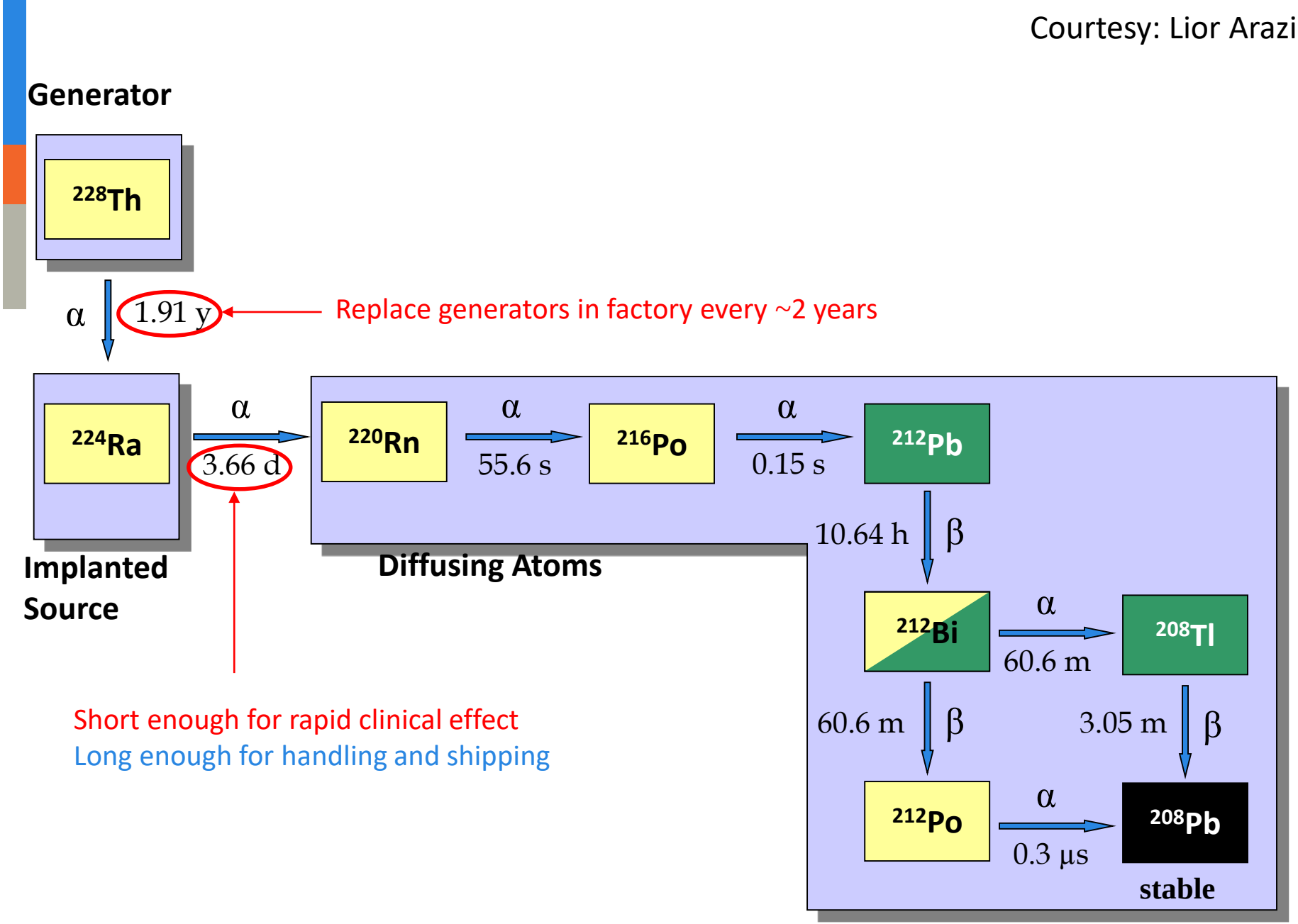


The DaRT seed emits from its surface **by recoil** a chain of alpha emitting *atoms*



The atoms disperse by diffusion, creating a 'kill region' over several mm

Courtesy: Lior Arazi



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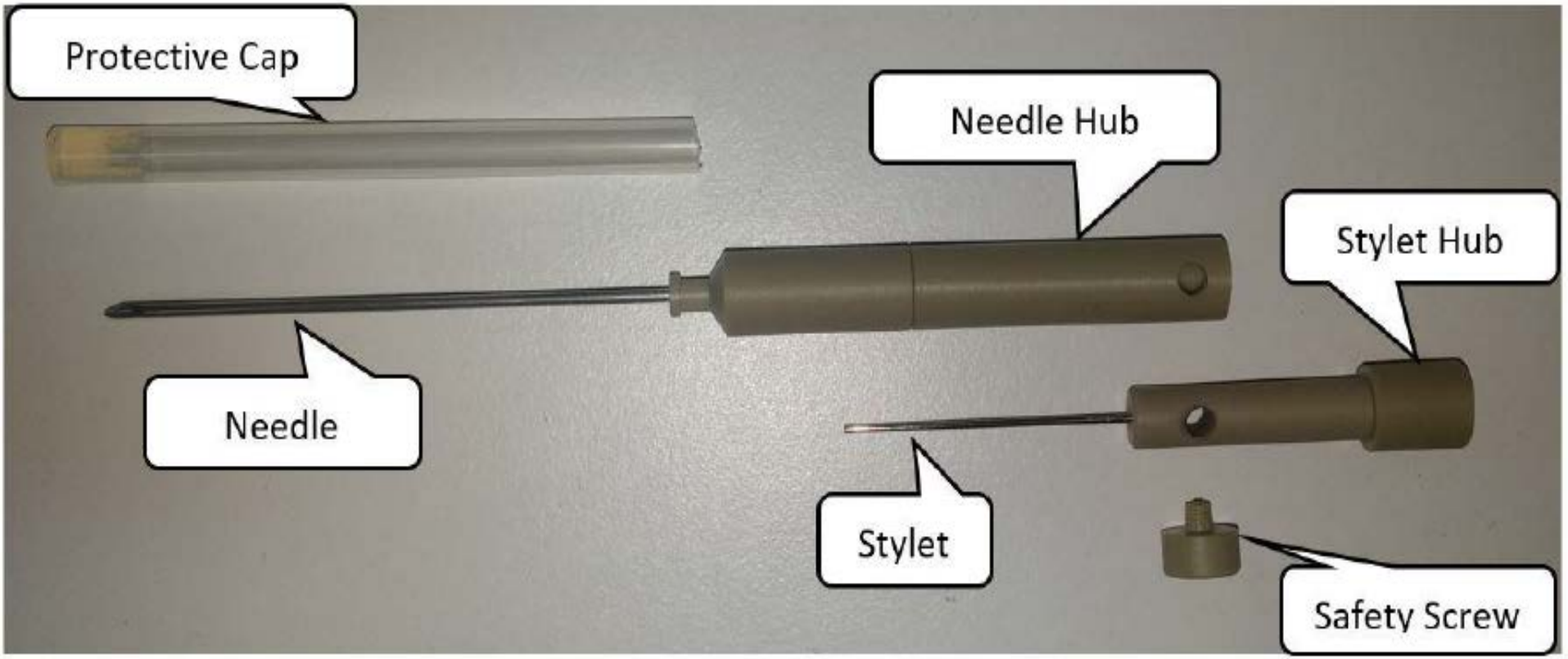
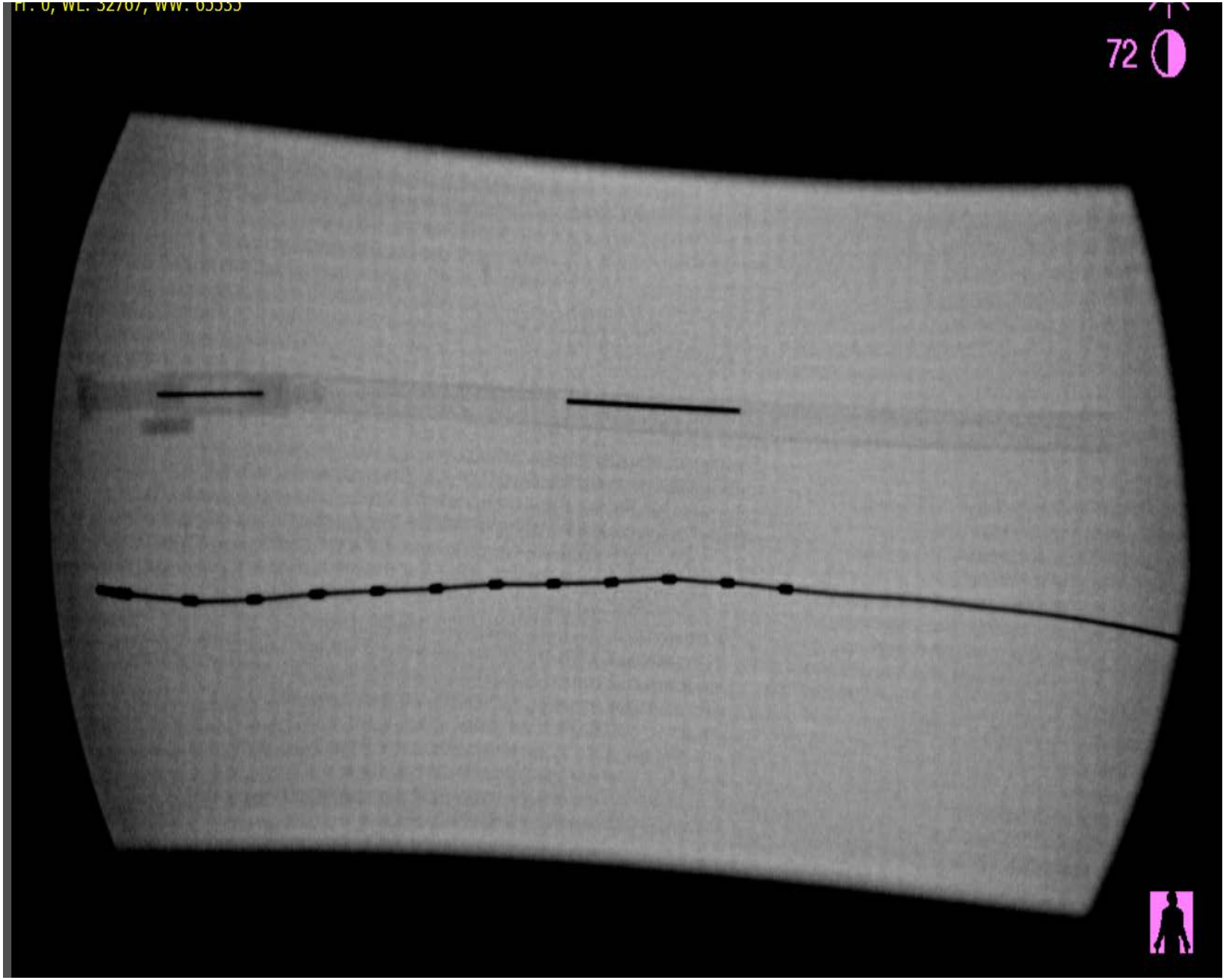
DaRT : a brachytherapy device

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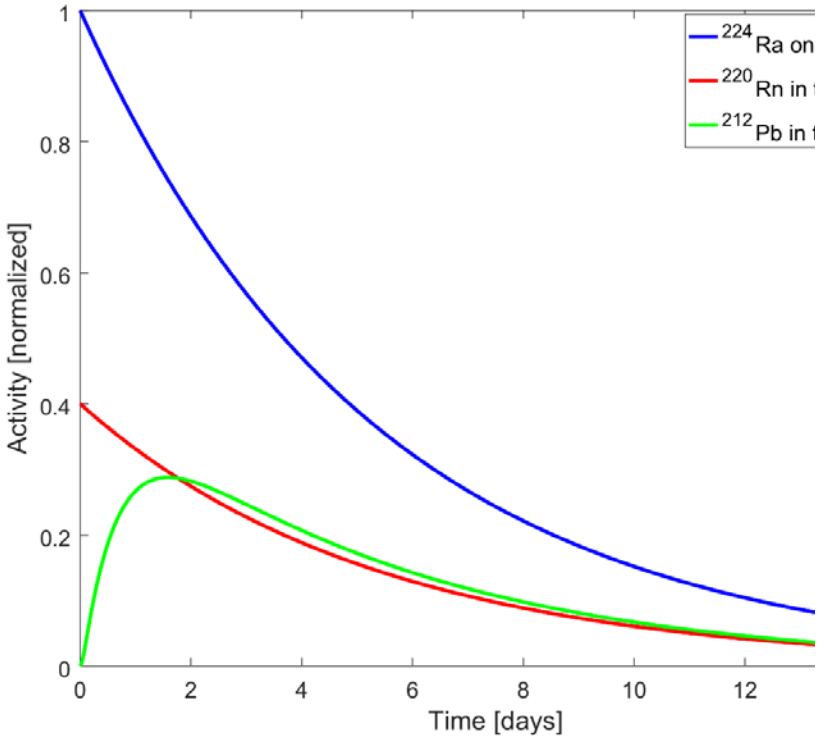
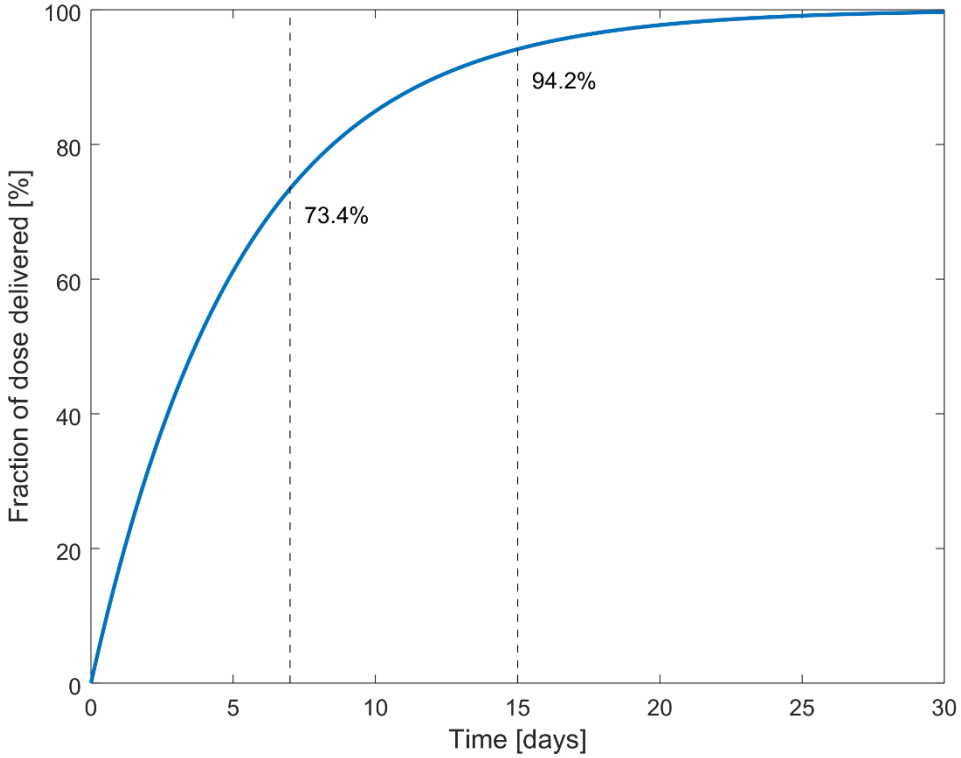
Temporal Profile





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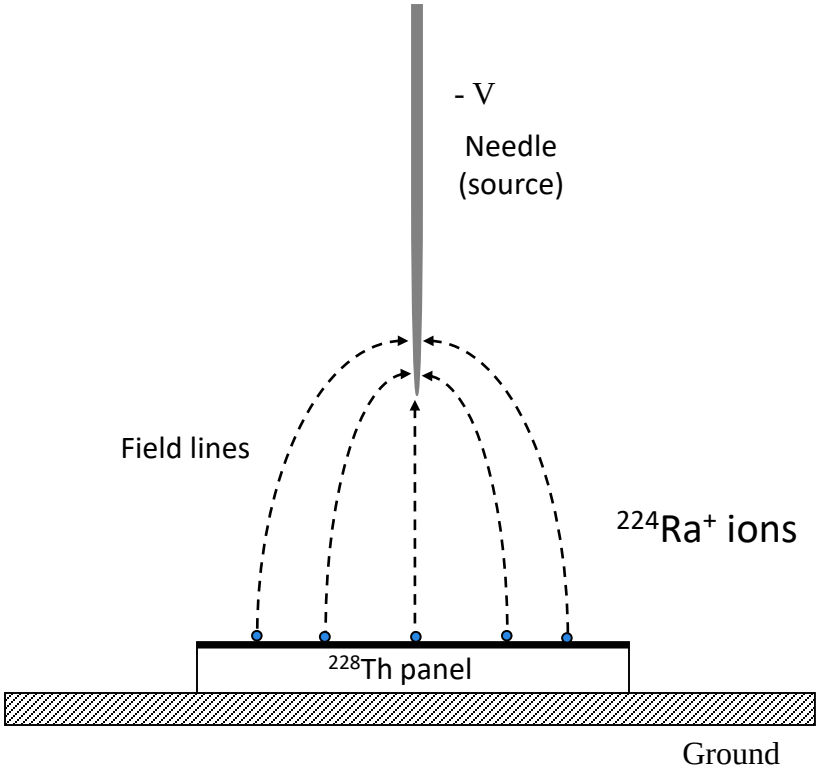
Source preparation: electrostatic collection of ^{224}Ra

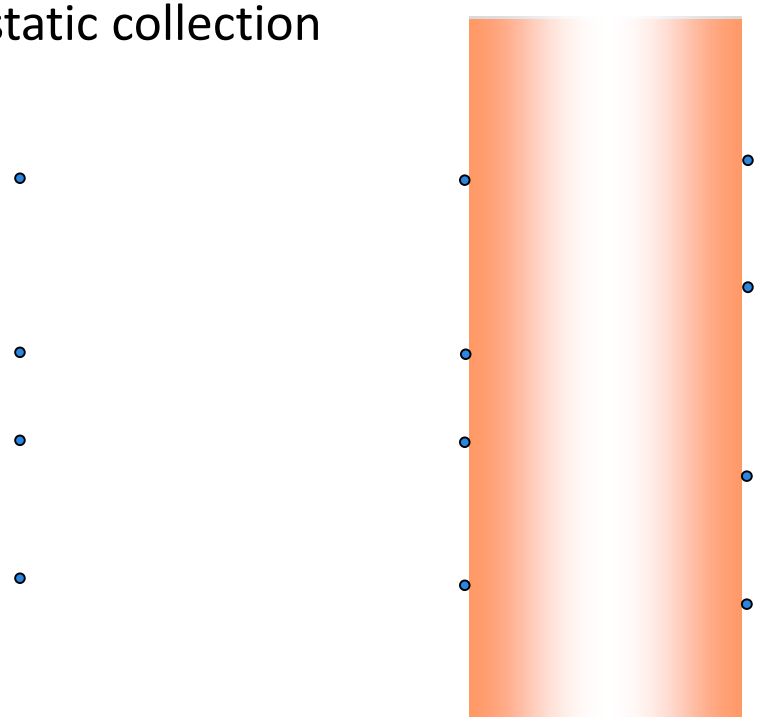
Courtesy: Lior Arazi



Source preparation: ^{224}Ra embedding on source

Courtesy: Lior Arazi

Electrostatic collection



Heat treatment

Courtesy: Lior Arazi

Current dosimetry model

Simplifying assumptions:

- The tumor tissue is homogeneous, isotropic and does not change with time
- Chaotic nature of tumor vasculature allows describing convective spread as effective diffusion
- Only ^{220}Rn and ^{212}Pb diffusion should be modeled, their short-lived daughters are in local secular equilibrium
- ^{220}Rn decays inside the tumor, ^{212}Pb removal by the blood modeled as a uniform “sink” term

Courtesy: Lior Arazi

Tissue transport: ^{220}Rn and ^{216}Po

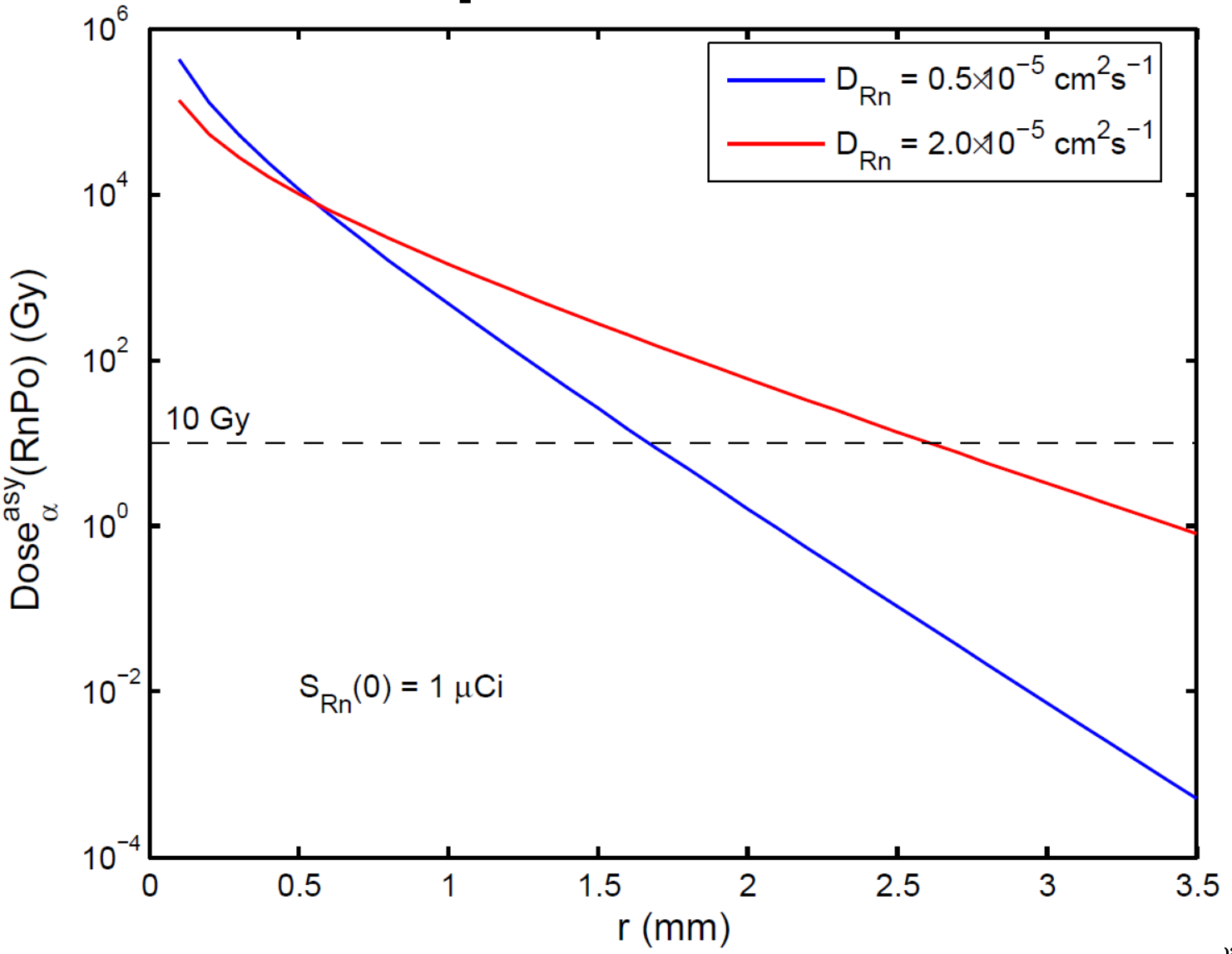
- ^{220}Rn emitted from source (seed) with 40% desorption probability
- Quickly neutralizes, continues as a noble-gas atom
- Diffusion coefficient in water $2 \cdot 10^{-5}$ cm^2/s, in stomach wall $0.5 \cdot 10^{-5}$ cm^2/s
- Hops on/off capillaries with random orientation → effective diffusion coefficient expected to be on same scale
- Because of its 1 min half-life does not escape tumor through blood
- ^{216}Po half-life 0.15 s → decays at the same site as ^{220}Rn

Courtesy: Lior Arazi

Tissue transport: ^{212}Pb and ^{212}Bi

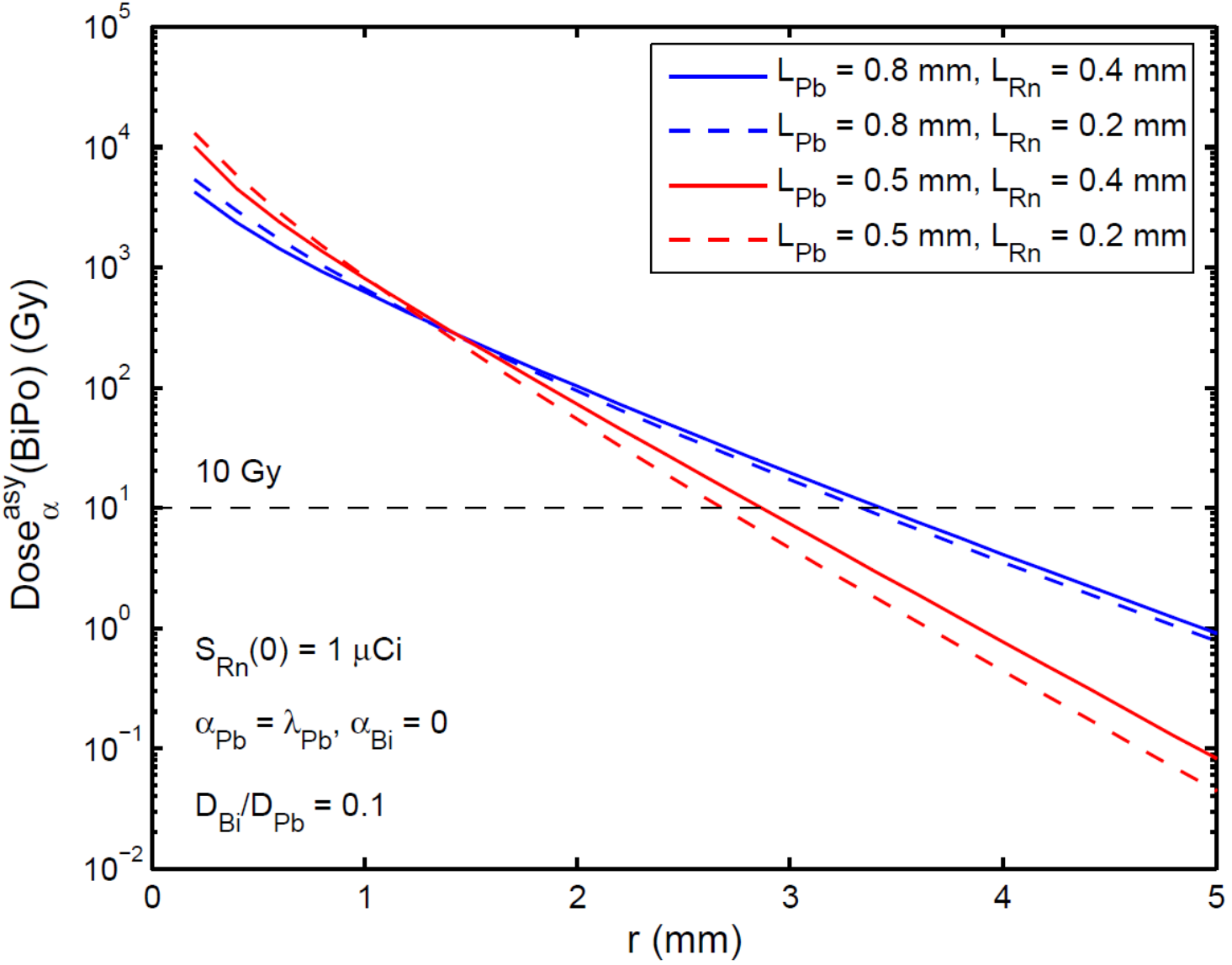
- ^{212}Pb emitted from source with ~55% effective desorption probability
- Likely starts as Pb^{2+}, then quickly binds to a variety of proteins of different masses, with effective diffusion coefficients of ~10^{-7} cm^2/s
- Because of its 10.6 h half-life can partially leave the tumor through the blood
- From preclinical and clinical data, typical time scale of ^{212}Pb leakage comparable to its half-life (~10-20 h)
- ^{212}Bi in local secular equilibrium with ^{212}Pb

Dose @ Depth



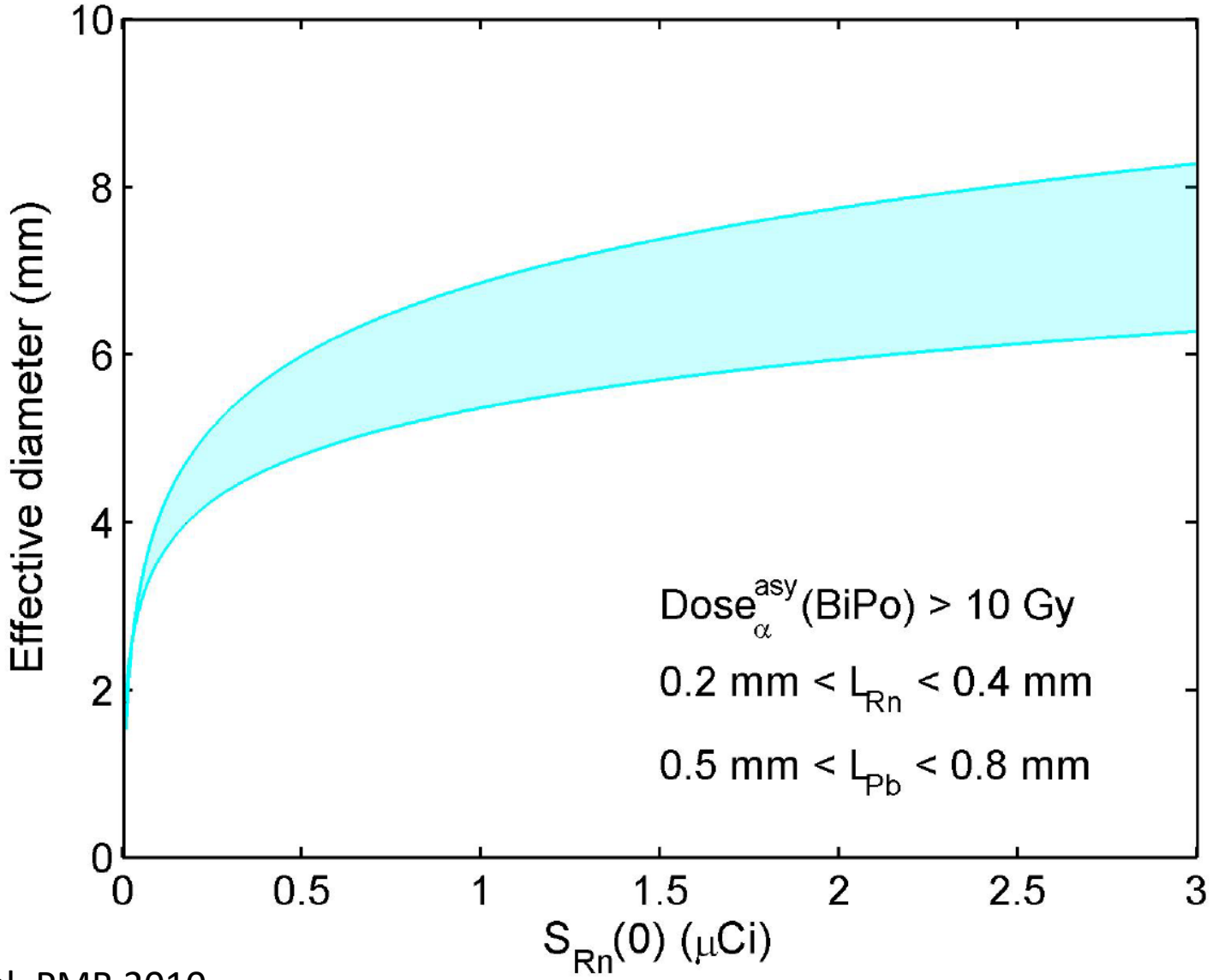
Arazi et al, PMB 2010

Dose @ Depth



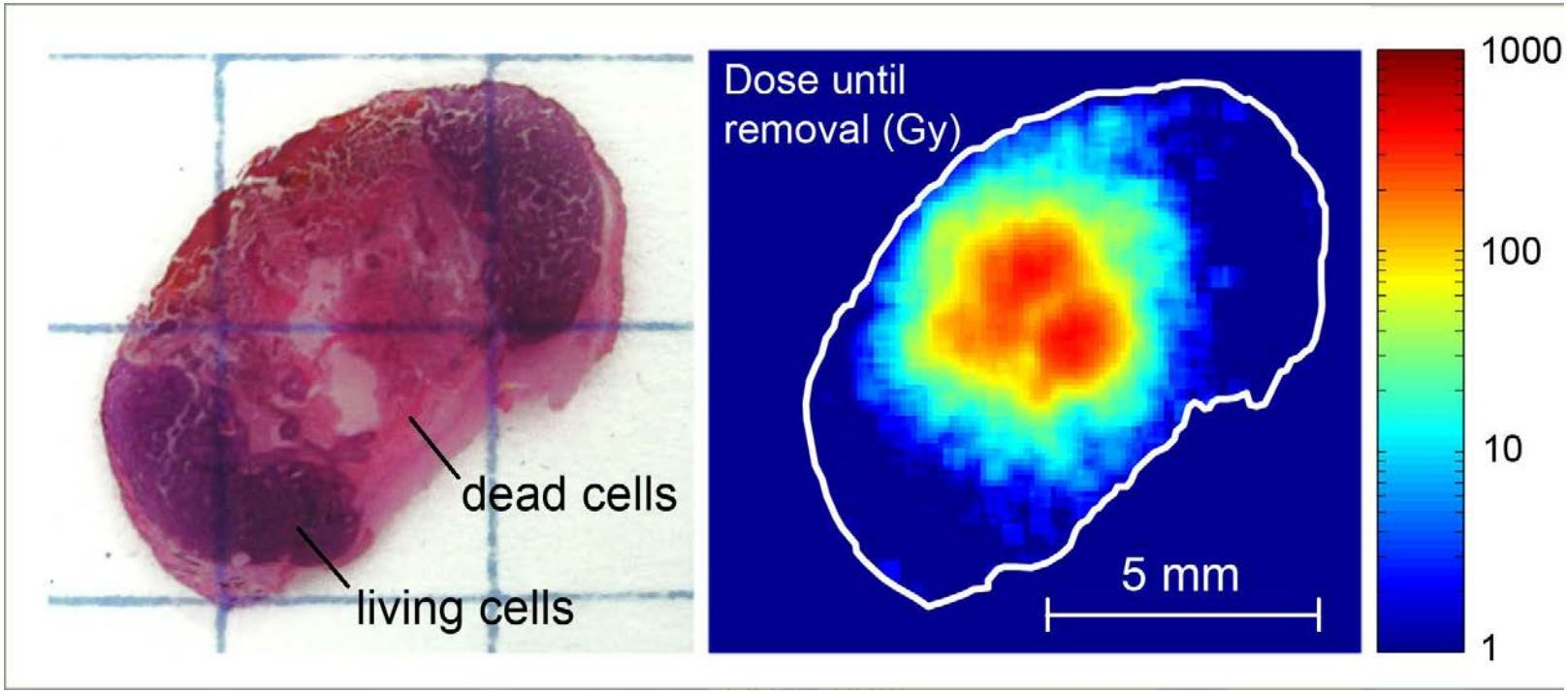
Arazi et al, PMB 2010

Effective Diameter



Arazi et al, PMB 2010

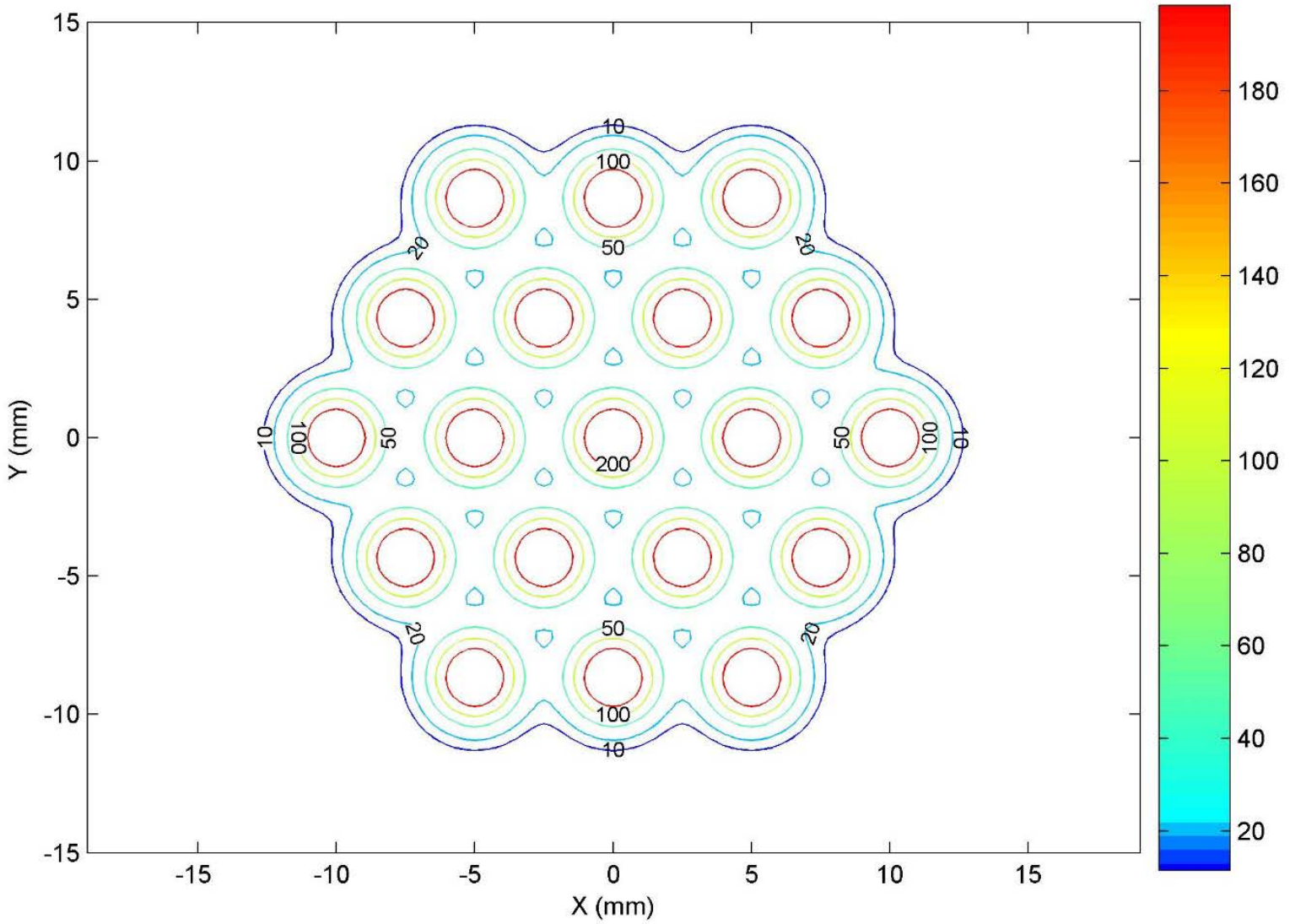
The distribution of radioactive atoms inside the tumor in comparison with the necrotic areas they cause



(Left) Hematoxylin-eosin (H&E) stained 5µm section taken from a SCC tumor treated with a ^{224}Ra DART source. Darker (purple) regions in (A) are composed of viable cells, lighter (pink) regions are necrotic.

(Right) The radiation pattern of the same section.

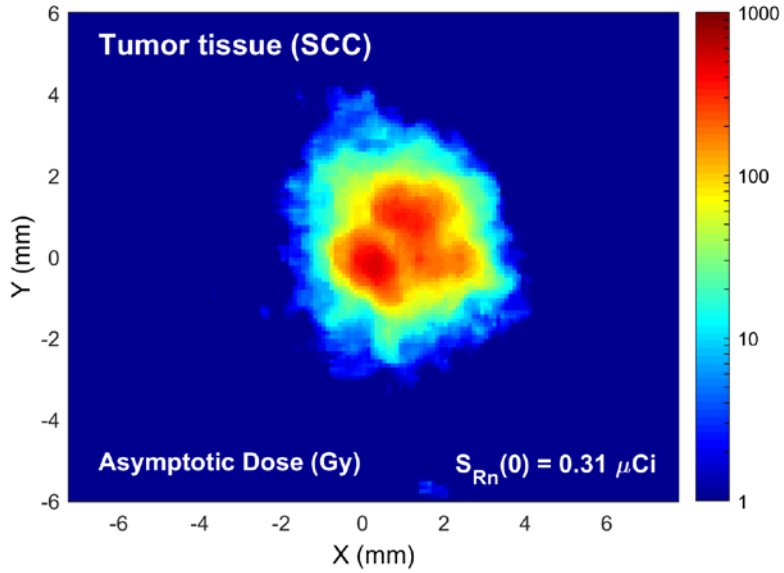
“TG43” distribution



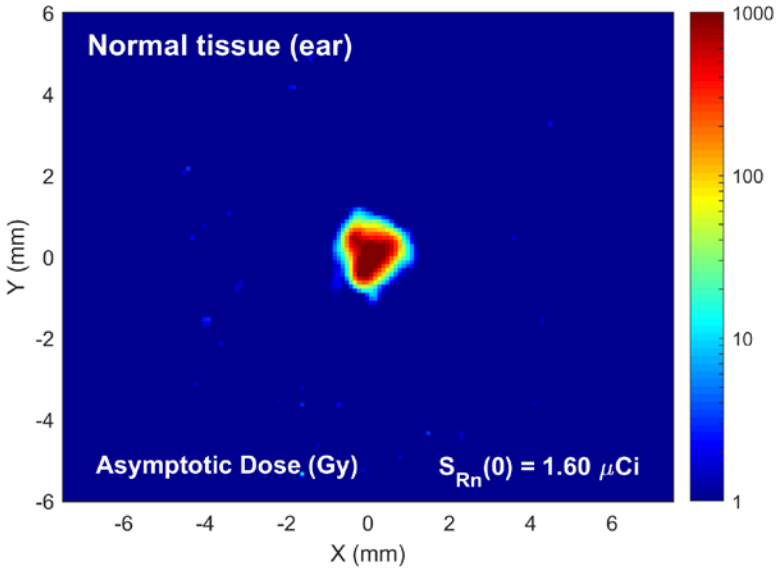
Courtesy: Lior Arazi

Safety – adjacent healthy tissue

- Negligible beta and gamma dose; rapid clearance of ^{212}Pb by ordered vasculature limits the kill region



Mouse SCC tumor



Pig's ear

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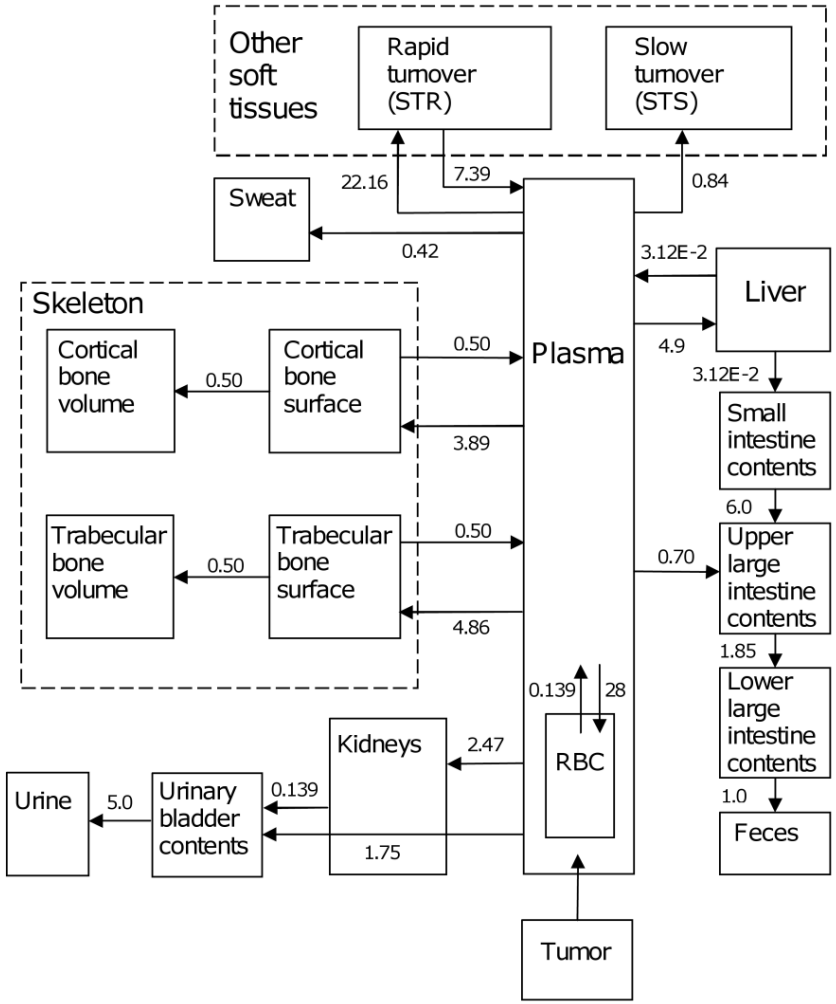
Courtesy: Lior Arazi

Safety – distant organs

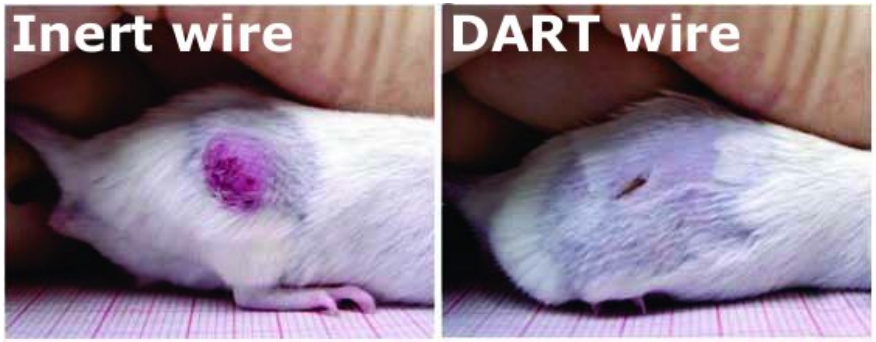
Distant organs: ^{212}Pb leaving tumor through blood spreads throughout the body. Biokinetic + internal dosimetry calculations show that organ doses in typical treatment are 1-2 orders of magnitude below tolerance levels.

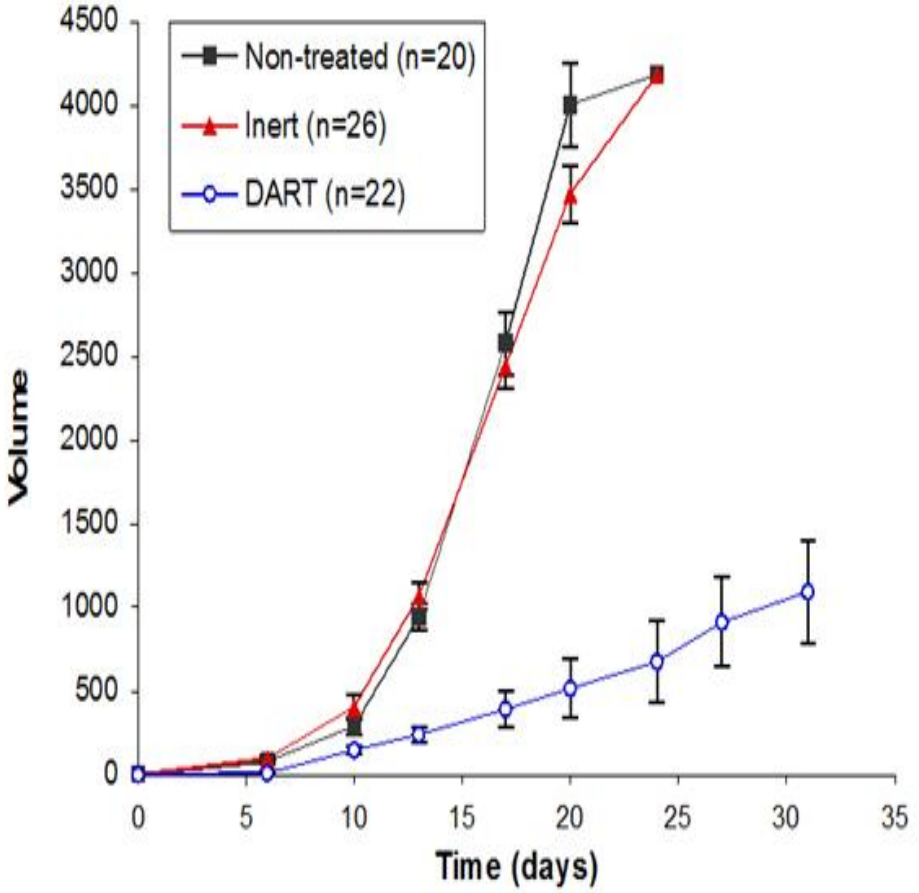


Courtesy: Keisari

Ra-224 DaRT wires inhibit the growth of squamous cell carcinoma (SCC) mouse tumors

DaRT wires were inserted into skin tumors and the growth of the tumors was measured for 32 days.





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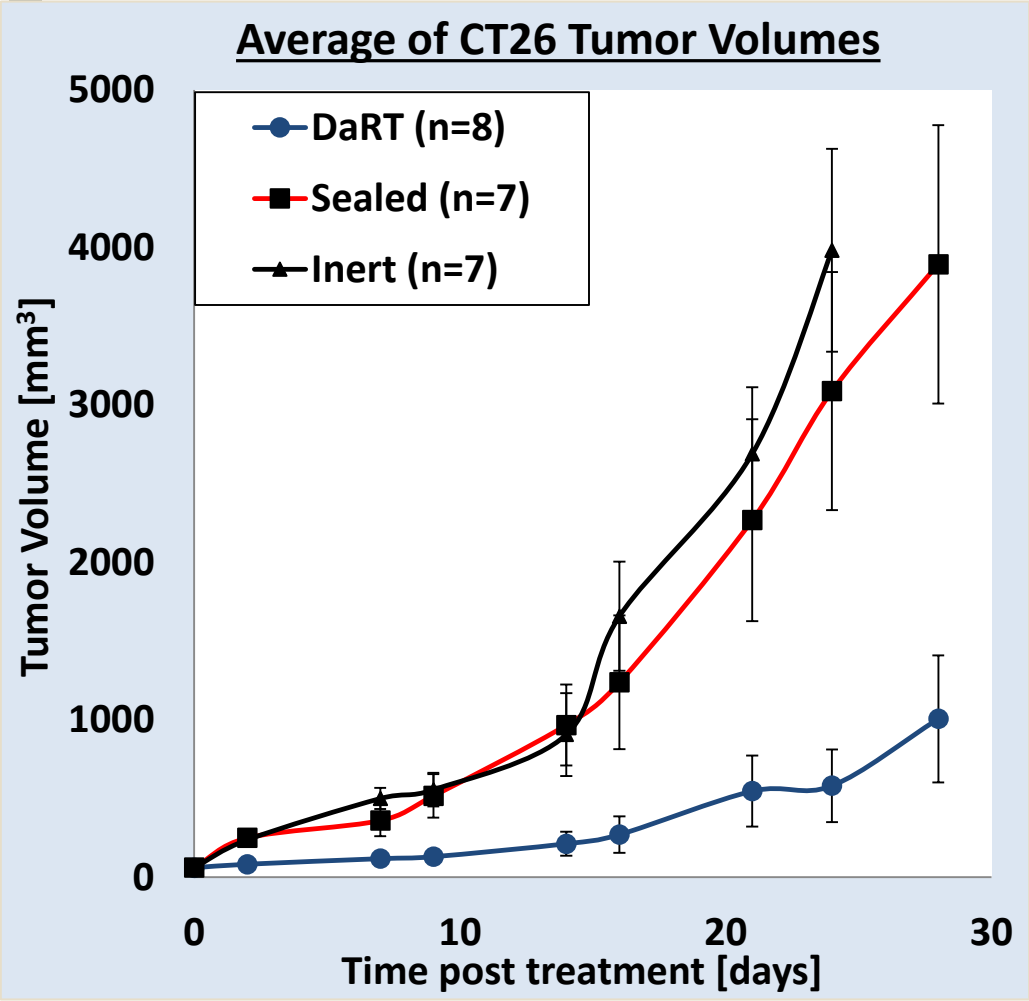
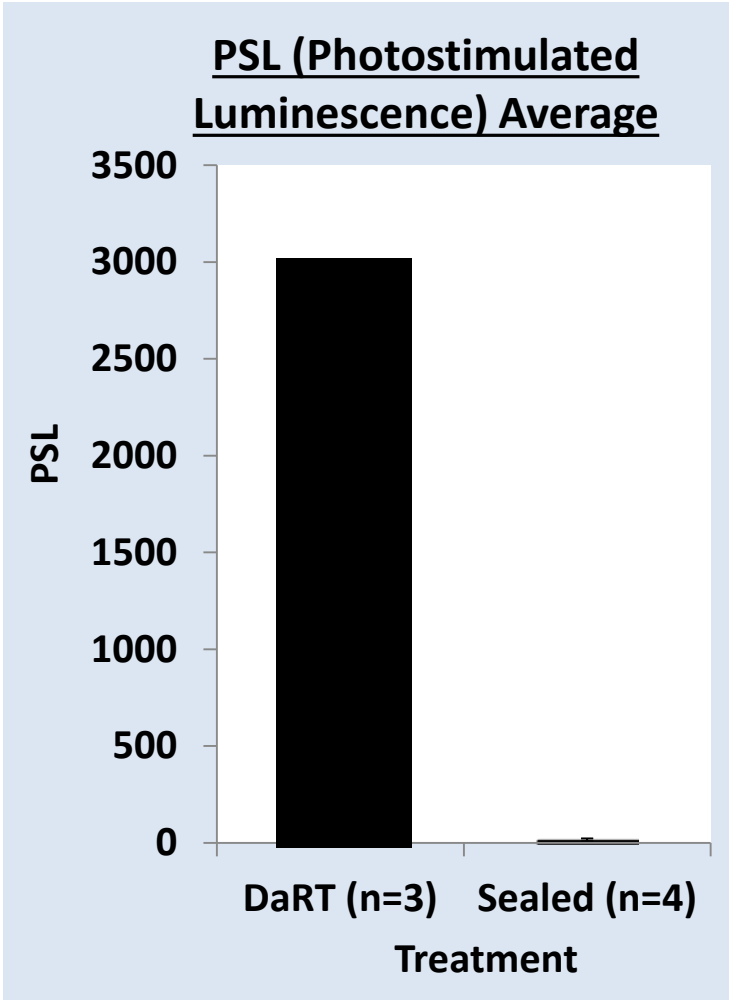
Courtesy: Keisari

Tumor Destruction by DaRT is Primarily Mediated by Alpha Particles





p<0.05 DaRT vs. controls

p<0.05 DaRT vs. sealed

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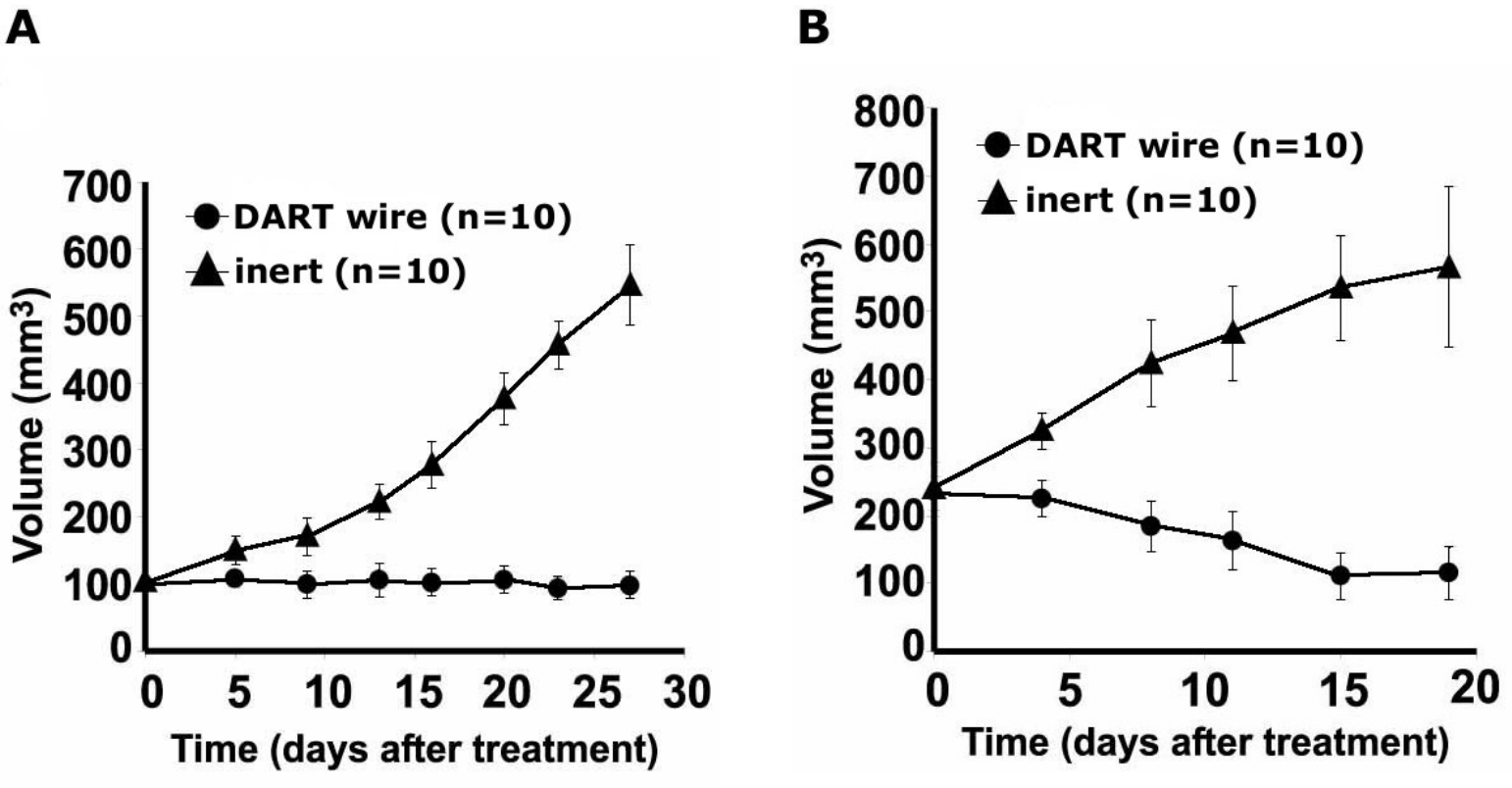
DaRT Wires Eradicating Human SCC in Nude mice

Effect of a single DART wire

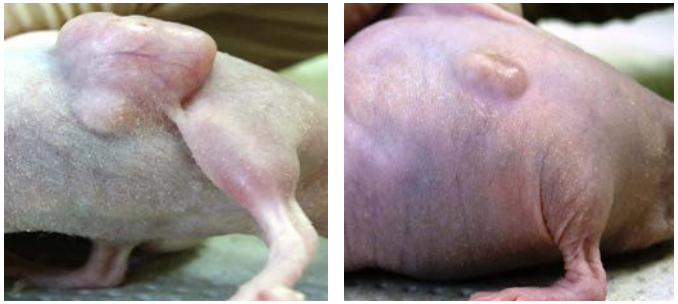


HNSCC

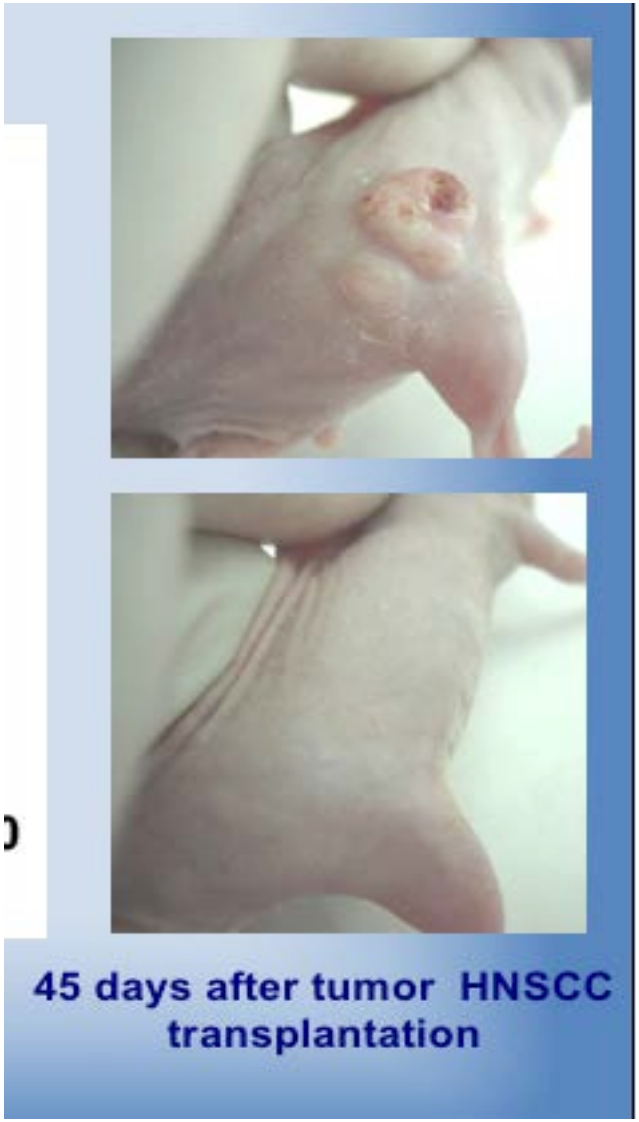
Lung SCC

DaRT Wires Eradicating Human Tumors in Nude mice

GBM



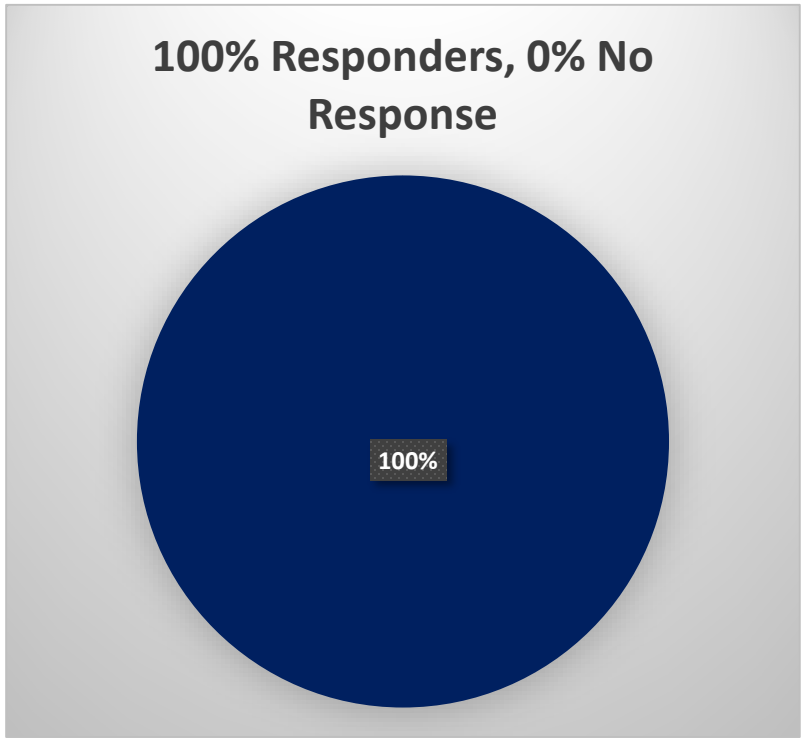
Human Prostate in Nude Mice

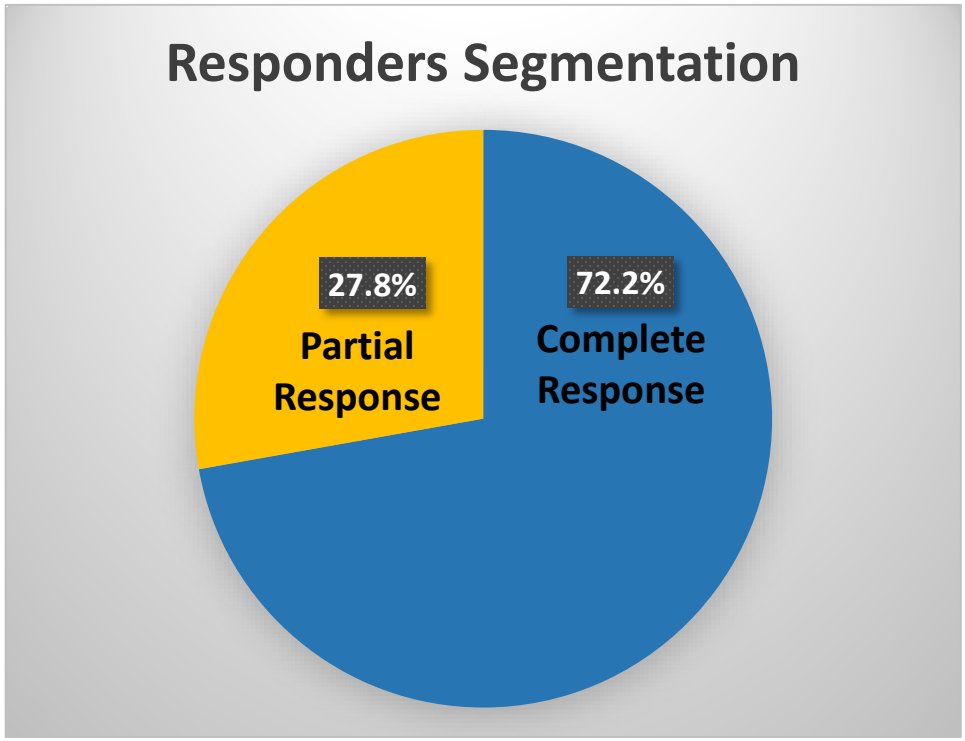


Safety/Efficacy Clinical Trial: Rabin Medical Center (N=17); others in the works in Italy and US

Patient	Age	Tumor Location	Previous RT	Response
1	87	Sub-Mandibular + Mandible	Yes	Partial
2	80	Ear	Yes	Complete
3	94	Tongue	Yes (x2)	Complete
4	80	Lip	Yes	Partial
5	75	Parotid	Yes	Partial
6	94	Tongue	Yes	Complete
7	69	Nose	Yes	Complete
8	81	Ear	Yes	Complete
9	91	Tongue	Yes	Complete
10	76	Cheek	No	Complete
11	78	Lip	Yes	Complete
12	70	Forehead	No	Partial
13	66	Lip	No	Complete
14	88	Parotid	Yes	Unknown

Safety/Efficacy Clinical Trial: Rabin Medical Center (N=17); others in the works in Italy and US





Challenges (source acceptance)

- Source characterization
  - No primary standard for DaRT
  - In-house absolute measurements with hpGe
  - Proposal : Initial multi-institution effort to standardize calibration until primary standard is available
  - Preliminary work done at MSKCC and IRST (Italy)

- Desorption probability
  - Rate of desorption of daughter elements from source is critical to dose calculation
  - Current MSKCC do not measure desorption
  - Is it necessary to perform in-house desorption measurements? With what frequency?

Challenges (dose calculation)

- Treatment planning system
  - “Spherical cow” model can be formalized in “TG43”-like tables
  - This is the only dose calculation system that will be available in the near future!

- Past the “spherical cow” model
  - Proposal to develop MC / finite elements models for diffusion accounting for heterogeneous medium, 4D effect (BGU, MSKCC)
  - Work on microdosimetry calculation underway (McGill)

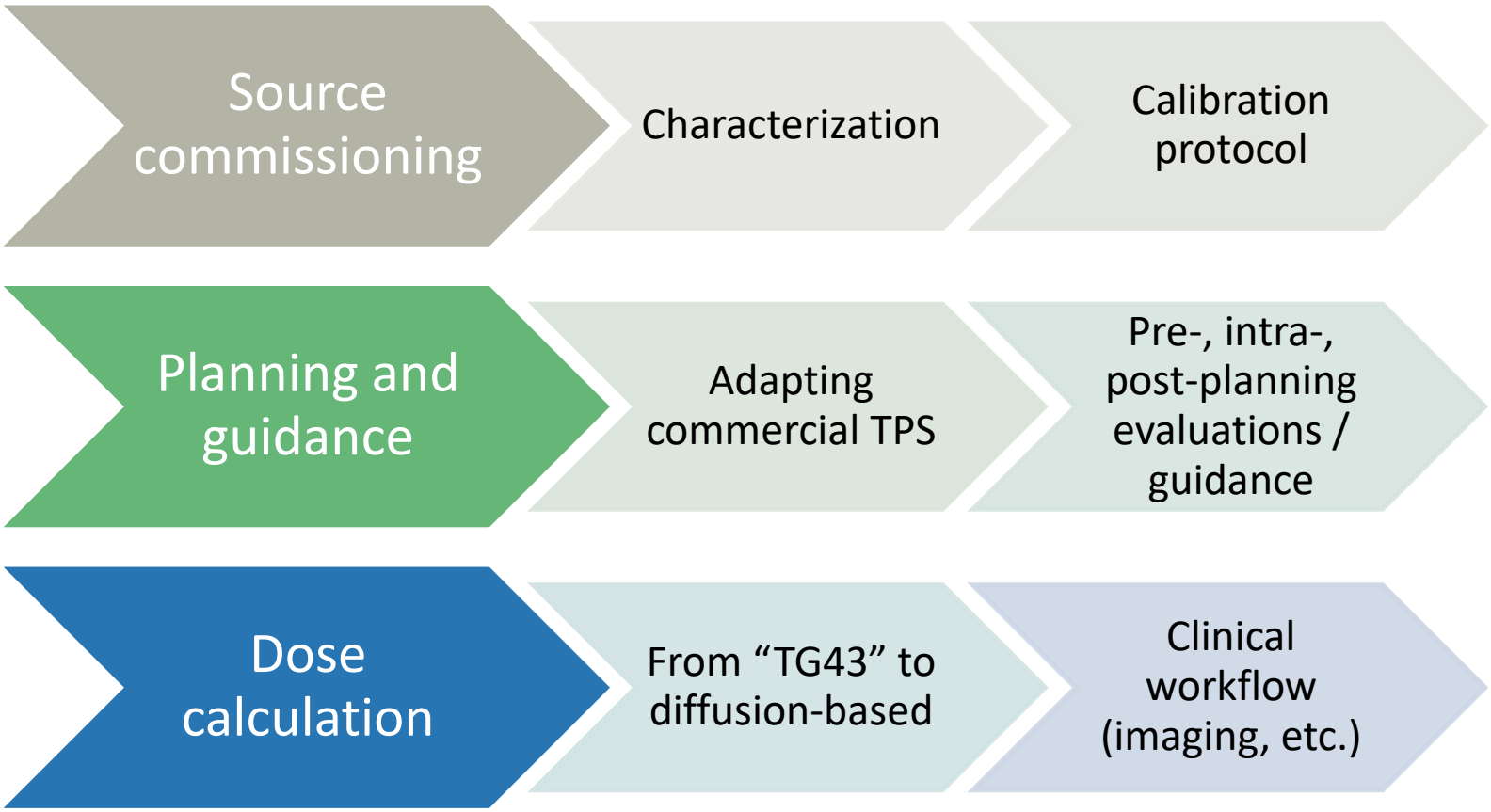
Challenges (known unknowns)

- Unknown diffusion / convection (TAU, McGill/Chum, BGU, U. of Wallangong)
  - Tissue type, vasculature, etc
  - Tumor response while DaRT is implanted
  - In-vivo dosimetry?
- Additional mechanism of tumor cell killing
  - Synergy with immunotherapy
  - Abscopal effect
- Micro / Nano effects
  - Is there a concern about tumor DNAs being shielded by membrane / convective effects?

Challenges (guidance)

- Pre-planning
  - Ordering of sources
  - Planning implantation with radiation oncologist / IR
- Managing possible cold spots inside tumor
  - Image guidance during implantation
  - Evaluation and insertion of additional sources
- Post implantation:
  - Gathering data necessary to evaluate efficacy / safety of DaRT

Roadmap


Source commissioning
Characterization
Calibration protocol
Planning and guidance
Adapting commercial TPS
Pre-, intra-, post-planning evaluations / guidance
Dose calculation
From “TG43” to diffusion-based
Clinical workflow (imaging, etc.)

Conclusion

- Promising initial clinical results
  - Novel device with brachytherapy and nuclear medicine aspects
  - Clinical protocols starting in the US; used clinically elsewhere
- Need a primary standard!
  - How to operate while we don't have one?
- Dose calculation
  - Simplified model developed by BGU/TAU
  - More complex model active area of research

1. Arazi, L., et al., *Treatment of solid tumors by interstitial release of recoiling short-lived alpha emitters.* Phys Med Biol, 2007. **52**(16): p. 5025-42.
2. Arazi, L., et al., *The treatment of solid tumors by alpha emitters released from (224)Ra-loaded sources-internal dosimetry analysis.* Phys Med Biol, 2010. **55**(4): p. 1203-18.
3. Cooks, T., et al., *Interstitial wires releasing diffusing alpha emitters combined with chemotherapy improved local tumor control and survival in squamous cell carcinoma-bearing mice.* Cancer, 2009. **115**(8): p. 1791-801.
4. Cooks, T., et al., *Growth retardation and destruction of experimental squamous cell carcinoma by interstitial radioactive wires releasing diffusing alpha-emitting atoms.* Int J Cancer, 2008. **122**(7): p. 1657-64.
5. Cooks, T., et al., *Local control of lung derived tumors by diffusing alpha-emitting atoms released from intratumoral wires loaded with radium-224.* Int J Radiat Oncol Biol Phys, 2009. **74**(3): p. 966-73.
6. Cooks, T., et al., *Intratumoral 224Ra-loaded wires spread alpha-emitters inside solid human tumors in athymic mice achieving tumor control.* Anticancer Res, 2012. **32**(12): p. 5315-21.