Low-Z linear accelerator targets

Options for image guidance
and dose enhancement in radiotherapy

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Disclosures

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Low-Z linear accelerator targets

1. Underlying physics
2. Beam characteristics
3. Imaging applications
   - Options with an MLC in the imaging beamline
4. Possibilities for therapy
   - Nanoparticle-aided radiotherapy

What is a low-Z target?

- A target with Z≤13, which is low in comparison to conventional tungsten (Z=74) or copper (Z=29) therapy target materials
  - Examples: beryllium, graphite, diamond, aluminum
- Used to recover a significant population of low-energy photons in a linac-generated beam
- Useful for imaging or dose enhancement

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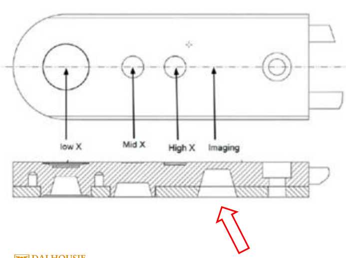
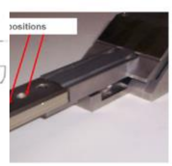
A look at the Truebeam target





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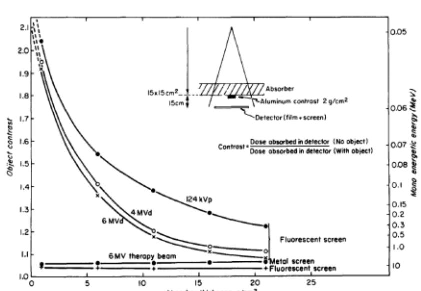
Early days: Galbraith (1989)
Beryllium and graphite targets



D Galbraith, Medical Physics 16 (5): 734–46

Low-Z targets: physical rationale

1. While diagnostic energy bremsstrahlung photons are created in high-Z and low-Z targets, **use of a low-Z target reduces the absorption of low-energy photons within the target** itself.
2. Electron-electron bremsstrahlung is more significant in low-Z targets compared to high-Z targets. **The spectrum produced has a lower peak energy** than electron-nuclear bremsstrahlung [2].
3. With regard to efficiency, while higher-Z targets give a greater yield of bremsstrahlung overall, **over the forward 0-15° angular range**, i.e. that subtended by a typical linac primary collimator in a linac, **the yield is roughly independent with Z.**

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1 (Motz 1955),
[2] (Motz 1955; Podgorsak, Rawlinson, and Johns 1975)
[3] Karzmark, 1998

Three modifications for a low-Z target beam

1. Reduce the Z of the target
2. Remove the flattening filtration
3. Lower the electron energy (optional)

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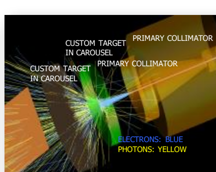
Experimental targets



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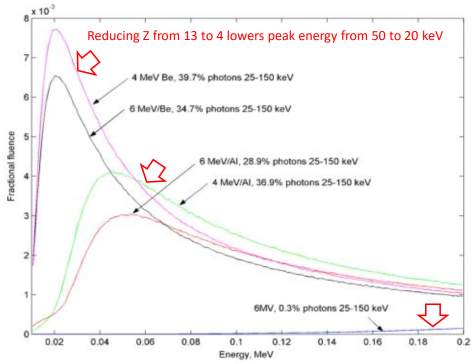
Choice of target material



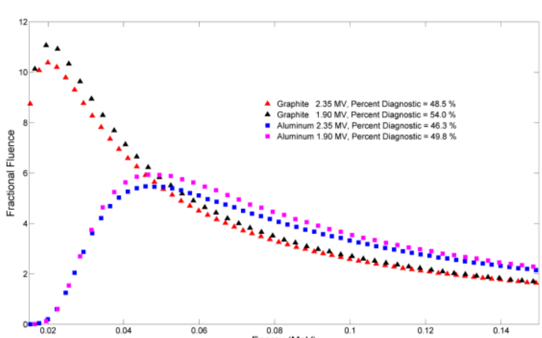
Orton, E J, and J L Robar, Physics in Medicine and Biology 54 (5): 1275–89, 2009.

Target material, thickness and energy

Author	Target thickness and material	Electron energy
Galbraith (Galbraith 1989)	14.2 mm graphite	6 MeV
Tsechanski(Tsechanski et al. 1998)	5 mm aluminum	4.0 MeV
Ostapiak (Ostapiak, O'Brien, and Faddegon 1998)	16.5 mm beryllium, 15.7 mm carbon	6.0 MeV
Flampouri (Flampouri et al. 2005)	6 mm aluminum	4 MeV
Faddegon (Faddegon et al. 2008)	13.2 mm graphite	4.2 MeV
Roberts (Roberts et al. 2008)	20 mm carbon (28%) nickel exit window (71%)	5.6 MeV (mean)
Orton (Orton and Robar 2009)	10 mm aluminum	6.0 MeV
Robar (Robar, Connell, Huang, and Kelly 2009a)	6.7 mm and 10.0 mm aluminum	3.5 and 7.0 MeV
Sawkey (Sawkey et al. 2010)	13.2 mm graphite, 13.2 mm sintered diamond	4.6 MeV and 6.4 MeV
Roberts (Roberts et al. 2011)	20 mm carbon (28%) nickel exit window (71%)	5.6 MeV (mean)
Fast (Fast et al. 2012)	13.2 mm graphite	4.2 MeV
Robar (Robar et al. 2012)	7.6 mm graphite	2.35 MeV
Parsons (Parsons and Robar 2012a)	7.6 mm carbon, 6.7 mm aluminum	1.85 to 2.35 MeV

DALHOUSIE UNIVERSITY   Carbon   Aluminum   Beryllium

Lowering the electron beam energy



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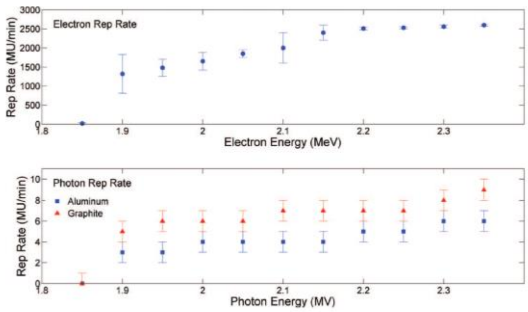
Parsons, David, and James L Robar, Medical Physics 39 (7): 4568–11, 2012.

Lowering the electron beam energy… there are limits



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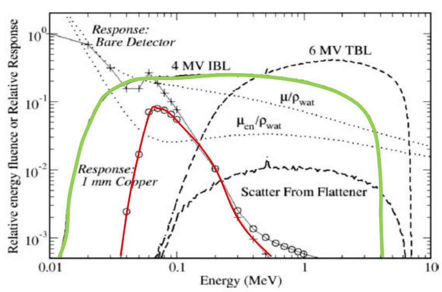
Parsons and Robar, Medical Physics 39 (7): 4568–11, 2012.

Siemens low-Z target



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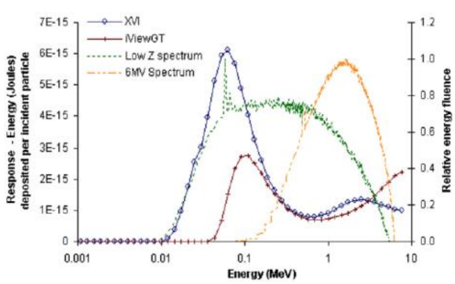
Faddegon *et al*, Medical Physics 35 (12): 5777–10.

Elekta low-Z target

… had a nickel vacuum window – this was the source of ~70% of the photons in the beamline!



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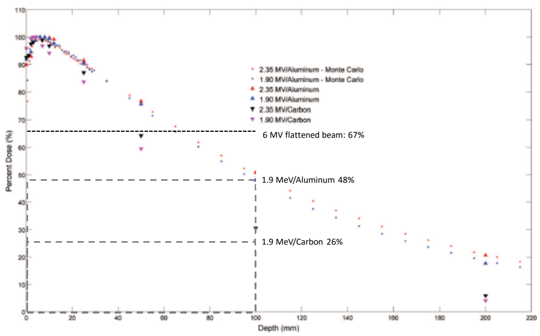
Roberts *et al*, Physics in Medicine and Biology 53 (22): 6305–19

PDDs examples: 1.9 to 2.35 MeV on Al and C



Low-Z targets
Imaging applications

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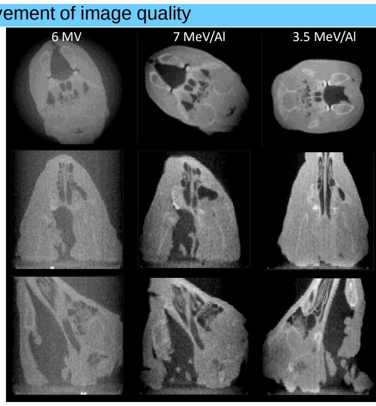
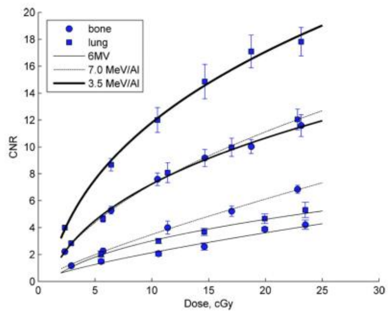
Improvement of image quality

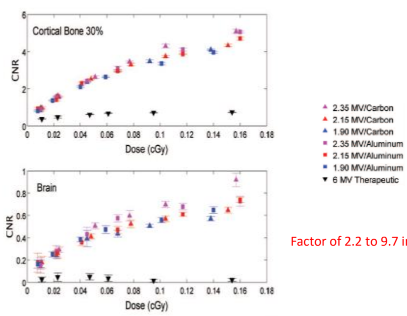


CNR versus dose compared to 6MV



Robar et al, Med Phys 36(9), 2009

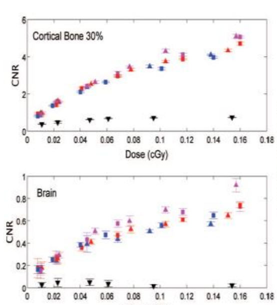
Improvement of CNR – BEV imaging

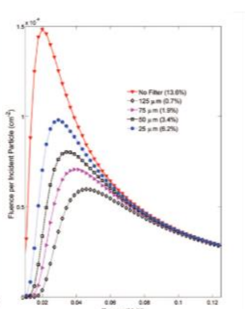


Factor of 2.2 to 9.7 improvement of CNR

Parsons and Robar, Medical Physics 39 (7): 4568–11.

Improvement of CNR – BEV imaging

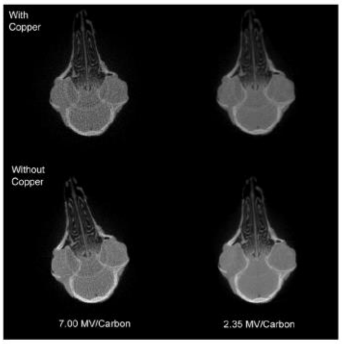




Thin layer of Cu on exit side of target.

Parsons and Robar, Medical Physics 39 (7): 4568–11.

Detector considerations – remove Cu layer



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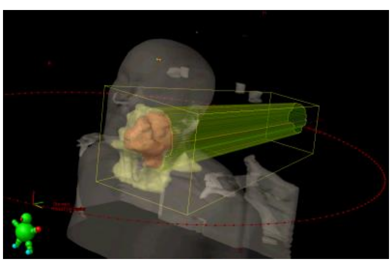
Experimental imaging with low-Z beams

Volume Of Interest CBCT imaging



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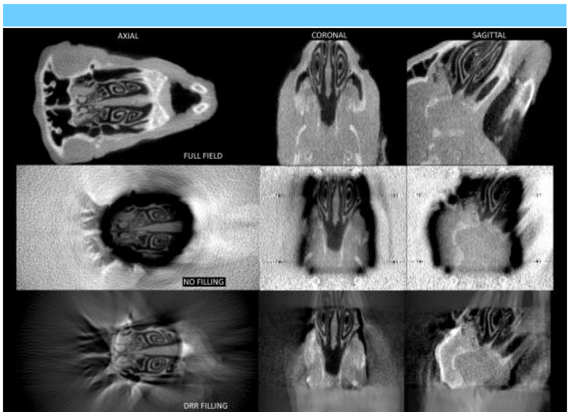
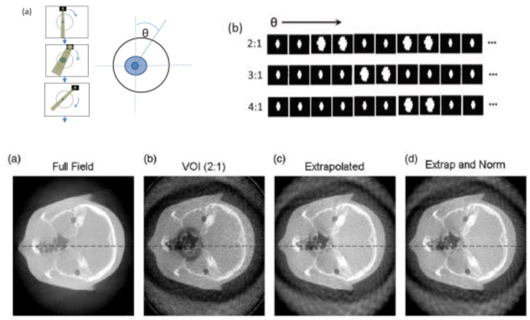
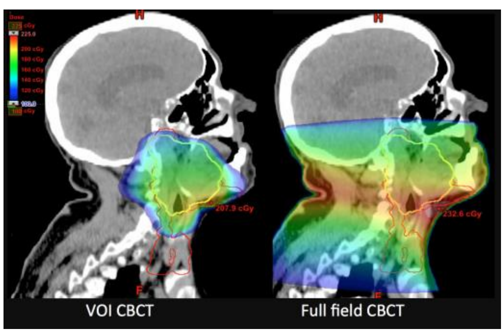


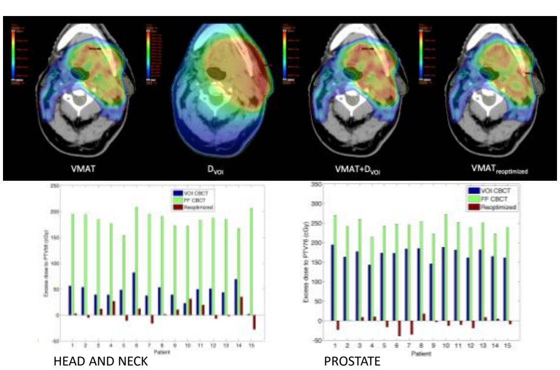
Spatially vary CNR with dynamic MLC sequences



Commission Eclipse with low-Z beam data



Compensate for imaging dose in treatment at planning time



Experimental high-Z / low-Z switching

- Prototype located in carousel of Varian Clinac platform
- ~ 250 ms switching between W/Cu and graphite targets
- Imaging application: periodic BEV imaging at high quality
- Imaging application – intrafractional BEV
- Therapy application: combination high-Z / low-Z treatment

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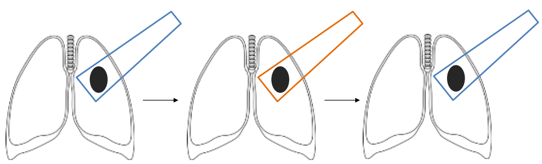
Intra-fractional imaging paradigm



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Low-Z targets
Therapeutic applications

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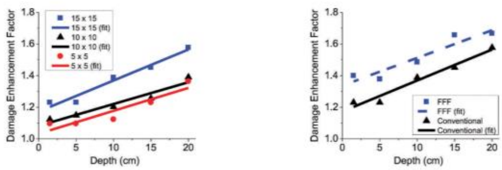
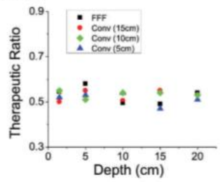
Au GNPs / HeLa cells with ɣ-H2AX staining





✓ Compelling evidence that photon energy will affect GNP dose enhancement *in vitro*

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Berbeco *et al*, Radiation Research 178, 2012

RESEARCH Open Access

AGuIX nanoparticles as a promising platform for image-guided radiation therapy

Alexandre Detappe[1,2*], Sijumon Kunjachan[1], Joerg Rottmann[1], James Robar[3], Panagiotis Tsiamas[1], Houari Korideck[1], Olivier Tillement[2] and Ross Berbeco[1*]

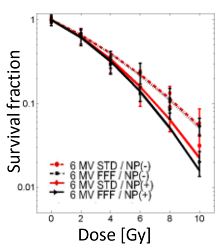

Table 1 Dose enhancement effect in terms of DEF, $DEF_{20\%}$ and SER_{4Gy} for Panc1 cells incubated with 0.5 mM AGuIX

Irradiation					
Preparation	220 kVp			6 MV FFF	6 MV STD
	AGuIX no incubation	AGuIX 1h incubation washing	AGuIX 1 h incubation unwashing	AGuIX 1 h incubation unwashing	
DEF	1.09	1.17	1.46	1.23	1.19
DEF 20 %	1.01	1.1	1.31	1.3	1.23
Sensitivity (SER4Gy)	1.05	1.19	1.41	1.2	1.12
p value	0.131	0.038	***	0.009	0.011

p values were calculated using a Kruskal Wallis to test the effect of the nanoparticles with the control

*** $p < 0.001$

6 MV FFF beam more effective at cell kill compared to standard 6 MV beam (p=0.014 Wilcoxon)

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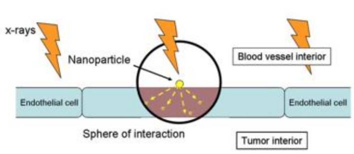
Low-Z targets for endothelial dose enhancement



$$\frac{N(x)}{N_0} = 1 - e^{-\left(\frac{\mu_{PE}}{\rho}\right)_{Au} \cdot \rho_{AuNP} \cdot d_{AuNP}} \approx \left(\frac{\mu_{PE}}{\rho}\right)_{Au} \cdot \rho_{AuNP} \cdot d_{AuNP} \quad \text{(Eq. 1)}$$

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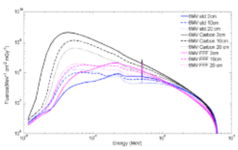
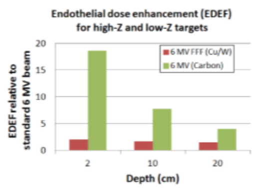
Berbeco *et al*, Int J Radiat Oncol Biol Phys, 81(1), 2011

Endothelial dose enhancement





Compared to a standard 6 MV beam, 6MV/Carbon provides

- **18.6 x** dose at d=2 cm
- **7.7 x** dose at d=10 cm
- **4.0 x** dose at d= 20 cm

6 MV Cu/W FFF beam provides 1.5 to 2.0 x dose

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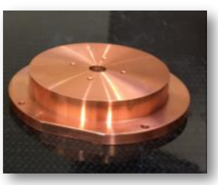
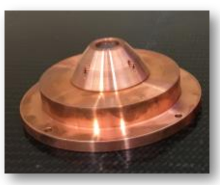
Berbeco *et al*, Med. Phys. 43(1), 2016

To do NP dose enhancement experiments, we need sufficient dose rate!



Mark I



Mark II

A new experimental low-Z target for Truebeam

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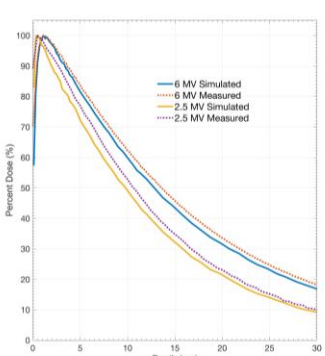
PDDs from new targets



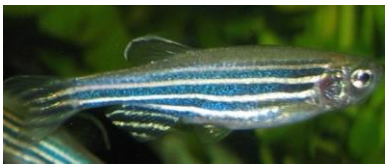
High dose rate possible!

Dose rate is ~67% of that for 6MV clinical beam @ dmax

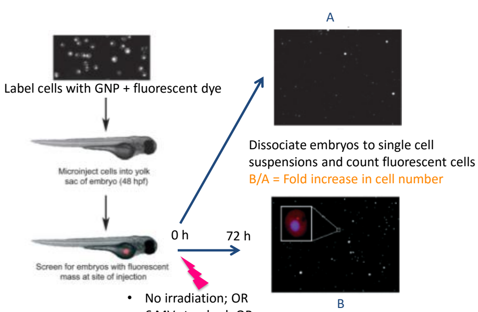
Zebrafish as a model organism

- *Danio* rerio is a tropical freshwater fish that has emerged as a useful model organism for studying vertebrate development and human cancers.

- Fully sequenced genome
- Embryos are produced in large numbers
- Develop rapidly outside the mother
- Optically clear
- Manny useful transgenic lines.
- Established protocols for xenografting cancer cells into zebrafish embryos and assessing cell migration and proliferation



CURRENT WORK Experiment 1: xenograft



- No irradiation; OR
- 6 MV standard; OR
- 6 MV low-Z target

Modified from Corkery *et al.*, *2011*

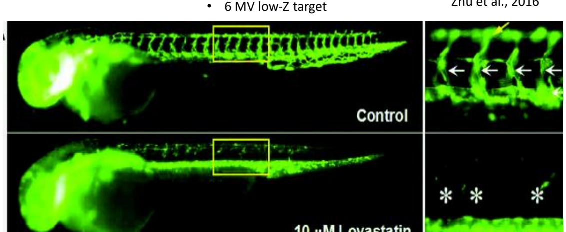
CURRENT WORK Experiment 2: GNPs targeting endothelial cells

Inject GNP IV → treatment → confocal microscopy

- No irradiation; OR
- 6 MV standard; OR
- 6 MV low-Z target

TG(fli1: EGFP)

Zhu et al., 2016



Summary

- Low-Z target beams can contain up to 50% of photons in the diagnostic energy range
- Imaging
  - Factor of 2-9 increase in CNR per unit dose compared to 6MV
  - New options to localize dose using MLC
  - Switching target may allow rapid, high-quality BEV imaging
- Therapy
  - Compelling evidence that GNP-aided radiotherapy will be more effective with low-Z target beams
  - Much more work to do here, but we have the tools

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