U O W

Geant4 Simulation Study on Nanoparticle Enhanced Microbeam Radiation Therapy

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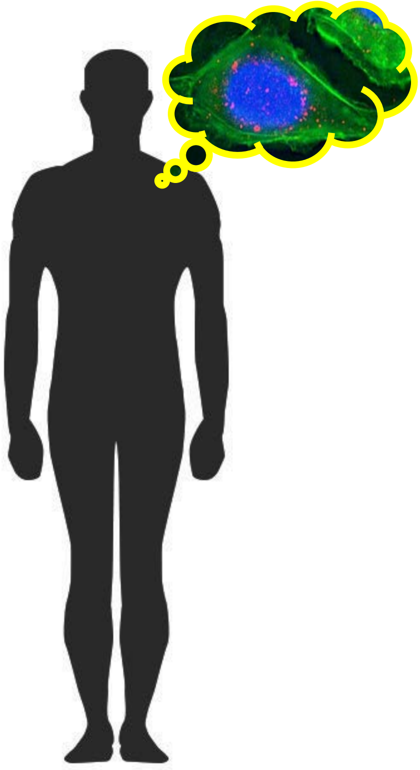
Nanoparticles for Radiotherapy?

- Nanoparticles are smaller than the size of cell structures:

- Nanomedicine: uses precisely engineered nano-materials developed for novel therapeutic and diagnostic modalities.



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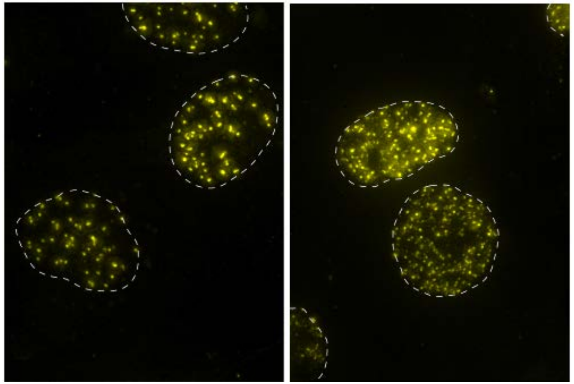
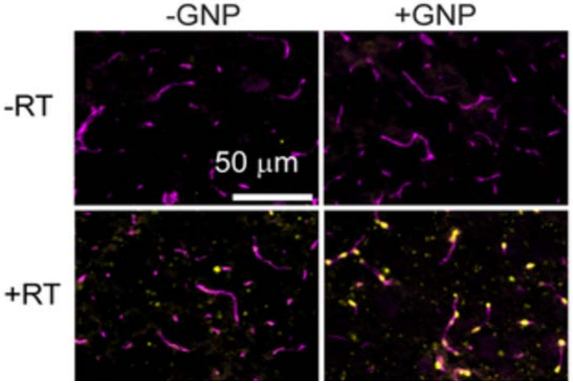
Nanoparticles for Radiotherapy?

- Nanoparticles are shown to produce additional DNA damage in the same radiation field, particularly for kV RT:



***in vitro* study:**
DSBs in glioblastoma cells without (right) and with GNPs (left) following a 4 Gy 150 kVp X-ray treatment.



***in vivo* study:**
Mouse brain tissues irradiated immediately following GNP injection leads to more DNA DSBs compared to those receiving RT alone

Joh et al. 2013, *Selective Targeting of Brain Tumors with Gold Nanoparticle-Induced Radiosensitization*. PLOS ONE 8(4): e62425.

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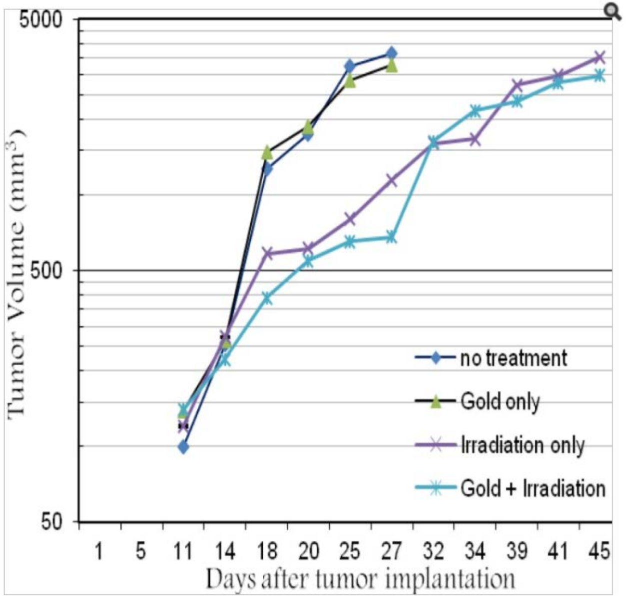
Mechanisms for Nanoparticle-Enhanced Radiation Damage



18 MV treatment of melanoma grown in mice (Anjidan *et al* 2013)

- Beam energy:
  - *in vivo* and *in vitro* experiments have shown significant NP radio-sensitization with kV radiation (Hainfeld et al 2004, 2008, 2013, Chattopadhyay et al 2012).
  - MV experiments have shown: NP-enhancement and no NP-enhancement (Anijdan *et al* 2013, Wolfe *et al* 2015)

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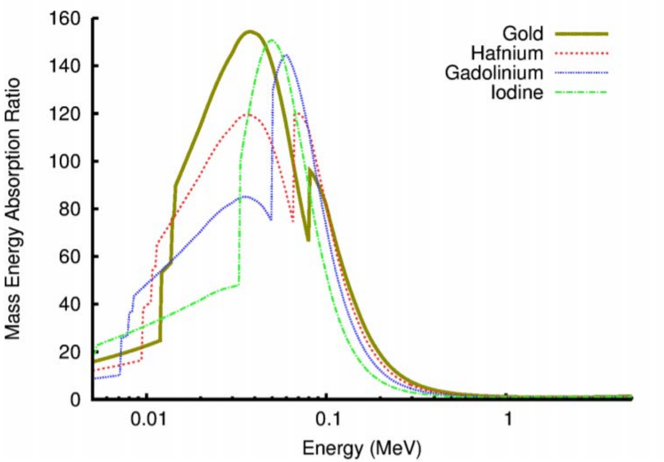
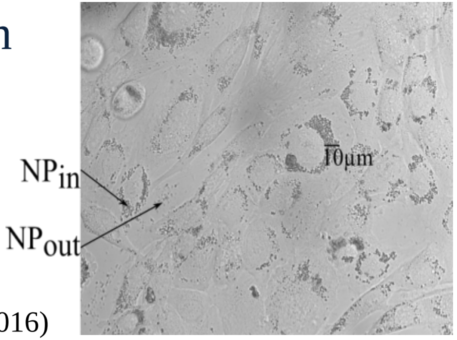
Mechanisms for Nanoparticle-Enhanced Radiation Damage

- High-Z: photon attenuation relative to water.
- Tumour uptake of NPs and localization relative to cellular DNA (Brun *et al* 2009, McKinnon *et al* 2016).
- AuNP size and concentration (McKinnon *et al* 2016, Butterworth *et al* 2012, Rahman *et al* 2009).



McMahon, Paganetti, Prise, 2015



(McKinnon *et al* 2016)

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Simulating Nanoparticles: Microscopic scale?

- Models based on track structures have begun to predict trends in NP enhancement from single or multiple NPs (Geant4-DNA).

- In order to relate microscopic and macroscopic NP enhancement trends, condensed history models are often adopted (Martinez *et al. 2011, McKinnon et al. 2016)*
  - Advantages include faster computation times and capability to accommodate more complex geometry.
  - Often with condensed history models, NP enhancement from a *nano-sized* single NP is not observed.
  - Approximations are made for NP-loaded water or tissue material.

- How accurately can these models predict trends in microscopic dose enhancement?

Study of the effect of ceramic Ta_2O_5 nanoparticle distribution on cellular dose enhancement in a kilovoltage photon field

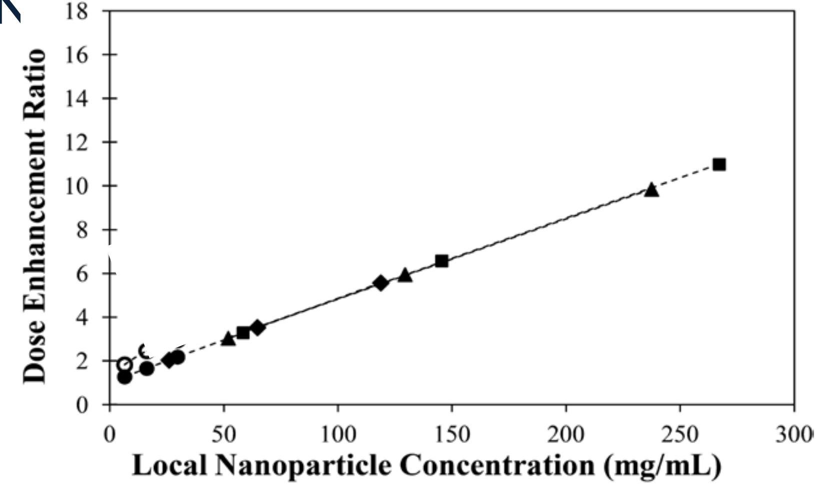
Sally McKinnon[1], Elette Engels[1], Moeava Tehei[1,2,3], Konstantin Konstantinov[2,4], Stéphanie Corde[1,5], Sianne Oktaria[1,2,3], Sebastien Incerti[6,7], Michael Lerch[1,2], Anatoly Rosenfeld[1,2], Susanna Guatelli[1,2]

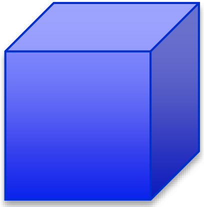
Physica Medica 2016
(DOI:
tp://dx.doi.org/10.1016/j.ejmp.2016.09.006)

Predicted Dose Enhancement with increasing NP concentration for N

Penelope Physics, G4v10.1
Auger electrons included
Clinical 150 kVp X-ray beam

$$DER = \frac{D_{NP}}{D_W}$$





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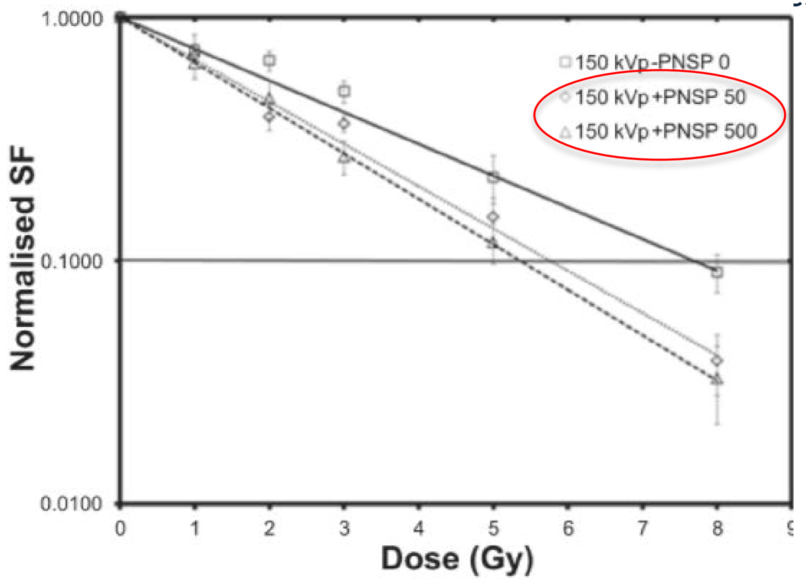
Actual Nanoparticle Dose Enhancement

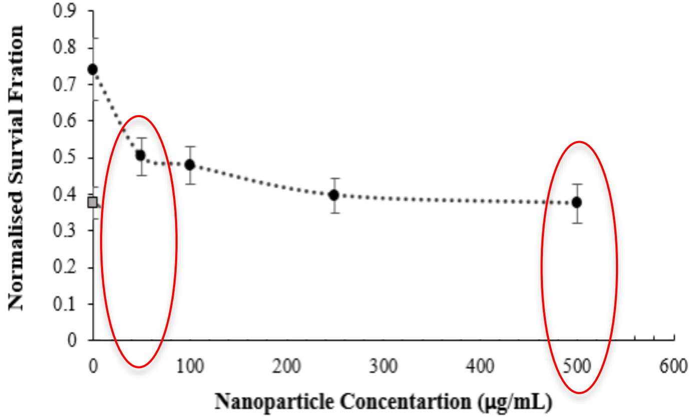
R. Brown et al. 2017: at 2 Gy:

My Result

Nanostructures, concentrations and energies: an ideal equation to extend
with Ta_2O_5 NPs therapeutic efficiency on radioresistant 9L tumor ce
nanostructured particles

9L gliosarcoma





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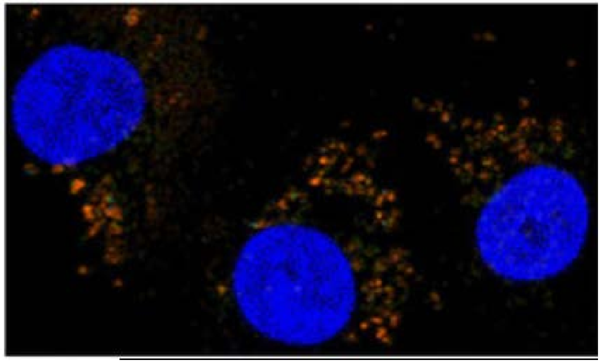
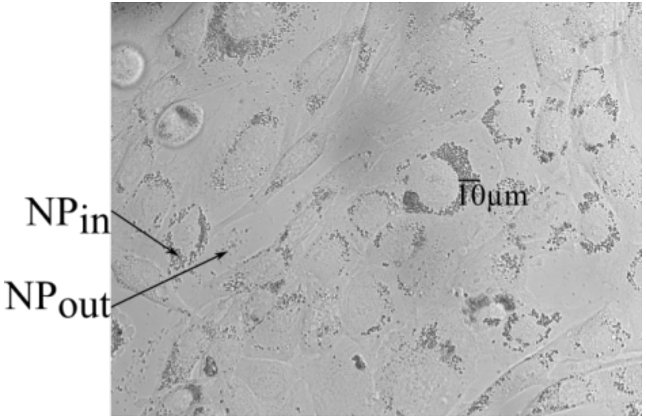
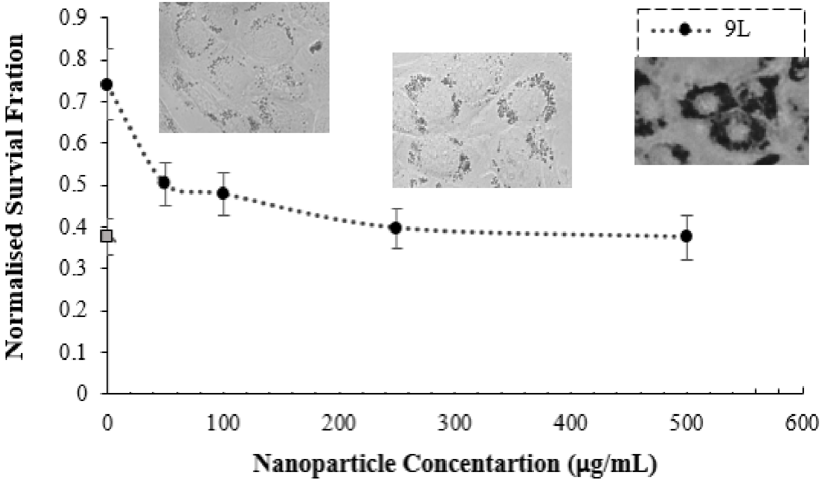
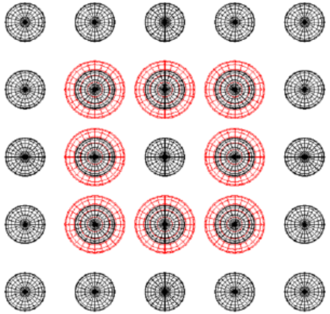
Simulating Nanoparticles: Considerations!

- Nanoparticle are never localized homogeneously.
- Localization and concentration begins to play a large role in the ability of the simulation to predict NP enhancement.
- Clusters of NPs can vary depending on the cell, NP and concentration.

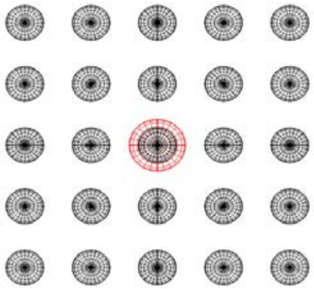








Penelope Physics, G4v10.1
Auger electrons included,
150 kVp beam



Study of the effect of ceramic Ta_2O_5 nanoparticle distribution on cellular dose enhancement in a kilovoltage photon field

Sally McKinnon[1], Elette Engels[1], Moeava Tehei[1, 2, 3], Konstantin Konstantinov[2,4], Stéphanie Corde[1,5], Sianne Oktaria[1,2,3], Sebastien Incerti[6,7], Michael Lerch[1, 2], Anatoly Rosenfeld[1, 2], Susanna Guatelli[1, 2]

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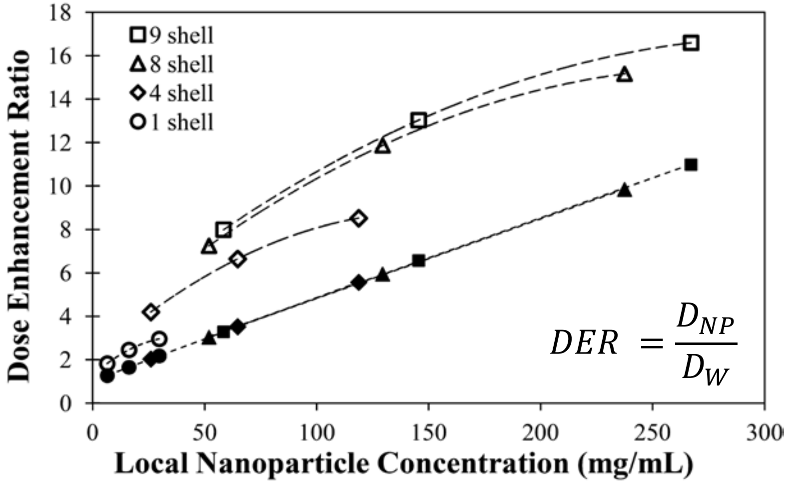
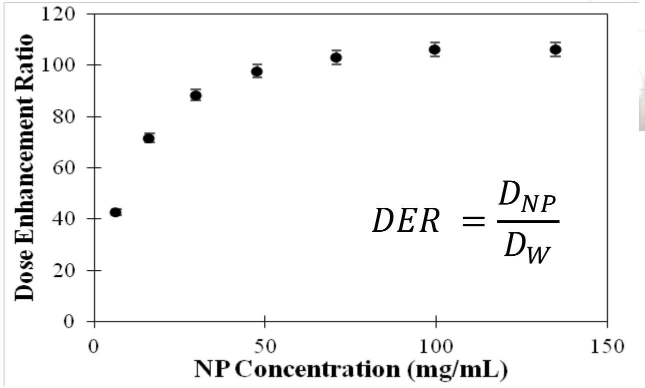
Physica Medica 2016
(DOI:
tp://dx.doi.org/10.1016/j.ejmp.2
016.09.006)

New Predicted Dose Enhancement:





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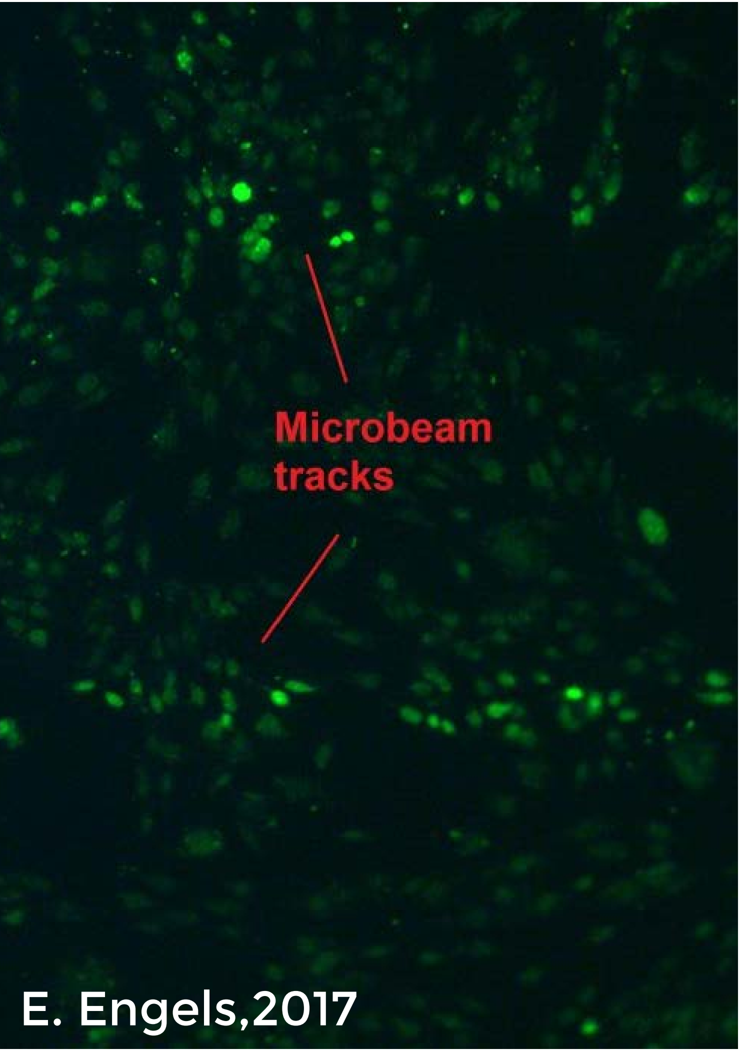
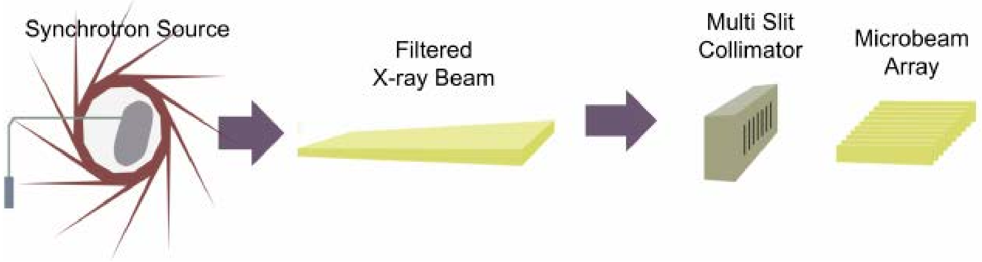


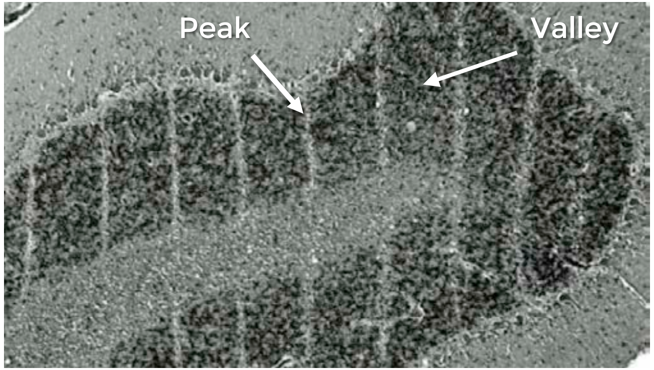
Clinical Outlooks for kV Radiation?

- kV radiation is used mostly for melanomas and cancers close to the surface of the skin.
- Can the benefit of NPs in the kV field be utilised therefore?

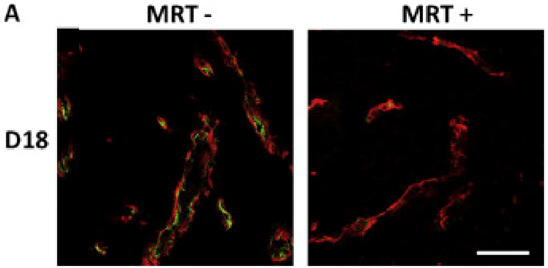
- Microbeam Radiation Therapy (MRT)
  - Administers devastating doses in order of 100s of Gy to the tumour.
  - The dose field is spatially fractionated



Why is MRT Effective?



Decrease in 9GLS tumor blood volume, vessel density and endothelial denudation



- High peak doses administered at high dose rates (40-2000 Gy/s), while low valley doses spare tissue.
- Several mechanisms have been suggested:
  - cytotoxic effects on tumor cells
  - a decrease in blood vessel number leading to decreased perfusion and tumor hypoxia
  - Modulation of the immune system
  - communication between lethally irradiated cells in the microbeam path and valley cells

Bouchet et al. Physica Medica 31 (2015) 634-641
Bouchet et al. International Journal of Radiation Oncology (2016)

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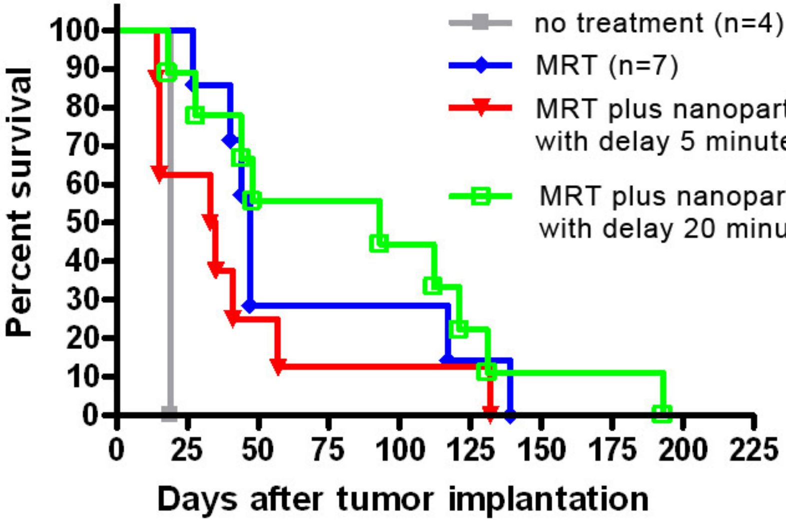
Nanoparticles in MRT

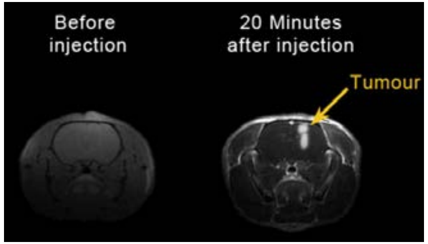
- Is there enhancement?

- Gadolinium-based nanoparticles (Le Duc *et al.* 2011):



in vivo increase in rodent survival observed with NPs present!

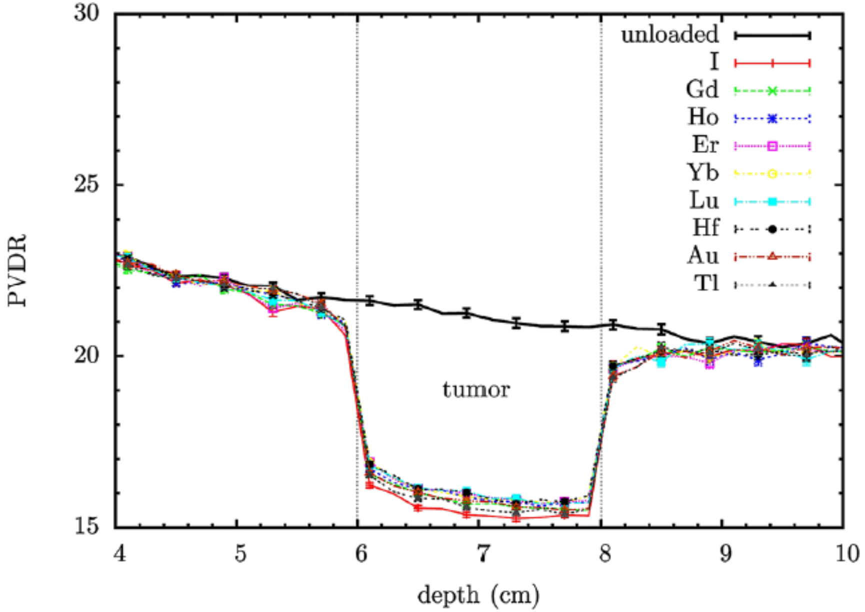
Both valley and peak dose is being enhanced in the kV field



Le Duc, ACS nano 5, 9566-74 (2011)

MRT and Nanoparticle Simulations

- NP-Loaded material with high-Z particles for MRT:



Martinez and Prezado, Medical Physics **38**, 4430 (2011);

- *Peak-to-valley dose ratio (PVDR) was considered.*
- *Small PVDR: valley dose → peak dose.*

- However, rarely NPs distribute homogeneously amongst and inside cells…
- **What implications do NP clusters have on NP-enhanced MRT?**

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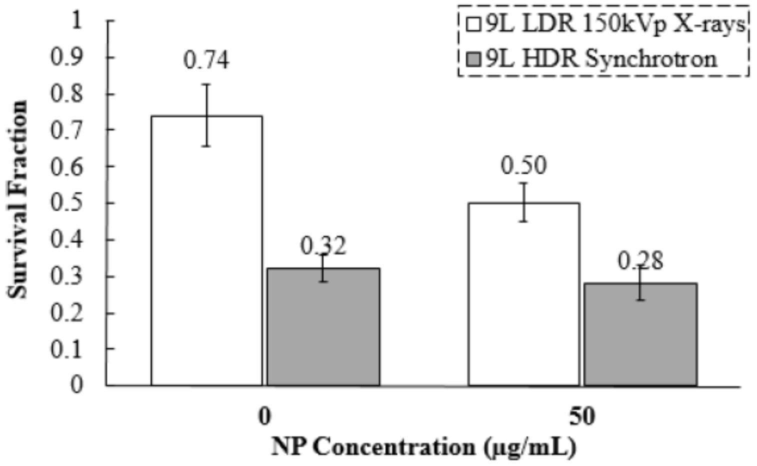
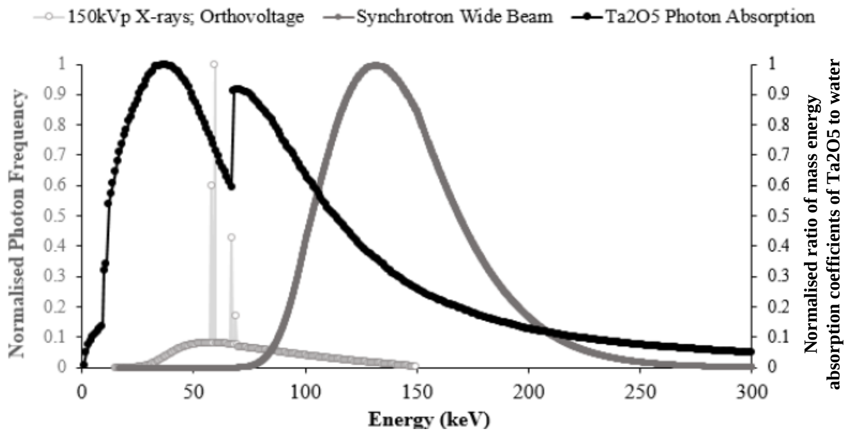
Experimental Results – Synchrotron Broad Beam

- **Tantalum Oxide Nanoparticles in Synchrotron Broad Beam**





Engels et al. Journal of Physics: Conference Series 777 (2017) 012011

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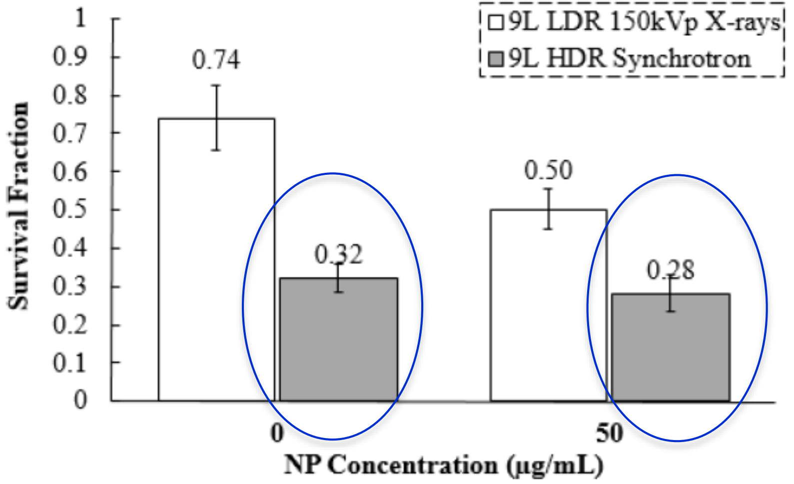
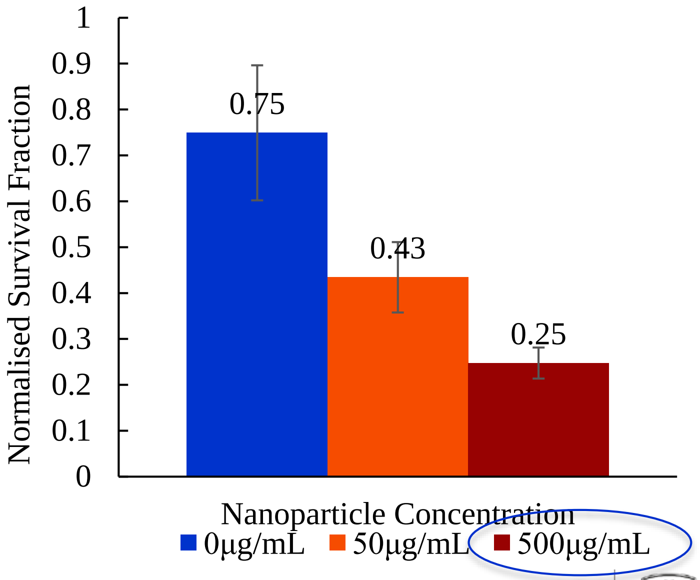
Experimental Results - MRT

Dose: 2 Gy
Synchrotron Energy: 90 keV



Valley Dose: 0.4 Gy
Energy: 90 keV



Engels et al. Journal of Physics: Conference Series 777 (2017) 012011
Engels et al. Physica Medica 32 (2016) 1852–1861

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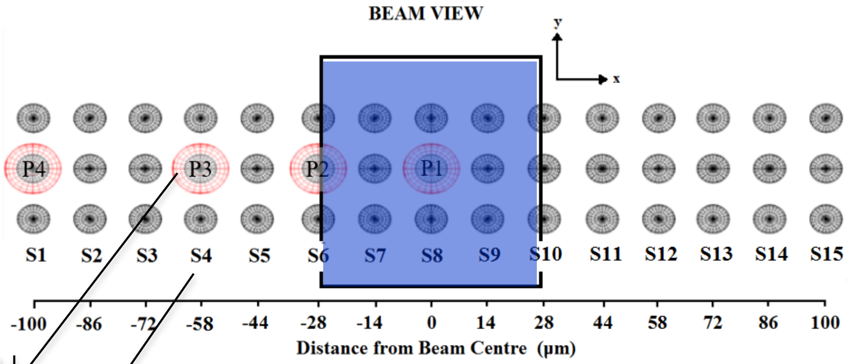
Optimizing dose enhancement with Ta_2O_5 nanoparticles for synchrotron microbeam activated radiation therapy

Elette Engels[1], Stéphanie Corde[1,5] Sally McKinnon[1], Konstantin Konstantinov[2,4], Sébastien Incerti[6,7], Anatoly Rosenfeld[1,2], Moeava Tehei[1,2,3], Michael Lerch[1,2], Susanna Guatelli[1,2].

Penelope Physics,
Auger electrons modelled
G4v10.1



Nanoparticle clusters in various locations

Sensitive volumes (nuclei) grouped as sections (S1-S15) at certain positions

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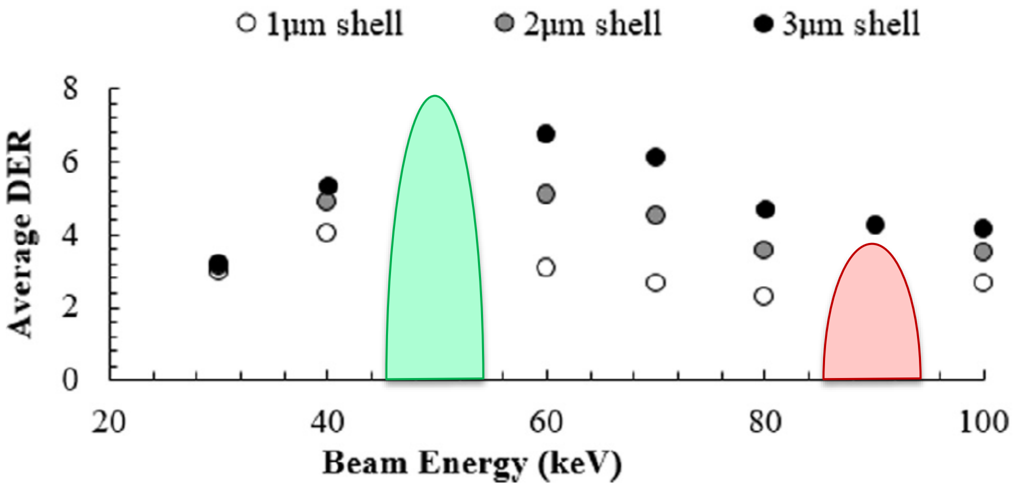
The Broad Beam Case:

- Why the lack of NP-cluster enhancement?
- Follows with the maximum in mass energy absorption coefficient

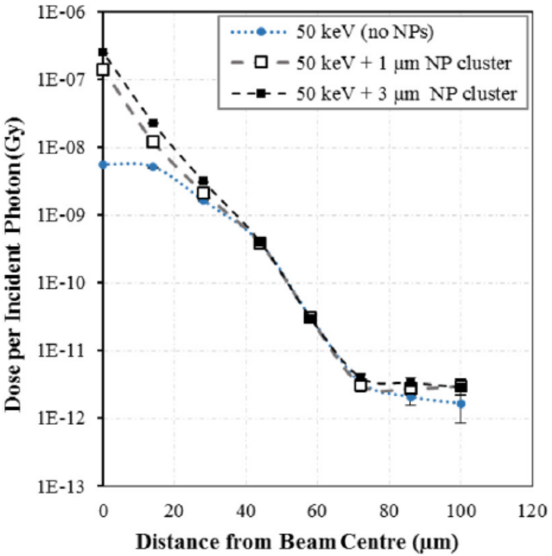


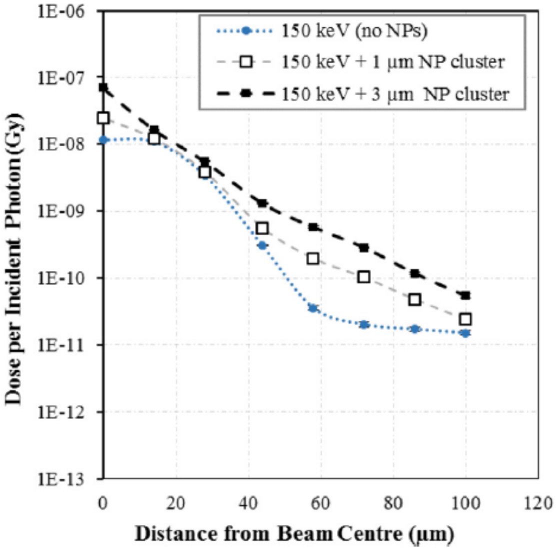
In the peak region or broad beam equivalent

Engels et al. Physica Medica 32 (2016) 1852–1861

Nanoparticle Clusters in the Peak Region

- Energy Dependence





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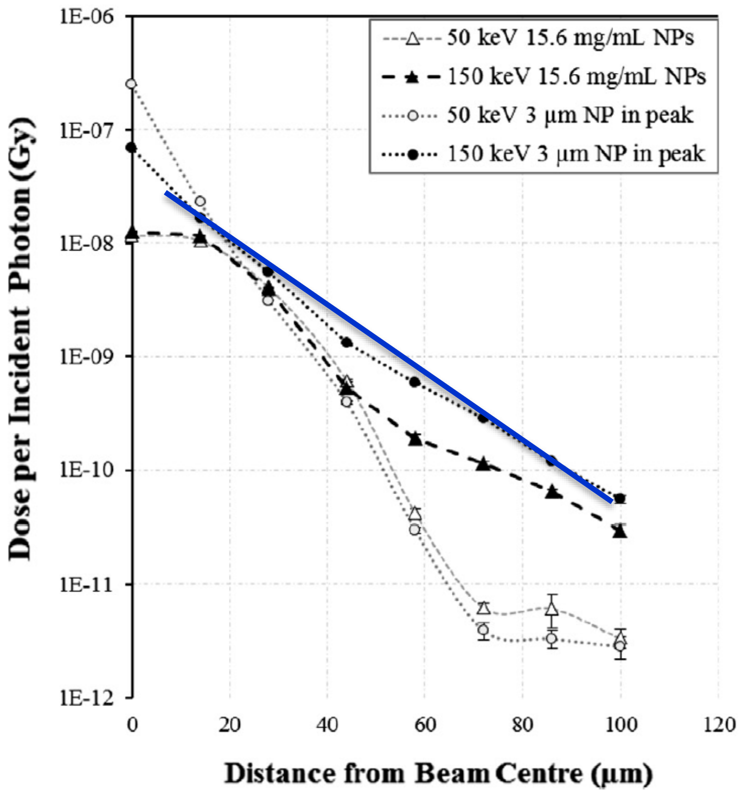
Nanoparticle Clusters in the Peak Region vs NP-loaded water

- Energy Dependence
  - Secondary electron range at high energies is enough to reach the valley - again!
  - Low energy with NP-loaded material shows little overall enhancement

- Any benefit to low energy MRT?



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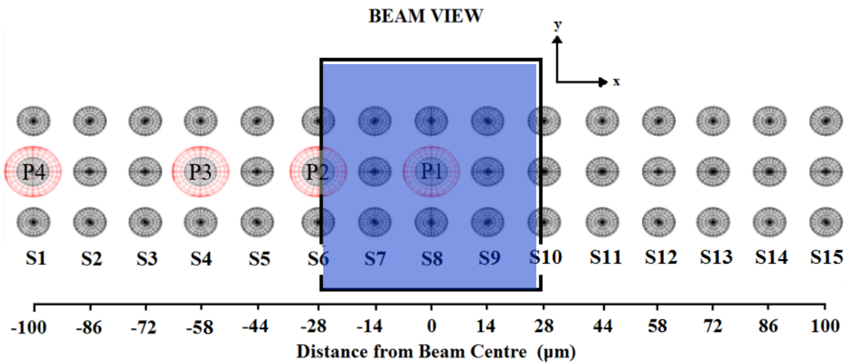
Low Energy MRT?

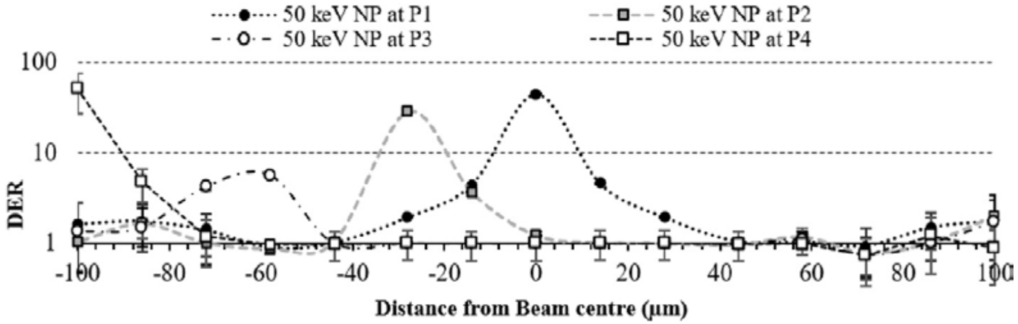
Lets look at more nanoparticle cluster.

- These “cells” benefit from the low energy photons that cause significant NP-cluster enhancements

- With low energy MRT, we now have **selective** NP enhancement to cells that can take up more nanoparticles!

  - tumour cell types





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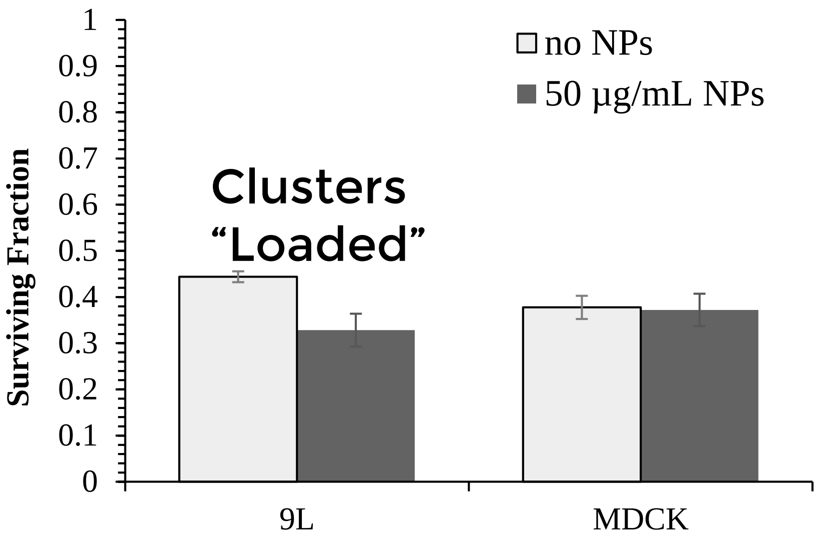
Does this agree Experimentally?

- **MRT:**
- **42 keV**
- **50/400** µm configuration
- 50 µg/mL



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Summary and Future Directions

- NPs have the ability to increase localised tumour dose
- Simulating the dose distribution in any field must model realistic NP configuration and concentration.

- We are now trialling new nanoparticles for NP-enhanced image-guided MRT both *in vitro* and *in vivo.*
- We begin *in vivo* experiments at the Australian Synchrotron.

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Thank you!

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Dr Stéphanie Corde
Dr Konstantin Konstantinov
Dr Sianne Oktaria
Dr Nan Li

<u>Co-collaborators:</u>
Dr Jeremy Davis
Dr Peter Lazarakis
Dr Sally McKinnon
Matthew Westlake
Nathan Thorpe
Dr Andrew Stevenson
Andrew Dipuglia
Marjorie McDonald
Matthew Cameron
Dr Sébastien Incerti
Lee Taylor
Kathrin Bogusz

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