RBE and DNA damage variation along monoenergetic and modulated Bragg peaks of a 62MeV therapeutic proton beam

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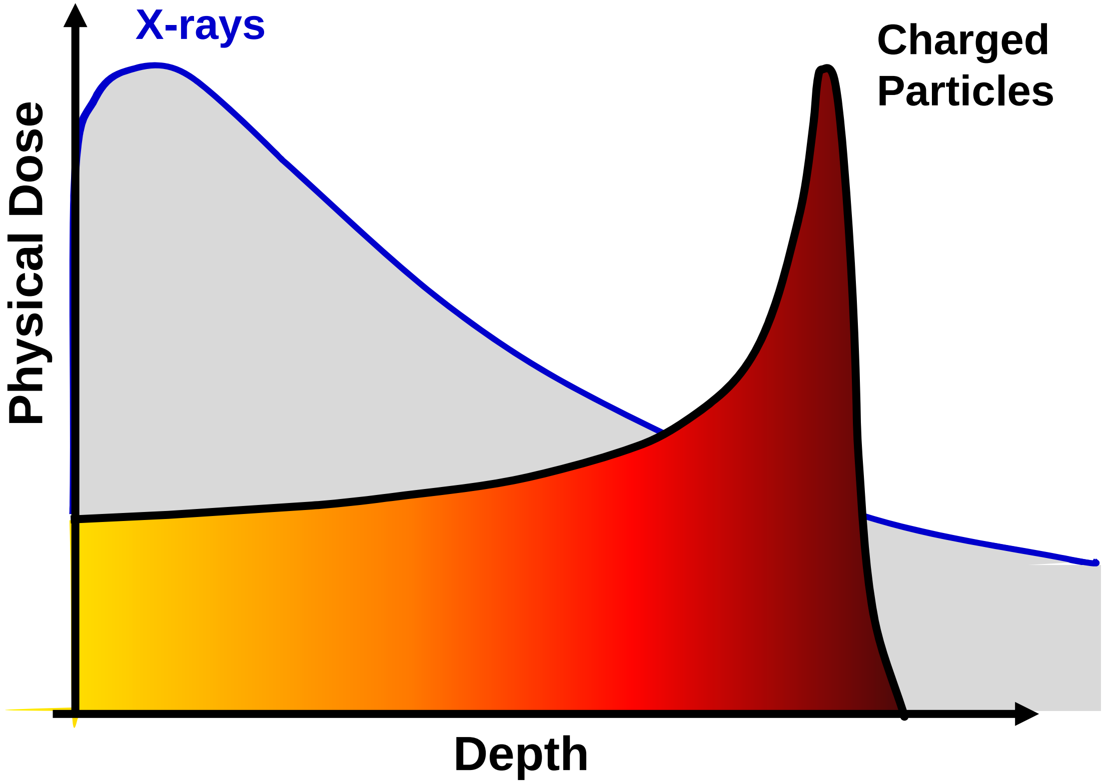
Background-1

Accelerated charged particles are being increasingly used in cancer treatment

- Inverse energy deposition → Selective dose localization
- Elevated RBE for cell killing → Improved tumour control



The Bragg curve does not represent the biological damage along the particle path since biological effects are influenced by the track structures of both primary and secondary particles.

Background-2

- A range of experimental studies *in vitro* and *in vivo* have been reported
- Average value at mid-SOBP over all dose levels of 1.2, ranging from 0.9 to 2.1.
- Studies using human cells show significantly lower RBE values compared with other cells owing to higher α/β ratios.
- The average RBE value at mid-SOBP in vivo is 1.1, ranging from 0.7 to 1.6.
- The majority of RBE experiments have used *in vitro* systems and V79 cells with a low α/β ratio, whereas most of the *in vivo* studies were performed in early-reacting tissues with a high α/β ratio.

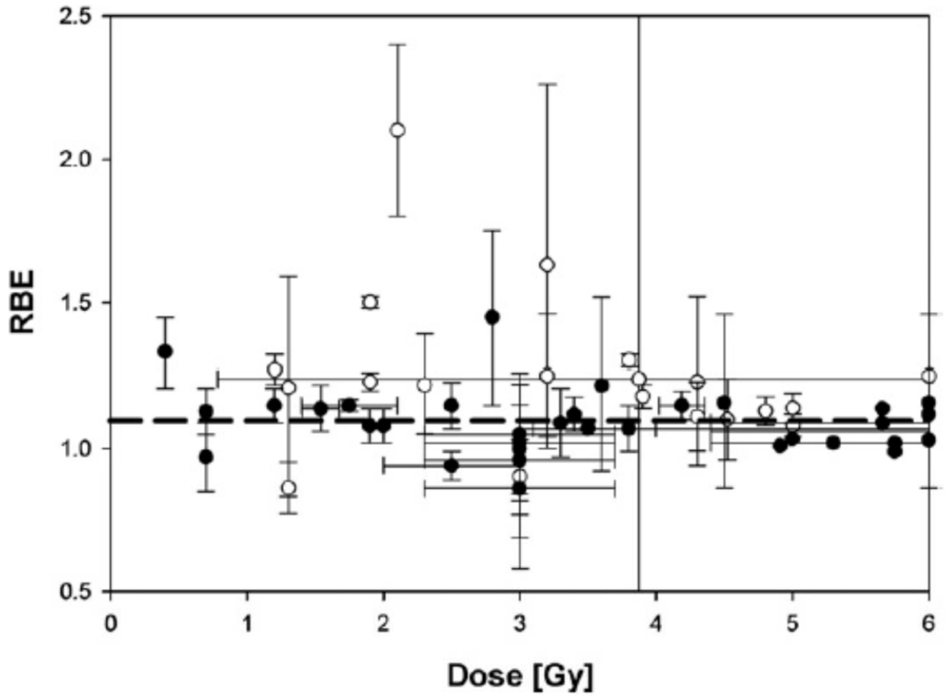


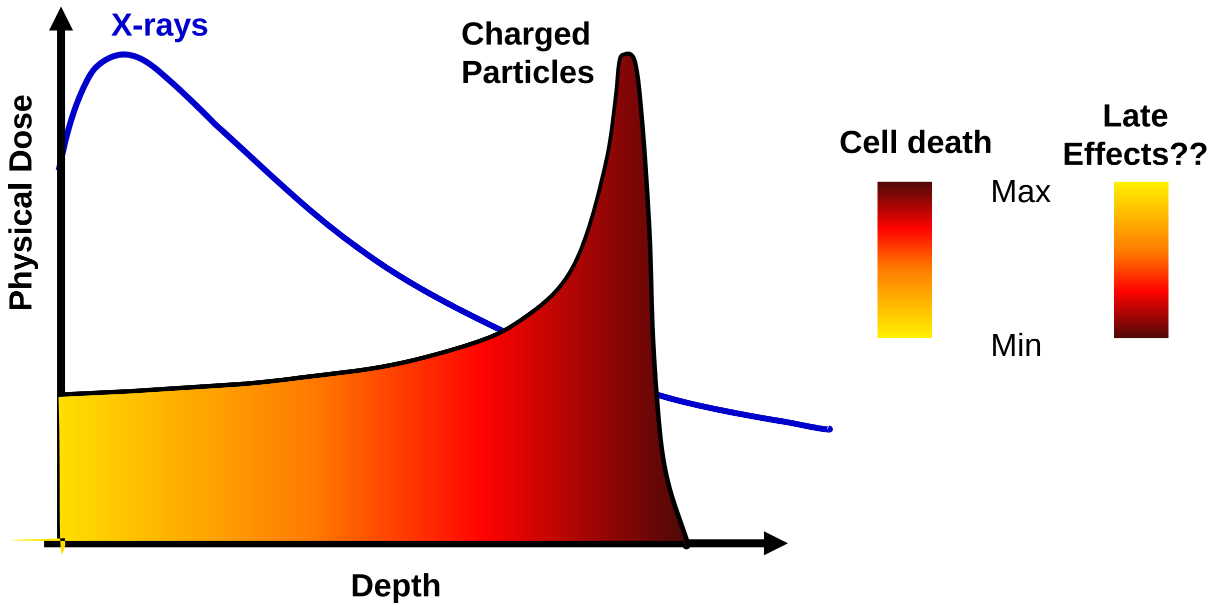
Figure 1 Experimental proton relative biological effectiveness (RBE) values (relative to ^{60}Co) as a function of dose/fraction for cell inactivation measured in vitro (open circles) and in vivo (closed circles). The thick dashed line illustrates an RBE of 1.1. Data taken from Paganetti et al.[15]

Paganetti and van Luijk, 2013, Sem Rad Oncol 23, 77-87

Long term effects

- **Ion beams are not only more efficient at cell killing but may also cause long-term effects such as mutation, transformation and carcinogenesis** *(e.g. Newhauser and Durante, Assessing the risk of second malignancies after modern radiotherapy, Nature vol. 11, 438-448, 2011)*

- **Sub-lethal exposure to charged particles appears very effective at causing *in vitro* stress-induced premature senescence in normal cells, potentially leading *in vivo* to normal tissue complications, organ failure (e.g. cardiovascular damage) and other non-cancer late effects** *(Ottolenghi et al, The risks to healthy tissues from the use of existing and emerging techniques for radiation therapy, Radiat. Prot. Dosim. Vol.143,533–535, 2011)*



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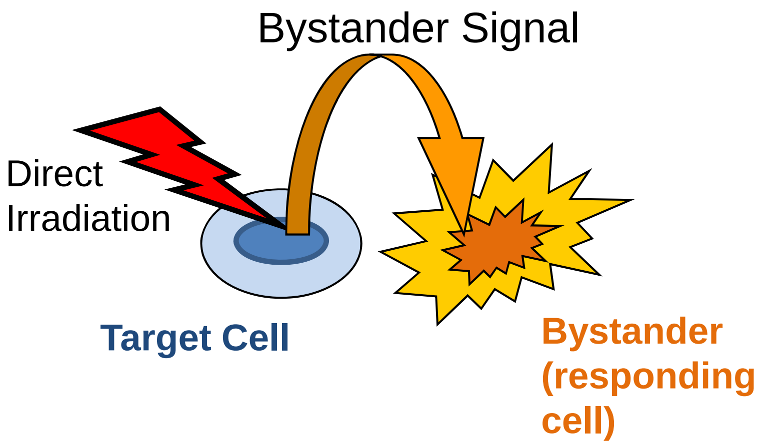
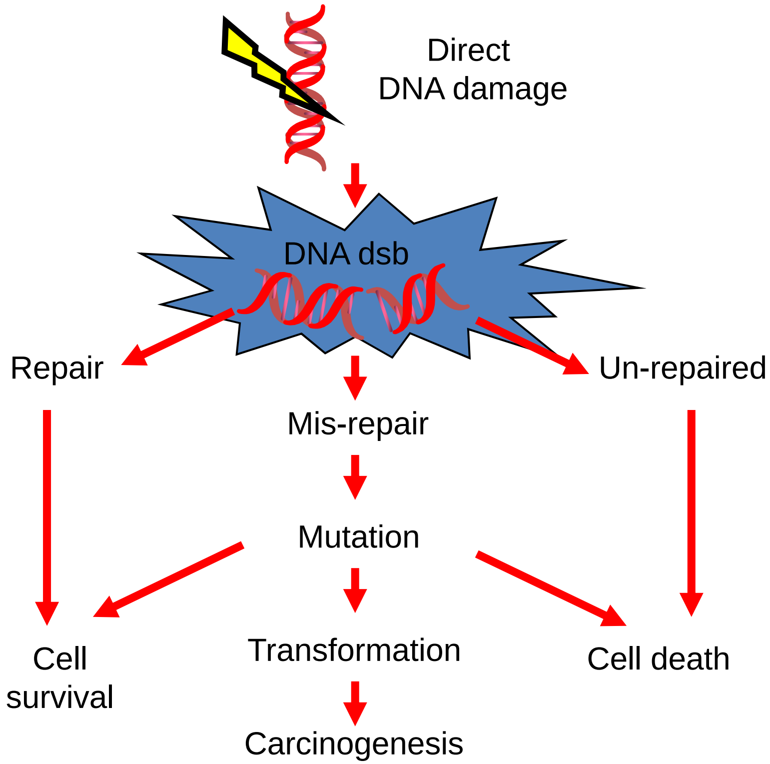
Bystander Effect

- **Recent radiobiological studies have challenged the tenet that biological effects are in direct proportion to energy deposited in nuclear DNA**
- **Evidence points to both *in vitro* and *in vivo* radiation effects also expressed in cells not “hit” but in proximity or in contact with directly damaged cells**





Overall aim

Combined assessment of early and late cellular response and DNA damage in a range of relevant cell lines to provide systematic detailed information to help developing a rigorous theory of ion radiation action at the cellular and molecular level.

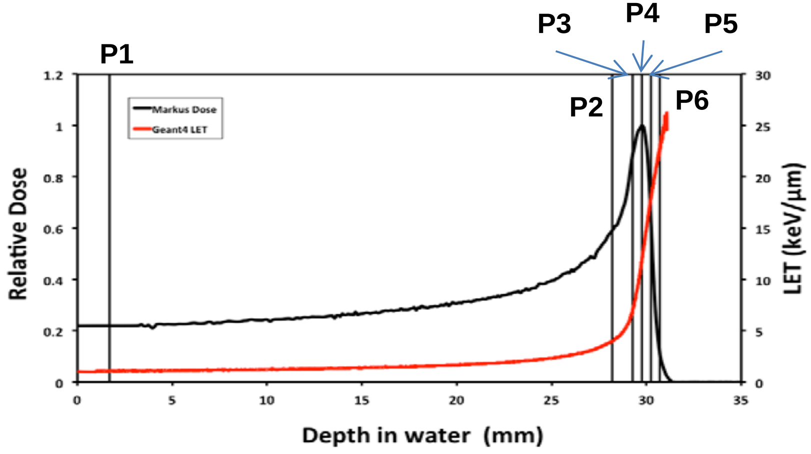
Q1. How does DNA damage and cell response vary across a pristine Bragg curve?

Q2. How biological effectives of a pristine curve relates to a Spread Out Bragg Curve?

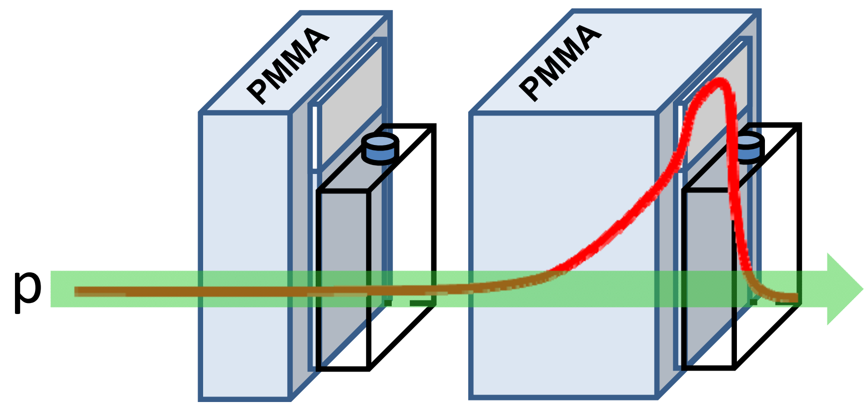
Q3. What is the contribution of radial dose to heavy ion track structure?

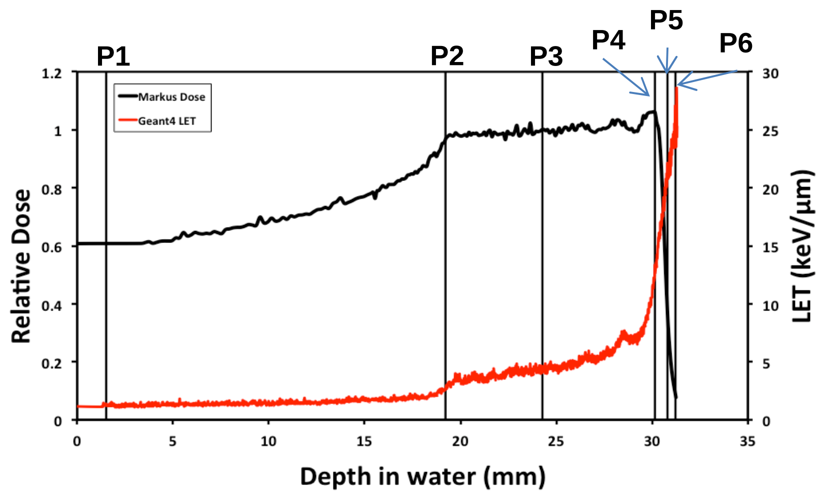
Q4. What is the contribution of cell signalling following heavy ion irradiation?

Irradiation Setup - Catania



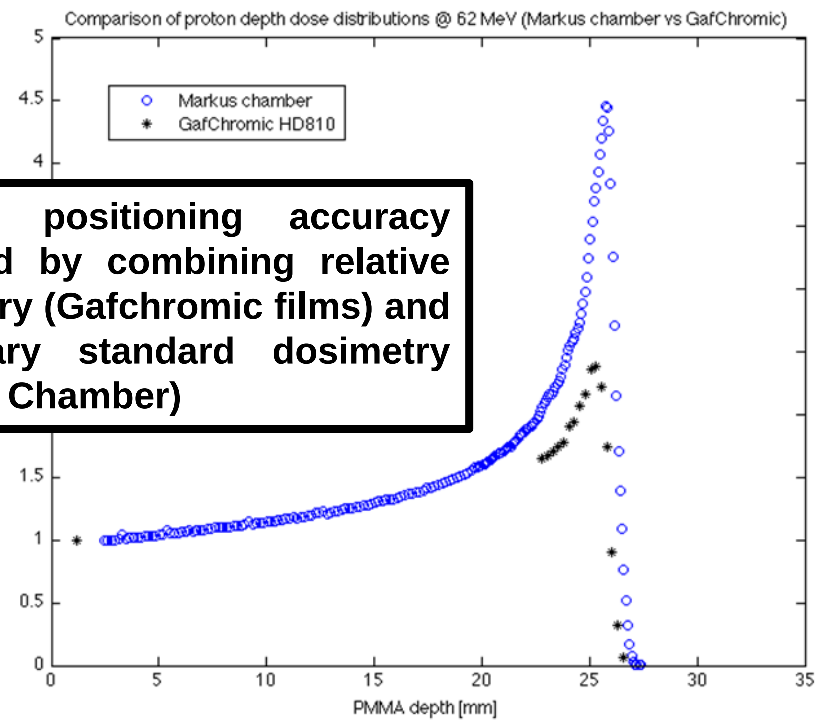
	P1	P2	P3	P4	P5	P6
Depth water [mm]	1.38	20.23	24.59	27.69	29.48	30.08
LET [keV/µm]	1.2	2.6	4.5	13.4	21.7	25.9





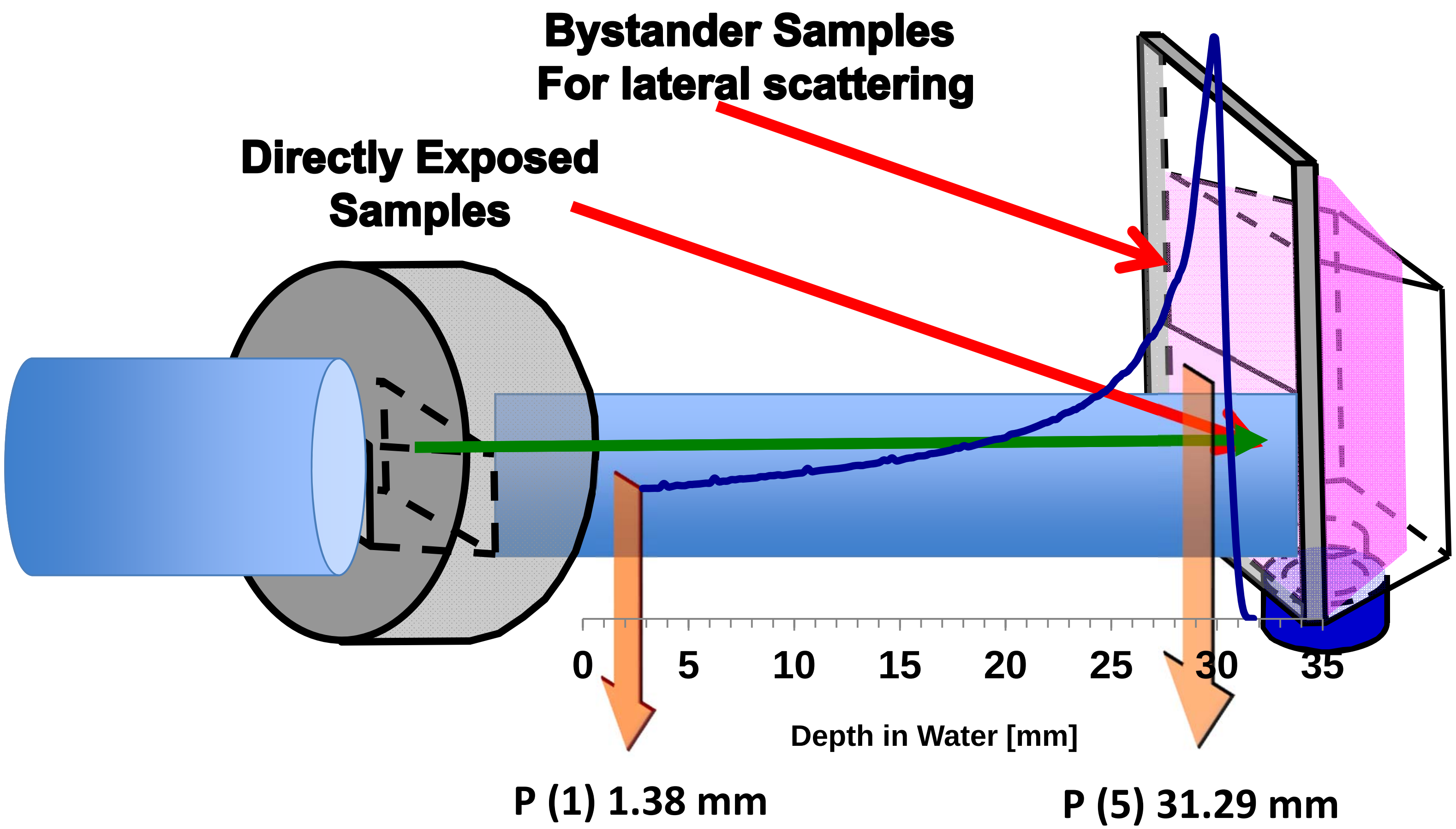
	P1	P2	P3	P4	P5	P6
Depth water [mm]	1.38	27.42	29.21	29.8	30.7	31.29
LET [keV/µm]	1.11	4.0	7.0	11.9	18.0	22.6

Prise, Schettino et al., submitted



50 µm positioning accuracy achieved by combining relative dosimetry (Gafchromic films) and secondary standard dosimetry (Markus Chamber)

Direct and bystander DNA damage



Prise, Schettino et al., unpublished

Conclusions

In this study RBE varies significantly across the Bragg curve with strong dependency on LET, Dose, and Radiosensitivity

- Differences between response to pristine and SOBP indicate that LET alone might not the best parameter for RBE predictions
- RBE variation for proton beams doesn't significantly extend the range of the SOBP (compared to fixed RBE = 1.1)
- Fixed RBE = 1.1 underestimates the dose delivered to the tumour volume
- Sub-lethal effects may also strongly vary along the Bragg curve and are higher than X-rays

Prise, Schettino et al., submitted

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