Proposition:
The more important heavy charged particle radiotherapy of the future is more likely to be with heavy ions rather than protons.

Against the Proposition

Al Smith, Ph.D.

To be Clear:

- I support, without reservation, clinical research using carbon ions.
- I have the greatest respect for my colleagues who are engaged in carbon ion clinical research.

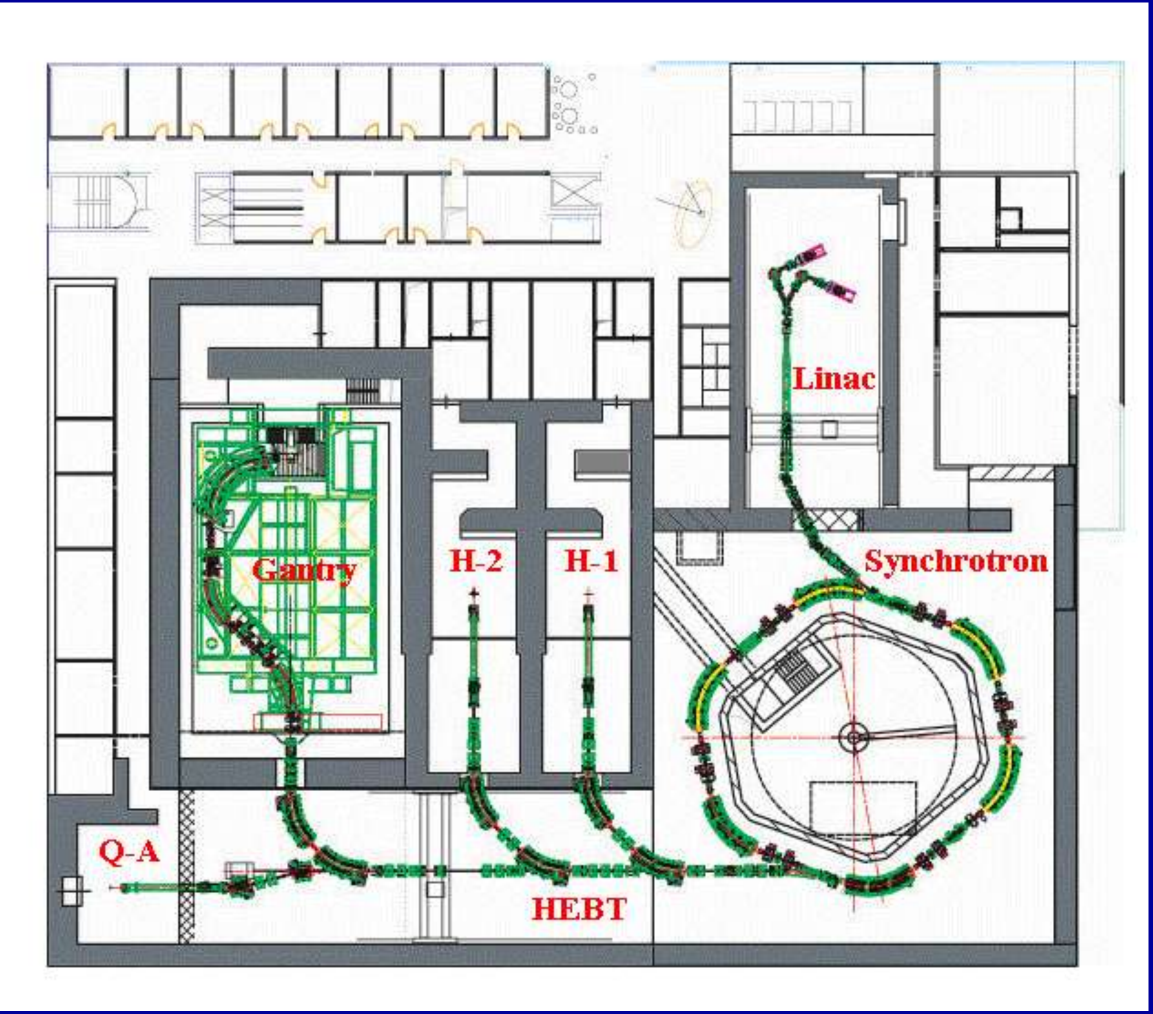
However: The proposition that carbon ions will be more <u>important</u> than protons for cancer therapy in the future is not supportable.

Things you should know about Carbon Ions

^{12}C treatment facility: DKFZ Heidelberg, Germany

Carbon facilities cost more than proton facilities:

- Equipment costs ~ **4 times** as much
- Total facility cost **2-3 times** as much



Heavy Ion Medical Accelerator at Chiba (HIMC)

Ministry of Science and Technology
(Mitsubishi, Sumitomo, Hitachi & Toshiba)

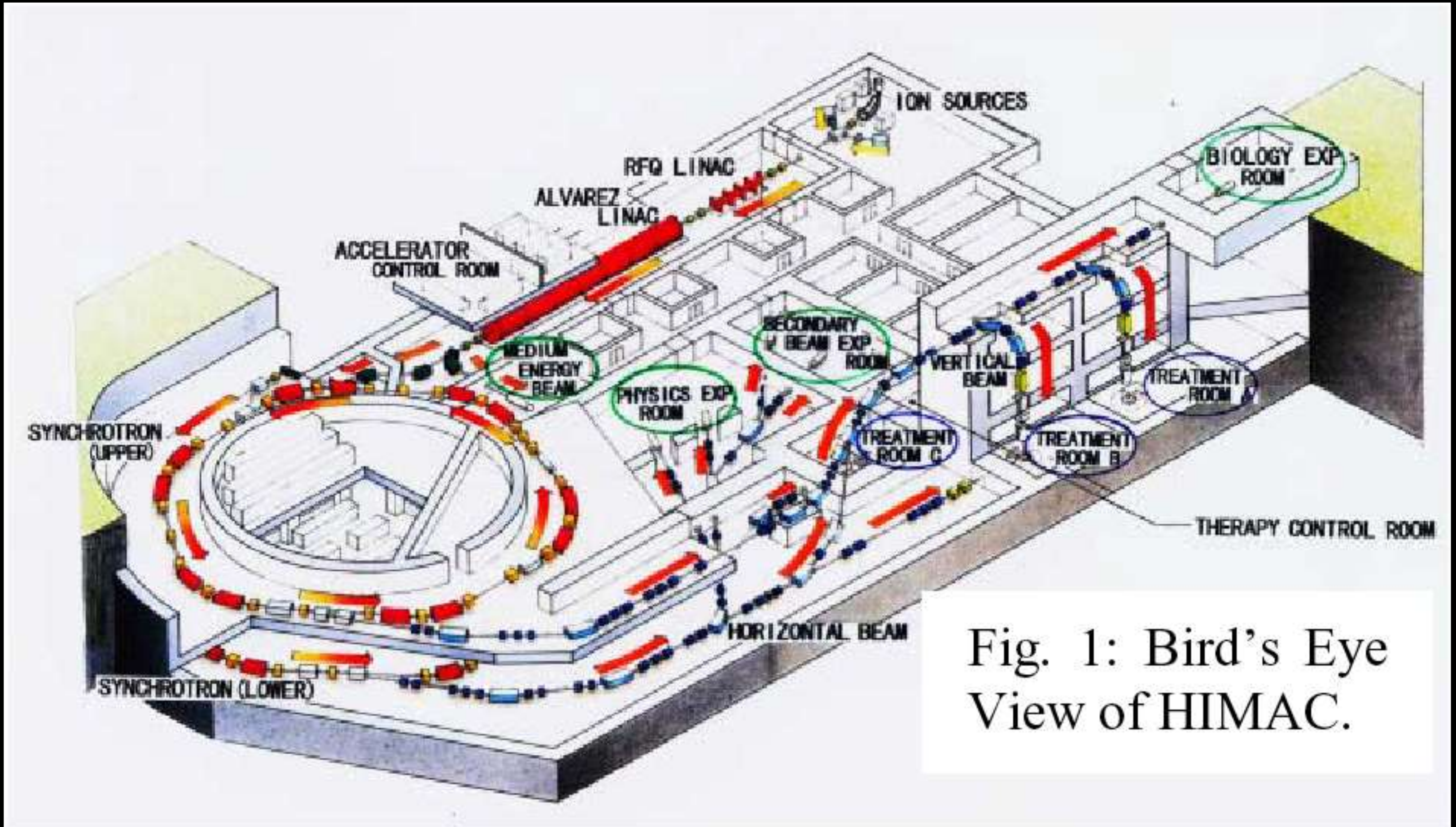


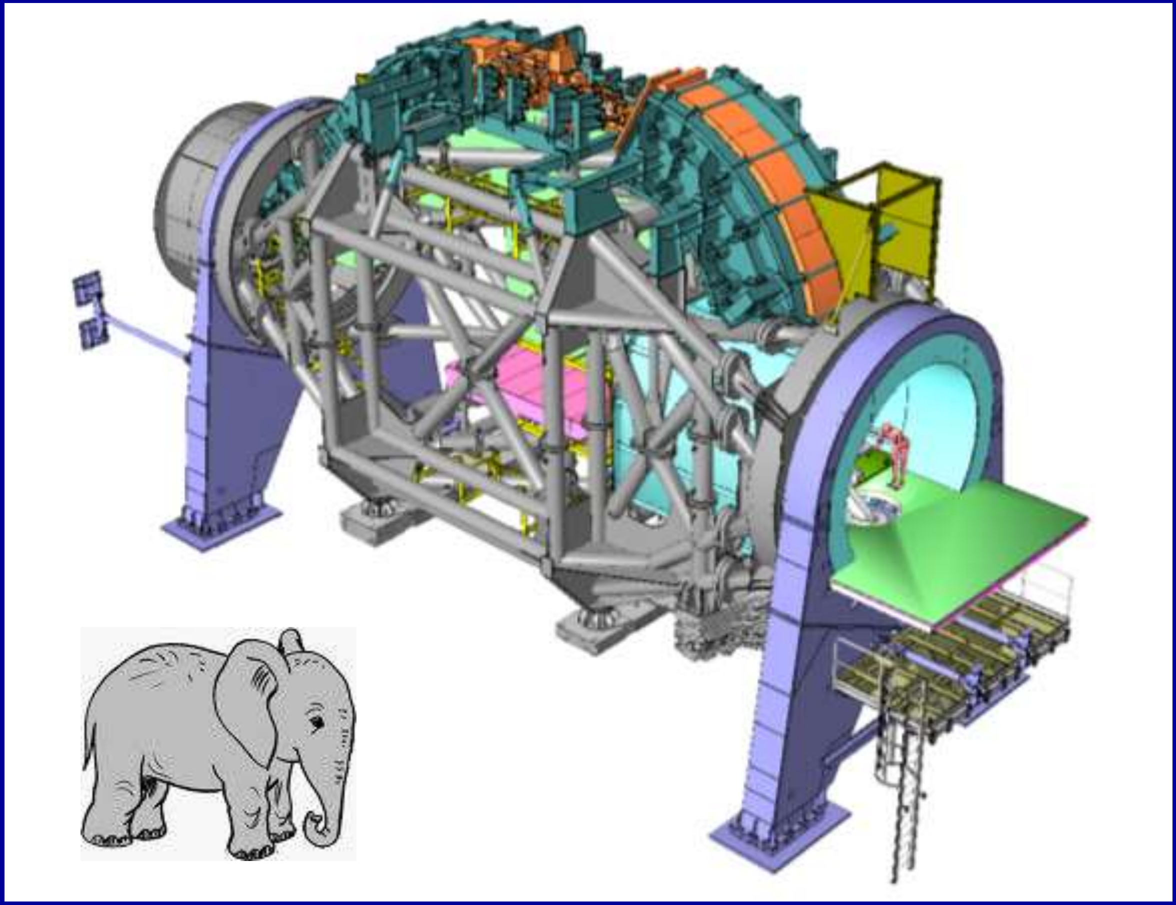
Fig. 1: Bird's Eye View of HIMAC.

The CNAO Synchrotron for protons and carbon ions

Scanning Ion Gantry: DKFZ Heidelberg, Germany

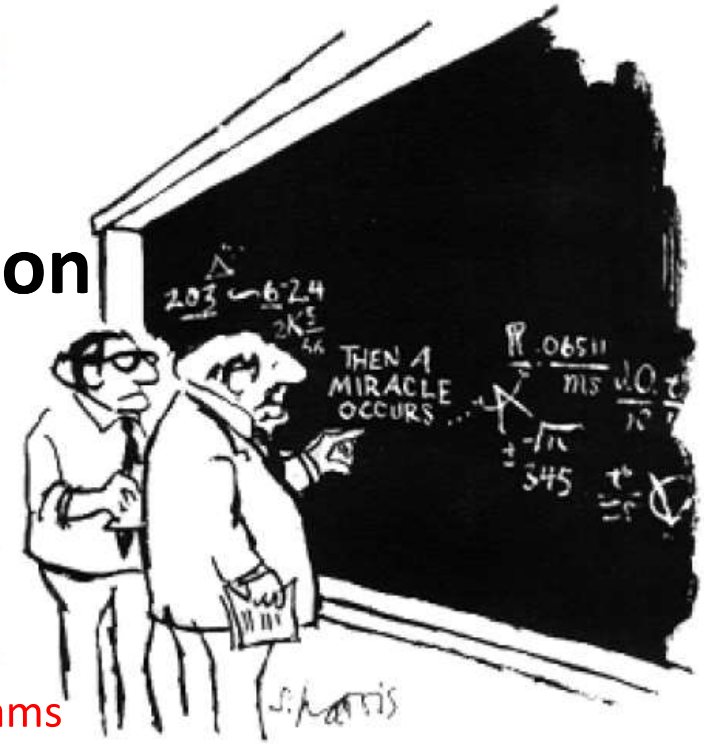
Isocentric gantries for carbon ions are large and expensive: 13 m diameter; 25 m length; **600 ton weight**. Therefore, most patients are treated with fixed beams.

Proton gantries:
360 ° proton gantries weigh 120 to 190 tons; 180 ° gantries weigh 70 to 90 tons.



RBE depends on

- energy/LET
- dose & fractionation
- tissue
  - late/early responding tissues
  - pO^2 status
  - position in cell cycle



"I think you should be more explicit here in step two."

"Treatment planning for ^{12}C ion beams is substantially more complex than for ^{1}H beams because varying LET and associated RBE values result in large uncertainties in RBE values .

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Harold Paganetti

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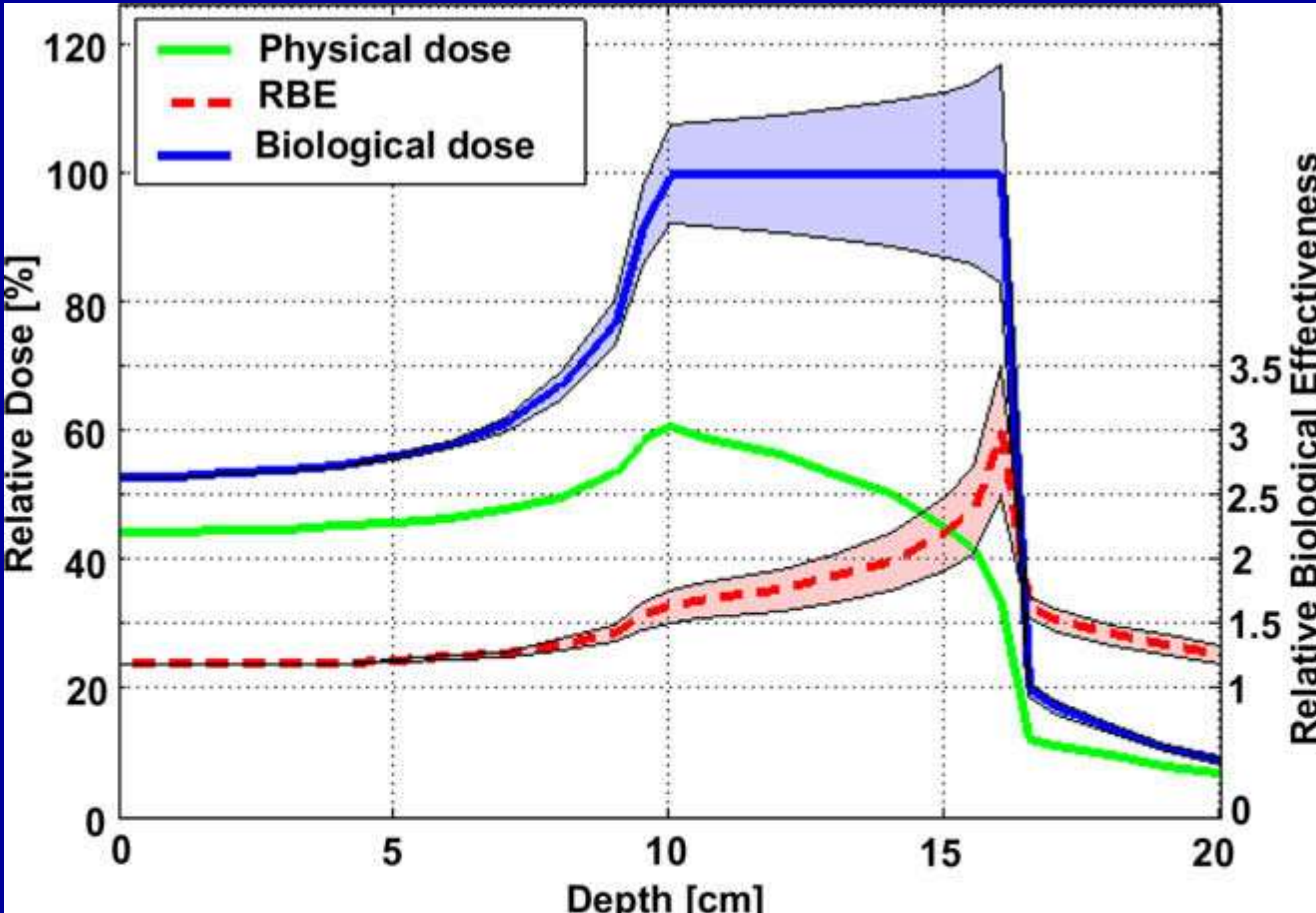
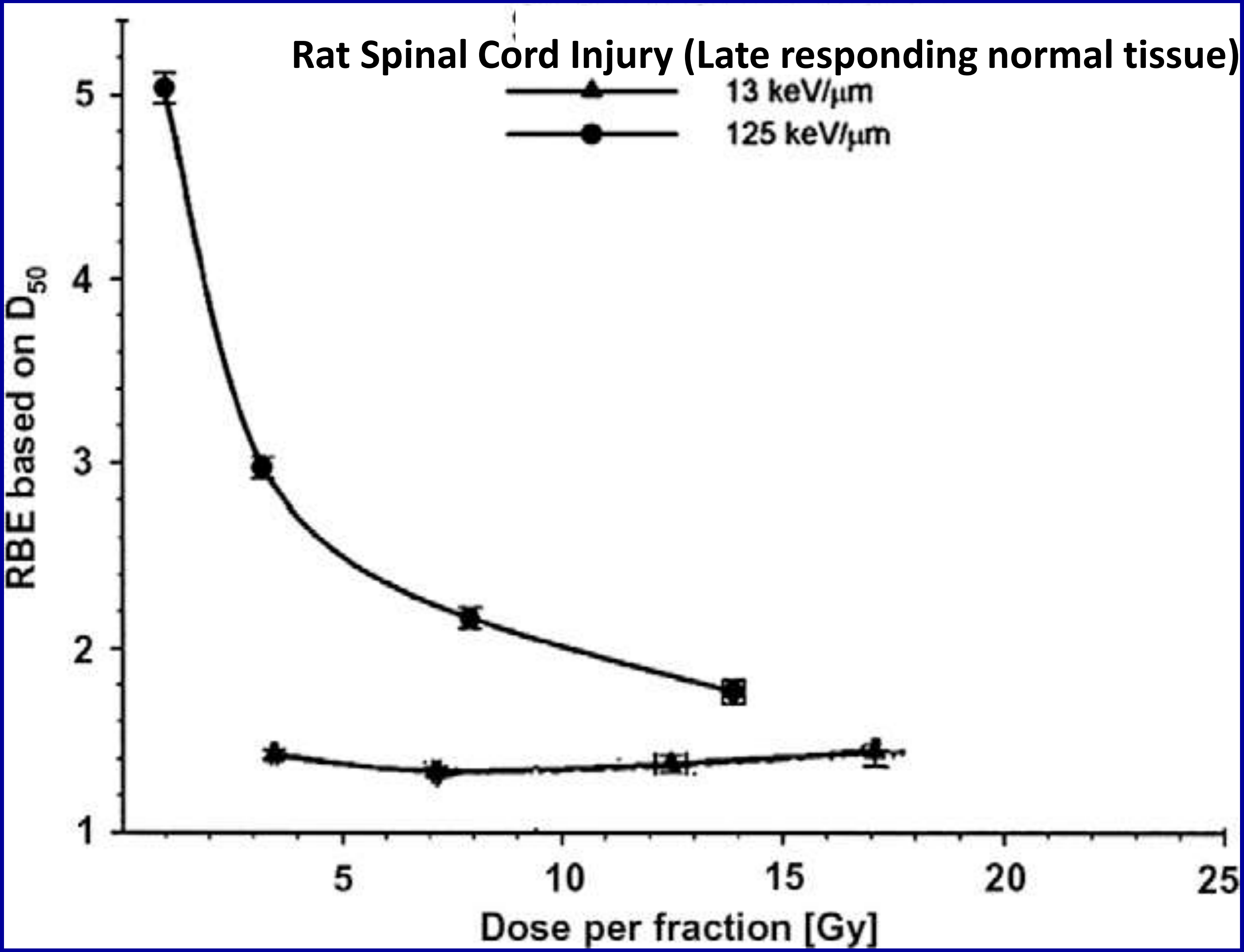
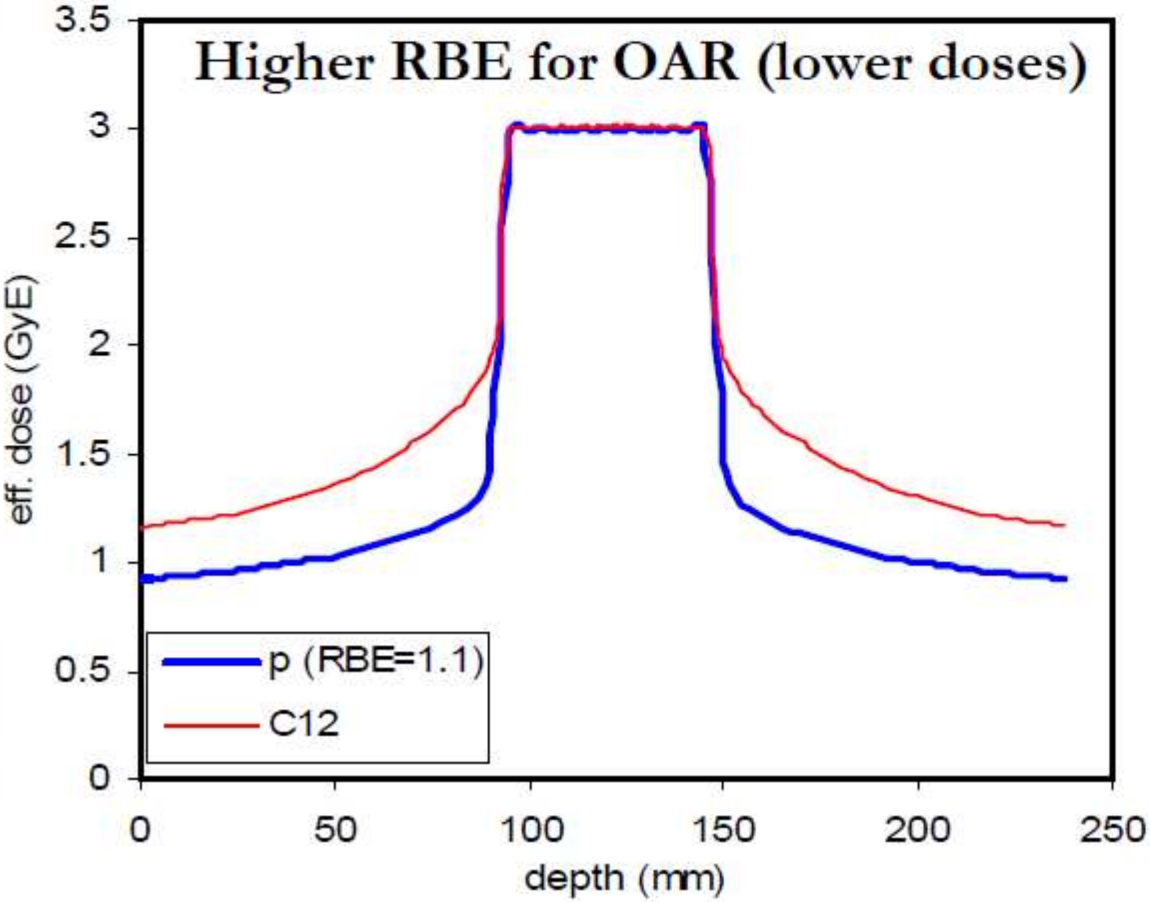


Design of a 290 MeV 12C ion beam with a 6 cm SOBP for an assumed maximum RBE of 3.0. The impact of an error in selecting the RBE were the true RBE in the range of 2.5–3.5 is represented by the uncertainty bands around the dose in Gy(RBE) across the SOBP. **The RBE for Protons is ~ 1.1.**



Karger C, Peschke P, Sanchez-Brandelik R, et al. Radiation tolerance of the rat spinal cord after 6 and 18 fractions of photons and carbon ions: experimental results and clinical implications. Int J Rad Oncol Biol Phys 2006;66: 1488–97.

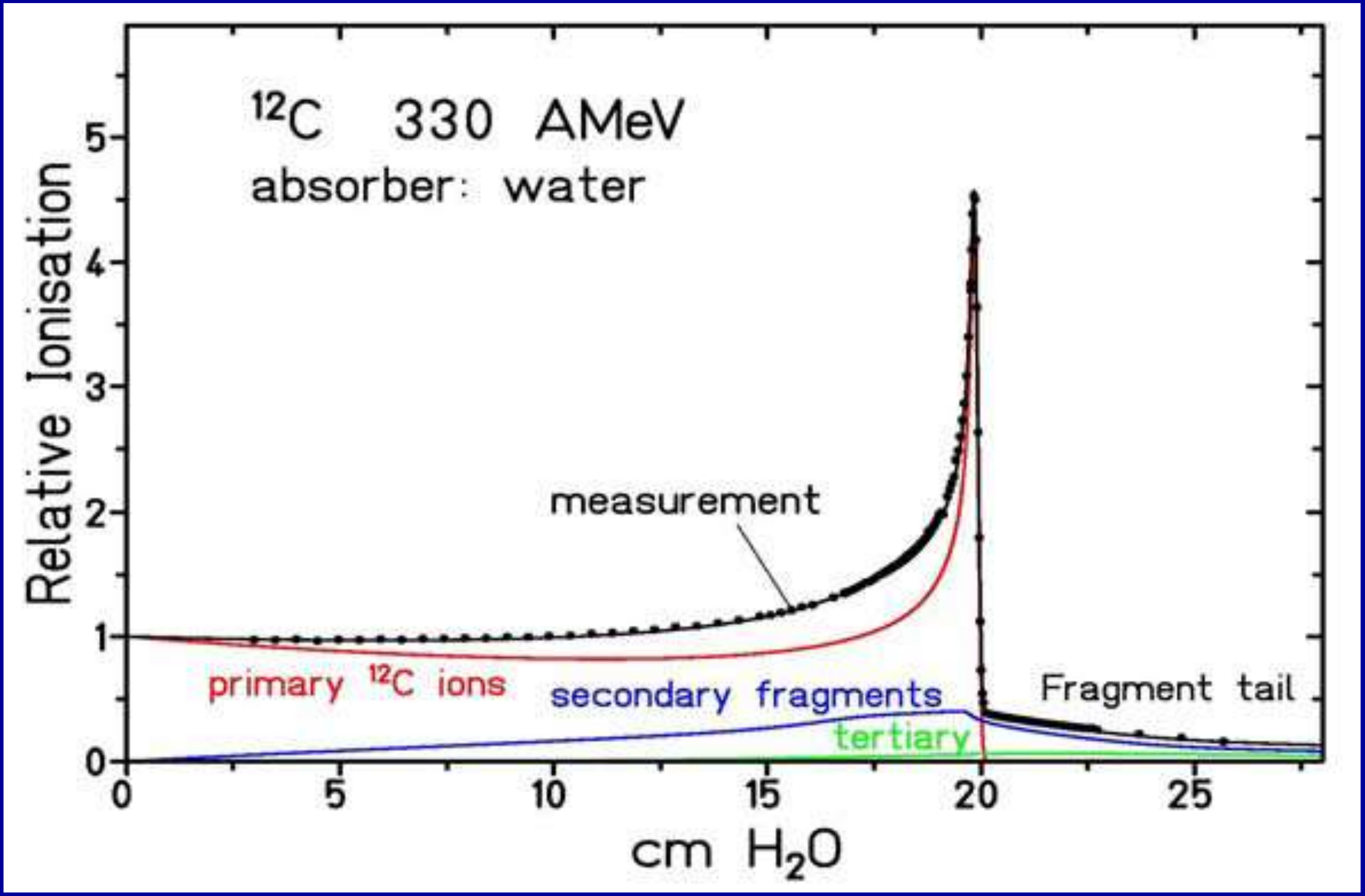
RBE as a function of dose



Wilkins and Oelfke:
Int. J. Radiat. Oncol. Biol. Phys. 2008

Carbon ion depth dose distributions have a tail of dose extending beyond the Bragg peak.

The tail develops from fragmentation of the carbon ions in the primary beam, due to nuclear interactions. Some fragments travel beyond the range of the primary beam for distances that depend on the energy of the primary beam. The tails are low physical dose and relatively high RBE with the net result being a non-negligible biologically effective dose in the fragmentation tail of carbon beams



SCHARDT, D., "Nuclear Fragmentation of high-energy heavy-ion beams in water", Adv. Space Res. 17 (1996) 87-94.

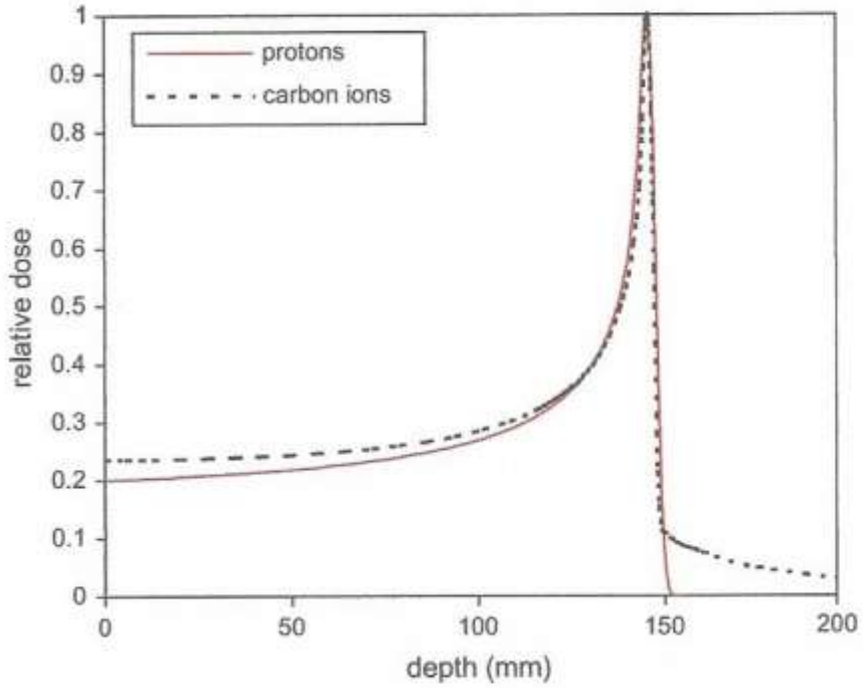


Fig. 1. Pristine Bragg peaks for a 145-MeV proton beam and a 276-MeV carbon beam (degraded with 3-mm ripple filter).

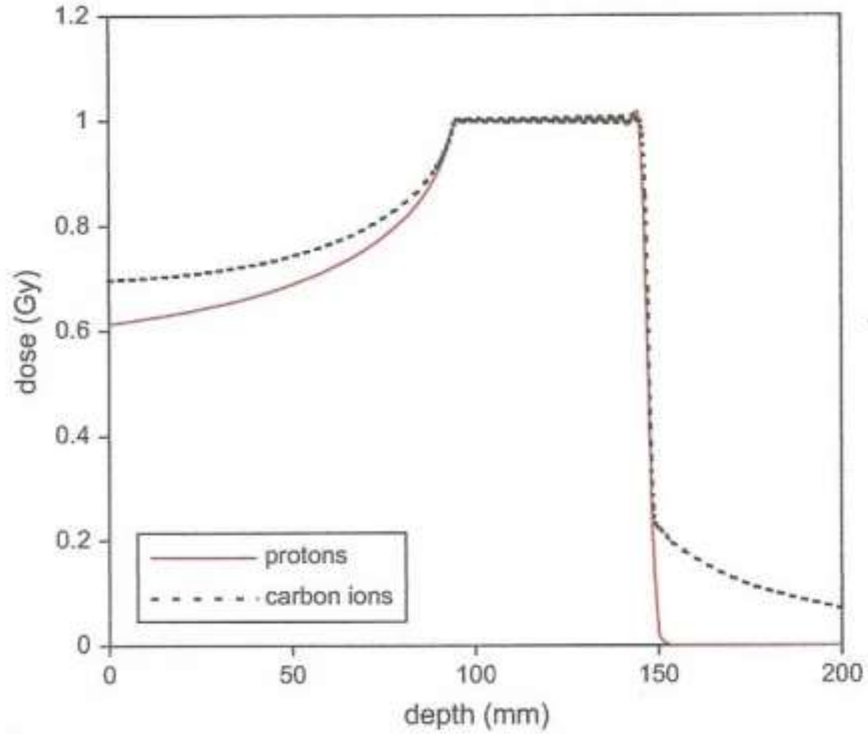
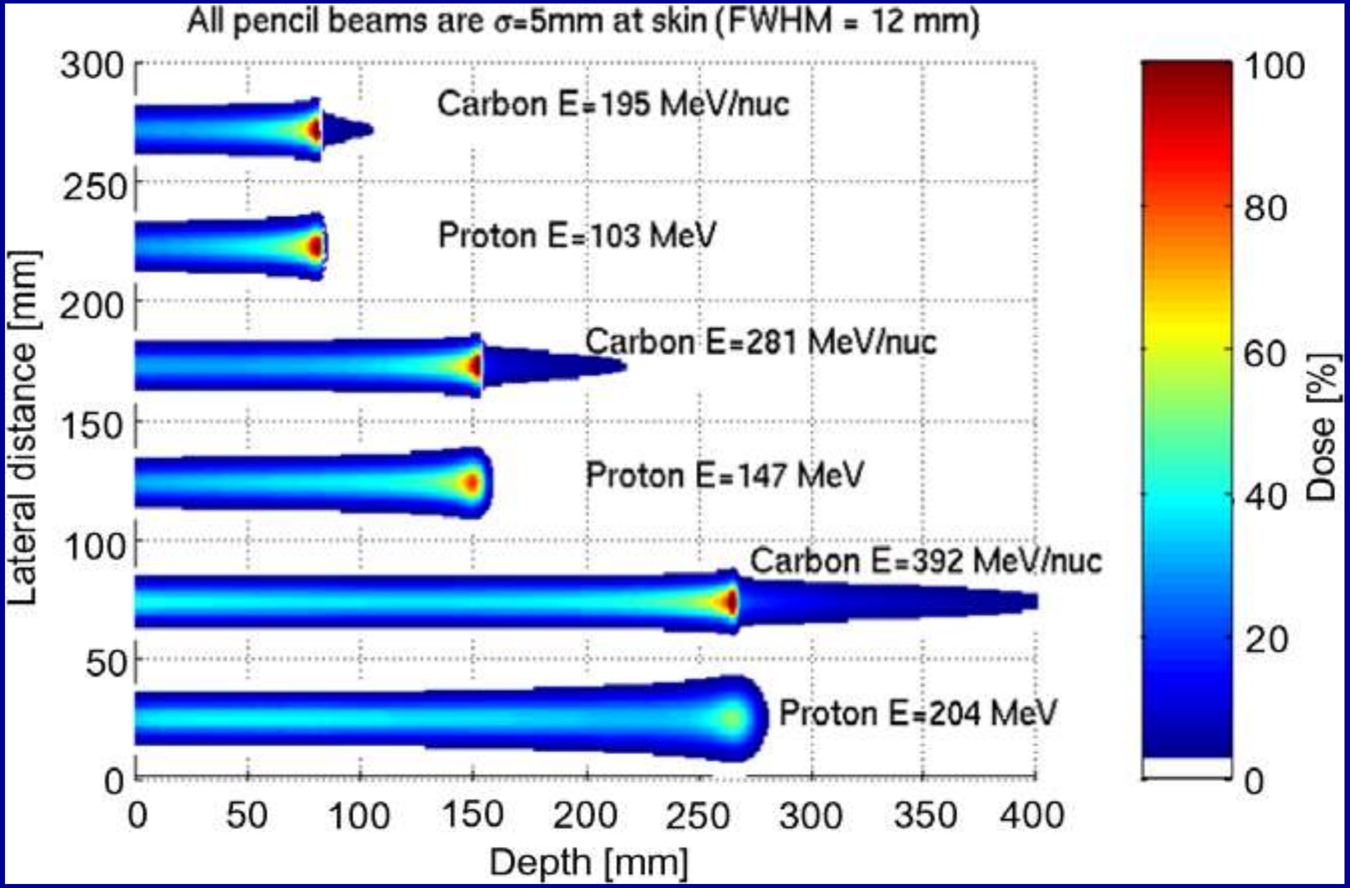


Fig. 2. Dose distribution for spread-out Bragg peaks that were optimized to yield a physical dose of 1 Gy in the target volume.

DIRECT COMPARISON OF BIOLOGICALLY OPTIMIZED SPREAD-OUT BRAGG PEAKS FOR PROTONS AND CARBON IONS : JAN J. WILKENS, PH.D., AND UWE OELFKE, PH.D.
Department of Medical Physics in Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany



Proton *vs.* carbon ion beams in the definitive radiation treatment of cancer patients: Herman Suit, et. al., Radiotherapy and Oncology 95 (2010) 3-22

"Should high LET provide a clinical advantage, one basis could be an inherently higher sensitivity of tumor than normal cells to high LET radiations, i.e. a higher RBE for tumor than normal cell irradiated under identical conditions. Substantial experimental data do not provide support such a differential sensitivity."

The potential gain from high RBE & LET may be due primarily to a lower OER for some tumor cells.

Proton *vs* carbon ion beams in the definitive radiation treatment of cancer patients: Herman Suit, et. al., Radiotherapy and Oncology 95 (2010) 3-22

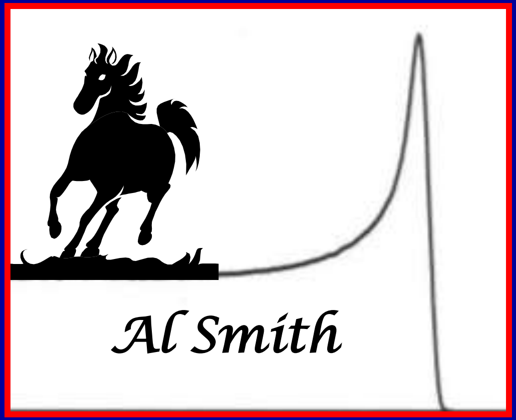
The "theoretical" advantages of carbon ions over protons have not been proven in a clinical setting. Studies performed thus far have shown an approximate clinical equivalence of both modalities.

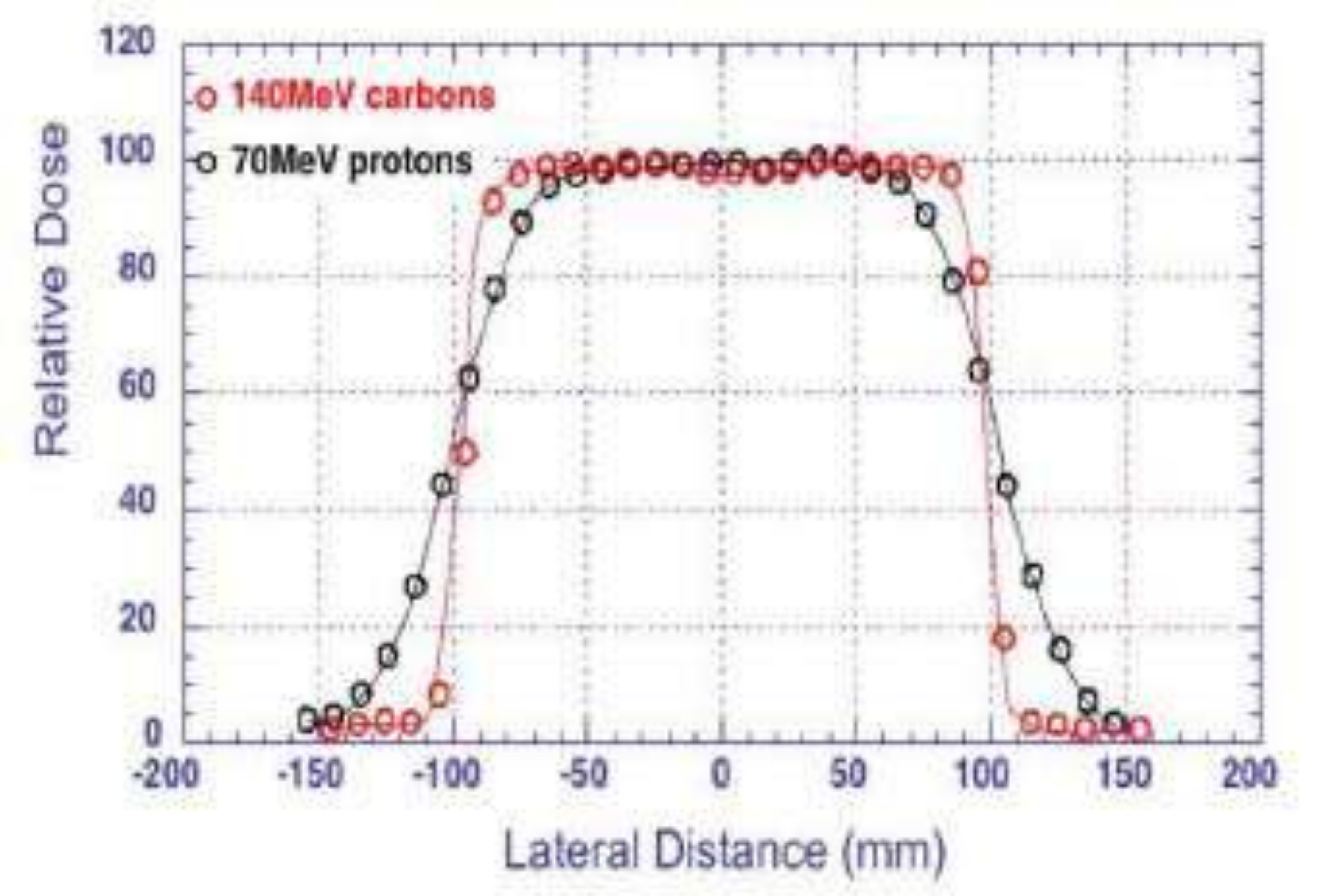
- H. Tsujii and T. Kamada, "A Review of Update Clinical Results of Carbon Ion Radiotherapy", Jpn J Clin Oncol, **42(8)**, 670–685 (2012)
- H. Suit, et al., "Proton vs. carbon ion beams in the definitive radiation treatment of cancer patients", Radiotherapy and Oncology **95,** 3–22 (2010)
- S. Komatsu, et al., "Clinical results and risk factors of proton and carbon ion therapy for hepatocullar carcinoma" Cancer **117(21),** 4890-4904 (2011)
- H. Iwata, et al., "High-dose proton therapy and carbon-ion therapy for stage I nonsmall cell lung cancer" Cancer **116(10)**, 2476-2485 (2010)

Proposition: The more <u>important</u> heavy charged particle radiotherapy of the future is more likely to be with heavy ions rather than protons.

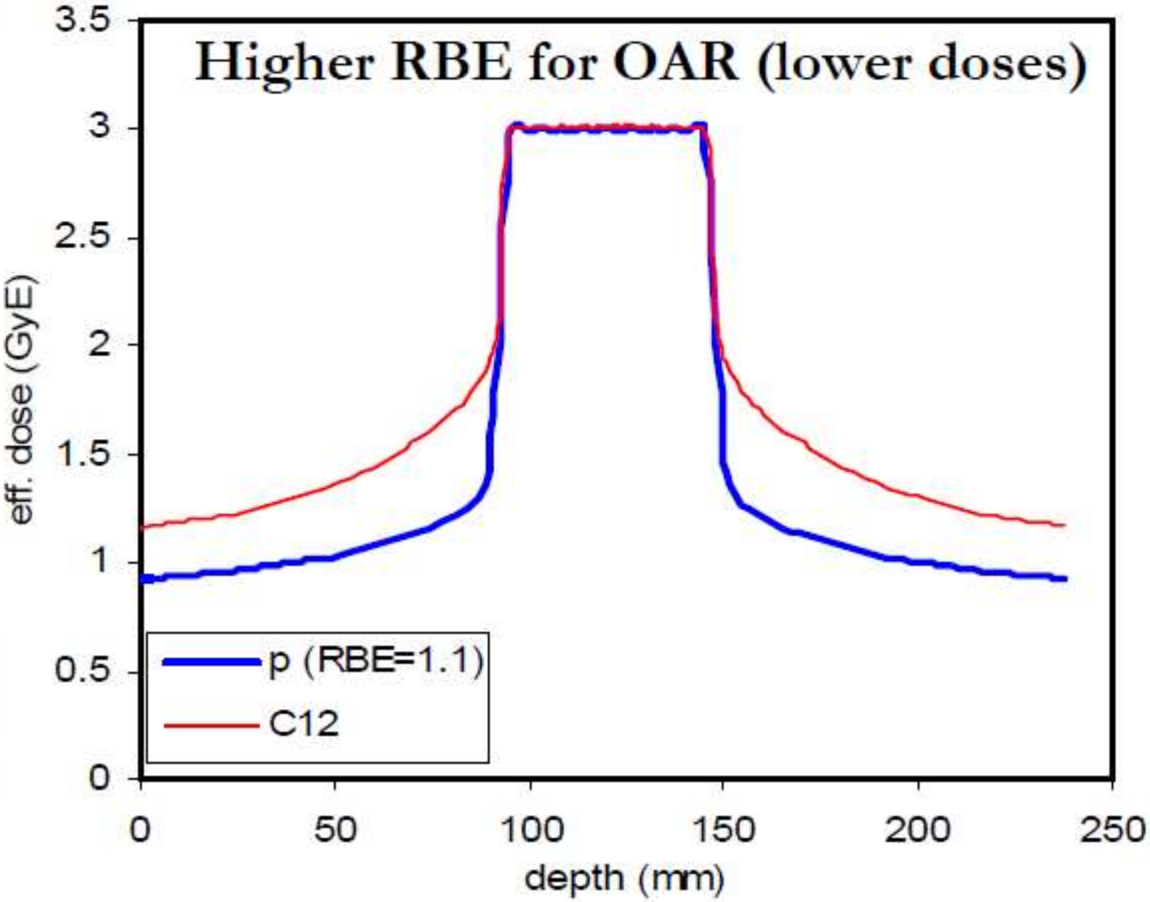
No matter how many ways I look at the word "**important**", I cannot find a way to support the proposition.

Thank You!




140MeV carbons
70MeV protons
Relative Dose
120
100
80
60
40
20
0
-200
-150
-100
-50
0
50
100
150
200
Lateral Distance (mm)

RBE as a function of dose



Wilkins and Oelfke:
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Present and Future Particle Facilities

- Facilities in operation worldwide:
  - Proton: 36 (93,895 patients treated)
  - Carbon: 6 (10,756 patients treated)
- Facilities in planning stage or under construction worldwide:
  - Proton: 31
  - Carbon: 5

It is not reasonable to expect that the number of carbon ion facilities will even overtake, much less outnumber, proton facilities in the foreseeable future. It has recently been reported that in the US 20 institutions are seriously considering proton therapy. Many more patients will be treated with protons than with carbon ions.

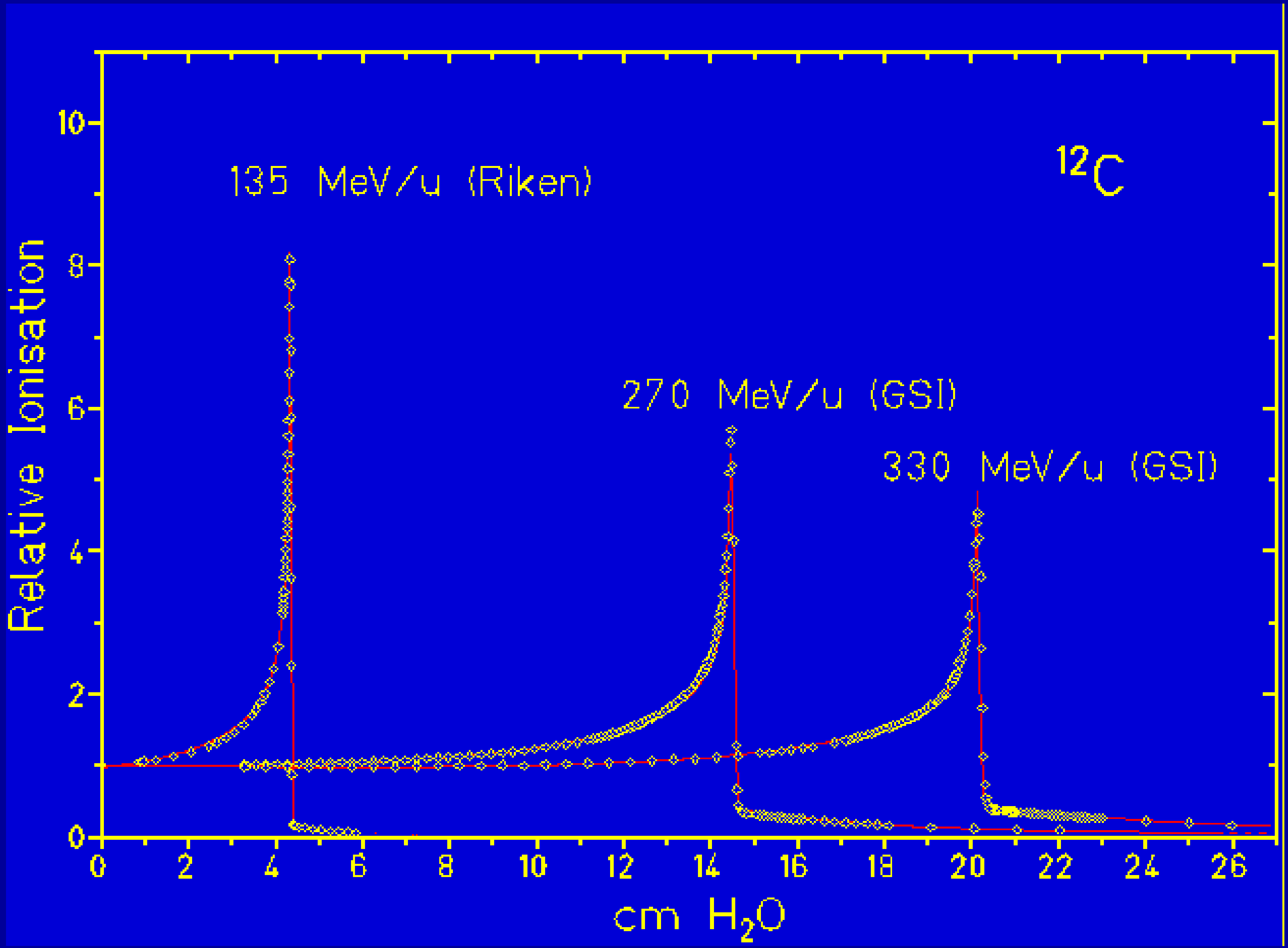
Additional hurdles for Carbon Ions in the United States

- Continued pressure to decrease the costs of medical care will make it very difficult to build expensive carbon ion facilities.
- There is no FDA approval for carbon ion equipment and no predicate facilities as a basis for an FDA 510(k) application.
- There is no established reimbursement for carbon ion therapy, therefore, there is little incentive for investment in carbon ion facilities.

Bottom Line

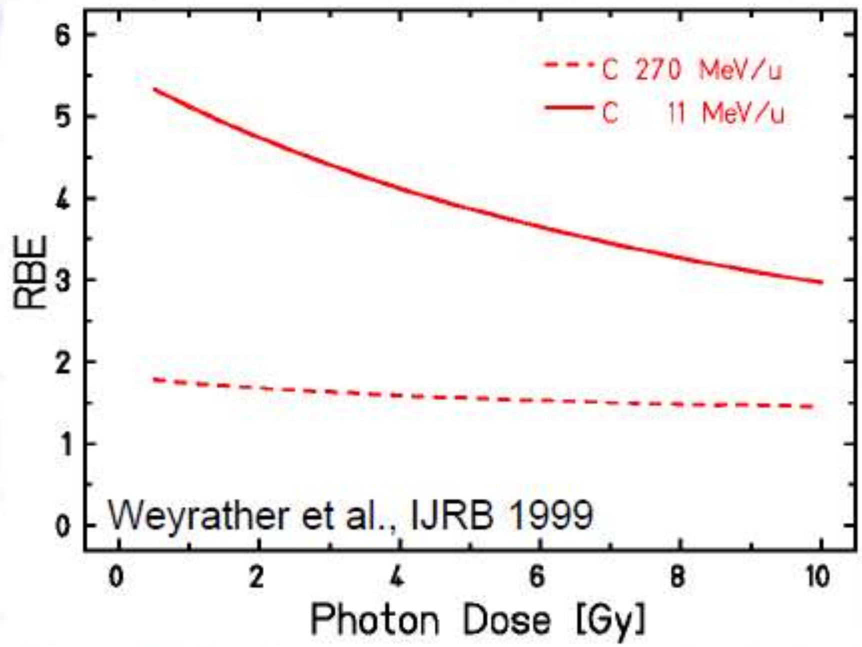
- Even should carbon ion therapy prove to be a good treatment for some cancers, its expense and complexity will likely prevent the building of many carbon facilities. In such case, carbon ions will not have a major impact on cancer cure, because, to do so, large numbers of patients need to be treated.
- Therefore, carbon therapy will not be a more important treatment modality than proton therapy in the future.

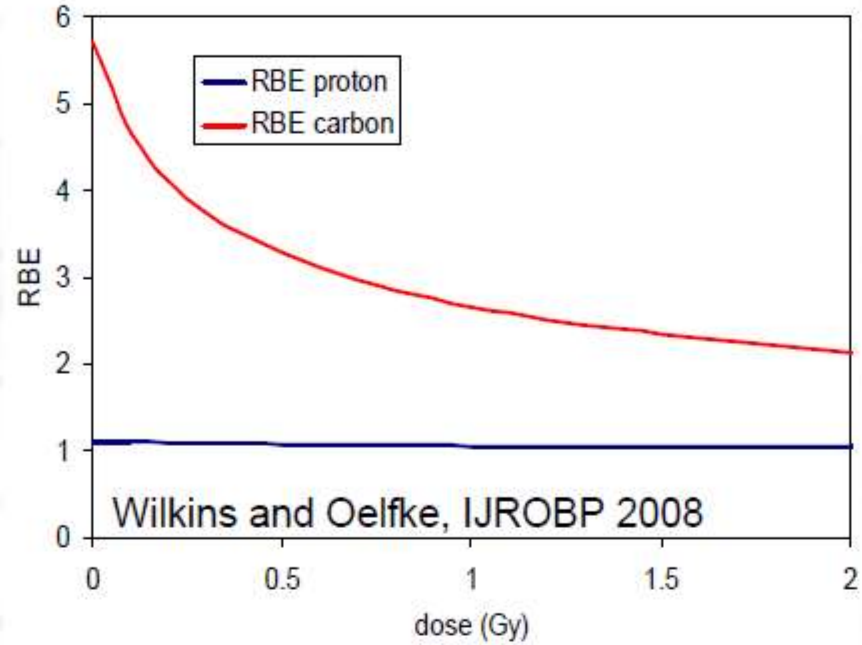
"Particles, particles, particles."



SCHARDT, D. et al., "Physical characterization of light-ion therapy beams", 5th Workshop on Heavy Charged Particles in Biology and Medicine (HCPBM), GSI Darmstadt, (1995), p.190.

RBE as a function of dose





- RBE decreases with increasing dose
- The lower the LET, the smaller the effect

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