International Workshop on Particle Therapy Research
UT Southwestern Medical Center
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RBEs, Normal Tissue Effects and Charged Particle Biology Research Challenges

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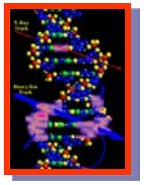
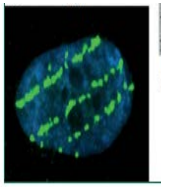
Disclosures

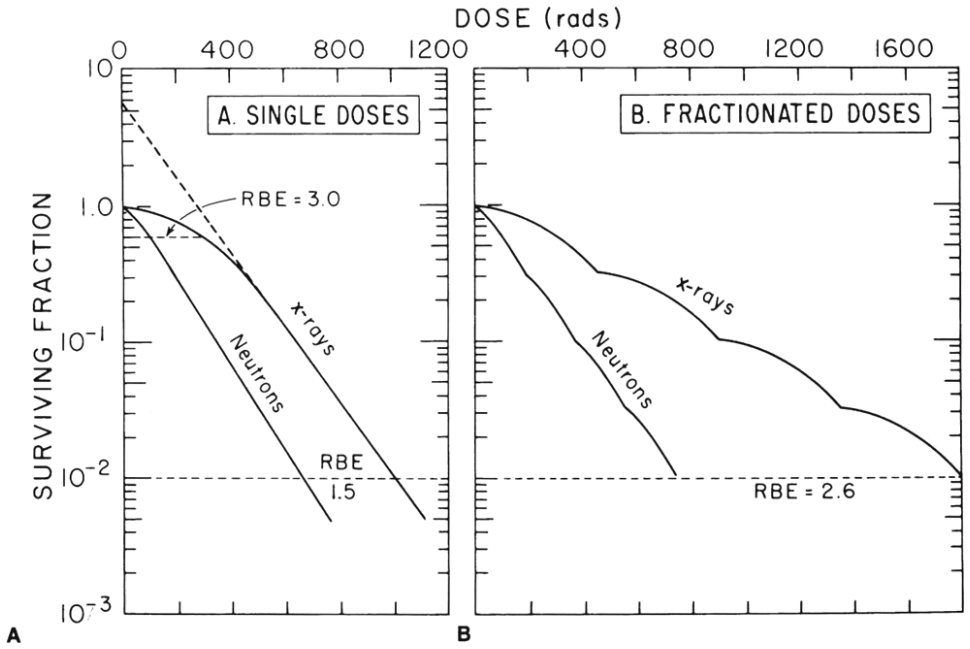
NONE

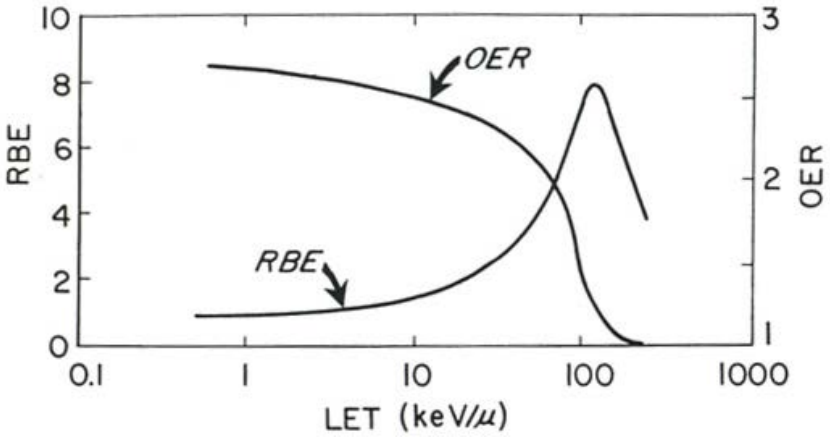


Carbon Ion RBEs for Normal Tissues: "Classic" Biology



- RBE is highly complex: depends on LET, ion species, dose, dose rate/fractionation, tissue/cell type, endpoint, microenvironment (and almost anything else you can think of!)

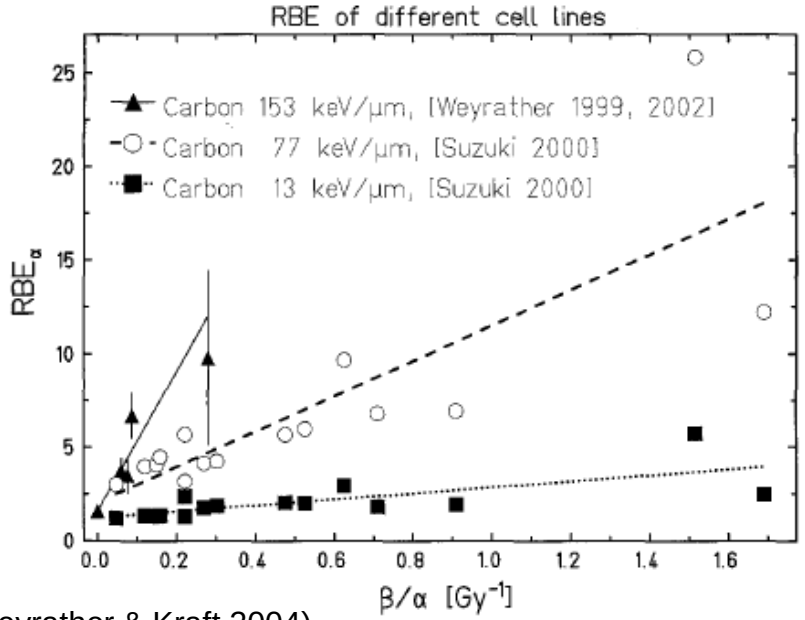




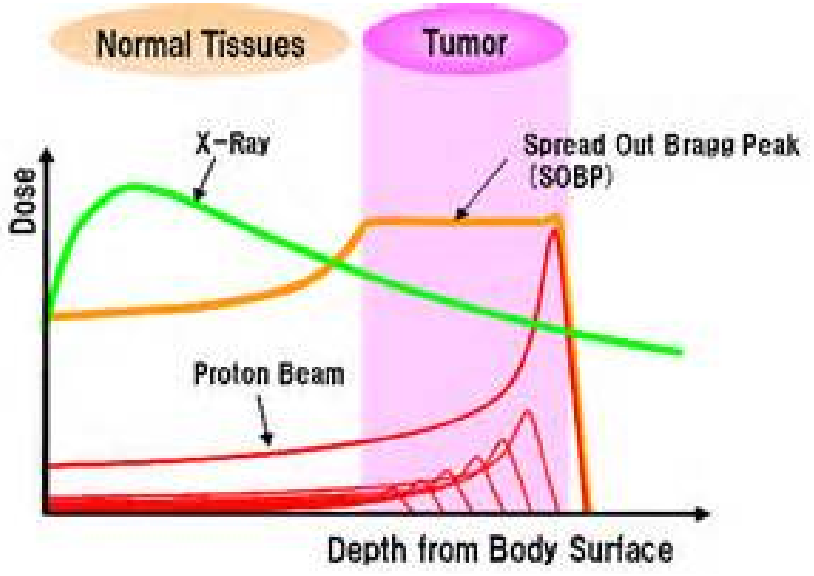
(from Hall 2000)

Carbon Ion RBEs for Normal Tissues: "Conventional Wisdom"

- Based on cell survival curves, late responding normal tissues (low α/β) should have larger RBEs than most tumors (high α/β) (bad news for carbon therapy) but with charged particles the normal tissues get lower dose and lower LET (good news).



(from Weyrather & Kraft 2004)



- Is it correct that late responding normal tissues have larger RBEs?

Carbon Ion RBEs: Survival Curves with Human Cells

- Ando and Kase (2009): ~ 40 curves, mostly for human tumors; 3 for human fibroblasts

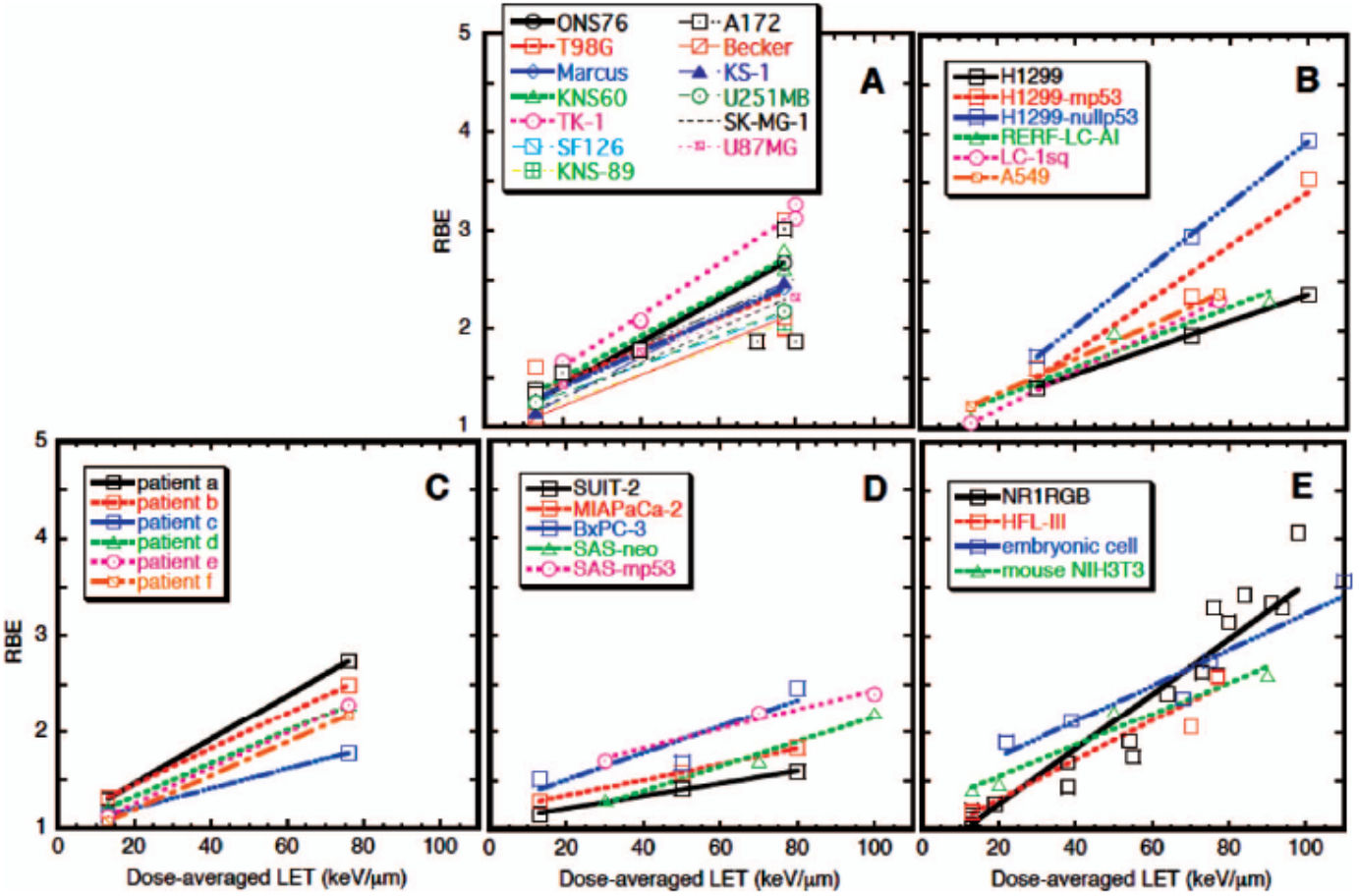


Figure 3. Relation between LET of carbon ions and RBE values for human cells. (A) Brain tumours, (B) lung tumours, (C) uterus tumours, (D) pancreas (SUIT-2, MIAPaCa-2, BxPC-3) and tongue (SAS-neo, SAS-mp53) tumours, (E) fibroblasts.

Carbon Ion RBEs: Survival Curves with Human Cells

- Suit et al. (2010) – some of same studies as previous slide

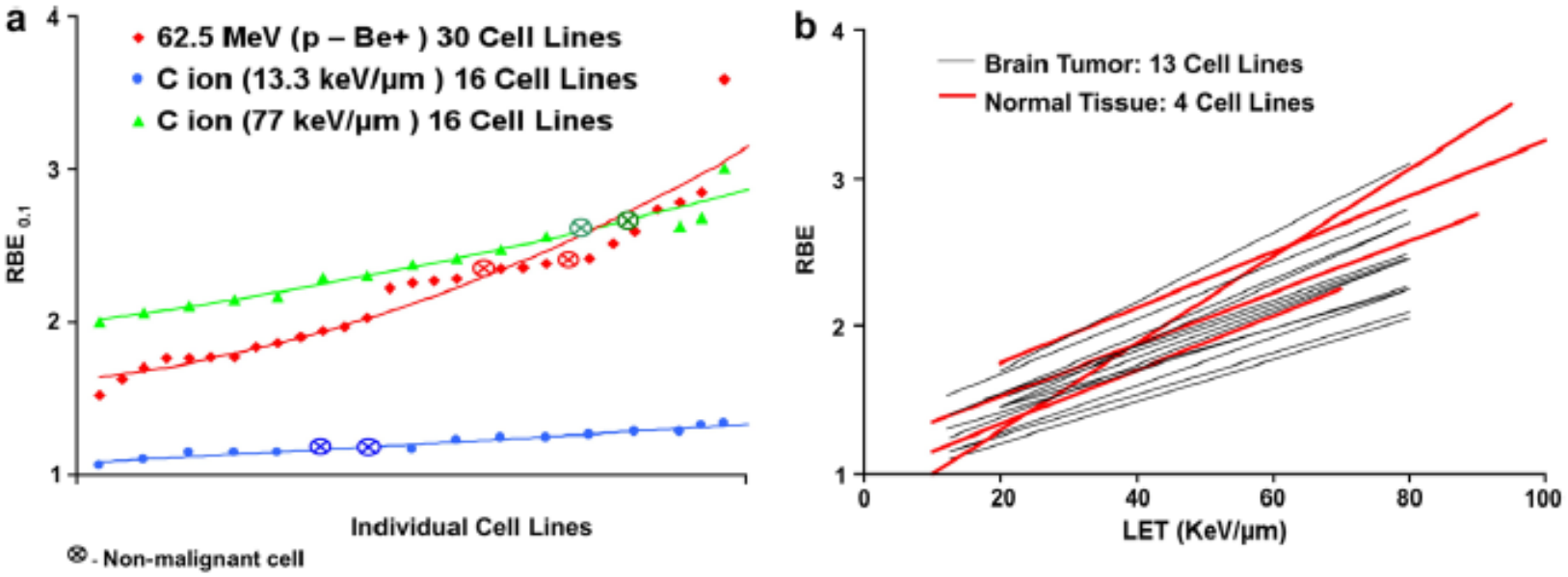
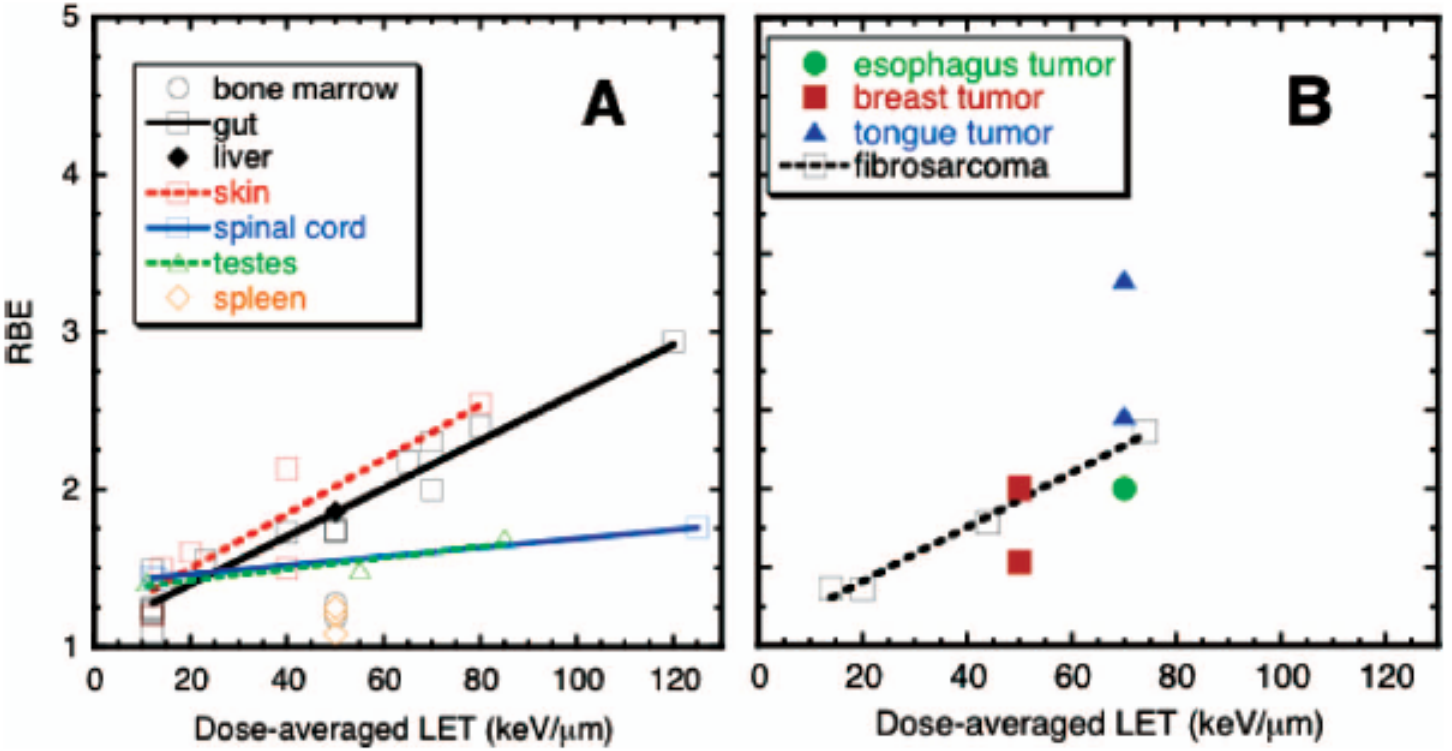


Fig. 7. RBE of tumor and normal cells *in vitro*. (a) Scattergrams of RBEs of 30 cell lines [two are normal cell lines] for 62 MeV neutron irradiation [33] and for 16 cell lines [two are normal cell lines] irradiated by ^{12}C ion beams at ~13 and ~80 keV/μm [34]. The large dots represent the normal cell lines. (b) RBE *vs* LET curves for 4 normal fibroblast cell lines and 13 brain tumor cell lines [35].

Conclusion from cell survival curves: Little evidence to support idea of consistently different RBEs for normal tissues than for tumors (if you think fibroblasts represent normal tissues).

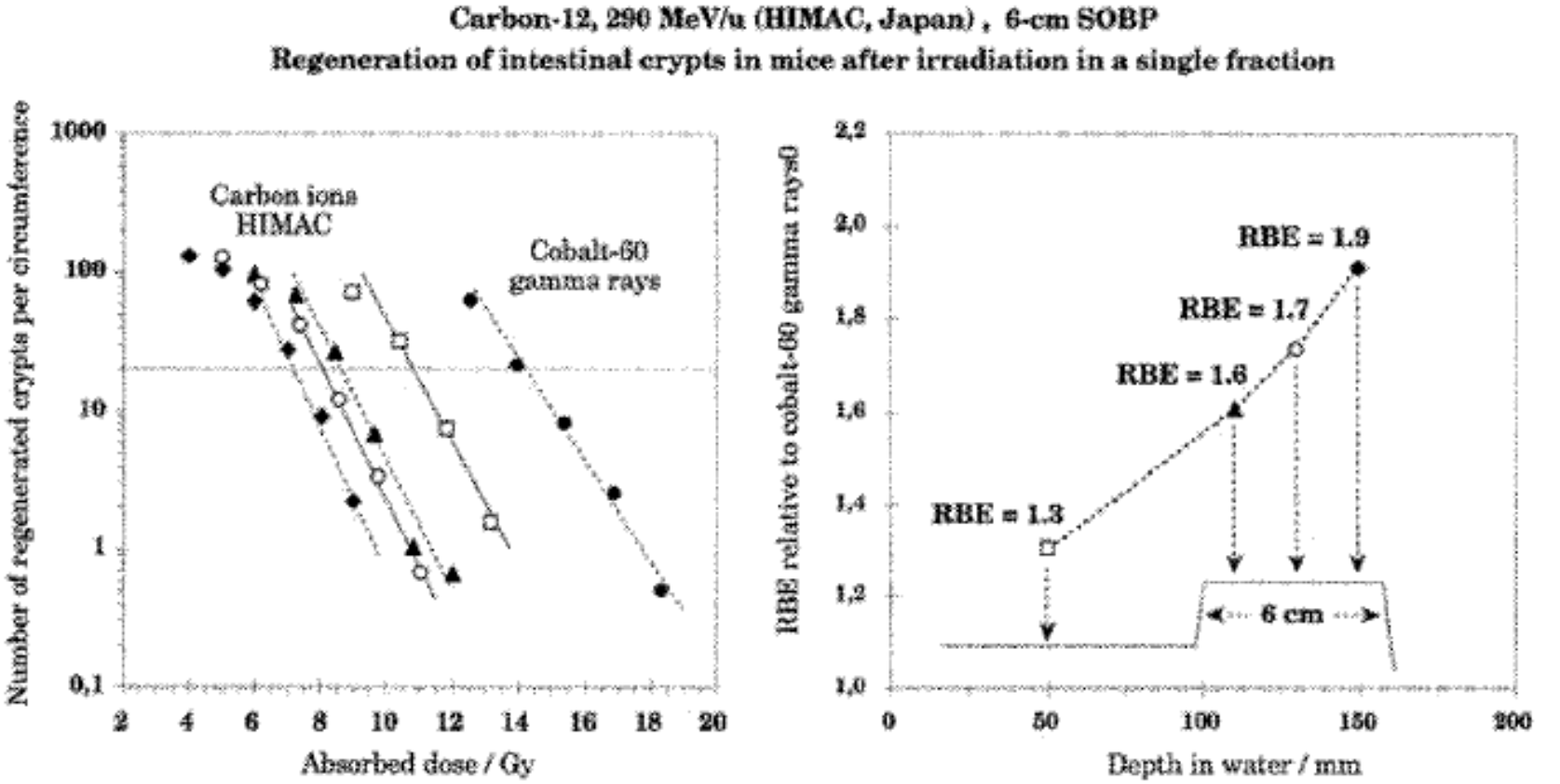
Carbon Ion RBEs for Normal Tissues *in Vivo*: Available Therapy-Relevant Data

- There is very little!
  - bit more for tumors
- Ando and Kase (2009): 82 RBE values for normal tissue effects of carbon ions in 17 papers



Carbon Ion RBEs for Normal Tissues: Available Therapy-Relevant Data

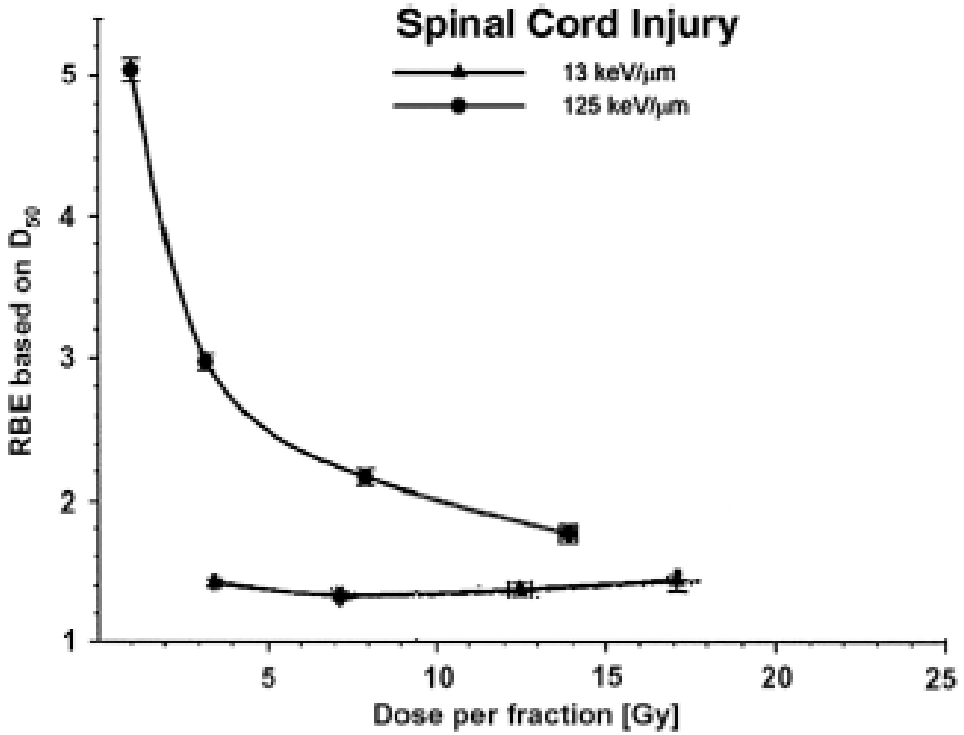
- Additional data on sensitivity of GI tract
- Note use of relatively large doses cf some survival curves



(from Gueulette *et al.* 2004)

Carbon Ion RBEs for Normal Tissues: Available Therapy-Relevant Data

- Bit more data on the spinal cord
- RBEs depend on fractionation at higher LET

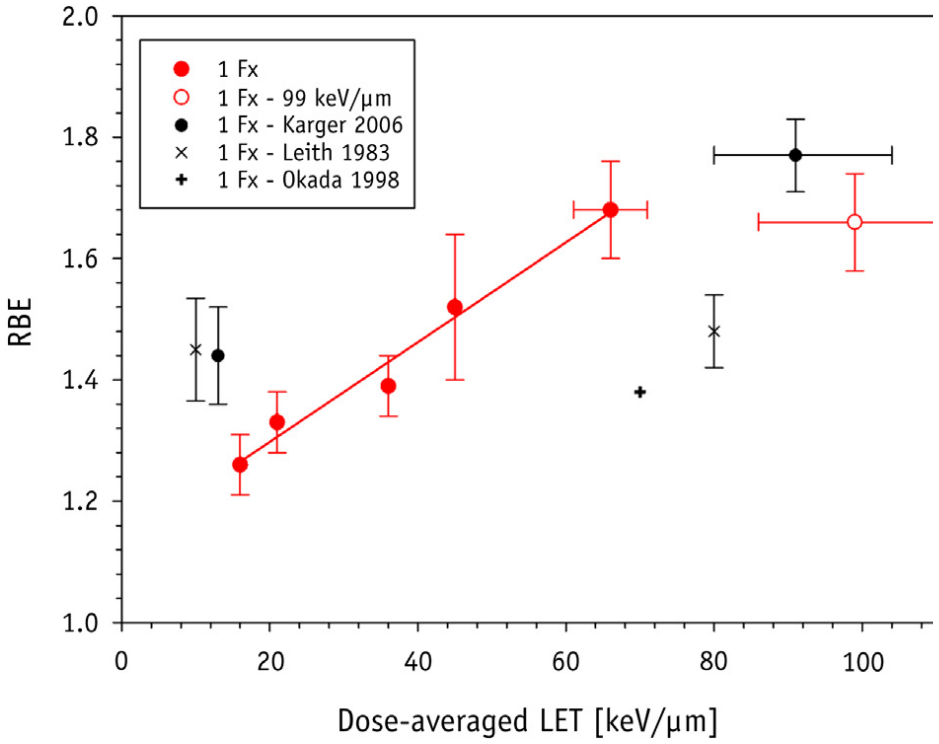


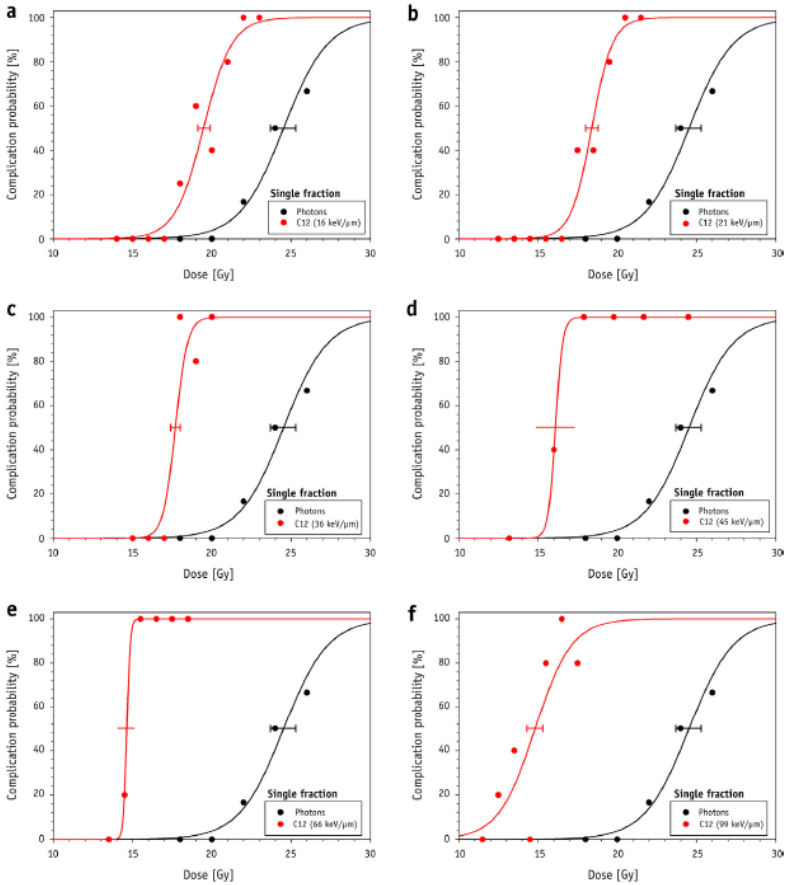
[from Suit *et al*. (2010); data from Karger *et al*. (2006)]

Fig. 10. RBE *vs* dose per fraction for late cervical spinal cord damage by ^{12}C ion *vs* 15 MV X-irradiation [38].

Carbon Ion RBEs for Normal Tissues: Available Therapy-Relevant Data

- Spinal cord damage with single fractions of carbon depends on LET
- RBEs not so large, but doses are

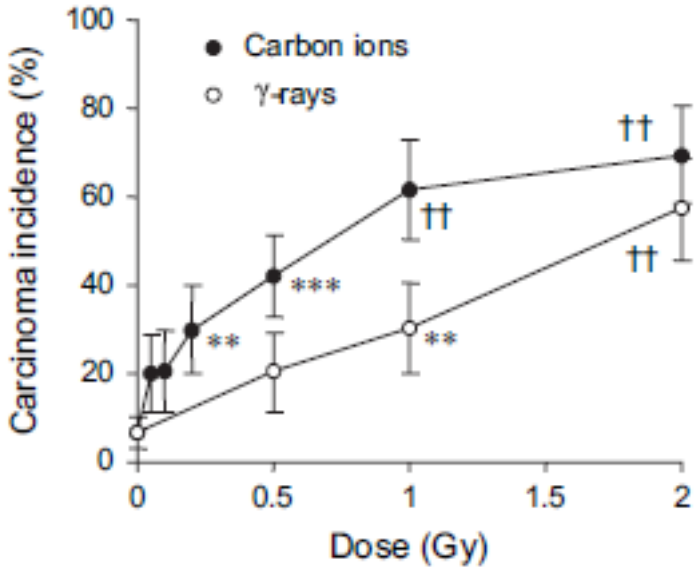




(from Saager *et al.* 2014)

Carbon Ion RBEs for Cancer Induction

- Some animal data show high RBEs (>5) for cancer induction with ions heavier than carbon, but only a few studies exist with carbon ions.

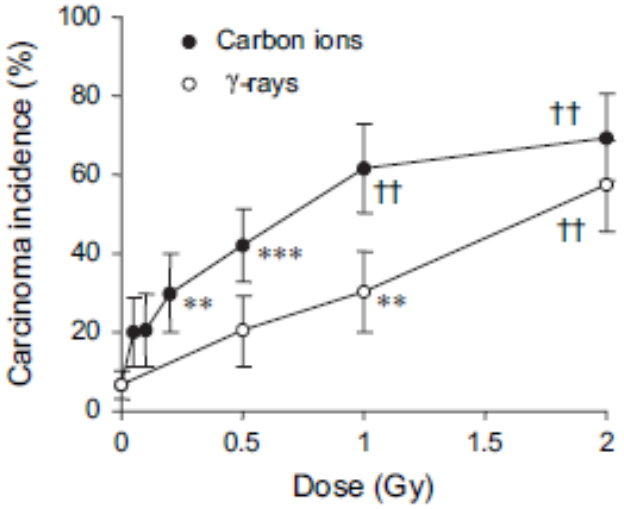


Sprague-Dawley rats (8 weeks old)
Mammary carcinoma
290 MeV/n C ions (6 cm SOBP)
RBE = 8.6 at 0.05 Gy
RBE = 1.9 at 1 Gy

(from Imaoka *et al*. 2007)

- Recent study of Imaoka *et al*. (2013) shows strong age dependence for RBEs: 0.2 at 1 week, 1.1 at 3 weeks and 3.3 at 7 weeks (with linear ERR dose responses for C ions)

Carbon Ion RBEs for Cancer Induction



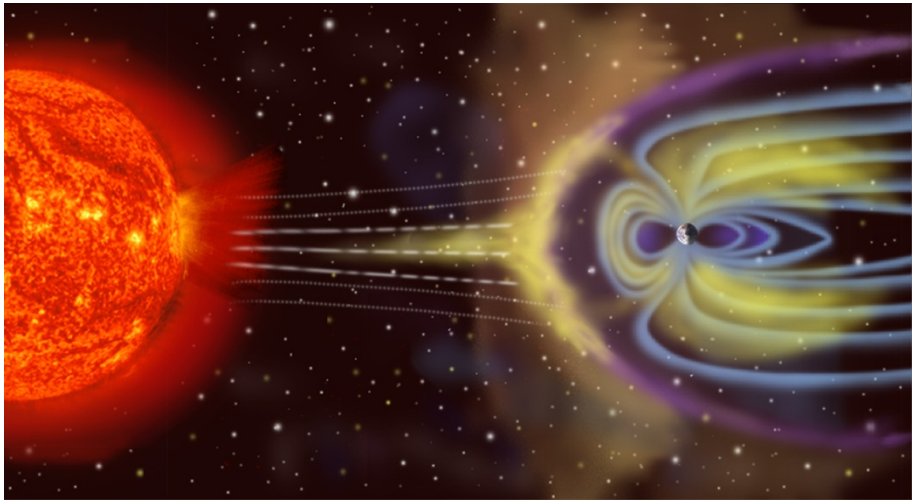
Sprague-Dawley rats (8 weeks old)
290 MeV/n C ions, 6 cm SOBP

RBE = 8.6 at 0.05 Gy; 1.9 at 1 Gy

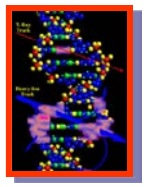
(from Imaoka *et al*. 2007)

- Often thought that cancer risk should be lower with carbon ions because the integral dose in normal tissue is reduced, but what if RBE goes up at low doses with high LET ions?
- On the other hand, in a human, most normal tissue will be in the entrance, not the SOBP, so will see low LET.

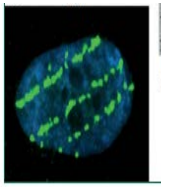
Space Radiation Biology Studies of Charged Particle RBEs



- Most emphasis has been on carcinogenesis and CNS effects
- Increasing amounts of data but much of it of limited relevance for therapy
  - Stresses lower doses
  - Mostly using ions heavier than carbon
  - Sometimes no photon reference

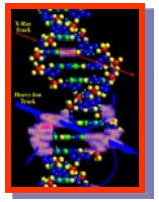


Carbon Ion RBEs – Some Thoughts

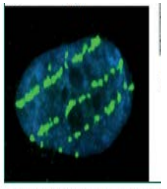


- How relevant are cell survival data for assessing normal tissue effects?
  - Maybe consider cytokines/inflammatory/fibrosis factors
- Dose heterogeneity in the normal tissues is a challenge
- Even for protons, “For NTCP, the variety of endpoints … and the large spread of results currently do not allow a comprehensive analysis towards a clinical RBE” (Paganetti 2014).
- Can clinical data be used to derive RBEs?

- Most relevant papers conclude:
  - “RBE of late effects should be studied”
  - “Uncertainty in RBE is the major problem in dose prescription for carbon ion therapy”



Biological Research Needs: Challenges and Opportunities



- How can we take advantage of this unique “drug”, heavy charged particles, to improve cancer therapy?

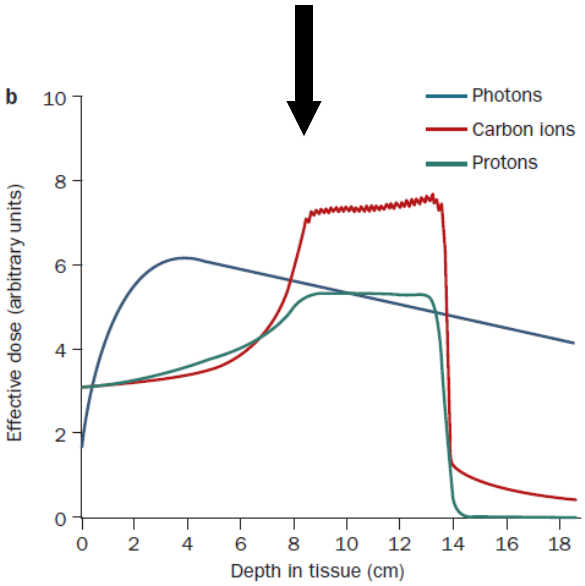
Challenges and Opportunities:
Some Research Needs in Charged Particle Biology
(summarized/selected from DOE-NCI Workshop, Jan., 2013)

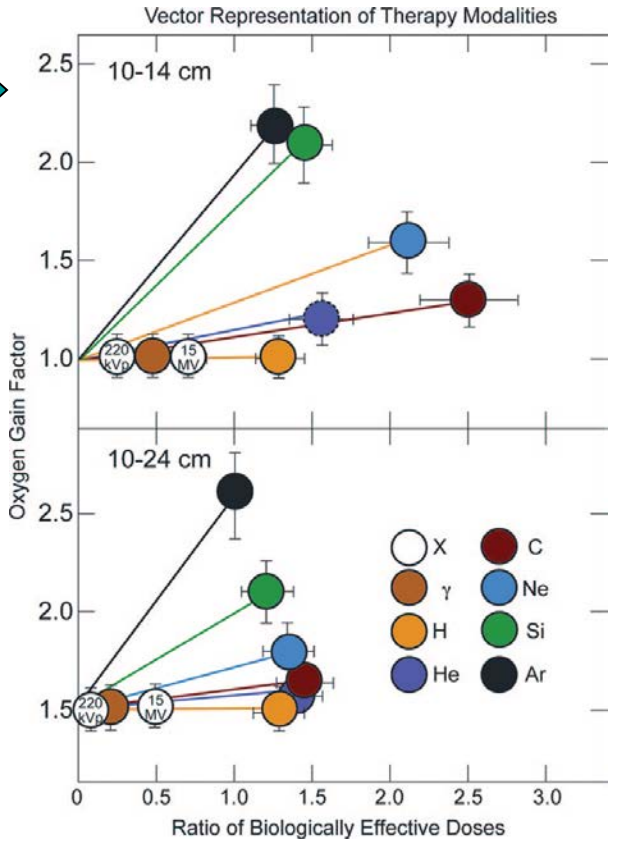
- Quantification of biologically-effective doses of ions in tumors and normal tissues – What's the "best" ion for any given tumor/normal tissues?
- Dose fractionation patterns – Is hypofractionation "better" for some tumors? What's it do to normal tissues?
- Role of hypoxia
- Combined radio + chemo/immunotherapy
- Induction of second cancers
- Individual sensitivity
- Biomarkers
- Molecular mechanisms?

Is Carbon the "Best" Heavy Ion?

Pioneering work of Blakely *et al*. suggested it is, based on ratio of peak to plateau BEDs.

Heavier ions may have better oxygen gain factors, but they tend to have declining "peak-to-plateau" ratios and produce more dose in the "tail", beyond the Bragg peak.





(from Blakely and Chang 2009)

But what about ions between Helium and Carbon or slightly heavier than Carbon?

What's the "best" ion?

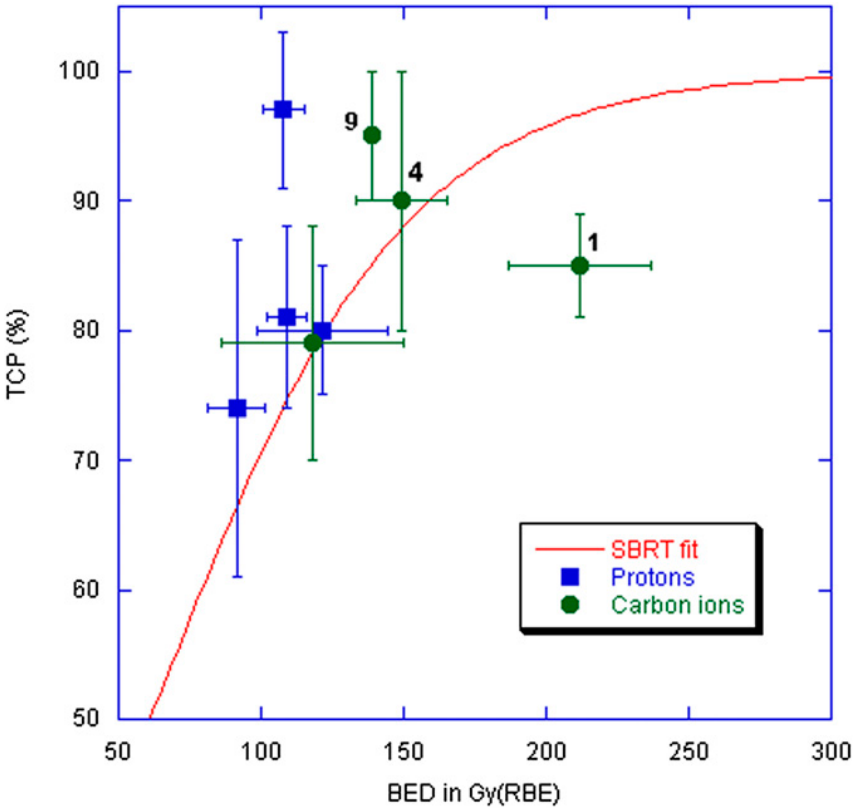
RBE depends on many factors, e.g., cell type, dose, dose rate, charged particle, etc.

NEED: Quantitative data on biologically-effective doses of ions in tumors and normal tissues

- Various ions (protons through oxygen)
- Various tumor types
  - With info on their genetic backgrounds
- Early versus late-responding normal tissues
- Integration into biophysical models and treatment planning

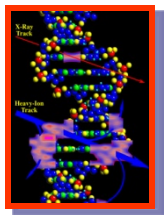
Why Is Hypofractionation of Ion Beams Effective in Tumors?

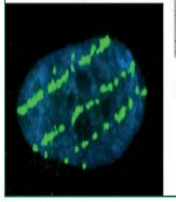
- Because of better dose localization, number of fractions can be reduced (down to 1-3 fractions) with dose per fraction increased
- Advantages to patient and economy from fewer fractions
- Biology studies suggest may be different/greater tumor damage
  - more vascular damage
  - target hypoxic regions
  - stimulation of immune response
- Are normal tissue reactions increased?



Stereotactic body radiotherapy and charged particles in NSCLC

(from Durante 2014)

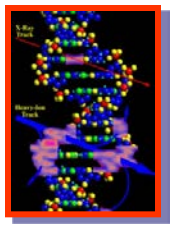




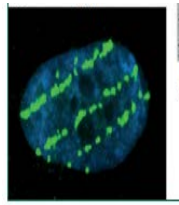
Molecular Mechanisms: Uniqueness of Track Structure

Differences in:

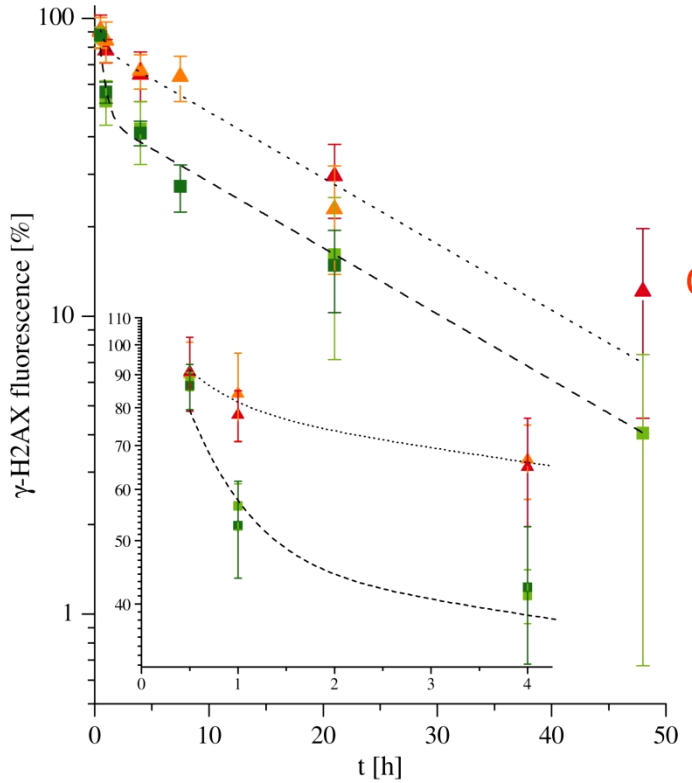
- types/complexity of DNA damages
- gene expression patterns
- effects on microenvironment
- intra- and inter-signaling
- immune system stimulation
- killing cancer stem cells



Molecular Mechanisms: Uniqueness of Track Structure



Differences in: types/complexity of DNA damages

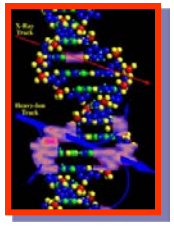


(from Schmid *et al*. 2010)

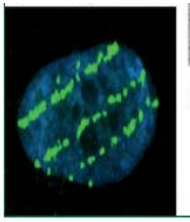
Slower and less complete repair of damage from carbon ions

Exploit by selecting DNA repair deficient tumors?

Enhance by combination with repair inhibiting drugs?



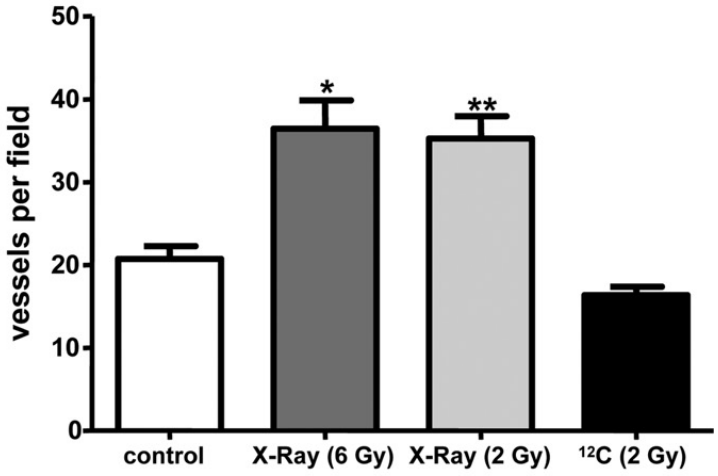
Molecular Mechanisms: Uniqueness of Track Structure

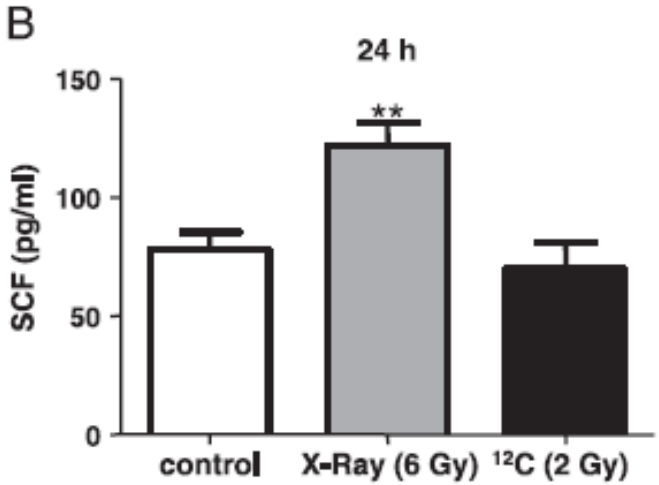


Differences in:

- gene expression patterns
- effects on microenvironment

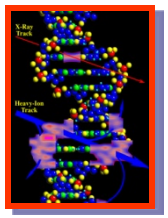
A549 lung cancer model



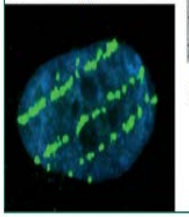


(from Kamlah *et al*. 2011)

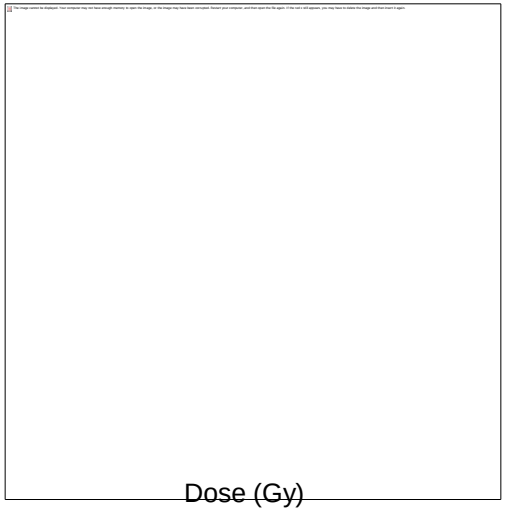
Are Carbon ions anti-angiogenic? If so, why?



Molecular Mechanisms: Uniqueness of Track Structure

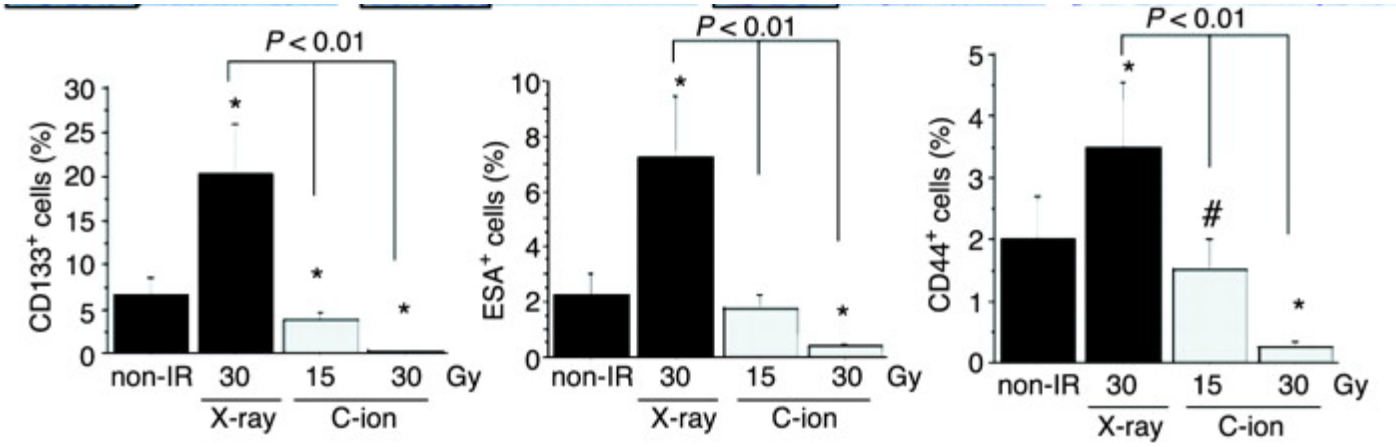


Differences in: killing cancer stem cells



Are charged particles more effective at killing “radiation resistant” cancer stem cells?

HCT116 Human colon cancer cells

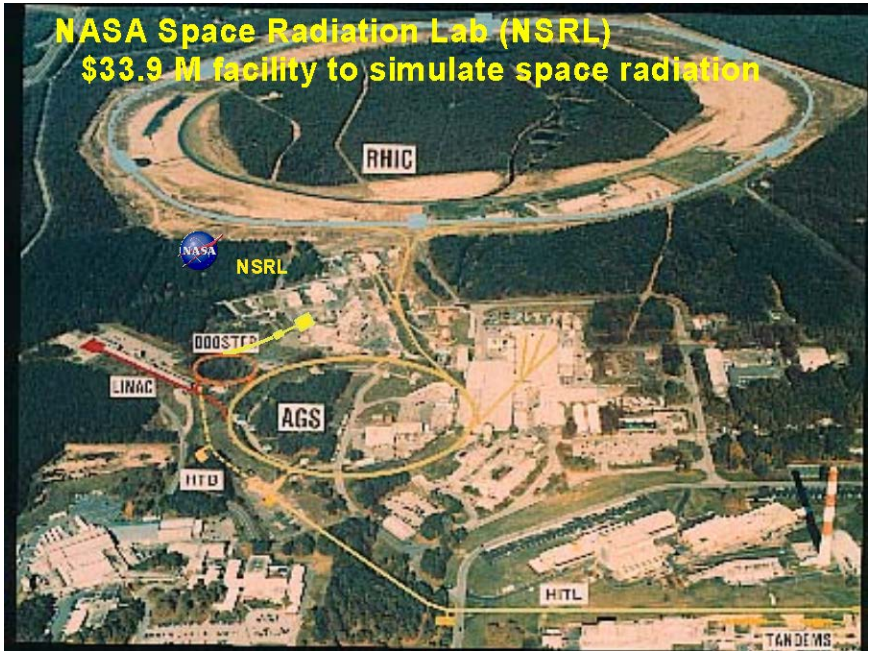


(from Cui *et al*. 2011)

Challenges and Opportunities

- Where can the needed basic biology and preclinical studies be done in the US?

NASA Space Radiation Laboratory (NSRL) at Brookhaven National Lab (BNL)

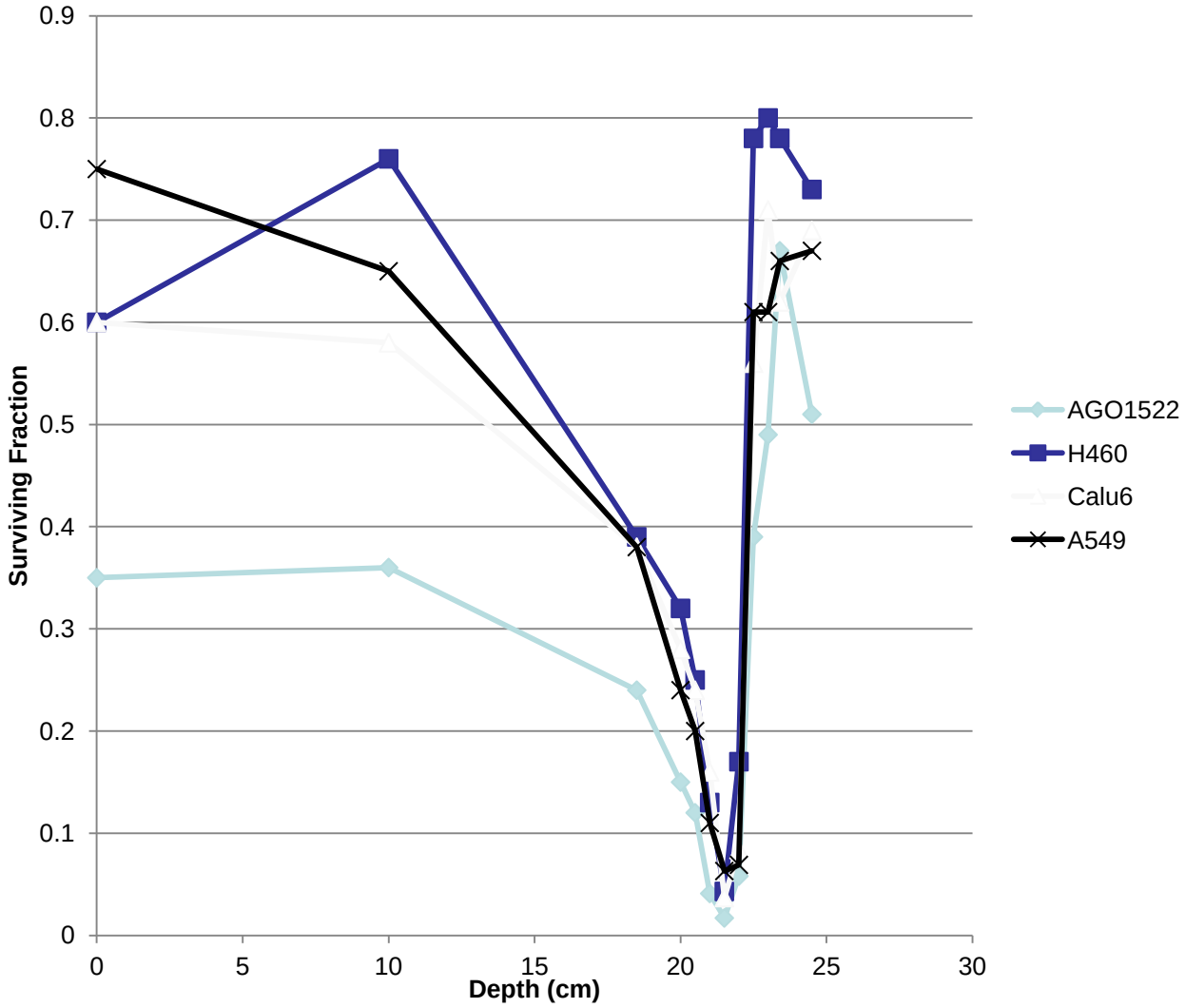


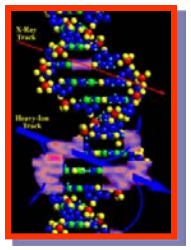
- Built through NASA-funded, DOE-managed collaboration
- Beams available: protons through uranium; energies of 50 to 2500 MeV/n
- Doses and dose rates: 100 particles/cm^2 up to ~4 Gy/min
- Well equipped biology labs and animal facilities at NSRL and in long-term support facility
- Knowledgeable, user-oriented support staff
- Non-NASA funded users pay hourly charge

- http://www.bnl.gov/medical/NASA/CAD/NSRL_Beam_Information_Guide.asp

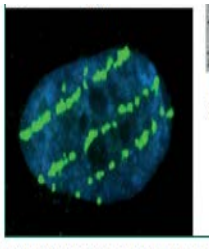
- Lowenstein et al., http://three.usra.edu/articles/NSRLatBNL.pdf

Carbon Ion Irradiations (done on 4-7-14)

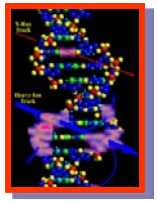




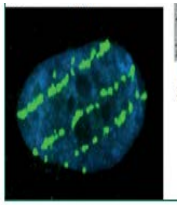
Summary



- Normal tissue RBEs for carbon ions are highly uncertain; little experimental data available.
- Biological research needs, challenges and opportunities are many.



Acknowledgments



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