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CYCLOTRON FACILITY

Genetic Mechanisms of the Dose Rate Effect:

Applications of RBE and LET

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Therapeutic Impact

How does Protracted Fraction Delivery affect the therapeutic window?

- Are there genetic markers for dose rate sensitivity?
- Can these markers be used for a predictive assay?
- Do we need to construct a “Biological Effectiveness” model to correct for low dose rate?

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Working Hypothesis

- The Low Dose Rate Effect is the result of differential physical damage

- Damage is repaired by different mechanisms/proteins

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Types of Damage

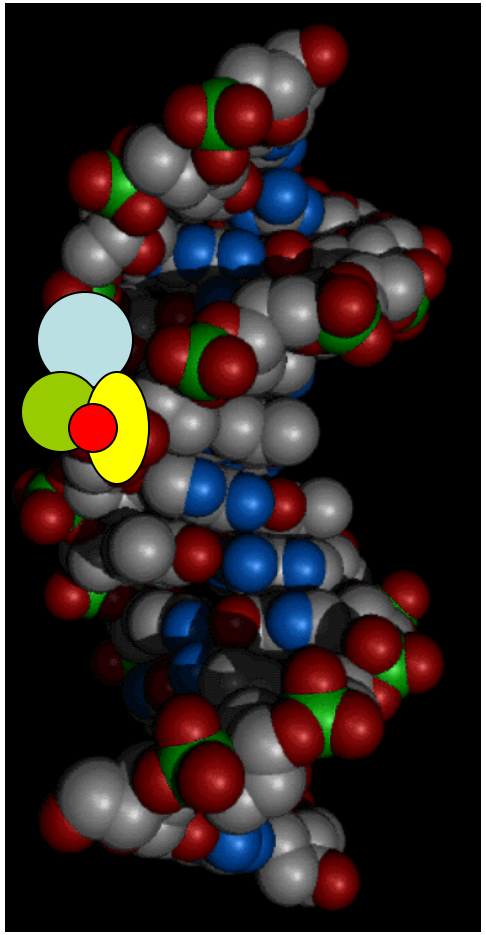
Single strand
Template available

Double strand
Template available

Double strand
No template

Large segment
missing

Mechanisms of Repair



Repair is effected by a complex of
- proteins
- enzymes
- Ribozymes, etc.

It seems reasonable to assume that different combinations of a mutual pool of components would be required to repair different types of damage.

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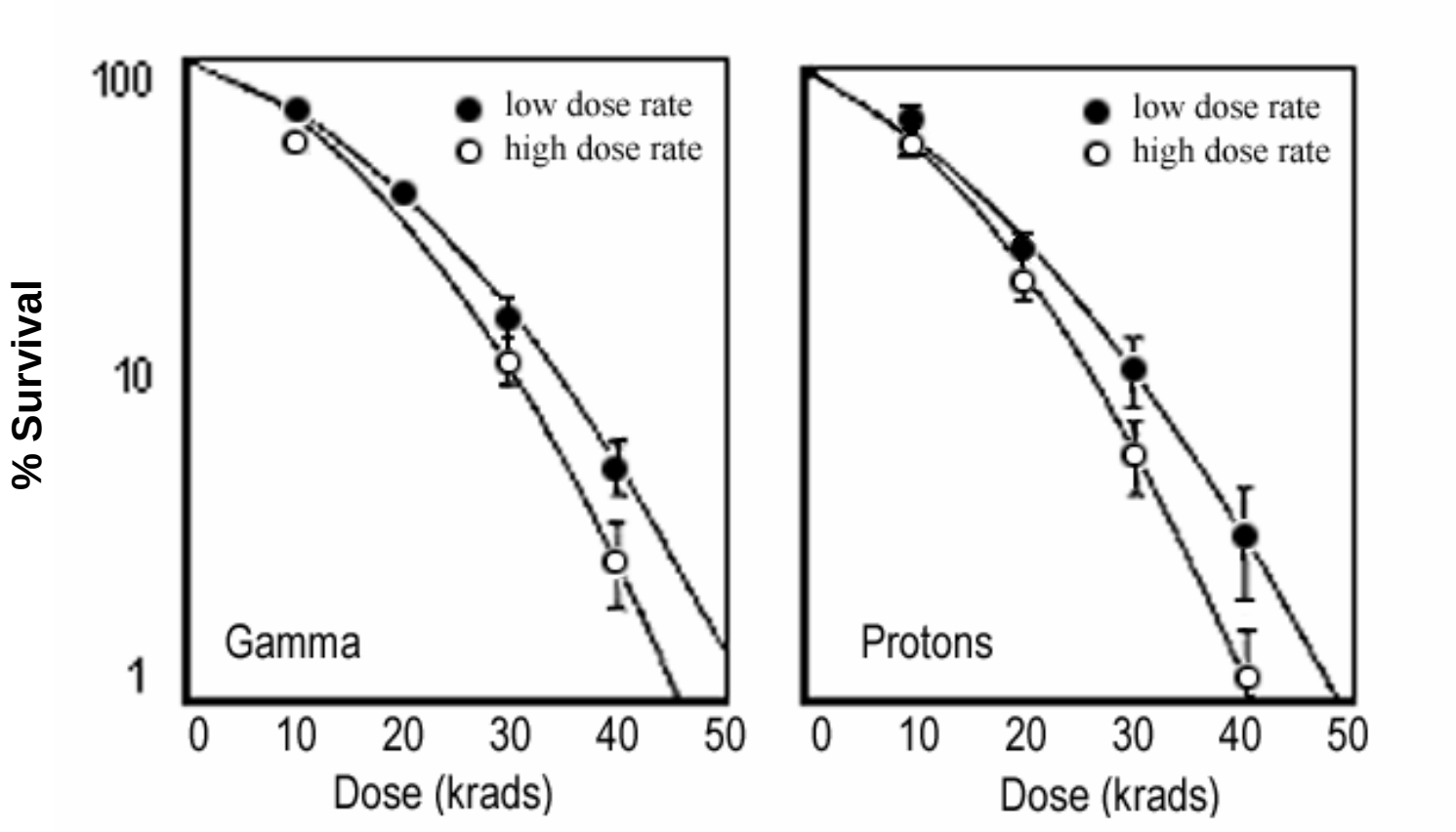
Low to mid-LET Dose Rate Effect



Wild-type *C. cinereus* Response

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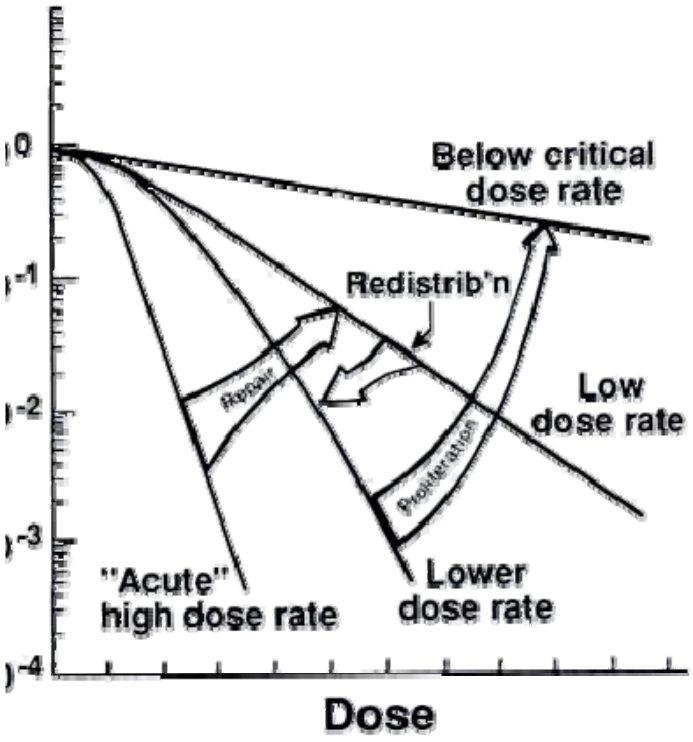
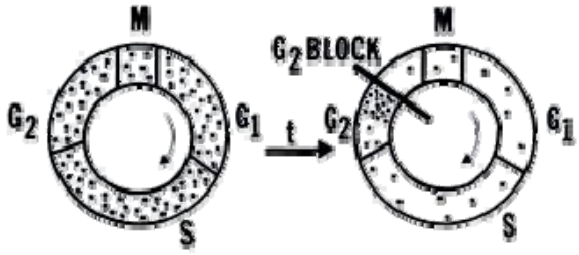
The Low Dose Rate Radiation Effect



Cell cycle:



From: Eric J. Hall, Lippincott Company, 1994

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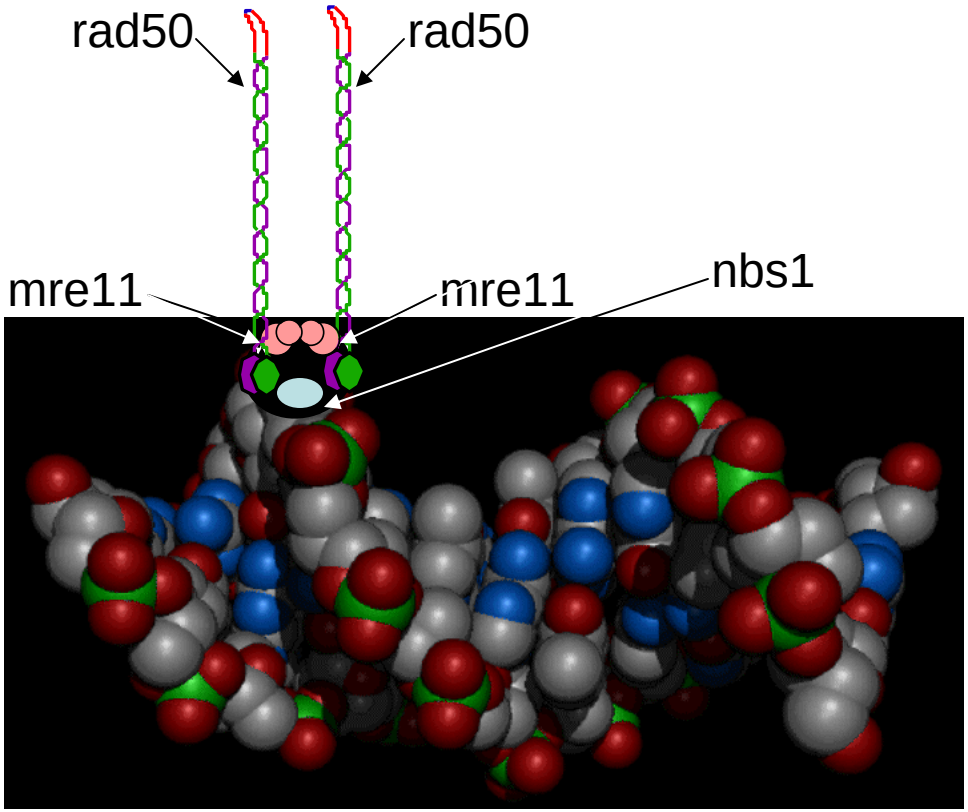
Coprinus/Human Genomics



Identified in Human genome

- **Mre11** binds to the 3' end of damaged DNA
- **nsb1** function is not well defined
- **rad50** binds to mre11 and has an ATP binding site
- **Delangin** effects gene expression

Identified *Coprinus* mutants

- **mre11**
- **rad50**
- **rad3** may be nbs1
- **Rad9** is delangin

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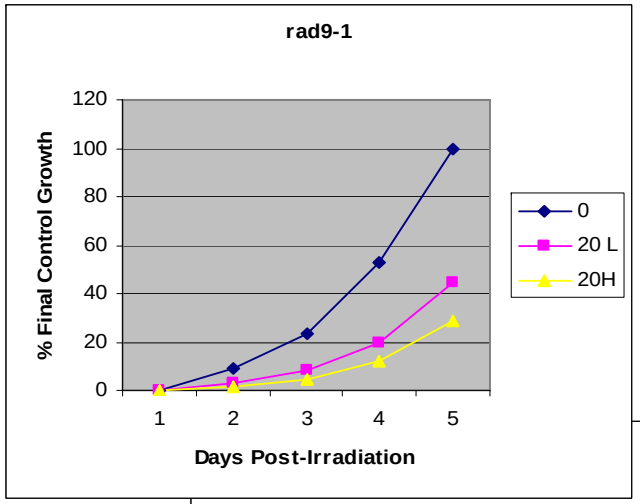
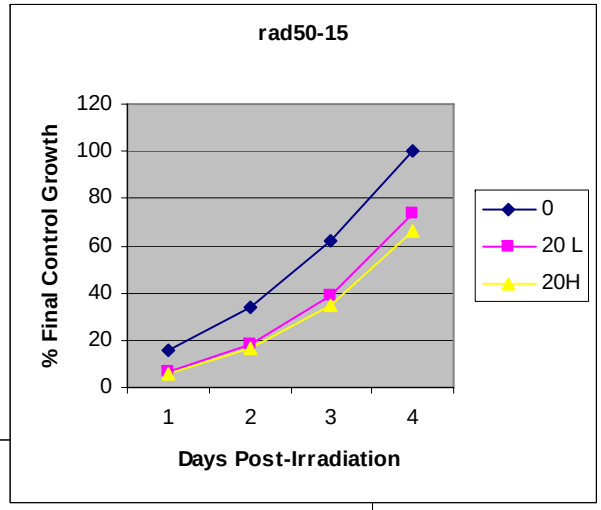
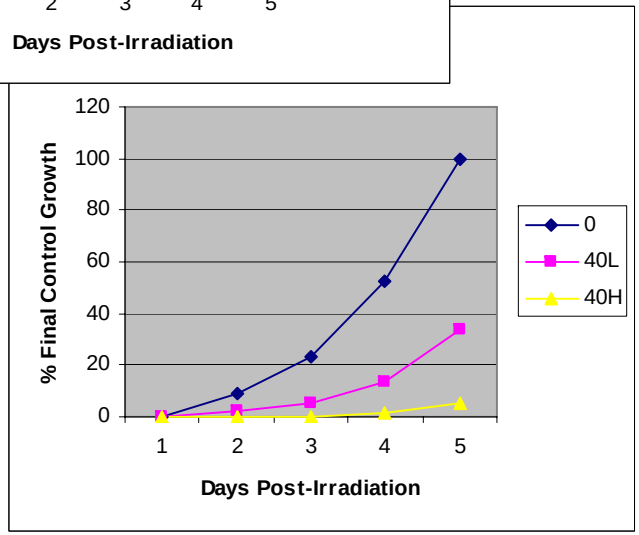
The effect is dose dependent

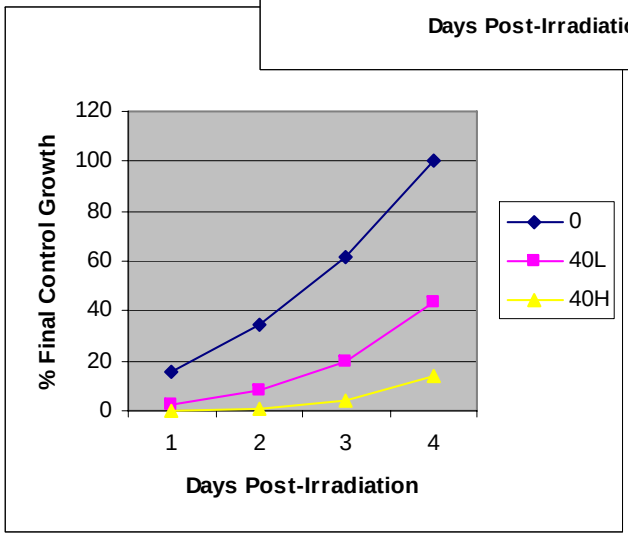


200 Gy



400 Gy





400 Gy

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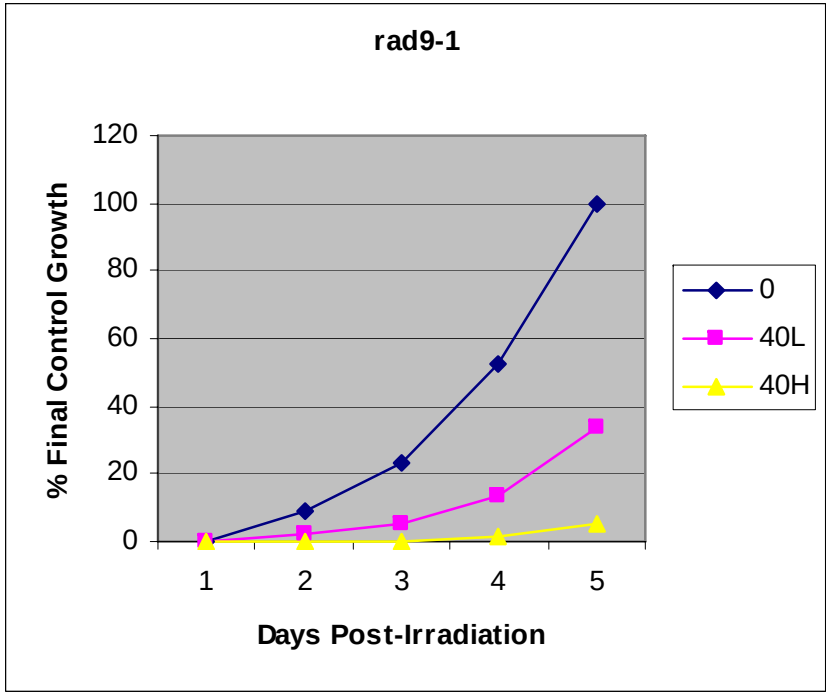
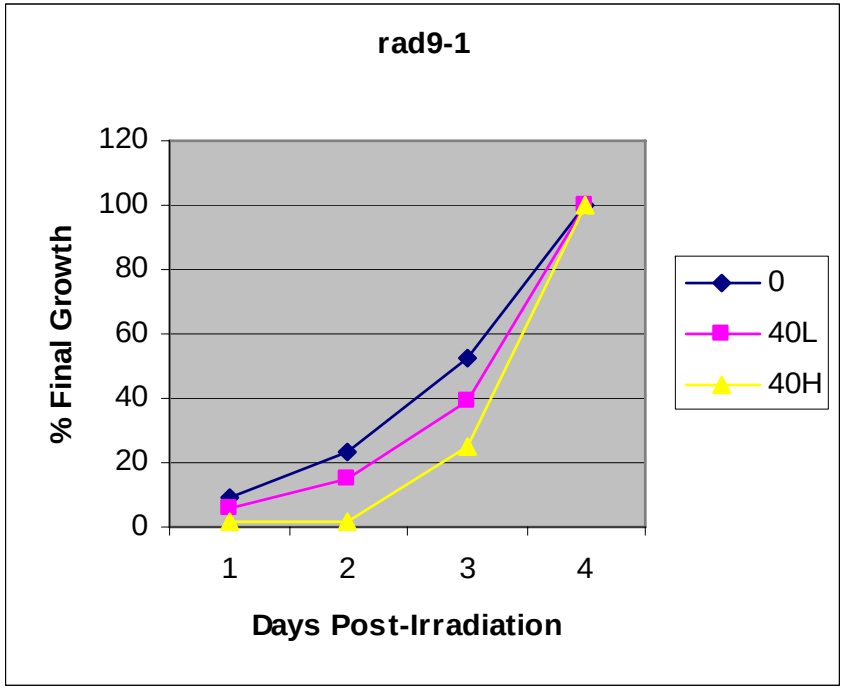
rad9-1





The effect is caused by a delay in the initiation of growth

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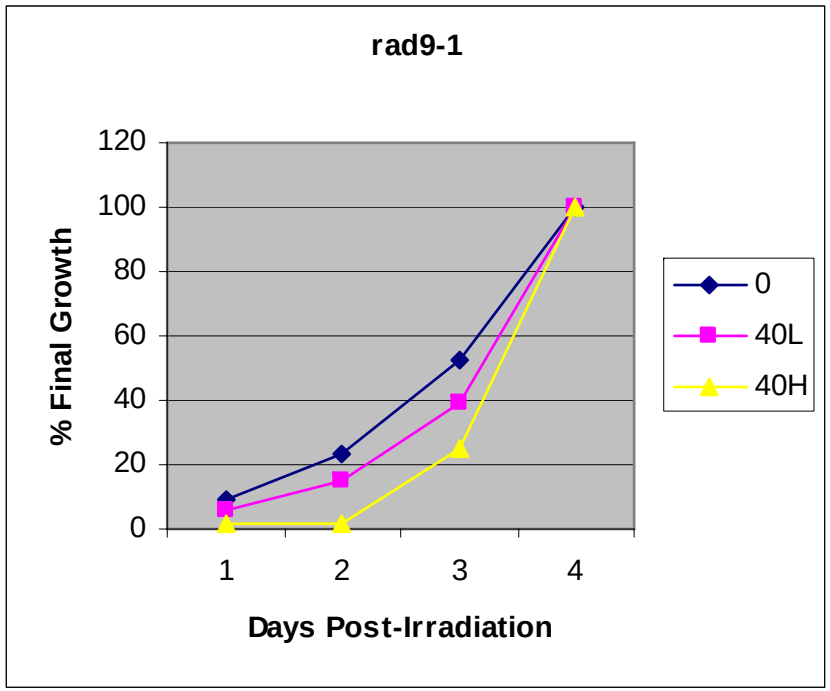
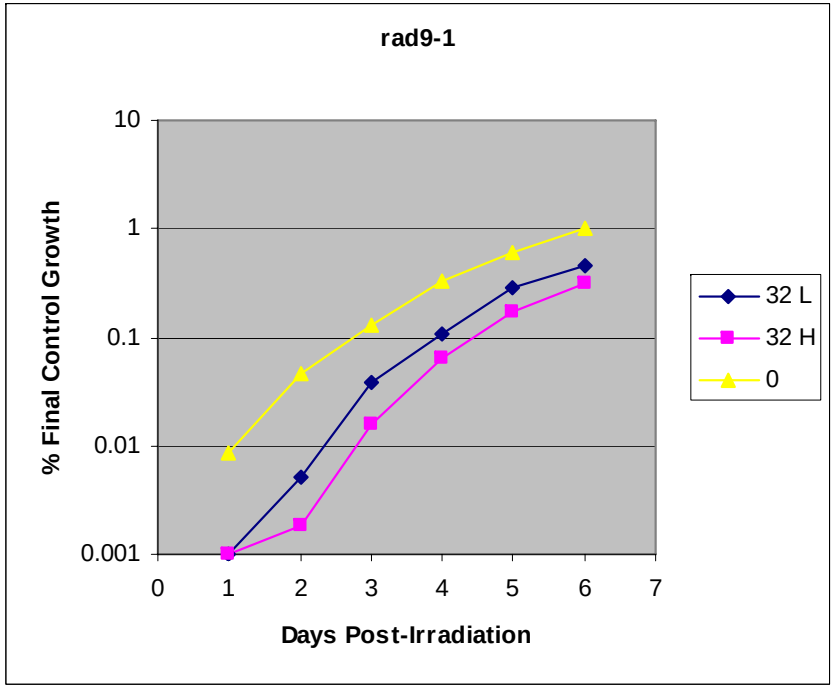
rad9-1





Semi-log plot of proton irradiated samples displays lag.

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rad9-1

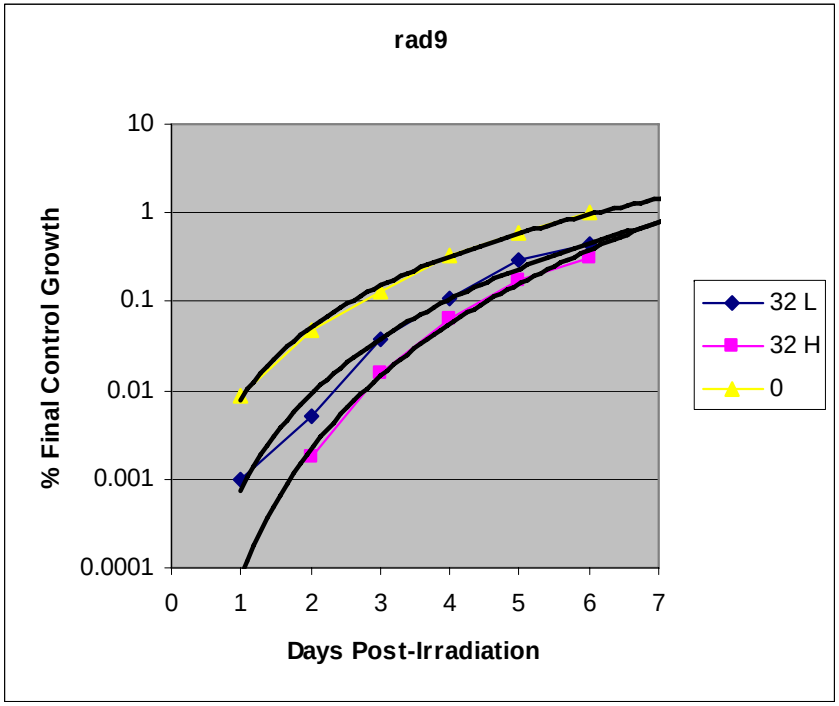
Growth = a t^{b}

$y = (0.008)t^{2.672}$

$y = (0.0007)t^{3.5731}$

$y = (0.00008)t^{4.7326}$

a = the lag
b= the mitotic rate



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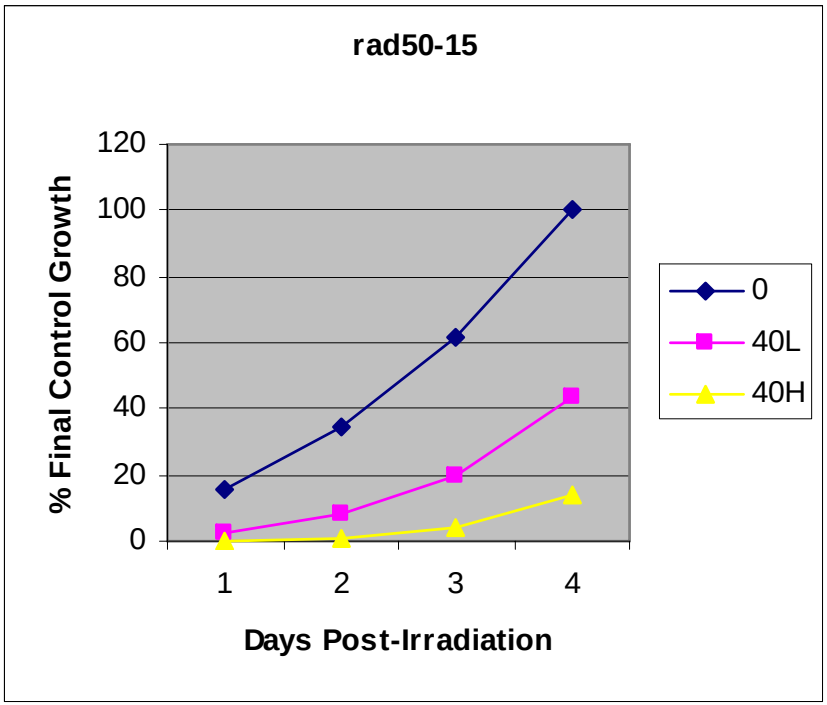
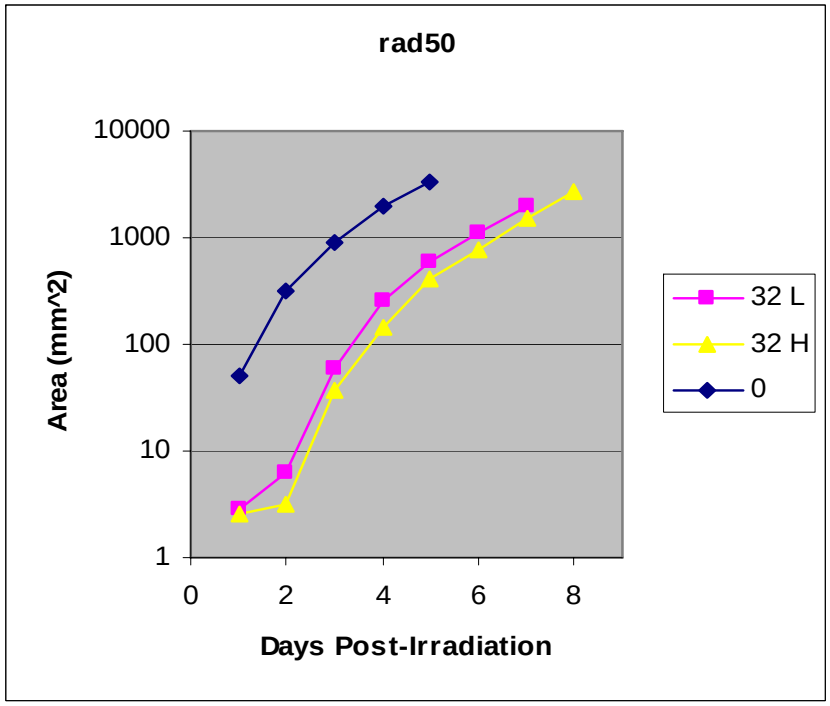
rad50





Implicated as a cell cycle checkpoint protein.

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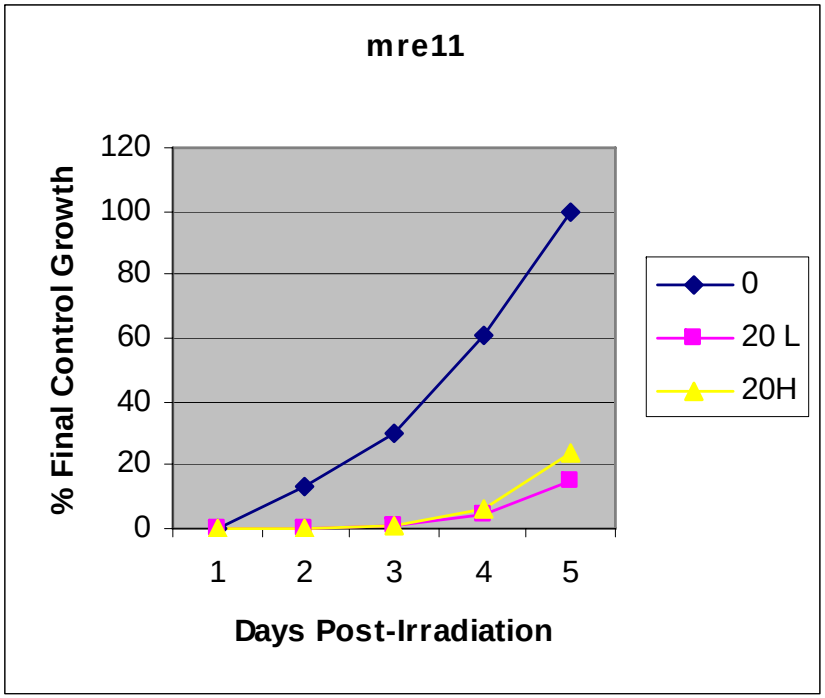
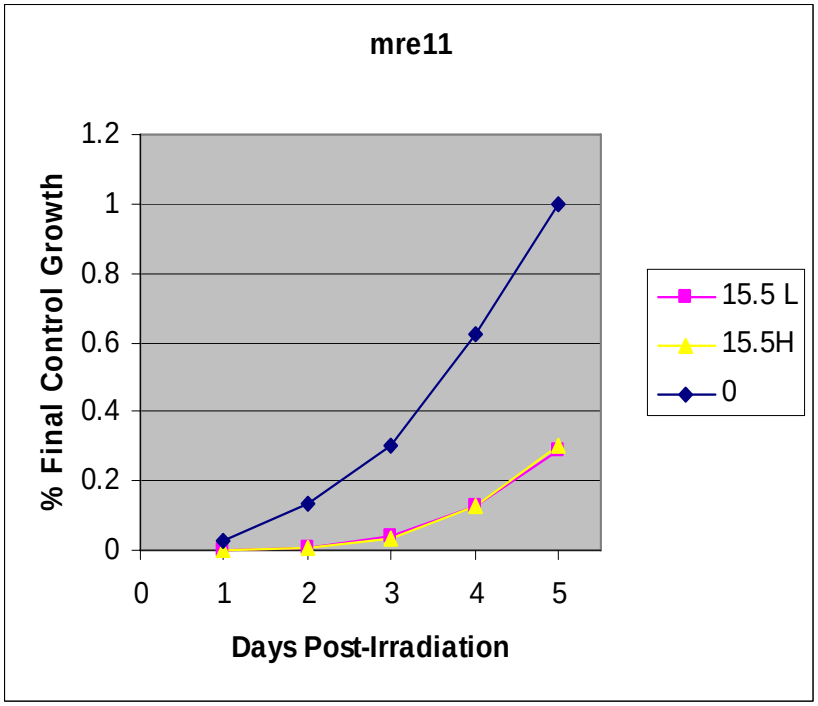
mre11



Gamma Radiation



Proton Radiation

Exhibits no dose rate effect & no lag effect.

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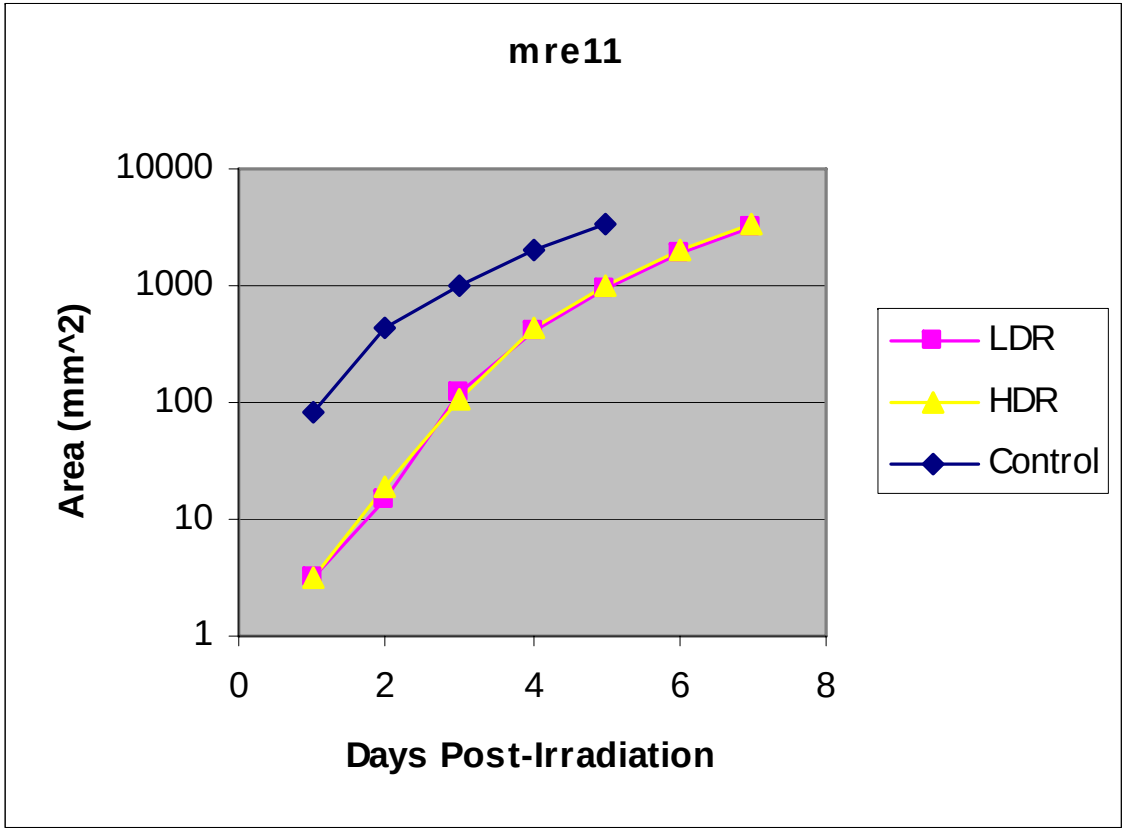
mre11



Exhibits no dose rate effect & no lag effect.

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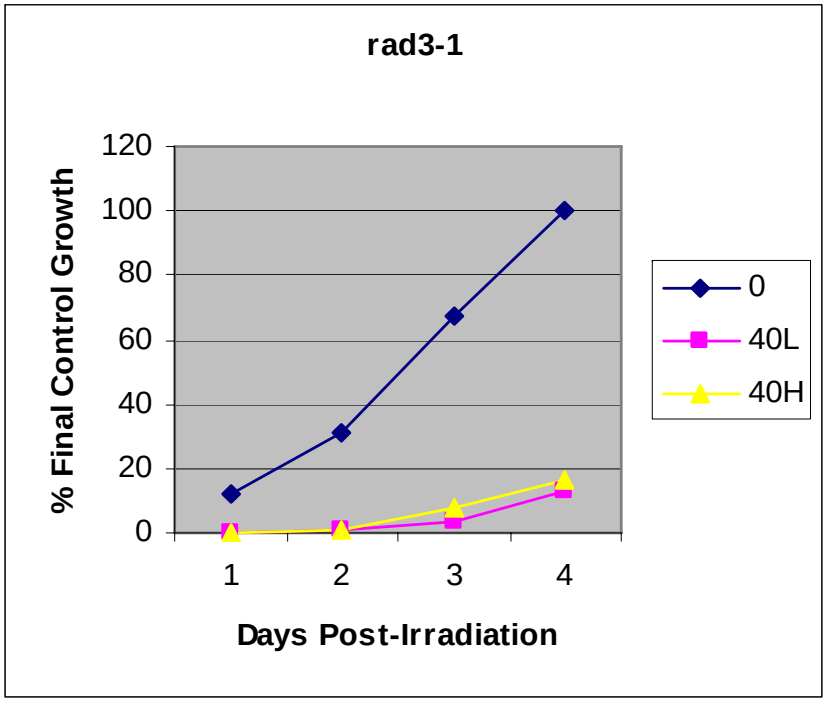
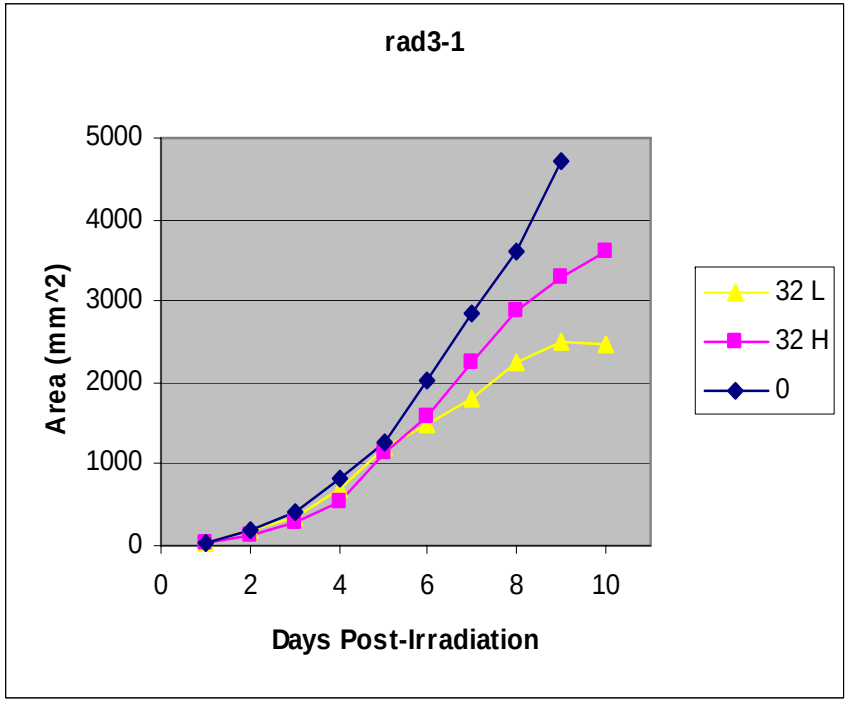
Rad3-1



Gamma Radiation



Proton Radiation

Exhibits inverse effect after day 5.

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Conclusions

- *The dose rate effect is significant for proton irradiation.*
- *The dose rate effect is most prominent near the optimal therapeutic dose.*
- *The effect is expressed as one or more of 3 modalities:*
  - *A lag in cell cycle initiation*
  - *An increase in cell cycle duration*
  - *A decrease in mitotic potential*
- *Some radiation responsive proteins are not associated with a dose rate effect.*

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Acknowledgements

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