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**INDIANA** UNIVERSITY

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



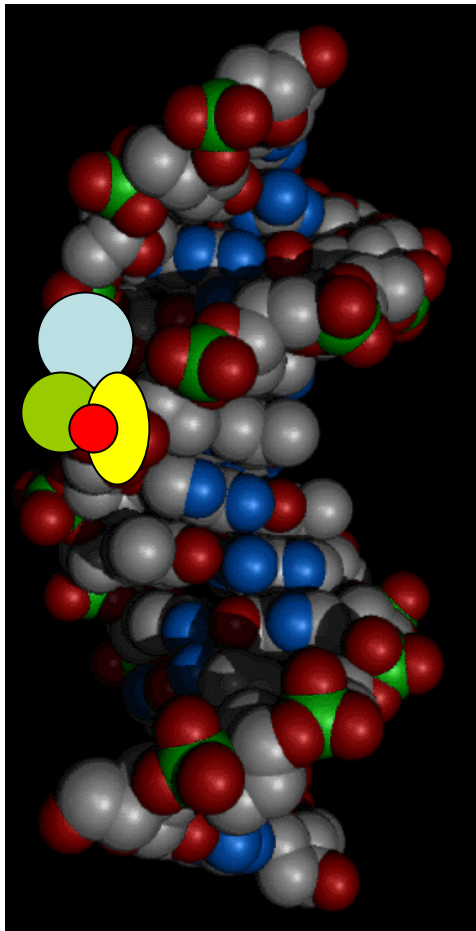
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## Mechanisms of Repair



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.



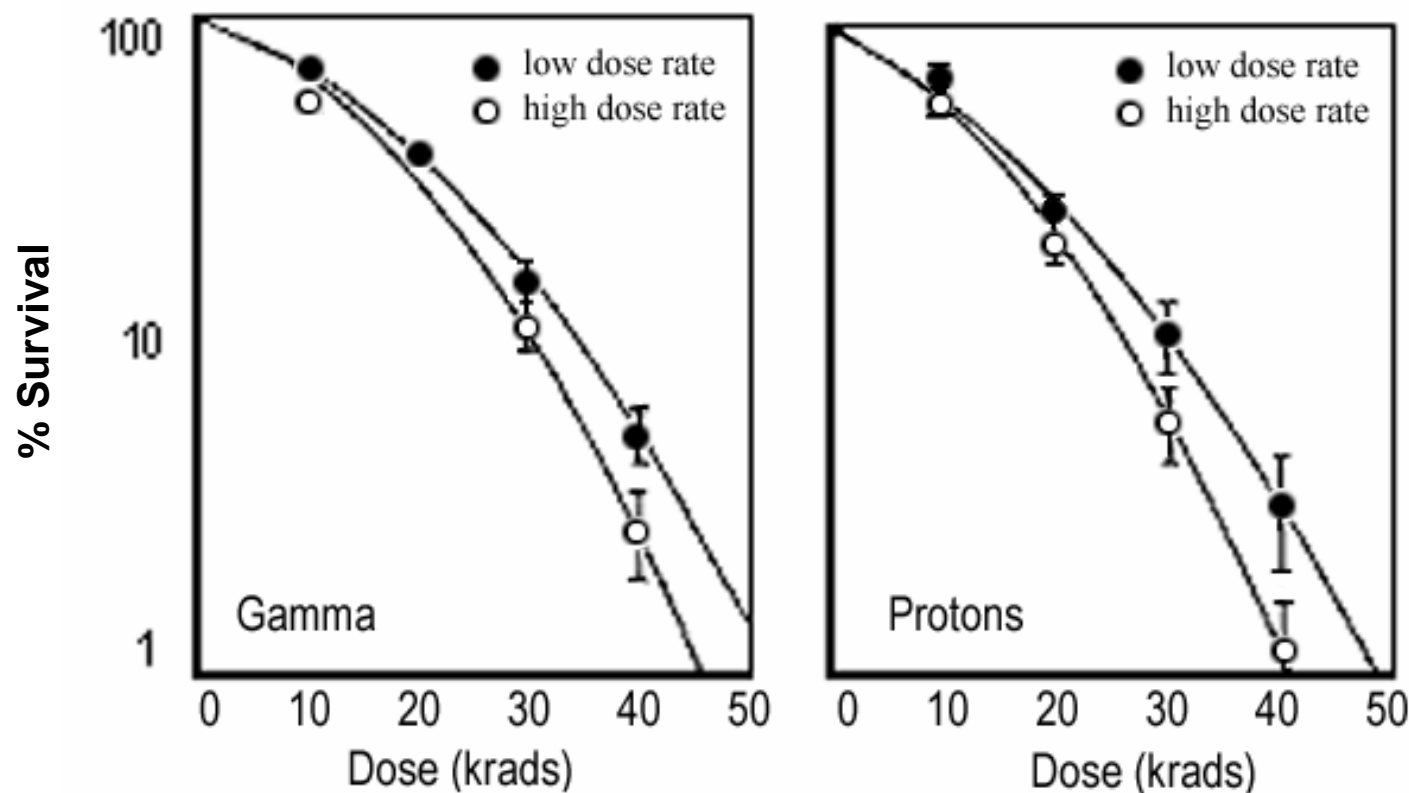
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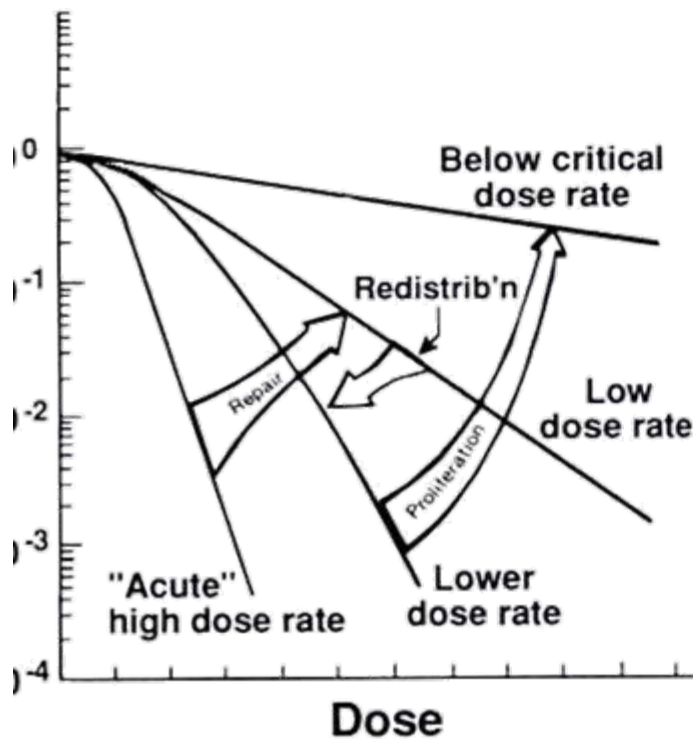
## Low to mid-LET Dose Rate Effect



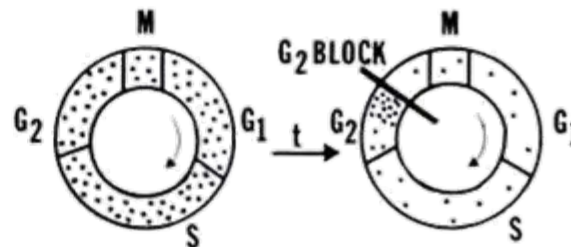
Wild-type *C. cinereus* Response



# The Low Dose Rate Radiation Effect



Cell cycle:



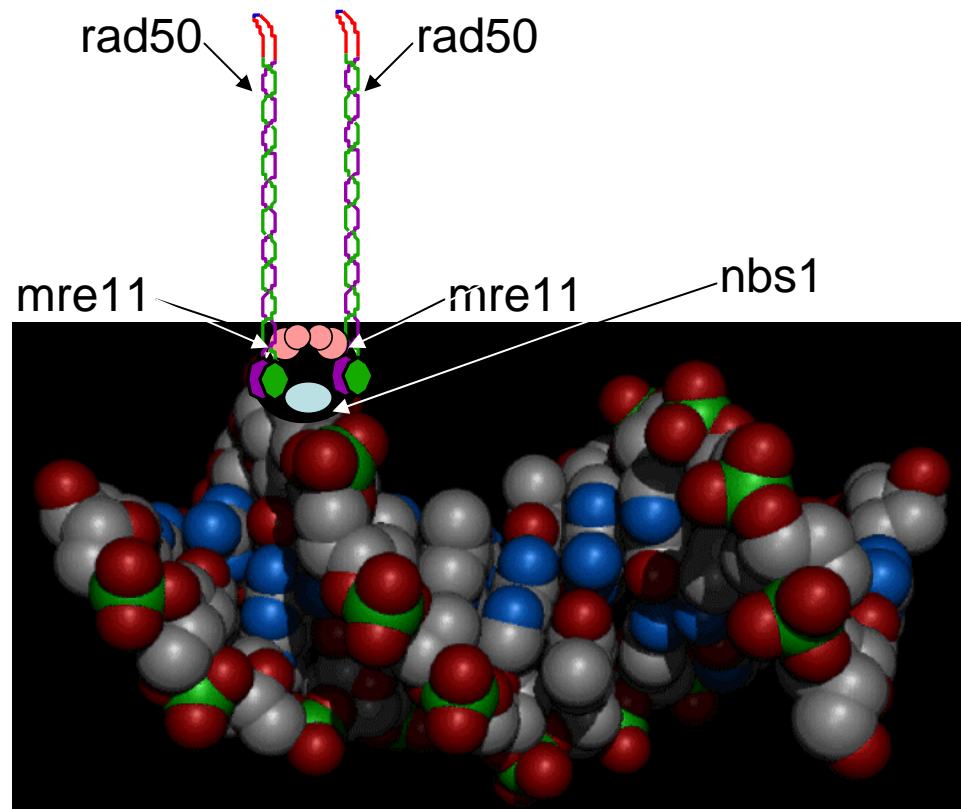


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## Coprinus/Human Genomics



### 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

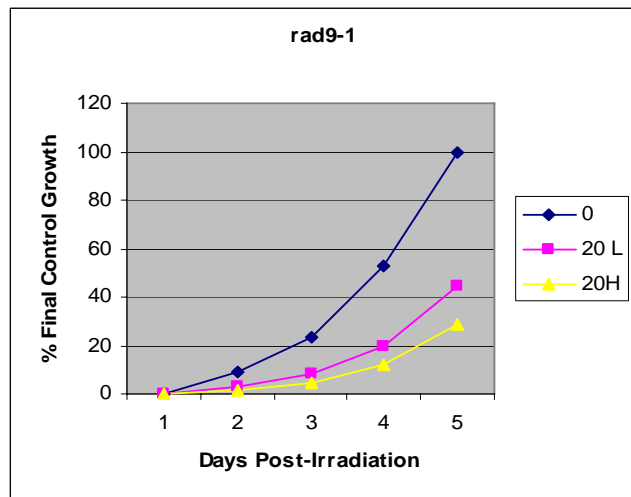
### Identified *Coprinus* mutants

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

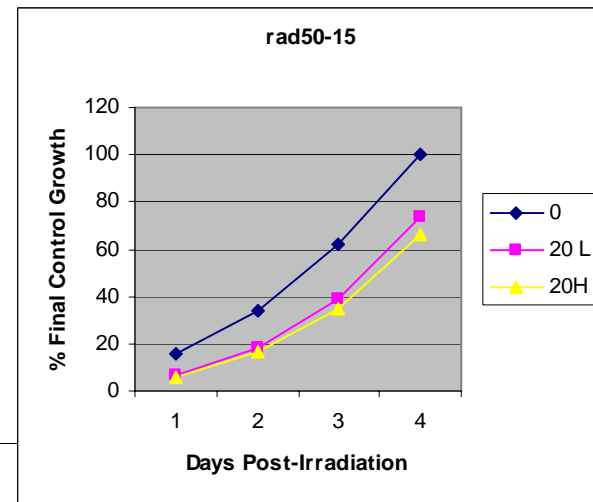




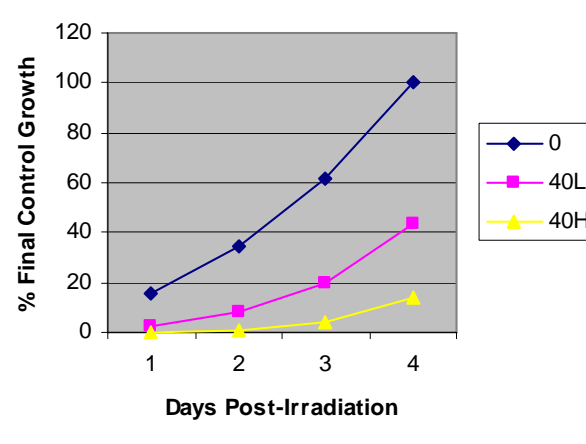
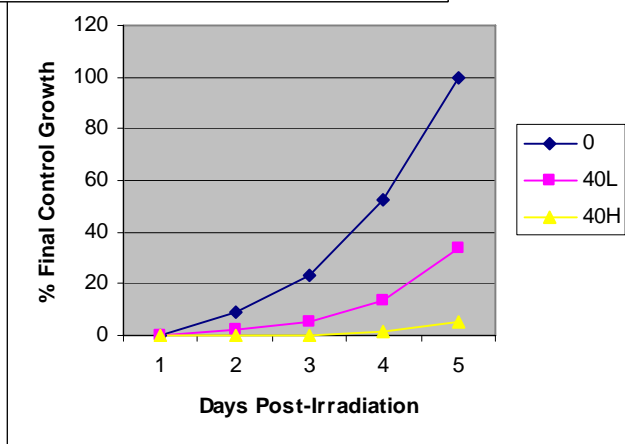
# The effect is dose dependent



200 Gy



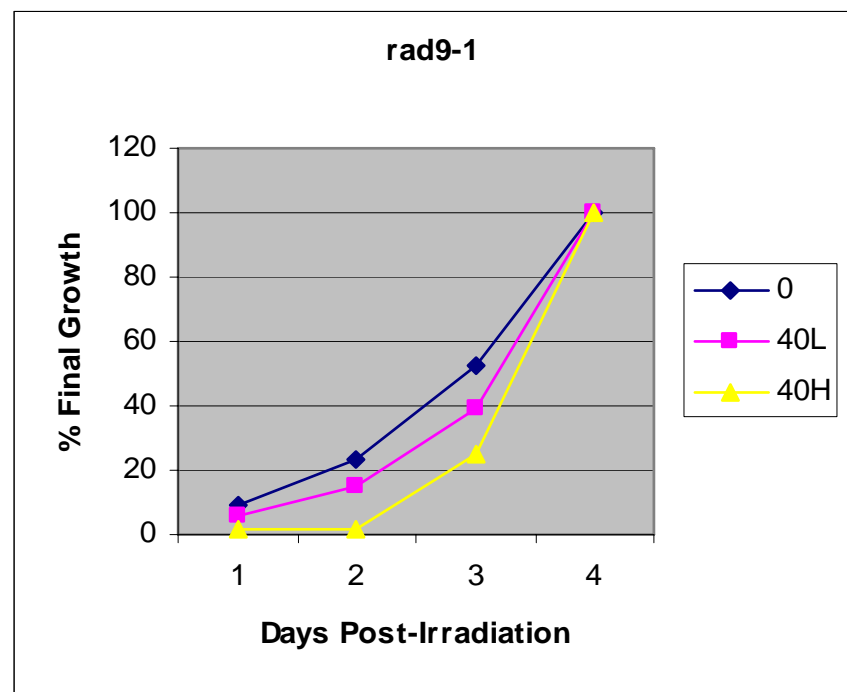
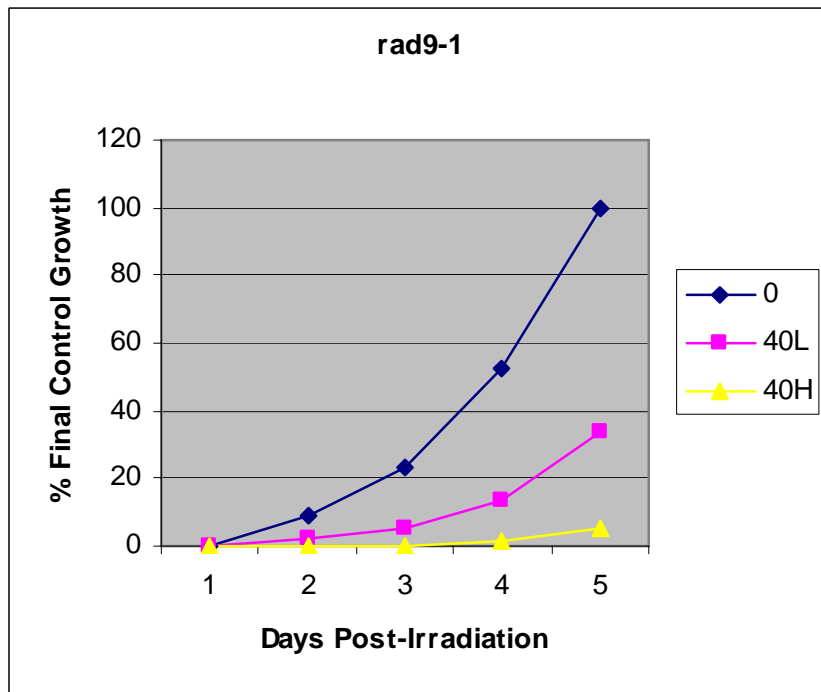
400 Gy



400 Gy



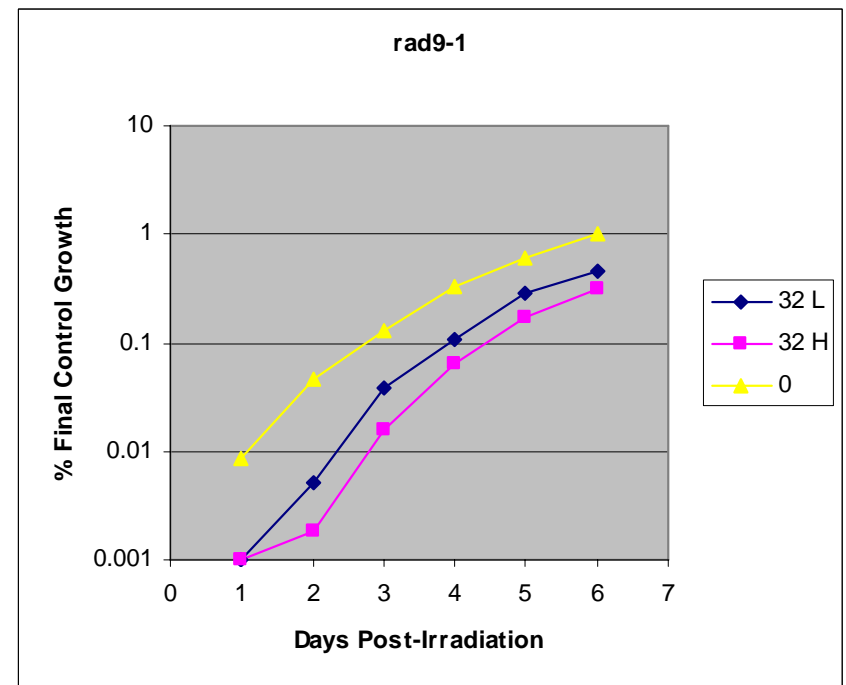
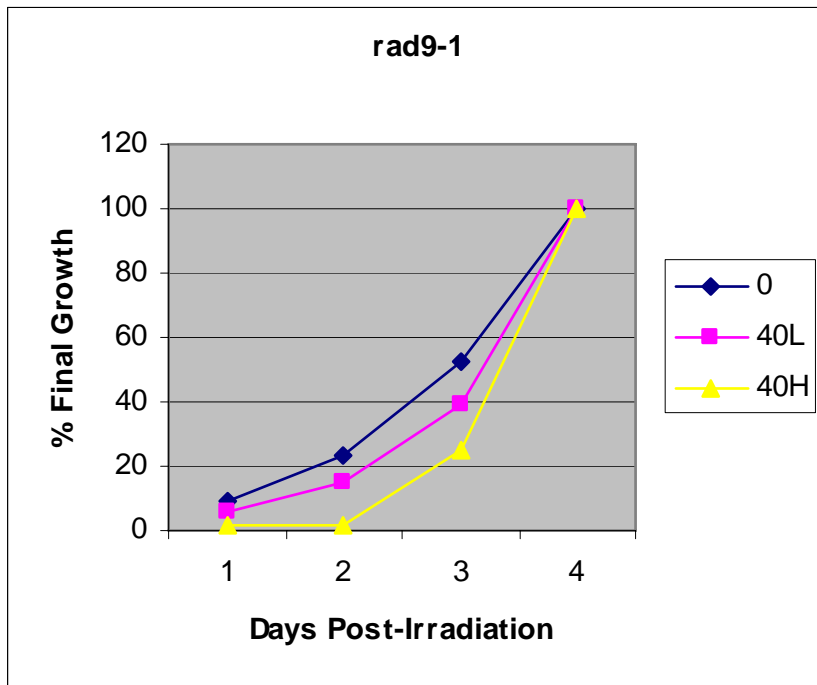
## *rad9-1*



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



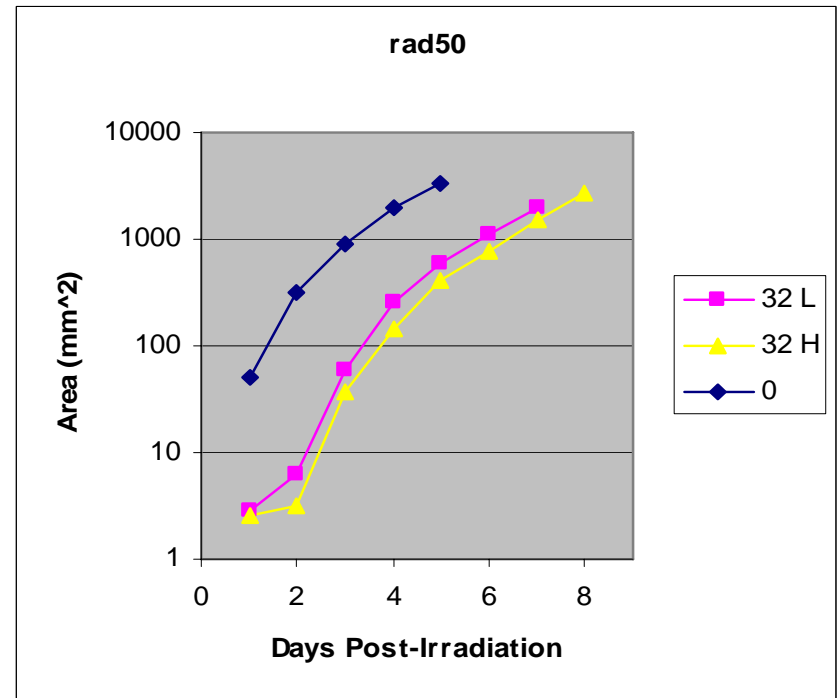
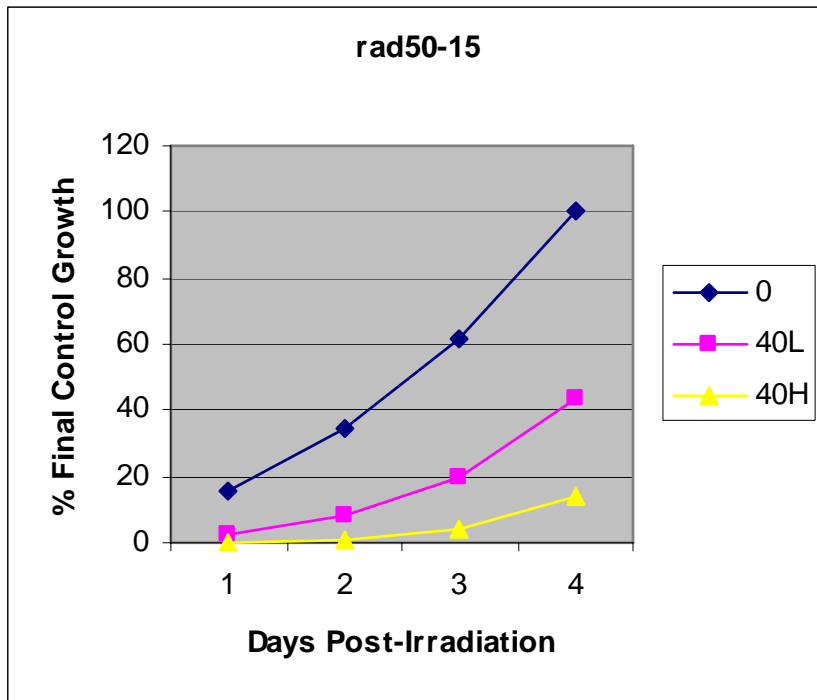
## *rad9-1*



Semi-log plot of proton irradiated samples displays lag.



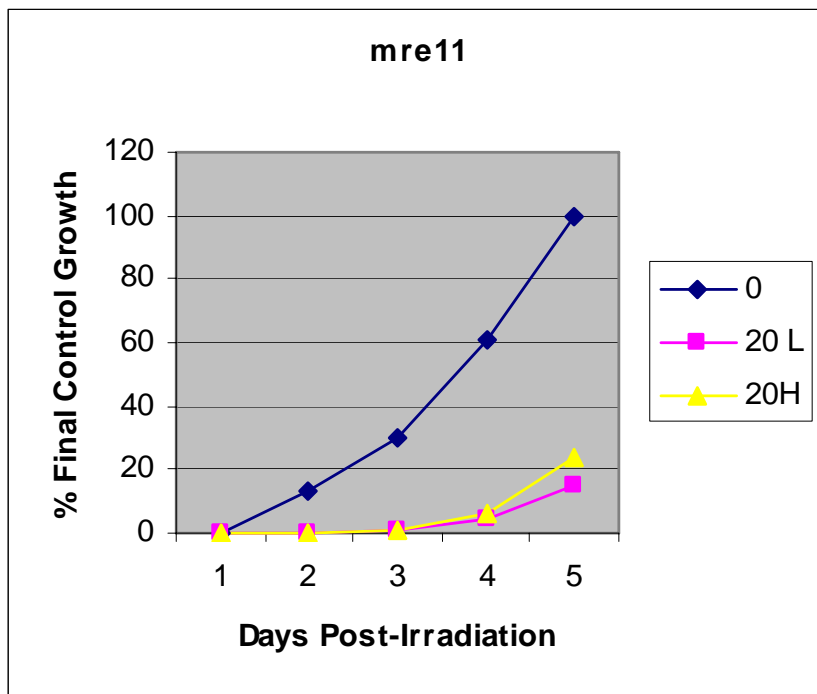
## *rad50*



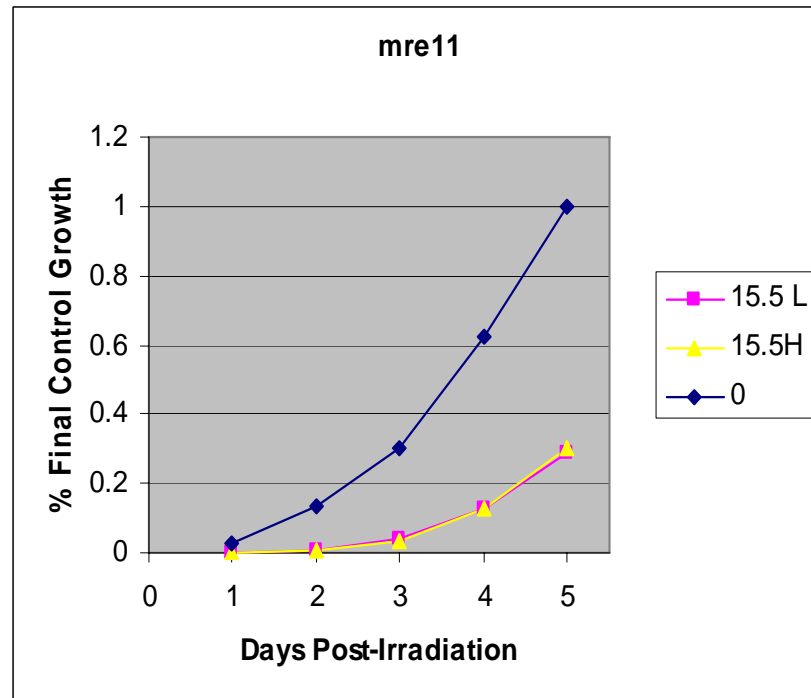
Implicated as a cell cycle checkpoint protein.



## *mre11*



Gamma Radiation



Proton Radiation

Exhibits no dose rate effect & no lag effect.



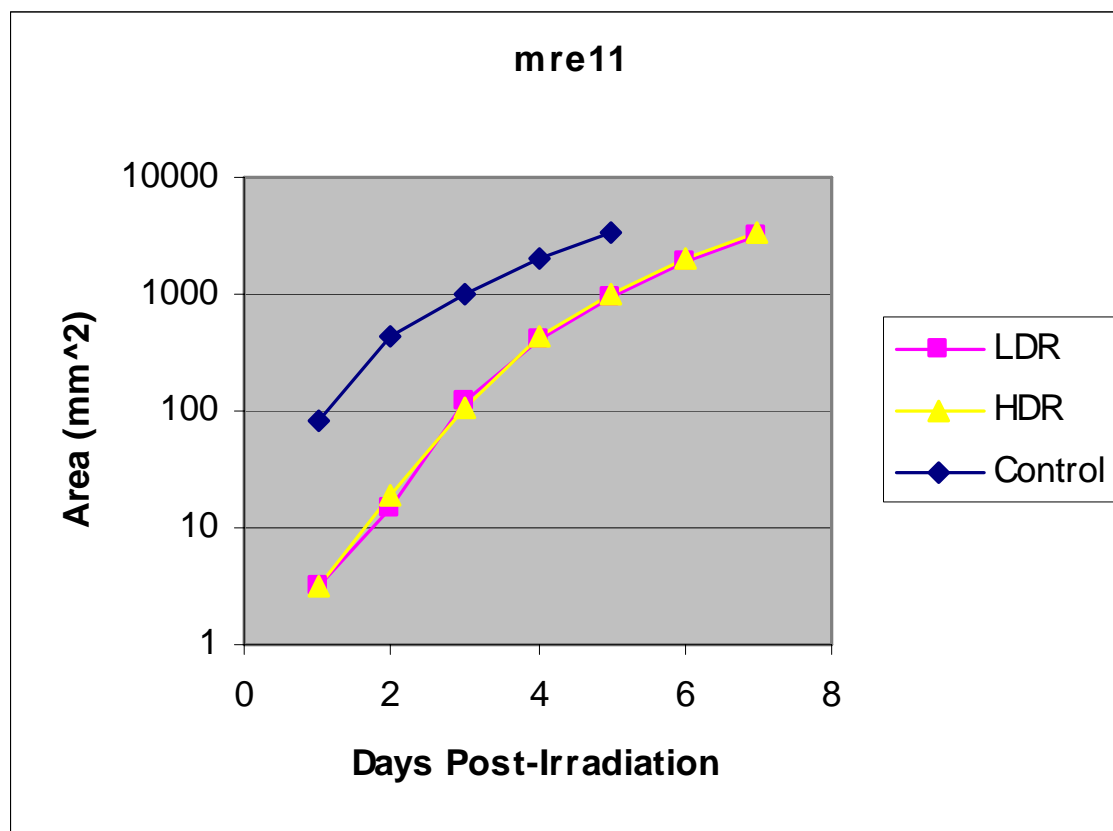
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## *mre11*



Exhibits no dose rate effect & no lag effect.



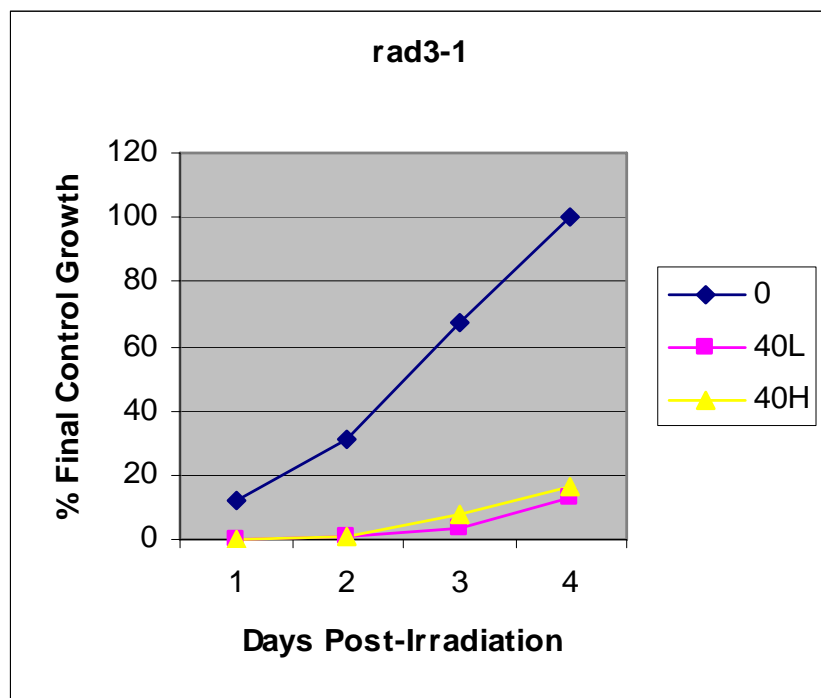
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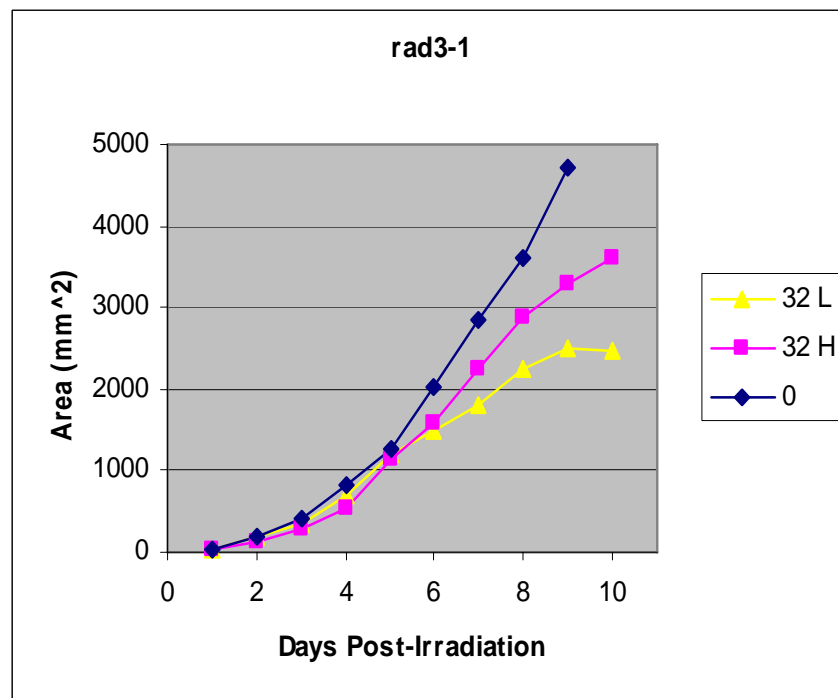
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## Rad3-1



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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