

Linear and non-linear dose-effect relationships at low dose IR

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Modeling of the dose-response curve

LNT, threshold, hypersensitive, hormesis?

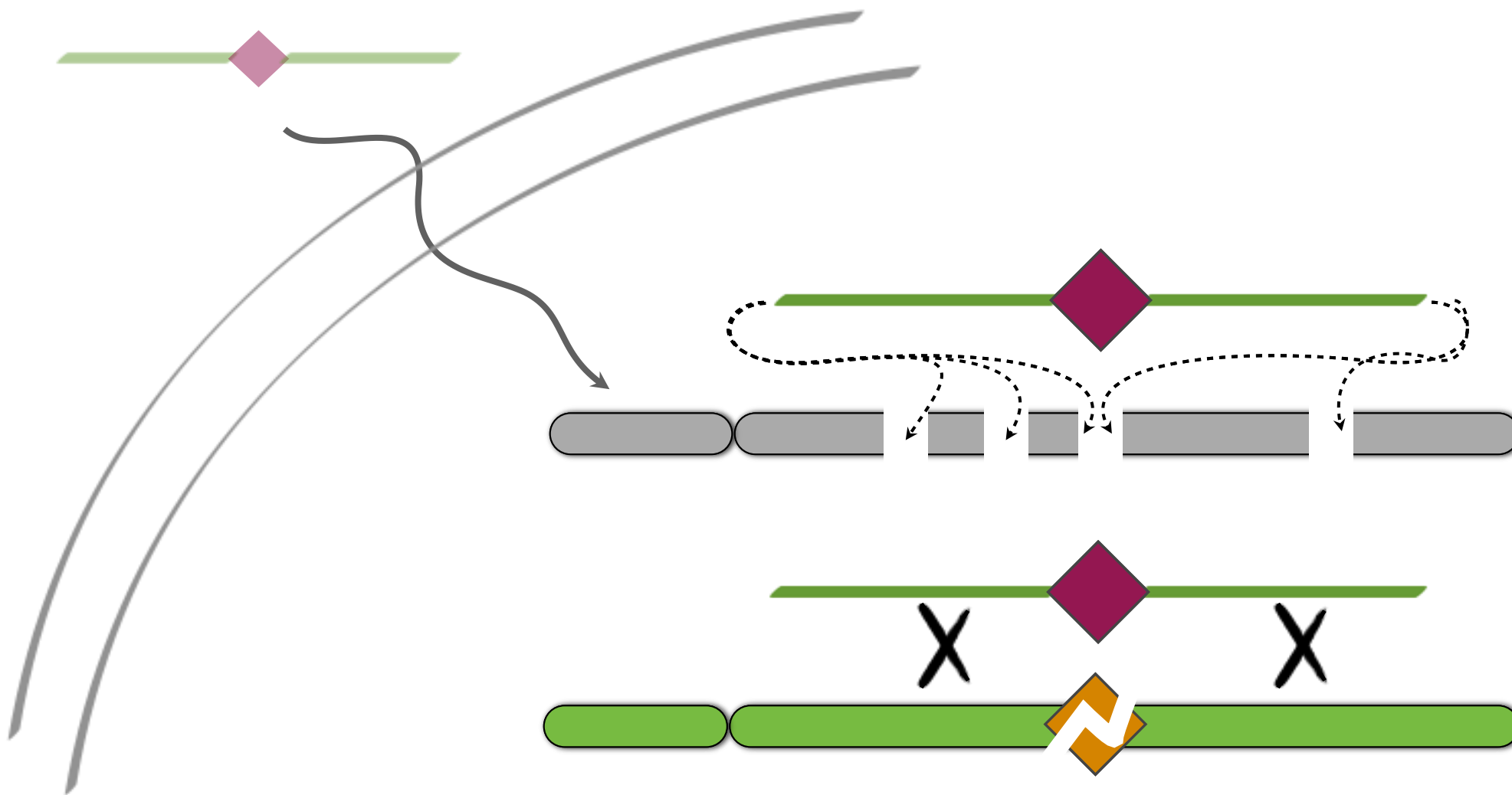
What can we measure at low dose?

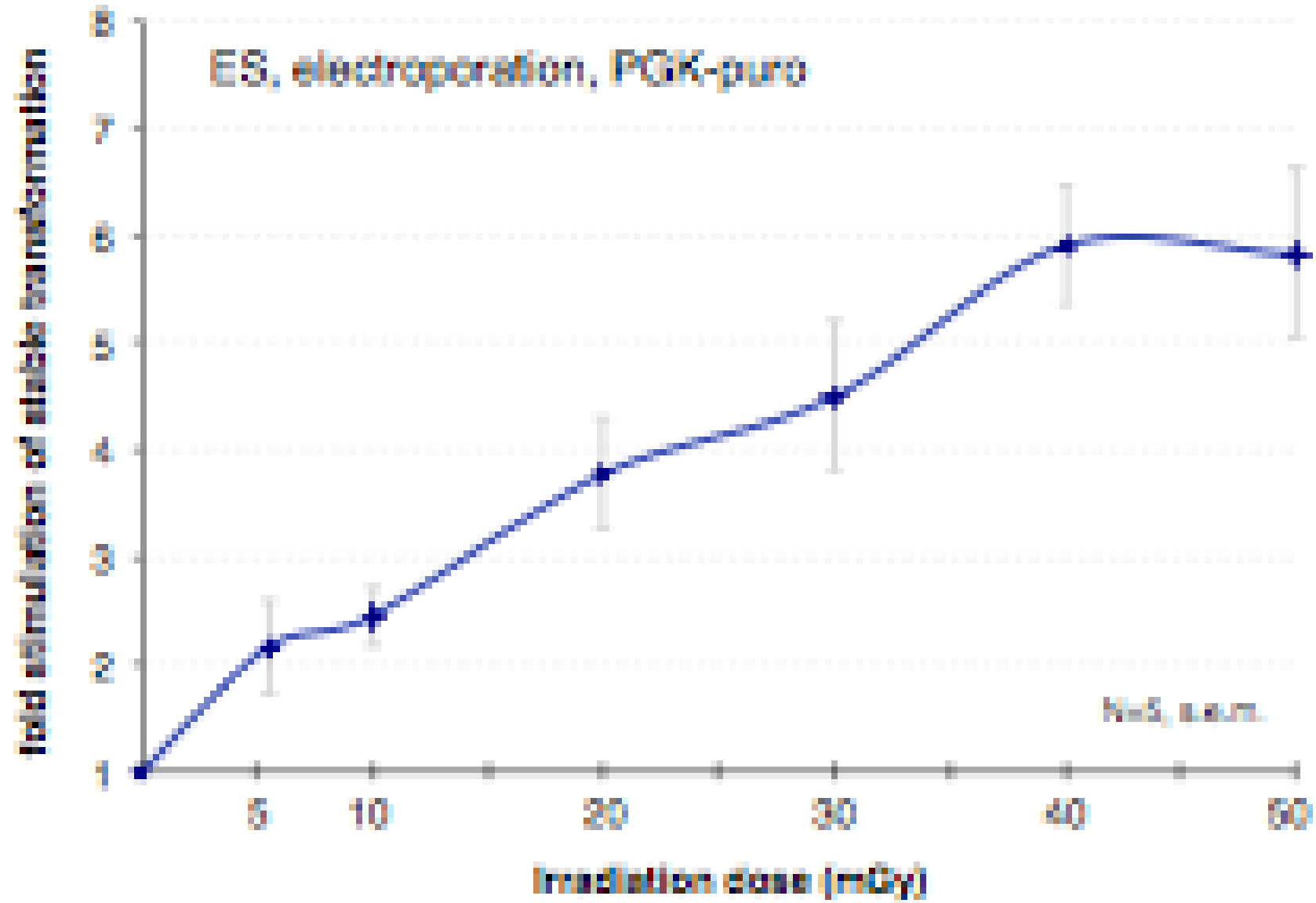
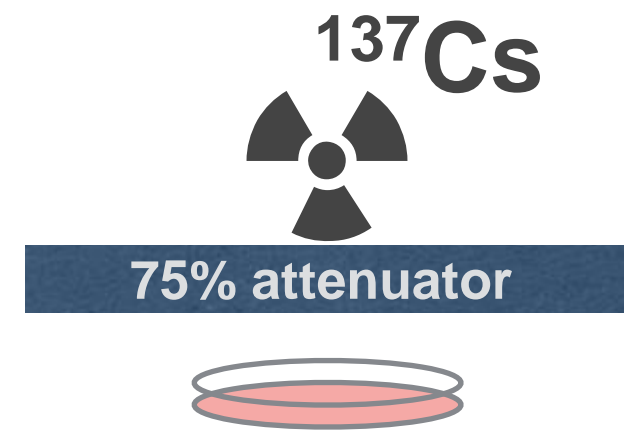
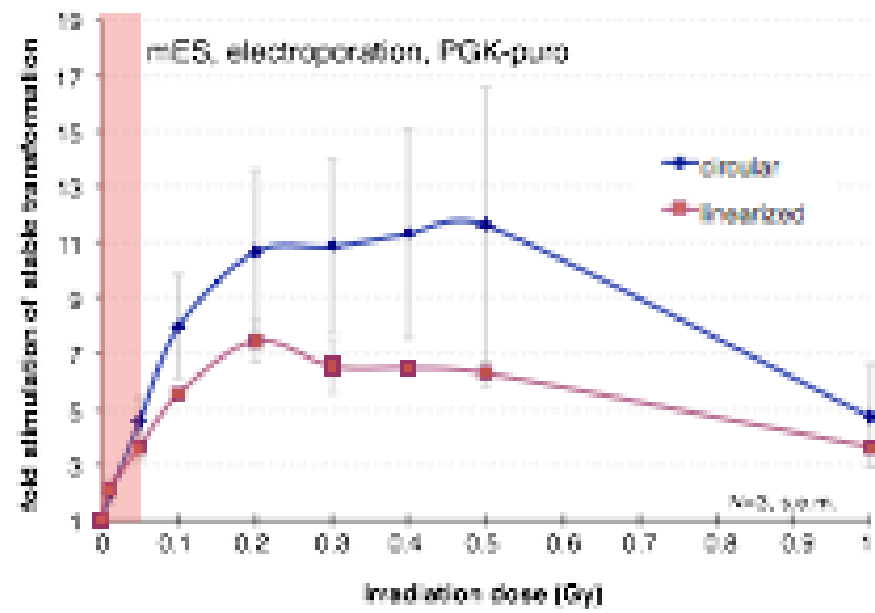
- DNA repair (linear 10-1000 mGy)
- micronuclei (linear)
- chromosomal translocation (linear)

What about uptake extrachromosomal DNA?

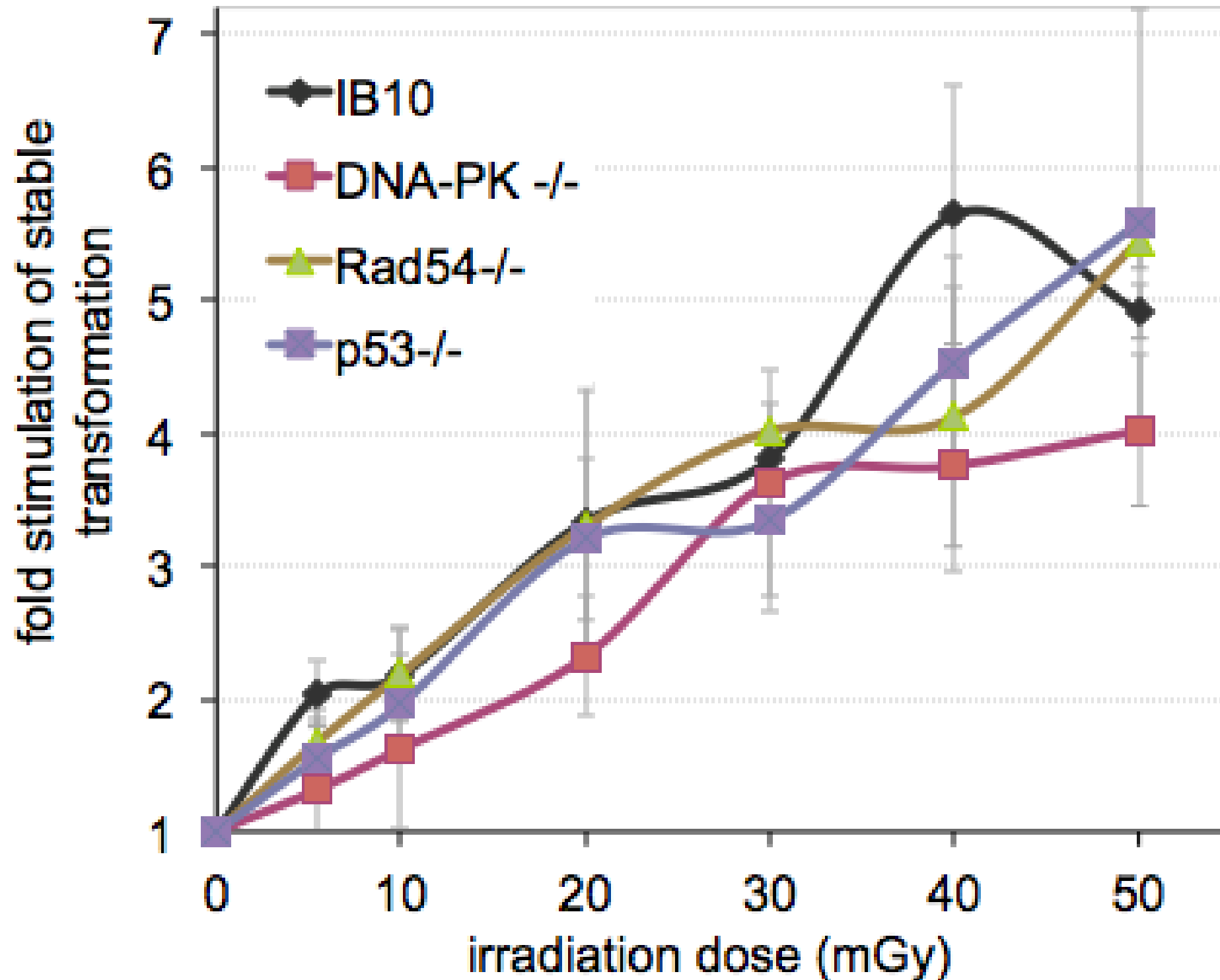
What about transcriptional responses?

Random integration assay

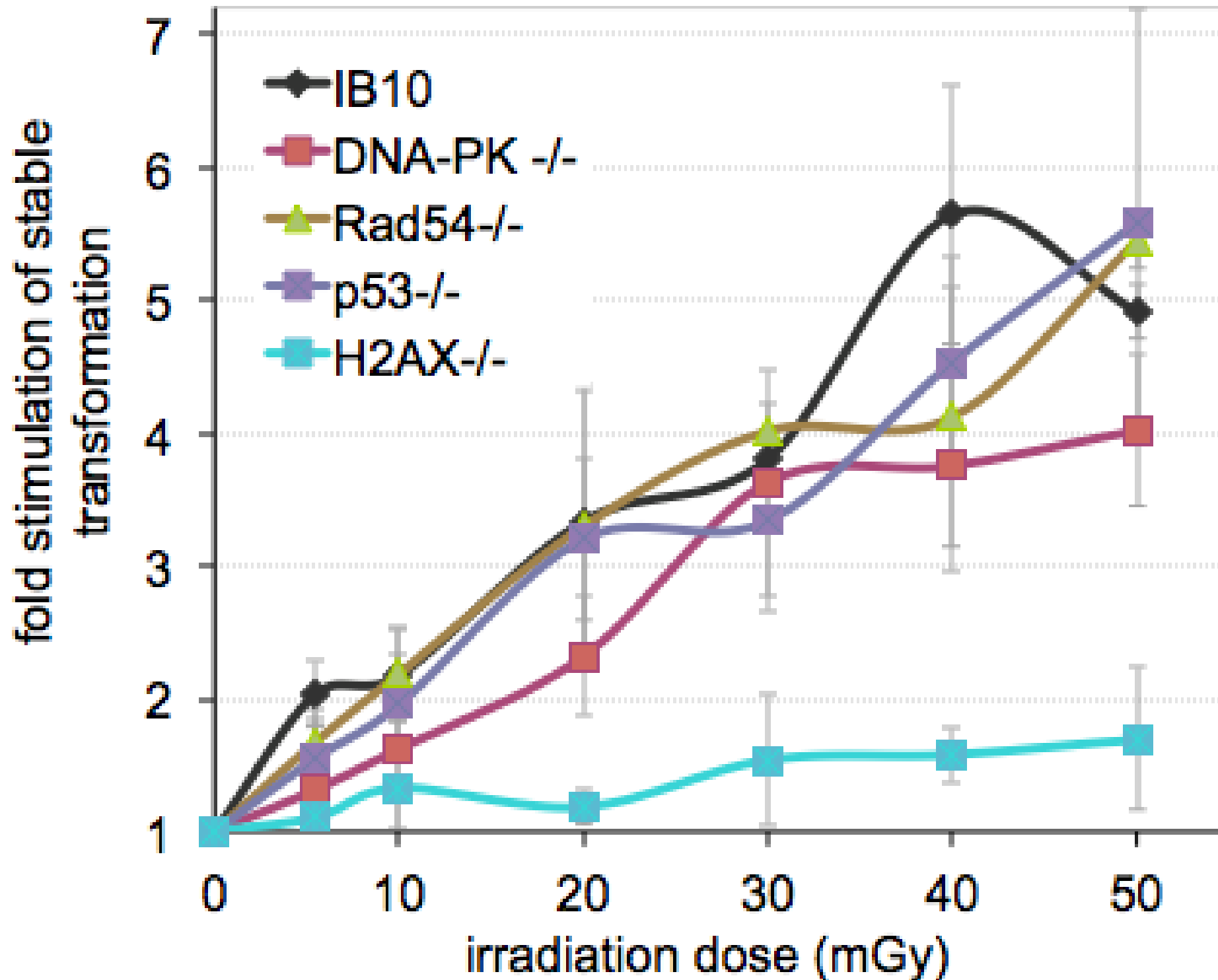




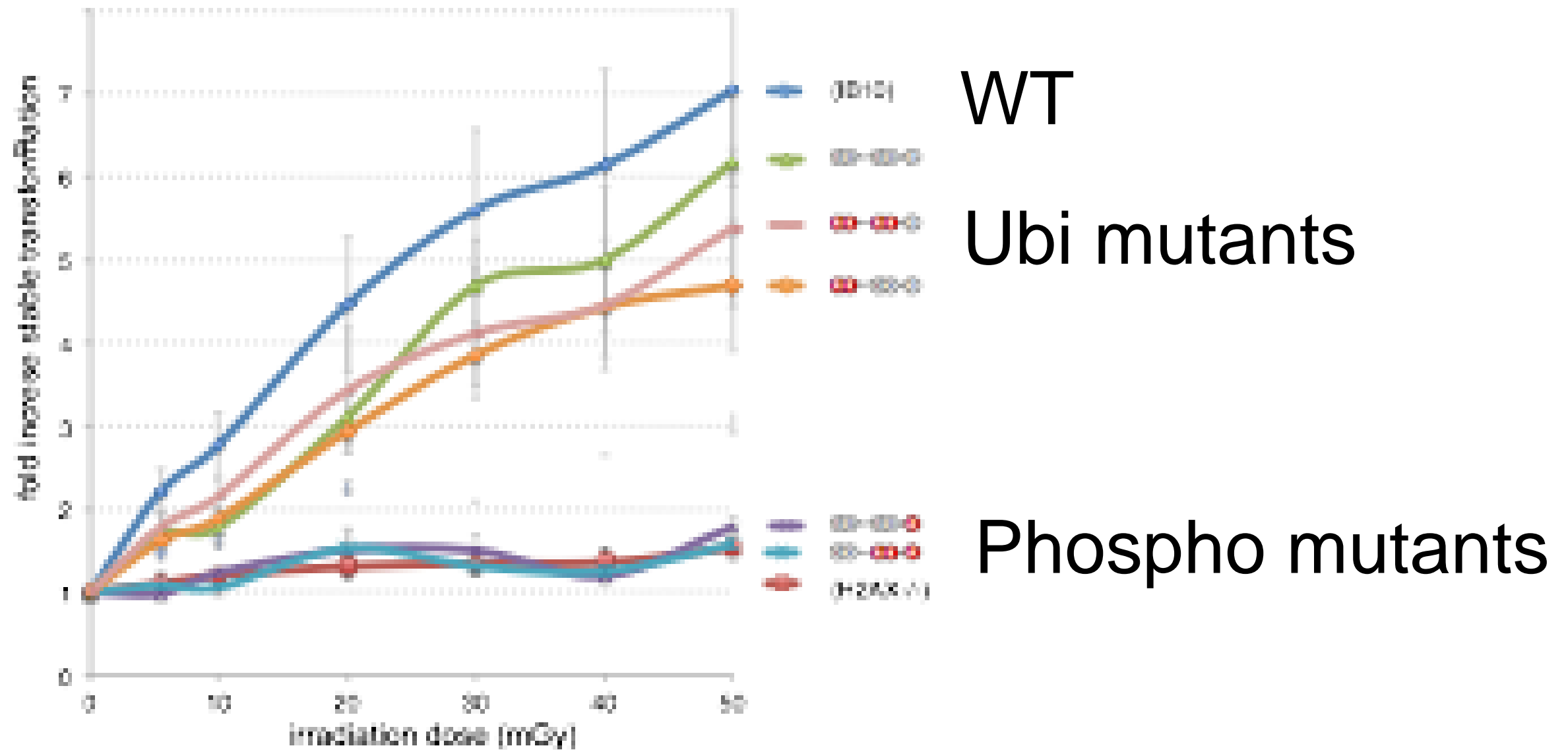
Repair mutants behave like wt



H2AX is required for stimulation

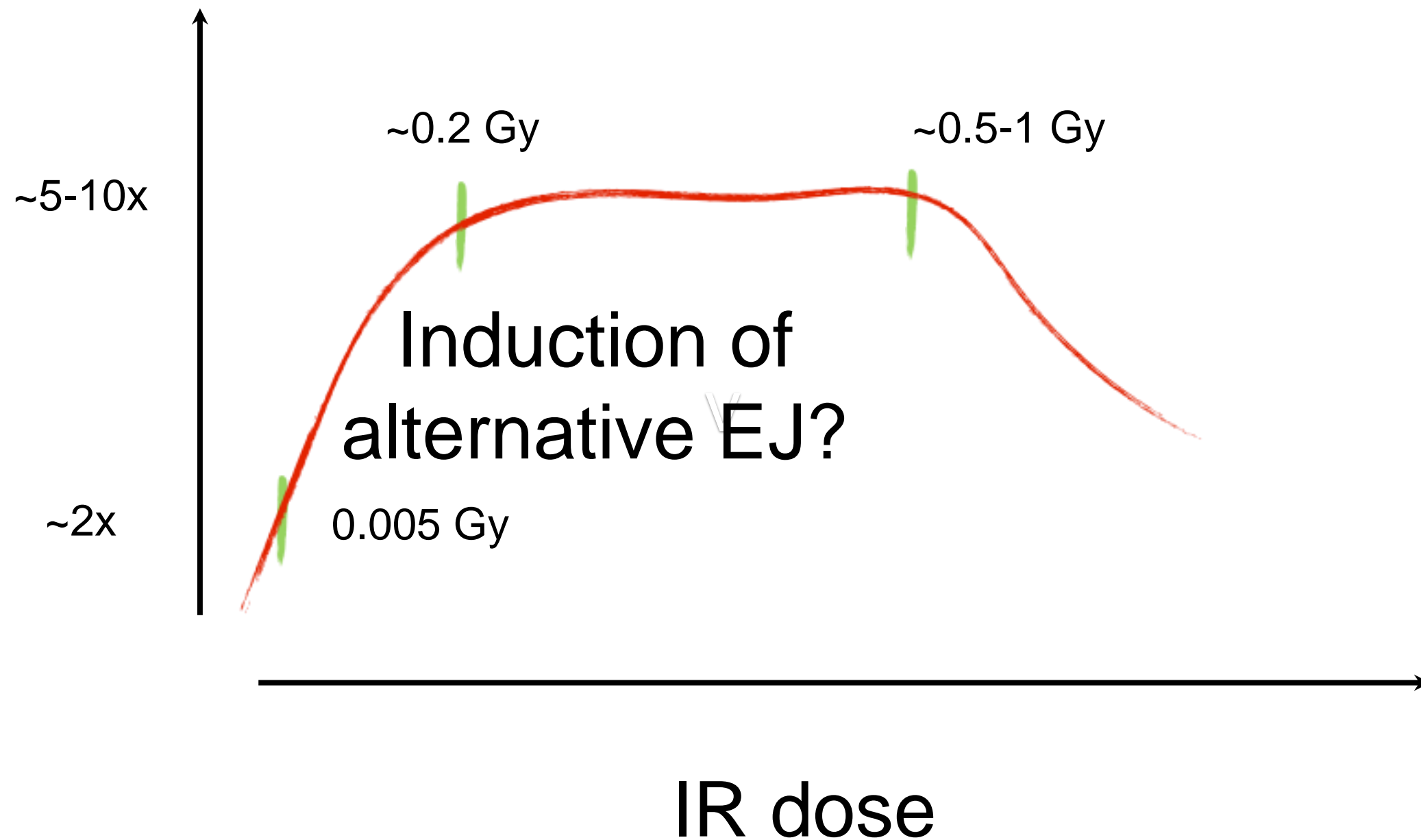


H2AX is required for stimulation

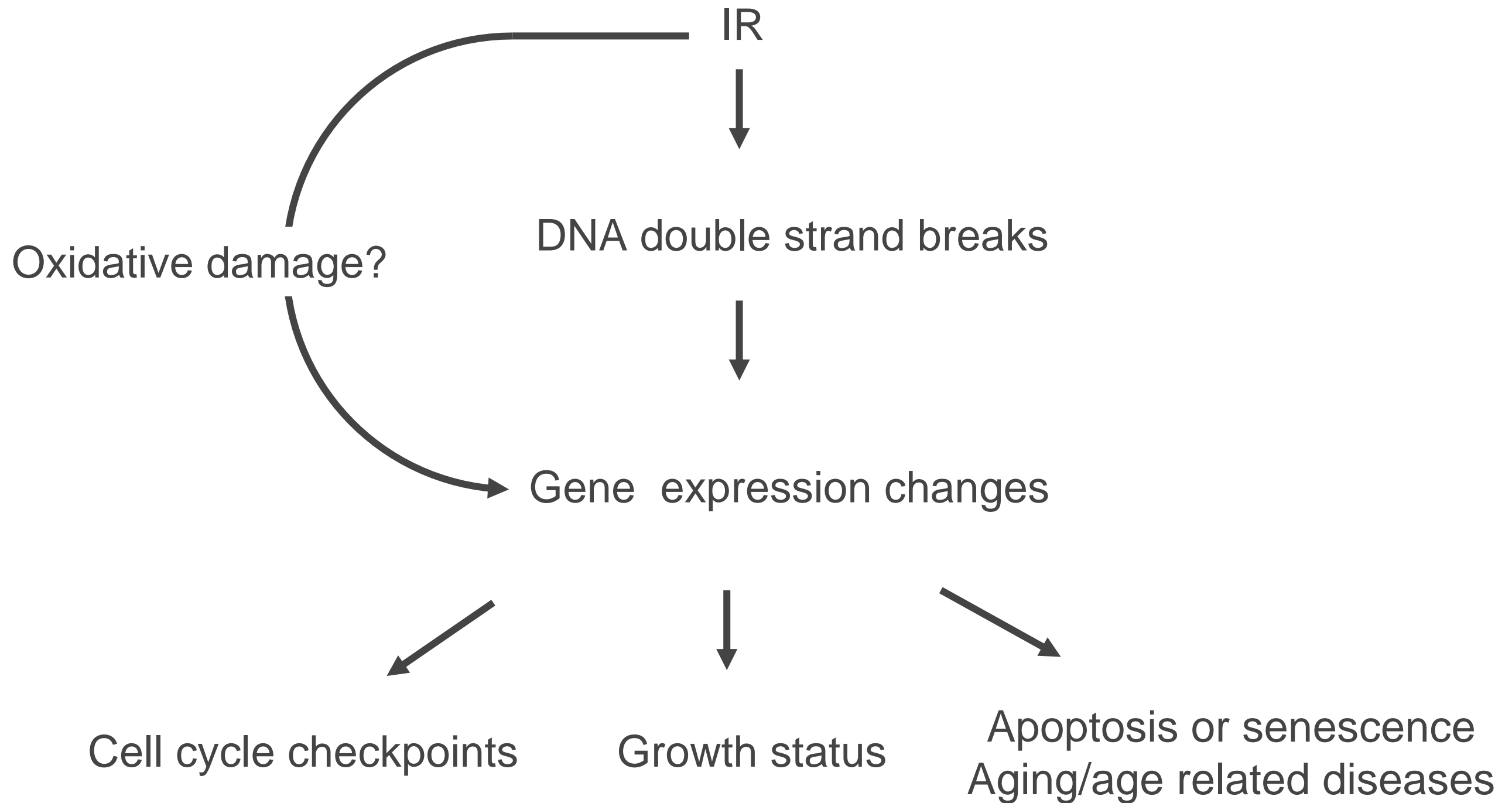


Plateau in dose-response

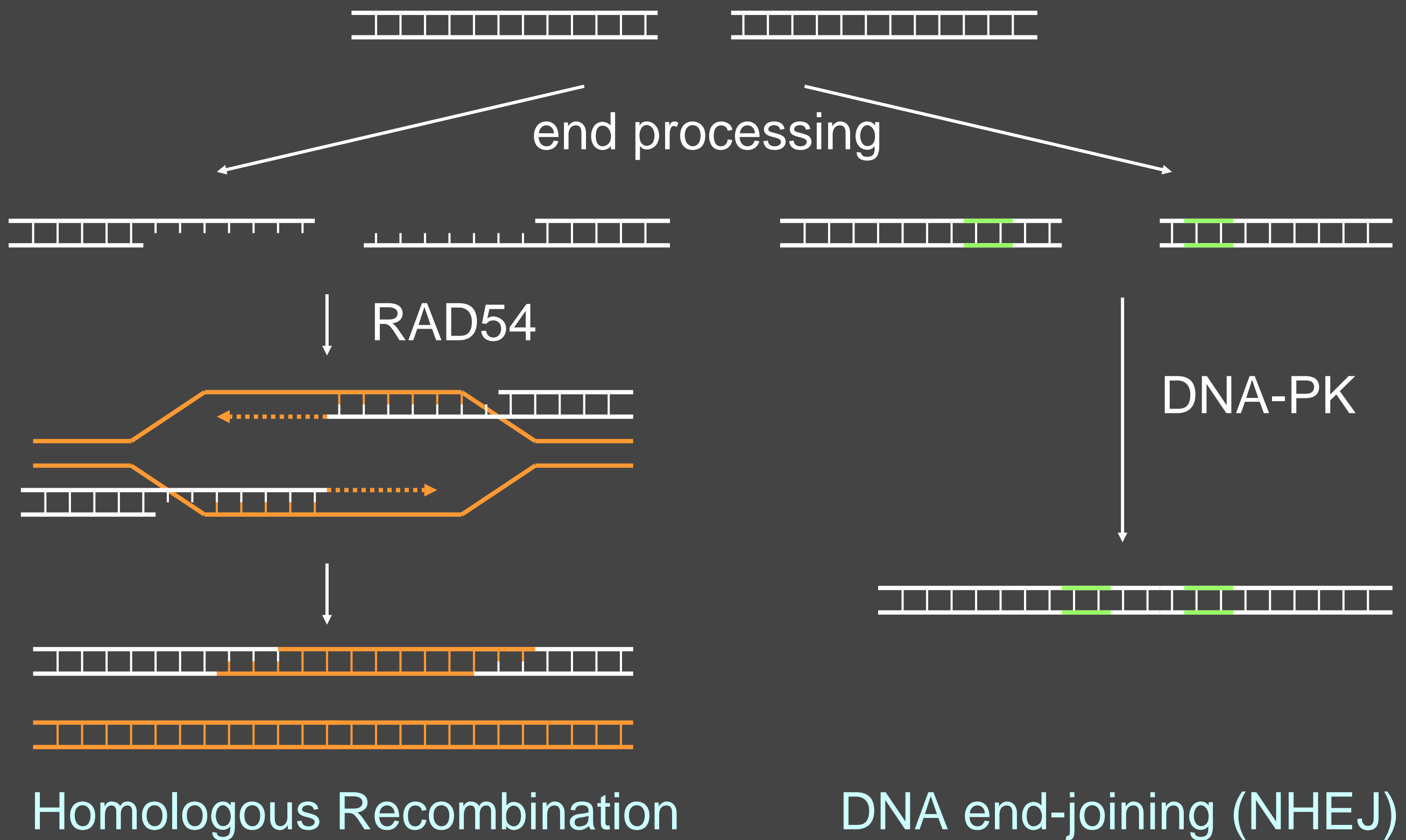
relative
integration



Regulation of the DNA damage response



Double-strand break repair pathways



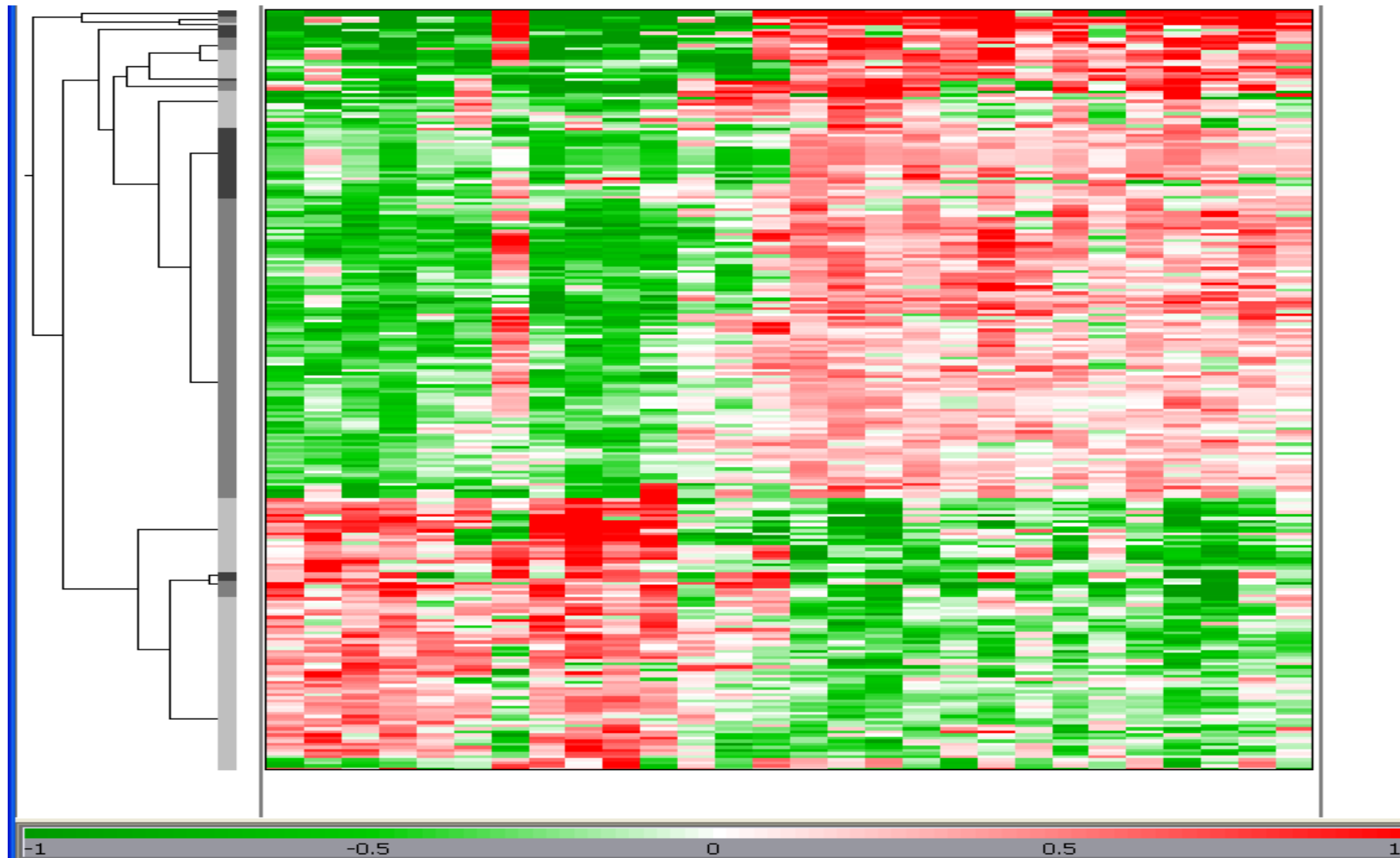
Low dose gene expression profiles

0 Gy

0.2 Gy

Wildtype
DNA-PK
Rad54
Rad54 DNA-PK

Wildtype
DNA-PK
Rad54
Rad54 DNA-PK

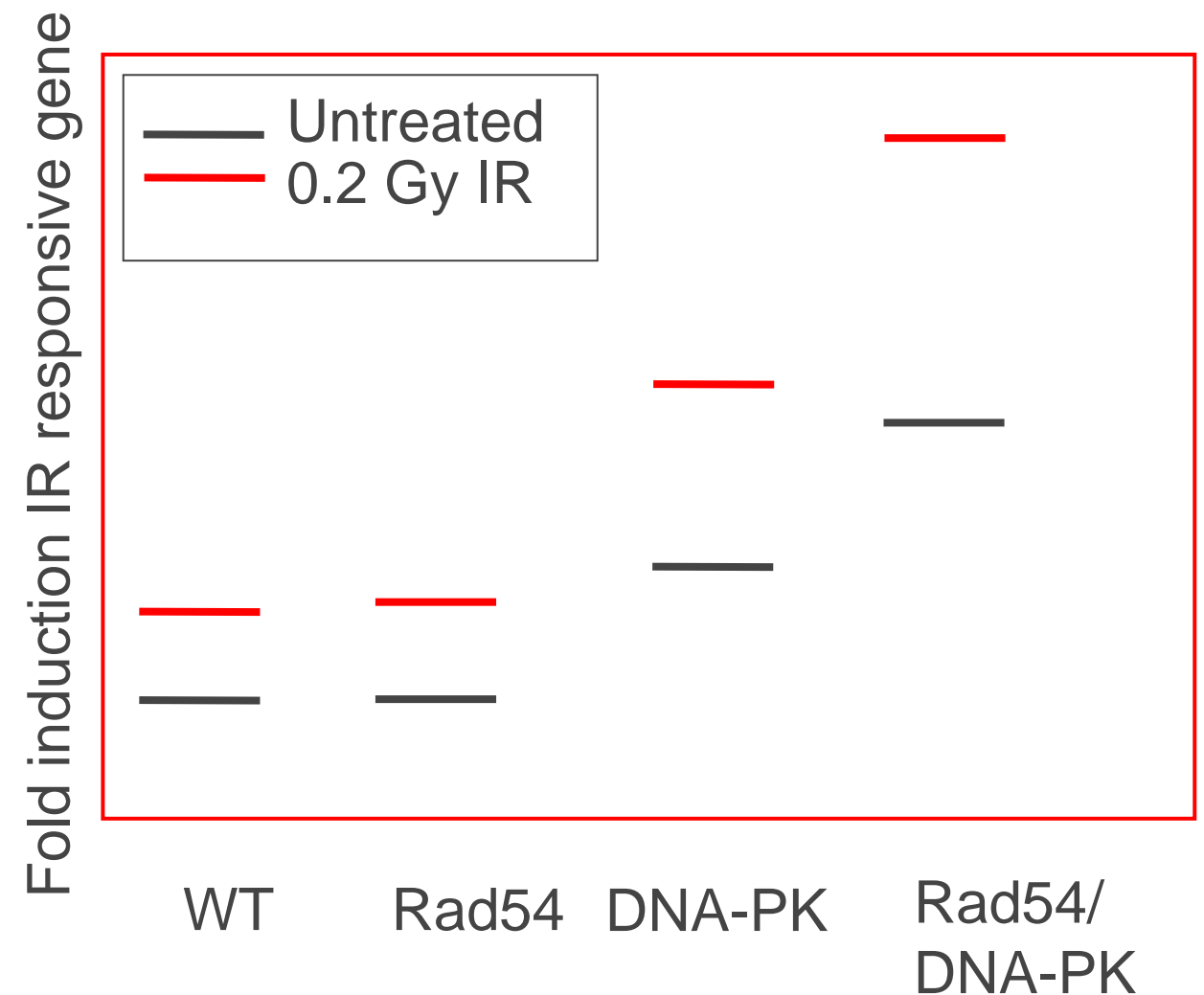


Mice irradiated 0.2 Gy,
0.2 Gy/hr
2 hours later, liver
isolated
mRNA isolation
Micro array analysis
Significant genes

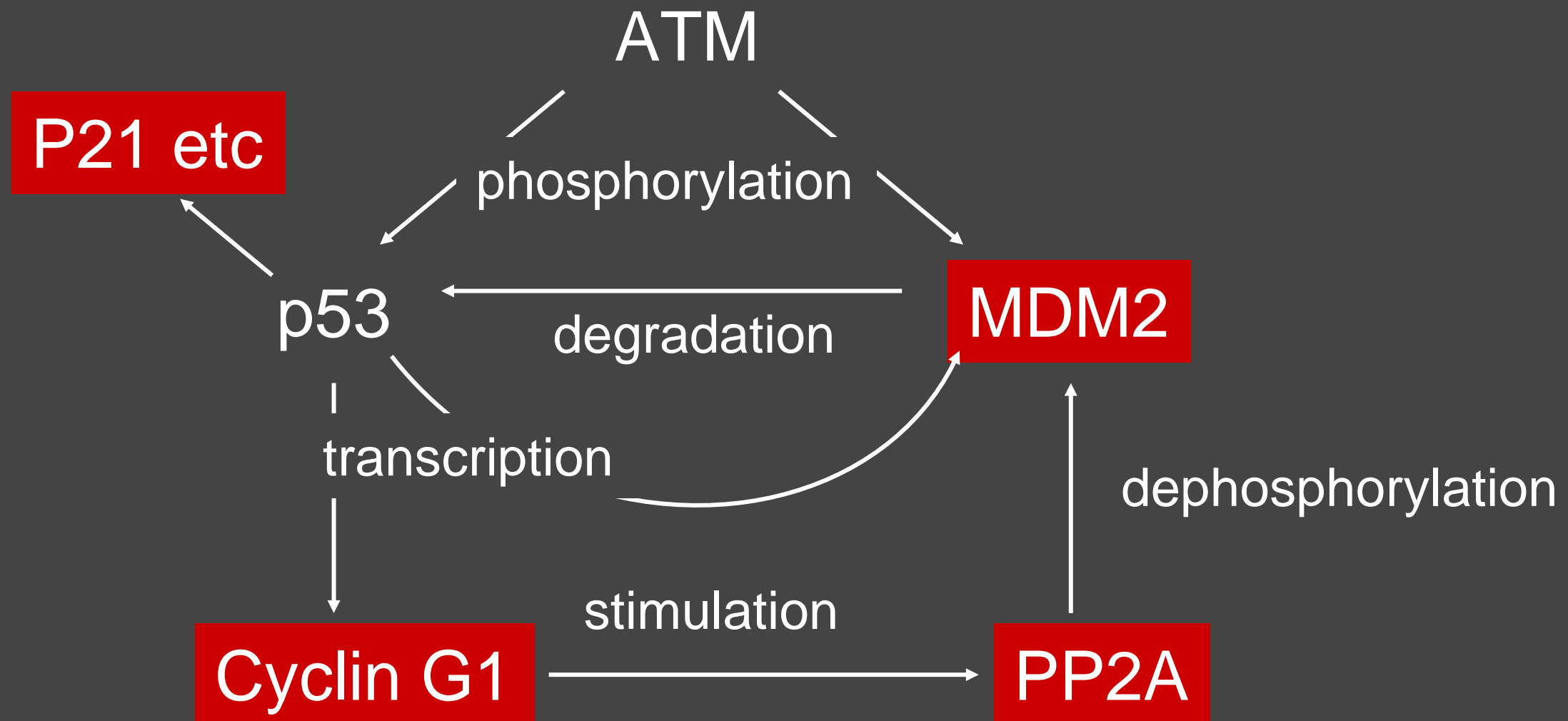
DSB induced genes

Known Responsive genes:

- Gadd45a/b
- P21 (CDKN1A)
- Sesn2
- cycB (Ccnb1)
- Puma (Bbc3)
- Atf3
- DDB2
- MDM2
- BAG3
- SLUG (Snai2)

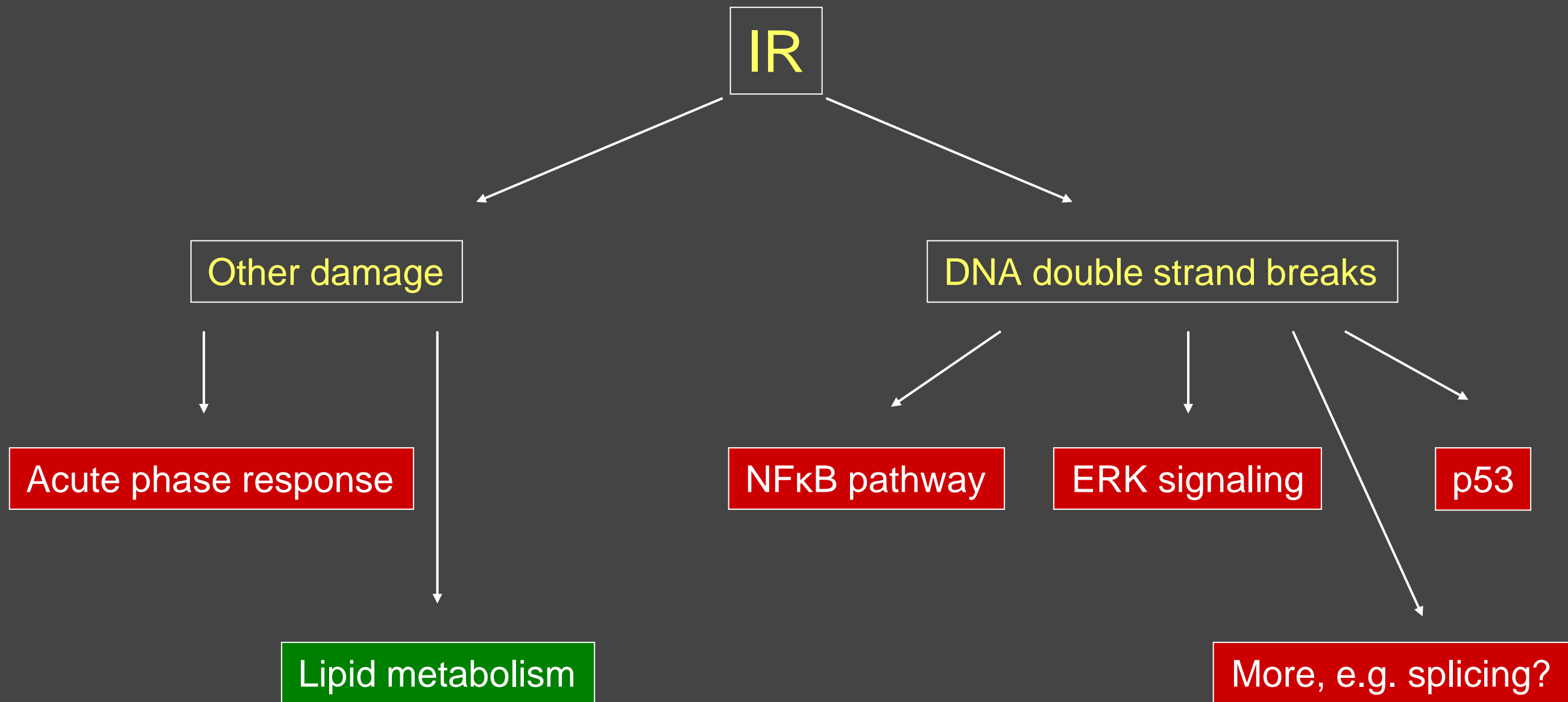


TP53 regulation



All genes that downregulate p53 are upregulated!

Regulation of gene expression after IR

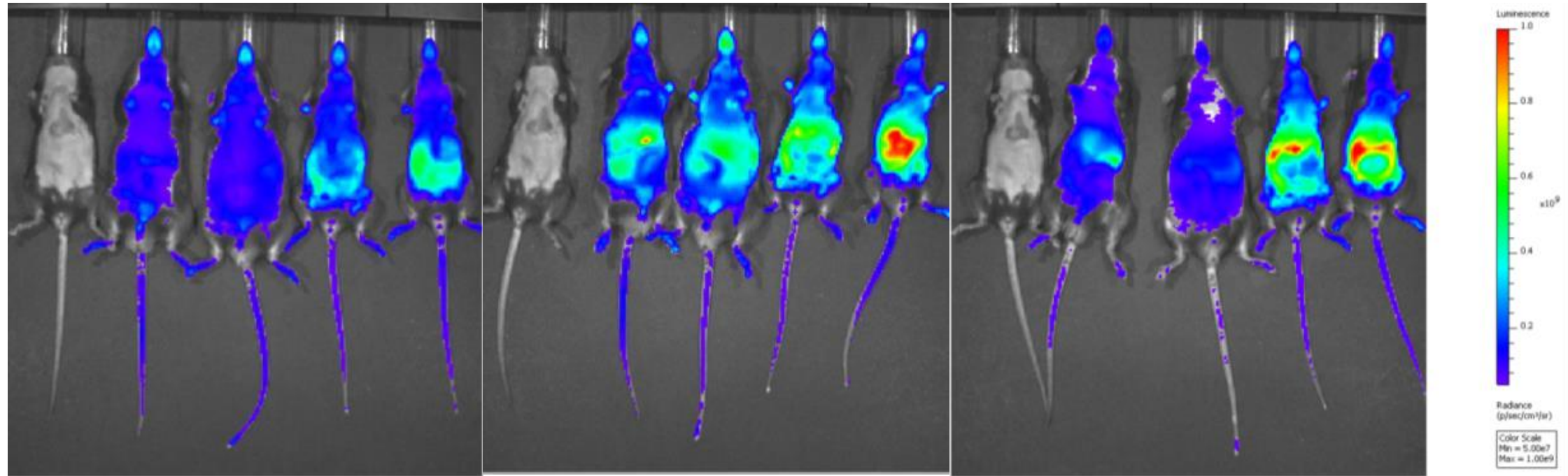


P21 reporter mice

unirradiated

0.2 Gy, 4 hours

0.2 Gy, 24 hours



No luciferase

Wt

RAD54

DNA-PK

double

No luciferase

Wt

RAD54

DNA-PK

double

No luciferase

Wt

RAD54

DNA-PK

double



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