



# Elucidating the role of XRN2-mediated DNA repair programs

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IECC2021

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# Take Home Messages

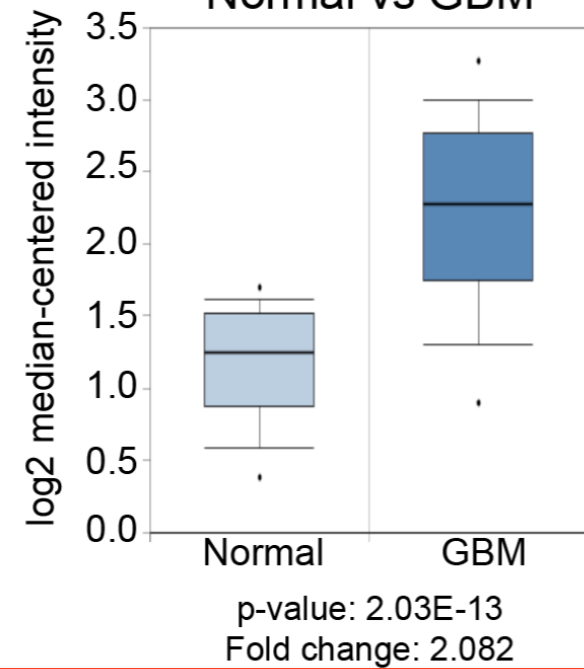
Goal: To determine the mechanism by which XRN2 mediates therapy resistance

- XRN2 expression is elevated in glioblastoma multiforme (GBM) and is correlated with poor survivorship rate
- XRN2 mediates multiple pathways in particular DNA damage repair
- XRN2's targets are required for efficient DNA repair
- XRN2's targets are potential lynchpins in cancer development

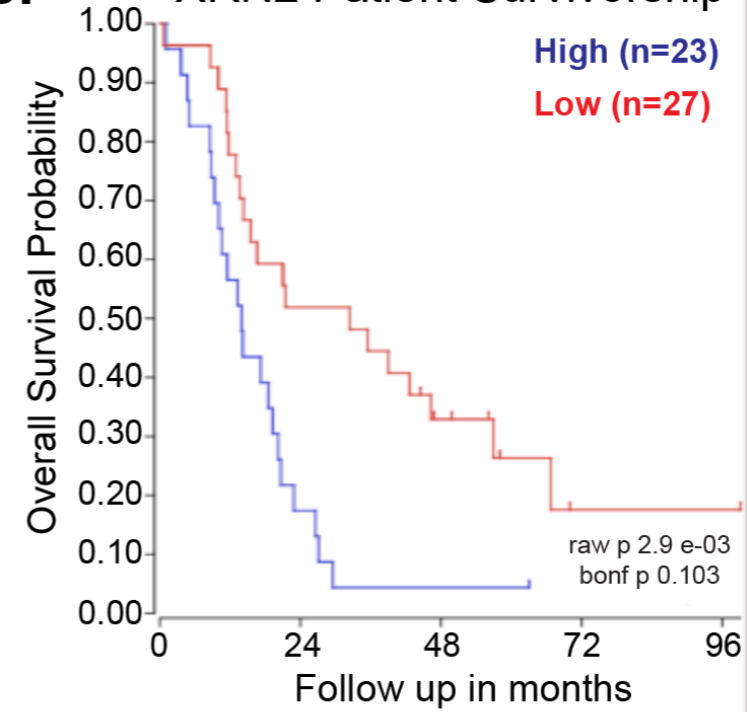


# XRN2 is elevated in GBMs

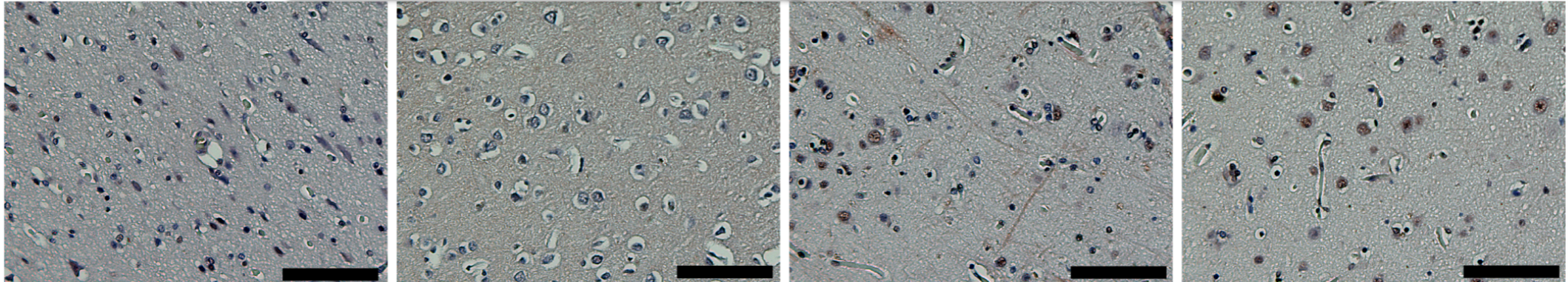
**A.** XRN2 expression  
Normal vs GBM



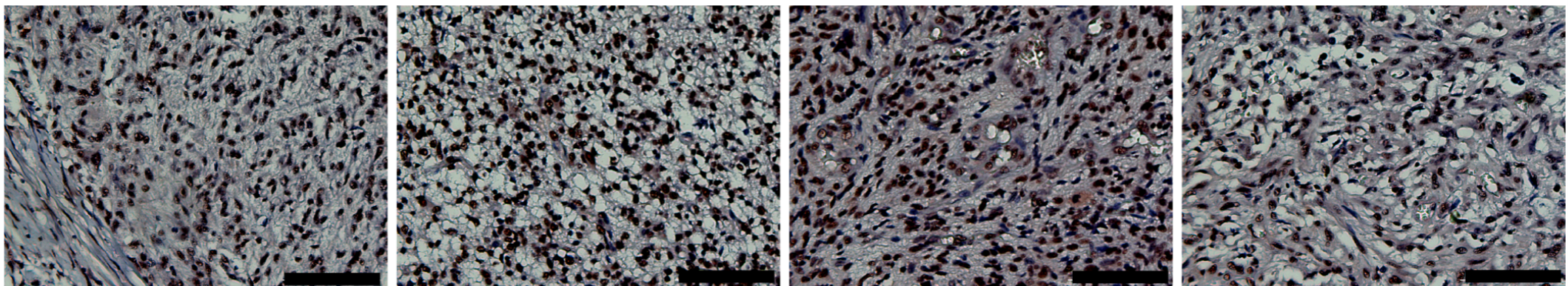
**B.** XRN2 Patient Survivorship



Normal

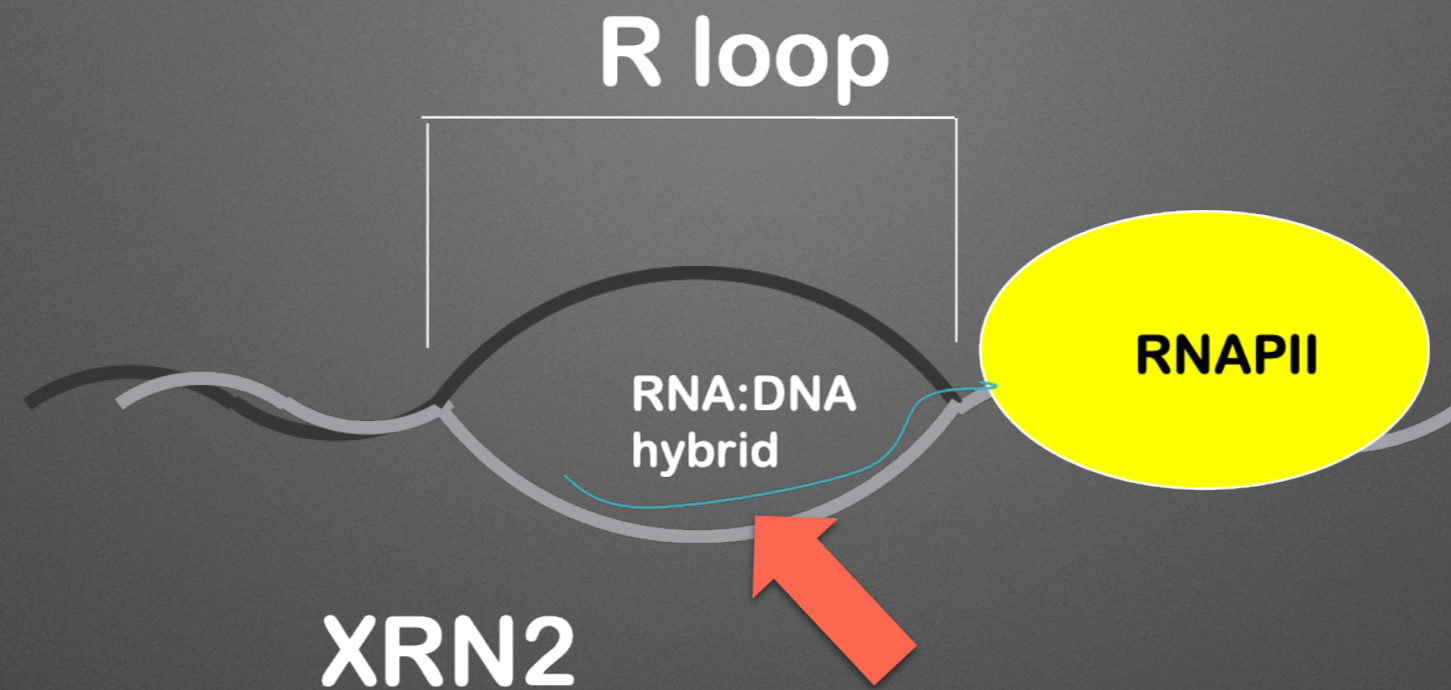


Glioblastoma





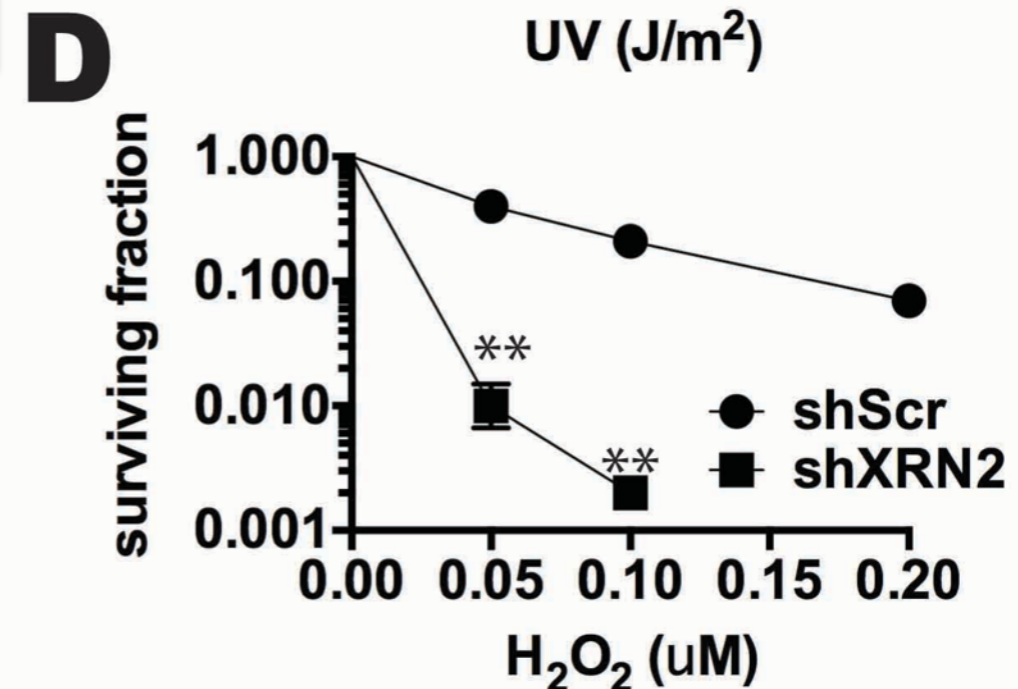
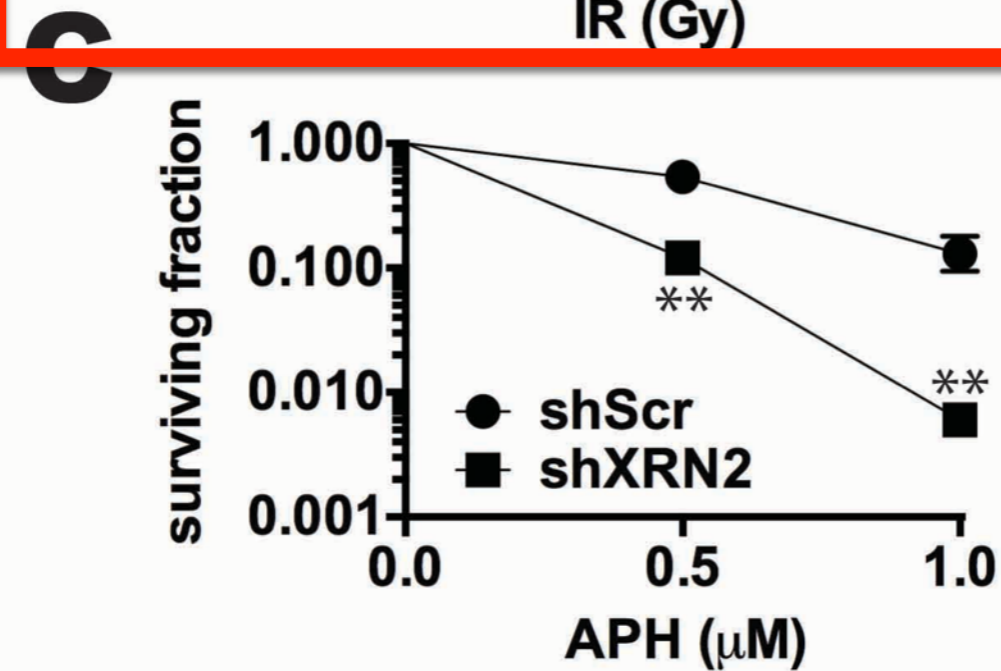
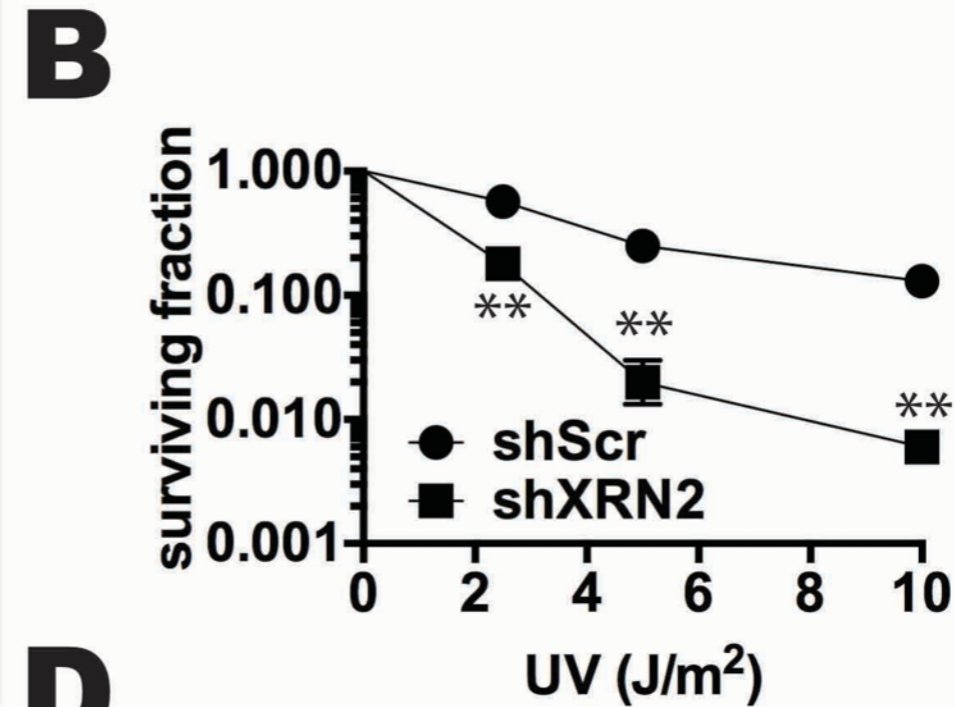
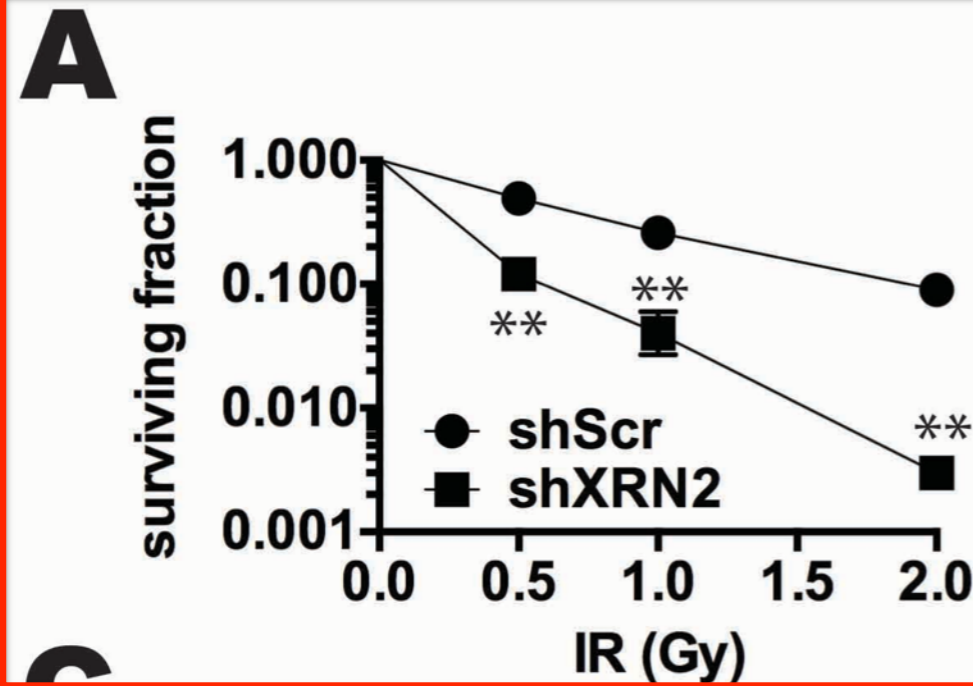
# XRN2, a 5'-3' exoribonuclease



- Involved in R-loop resolution during transcription termination (Manley and Proudfoot groups)
- Loss of XRN2 leads to a global increase in R loop formation (Morales, J et.al. PLOS Genetics, 2016)
- Recently found to be involved in DNA double stranded break repair (Dang, T et. al Cancers, 2020)



# XRN2 is required for cell survival against genotoxic agents

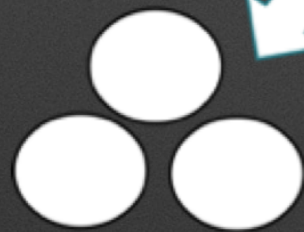




# XRN2 affects DNA double stranded break repair

Reporter cell line for HR or NHEJ repair

+ I-SceI (introduces double stranded breaks)

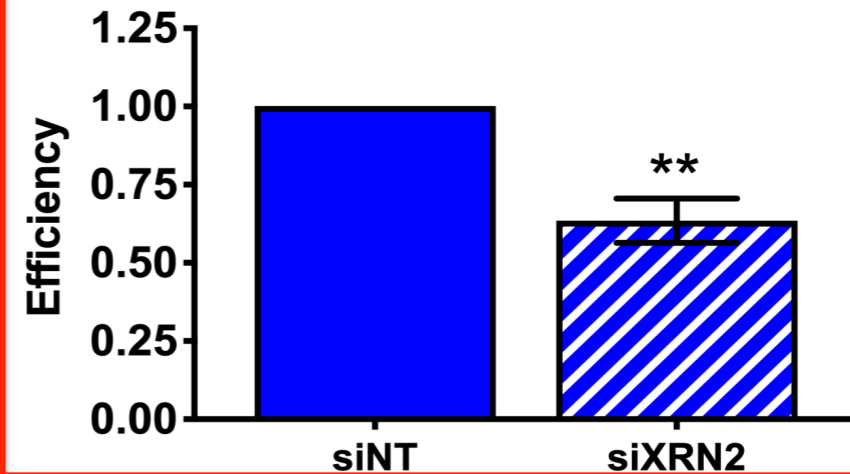


Unsuccessful repair

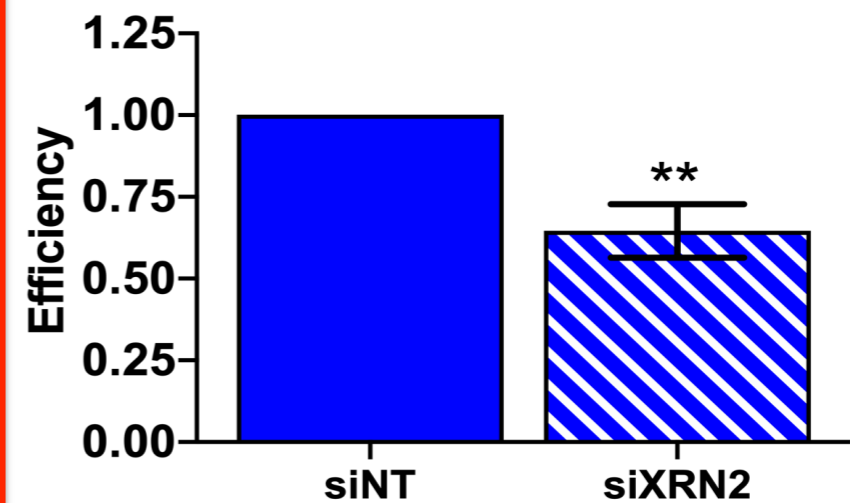


Successful repair

Homologous Recombination



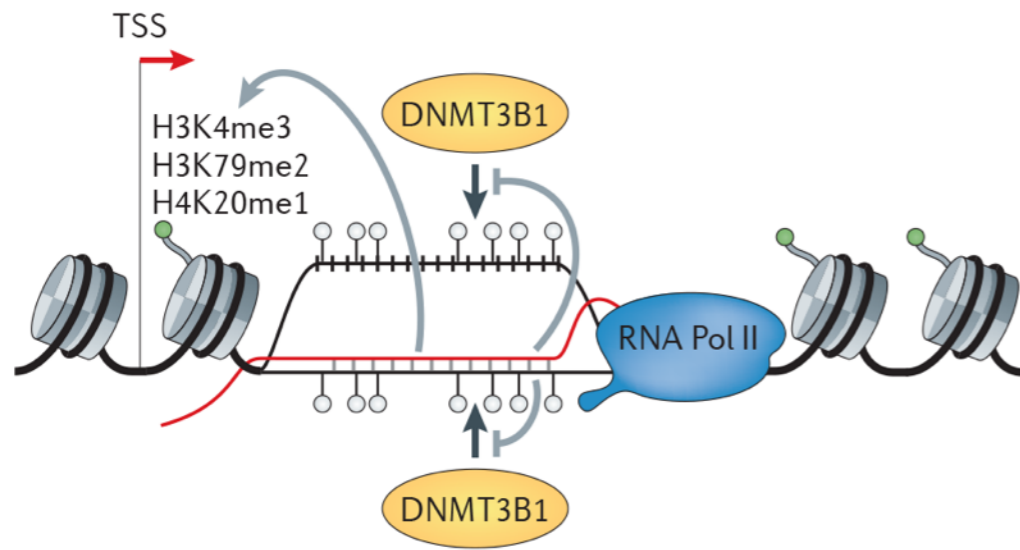
Non-Homologous End-joining Repair



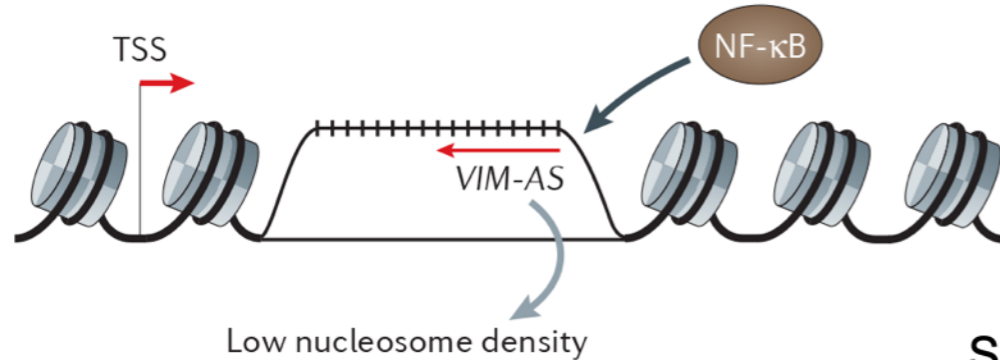


# R loops can mediate gene expression

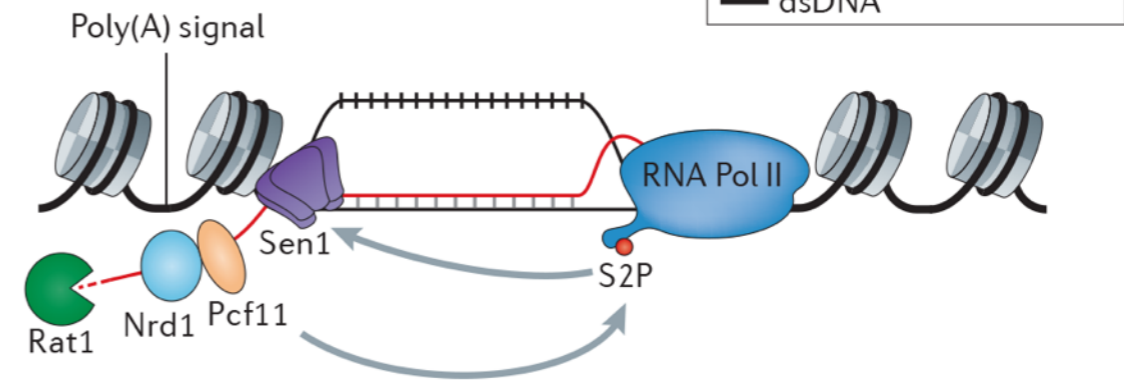
**a** Transcription activation at CpG island promoters



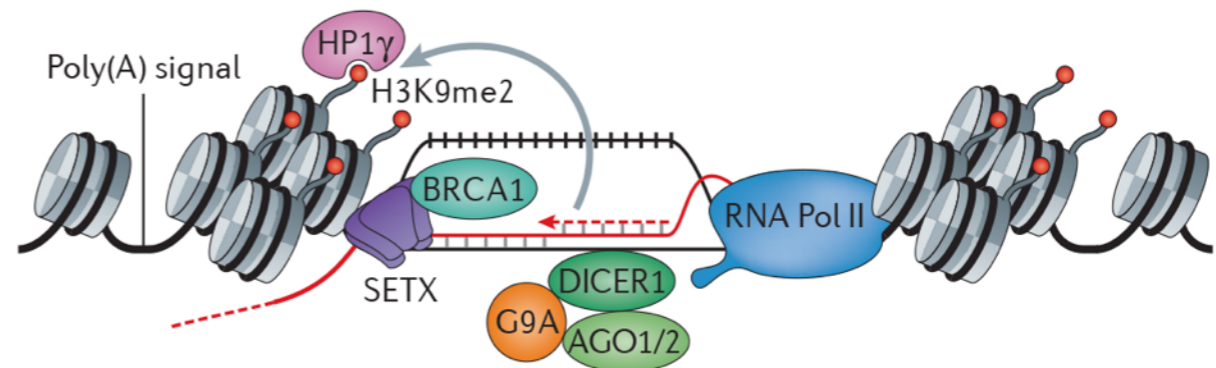
**b** Transcription activation at the *VIM* promoter



**d** Transcription termination in yeast cells



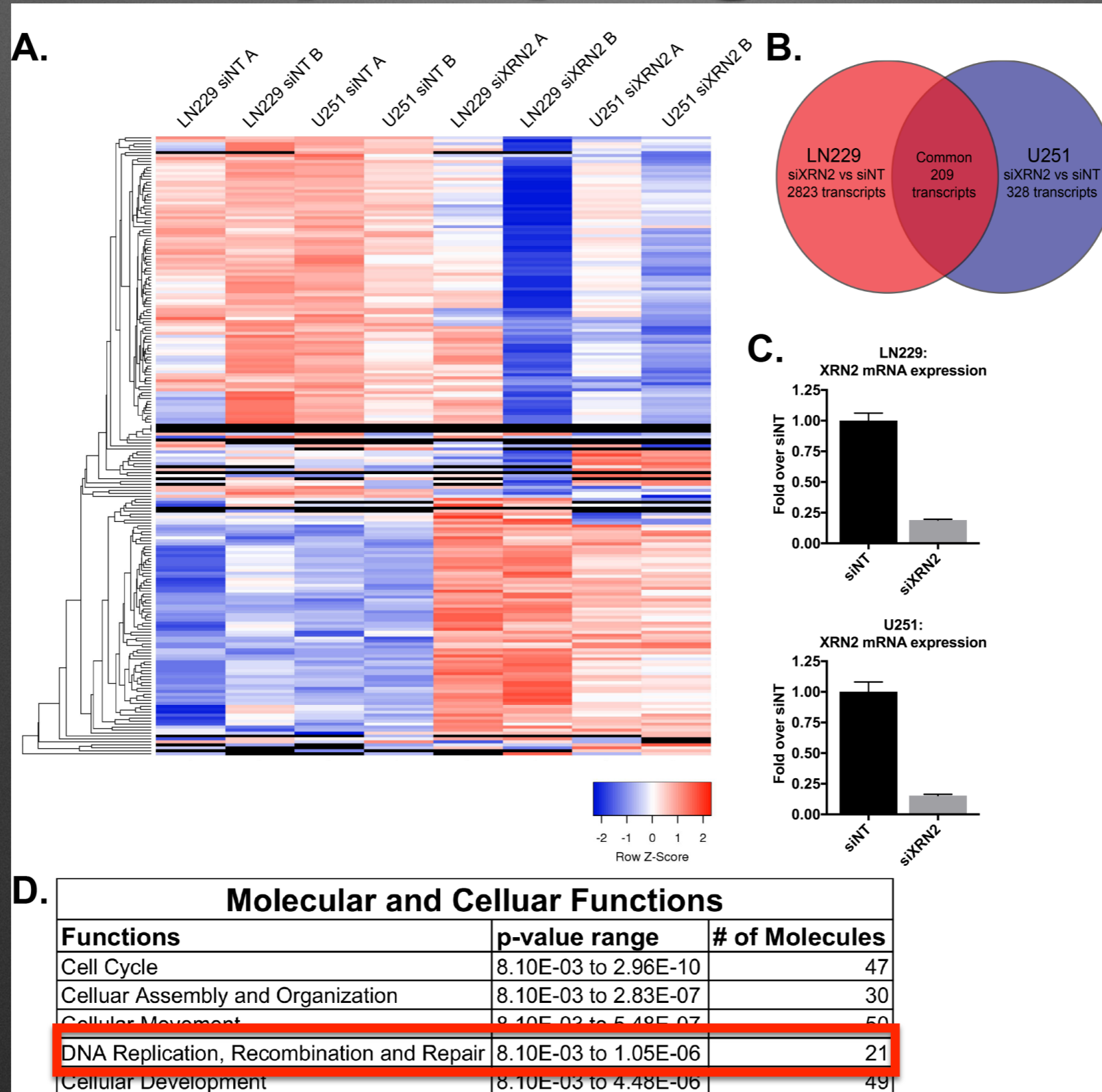
**e** Transcription termination in human cells



Santos-Pereira JM and Aguilera A. Nature Review Genetics, 2015

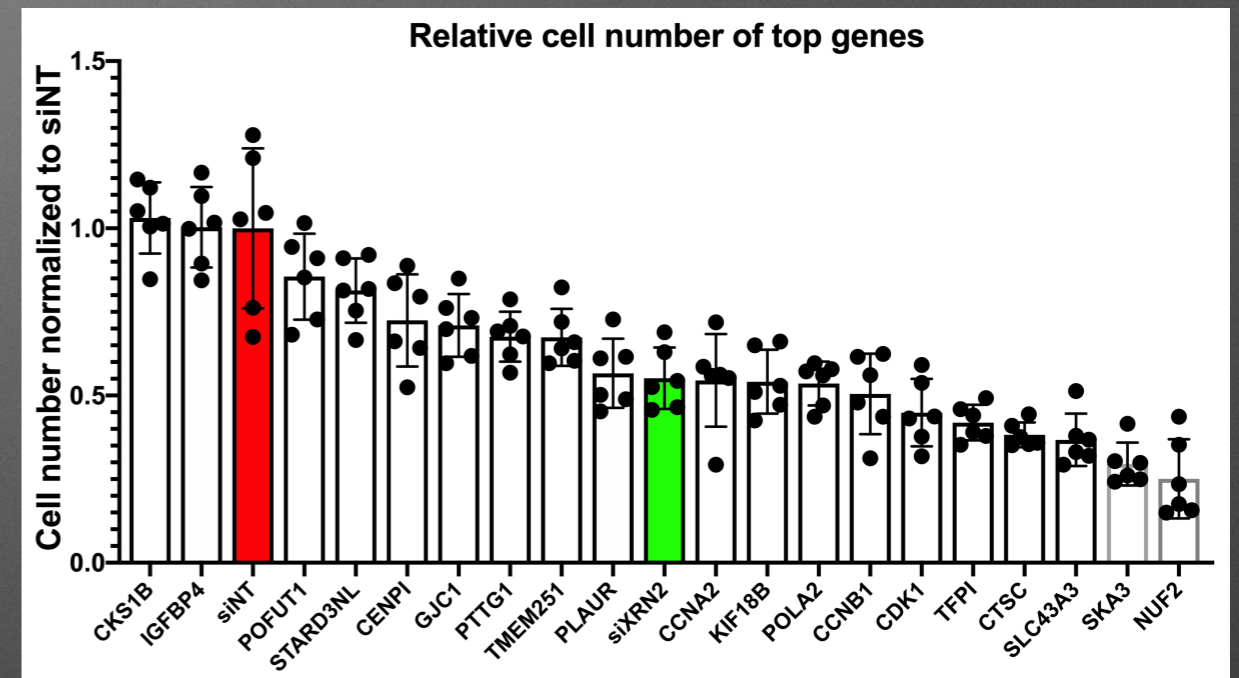
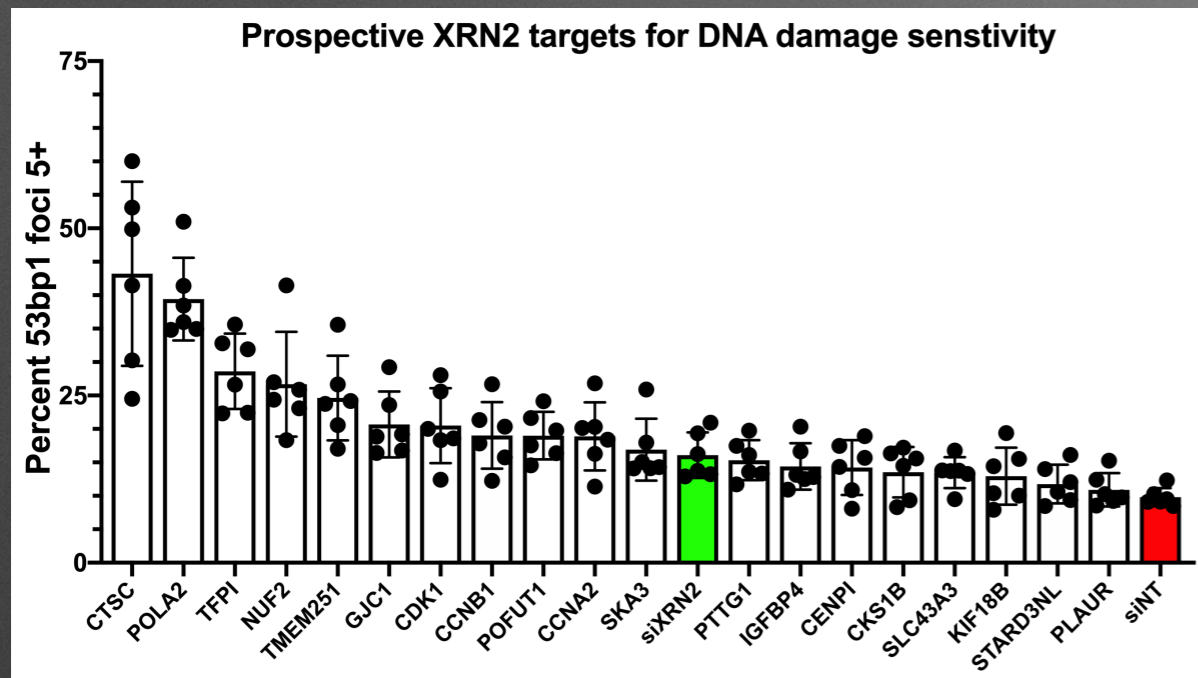


# XRN2 regulates DNA damage repair program





# Loss of XRN2 targets increases DNA damage



## Cherry pick list for HR and NHEJ assays (6):

POLA2 (DNA polymerase alpha 2, accessory subunit)

CDK1

CCNB1

CENPI (centromere protein I)

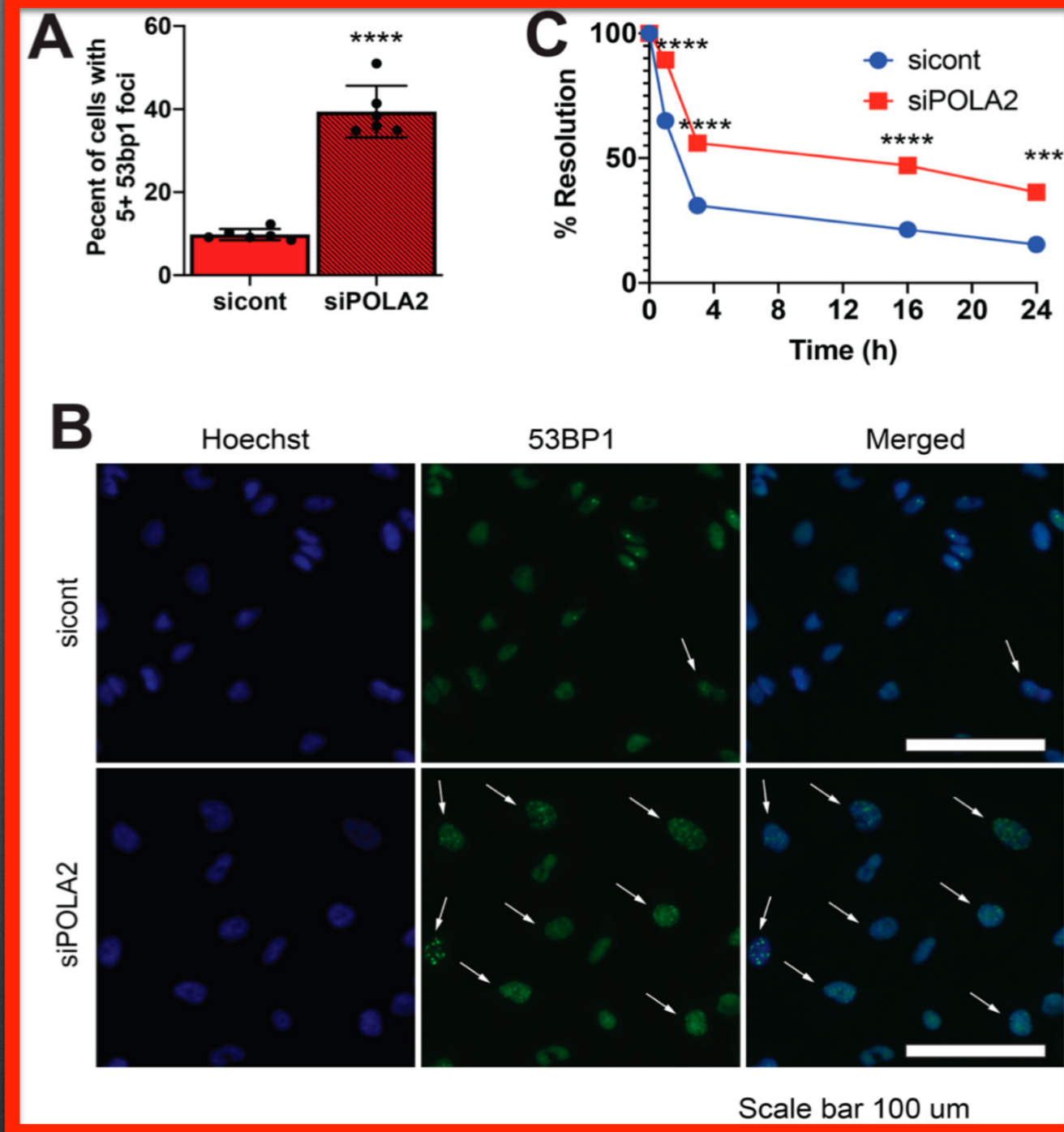
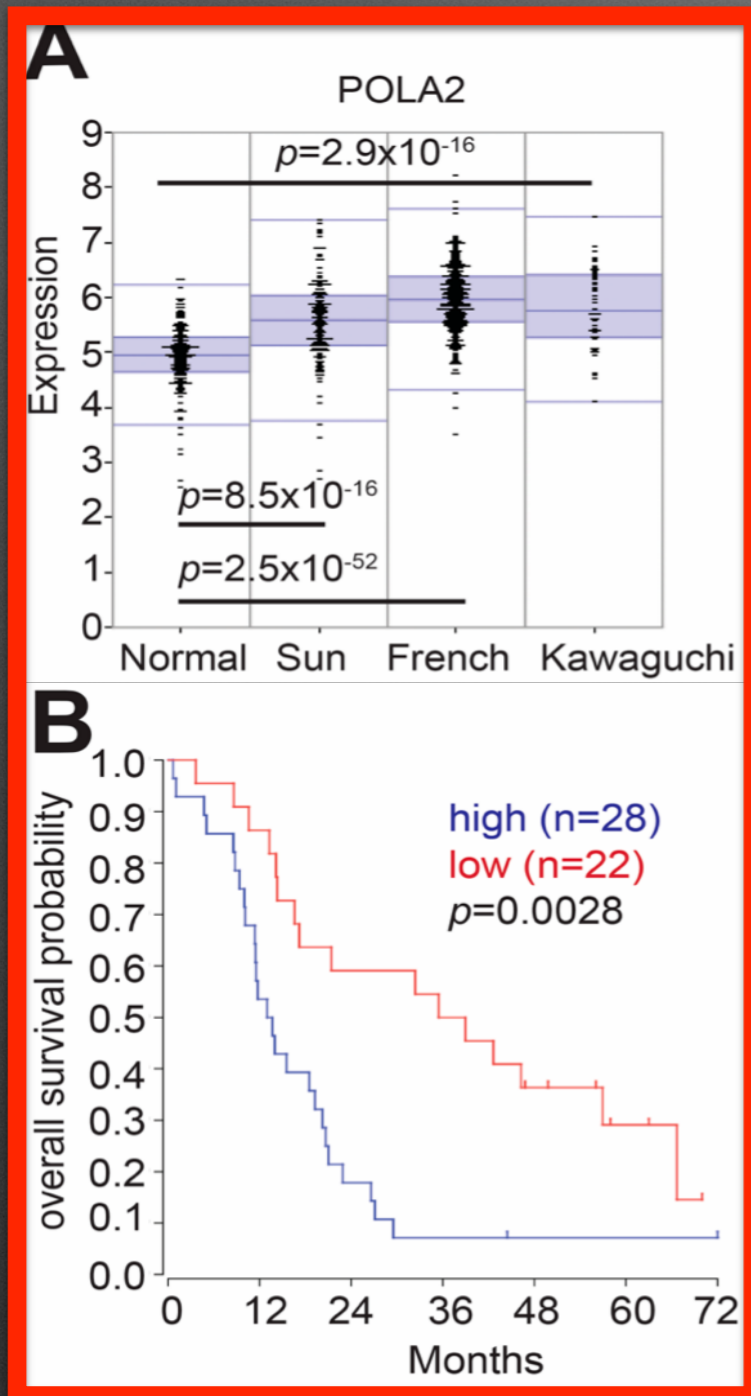
CCNA2

PTTG1 (securin, pituitary tumor-transforming 1)



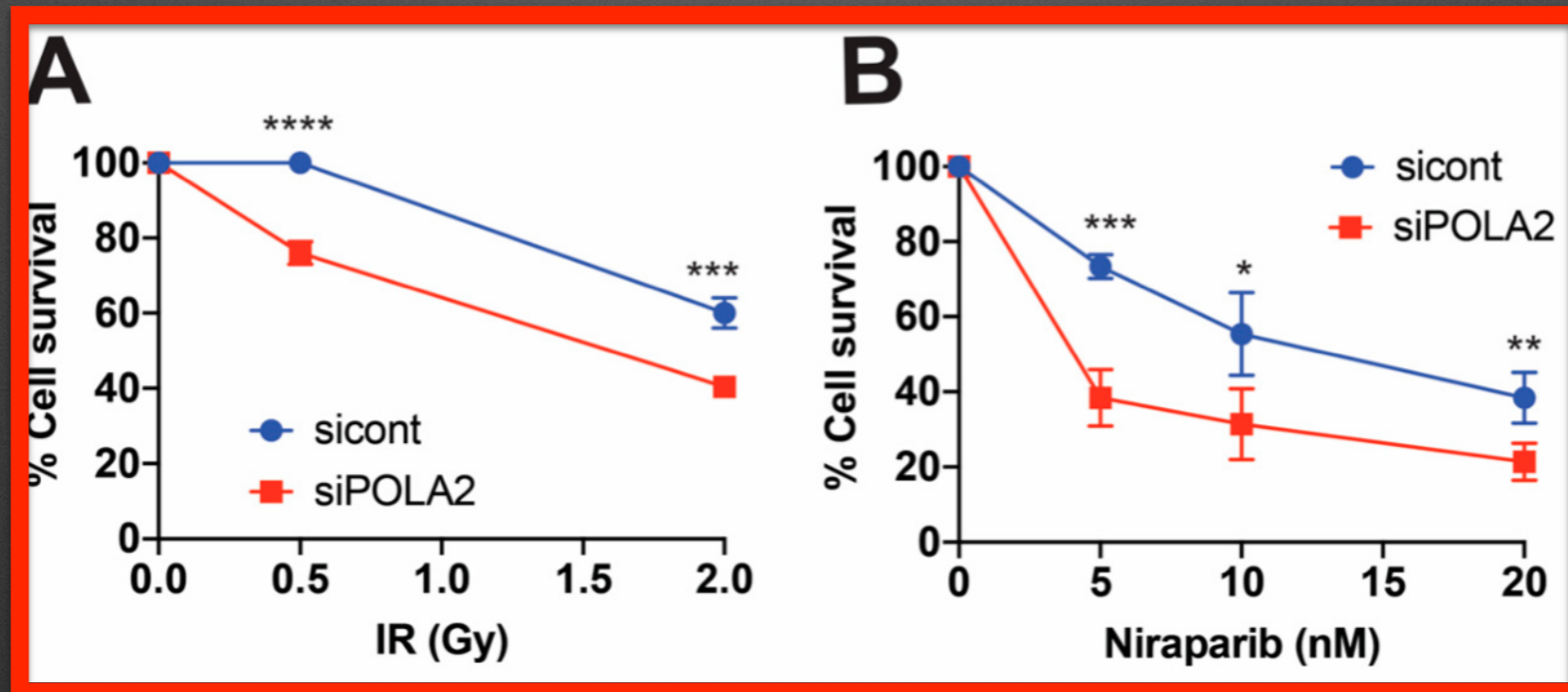
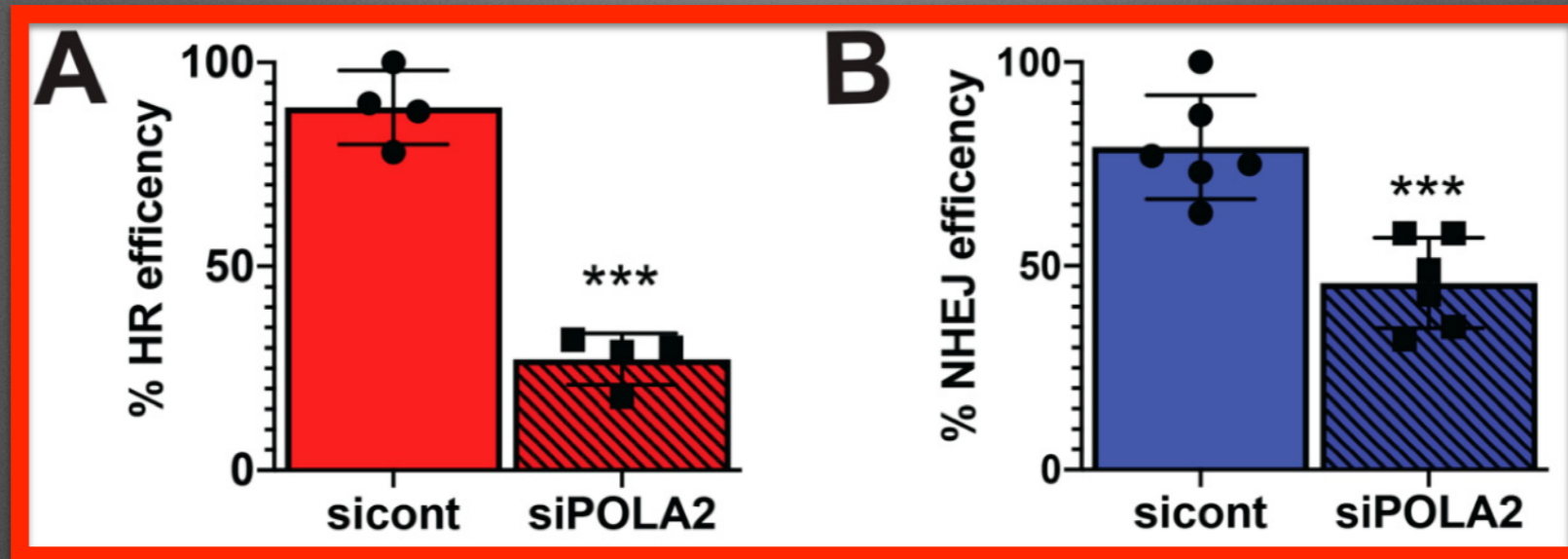


# POLA2 is upregulated in GBM patients





# POLA2 required for efficient DNA repair



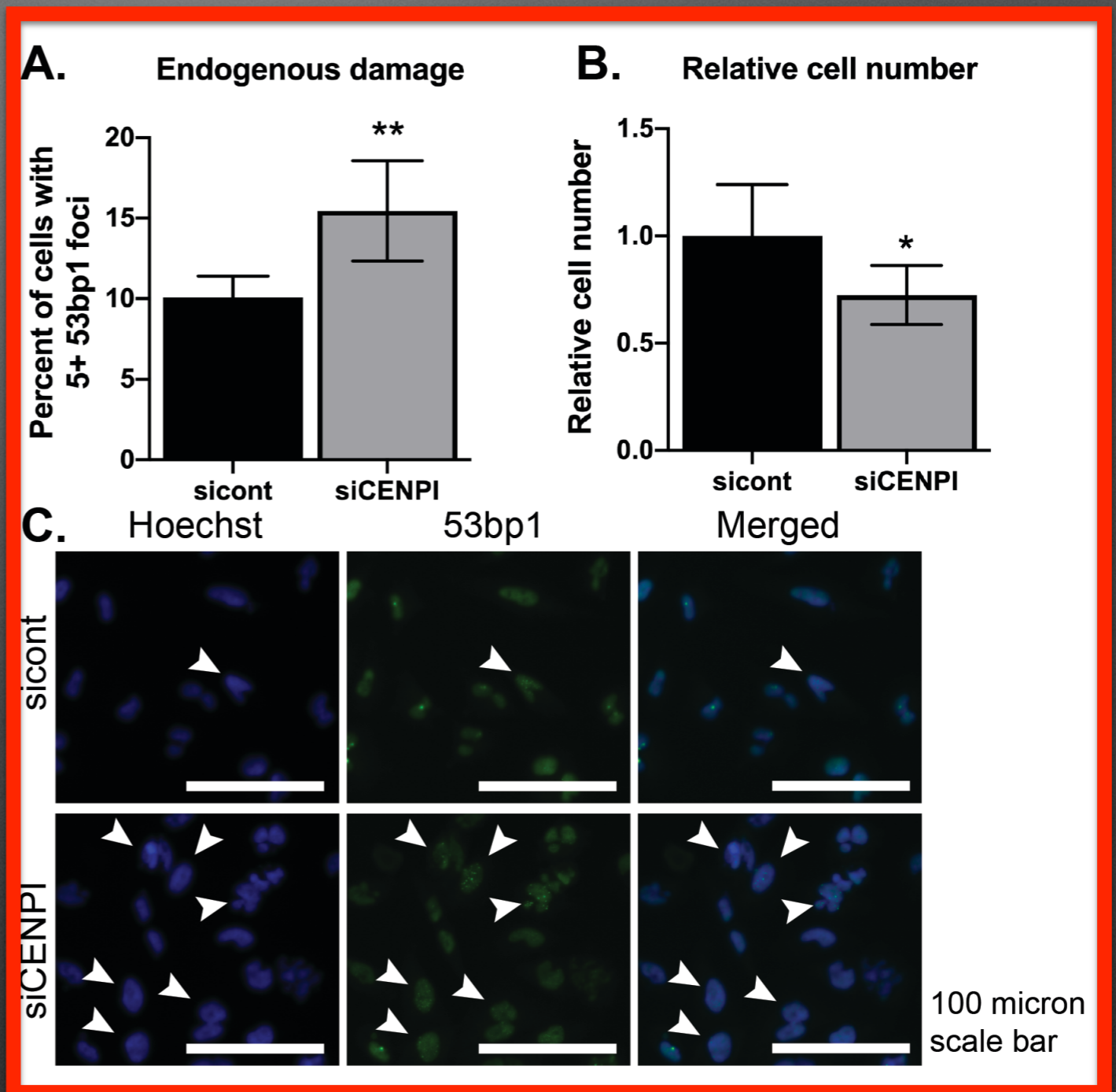
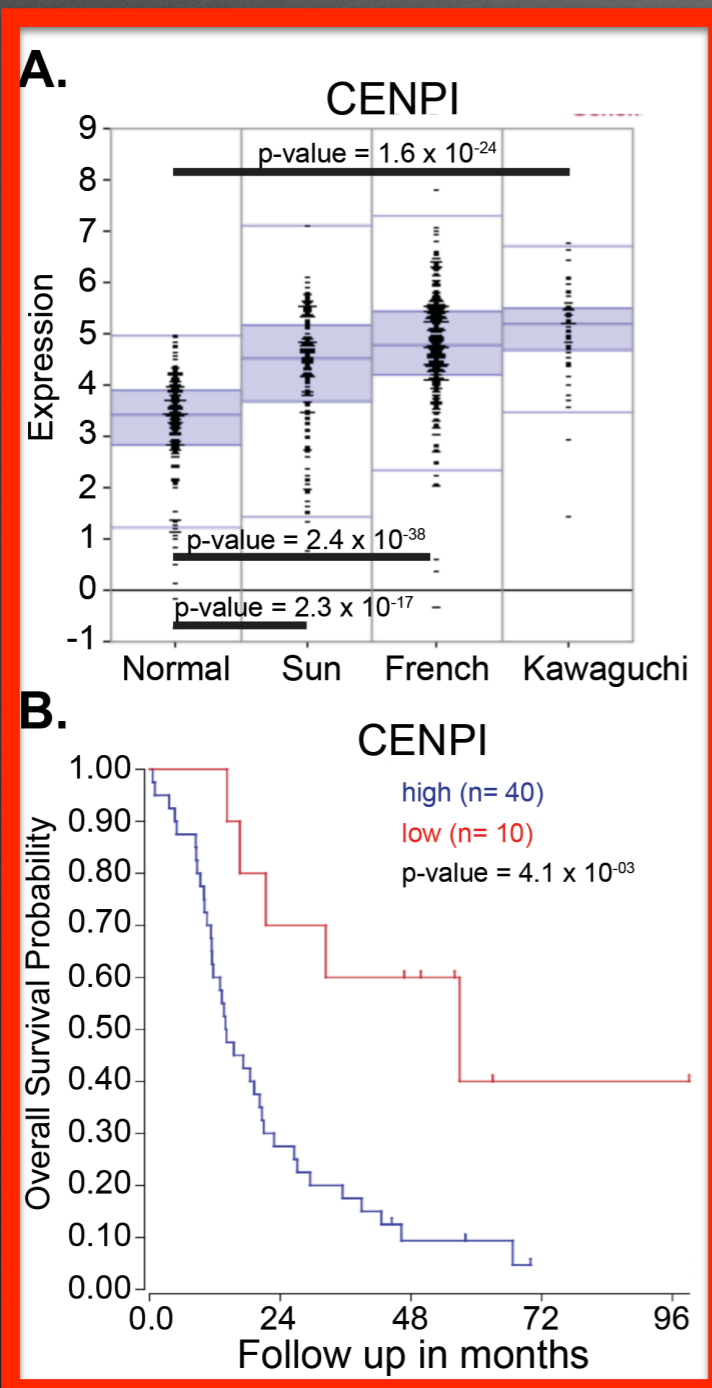


# POLA2 is required for the efficient repair of DNA double stranded-breaks

- POLA2 is up-regulated in GBM tumors
- High expression of POLA2 confers with poorer patient outlook
- POLA2 is required for efficient repair of DNA double stranded breaks through HR and NHEJ
- Loss of POLA2 sensitizes cells to IR and Parp-1 inhibition

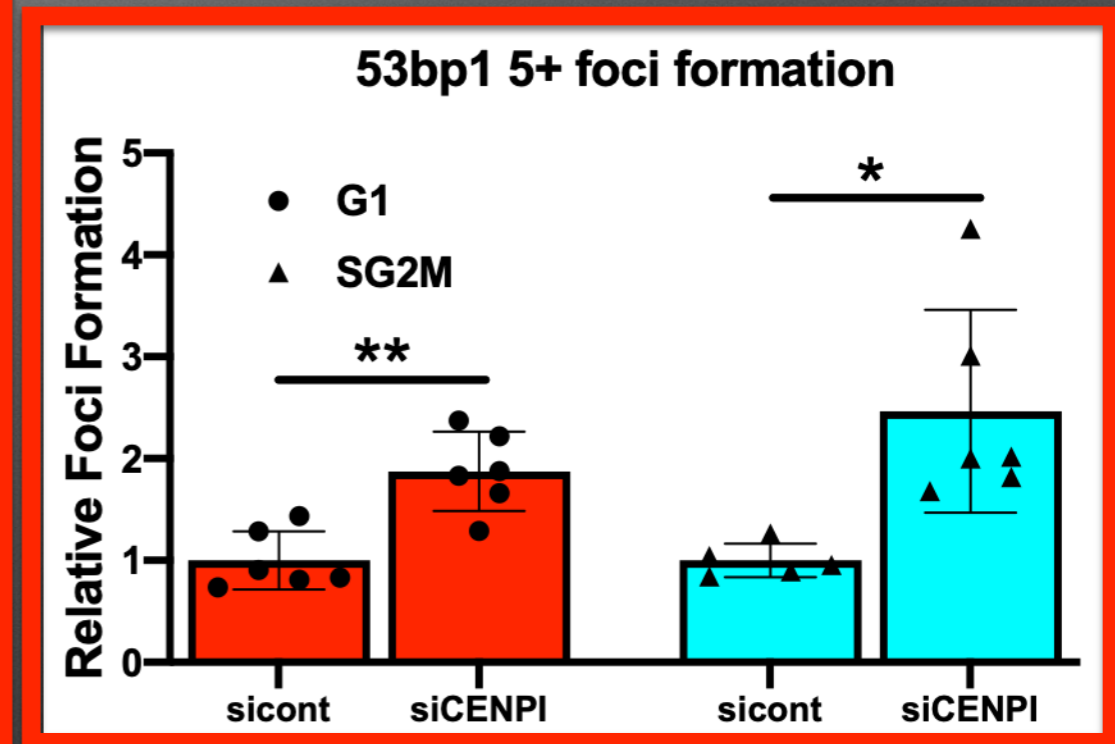
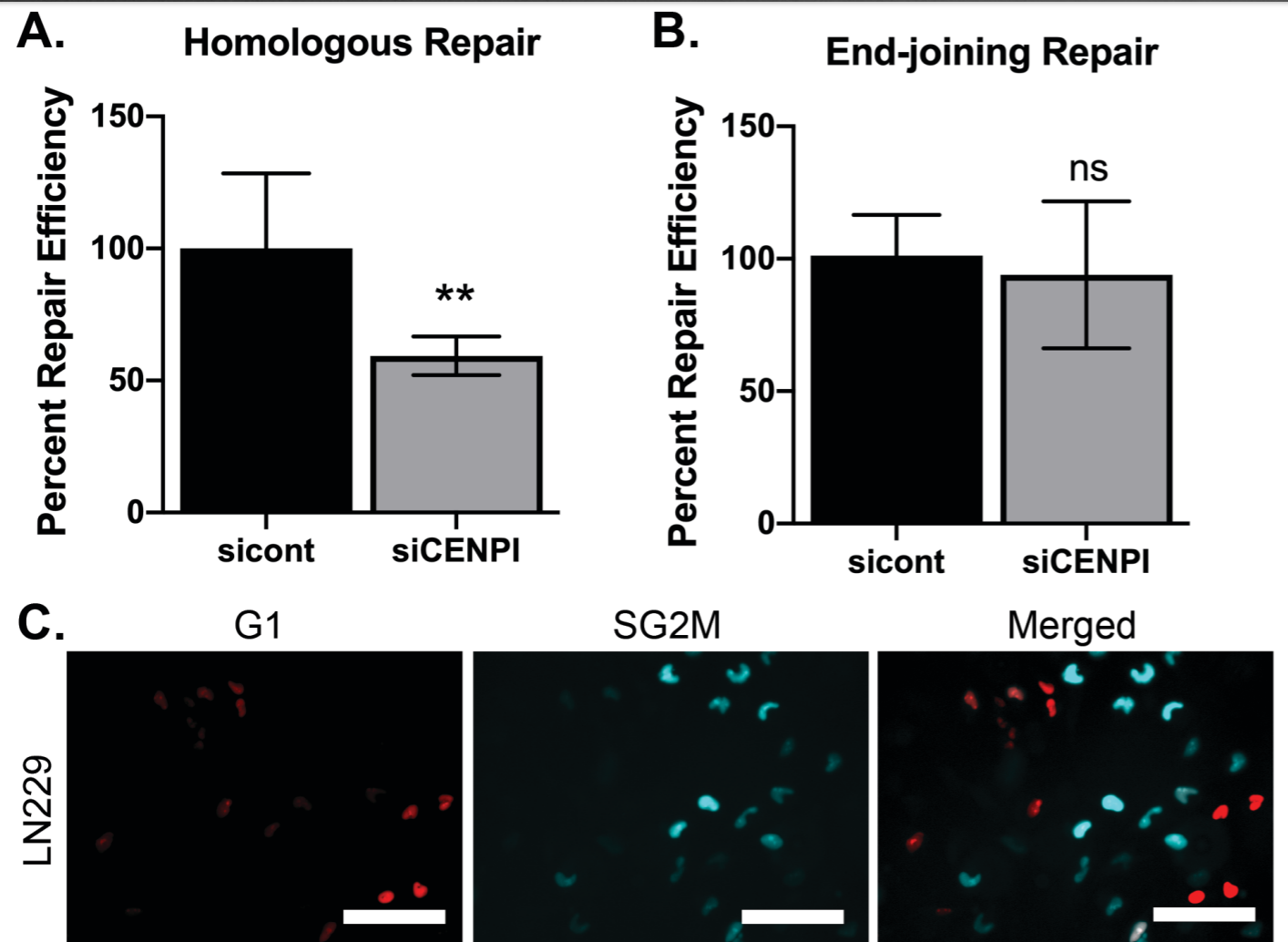


# Upregulation of CENPI is detrimental to GBM patients



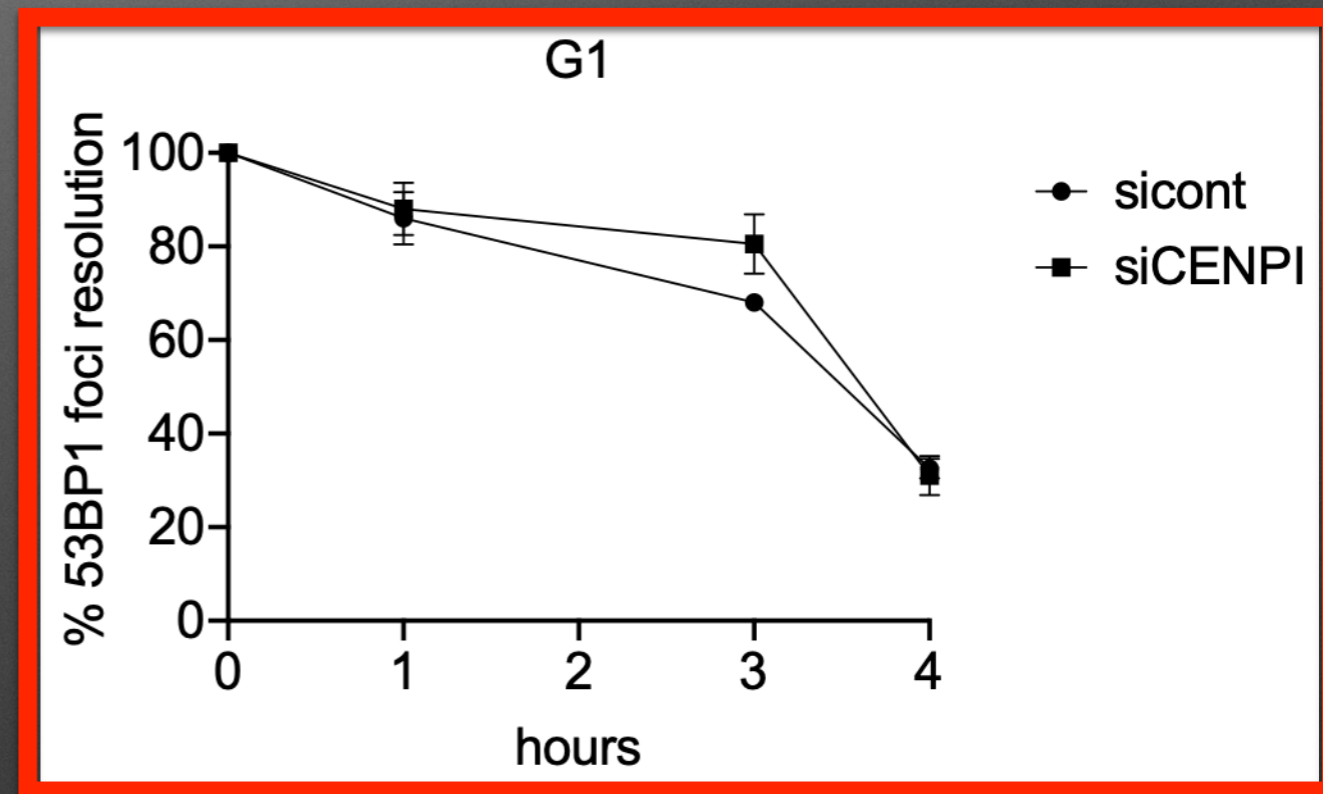
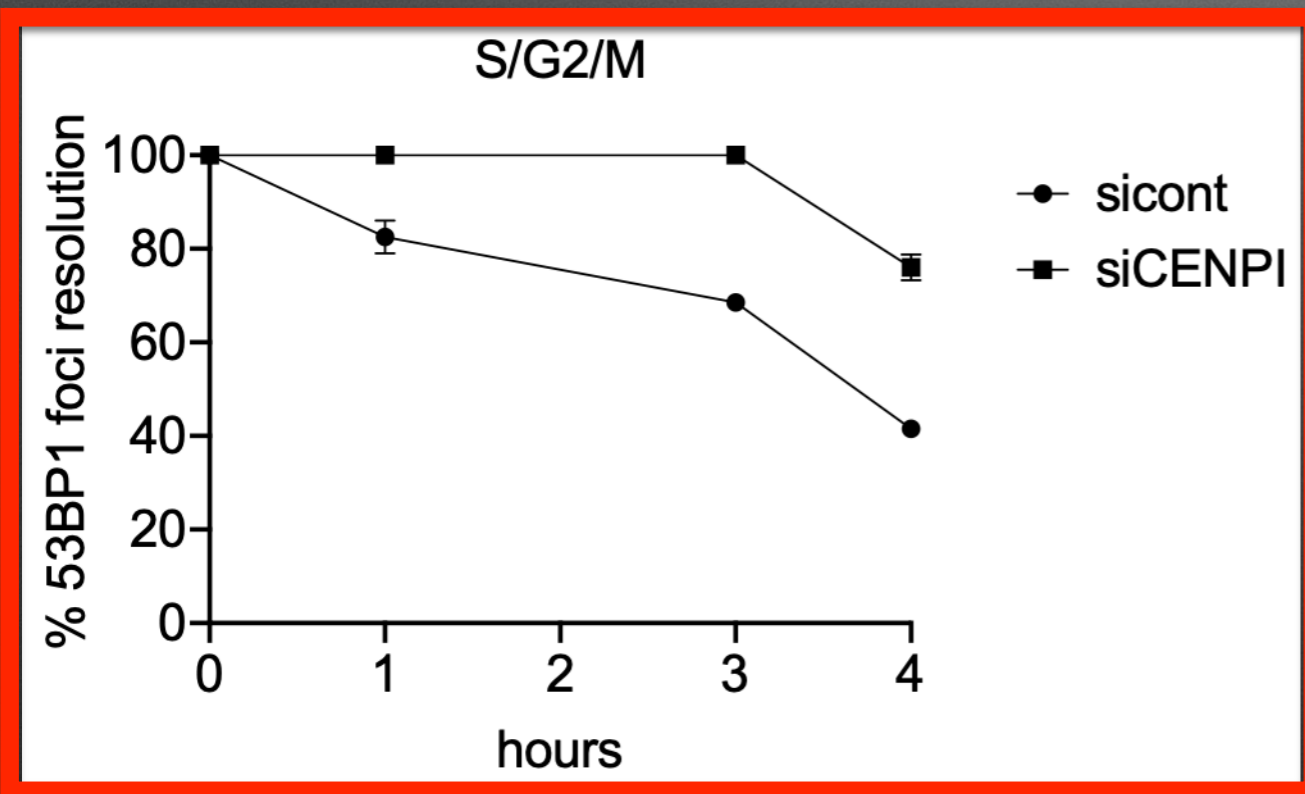


# CENPI is required for efficient HR repair





# Loss of CENPI impair DNA repair kinetics in S/G2/M





# CENPI is required for the efficient repair of DNA double stranded-breaks through HR

- CENPI is up-regulated in GBM tumors
- High expression of CENPI confers with poorer patient outlook
- CENPI is required for efficient repair of DNA double stranded breaks through HR and not NHEJ



# XRN2 and its targets are novel regulators of DNA repair programs

- XRN2 and its targets are required for efficient DNA double stranded break repair
- Loss of expression in XRN2 or its targets sensitizes cells to DNA damaging agents
- POLA2 is required for efficient repair of DNA double stranded breaks through HR and NHEJ
- CENPI is required for efficient homologous repair of double stranded breaks



# Acknowledgements

Morales Lab

Dr. Julio Morales

Stark Lab

Dr. Jeremy Stark

OUHSC Genomics Core

Dr. Allison Gillaspy

Jenny Gipson

Funding: P20GM103639 granted to JCM





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