

Screen of DNA Repair Genes in Colorectal Cancer

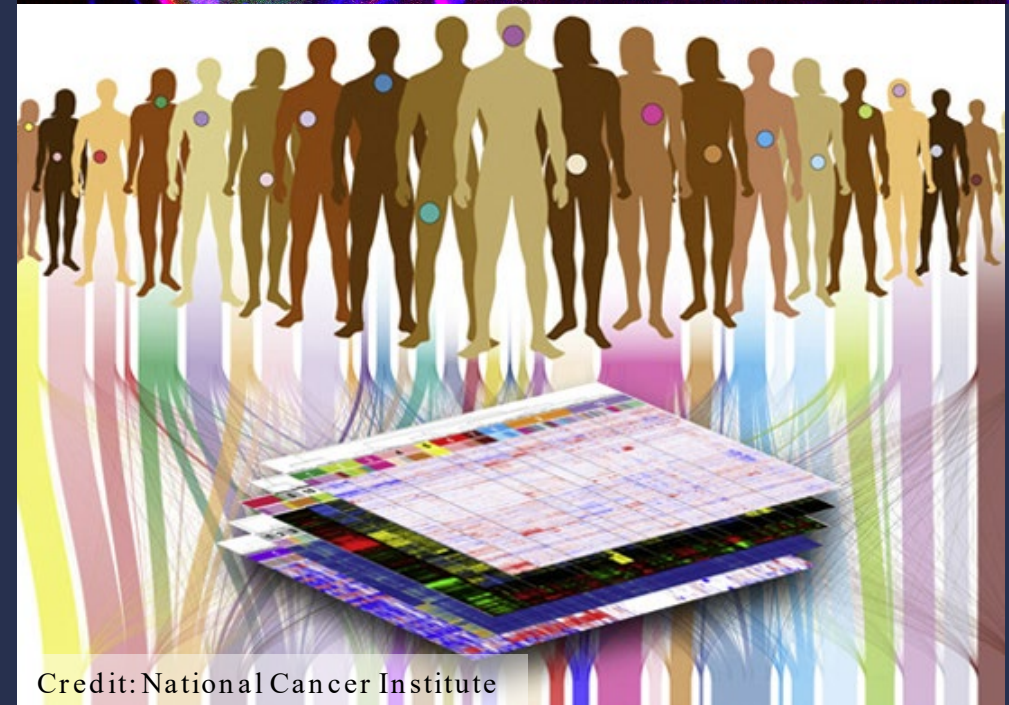
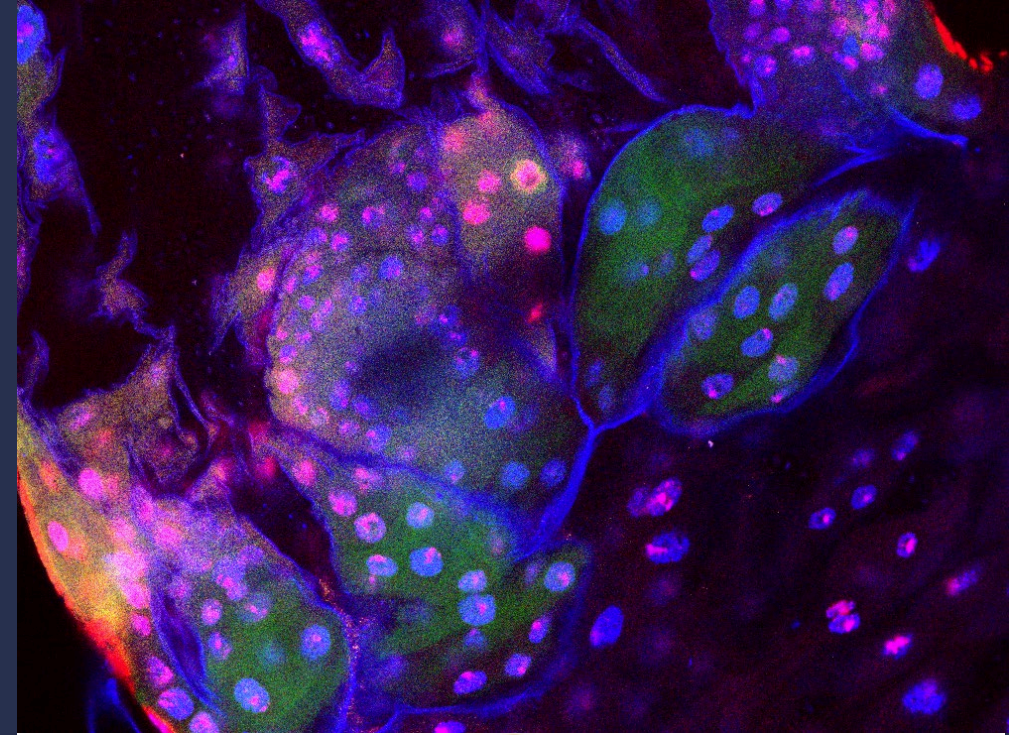
Andrew Taylor

Helen Louise Lee Undergraduate Research Award

Supervising Professor: Dr. Erdem Bangi

Colorectal Cancer

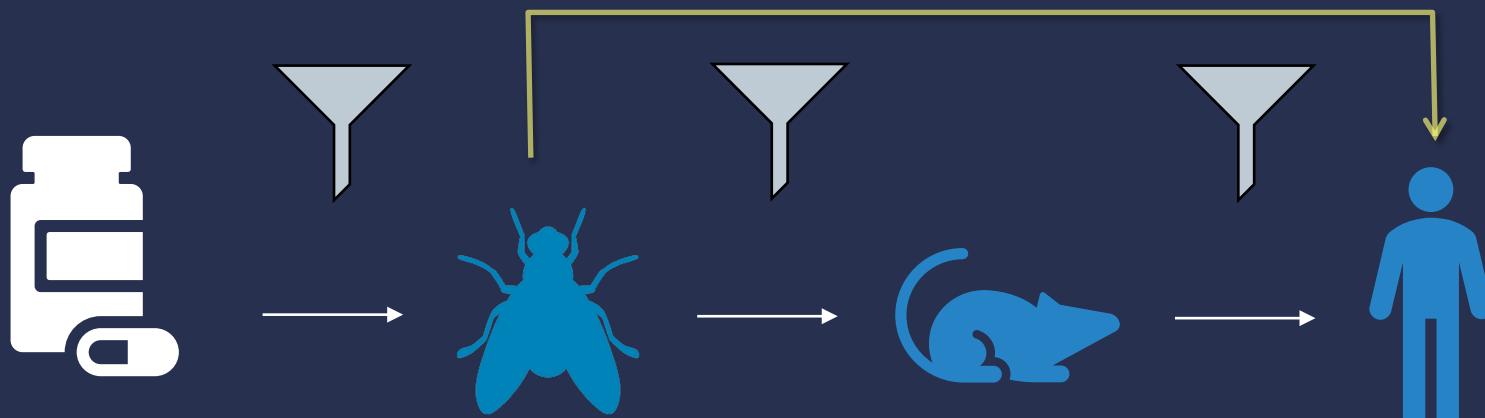
- 2nd Leading cause of cancer related death in the western world
- 1 in 20 people in the United States expected to have it over course of lifetime
- Drug trials have low FDA approval rates (<5%)
- Genetically complex and diverse disease
- Age of bioinformatics
- "Omics" data sets constantly expanding: transcriptomics, genomics, proteomics, epigenomics



Credit: National Cancer Institute

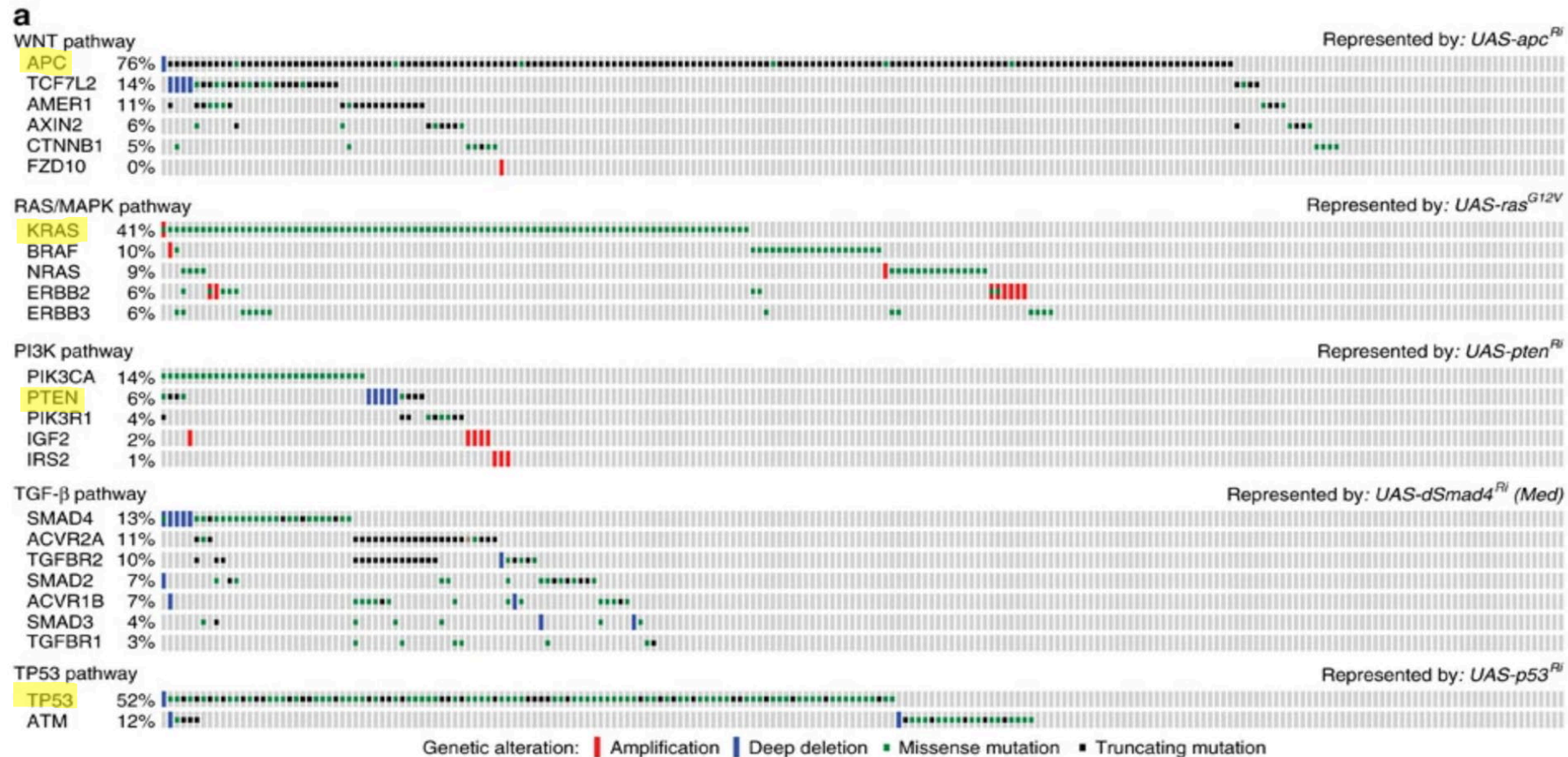
Drosophila Based Approach

- Over 90% of genes mutated in cancer have fly orthologs
- Practical Advantages as Model Organism: History, Life Cycle, Maintenance, Genetic Tools
- Drug Discovery Pipeline
- Fruit Fly Avatars of Human Patients



RPPA Cancer Model in Drosophila

- Models 4 of the most frequently mutated genes in human colorectal cancer



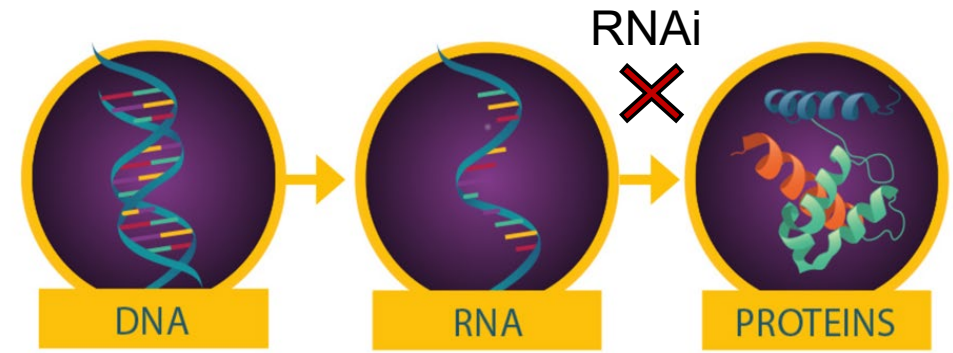


RPPA Cancer Model

- Uses gene overactivation and knockdown to simulate cancer driving mutations in flies
- Cancer expression is

a) Inducible

b) Tissue Specific

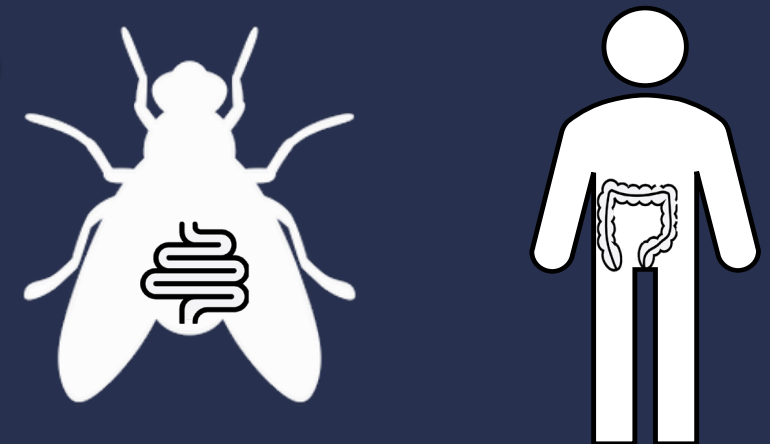


Credit: National Cancer Institute

a)

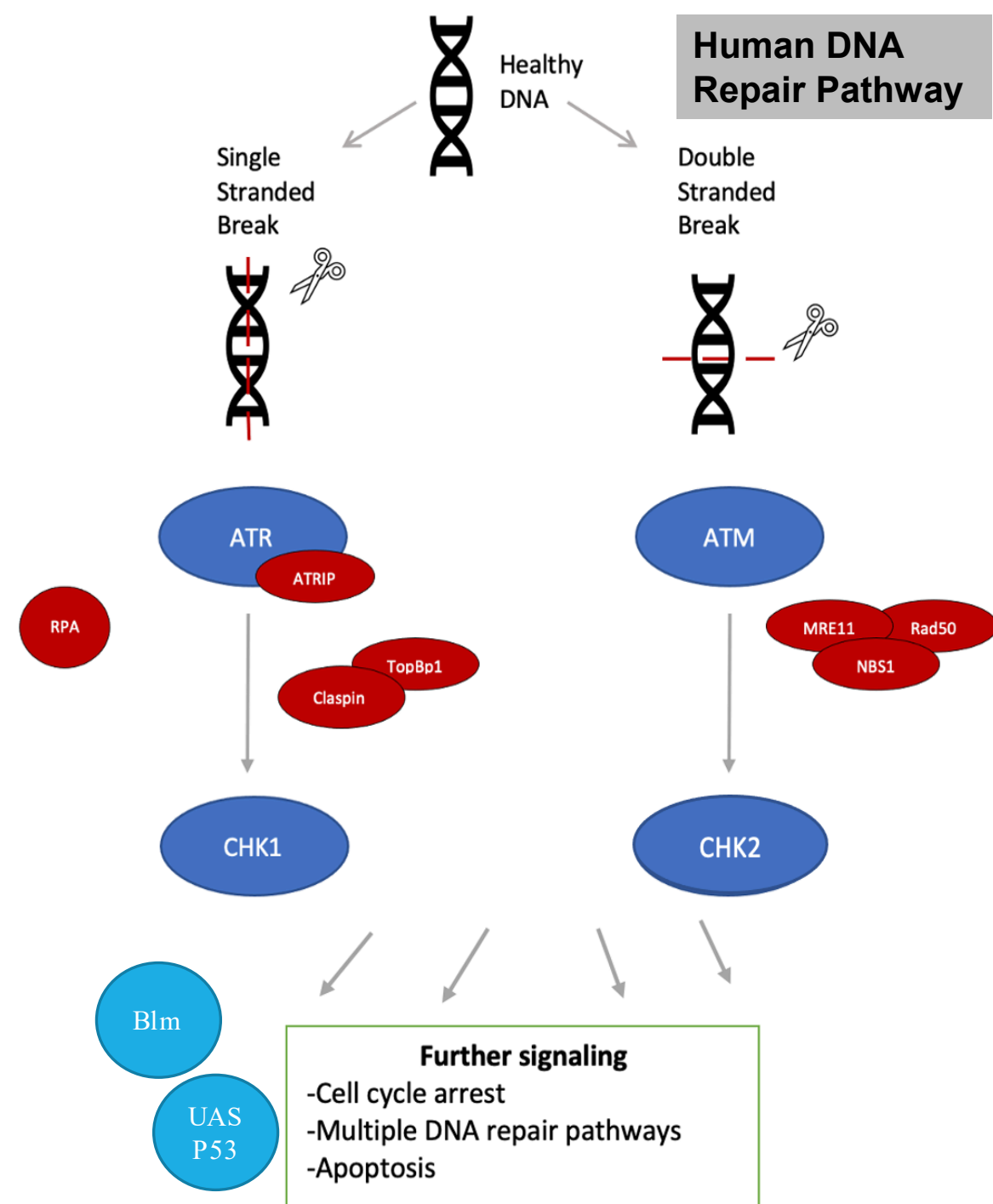
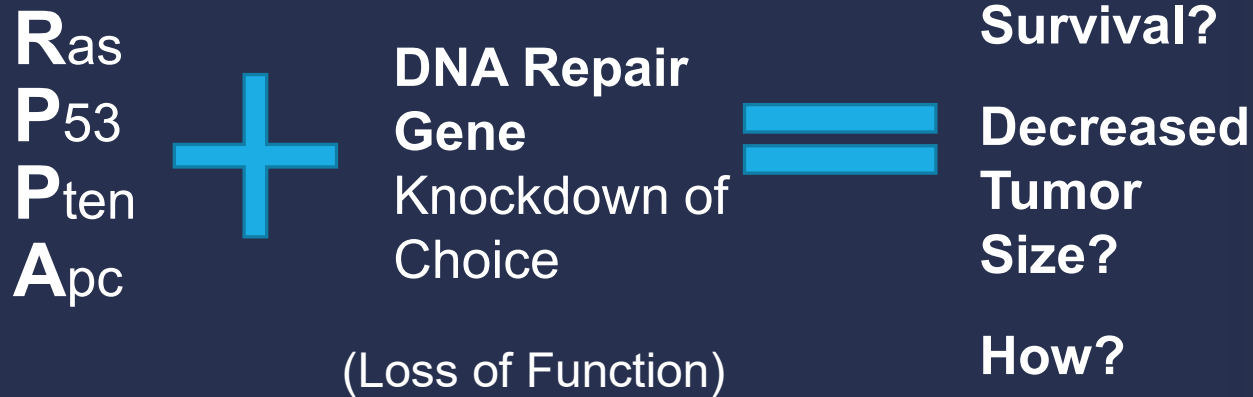


b)



IDEA Grant Project

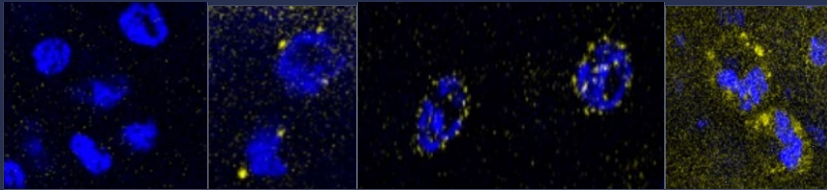
- **Primary Question: How does reduced DNA repair gene expression affect tumor cells?**
- DNA Damage Response essential for life
- DNA repair gene loss of function studied in RPPA Background



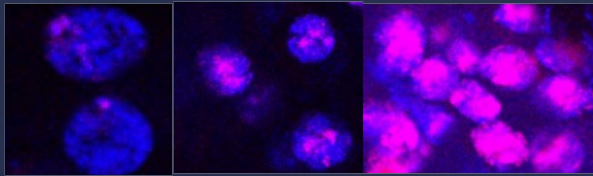
Functional Changes

3 measures used to examine tumors

1. Analysis of cancer relevant proteins



Y-H2AV (DNA Damage)

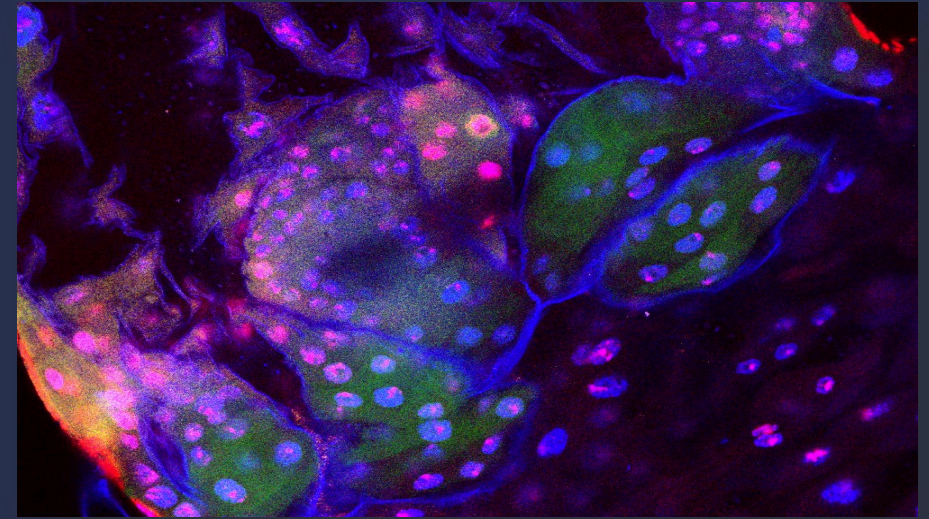


H3K9me3 (Senescence)

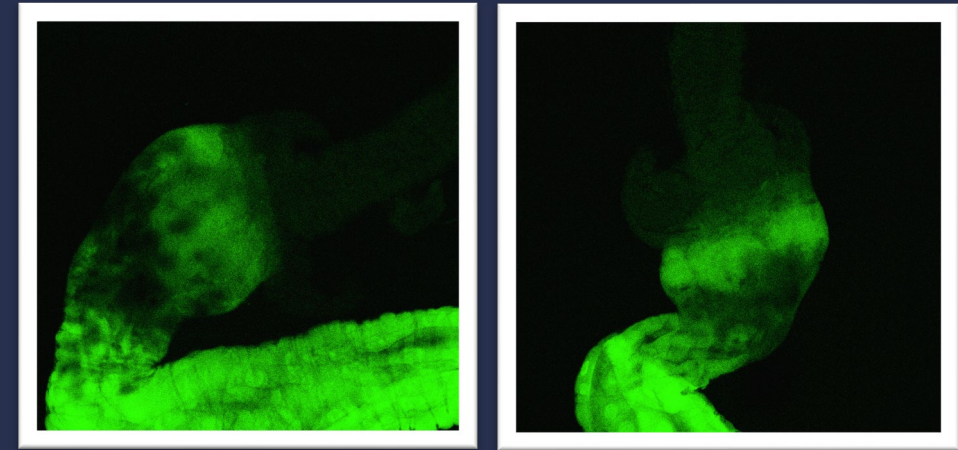
2. Tumor size quantification

3. Organismal lethality

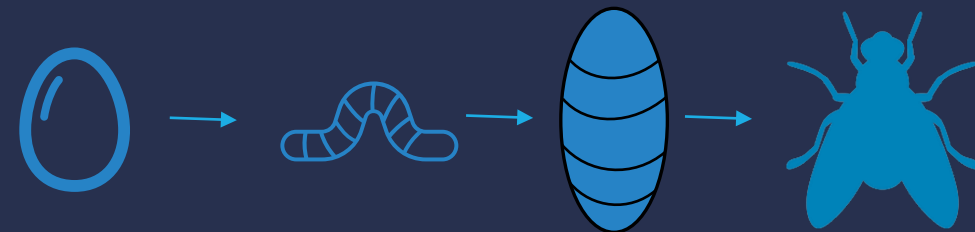
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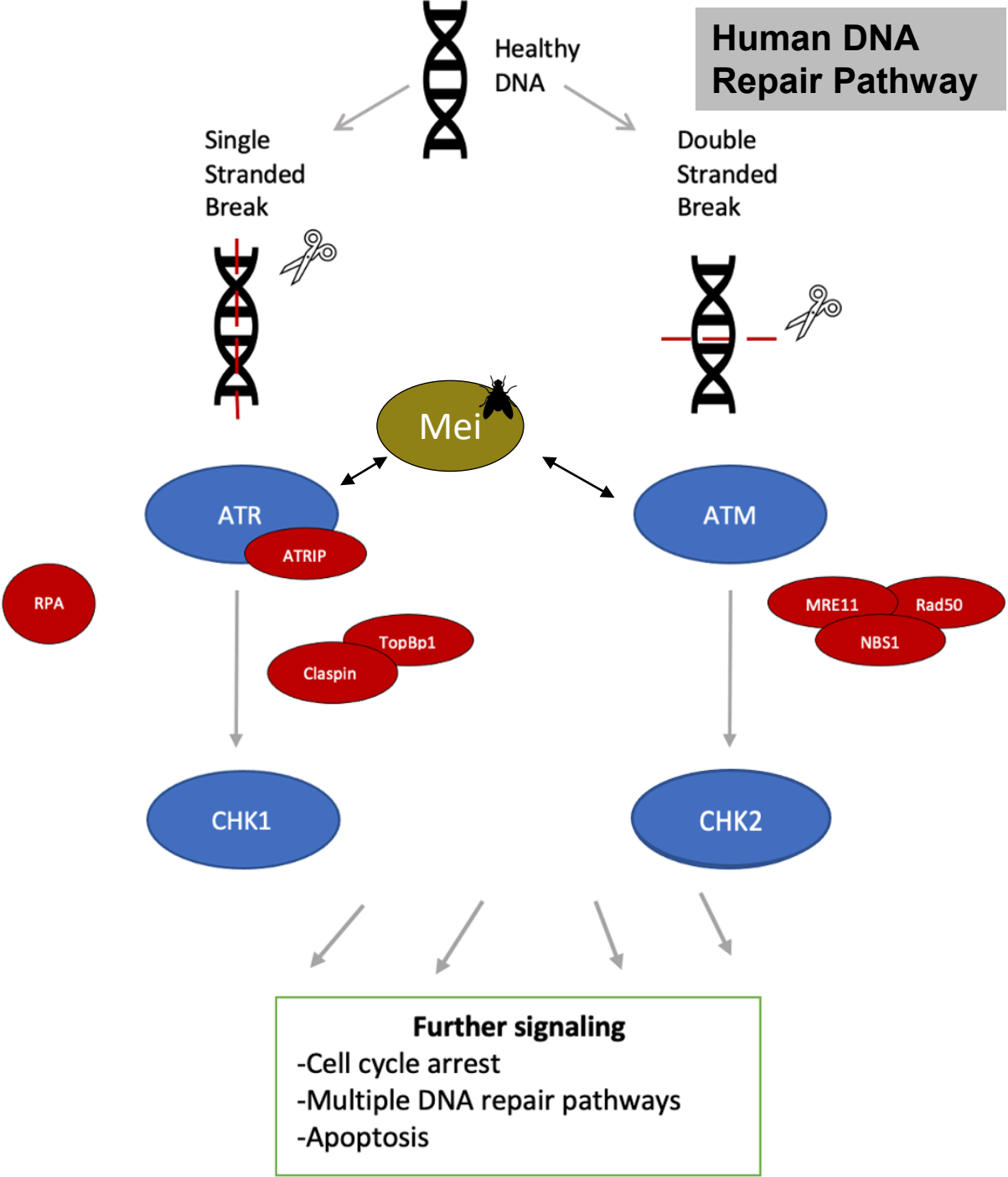
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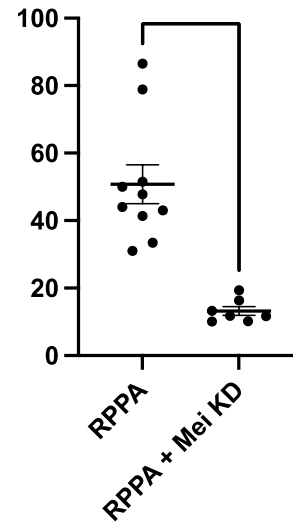
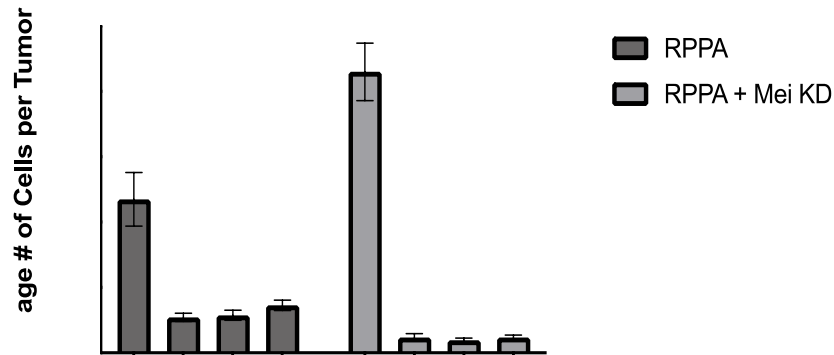


Mei/ATR

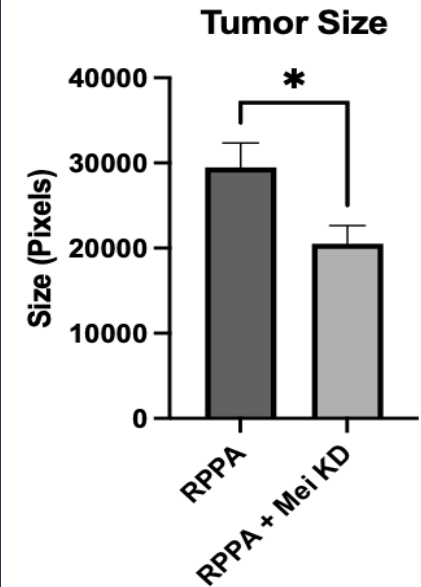


Results – Mei/ATR

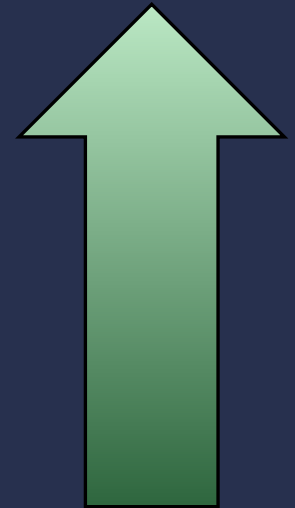
DNA Damage Marker



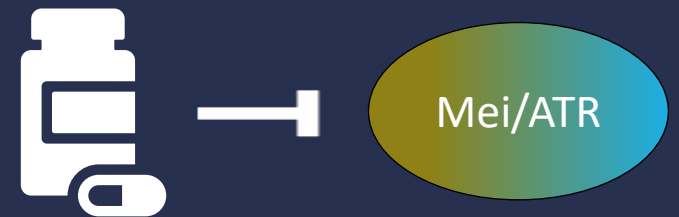
Tumor Size



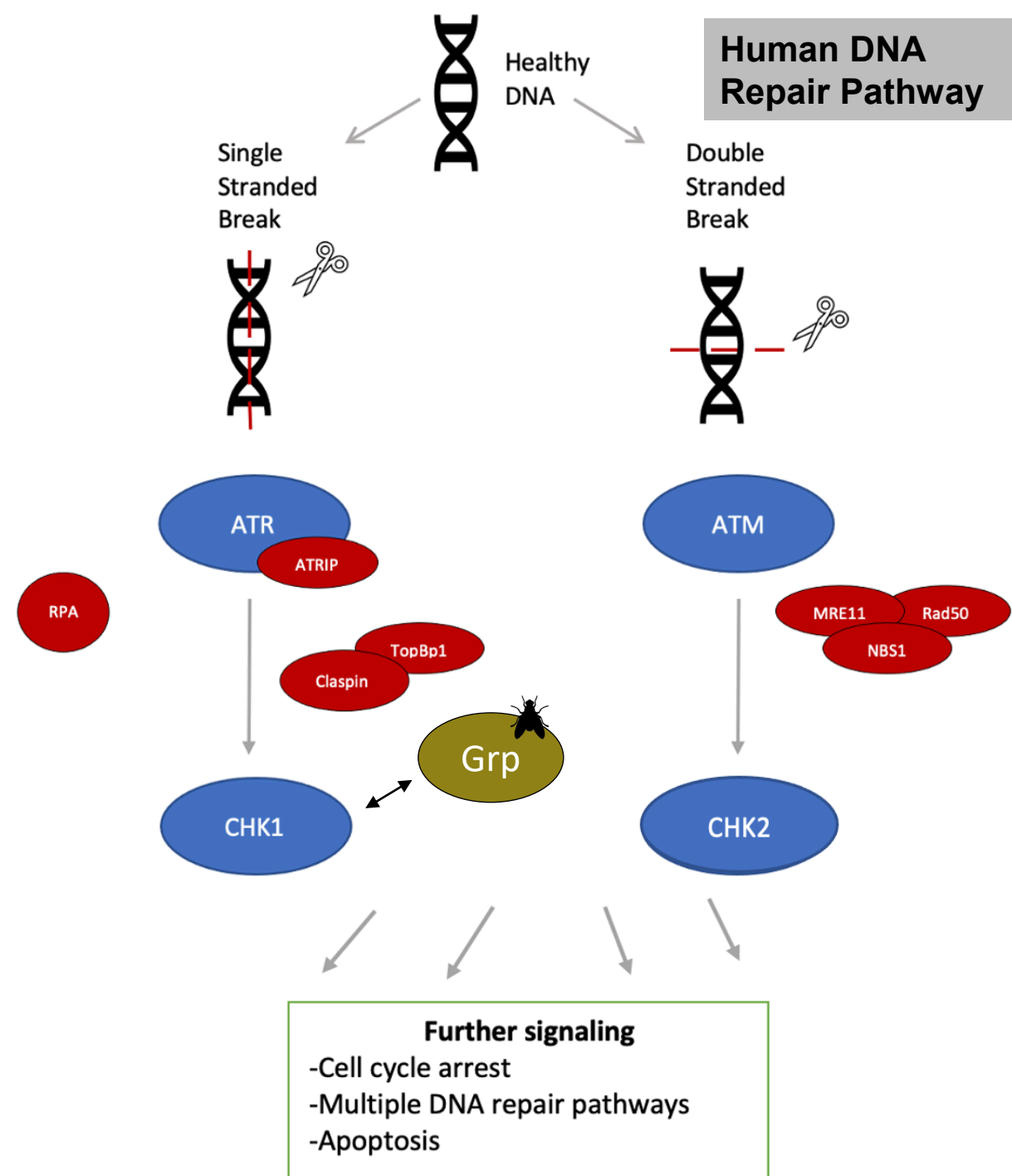
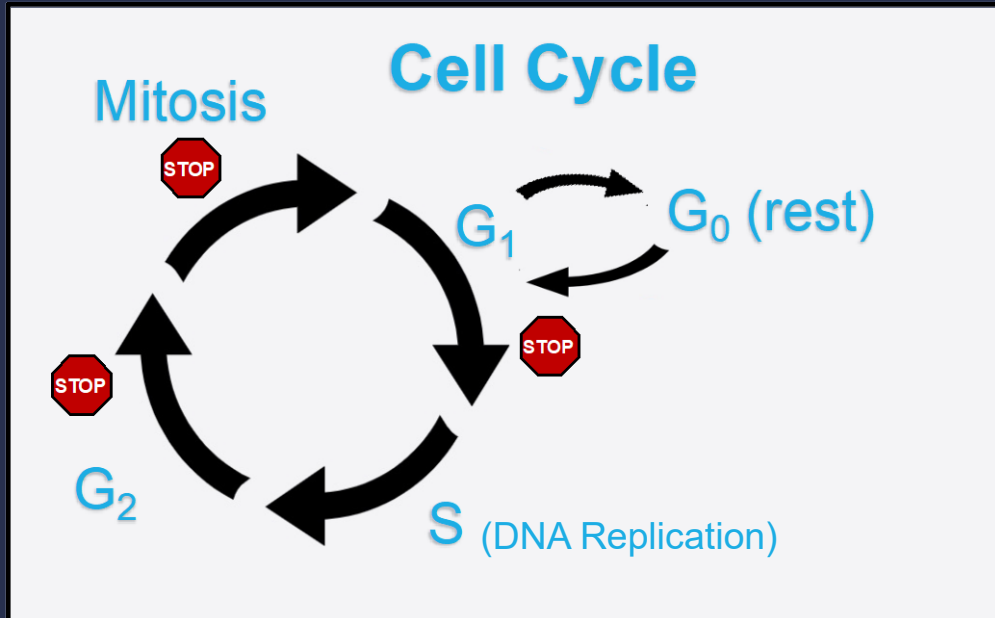
Survival (Preliminary)



Conclusion: Decrease in activity of Mei/ATR might preferentially harm/limit tumor cells via some mechanism involving DNA Damage Detection



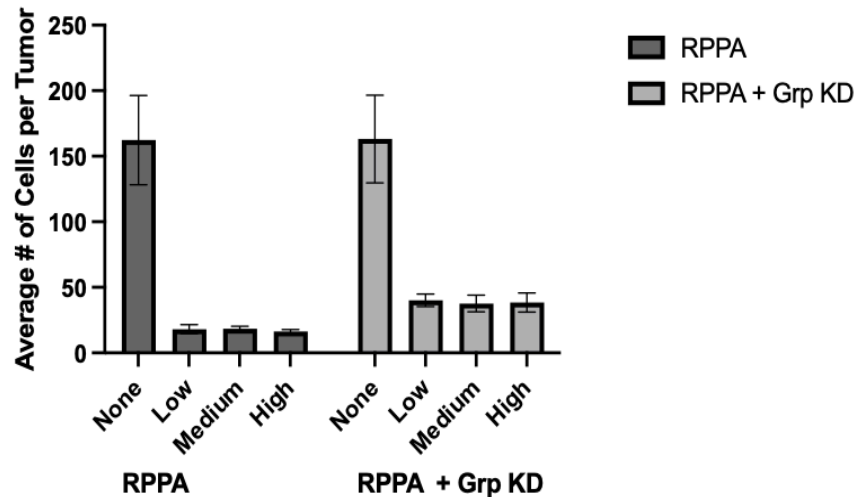
Grp/CHK1



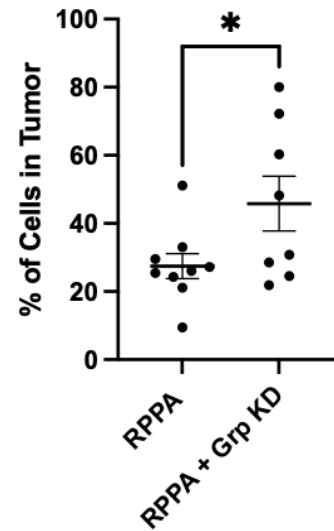
Results – Grp/CHK1

DNA Damage Marker

Average Number of Cells per Tumor Sorted by DNA Damage Marker Intensity



All Cells with DNA Damage

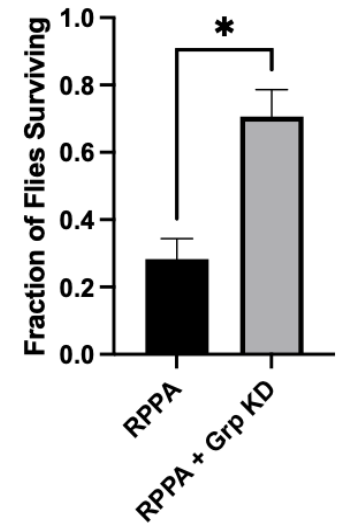


Tumor Size

No
Significant
Difference

Survival

Survival



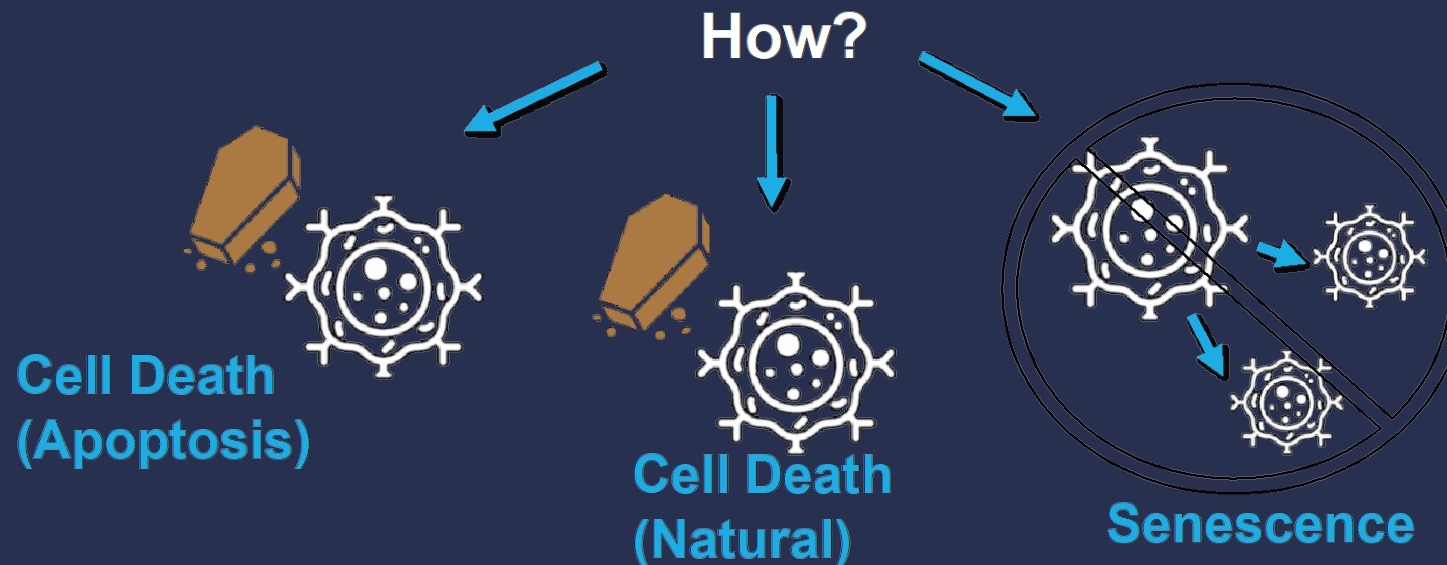
Conclusion: Decrease in activity of Grp/CHK1 enhances survival through some mechanism involving DNA Damage



Discussion - Survival

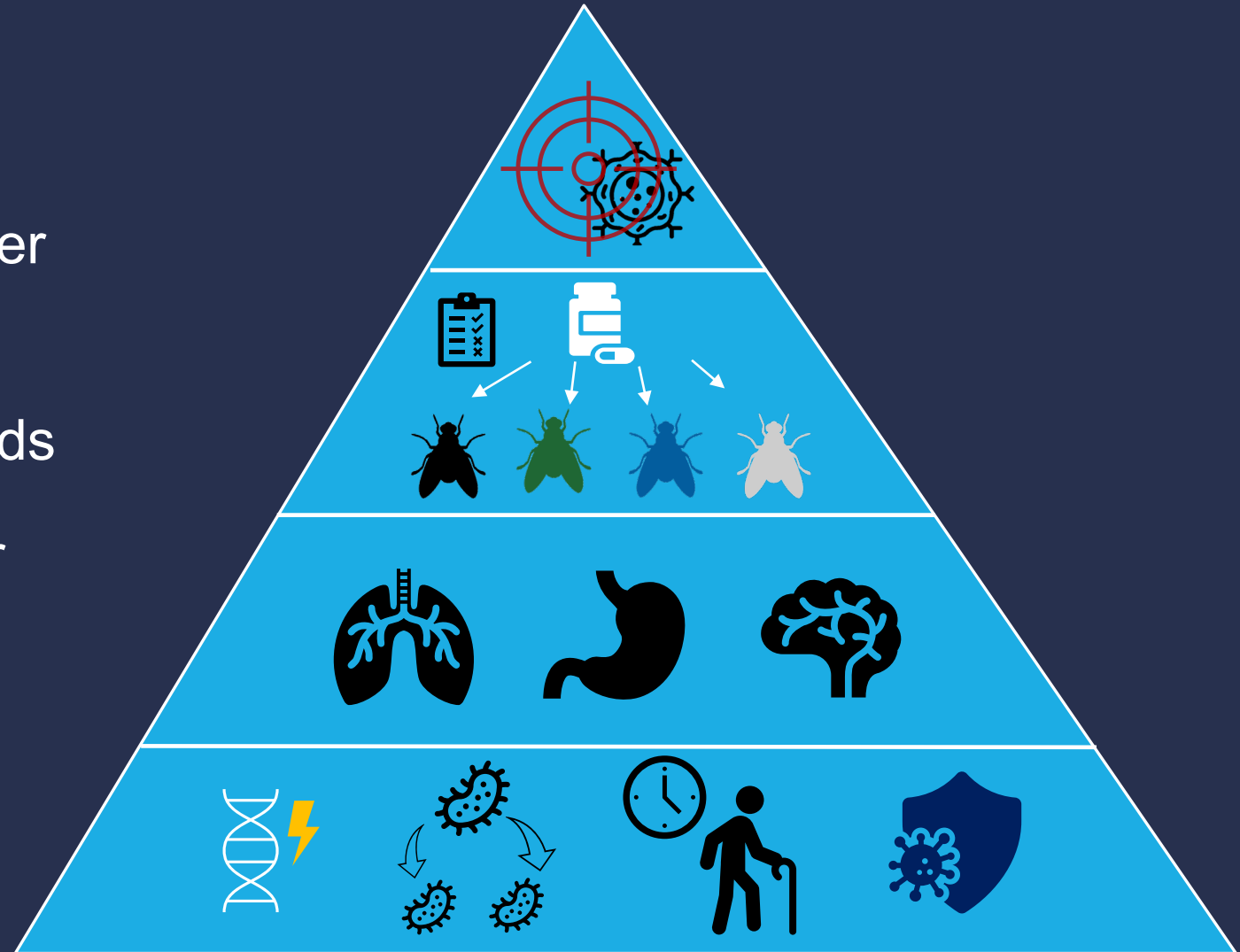
- Decrease in DNA Repair Gene Expression = Increased Survival

Gene Knockdown	Mei	Tefu	Grp	Lok	Blm	UAS P53	Nbs	Mus 304	Mus 101	Mre11	RPA-70	Claspin
Survival (Preliminary)	↑	↑	↑*	↓	↑	↑	↑	↑	↑	↑	↑	↑



Closing Remarks – Why is this important?

1. Actionable targets for anti-cancer drugs
2. Screening in unique backgrounds
3. Better understanding of cancer
4. Broader applications



Acknowledgements

- Dr. James Lee – for funding the project & living costs over 15 weeks
 - Helen Louise Lee Undergraduate Research Award
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