

20.109 MOD1

Genomic Instability

Fall 2022
Day 6

Bevin P. Engelward, *Sc.D.*
Professor of Biological Engineering

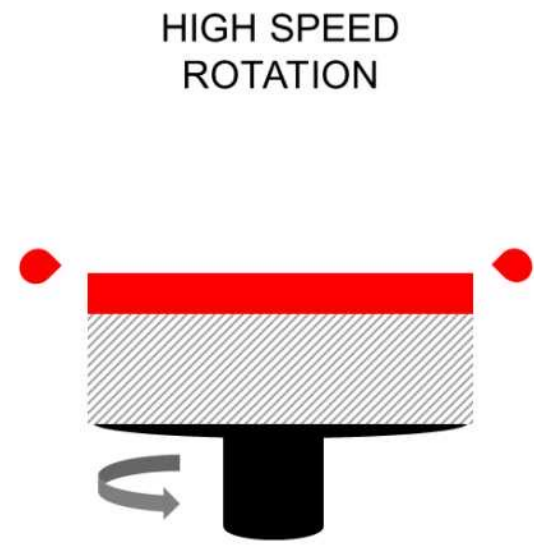
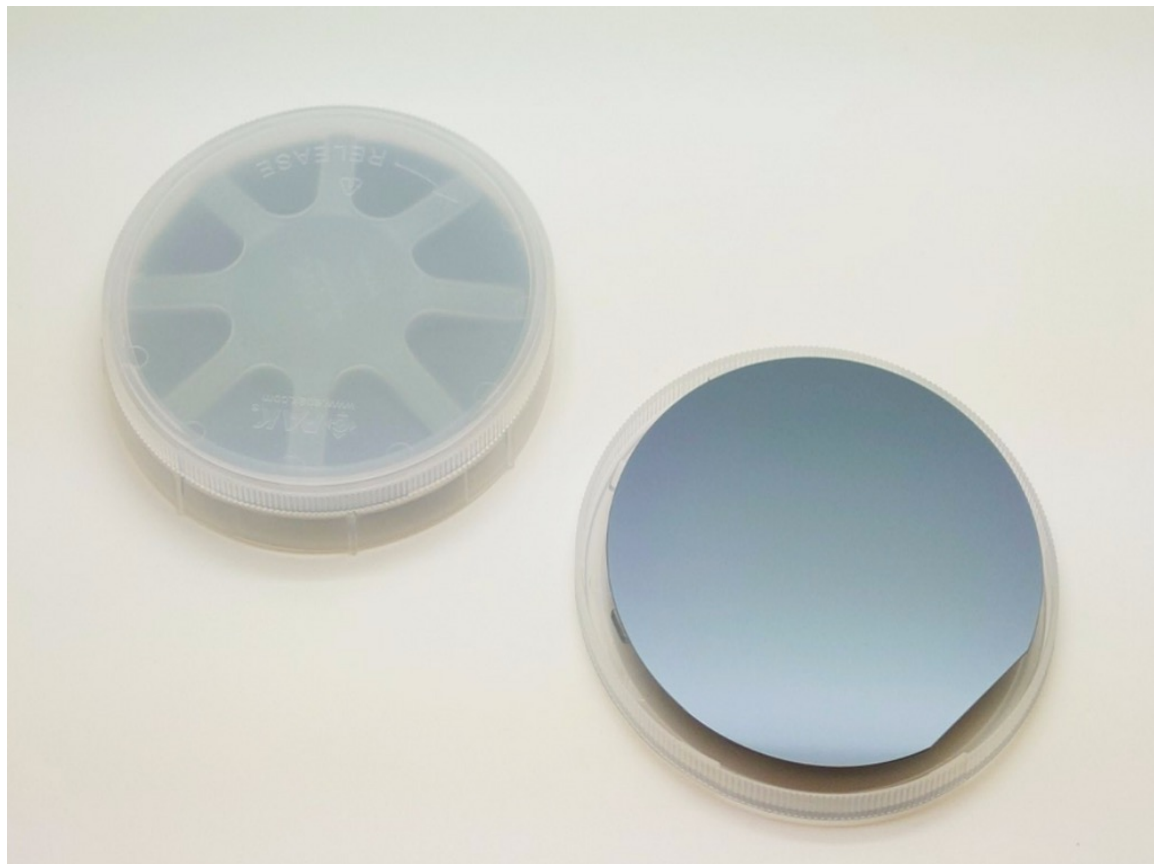
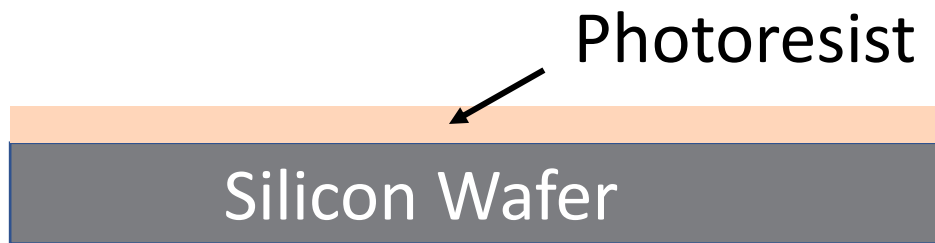
How the CometChip was made

How to Measure Repair Capacity using a Time Course Experiment

Inter-individual Variation in DNA Repair Capacity

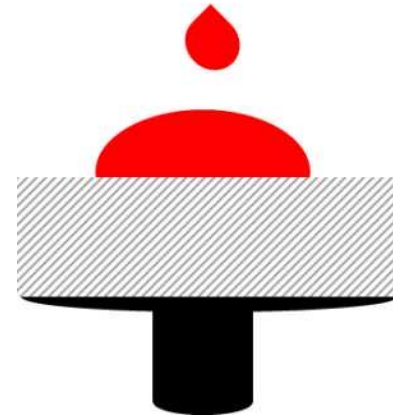
Impact of Variable DNA Repair Capacity on Cancer Risk

Review of our Central Hypothesis

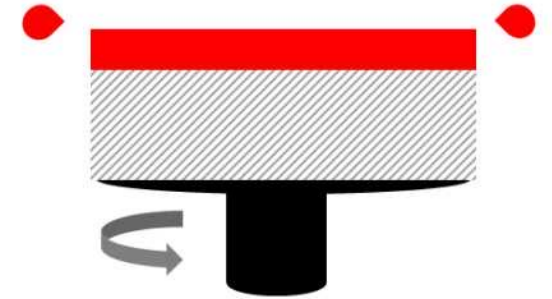


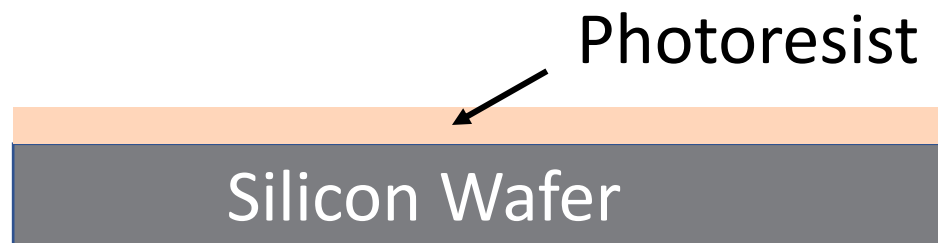


DISPENSING
OF RESIST

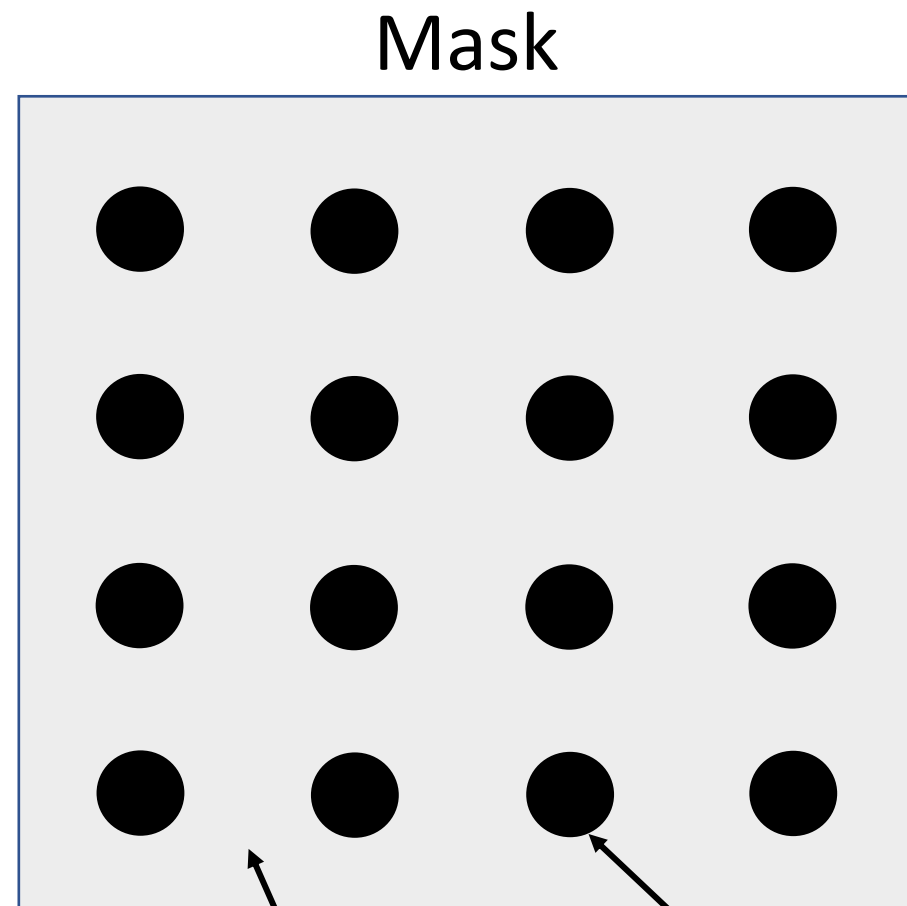


HIGH SPEED
ROTATION



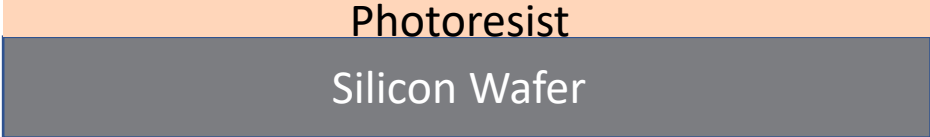


Mask

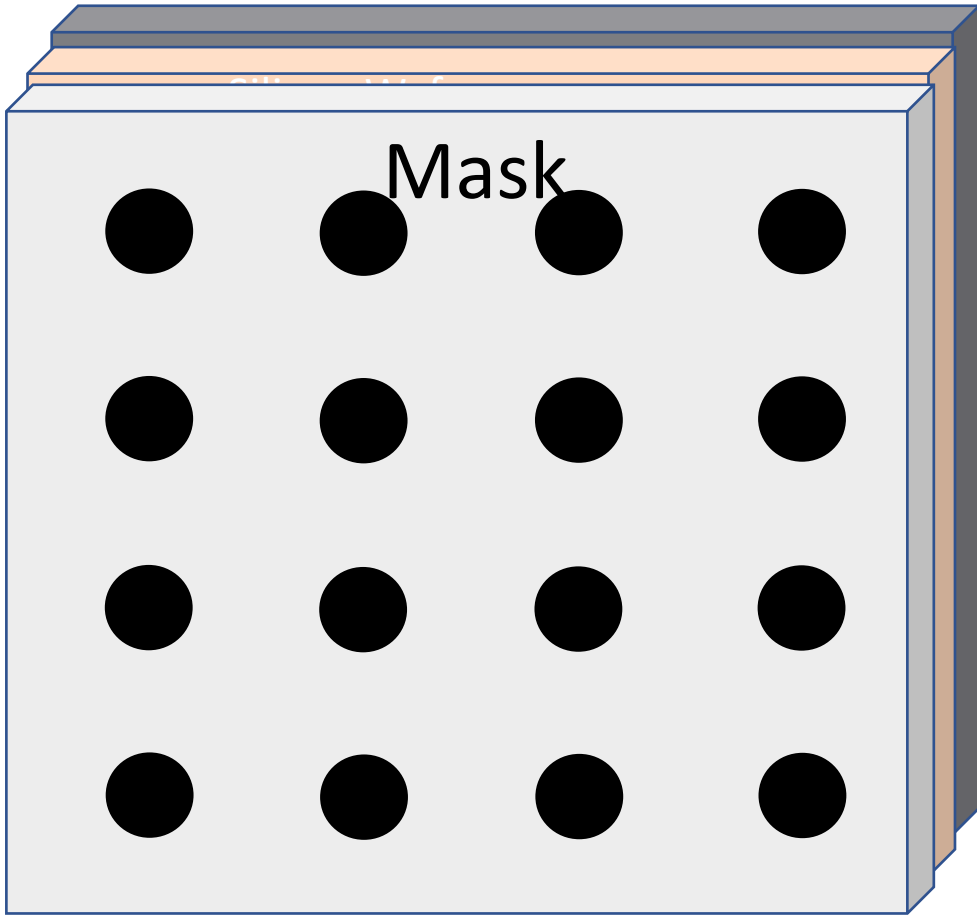


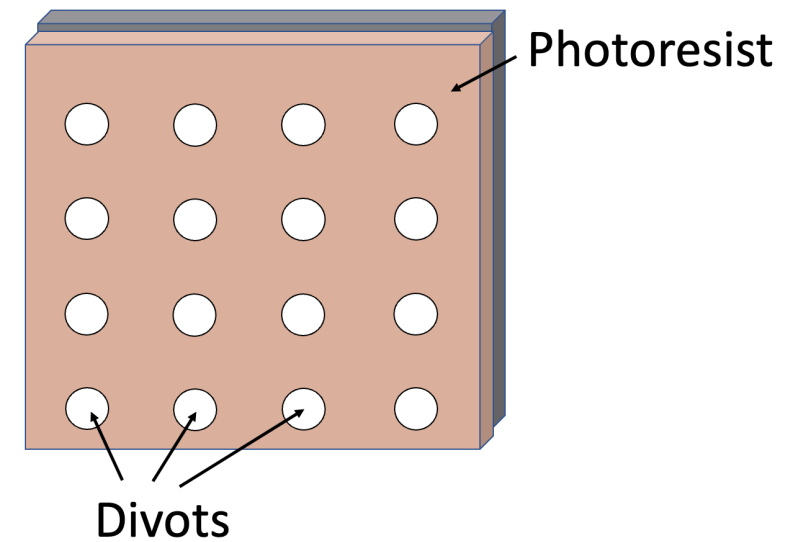
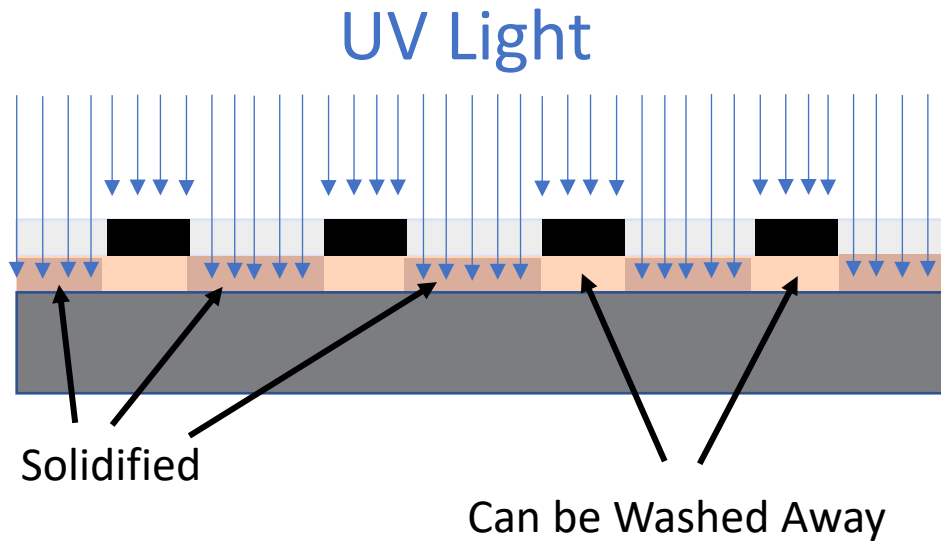
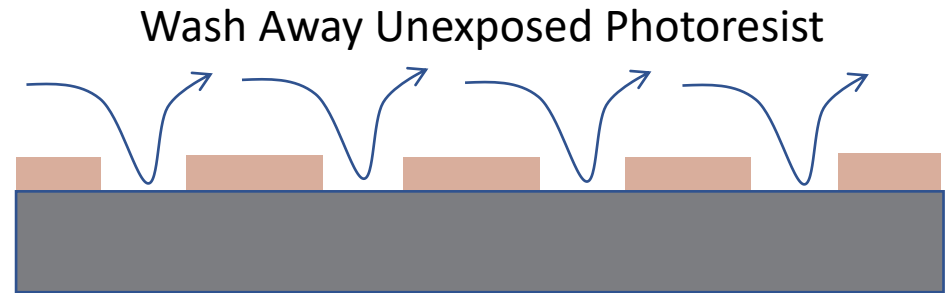
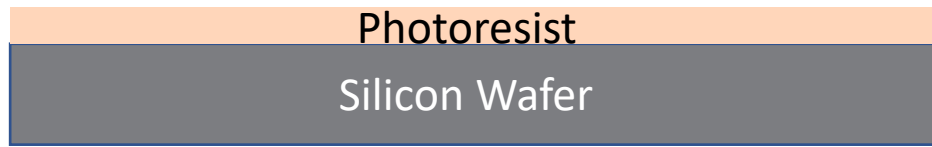
Transparent

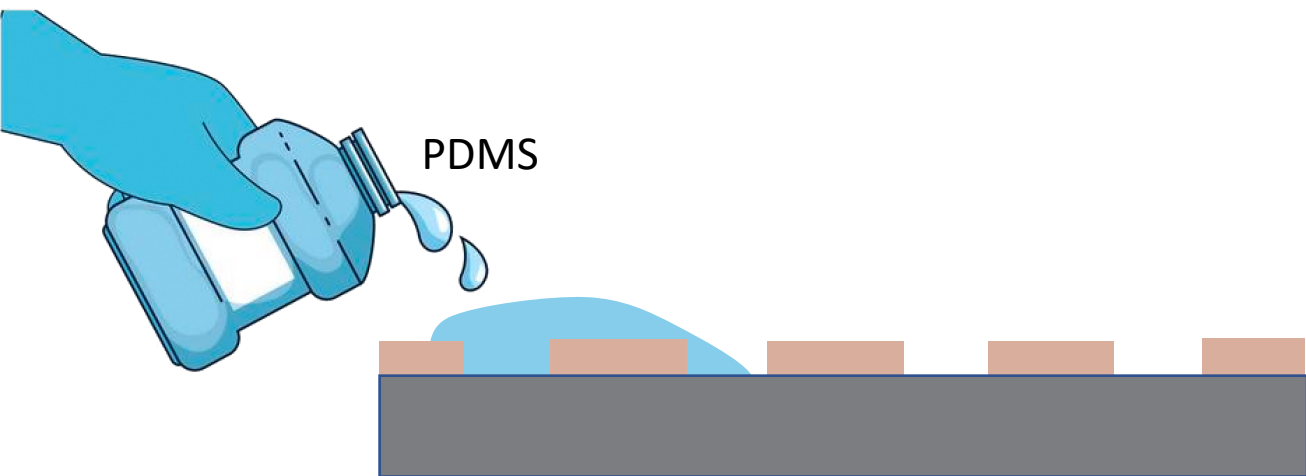
Opaque
(Blocks UV)



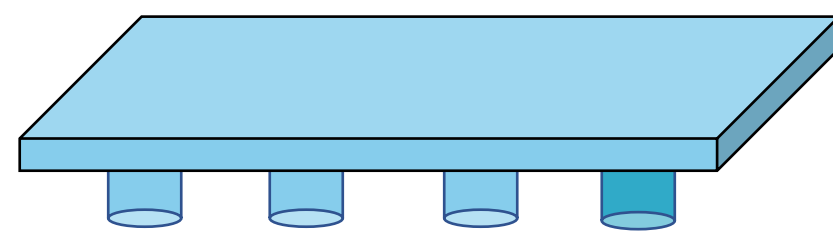
Mask





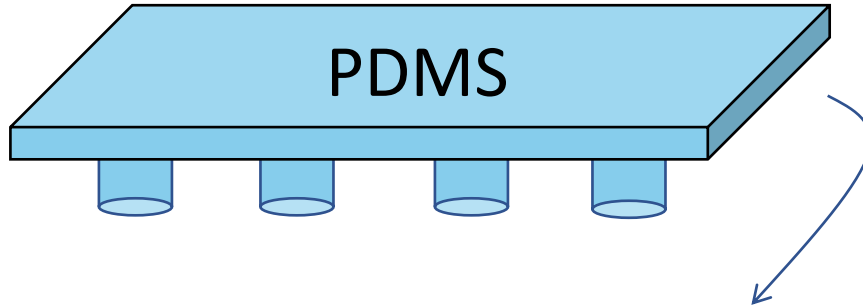


PDMS is an Array of Pegs



Pegs roughly
the diameter
of a single cell

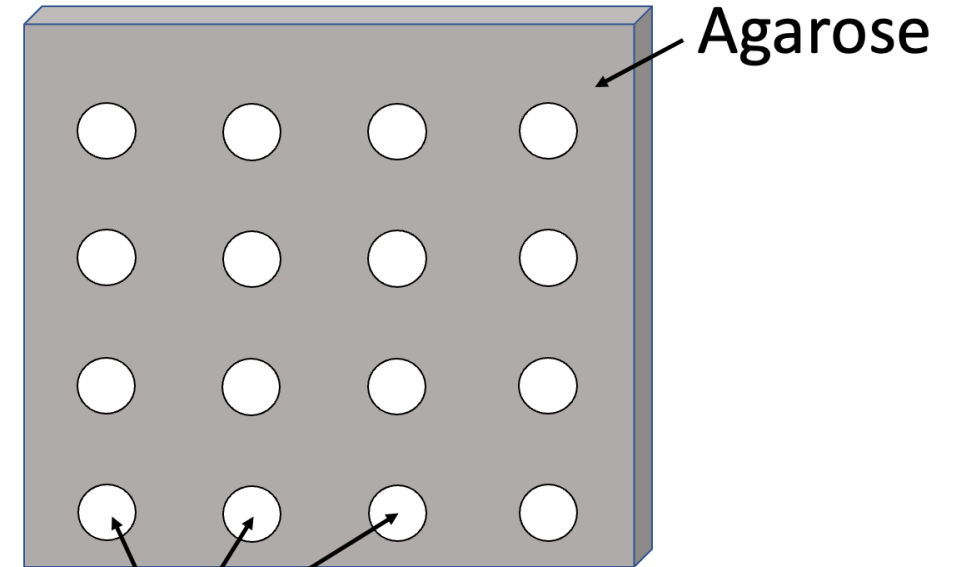
PDMS is an Array of Pegs



Molten Agarose



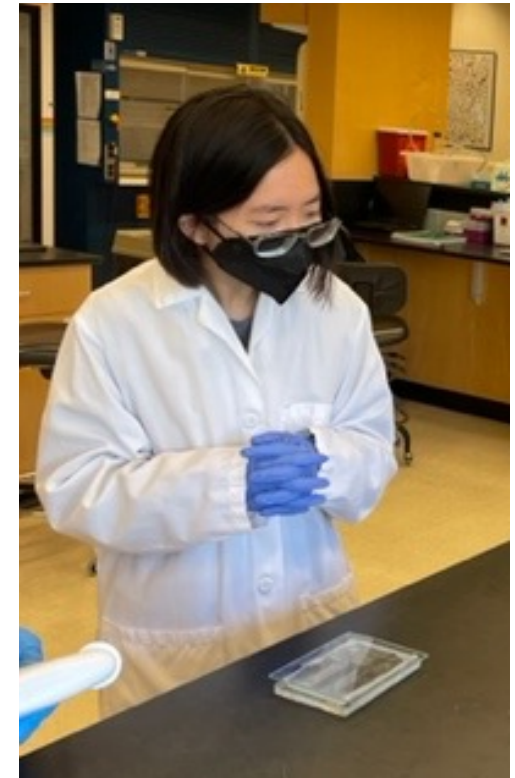
Pegs



Divots =
Microwells



Kam
demonstrating
how the
CometChip
Chip is made.







How the CometChip was made

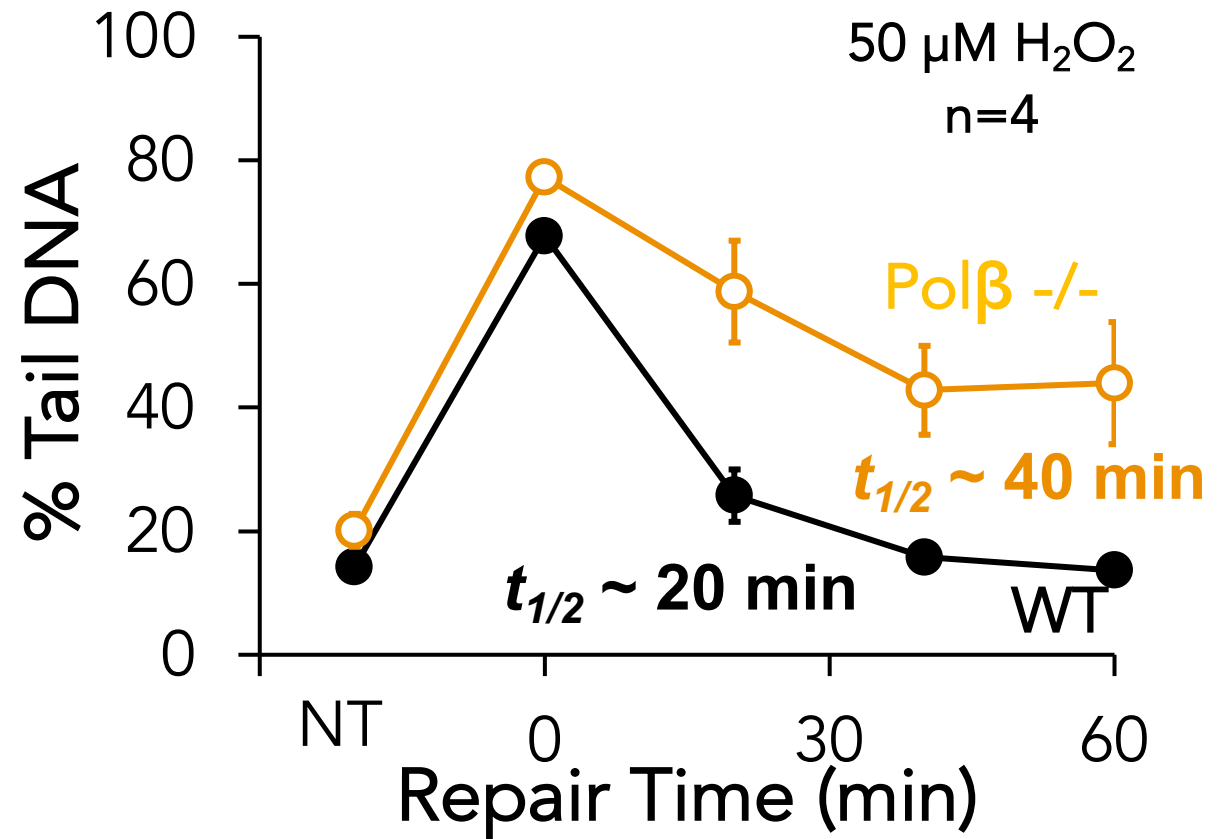
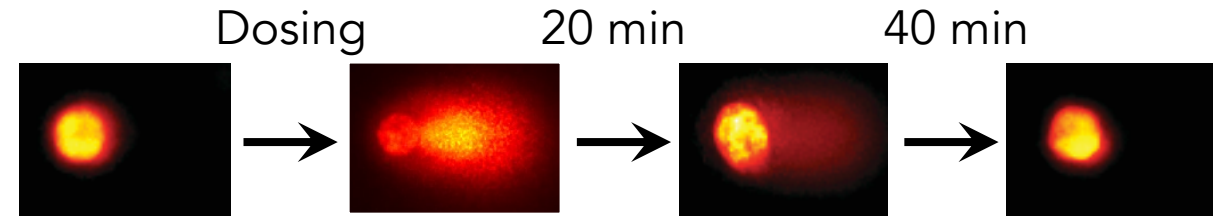
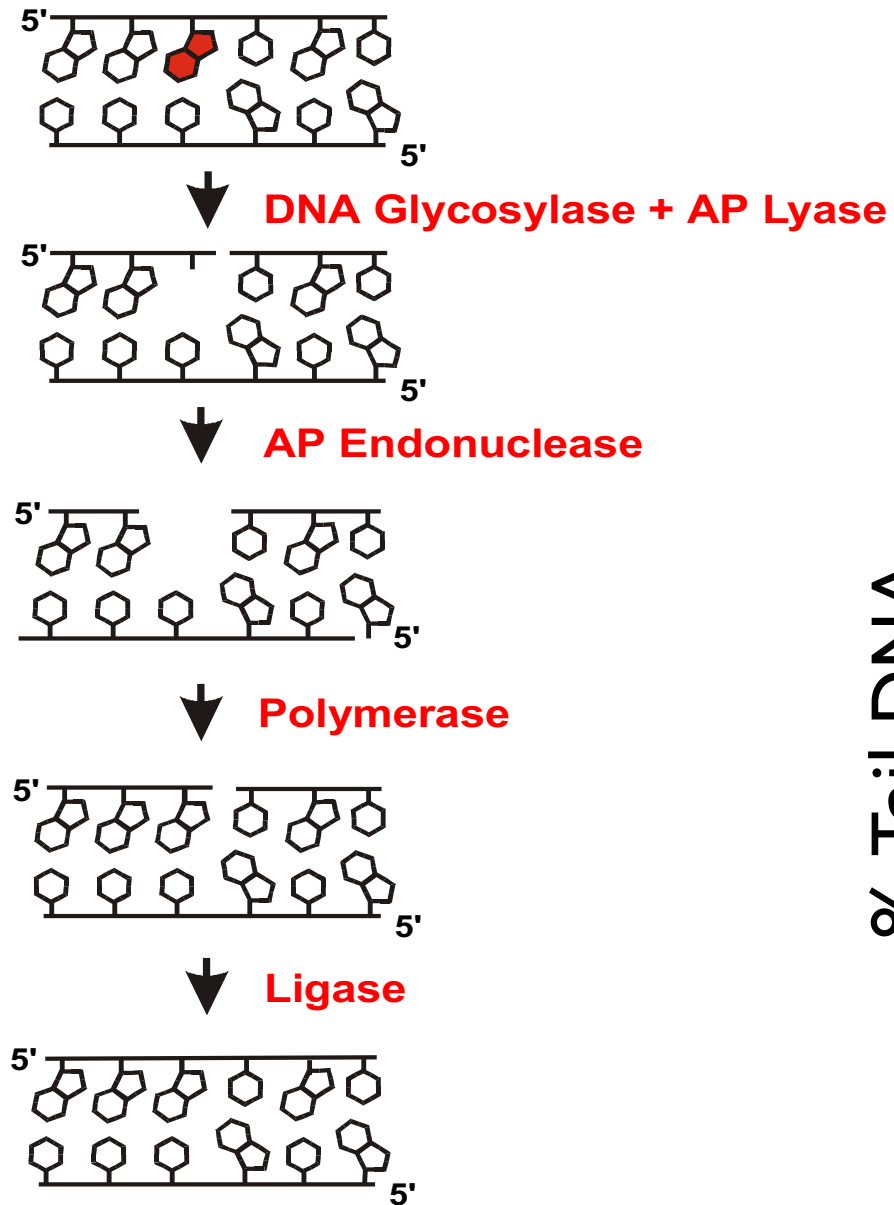
How to Measure Repair Capacity using a Time Course Experiment

Inter-individual Variation in DNA Repair Capacity

Impact of Variable DNA Repair Capacity on Cancer Risk

Review of our Central Hypothesis

DNA Repair



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Precision Prevention:
What makes some
people more
susceptible to cancer
than others?

How Different is Our DNA Repair Capacity?

Everyone is different

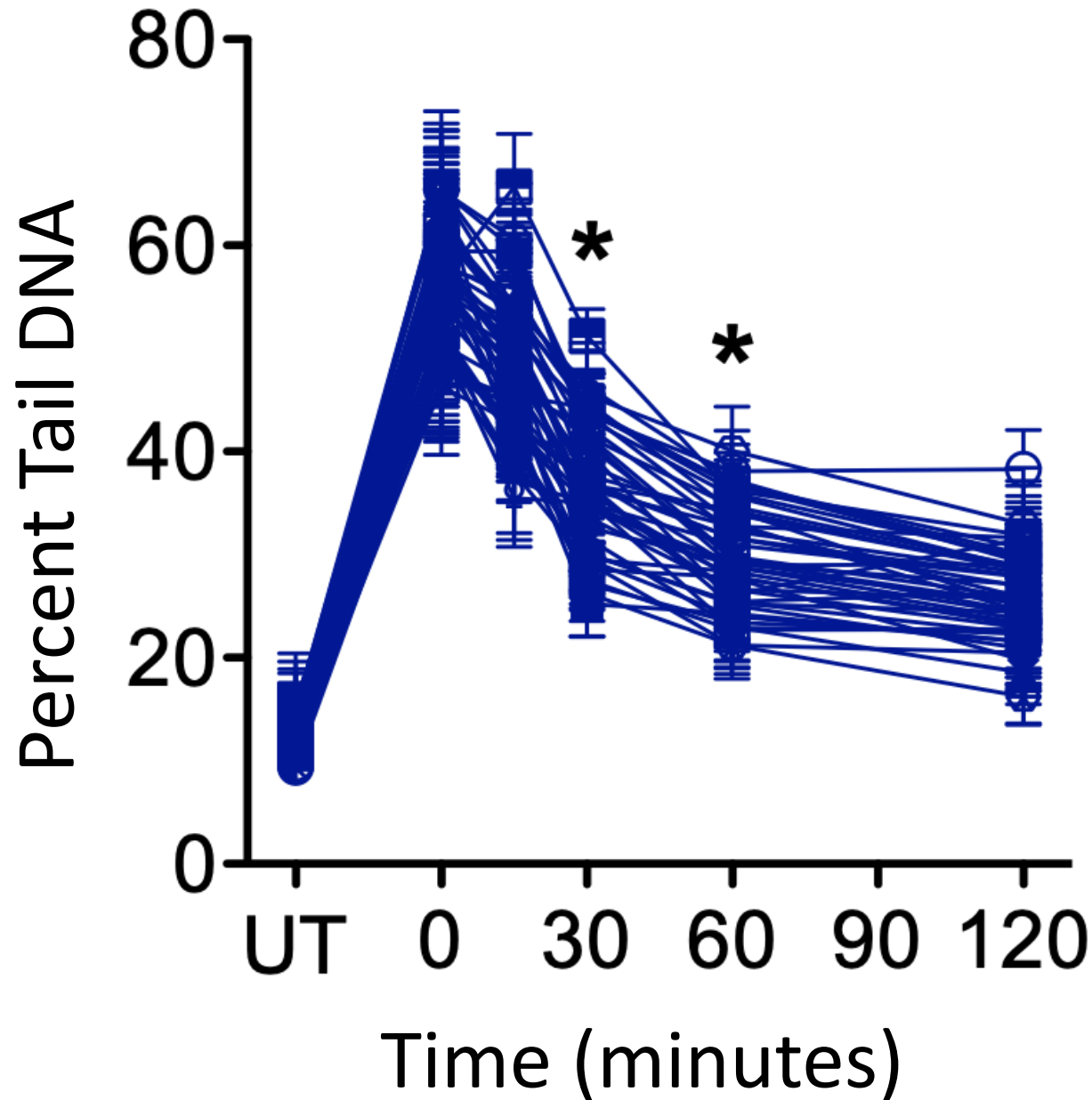


Genetics

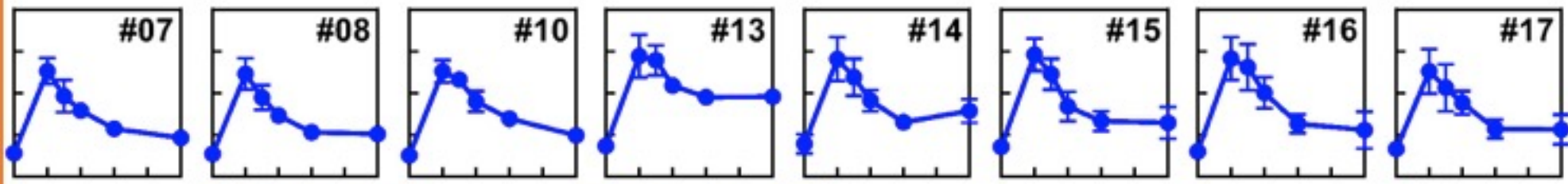
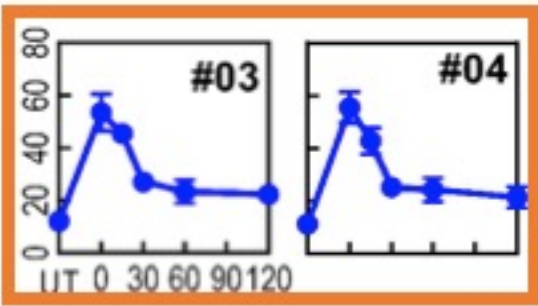


Lifestyle

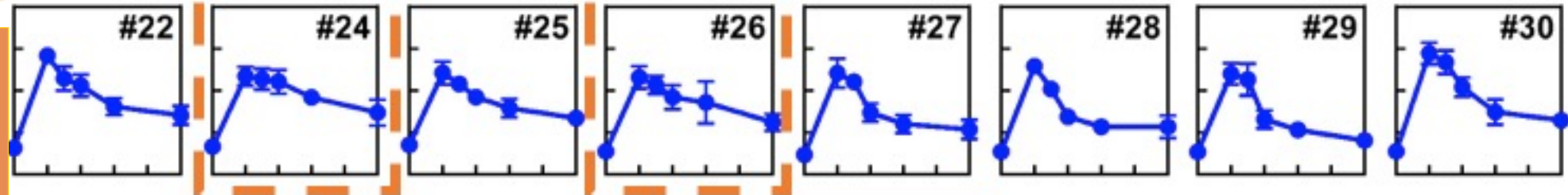
DNA Repair Kinetics are Variable Among 50 People



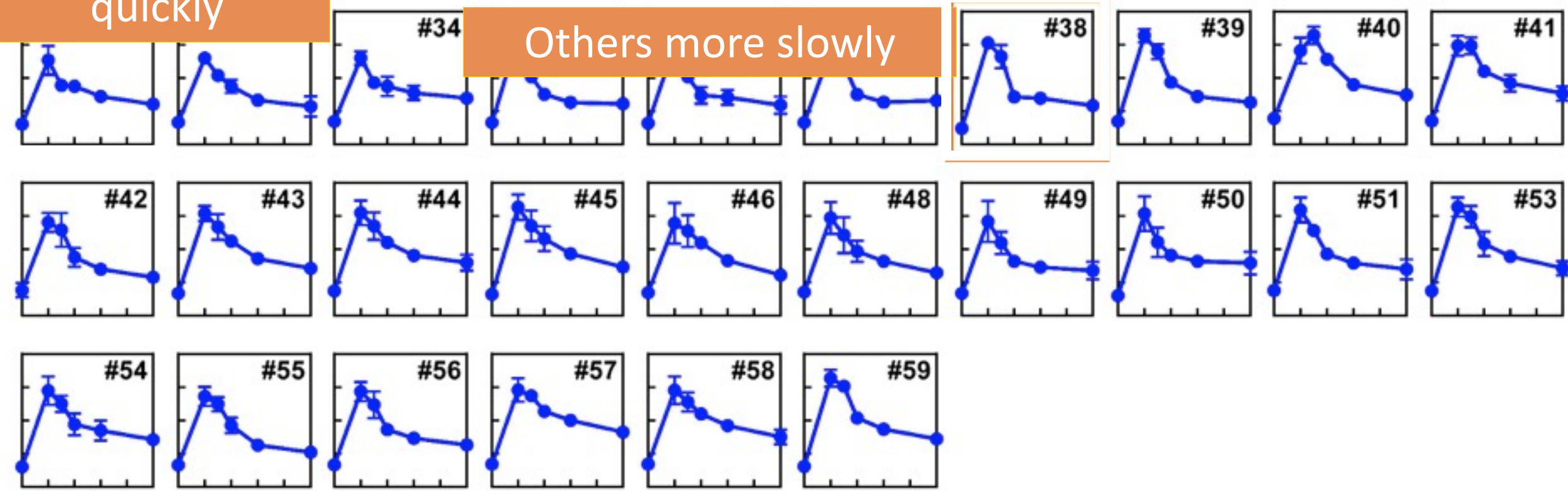
**Dr. Le P. Ngo
(Lizzie)**



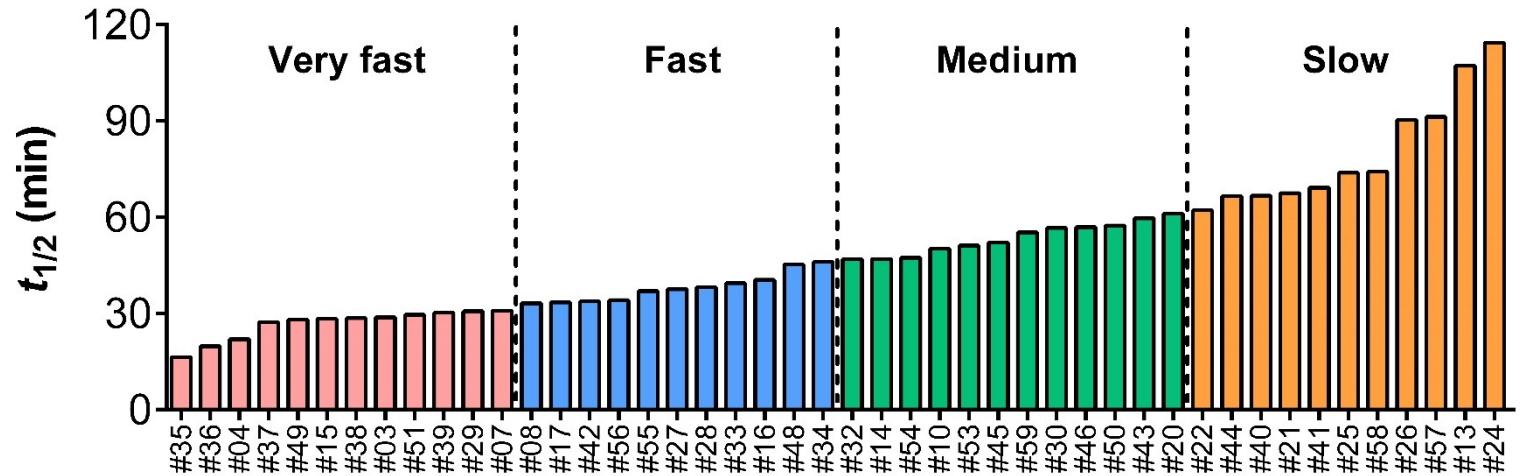
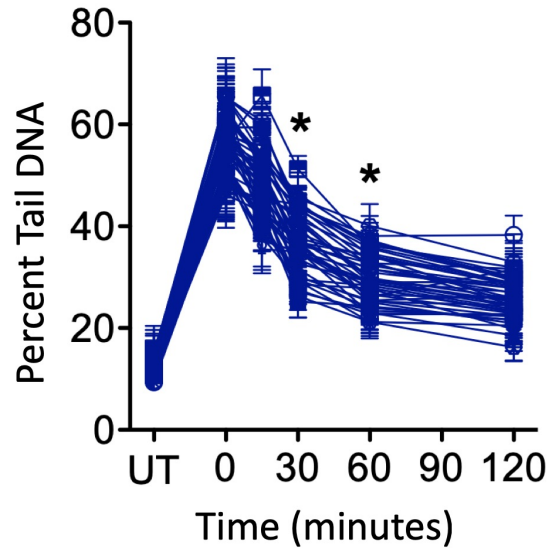
Some people
repair DNA
quickly



Others more slowly



People Have Variable Rates of Repair



Strengths and weaknesses of this study

Now have a higher throughput way to look at inter individual variation in DNA repair.

But:

- WBC's don't necessarily reflect tissues
 - WBC's are a mix of cell types
- It would be nice to know about DNA damage in the person, rather than response of cells *ex vivo*

How the CometChip was made

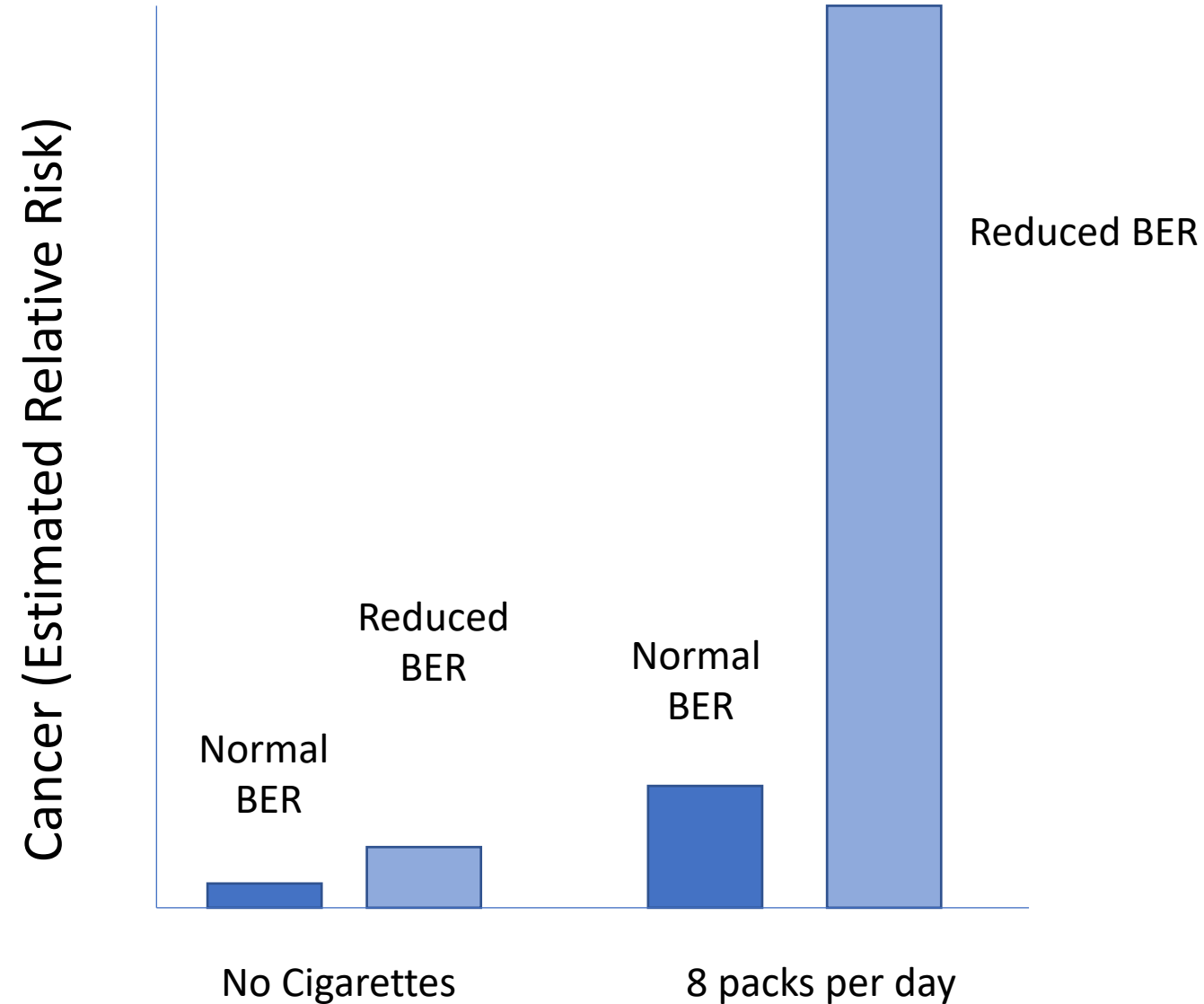
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Differences in Repair Capacity Among People Affects Cancer Susceptibility



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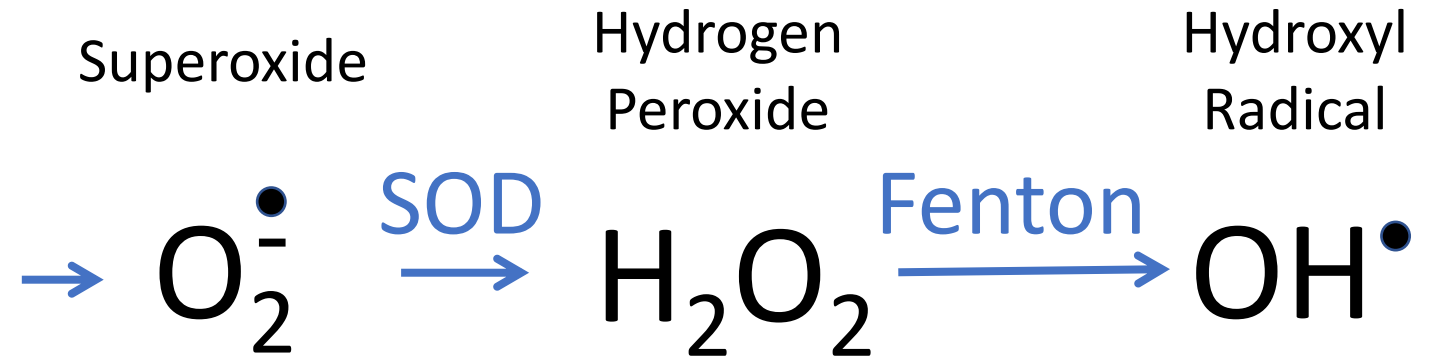
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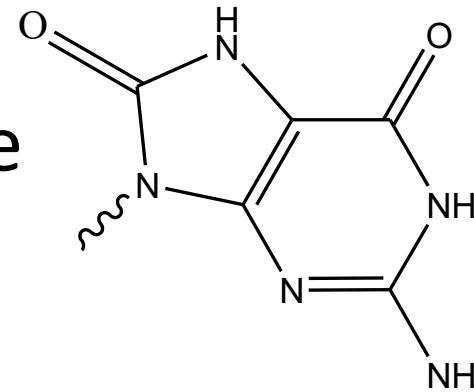
Electrons Escape
and form Superoxide

SOD = Superoxide Dismutase

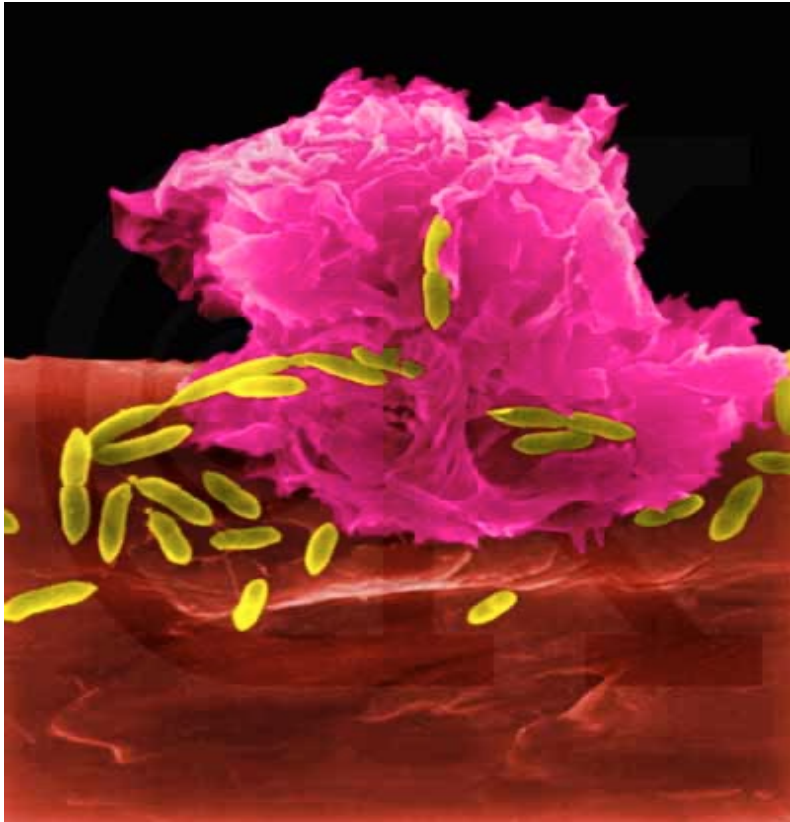
CNRI/Science Photo Library/Getty Images



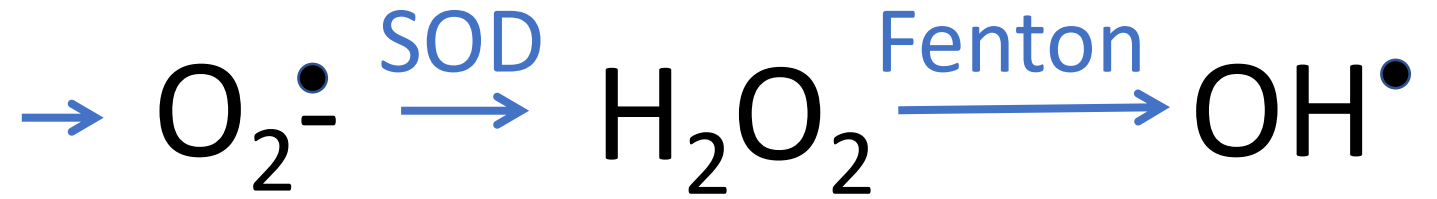
8-oxoguanine



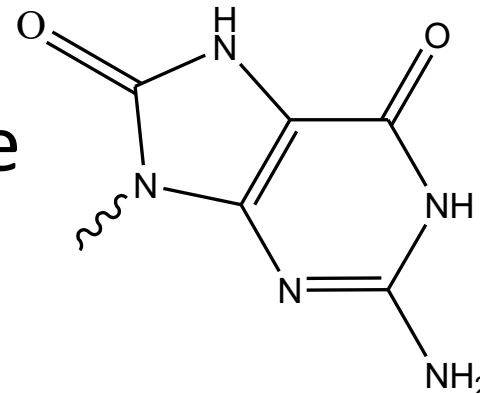
Plus Dozens of Other Types of Base Damage



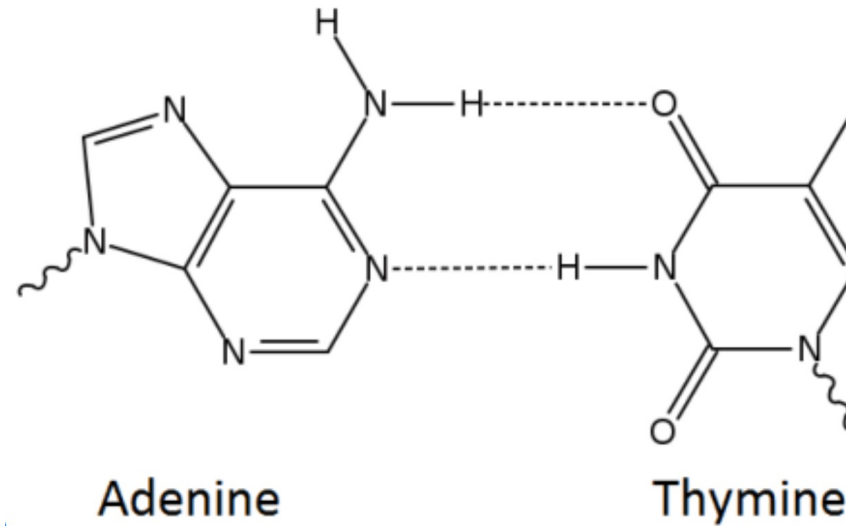
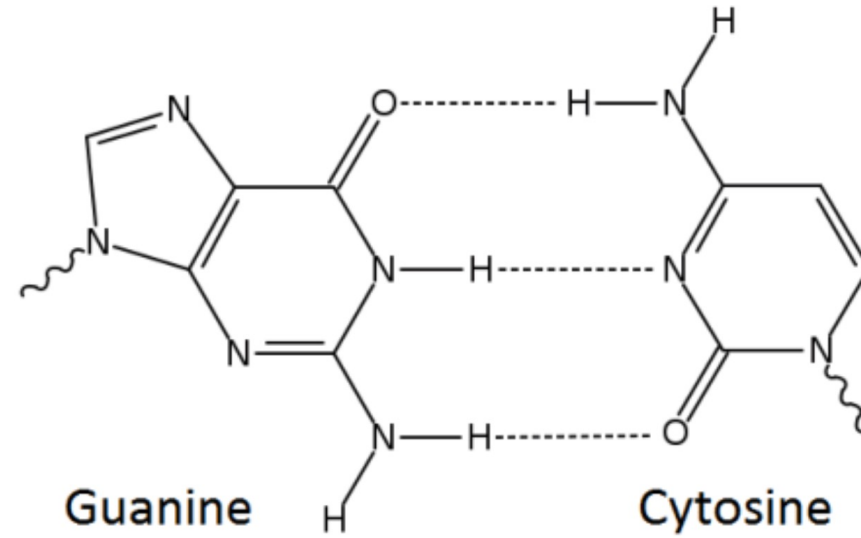
SEM (x10.000)
www.DennisKunkel.com

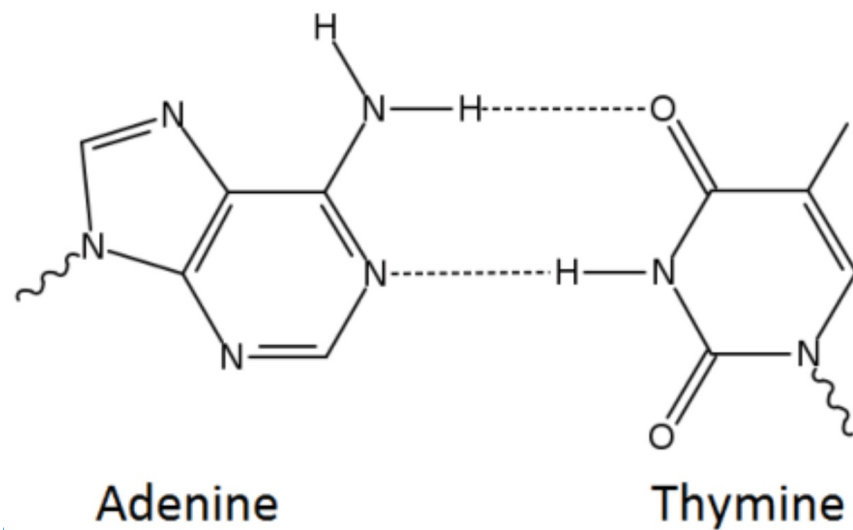
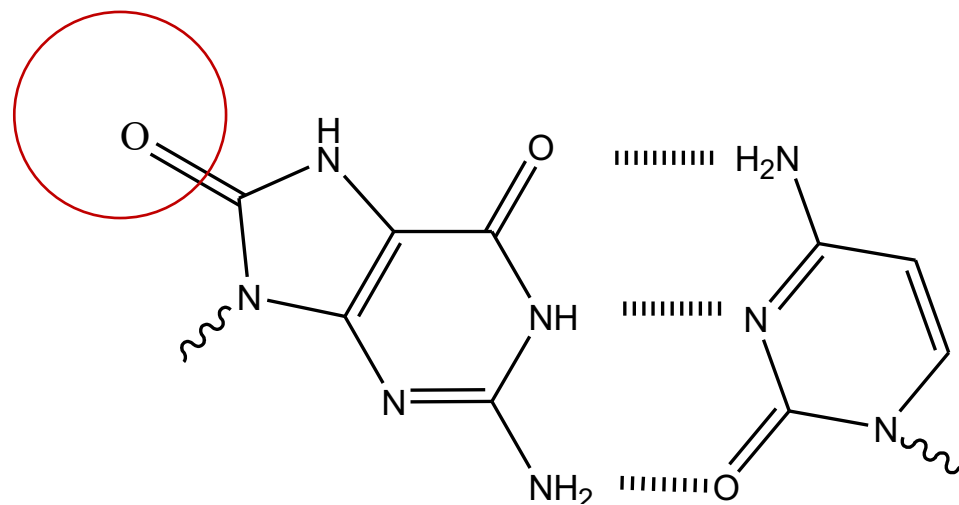
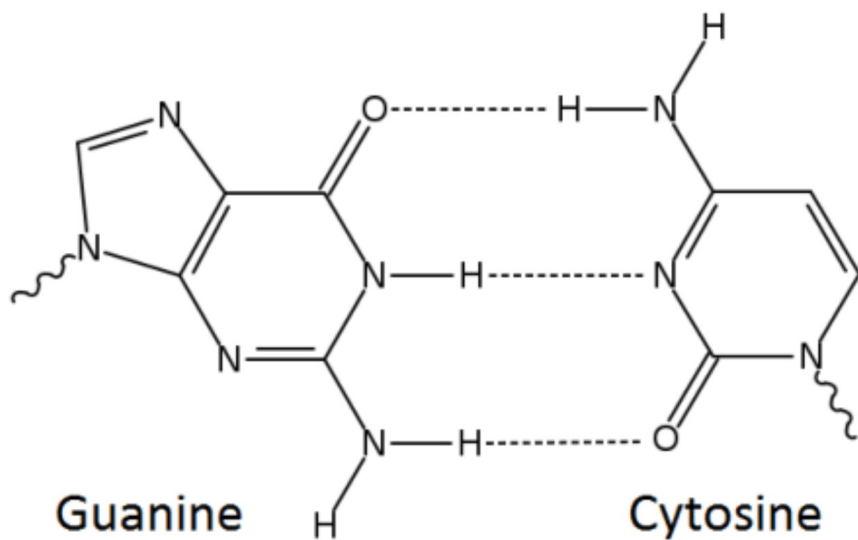


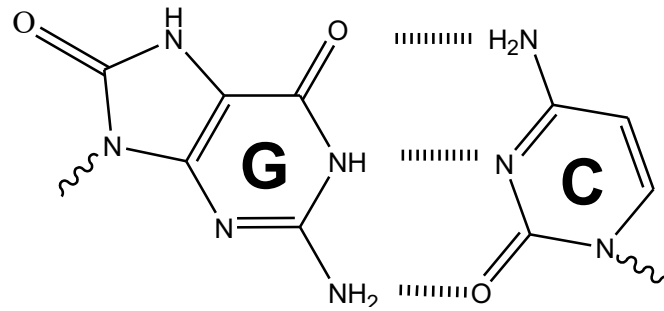
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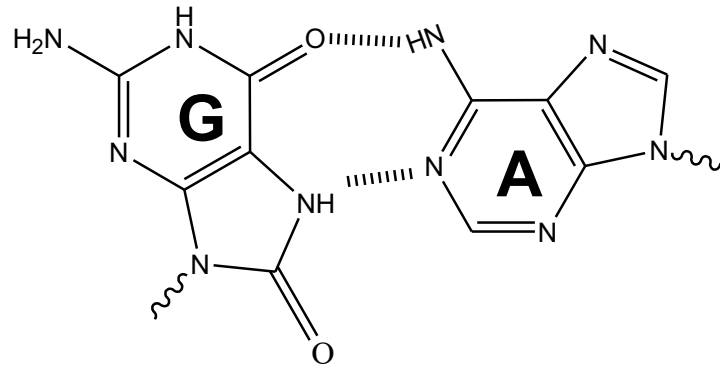
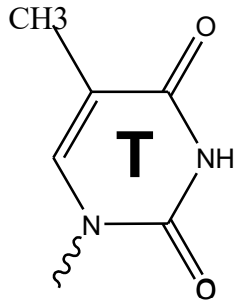
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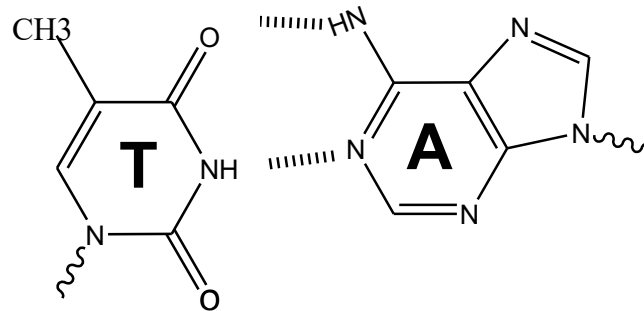




↓ DNA Replication



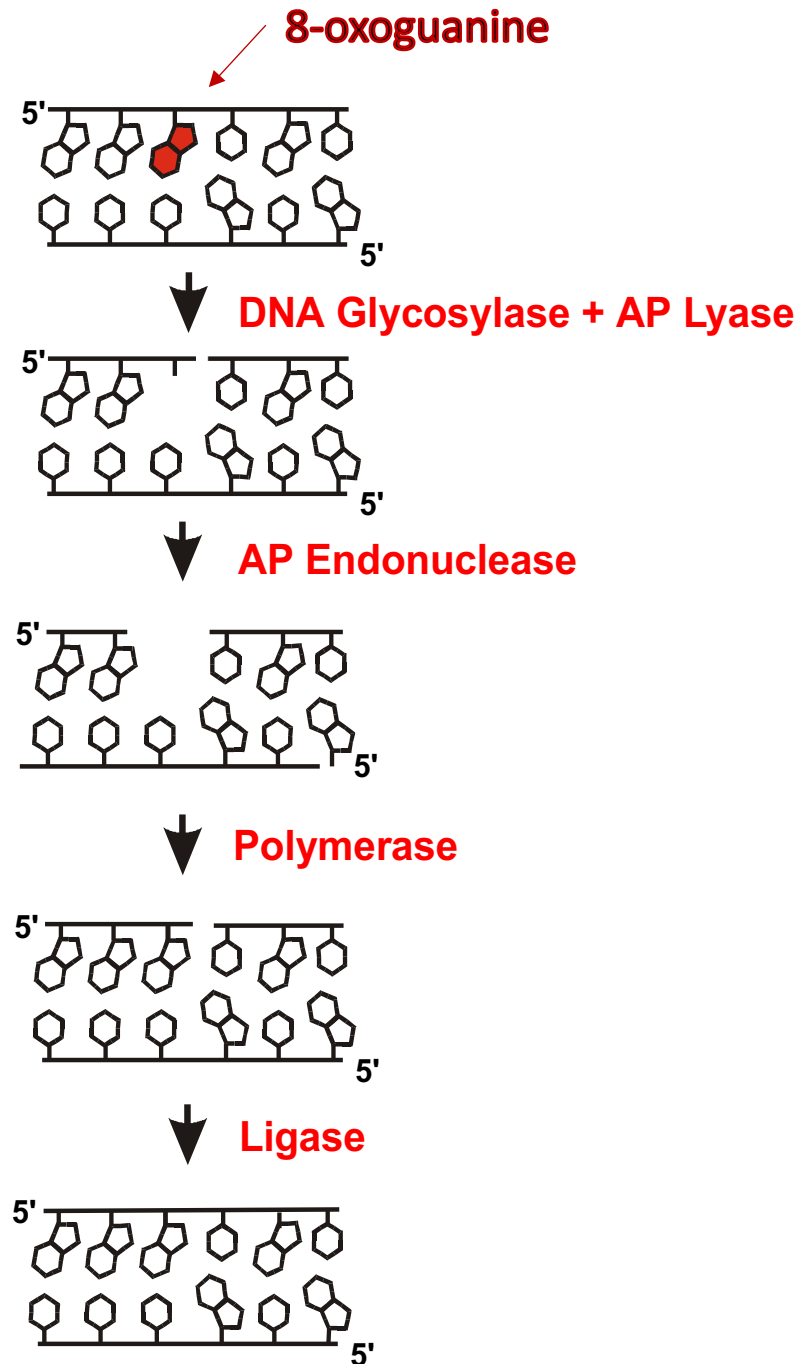
↓ DNA Replication



A change in
structure leads to
a change in
information.

GC → TA

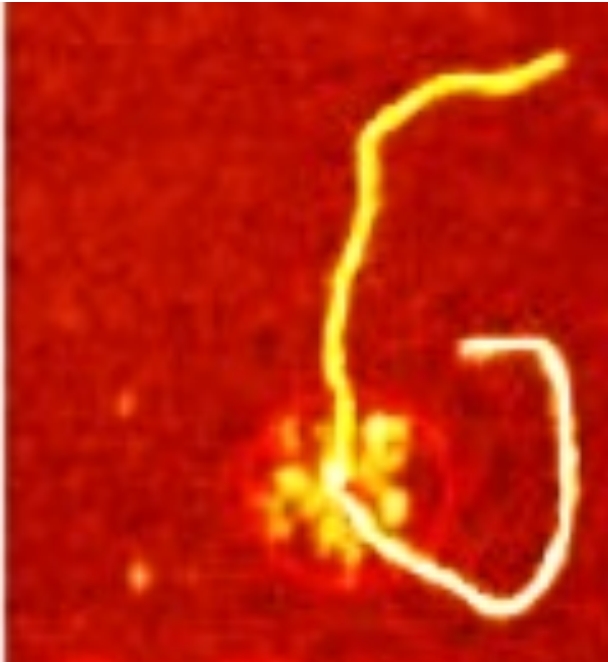
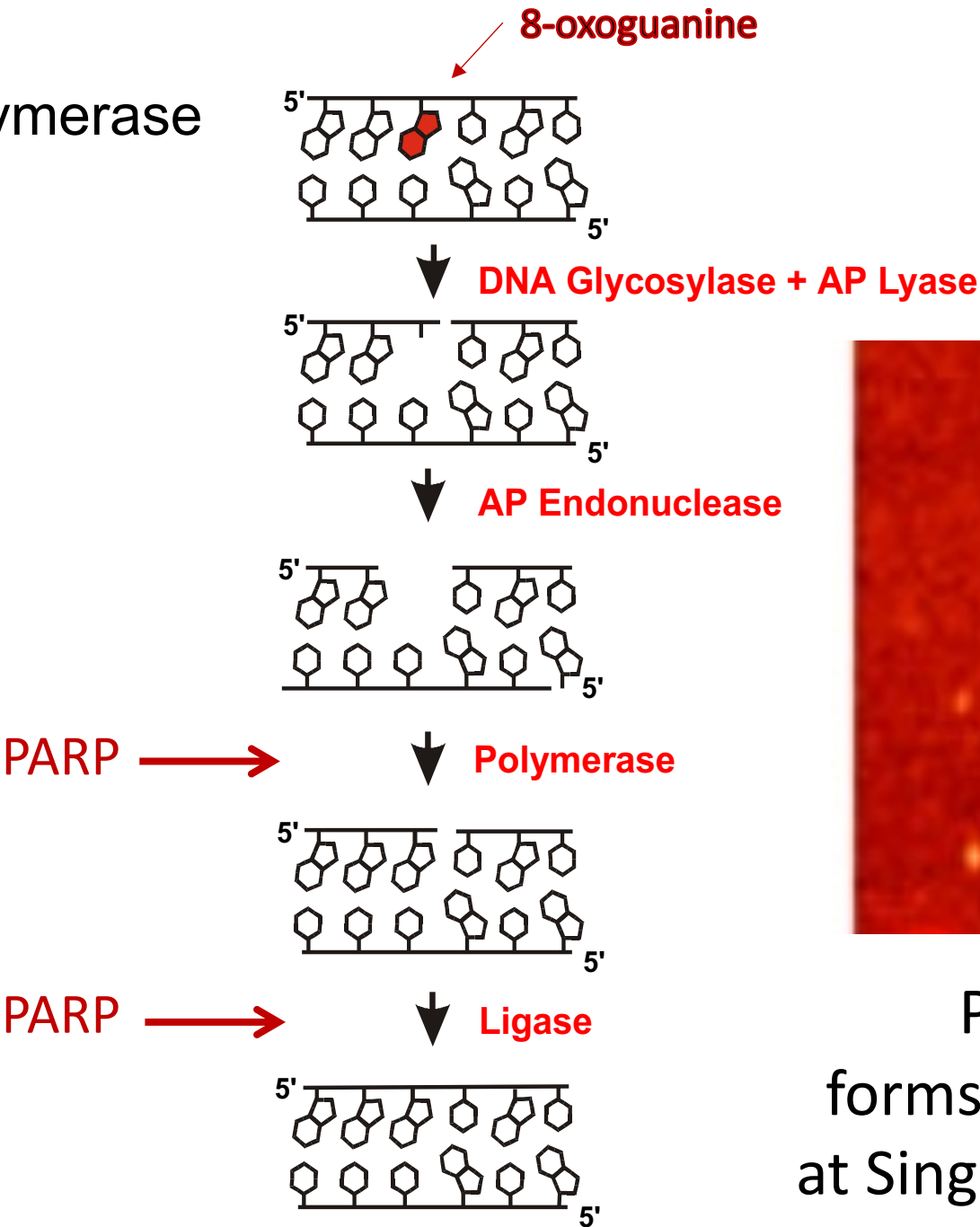
Base Excision Repair Pathway



PARP =
Poly (ADP-Ribose) Polymerase

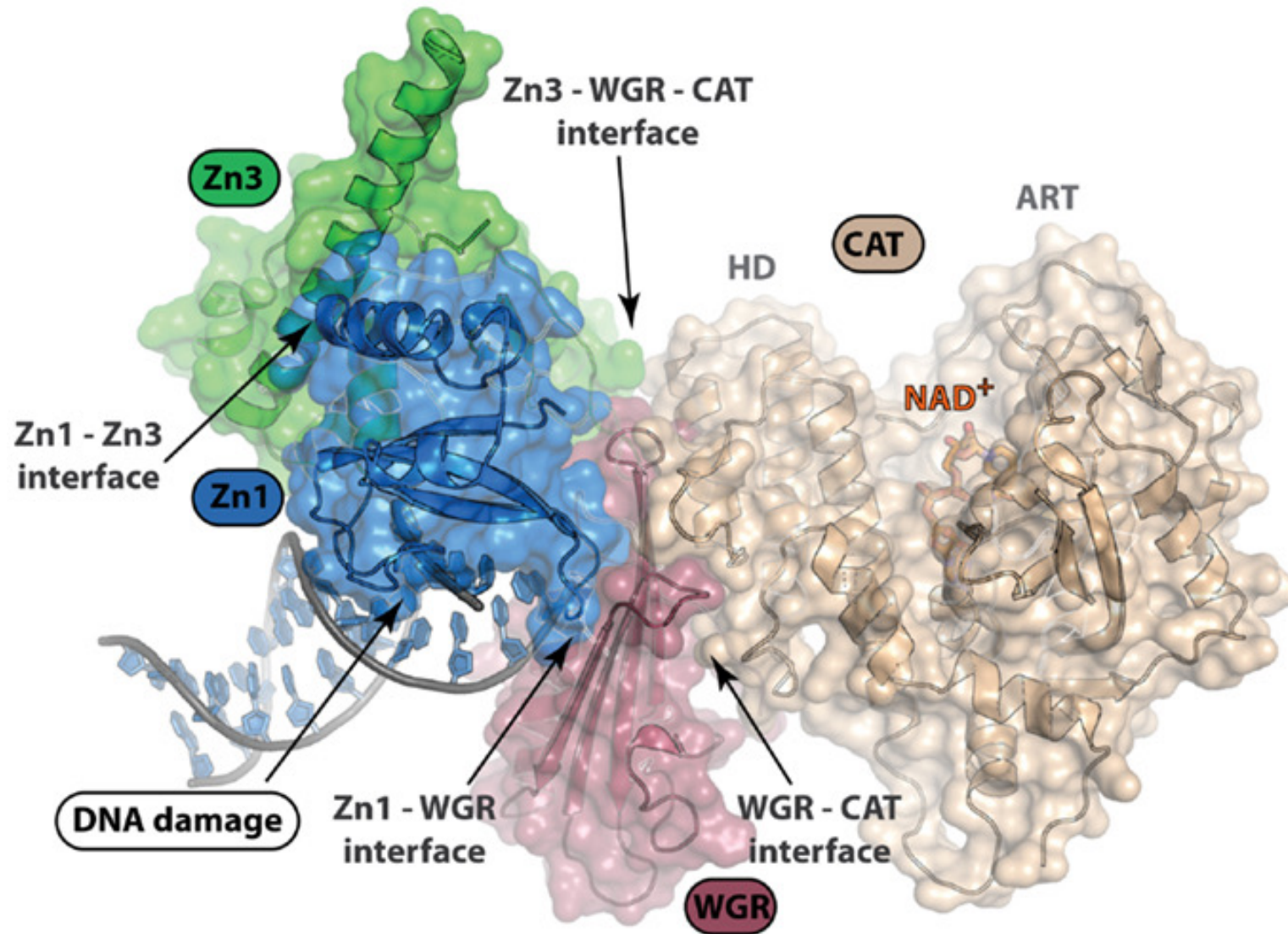
PARP Promotes BER

As inhibits PARP

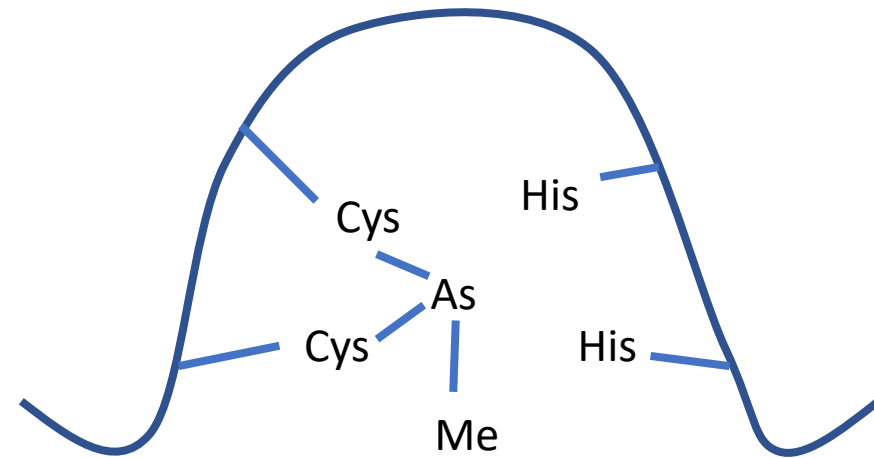
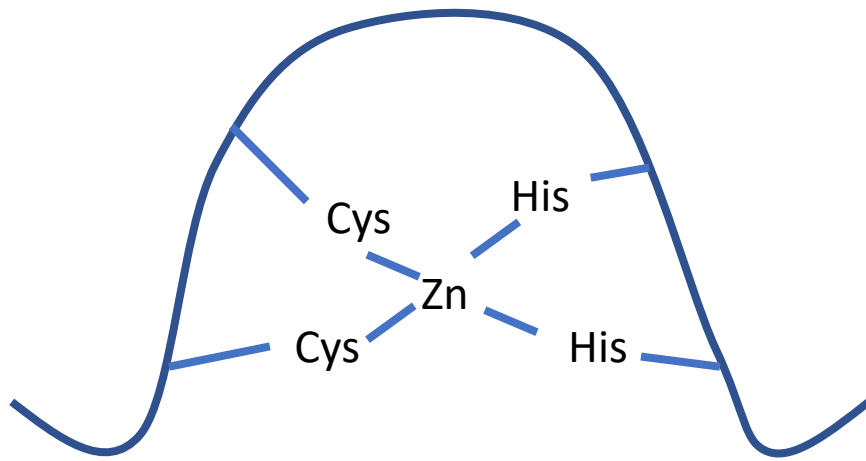


Poly(ADP)-ribose
forms a branched structure
at Single Strand Breaks (SSBs)

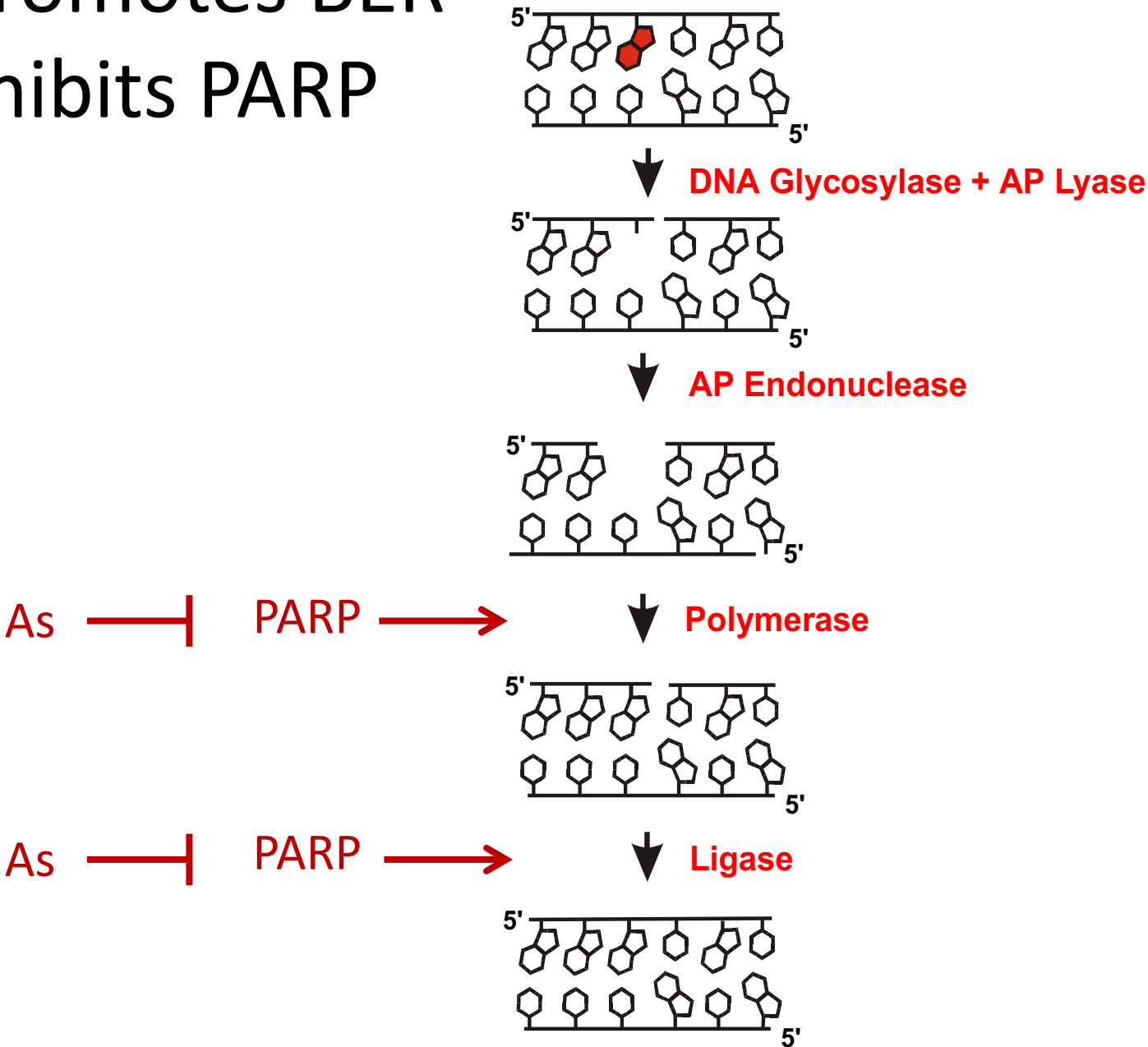
PARP has Zinc Fingers



Arsenic Disrupts Zinc Fingers

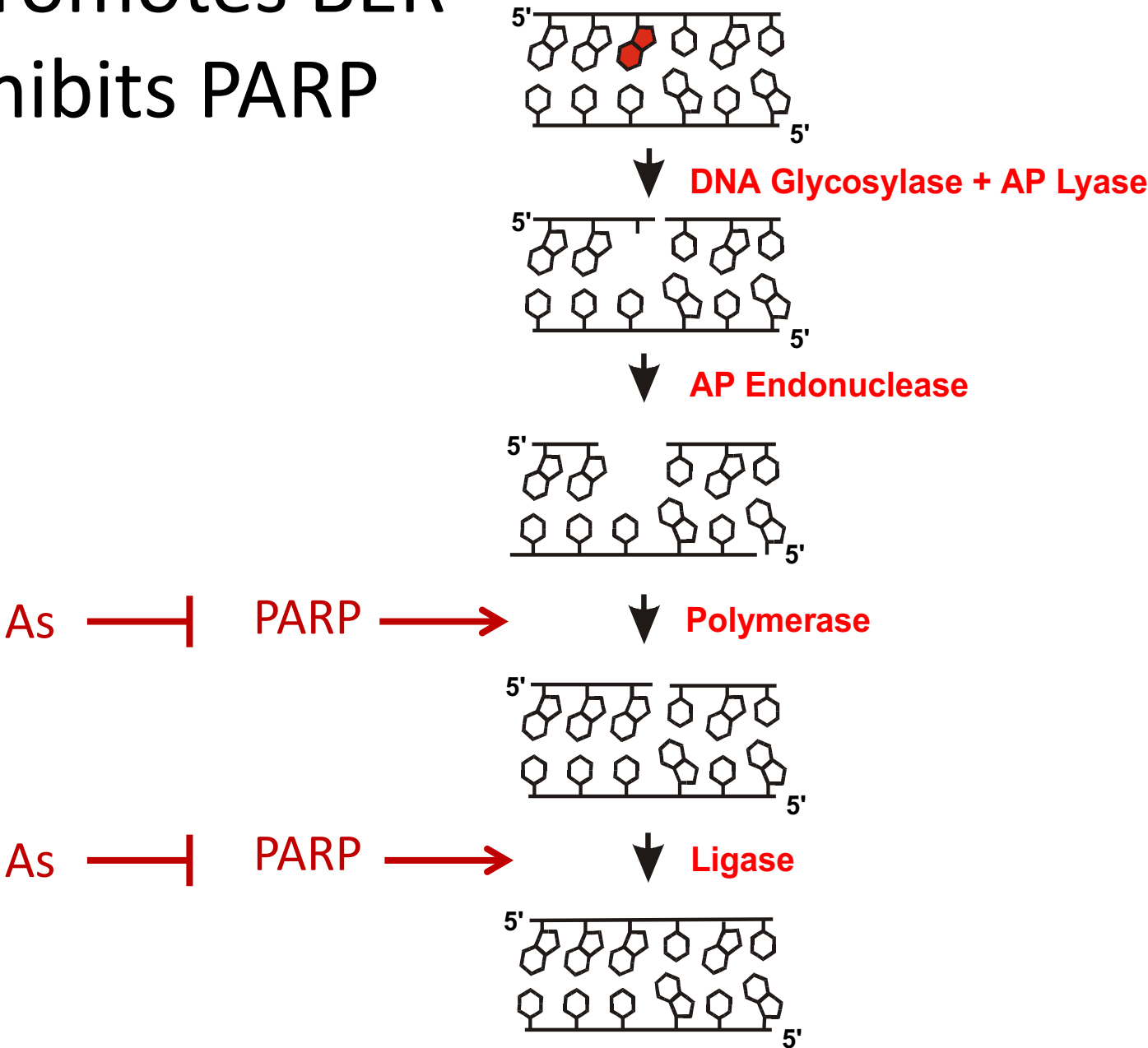


PARP Promotes BER As Inhibits PARP



Suppression
of PARP
Reduces
Recruitment
of DNA
Repair
Proteins

PARP Promotes BER As Inhibits PARP



Suppression
of PARP
Might Lead to
an Increase in
Single Strand
Breaks

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