20.109 MOD1
Genomic Instability

Fall 2023
Day 2

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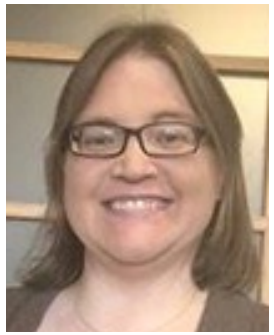
Professor of Biological Engineering

20.109 MOD1 Fall 2023 – The Fabulous Team

Dr. Noreen Lyell
Sr. Lecturer



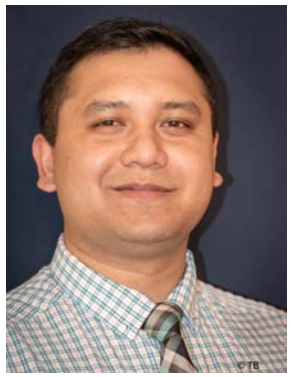
Dr. Becky Meyer
Lecturer

Jamie Zhan
Instructor

Chiara Ricci-Tam
BE Communication
Lab Manager &
Lecturer

Simone Wall

TA

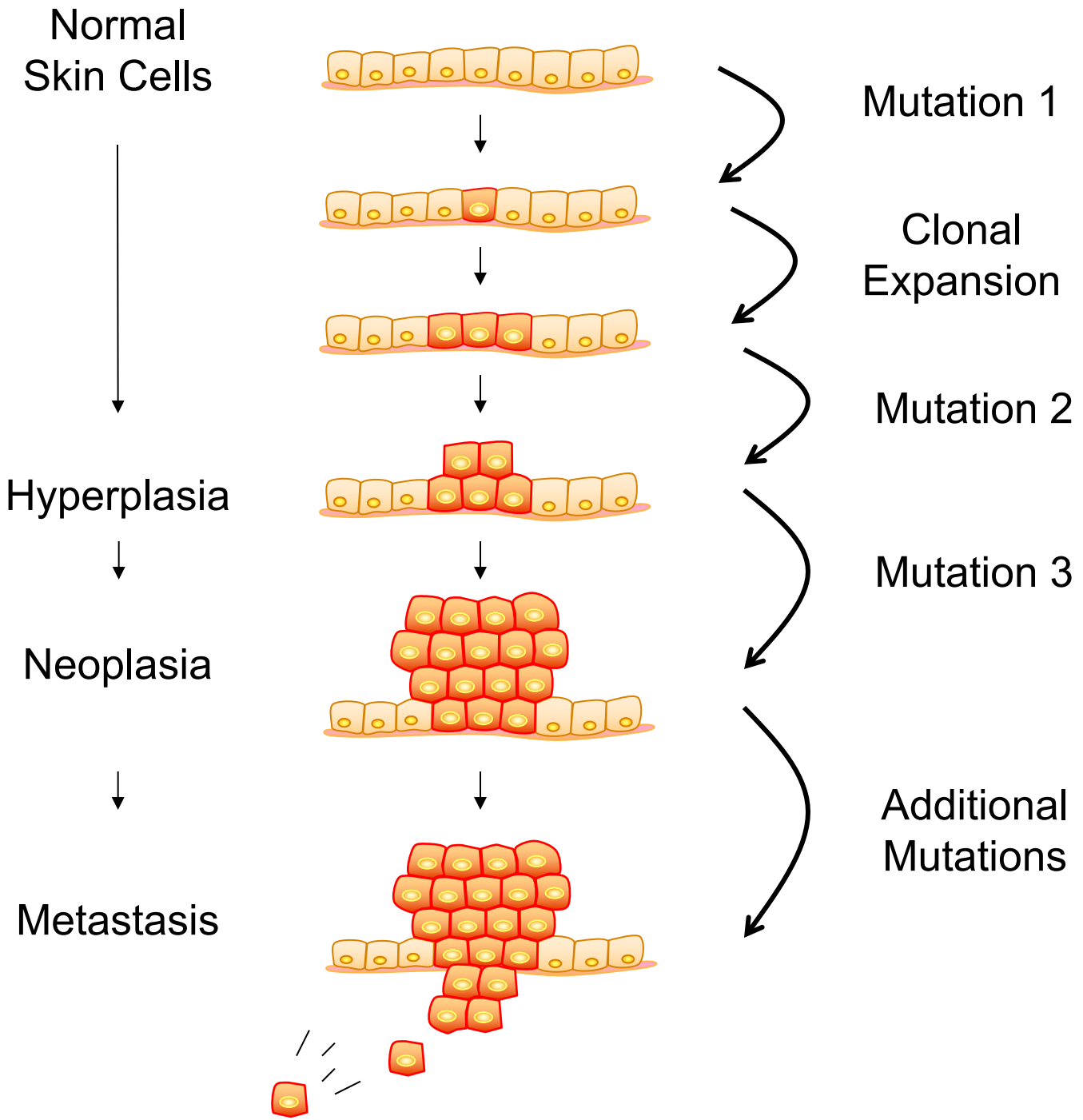


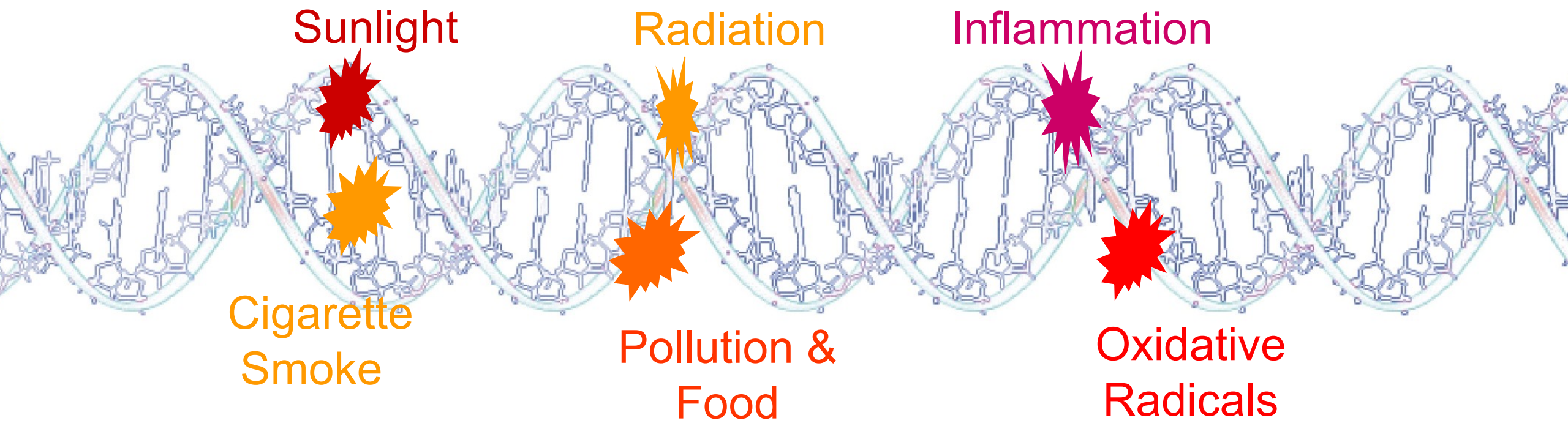
Bishal Thapa

TA

Abby Dzordzorme

TA

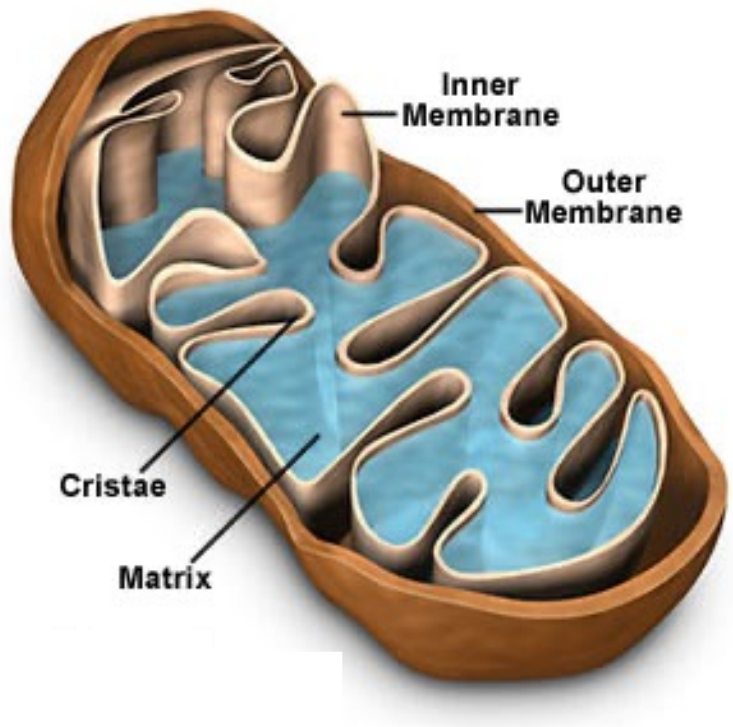

Normal
Skin Cells
Hyperplasia
Neoplasia
Metastasis
Mutation 1
Clonal
Expansion
Mutation 2
Mutation 3
Additional
Mutations

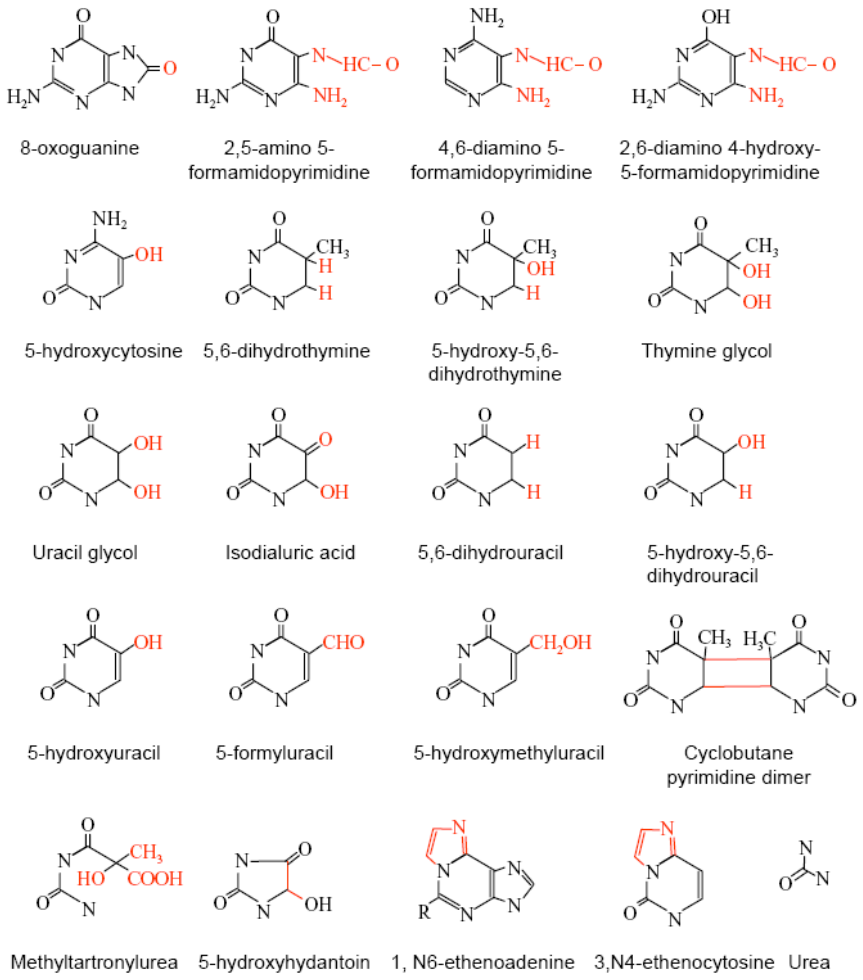


Mutations, Toxicity, Cellular Defects

Cancer, Aging, Heritable Diseases

Reactive Oxygen Species Damage DNA Bases

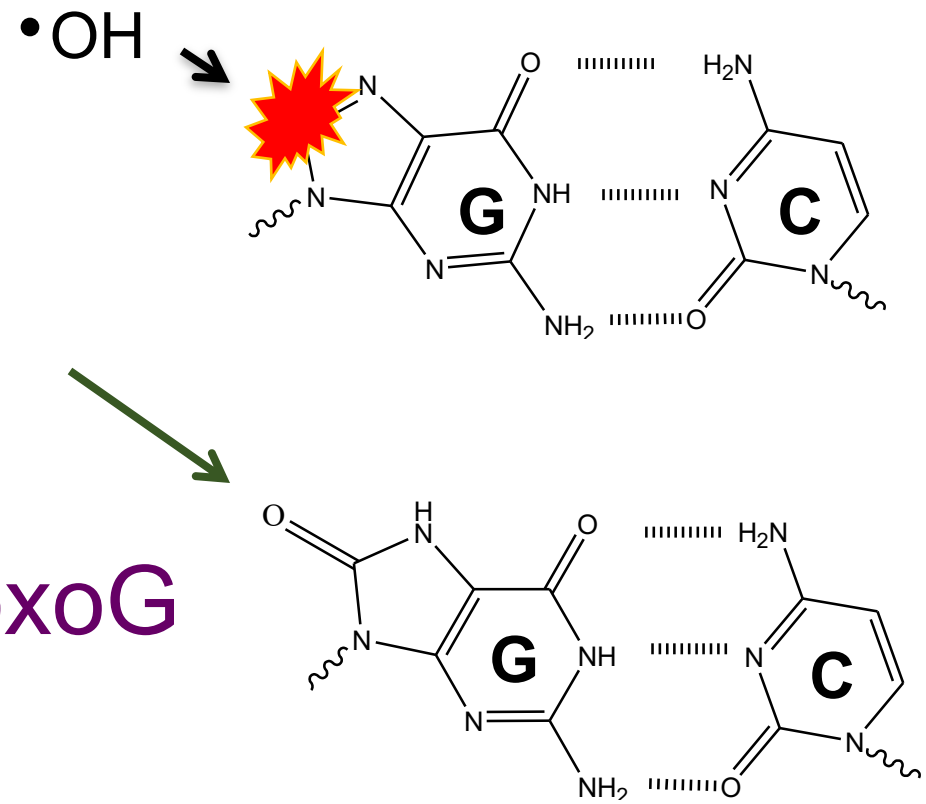


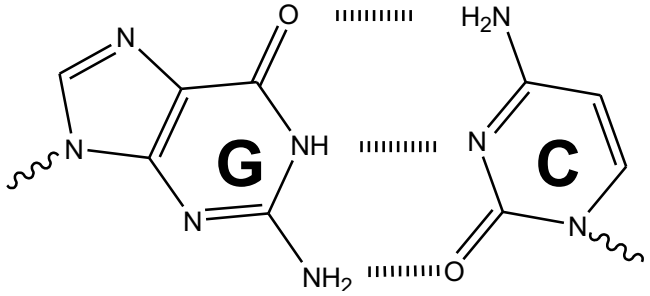


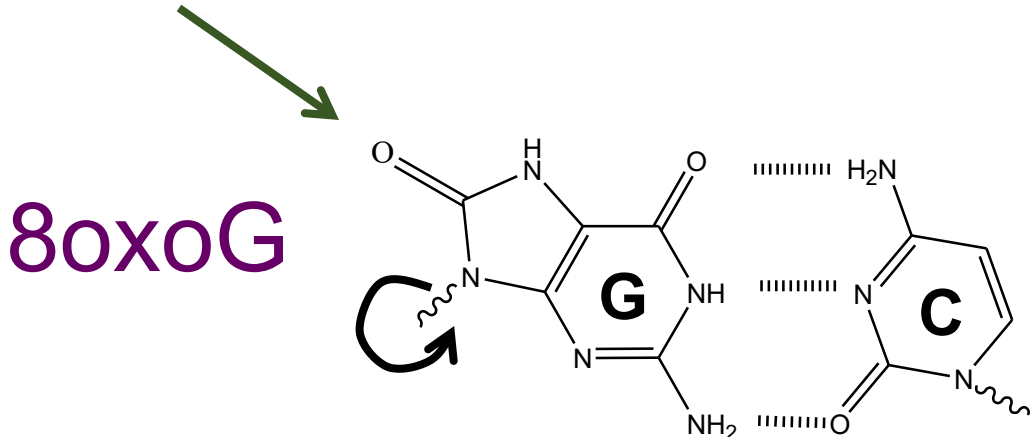
From Slupphaug, Kavli and Krokan

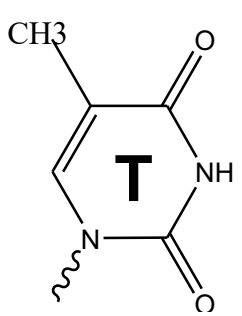
What can happen if DNA structure is broken

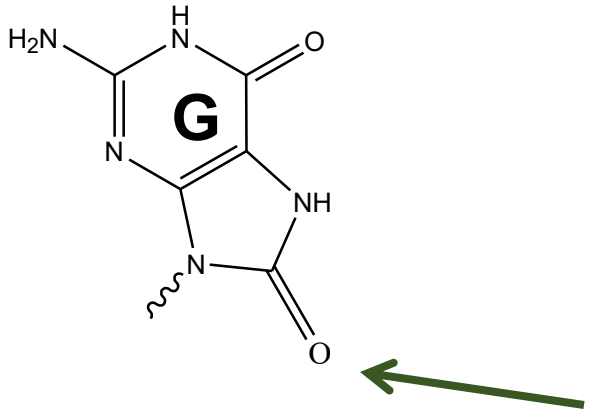
8oxoG

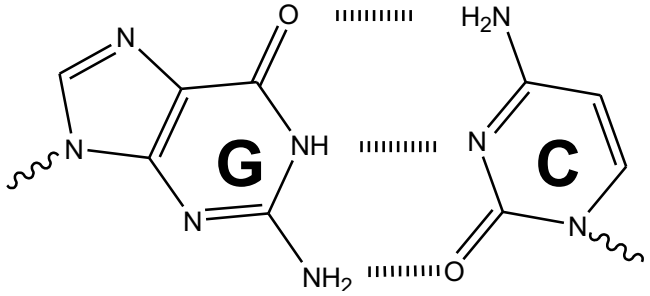

•OH
8oxoG
G
C
NH
NH2
H2N
O
N
H

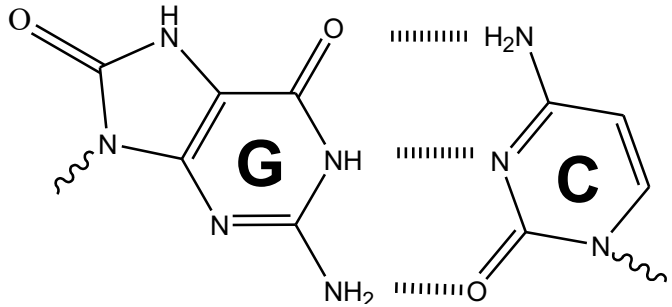

O
N
H2N
N
G
NH
N
C
N
NH2
O

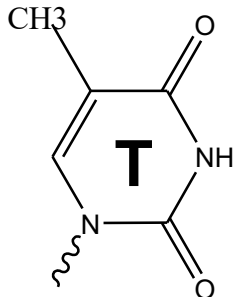

8oxoG
O
H
N
O
H2N
N
G
NH
N
C
N
NH2
O

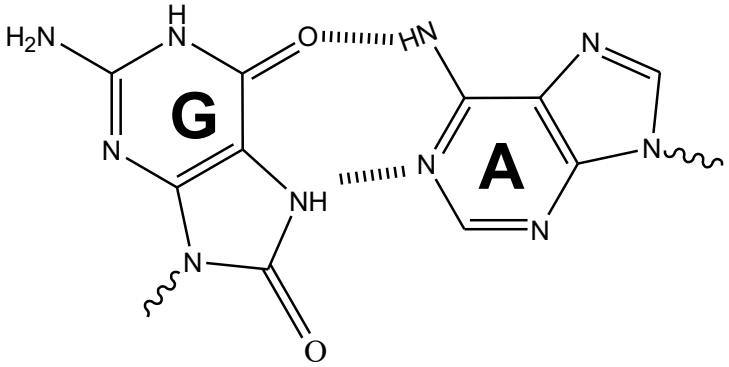

CH3
O
T
NH
N
O


H2N
H
N
O
G
N
NH
N
O









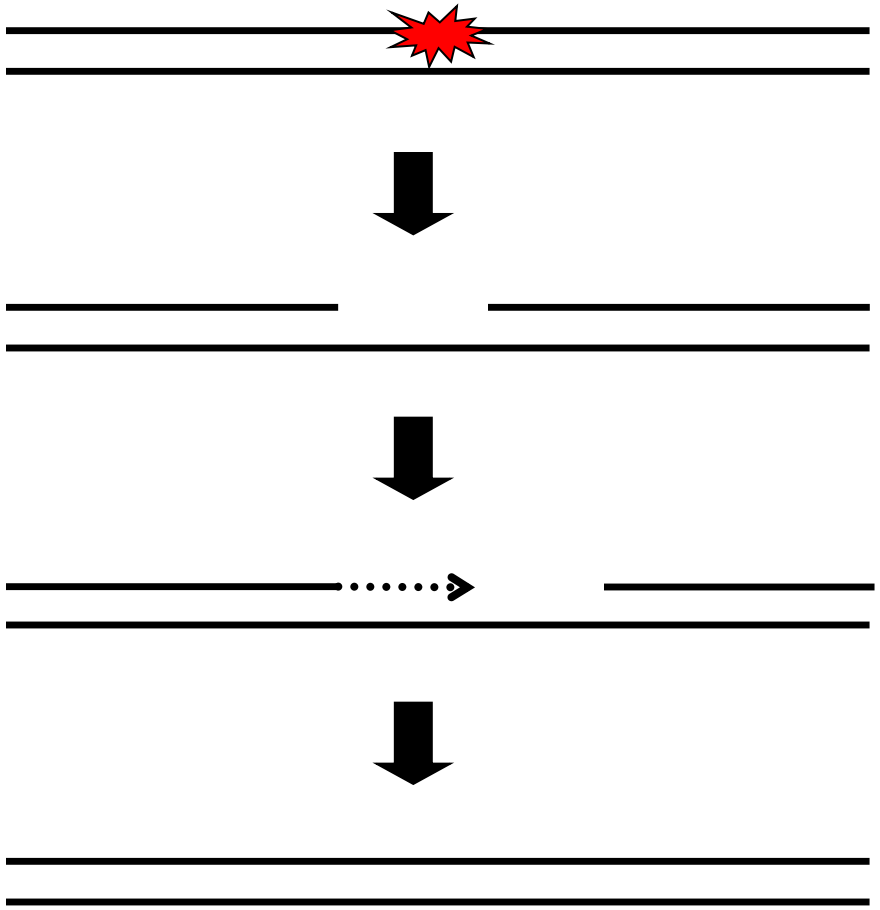
Structure is information!

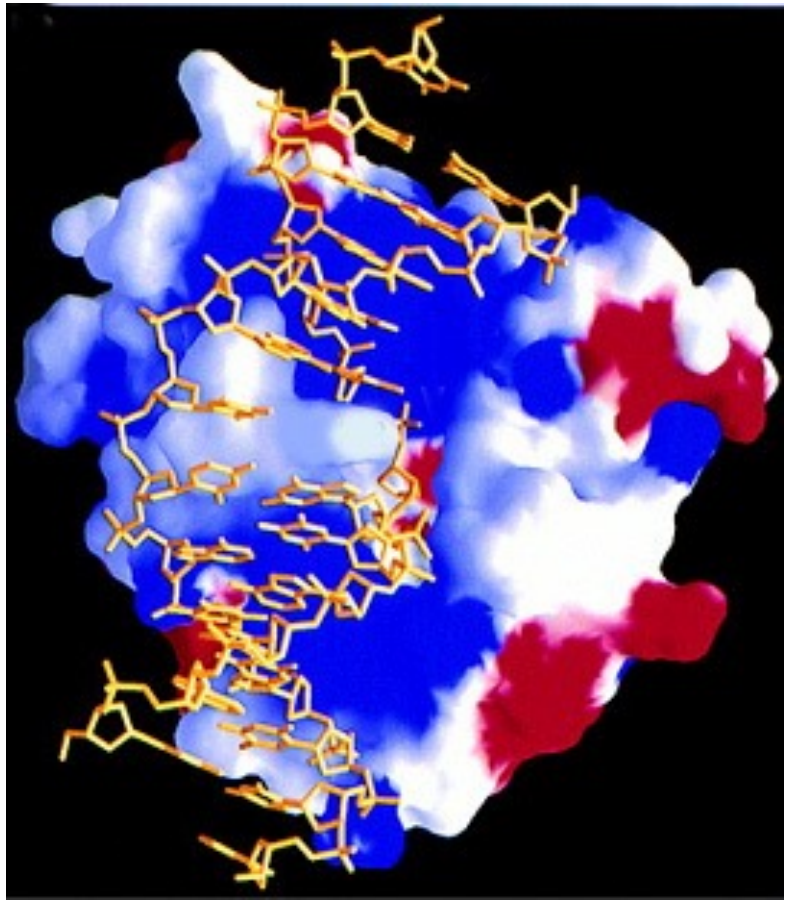
Tiny Changes can have Big Effects

GC →TA

Broken DNA can be Fixed

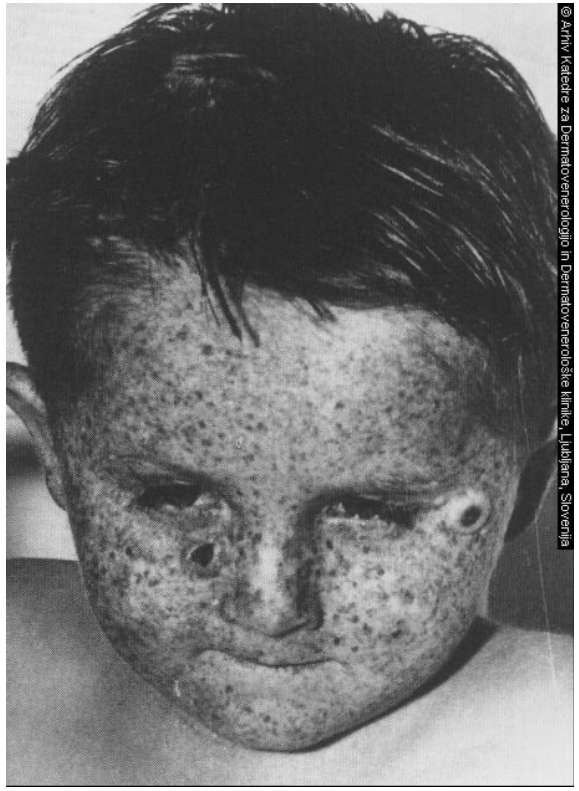
One Way to Prevent Mutations is to Repair DNA





A. Lau and T. Ellenburger; Harvard.

DNA Repair impacts Risk of Cancer



People lacking repair of UV dimers have a 2000X increased risk of skin cancer.

Xeroderma Pigmentosum – A rare human disease

The Base Excision Repair Pathway

Arsenic is a Major Public Health Problem

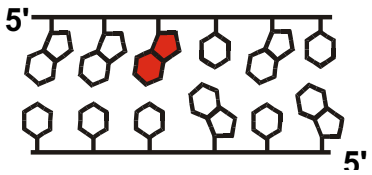
How PARP promotes DNA repair and how As inhibits PARP

The Base Excision Repair Pathway

Arsenic is a Major Public Health Problem

How PARP promotes DNA repair and how As inhibits PARP

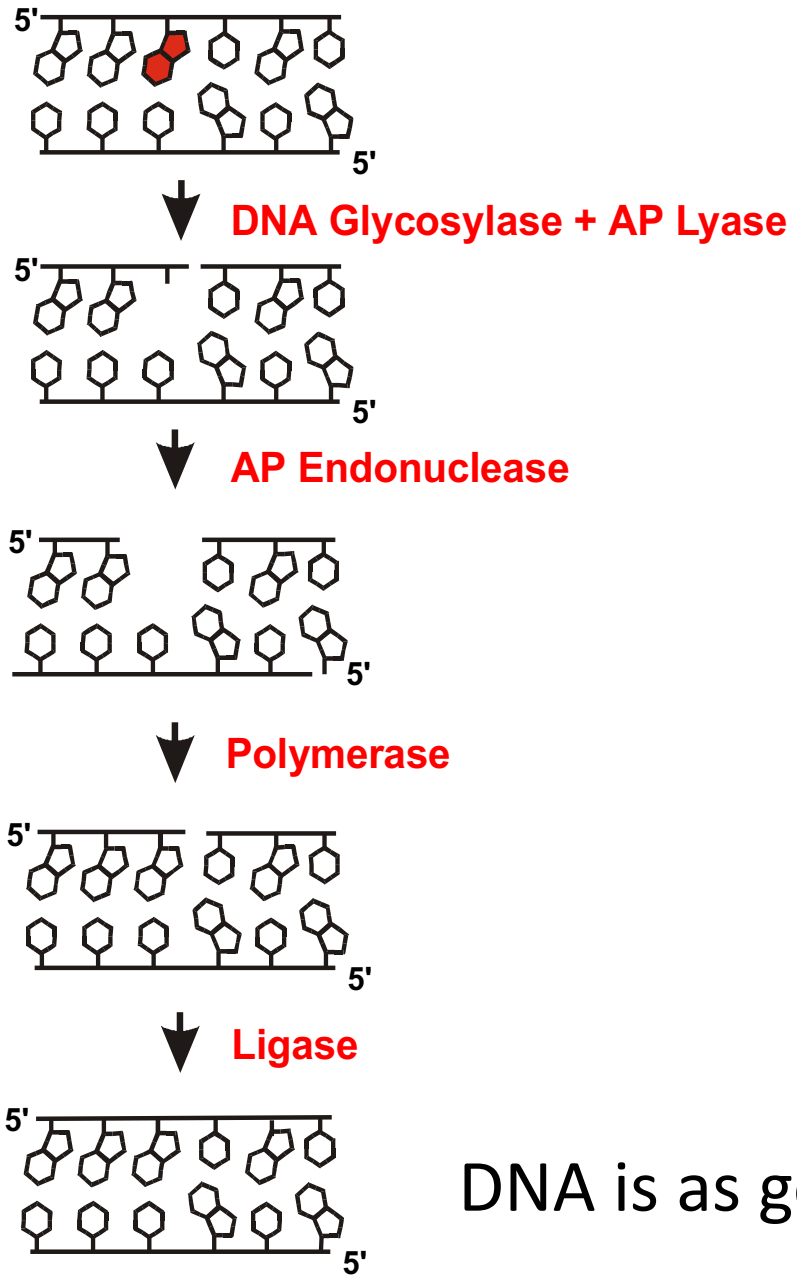
Base Excision Repair Pathway (BER)



Ogg1 Glycosylase

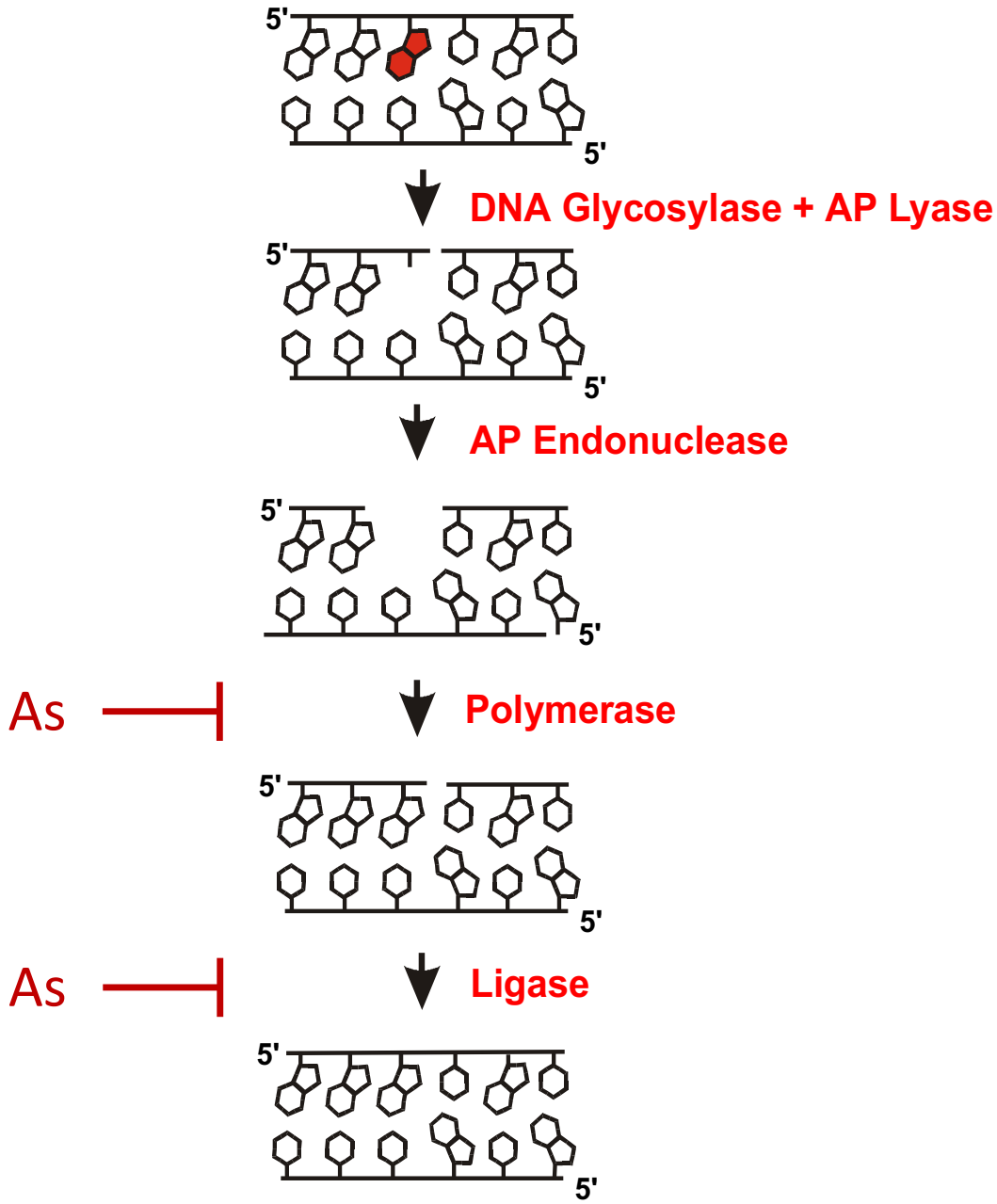
Verdine, G.L., Crenshaw, C.M., Oo, K.S., Kutchukian, P.S.

Base Excision Repair Pathway (BER)



DNA is as good as new!

Arsenic interferes with DNA repair



The Base Excision Repair Pathway

Arsenic is a Major Public Health Problem

How PARP promotes DNA repair and how As inhibits PARP

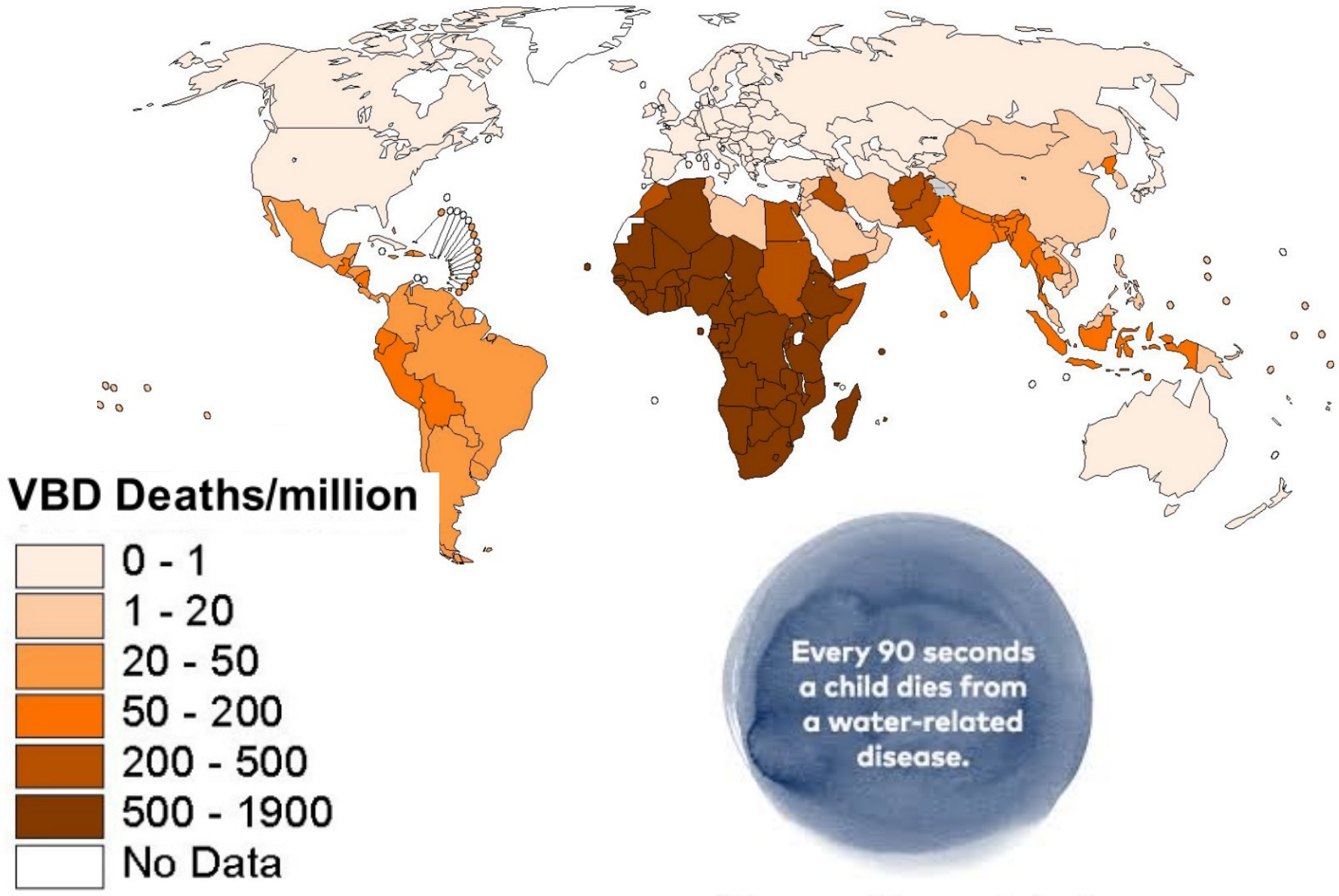
Public Health:

How Bangladesh came to have a major public health crisis due to Arsenic

Public Health:

The initial problem in Bangladesh was infectious disease.

Deaths from Vector-Bourn Diseases

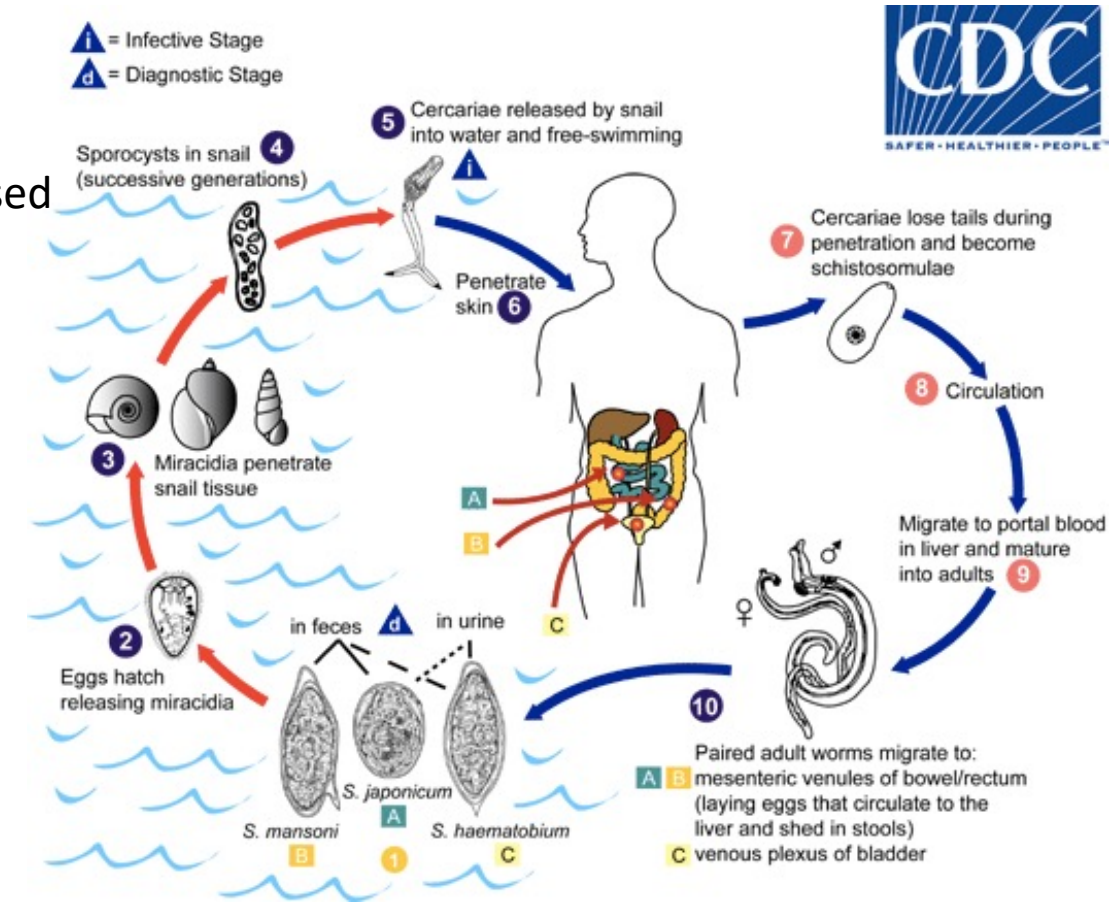


Example of a Water-bourn Disease: Schistosomiasis

Parasitic trematode flatworm Schistosoma

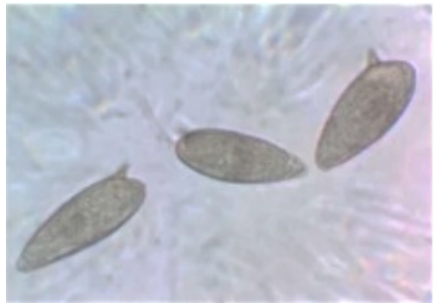
Cercariae are released from snails

Cycle of the Schistosomiasis

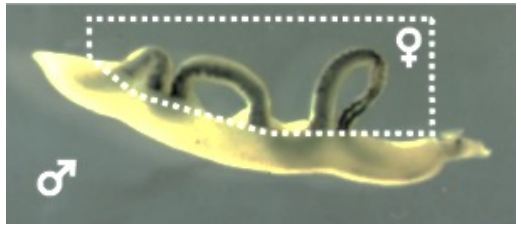


Schistosomula

Circulation then to Liver
Then to Bowel
Then eggs to into the water



Eggs hatch and enter the snail



Adult Worms

Schistosomiasis is a major neglected tropical disease with more than 700 million at risk.

The disease burden is estimated to exceed 70 million disability-adjusted life-years.

~23,000 Publications on Schistosomiasis

~4,400,000 Publications on Cancer

What is our responsibility for diseases that don't affect people in the US?

Joseph Jeune had HIV/AIDS and TB

Recovery after treatment for HIV/AIDS and TB.

We work hard to combat mortality.

We work hard when we can see how powerful treatment can be.

We need to also work hard to prevent suffering, especially when it isn't visible.

MIT has saved more lives than Harvard, Tufts and BU combined…. Even without a hospital!

How?

Ellen H. Swallow Richards

Women's Advocate, Sanitation Engineering Pioneer

One of America's first female professional chemists

The first woman to be accepted by a scientific school

Pioneer in the field of sanitary engineering.

Richards performed an unprecedented survey in 1890 that led to **the first water-quality standards in the nation**.

Connecting the Dots between Clean Water and Arsenic Poisoning

Bangladesh Had Significant Water Bourn Diseases

1980s
World Health Organization Sponsored Digging of Wells

Unfortunately, naturally occurring arsenic led to wide-spread poisoning.

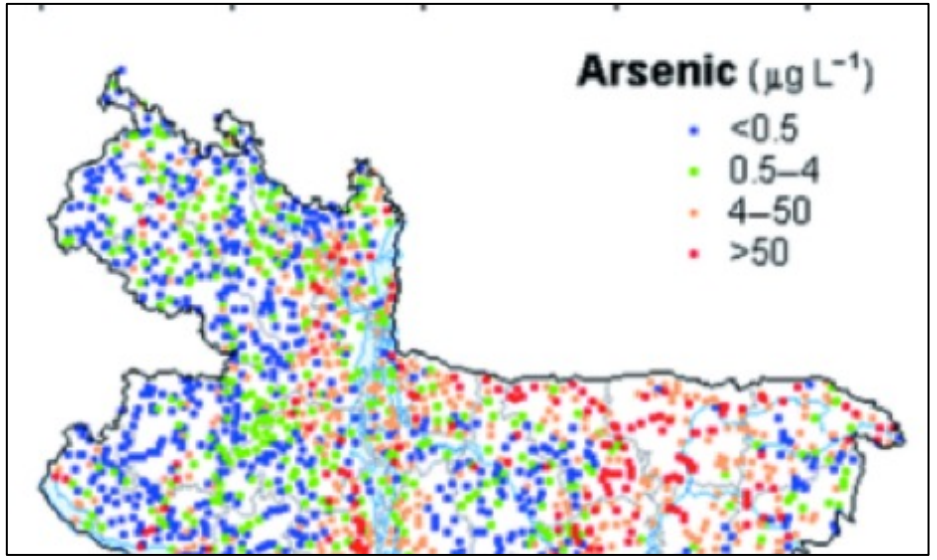
Unfortunately, naturally occurring arsenic led to wide-spread poisoning.

•Acute exposure:
- Nausea, vomiting, diarrhea,
- Weakness,
- Loss of appetite
- Cough and headache

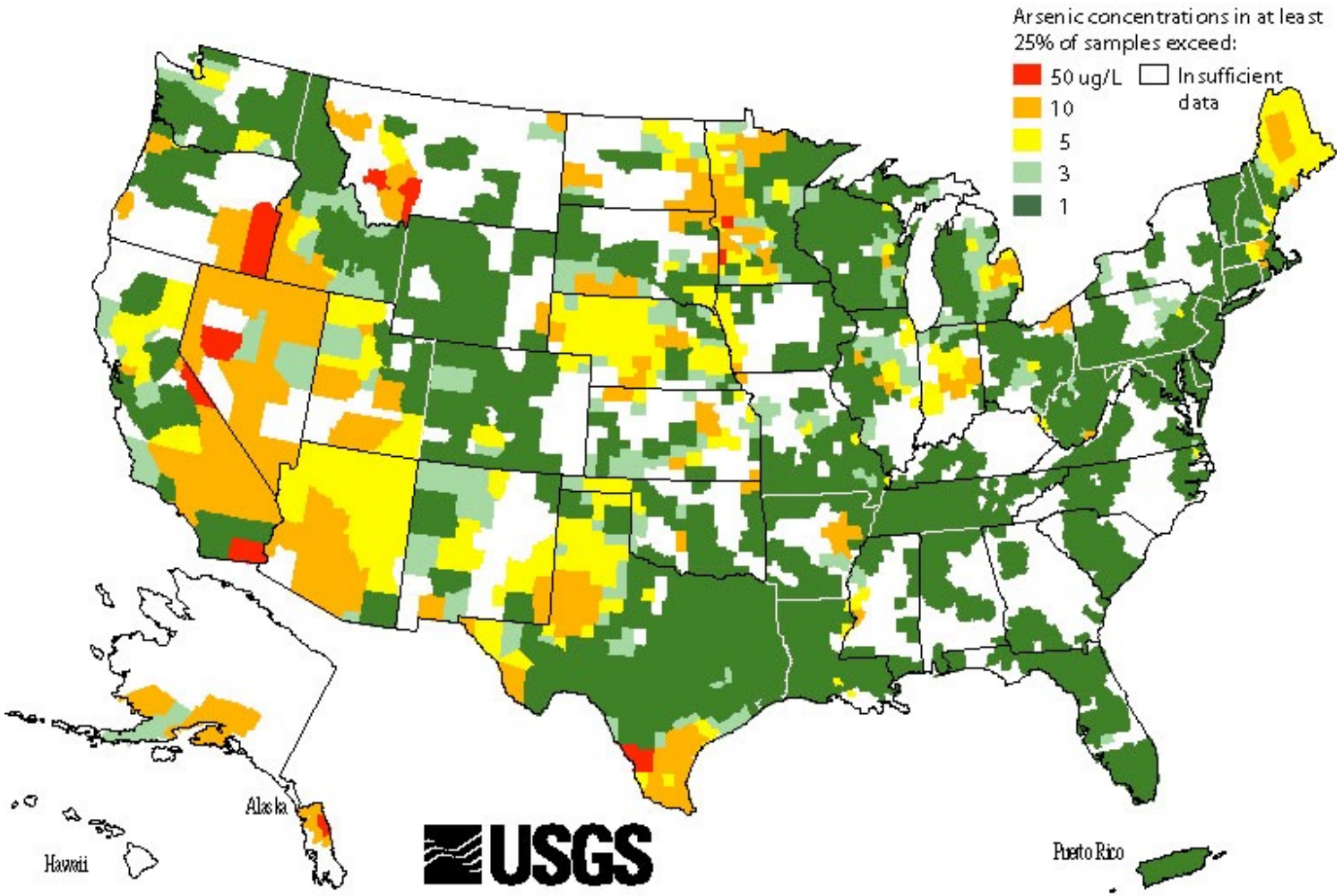
•Chronic exposure:
- Abnormal skin pigmentation,
- Cardiovascular disease
- Diabetes

Cancer:
Skin (non-melanoma)
Kidney,
Bladder,
Lung,
Prostate
Liver

Unfortunately, naturally occurring arsenic led to wide-spread poisoning.

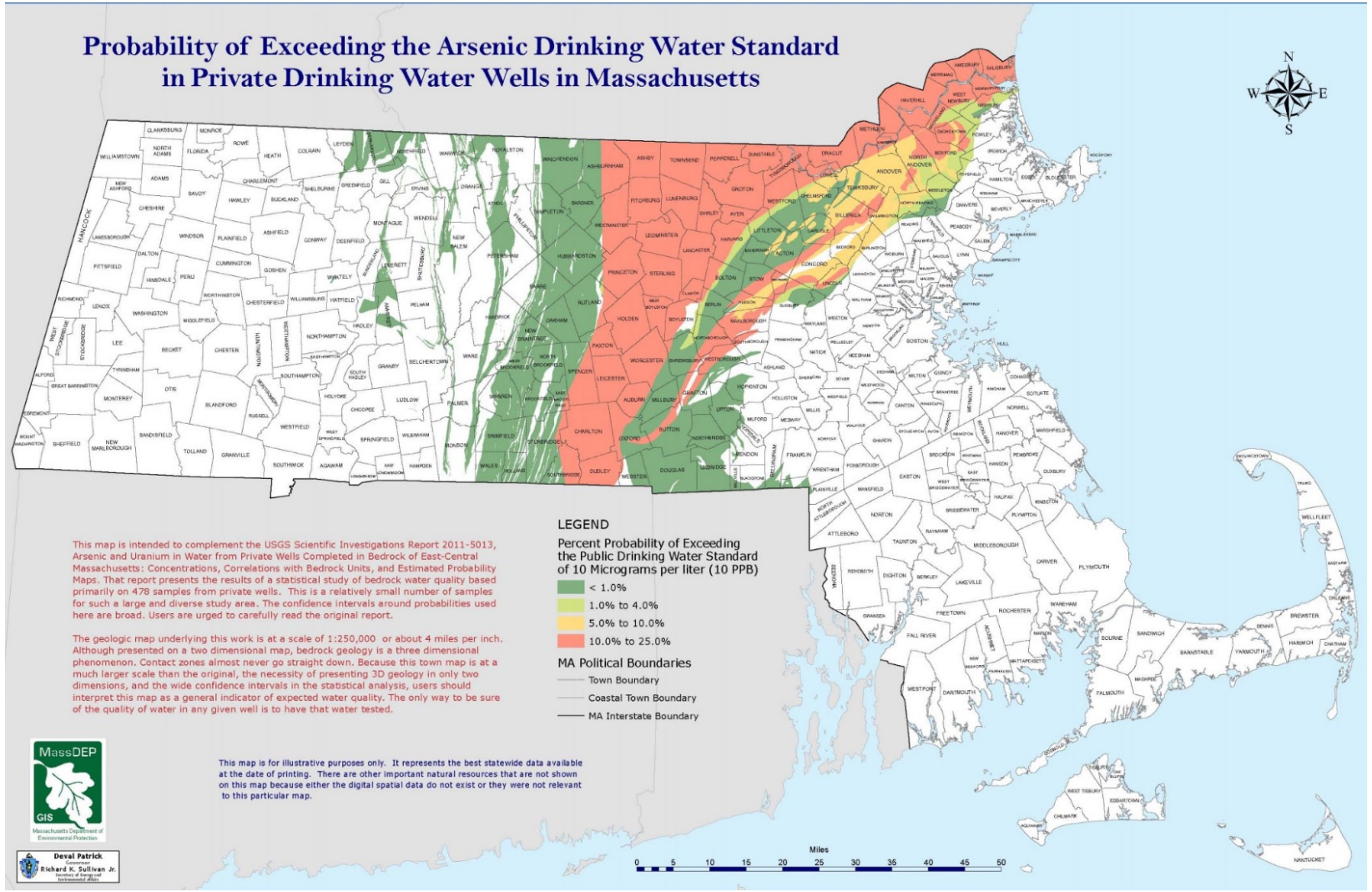


Arsenic Levels in the US



World Health Organization Guideline is that the levels should be under 10 ug/L (10 ppb)

25 million people are chronically exposed to high levels of arsenic



10-25% Chance of Arsenic at > 10 PPB

The Base Excision Repair Pathway

Arsenic is a Major Public Health Problem

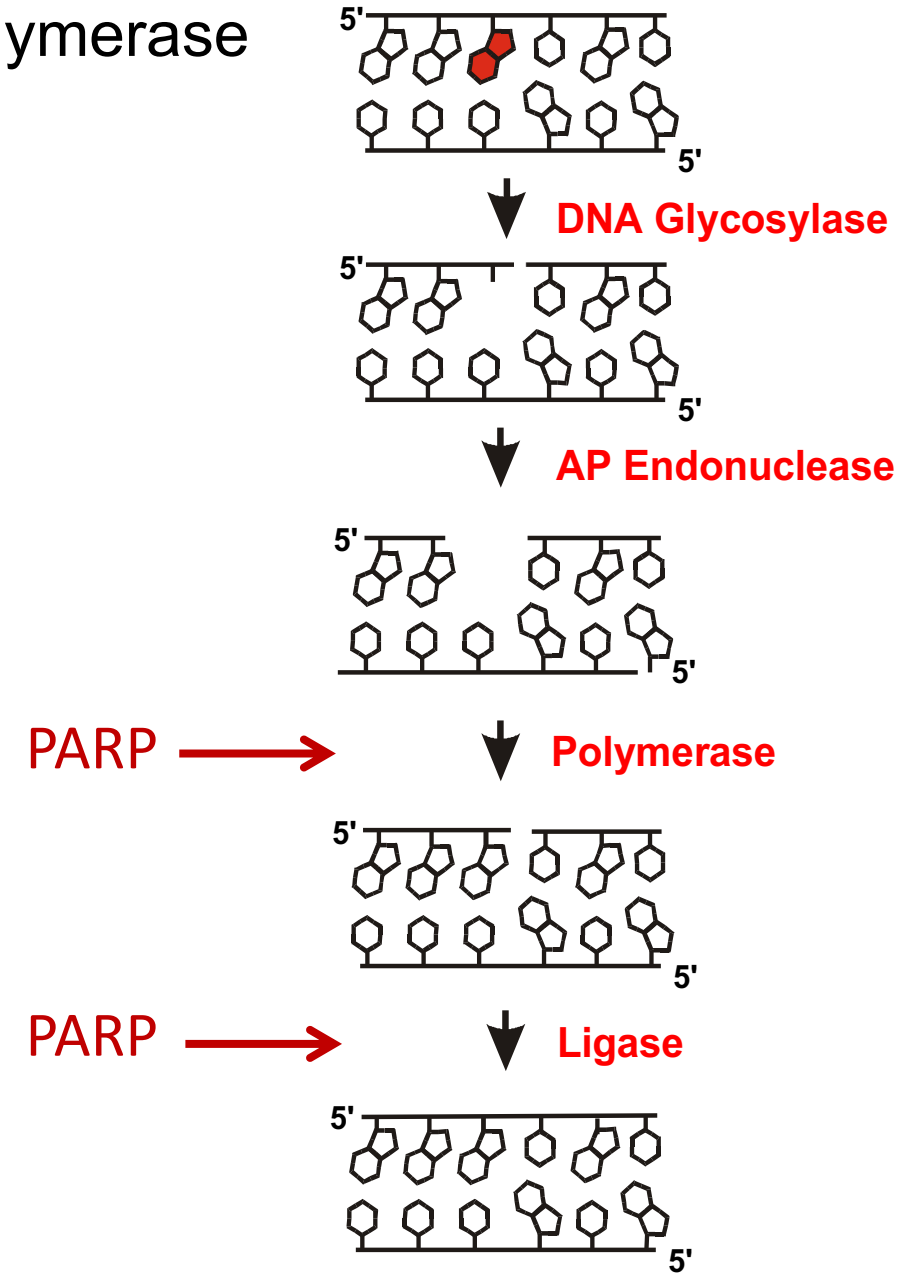
How PARP promotes DNA repair and how As inhibits PARP

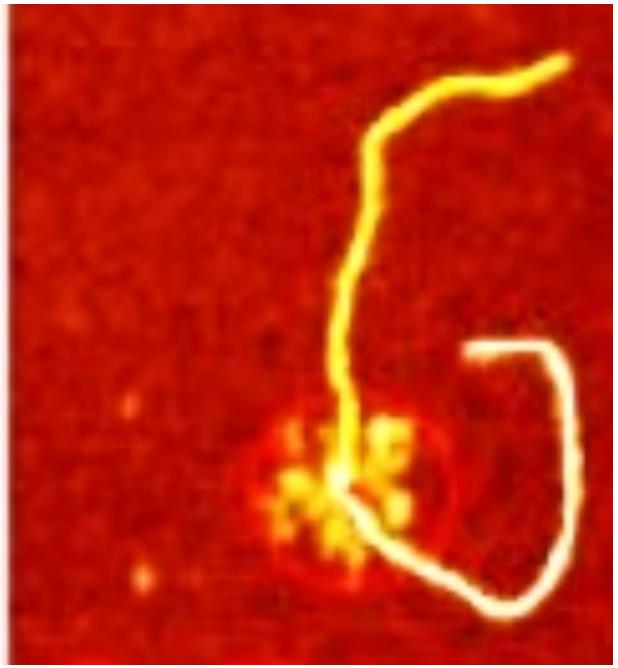
Arsenic Interferes with Base Excision Repair

PARP =
Poly (ADP-Ribose) Polymerase

PARP Promotes BER

As inhibits PARP





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

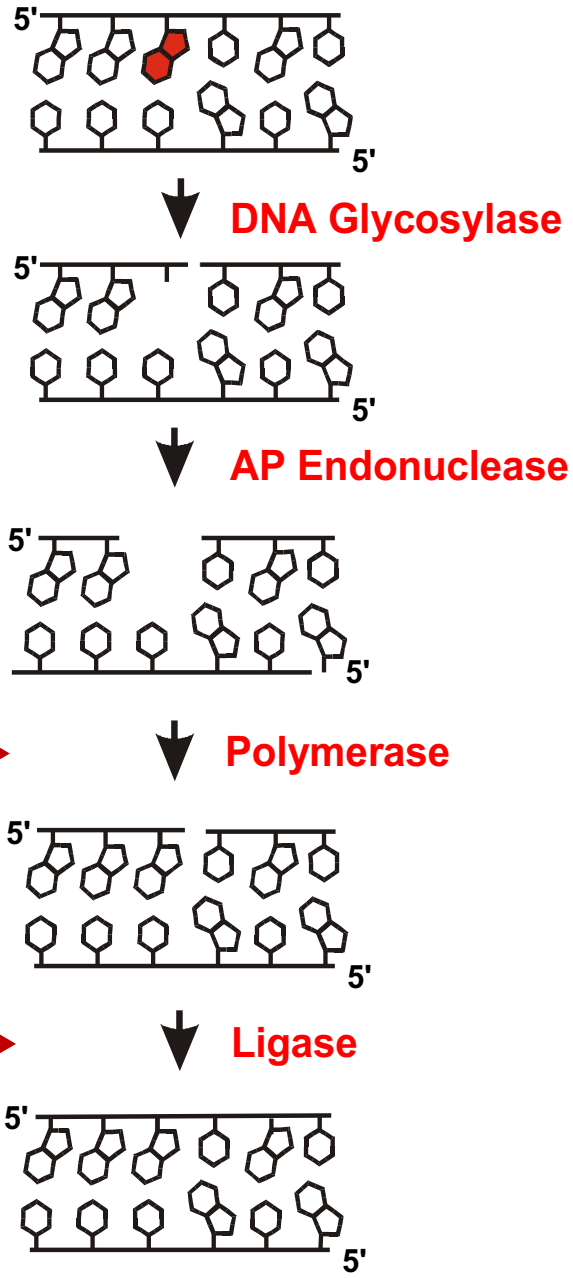
PARP =
Poly (ADP-Ribose) Polymerase

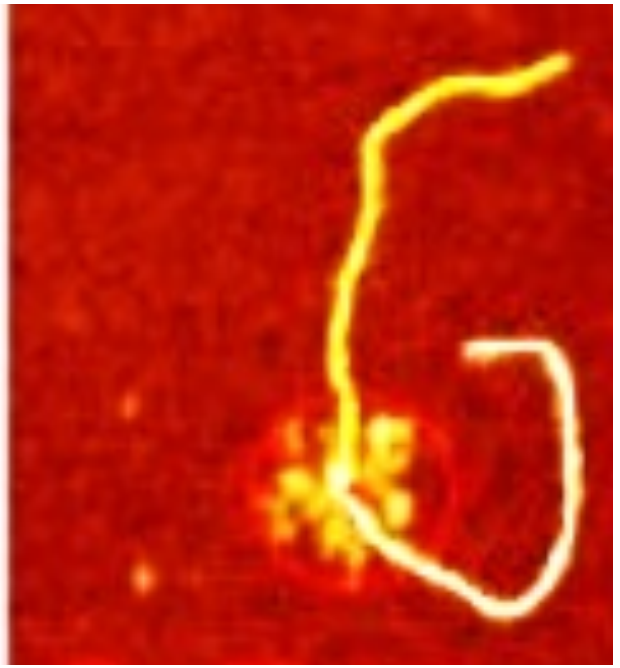
PARP Promotes BER

As inhibits PARP

PARP binds to SSBs

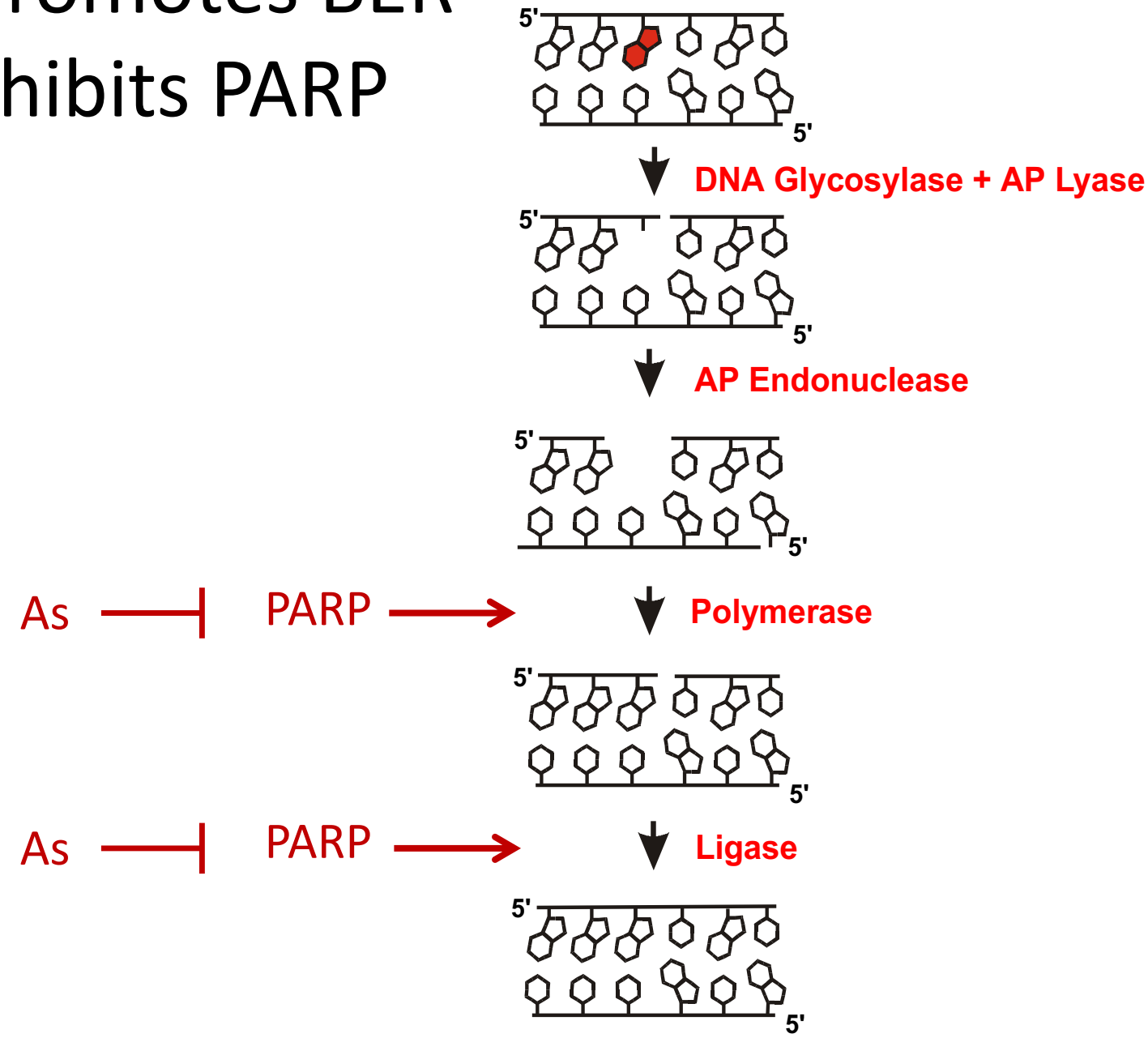
PARP forms
a PAR "beacon"
that Recruits
BER Enzymes





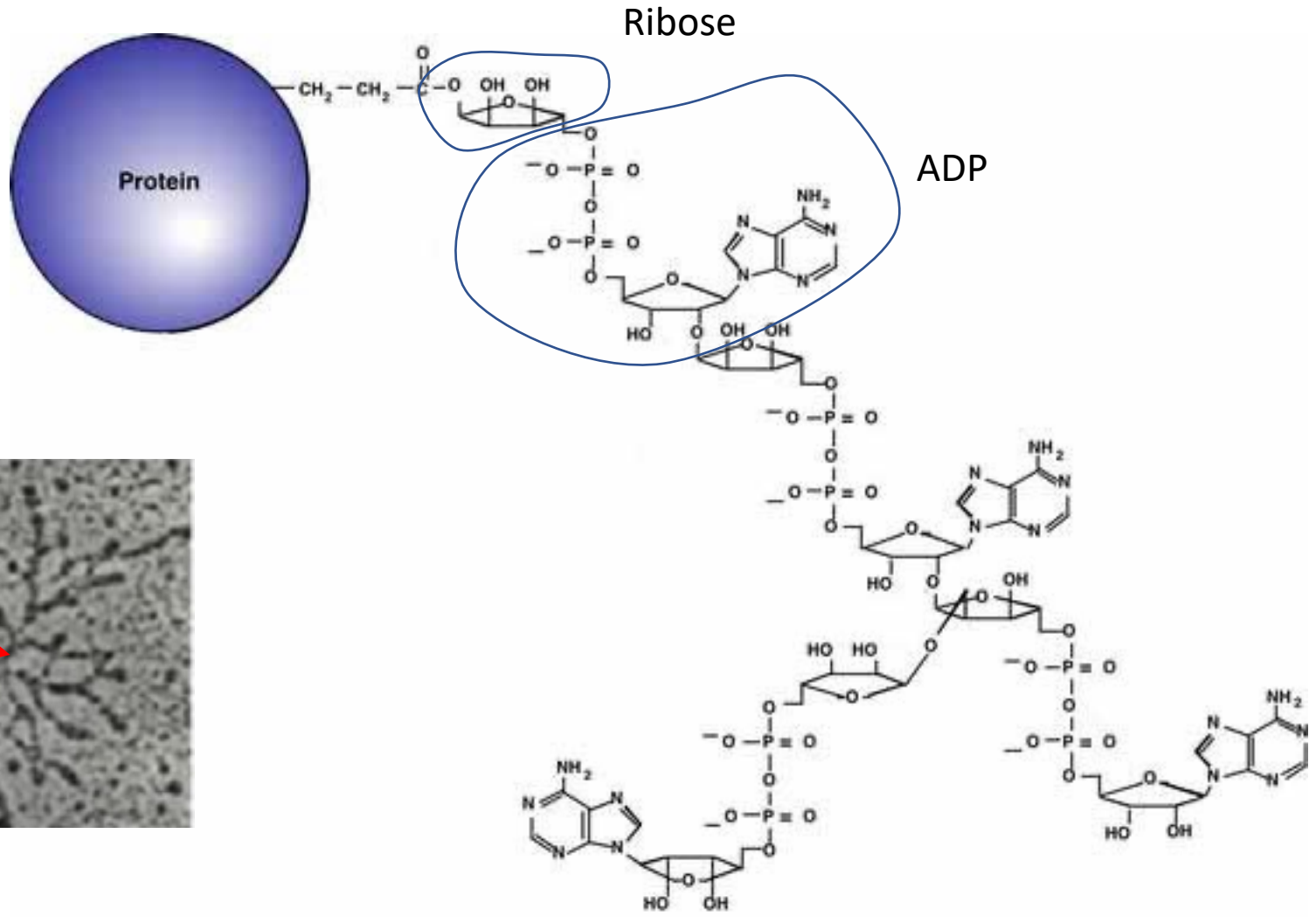
Poly(ADP)-ribose
forms a branched structure
at Single Strand Breaks (SSBs)

PARP Promotes BER As Inhibits PARP

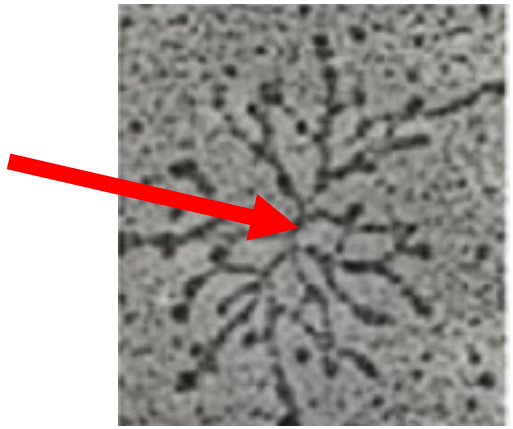


Suppression of PARP Reduces Recruitment of DNA Repair Proteins

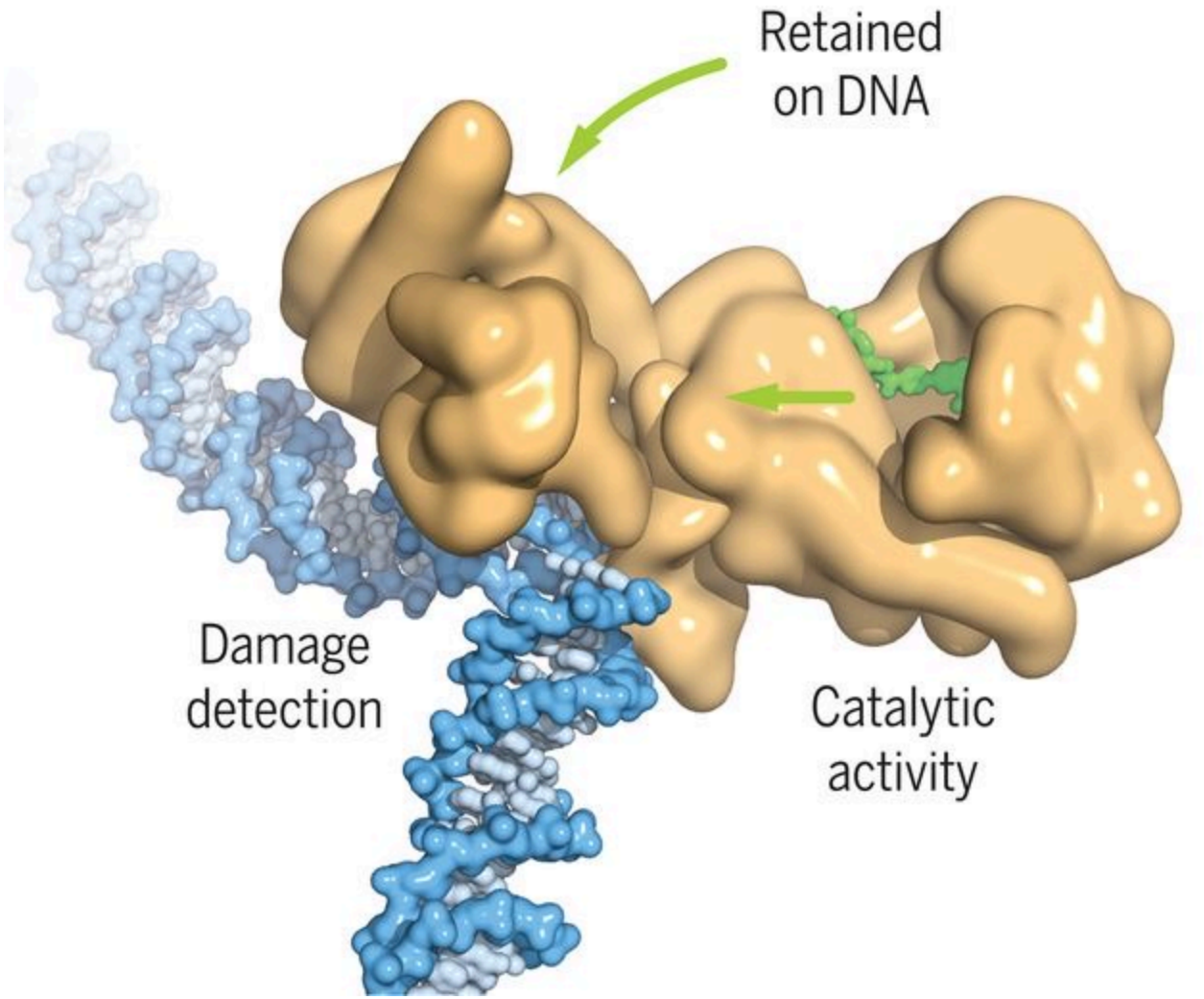
PARP Automodification Creates a Branched Structure



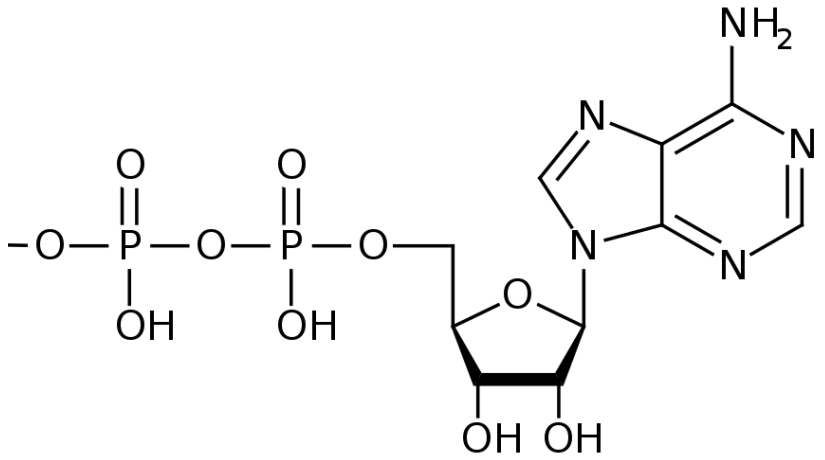
PARP is in the middle



Poly(ADP-Ribose) Polymerase (PARP)



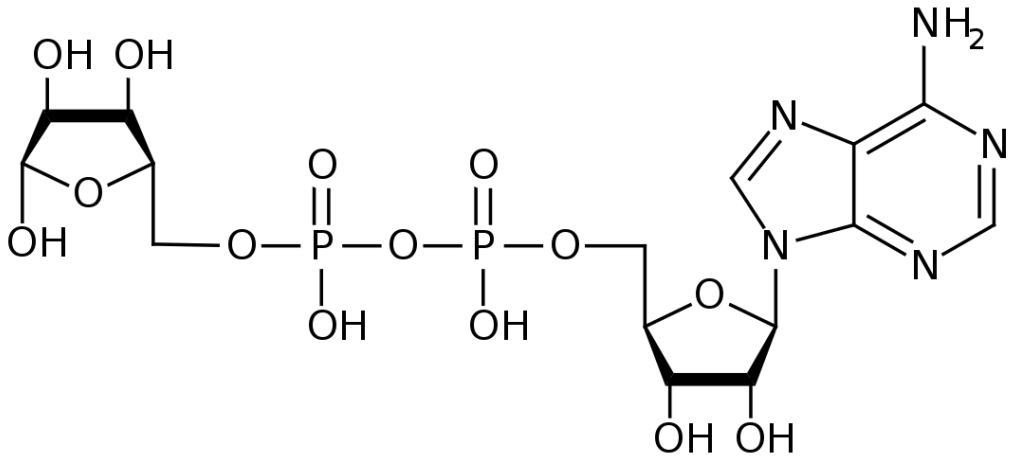
Poly (ADP)-Ribose [PAR] is made from ADP-ribose



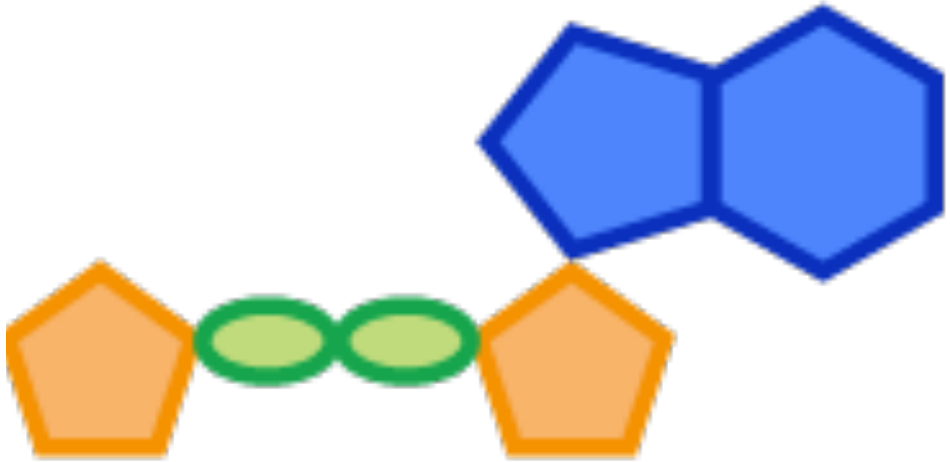
Adenosine diphosphate (ADP)

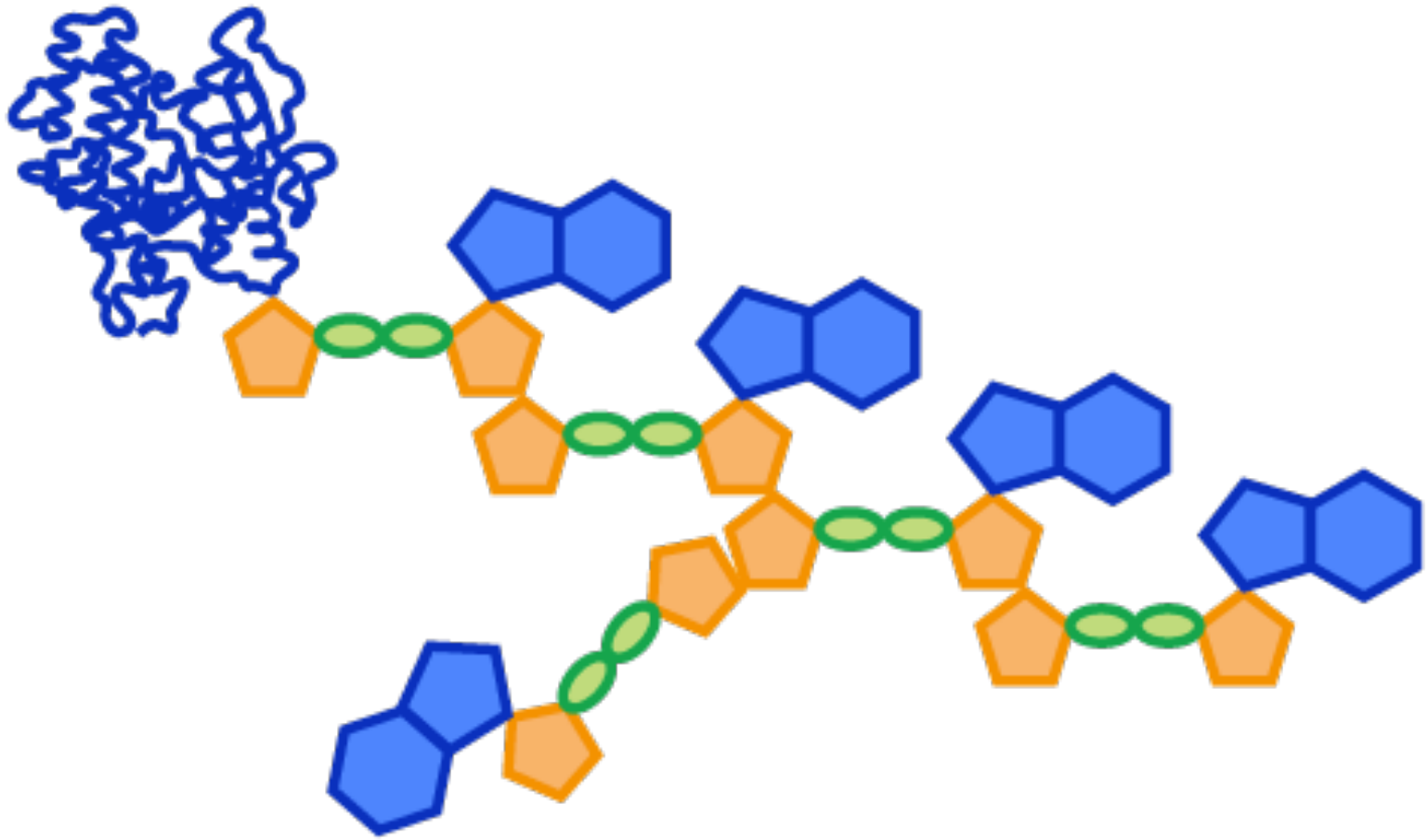
Poly(ADP)-Ribose is made from ADP-ribose

ribose ADP

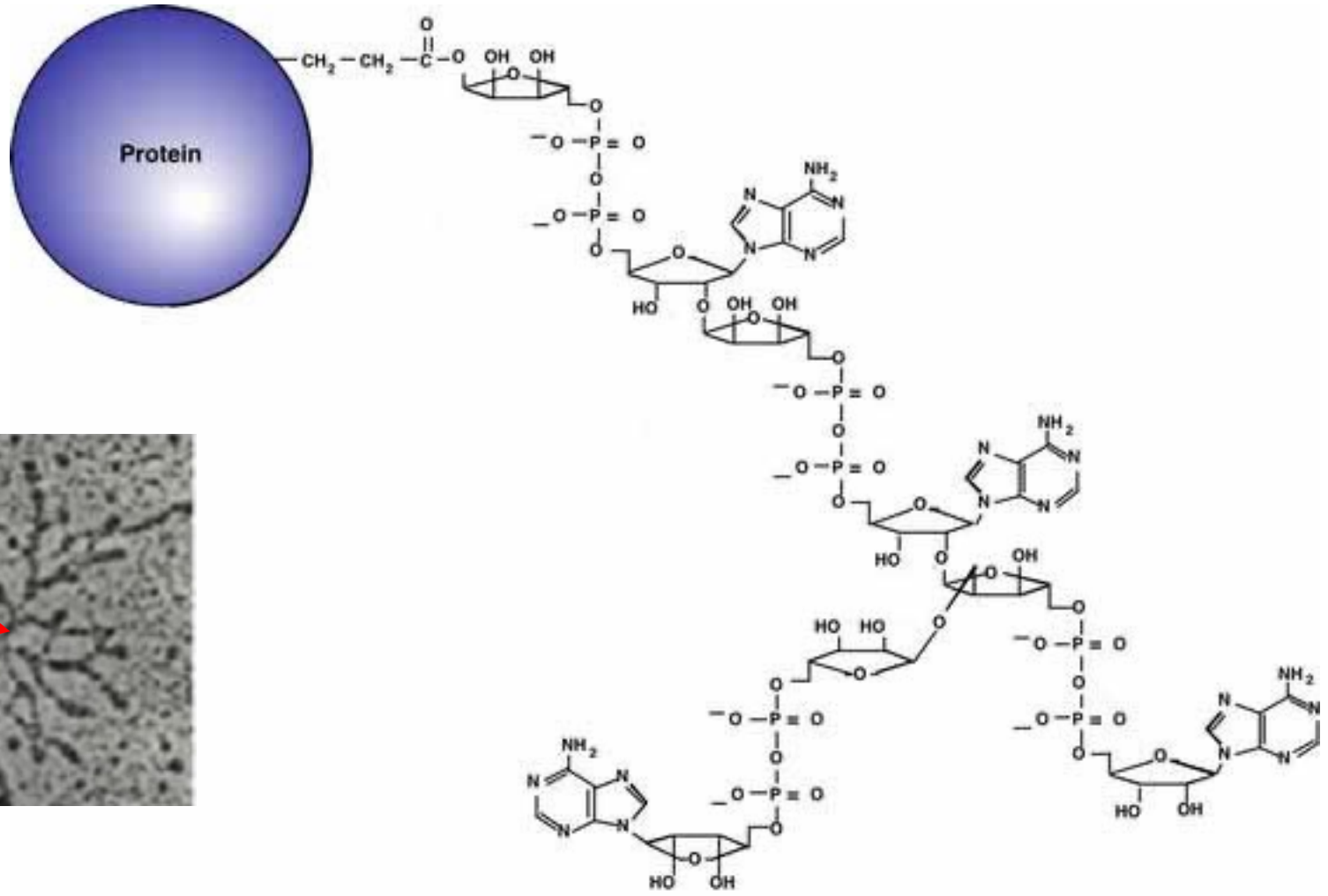


ADP-ribose

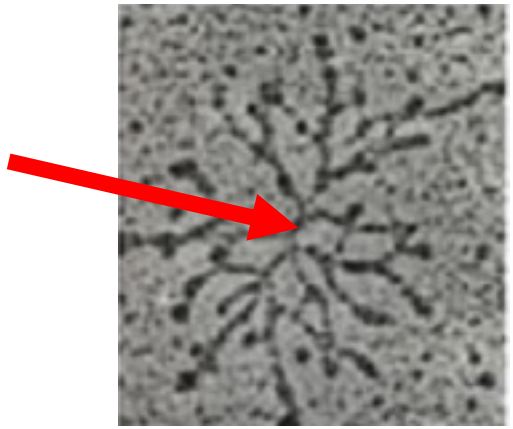




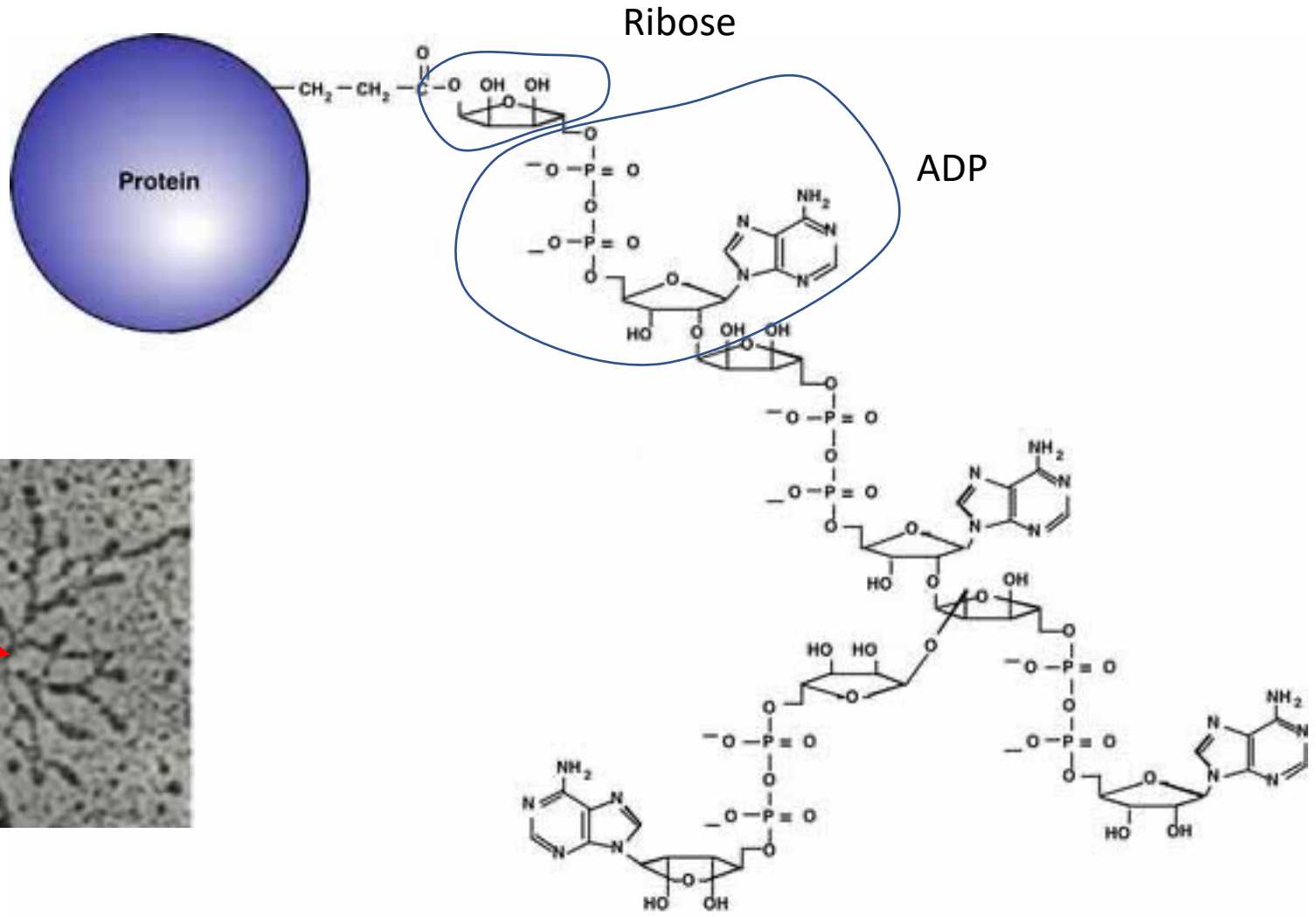
PARP Automodification Creates a Branched Structure



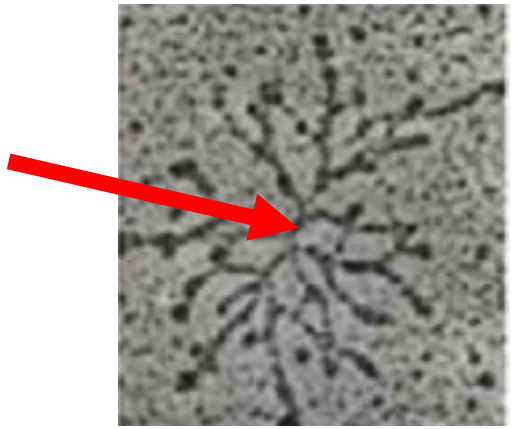
PARP is in the middle



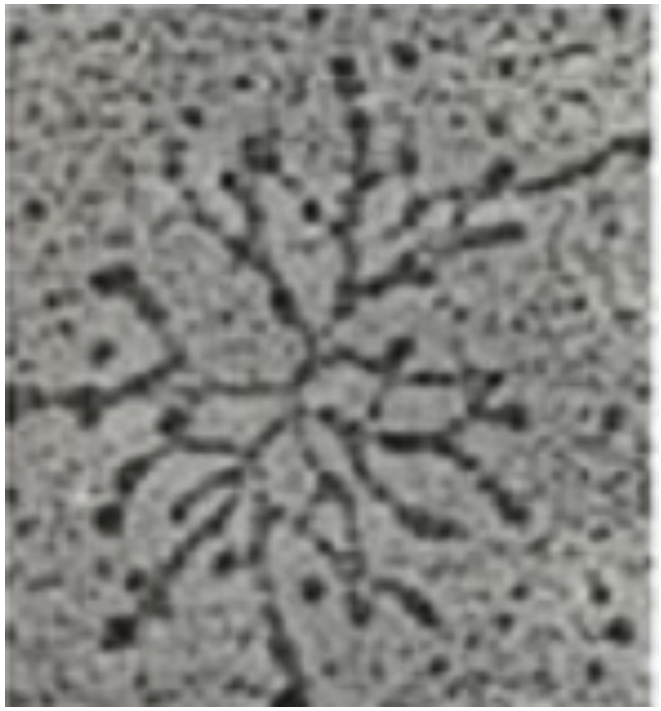
PARP Automodification Creates a Branched Structure



PARP is in the middle



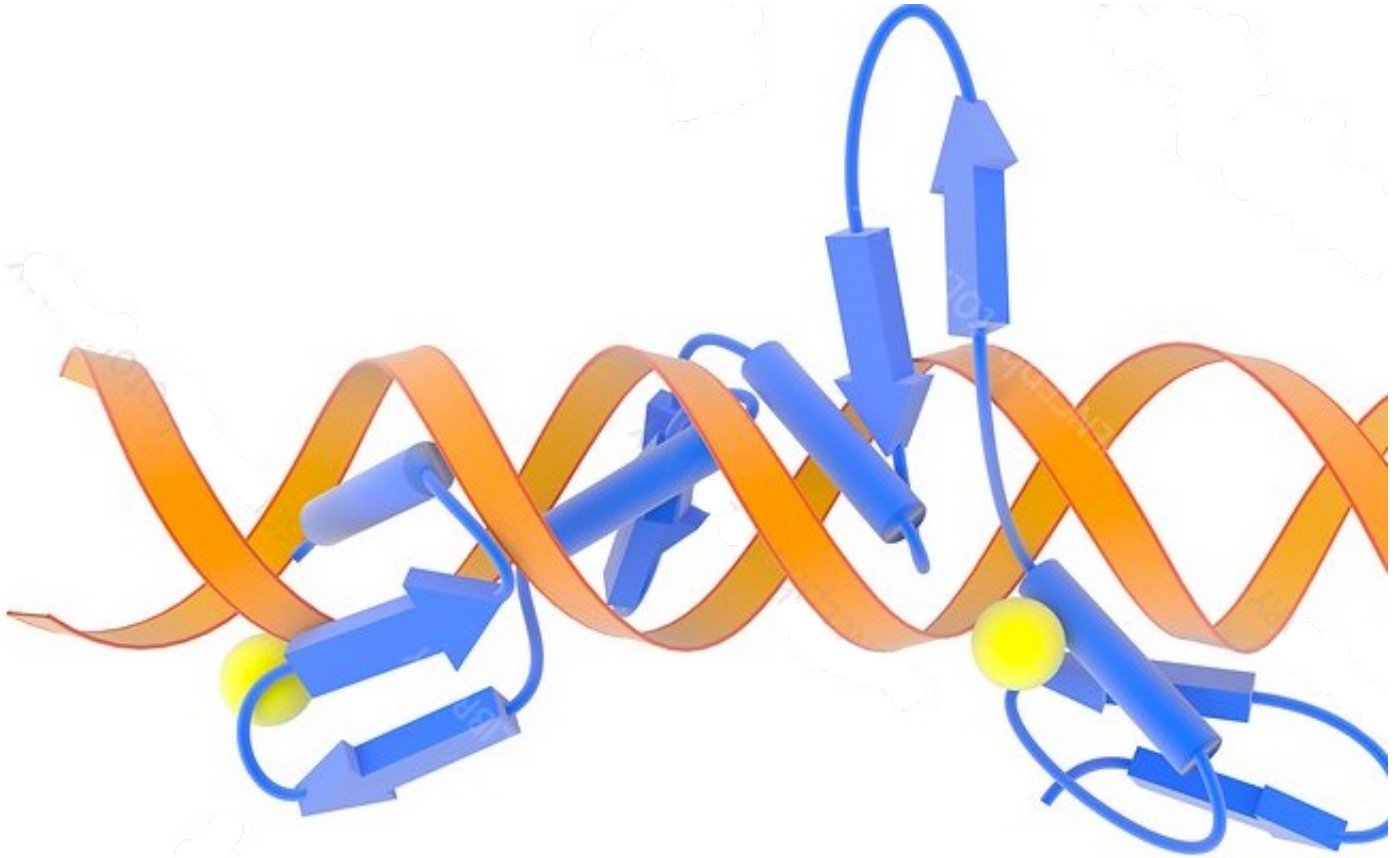
SSB-induced Poly(ADP-Ribose) [Parylation]



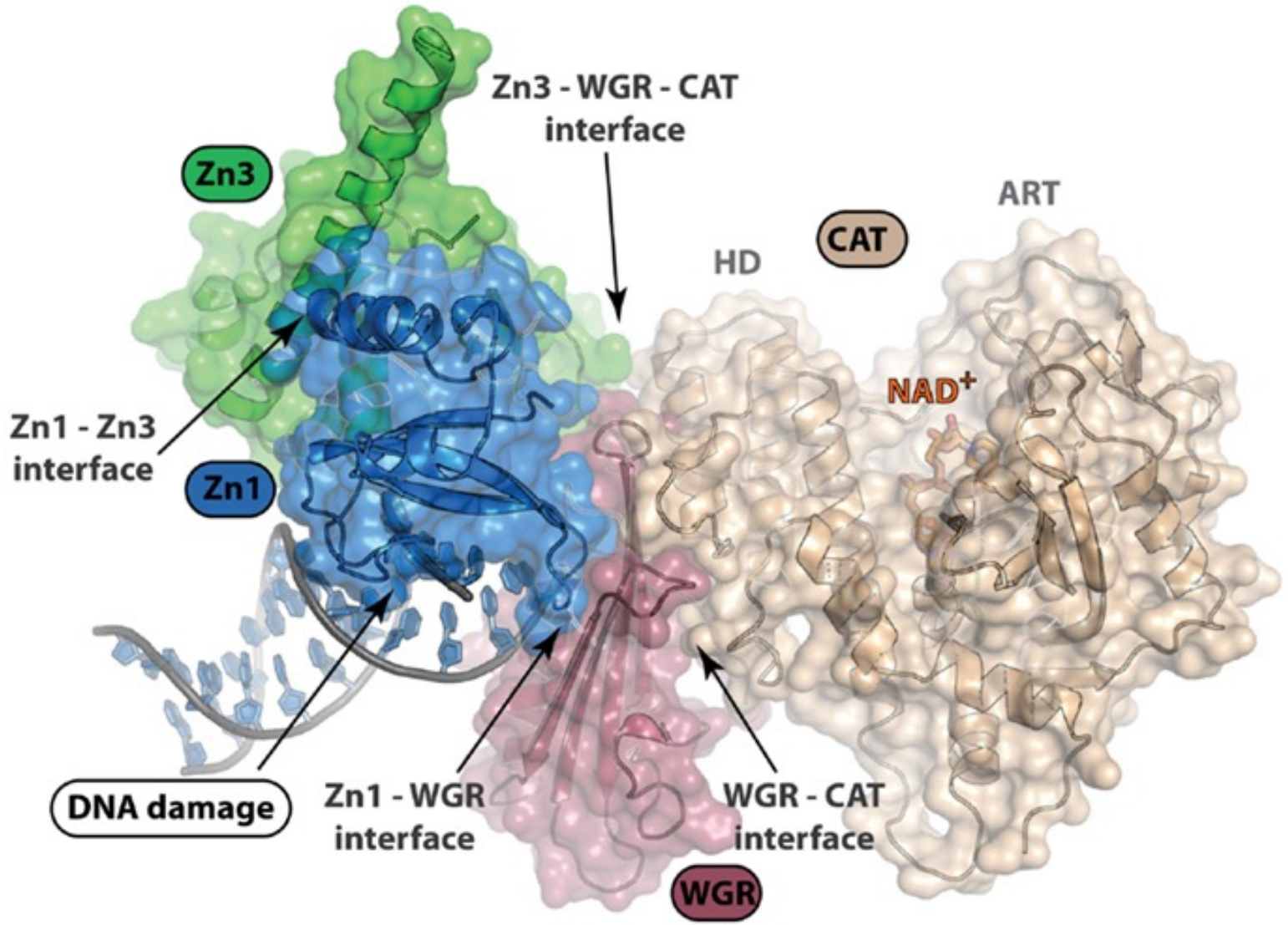
BER Components
Interact with PAR

PAR Recruits
XRCC1 – Scaffold
Polβ
Ligase III

Zinc Fingers Interact Tightly with DNA

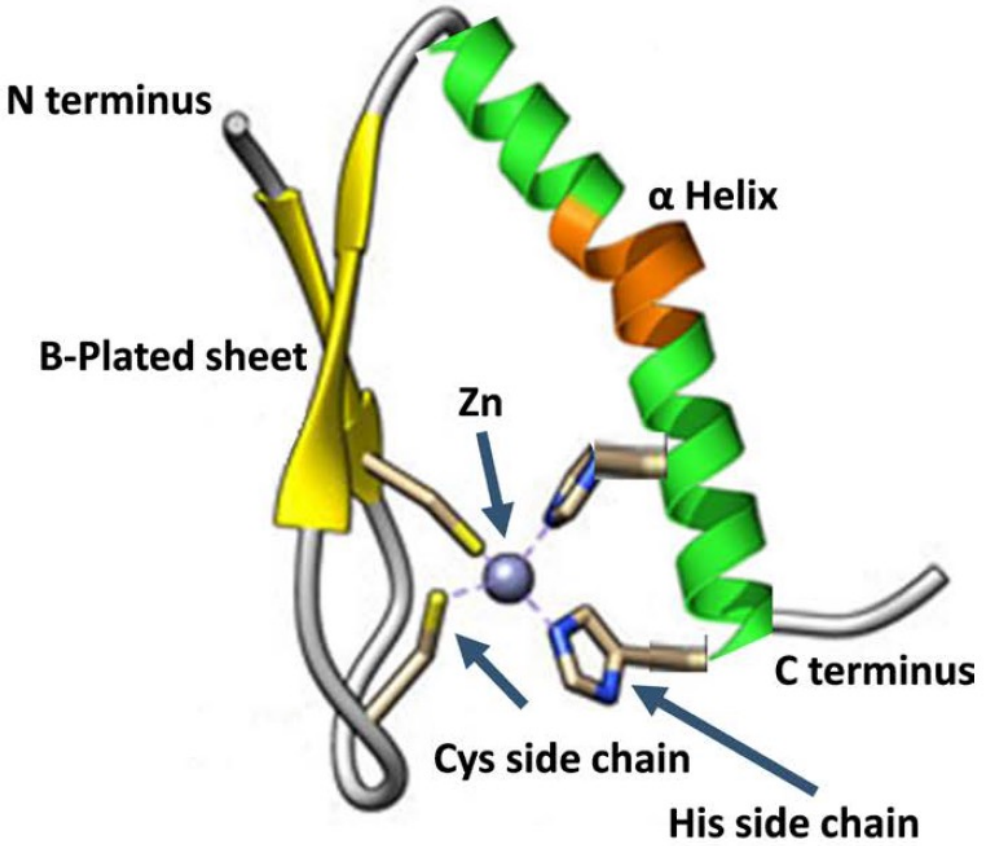


PARP has Zinc Fingers

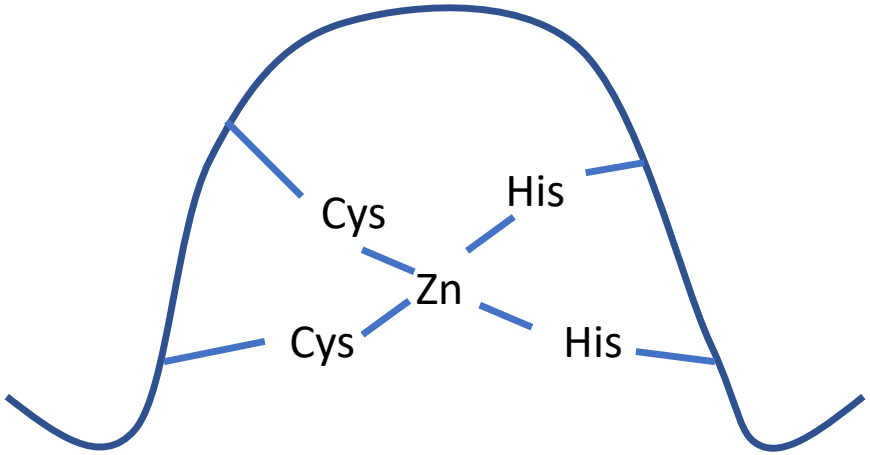


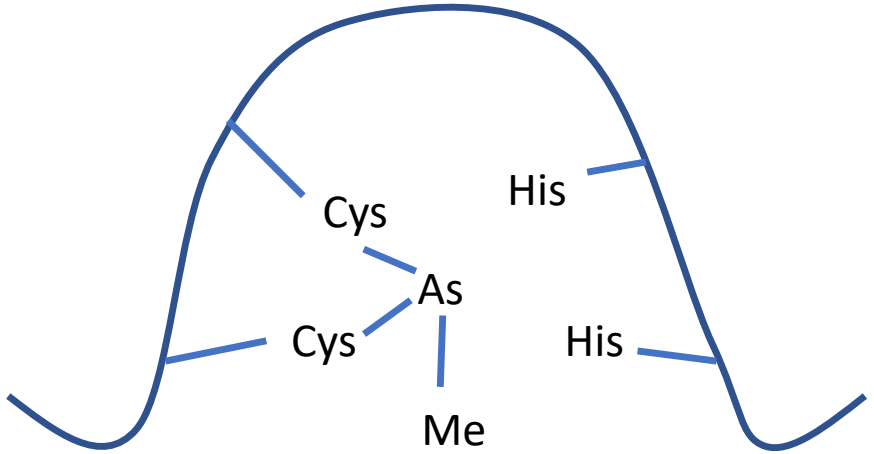
Jamin, Brody, Armen, Pascal

Zinc Fingers have Amino Acids that Bind Zinc



Arsenic Disrupts Zinc Fingers



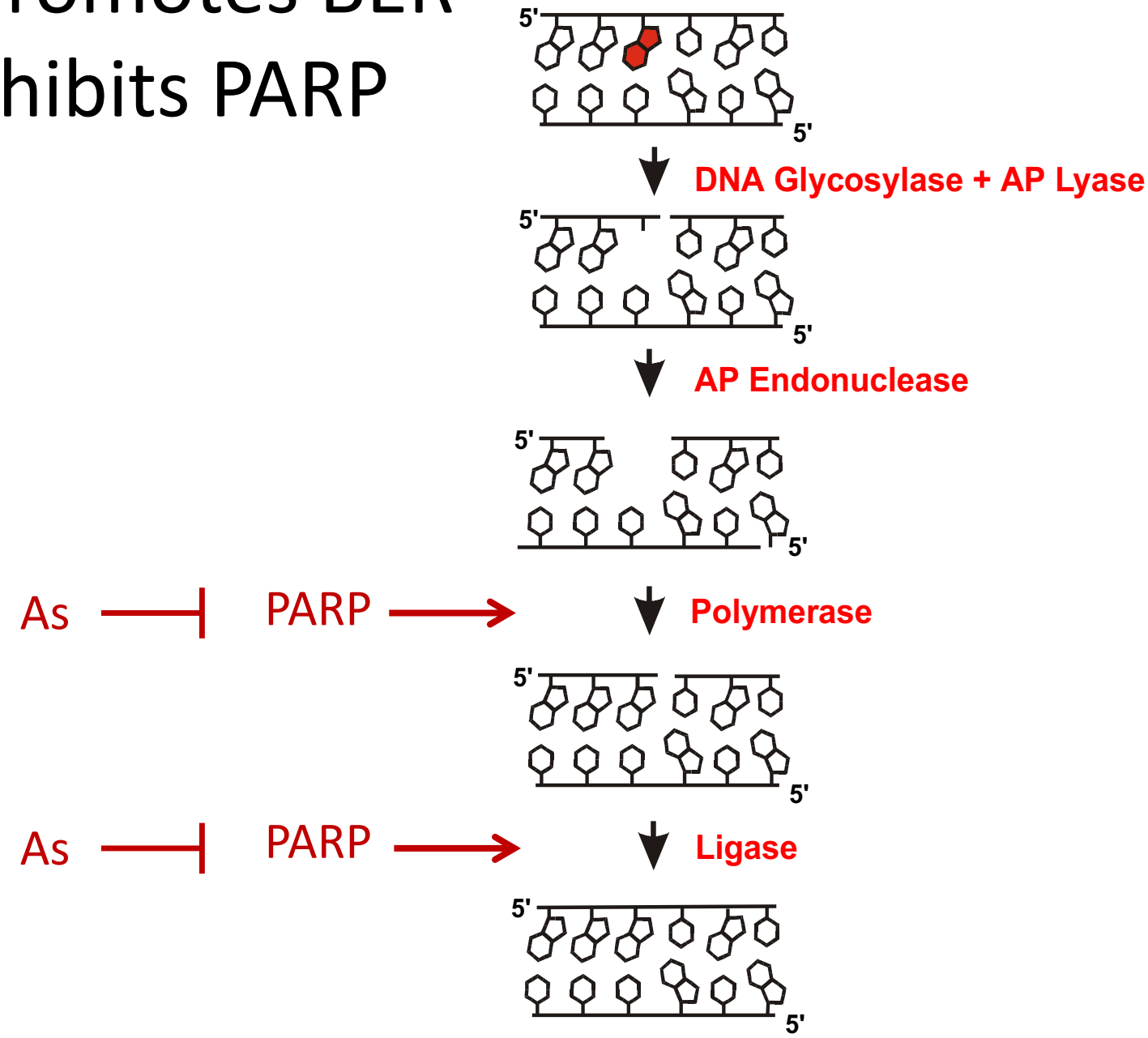


Replacement of Zinc with Arsenic Changes the Structure of PARP

Arsenic leads to PARP inhibition

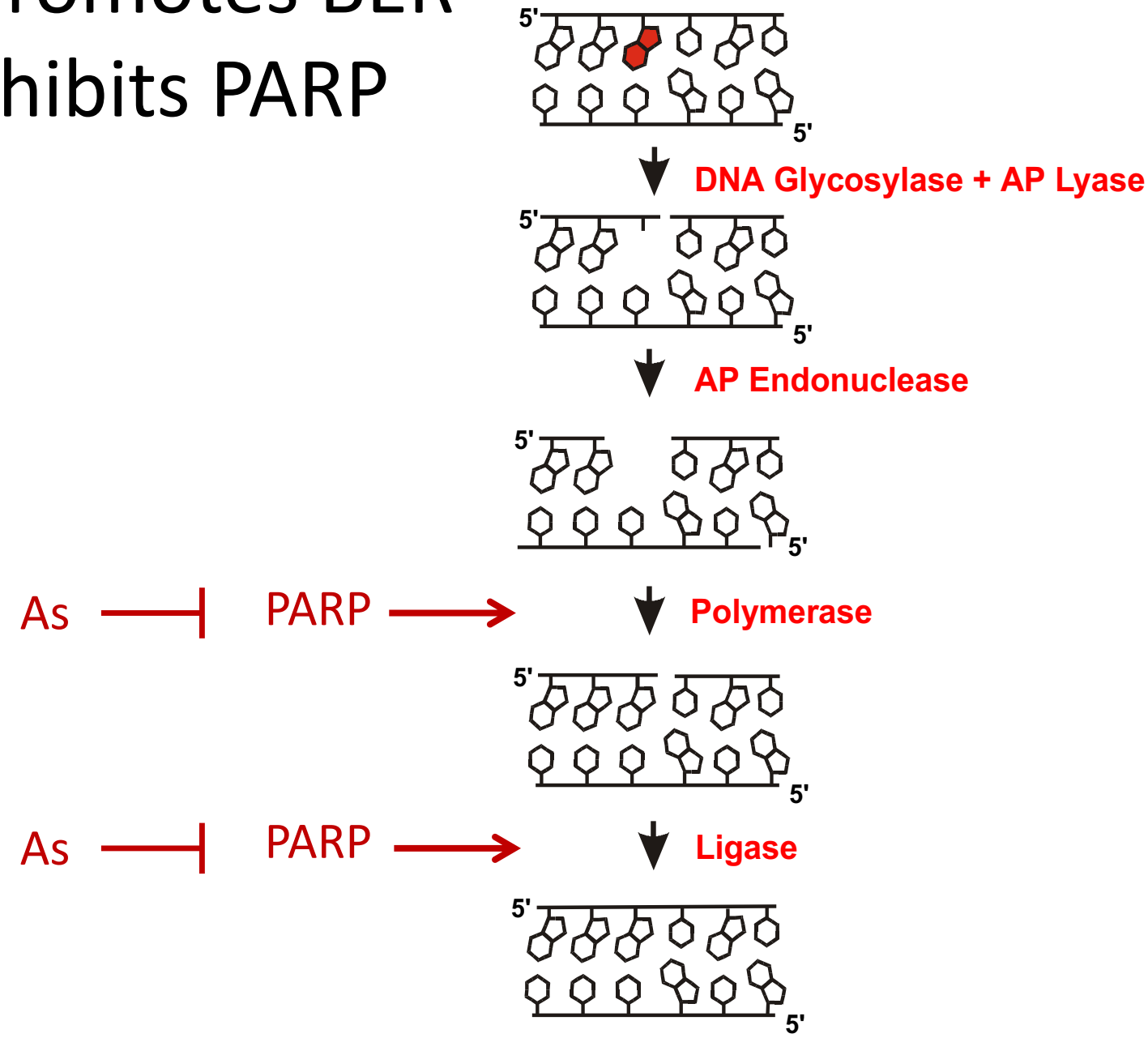
PARP inhibition slows BER

PARP Promotes BER As Inhibits PARP



Suppression of PARP Reduces Recruitment of DNA Repair Proteins

PARP Promotes BER As Inhibits PARP



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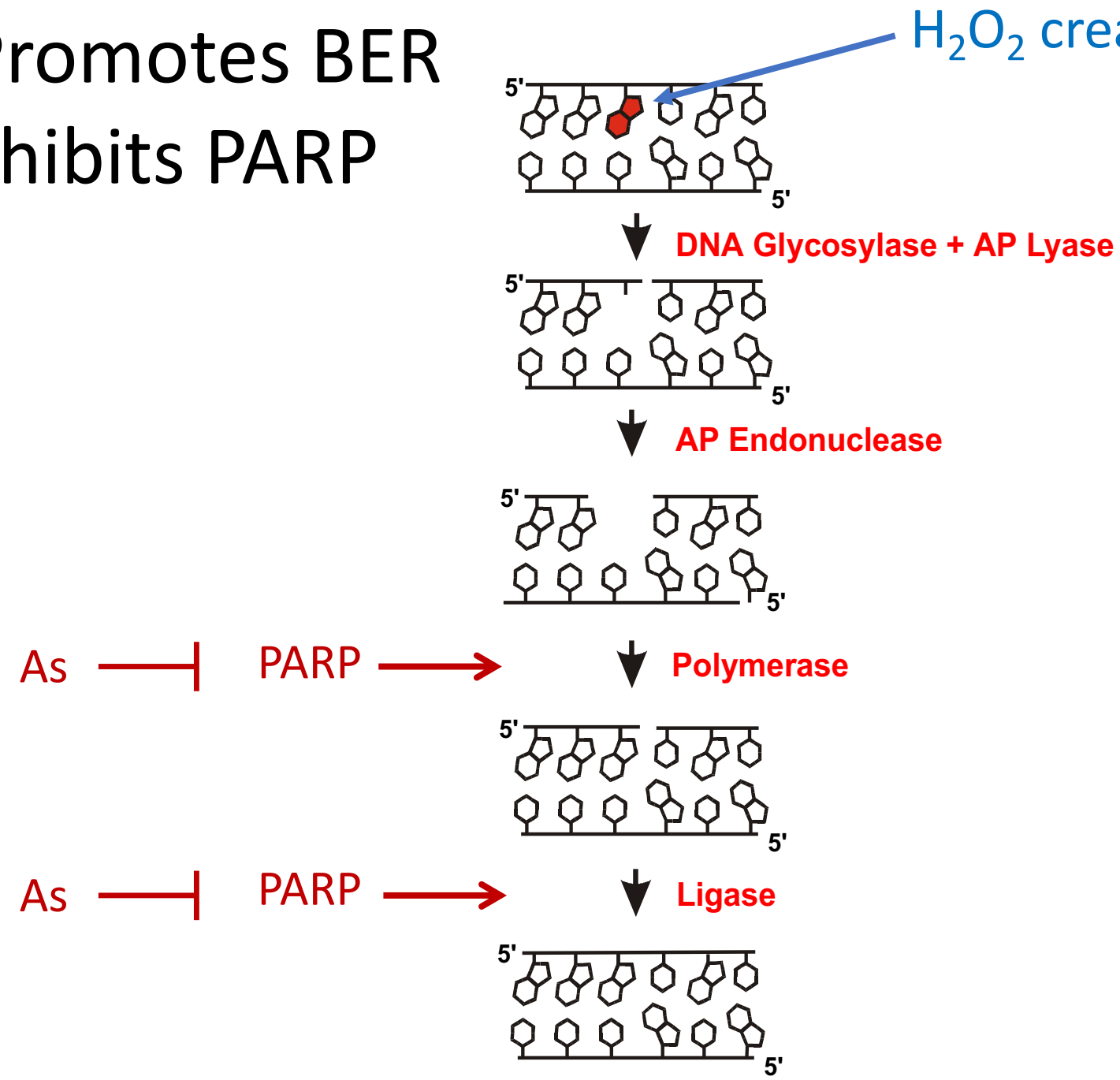

Suppression of PARP Reduces Recruitment of DNA Repair Proteins

As Inhibition of PARP leads to Increased Single Strand Breaks

Closely Opposed Single Strand Breaks lead to Double Strand Breaks

How structural changes to the DNA lead to mutations

How DNA damage is repaired via Base Excision Repair

Arsenic is a Major Public Health Problem

How PARP promotes DNA repair and how As inhibits PARP

-Oxidative damage is happening even without exposures
-Inflammation induces high levels of ROS