Our Glorious diversity: Genome (in)stability and the Road Ahead

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Biovision 2016

Outline

1- Overview of what we study in the lab

2- Brief examples from ongoing research

3- The future of Medicine: make it more precise

- Understand more about genetic differences
- Improve delivery (Gene Therapy)

4- The big picture

We are here because NOTHING is stable if you give it enough time

2015 NOBEL PRIZE IN CHEMISTRY

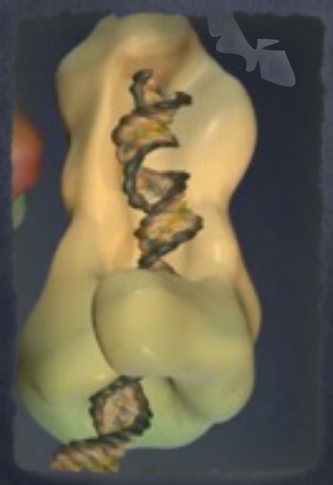
Tomas Lindahl

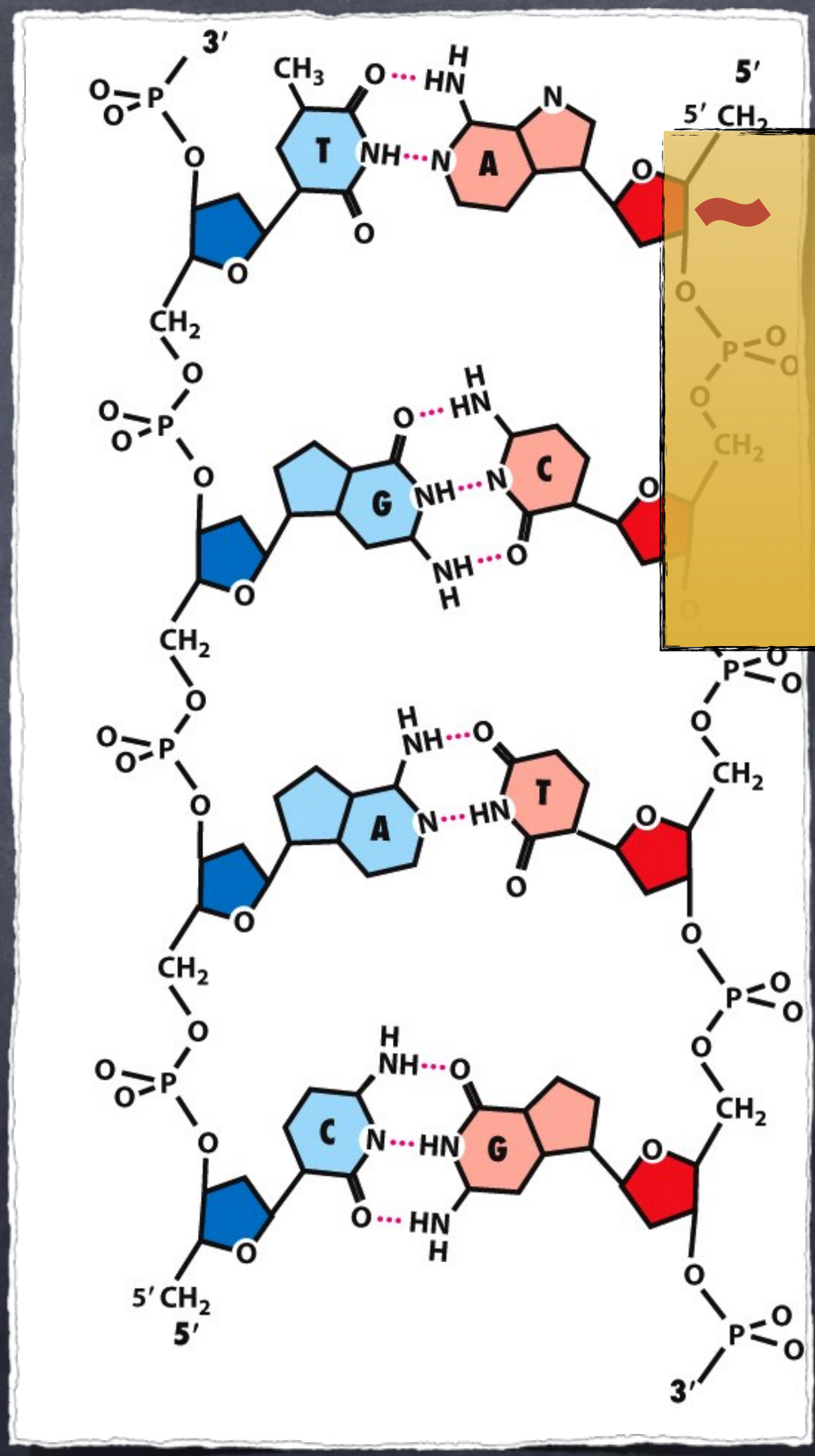
Nobelprize.org
The Official Web Site of the Nobel Prize

"DNA decays at a rate that ought to have made the development of life on Earth impossible" Lindhal, Nature 1970

O_2^-

OH^-





~ 7 lesions cell / minute

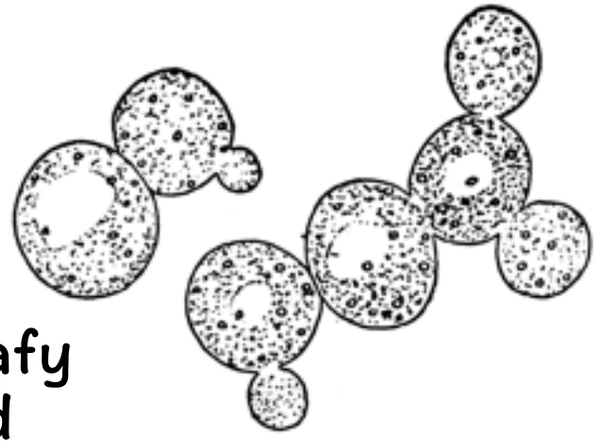
Consequences of Genome stability

Cell death

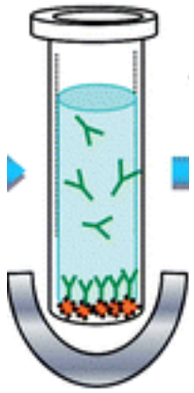
Degenerative Disease & Ageing

Cell survival

Cancer



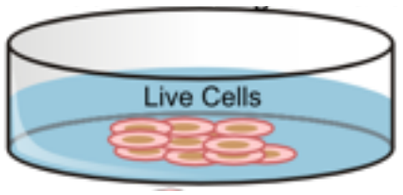
Menna El-Serafy
Ahmed Awad



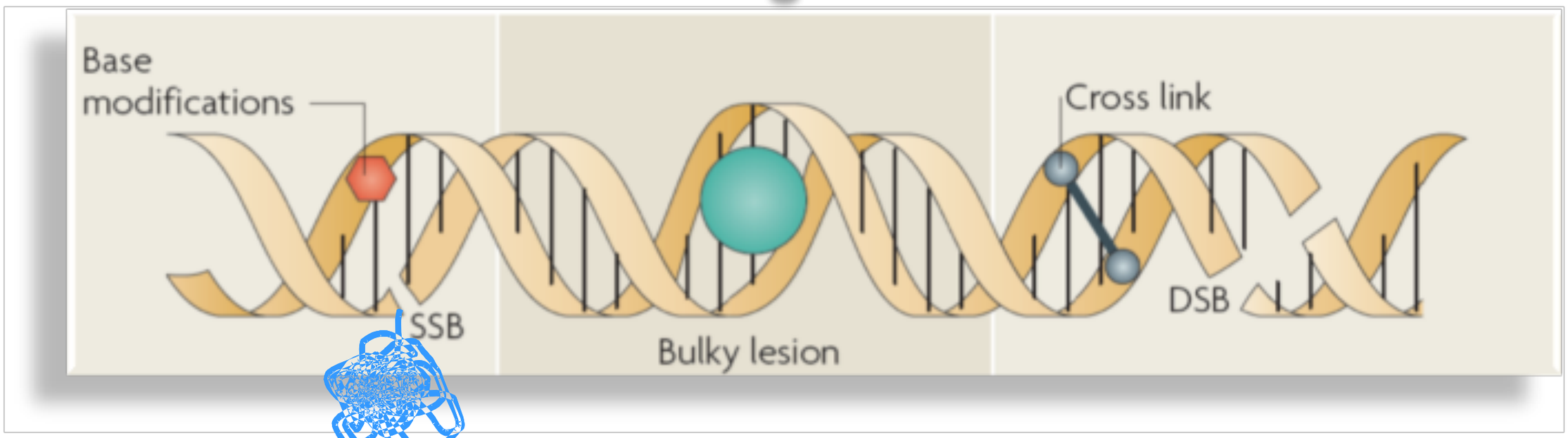
Reham Atteya
Mohamed Farah

Tools

Mohamed Ashour
Walaa Ramadan
Waheba El-Sayed
Lamia El-Shafei

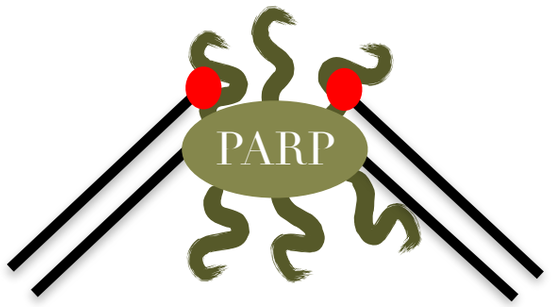


Freek Van Eeden

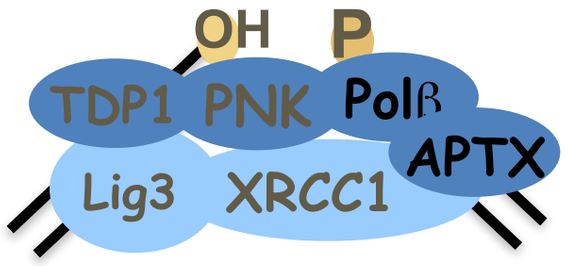

Base
modifications
Cross link
SSB
Bulky lesion
DSB

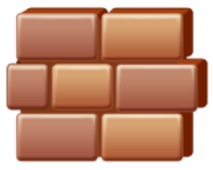
DNA Repair

Damage Detection

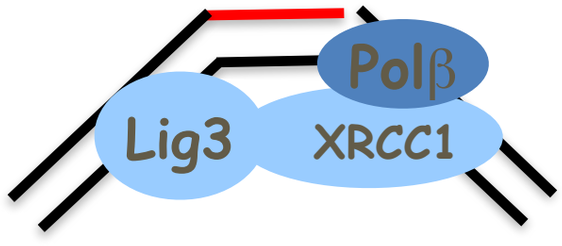


End Processing

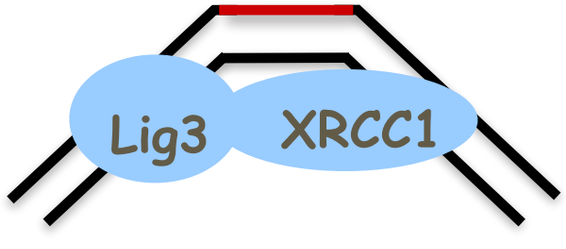


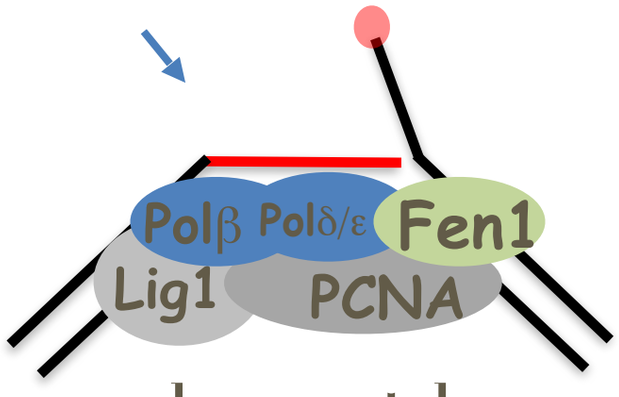


Gap Filling

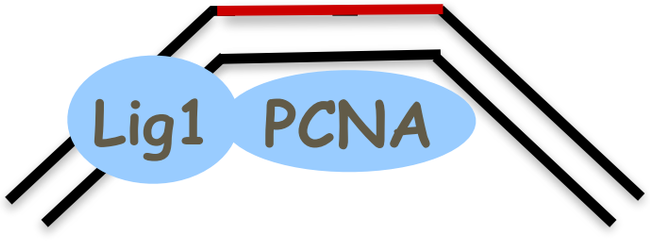


Short-patch



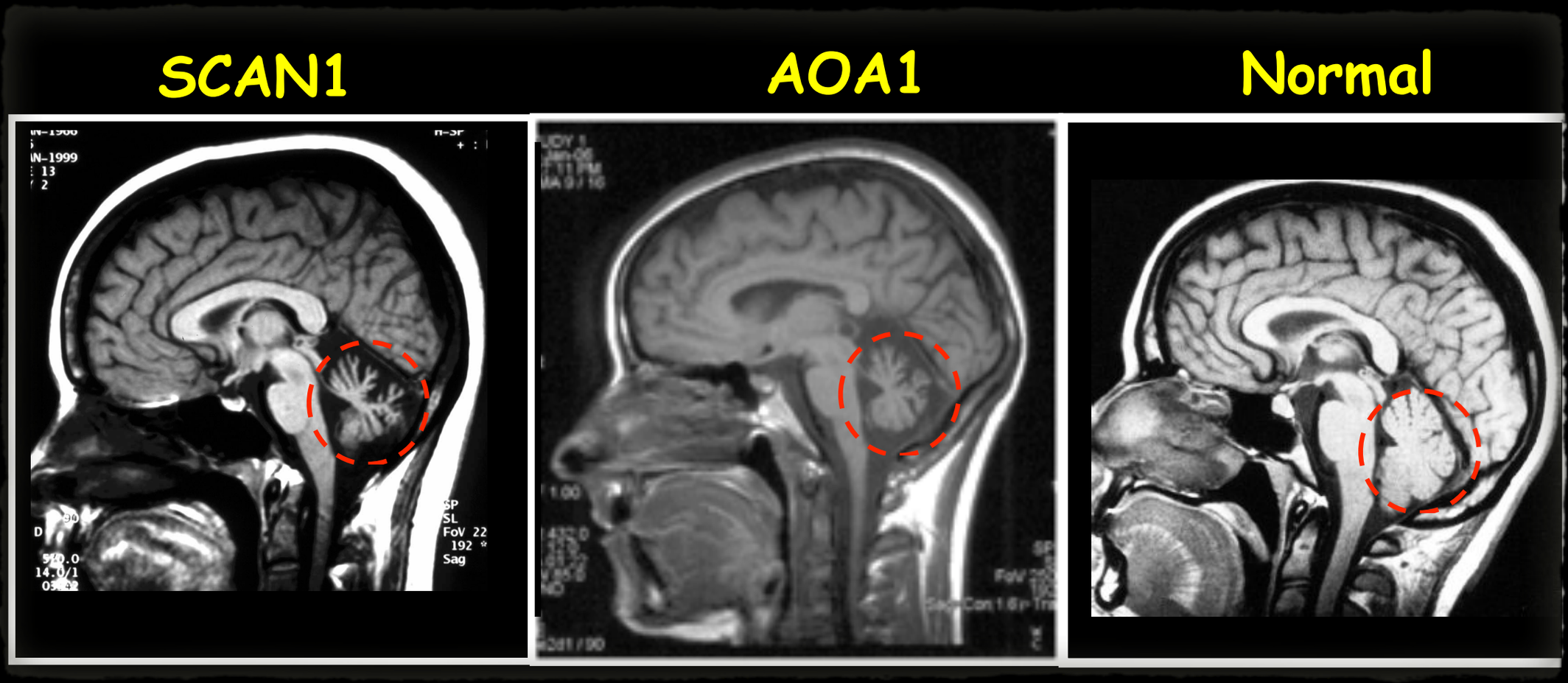


long-patch



Ligation

Spinocerebellar Ataxia with Axonal Neuropathy-1 (SCAN1)



pathology largely restricted to nervous system (no predisposition to cancer)

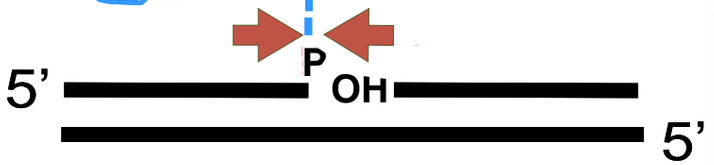
variable onset (~15 yrs)

cerebellar degeneration

spinocerebellar ataxia

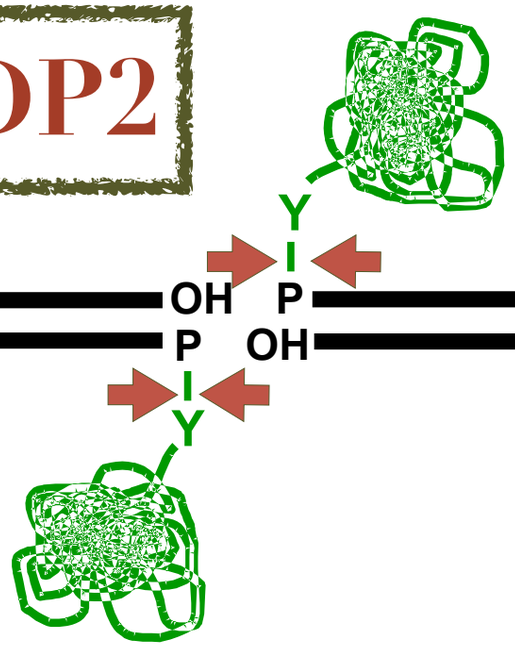
Top1

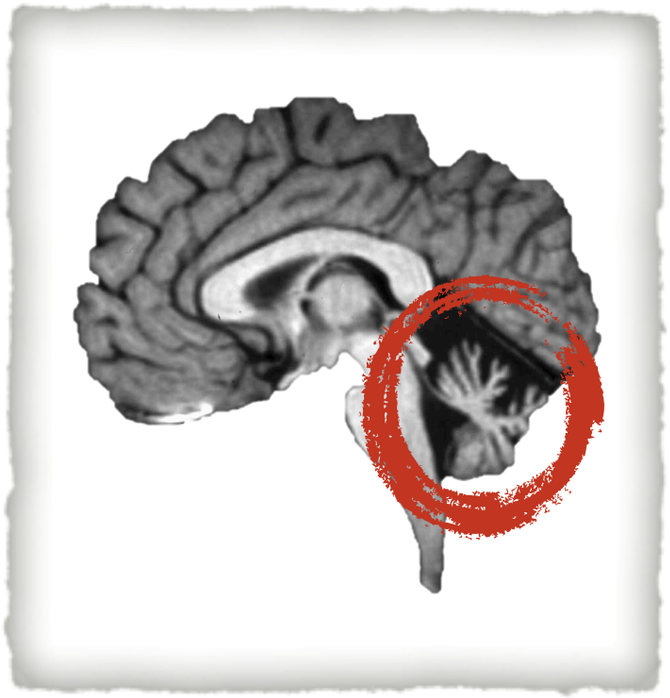
TDP1

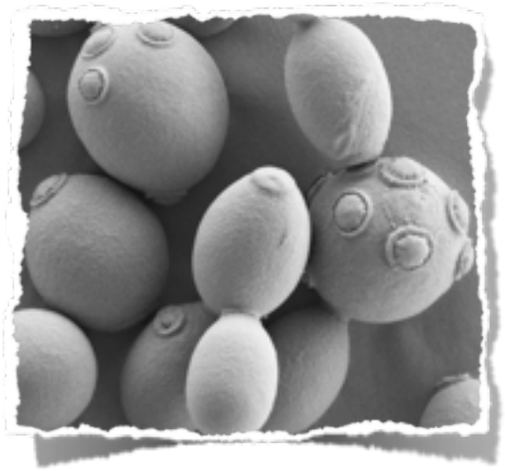


TDP2

Top2







Ledesma & El-Khamisy et al.

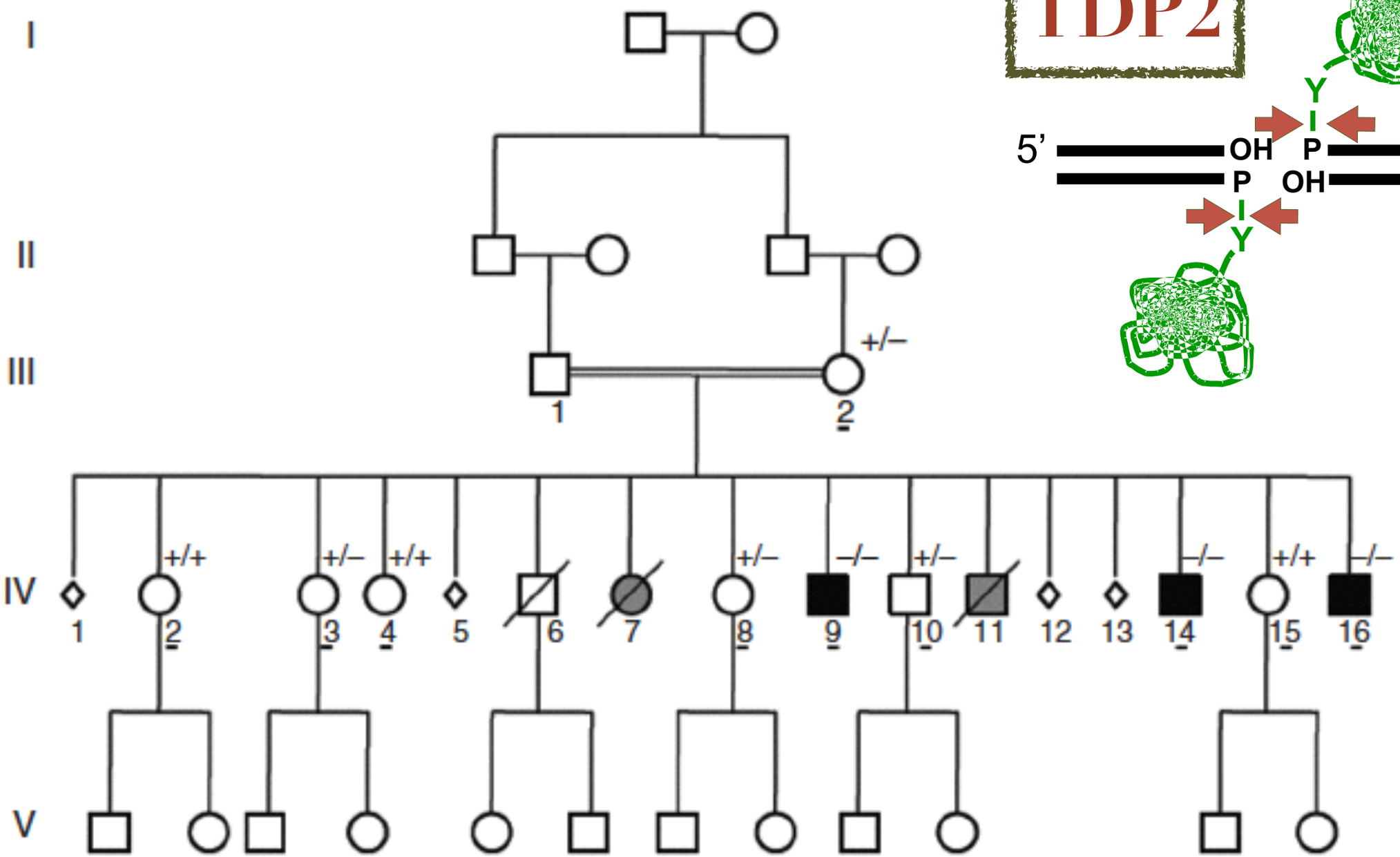
***Nature* 2009**

El-Khamisy et al., *Nature* 2005

Ahel & El-Khamisy et al., *Nature* 2007

El-Khamisy, *EMBO Mol Med* 2011

PDBs arising from TDP2 defect also cause neurodegeration



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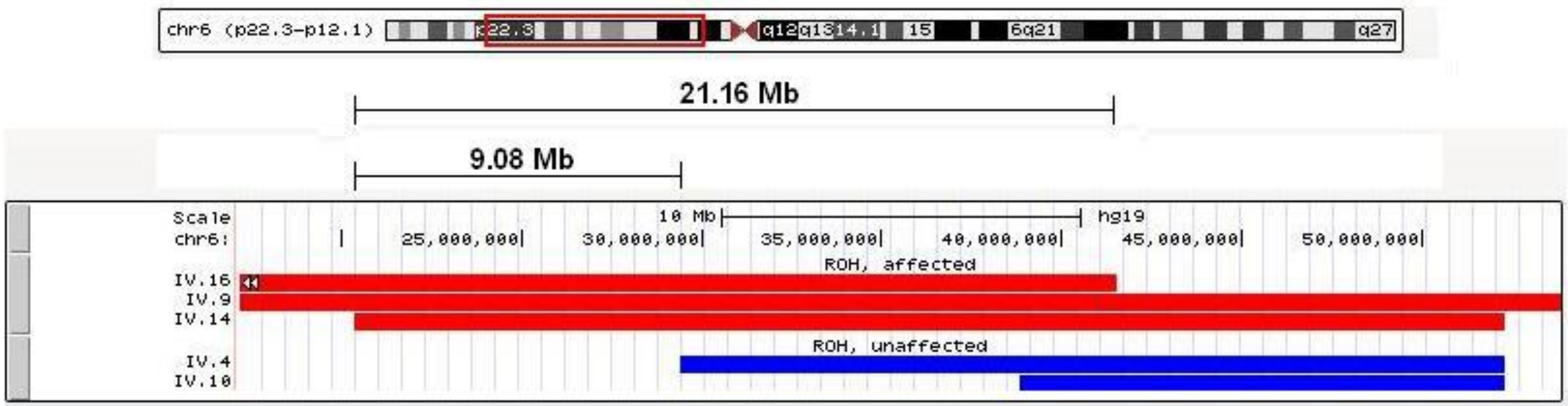
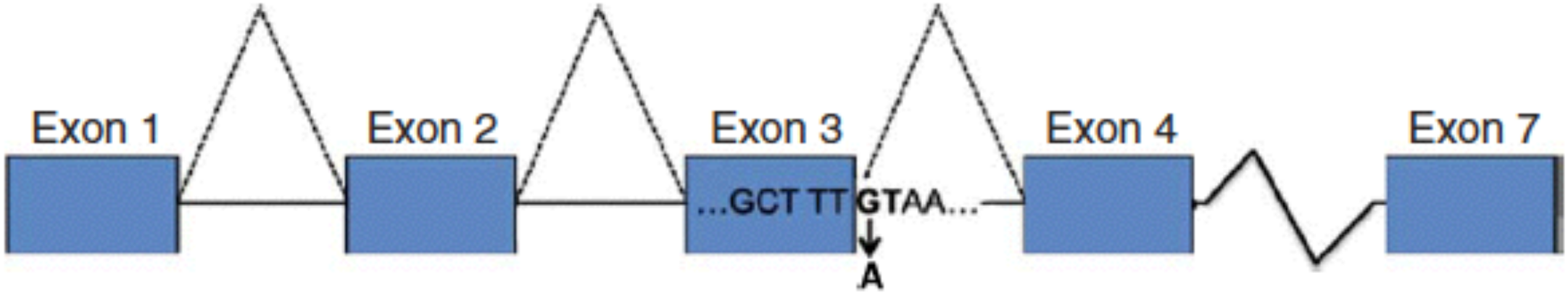
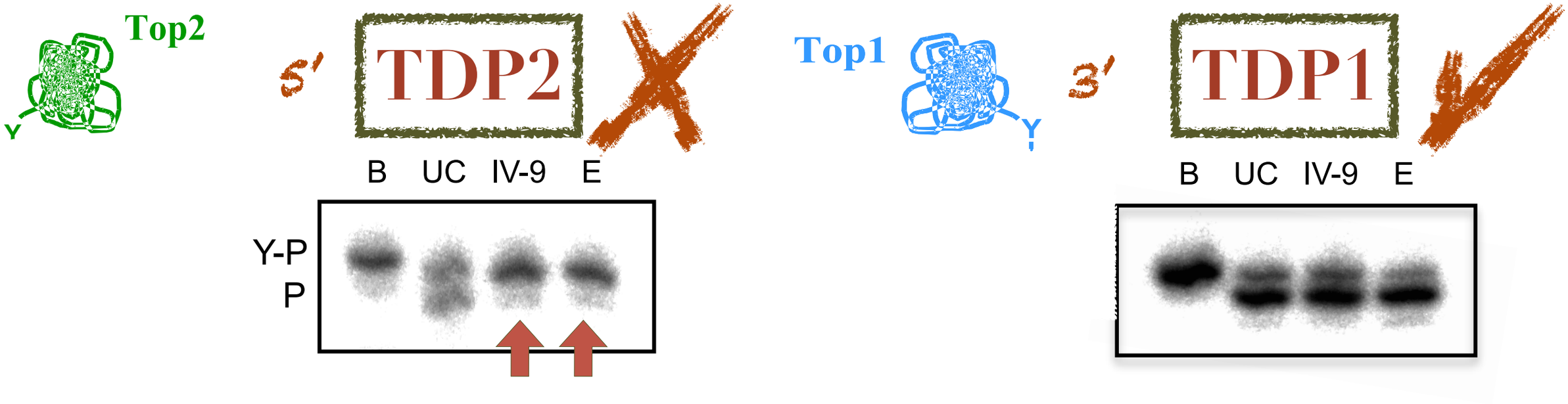
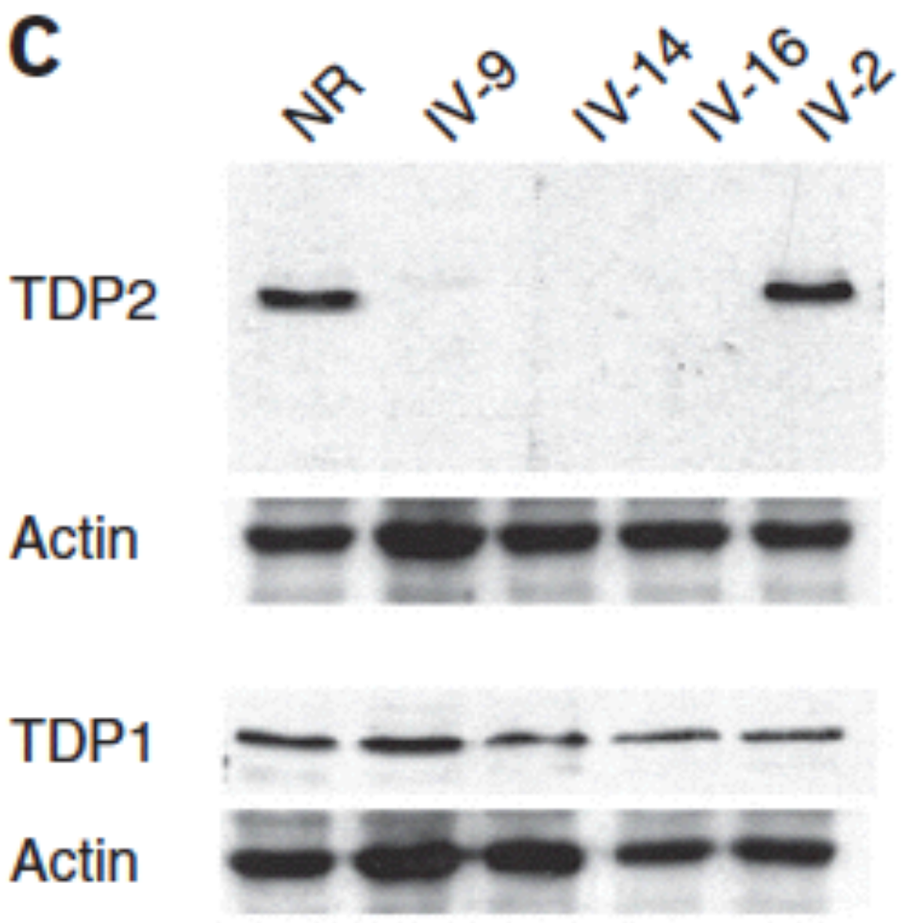


TDP2

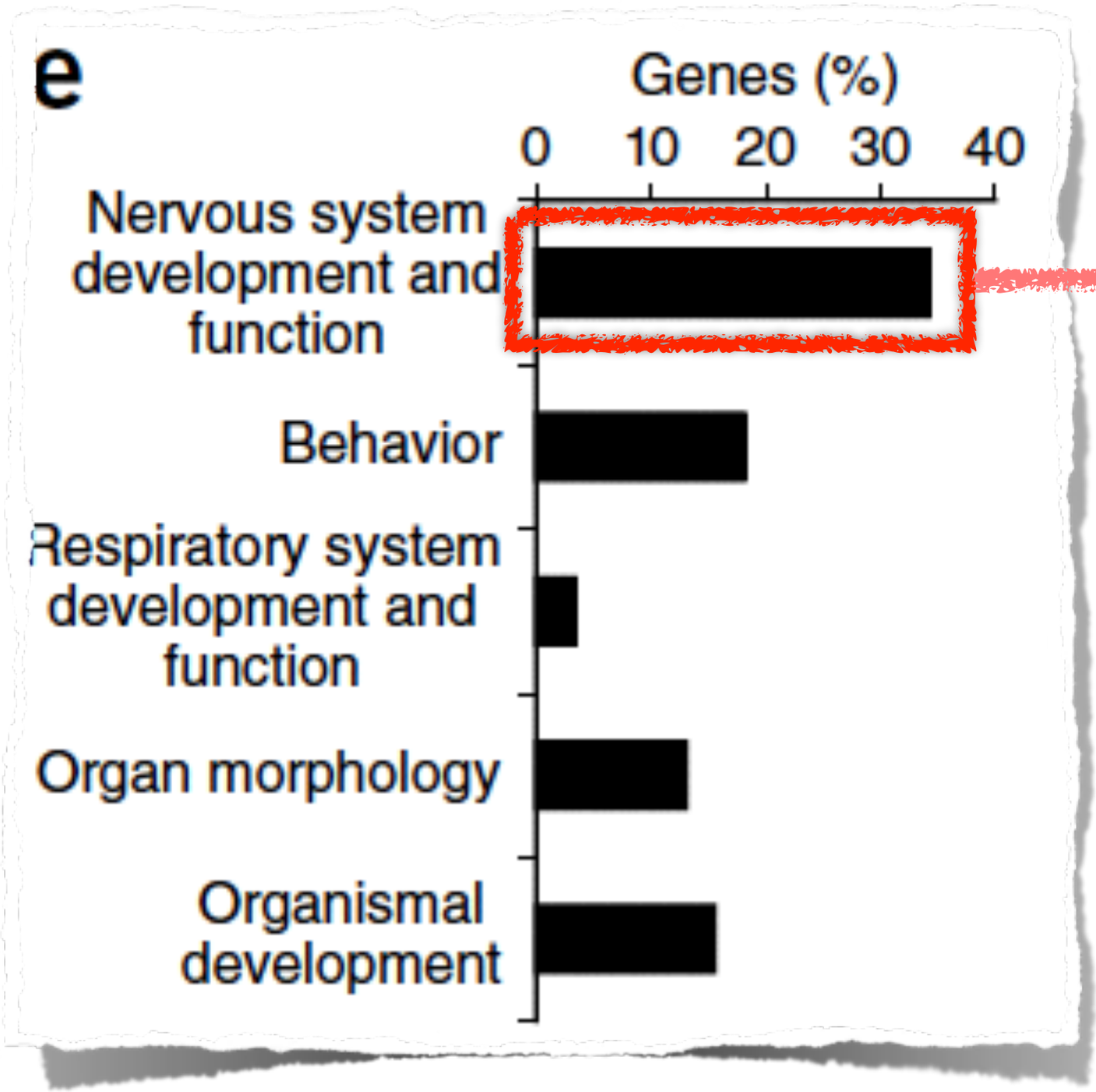


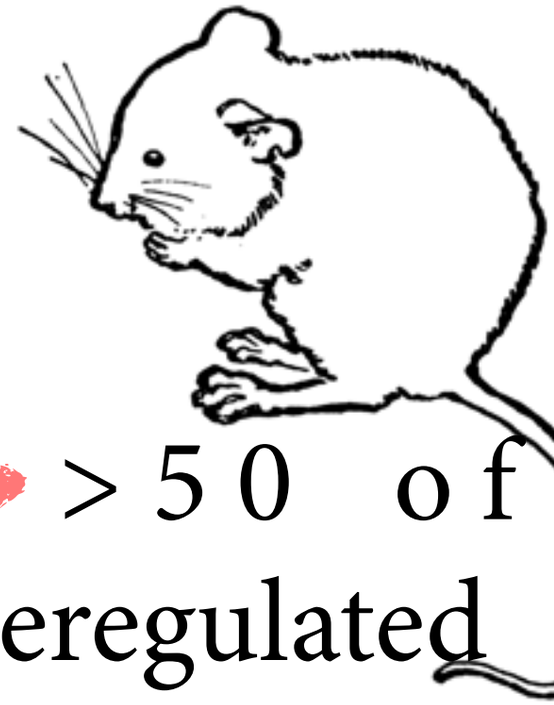
Absence of TDP2 activity in Irish and Egyptian patients harbouring homozyous truncation mutations in TDP2



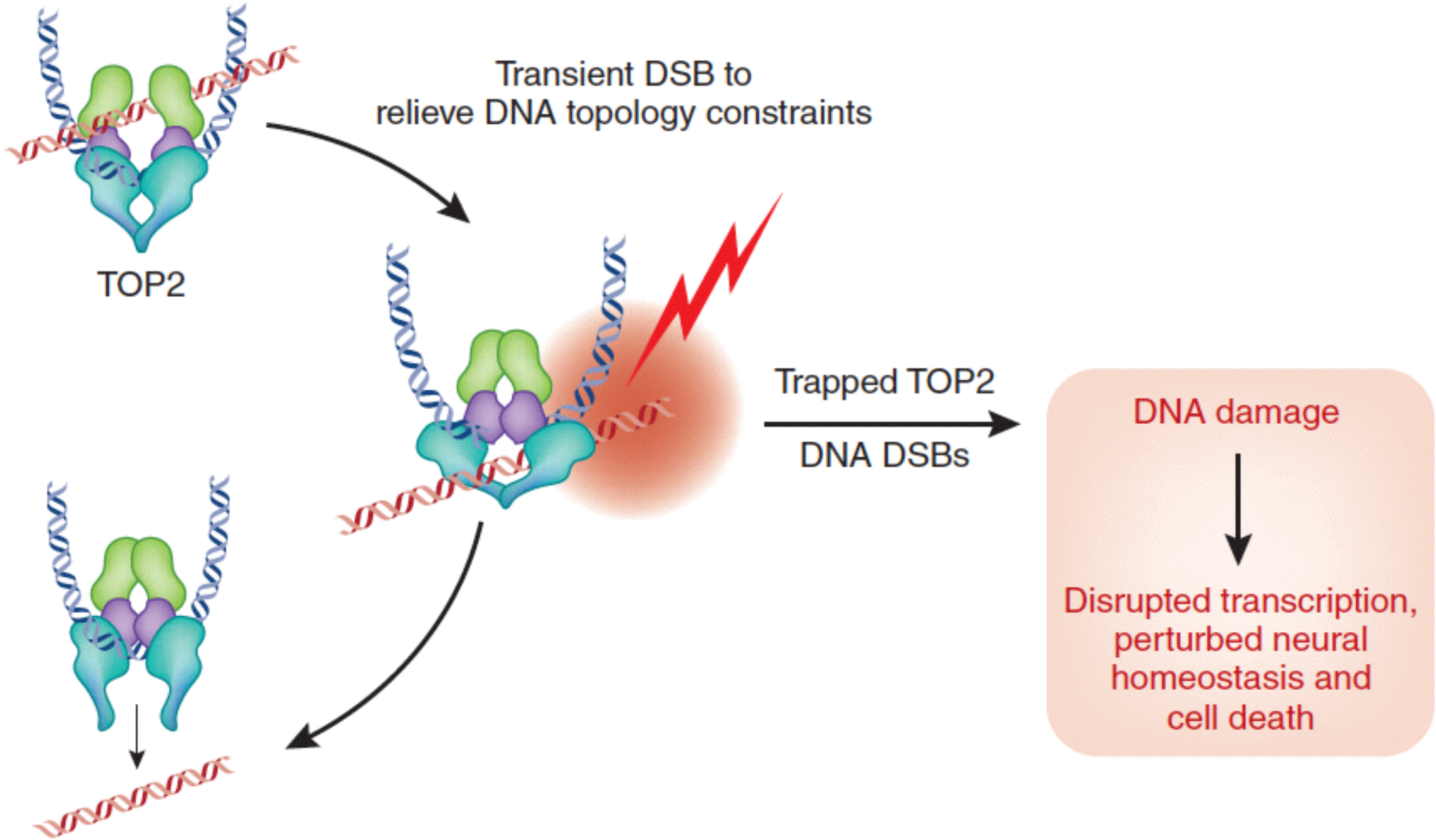


Do PDBs arising from TDP2 defect also cause neurodegeration ?



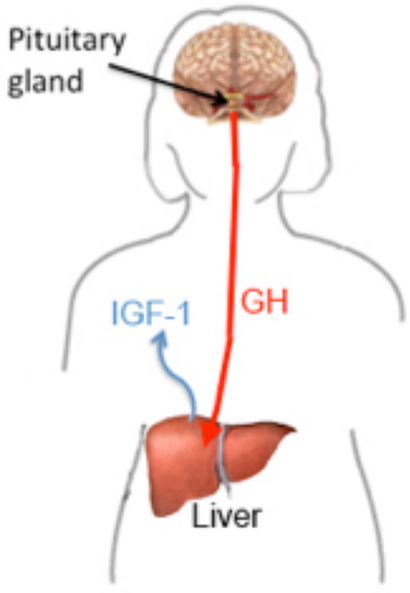


> 50 of the deregulated genes are associated with neurological disease in humans



Gómez-Herreros, …..El-Khamisy, Nature Gent 2014

Does defective PDB repair (in the nervous system) trigger hallmarks of Ageing (systemically) ?



ODBs / PDBs

Ageing

The Future of Medicine

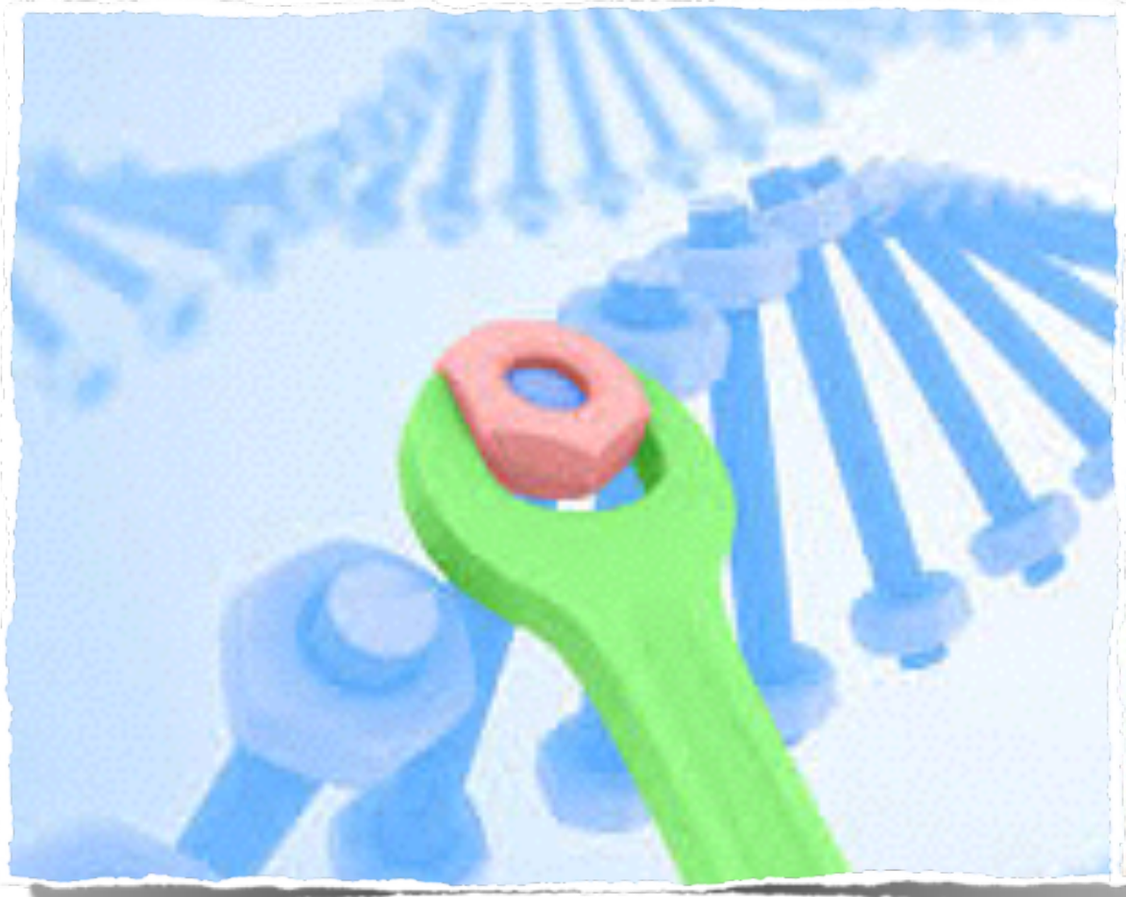
(Improve Precision)

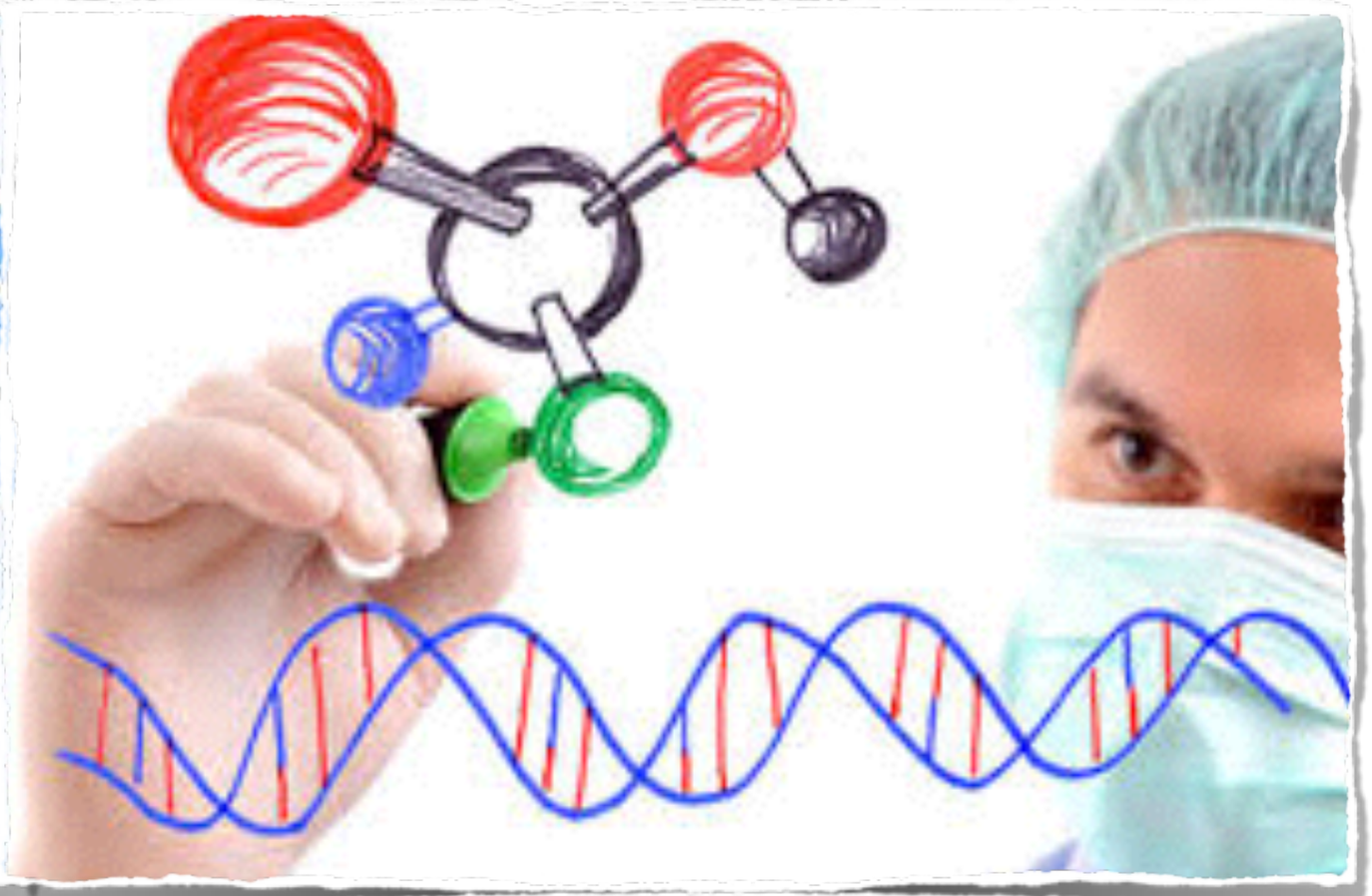
Utilise differences

- Genetic
- Epigenetic

Improve delivery

- Gene Therapy
- Nanoformulations





Genetic

Pharmacologic

New tools for genome editing

Clustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats
(CRISPR)

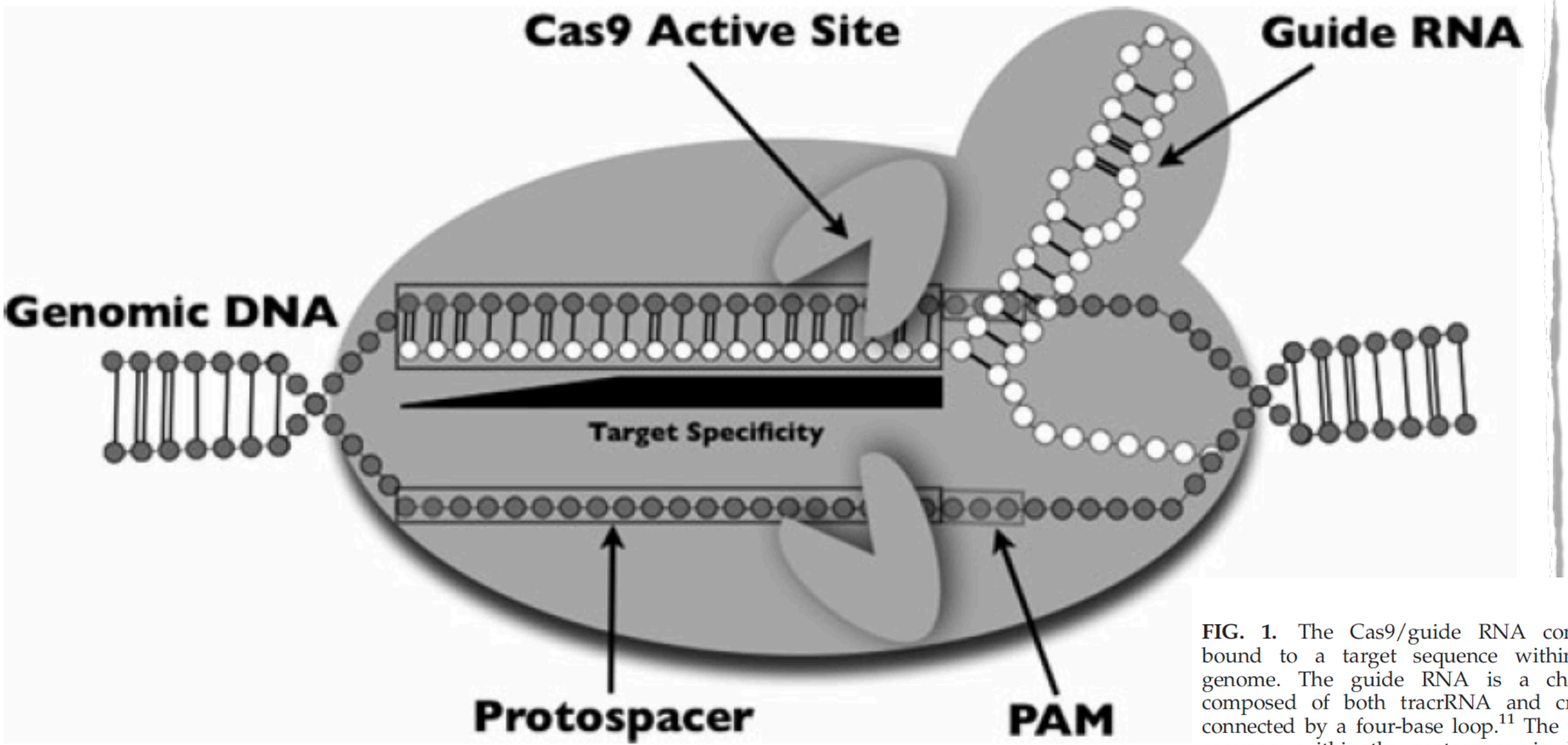
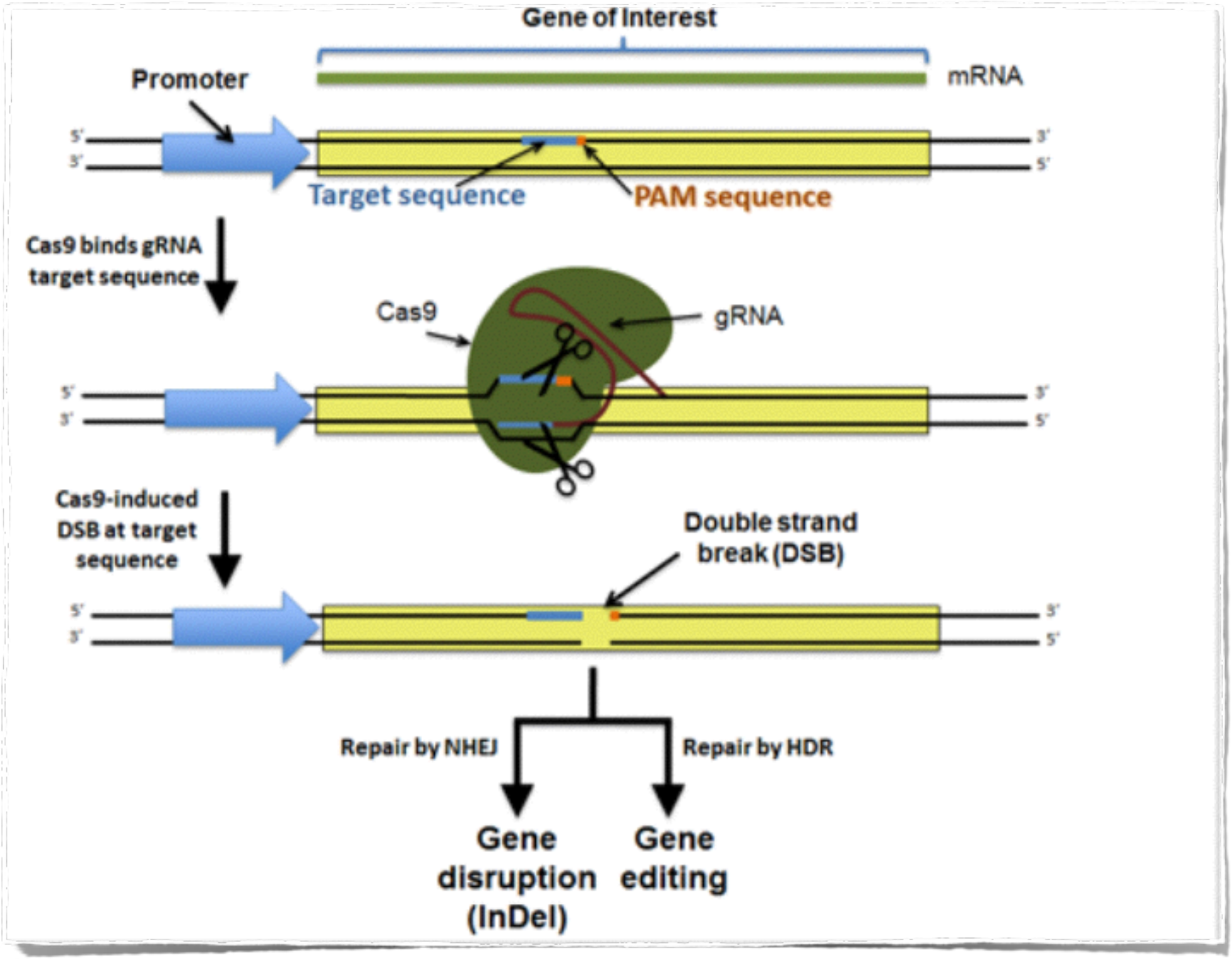


FIG. 1. The Cas9/guide RNA complex bound to a target sequence within the genome. The guide RNA is a chimera composed of both tracrRNA and crRNA connected by a four-base loop.[11] The target sequence within the protospacer is shown base-paired with the guide RNA. The Cas9 endonuclease active sites cut between 3 and 7 bases upstream of the PAM (protospacer adjacent motif) on both strands.[11] The first 8—12 bases directly upstream of the RAM seem to be essential for Cas9 cleavage.[13] The importance of the remaining 8–12 bases is unclear.[13]

New tools for genome editing

Clustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats (CRISPR)



Consequences of Genome (in)stability

Cell death **Cell survival**

Cancer

Ashour, Atteya, and El-Khamisy, Nature Rev Cancer 2015

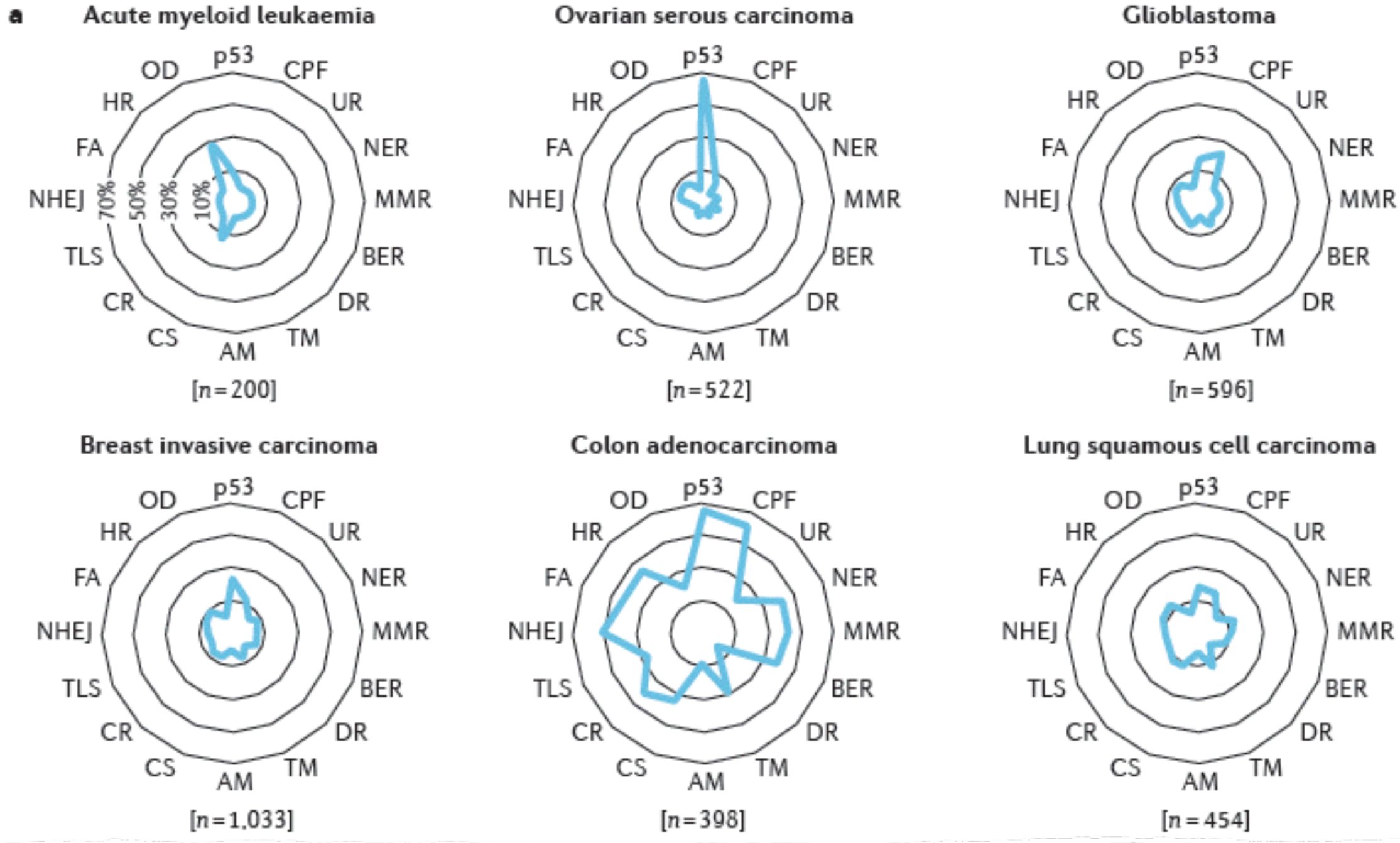
Chemotherapy and radiotherapy

Damage the genome

Synthetic Lethality

"The exploitation of genetic defects essential for tumour cell survival by combining the defect in an affected pathway with a pharmacologically induced defect in a compensatory pathway"

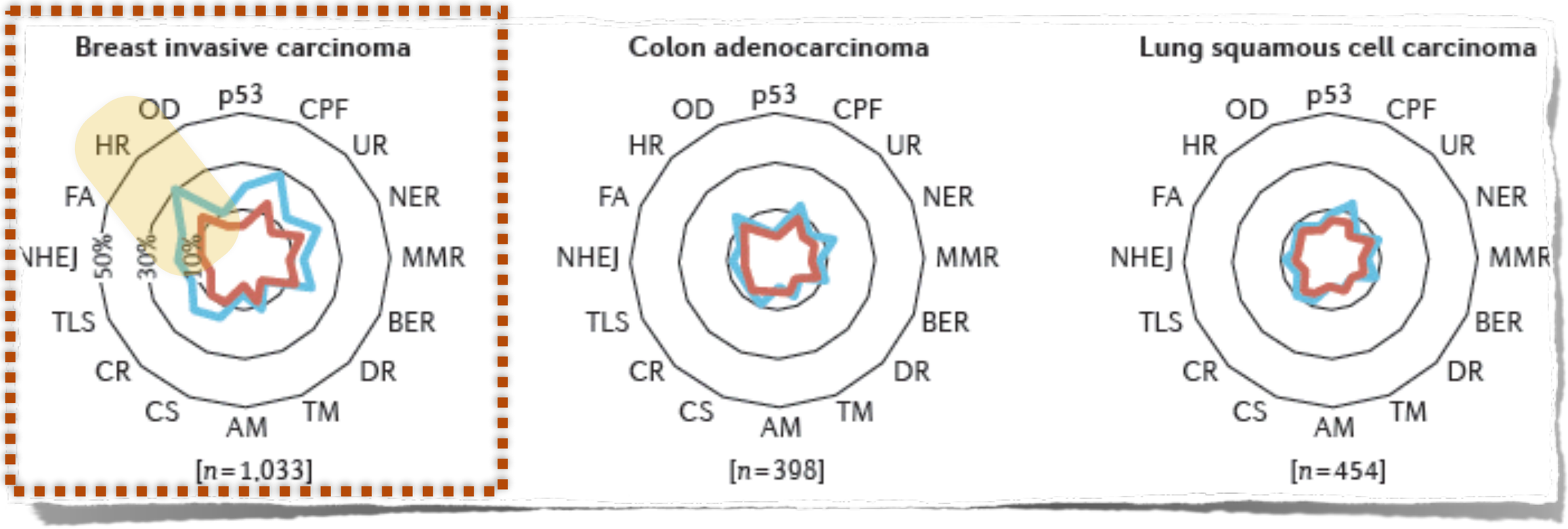
DDR Cancer Signatures



Pearl et al., Nature Rev Cancer. March 2015, doi:10.1038/nrc3891

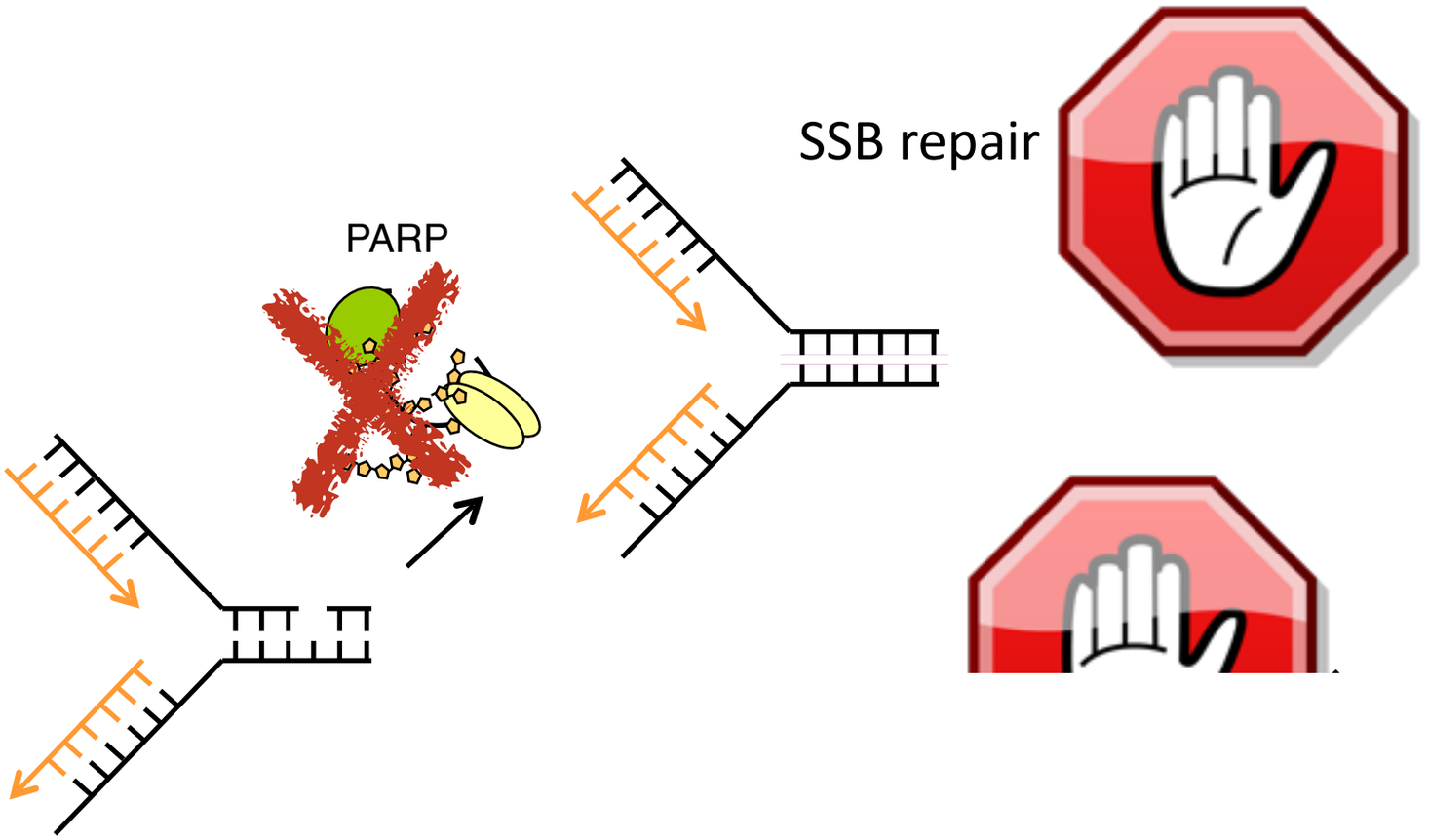
DDR Cancer Signatures

Copy Number variations (CNVs)



Pearl et al., Nature Rev Cancer. March 2015, doi:10.1038/nrc3891

Success in Personalised Therapy
Synthetic Lethality



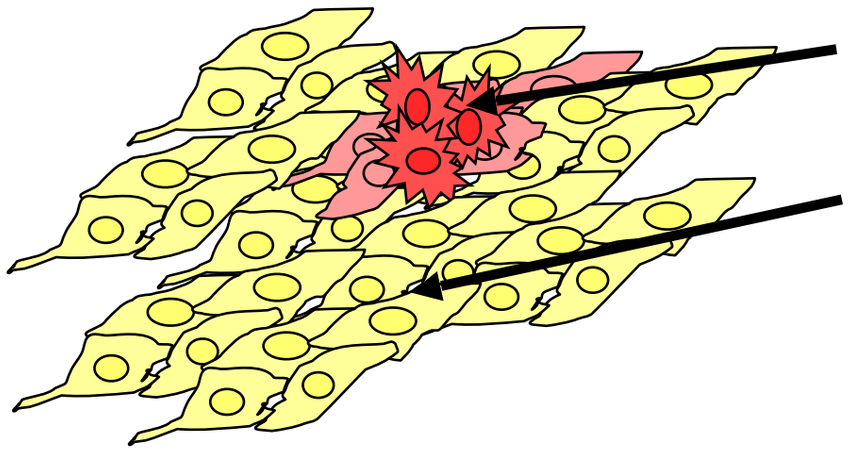
Cell Death

Pharmacologic

Genetic

In clinical use....

Highly specific
No need for other DNA damaging agents
PARP knockout mice are healthy

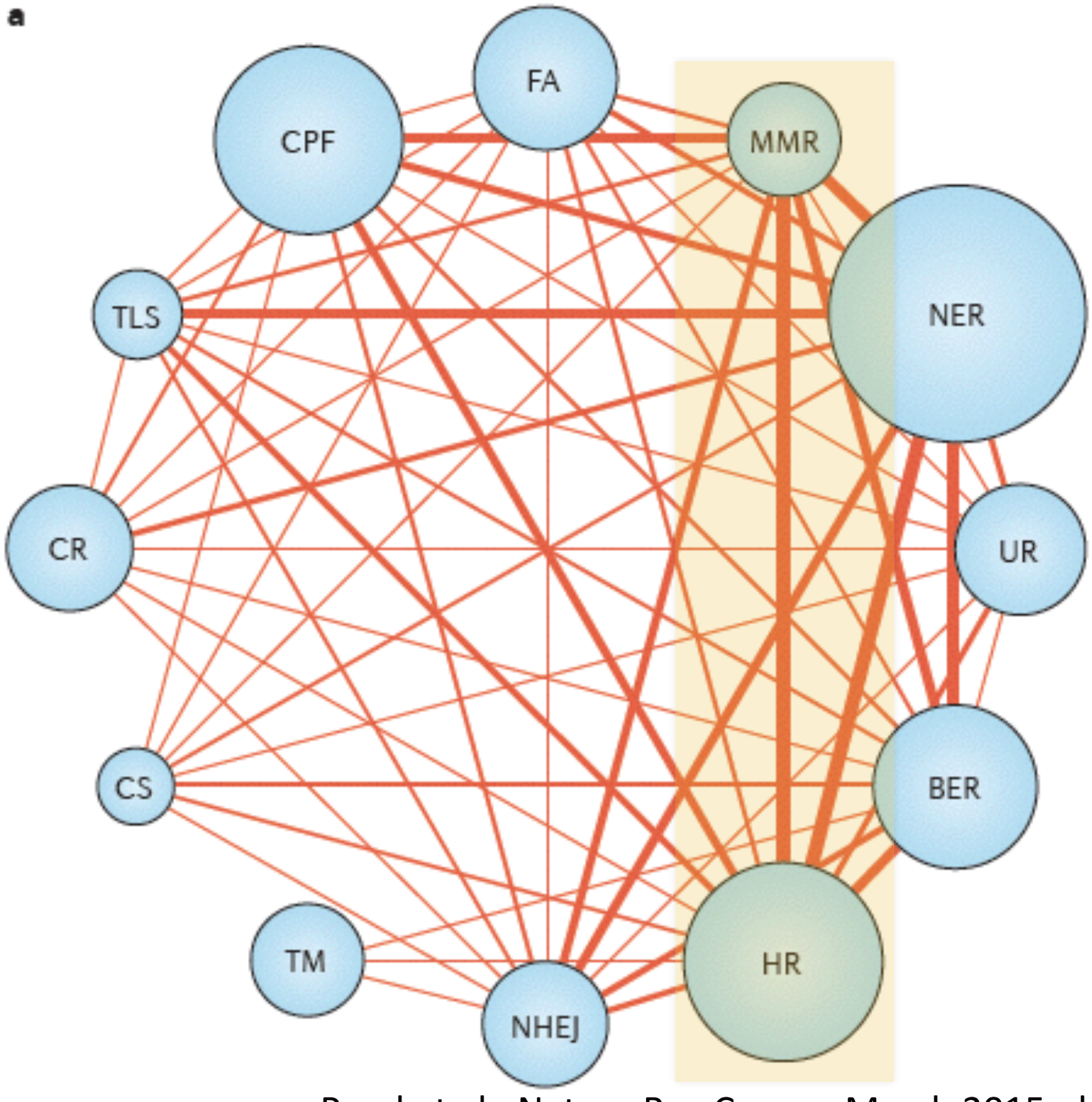


BRCA2-/- sensitive to PARP inhibitors

BRCA2+/- insensitive to PARP inhibitors

Olaparib (AZD-2281) has been approved by the FDA in Dec 2014

The Road Ahead >>>> The Future for S.L.



Pearl et al., Nature Rev Cancer. March 2015, doi:10.1038/nrc3891

Thank You !

Past Lab Members
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Cornelia Meisenberg
Meryem Alagoz
Jean Carroll
Chris Rockyard
Owen Well
Kay Osborn
Abhishek Sharma
Poorvi Patel
Limei Ju

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Simon Ward
Richard Angell

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