Cancer: from Cause to Cure

Wednesday 25th September 2013

Breast cancer genetics & Target Discovery

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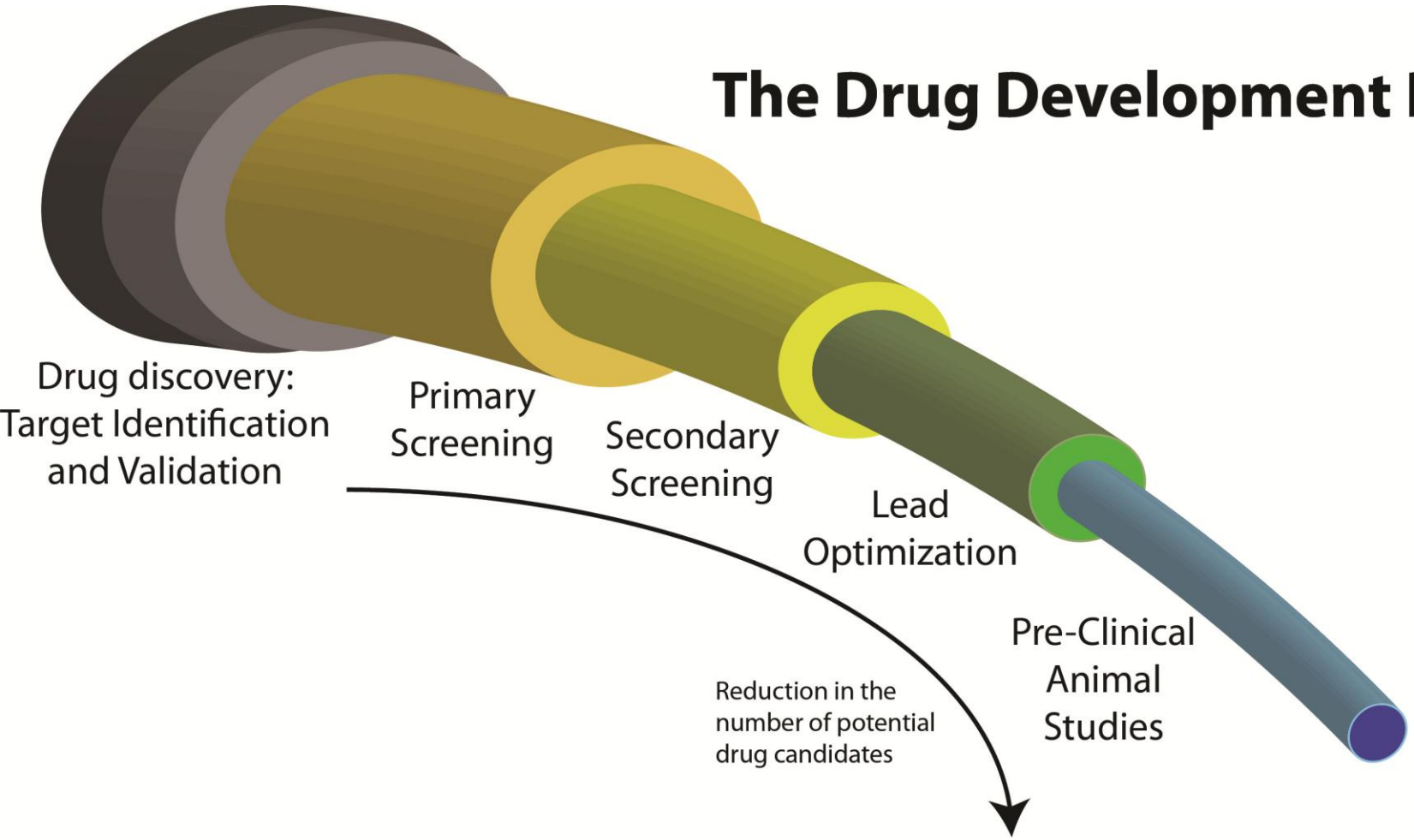
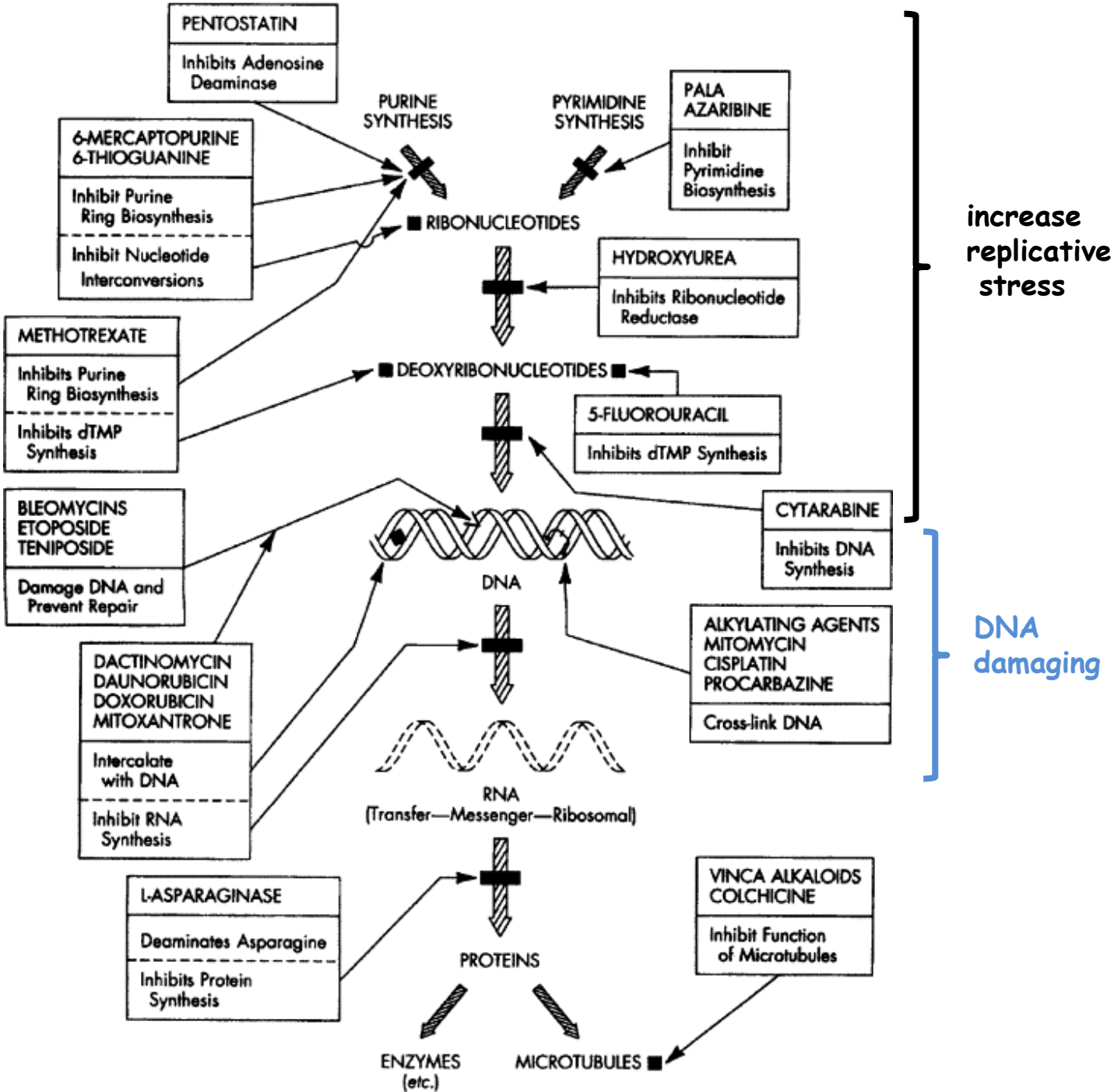
science capital

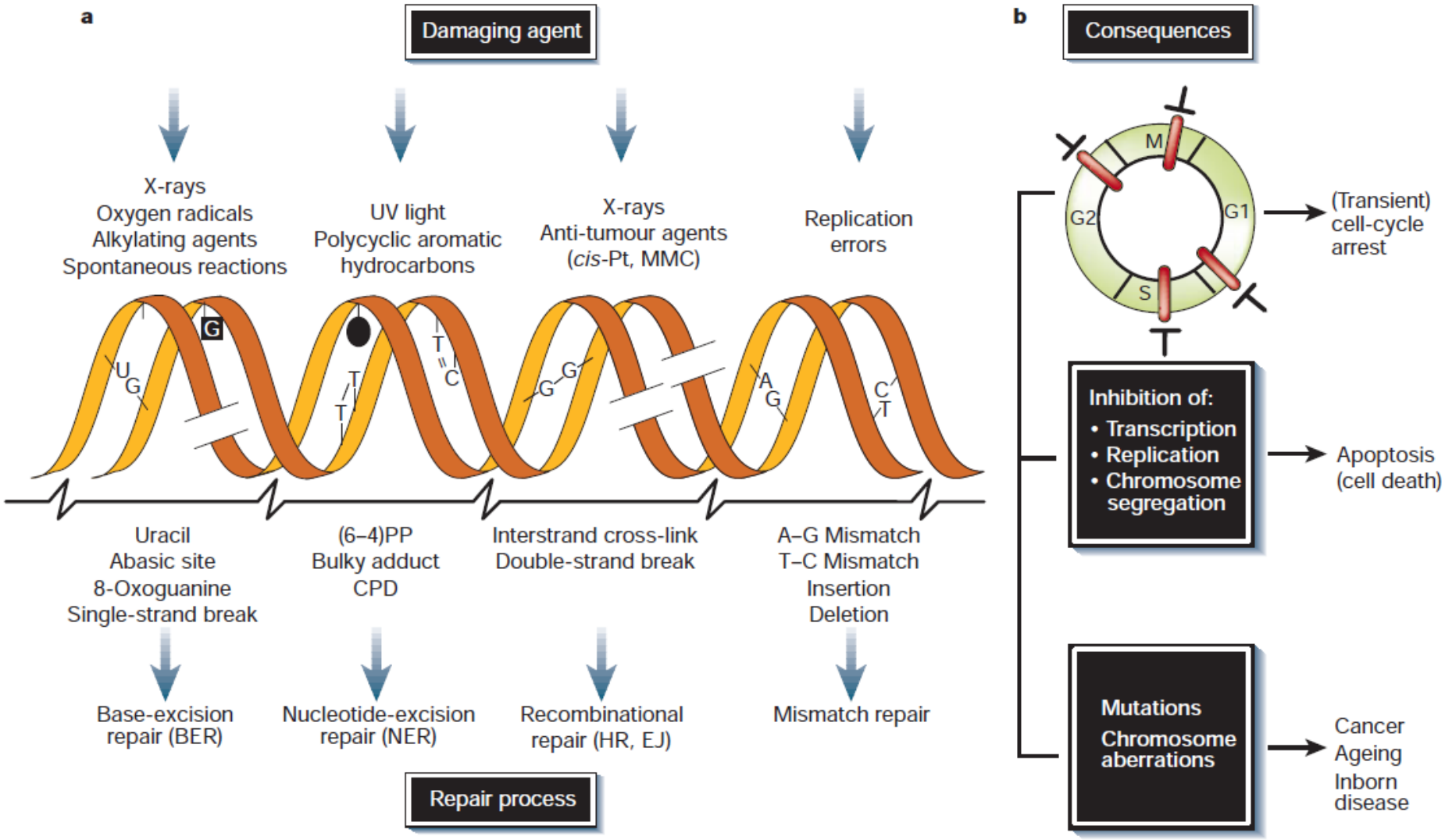
UNIVERSITY OF BIRMINGHAM


The Drug Development Pipeline
Drug discovery:
Target Identification
and Validation
Primary
Screening
Secondary
Screening
Lead
Optimization
Pre-Clinical
Animal
Studies
Reduction in the
number of potential
drug candidates

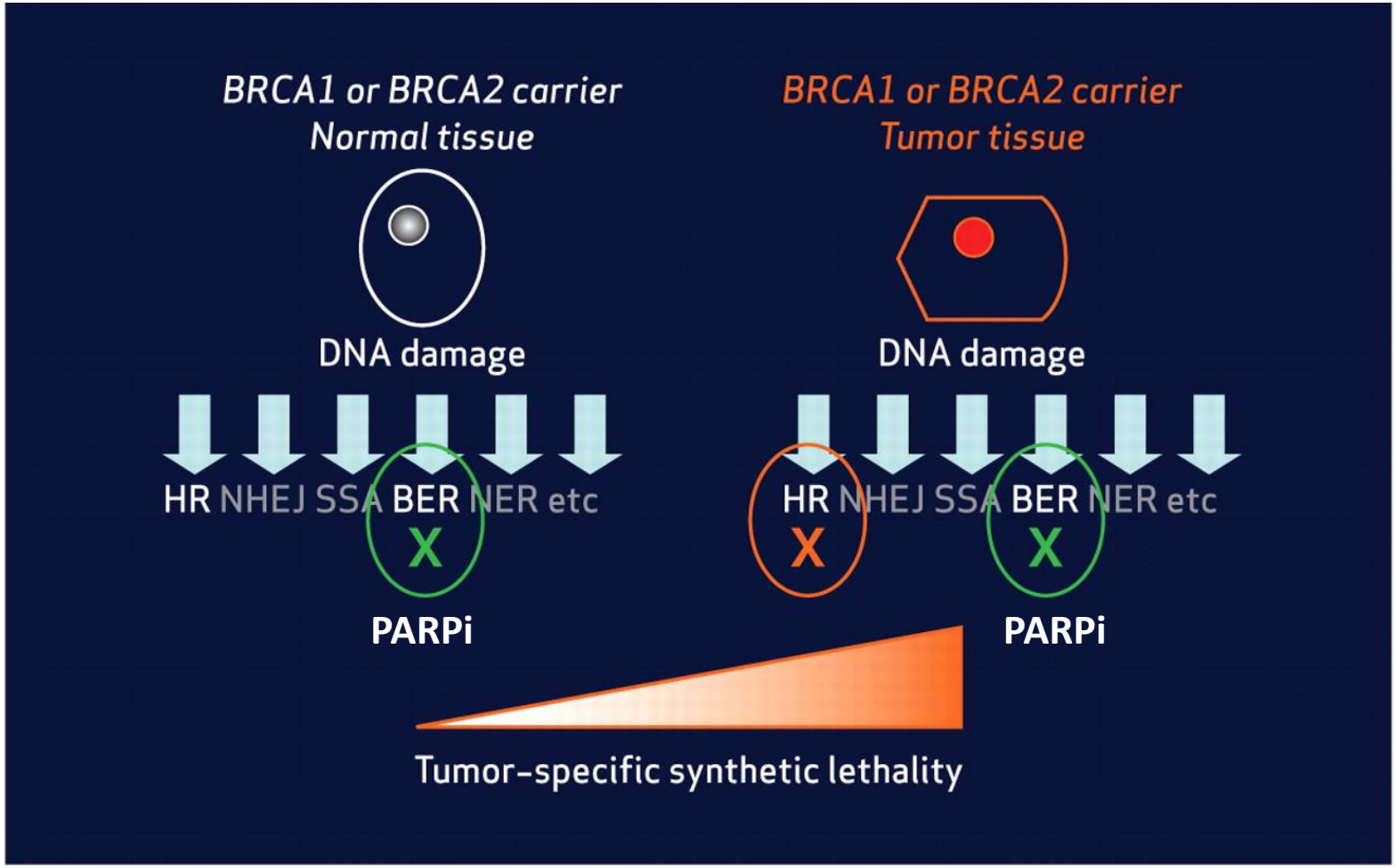
"Standard" Anticancer drugs



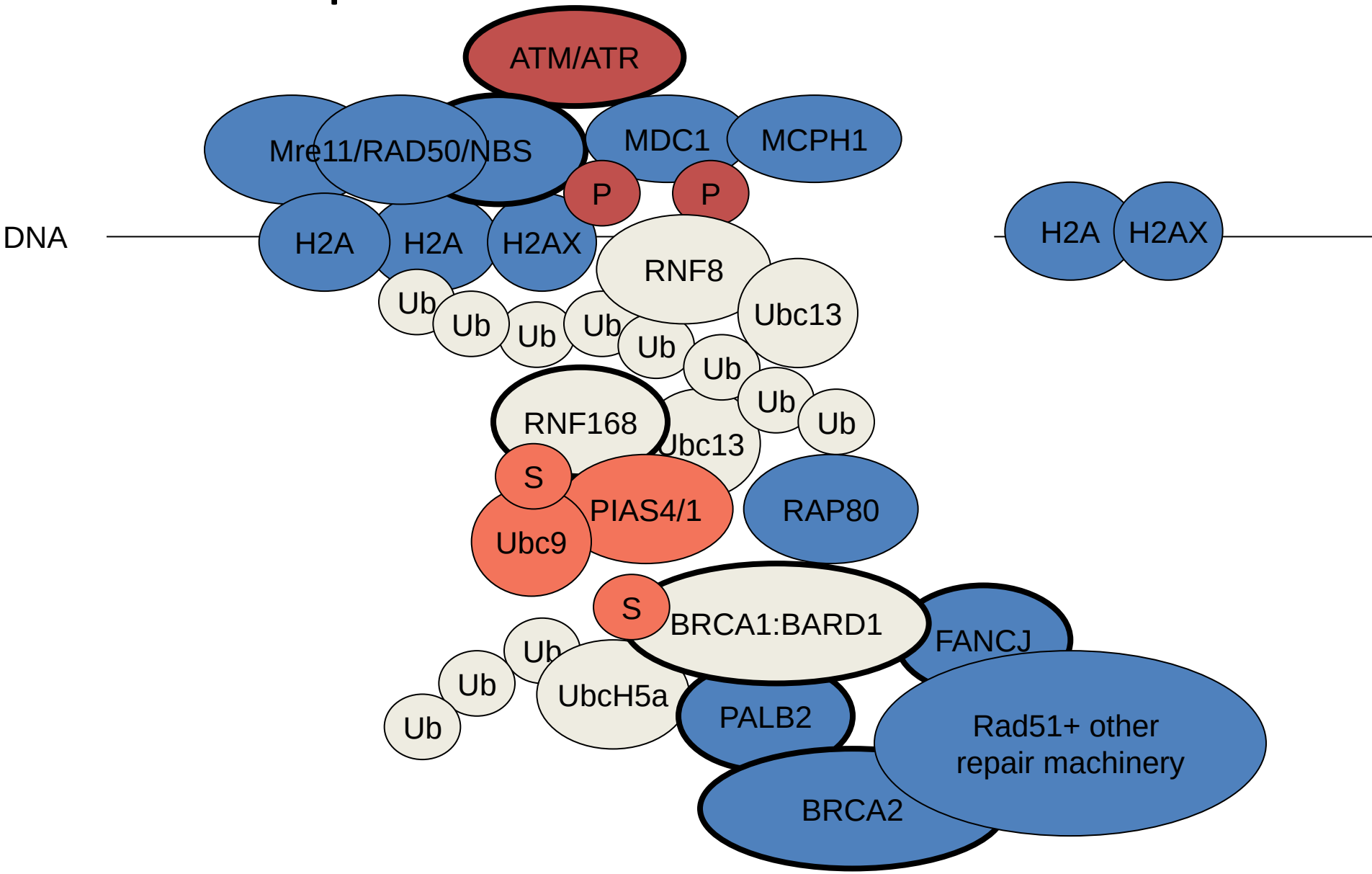
Means of DNA repair



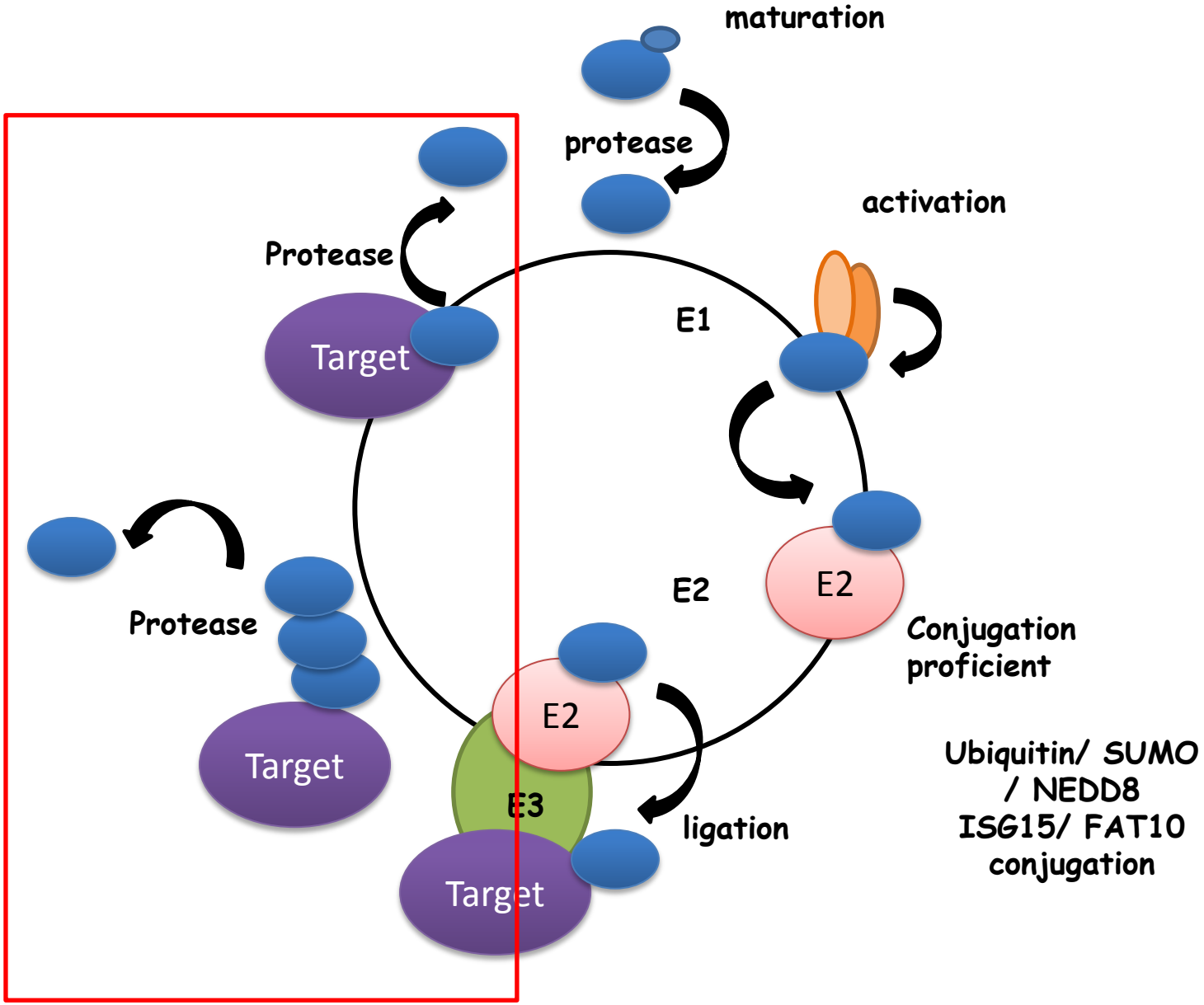
Biological proof of principle



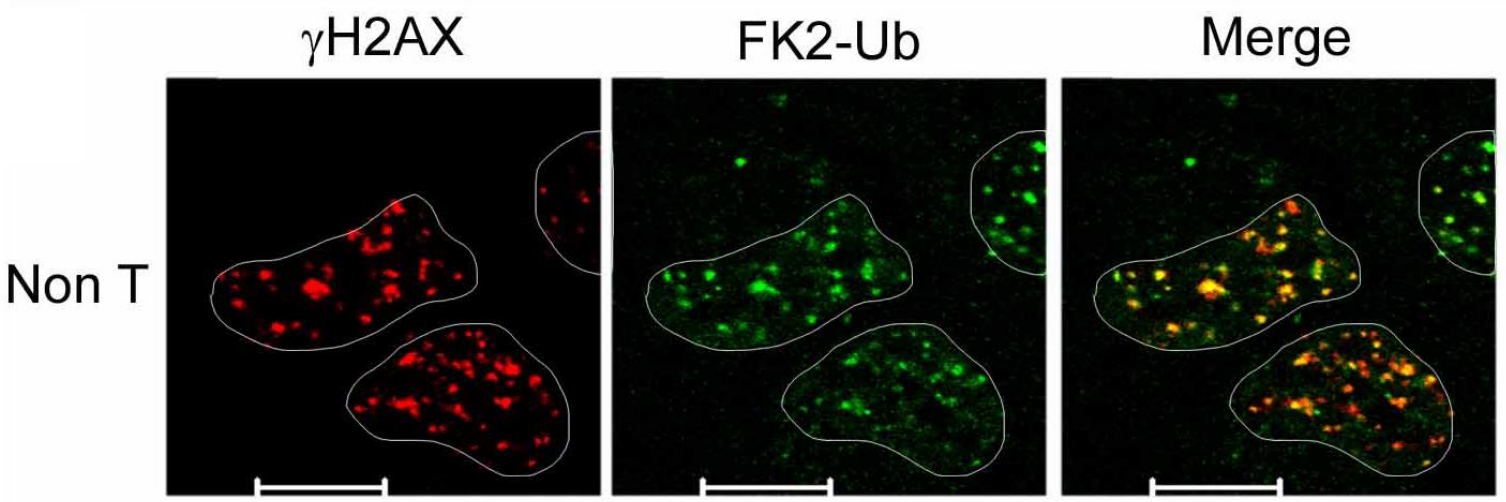
PTMs in response to DSBs

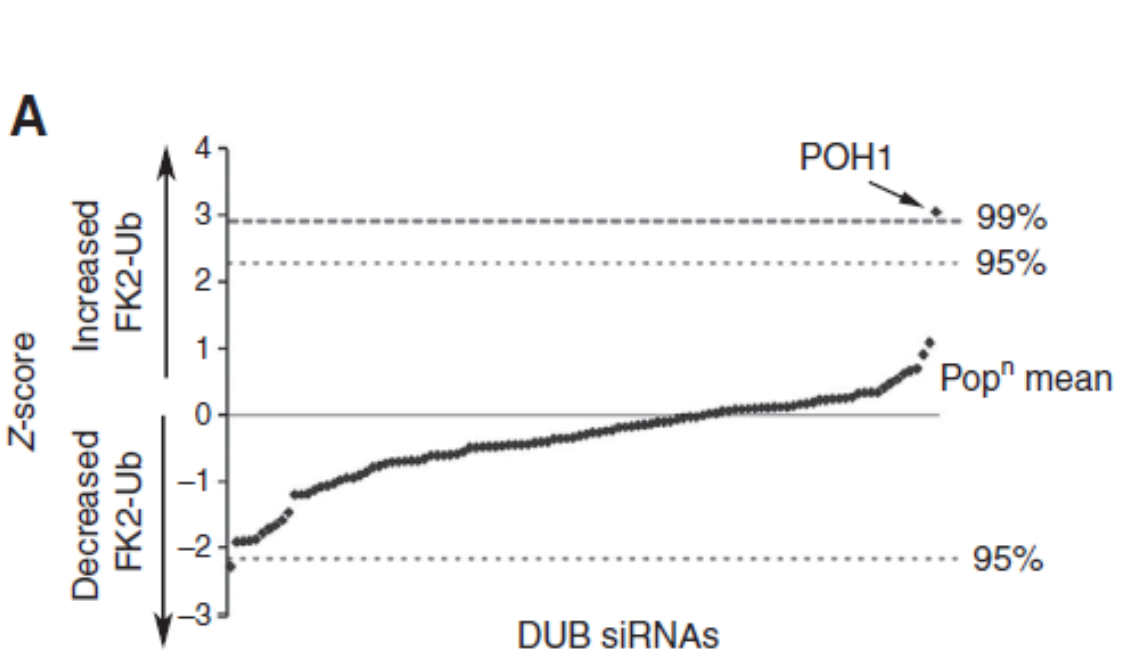


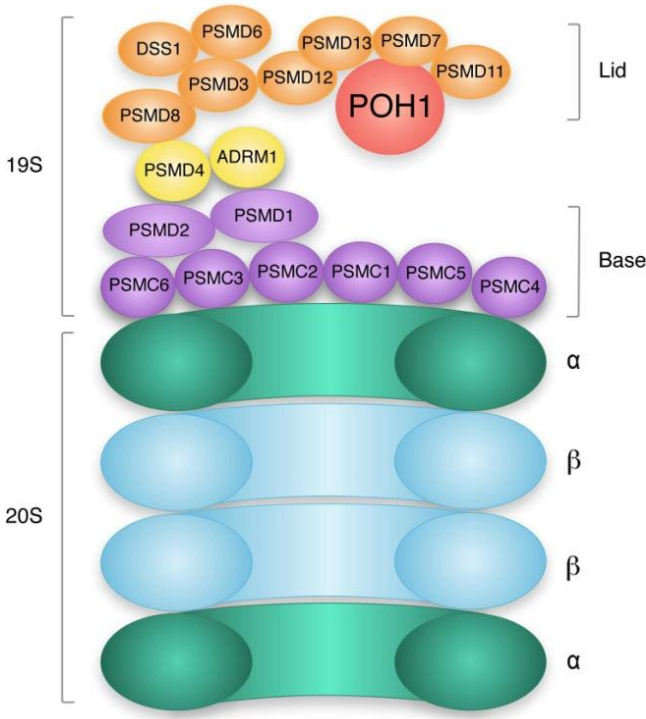
Protein modifiers



De-Ubiquitinating Enzymes as targets or bio-markers







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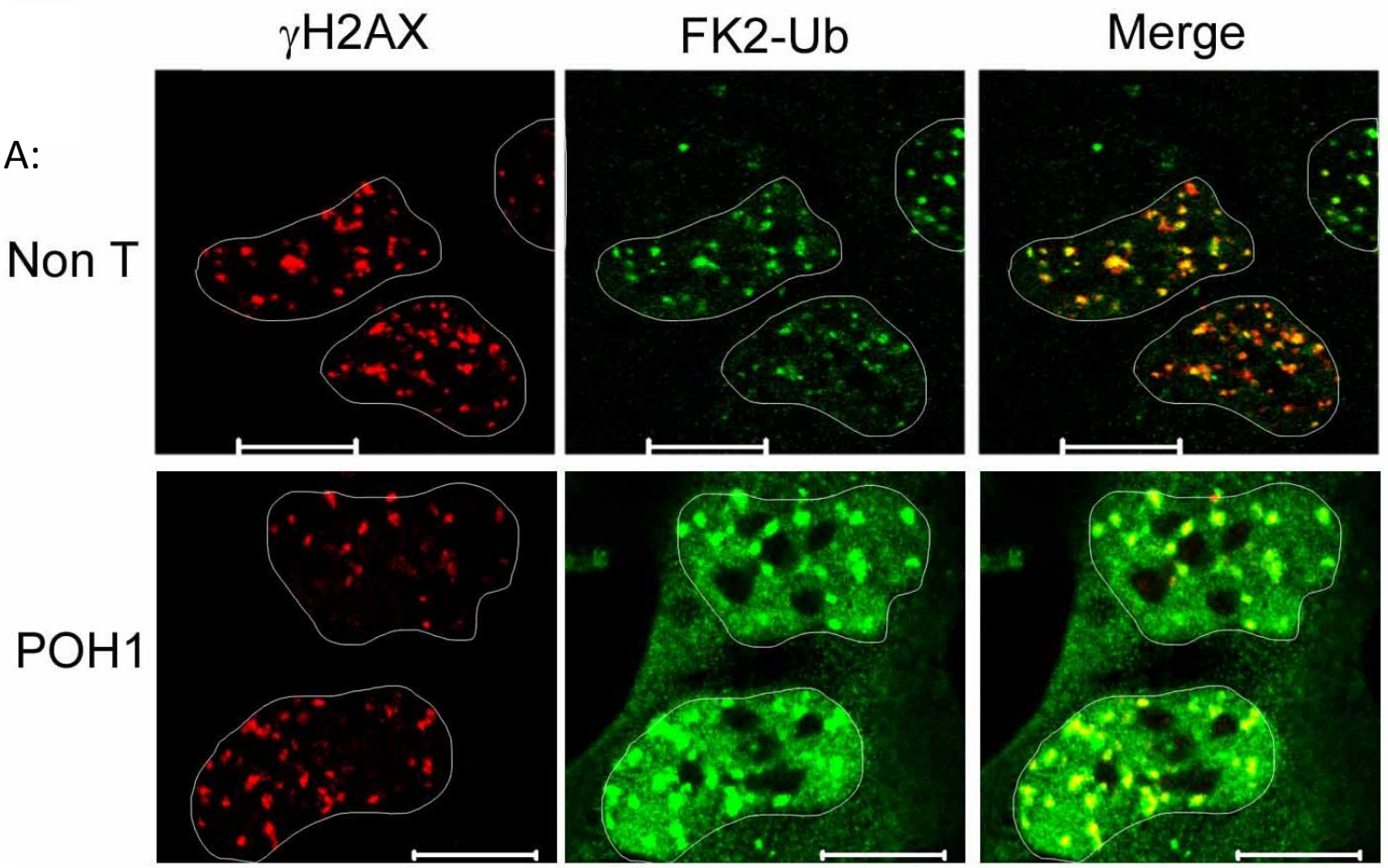

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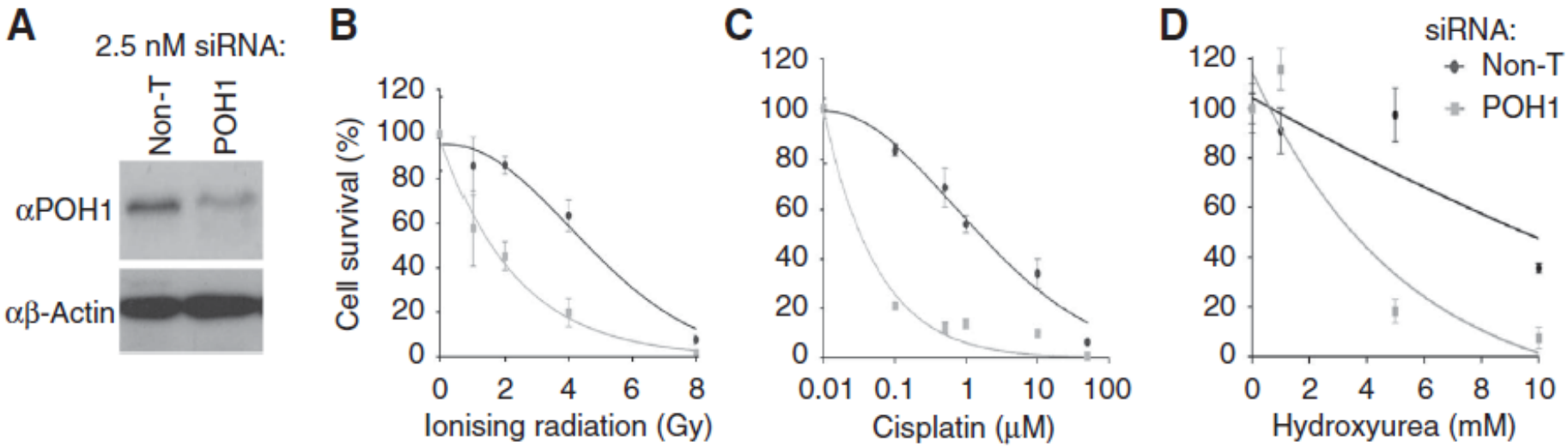
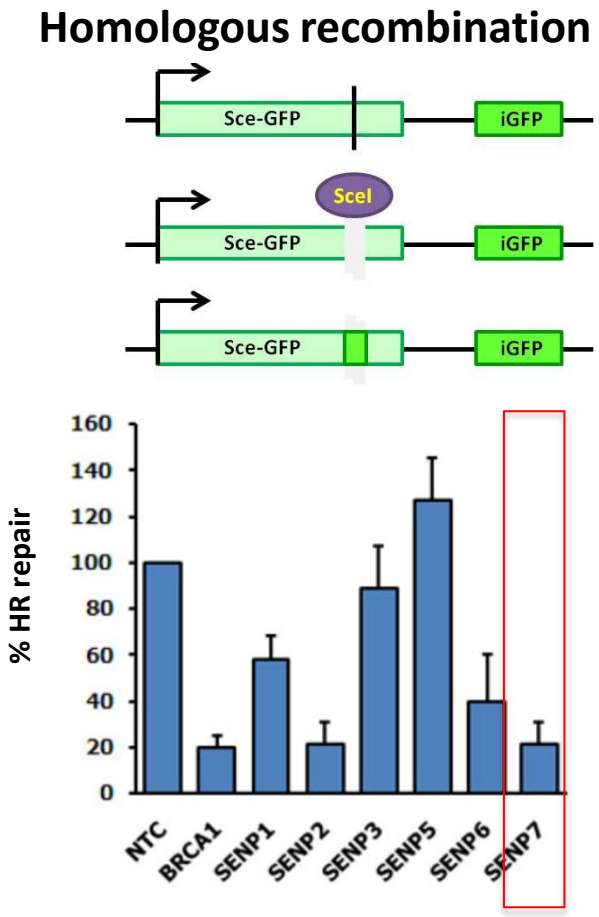


Butler LR, et al (2012) The proteasomal de-ubiquitinating enzyme POH1 promotes the double-strand DNA break response. *EMBO J* 31: 3918–3934

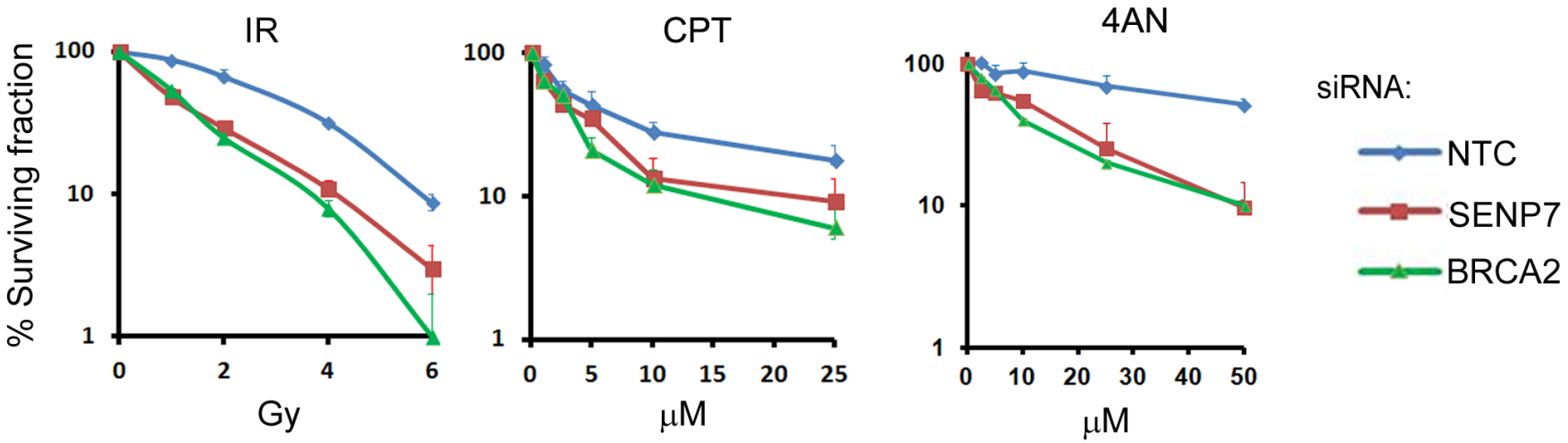
De-SUMOylating Enzymes as targets or bio-markers

SENP depletion in Enzyme-based reporter assays for DSB repair



De-SUMOylating Enzymes as targets or bio-markers

Colony survival assays in HeLa cells treated with drugs that induce DSB's.



Garvin AJ, et al (2013)
The deSUMOylase SENP7 promotes chromatin relaxation for homologous recombination DNA repair.
*Embo Reports (*Epub ahead of print)

PMT Enzymes as targets or bio-markers?

De-Ubiquitinating Enzymes as targets or bio-markers

Mini Rev Med Chem. 2012 Oct;12(12):1184-92.

Diethyldithiocarbamate complex with copper: the mechanism of action in cancer cells.

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Abstract

The idea of "repurposing" of existing drugs provides an effective way to develop and identify new therapies. Disulfiram (Antabuse), a drug commonly used for the treatment of alcoholism, shows promising anticancer activity in both preclinical and clinical studies. In the human body, disulfiram is rapidly converted to its reduced metabolite, diethyldithiocarbamate. If copper ions are available, a bis(diethyldithiocarbamate)-copper(II) complex is formed. Disulfiram's selective anticancer activity is attributed to the copper(II) complex's ability to inhibit the cellular proteasome. It is assumed that the complex inhibits the proteasome by a mechanism that is distinct to the clinically used drug bortezomib, targeting the 19S rather than the 20S proteasome. This difference could be explained by inhibition of the JAMM domain of the POH1 subunit within the lid of the 19S proteasome.

1881

- A Berlin chemist, M. Grodzki reported synthesized a new compound C10H20N2S4 .

1900

- disulfiram used by the rubber industry to accelerate the vulcanization of rubber.

1937

- E. E. Williams, a plant physician in the American rubber industry, described how workers in the plant, processing tetramethylthiuram monosulfide and disulfide, suffered trouble when ingesting alcohol.

1940s

- tetraethylthiuram monosulfide was a promising drug against scabies/worms in domestic animals.

1945

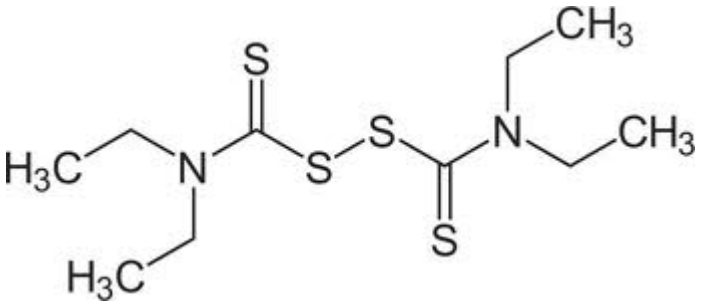
- 1945 Danish researchers Jacobsen and Martensen start work on disulfiram for worms

1948

- J. Hald and E. Jacobsen, "A Drug Sensitising the Organism to Ethyl Alcohol," *The Lancet, **1948, 252, 1001***-1004.
- O. Martensen-Larsen, "Treatment of Alcoholism with a Sensitising Drug," *Lancet, **1948, 252, 1004-1005.***

1950

- Dominant procedure for treating alcohol misuse in the Danish health system.
- FDA approval, 1951 (250,000/prescriptions /year in US)



~ 120,000 people world wide take antabuse for misuse of alcohol (20% in Denmark)

"Drug for Drunks" in *Time of December 6, 1948*
Copenhagen's Dr. Erik Jacobsen, 45, likes to try out new drugs on himself before giving them to his patients. One night before going to a dinner party he swallowed a couple of pills made of tetraethylthiuram-disulfide; they were supposed to be good for intestinal worms. To his surprise, Dr. Jacobsen found that any form of alcohol revolted him. When he sipped even a small glass of beer, his face got red, his heart started to pound, and he had trouble getting his breath.

1966
1975

- Schirmer HK, Scott WW. Disulfiram and tumor inhibition (Trans Am Assoc Genitourin Surg. 1966;58:63-6.),
- Wattenberg dietary disulfiram inhibited chemical induction of bowel cancer in mice (JNCI, 1975 Apr;54(4):1005-6).

1989

- Disulfiram potentiated the cytotoxicity of nitrogen mustard chemotherapy in rodents (Cancer Res. 1989 Dec 1;49(23):6658-61).

1990

- Phase II trial (16 in group I, 14 in group II) –no difference between cisplatin and cisplain + Disulfiram (Am J Clin Oncol. 1990 Apr;13(2): 119 -24)(looking for nephroprotection actually 1 patient had complete response group II)

2000

- Disulfiram potentiated the cytotoxicity of nitrogen mustard and 5FU chemotherapy effects on leukemia and colorectal cells respectively. (JNCI 2000 Jun 7;92(11):898-902).

2004

- 1 patient with advanced metastatic disease (Combination of oral zinc gluconate and disulfiram at approved doses for alcoholism induced >50% reduction in hepatic metastases and produced clinical remission in a patient with stage IV metastatic ocular melanoma, who has continued on oral zinc gluconate and disulfiram therapy for 53 continuous months with negligible side effects. (1 patient!) Mol Cancer Ther. 2004 Sep;3(9):1049-60.

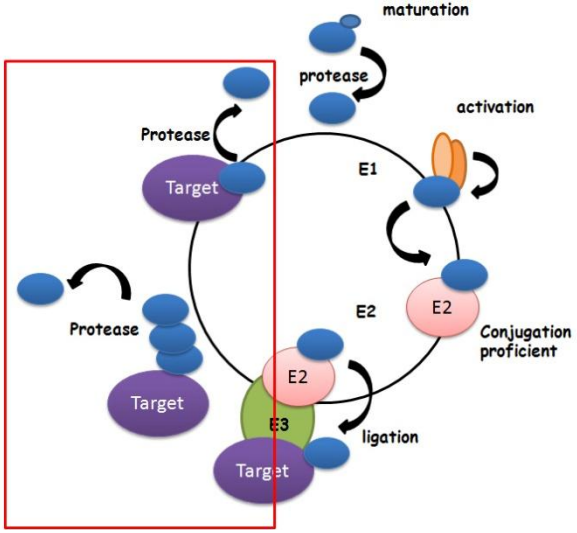
2012

- In a library screen of 1200 compounds, disulfiram, identified as an enhancer of the cytotoxic effects of cisplatin Anticancer Res. 2012 Jul;32(7):2679-88.)

now

- clinical trials of disulfiram with copper gluconate against liver cancer in Utah (ClinicalTrials.gov Identifier: NCT00742911) –just completed not yet reported (only 21 patients)
- disulfiram as adjuvant against lung cancer in Israel (ClinicalTrials.gov Identifier: NCT00312819) – completed not yet reported (60 patients)

Enzymes that remove PTMs in DNA repair (De-Ubiquitinaing and de-SUMOylating enzymes) are potential biomarkers and targets *with the potential to improve cancer treatment*.



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Press Release

Forma therapeutics and Cancer Research Technology to discover cancer drugs targeting deubiquitinating enzymes (DUBS)

Tuesday 9 July 2013

Cancer Research Technology Press Release

Forma Therapeutics and Cancer Research Technology, Ltd. (CRT), the commercialisation company of Cancer Research UK, announced today a bold research initiative to discover innovative tools, technologies and therapeutic drug candidates against a variety of protein homeostasis regulators called, deubiquitinating enzymes (DUBs).

Under this agreement, FORMA will pair its ultra-efficient drug discovery capabilities with CRT's expertise in translating academic discoveries through its Discovery Laboratories (CRT-DL) and the exclusive world-class academic network of Cancer Research UK Principal Investigators.

"This initiative with CRT and Cancer Research UK has the potential to significantly accelerate our understanding of the relevant biological applications of DUBs, a key class of enzymes involved in regulating protein homeostasis," said Steven Tregay, Ph.D., President and CEO, FORMA

Thank you

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