IMPAKT
BREAST CANCER CONFERENCE

IMPROVING CARE AND KNOWLEDGE THROUGH TRANSLATIONAL RESEARCH IN BREAST CANCER

WELCOME TO IMPAKT

Brussels, Belgium **7-9 MAY 2015**

IMPAKT Chairs: Nicholas Turner London, UK and Carsten Denkert, Berlin, Germany

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BASICS IN DNA REPAIR

Brussels 5th May 2015

Jean Feunteun
Gustave-Roussy Villejuif France

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- Any financial interest in, or arrangement with, a competing company: NO

- Any other financial connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated – including pertinent commercial or other sources of funding for the individual Speaker or for the associated department or organization, personal relationships, or direct academic competition. NO

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Summary

- Dynamics of genetic information
- DNA damage and cancer cells selection
- Types of DNA Damages
- DNA lesions: cause of cancer and cancer treatment
- Pharmacological targeting of DNA Damage Response:
  →Synthetic lethality

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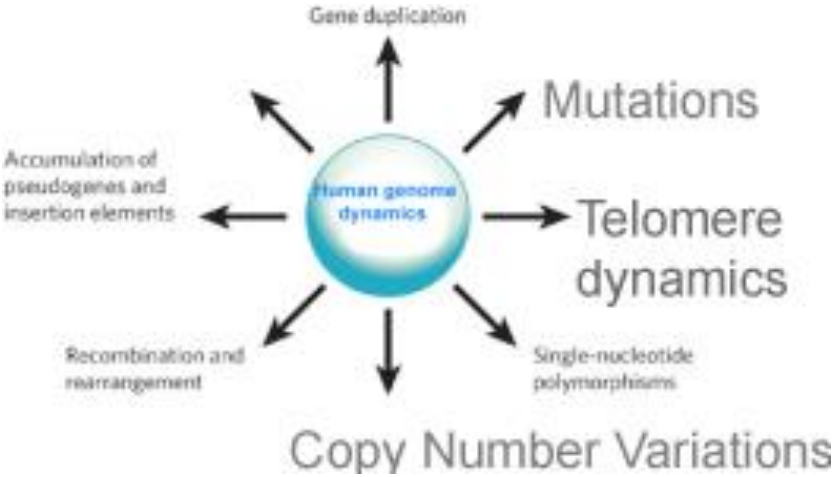
Dynamics of genetic information

DYNAMICS OF GENOMES (DNA)



- Implies mechanisms of surveillance
  = DNA Damage Response

DYNAMICS OF GENE EXPRESSION (RNA):

Differential splicing…..

- Implies mechanisms of surveillance de l'information:
  Nonsense-Mediated Decay (NMD)…..

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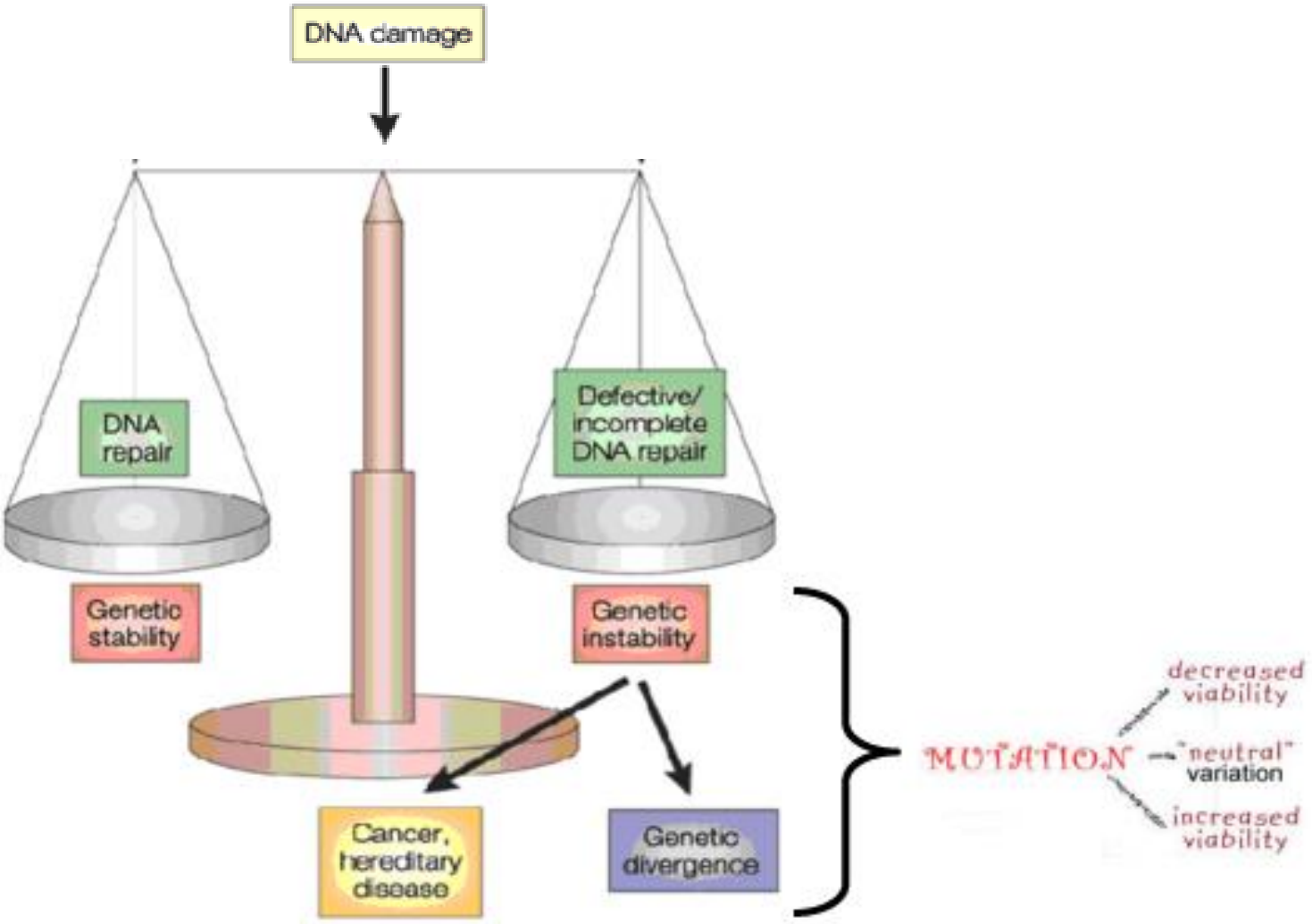
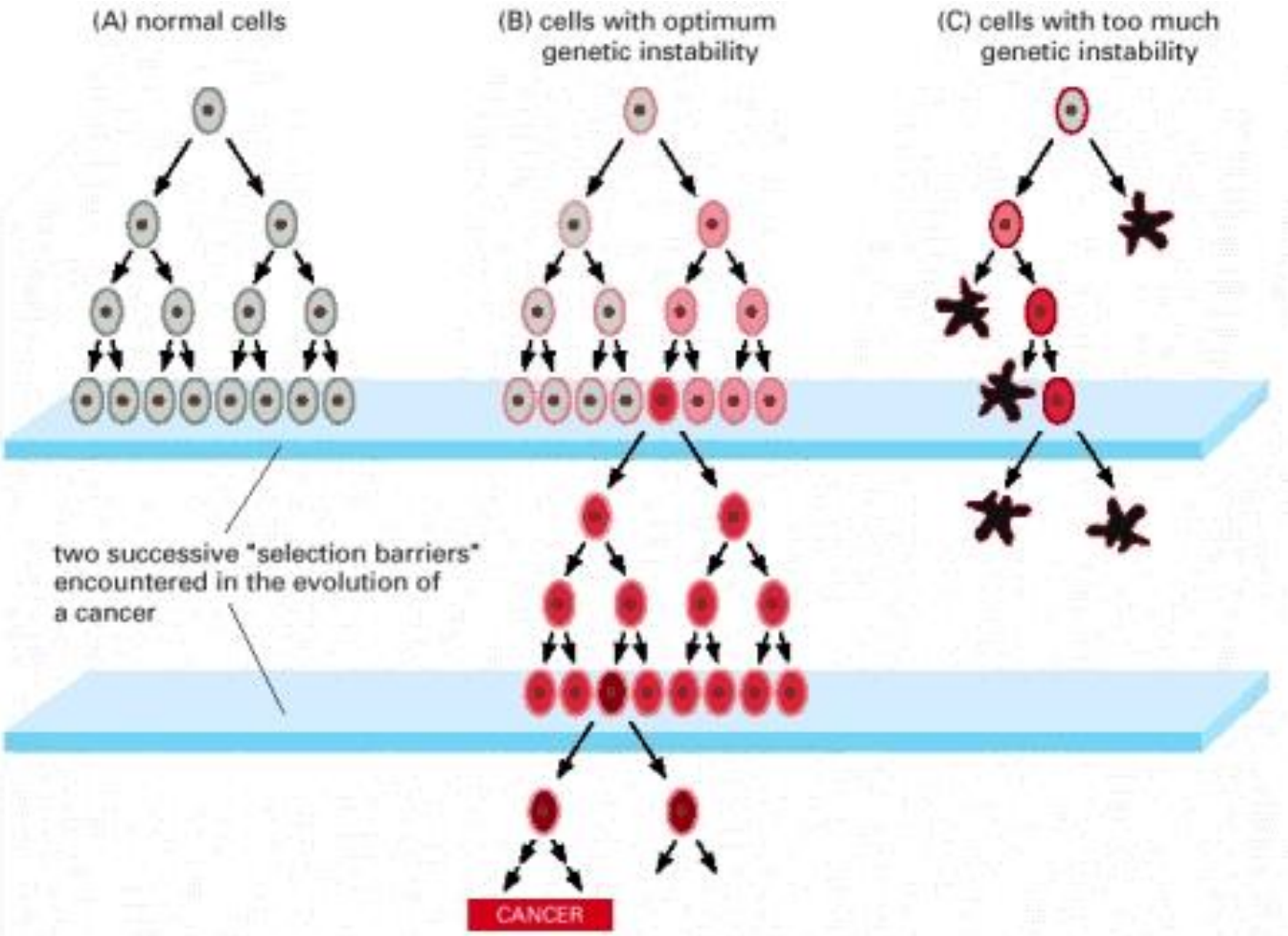
DNA damage and cancer cells selection



Genetic instability
Cause and consequence of cancer



From NCBI » Bookshelf » Molecular Biology of the Cell »

DNA Damage Response: Surveillance at work

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Drivers or Passengers

Mutations in cancers are either drivers or passengers.

- Driver mutations are the ones that cause cancer cells to grow.
- Passengers are co-travellers that make no contribution to cancer development.

Most mutations in cancers are passengers

Human familial cancer syndromes due to inherited defects in DNA Damage response

Name of syndrome	Name of gene	Cancer phenotype	Enzyme or process affected
HNPCC	(4–5 genes)[a]	colonic polyposis	mismatch repair enzymes
XP[b]	(8 genes)[b]	UV-induced skin cancers	nucleotide-excision repair
AT[c]	*ATM*	leukemia, lymphoma	response to dsDNA breaks
AT-like disorder[c]	*MRE11*	not yet determined	dsDNA repair by NHEJ
Familial breast, ovarian cancer	*BRCA1, BRCA2*[d]	breast and ovarian carcinomas	homology-directed repair of dsDNA breaks
Werner	*WRN*	several cancers	exonuclease and DNA helicase[e], replication
Bloom	*BLM*	solid tumors	DNA helicase, replication
Fanconi anemia	(9 genes)[f]	AML, HNSCC	repair of DNA cross-links and ds breaks
Nijmegen break[g]	*NBS*	mostly lymphomas	processing of dsDNA breaks, NHEJ
Li–Fraumeni	*TP53*	multiple cancers	DNA damage alarm protein
Li–Fraumeni	*CHK2*	colon, breast	kinase signaling DNA damage

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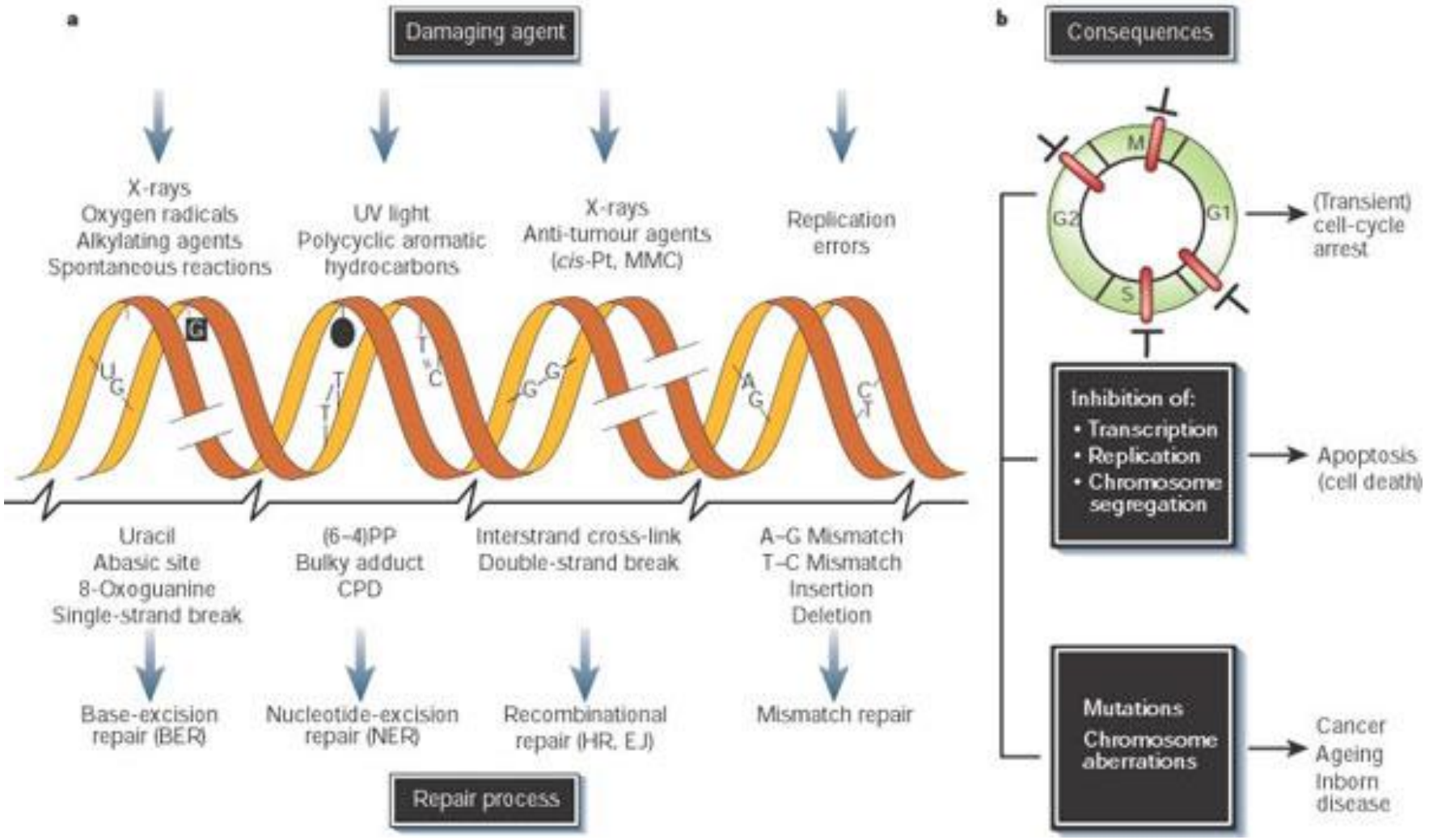
Adapted in part from B. Alberts et al., Molecular Biology of the Cell, 4th ed. New York: Garland Science, 2002; and from E.R. Fearon, *Science* 278:1043–1050, 1997.

DNA Damages



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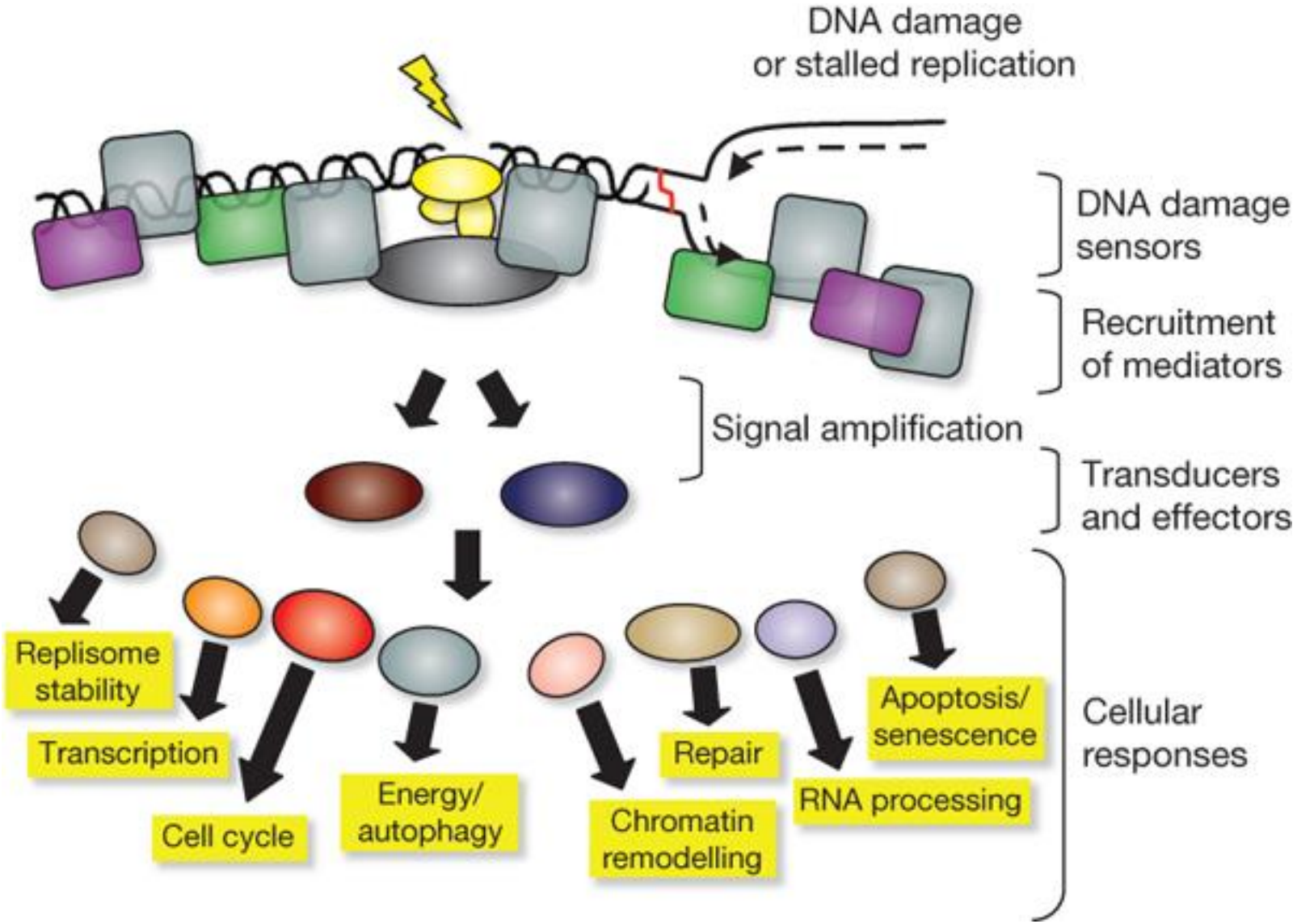
Jan H. J. Hoeijmakers Nature 411, 366-374 (2001)

Integrated DNA Damage Response.



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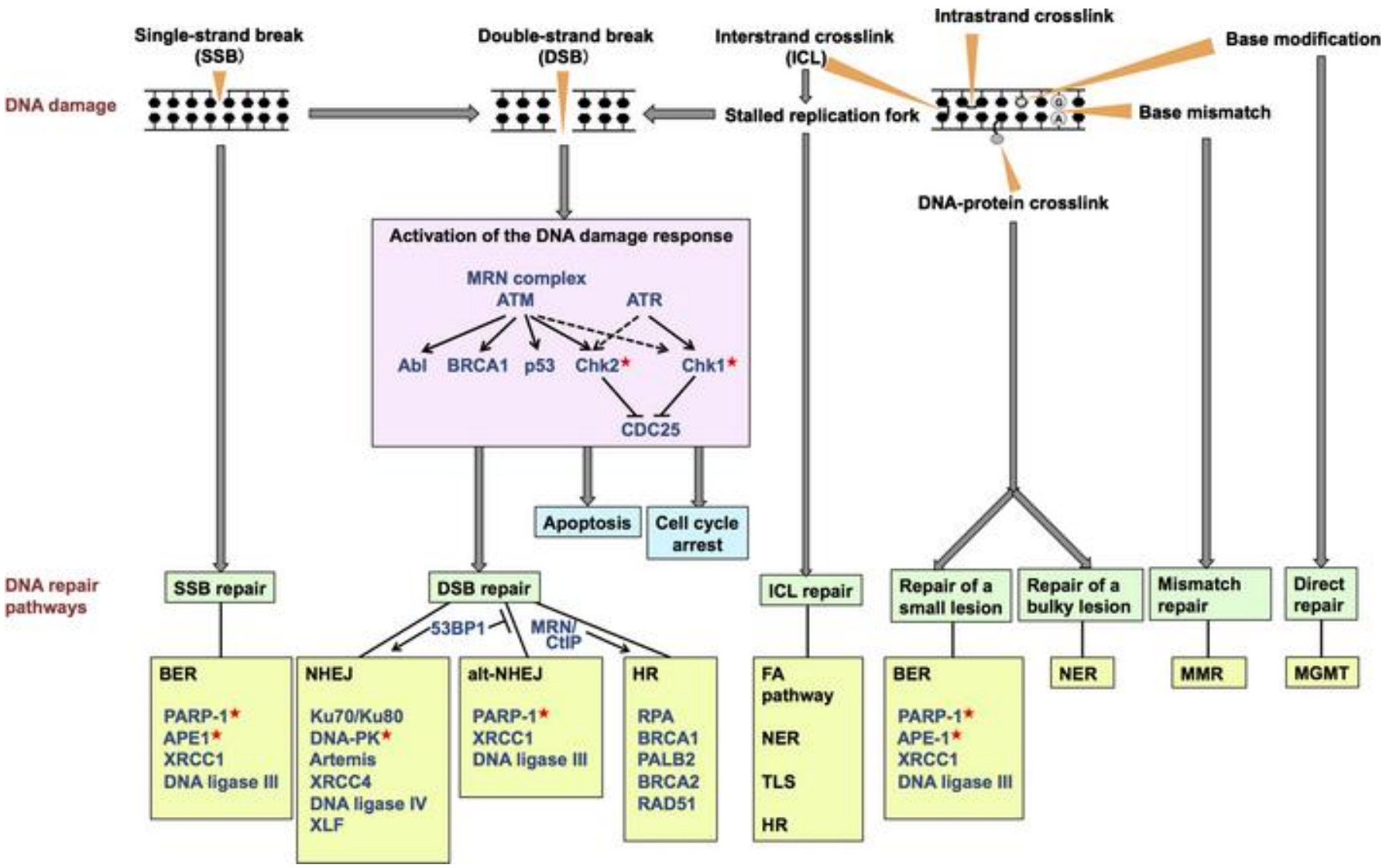
SP Jackson & J Bartek *Nature* **461**, 1071-1078 (2009)

The DNA damage responses



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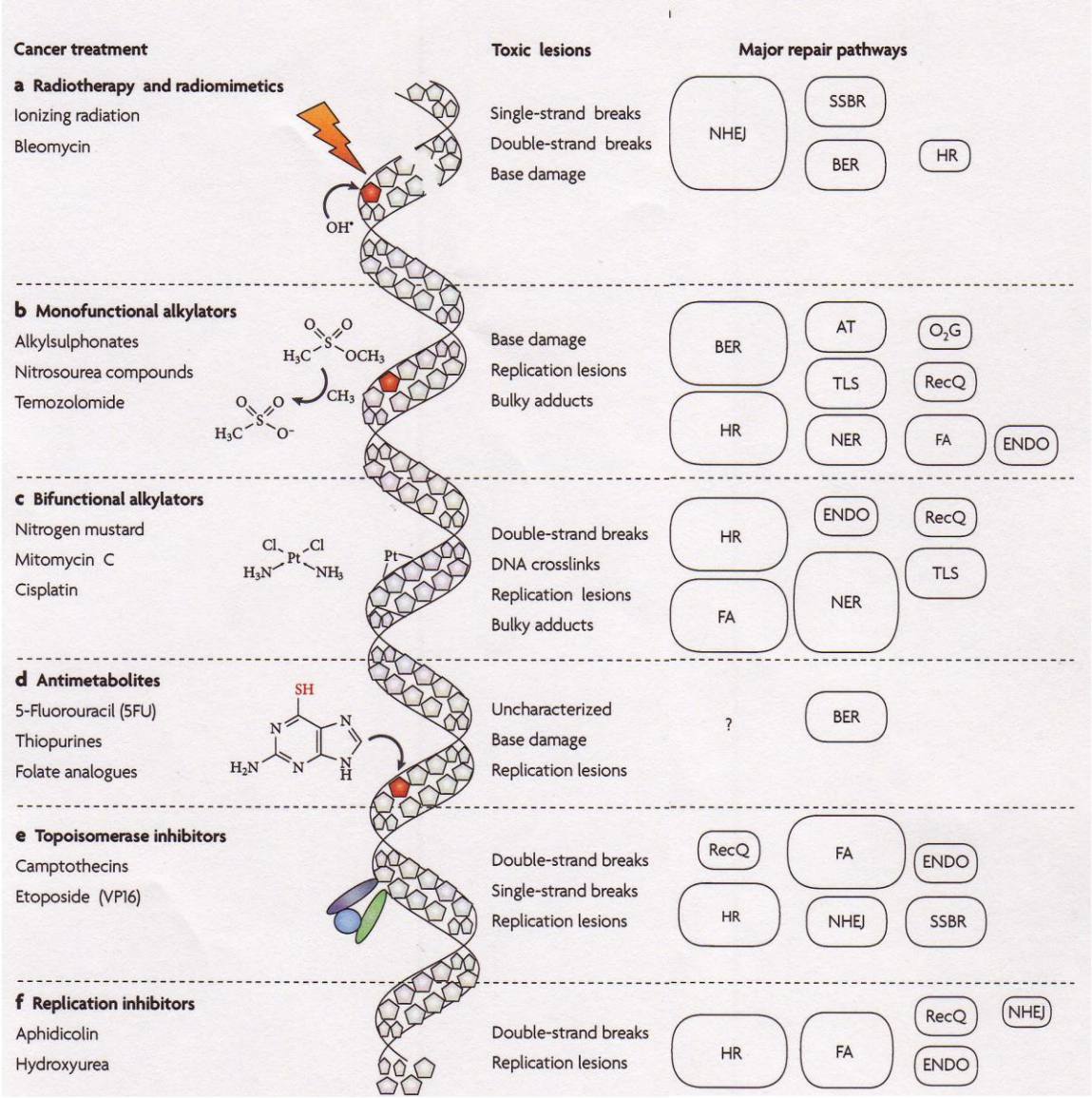
Hosoya N. and Miyagawa K. Cancer Science 105, 370–388, 2014

DNA lesions: cause of cancer and cancer treatment



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DNA Damage Response inhibitors

Table 2. Examples of DNA damage response inhibitors in preclinical studies

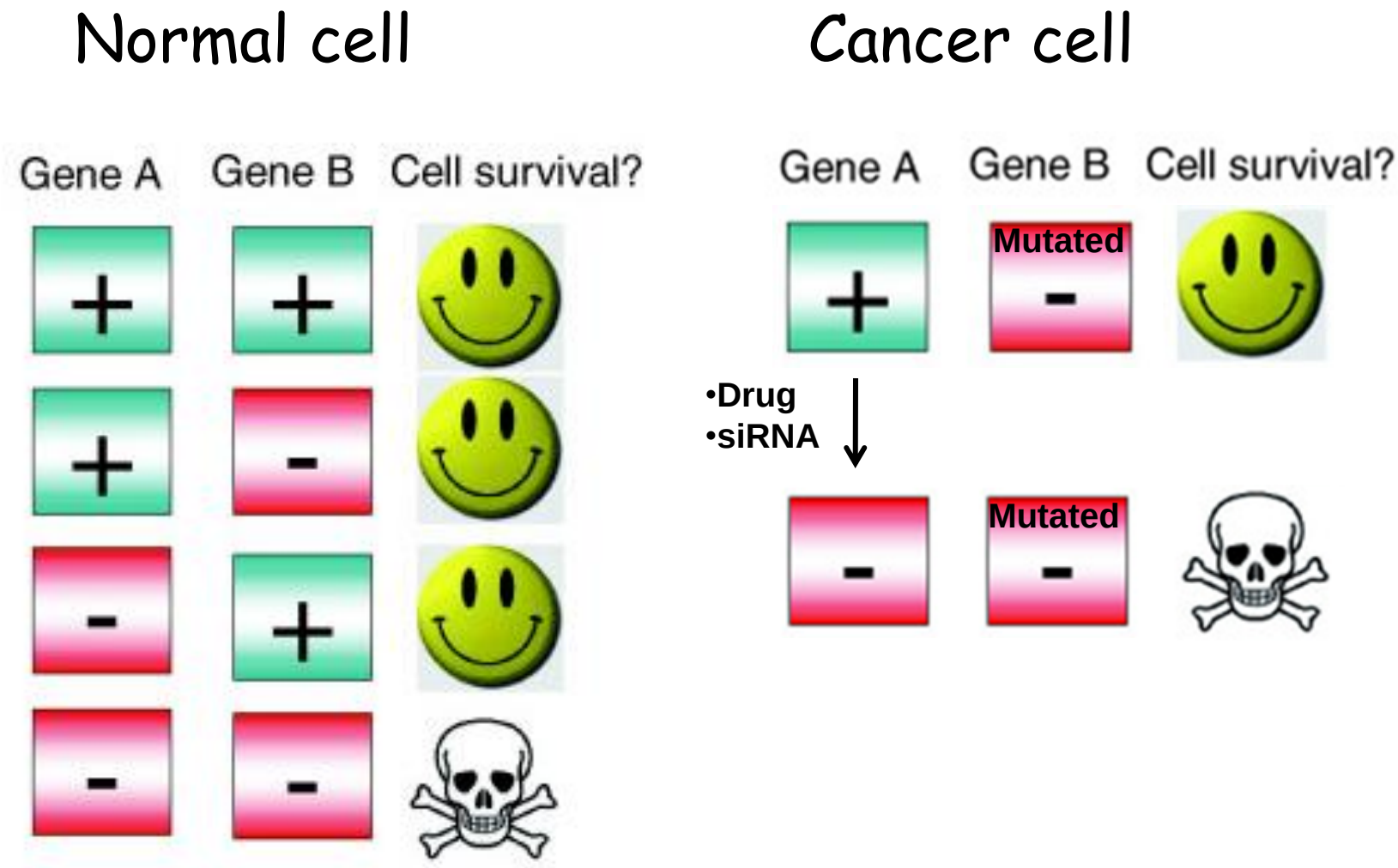
Pathway	Target(s)	Name(s)	Preclinical evidence
DNA damage sensors and mediators	MRE11	Mirin, telomelysin	Sensitization to ionizing radiation
	ATM	KU55933, KU60019, CP466722	Sensitization to ionizing radiation and topoisomerase inhibitors
	ATR	Schisandrin B	Sensitization to UV treatment
		NU6027, VE-821	Sensitization to ionizing radiation and a variety of chemotherapy
Cell cycle checkpoints	Chk1	SAR-020106	Sensitization to irinotecan and gemcitabine
	Chk2	VRX0466617	Sensitization to ionizing radiation
Non-homologous end joining	DNA-PK	NU7026, NU7441	Sensitization to ionizing radiation and topoisomerase II inhibitors
	DNA-PK and PI3K	KU-0060648	Sensitization to etoposide and doxorubicin
	DNA ligase IV	SCR7	Sensitization to ionizing radiation and etoposide
Alternative non-homologous end joining	DNA ligases I and IIIα	L67	Sensitization to ionizing radiation and methyl methanesulfonate
Homologous recombination (HR)	RAD51	B02, A03, A10	Identified by high-throughput screenings of RAD51 inhibitors

Table 3. Examples of DNA damage response inhibitors in clinical trials

Pathway	Target(s)	Name	Combination	Type of cancer	Clinical trial number	Stage	Trial periods
Cell cycle checkpoints	Chk1	UCN-01	Combination therapy				
			Carboplatin	Advanced solid tumor	NCT00036777	Phase I	Completed
			Irinotecan	Metastatic or unresectable solid tumor, triple negative breast cancer	NCT00031681	Phase I	Completed
			Cytarabine	Refractory or relapsed acute myelogenous leukemia, myelodysplastic syndrome	NCT00004263	Phase I	Completed
			Perifosine	Relapsed or refractory acute leukemia, chronic myelogenous leukemia, high risk myelodysplastic syndrome	NCT00301938	Phase I	Completed
			Gemcitabine	Unresectable or metastatic pancreatic cancer	NCT00039403	Phase I	Completed
			Topotecan	Relapsed or progressed small-cell lung cancer	NCT00098956	Phase II	Completed
			Cisplatin	Advanced malignant solid tumor	NCT00012194	Phase I	Terminated
			Fluorouracil	Metastatic pancreatic cancer	NCT00045747	Phase II	Completed
			Prednisone	Refractory solid tumor, lymphoma	NCT00045500	Phase I	Completed
			Irinotecan	Advanced solid tumor	NCT00047242	Phase I	Completed
			Fluorouracil, leucovorin	Metastatic or unresectable solid tumor	NCT00042861	Phase I	Completed
			Topotecan	Advanced ovarian epithelial, primary peritoneal, fallopian	NCT00072267	Phase II	Completed

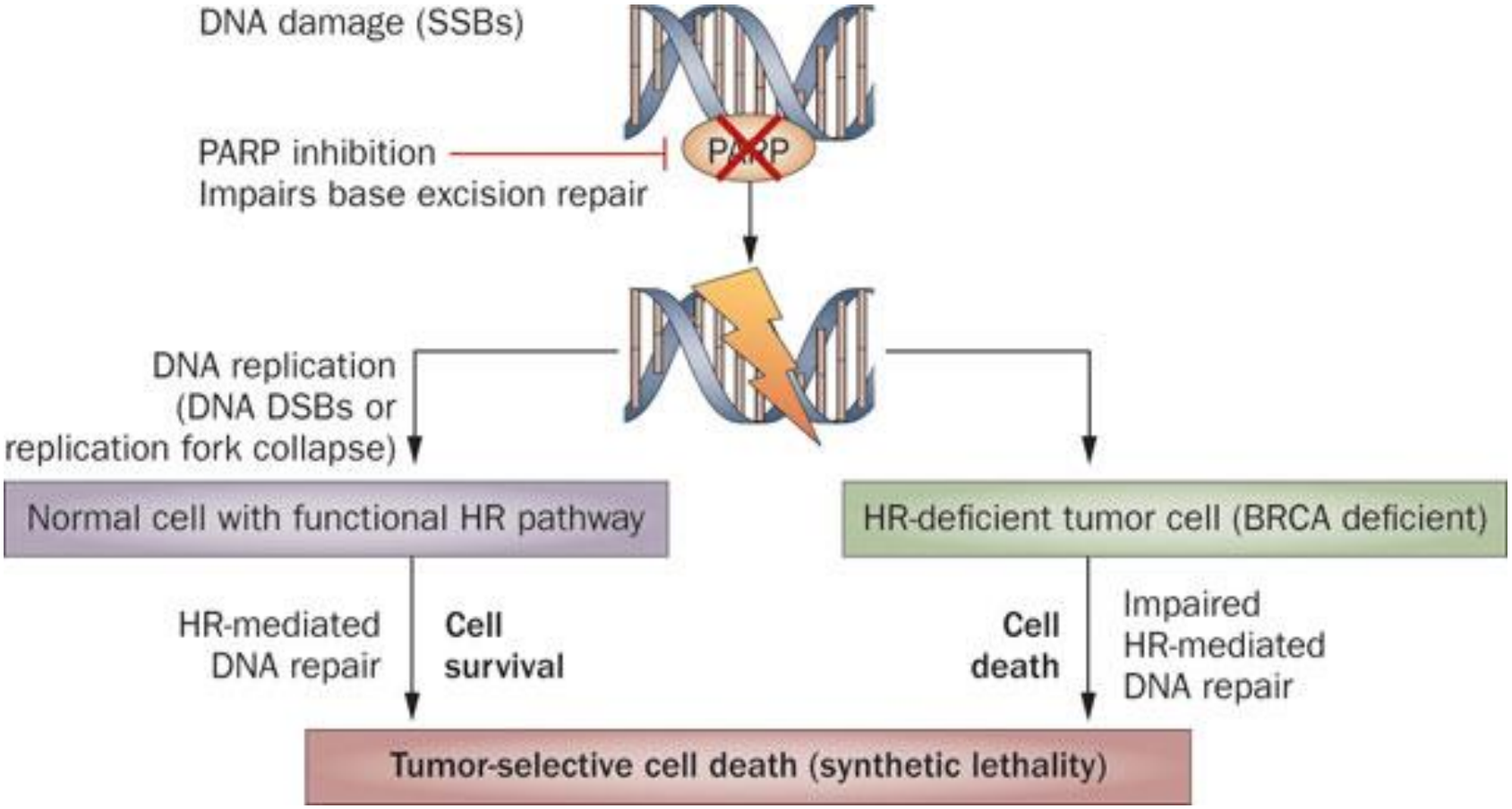
Hosoya N. and Miyagawa K. *Cancer Science* 105, 370-388, 2014

Pharmacological targeting of DNA Damage Response: Synthetic lethality (1)



Synthetic lethality (2)

Mechanism of synthetic lethality between *BRCA* deficiency and PARP inhibition



Banerjee, S. *et al.* (2010) Making the best of PARP inhibitors in ovarian cancer *Nat. Rev. Clin. Oncol.*

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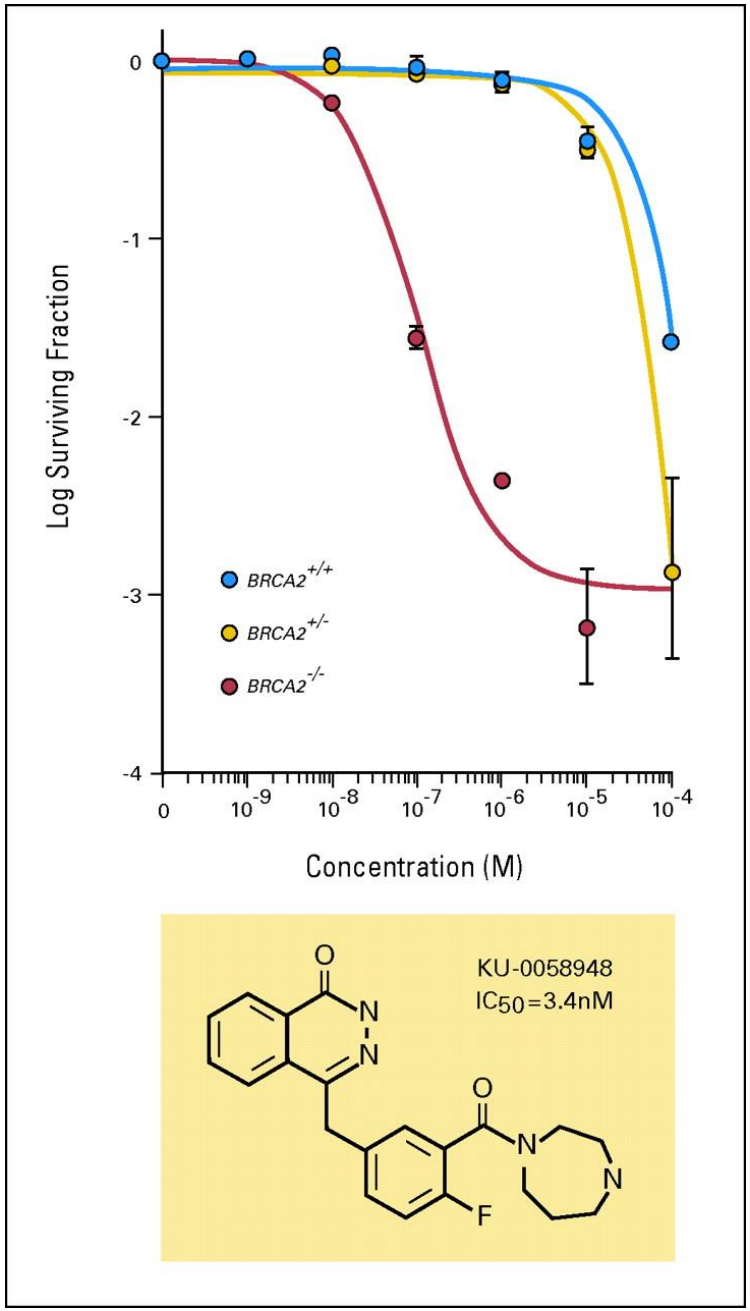
Synthetic lethality (3)



IMPAKT JOURNAL OF CLINICAL ONCOLOGY

Ashworth A JCO 2008;26:3785-3790

Conclusions

DNA Damage Response at the heart of cancer cell biology:

- Defects in DDR drive cancer selection
- DDR pathways = pharmacological targets