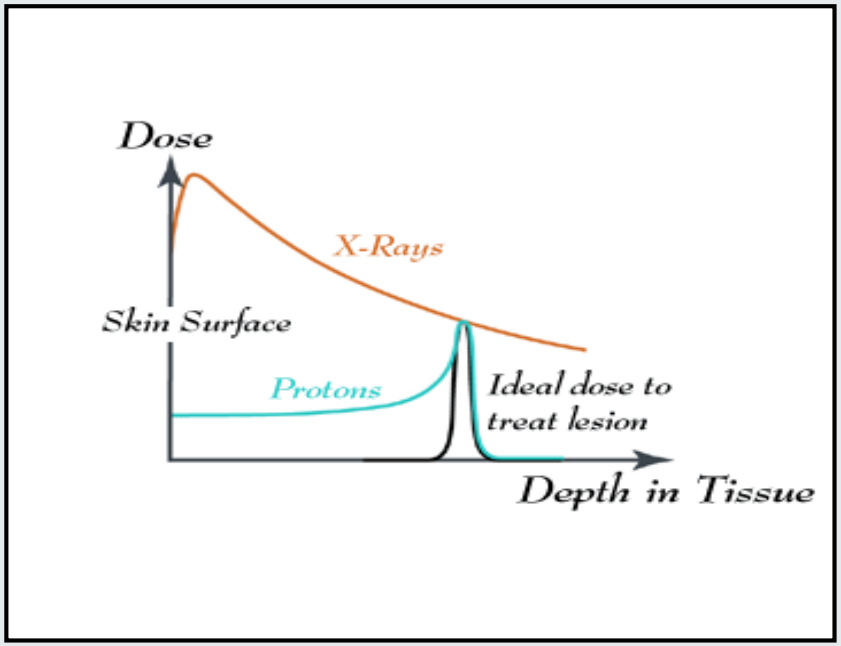
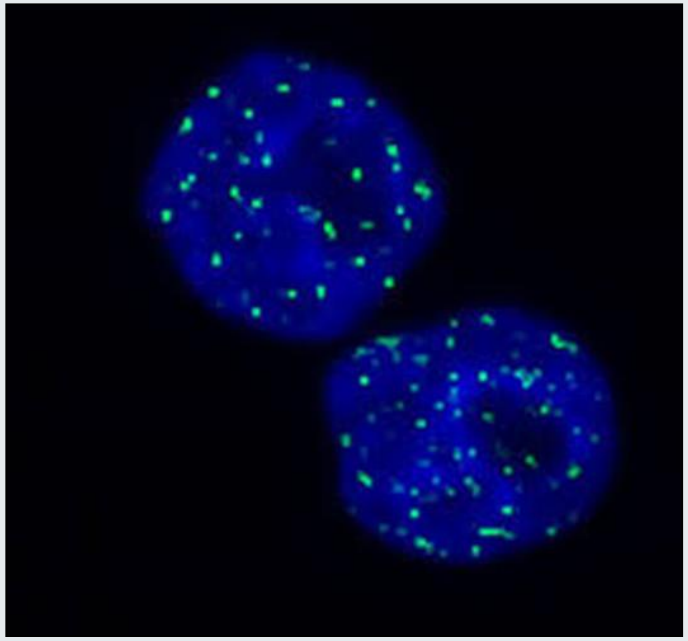
BASICS in RADIATION BIOLOGY
(from the biological perspective)





UniversityHospital
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Dept. Radiation Oncology
University Hospital Zurich

Radiobiology

Fact: We deliver a known physical dose with a high degree of accuracy to similar tumors

Observation: The radiocurability of tumors varies widely

Aim: Understand the biological factors that influence the sensitivity of tumors to radiation

Radiobiology

The response to radiation is different in normal tissues and cancer:

- at the cellular level
- at the tissue level

These differences are due to the underlying biological properties of different tissues and cancers

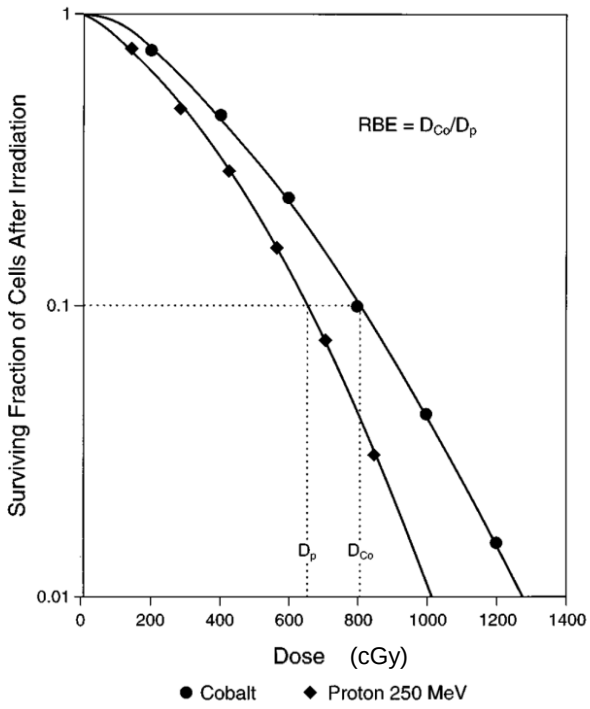
What is the relevance of these differences?

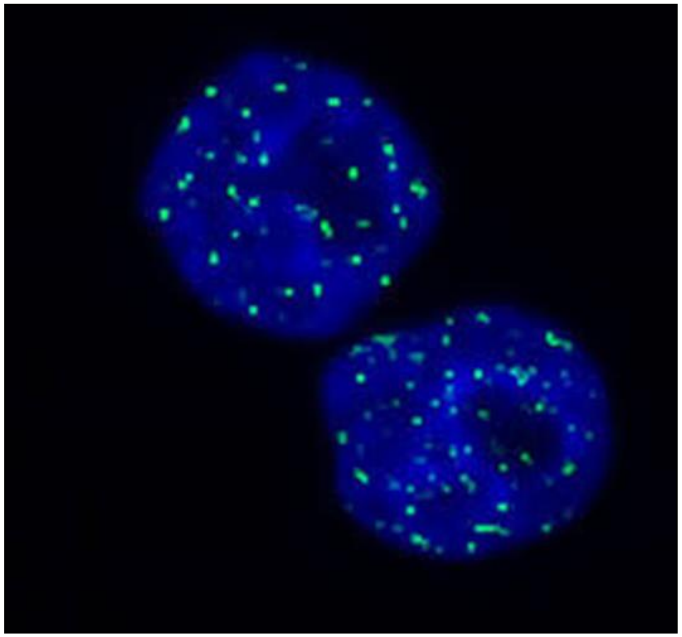
How do they have to be taken into consideration?

How can we exploit them?

Photon- and Particle-based Radiobiology:

Understand the biological factors that influence the sensitivity to different types of ionizing radiation



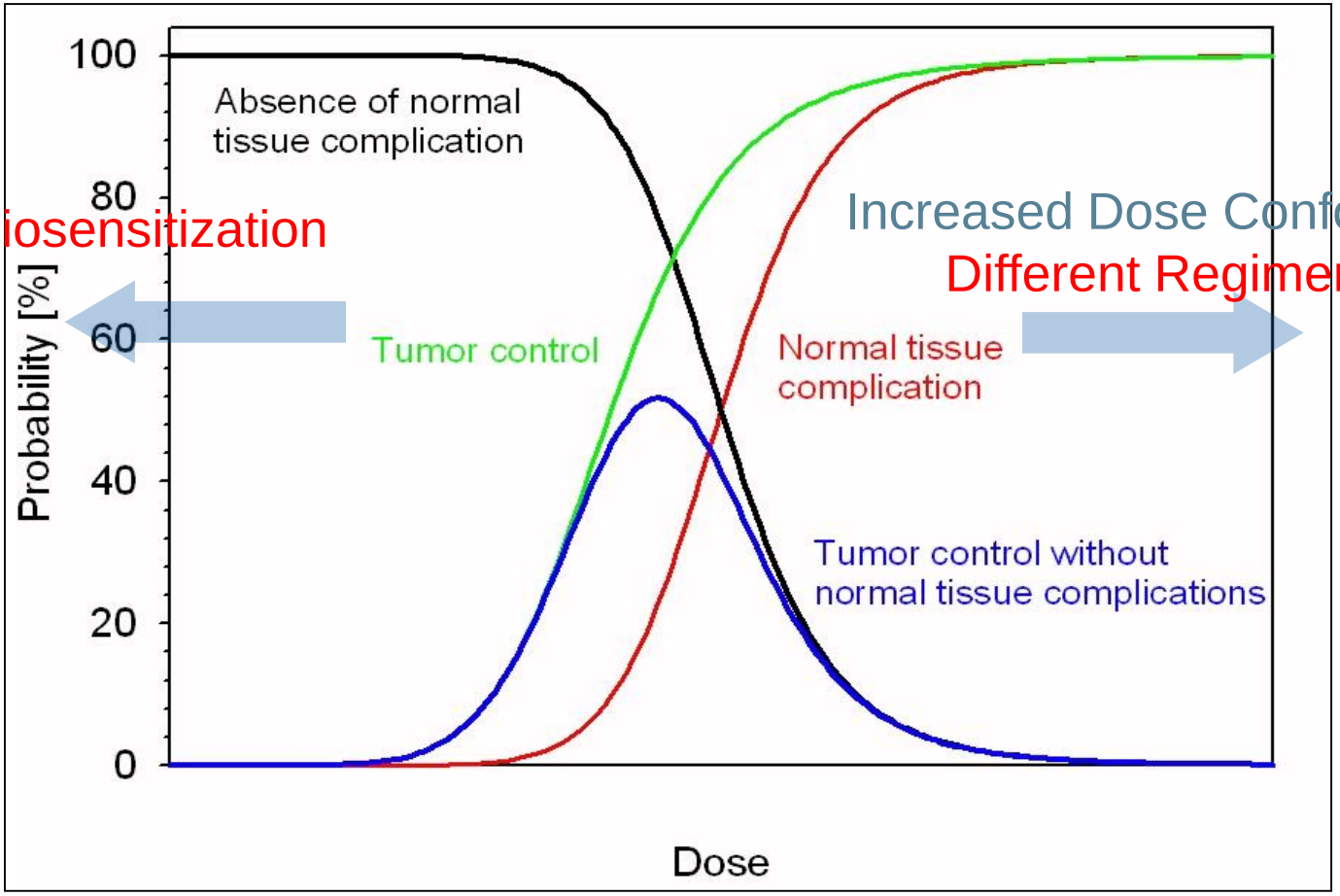


γH2AX-foci in response to IR

- How can we define these differences?
- How do they have to be considered?
- Where do these differences derive from?

see upcoming lecture, RBE

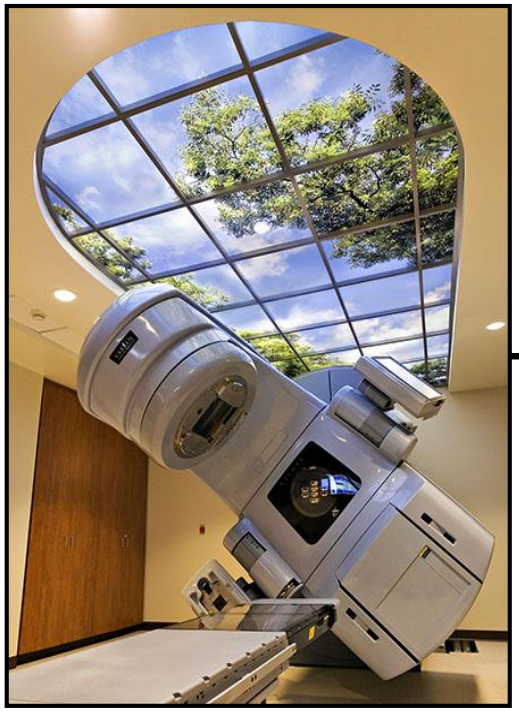
The Therapeutic Window

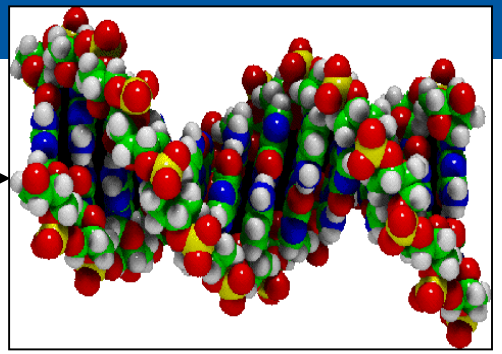


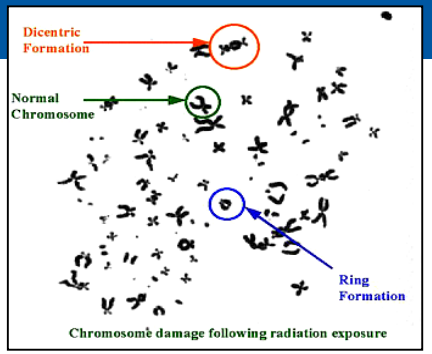
Radiosensitization

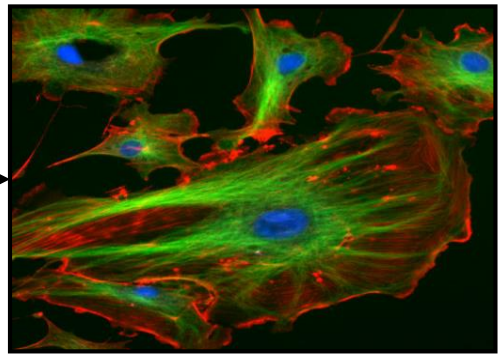
Increased Dose Conformity;
Different Regimens

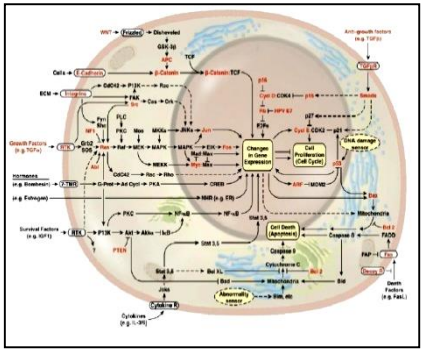
Therapeutic Index

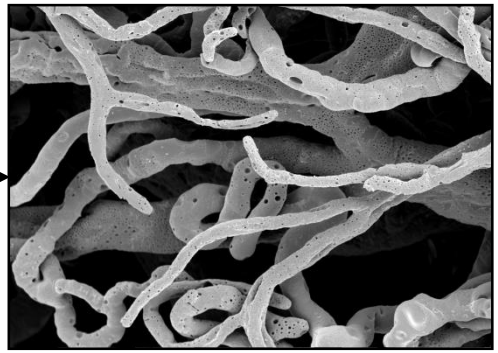


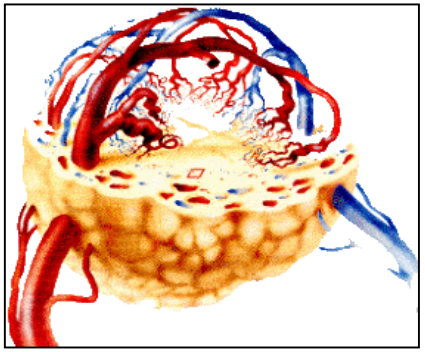


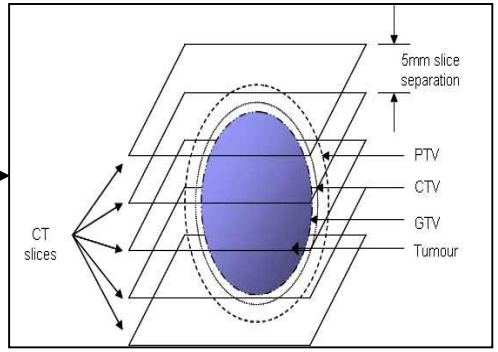

Dicentric Formation
Normal Chromosome
Ring Formation
Chromosome damage following radiation exposure

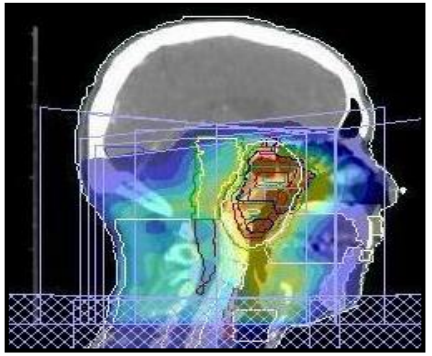




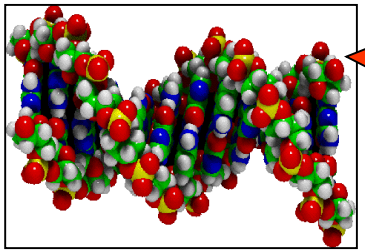




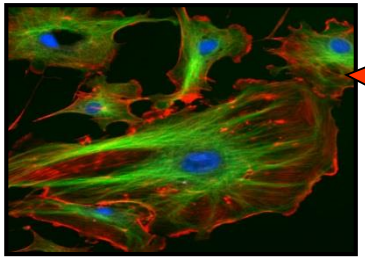

5mm slice separation
PTV
CTV
GTV
Tumour
CT slices



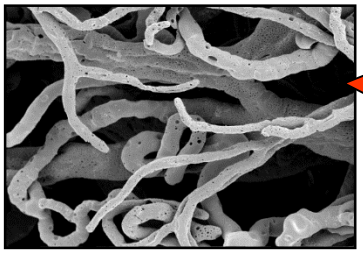
Radiation-Induced Biological Processes



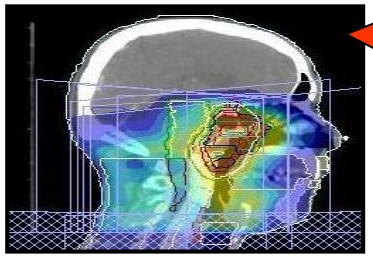
DNA-Repair-1 → DNA-Repair-2 → DNA-Repair-3



Tumor cell signal-1 → Tumor cell signal-2 → Tumor cell signal-3

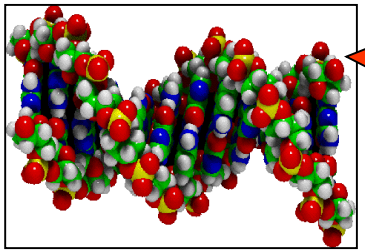


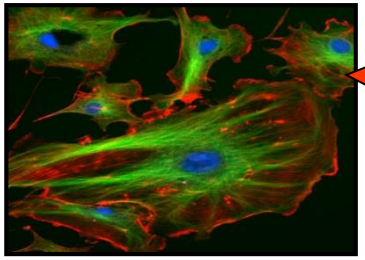
Tumormillieu-1 → Tumormillieu-2 → Tumormillieu-3

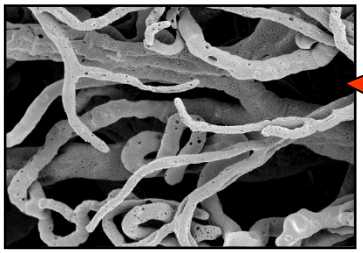


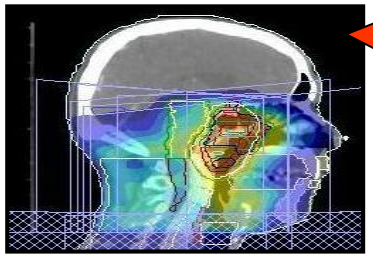
NT-Change-1 → NT-Change-2 → NT-Change-3

Complexity of Radiation-Induced Biological Processes









DNA-Repair-1

DNA-Repair-2

DNA-Repair-3

Tumor cell signal-1

Tumor cell signal-2

Tumor cell signal-3

Tumormillieu-1

Tumormillieu-2

Tumormillieu-3

NT-Change-1

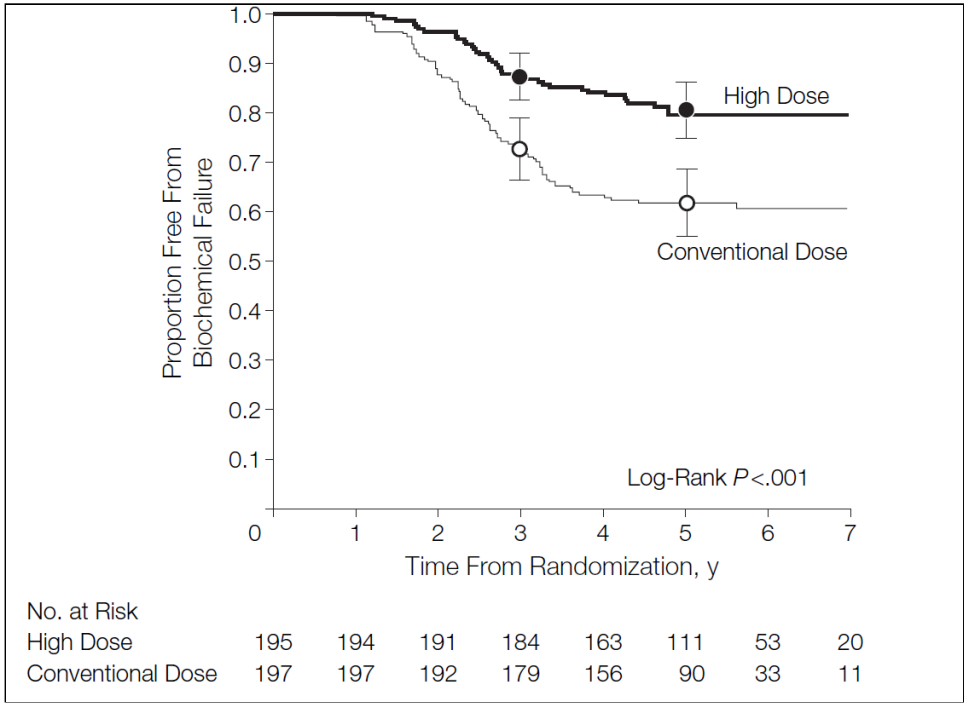
NT-Change-2

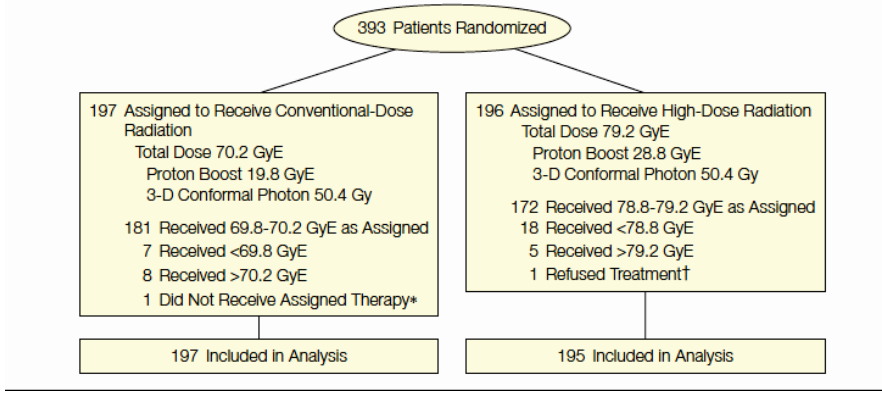
NT-Change-3

Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate

A Randomized Controlled Trial

(Reprinted) JAMA, September 14, 2005—Vol 294, No. 10 **1233**





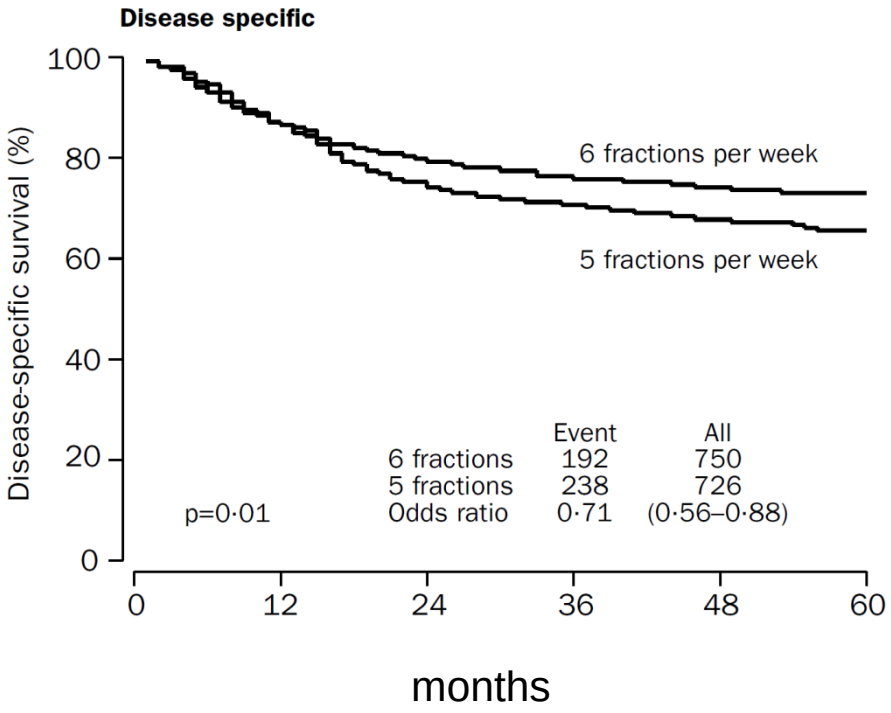
Freedom from Biochemical Failure
(Zietman et al., 2005)

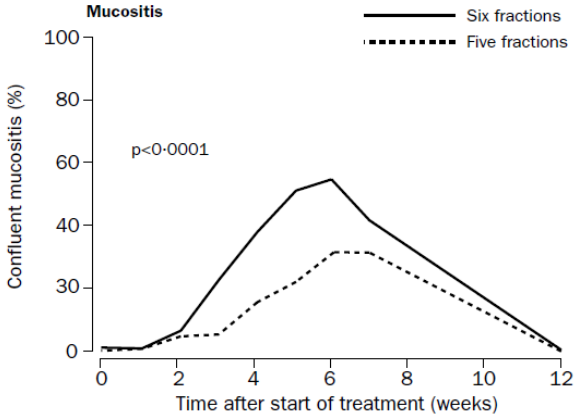
Articles

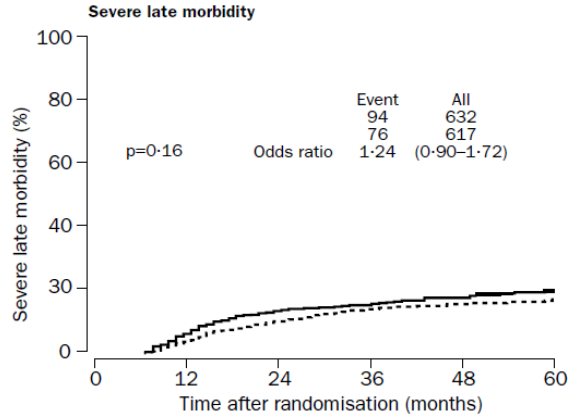
Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial

Jens Overgaard, Hanne Sand Hansen, Lena Specht, Marie Overgaard, Cai Grau, Elo Andersen, Jens Bentzen, Lars Bastholt, Olfred Hansen, Jørgen Johansen, Lisbeth Andersen, Jan F Evensen, on behalf of the Danish Head and Neck Cancer Study Group

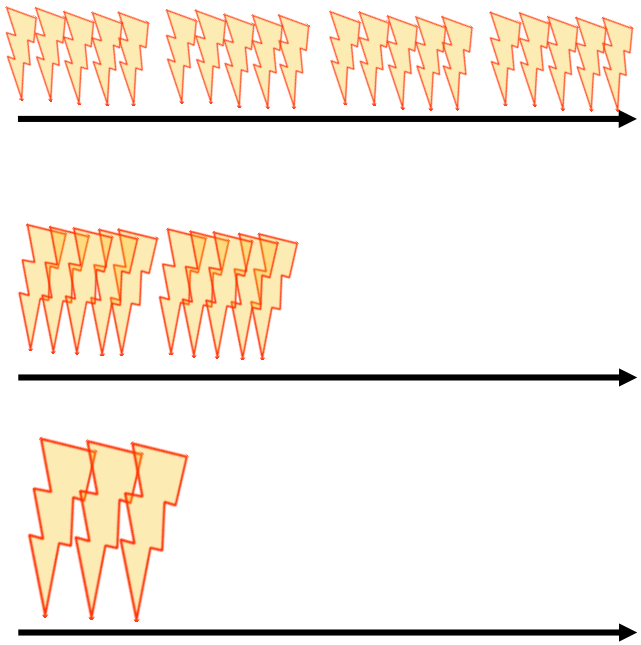
Lancet 2003; **362:** 933–40

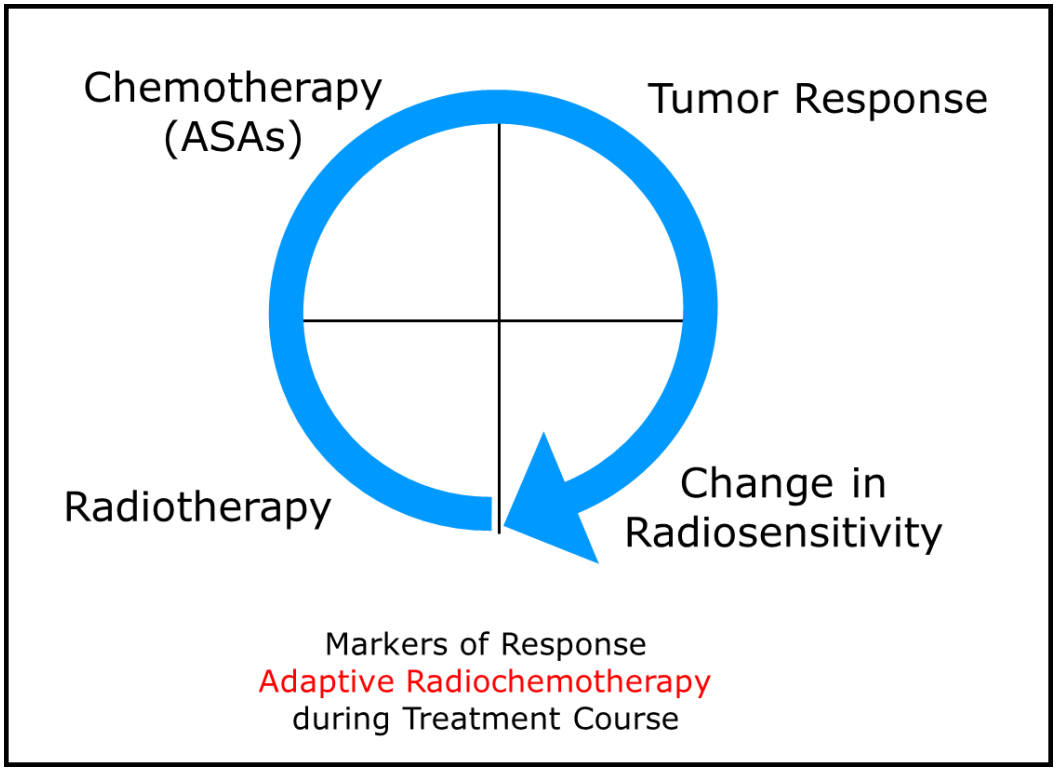






Defining (Personalized, Combined) Treatment Modalities





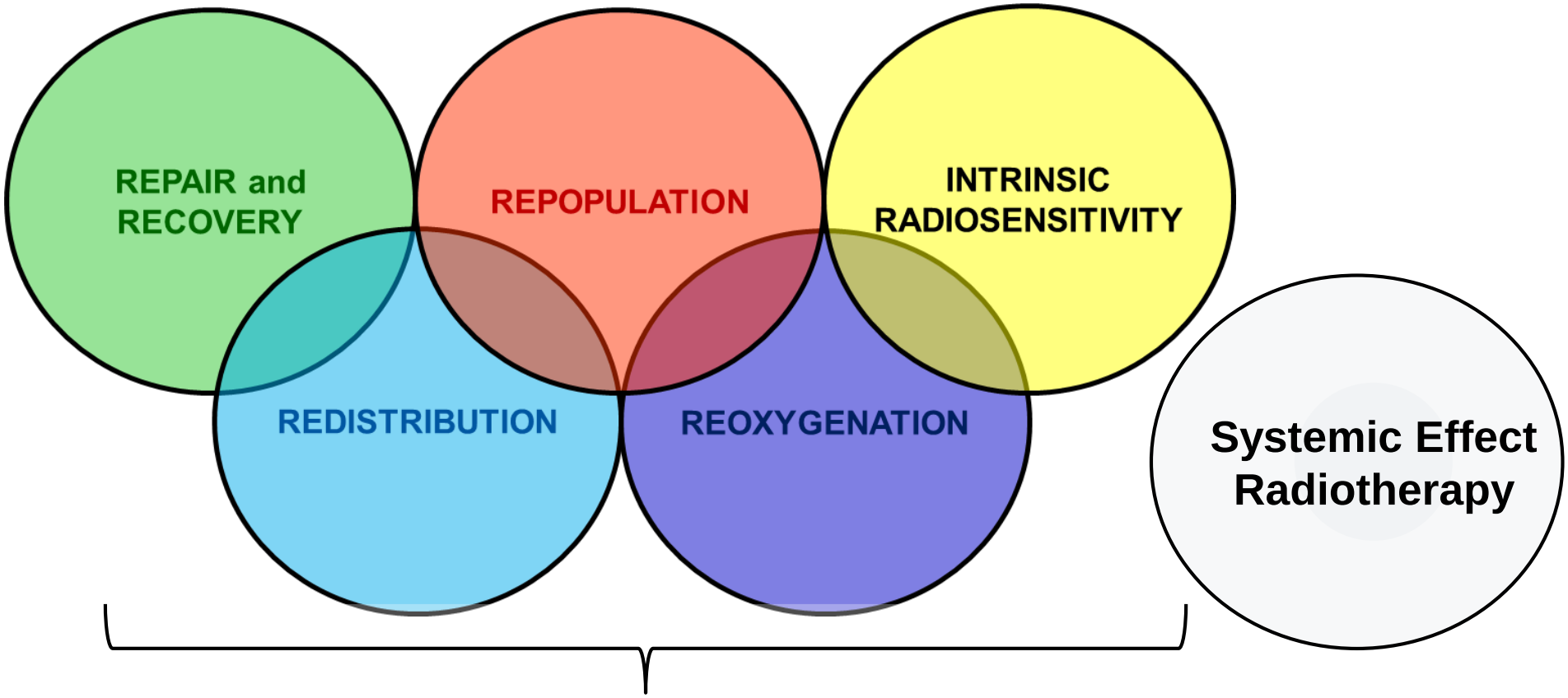
Dynamic Treatment Response to
Different Treatment Modalities

FACTORS INFLUENCING LOCAL TUMOR CONTROL (5 R‘s of RADIOTHERAPY: Alterations of Tumor Biology)

- Repair
- Reassortment of Cell Cycle (Redistribution)
  (redistribution into more sensitive/resistant cell cycle phase)
- Repopulation
  (rapid repopulation of clonogenic tumor cells during treatment)
- Reoxygenation:
  (hypoxic clonogenic cells become better oxygenated after RT-fraction)
- (Intrinsic) Radiosensitivity

HR. Withers, 1975
GG Steel, 1989

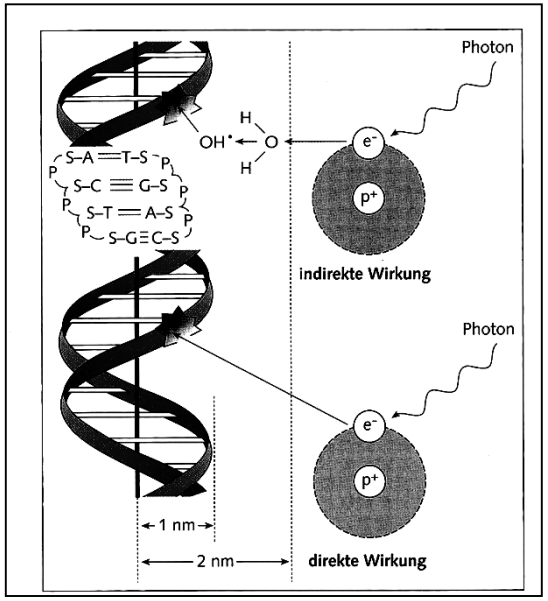
«HALLMARKS OF RADIOTHERAPY»
FACTORS INFLUENCING LOCAL TUMOR CONTROL

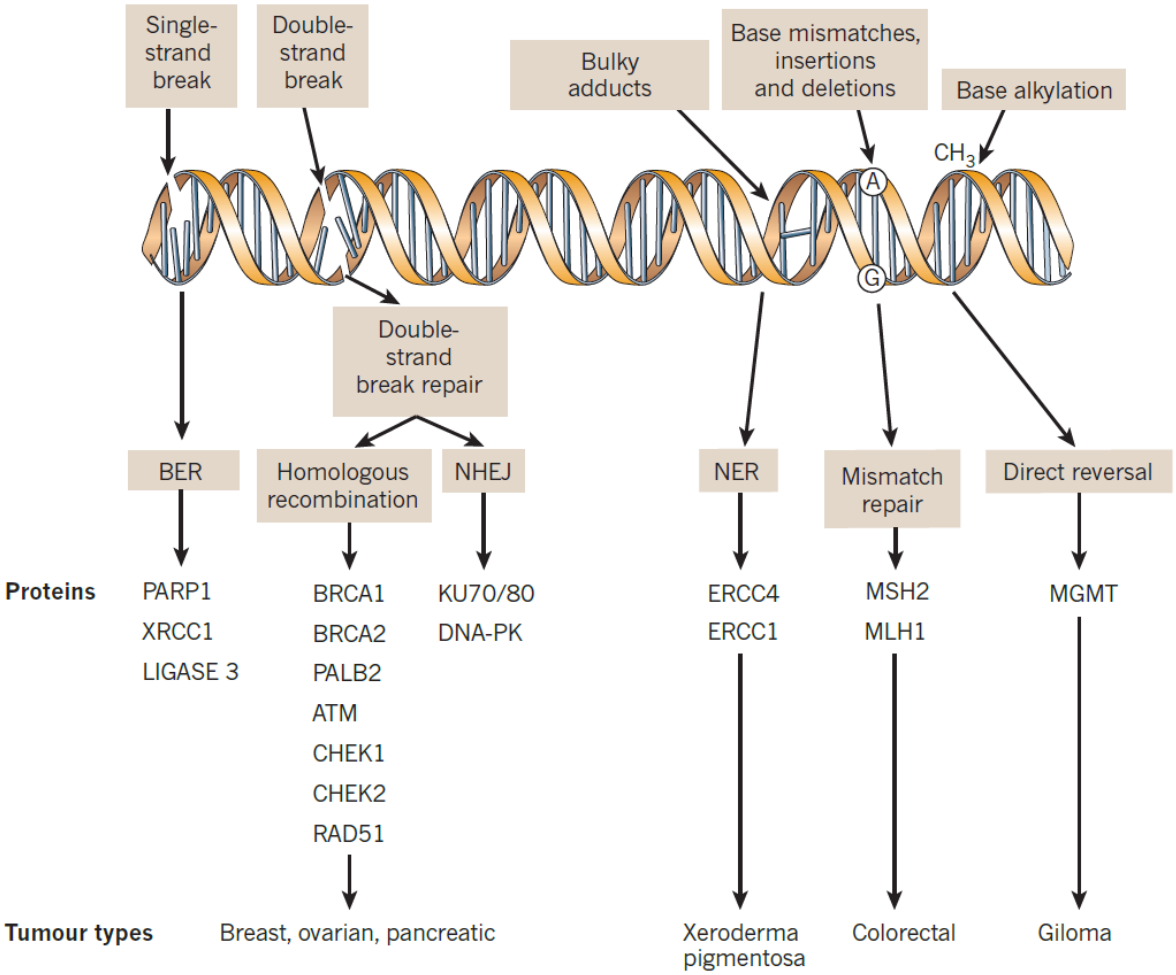


«5 R's of Radiotherapy»
(local tumor effect)

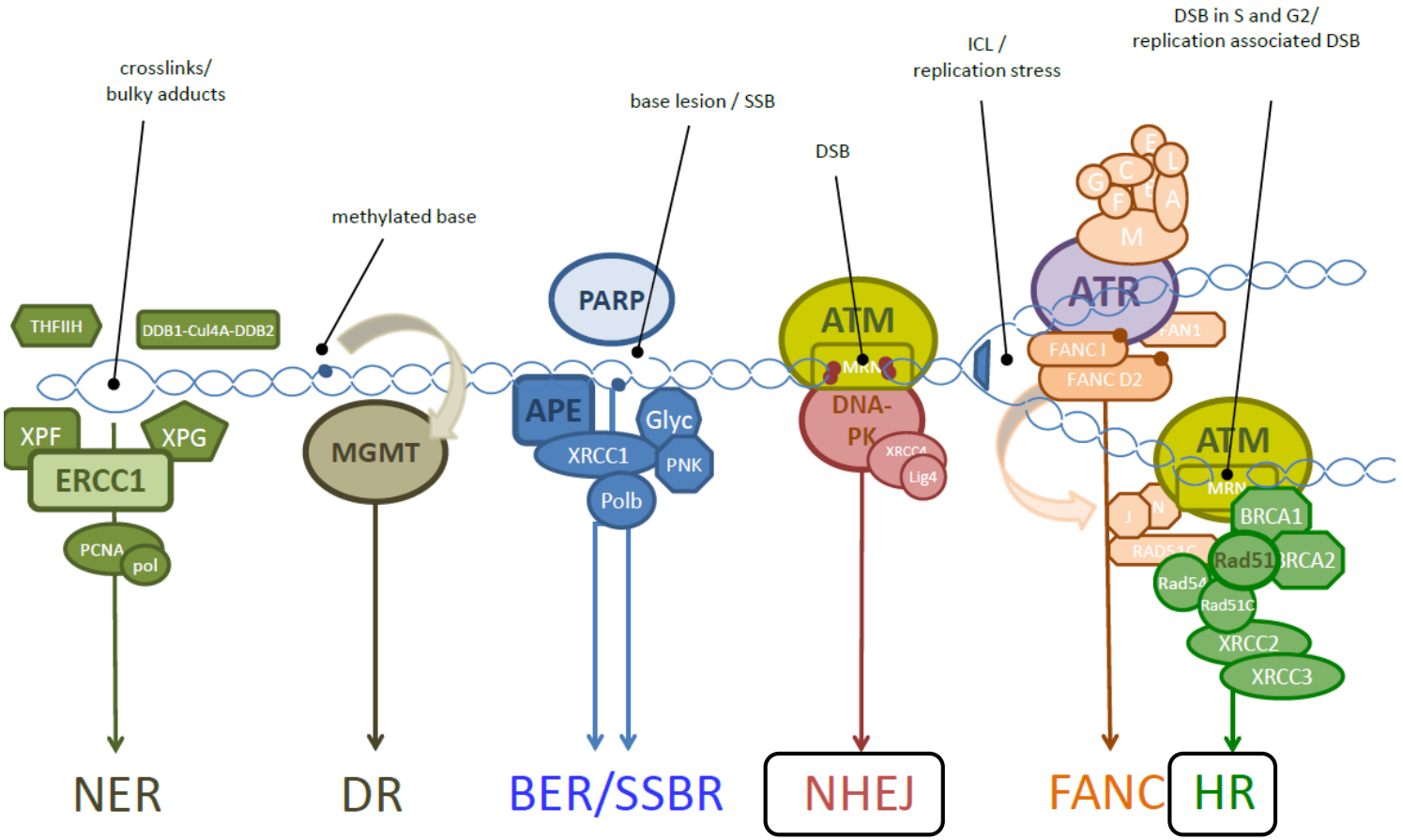
HR. Withers, 1975
GG Steel, 1989

DNA is the Major Target



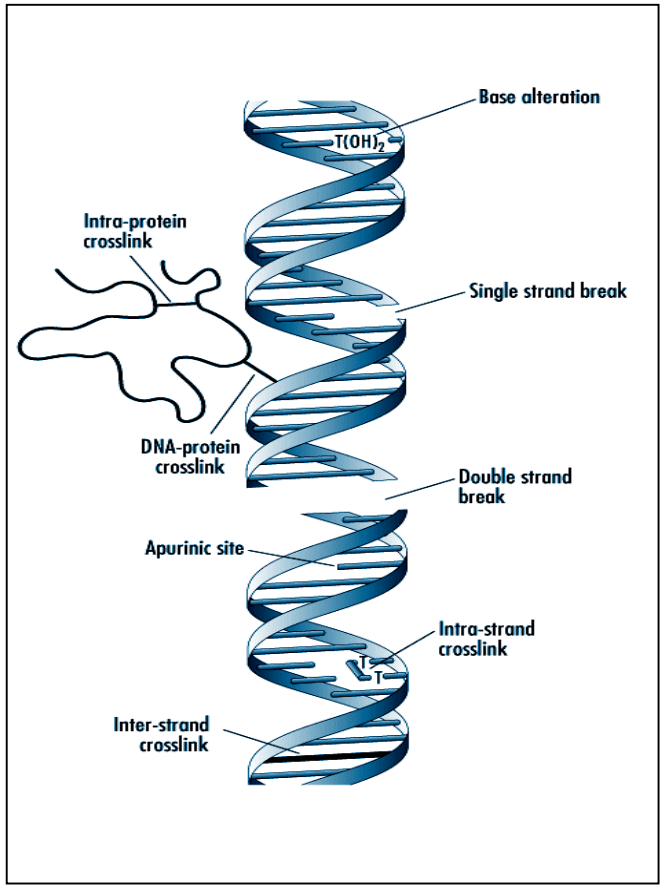


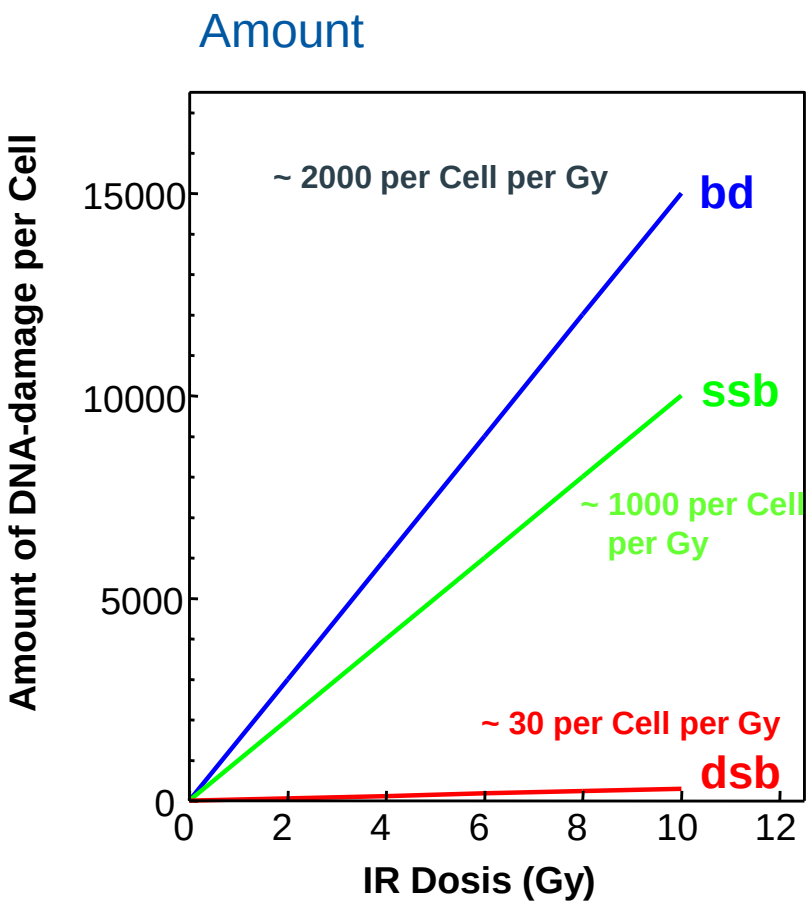
Several DNA Damage Specific Repair Machineries



DNA Damage Response and Repair

Radiation-induced lesions in DNA





DSB’s are unique forms of damage produced by radiation and by only a few drugs

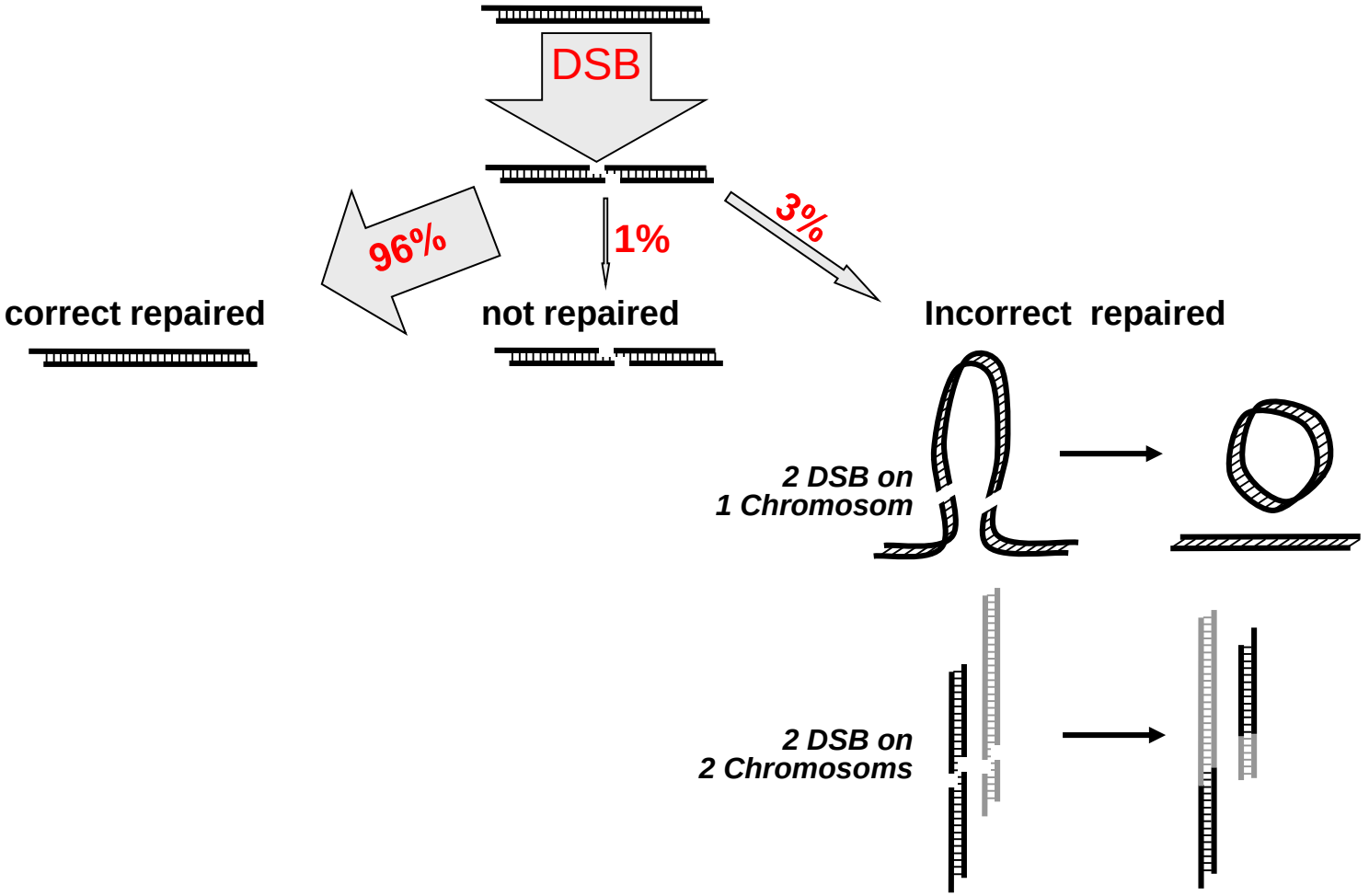
An unrepaired DSB leads to loss of genetic information at mitosis

DSB’s are extremely toxic. It takes only 1 unrepaired DSB to kill a cell

Evidence suggests that DSB’s are the most important lesions produced by ionizing radiation

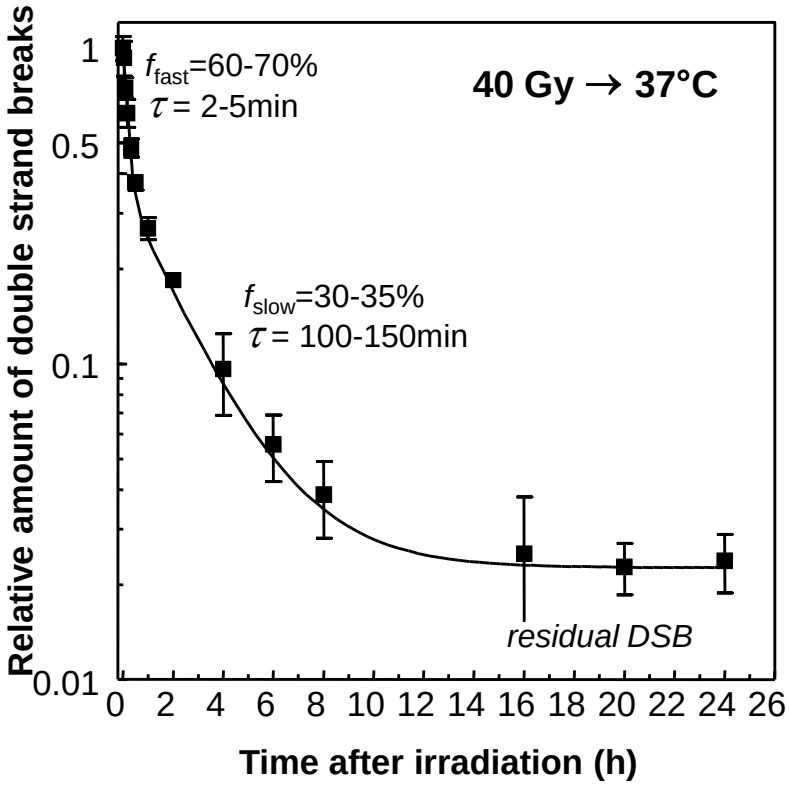
High Efficacy of DNA Repair

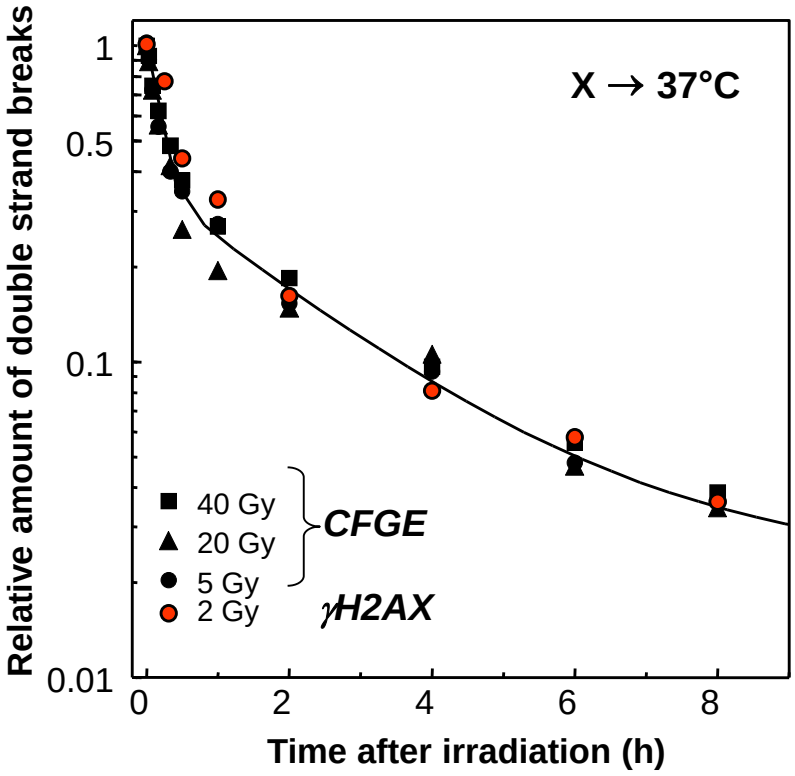
Double strand breaks



Repair Kinetics

- **Double strand breaks**



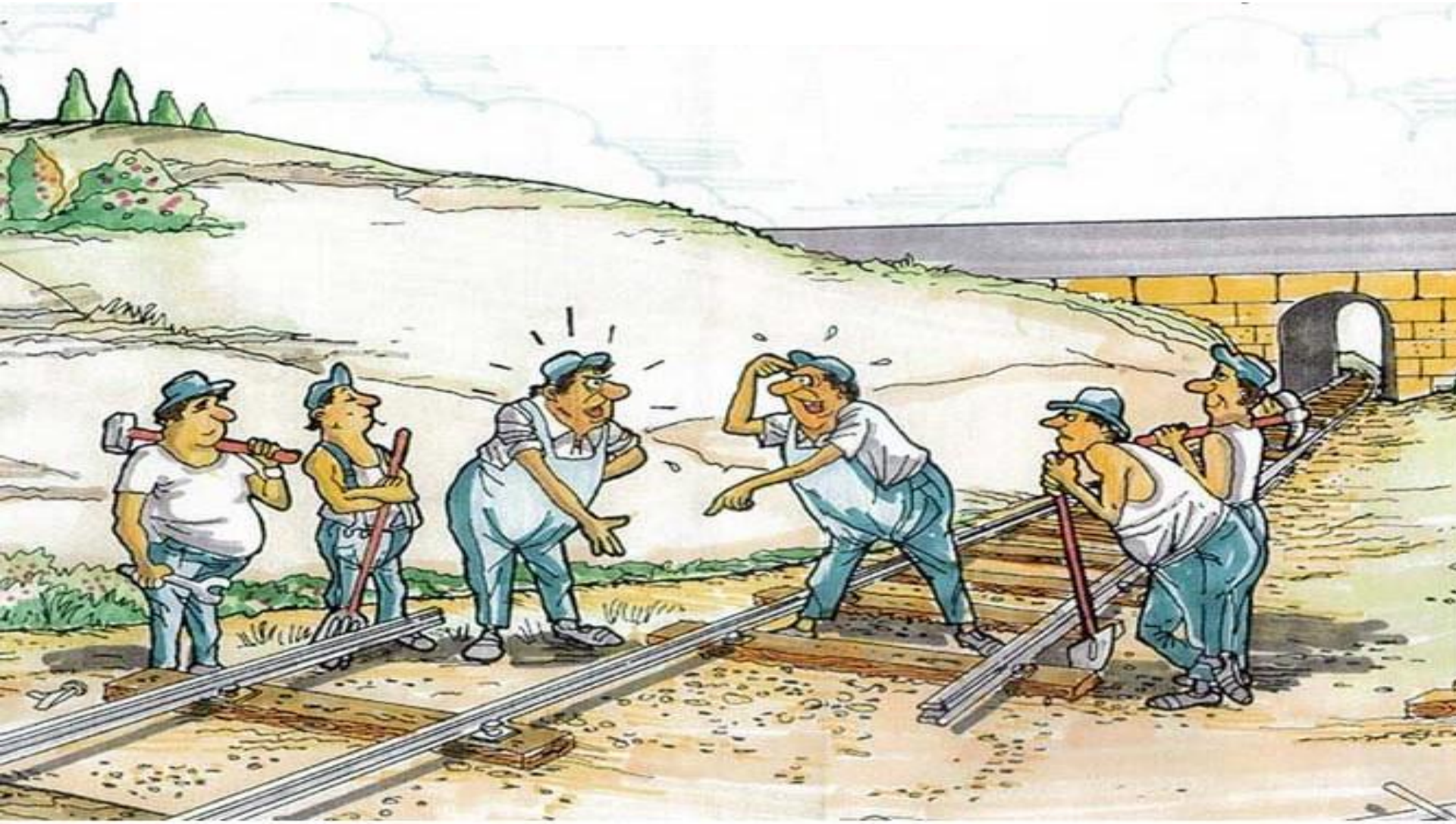


Dikomey and Brammer 2000 Int J Radiat Biol 76, 773-781

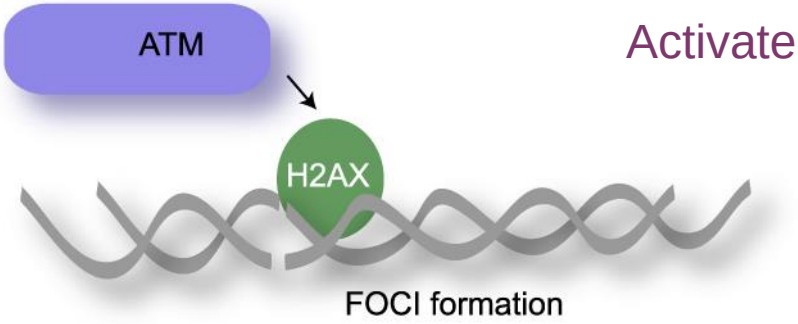
Fast and slow repair of DSB
Repair is finished after 12 h (98% will be repaired in normal fibroblasts)
Repair kinetics is independent of dose

CFGE: constant field gel electrophoresis

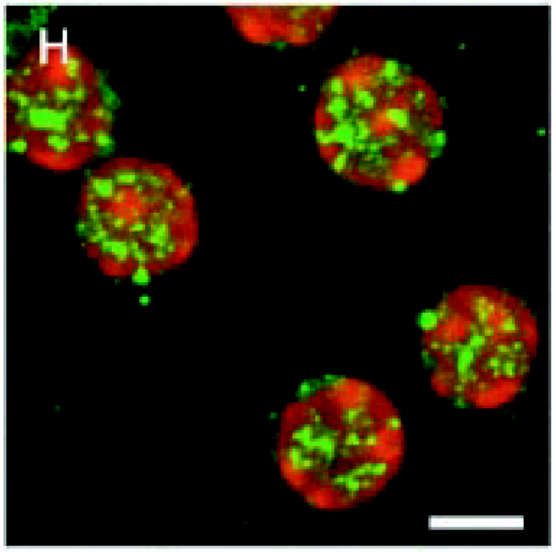
How are DNA double strand breaks repaired ?



DNA Damage Response & Repair



Activated ATM phosphorylates Histone H2AX



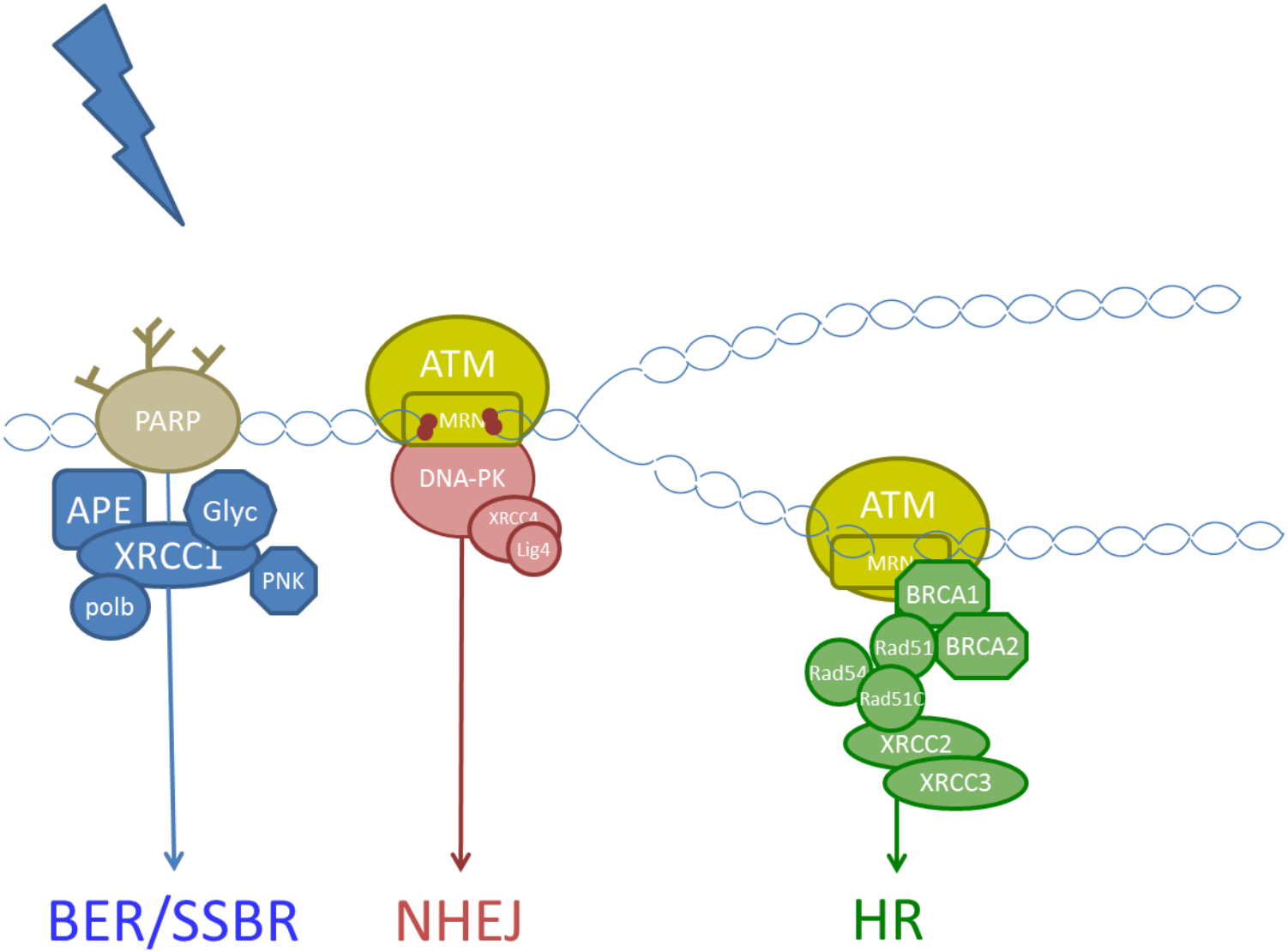
Phosphorylation of histone H2AX

Form within minutes at every DSB in the cell

Opening up of DNA to allow access of other repair factors; recruits repair proteins

Phosphorylated H2AX (γH2AX)
often used as a marker for DSBs

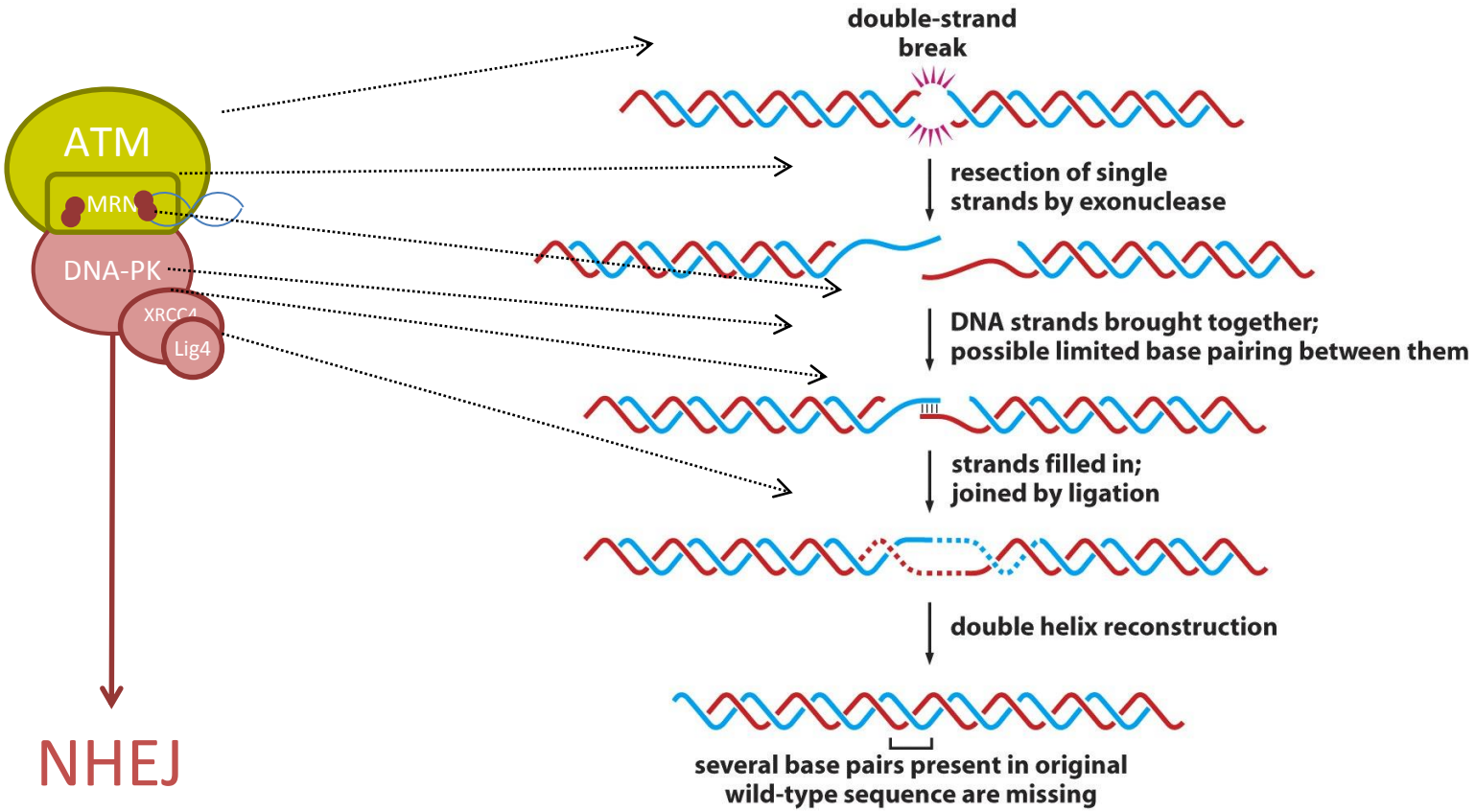
DNA Damage Response & Repair



NHEJ: Non-homologous end joining

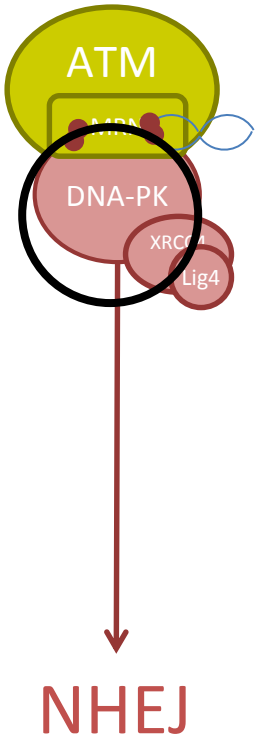
HR: Homologous recombination

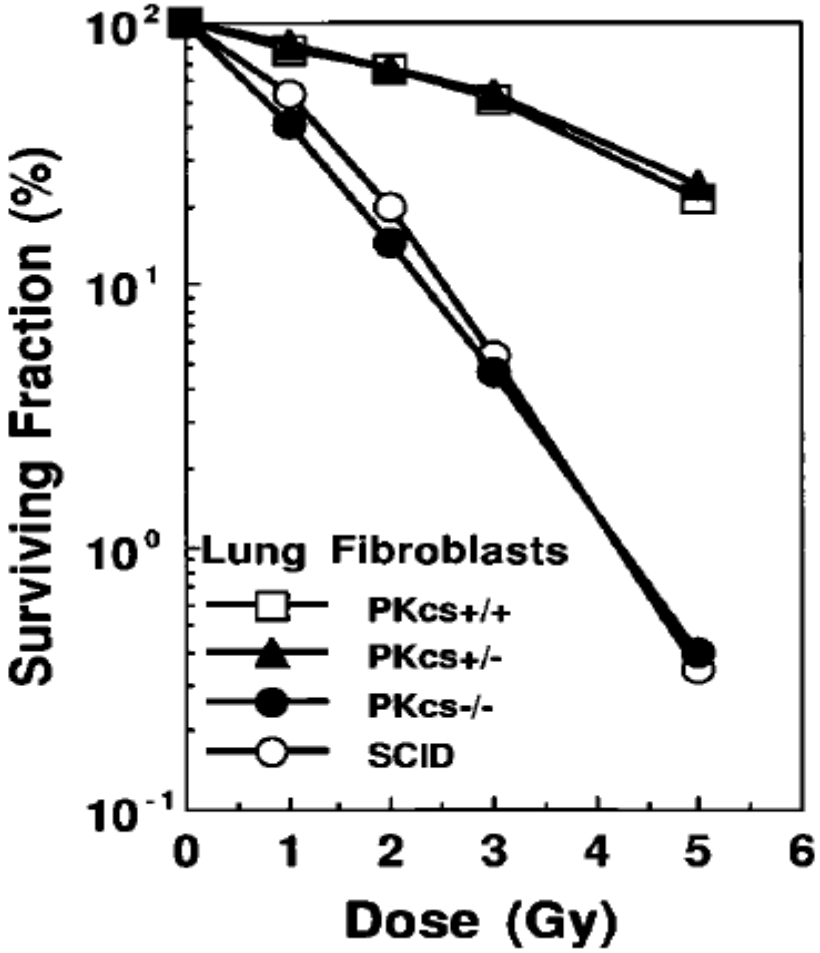
DNA Damage Response & Repair



DNA Damage Response & Repair

Non-homologous endjoining defects affect radiosensitivity



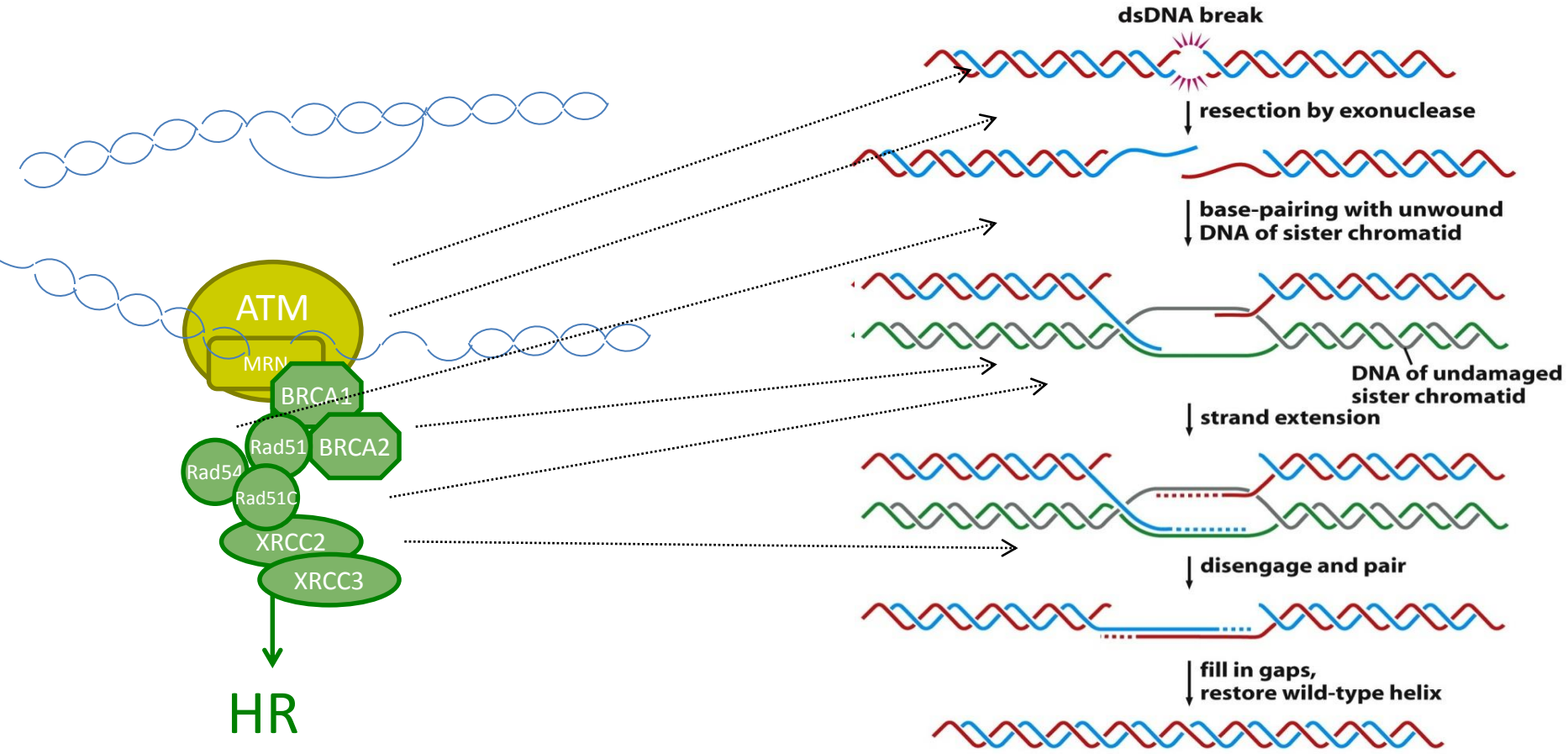


NB. PKcs = DNA-PKcs = PRKDC

Kurimasa A et al PNAS 1999

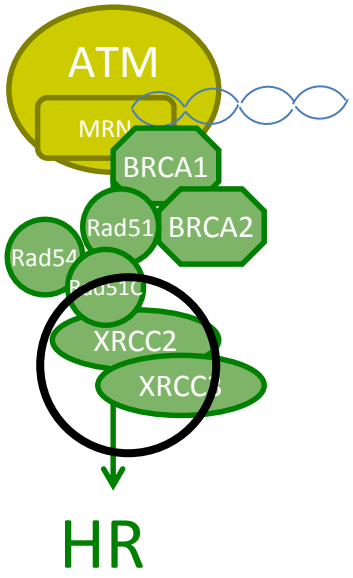
Erami A et al NAR 1998

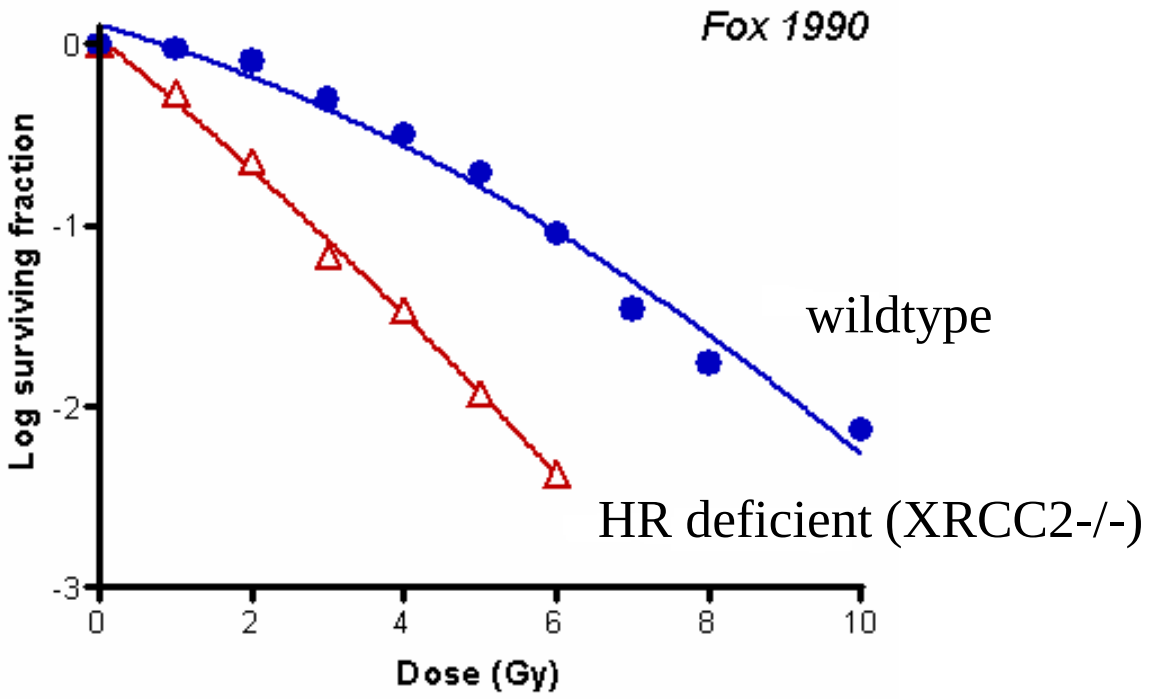
DNA Damage Response & Repair



DNA Damage Response & Repair

Homologous recombination defects affect radiosensitivity

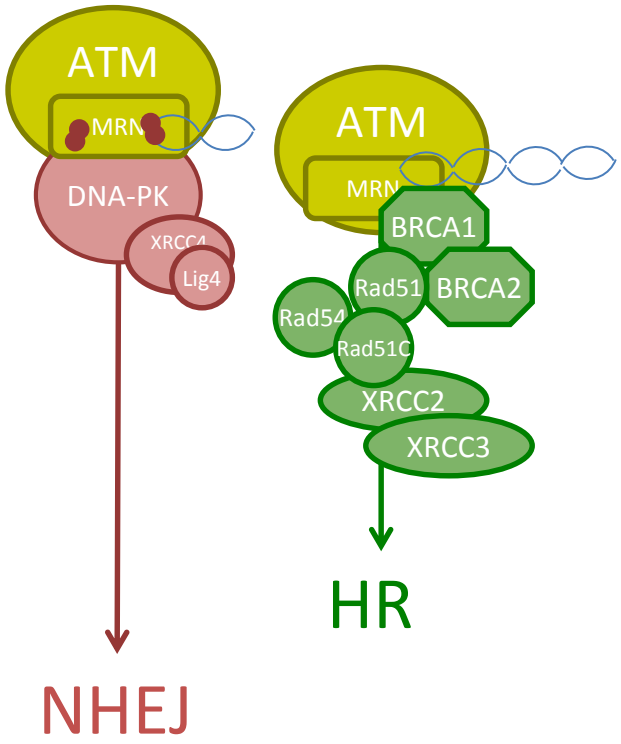




Kurimasa A et al PNAS 1999

Erami A et al NAR 1998

DNA Damage Response & Repair

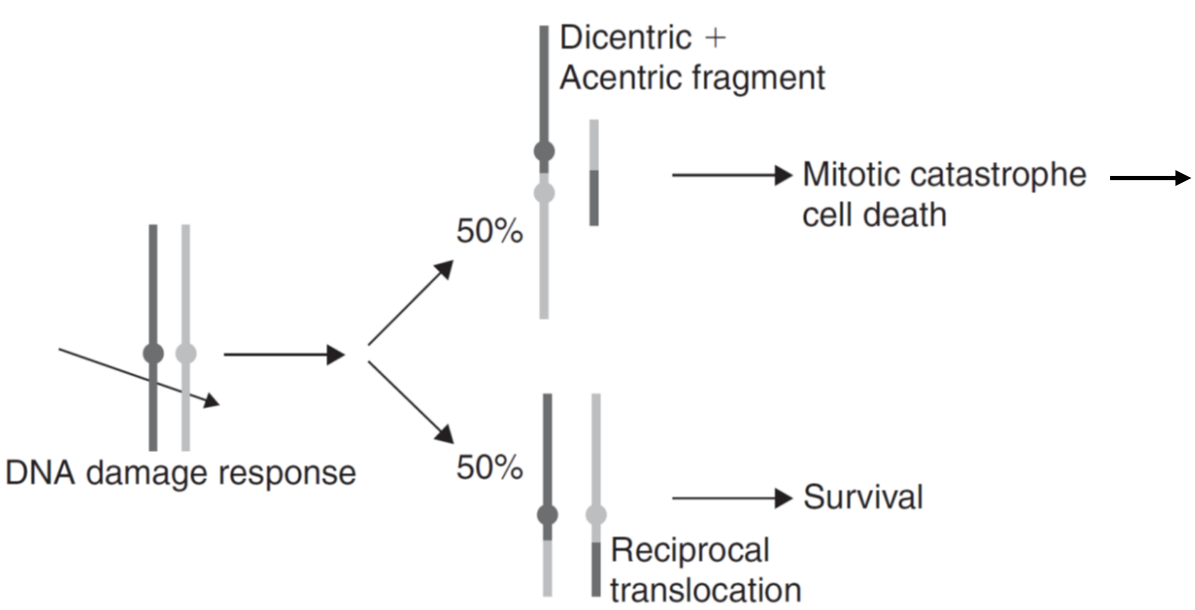


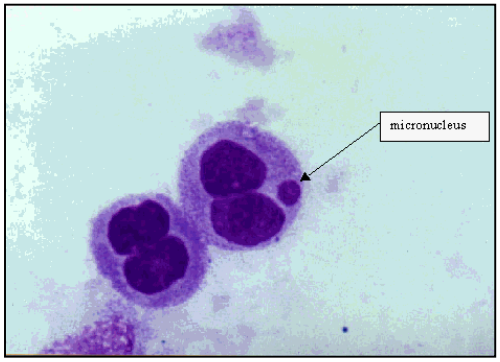
NHEJ:
- repairs DSBs
- strongly determines radiosensitivity in cells, animals and humans
- acts throughout the cell cycle

HR:
- repairs DSBs in S and G2
- determines radiosensitivity in S and G2
- error-free since using the sisterchromatid as template
- also relevant for replication associated DSB repair

SSBR:
- Repairs SSBs
- Determines radosensitivity
probably due to the conversion of SSBs to DSBs

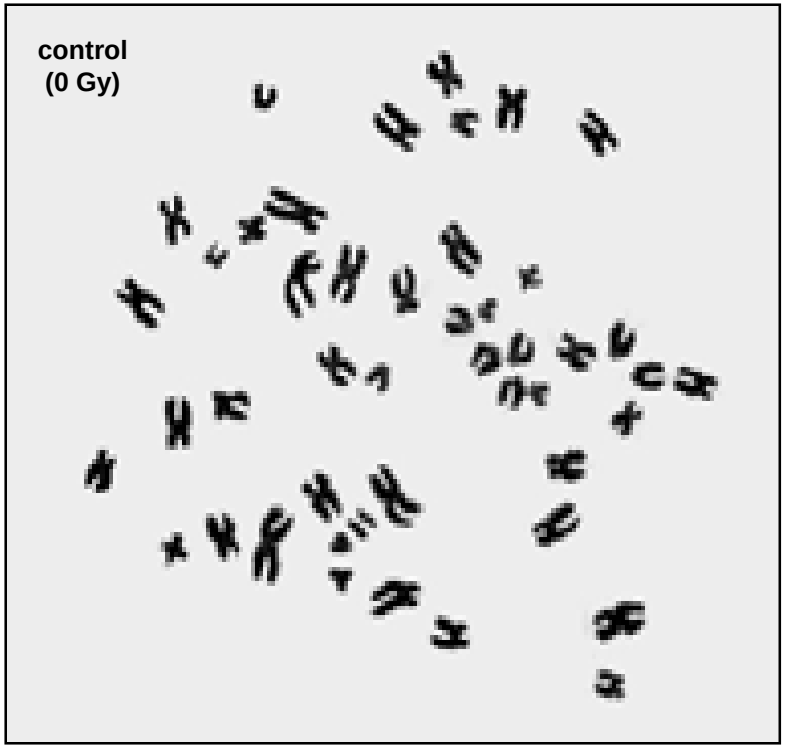
Chromosomal aberrations by Ionizing Radiation → Loss of clonogenicity (Inactivation)

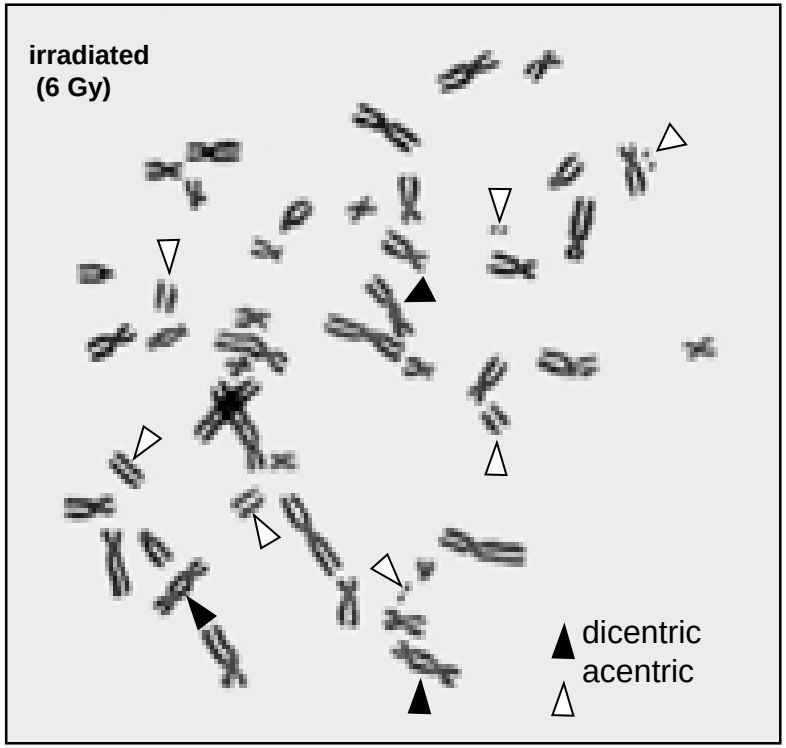


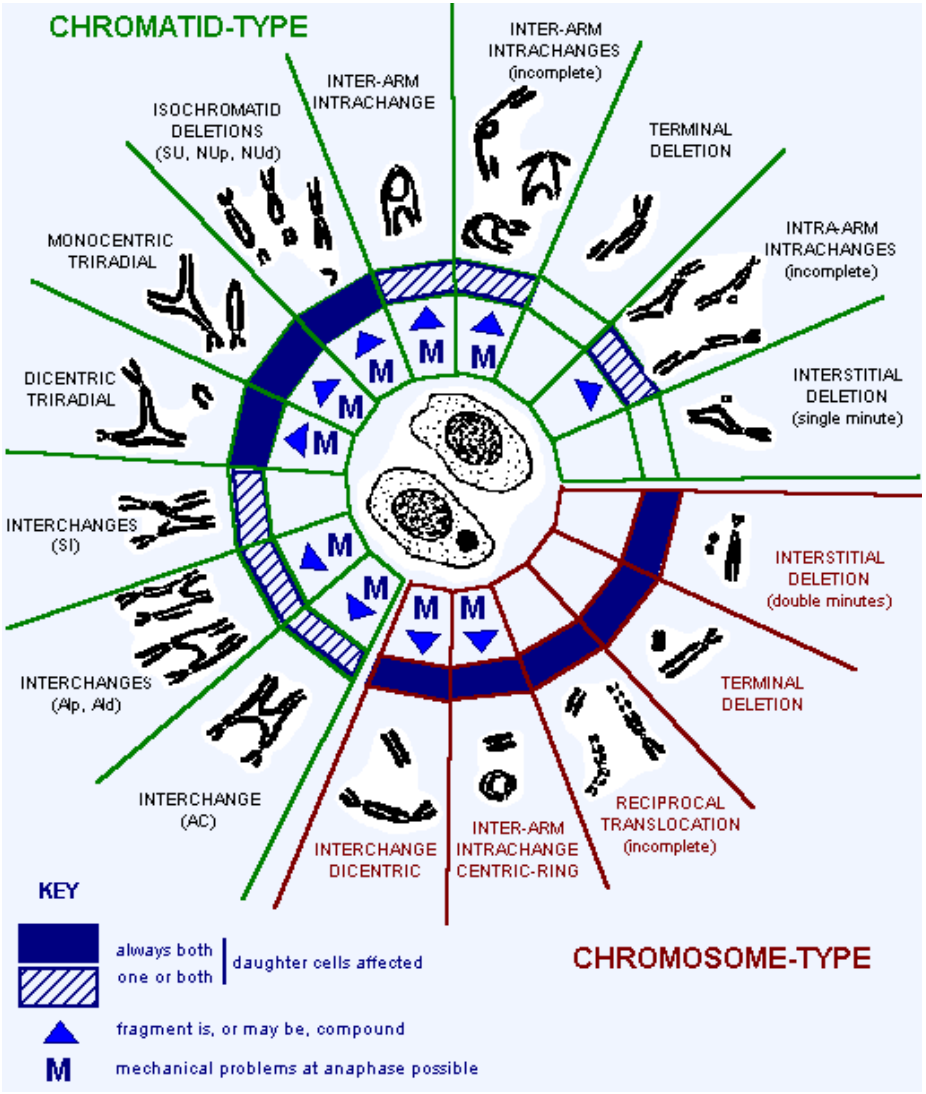


- Formation of anaphase bridges and azentric fragments
- Azentric fragments are removed via micronuclei : loss of DNA :: Loss of essential proteins
- Dicentric fragments/anaphase bridges will lead to mitotic catastrophe

Chromosomal aberrations







Examples of 2-lesion *Chromosome-type* aberrations

	INTERCHANGE	INTER-ARM INTRACHANGE	INTRA-ARM INTRACHANGE	"BREAK" DISCONTINUITY
A	dicentric	centric-ring	interstitial deletion	
S	reciprocal translocation	pericentric inversion	paracentric inversion	

http://atlasgeneticsoncology.org/Deep/Chromaber.html

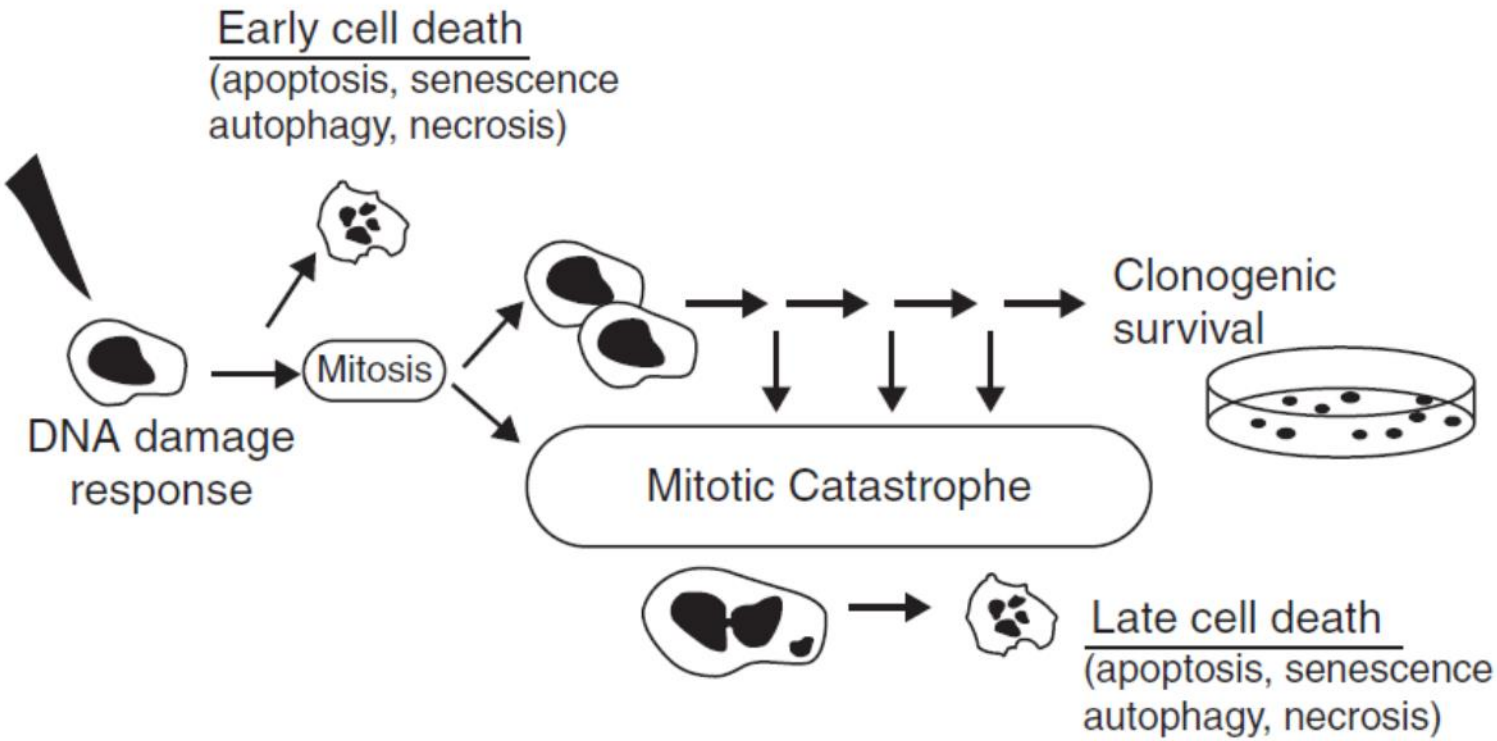
Examples of 2-lesion *Chromatid-type* aberrations

	INTERCHANGE	INTER-ARM INTRACHANGE		INTRA-ARM INTRACHANGE		"BREAK" DISCONTINUITY
		intra-chromatid	inter-chromatid	intra-chromatid	inter-chromatid	
A	dicentric	(=centric ring)	(=dicentric)	interstitial deletion	isochromatid deletion	
S	reciprocal translocation	pericentric inversion	duplication/ deletion	paracentric inversion	(=duplication/ deletion)	some are incomplete intra-arm intrachanges

Chromatid-type where the breaks and re-joins affect only one of the sister-chromatids, at any one locus

Chromosome-type where the breaks and re-joins always affect both sister-chromatids at any one locus

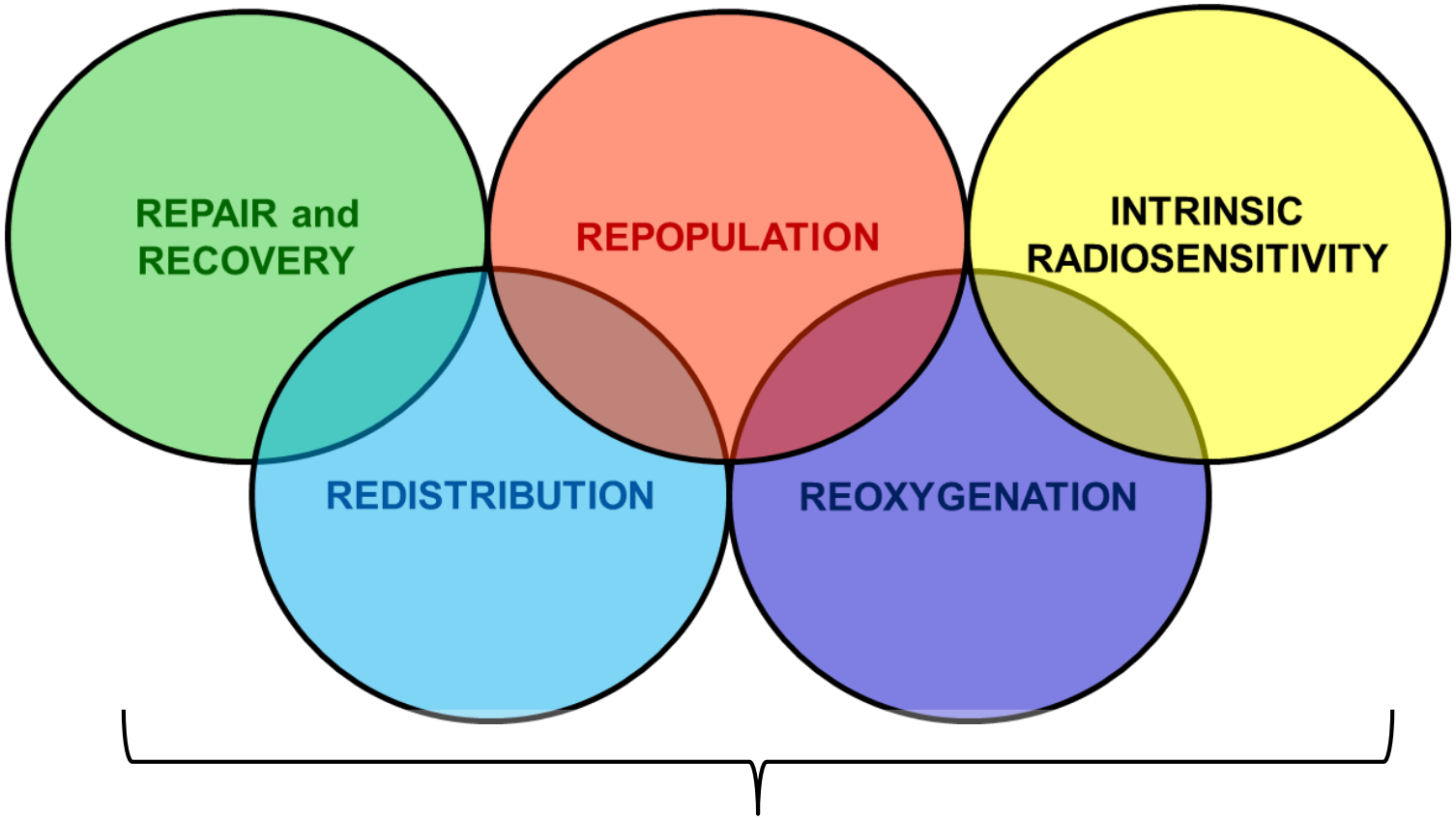
Early and Late Cell Death



1) IR-induced DNA damage elicits activation of DNA damage response
2) In certain rare cells: induction of apoptosis and other forms of cell death
3) In most cases, cells die after attempting mitosis
4) Improperly repaired damage causes mitotic catastrope, which can take place after the first attempt at cell division or after several rounds of proliferation

➢ late cell death

«HALLMARKS OF RADIOTHERAPY»
FACTORS INFLUENCING LOCAL TUMOR CONTROL



«5 R's of Radiotherapy»
(local tumor effect)

HR. Withers, 1975
GG Steel, 1989

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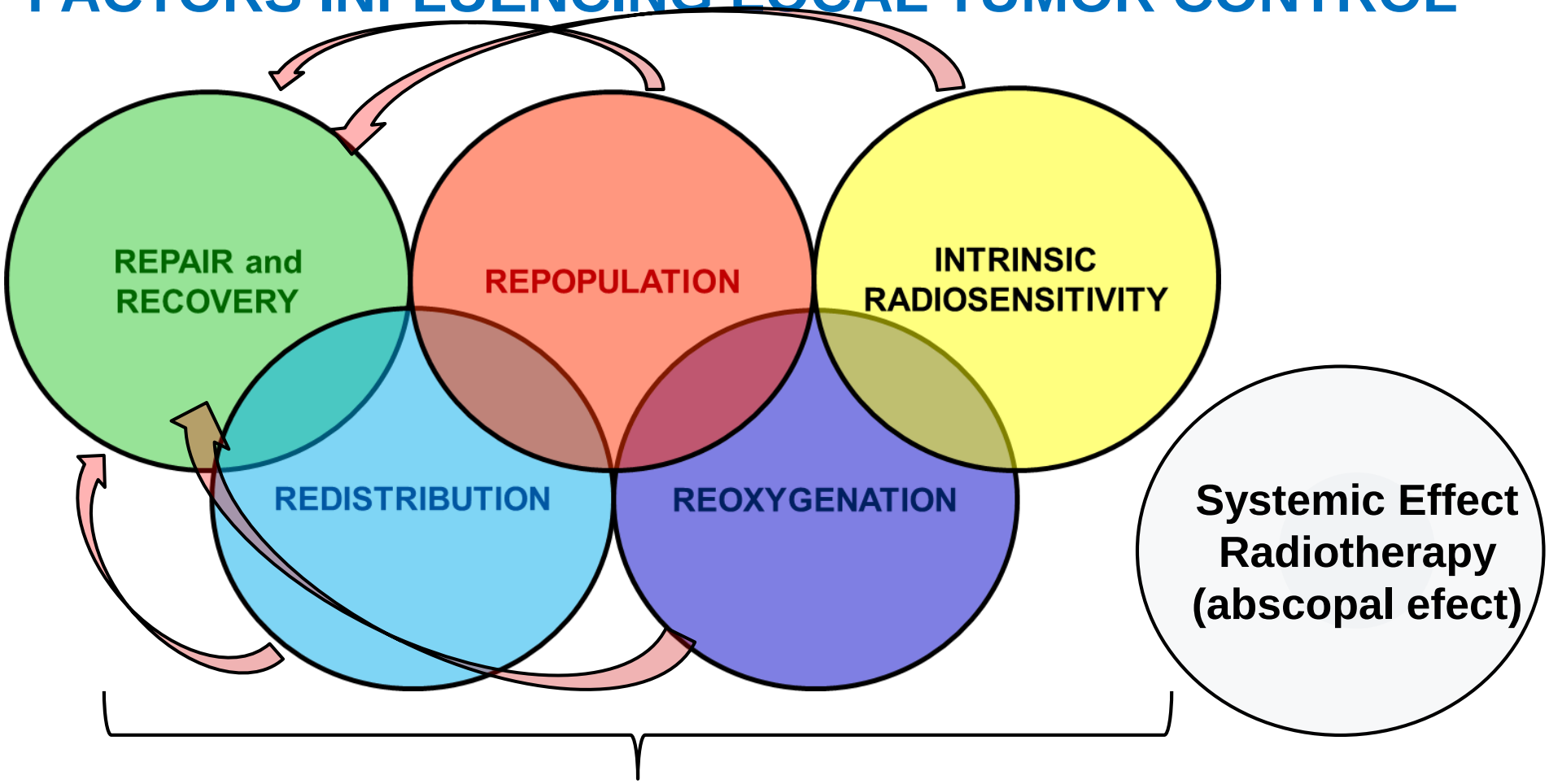

«5 R's of Radiotherapy»
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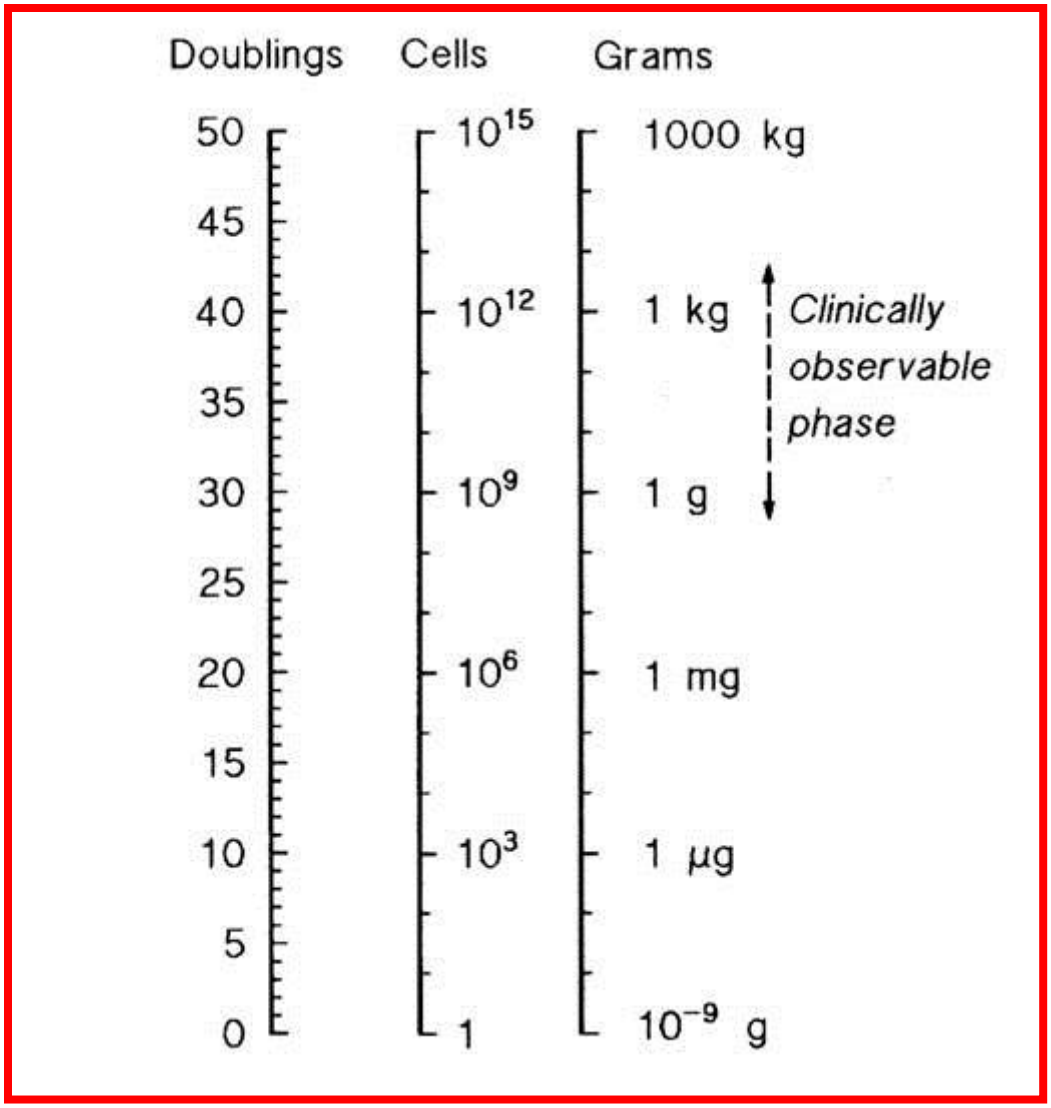
Cure = min kill of 10^9 cells



Summary

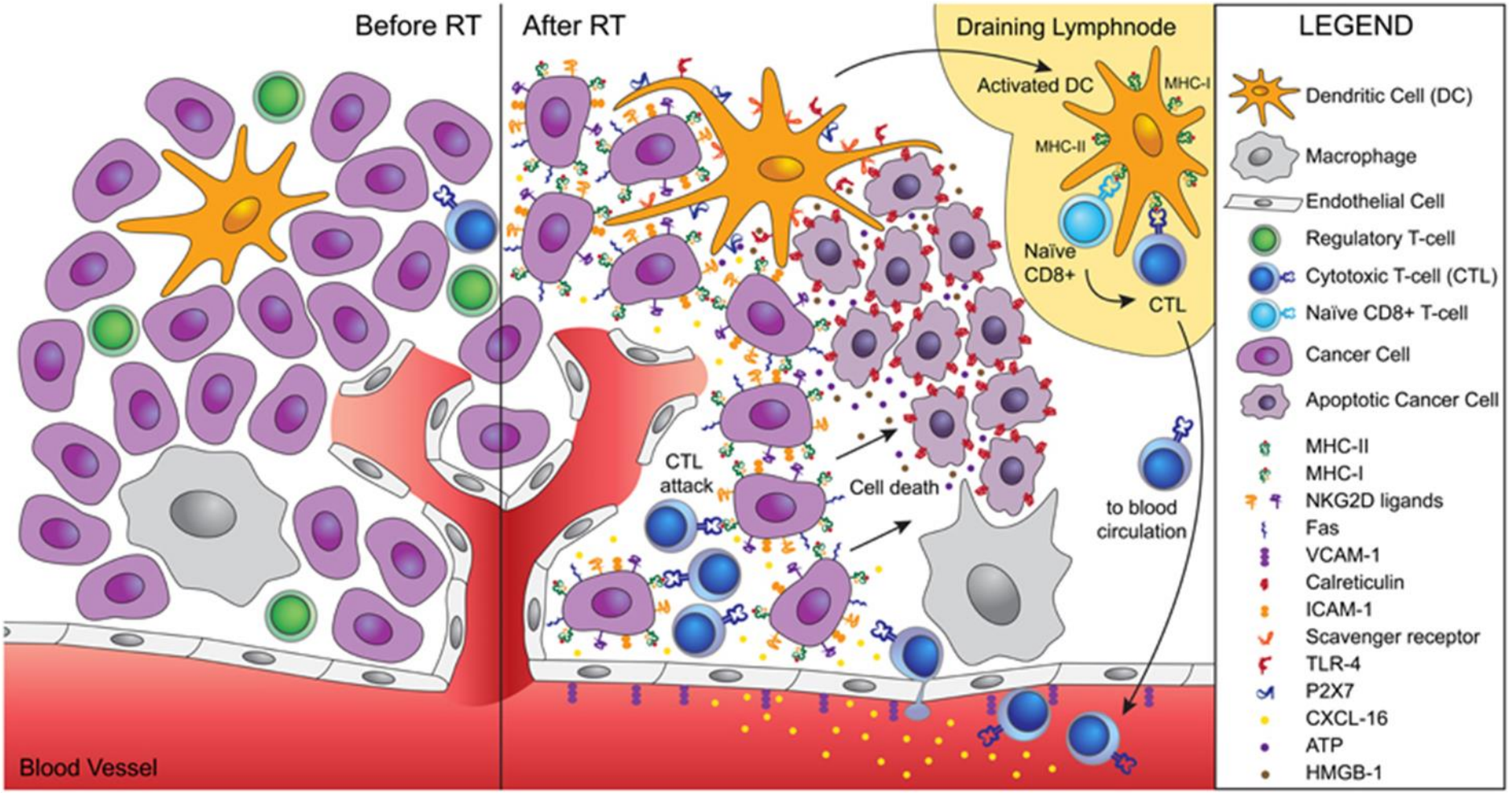
The classic 5 R's of Radiotherapy are nowadays understood on the molecular level

RT-induced DNA-damage is (still) the most relevant RT-induced insult

RT-induced processes on the molecular, cellular, tumor microenvironment level act as targets for combined treatment modalities

Is Rejection of neoplastic lesions by immune system a novel «R»?

Irradiated Tumor: In Situ Individualized Vaccine ?

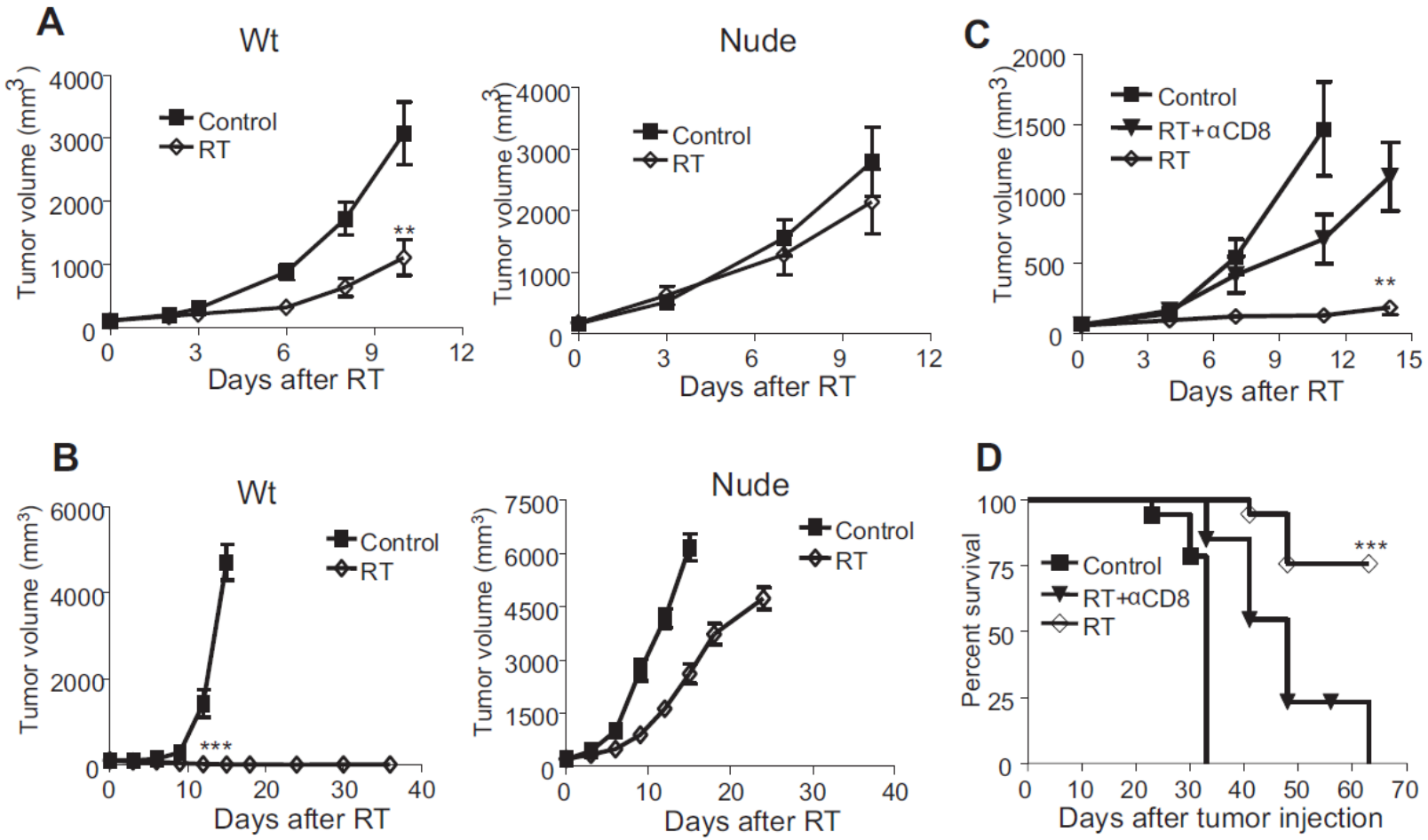


Demaria; Formenti et al. 2012,

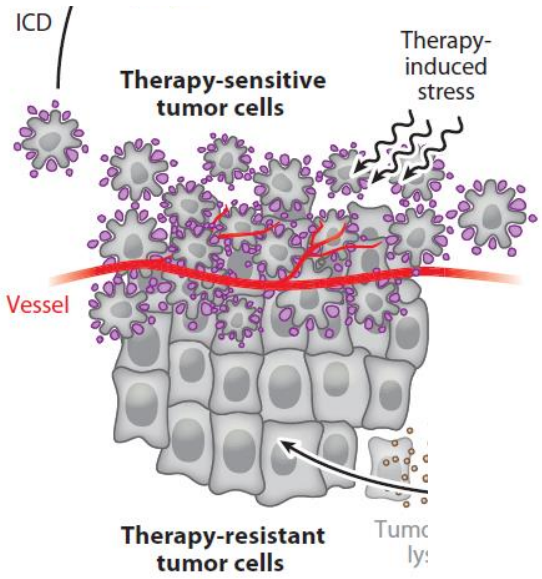
➢ Immunogenic Cell Death

Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment

*Youjin Lee,[1] *Sogyong L. Auh,[1] Yugang Wang,[1] Byron Burnette,[1] Yang Wang,[1] Yuru Meng,[2] Michael Beckett,[2] Rohit Sharma,[3] Robert Chin,[1] Tony Tu,[1] Ralph R. Weichselbaum,[2] and Yang-Xin Fu[1]



Immunogenic Cell Death induced by RT



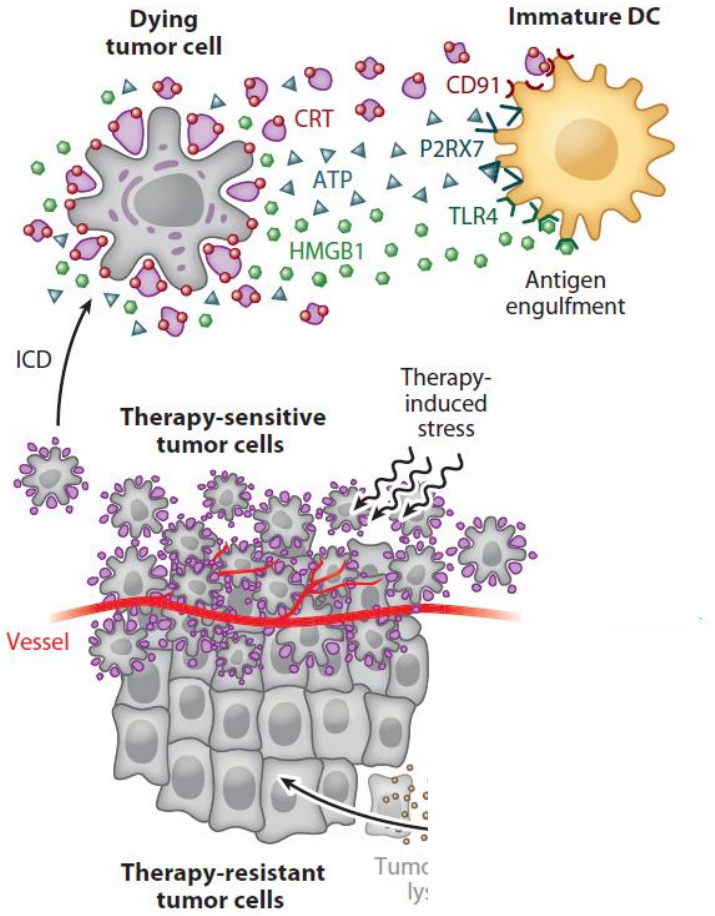
Properties of Immunogenic Cell Death:

a) Exposure of calreticulin, secretion of ATP, release of HMGB1

b) Recruitment of DCs into tumor bed, optimal antigen presentation to T cells

c) Followed by potent immune-response

Immunogenic Cell Death induced by RT



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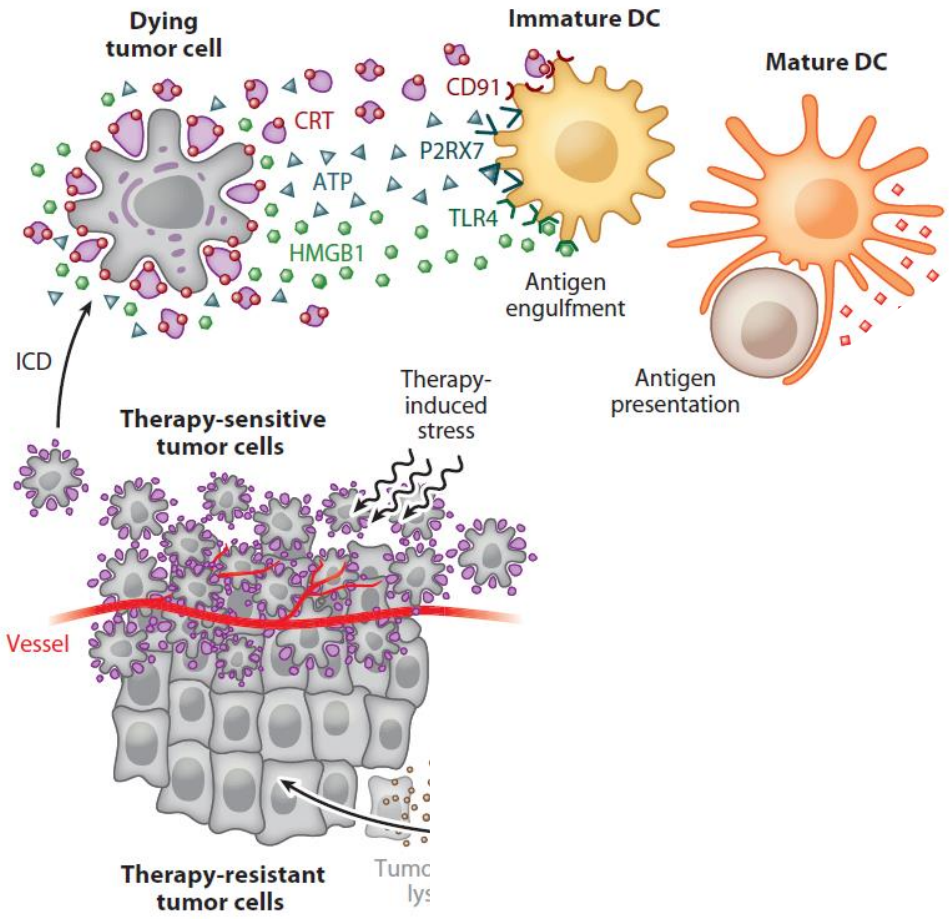

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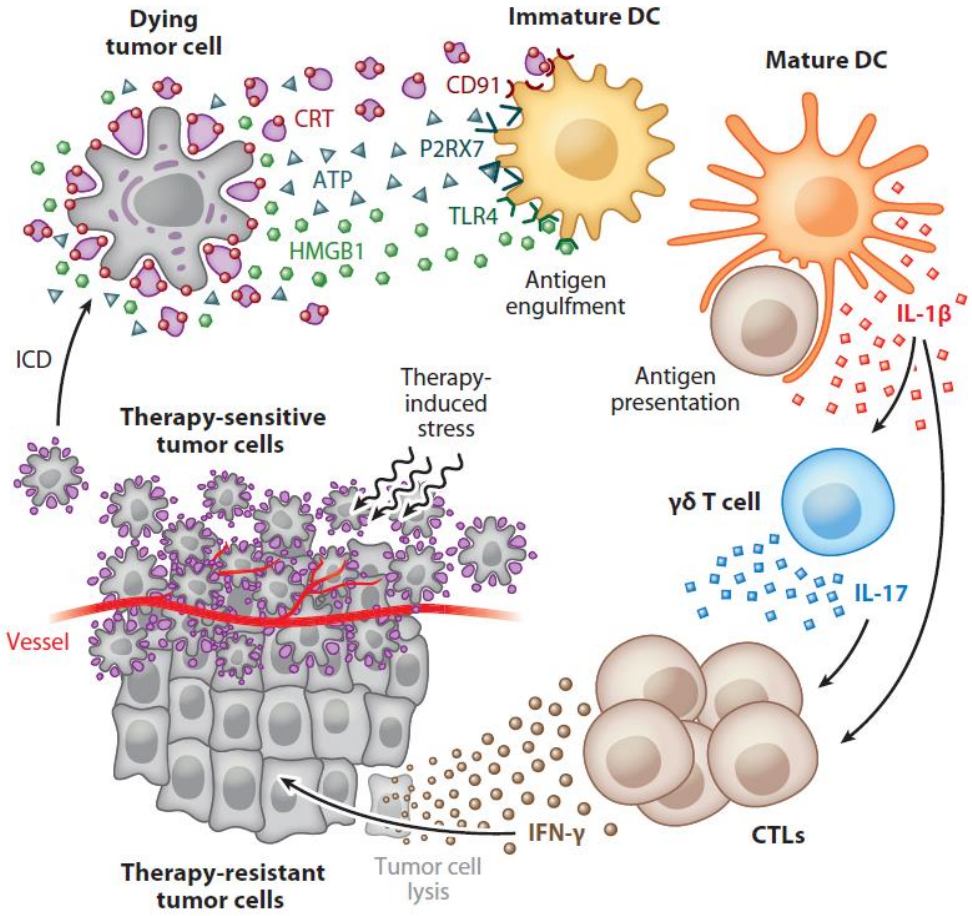

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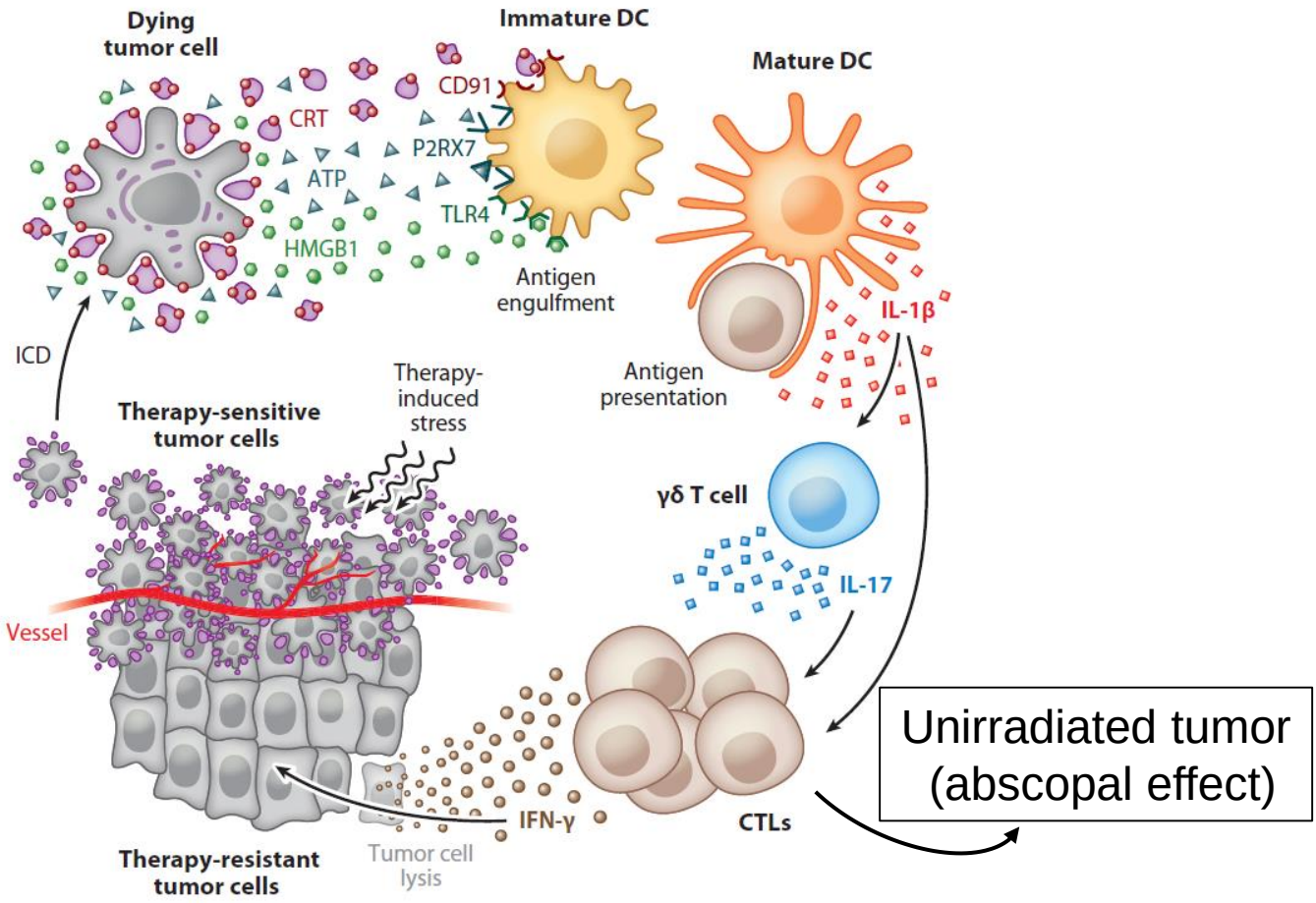

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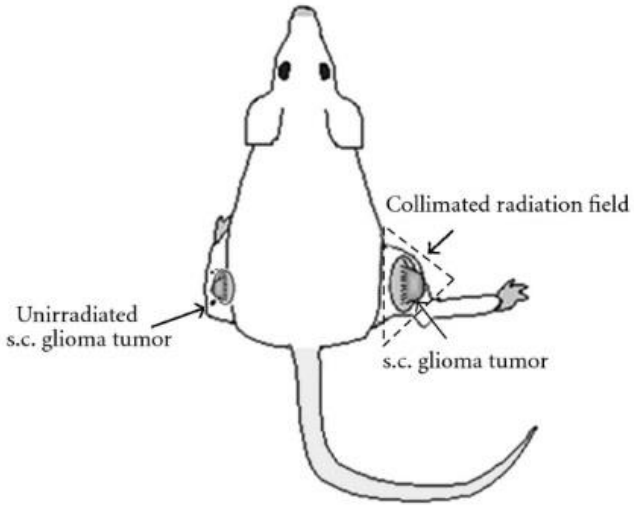
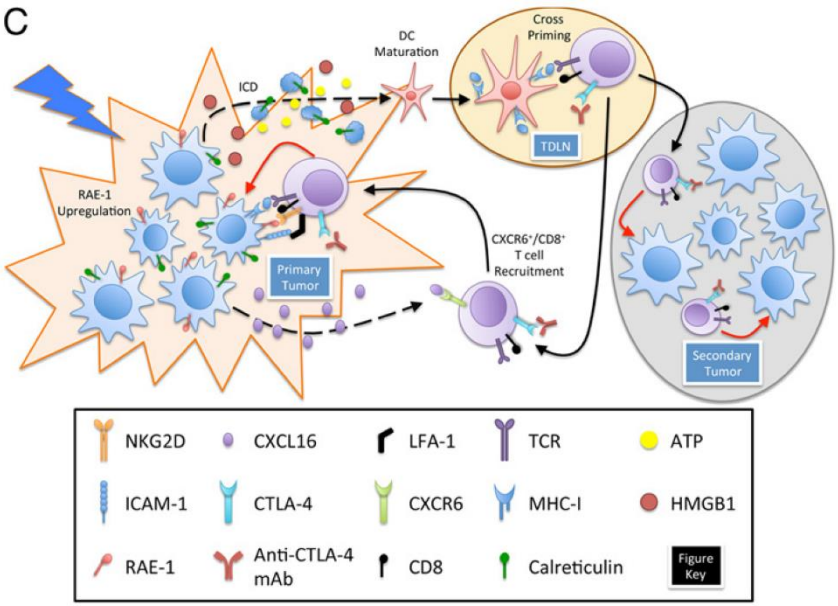
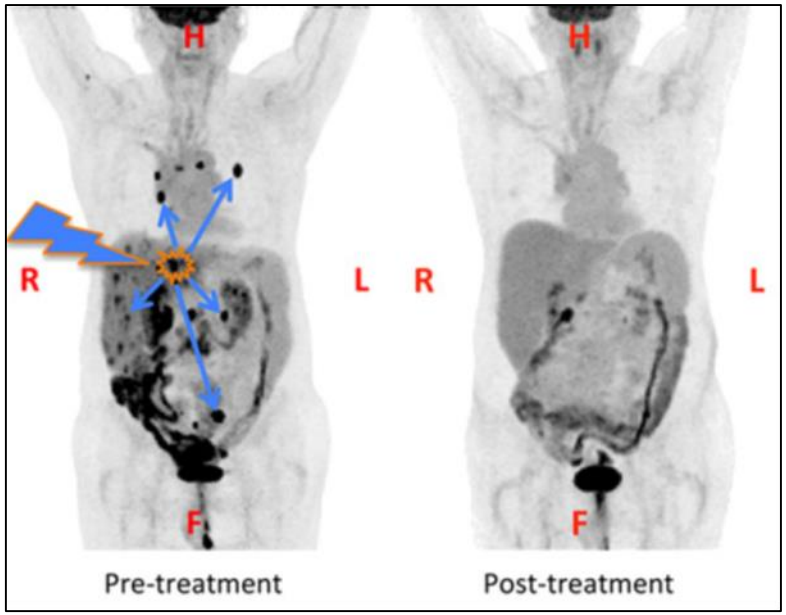
Abscopal effect







Pre and 1 y post-treatment PET:
lung cancer patient treated for single intrahepatic metastasis (RT plus ipilimumab)

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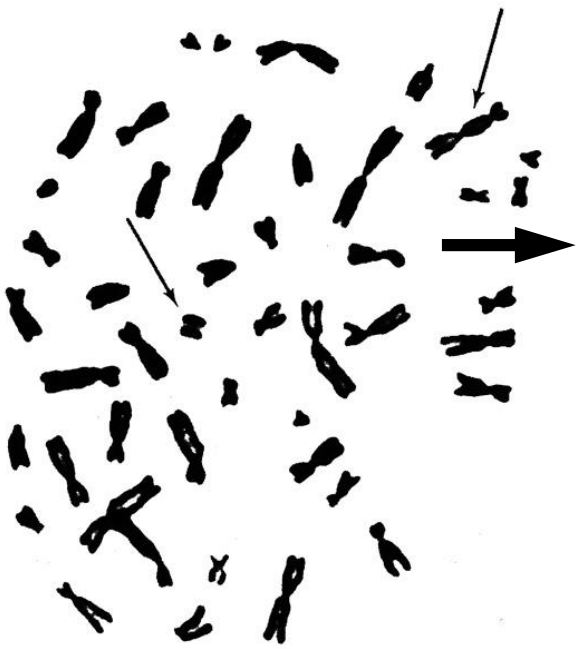
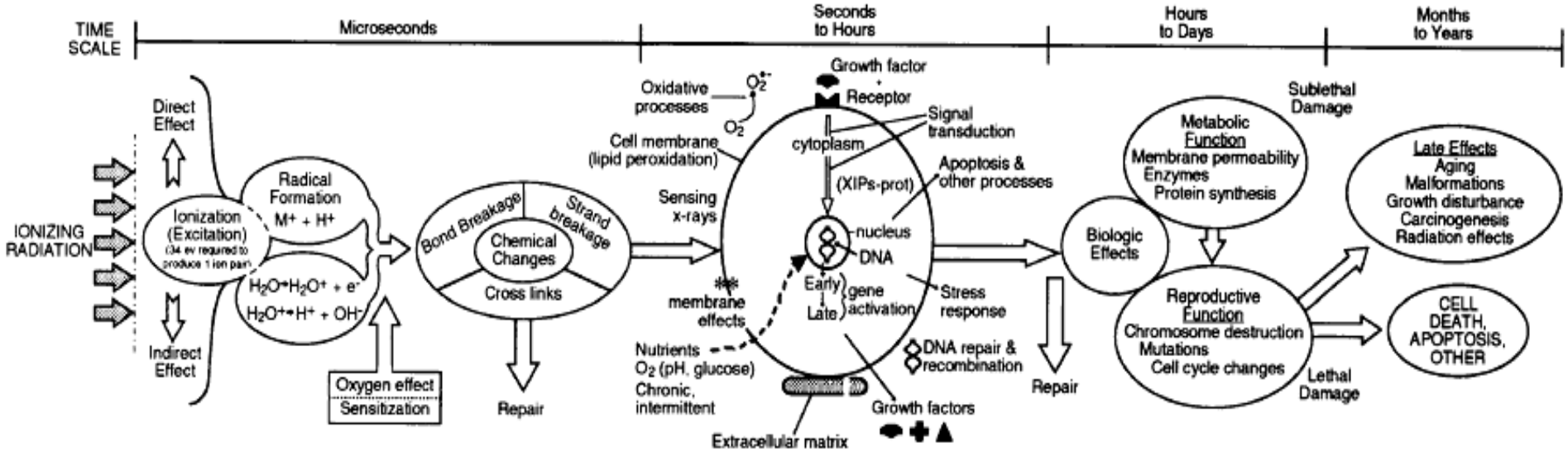
Is Rejection of neoplastic lesions by immune system a novel «R»?

UniversityHospital
Zurich

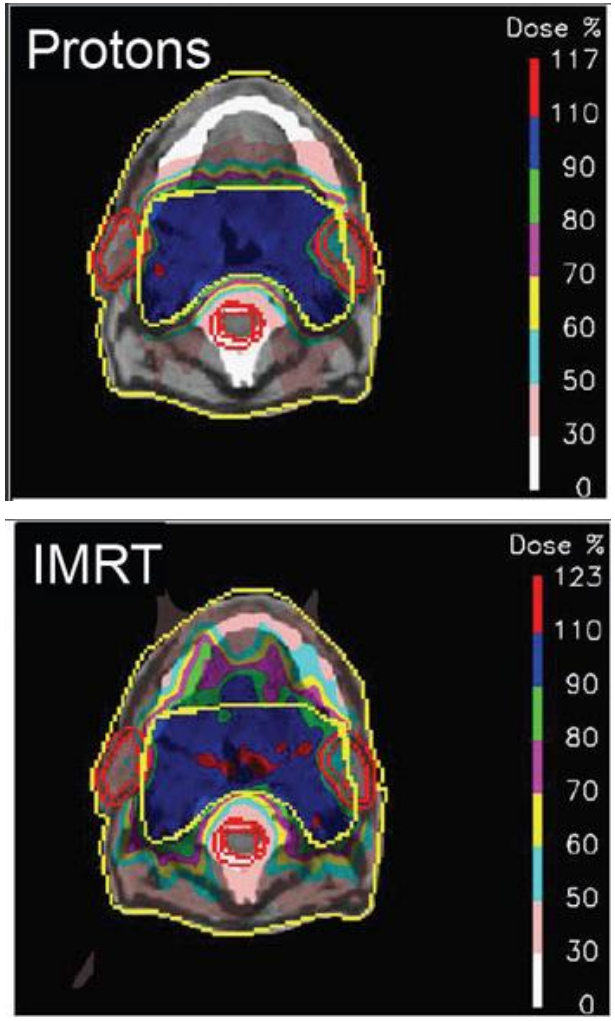
Ionizing Radiation Induced Processes



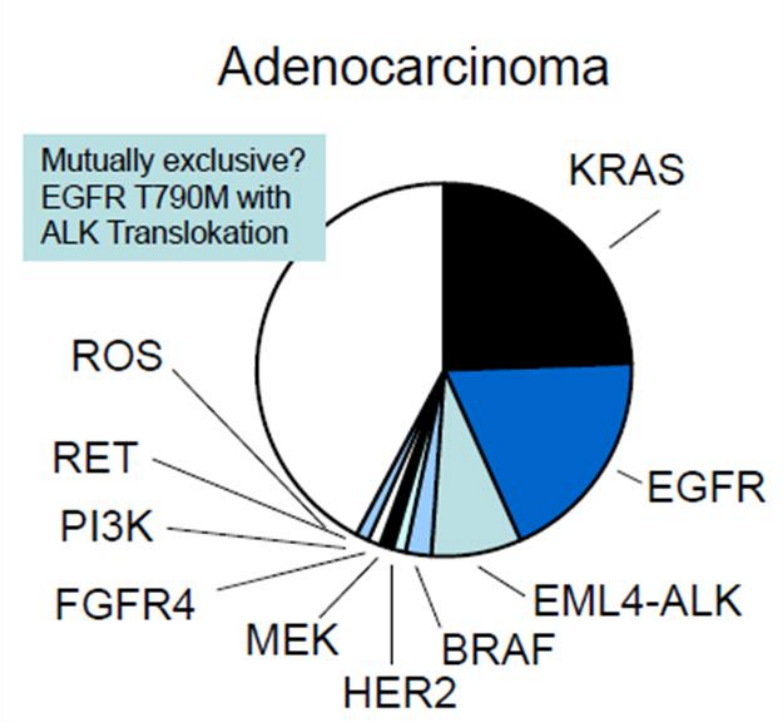
Micronucleus



Major Challenge: Personalized Treatment



The integral dose difference between protons and IMRT



Biology-based Personalized Protocols

Stratification not only based on Clinical Parameters