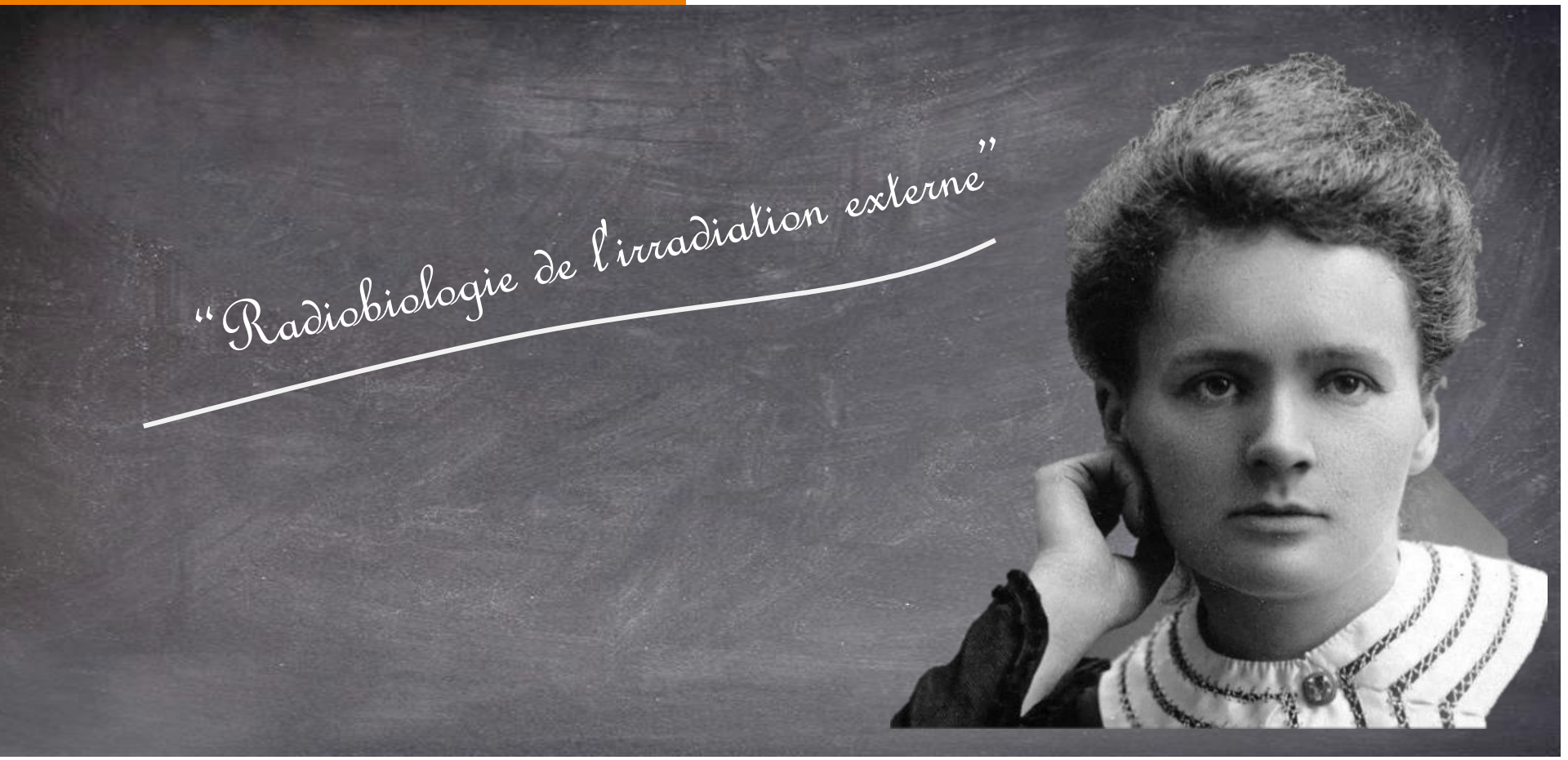
DUTREIX Marie

RIV meeting, Montpellier

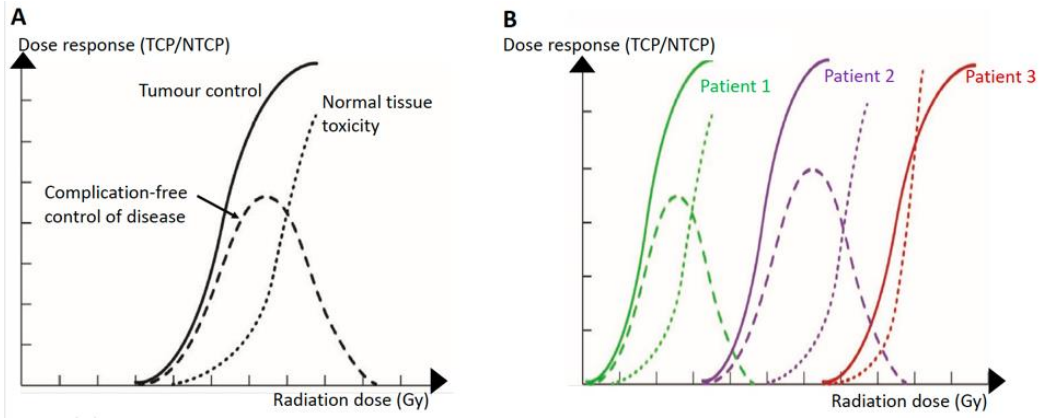
- 16/03/2022



ENSEMBLE, PRENONS
LE CANCER DE VITESSE

institut Curie

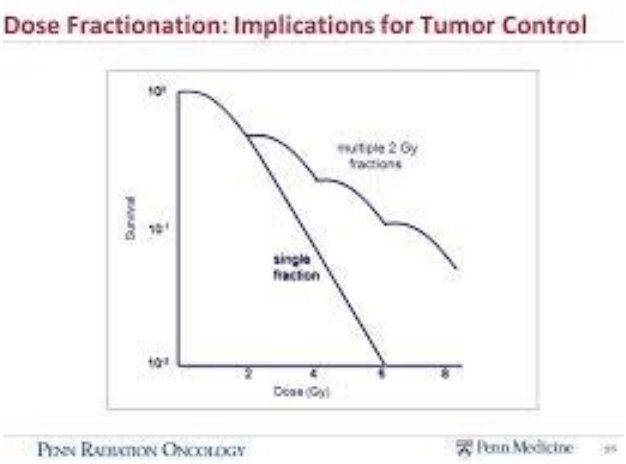
Radiotherapy is a compromise between toxicity and efficacy



Kaidar-Person O, et al. Lancet Oncol. 2021 Aug 4:S1470-2045(21)00411-3. doi: 10.1016/S1470-2045(21)00411-3. Online ahead of print.

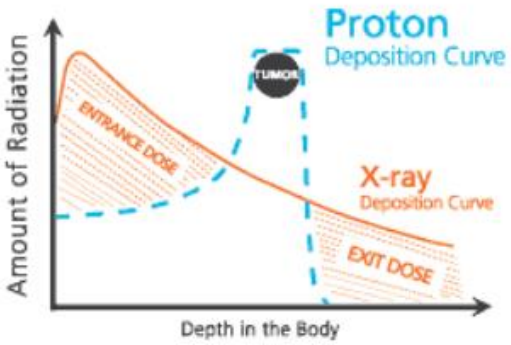
Fractionation of the treatment in sessions→ the best way to decrease toxicity

Delivering a small fraction of the total radiation dose **allows time for normal cells to repair themselves between treatments, thereby reducing side effects**.



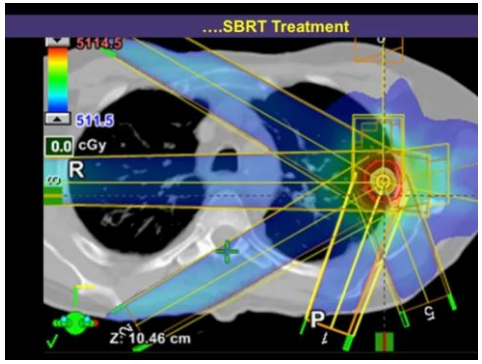
Techniques de radiothérapie modernes

Hadronthérapie



- Faible dose d'entrée
- Pas de dose de sortie

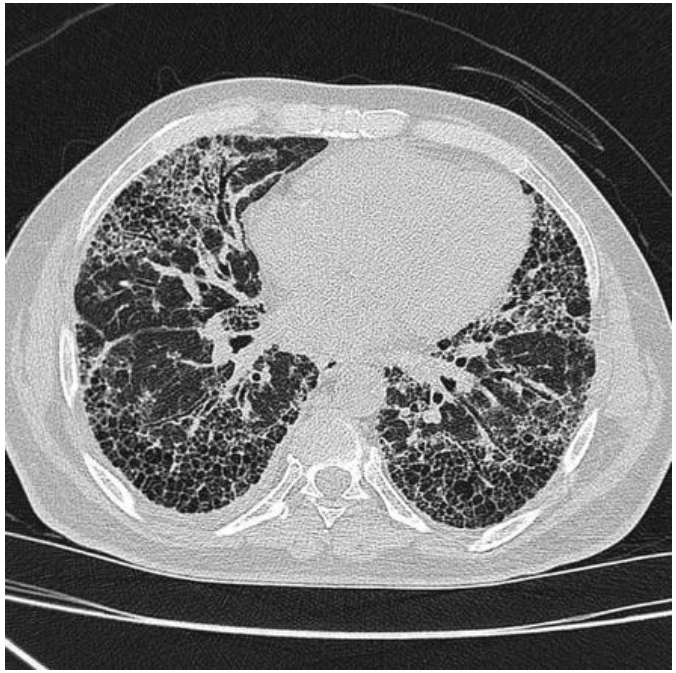
Radiothérapie stéréotaxique



- Faisceaux se rejoignant à la tumeur

Conclusion : Des améliorations récentes ont permis d'augmenter **l'effet différentiel** des rayonnements entre les tumeurs et les tissus sains.

Cependant …



➢ Des toxicités tardives comme la fibrose radio-induite surviennent chez **2 à 9 %** des patients traités par radiothérapie.

2 strategies developped in the Center of Research of Institut Curie

Use less toxic irradiation mode

FLASH

www.ScienceTranslationalMedicine.org 16 July 2014 Vol 6 Issue 245 245ra93

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

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*Corresponding author. E-mail: vincent.favaudon@curie.fr

REPORTS

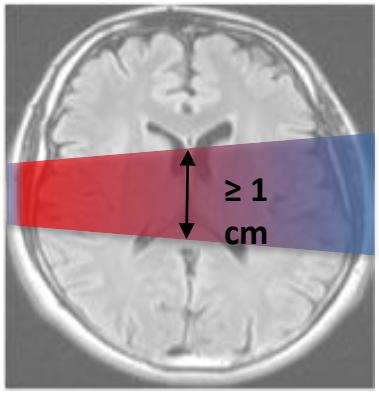
MiniBeam

Advancing proton minibeam radiation therapy: magnetically focussed proton minibeams at a clinical centre

Dutreix-RIV Montpellier

Spatially Fractionated Radiation Therapy (SFRT)

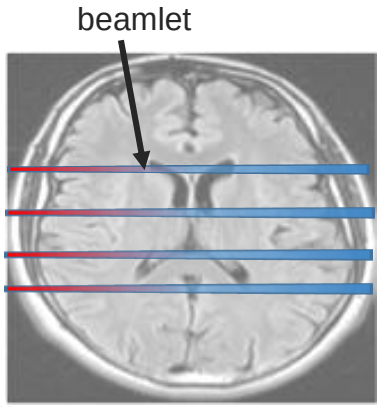
Standard RT

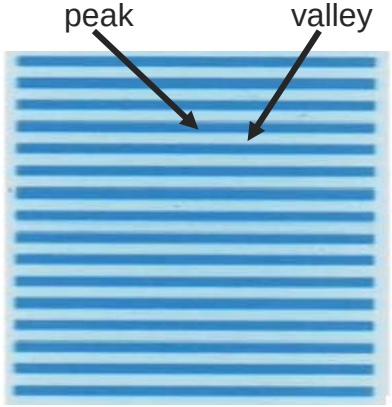


- large fields (≥ 1 cm)
- laterally homogeneous dose distributions

spatially fractionated RT techniques: GRID, Lattice, MBRT

SFRT



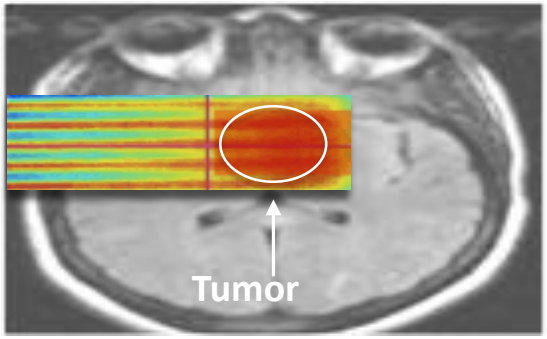


- field composed of smaller **beamlets**
- laterally **heterogeneous** dose distributions (*peaks* and *valleys*)

→ **increase** of **normal tissue tolerance**

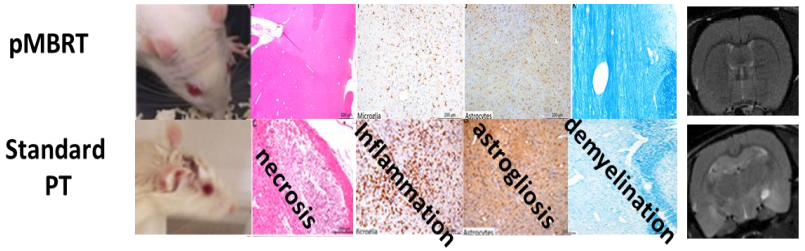
*PROTON*MBRT: an innovative therapeutic approach

Proton Minibeam Radiation Therapy
pMBRT



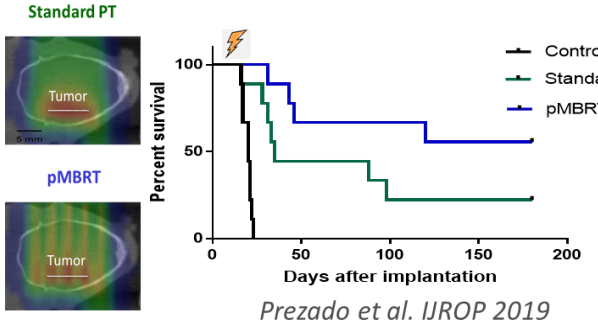
Prezado et al. 2013

Net reduction of neurotoxicity
(histology, IHC, MRI, and behavioral tests)

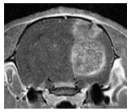


Prezado et al, 2017, Lamirault et al. 2020

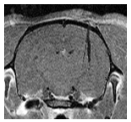
Equivalent or superior tumor (rat glioma) control than standard proton therapy (PT)



Prezado et al. IJROP 2019



5 days after IR

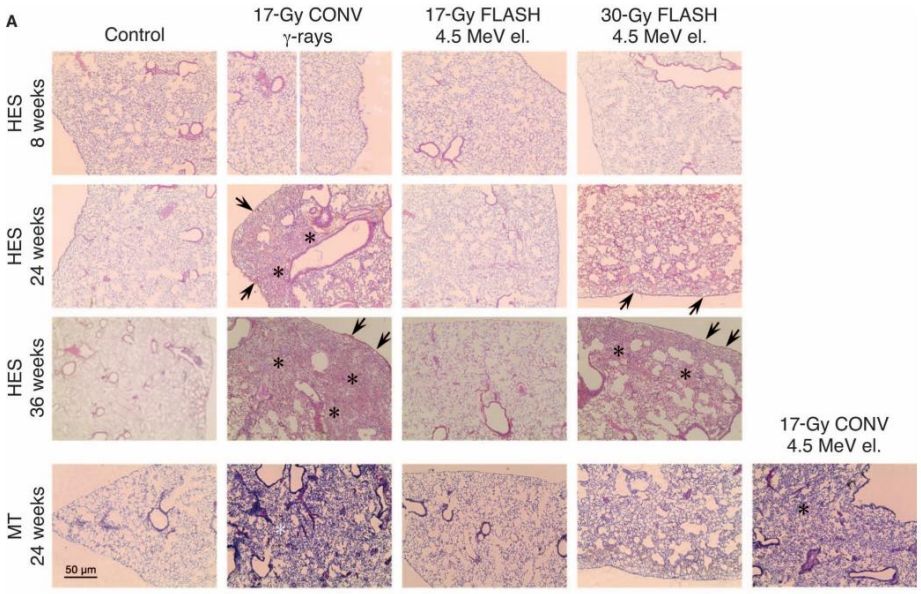


26 days after IR

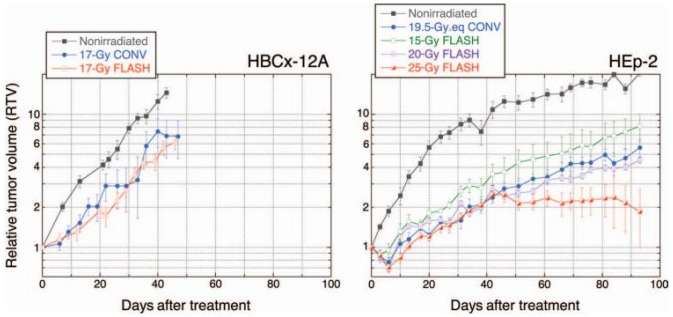
Time Fractionated Radiation

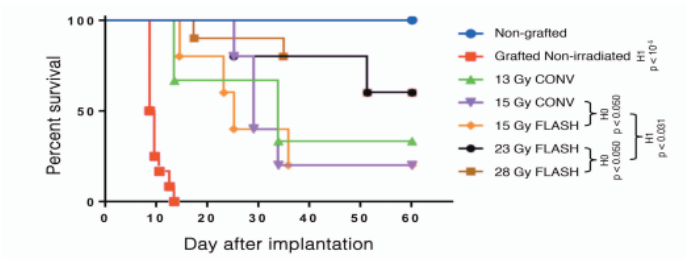
FLASH: an innovative therapeutic approach

Sparing of healthy tissues



Iso-efficacy on tumors





These results have been reproduced over the world using various instruments and target organs.
It seems to be a property of the irradiation mode of irradiation with high dose rate

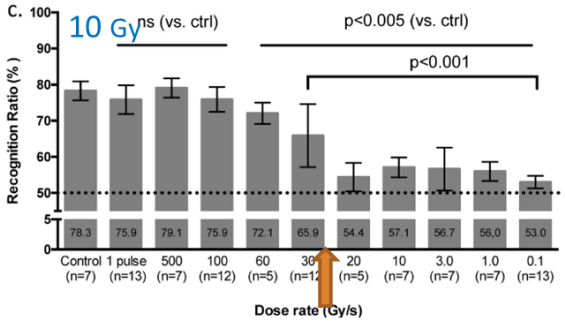
FLASH irradiation : dose delivery time ≤ 500 ms
dose rate ≥ 40 Gy/s

Time Fractionated Radiation Therapy & FLASH

FLASH irradiation

BRAIN

P. Montay-Gruel et al., Radiotherapy and Oncology (2017)

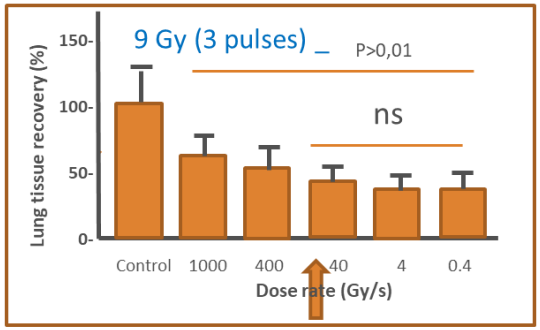


100% gain
FLASH vs CONV

- Preservation of memory and learning skills
- Preservation of neural stem cells

LUNG

C. Fouillade unpublished

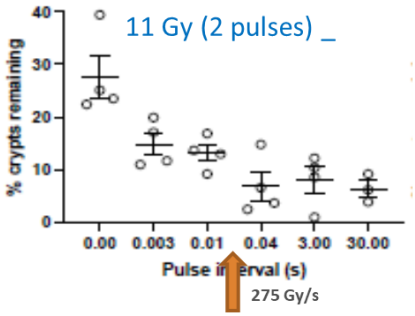


50% gain
FLASH vs CONV

- Proliferation capacity
- Preservation of lung stem cells

INTESTINE

J-L Ruan et al., Int J Radiation Oncology (2021)



50% gain
FLASH vs CONV

- crypts number
- Preservation of intestine stem cells

Same profiles
A dose rate threshold around 100Gy/s

The molecular mechanisms involved in tissues protection by FBRT or FLASH are not fully understood.

Radiation effect is a complex molecular effect

- **In direct action** the radiation interacts directly with the critical target in the cell. The atoms of the target itself may be ionized or ex cited through Coulomb interactions leading to the chain of physical and chem ical events that eventually produce the biological dam age. Direct action is the dominant process in interaction of high LET particles with biological materials.

- **For the indirect action** of x-rays

Physic	Step 1: Primary photon interaction (photoelectric effect, Compton effect, pair production) produces a high energy electron.
Chemistry	Step 2: The high-energy electron in moving through tissue produces free radicals in water.
Radiobiology	Step 3: The free radicals m ay produce changes in DNA from breakage of chemical bonds.
	Step 4: The changes in chemical bonds in many other targets than DNA (lipids, proteins, membranes….) result in biological effects.

Spontaneous and radio-induced DNA damage

Nature of the damage	Spontaneous (per cell/day)	Radio-induced (per Gy/cell/day)
Single strand break	10 000-55 000	1 000
Loss of base	12 600	?
Base damage	3 200	1 000
Double strand break	8	40
DNA-DNA crosslink	8	30
Protein-DNA crosslink	few	150
Multiple damage sites	few?	few

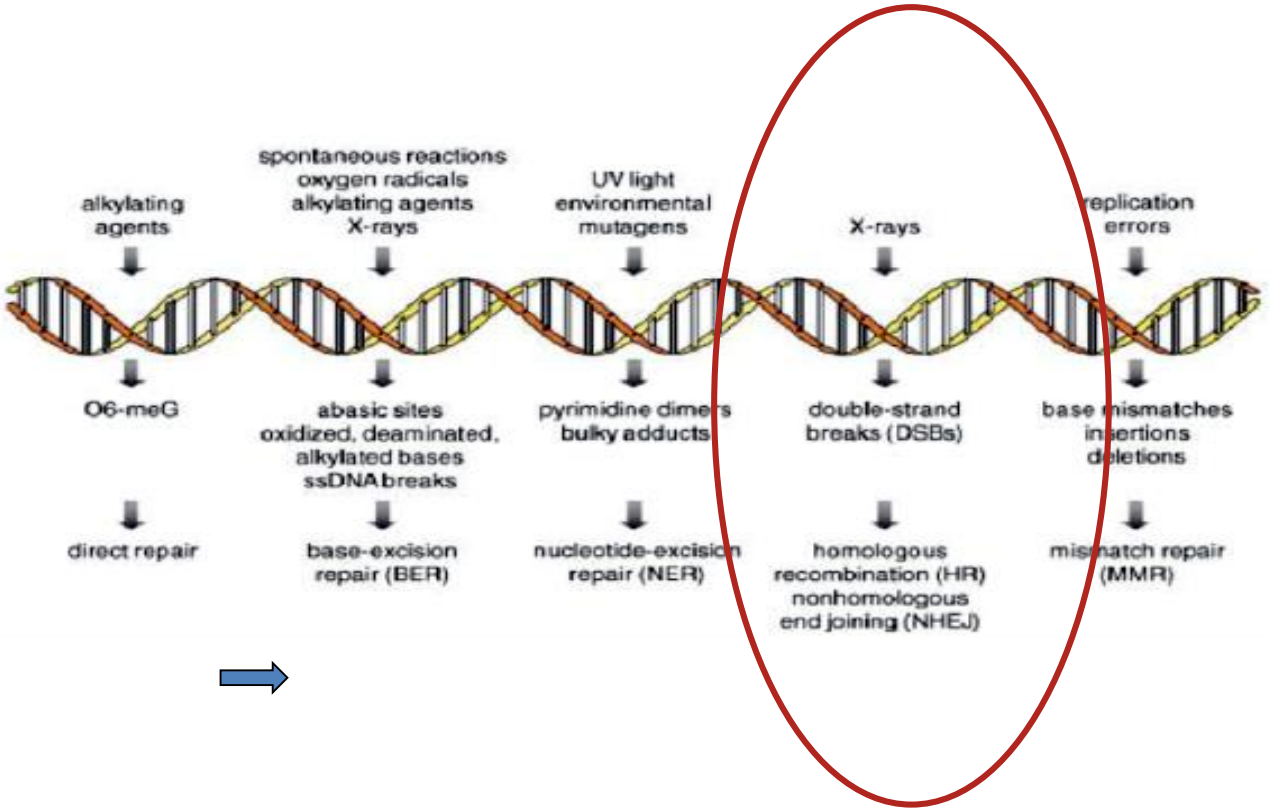
(from Burkart et al. CR Acad Sci III 1999; 322: 89-101
Ward Prog Nucl Acids Res Mol Biol. 1988; 35: 95-125)

Among DNA damage, DNA breaks are considered to be lethal DNA lesion within the cells if not repaired or misrepaired

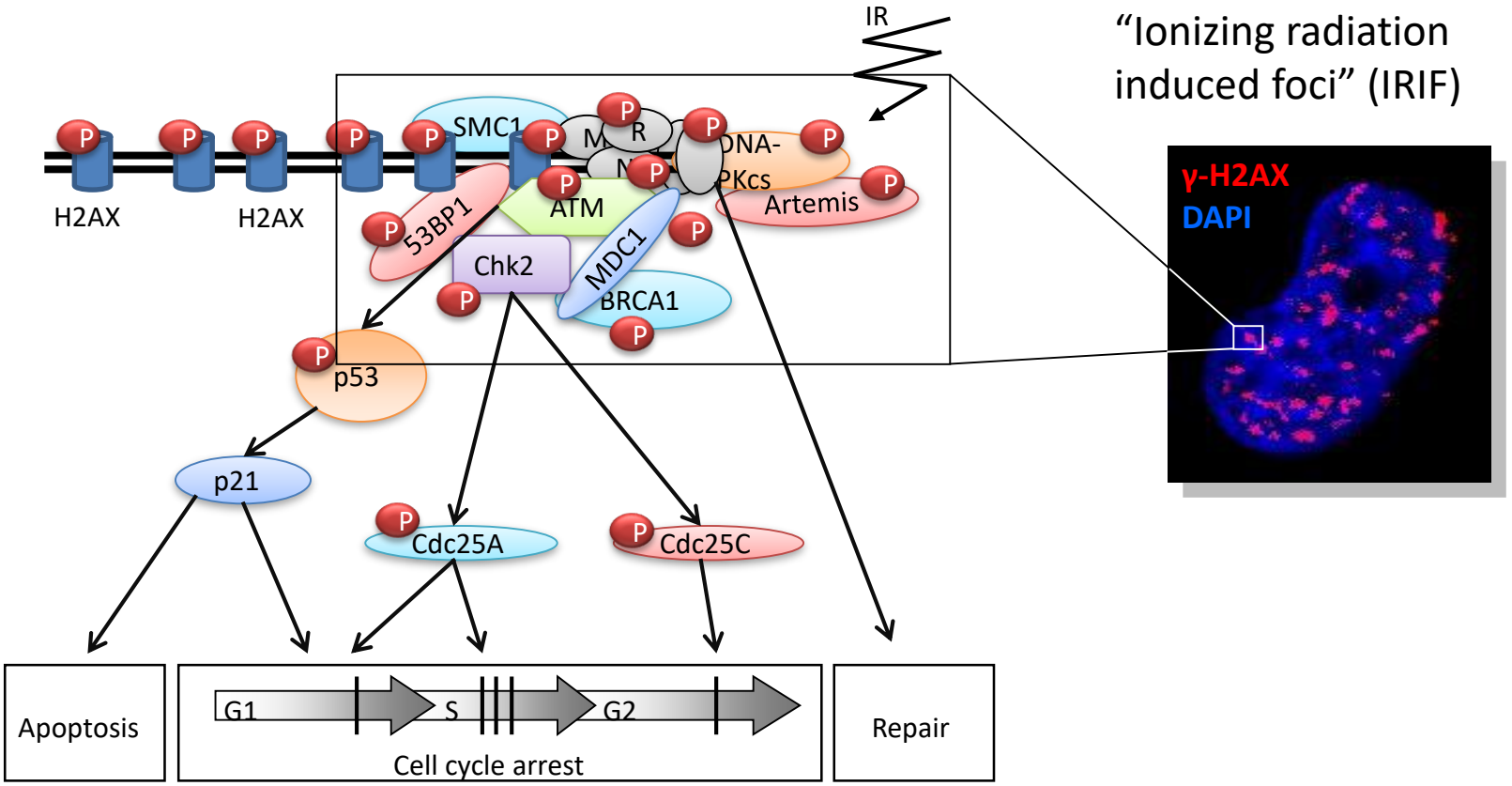
DNA repair pathways are a complex network of inter-related activities

- Unrepaired damage are converted to double-strand breaks during replication
- Unrepaired double-strand breaks are lethal
  dividing cells are more sensisitive to treatment than quiescent cells

- Several pathways (HR, NHEJ, b-NHEJ) can repair double-strand break

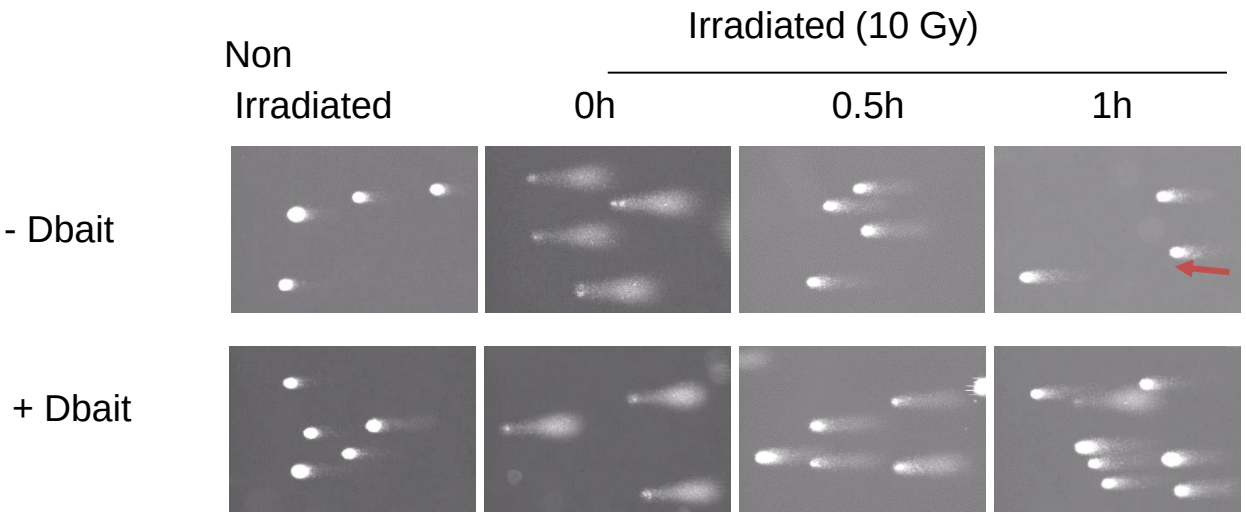


IrRadiation Induced Foci (IRIF)

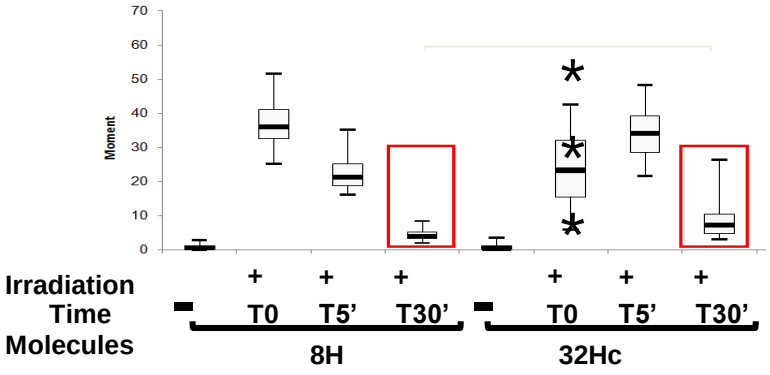


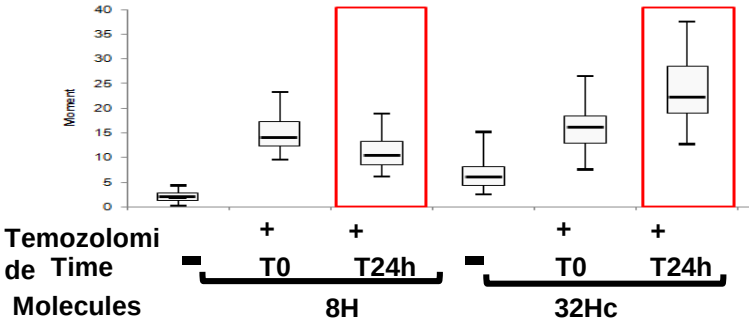
After irradiation, signaling and repair proteins concentrate at damage site to form repair foci (IRIF) often detected as γ-H2AX foci

Inhibition of damage repair by Dbait32H

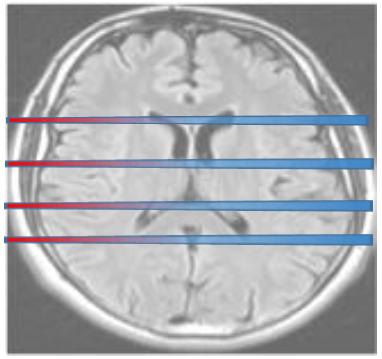


DNA Repair is evaluated by « comet assay » after various treatments: Dbait inhibits the repair of damage induced by Irradiation, or chemotherapy (TMZ, 5-FU, CPT11…)

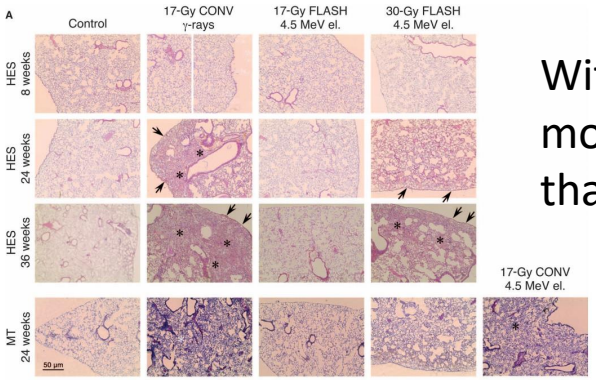




How to explain the recent results with MBRT and FLASH?

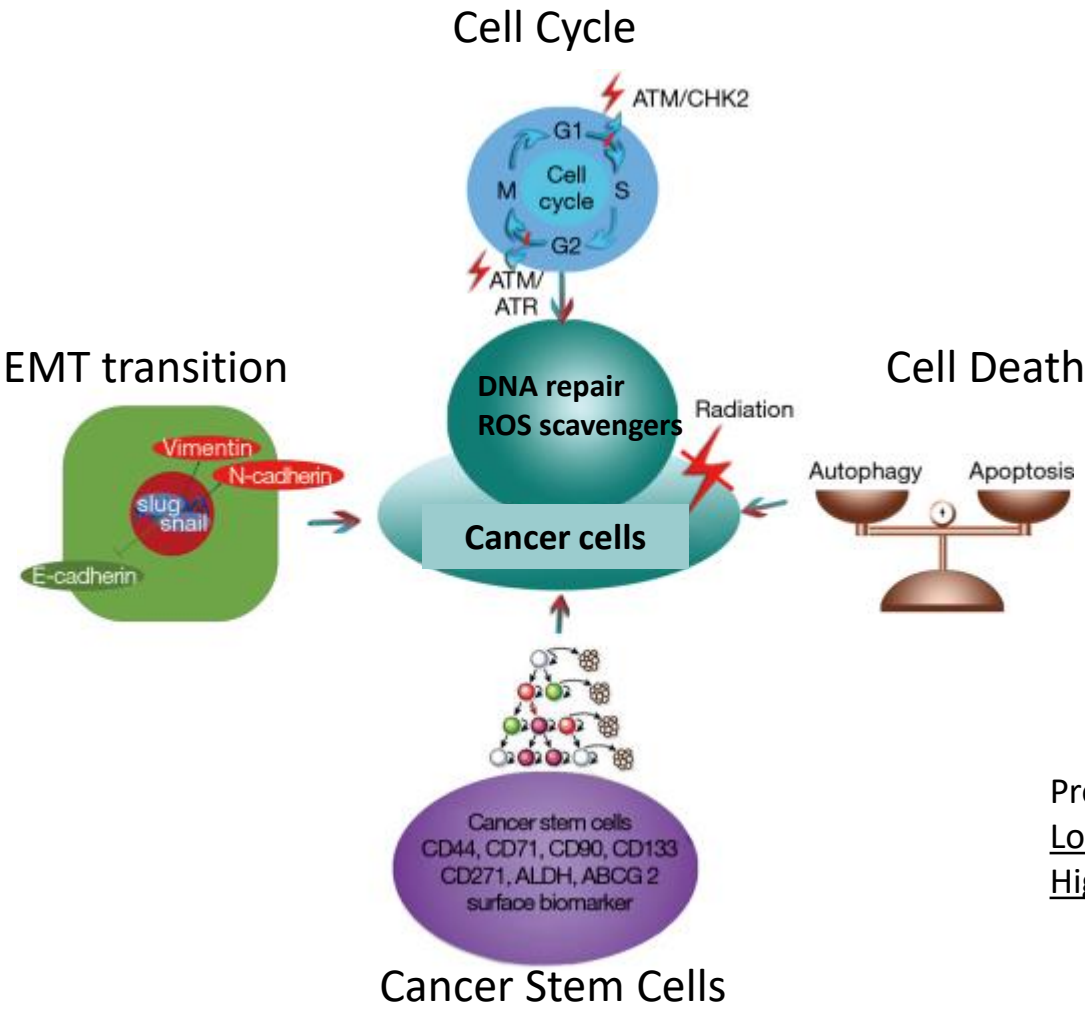


With minibeam the distribution is heterogenous: healthy tissues receive highly toxic dose in the pic and some tumor cells may get very low doses in the valleys



With FLASH the dose is the same with the two modes of irradiation but CONV is more toxic than FLASH in normal tissues

The mechanisms of radioresistance

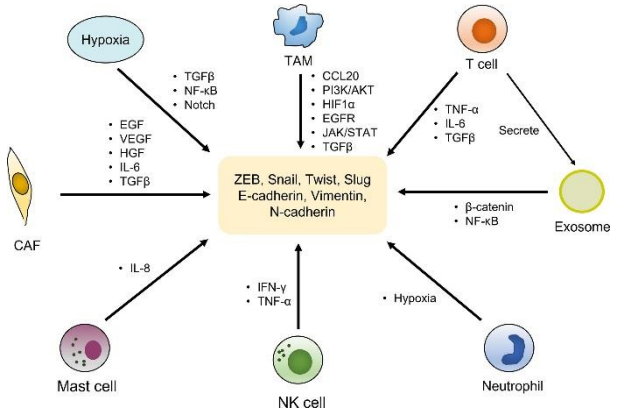


Necrosis
Mitotic catastrophe
Senescence

Preferential death
Low doses: apoptosis
High doses: necrosis

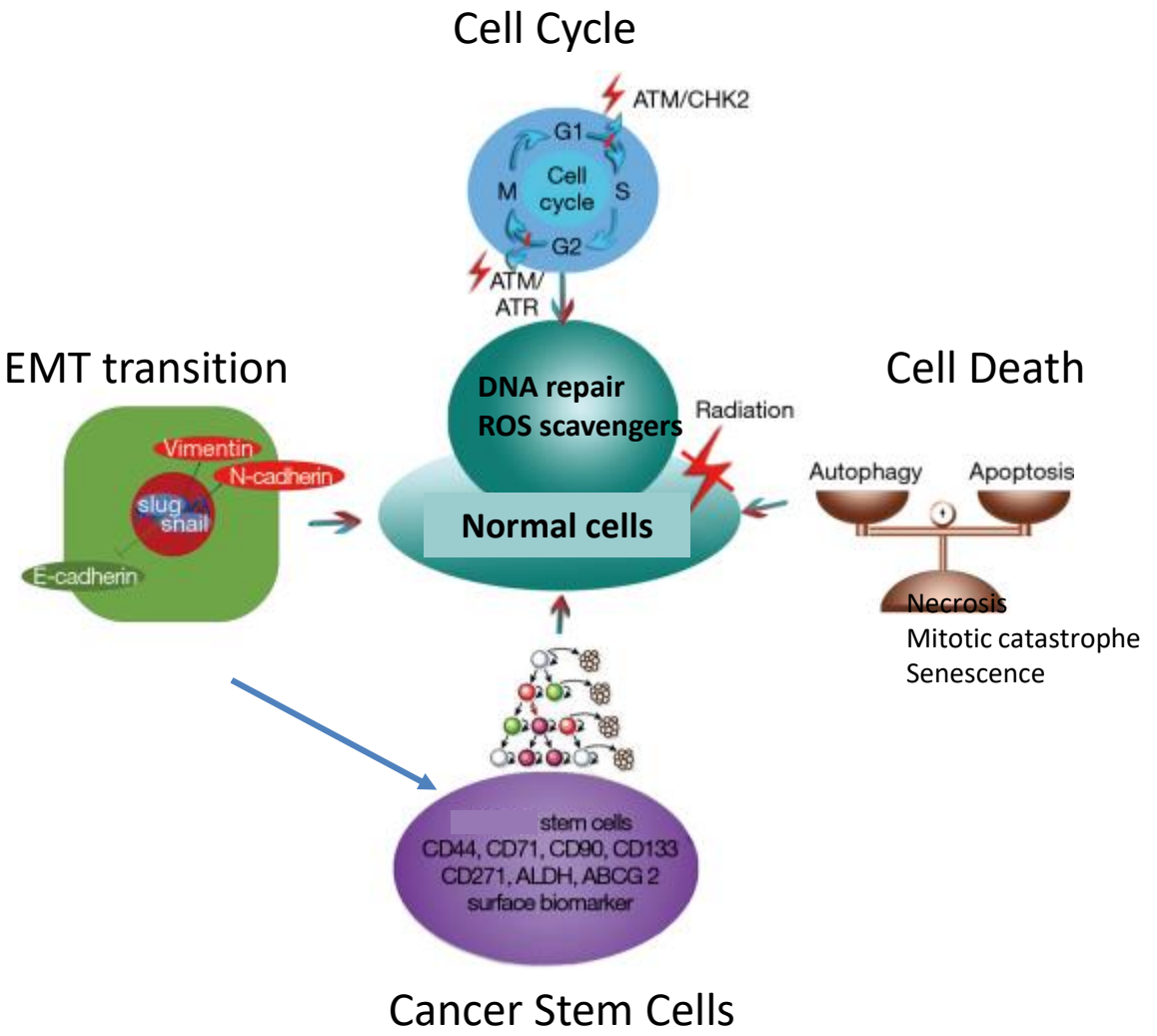
Modified from Chen G-Z. et al., J Thorac Dis 2017;9(3):849-859

The mechanisms of radioresistance



Microenvironment

lymphocytes (T cells, B cells and NK) are among the most radiosensitive cells, followed by monocytes, macro-phages and antigen-presenting cells (APCs), Dendritic cells (DC), have a higher radioresistance.



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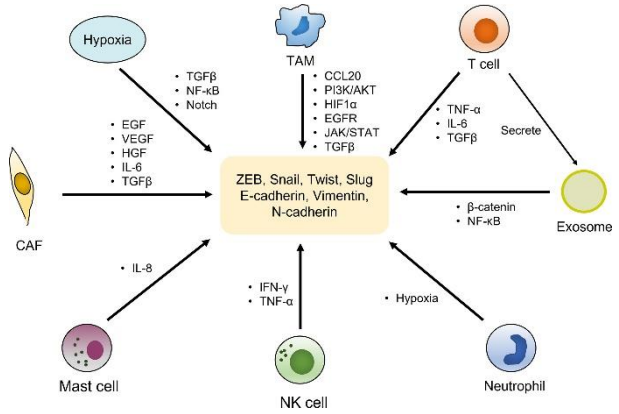
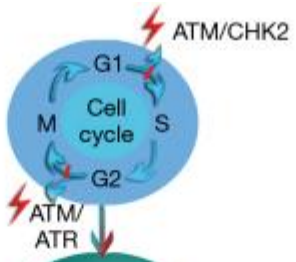
The mechanisms of radioresistance

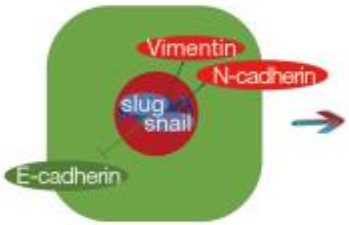


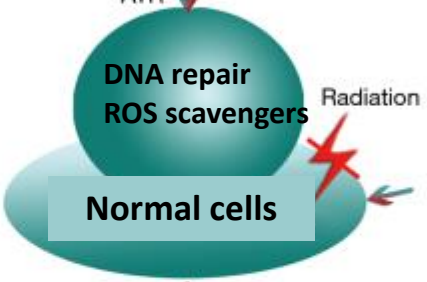
Microenvironment

Cell Cycle

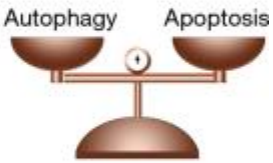


EMT transition





Cell Death



Necrosis
Mitotic catastrophe
Senescence

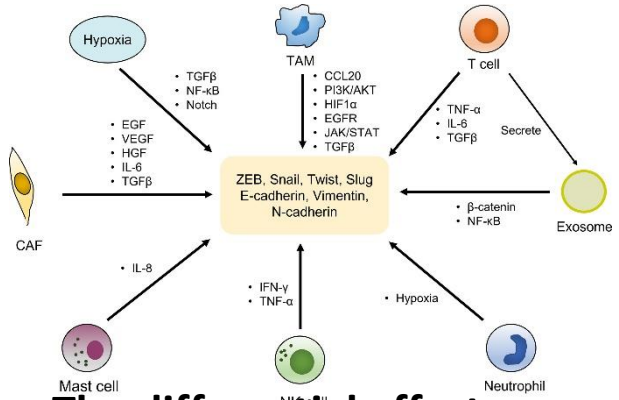
Currently, no consensus about the optimal dose schedule to stimulate the immune system
- a dose sufficient to promote immunogenic cell death
- a dose that does not induce Trex

Cancer Stem Cells

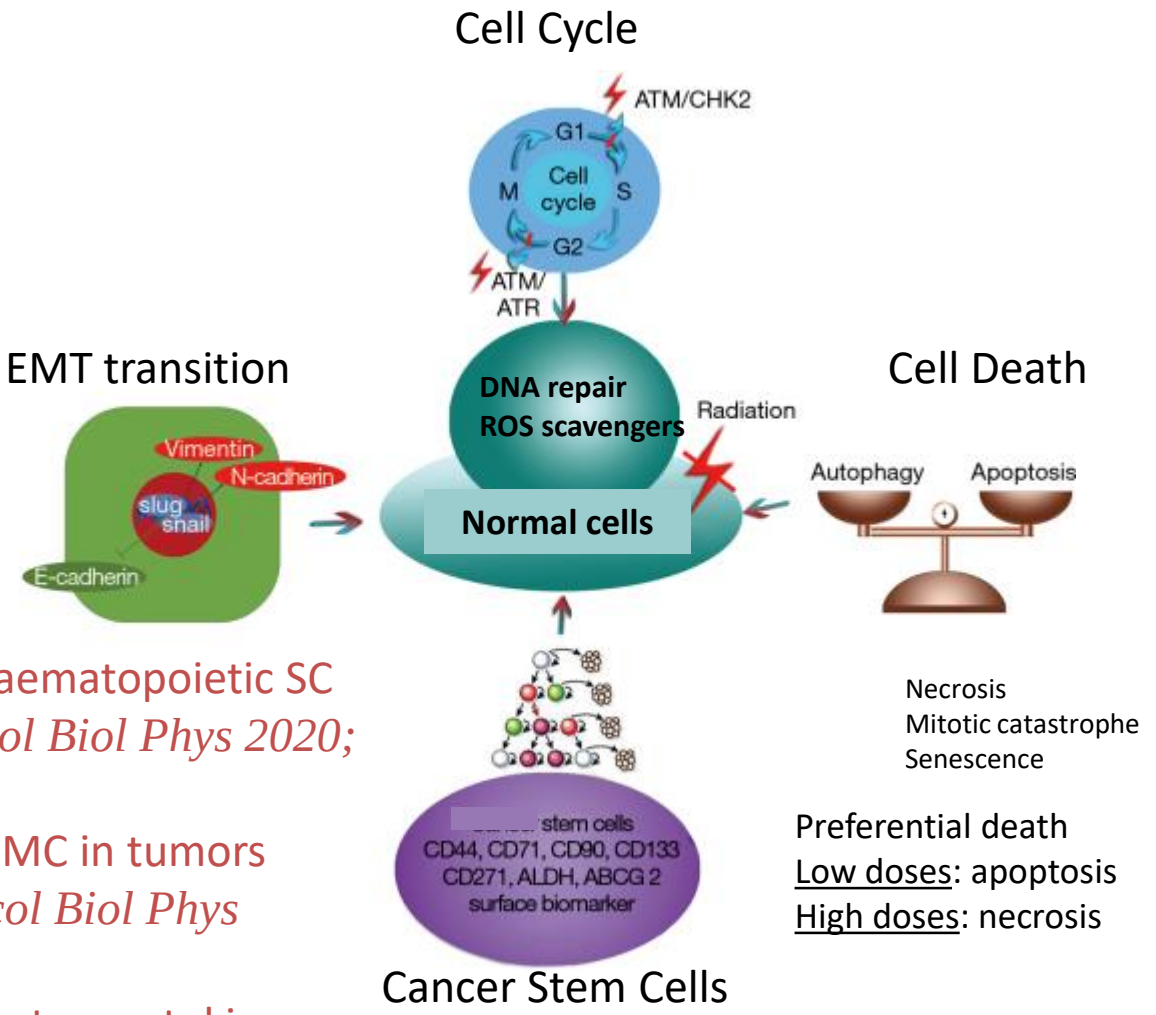
Preferential death
Low doses: apoptosis
High doses: necrosis

Modified from Chen G-Z. et al., J Thorac Dis 2017;9(3):849-859

The mechanisms of FLASH radioresistance



The differential effect on microenvironment:



Favored hypothesis

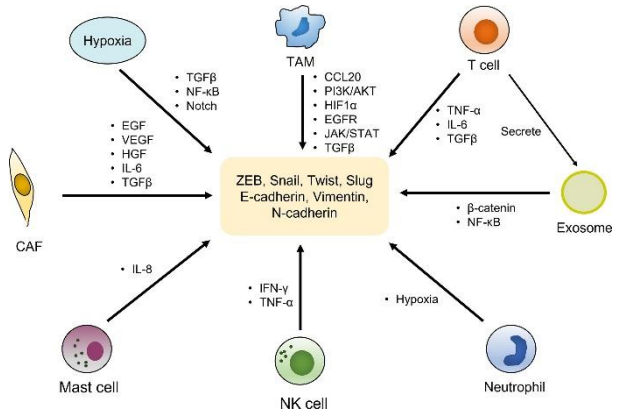
1- FLASH reduces damage on haematopoietic SC *(Chabi S, et al.Int J Radiat Oncol Biol Phys 2020; 109(3):819e829)*

2- FLASH induces infiltration of MC in tumors (*Kim YE, et al. Int J Radiat Oncol Biol Phys 2021;109(5):1440e1453.)*

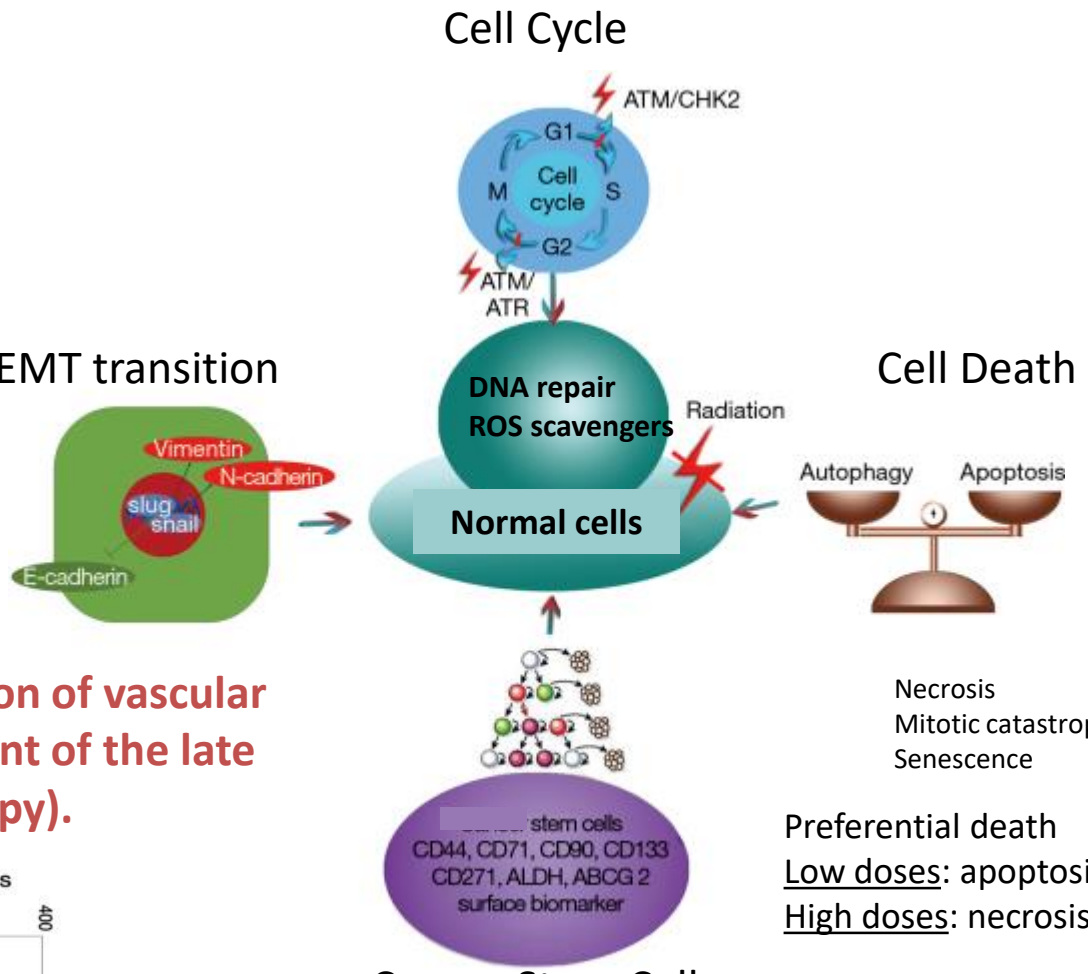
3- FLASH decreases proinflammatory cytokines secretion (*8 ref; Fouillade et al., Clin Cancer Res 2020;26(6):1497e1506*)

Modified from Chen G-Z. et al., J Thorac Dis 2017;9(3):849-859

The mechanisms of FLASH radioresistance



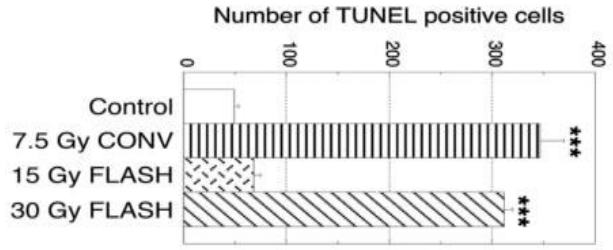
The differential effect on microenvironment:



Necrosis
Mitotic catastrophe
Senescence

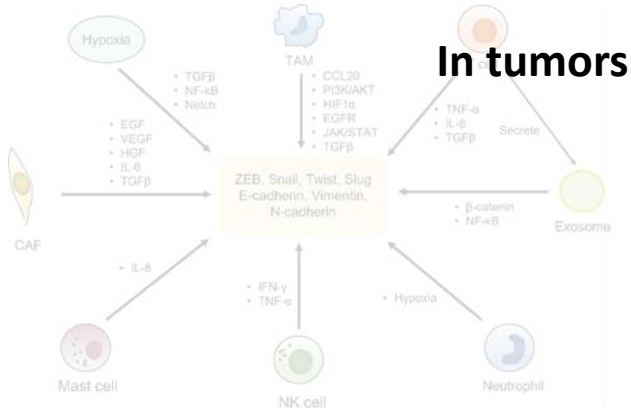
Preferential death
Low doses: apoptosis
High doses: necrosis

FLASH elicite a dramatic reduction of vascular apoptosis (important determinant of the late complications of radiation therapy).



Modified from Chen G-Z. et al., J Thorac Dis 2017;9(3):849-859

Vectorised radiobiology



In tumors:

Heterogeneity of dose distribution

Decreasing dose with time

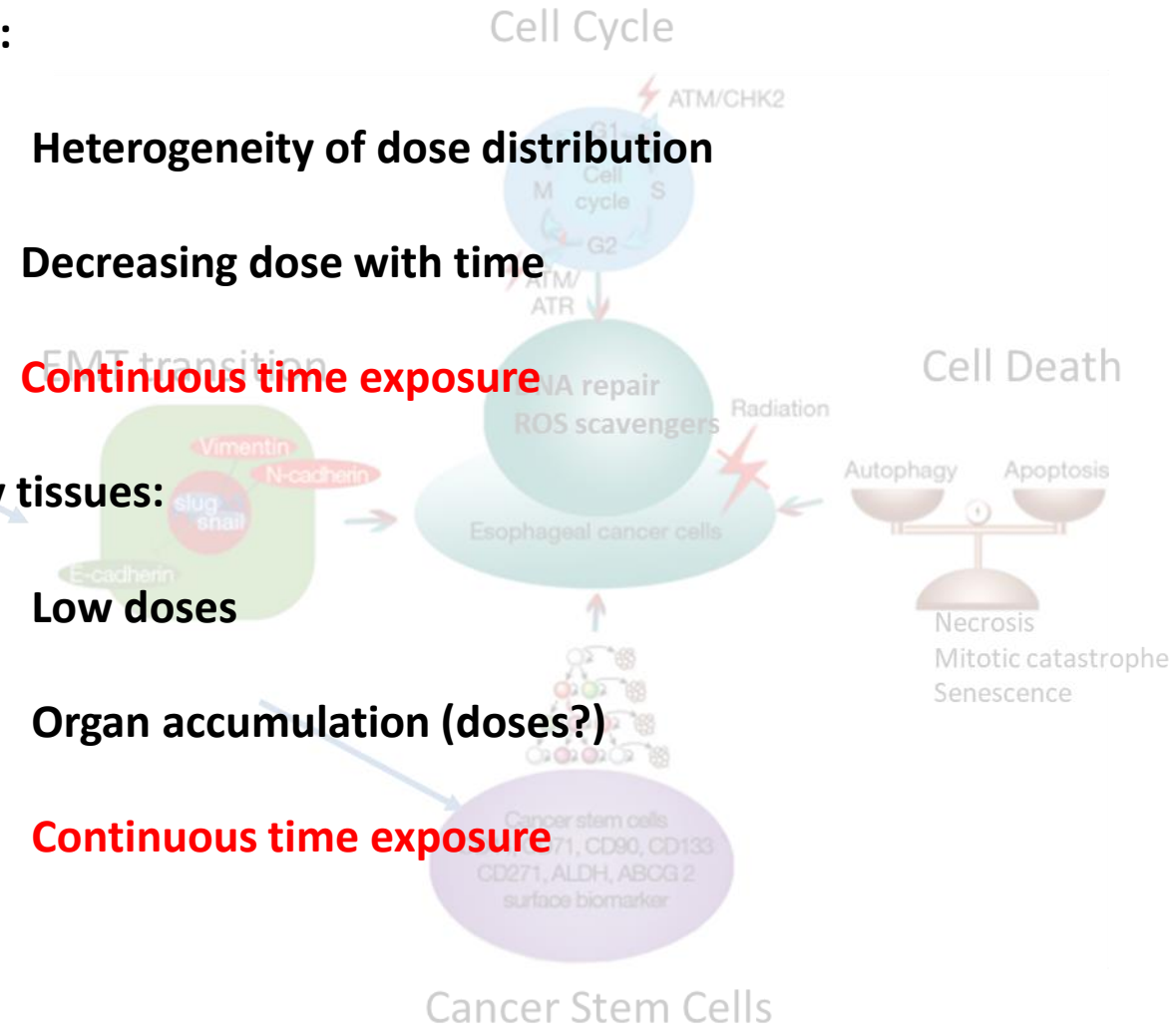
Continuous time exposure

In healthy tissues:

Low doses

Organ accumulation (doses?)

Continuous time exposure



The work of MANY people

Current members
Marie Dutreix, PhD
Sophie Heinrich, PhD
Charles Fouillade, PhD
Vincent Favaudon, PhD
Pierre-Marie Girard, PhD
Delphine Javelaud, PhD
Lucie Portier, PhD
Nathalie Berthault, AI
Pauline Dubreuil, T
Lucia Giuliano, PhD student
Floriane Peirera, PhD student
Anouk Sesink, PhD student
Maxime Dubail, M2 student
Lilia Kadi Aggar, M2 student

And all the former members of the lab

Institut Curie research center

Histology platform
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Microscopy platform
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MR imaging
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Transcriptome analysis and interpretation
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Thank you for your attention