IRCCS Azienda Ospedaliera Universitaria
San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro

Microambiente e radiorisposta in emato-oncologia trapiantologica

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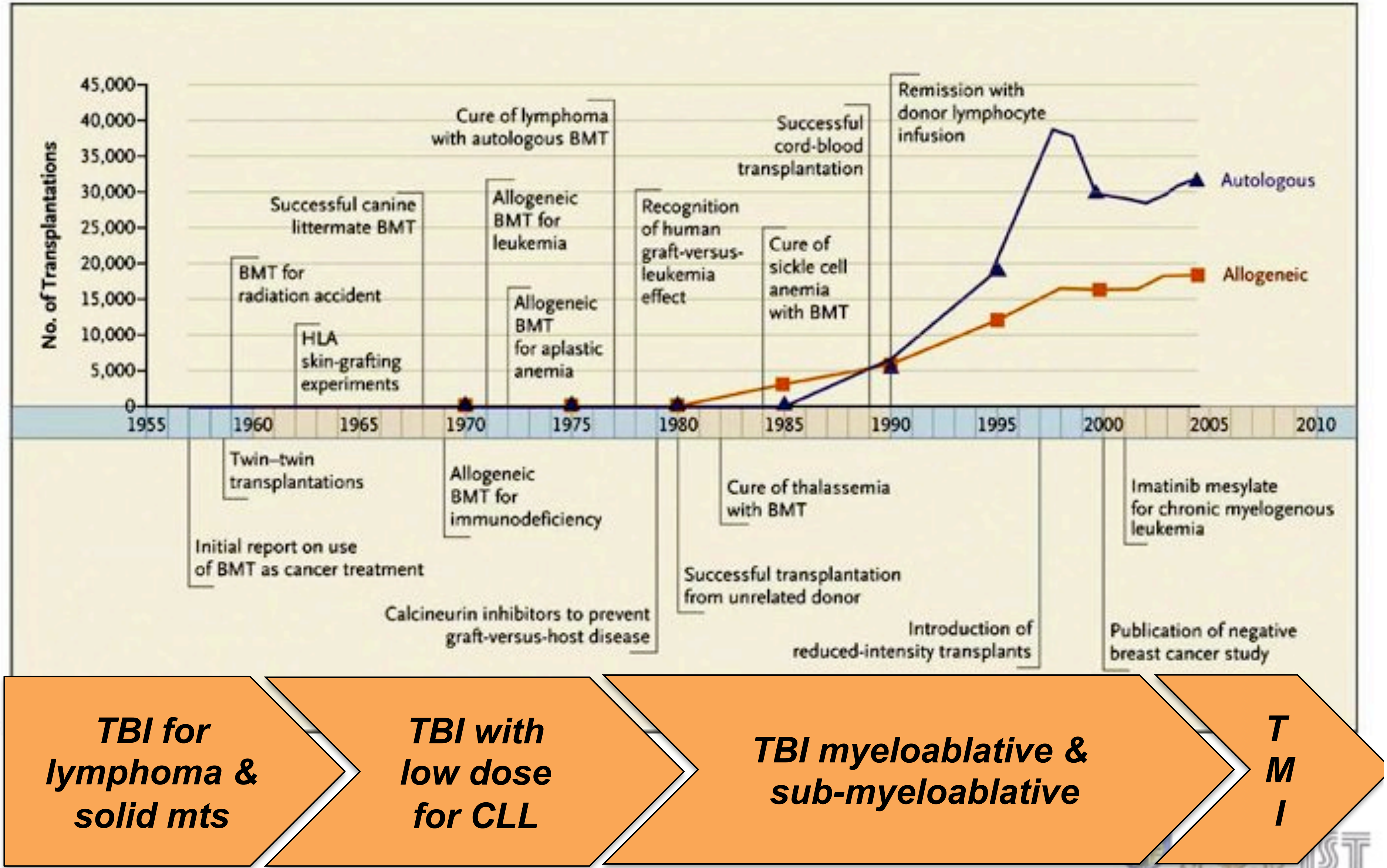
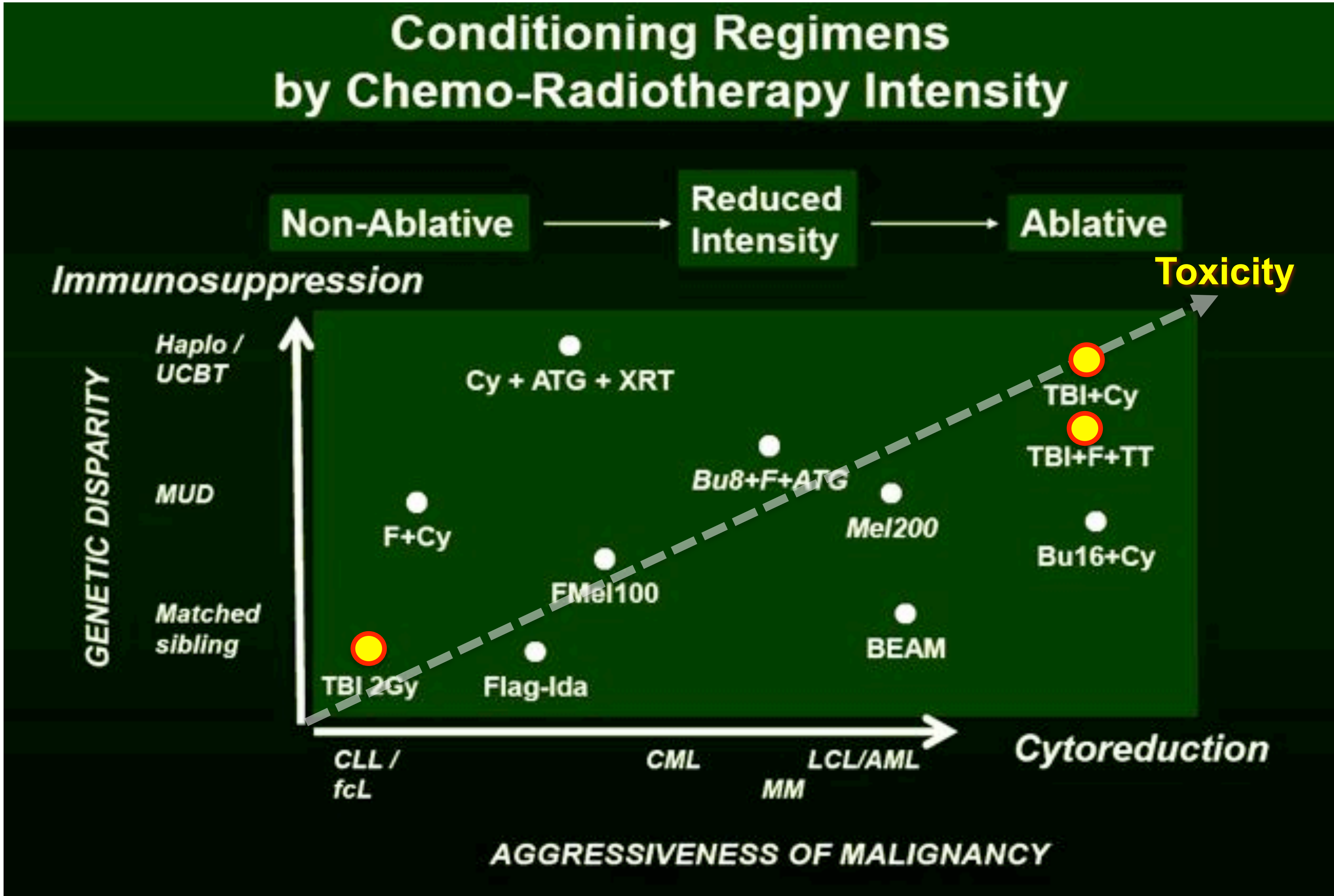
Genoa (IT)

Hematopoietic Stem Cell Transplantation

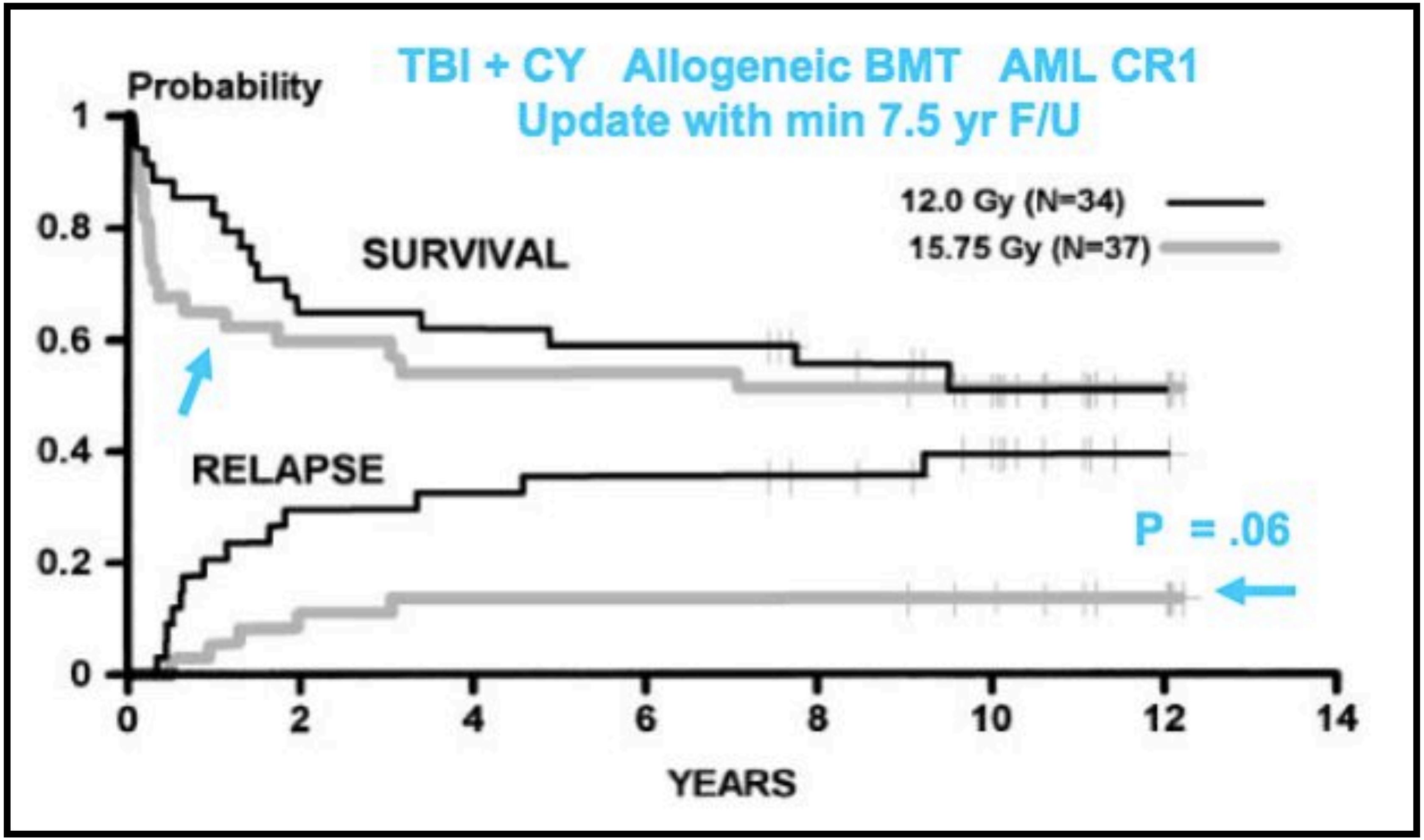
A long-time history



Role of Radiotherapy

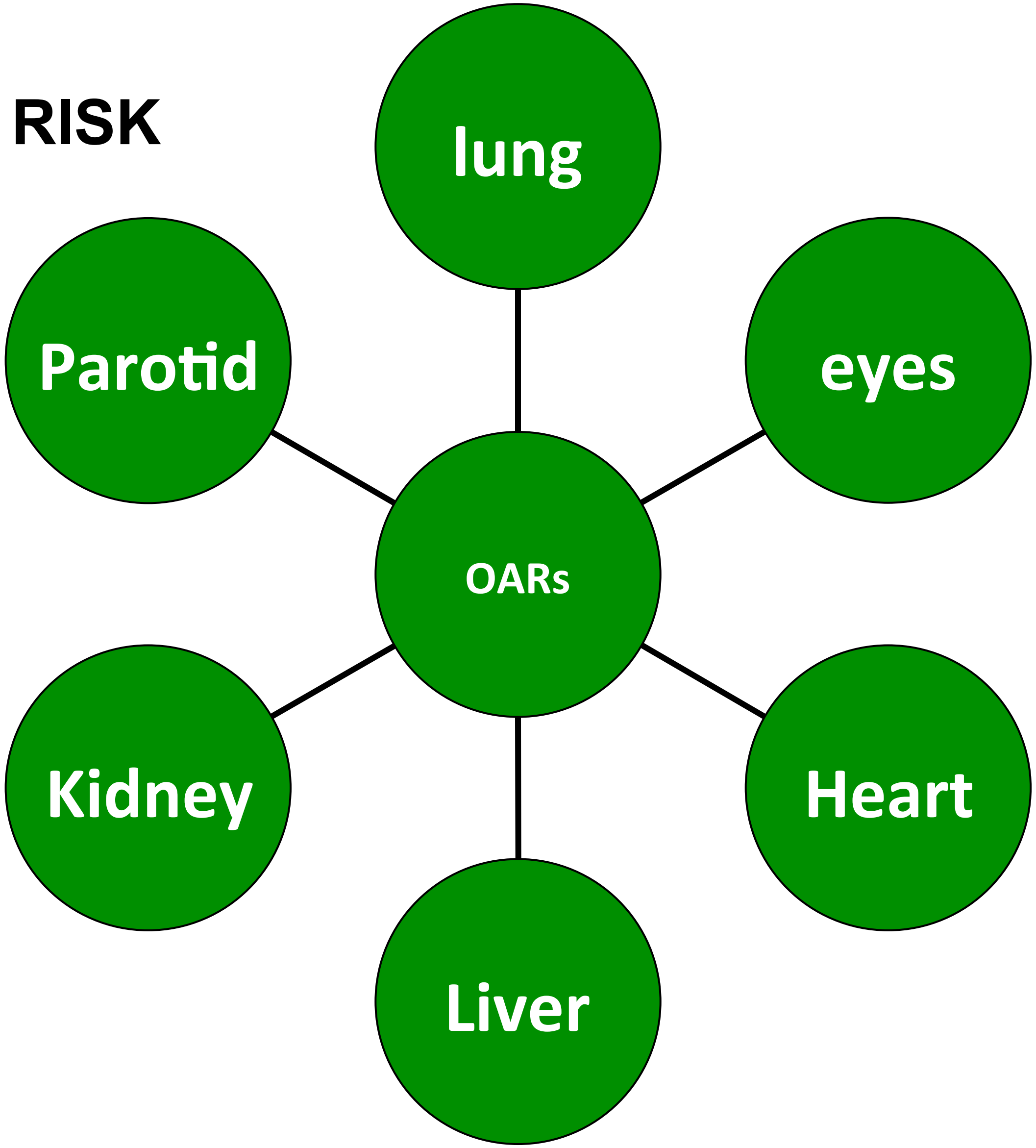


TBI dose escalation:
conventional 12 Gy vs 15.75 Gy



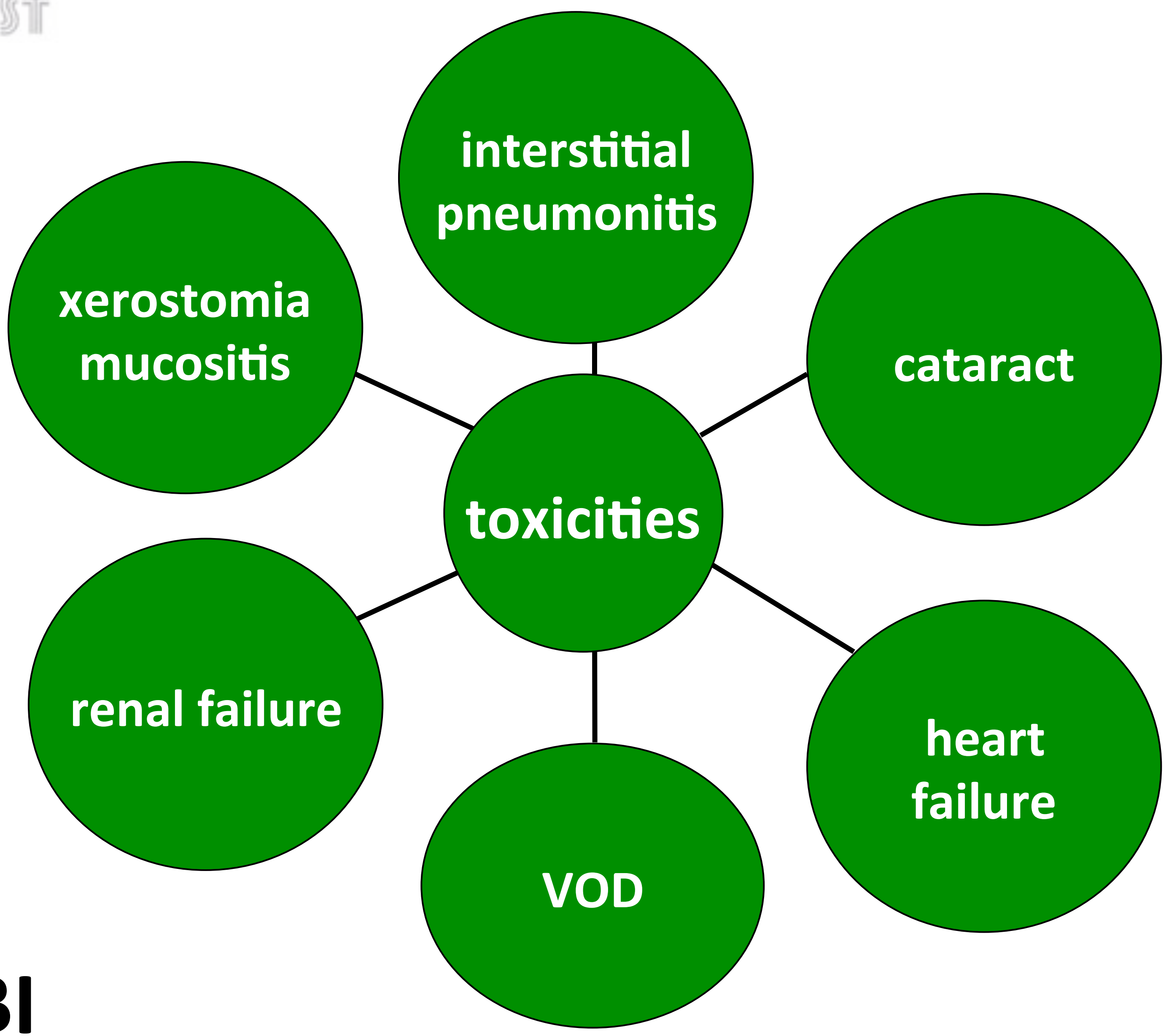
Clift et al, Blood 1998

ORGANS at RISK



TBI

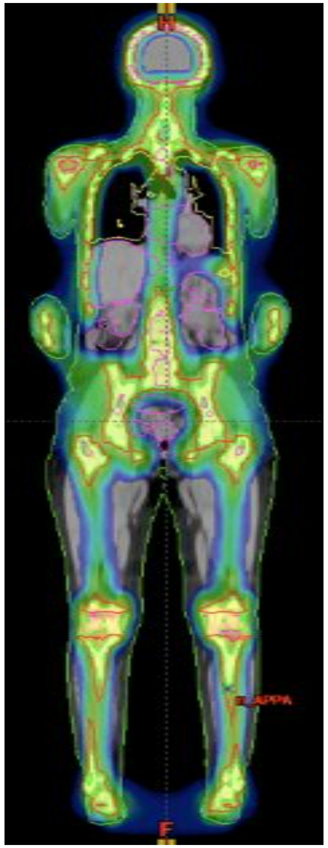
RISK FOR TOXICITIES

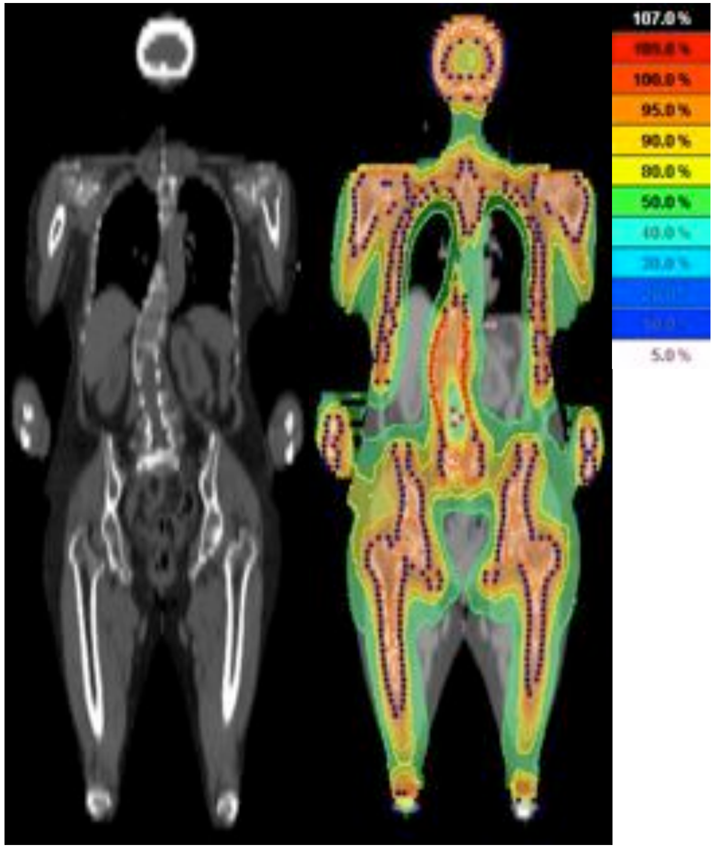


TBI

RISK FOR TRANSPLANT-RELATED MORTALITY

What's New in Radiotherapy





- High target conformity
- Precise delivery
- Dosimetric informations
- Large dose reduction to Organs at Risk

 # IGRT & HELICAL / VOLUMETRIC MODULATED ARC THERAPY

Clinical TMI data in leukemia

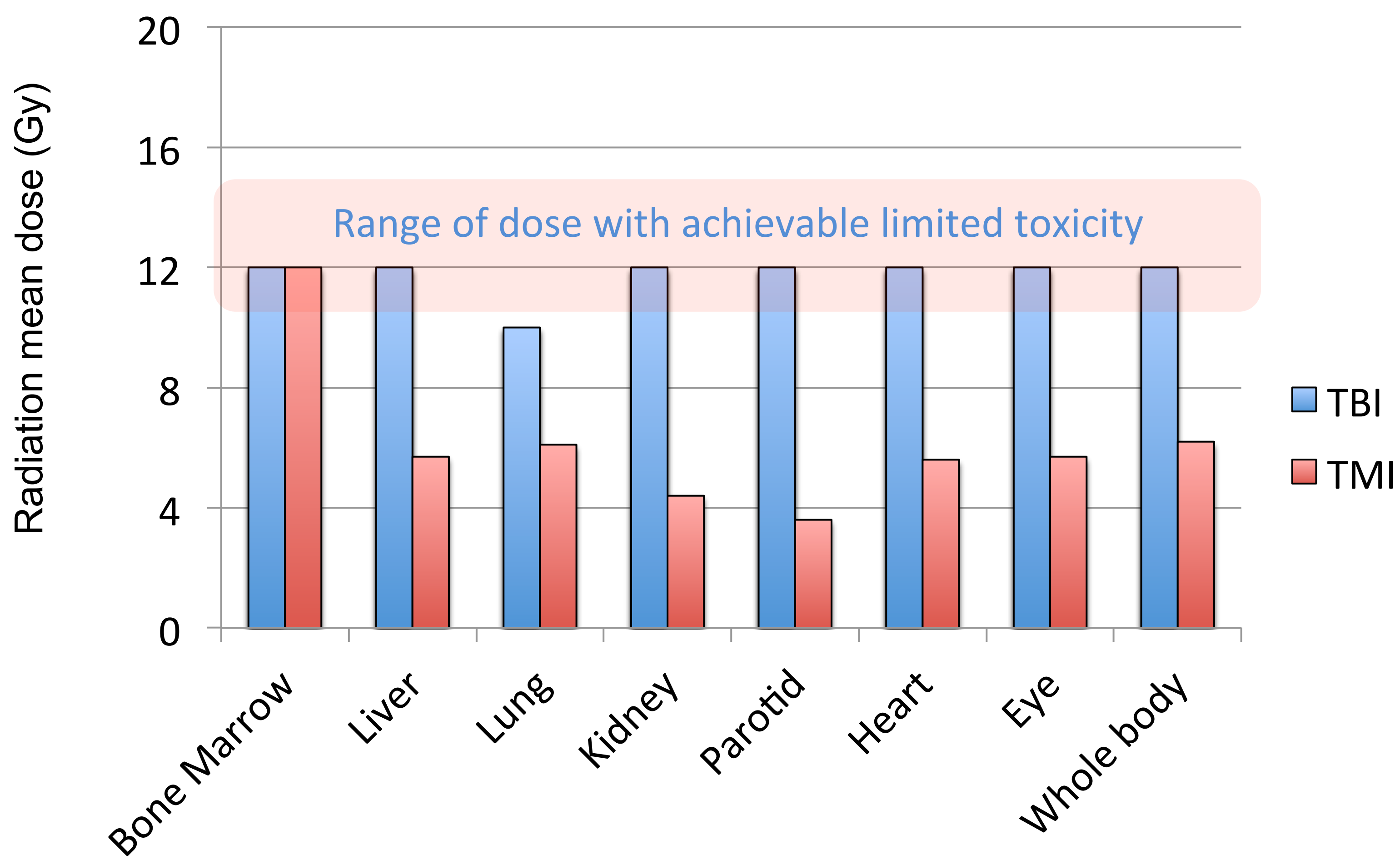
Author	Nº of patients	Study phase	TMI total dose	CT
Corvò R Radiother Oncol 2011	15	Phase I	**14 Gy**	Cy
Rosenthal J Blood 2011	24	Phase I	12 Gy	RIC Flu/Mel
Wong JYC Int J Radiat Oncol Biol Phys 2012	32	Phase I	**12 Gy to 16 Gy**	Cy/VP16 Vs Bu/VP16

Clinical data in Multiple Myeloma

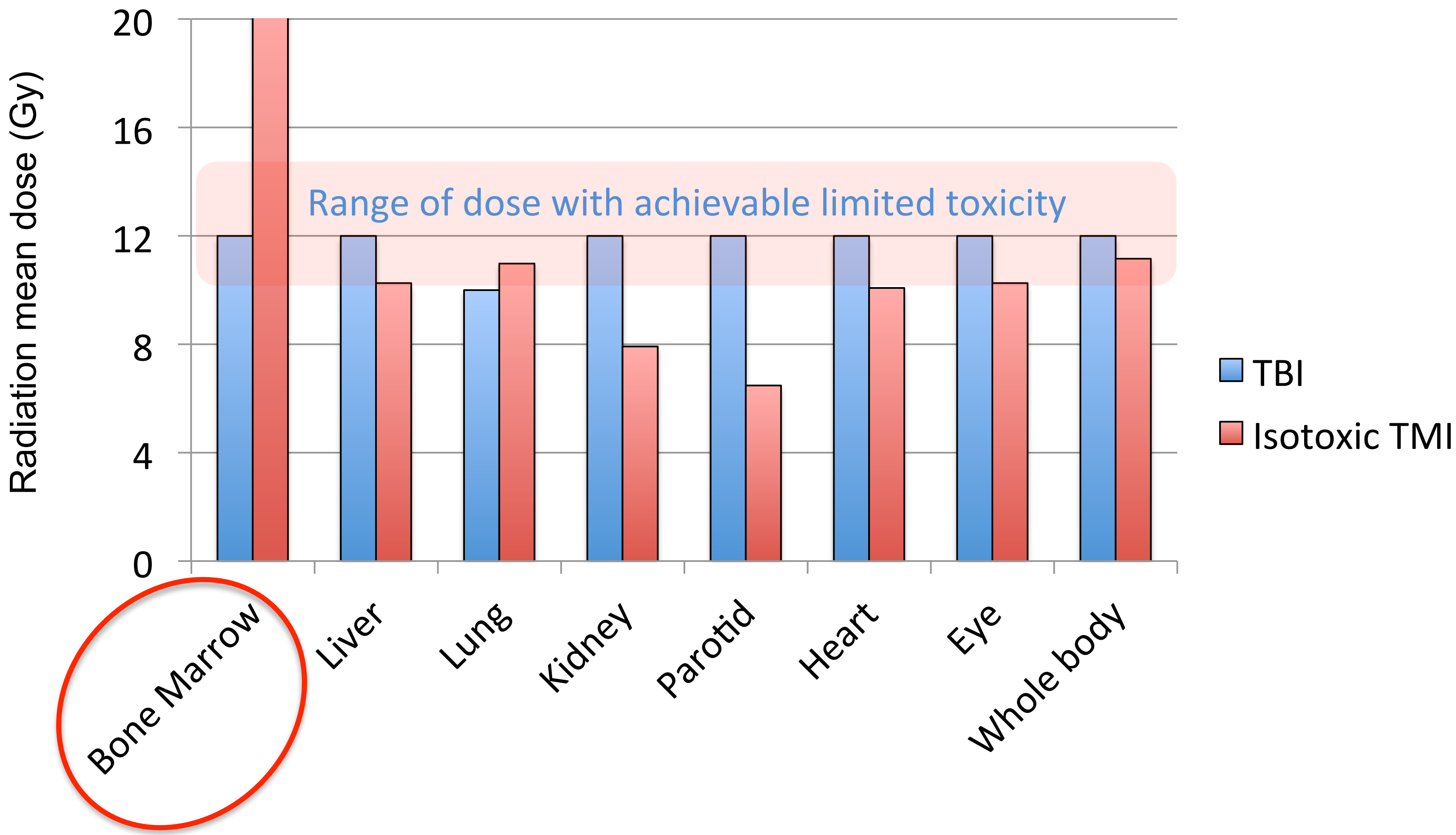
Author	Nº of patients	Study phase	TMI total dose	CT
Somlo Clin Ca Res, 2010	22	Phase I	**12 Gy up to 18Gy**	Tandem MEL 200
Lin SC Biomed Res Int 2013	9	Phase I/II	8 Gy	MEL 140

 # Dose escalation

What's New in Radiotherapy



What's New in Radiotherapy



20 Gy is it feasible ?

The Bone Marrow as Target

First trhee phases of myeloablative approach to allographting

Components	*Purpose*
1. Myeloablative conditioning pretransplant	Host immunosuppression Eradication of underlying disease Creation of Marrow Space
2. Stem Cell Graft	Rescue from myelosuppression Establishment of normal hematopoiesis Graft-versus-tumor
3. Postgrafting immunosuppression	Prevent rejection Control of GVHD

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 # Which mechanism regulate BM radiation injury

Hematopoietic System

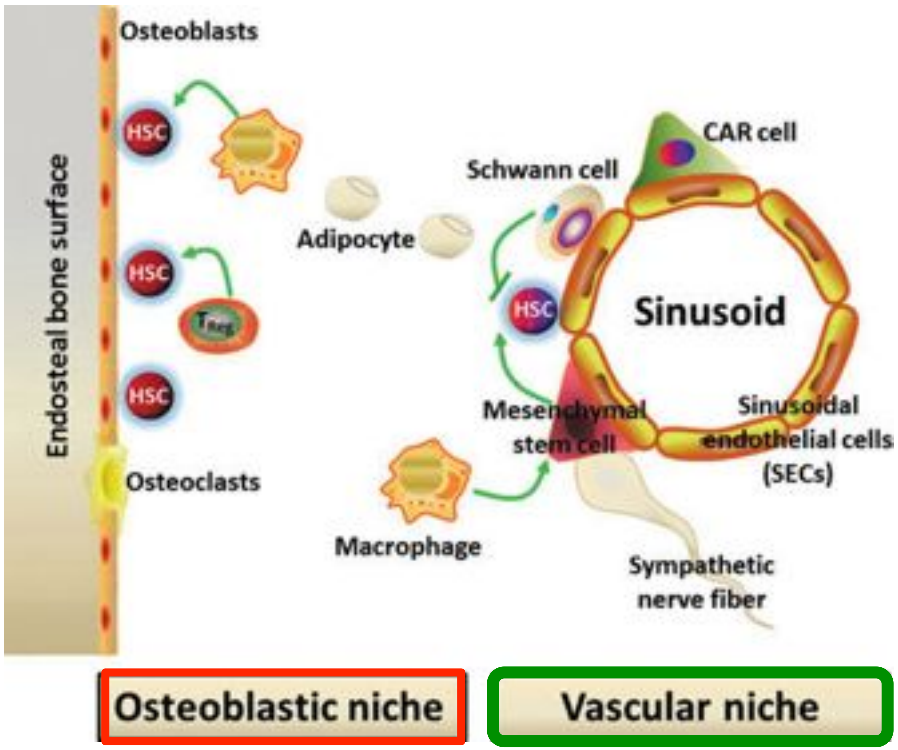
- ***Most radiosensitive tissue of the body***
  - Severity and duration of hematopoietic syndrome is dose dependent at TBI > 1Gy
  - Acute and transient myelosuppression if TBI < 3.5 Gy
  - Persistent myelosuppression if TBI > 4 Gy

- ***Hematopoietic Stem Cells***
  - Pluripotency differentiation
  - Self-renewal ability

- ***Bone Marrow Microenvironment***
  - regulate the maintenance of HSCs
  - regulate the production and maturation of hematopoietic progenitors

IST

Microenvironment: Niches

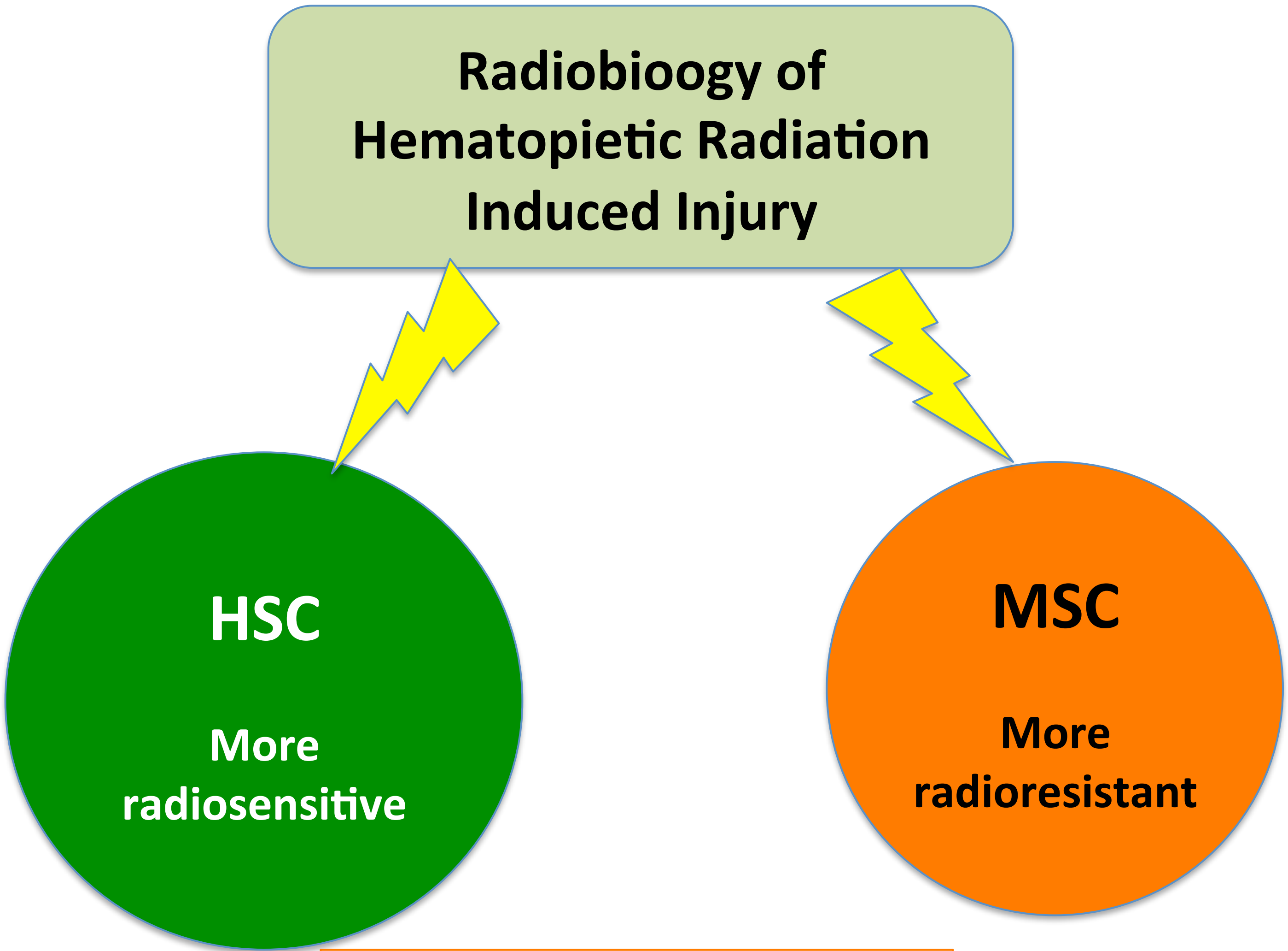


HSCs
Maintenance
Quiescence
Retention

HSCs
Self-renewal
Mobilization
Differentiation

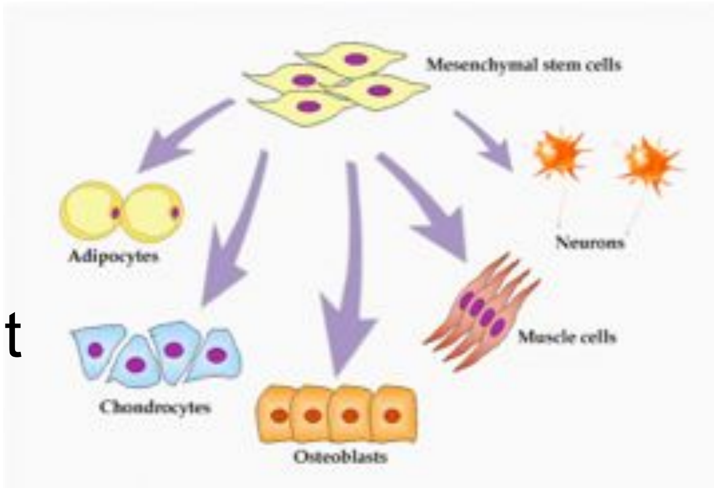
- Mesenchimal Stromal Cells (stem)
- Osteoblast (VCAM-1; Annexin II)
- CAR cell (CXCL-12)
- Neurons
- MSCs nestin+
- Perivascular Stromal Cell (leptin receptor)

Key players of myelosuppression rescue



Stem Cells with different mechanism of response

Mechanisms of MSCs IR Injury



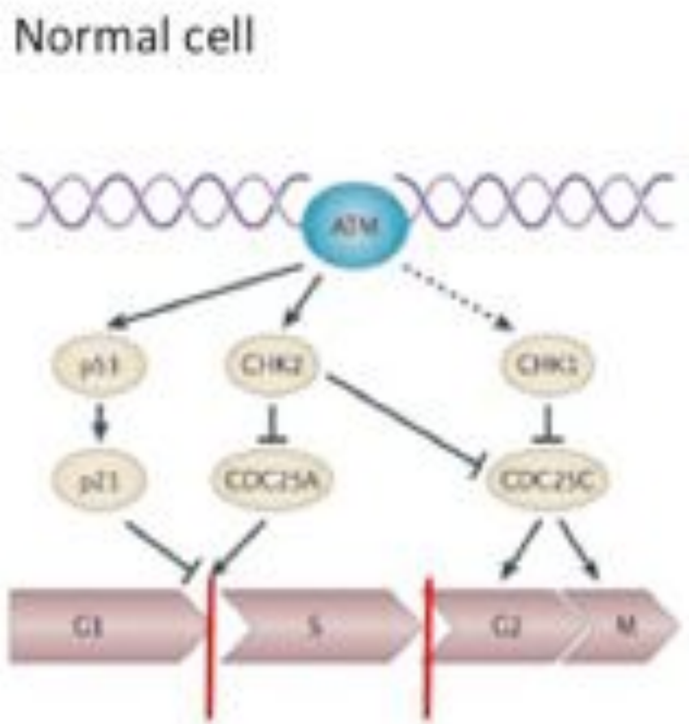
- Host derived MSCs survive irradiation
- Sustain the “donor” HSCs engraftment
- Co-transplantation of MSCs promote the recovery of bone marrow
- MSCs from different anatomical bone site display variable response to IR (maxilla and mandibular bones MSCs are more radioresitant that Iliac ones)
- The natural function of maintain tissues homoeostasi of MSCs after IR vary between cell types.

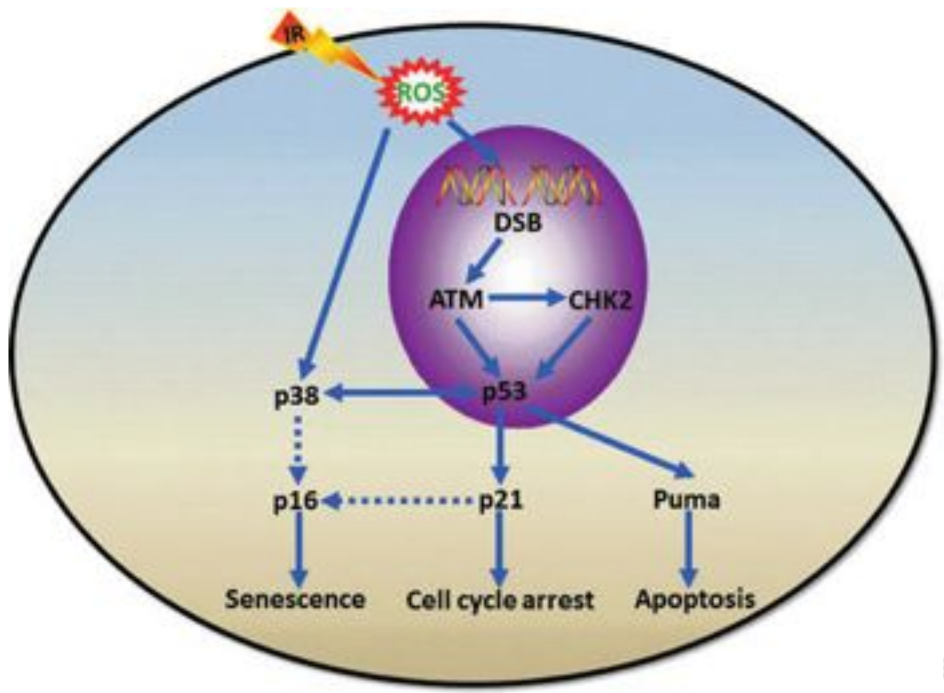
Mechanisms of MSCs IR Injury

Ability to recognise and repair DNA damage (DDR)

Activation of DNA damage cekhpoints facilitate DNA repair by providing more time for DNA damage to be removed before next phase of cell cycle

- y- H2AX formation -------- ATM phosphorilation
- p21 important player for MSCs response to IR

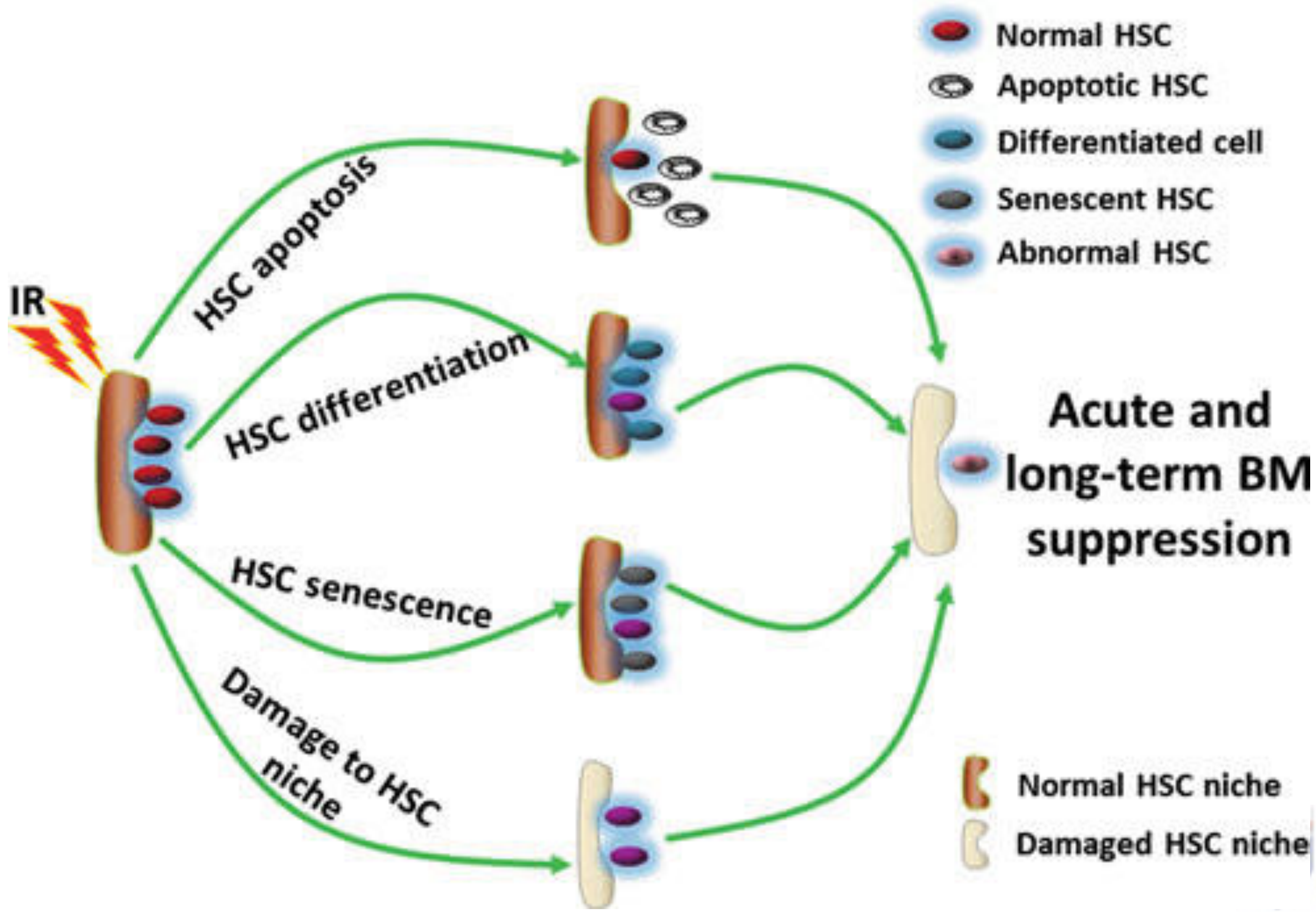




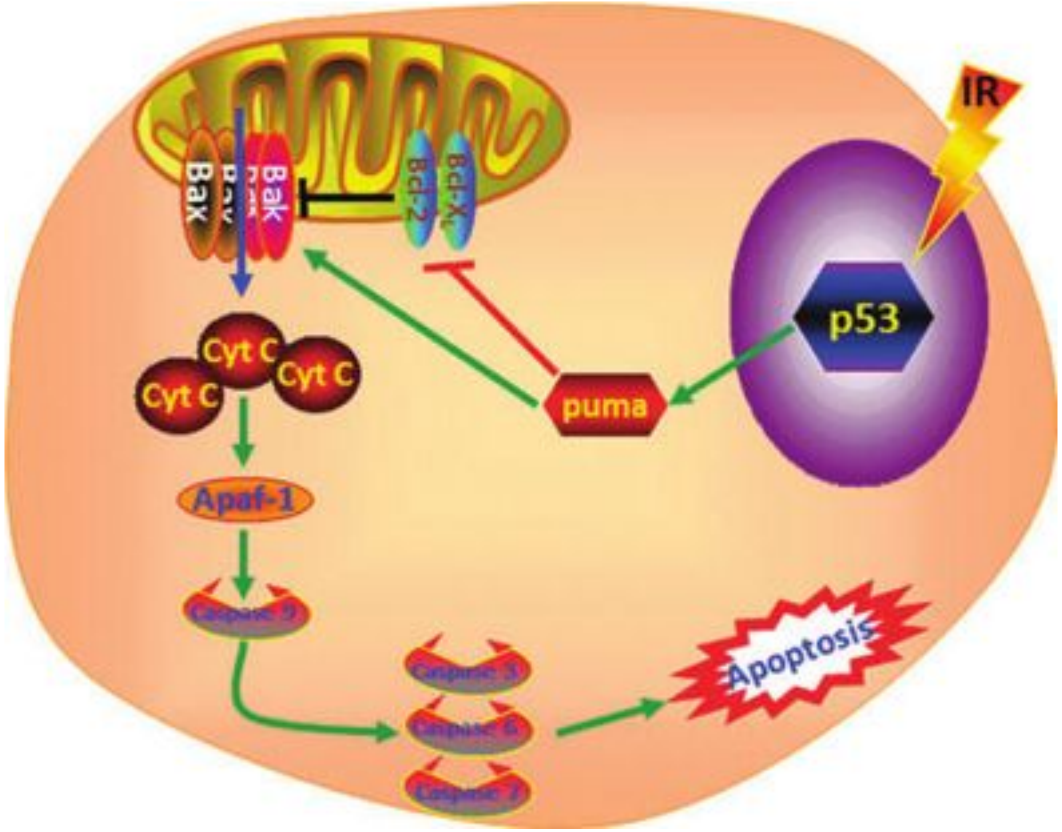
Mechanisms of HSCs IR Injury

IR generate hematopoietic reduction

- **Qualitative**: canghe in replicative functions as senescence
- **Quantitative**: reduction due to cell death or proliferation

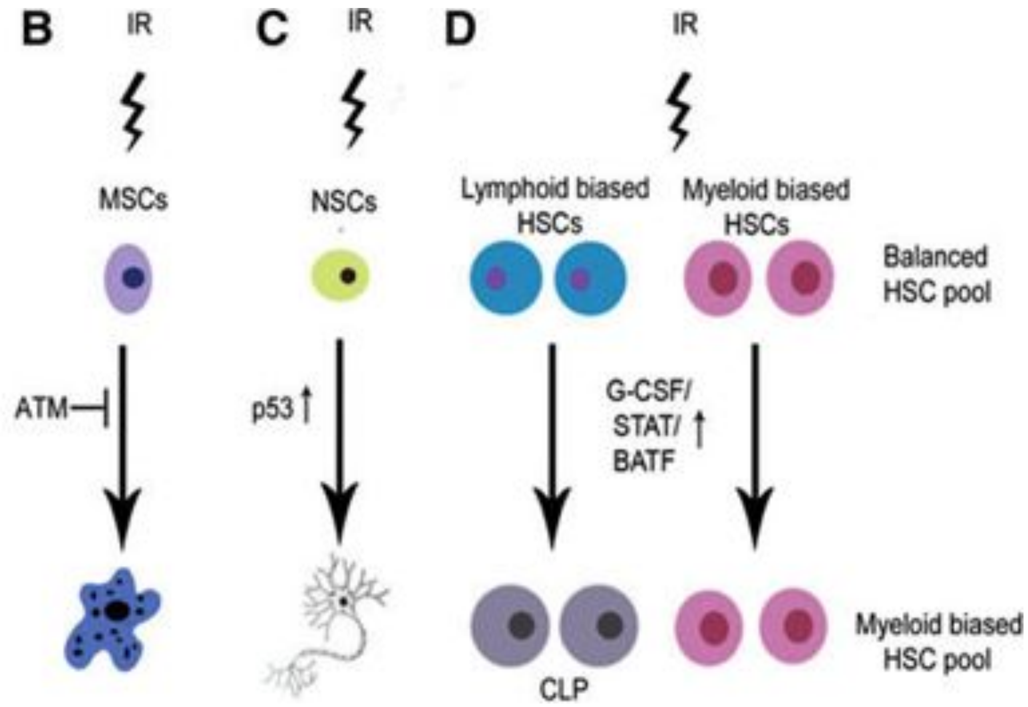


Apotosis death of HSCs by IR Injury



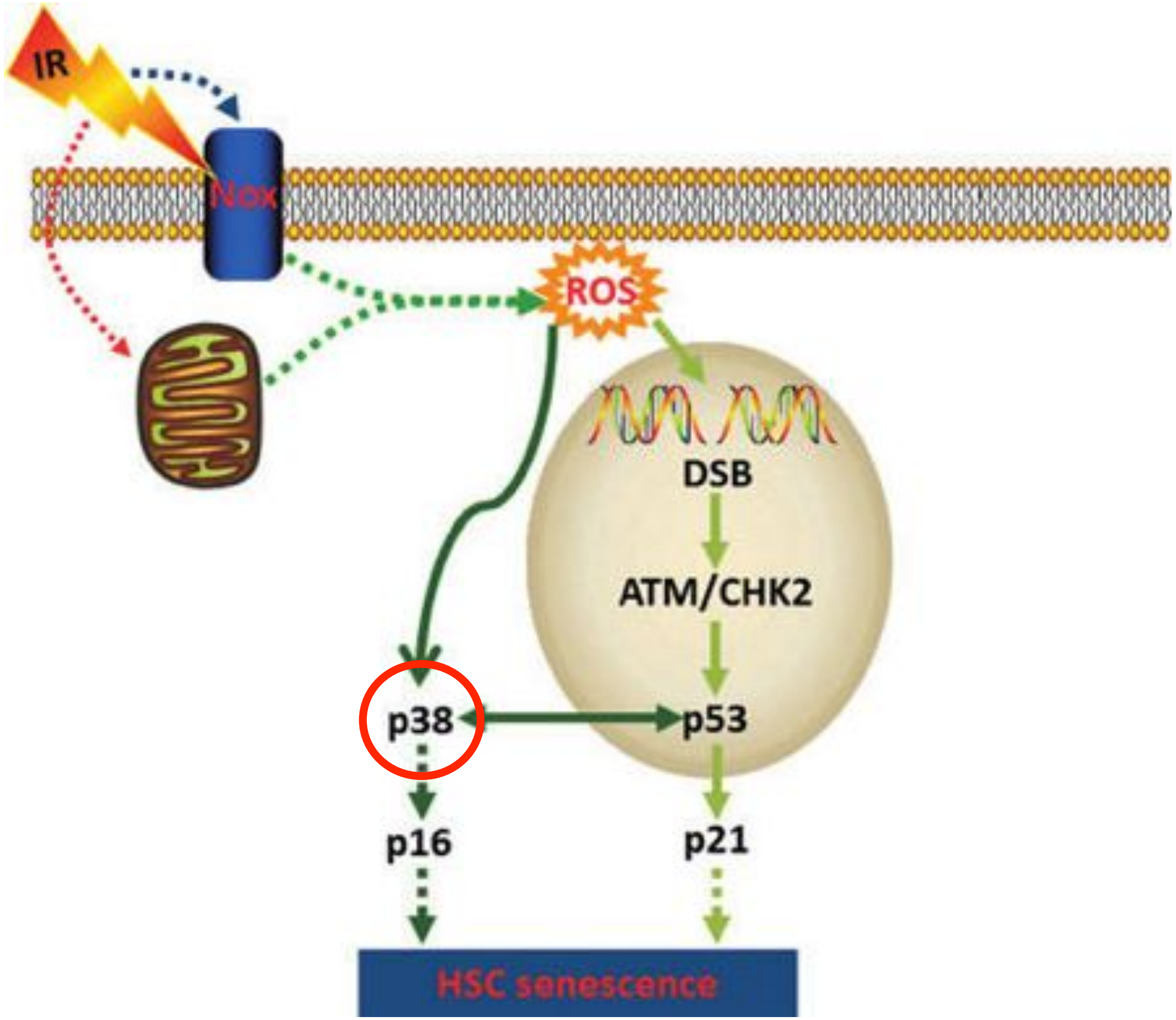
- Primary cause of IR induced HSCs depletion
- PUMA is selectively induced by IR
- PUMA blok the interactions of antiapoptotic proteins with the proapototic BAK

Differentiation of HSCs by IR Injury

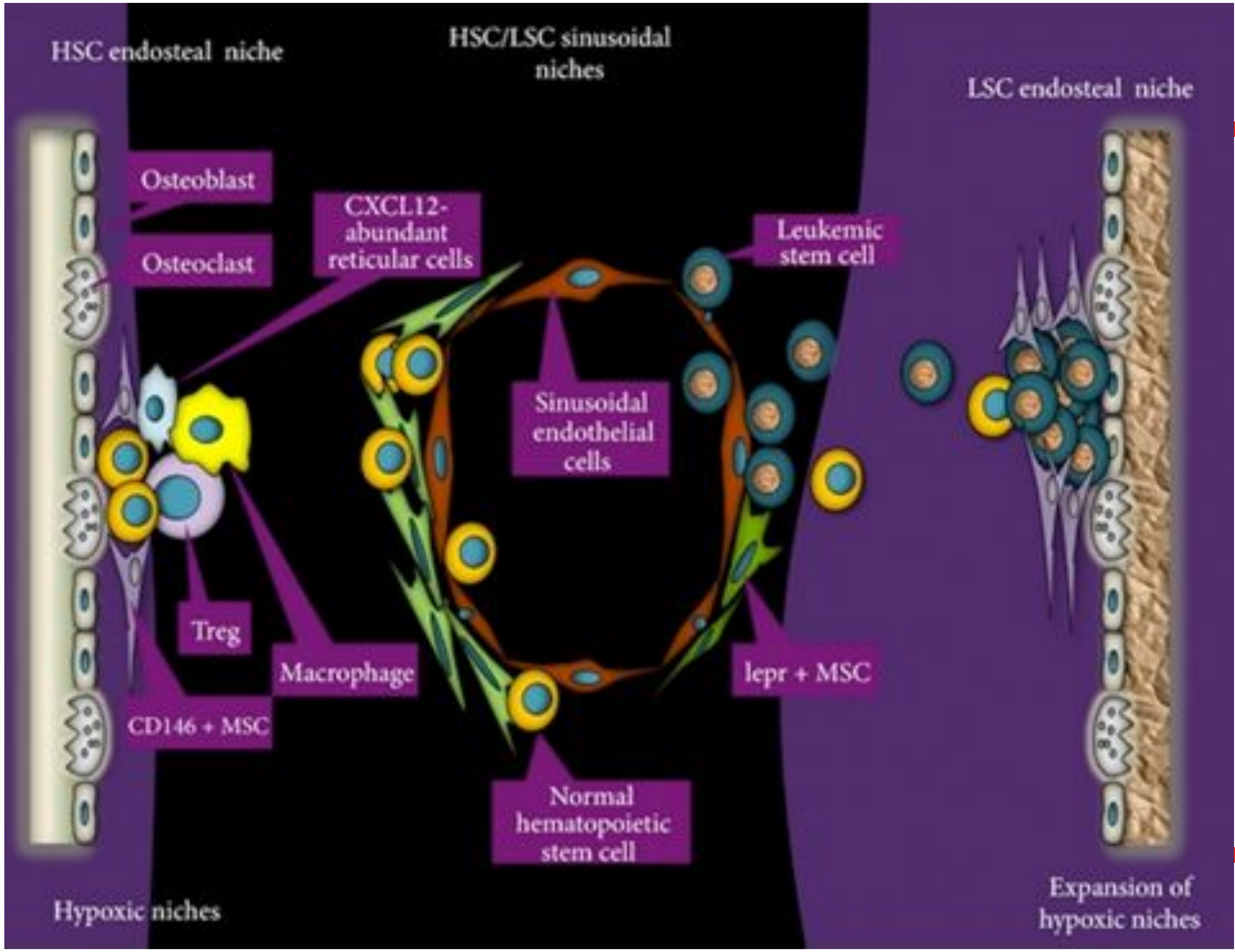


HSCs self- renewal and differentiation have to be tightly regulated to avoid abnormal HSC expansion and leukemia or HSC premature exhaustion and BM failure

Senescence of HSCs by IR Injury



Leukemic Stem Cells



Larger hypoxic endosteal niche:
- More radioresitant
- Detectable?

New advances in Imaging

JOURNAL OF MAGNETIC RESONANCE IMAGING 38:1578–1584 (2013)

Technical Note

Water–Fat MRI for Assessing Changes in Bone Marrow Composition Due to Radiation and Chemotherapy in Gynecologic Cancer Patients

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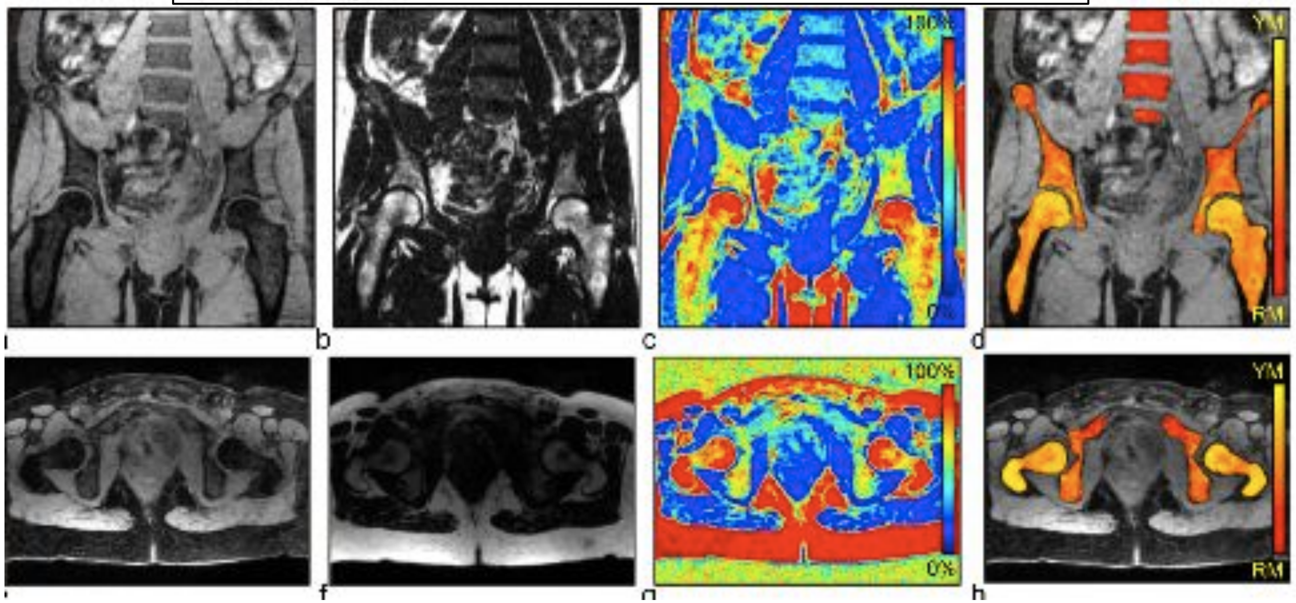

IR reduce the number of hematopoietic cells and can increase MSc adiposis differentiation----from RED to YELLOW marrow—higher FAT Fraction

3T MRI Whater Fat Fraction can detect modifications

New advances in Nanothecnology

Review

Nanoparticles Based Stem Cell Tracking in Regenerative Medicine

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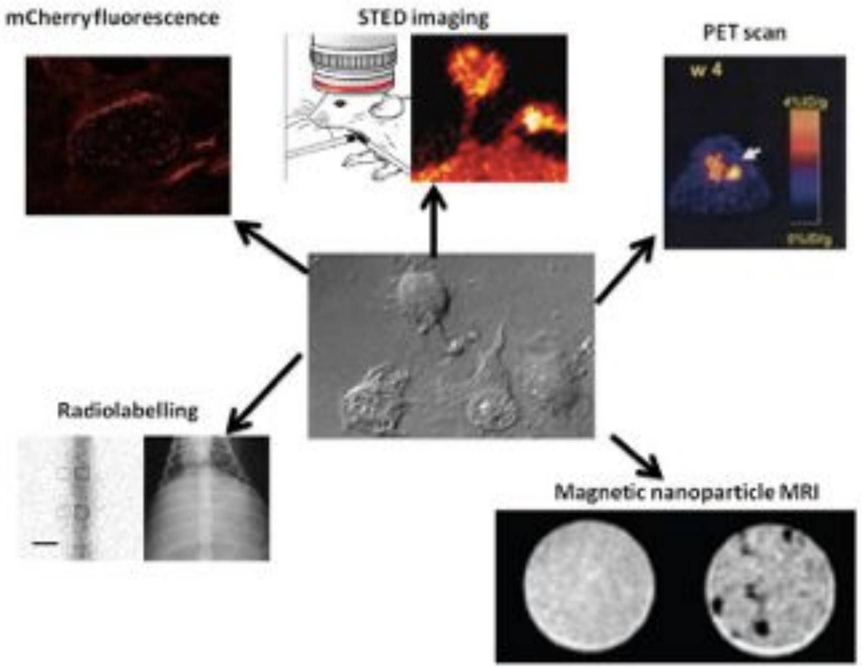

- Magnetic core into SCs
- High resolution non invasive
- 3D MRI nanoparticles tracks grafted stem cells
- no patient discomfort
- still exist some limitations

Point the Way

- Bone marrow microenvironment is a new “old” field of research (most of the radiobiological research is from ‘80s)

- New radiobiological data from human are lacking due to the “limitation” in progress of conventional radiotherapy technique

- In the ideal world the Imaging modality should show burden areas of leukemic cells (hypoxic endosteal niche) and allow to mapping sites with radioresitant MSc. “**Dose painting**”

- Patients treated with TMI are limited in number and a long time is needed to prospectively consolidate new fractionation schedule

- Biological effects of dose rate from new FFF beams are to be investigated


IC - TMI

- ***UZ Bruxelles (BE)***
- ***IRCCS San Martino IST Genoa (IT)***
- ***Masonic Centre Minnesota (US)***
- ***ICORG Nantes (FR)***
- ***Tokyo Univeristy (JP)***
- ***Maria Skwlodoska – Curie Memorial Cancer Centre, Gliwice (PL)***

- *Collaborative intent to write common protocols*
- *Improving the feasibility of the technique*
- *Creation of a common database of toxicities*
- *Analyze data from different fractionation schedule*
- *Share patients bone marrow samples to be centrally analyzed*

..taking the first steps towards…

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Physics Contribution

Multi-institutional Feasibility Study of a Fast Patient Localization Method in Total Marrow Irradiation With Helical Tomotherapy: A Global Health Initiative by the International Consortium of Total Marrow Irradiation

Thank you