European Joint Programme for the Integration of Radiation Protection Research – CONCERT

Topic 1: Improvement of health risk assessment associated with low dose/dose rate radiation

Daniela Kraft — **GSI, Darmstadt**

Lisa Wiesmüller — **Gynecological Oncology, Ulm University**

Research focus:
Low-fidelity DNA double strand break repair in leukemia-cells-of-origin

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DLR/BMWi
50WB1225

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Eric Metzler
Aljona Groo
Lea Bauer
Marco Durante

Halvard Bönig

Elena Nasonova, Dubna, JINR, Russia

Radiation facilities (GSI, Darmstadt)

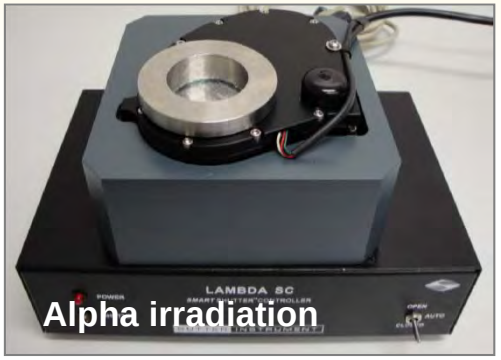
<u>low and high LET radiation exposure</u>

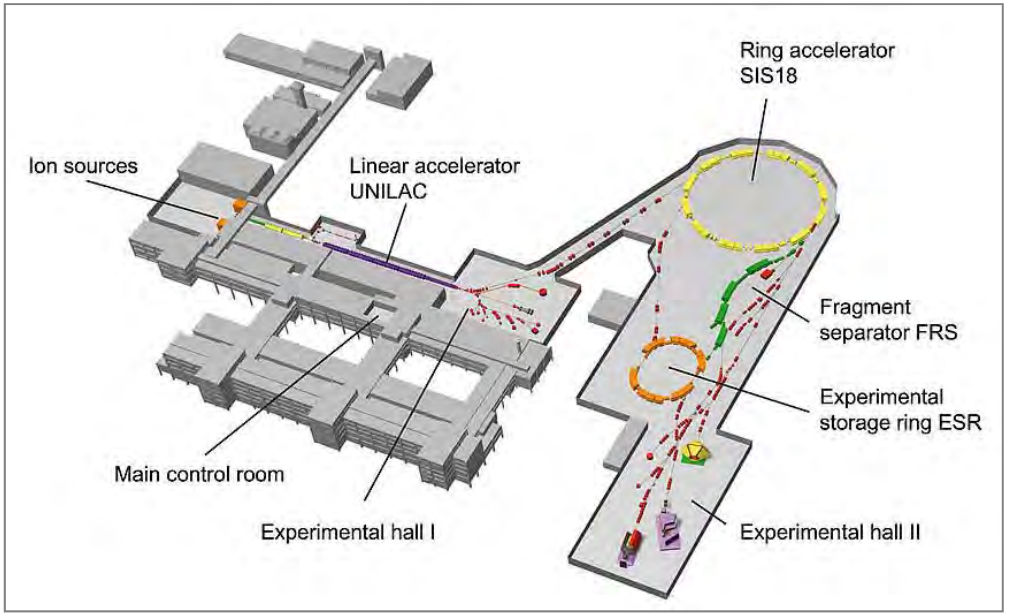
a) photons

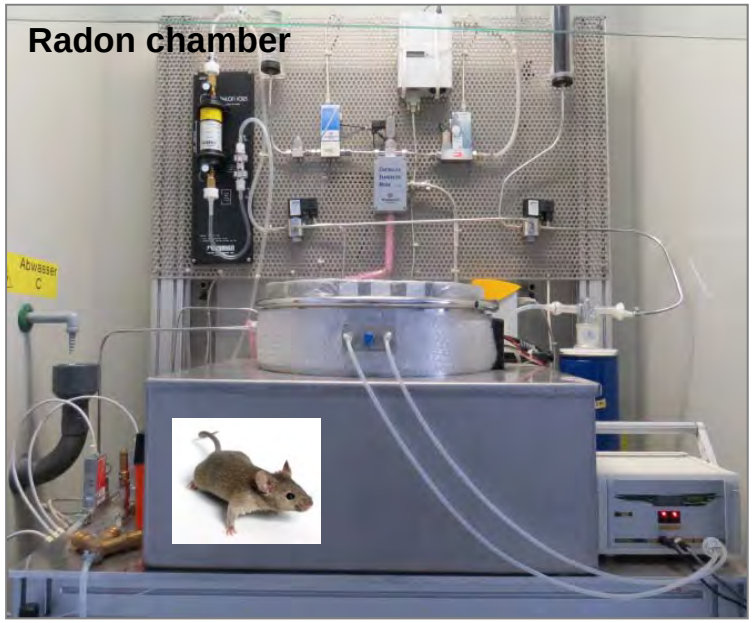
b) **heavy ion** accelerators

c) **alpha particles**, ^{241}Am-source, max. energy: 5.49 MeV, mean LET 153±45 keV/µm

d) **Radon** exposure (cell cultures/small animals), simulate conditions like in radon-galleries, max. radon concentration 620 kBq/m^3

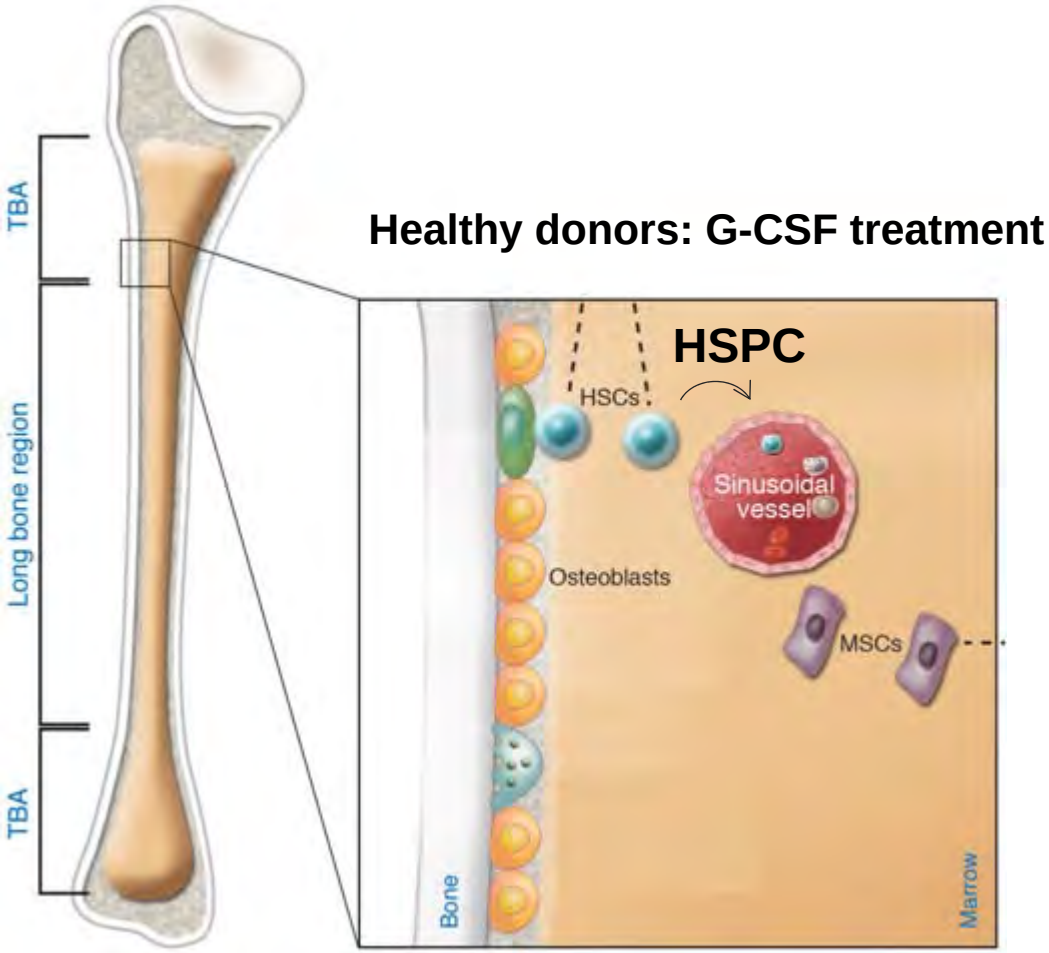






Radiation impact on **human bone marrow stem cells**

(A) Hematopoietic stem and progenitor cells (HSPC)

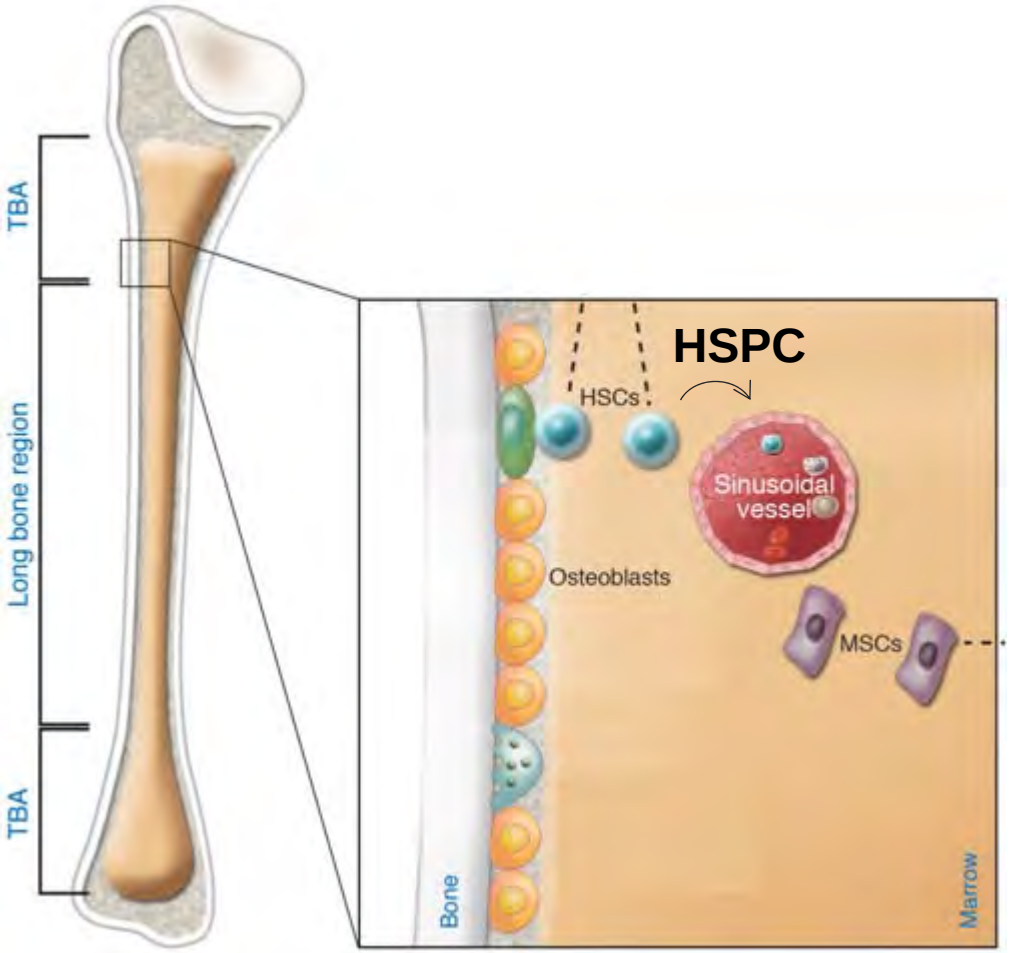


(Yin and Li 2006) modified

Radiation impact on **human bone marrow stem cells**

(A) Hematopoietic stem and progenitor cells (HSPC)

Stem cell apheresis
CD34+ positive enrichment

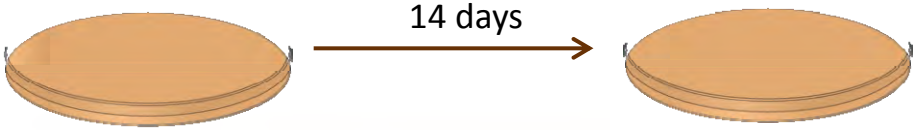


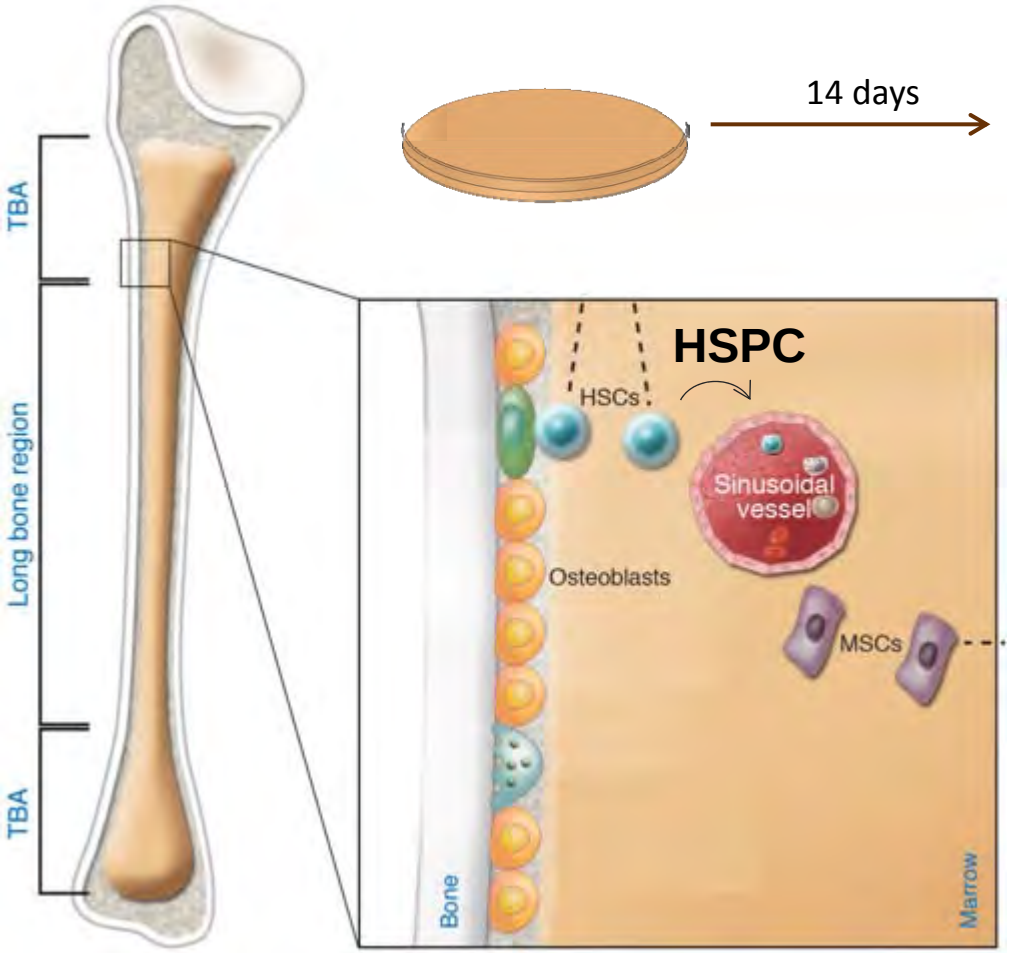
(Yin and Li 2006) modified

Radiation impact on **human bone marrow stem cells**

(A) Hematopoietic stem and progenitor cells (HSPC)

Culture & Differentiation
Colony Forming Unit (CFU)
Assay





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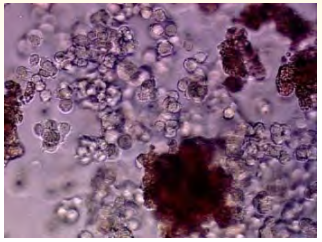
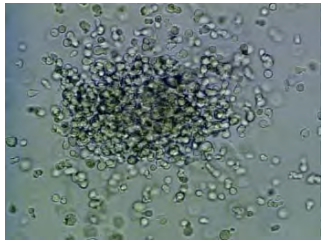
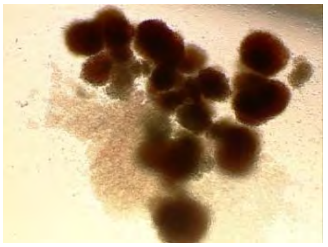


Progenitors



Granulocytes/
monocytes



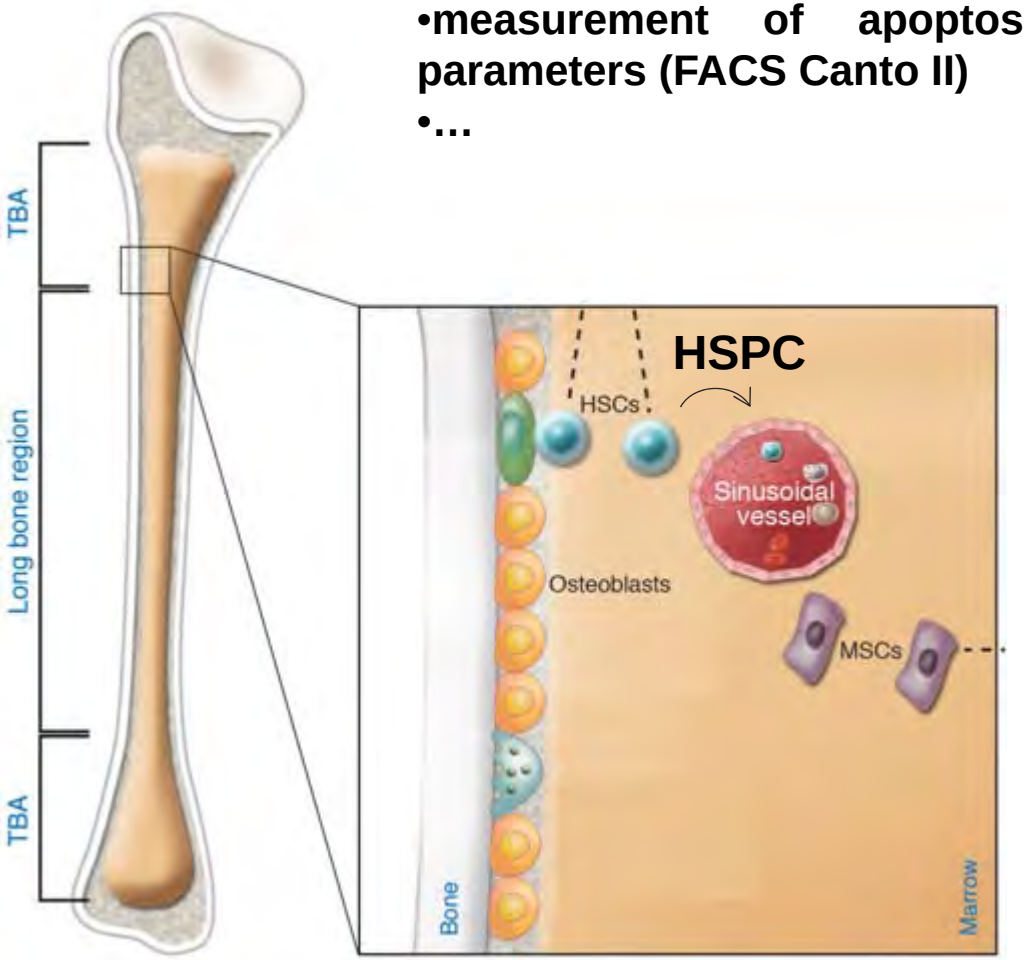
erythroctyes

Radiation impact on **human bone marrow stem cells**

(A) Hematopoietic stem and progenitor cells (HSPC)

Analytical tools

- **Cytogenetics (interphase and multicolour fluorescence in situ hybridization (FISH)**
- **measurement of apoptosis and cell cycle parameters (FACS Canto II)**
- **…**



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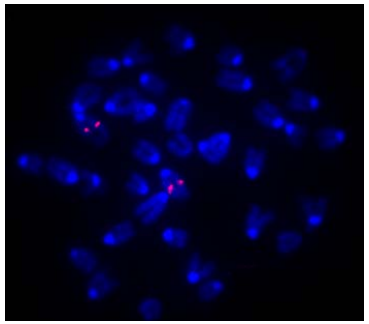
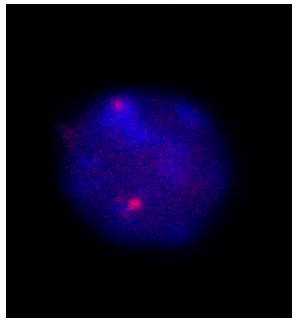
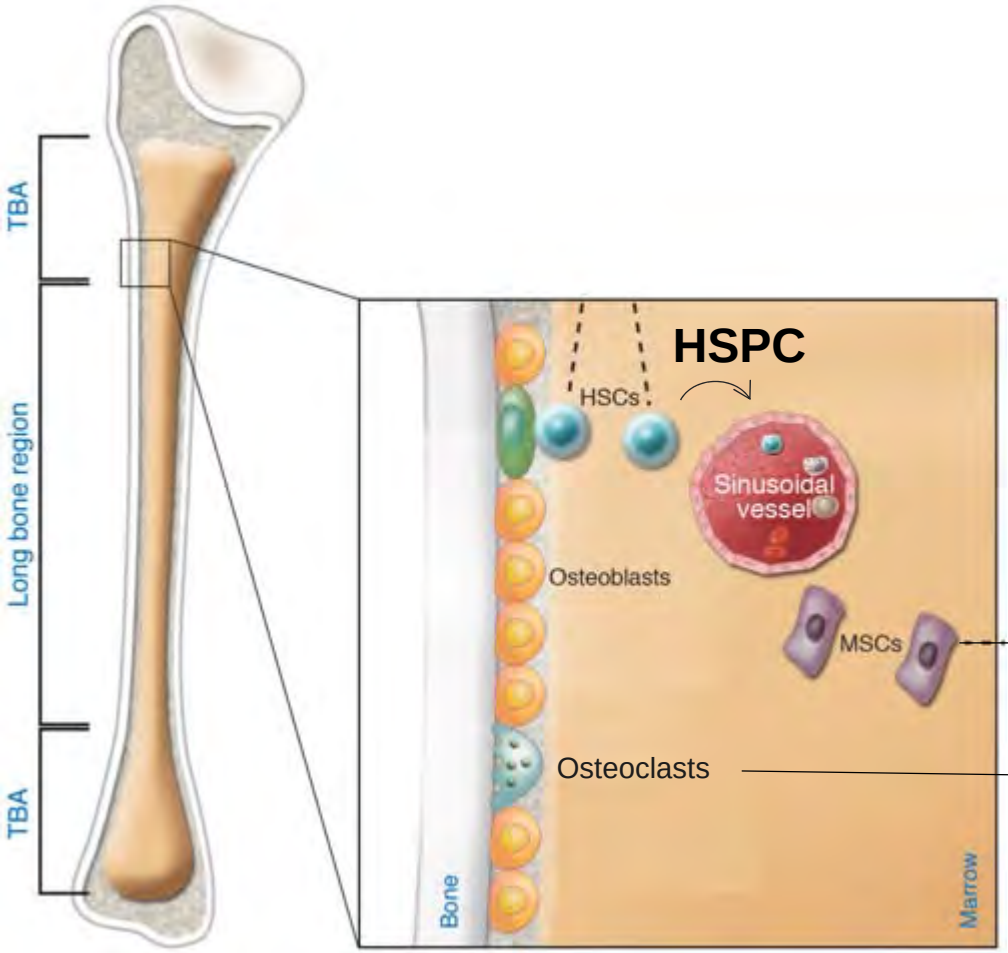


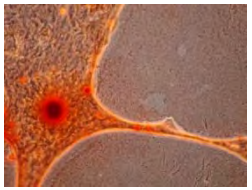


Radiation impact on **human bone marrow stem cells**

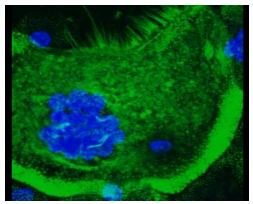


(Yin and Li 2006) modified

(B) Bone forming and resorbing cells



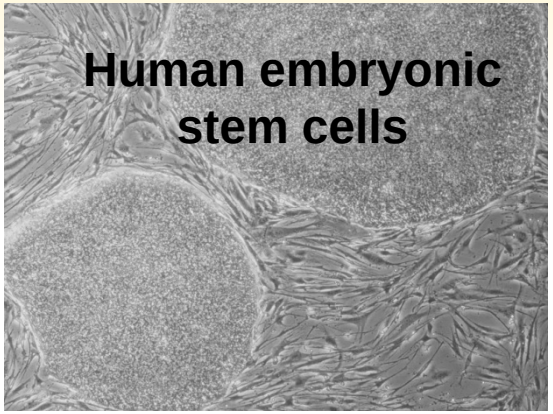
Osteoblasts



Osteoclasts

Radiation impact on early development and regeneration

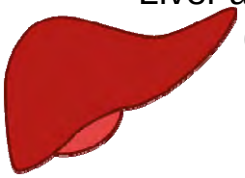
Dr. Sylvia Ritter



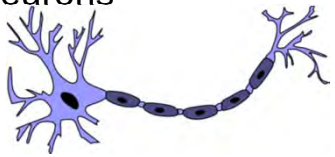
Differentiation into all cells of the body

Dr. Insa Schröder

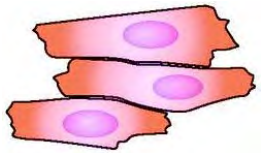
Liver and pancreas cells
(endoderm)



Neural stem cells, neurons
(ectoderm)



Beating cardiomyocytes
(mesoderm)



Analytical tools:

mRNA arrays (Stem cell signaling, DNA repair)
miRomics
chromosome analyses (mFISH)
electrophysiology (micro electrode arrays)

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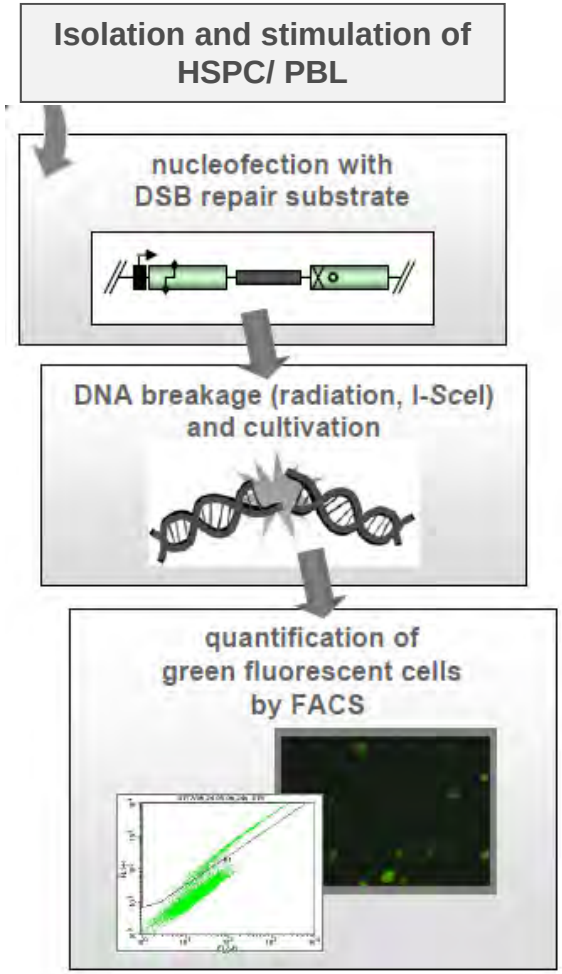
NF-κB-dependent DNA damage-signaling differentially regulates DNA double-strand break repair mechanisms in immature and mature human hematopoietic cells

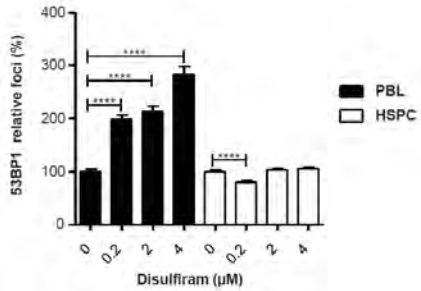
D Kraft[1,4], M Rall[2,4], M Volcic[2,4], E Metzler[1], A Groo[1], A Stahl[2], L Bauer[1], E Nasonova[1,6], D Salles[2], G Taucher-Scholz[1], H Bönig[3], C Fournier[1,5] and L Wiesmüller[2,5]

Leukemia advance online publication, 3 March 2015; doi:10.1038/leu.2015.28



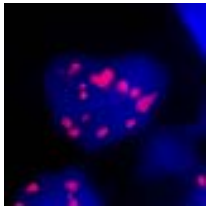
DSB repair in HSPC vs. PBL

- capacity and fidelity of DSB repair reduced (fluorescence-based DSB repair assay system - EP1399576, quantitative immunofluorescence multiparameter microscopy, radiation/drug sensitivities, screening)

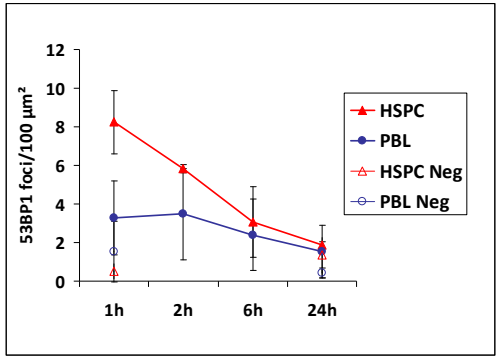


Identification of druggable mechanism

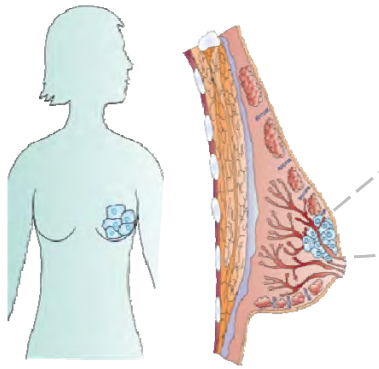
- PARP1-NF-κB signalling inactive



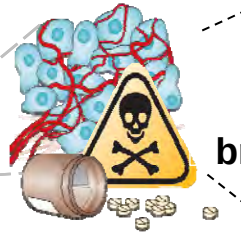
53BP1



MLL breakpoint cluster region (*MLL*bcr), a hotspot for radiation-induced fragility

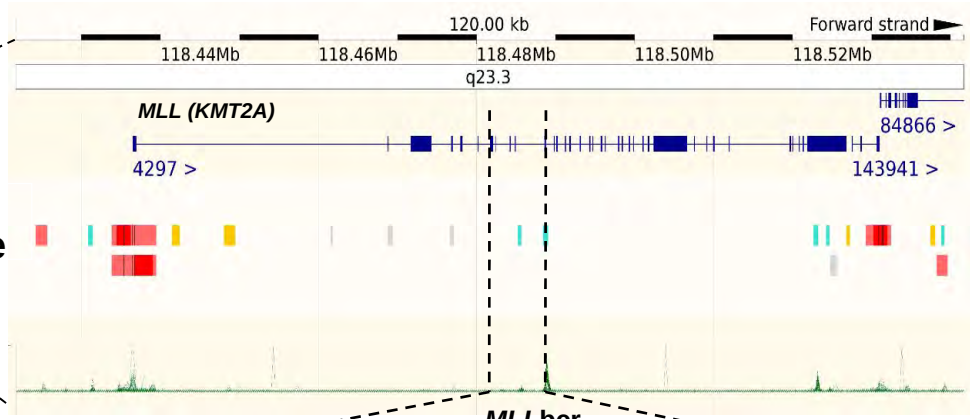


Chemo-/ Radiotherapy

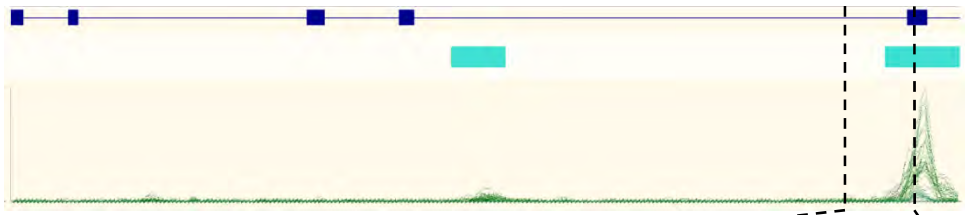


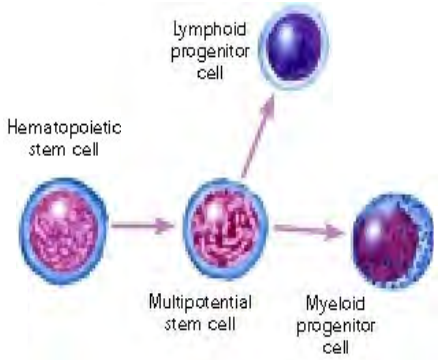
DNA breakage

Chromosome 11



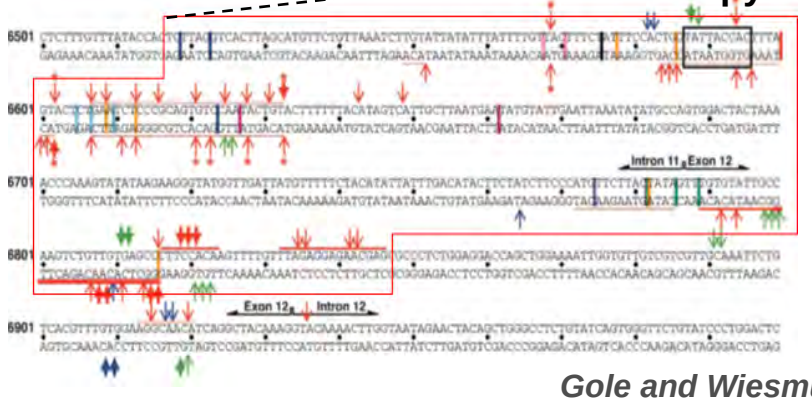
***MLL*bcr**

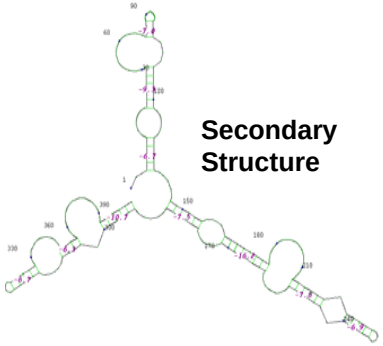




Therapy-induced *MLL* rearrangements and leukemia (6-35%)

Therapy-related *MLL*bcr hotspot





Secondary Structure

Gole and Wiesmüller 2015 Front Dev Biol

Arch Toxicol (2014) 88:1141–1159
DOI 10.1007/s00204-014-1229-3

GENOTOXICITY AND CARCINOGENICITY

Fluorescence-based recombination assay for sensitive and specific detection of genotoxic carcinogens in human cells

Ivanildce C. Ireno · Cindy Baumann · Regina Stöber · Jan G. Hengstler · Lisa Wiesmüller

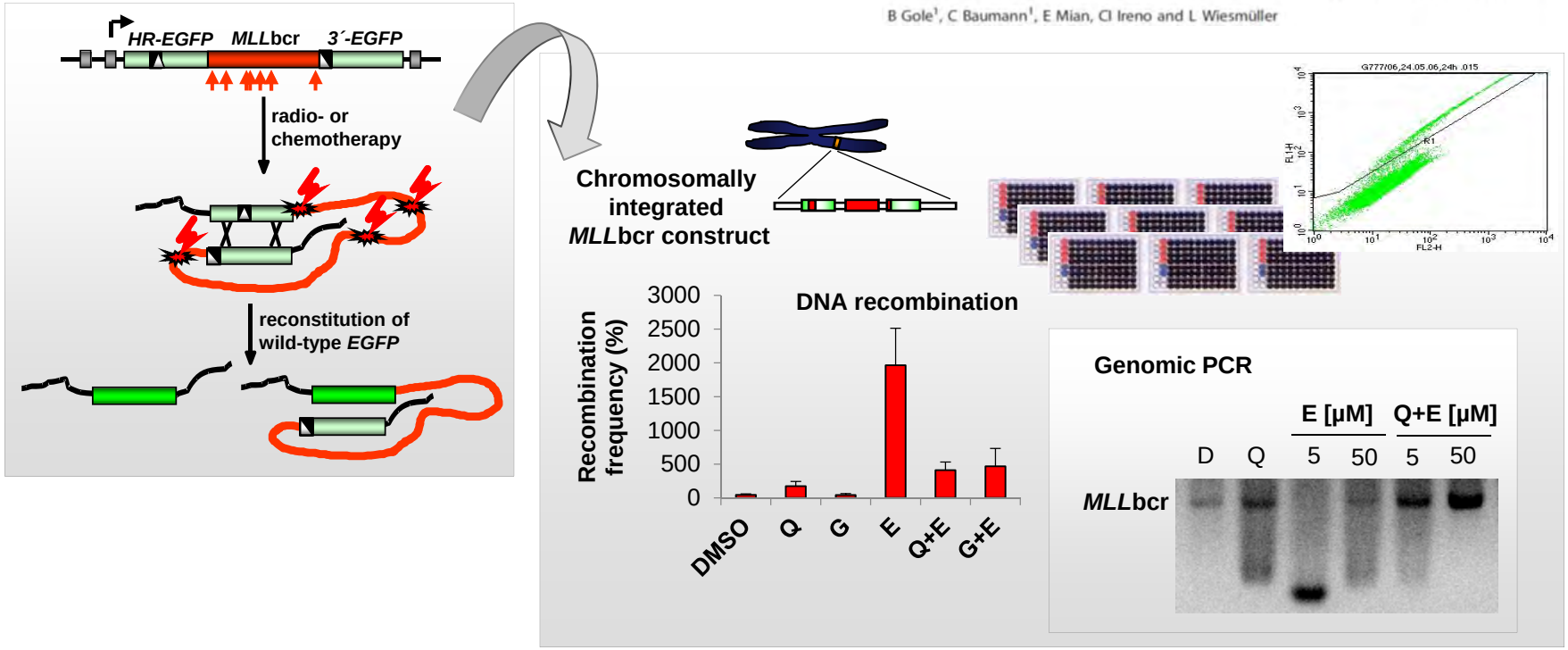
Oncogene (2014), 1–11

www.nature.com/onc

ORIGINAL ARTICLE

Endonuclease G initiates DNA rearrangements at the *MLL* breakpoint cluster upon replication stress

B Gole[1], C Baumann[1], E Mian, CI Ireno and L Wiesmüller



Model system for *MLL*bcr rearrangements for leukemia risk assessment

- Sensitive detection of radiation-induced *MLL*bcr rearrangements in HSC
- Screen-based identification of molecular targets/radiation mitigator drug