

Radiobiology I

Research and Lab Environment

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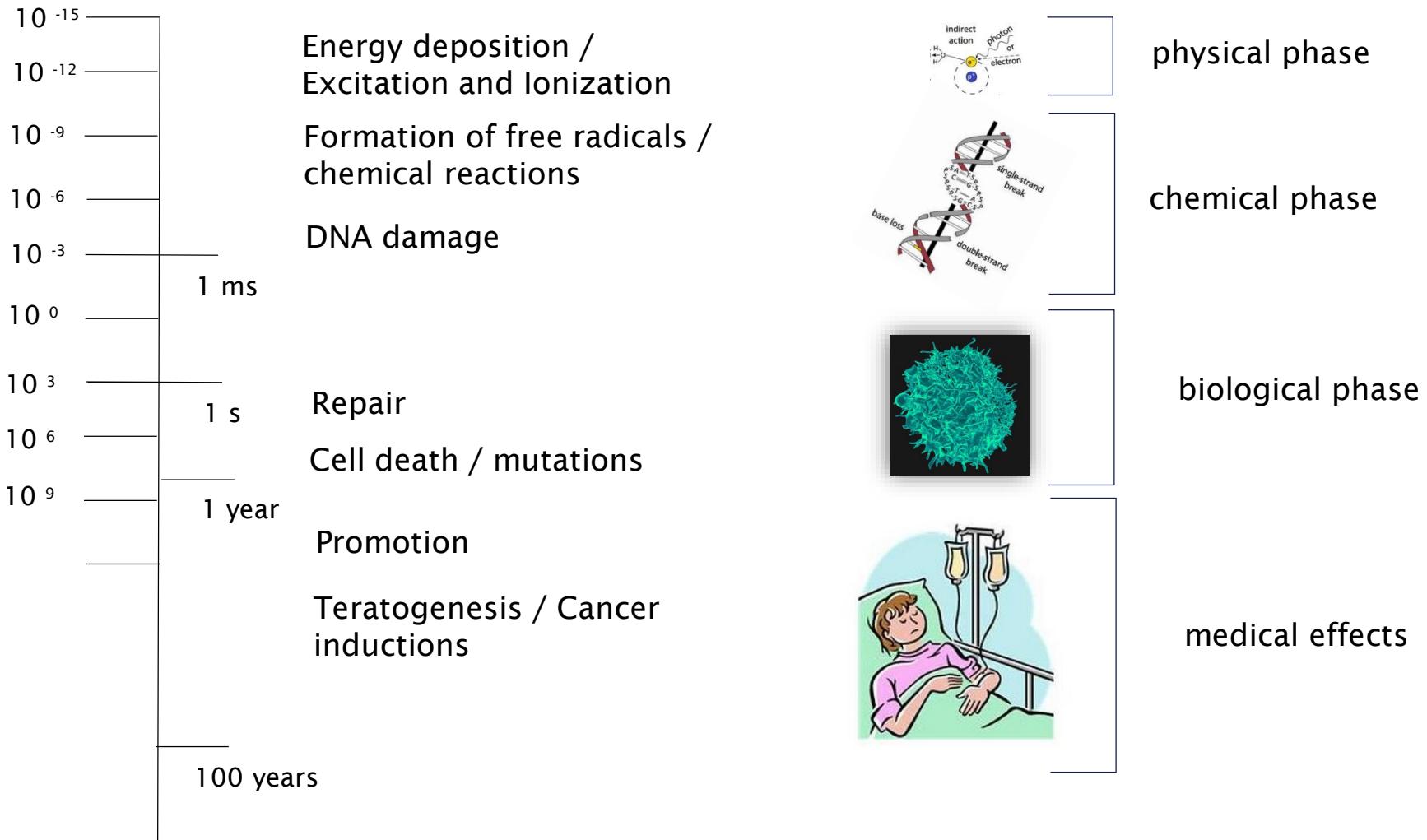
1. Basics of Radiobiology

1. DNA damage
2. DNA damage repair
3. Cellular survival influencing factors

2. Ion Beam Radiobiology at MedAustron

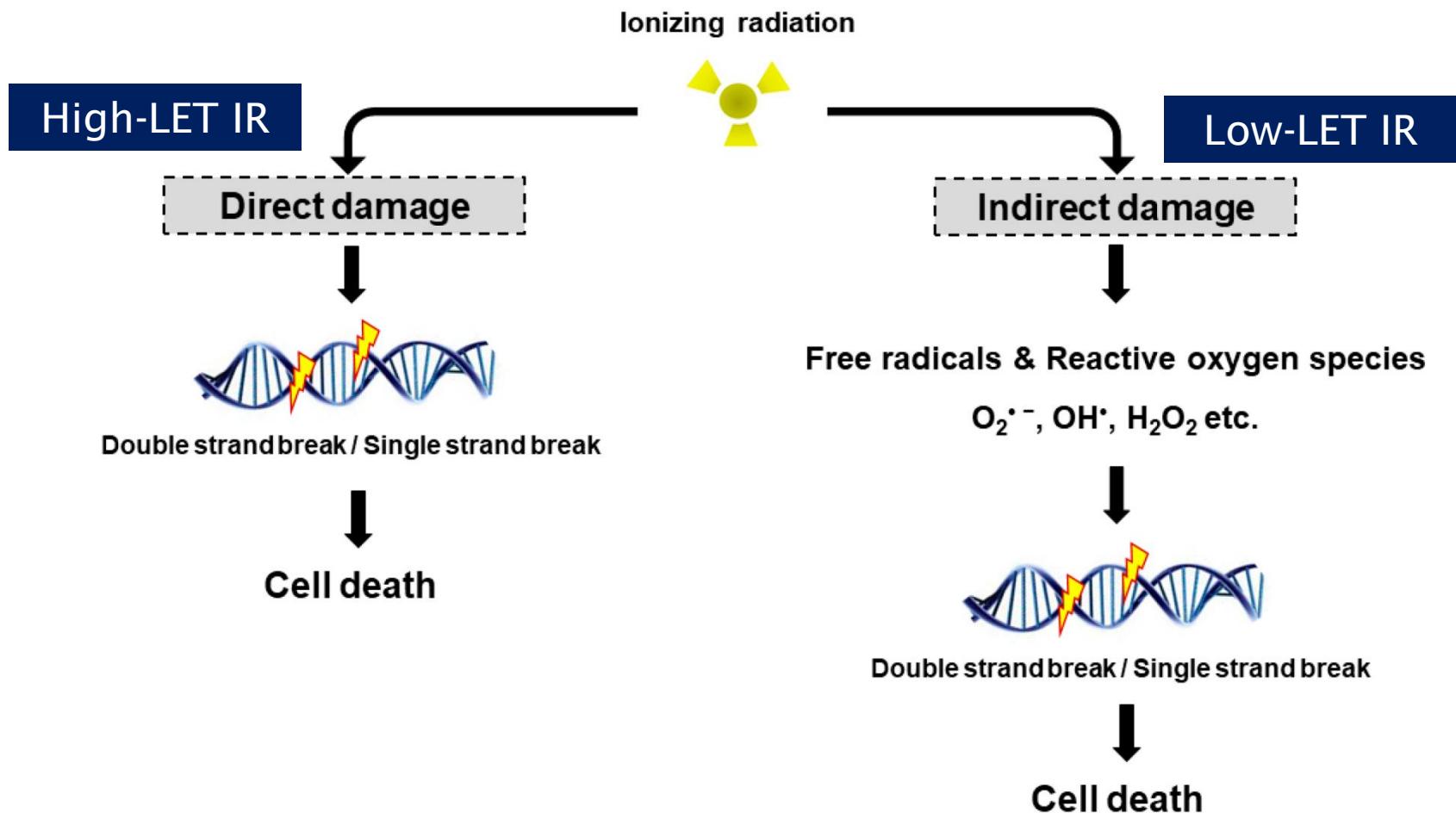
1. Ion beam therapy motivation – a biologist's point of view
2. Focus of radiobiological research at MedAustron
 1. Relative Biological Effectiveness of Particles and its Dependencies
 2. Synergistic IBT effects and combinations
 3. Advanced cell culture and in vivo models

Chronology of Radiation Effects



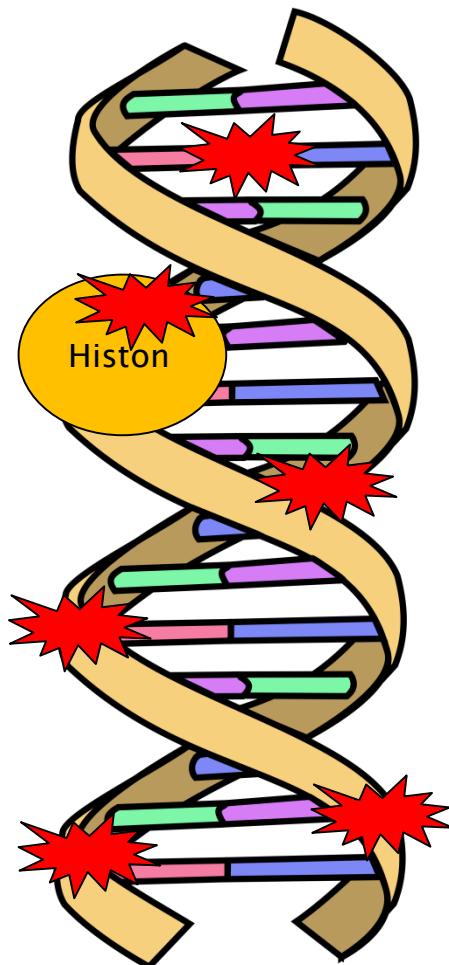
DNA damage

Direct vs. indirect



DNA damage – 1 Gy

- = Adenin
- = Thymin
- = Cytosin
- = Guanin
- = Phosphat-
desoxyribosc
Strang



base damage

4000-5000 incidents

DNA-protein crosslinks

150 crosslinks

sugar changes

800 – 1500 changes

single strand breaks

1000 SSB

double strand breaks

30- 60 DSB

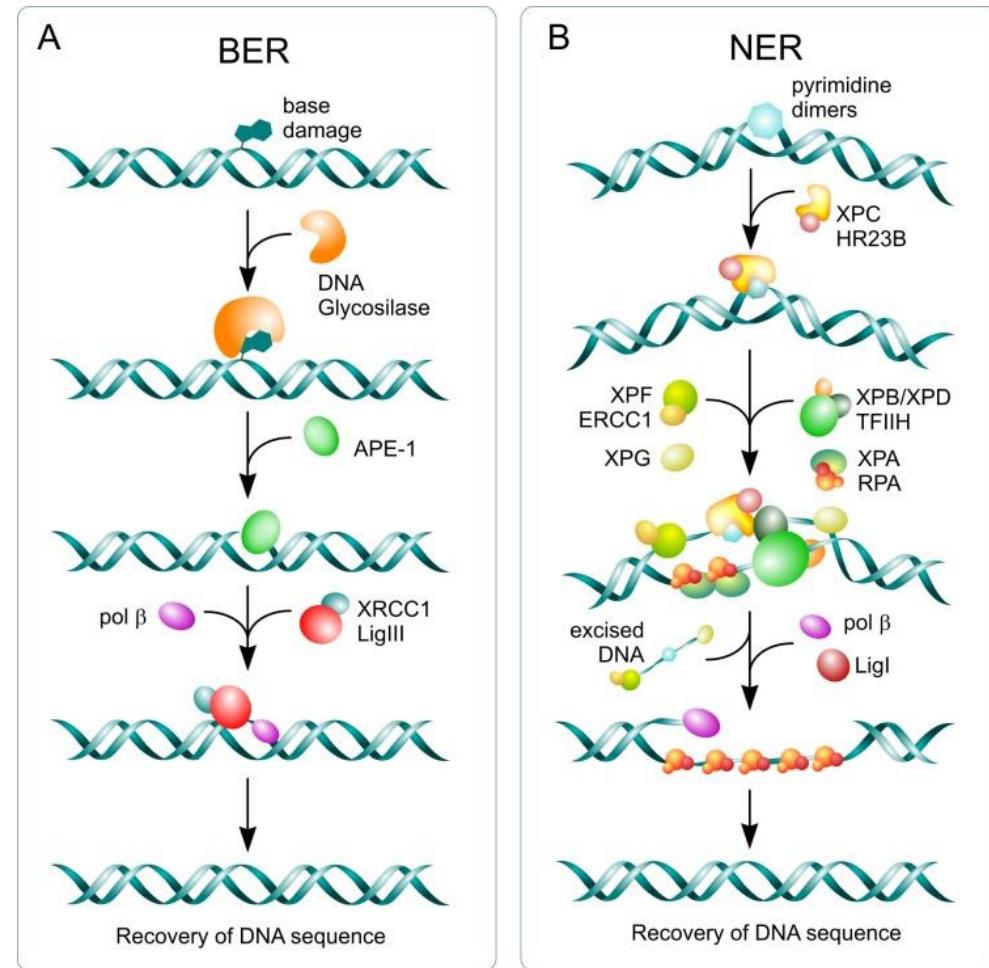
DNA damage repair – Single Strand Breaks

Baseexcision repair

- base damage
- induction of SSB
- synthesis of missing bases
- annealing

Nucleotideexcision repair

- bulky lesions
- induction of SSB
- excision of 20-30 BP
- synthesis of missing bases
- annealing



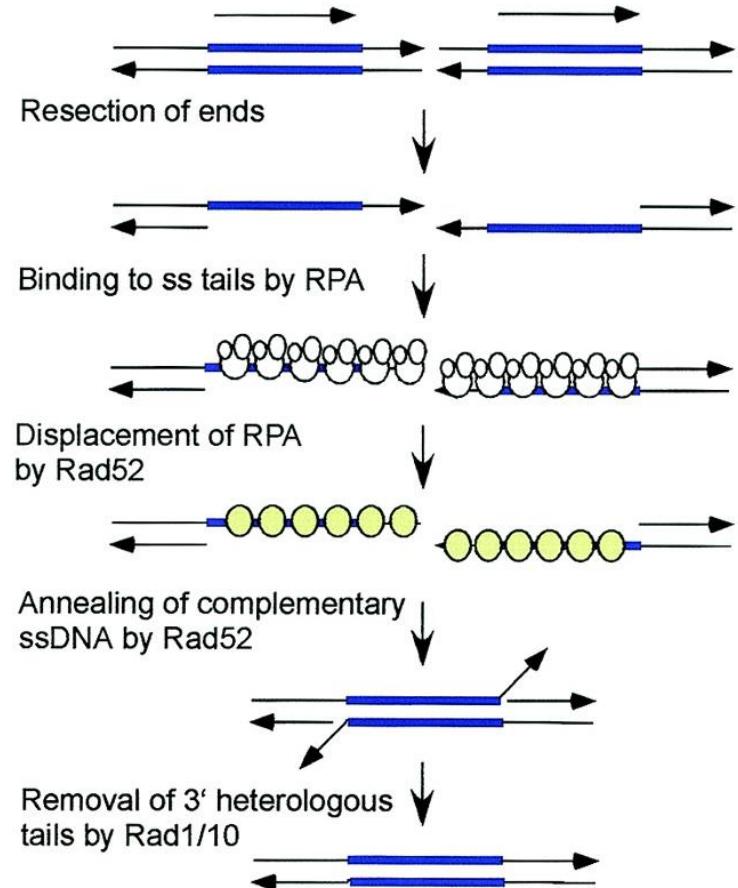
The Journal of Biological Chemistry, 285, 9762-9769, March 26, 2010

DNA damage repair – Double Strand Breaks

Single Strand Annealing

- only if DSB occurs between 2 repetitive sequences
- generation of ESB
- annealing of complementary sequences
- removal of tails

error prone



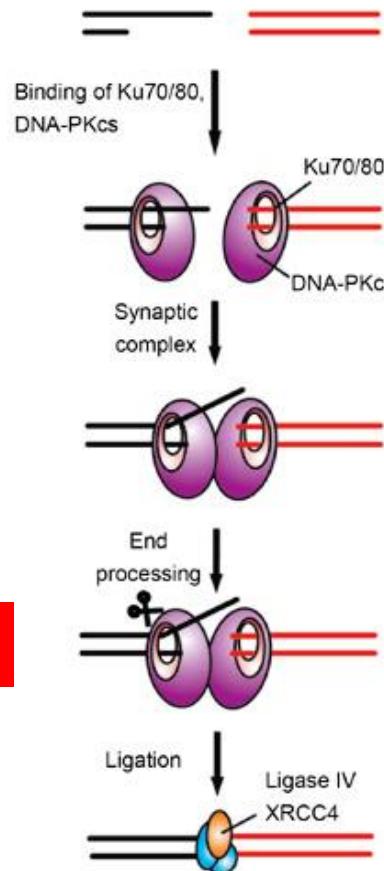
Microbiol. Mol. Biol. Rev. 2002;66:630-670

DNA damage repair – Double Strand Breaks

Nonhomologous endjoining Homologous recombination

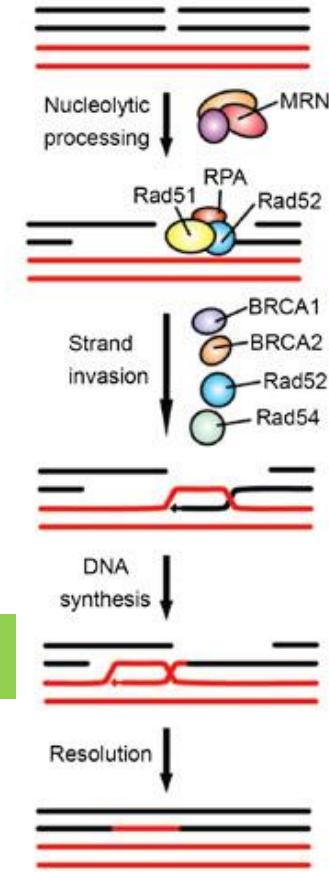
- >80 % of DSB
- G0 and G1 cell cycle phase

error prone



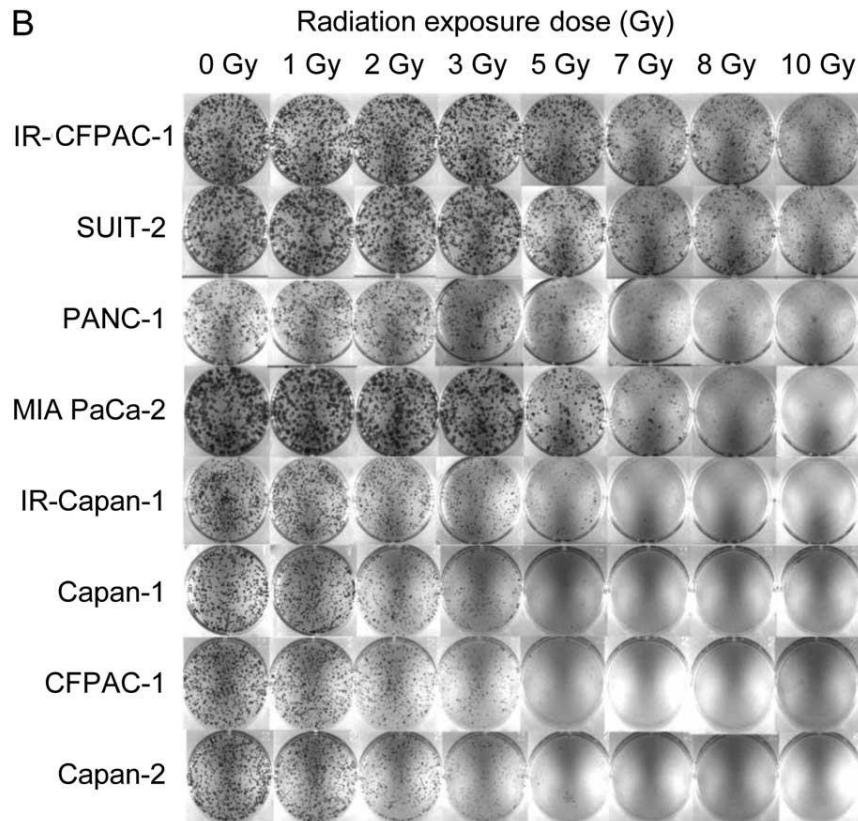
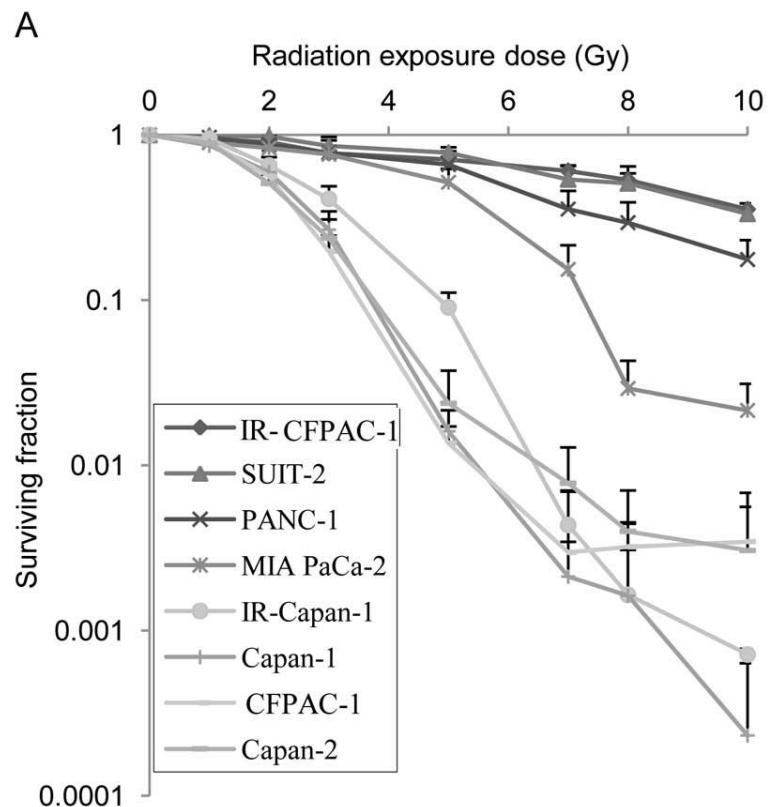
- < 20% of DSB
- S and G2 cell cycle phase

error free



Survival influencing factors

Intrinsic Radiosensitivity



Kozono et al, Oncol. Rep. 2013 Oct;30(4):1601-8.

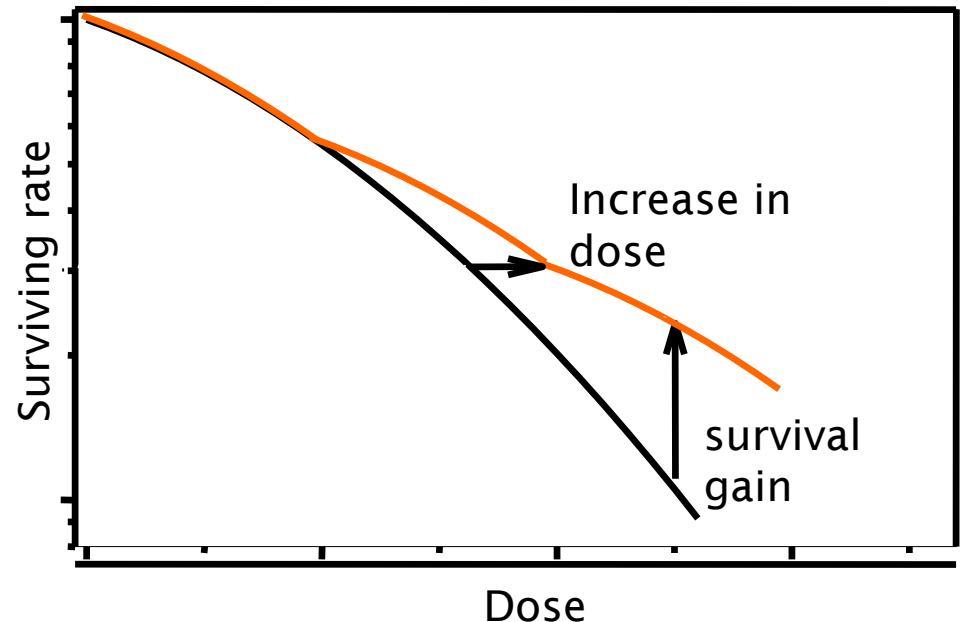
Survival influencing factors

Repair and Recovery

- Repair = function of macromolecule is restored
- Recovery = refers to increase in survival when TIME is increased
 - recovery from sublethal damage



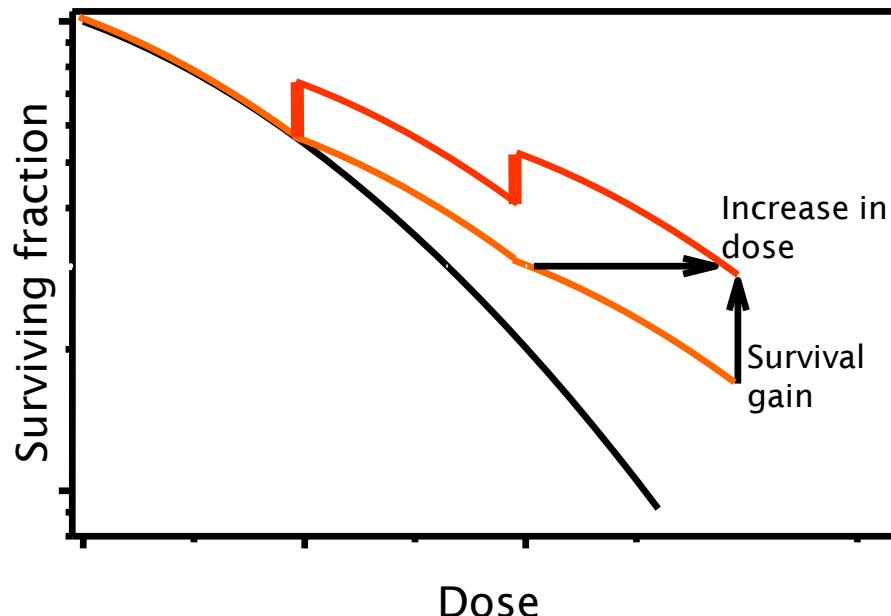
fractionation effect



Survival influencing factors

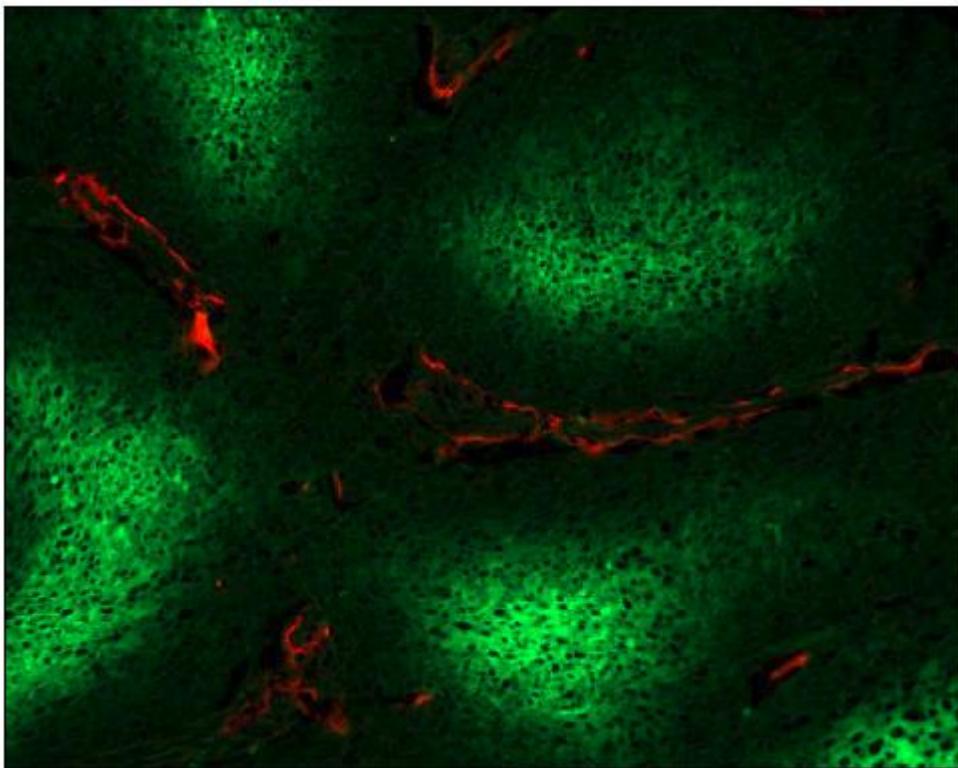
Repopulation

- Proliferation between fractions – increase in cell numbers
- Increased radiation tolerance with increasing treatment time

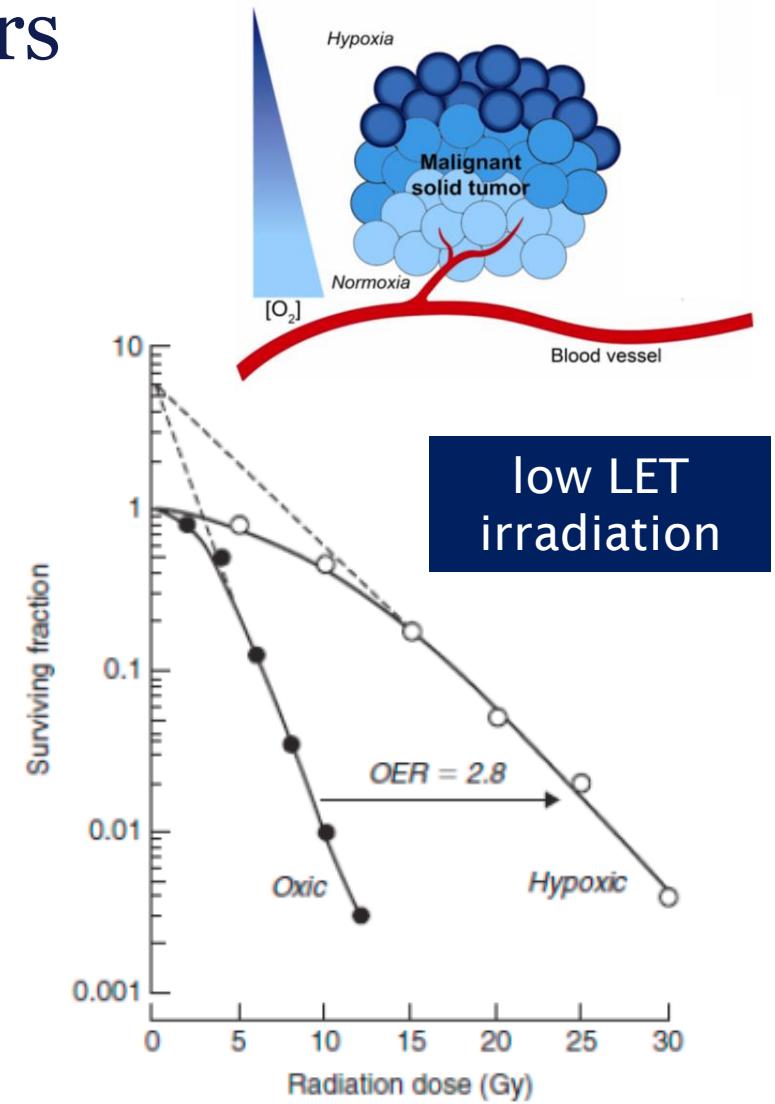


Survival influencing factors

Hypoxia/Reoxygenation

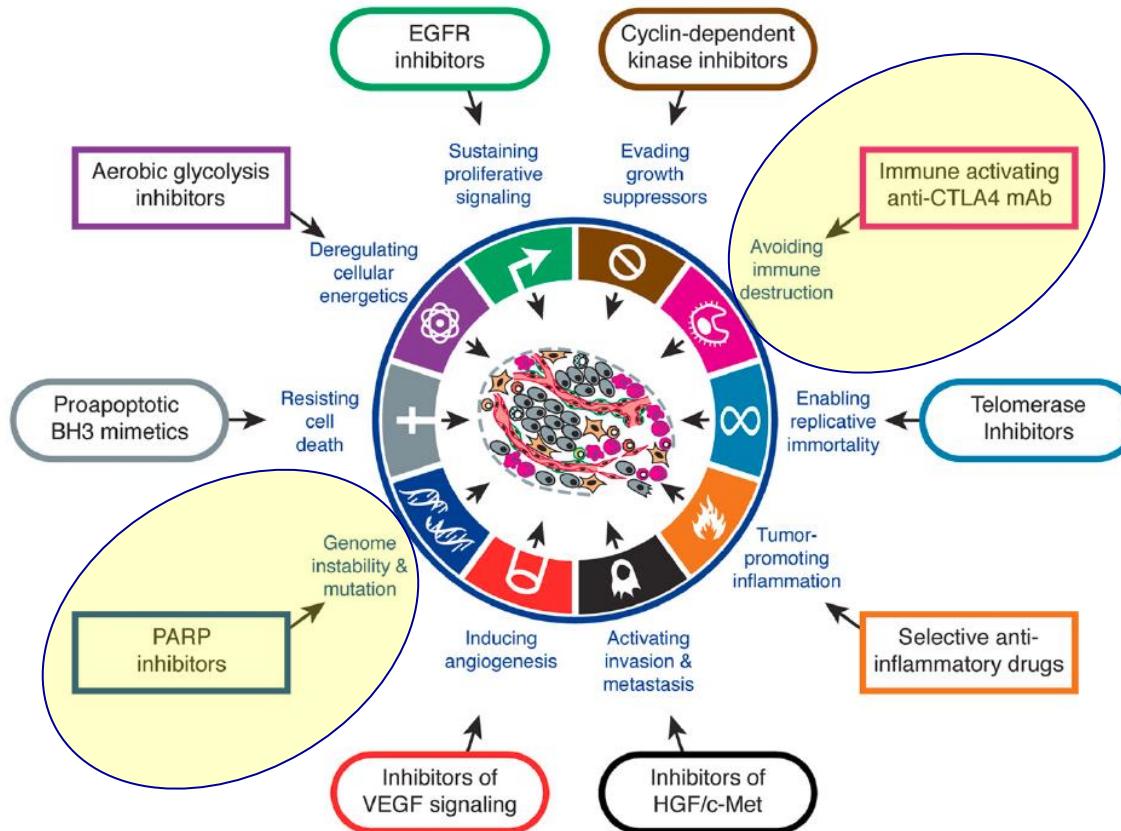


green: pimonidazole
red: vasculature

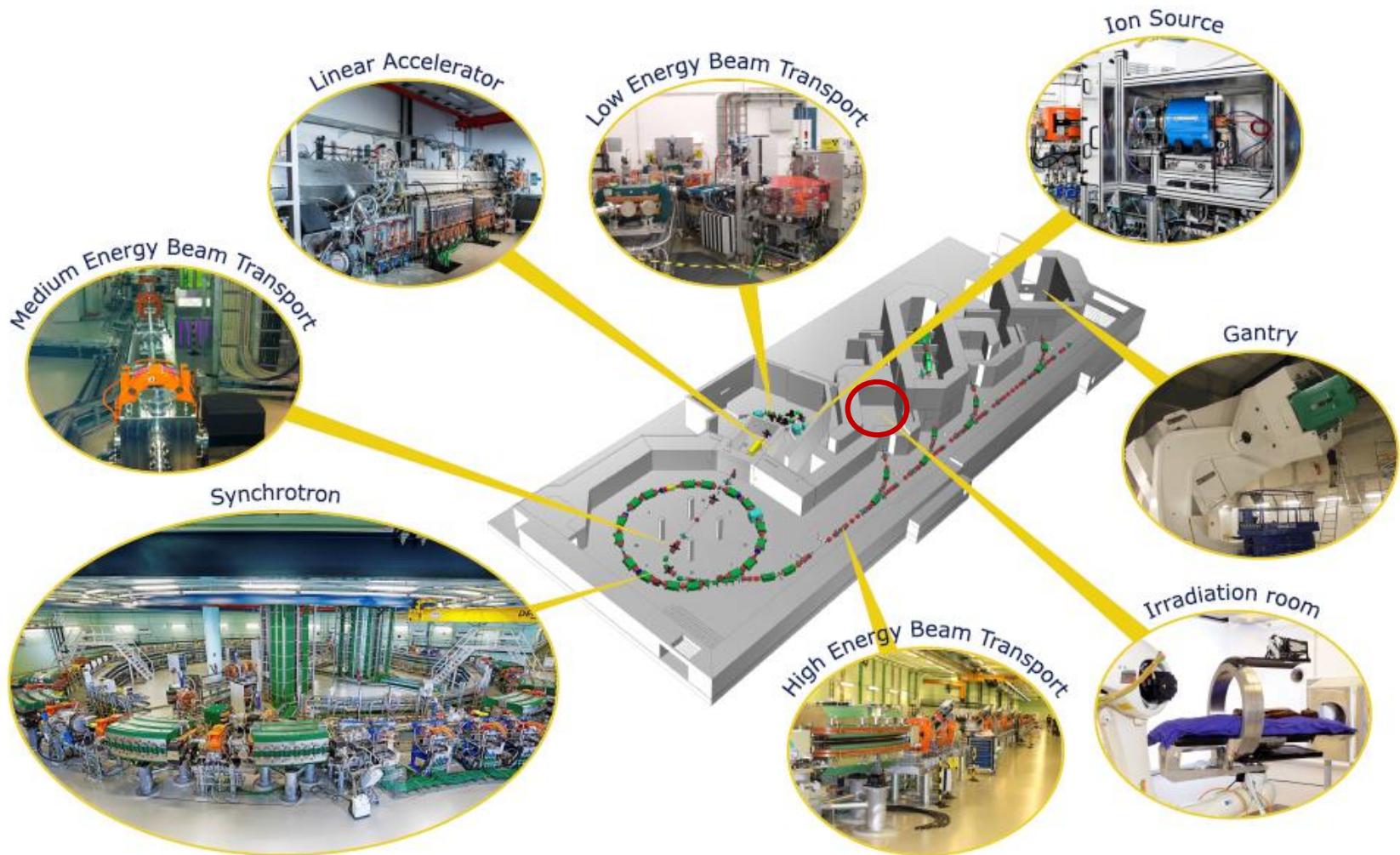


Survival influencing factors

molecular Radiopathology



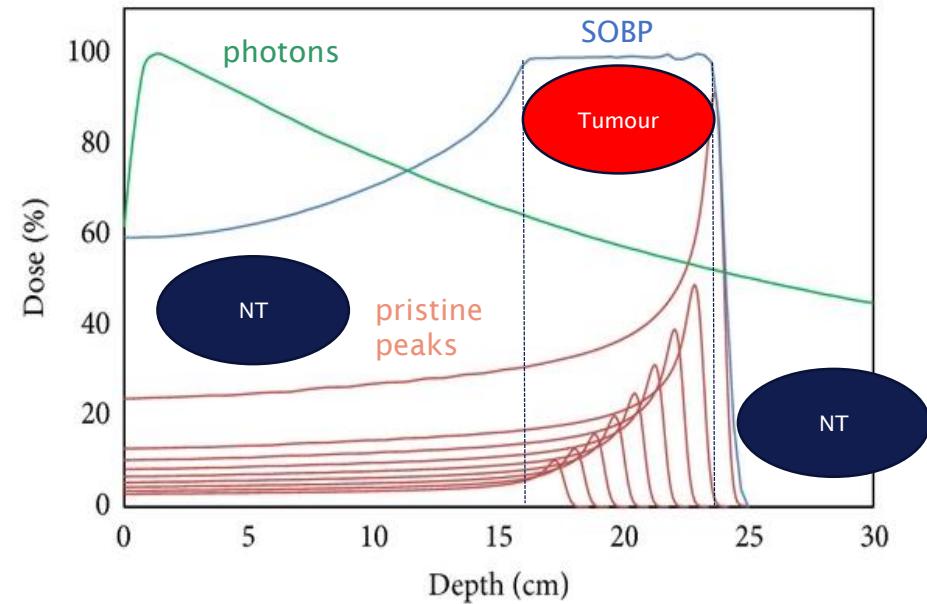
Ion Beam Radiobiology



Biologist's point of view: Physical Motivation

Superior dose distribution

1. inverted depth dose profile
 - highest dose to the tumour
2. defined penetration depth and reduction of integral dose
 - effective sparing of NT
3. reduced lateral scatter
 - high conformity



reduced dose in organs at risk

Biologist's point of view: Medical Motivation

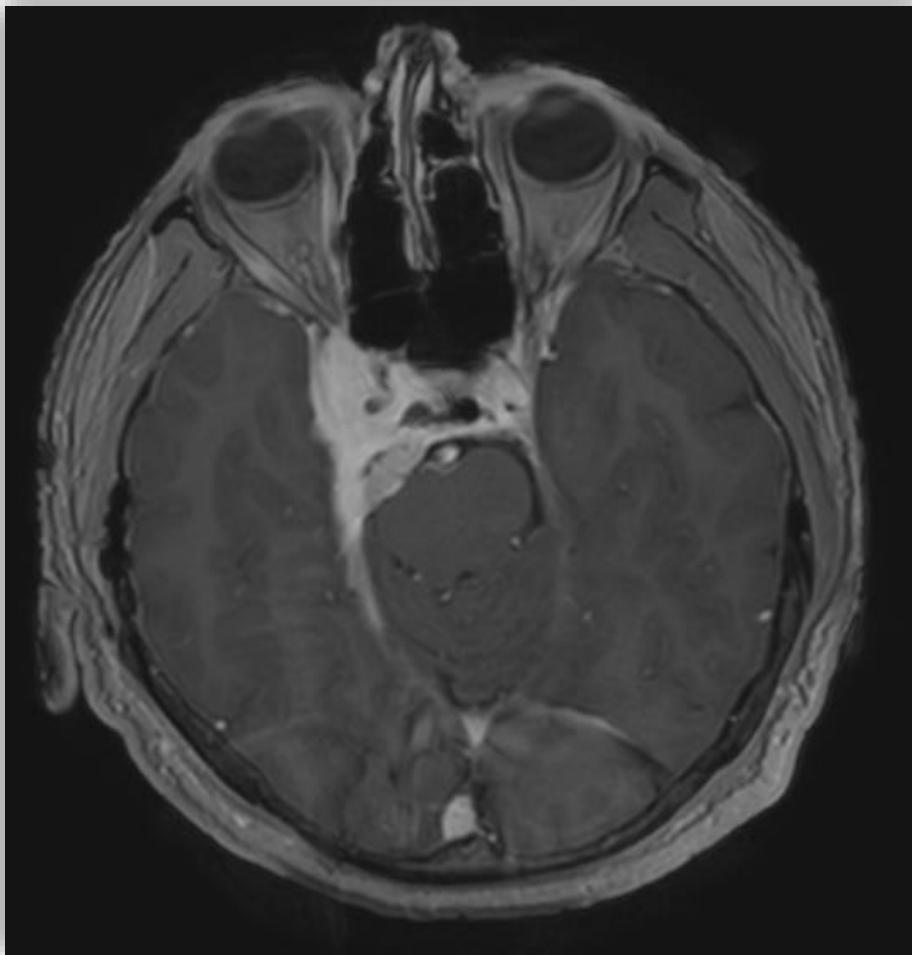


Image: Dr. Markus Stock, MedAustron

Ion Beam Therpay: Medical Motivation

Photons vs. protons

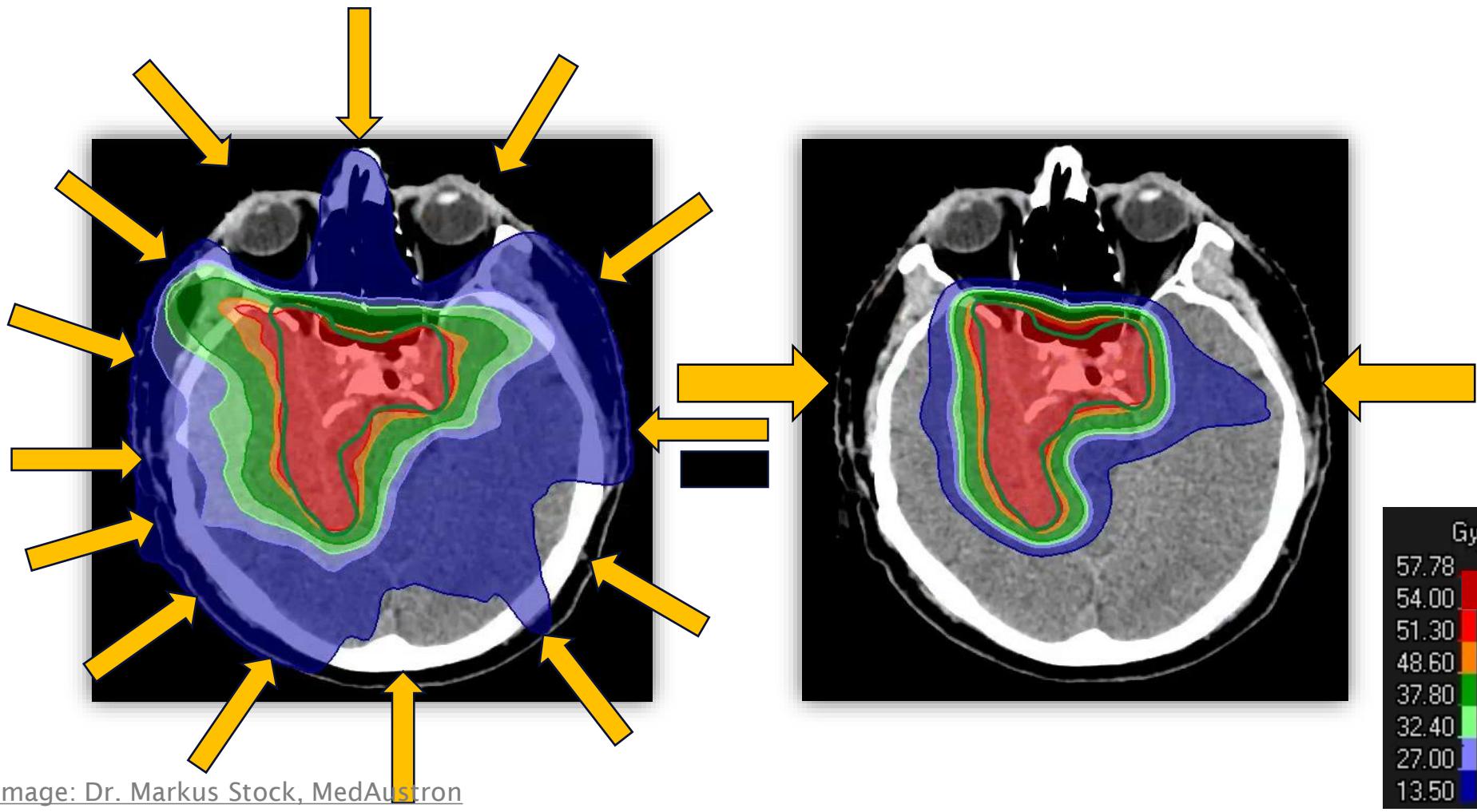


Image: Dr. Markus Stock, MedAustron

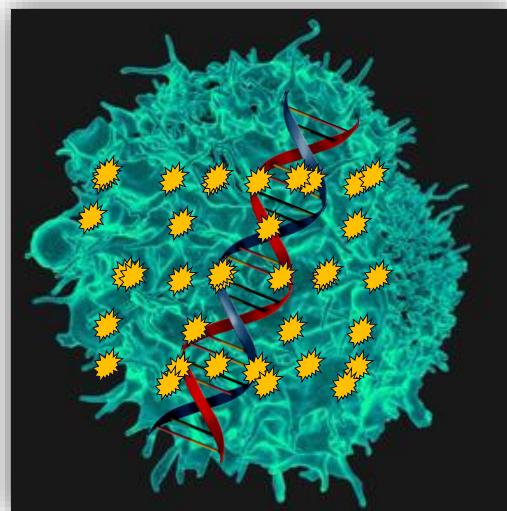


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Ion Beam Therapy: Biological Motivation

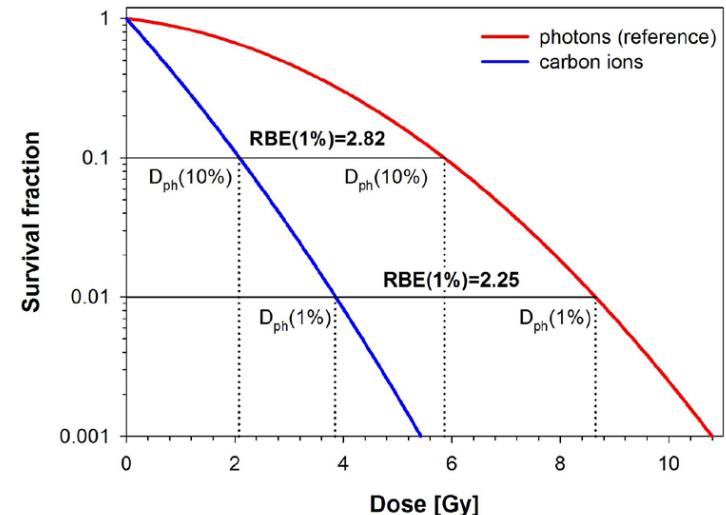
Increased Effectiveness

- Increased relative biological effectiveness (RBE)
 - Proton RBE (generic): 1.1 → clinically used
 - Carbon RBE: values >3 reported



sparsly vs. densely ionizing irradiation

↓
same physical dose results
in increasingly complex DNA
damage pattern

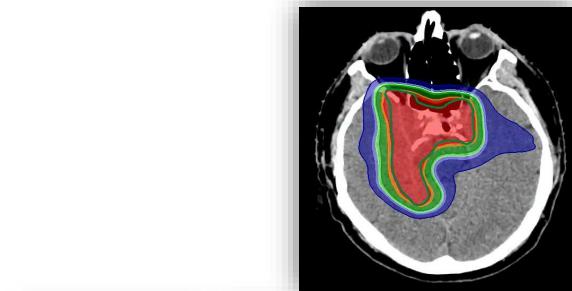


Karger and Peschke 2018 *Phys. Med. Biol.* 63

Ion Beam Therapy: Indications

1. Tumours close to critical organs at risk
2. Pediatric tumours
 - reduced risk of secondary tumours
 - reduced developmental impairment
3. Reirradiations
 - occult irreversible radiation injury
4. Resistant tumours – increased relative biological effectiveness (RBE)

→ depth dose profile



growing bone



Osteosarcoma

→ increased RBE

Staff



PhD Students



Timeline of Radiobiology Research at MedAustron

2015

2016

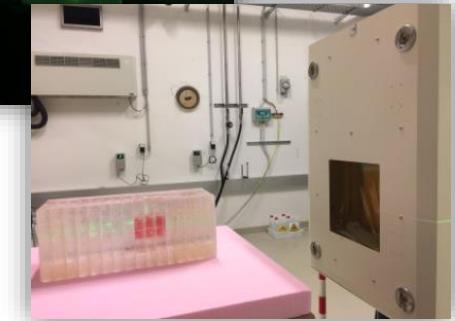
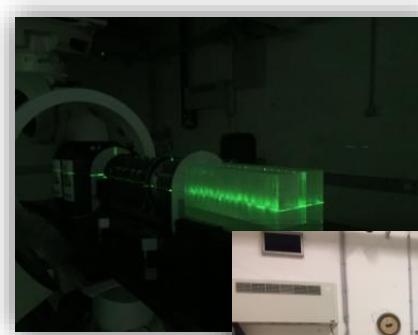
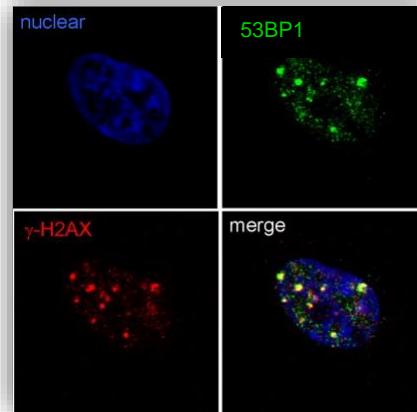
2017

2018

equip the labs

commissioning of
infrastructure10/16: proton
beam in IR1implementation of methods
and techniques04/17: first cell irradiations in
IR1 → RBE dependencies

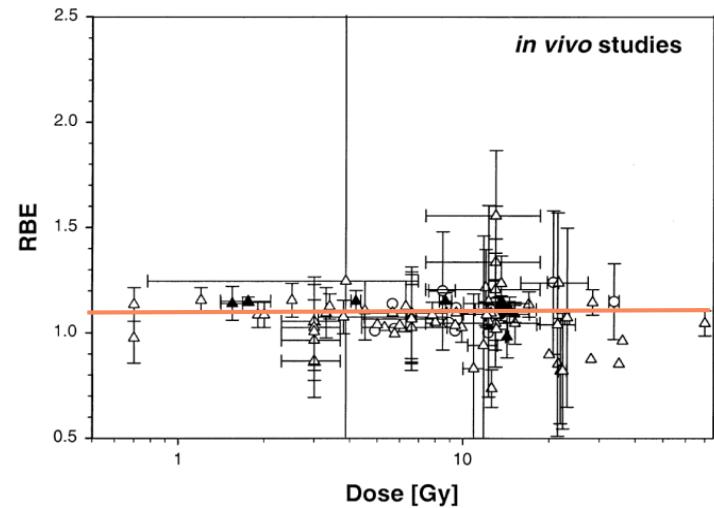
3D models



Focus of Radiobiological Research at MedAustron I

Challenging the RBE

- Generic RBE for PBT: 1.1
- Influencing factors
 - **Tissue Characteristics**
 - **Linear Energy Transfer (LET)**

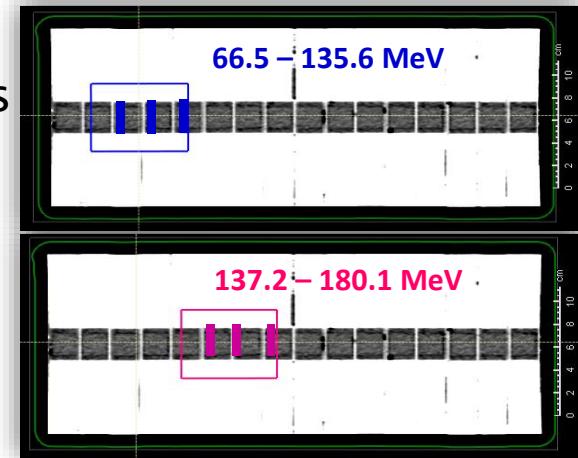
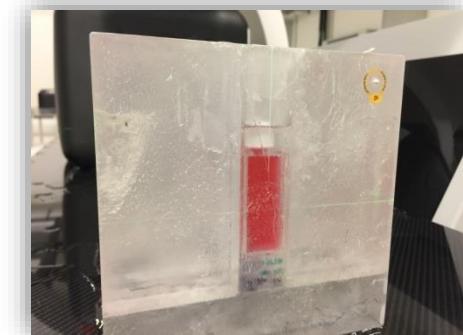


RBE of protons relative to CO^{60}
Mice data: crypt regeneration,
lung tolerance, skin reaction,
fibrosarcoma

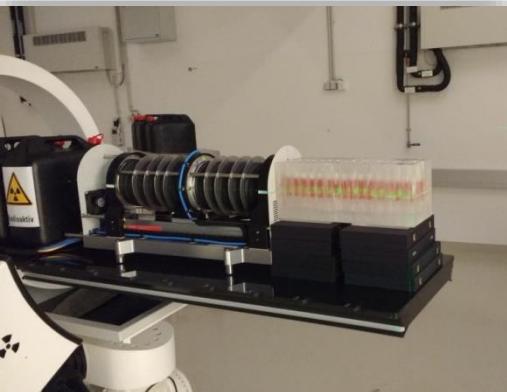
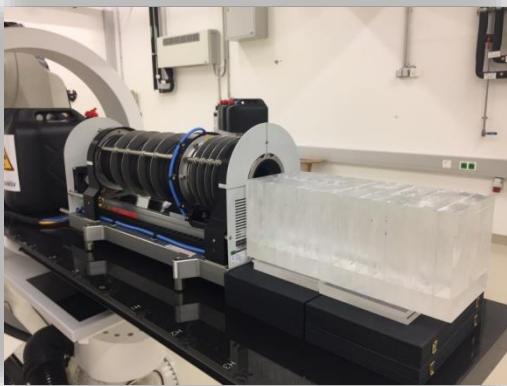
Paganetti et al, Int J Radiat Oncol Biol Phys. 2002 ;53(2)

RBE Dependencies: LET

- Development and implementation of a **dedicated irradiation setup** in cooperation with Medical Radiation Physics
- Key requirement 1:
 - Simultaneous irradiation of multiple samples
 - investigation of end-of-range effects (LET)
- Key Requirement 2:
 - Variation of target depth
 - investigation of target coverage energy effects



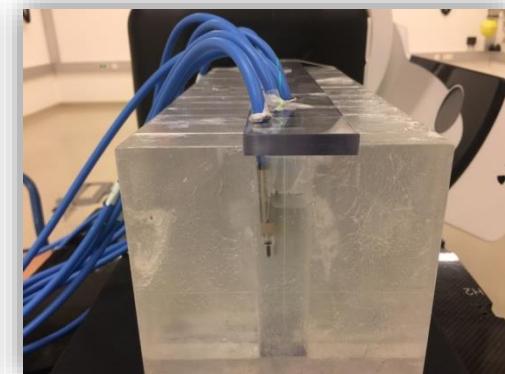
Dosimetry Aspects



Range measurements

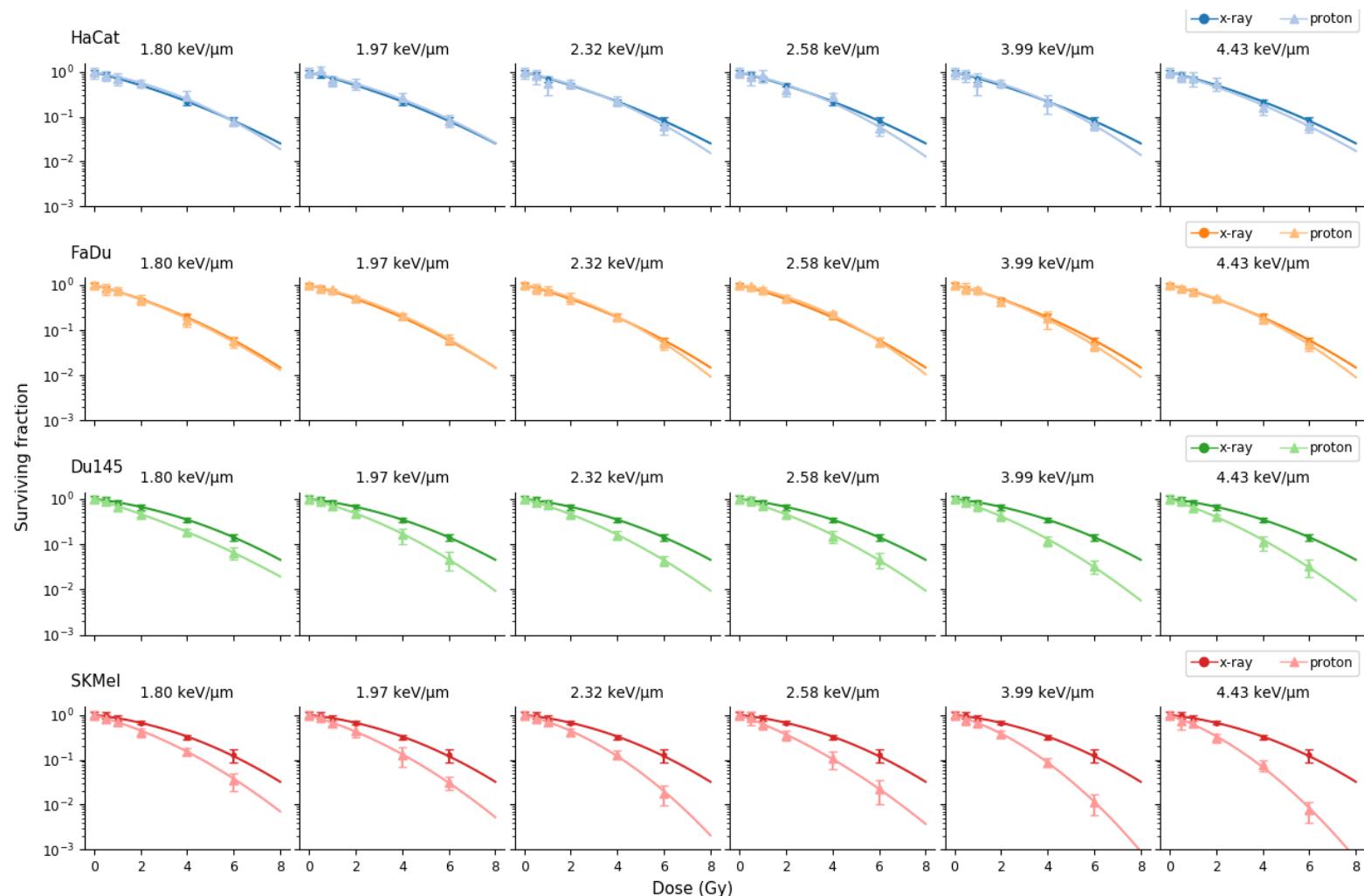


Dosimetry: films

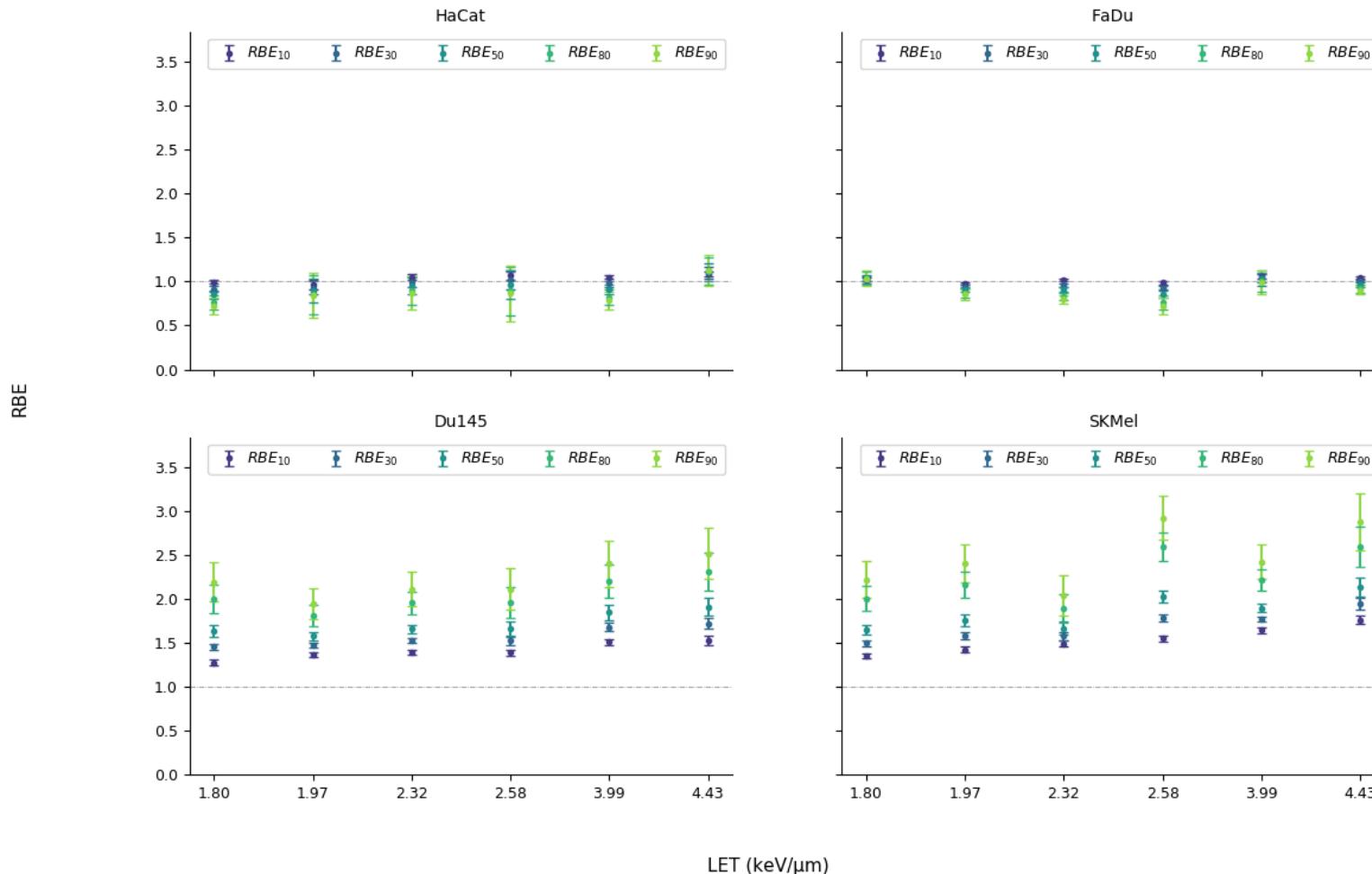


Dosimetry: ionisation chambers

The RBE of protons: an α/β – LET relationship



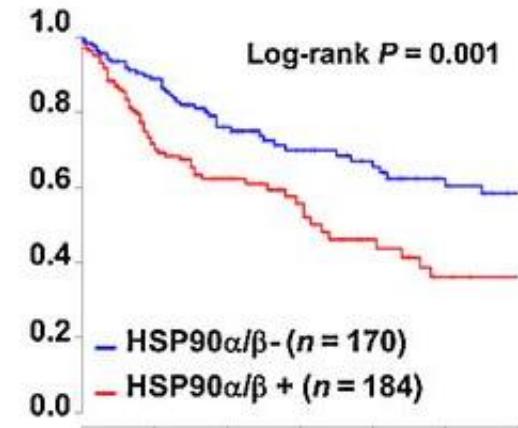
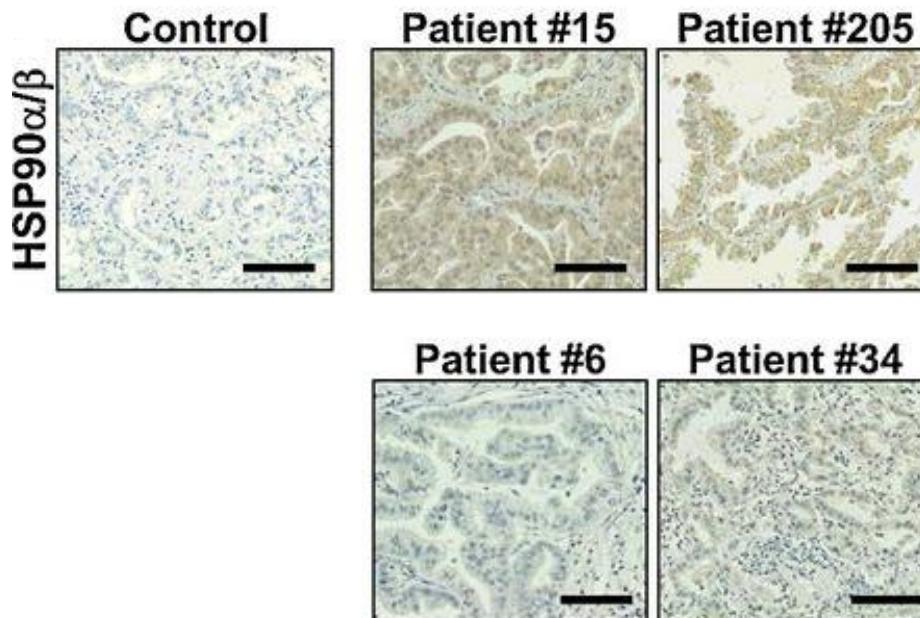
The RBE of protons: an α/β – LET relationship



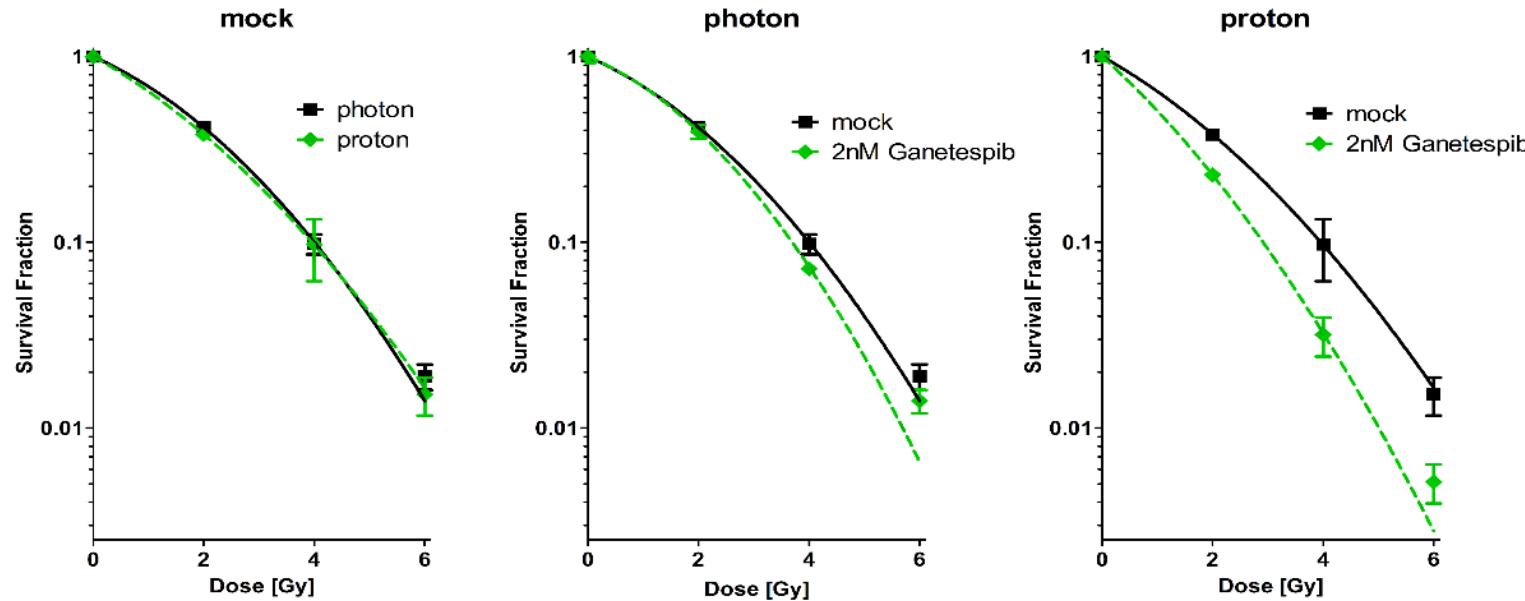
Focus of Radiobiological Research at MedAustron II

Identification of synergistic therapy mechanisms

Targeting of HSP90 in HNSCC and NSCLC

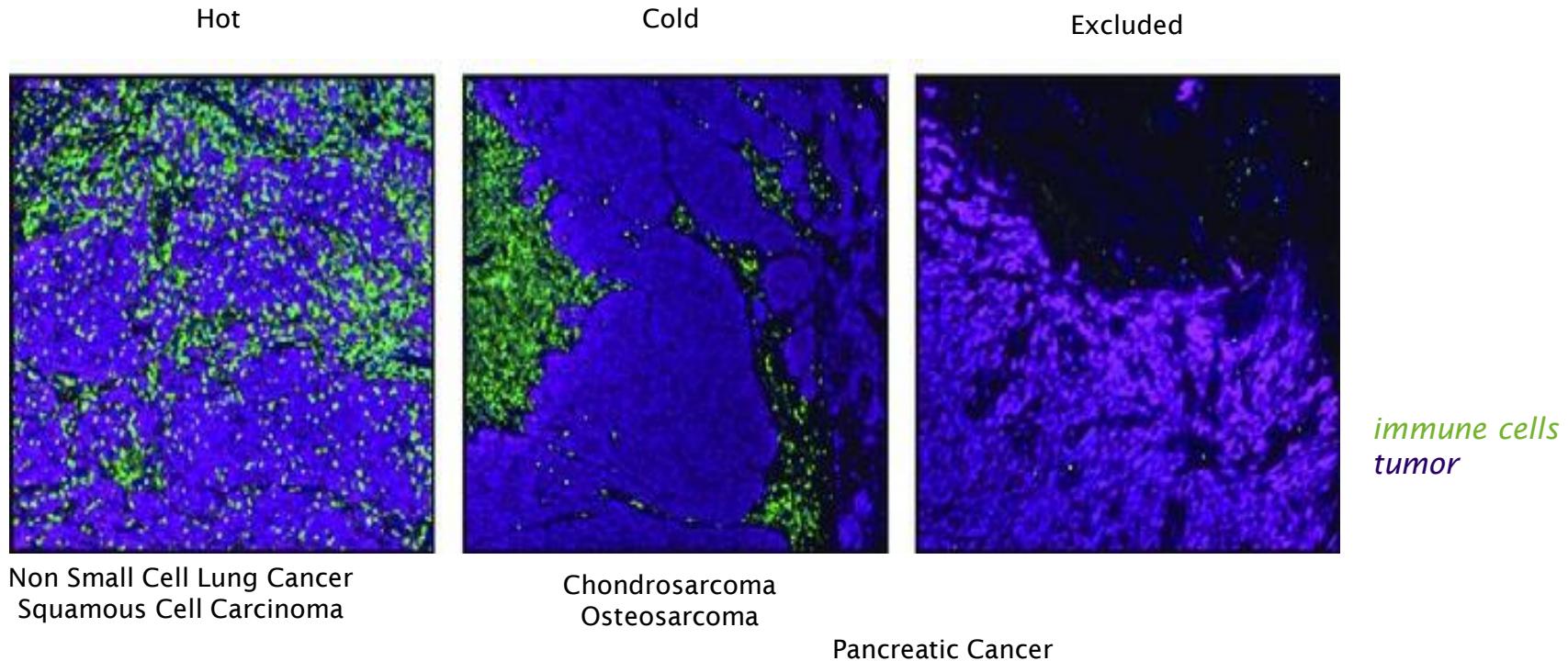


Synergistic effect of HSP90 inhibition in NSCLC



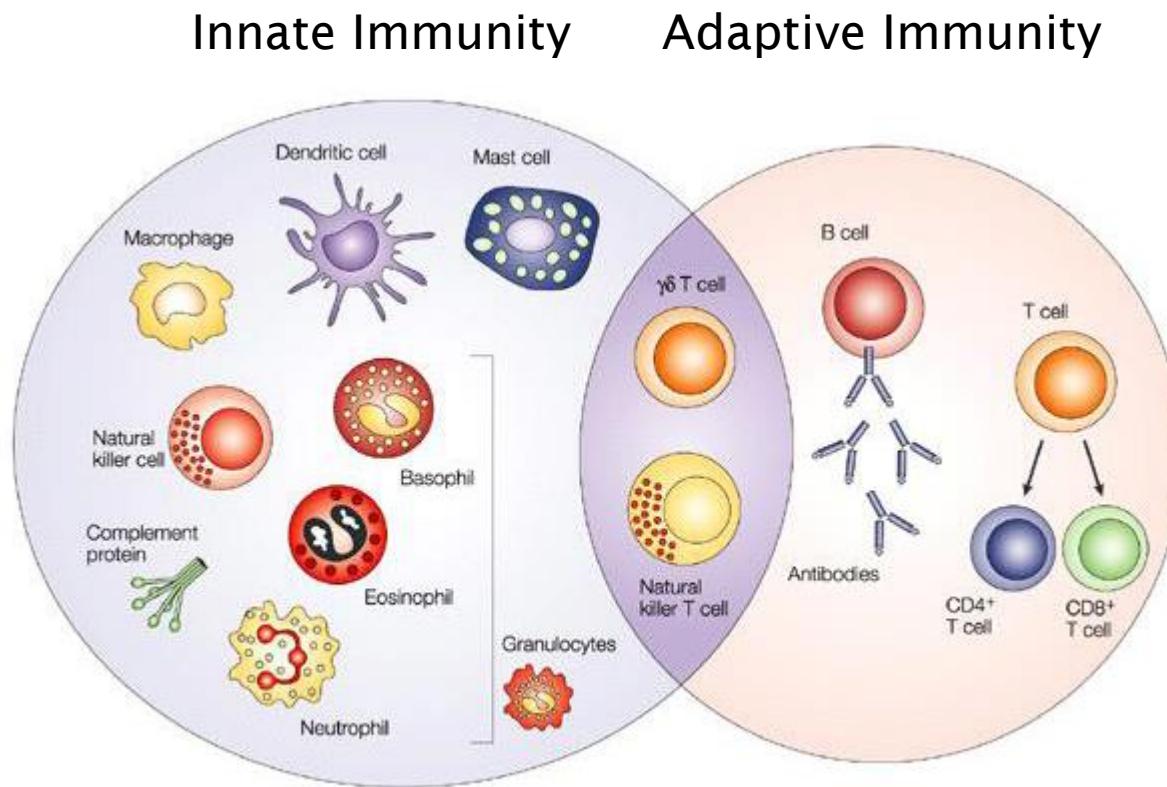
Synergistic effects of IBT: enhanced immune recognition

Hot vs. cold tumors



Van der Woude, Trends Cancer. 2017

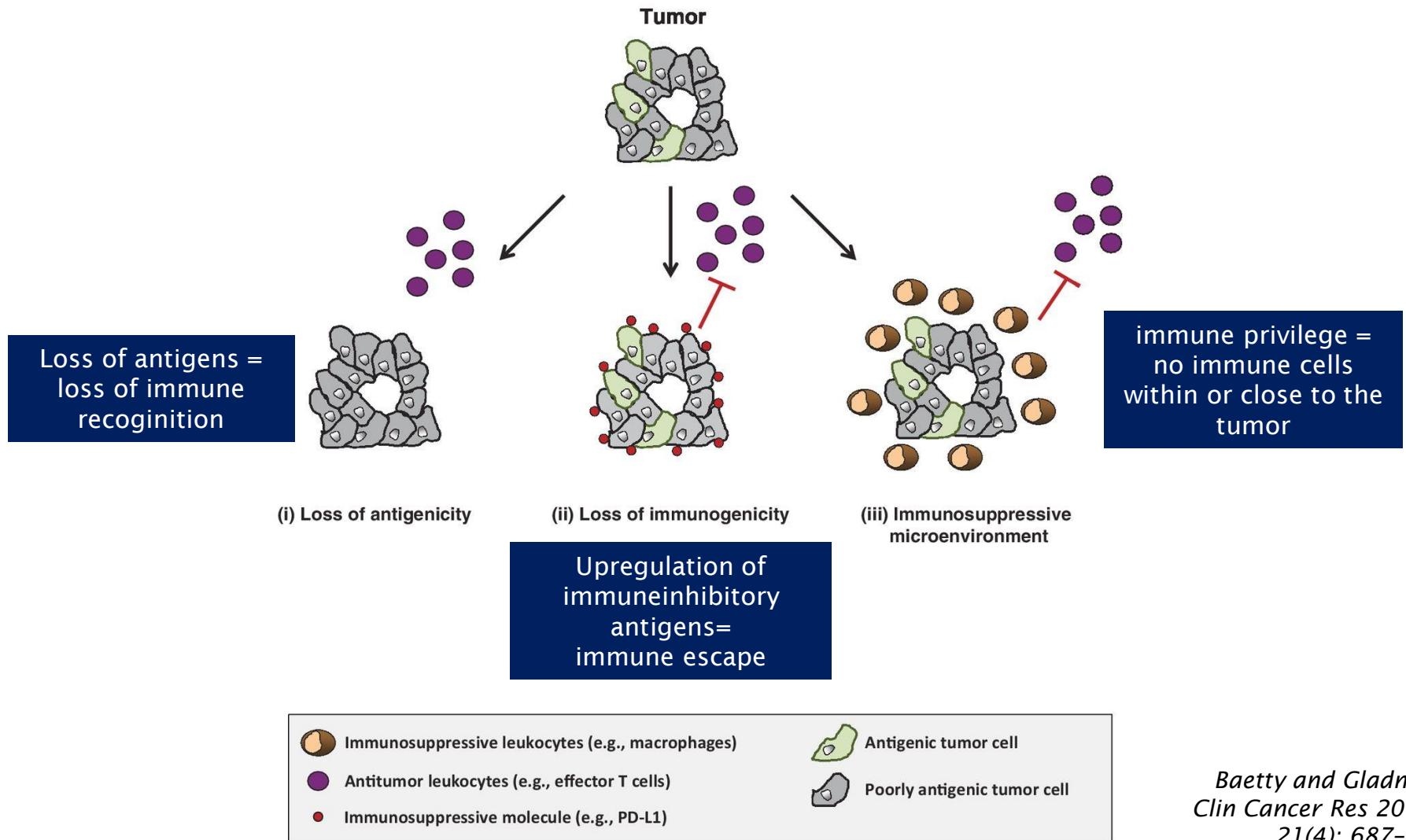
Immune System Function and Response



Identify and destroy non-self antigen presenting cells

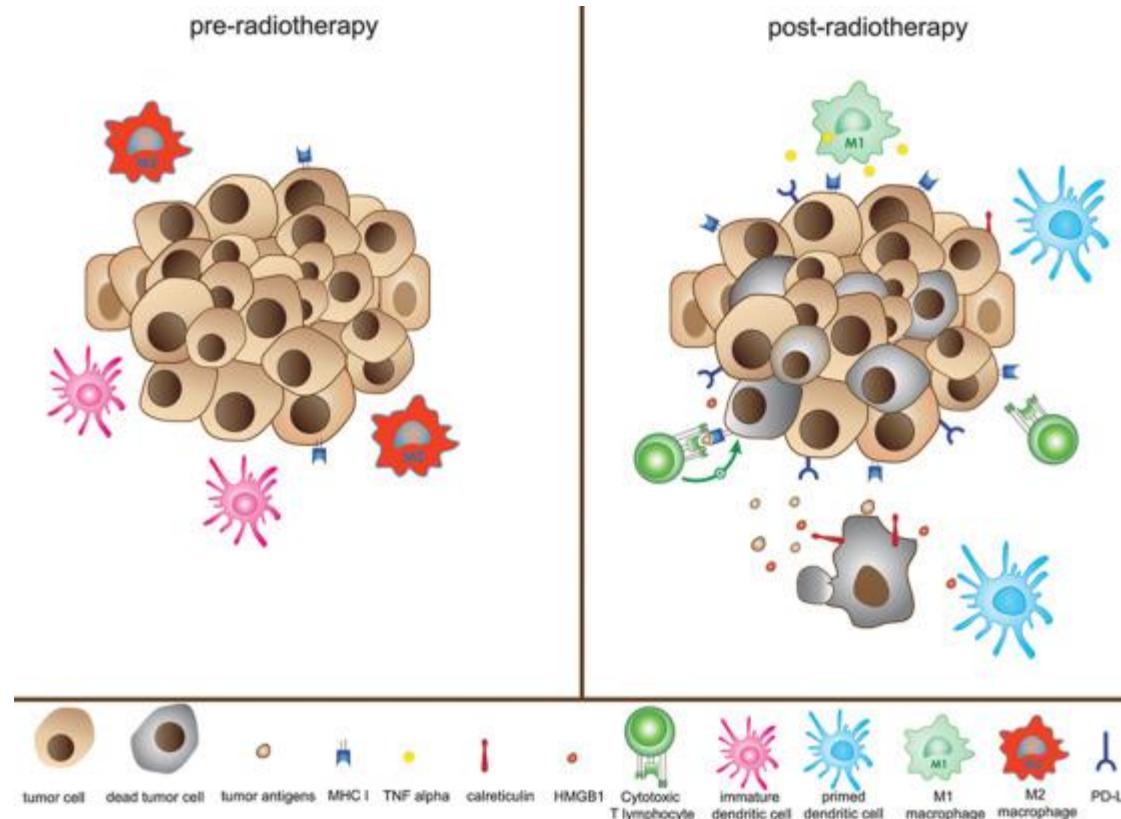
Macmillan , Nature Reviews Cancer, 2004

Mechanisms of Immune Escape



Baetty and Gladney,
Clin Cancer Res 2015;
21(4); 687-92.

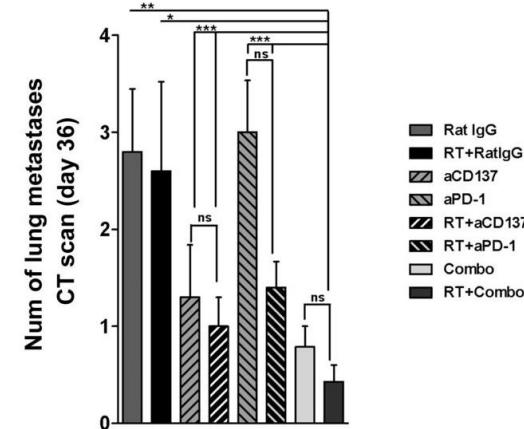
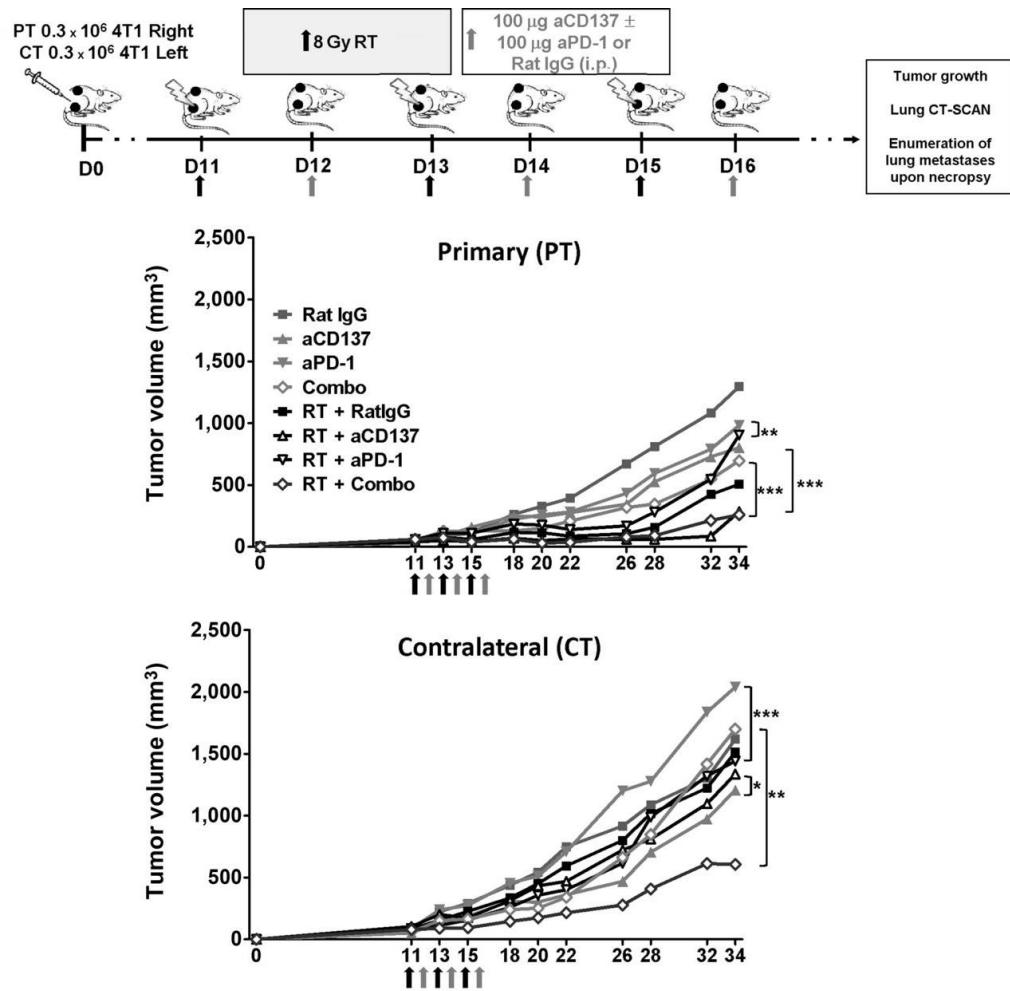
Stimulation of immune recognition with radiotherapy



in situ vaccine

Daly et al, J.Thor.Oncol 2015; 10(12); 1685-93.

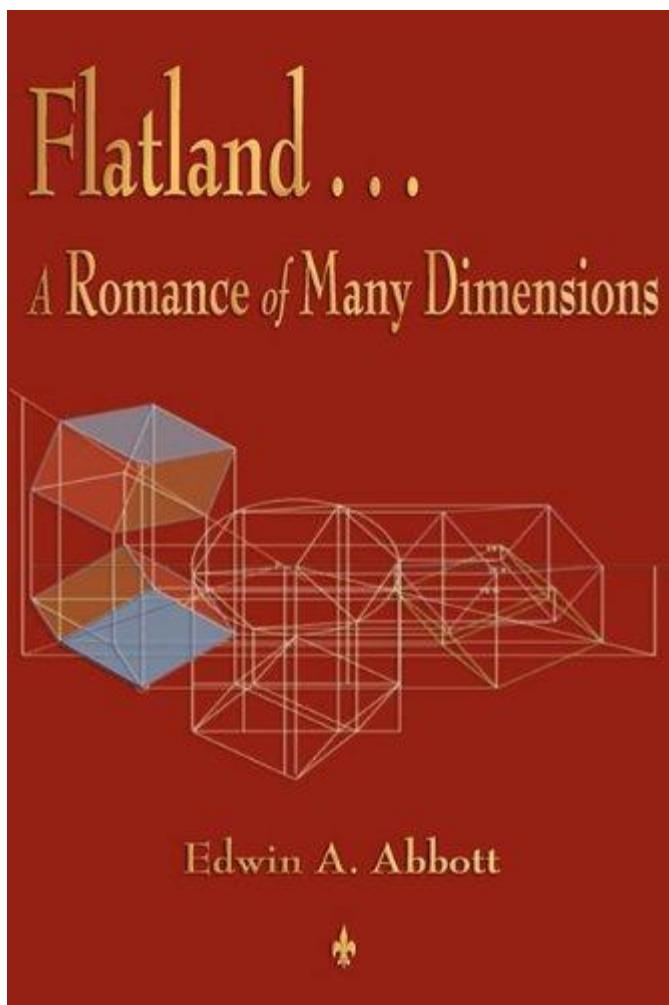
Stimulation of immune recognition with radiotherapy



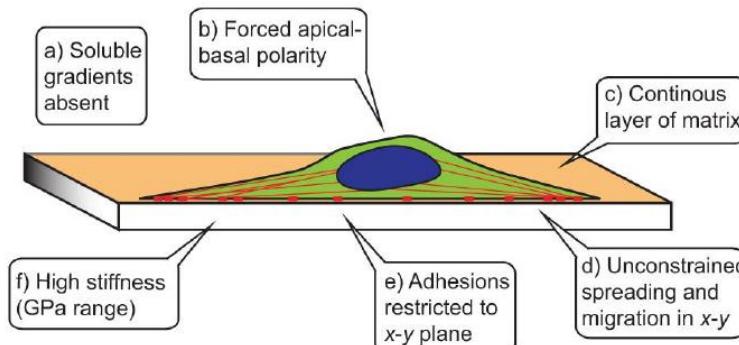
enhanced effect of
particle radiotherapy?

Rodriguez-Ruiz et al, Cancer Res 2016; 76(20)

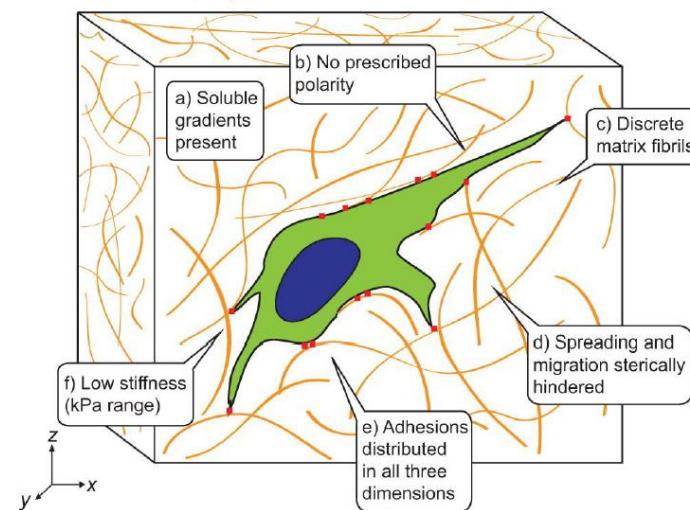
A 3D World



Collagen-coated glass (2D)



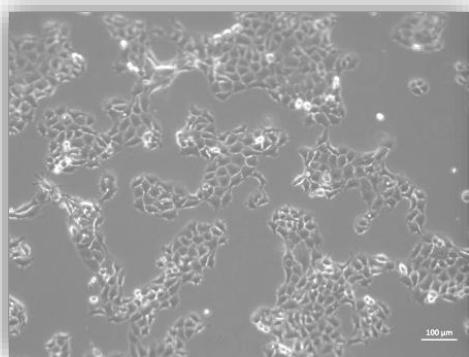
Collagen gel (3D)



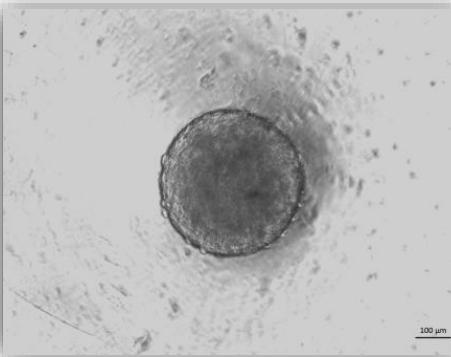
Baker and Chen, J Cell Sci 2012 125: 3015-3024

Focus of Radiobiological Research at MedAustron III

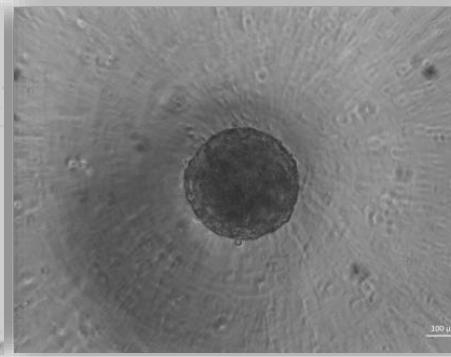
Advanced Cell Culture models



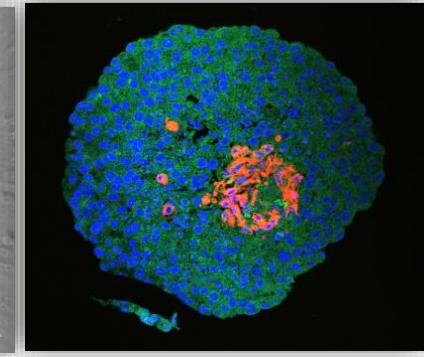
Squamous cell carcinoma
cells 2D



SCC 3D



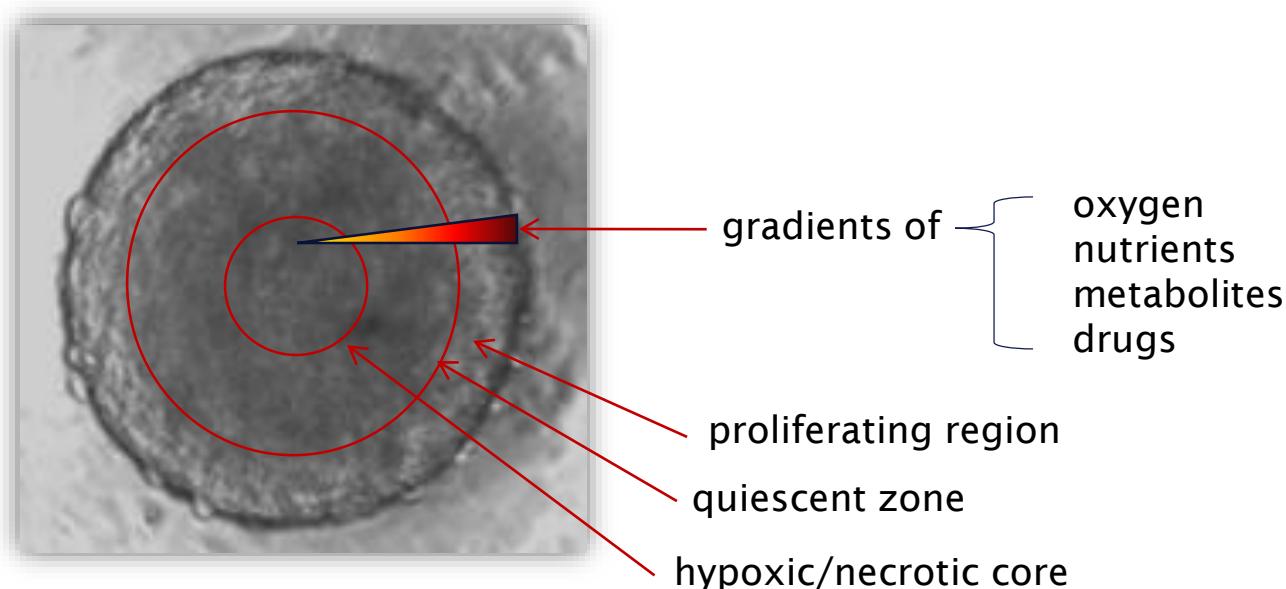
SCC 3D + ECM mimetic



SCC 3D + ECM mimetic
+ fibroblasts

head-and-neck squamous cell carcinoma
prostate carcinoma
pancreatic ductal adenocarcinoma
osteosarcoma
chondrosarcoma

Advances Cell Culture Models: Multicellular Tumor Spheroids

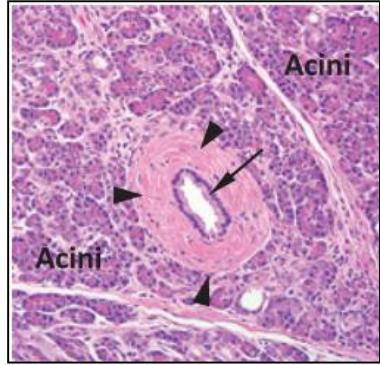


Focus of Radiobiological Research at MedAustron IV

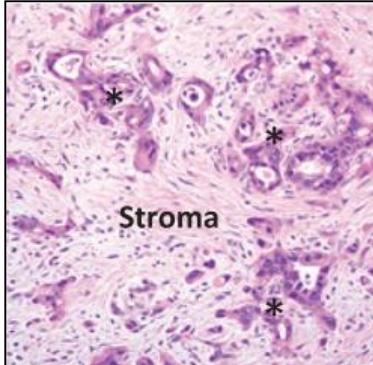
Effect of particle beams on the tumor microenvironment/stroma

Pancreatic ductal adenocarcinoma (PDAC)

normal pancreatic duct



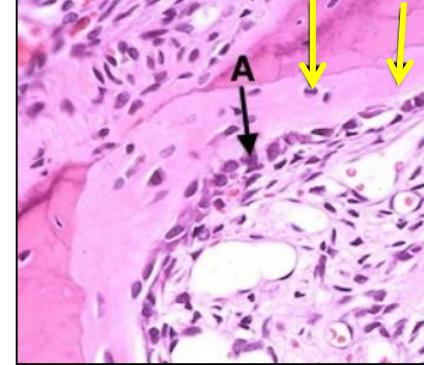
PDAC



Christine A Iacobuzio-Donahue; Gut (2011)

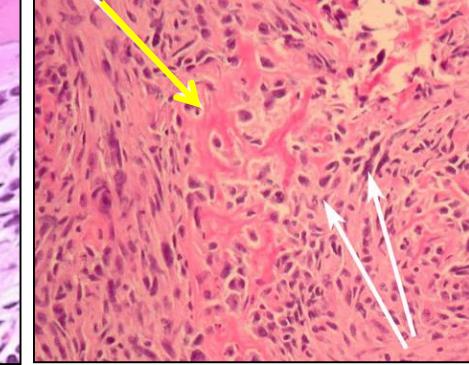
Osteosarcoma (OS)

normal bone tissue



Yale Histology (2018)

osteosarcoma



Klein, Siegal; AJCP (2006)

Malignant osteoid

Tumor-stroma interactions affect:

Tumor growth, hypoxia, aggressiveness, immune phenotype

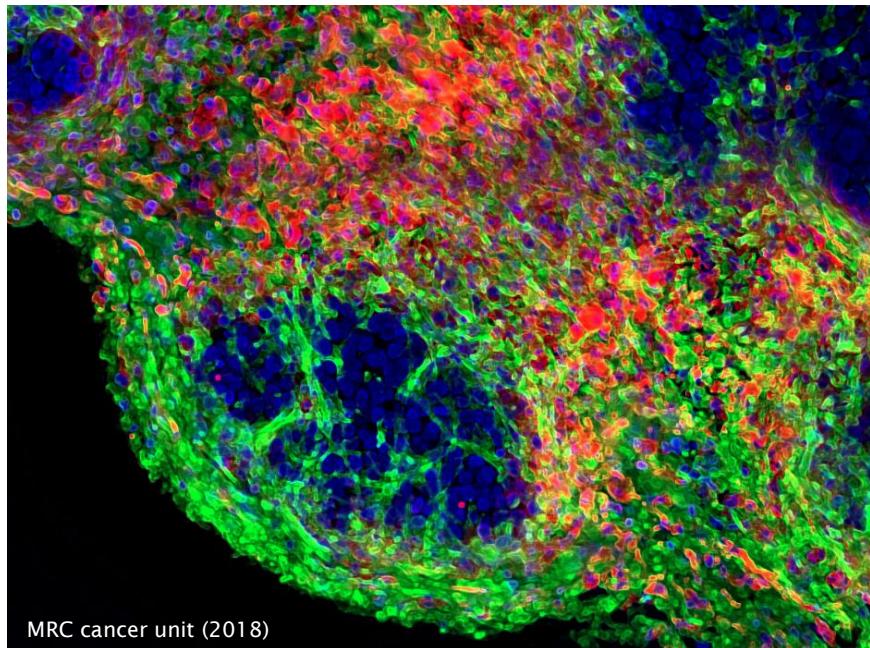
→ Therapy resistance and relapse

In vivo studies

Heterogeneous tumor

Biological targeting

Dose painting

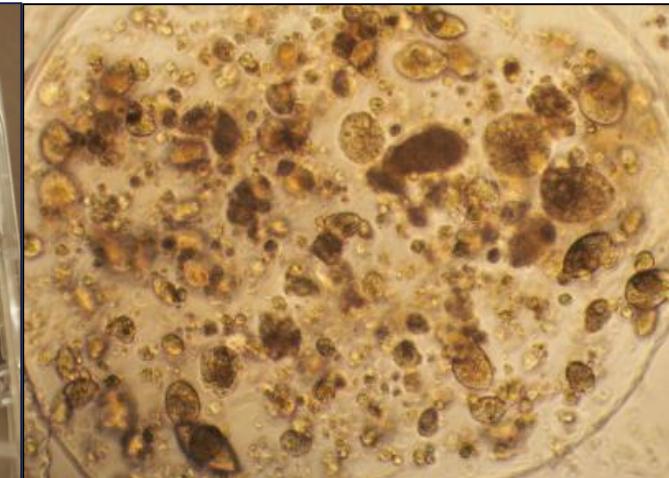
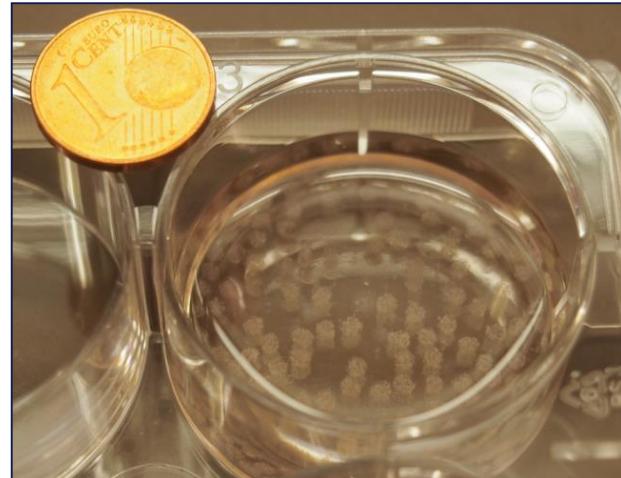


Beneficial effect of particle beam therapy?

Xenograft model (nude mice)



Heterogeneous cell suspension or spheroid injection



Alginic transplantation



DEPARTMENT OF RADIOTHERAPY
MEDICAL UNIVERSITY OF VIENNA

Acknowledgement

<http://www.meduniwien.ac.at/hp/radonc/>

Colleagues and Advisors

- Radiobiology Team MedAustron
 - Elisabeth Mara: RBE dependencies /3D Pancreatic cancer model
 - Simon Deycmar: synergistic mechanisms
 - Jakob Kowaliuk / Susanna Zakaria: in vivo studies
- Prof. Dietmar Georg – Head of Medical Physics and Oncotechnology
- Medical Physics and Oncotechnology Team
- Dr. Thomas Schreiner – Coordinator Non Clinical Research
MedAustron
- Prof. Eugen Hug – Medical Director MedAustron

