

Radiobiology Research at MedAustron – Ion Therapy and Research Centre

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Medical University of Vienna

High Energy Physics Seminars

Imperial College London

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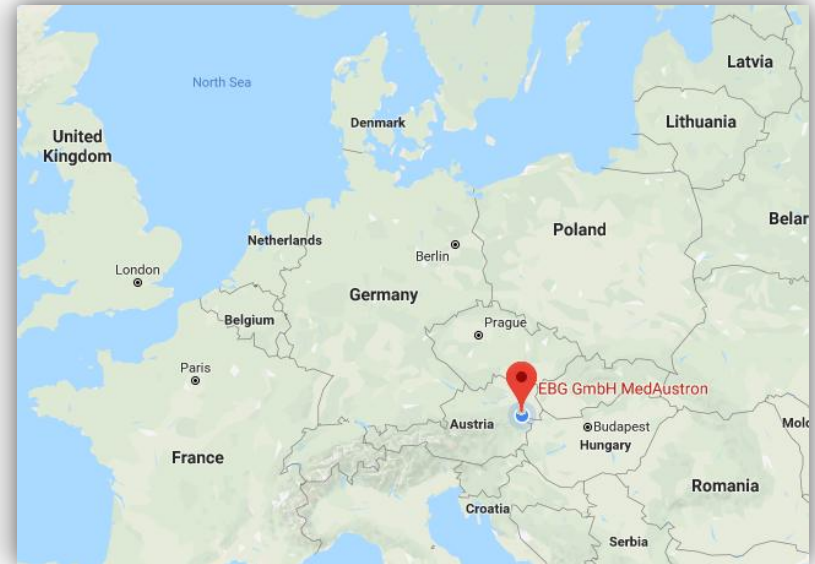
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2. Tumour Treatment with Ion Beam Therapy
3. Facility Overview

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1. Applied and Translational Radiobiology at MedAustron
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The MedAustron Centre



Ion Therapy and Research Centre

- Outpatient clinic
- Non clinical research
 - Medical physics, radiation physics and radiobiology

Image: MedAustron

A Brief History

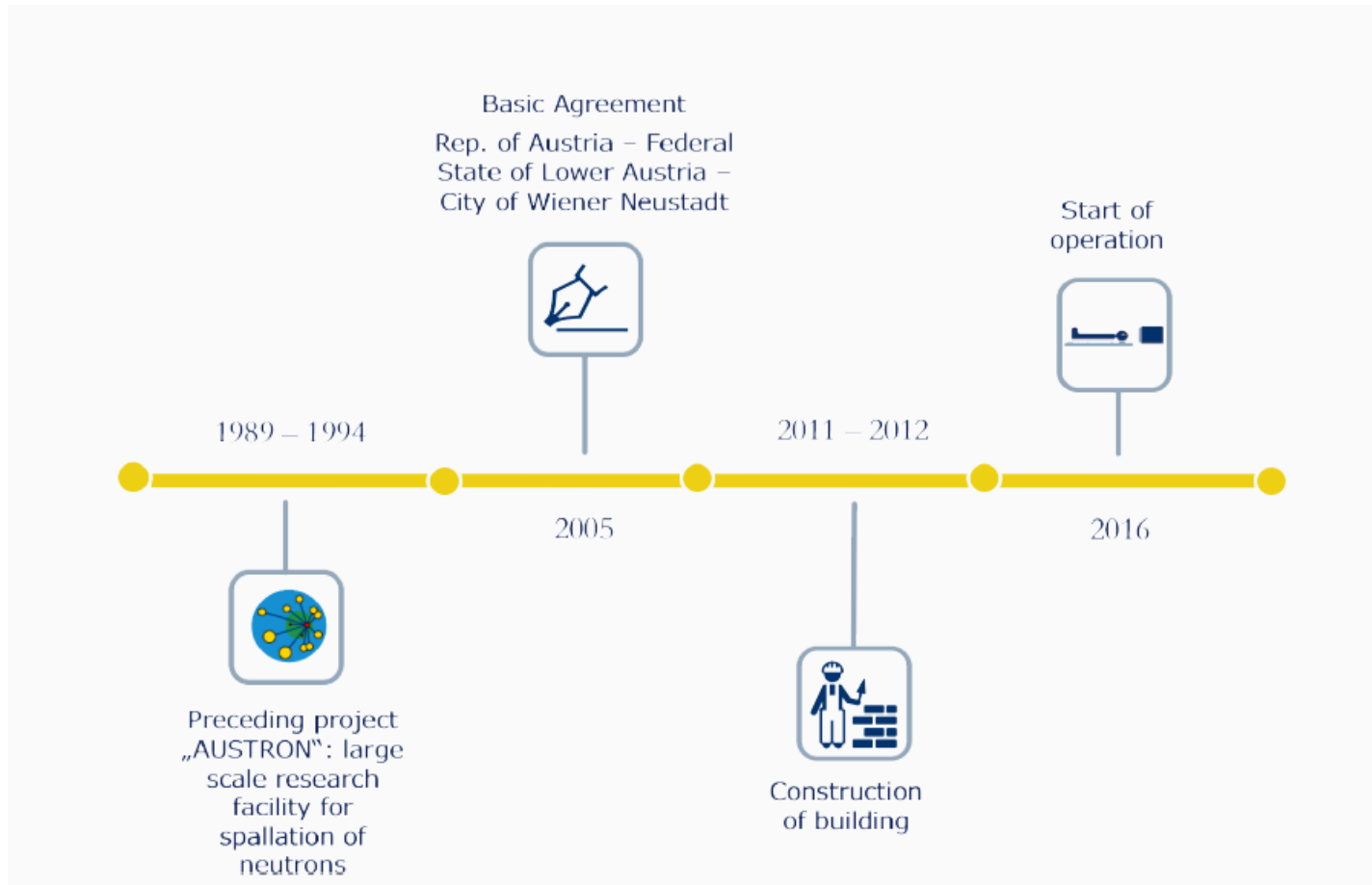


Image: MedAustron

Tumour Therapy Options



Surgery



Radiation Therapy



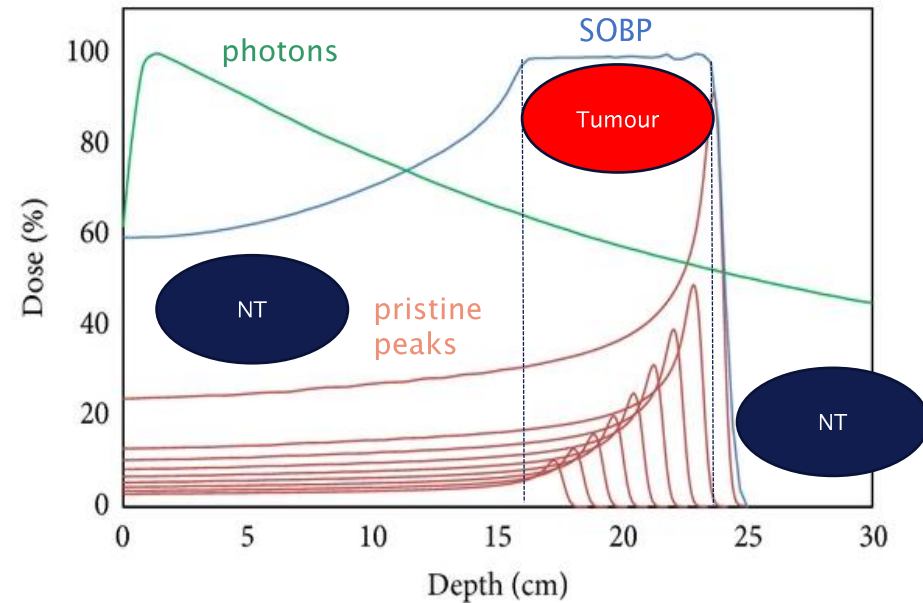
Chemotherapy

Image: MedAustron

Ion Beam Therapy: 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

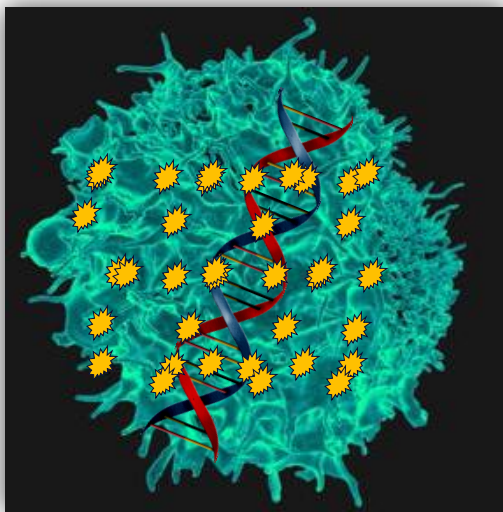


reduced dose in
organs at risk

Ion Beam Therapy: Biological Motivation

Increased Effectiveness

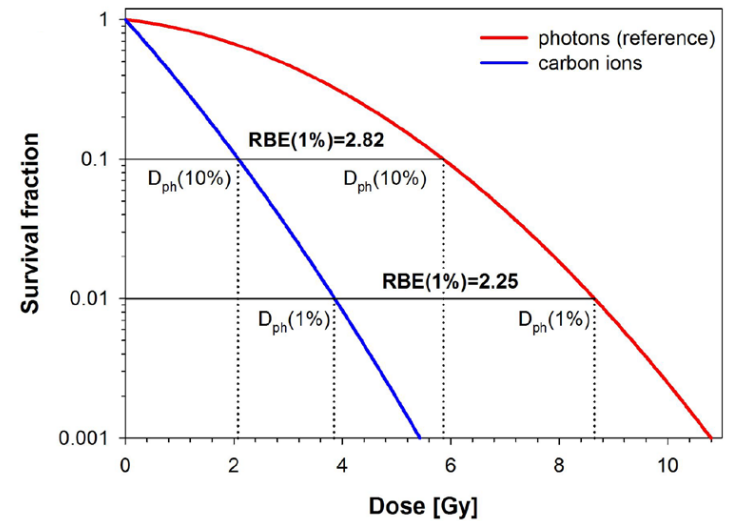
- Increased relative biological effectiveness (RBE)
 - Proton RBE (generic): 1.1 → clinically used
 - Carbon RBE: values >3 reported



sparsely vs. densely
ionizing irradiation

↓

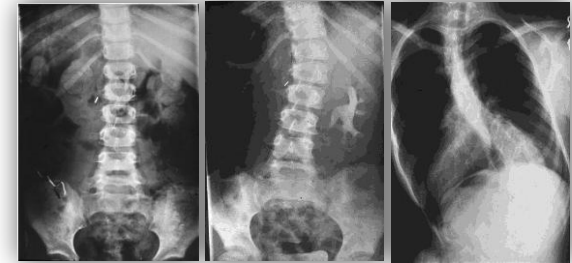
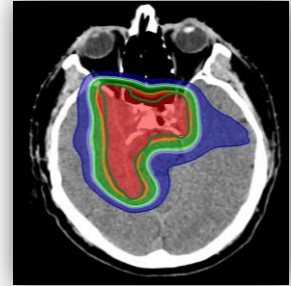
same physical dose results
in increasingly complex DNA
damage pattern



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. Resistent tumours – increased relative biological effectiveness (RBE)



growing bone



Osteosarcoma

depth dose profile

increased RBE

Facility Layout

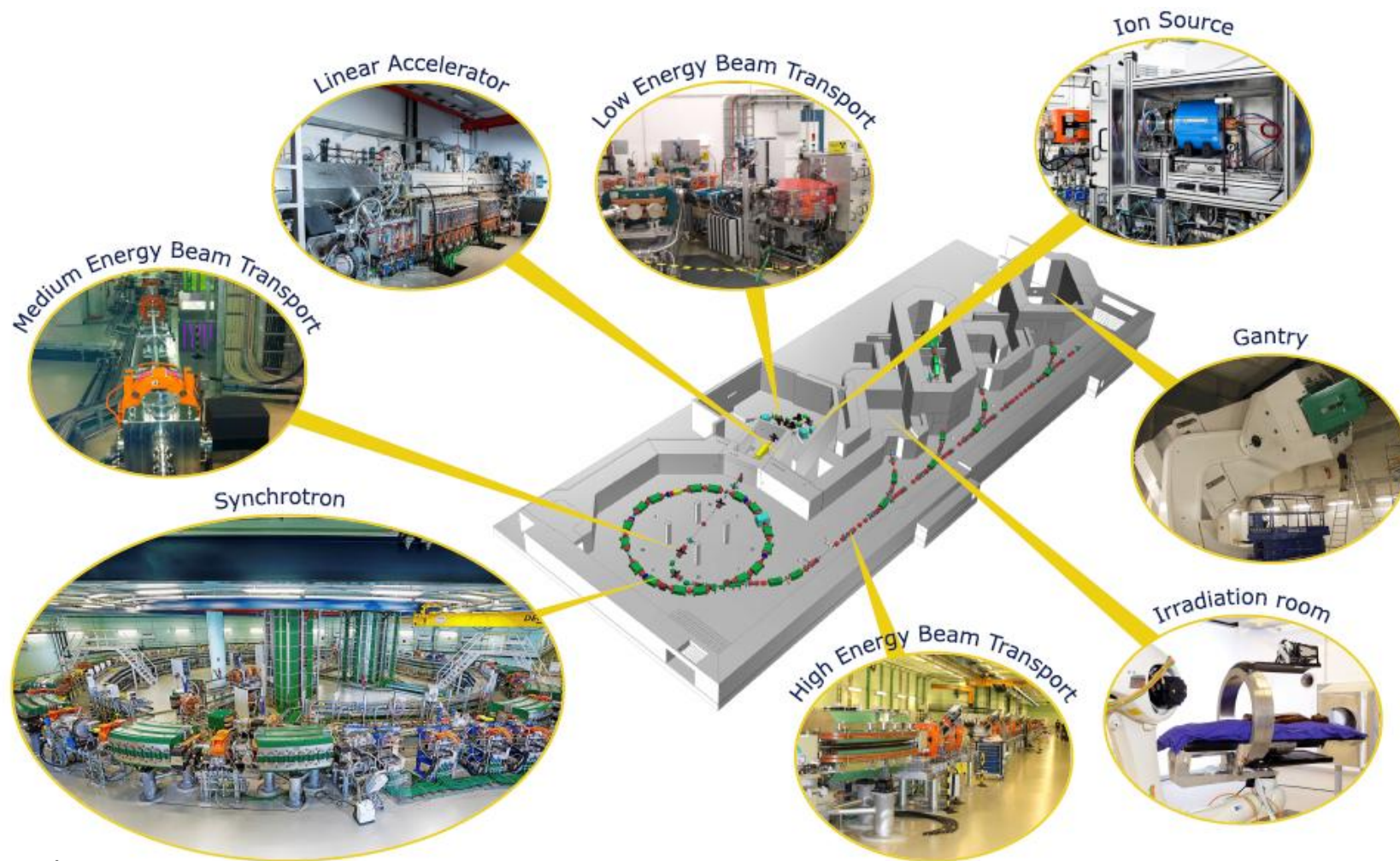
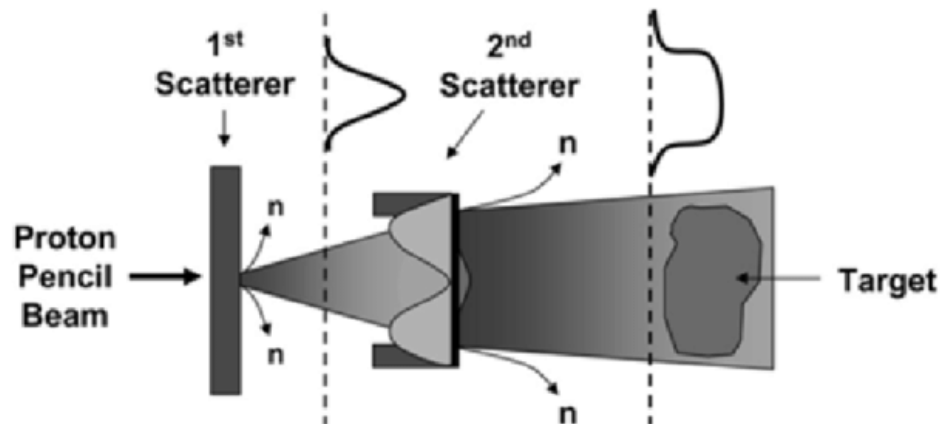


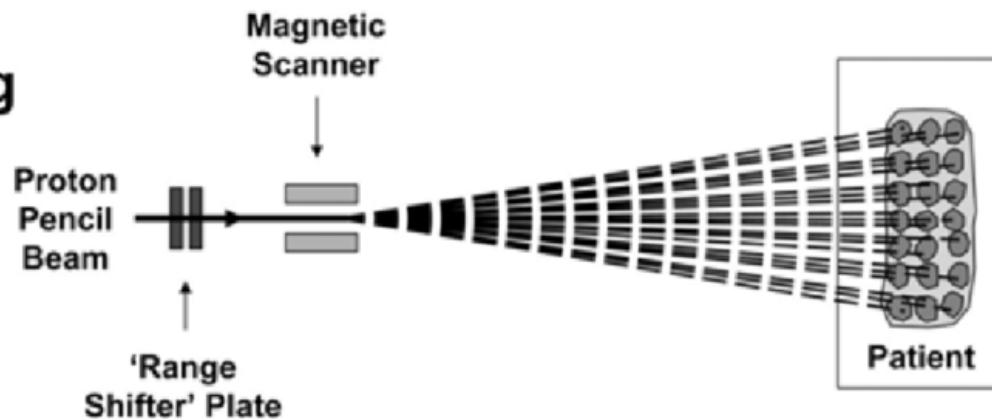
Image: MedAustron

Pencil Beam Scanning

Passive Scattering



Active Scanning



KCE Reports 235. D/2015/10.273/05.

Irradiation Rooms

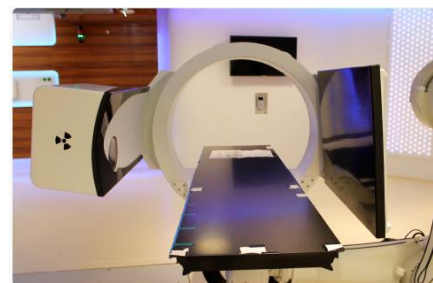
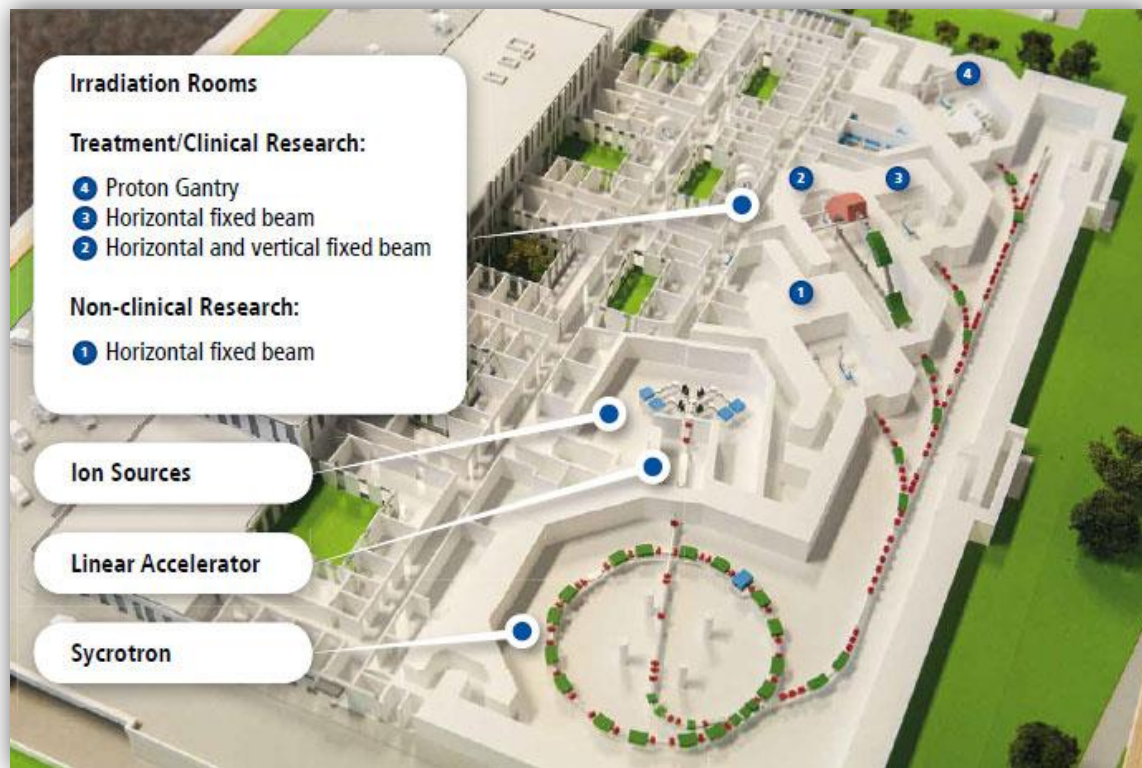


Image: MedAustron

Irradiation Rooms – Patient Treatment

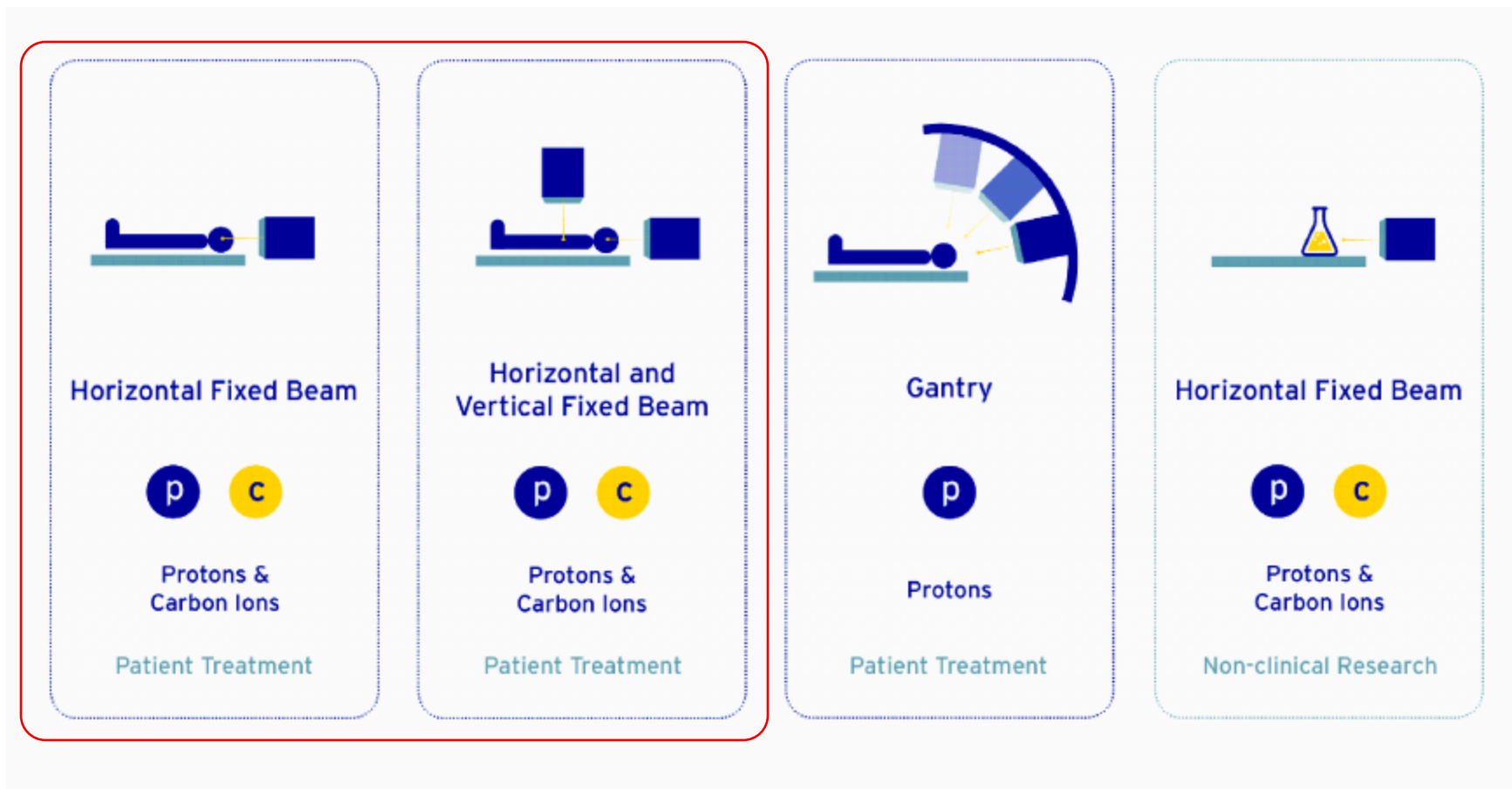
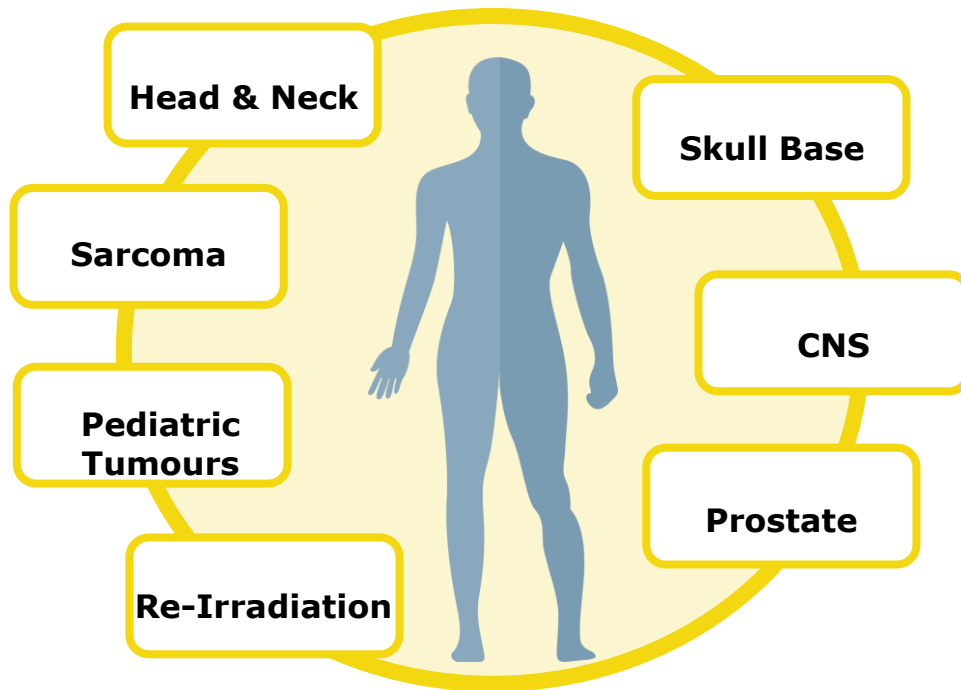


Image: MedAustron

Current Treatments at MedAustron



Indication	%
Meningioma	44
Head & Neck	16
Skull Base	11
Re-Irradiation	11
Pediatric Tumours	10
Sarcoma	4
Prostate	3
Gastrointestinal	1

- 167 patients since 12/2016
- status: 05/2018

Image: MedAustron

Irradiation Rooms - Research

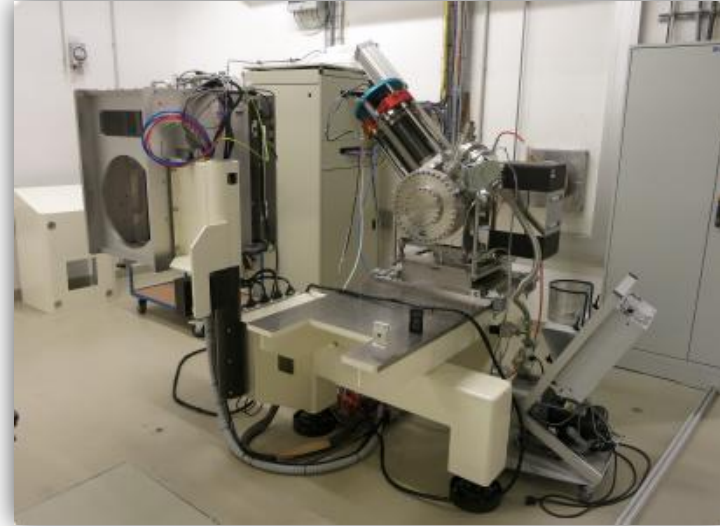


Image: MedAustron

Irradiation Room 1



- dedicated for NCR
- protons since 10/16
- carbon ions Q3 19



- 2 isocenters
- robotic couch
- laser positioning system
- suitable for high energies

Image: MedAustron

Non Clinical Research Groups

Medical Radiation
Physics with Special-
isation in Ion Therapy

Medical Radiation
Physics and
Oncotechnology

Applied and
Translational
Radiation Biology



Lembit Sihver



Dietmar Georg



MEDICAL UNIVERSITY
OF VIENNA



Wolfgang Dörr

Applied and Translational Radiobiology Team

PostDoc



Sylvia Gruber



Head
Wolfgang Dörr

Scientific Assistance



Karin Posch



Clara Pessy

PhD Students

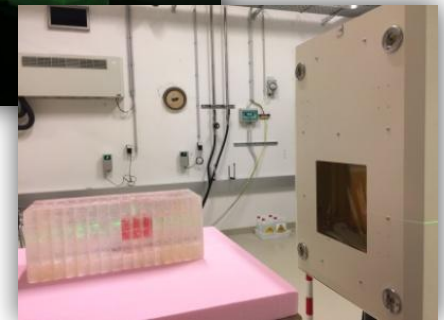
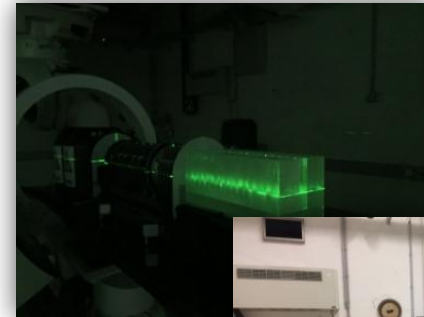
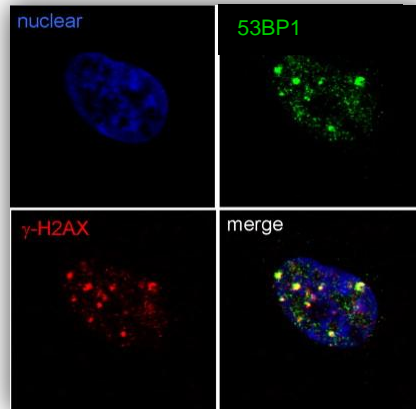
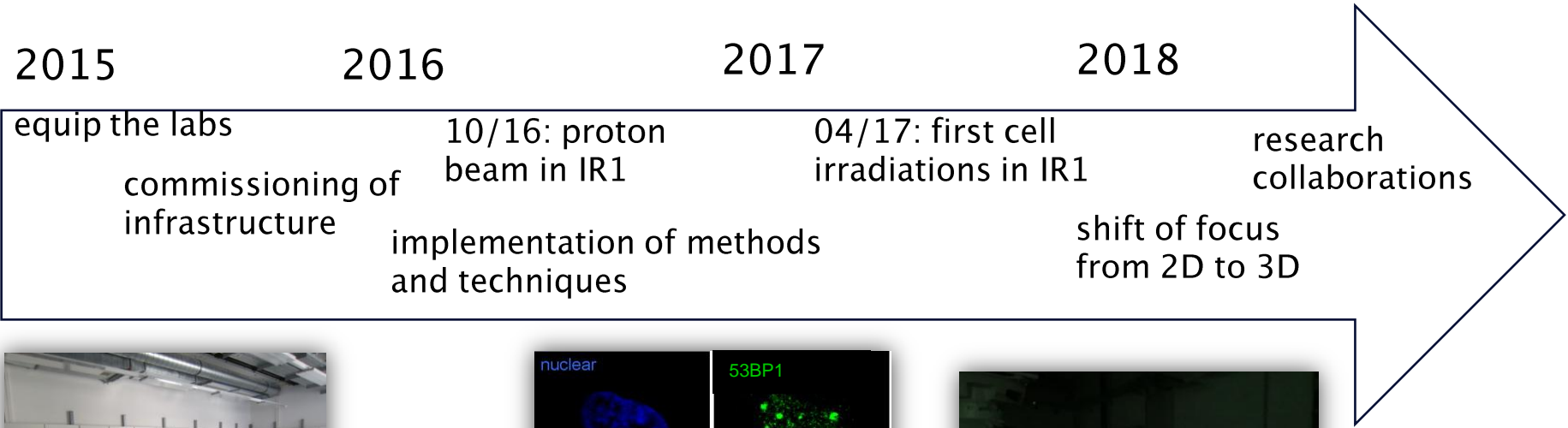


Suphalak
Khachonkham



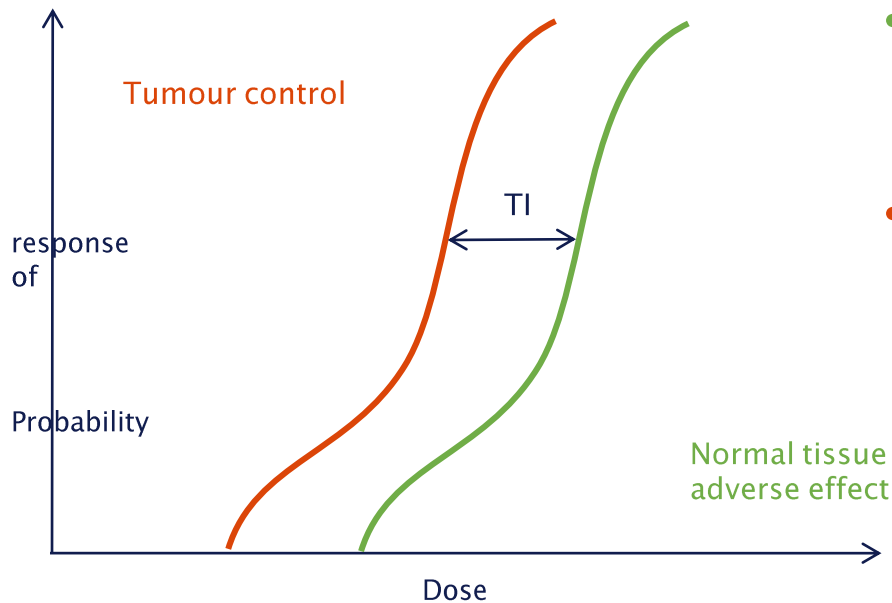
Elisabeth
Mara

Timeline of ATRAB at MedAustron



Mission

Broadening of the therapeutic index



- **Decrease** radiosensitivity of organs at risk
- **Increase** radiosensitivity of tumours

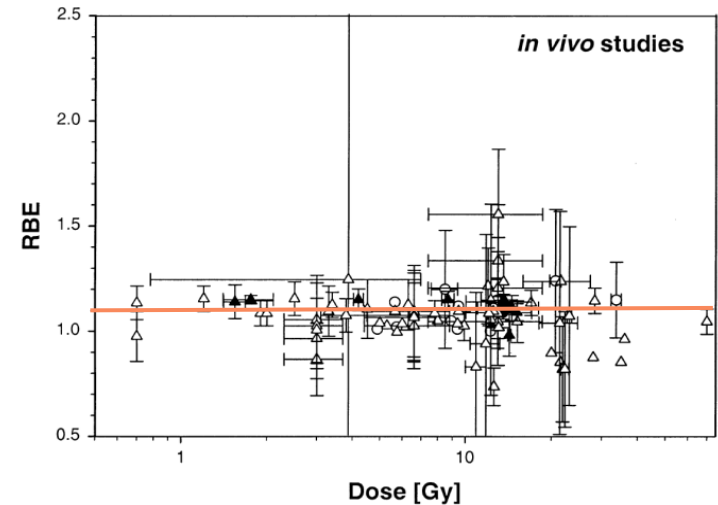


Selective protective /
targeting strategies

Focus of Radiobiological Research at MedAustron

Challenging the RBE

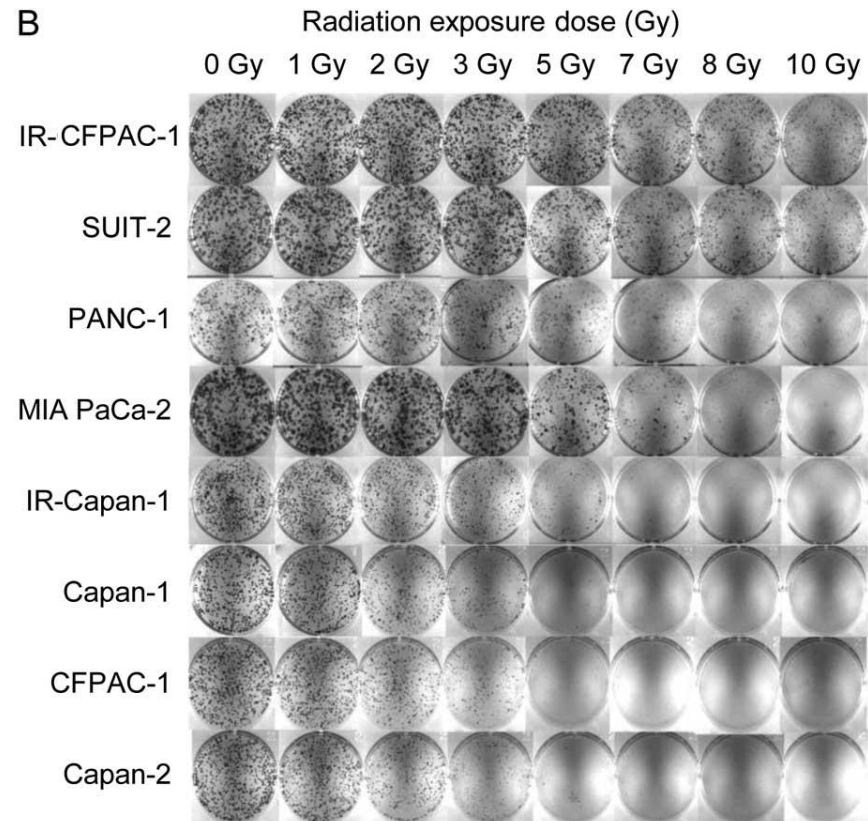
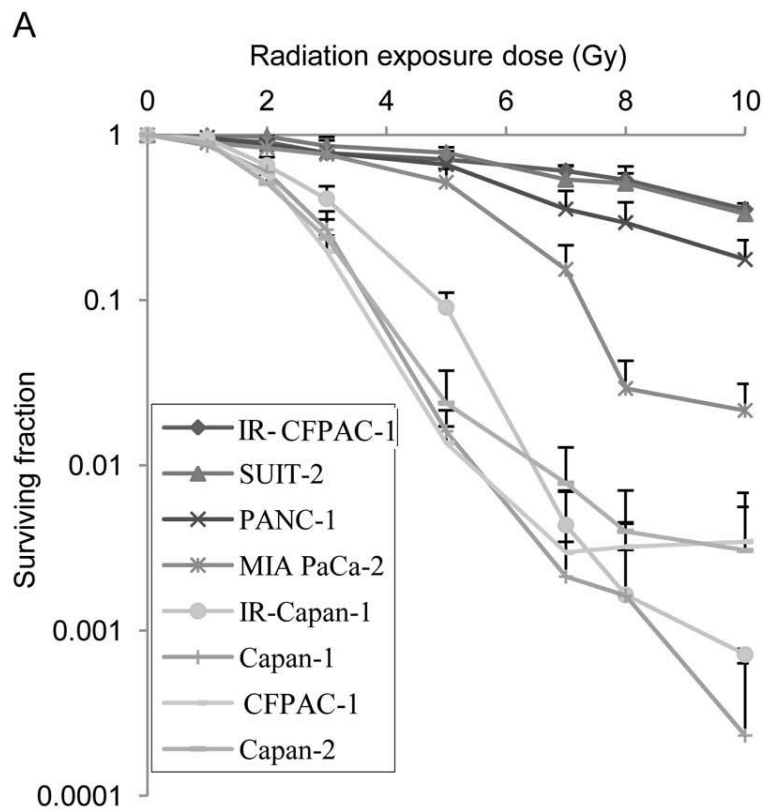
- Generic RBE for PBT: 1.1
- Influencing factors
 - **Tissue Characteristics**
 - **Linear Energy Transfer (LET)**
 - **Energy**



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: Tissue Characteristics



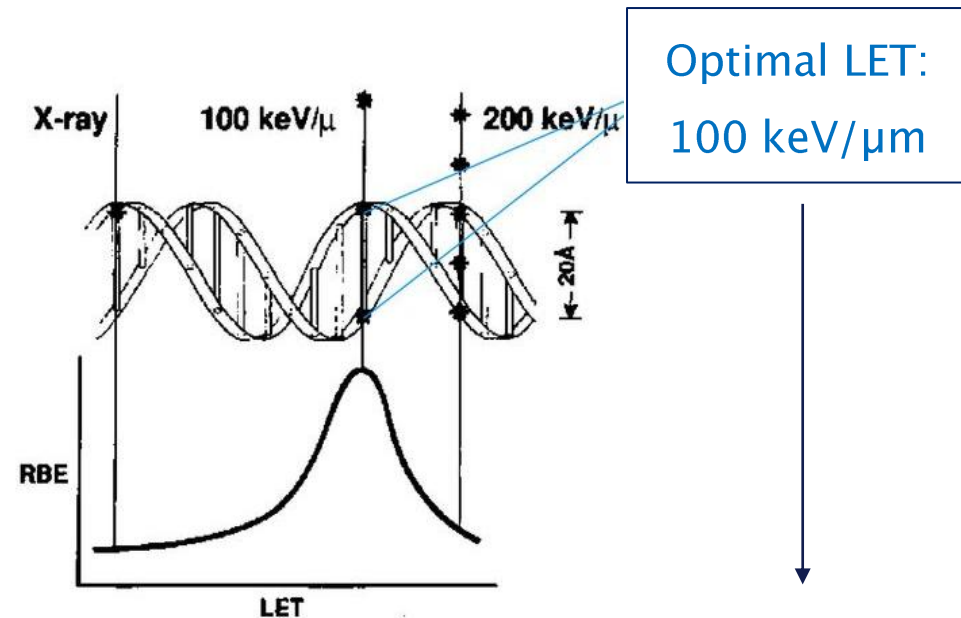
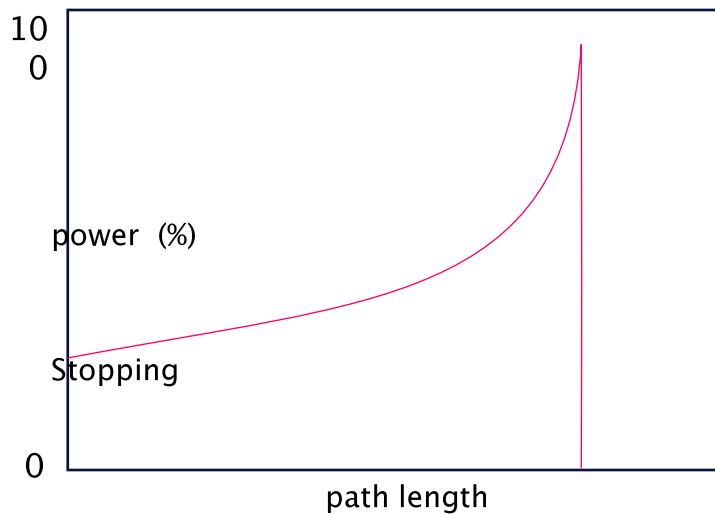
RBE depends on the intrinsic radiosensitivity of a tissue

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

RBE Dependencies: LET

Linear Energy Transfer:

- Amount of energy transferred to the material transversed per unit distance



Average ionization events
separation =
DNA doublehelix diamter

RBE Dependencies: LET

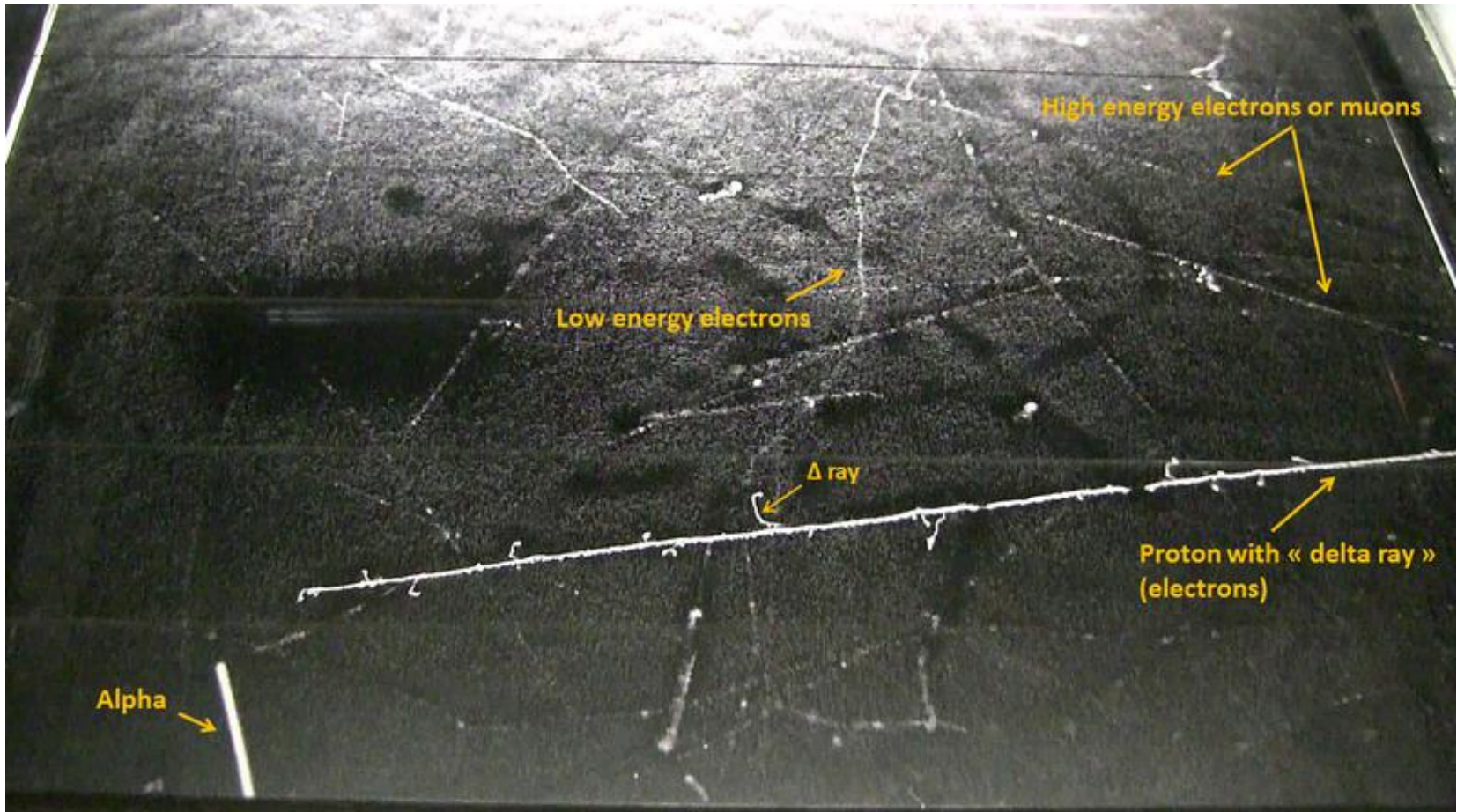


Image: Cloudylabs

RBE Dependencies: Target Coverage Energy

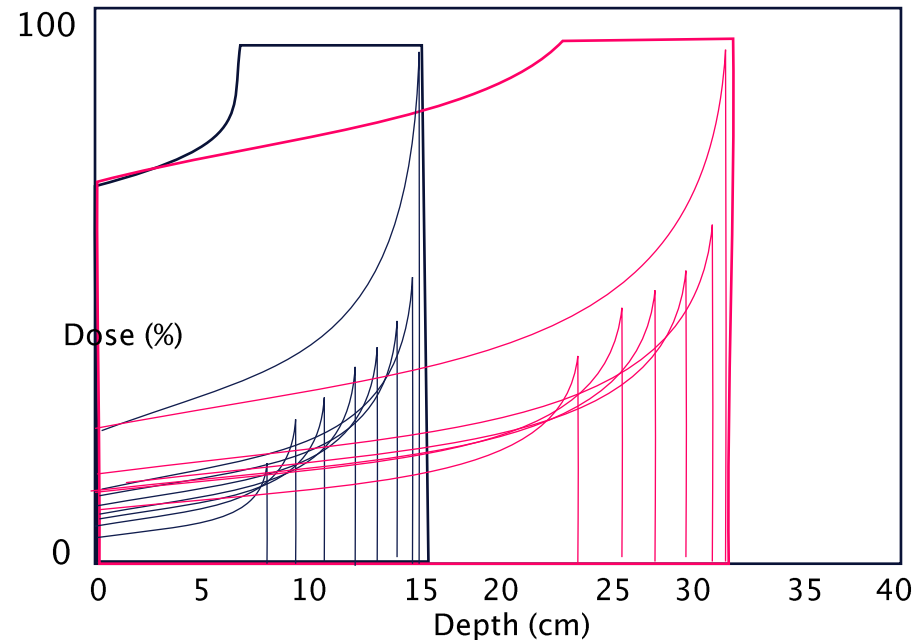
Lower energies:

- sharp penumbras
- higher number of BPs required for target coverage

Higher energies:

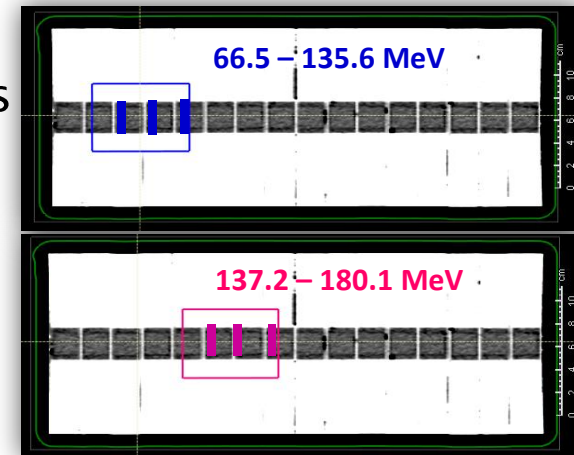
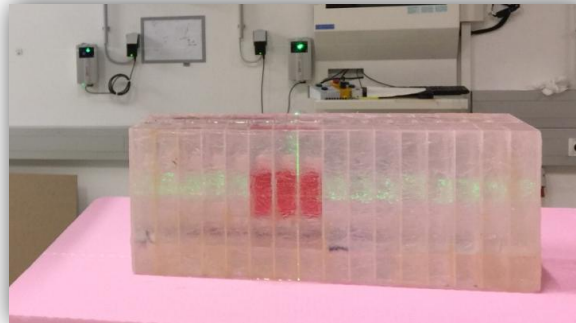
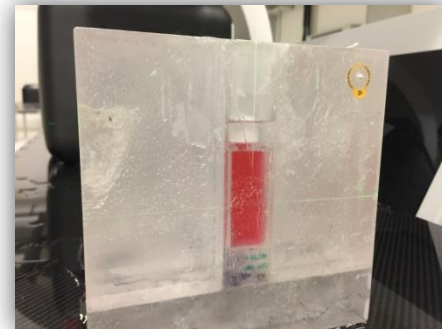
- reduced lateral penumbra sharpness
- less BPs required for TC

RBE expected to be higher with lower energies

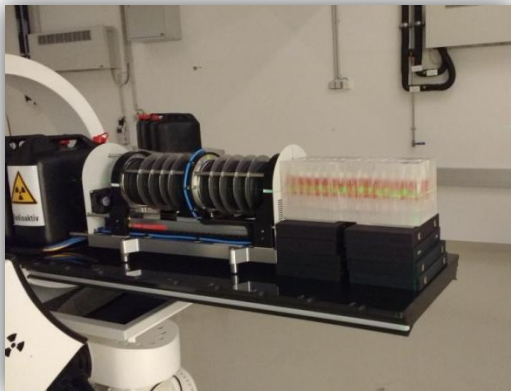
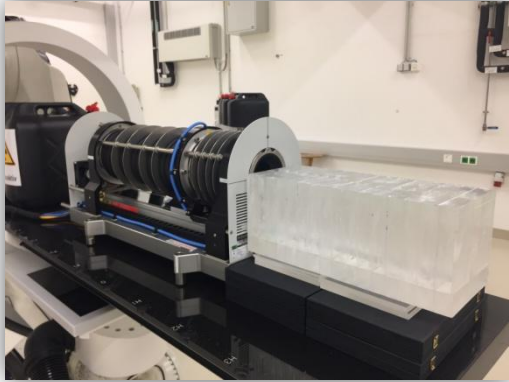


RBE Dependencies: Target Coverage Energy and LET

- 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



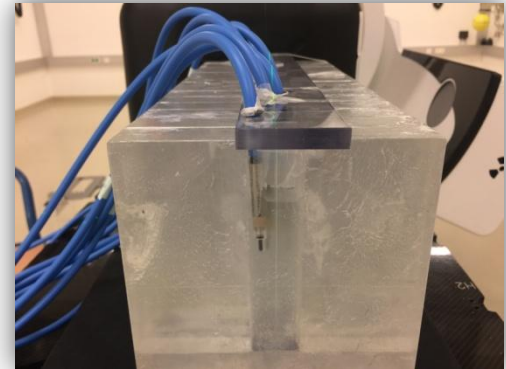
Dosimetry Aspects



Range measurements

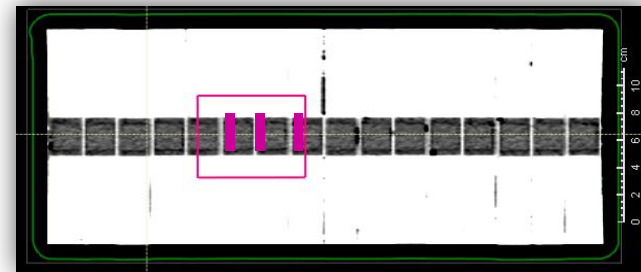
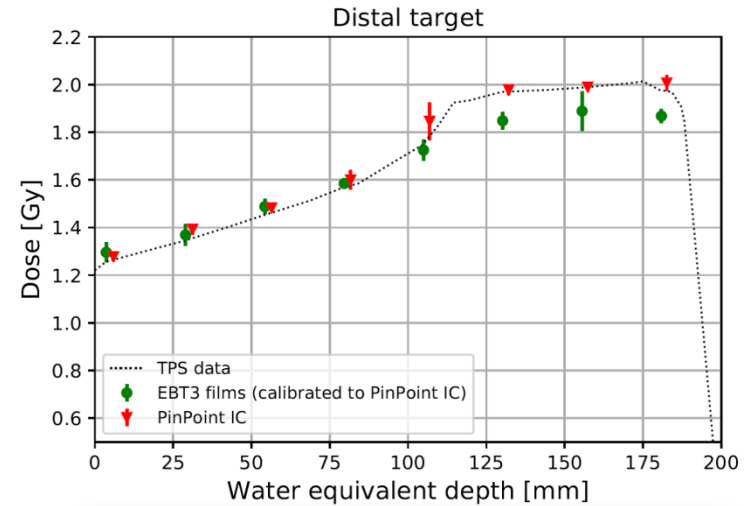
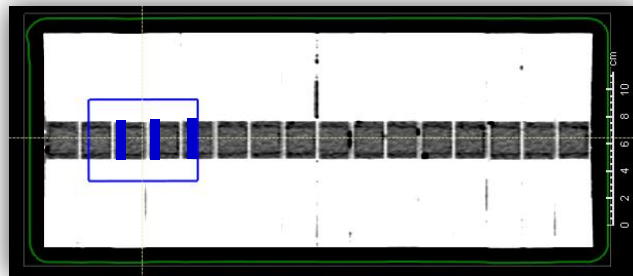
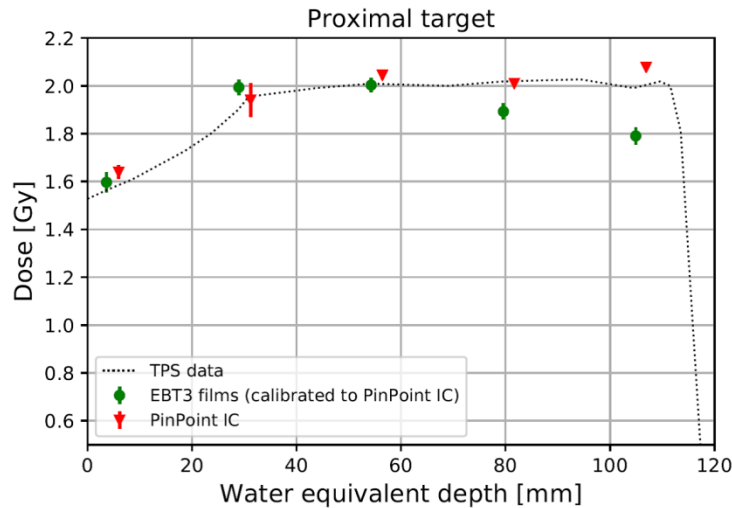


Dosimetry: films



Dosimetry: Ionisation chambers

Dosimetry Aspects

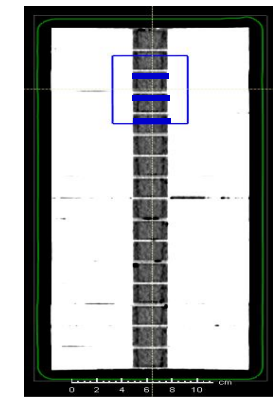
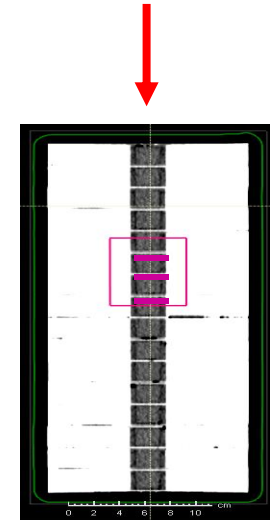
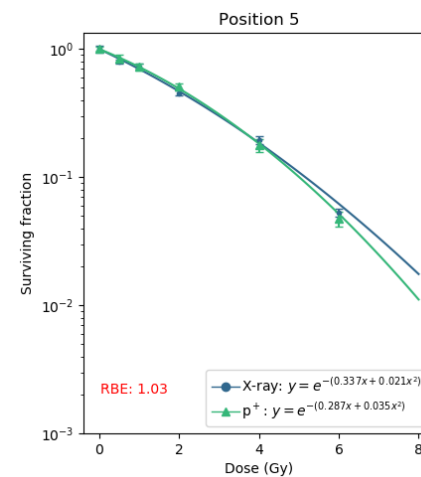
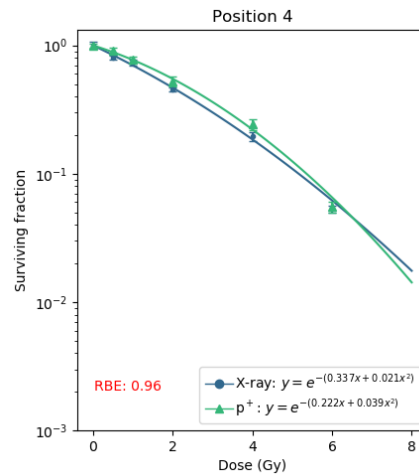
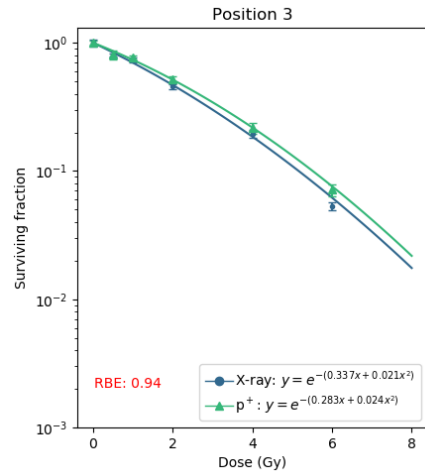
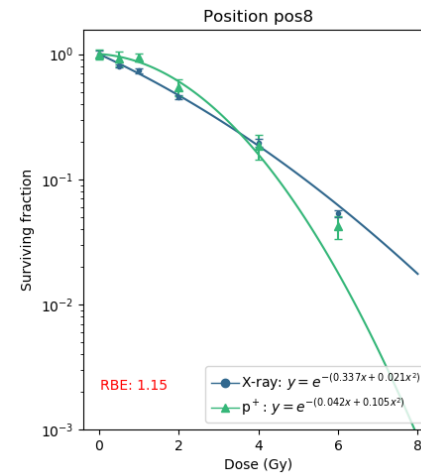
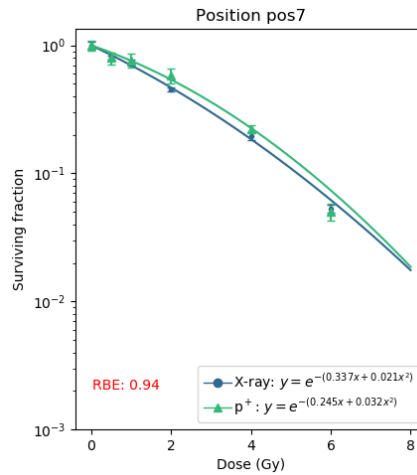
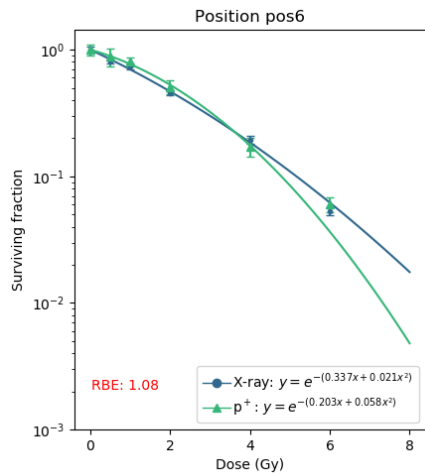


Quenching effect:

→ undervalue dose near the BP

Clausen et al, to be submitted

Squamous Cell Carcinoma Cells

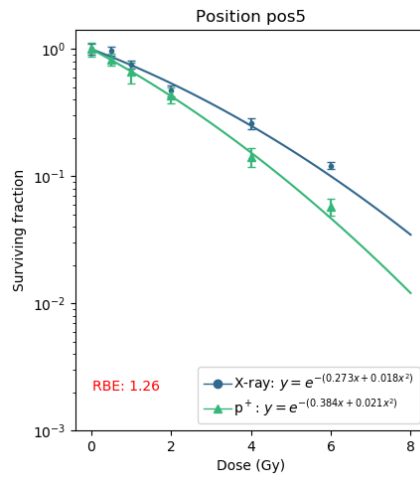
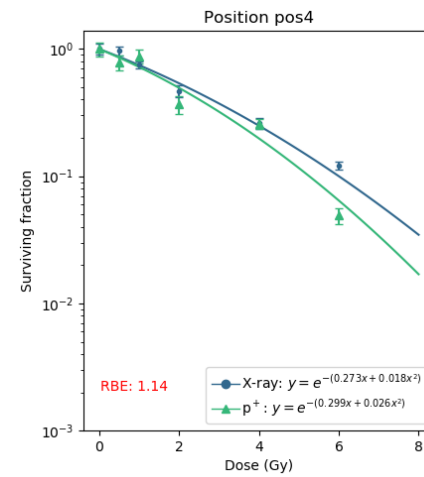
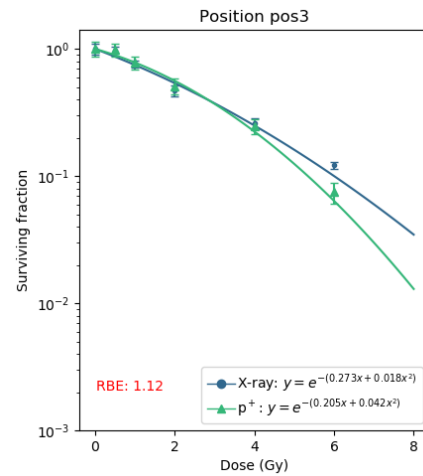
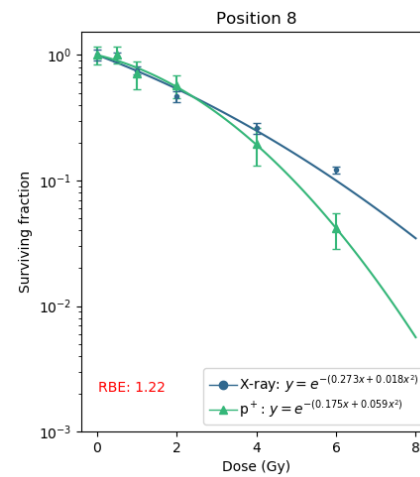
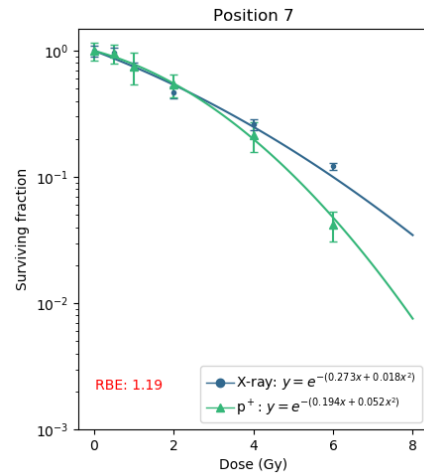
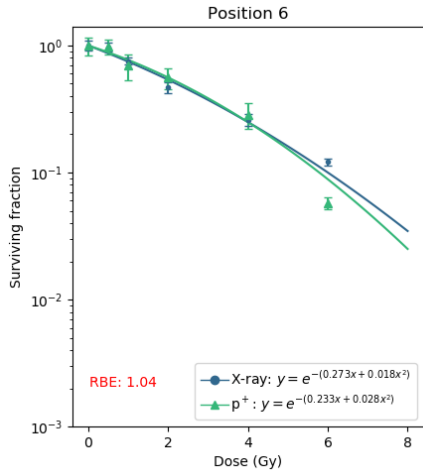


proximal

middle

distal

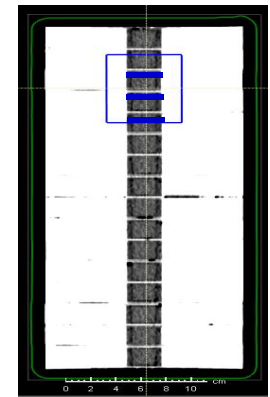
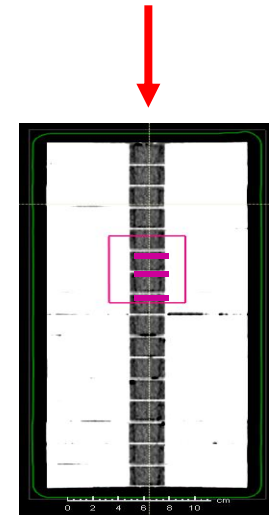
Normal Skin Keratinocytes



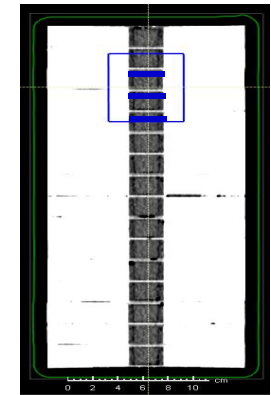
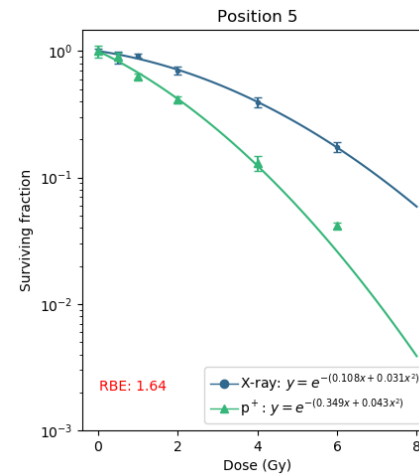
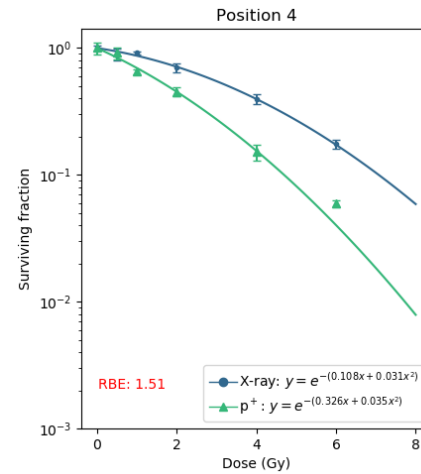
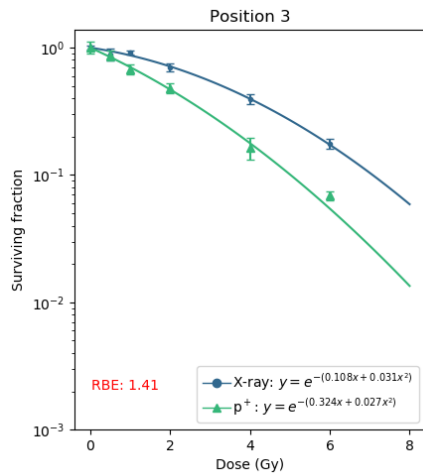
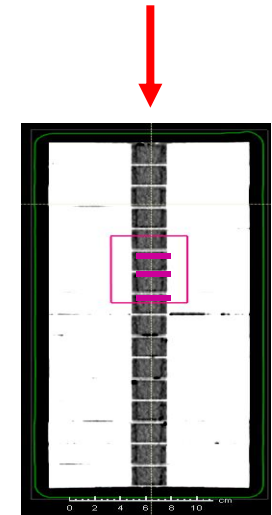
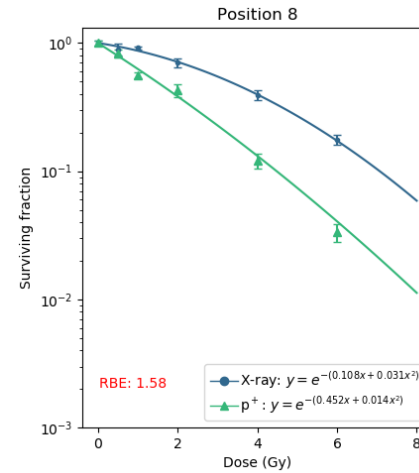
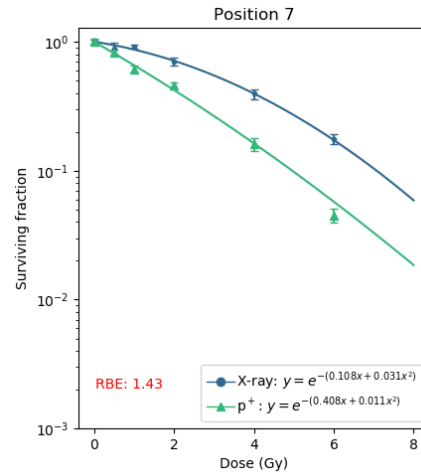
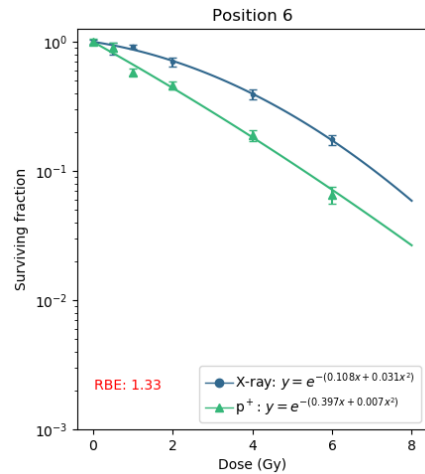
proximal

middle

distal



Prostate Carcinoma Cells

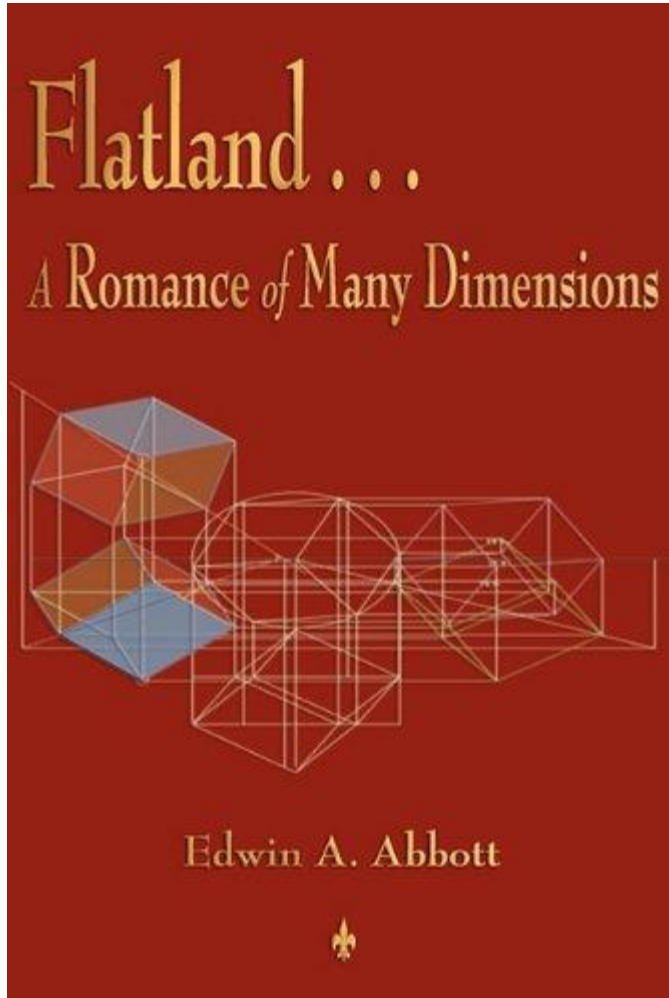


proximal

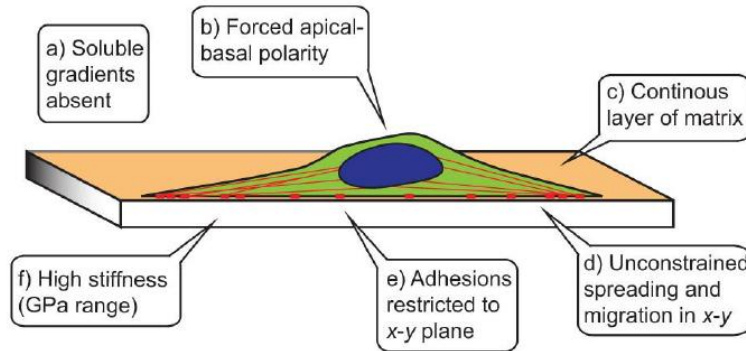
middle

distal

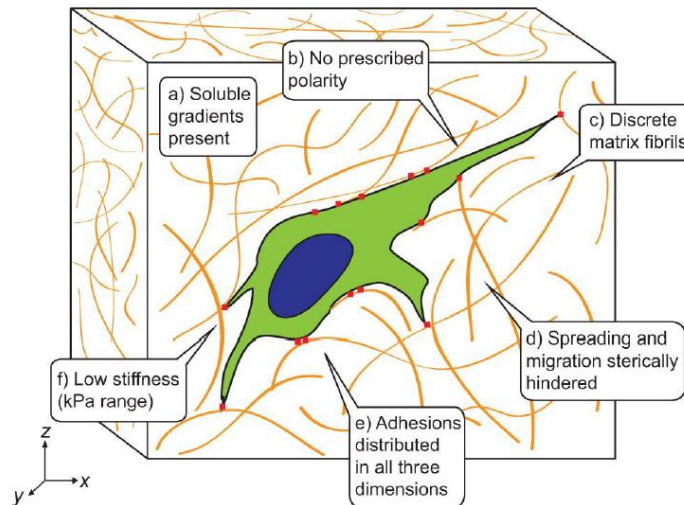
A 3D World



Collagen-coated glass (2D)

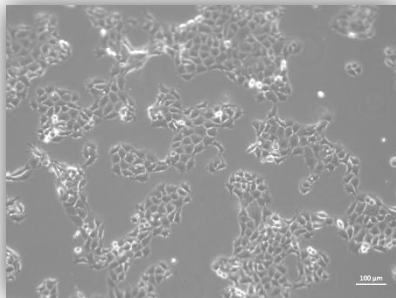


Collagen gel (3D)

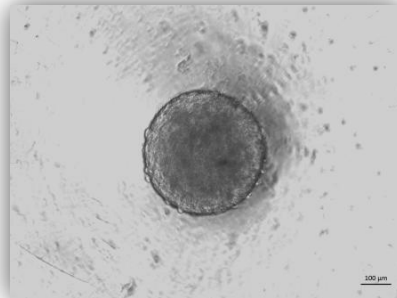


Baker and Chen, *J Cell Sci* 2012 125: 3015-3024

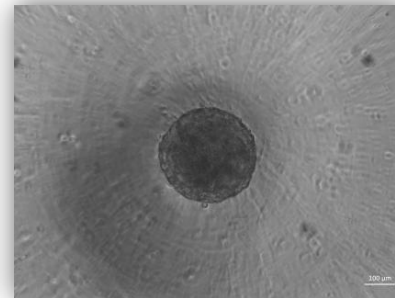
Advances Cell Culture Models: Multicellular Tumor Spheroids



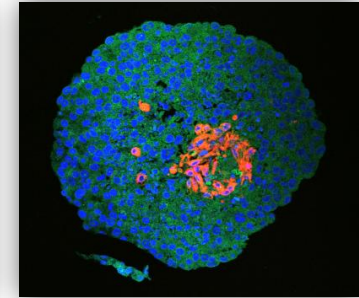
Squamous cell carcinoma cells 2D



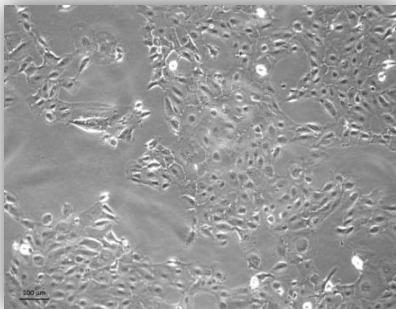
SCC 3D



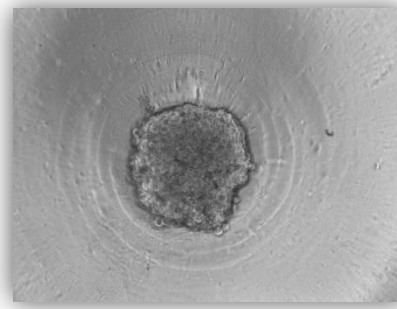
SCC 3D + ECM mimetic



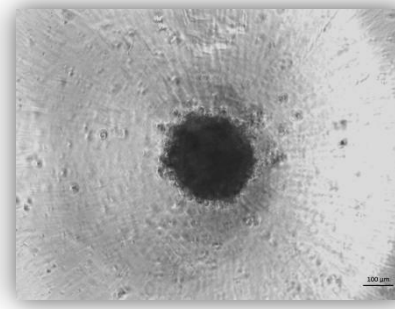
SCC 3D + ECM mimetic + fibroblasts



Prostate Carcinoma Cells 2D

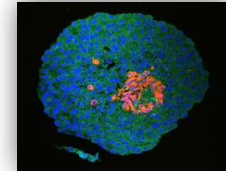
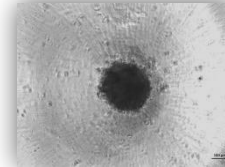
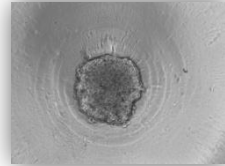
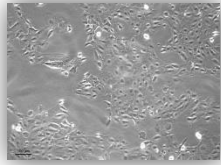


PC 3D



PC 3D + ECM mimetic

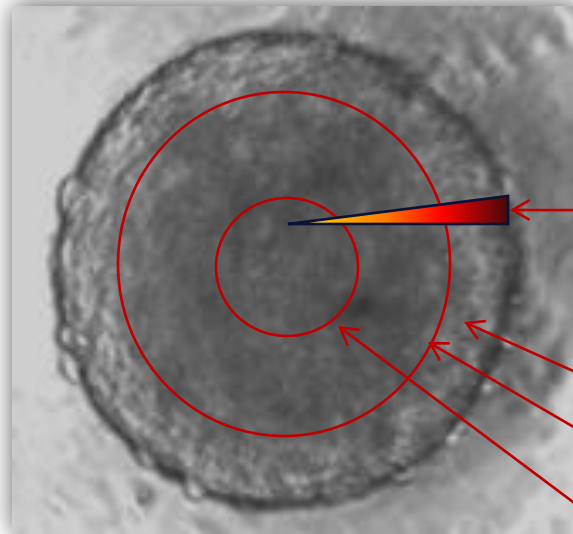
Advances Cell Culture Models: Multicellular Tumor Spheroids



biological function

Low

High



gradients of

oxygen
nutrients
metabolites
drugs

proliferating region

quiescent zone

necrotic core

Therapy-relevant Factor: Hypoxia

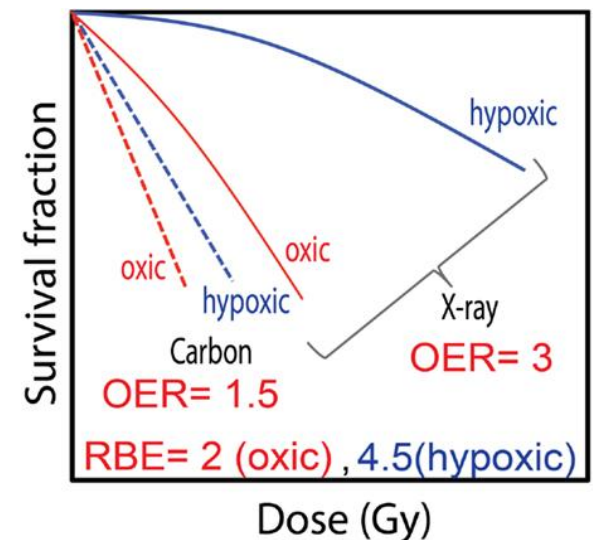
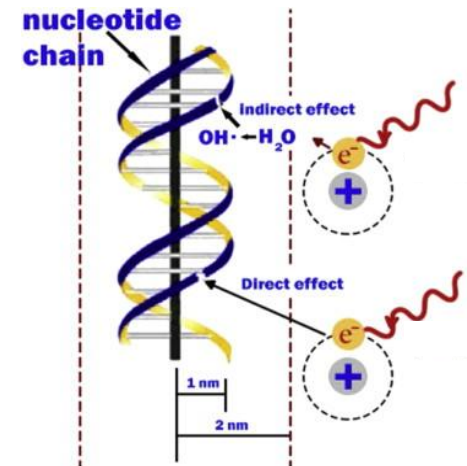
Indirect vs. direct DNA damage

Indirect DNA damage

- Ionisation of water molecules
- generation of radicals
- requires oxygen

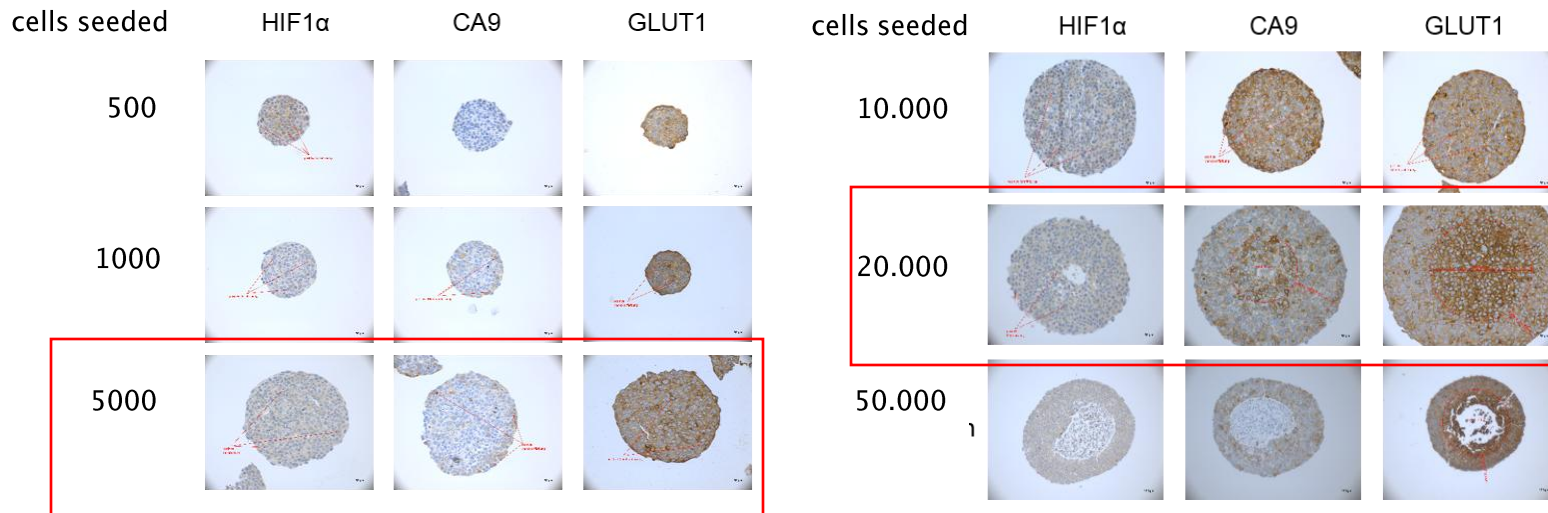
Direct DNA damage

- ionisation of target structure
- does not require oxygen



Held et al, *Front Oncol.* 2016 Feb 12;6:23.

Spheroid Size determines Oxygen Gradient

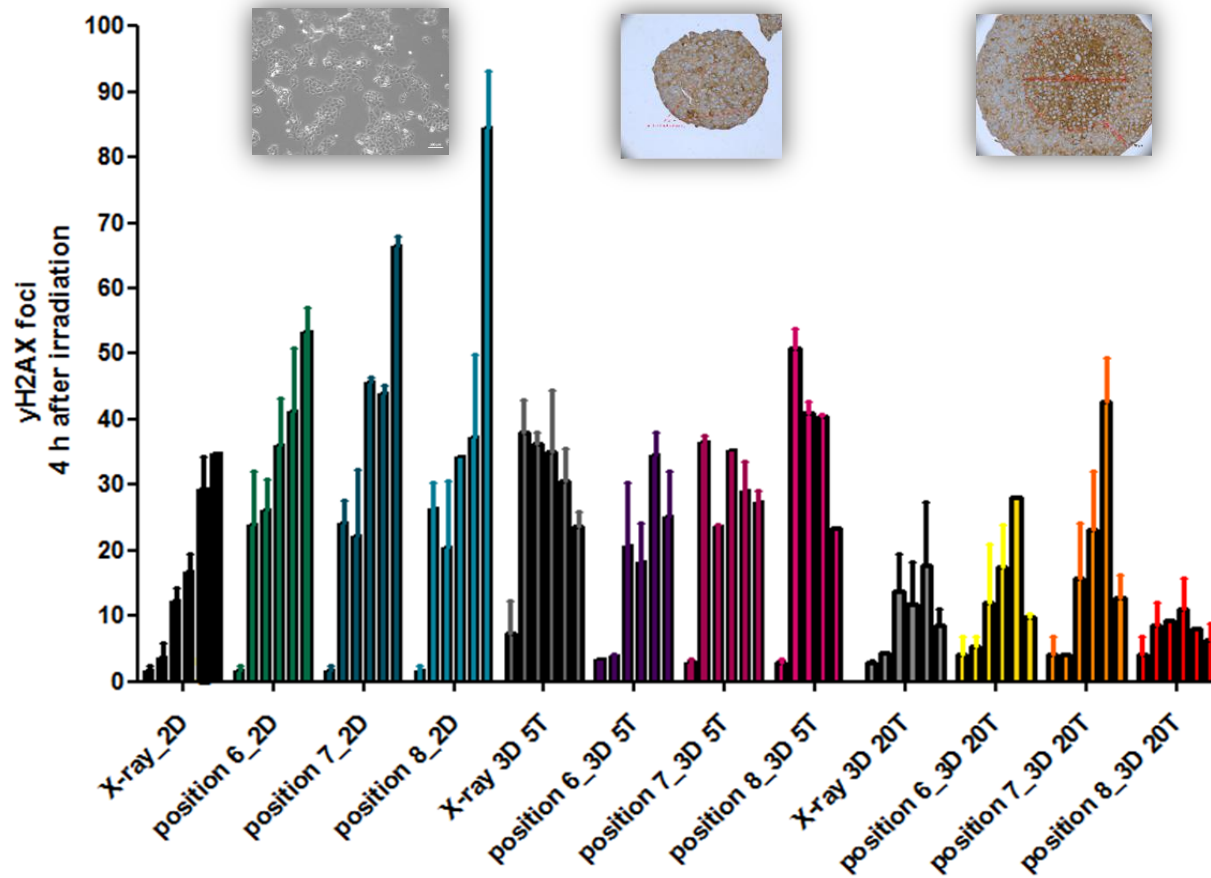


Initial experiments: relevance of hypoxia

- Comparison of oxygenated and hypoxic spheroids
- DNA damage after irradiation

DNA Damage: Influence of 3D Tissue Architecture

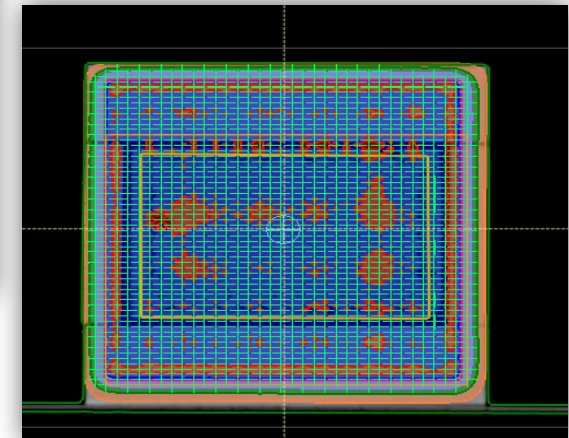
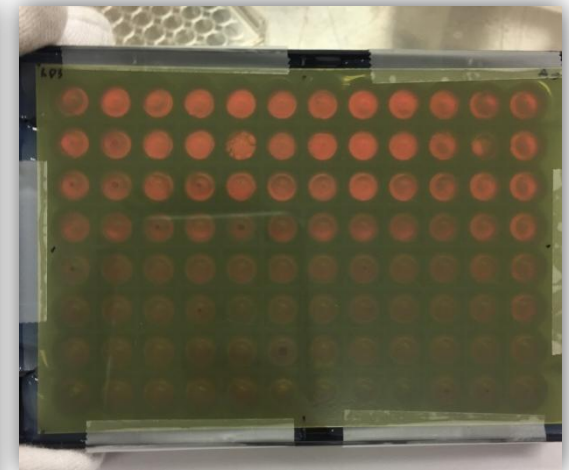
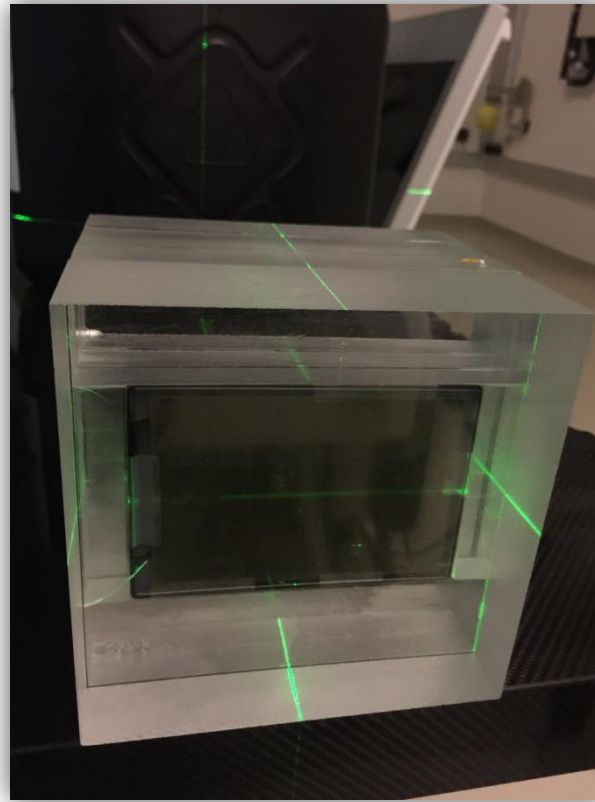
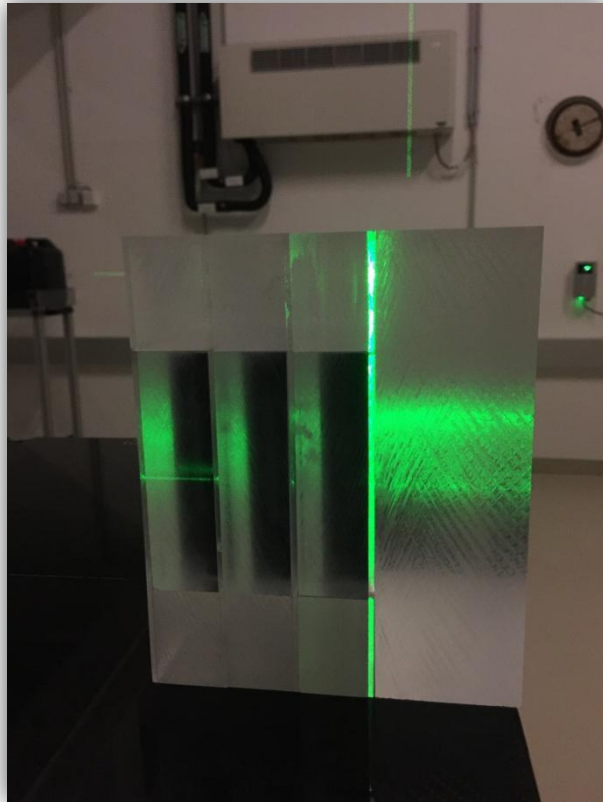
Squamous Cell Carcinoma Spheroids



Tumor Spheroids: Irradiation Setup



Tumor Spheroids: Irradiation Setup



Résumé and Workaround

- high uncertainties
 - heterogenous air bubbles
 - leakage
- high contamination risk
- long irradiation times

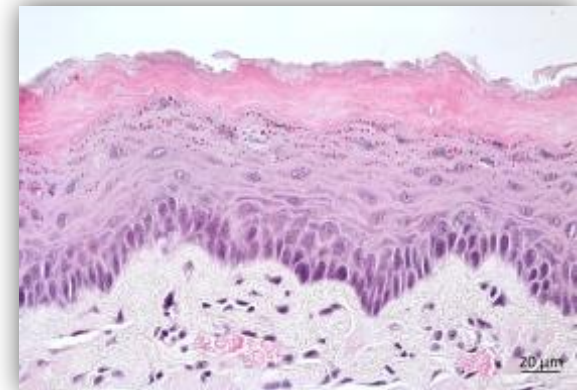
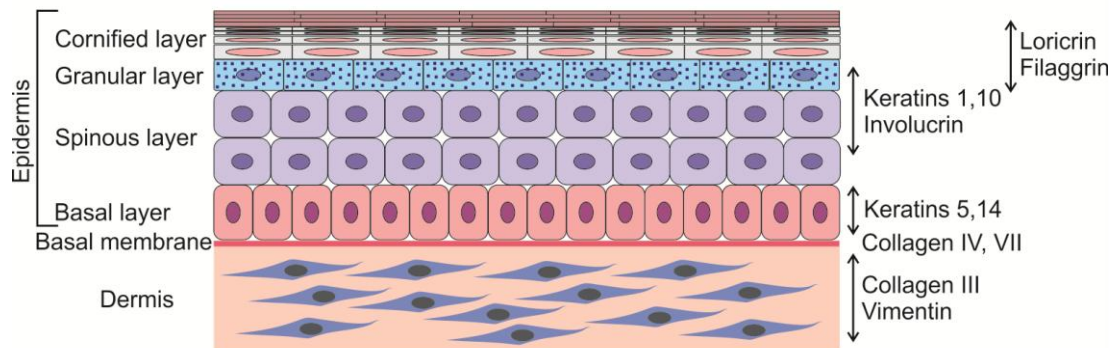
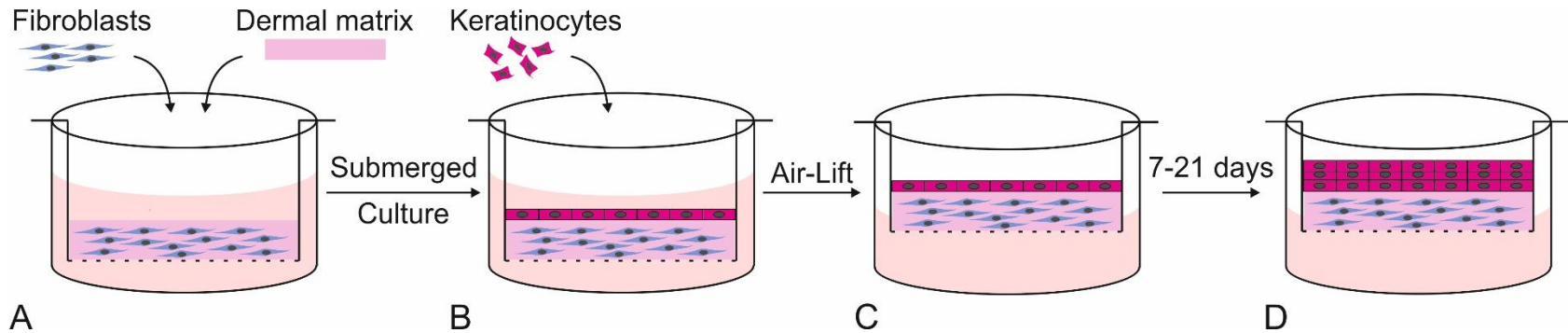
cannot be used in
experimental routine

Workaround:

collection of spheroids in tubes
and positioning of tubes in the
Lab-Tek chamber slides



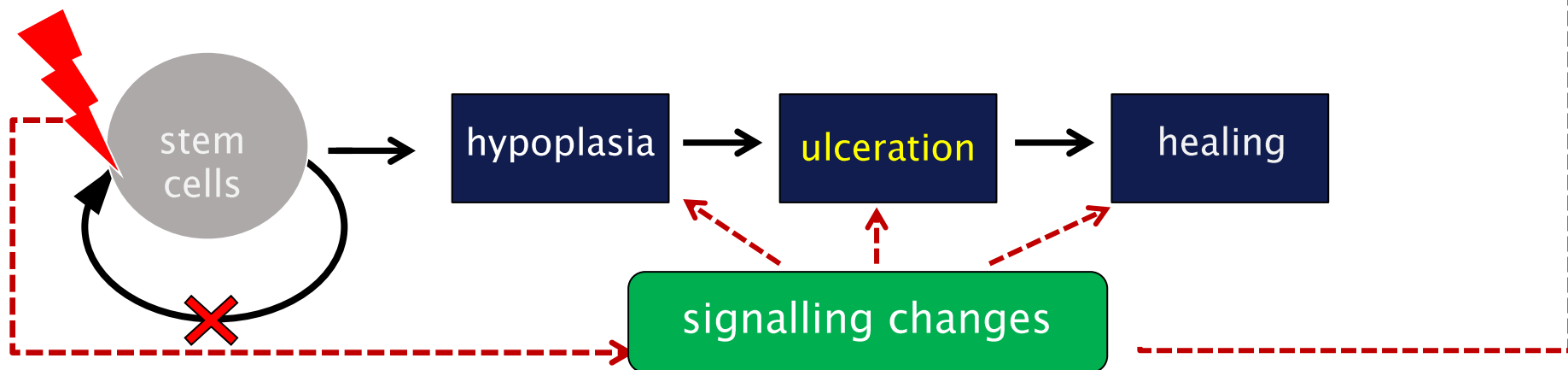
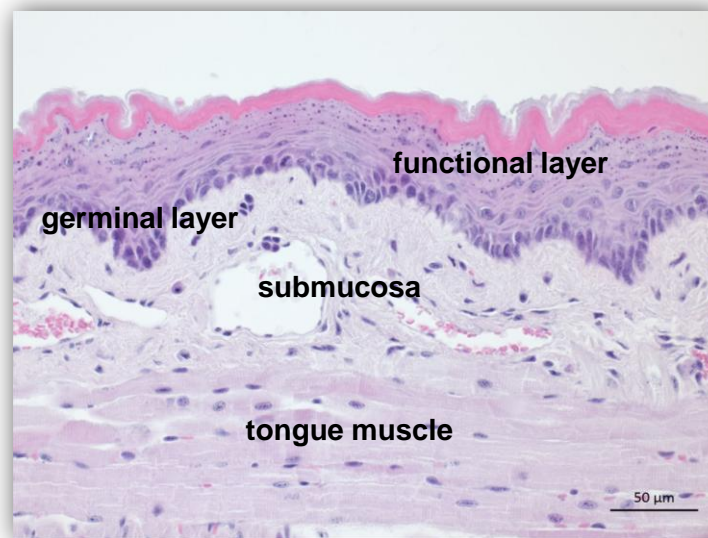
Advances Cell Culture Models: Biomimetic Epithelium



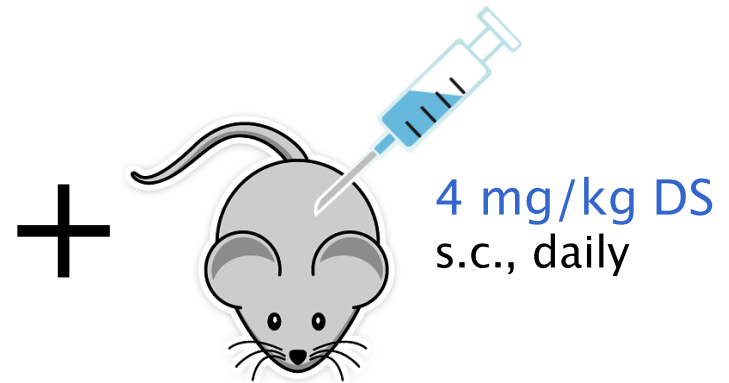
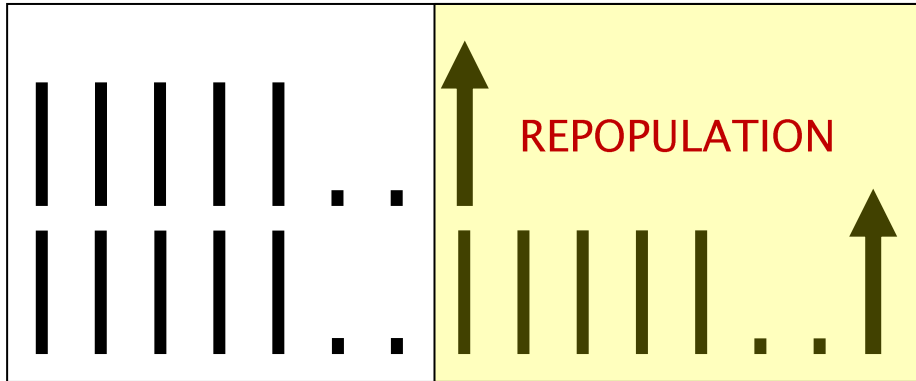
Radio sensitivity

Georgeta Zemora, ATRAB Vienna

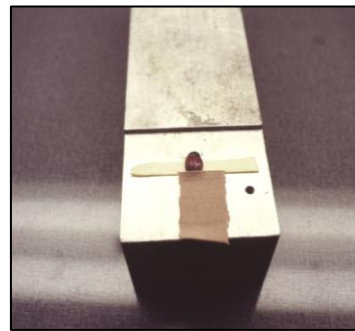
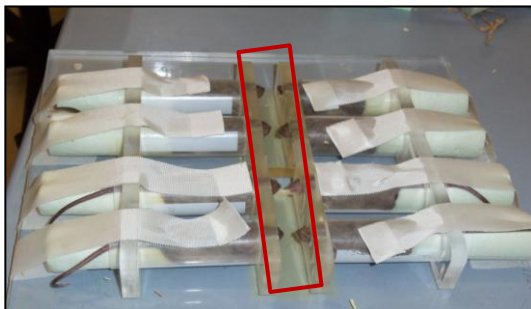
Radiobiology of Normal Tissue Reactions



The Oral Mucositis Mouse Model



Fractionated snout irradiation

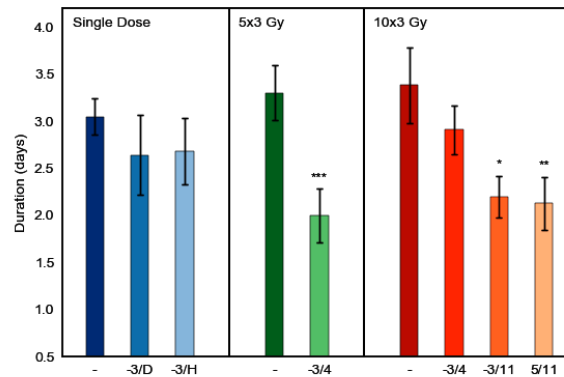
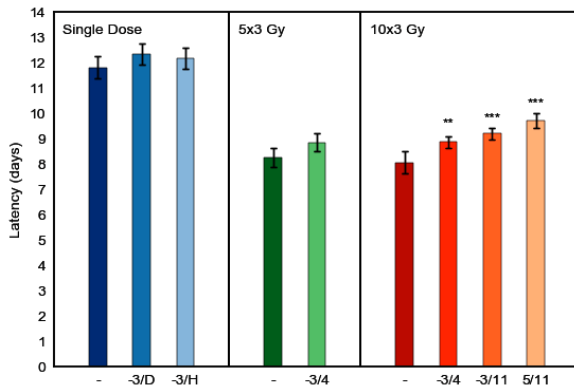
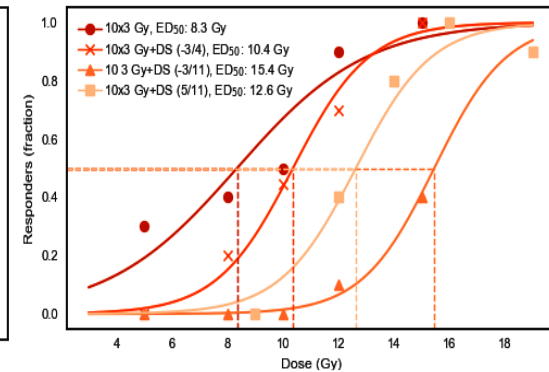
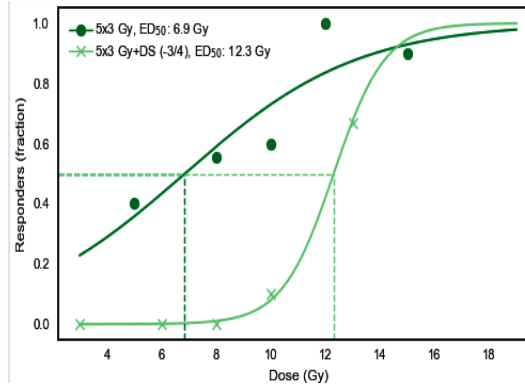
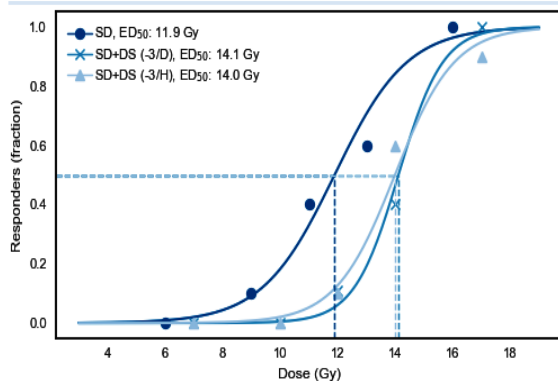


Local tongue irradiation



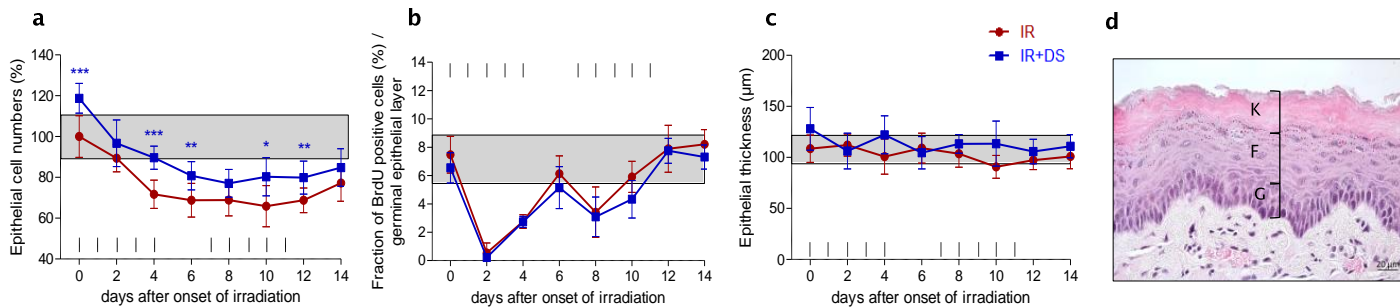
Limitation of the ulceration to a
3x3 mm² area of the lower tongue surface

Normal Tissue Protection: Dermatane Sulfate for OM Mitigation



Dermatan sulfate protects oral mucosa – mechanisms?

DS-mediated radioprotection: not stimulation of proliferation but junctions



β-catenin

E-cadherin

Claudin-1

Occludin

IR

IR+DS

IR

IR+DS

IR

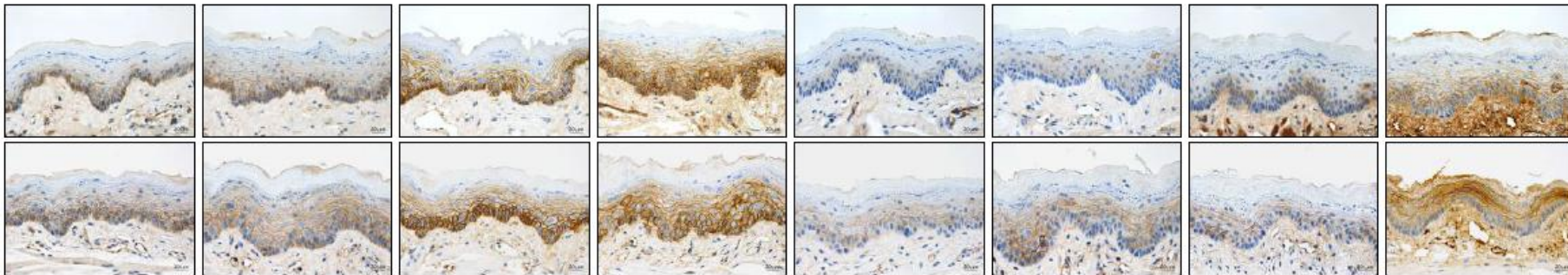
IR+DS

IR

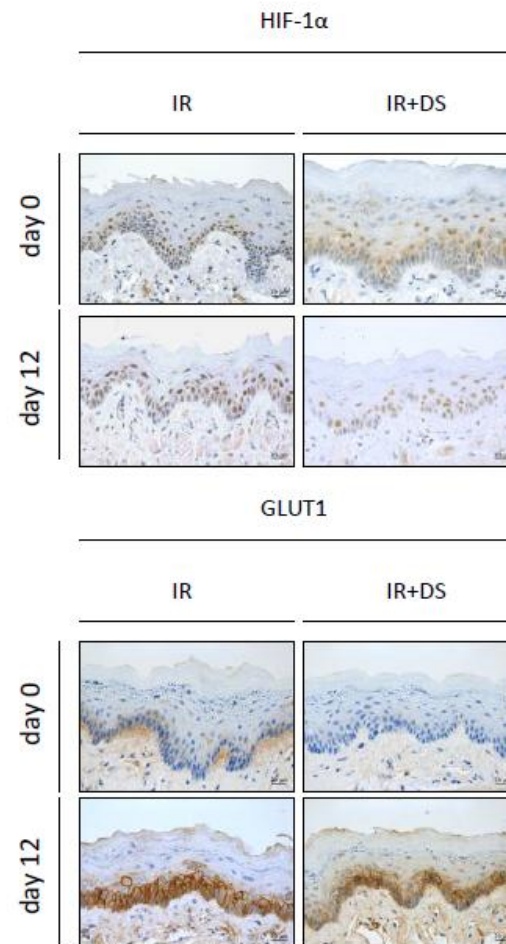
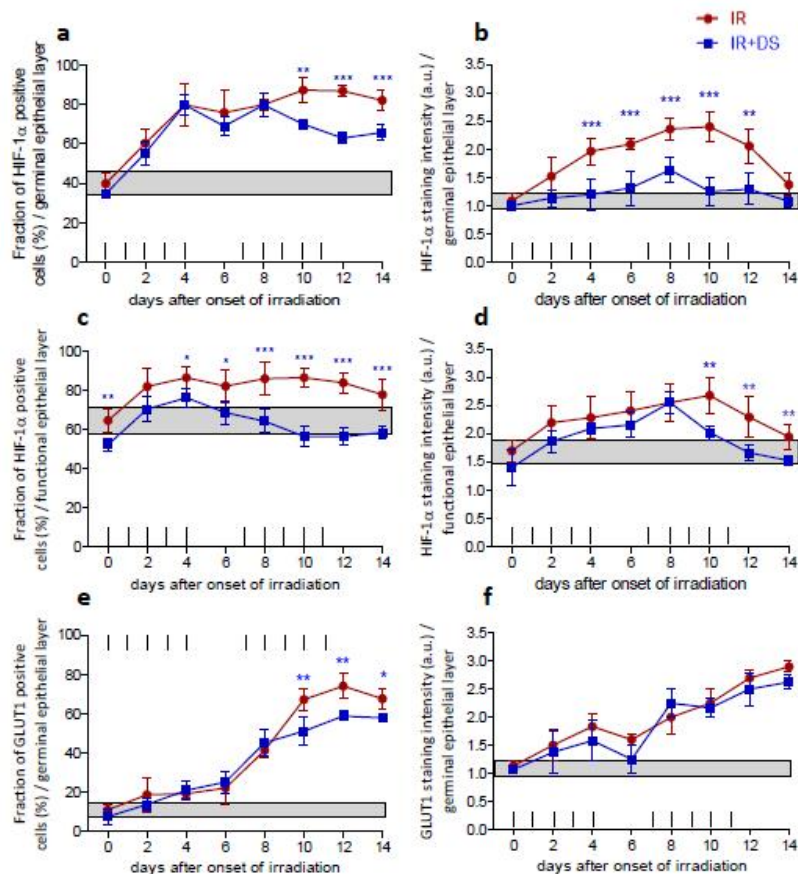
IR+DS

day 0

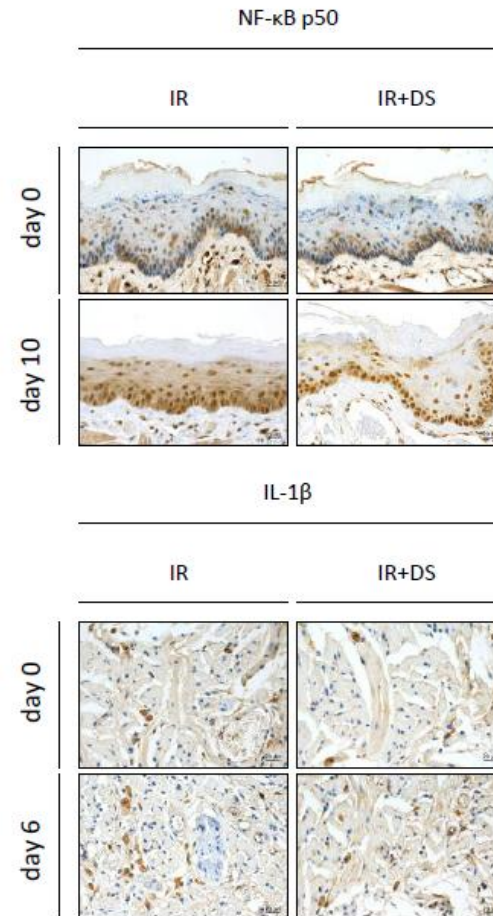
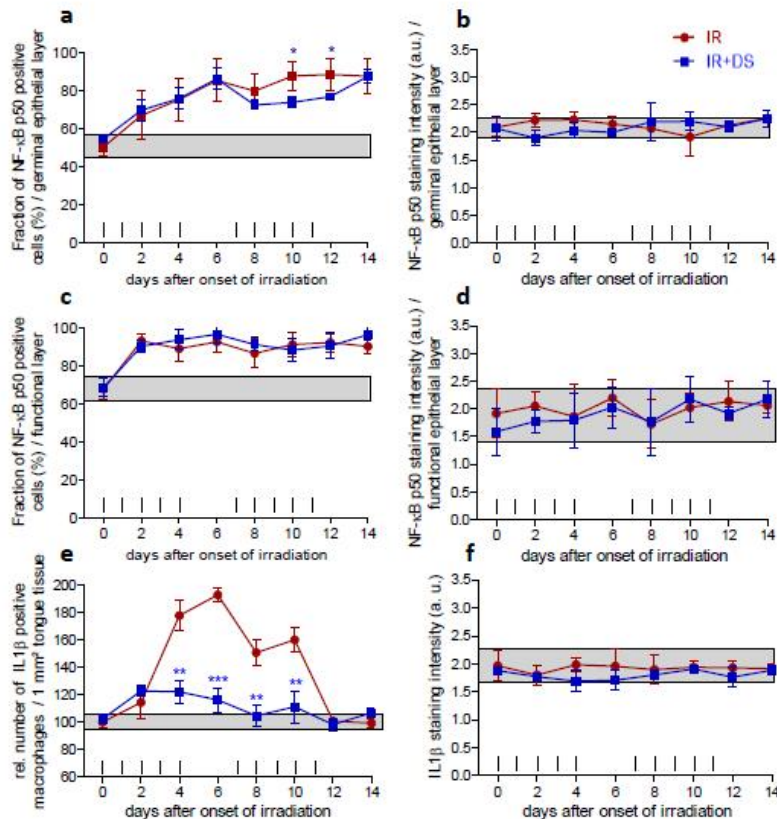
day 14



DS-mediated radioprotection: reduced hypoxia

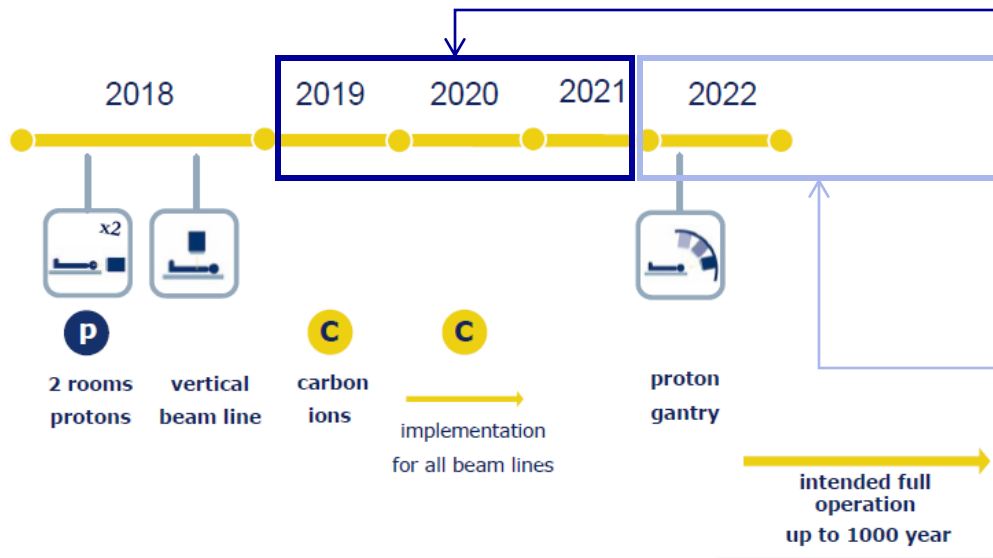
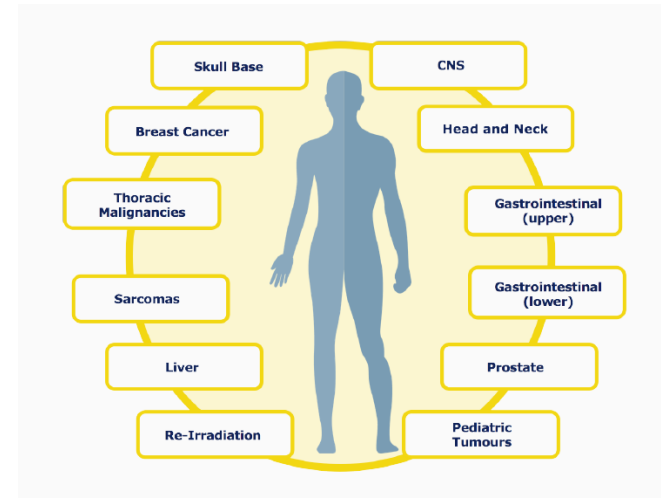


DS-mediated radioprotection: reduced inflammation



MedAustron - Outlook

- commissioning of the proton gantry – 2022
- carbon ions and 800 MeV protons in IR1 (research room) – 2019
- carbon ions in IR2 and IR3 – 2019 and 2020



Research Period II:
LET and Biology
LET-dependent signalling

Radioimmunotherapy
Therapy Personalization

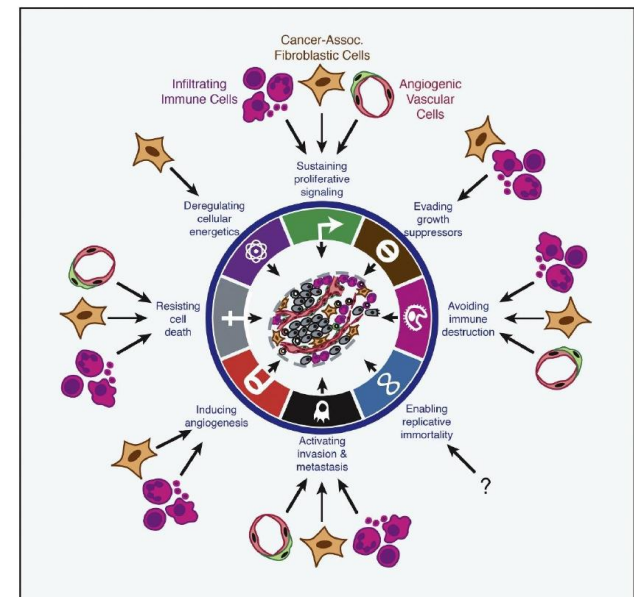
Image: MedAustron

Research Outlook– 2019-2021

Correlation of LET and signalling events

- Regulation of gene activation in response to CIRT vs. PhRT
- Radiation response of tumour cells AND tumour stroma
- Immunotherapy–relevant signalling
 - Immunogenic cell death
 - Immune evasion

Is CIRT more immunogenic than
PhRT?



Acknowledgement

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

Colleagues and Advisors

- ATRAB Team MedAustron
- ATRAB Team MUW: Verena Kopatz and Georgeta Zemora
- 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



MedAustron 



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Supplementary

Accelerator Components – Ion Sources

- 3 identical electron cyclotron resonance sources
 - H_3^+
 - C_4^+
 - redundant source
 - position for 4th source prepared
- micro-wave with 14.5 GHz frequency
- extraction potential difference: 30 kV
- extraction energy: 8 keV



Image: MedAustron

Accelerator components – Low Energy Beam Transfer Line

- switching dipoles to choose the source / particle species
- constant beam current
- fast deflector to create short pulses for LINAC
- beam monitors
- Purpose:
 - transport particles from source to the LINAC

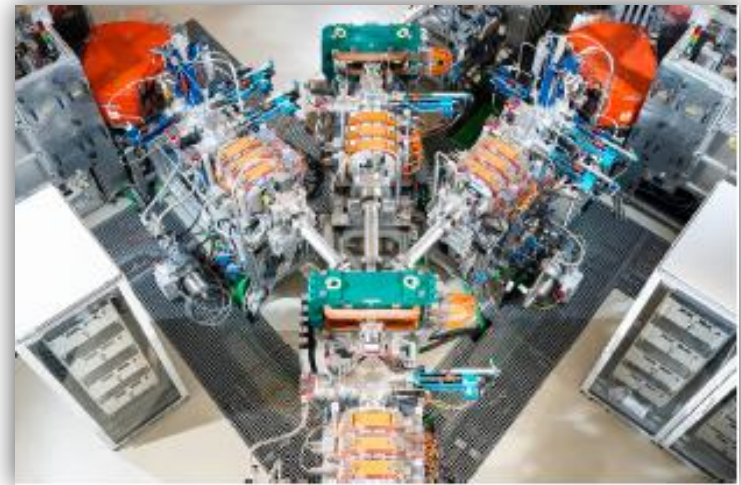


Image: MedAustron

Accelerator components – Linear Accelerator

RFQ (Radiofrequency quadrupole):

- bunching, focusing, acceleration of particles
- extraction energy: 400 keV

IH (interdigital H-mode structure) tank:

- acceleration
- alternating opposite electrodes
- extraction energy: 7 MeV

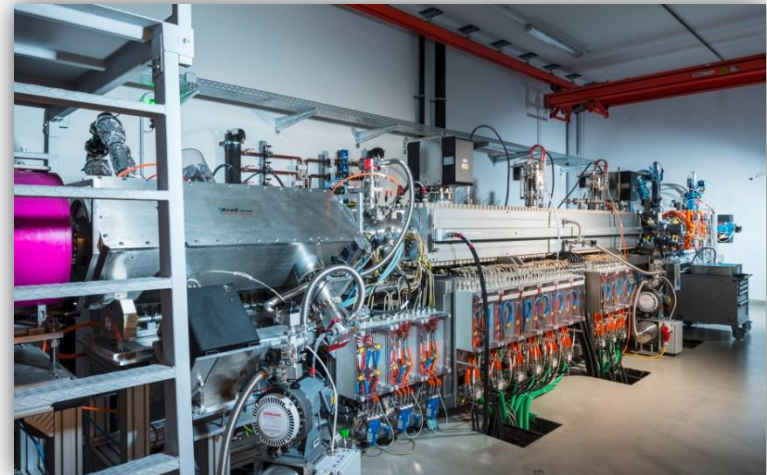
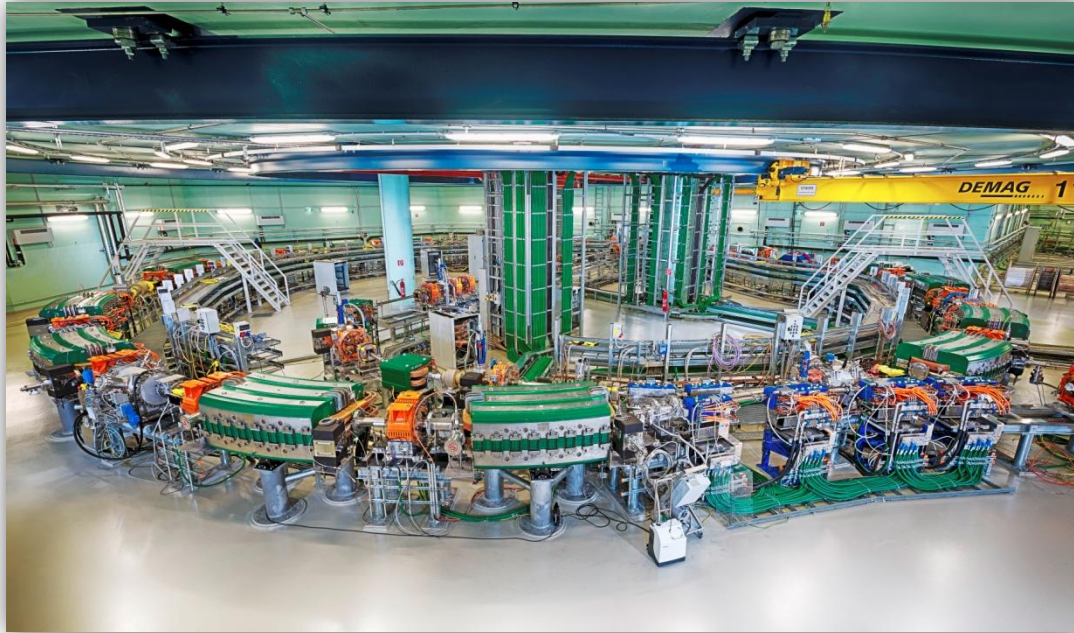


Image: MedAustron

Accelerator components – Synchrotron



- circumference: 78 m
- 16 main dipole magnets
- 24 quadrupole magnets
- 1 RF cavity for acceleration
- protons and carbon ions
- extraction energy:
 - Protons: 60 MeV – 800 MeV
 - Carbon: 120 MeV/u – 400 MeV/u

Image: MedAustron

Accelerator components – High Energy Transfer Line

- dipole magnets for transversal corrections
- quadrupole magnets for focusing / defocusing
- switching dipoles for individual irradiation rooms
- in-room: fast scanning magnets for active scanning of target
- Purpose:
 - transfer of particles from synchrotron into the irradiation rooms



Image: MedAustron