Marburg Ionbeam-Therapycenter (MIT)

MIT
Marburger Ionenstrahl-Therapiezentrum

Innovations in Physics and Radiobiology

Dr. Ulrike Schötz
Dr. Kilian Baumann
Prof. Dr. Klemens Zink

HITRI plus
Heavy Ion Therapy Research Integration

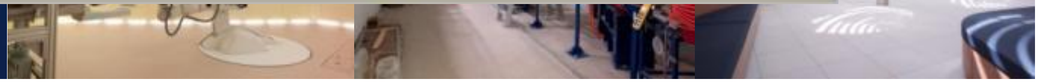
Marburg Ionbeam-Therapycenter (MIT)

MIT Marburger Ionenstrahl-Therapiezentrum

Prof. Dr. Klemens Zink
Medical Physicist
Technical and Scientific Director MIT

Marburg
about 80 km north from Frankfurt

HITRI plus
Heavy Ion Therapy Research Integration



History of MIT

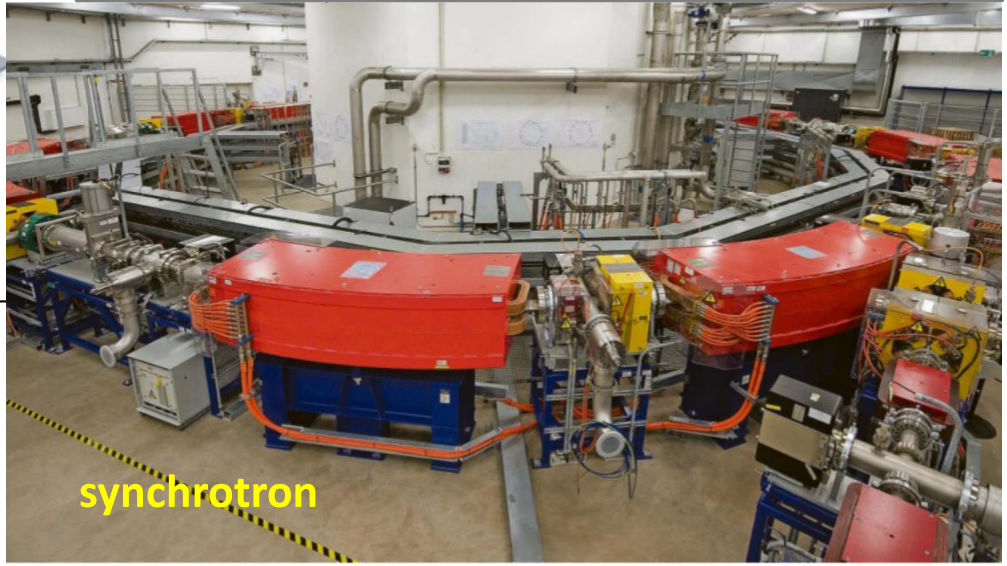
Constructed by Siemens Healthineers

2 facilities in operation: Marburg and Shanghai

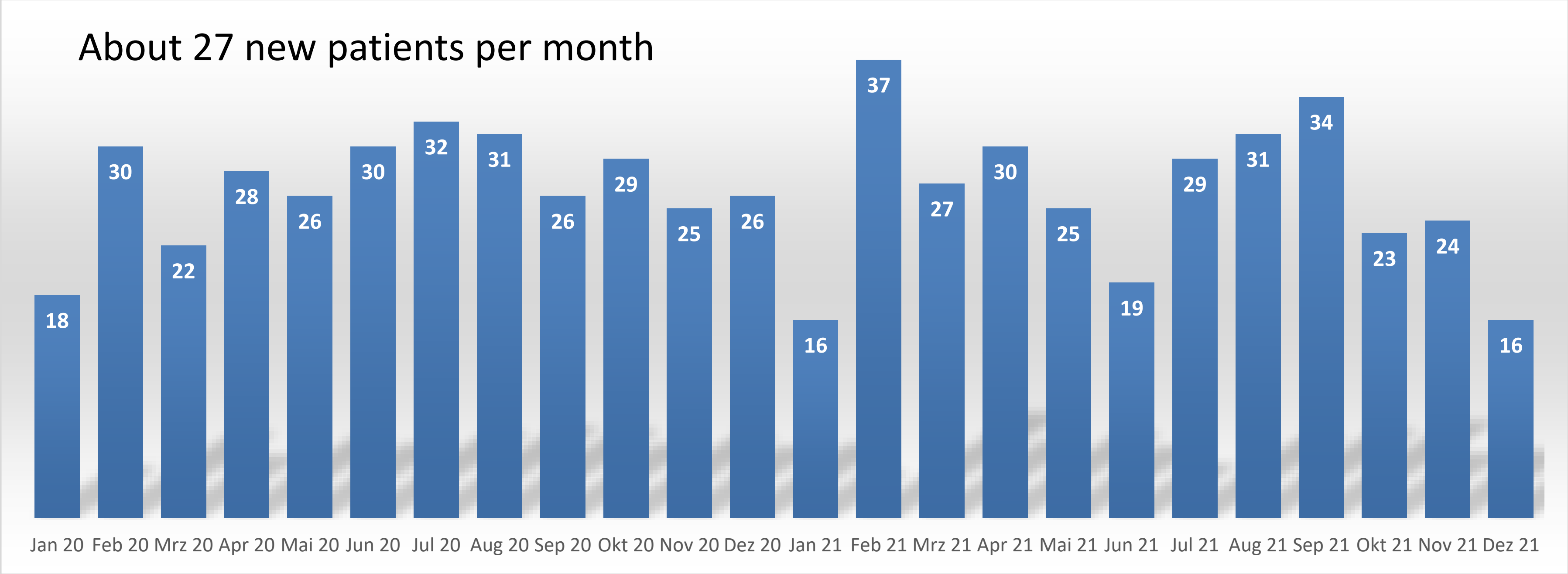
Start of construction:	09/2007
End of construction:	04/2009
Installation accelerator:	08/2008
First beam in treatment room:	02/2010
First patient treatment: (planned)	2011
Shut down:	2011
Restart (leadership HIT):	2015
First patient treated:	2015
Change ownership HIT -> UKGM:	08/2019

Technical Equipment

- Synchrotron:
  - up to 430 MeV/u ^{12}C
  - up to 250 MeV protons
- active raster scanning
- 3 treatment rooms with horizontal beam
- 1 treatment room with 45° beam line



Patient statistic



year	number of patients
2018	251
2019	293
2020	323
2021	311

Treatments:
- 66% Primary
- 34% Boost

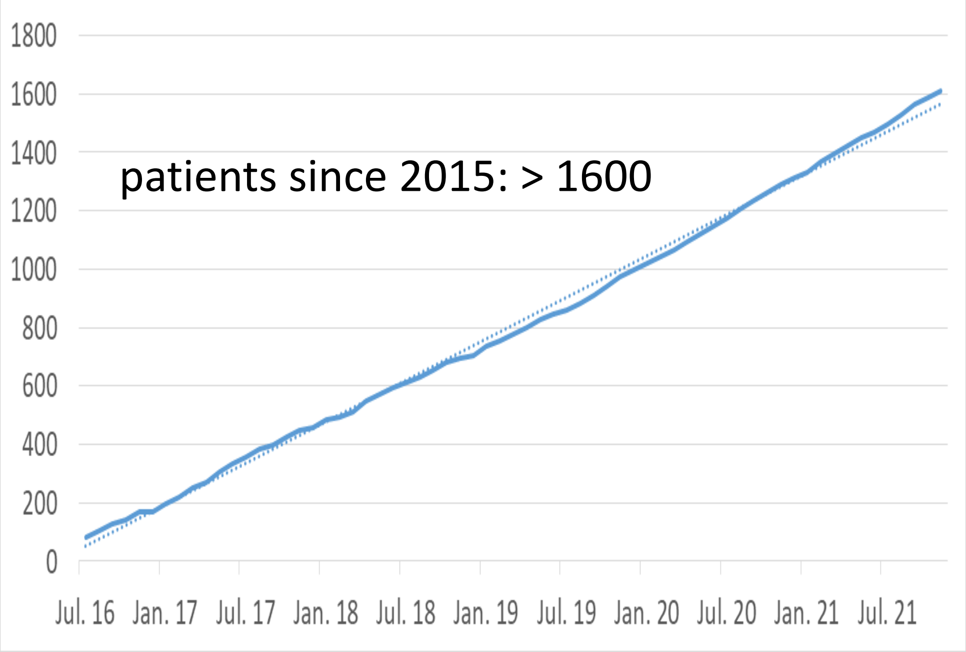
Treatments:
- 40% ^{12}C
- 60% Protonen

Patient statistic

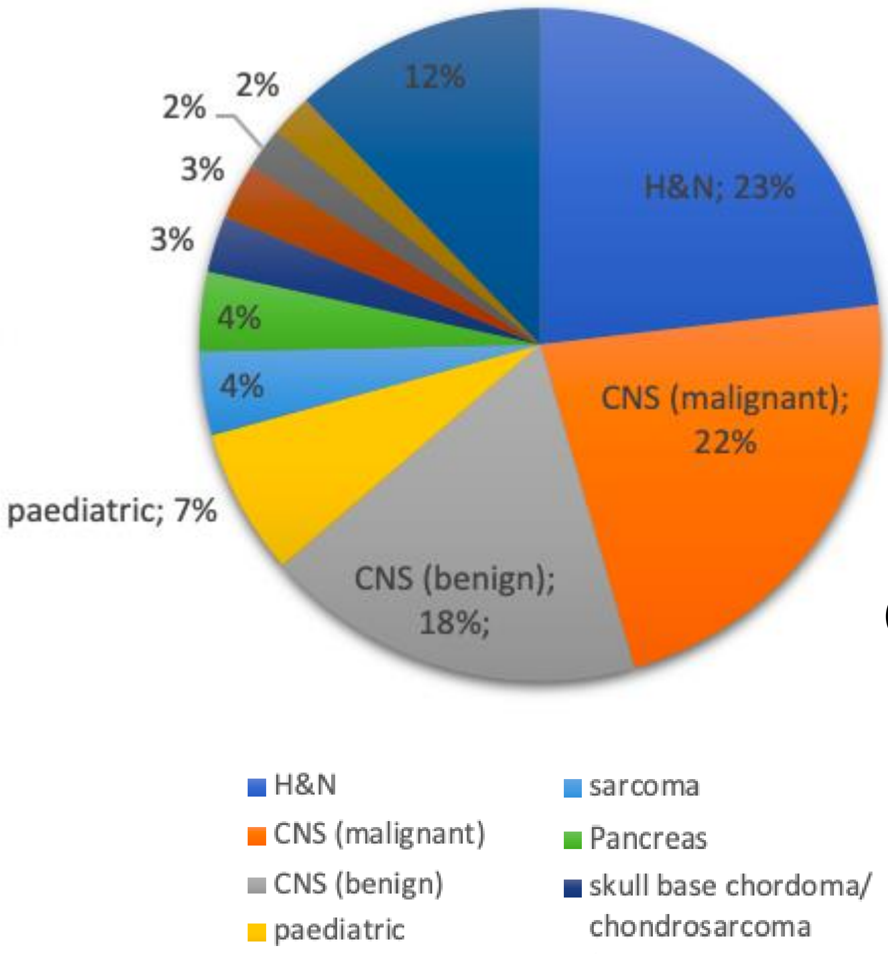
year	number of patients
2018	251
2019	293
2020	323
2021	311

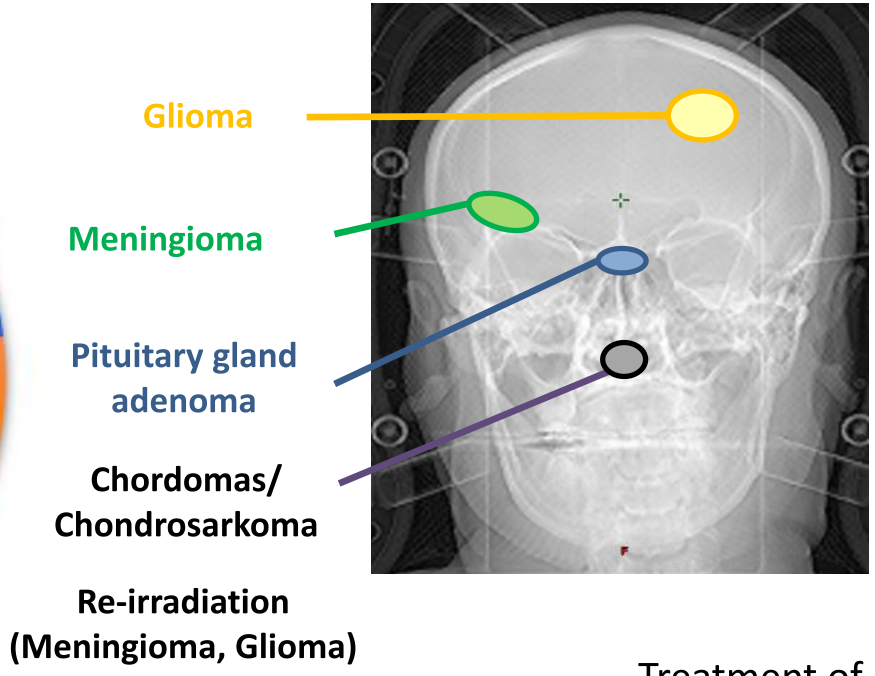
Treatments:

- 40% ^{12}C
- 60% Protonen

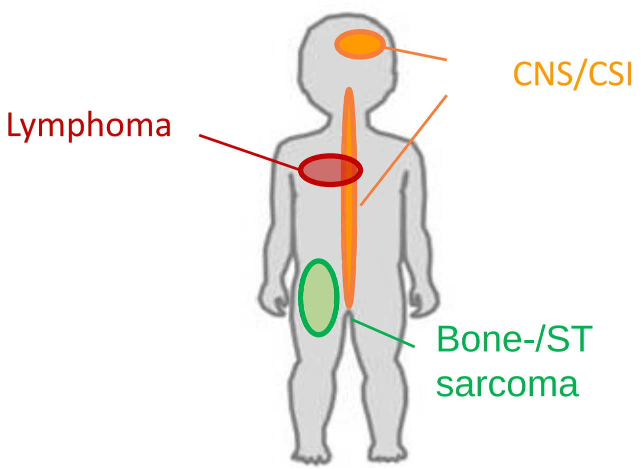


Treated tumor entities

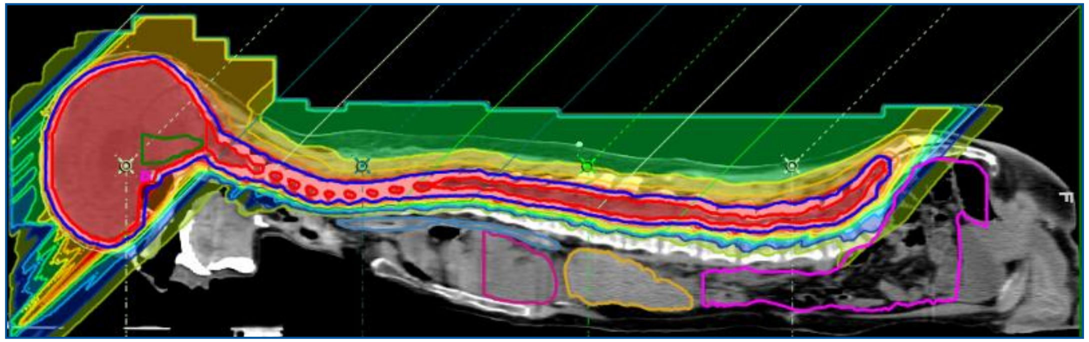




Pediatric tumors



Treatment of neuro axis with protons at MIT



Clinical trials initiated by MIT

MIT Marburger Ionenstrahl-Therapiezentrum

GliProPh (phase III)

GliProPh – Version V.07 vom 25.09.2017

Studienplan

Phase III Studie zum Vergleich einer Protonen- vs. Photonen-Strahlentherapie für Patienten mit WHO Grad II-III Gliomen (GliProPh)

Phase III trial of radiotherapy with protons vs. conventional radiotherapy with photons for patients with WHO grade II-III glioma (GliProPh)

Version V.07 vom 25.09.2017

grade 2 and 3 glioma

protons vs. photons

multicentric
prospective randomised

recruiting

INSPIRE

Intensitätsmodulierte Partikeltherapie im Raster Scan Verfahren mit Protonen und C12-Schwerionen:
INSPIRE
-Beobachtungsstudie-

registry

all patients out of prospective trials

monocentric
prospective

recruiting

GIRO (phase III)

Re-Bestrahlung von Glioblastomrezidiven mit Kohlenstoffionen (C12) versus stereotaktische Re-RT mit Photonen

(GIRO)

multizentrische zweiarmige prospektive Phase III Studie

recurrent glioblastoma

C^{12} vs. photons

multicentric
prospective
randomised

start in Q3/2021

KOENIG (phase I/II)

Klinisches Studienprotokoll
Kohlenstoffionentherapie beim primären Glioblastom
Die KOENIG Studie

Version 1.0
26.8.2019

glioblastoma

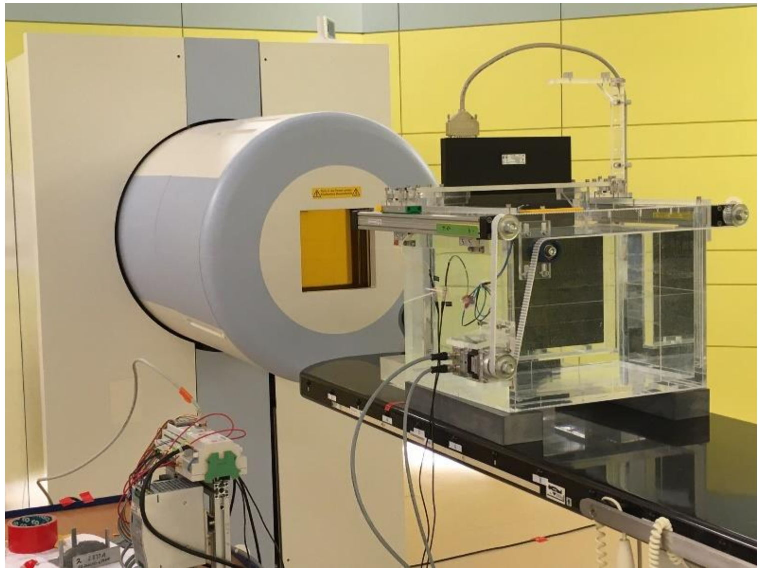
C^{12}

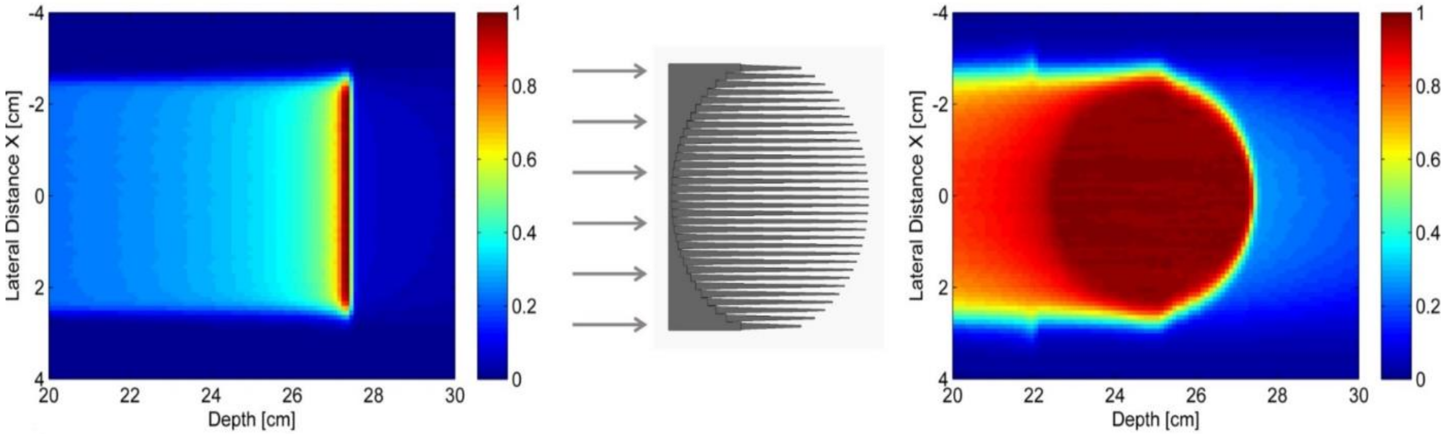
monocentric
prospective
one armed

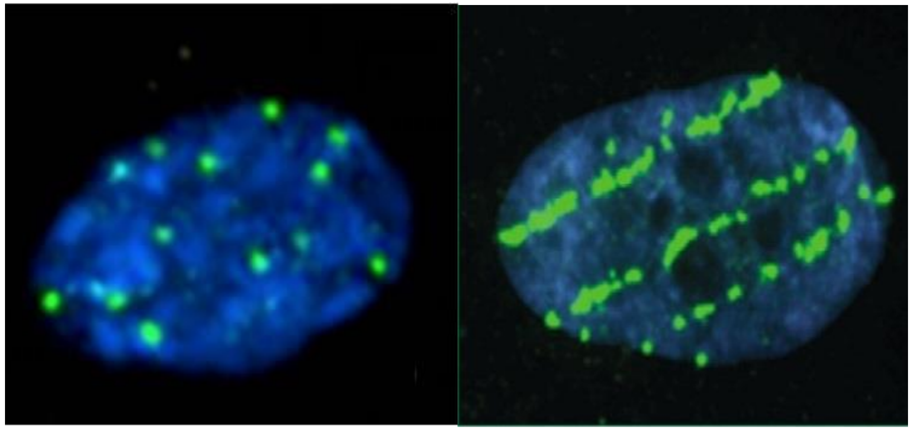
start in Q1/2022

Research@MIT

- Since 2018 MIT hosted about 18 scientific projects and groups
  - Radiobiology
  - Medical physics
  - Particle physics
- Annual grants for beamtime for hessian research groups



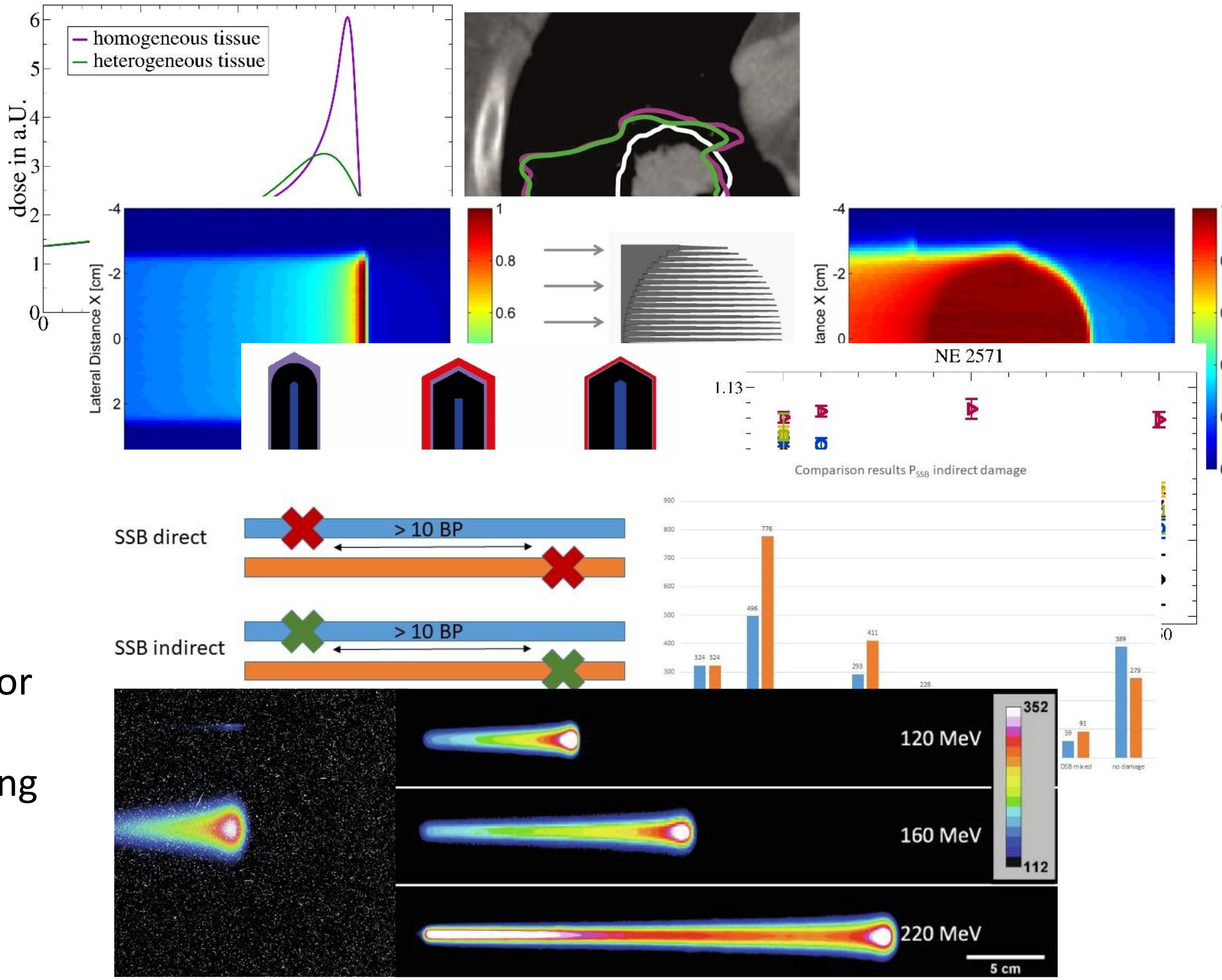




Medical physic projects@MIT

Medical Physics Research at MIT

Kilian-Simon Baumann
- Postdoctoral Researcher at Philipps-University Marburg
- Medical Physicist at MIT

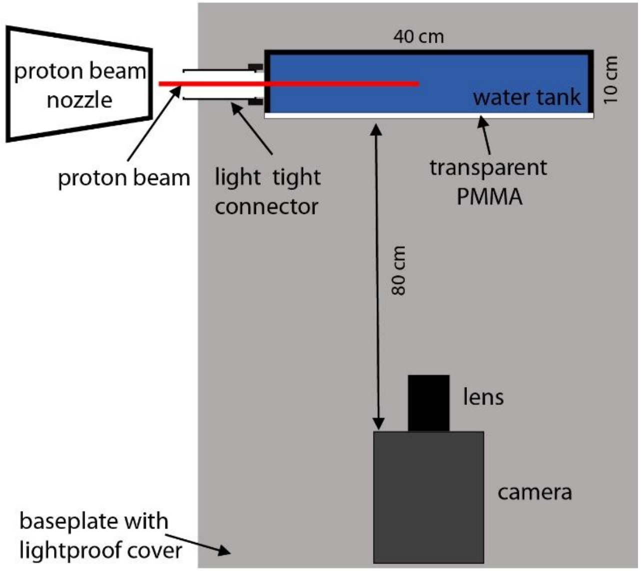


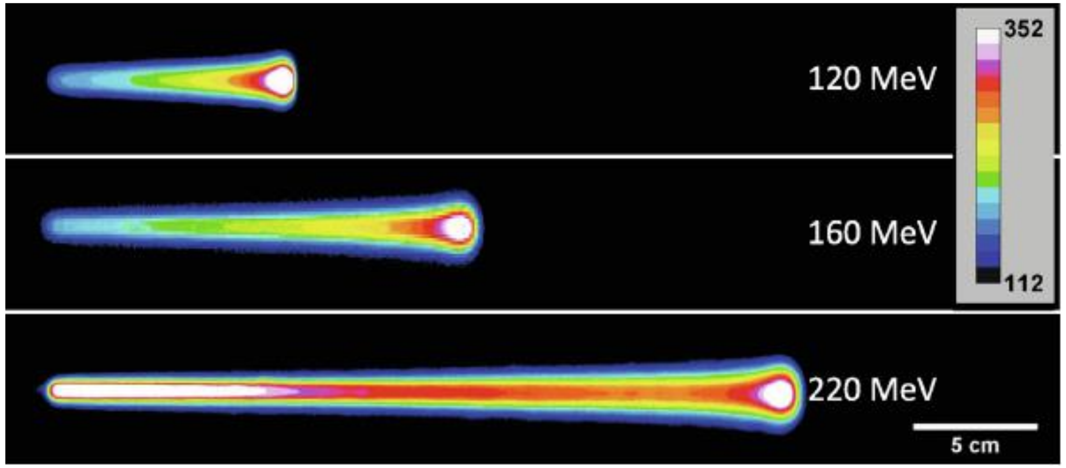
Research topics:

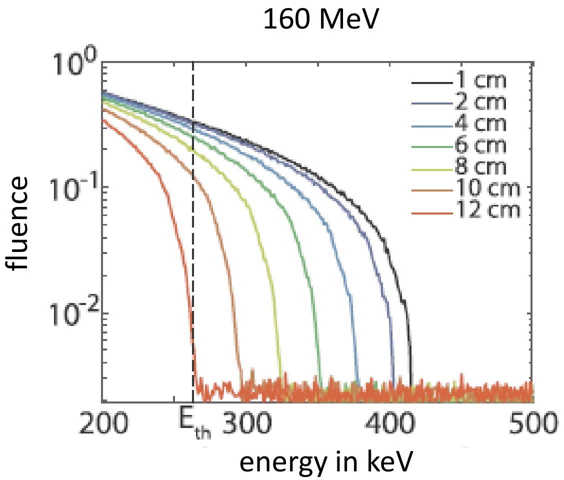
- Particle therapy of lung cancer patients
  - Investigation of lung modulation effects
  - Development of 3d range modulator
- Monte-Carlo based dosimetry on microscopic and macroscopic scales
  - Calculation of beam quality correction factors for air-filled ionization chambers
  - Track structure simulation on cellular scales using Geant4-DNA
- Optical range verification

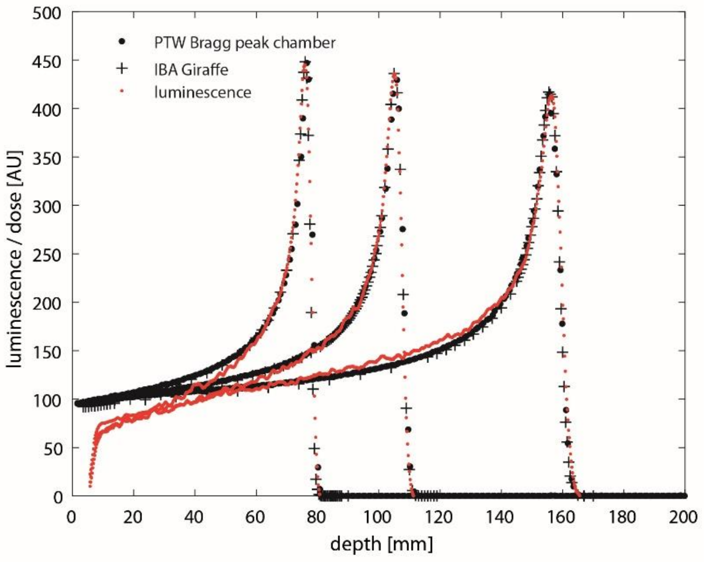
Medical Physics Research at MIT – optical range verification

- CMOS camera is used to collect light emitted by protons
- Range of protons can be determined on the sub-millimetre scale
- Results verified against PTW Bragg peak chamber and IBA Giraffe
- Changes in energy smaller than 0.5 MeV detectable
- Source of light:
    - Cherenkov radiation only at entrance region
    - Measurements of spectral fluence



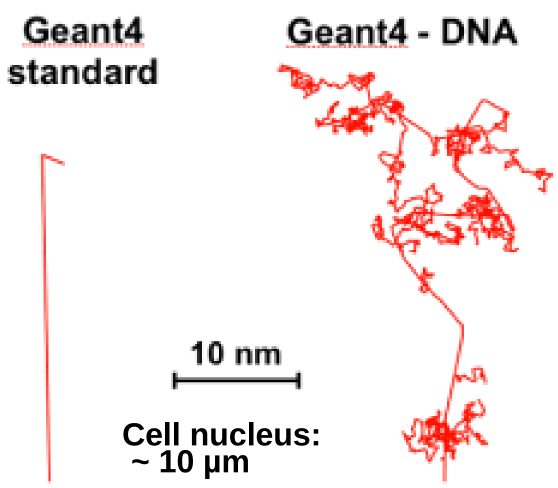


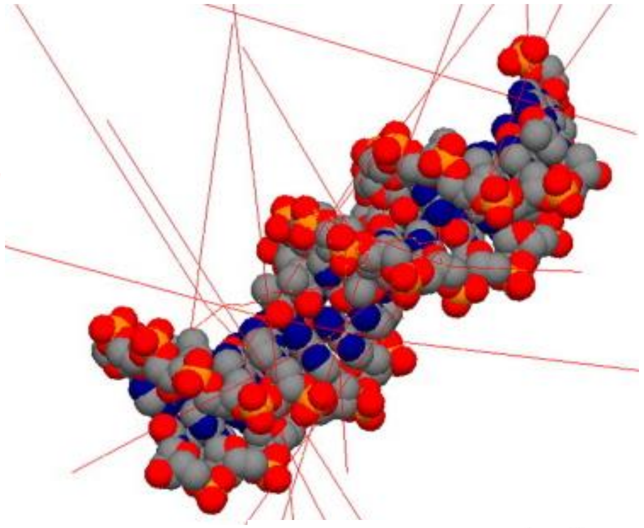


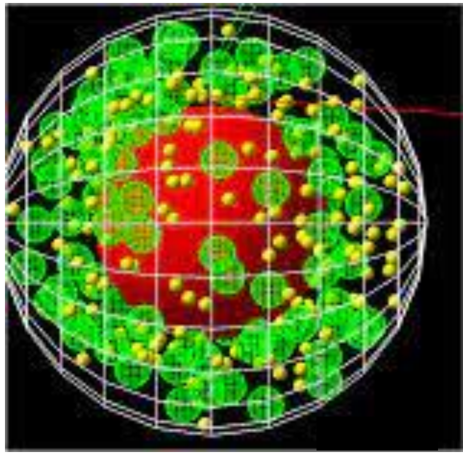


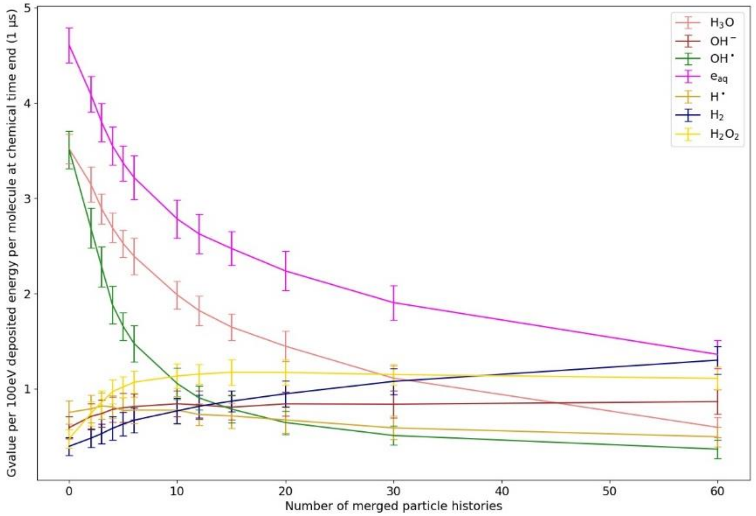
Medical Physics Research at MIT – track structure simulations

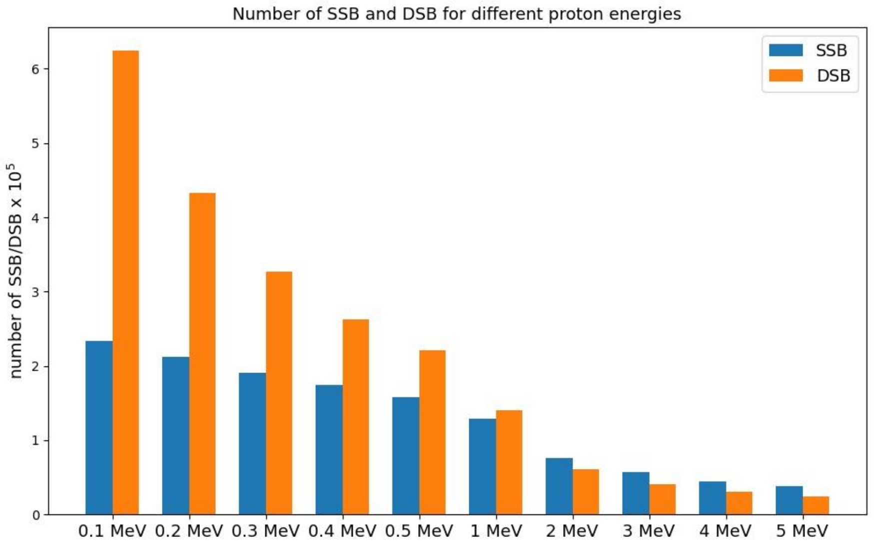
- Geant4-DNA is able to simulate track structures on the nm scale and dose deposition down to several eV
- Simulation of chemical stage as well as biological scale
- Determination of quantity and quality of DNA damage
- Influence of FLASH irradiation
- Simulations will be used to support cell experiments
- Overall goal is optimization of RBE models





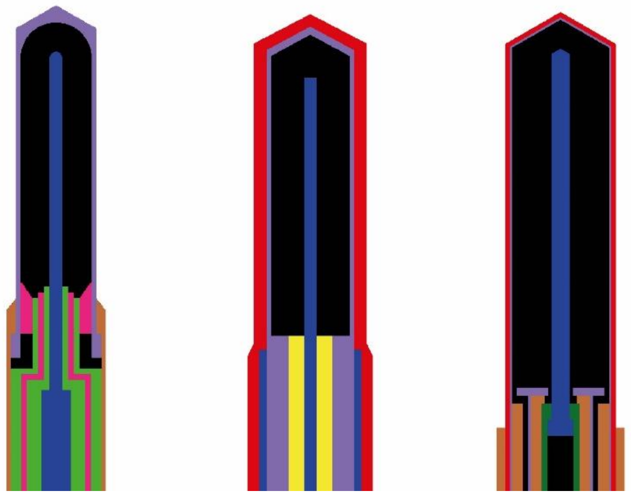


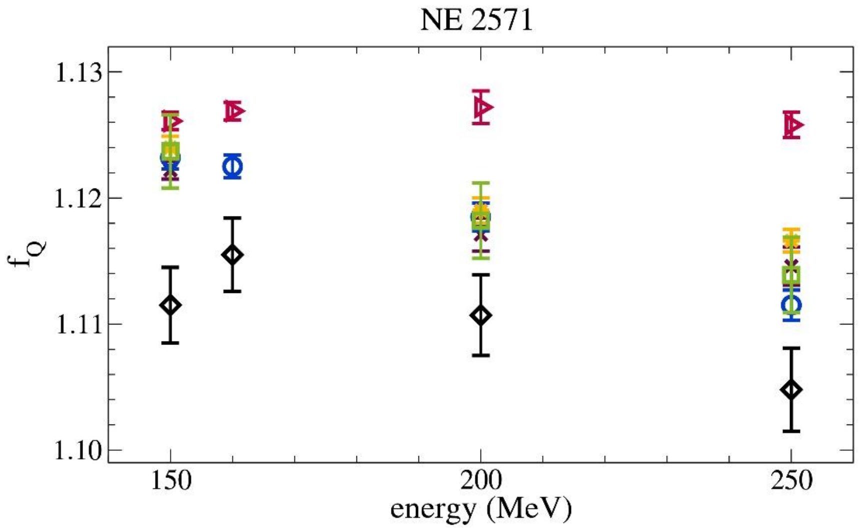


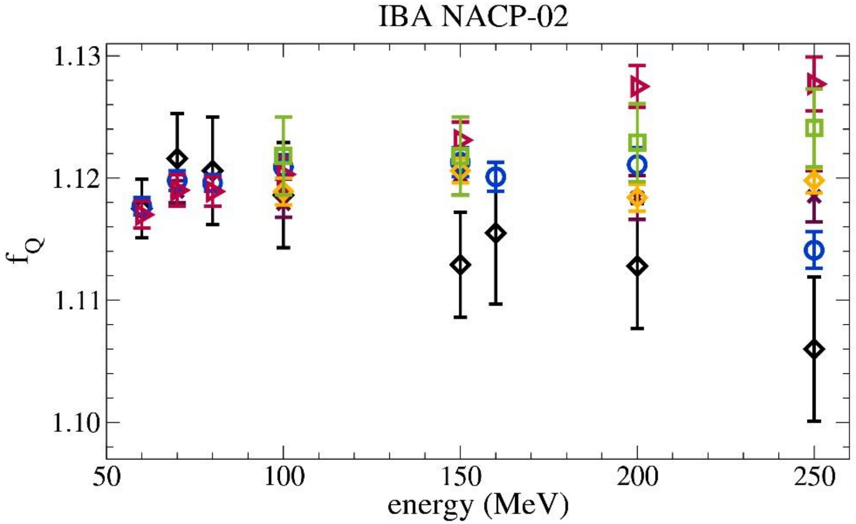


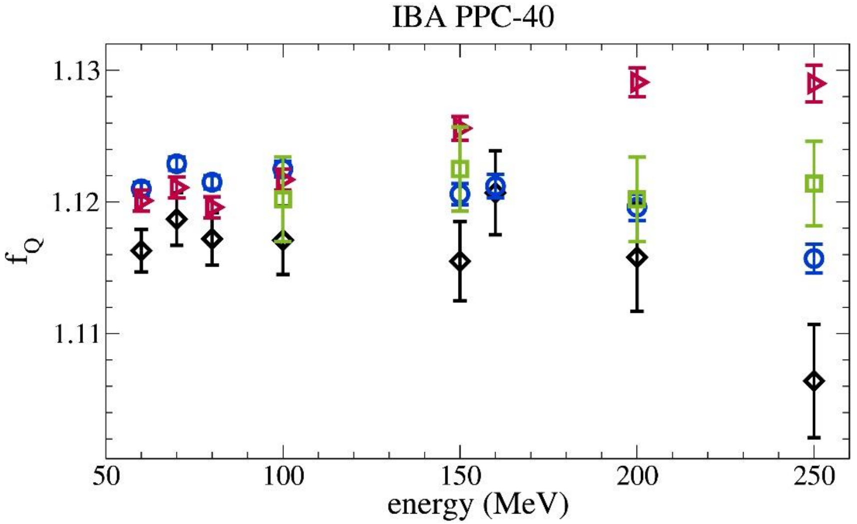
Medical Physics Research at MIT – macroscopic dosimetry

- Modelling of air-filled ionization chambers in FLUKA and Geant4
- Calculation of f_Q and k_Q factors as function of energy
- Update of IAEA TRS-398
- Intercode comparison:
  - Good agreement for low and medium energies
  - Divergence for high energies
- Investigation of role of nuclear interactions



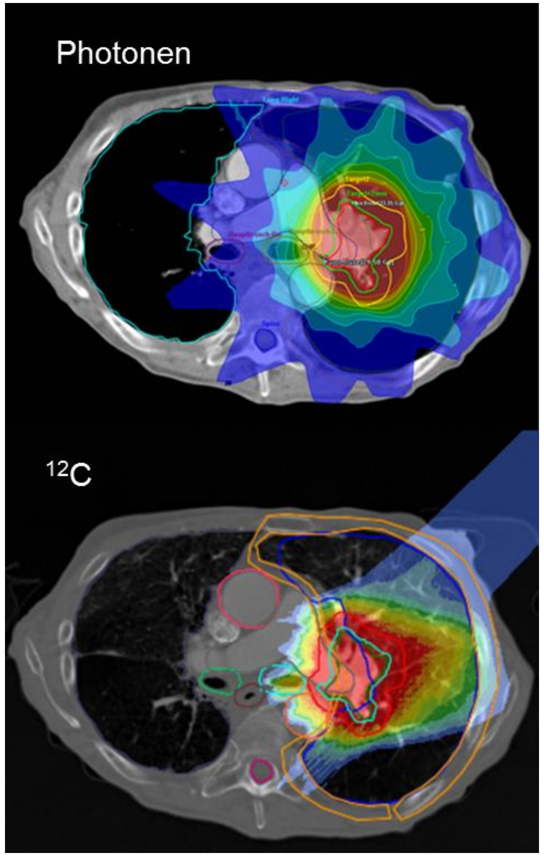


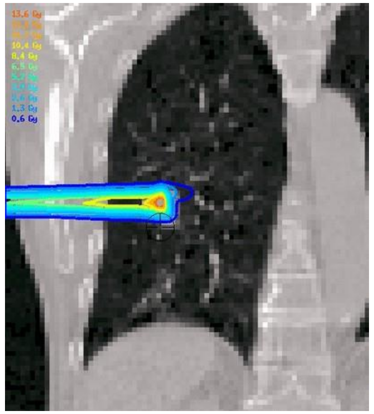




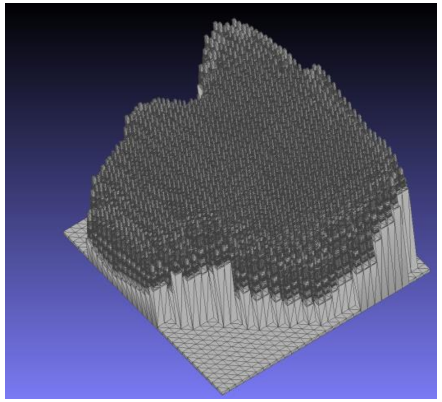
Medical Physics Research at MIT – PT of thoracic tumors

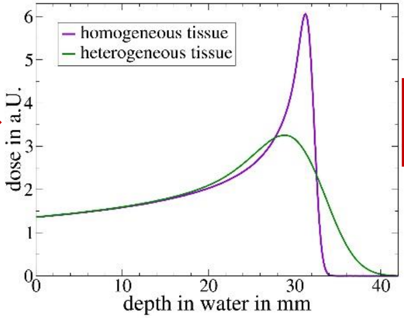
- Particle therapy promising alternative to photon-based radiotherapy for lung cancer patients
    - Conformal dose deposition in tumor and significantly better sparing of normal tissue
    - Higher biological effectiveness for carbon ion
- However: major challenges!
    - Motion
    - Lung modulation effects

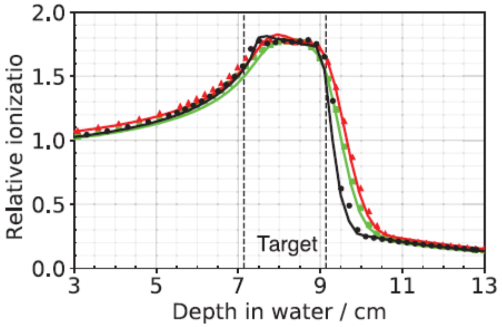




C. Graeff, GSI

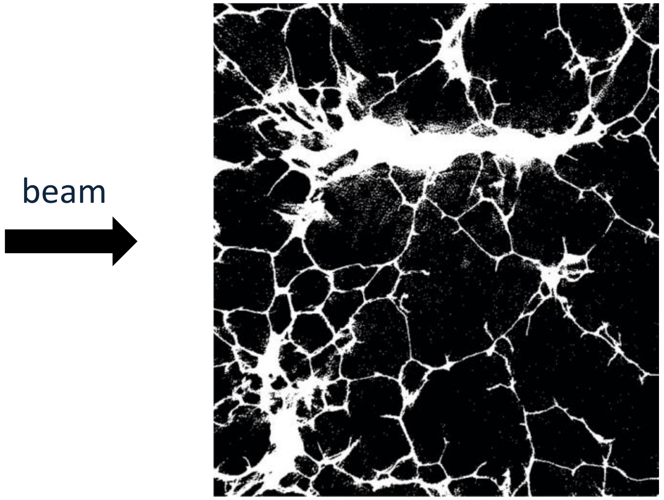


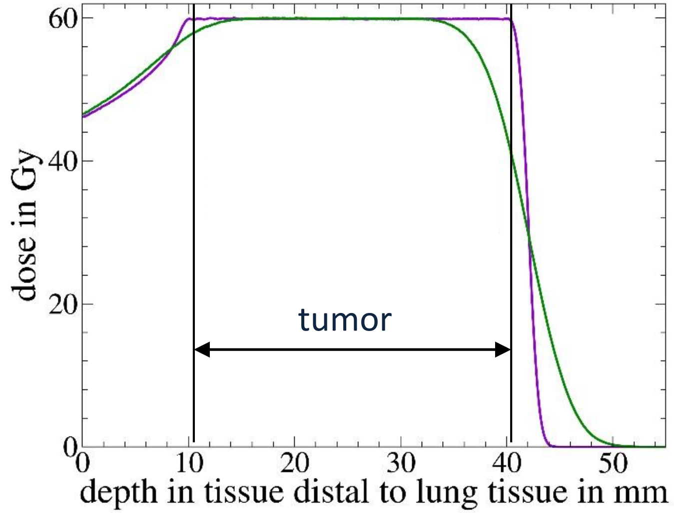


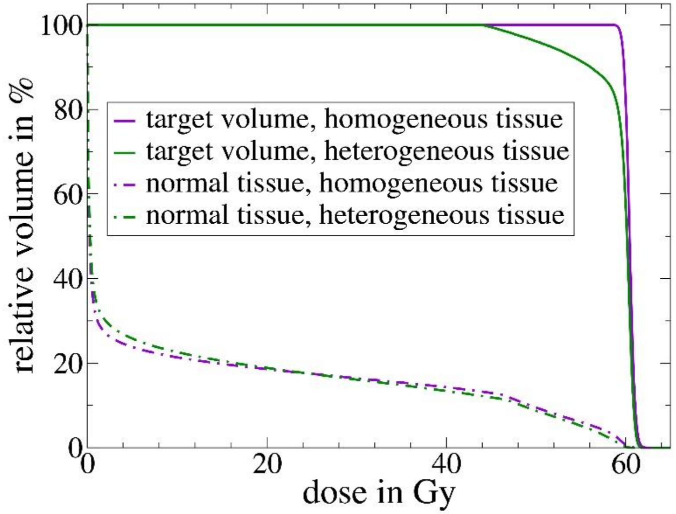


Medical Physics Research at MIT – lung modulation effects

- Heterogeneous structure of lung tissue leads to degradation of Bragg peak
- Potential underdosage of target volume and overdosage of distal normal tissue
- Effect should be considered in treatment planning
- Problem: Structure of lung tissue is not sufficiently resolved in treatment-planning CTs
  - More homogeneous
  - Consideration of effects hardly possible

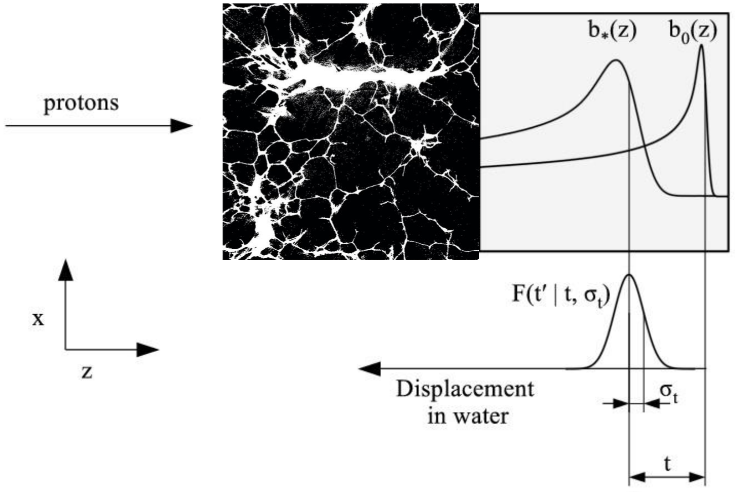






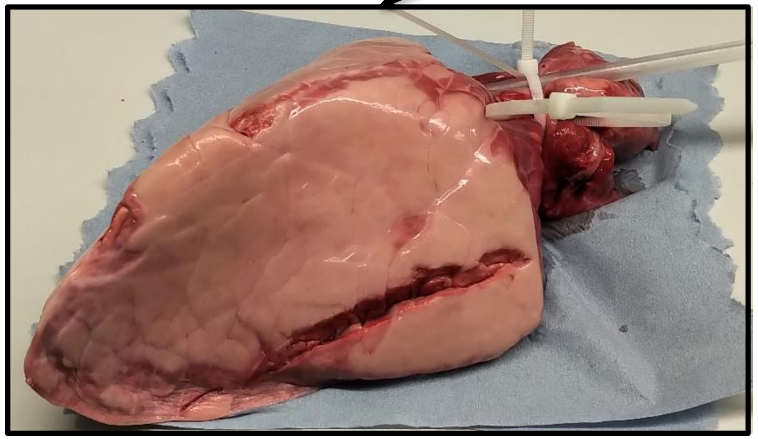
Medical Physics Research at MIT – lung modulation effects

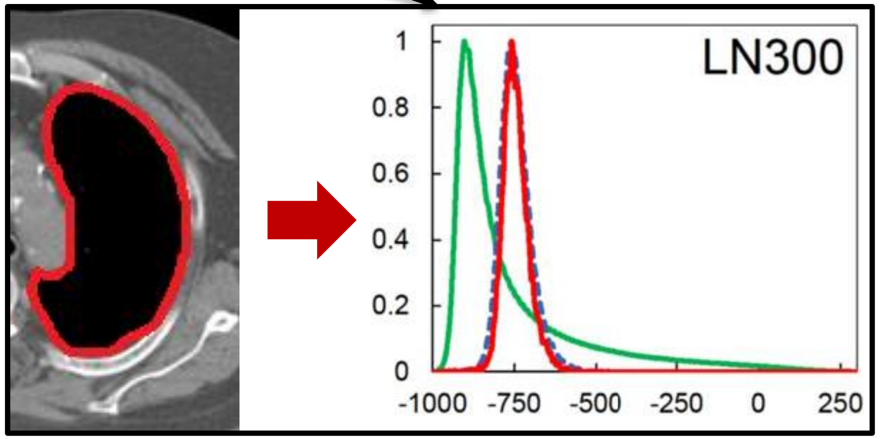
- Mathematical description of Bragg peak degradation by convolution with normal distribution
- Definition of material characteristics **modulation power** P_{mod}
- Modulation power can be determined experimentally
    - Applicability for human lung tissue?
- Estimation of modulation power on basis of clinical CT-images with the help of a histogram analysis



$$b_*(z) = (F \times b_0)(z) = $$
$$= \int_{-\infty}^{\infty} F(t'|t,\sigma_t)\, b_0(z+t')\, dt'$$

$$P_{\text{mod}} \equiv \frac{\sigma_t^2}{t}$$

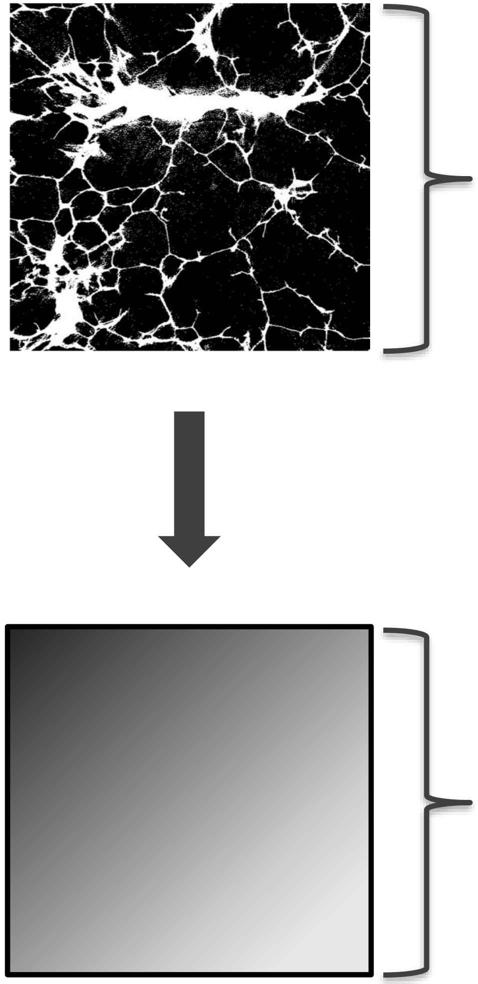




Medical Physics Research at MIT – lung modulation effects

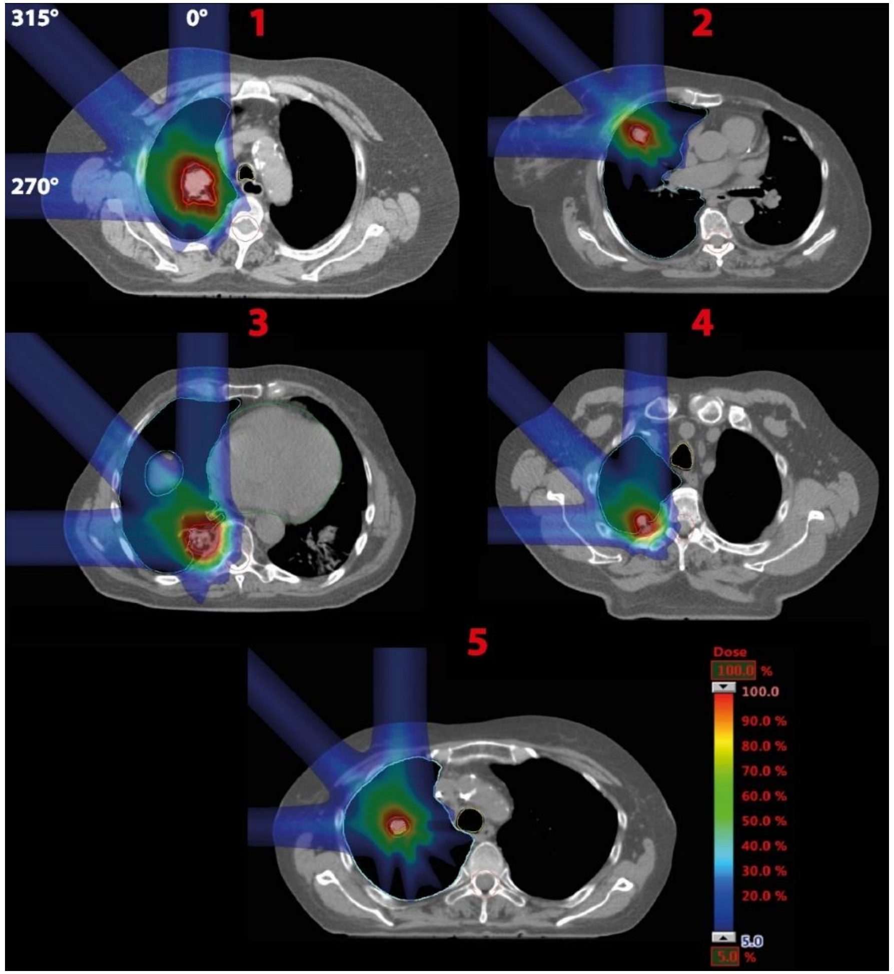
MIT Marburger Ionenstrahl-Therapiezentrum

- Monte-Carlo based solution to reproduce lung modulation effects on clinical CT-images
- Modulation of physical density of lung voxels
- Investigation of dose uncertainties for clinical treatment plan
- Different tumor volumes, positions within the lung, and irradiation strategies



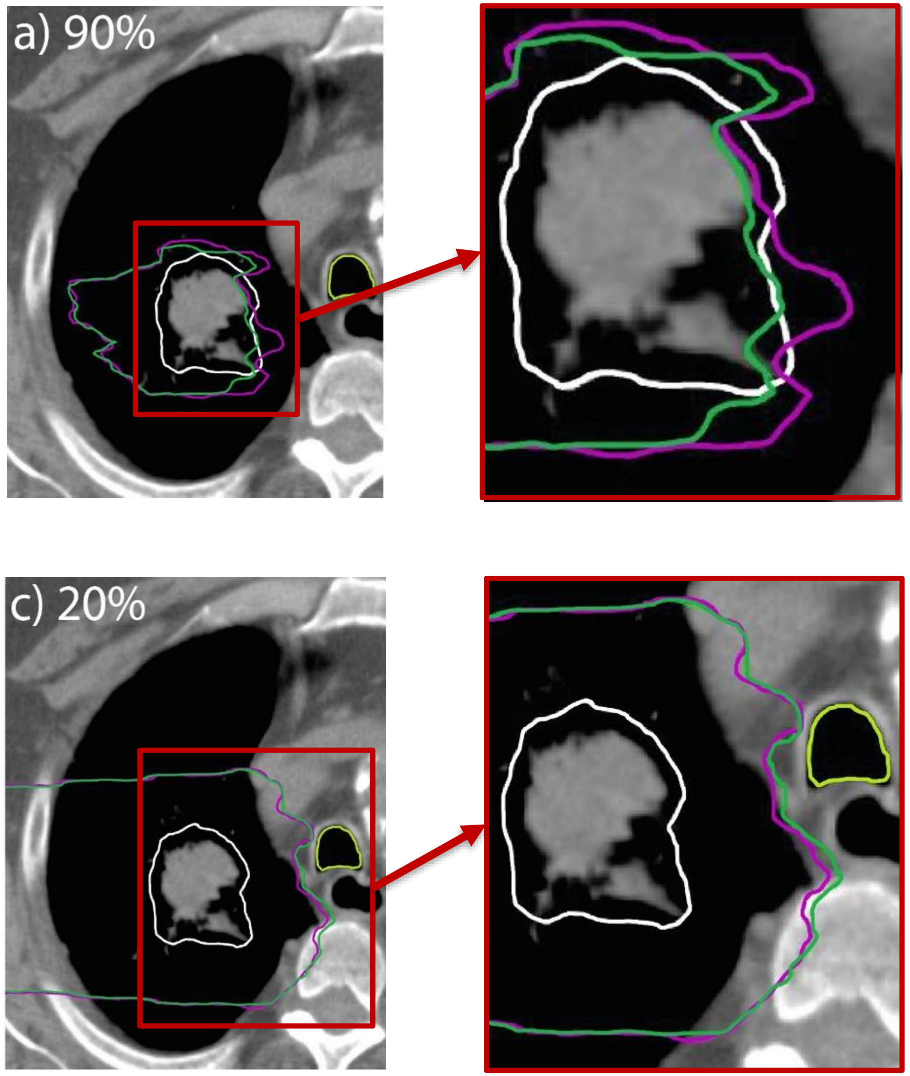
- Binary density distribution
- Heterogeneous fine structure not depicted in CT-images

- Rougher structure (CT-voxel)
- Modulation of mass density



Medical Physics Research at MIT – lung modulation effects

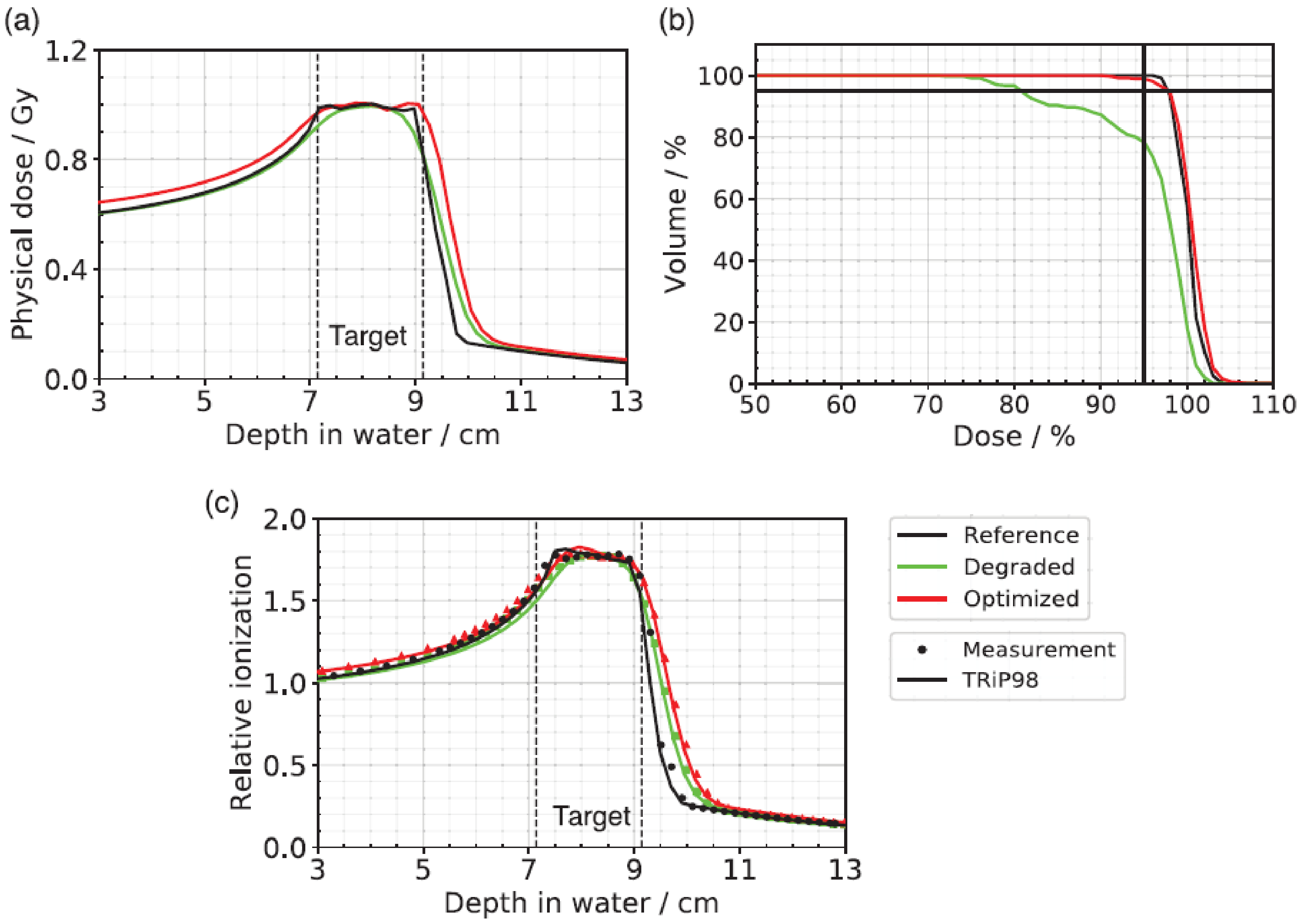
- Lung modulation effects lead to smaller region of high dose
    - Range uncertainties of up to 10 mm
- The region of low dose is smaller and reaches farther
    - Range uncertainties of up to 5 mm
- Underdosage of CTV up to -5% for protons
- Effects significantly more pronounced for carbon ions



Patient	Underdosage in terms of average dose in CTV
1	**-2.1%**
2	**-3.1%**
3	**-1.8%**
4	**-2.2%**
5	**-4.9%**

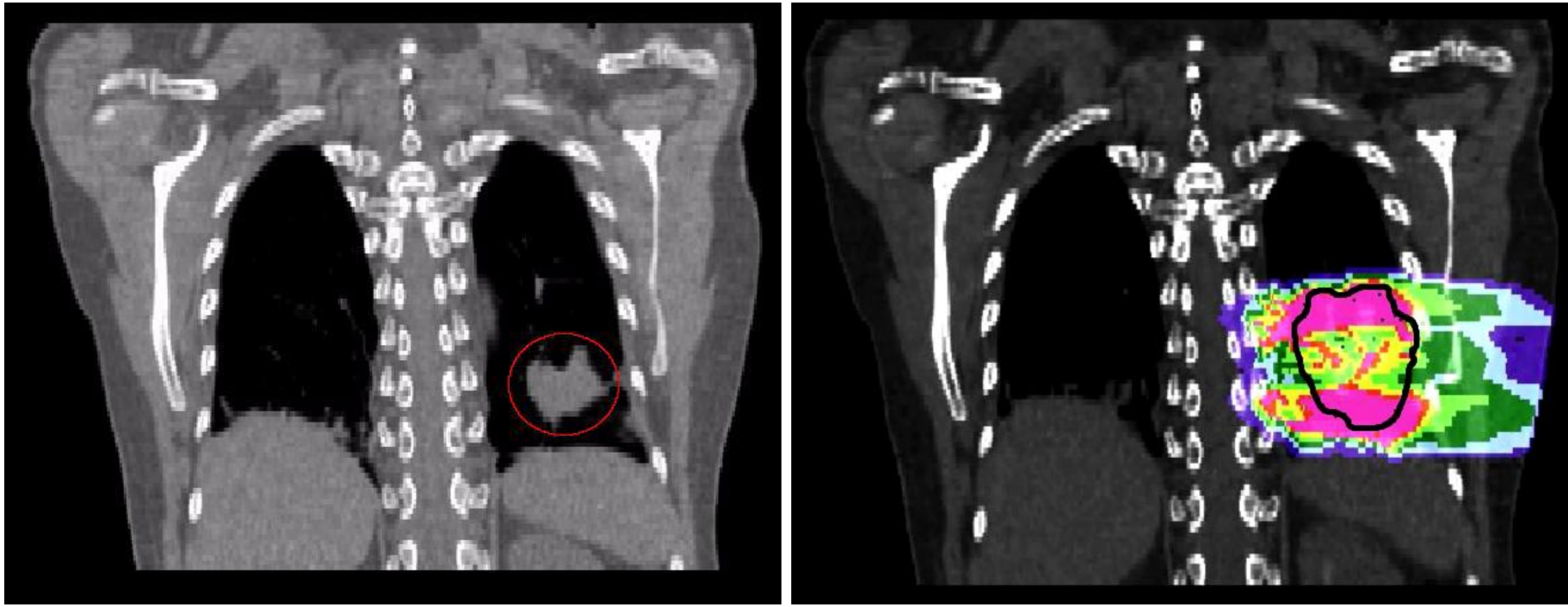
Medical Physics Research at MIT – lung modulation effects

- Consideration of lung modulation effects in treatment planning
- Degradation of base data depth dose curves for dose calculation and optimization
    - Reference plan optimized without consideration of lung modulation effects
    - Lung modulation effects lead to underdosage of target volume
    - Improved optimization reduces dose uncertainties to <0.5%



Medical Physics Research at MIT – Range Modulator

- Background: Particle therapy of lung cancer patients
- For active scanning interference between tumor motion and movement of the particle beam
  → Interplay effects
- Potential hot and cold spots negatively influencing therapy outcome



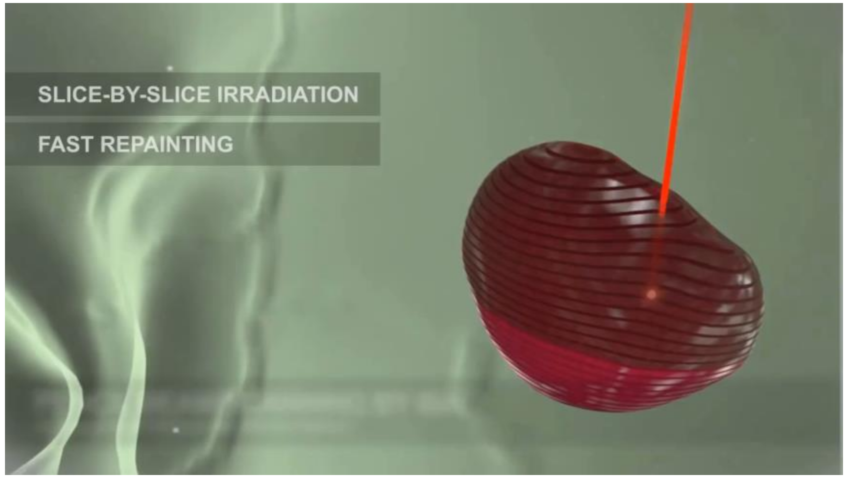
C. Graeff, GSI

Can we achieve a sufficient reduction in irradiation time enabling an irradiation under breath hold?

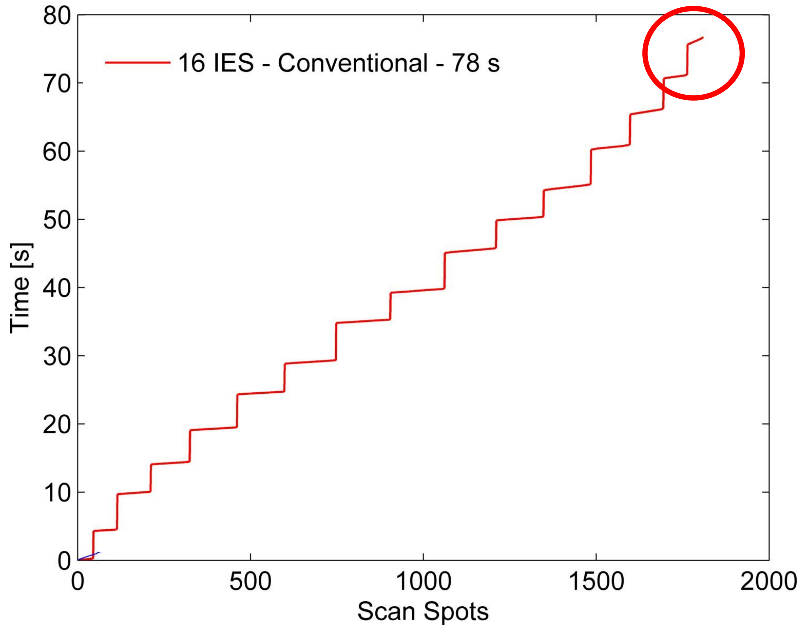
Medical Physics Research at MIT – Range Modulator

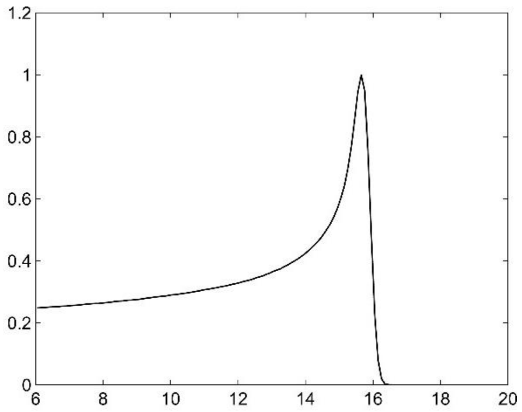
MIT Marburger Ionenstrahl-Therapiezentrum

- For synchrotron-based facilities an acceleration of particles is necessary for each iso-energy layer that is being irradiated
- Acceleration takes time in the order of seconds
- For an exemplary treatment plan with 16 iso-energy layers, the total irradiation time is 78 seconds
- Is there a possibility to enlarge high-dose region of depth dose curve?

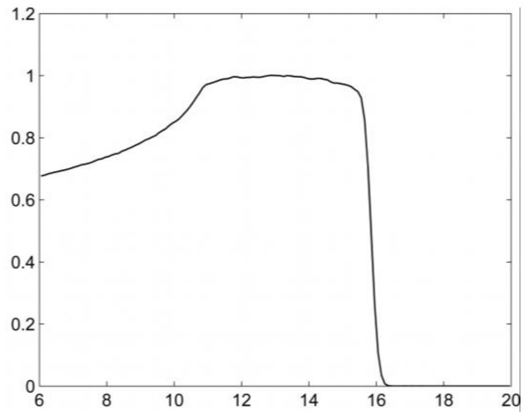


With courtesy of IBA



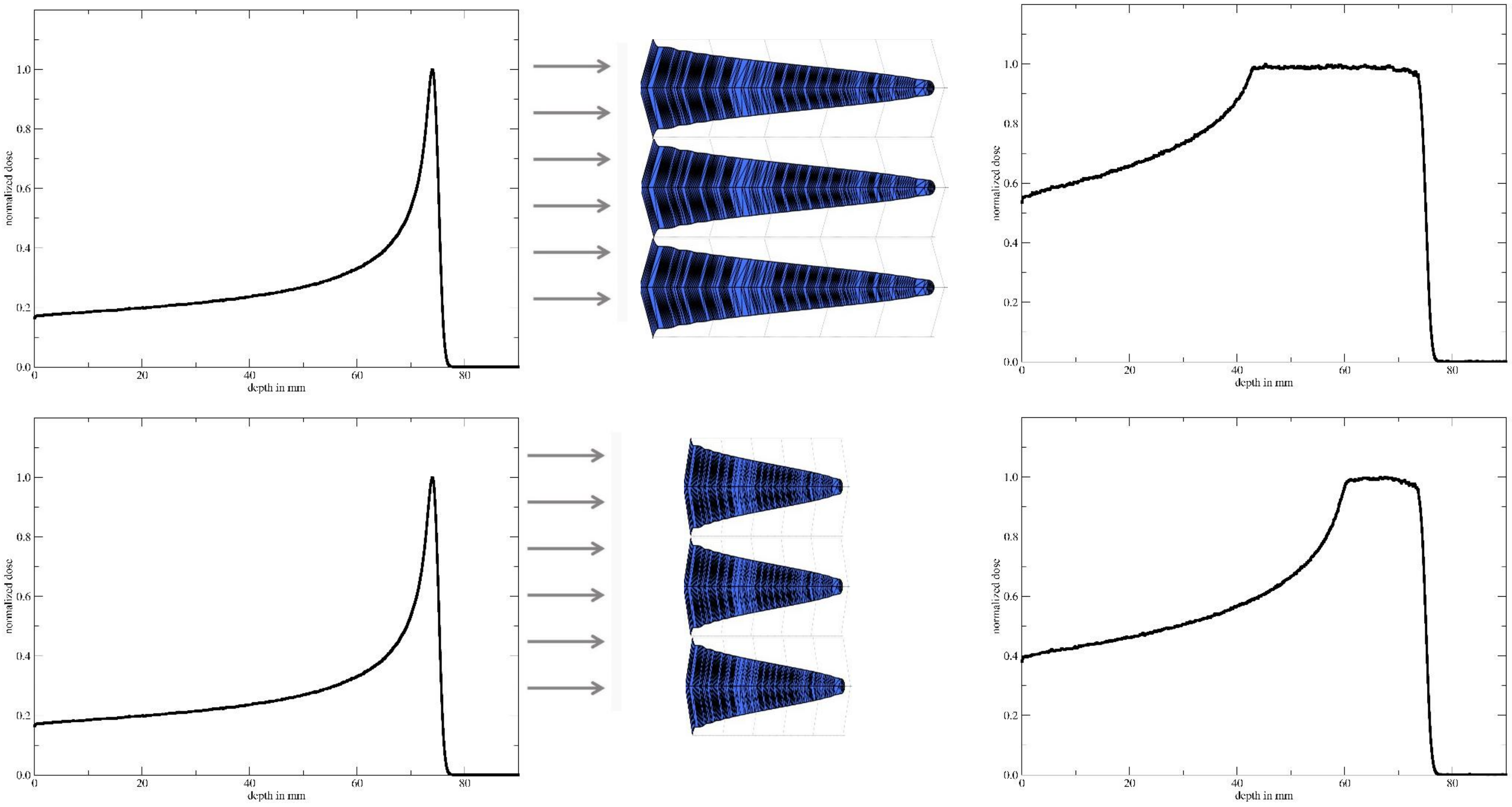


?



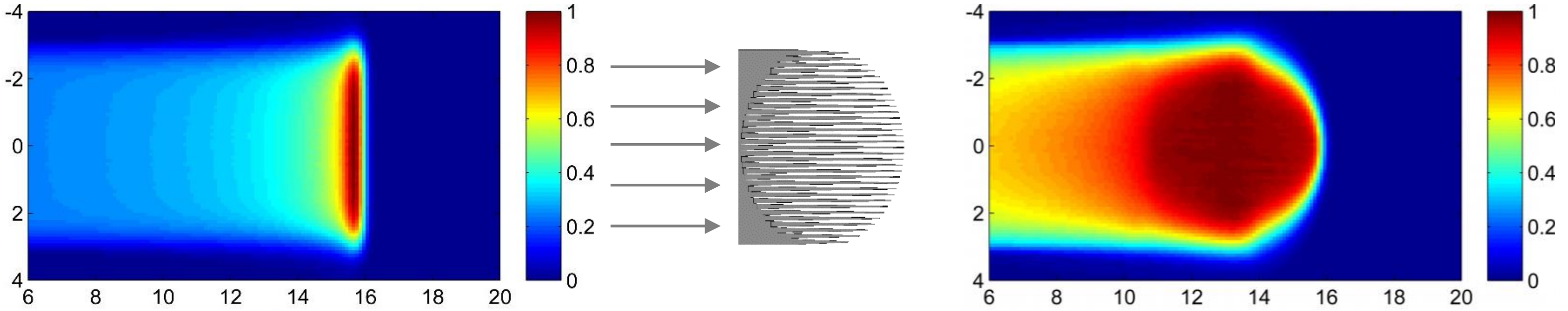
Medical Physics Research at MIT – Range Modulator

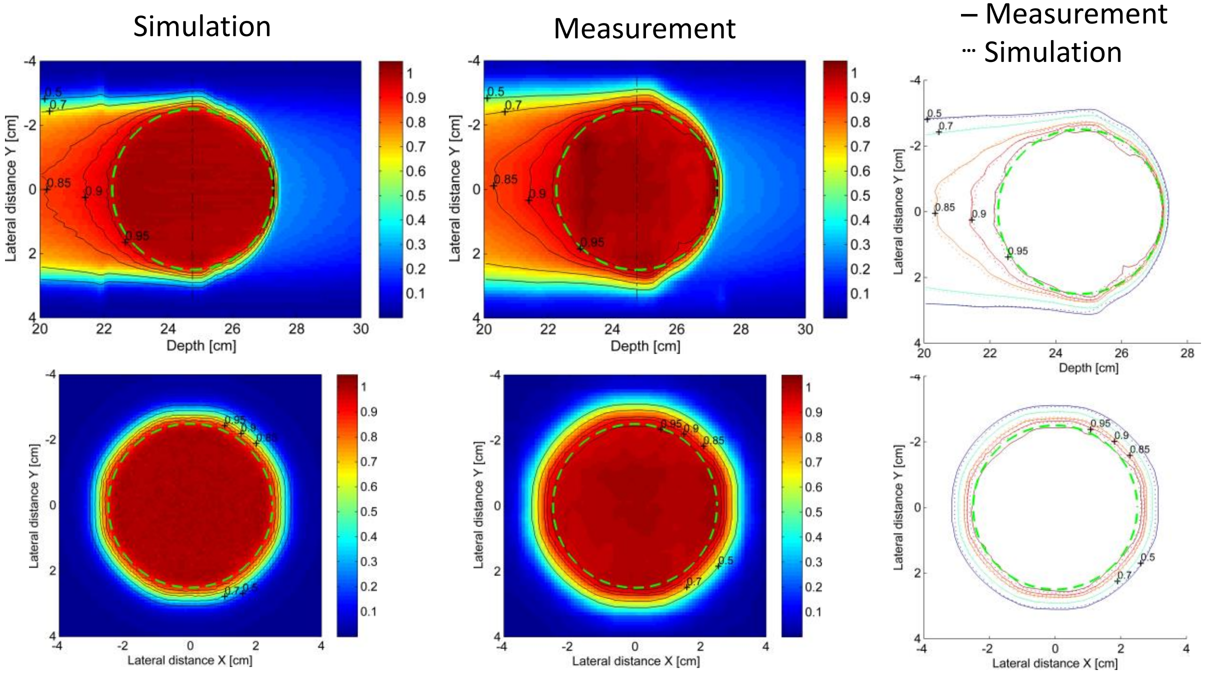
- Approach: Use passive Range Modulator similar to Ripple Filter to enlarge Bragg Peak
- Range Modulator consists of Pins
- Energy loss and hence range depend on the particle's trajectory through the pin
- Length of Pin defines width of Spread-Out Bragg Peak
- Only 1 energy needed to apply Spread-Out Bragg Peak

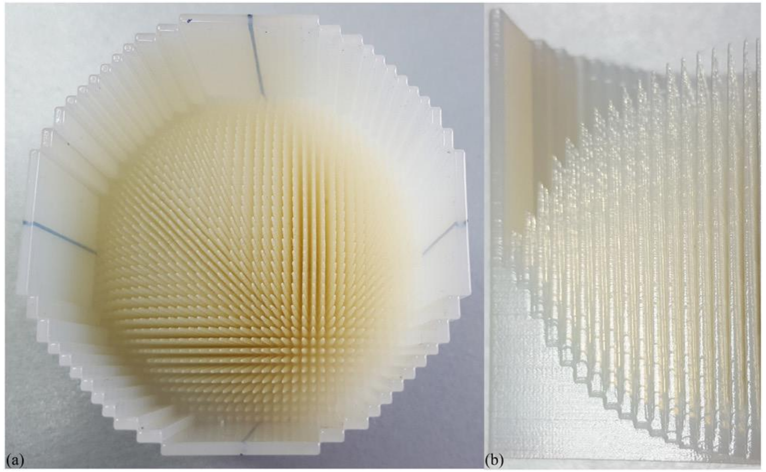


Medical Physics Research at MIT – Range Modulator

- By arranging different pins, 3D dose distributions can be created
- 3D Range Modulators can easily be 3d-printed
- Verification with measurements at MIT

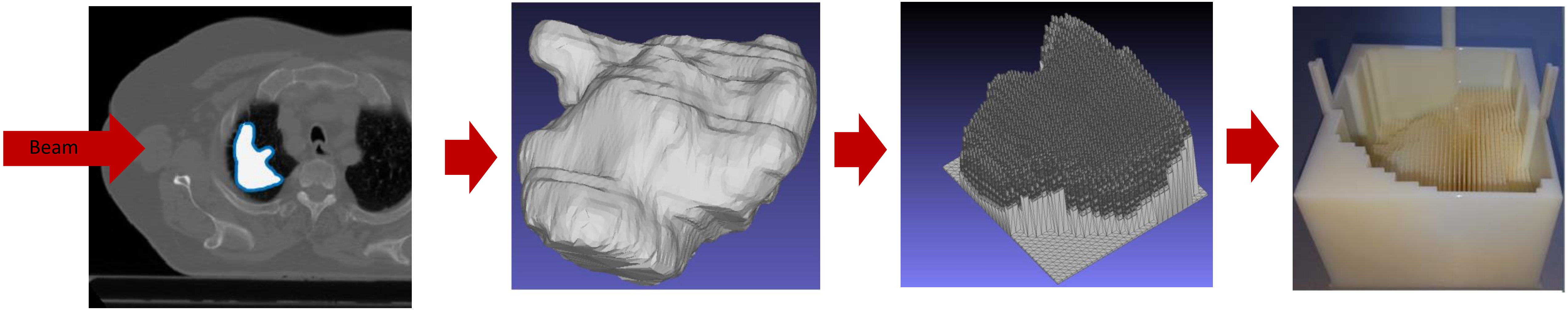


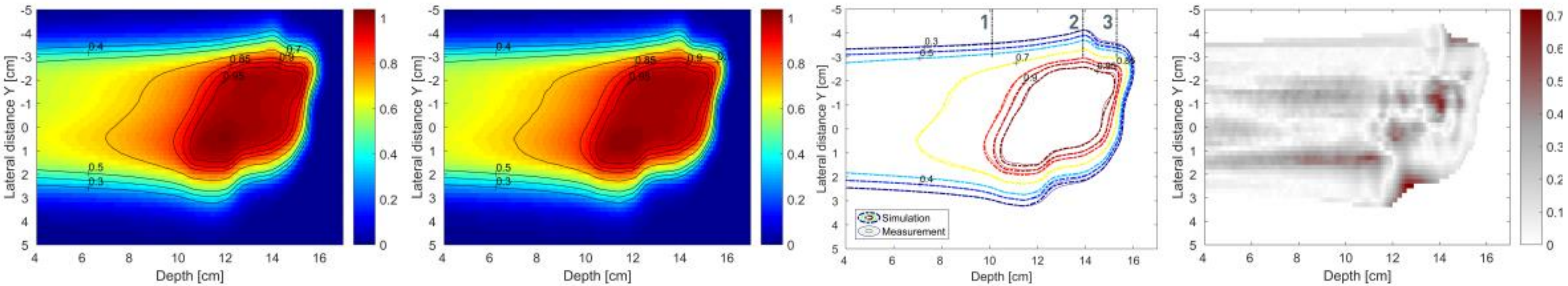




Medical Physics Research at MIT – Range Modulator

- 3D Range Modulator for complex tumor geometries designed patient individually

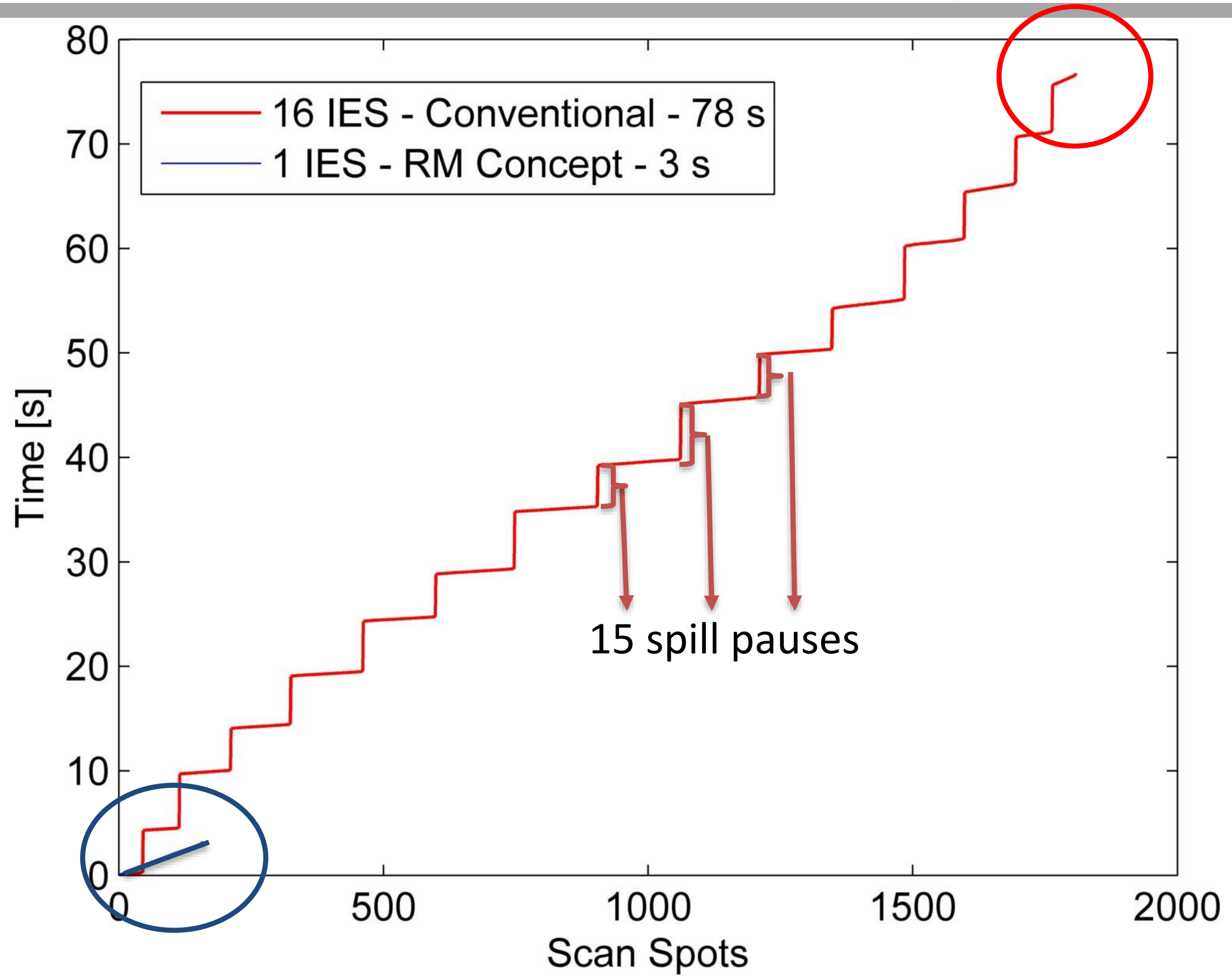




Medical Physics Research at MIT – Range Modulator

- Reduction in treatment time due to 3D Range Modulator:
  - 78 seconds without RM
  - 3 seconds with RM

Pencil Beam Scanning	3D Range modulator
Very good dose conformity	Dose conformity comparable to PBS
Slow due to energy switching	Only one energy needed
Interplay effects in moving target	Treatment time in order of seconds



3D Range Modulator also essential for FLASH irradiation with active scanning and "slow" energy selection!

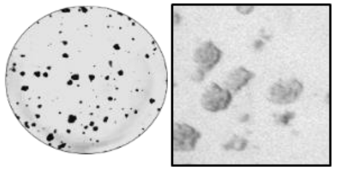
Radiobiology projects@MIT

Radiobiology – Projects

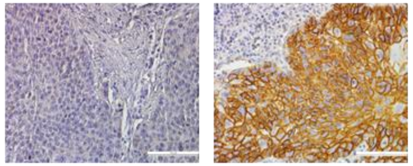
Ulrike Schötz

Photon and carbon ion irradiation

Head and neck squamous cell carcinoma (HNSCC)



In vitro (2D, 3D)



Tumor specimen

Parameter:

Molecular mechanisms of radioresistance

HPV infection

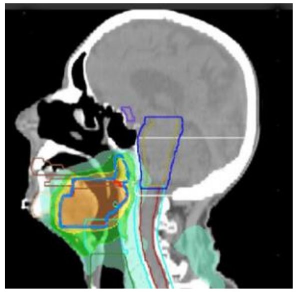
DNA damage response

Senescence/ Inflammation

DNA repair

CXCR2, IL1 **CD44v6** **Replication**

HNSCC **NSCLC**



Radioresistance

Mechanisms

Targeting

Biomarker

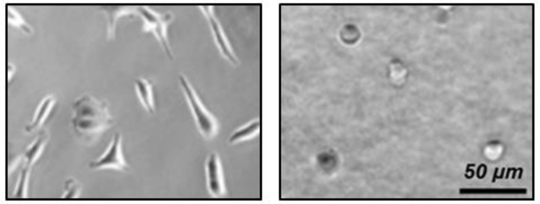
Particle Irradiation

Mechanisms

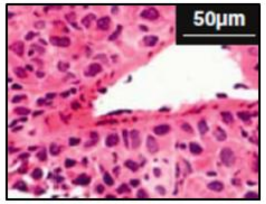
Improved treatment response

Photon and carbon ion irradiation

Non-small cell lung cancer (NSCLC)



in vitro (2D, 3D)



in vivo

Parameter:

Molecular mechanisms of radioresistance

Hypoxia

Pulmonary infection

MAPK **AKT**

HIF **SCF/c-Kit** **TLR-4/CREB**

Pathogenesis of head and neck squamous cell carcinoma (HNSCC)

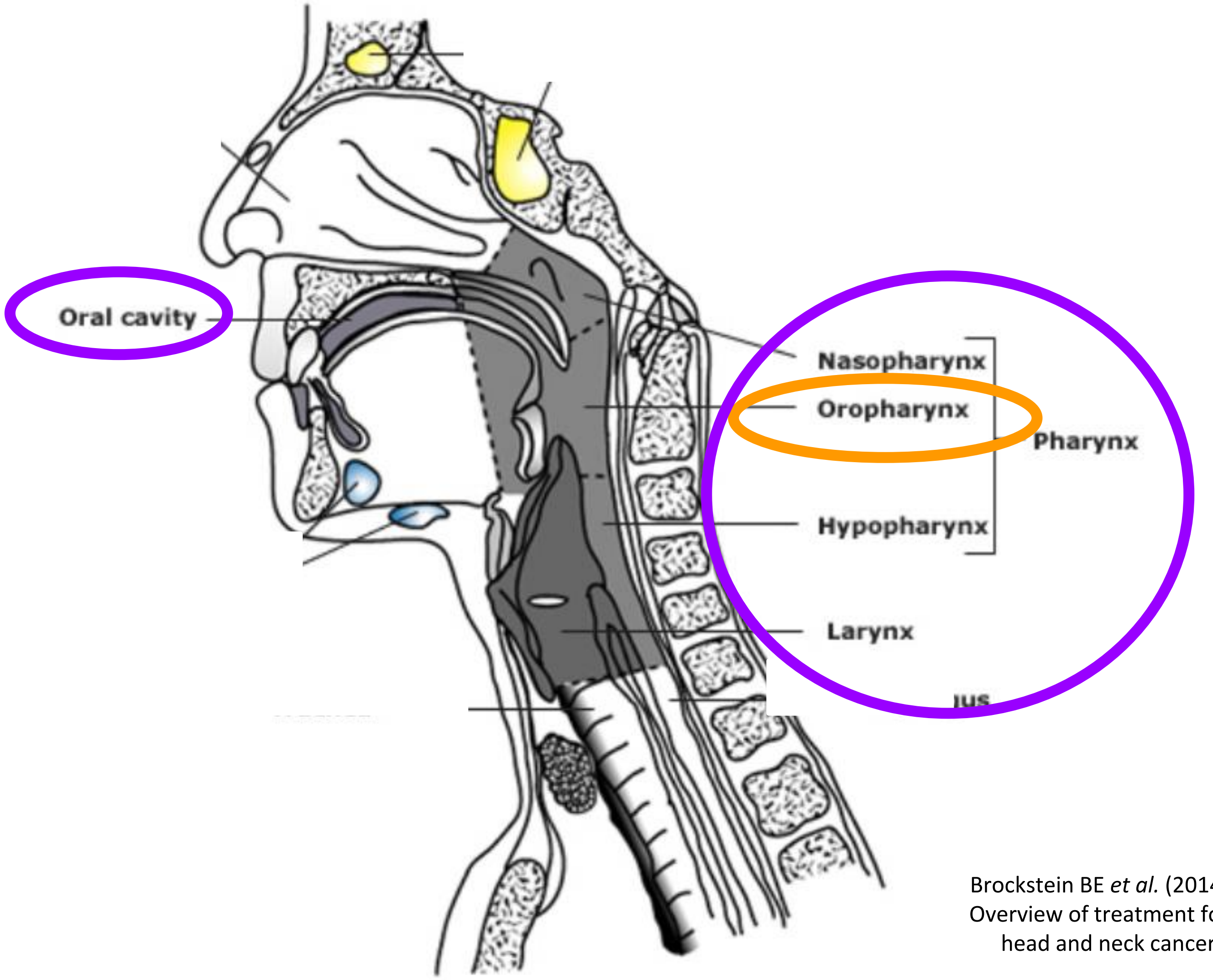
Incidence:

Male: 6. most prominent
Tumor disease
Female: 15.

Risk factors:

→ Smoking / alcohol (HPV-negative)

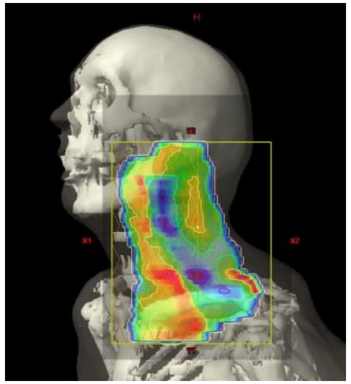
→ HPV-16 (Oropharynx) (HPV-positiv)
→ Increasing incidence (app. 30%)



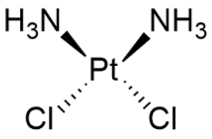
Brockstein BE *et al.* (2014)
Overview of treatment for
head and neck cancer.)

First line therapy, curative intention

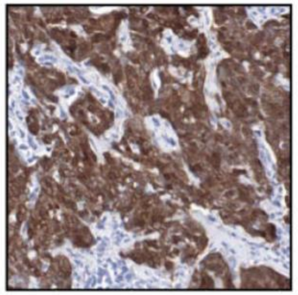
- **Surgery**
  - complete resection (R0)



- **Radiotherapy**
  - 60 Gy to 74 Gy
  - Fractions, 6-8 weeks
- **Concomitant chemotherapy**
  - Common: Cisplatin / 5-FU



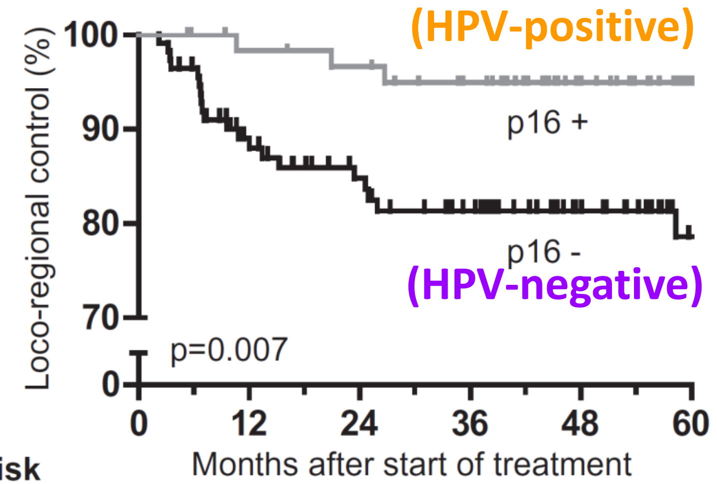
Cisplatin



- **Pathology**
  - p16-status (histology) is surrogate marker for HPV-infection
  - prognostic marker
  - No influence on therapy

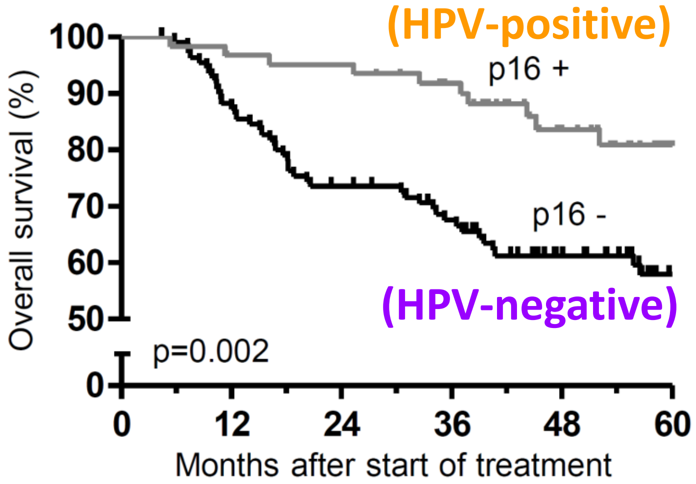
Standard Treatment in Germany: DKTK-HNSCC

Lokal tumor control



Patients at risk						
negative	112	88	74	63	46	27
positive	63	59	57	49	33	17

Overall Survival



112	96	78	67	48	28
63	59	58	50	34	17

Optimization of therapy is needed!!

- **HPV-negative**:
  - in 20% of cases no sufficient
- **HPV-positive:**
  - Good

- **HPV-negative**:
  - Overall Survival 60%
- **HPV-positive:**
  - Overall Survival 80%

Linge and Schötz et al., Radiotherapy and Oncology, 127 (2018)

Particle irradiation is an alternative treatment option

- **Standard therapy**
  - Maximum Dose is reached already
  - No escalation feasible due to high normal tissue complications
  - Therapy sensitizer / current optional therapy concepts are not superior to standard therapy

- **HPV negative**
  - Low survival rate requires therapy optimization
  - Strong side effects needs to be reduced

- **HPV positive**
  - Deescalation concepts are discussed to reduce normal tissue complications

Particle irradiation of HPV-positive and HPV-negative HNSCC

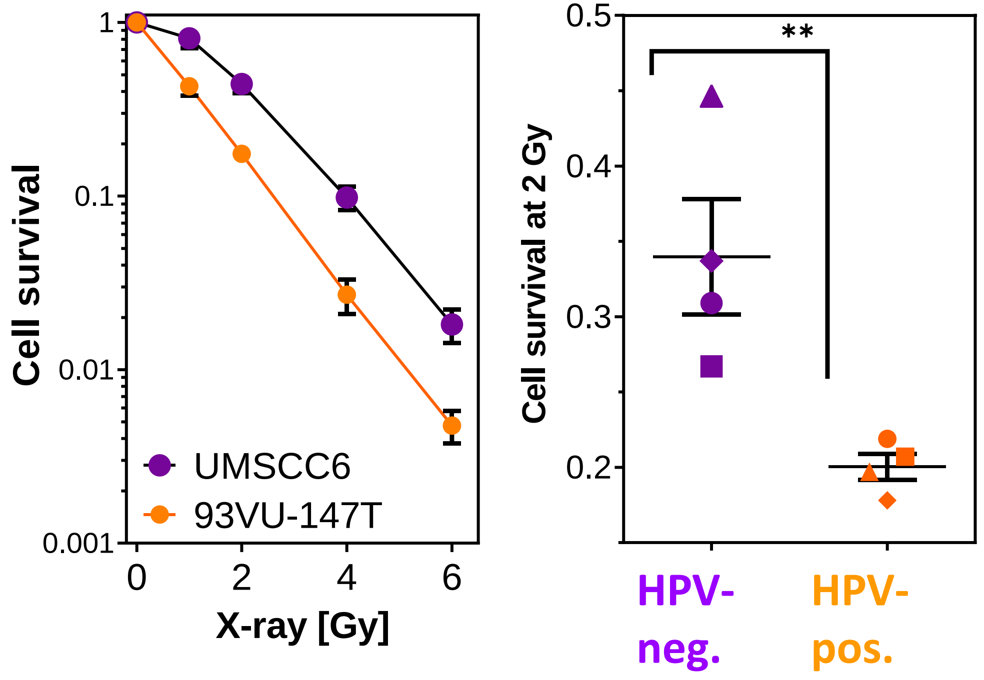
We have to understand, why

HPV-positive show good response towards photon therapy, whereas HPV-negative often do not.

We want to clarify, How the two entities behave towards particle therapy with Carbon ions (12C).

HPV-positive cells show a higher radiosensitivity towards photon irradiation than HPV-negative do

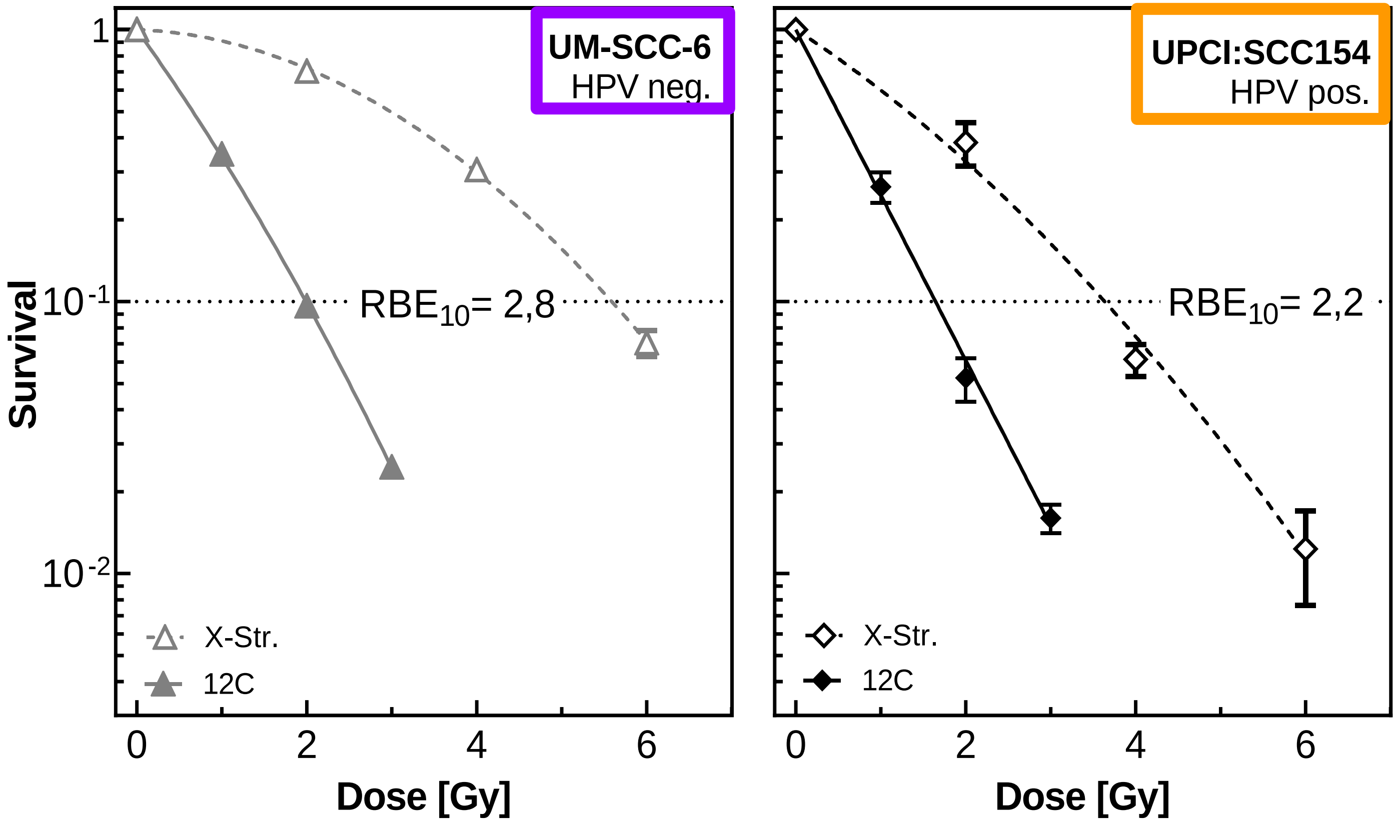
In vitro:



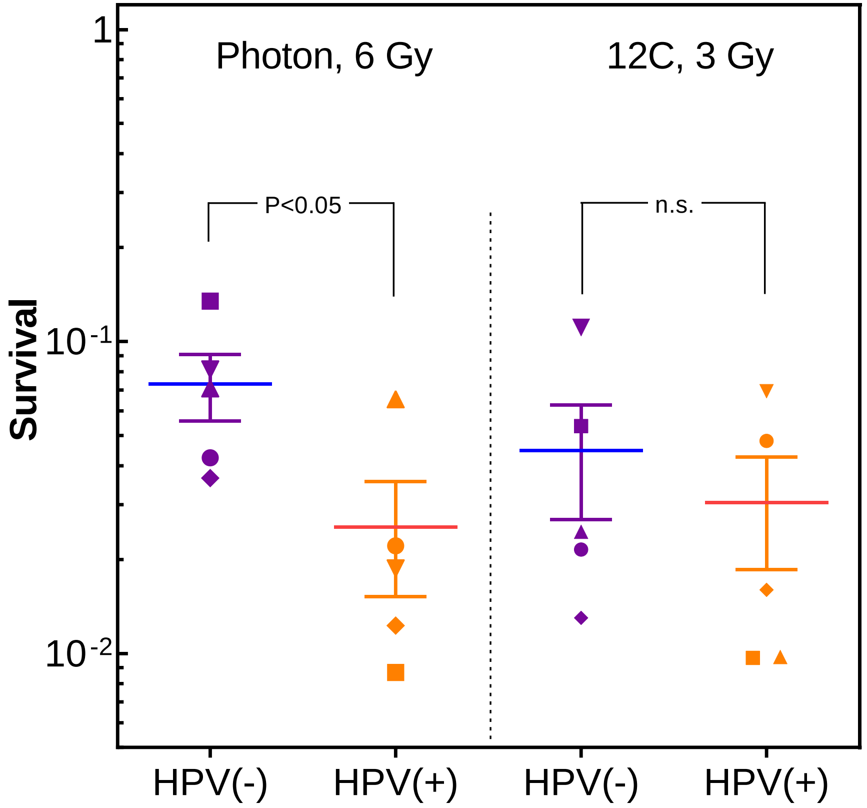
Arenz et al., Strahlenther Onkol, 190 (2014)

Radiosensitivity after Carbon Ion Therapy

HPV-positive show a lower RBE than HPV-negative



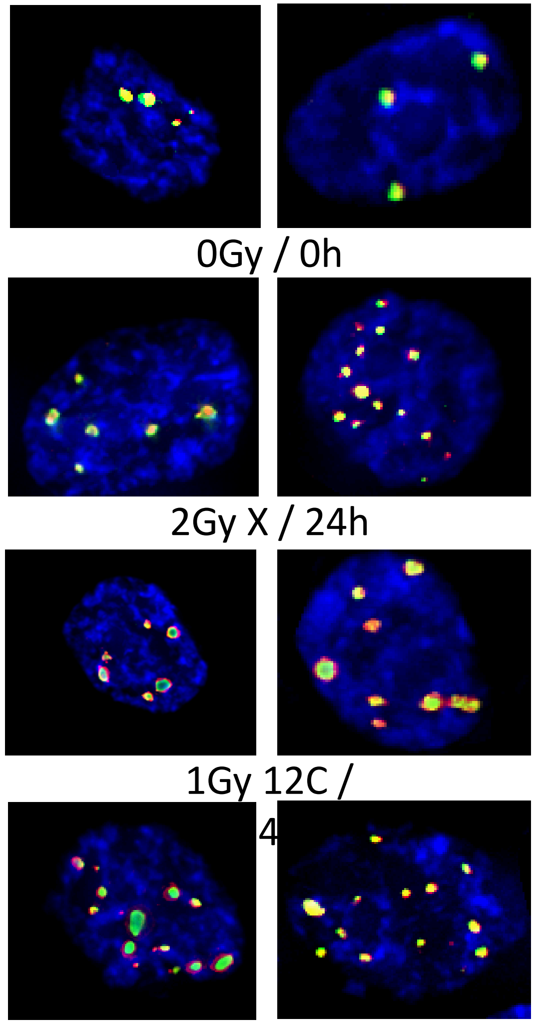
The difference in radioresistance observed after photons, decreases after 12C.



DNA DSB repair after Carbon Ion Therapy

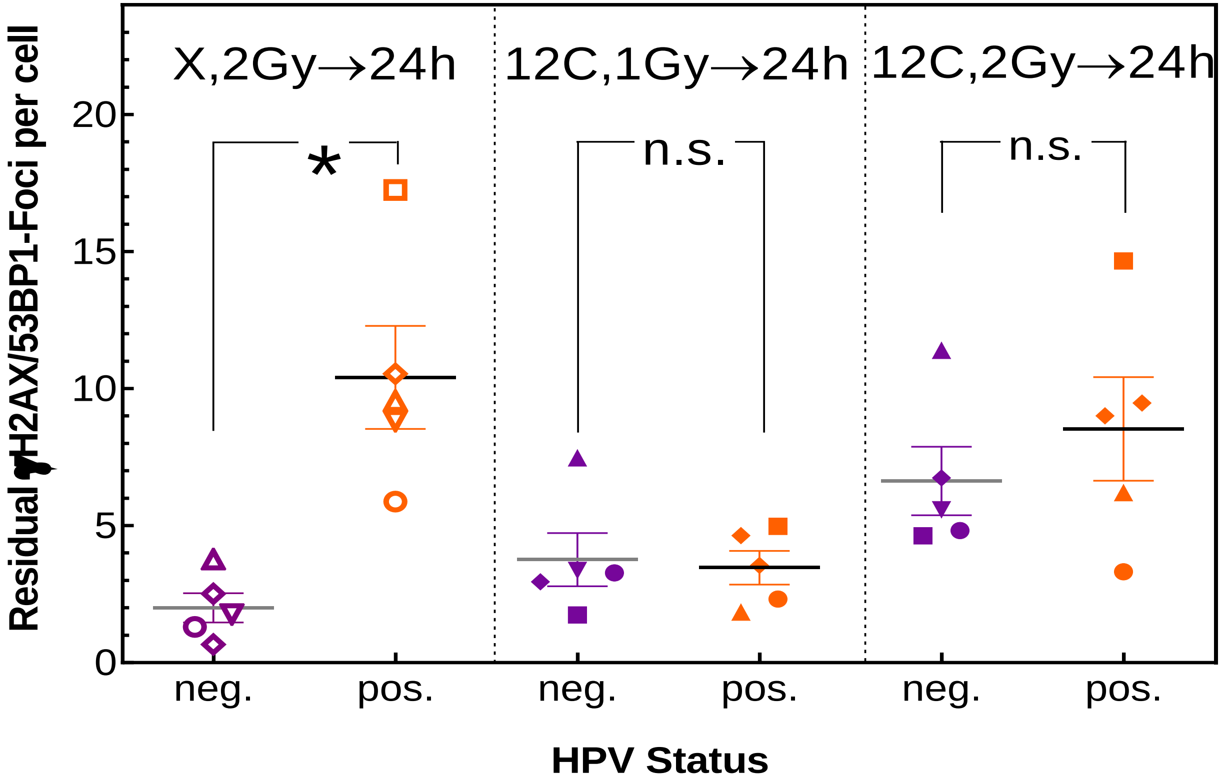
MIT Marburger Ionenstrahl-Therapiezentrum

HPV-negative HPV-positive



Photons: significant difference in the amount of residual foci

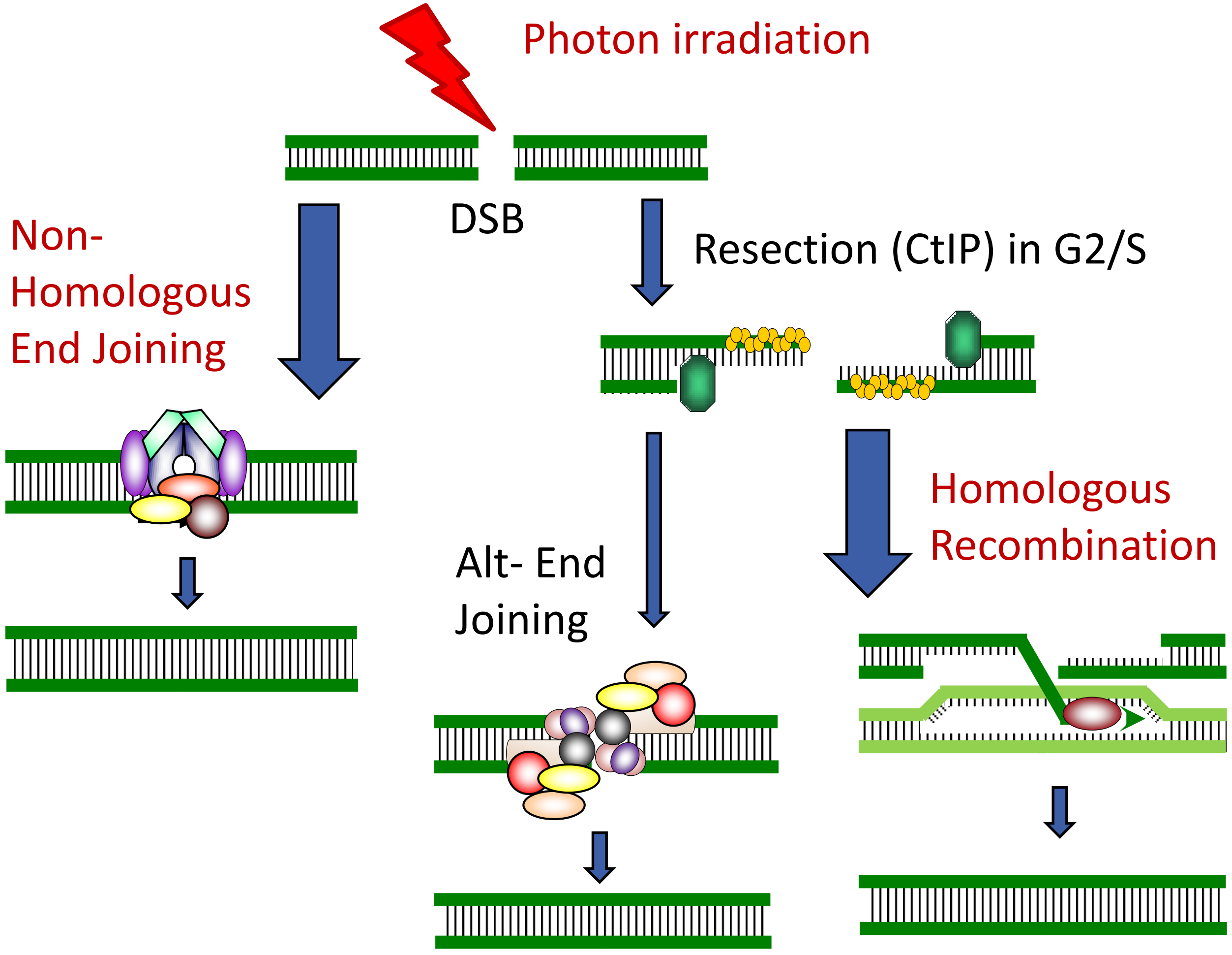
12C: no significant difference between **HPV-positive** **and** **HPV-negative** HNSCC cells



HPV-positive cells harbour a defect in homologous recombination (HR)

In contrast to photon irradiation, **after 12C** irradiation there is **no significant difference** in radiosensitivity and DSB repair capacity between **HPV-positive** and **HPV-negative** **HNSCC cells**

How can the apparent higher radioresistance of HPV-positive cells towards 12C be explained?

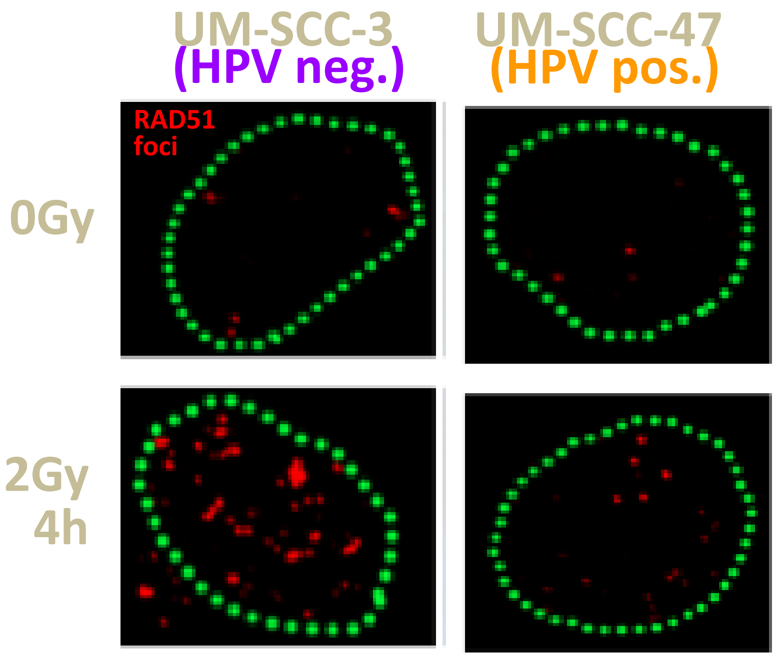


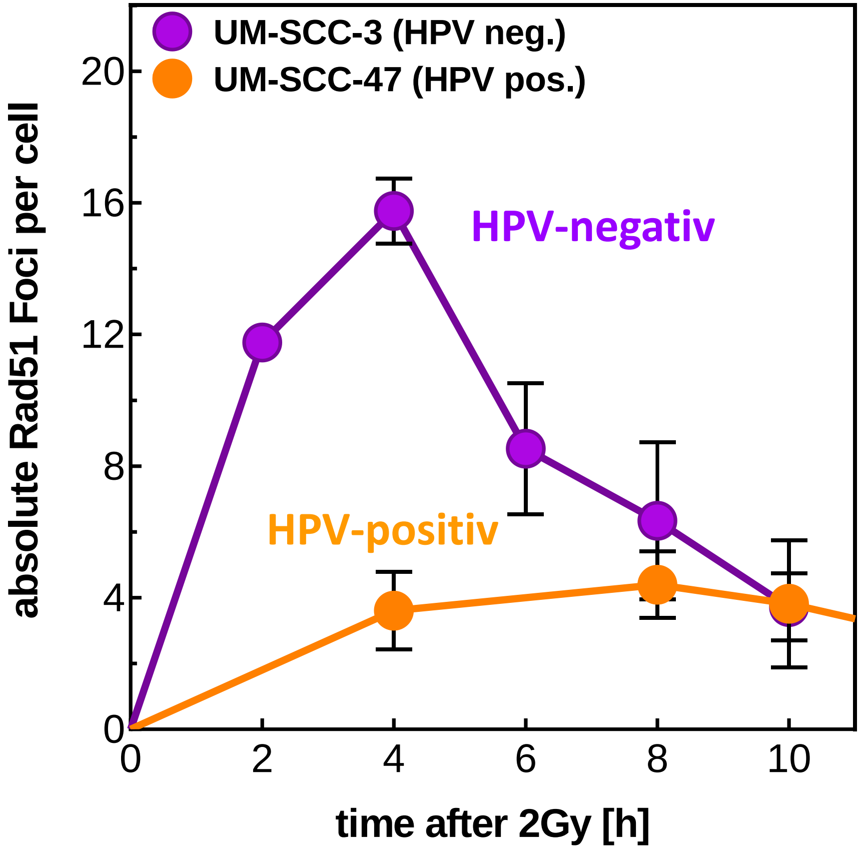
Dikomey et al. (2016), Elsevier

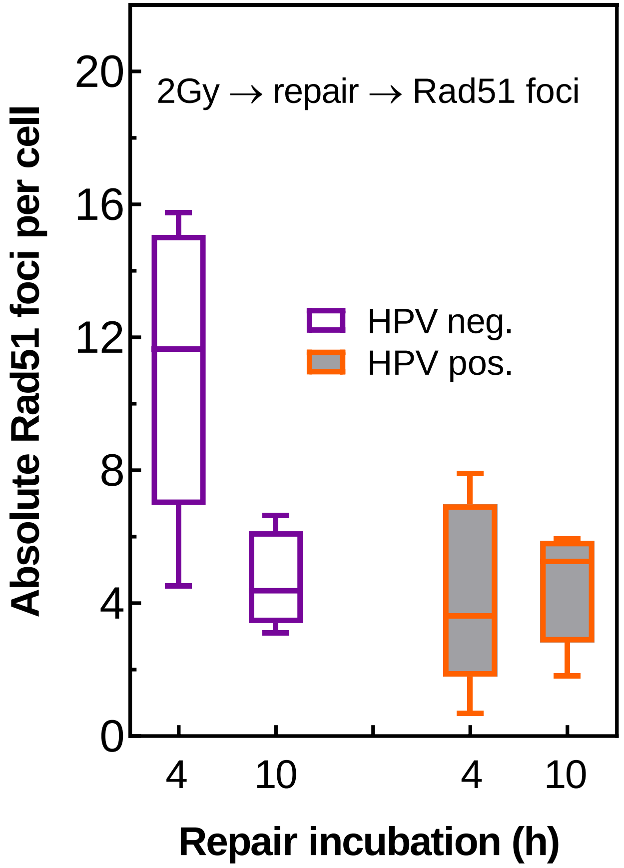
Marburg Ion-Beam Therapy Center (MIT)

HPV-positive cells harbour a defect in homologous recombination (HR)

HPV-positive cells have a defect in Rad51 recruitment







Ziemann et al.,
Oncotarget 8 (2017)

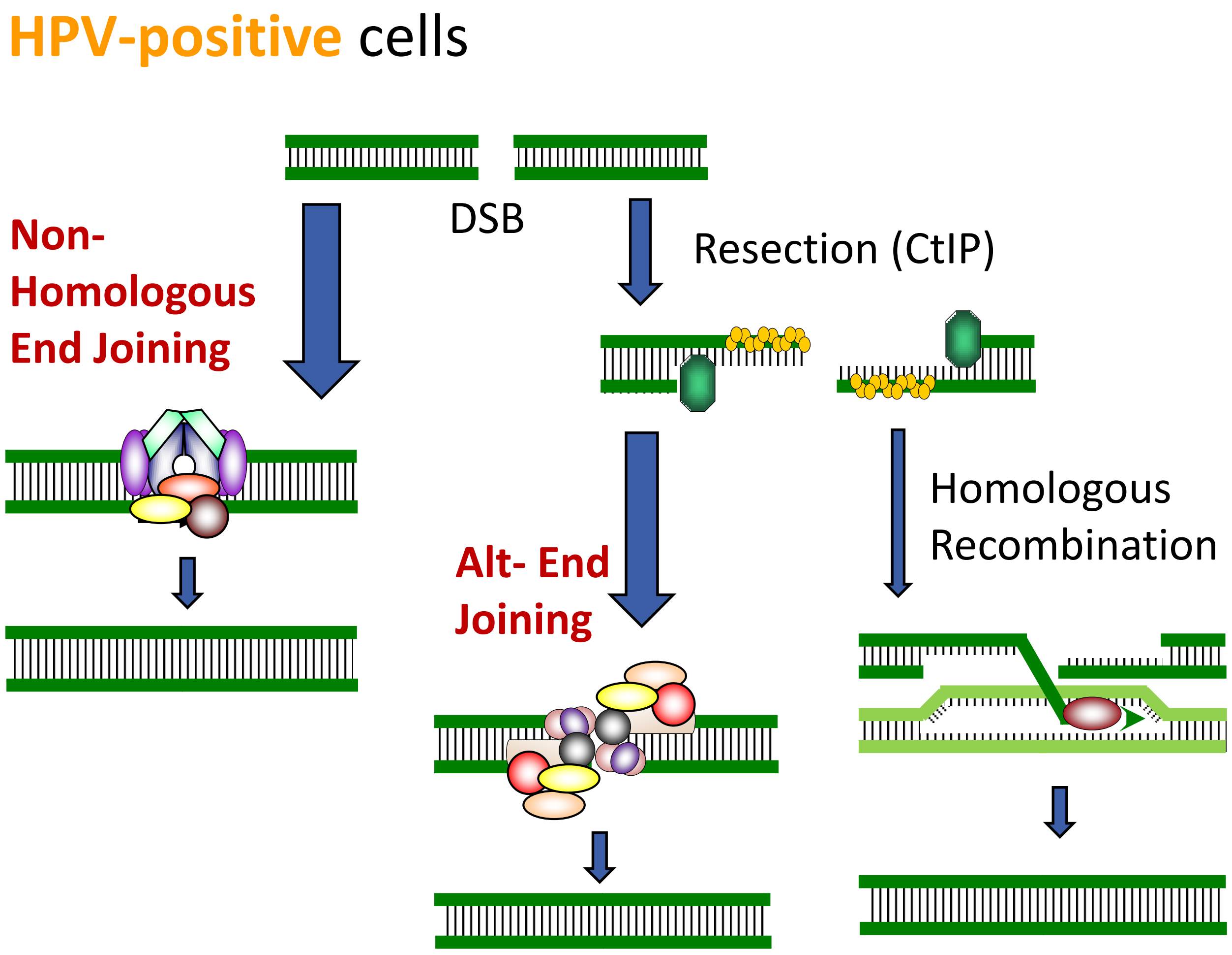
HPV-positive cells harbour a defect in homologous recombination (HR)

HPV-positive HNSCC-cells

shift their repair pathways from

Homologous Recombination towards

Alt- End Joining



Schoetz et al., Cancers (2021)

Liu et al., Clin Can Res (2018)

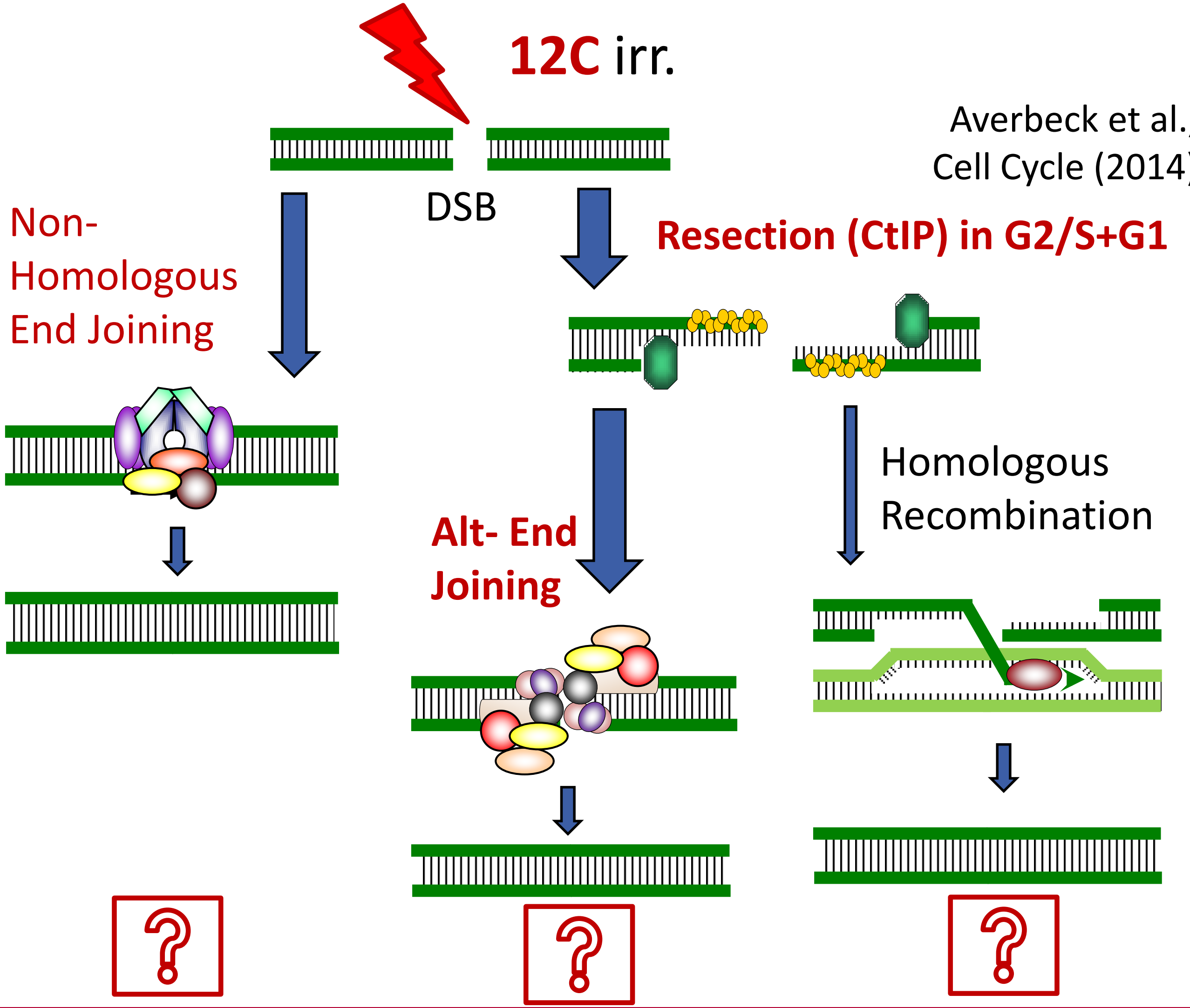
Ziemann et al., Oncotarget 8 (2017)

HPV-positive cells harbour a defect in homologous recombination (HR)

Considering 12C-ion induced DNA lesions:

There is a predominant End Resection taking place

Major repair mechanisms are not entirely clarified



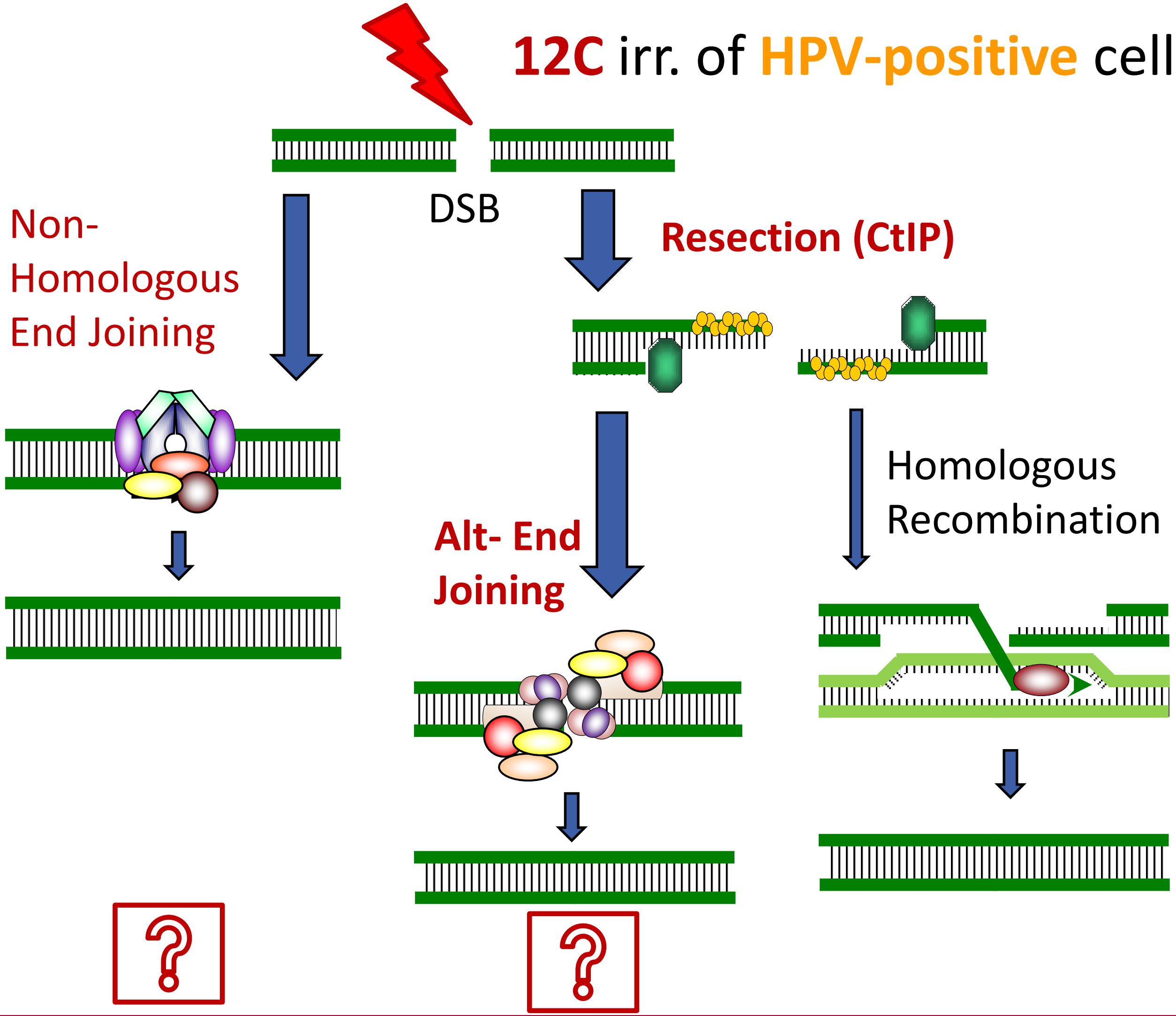
Averbeck et al., Cell Cycle (2014)

HPV-positive cells harbour a defect in homologous recombination (HR)

Hypothesis considering 12C-ion irradiation of HPV-positive HNSCC-cells :

HPV-positive HNSCC-cells
Exhibit a survival advantage
due to improved
Alt- End Joining
in combination with
a predominant
End Resection
observed after 12C

12C irr. of HPV-positive cells



Carbon Ion Irradiation of HNSCC cells

Conclusion:

- The impact of HR in repair of 12C-induced lesions is low in HNSCC cells.
- While HPV pos. cells are significantly more radiosensitive to photons than HPV neg. cells, no significant difference was seen after 12C.
- This needs to be considered when planning new protocols for the treatment of HPV pos. tumors with 12C.

Outlook:

The lab proceeds with further 12C irradiation experiments:

- **Characterization** of HR via **Rad51** knockdown and of **replication-associated HR**
- Examination of **alt-Endjoining capacity after 12C**

Thanks for your attention!

MIT
Marburger Ionenstrahl-Therapiezentrum

Physicians:
- Prof. Dr. Rita Engenhart-Cabillic
- Dr. Fabian Eberle
- Dr. Markus Schymalla

Physicists:
- Prof. Dr. Klemens Zink
- Dr. Kilian Baumann
- Dr. Veronika Flatten
- Dr. Sonja Lahrmann
- M.Sc. Yannik Senger
- M.Sc. Yuri Simeonov
- M.Sc. Petar Penchev
- M.Sc. Matthias Witt

Biologists:
- Dr. Ulrike Schötz
- Prof. Dr. Ekkehard Dikomey
- PD Dr. Florentine Subtil
- Stefanie Preising
- Leoni Piepke
- Sibylla Kohl

Federal Ministry of Education and Research

Federal Ministry of Economics and Technology

LOEWE
Exzellente Forschung für Hessens Zukunft

HITRI plus
Heavy Ion Therapy Research Integration

EMPIR EURAMET
The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

varian
A Siemens Healthineers Company

Partners:
- Dr. U. Weber (GSI)
- Dr. Ch. Schuy (GSI)
- PD Dr. W. Mansour (UKE)