PARticle Therapy REsearch Center (PARTREC)
From Nuclear Physics to Medicine

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  - Microdosimetry
  - Fast Irradiations
    - FLASH
    - VHEE
  - Novel Gantries
  - Patient Imaging

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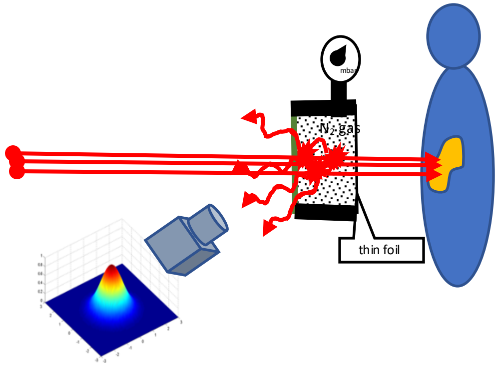

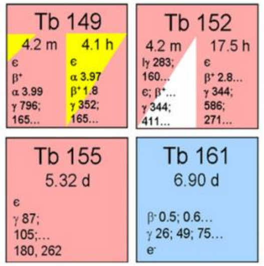

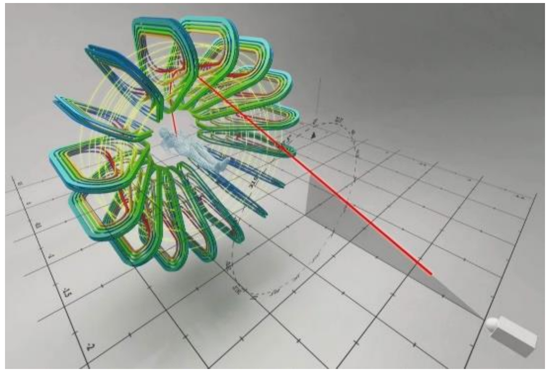

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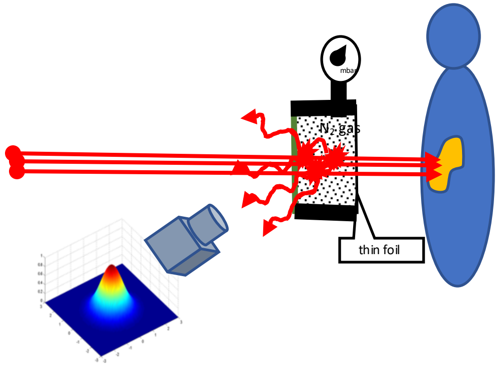

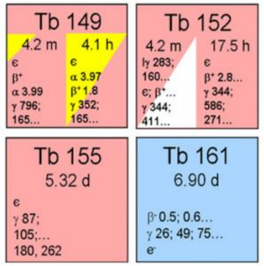

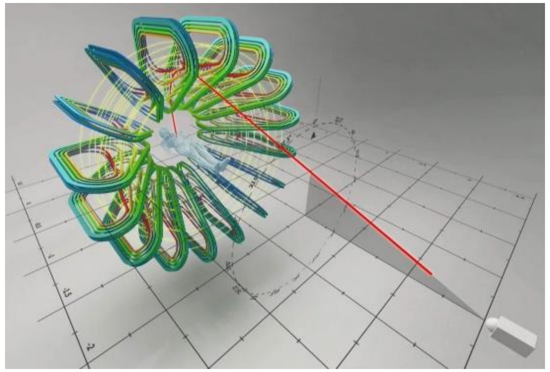

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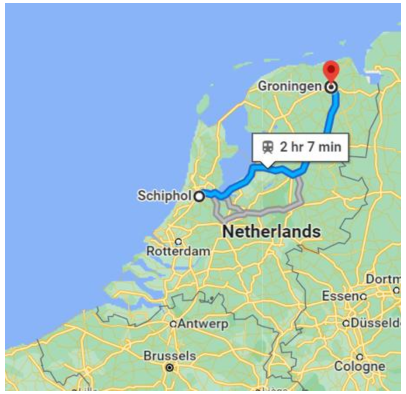
Groningen University

- Rijksuniversiteit Groningen (RUG):
  - Founded in 1614 (second oldest in the Netherlands)
  - Ranked 76th in the world, 2nd in the Netherlands (Shanghai University Ranking)
  - Discoveries/Inventions
    - Calculus (Bernoulli 1720's and later)
    - Electric cars (Stratingh, 1837)
    - Vitamine C (Szent-Györgyi, 1928)
    - Phase contrast microscopy (Zernike, 1930s) and much more!
  - 4 Nobel Prize winners, incl. Feringa (Chemistry, 2016)
- KVI/PARTREC
  - Only accelerator physics institute in NL
  - Reorganization, inclusion of medical and radiobiological research

    -> Re-established as PARticle Therapy REsearch Center (PARTREC)



World Rank	Institution	Country/Region	National/Regional Rank	Total Score	Alumni
76	University of Groningen		2	28.1	12.8

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Integrated with Medical Faculty of University of Groningen

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Integrated into UMCG in 2019

GPTC
UMC Groningen Protonen Therapie Centrum

First patient in 2018

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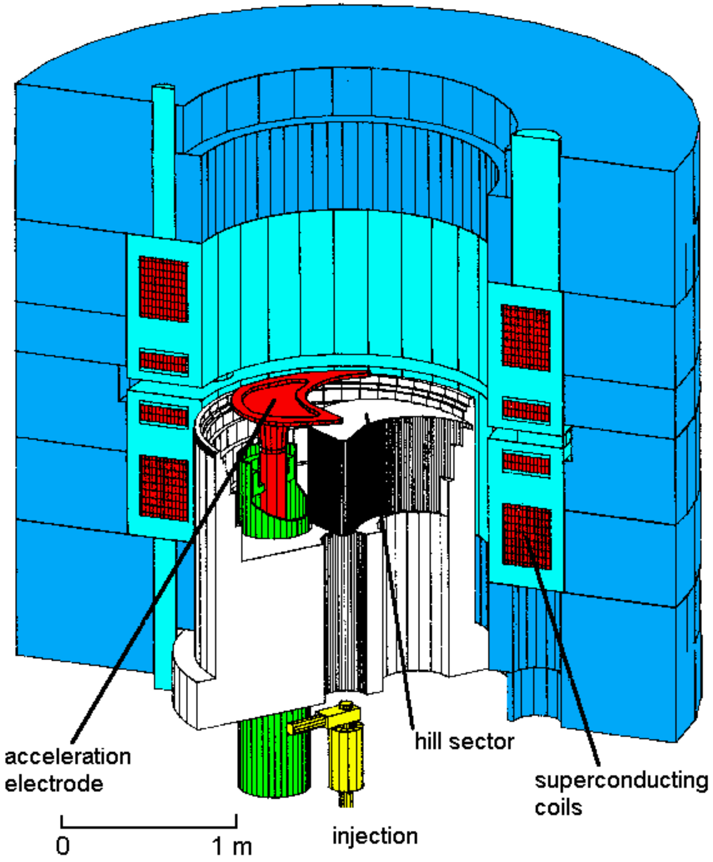
AGOR Cyclotron

- Superconducting AGOR cyclotron is a multi-particle, variable energy AVF-cyclotron
- French-Dutch collaboration built 1987 – 1994
- Operational since 1996
- Magnetic field (1.7 to 4.1 T) produced by
  - Two pairs of superconducting main coils
  - fifteen trim coils
  - three iron hill sectors for focussing
- 3 halfwave RF cavities, 24 - 62 MHz; h = 2, 3 or 4
- Three external ion sources (two ECR sources for protons and heavy ions, multi-cusp source for light ions) are axially injected
- Extraction
  - 300 - 500 turns depending on harmonic mode
  - extraction radius 870 - 890 mm depending on E/A
  - turn separation at extraction 2 - 3 mm ~ beamwidth



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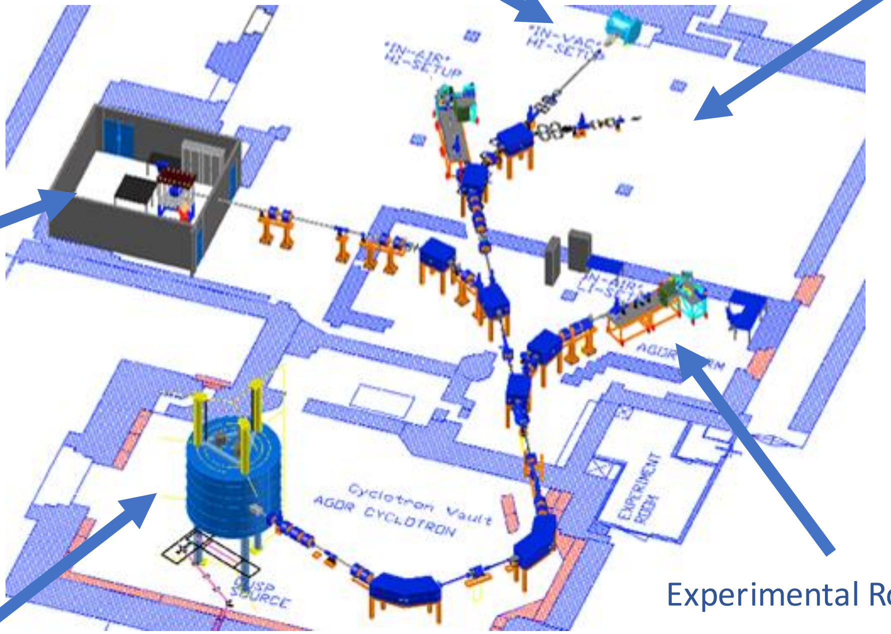
Beams and Test Rooms

Large in-vacuum irradiation setup

Nuclear physics experiment (NEXT)

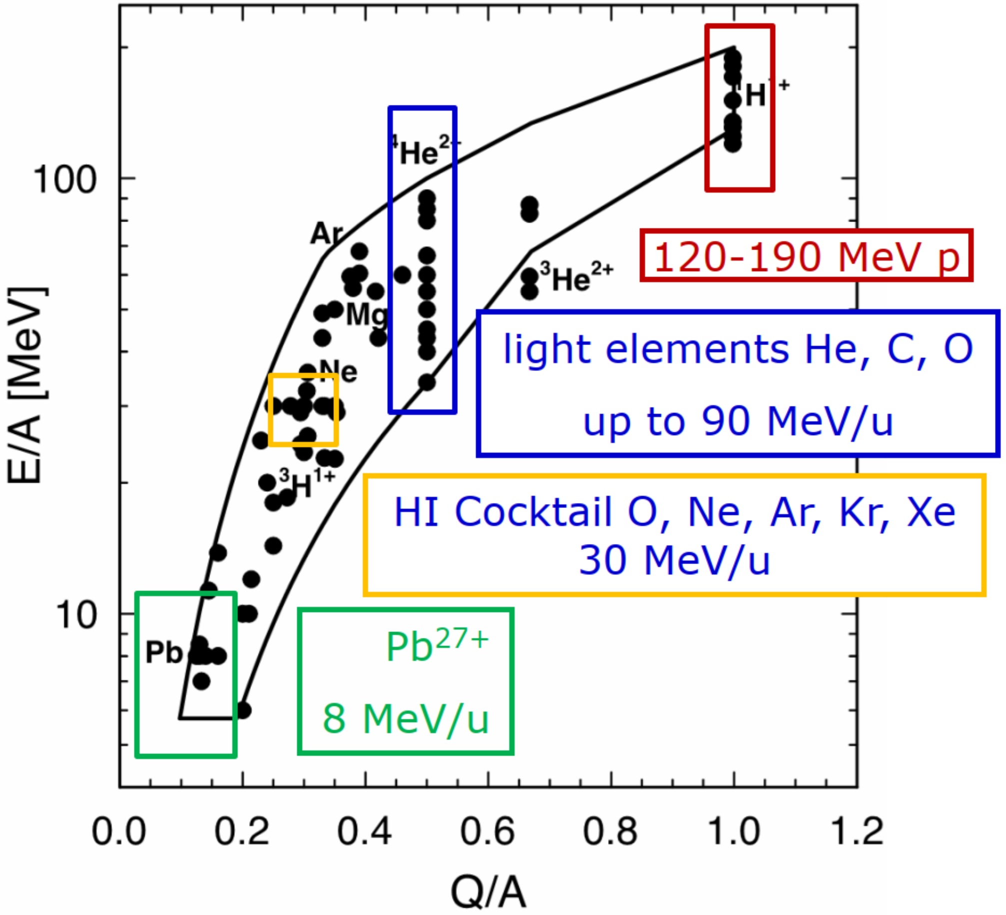
New animal facility IMPACT (A-cell)



Experimental Room (H-cell)

Accelerator (AGOR)

AGOR can deliver beams of all elements up to Xe



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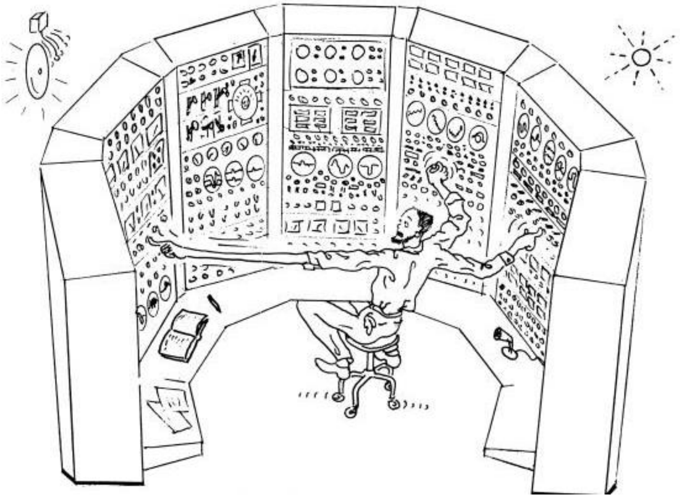
Our Team

- Faculty (4)
- Post-doc, PhD-students (~10)
- Technical staff (25)
  - Operators
  - Experimental and project support
  - Cryogenics, cooling and vacuum
  - Design/Mechanical
  - Electronics
  - IT Support
- Operational 120 hours/week, 26 weeks/year
- Users: Medical Physics, Radiobiology, ESA, Detectors, Commercial
- Beam requests: irradiations.partrec@umcg.nl



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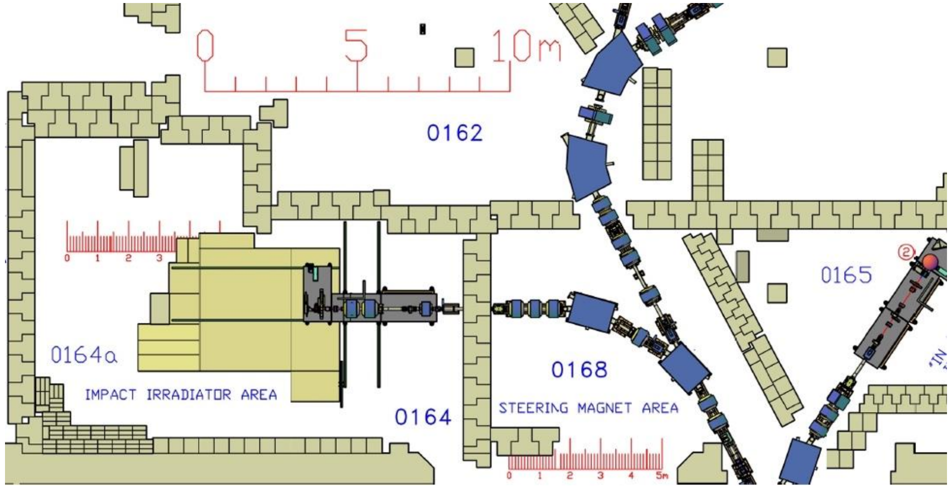
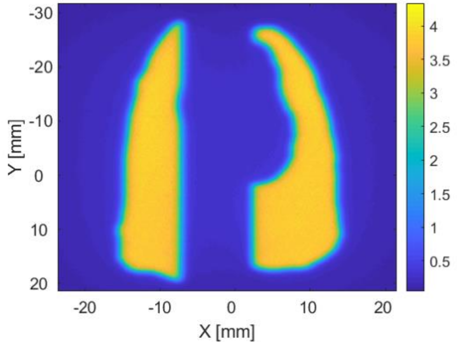
IMPACT Beam Line

- >3 MEUR grant from KWF
- Designed for small animals
- New beam line
  - Pencil beam scanning (10 cm x 10 cm)
  - Shoot-through or SOBP
  - Collimator for penumbra
- Combined on-line 3D X-ray imager and X-ray irradiator
- Irradiation planning
- First beam: 04.10.2024
- Fully operational: 2025





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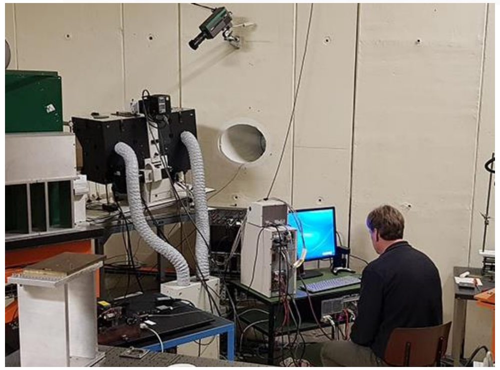
One Stop Shop

- Experiment development
- Ethics authorisation process
- Animal procurement logistics
- On site animal accommodation with IVCs
    - capacity 200 rats and mice
    - no long term stay
    - two additional accommodations planned
- "Twin Beam" Irradiation
- Laboratory for animal handling prior and post irradiation
    - GronSAI imaging center:
      optical, molecular, CT, MRI, PET
- Data management facilities



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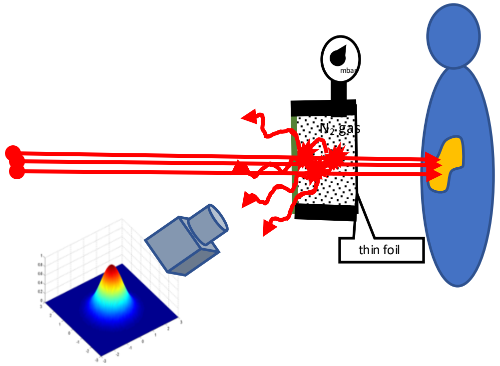
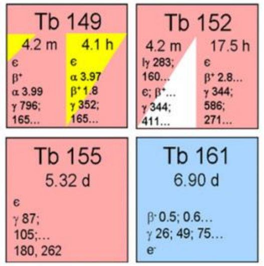
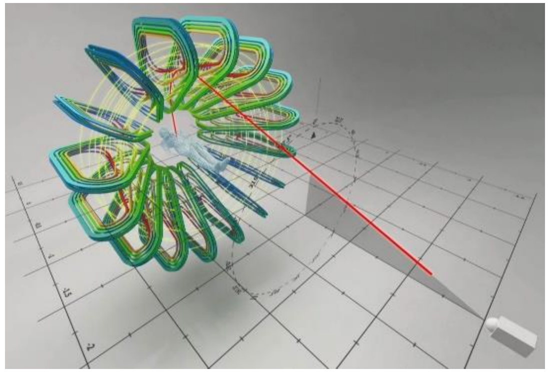




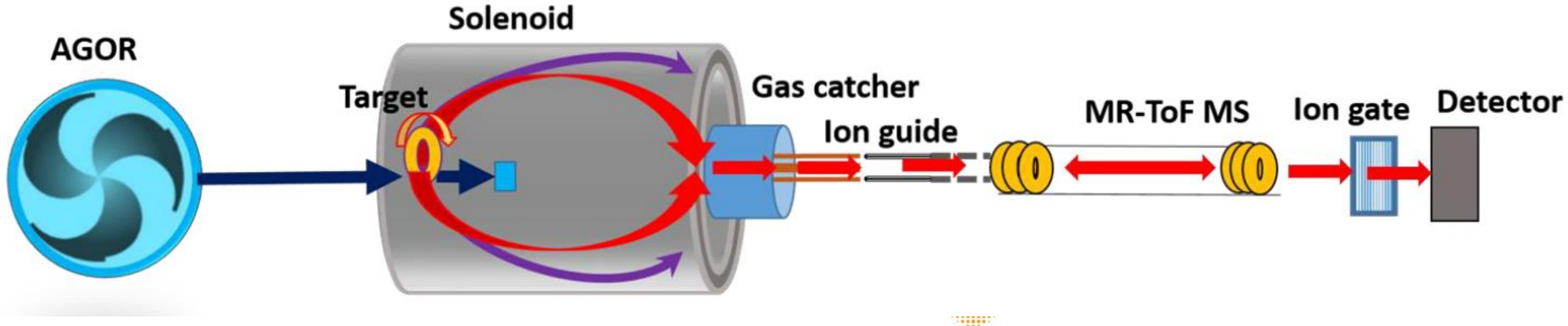


Heavy Ion Beams

- AGOR can deliver beams of all elements up to Pb
- Research areas
  - Radiobiology (RuG, UMCG, PSI)
  - Detector tests & development (ESA)
  - Experiment development (ESA)
  - Radiation hardness (ESA, companies)

NEXT (J. Even)

- New experimental research on the production of neutron-rich heavy nuclei using multi-nucleon transfer reactions between heavy nuclei (e.g. ^{136}Xe on ^{208}Pb) has recently been started
- ECR ion source development, improvement of transmission from source to extraction
- A new experimental station consisting of a 3 T superconducting solenoid fragment separator and MR-ToF mass spectrometer is developed with RUG has been installed



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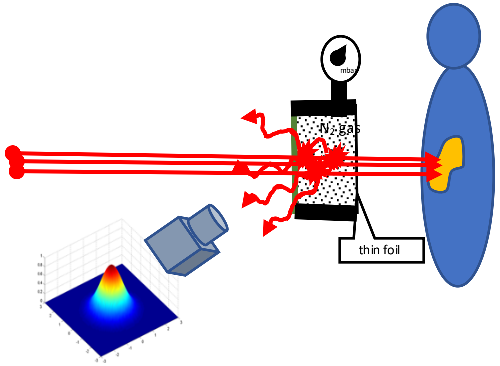

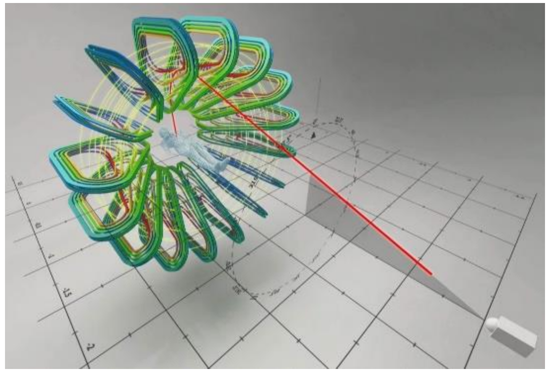

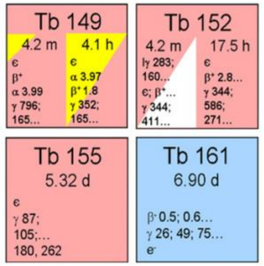

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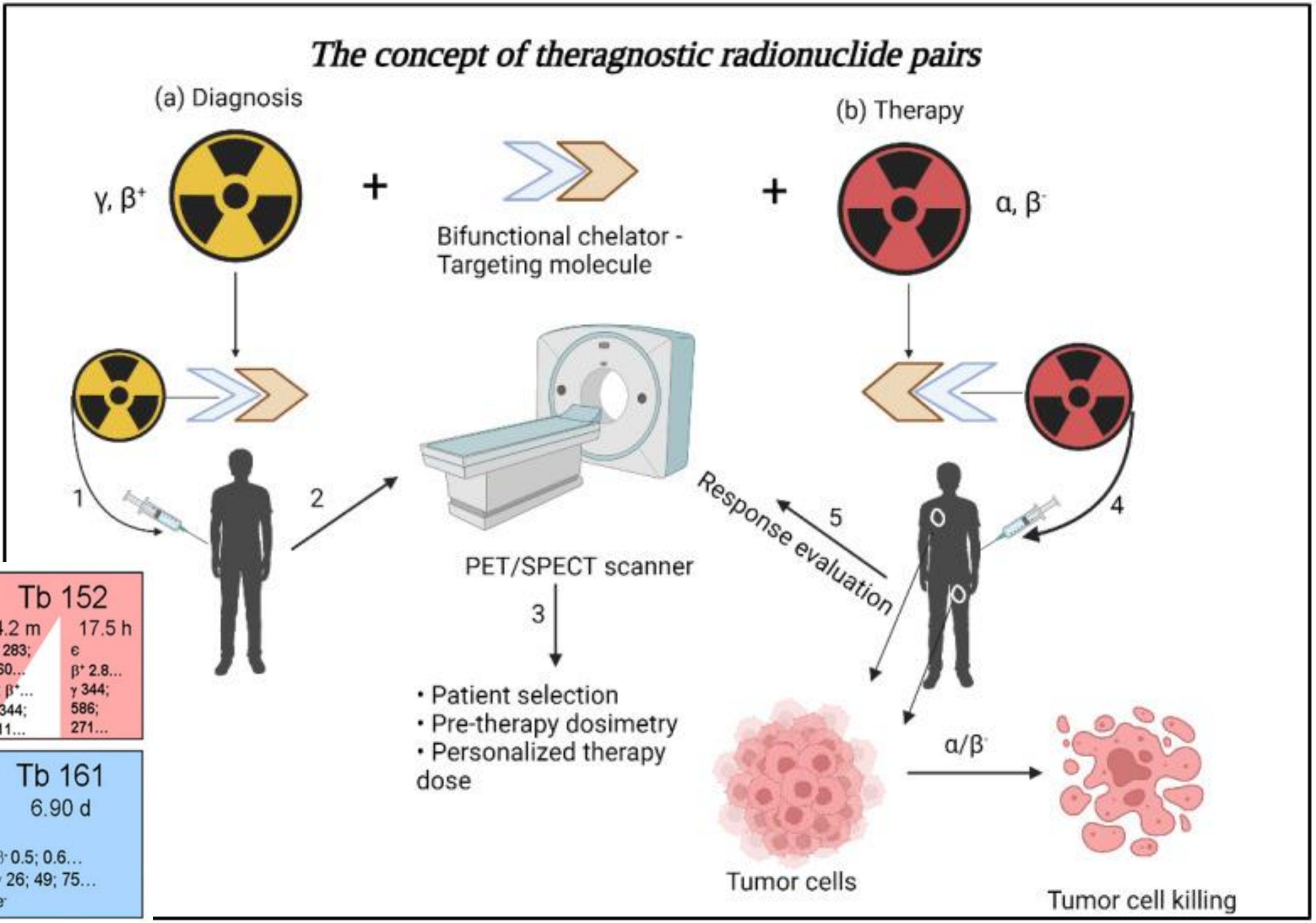
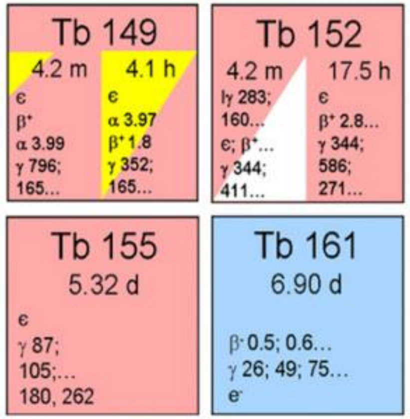
Terbium Theragnostics

- >10 MEUR grant from IPCEI
- Produce four Terbium isotopes for patient diagnostics and treatment
- Partners: SHINE, UMCG

SHINE™





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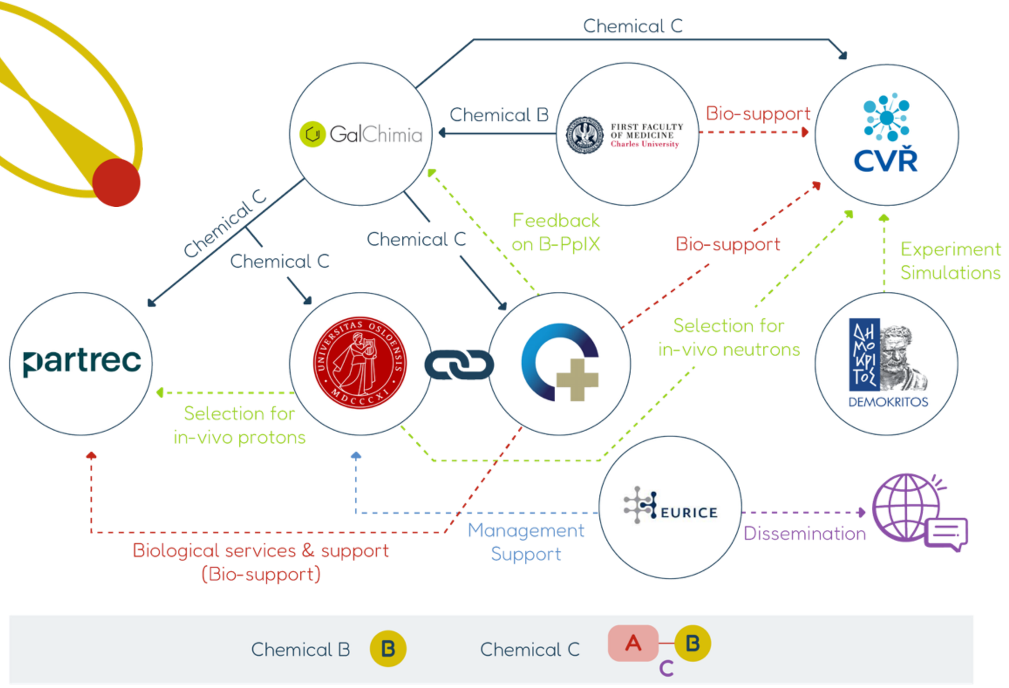
NuCapCure

- Consortium of eight parties
- Goal: Treat Glioblastoma (presently <10% 5-year survival)
- Envisaged radiation effect:
  - Higher in tumour due to boron proton capture
  - Lower in healthy tissue due to FLASH
- > 5 MEUR from EIC Pathfinder Open 2023
- Ranked 1st (788 proposals submitted, 56 funded)



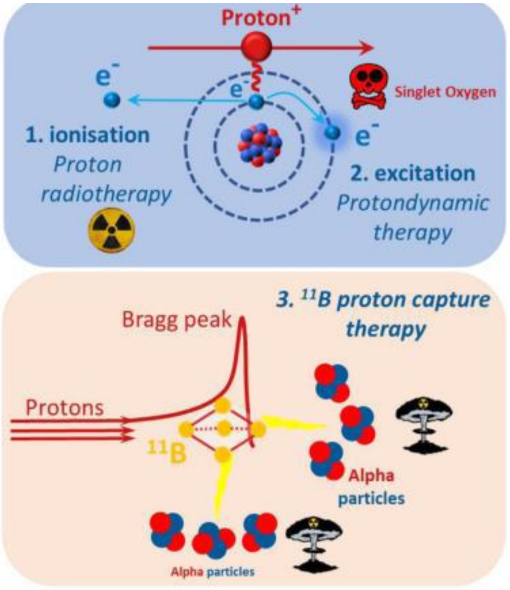


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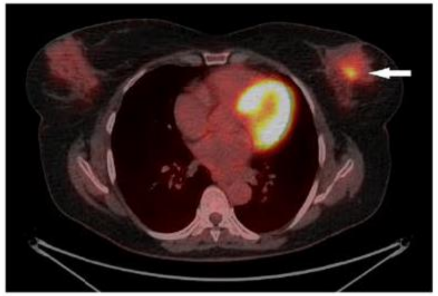
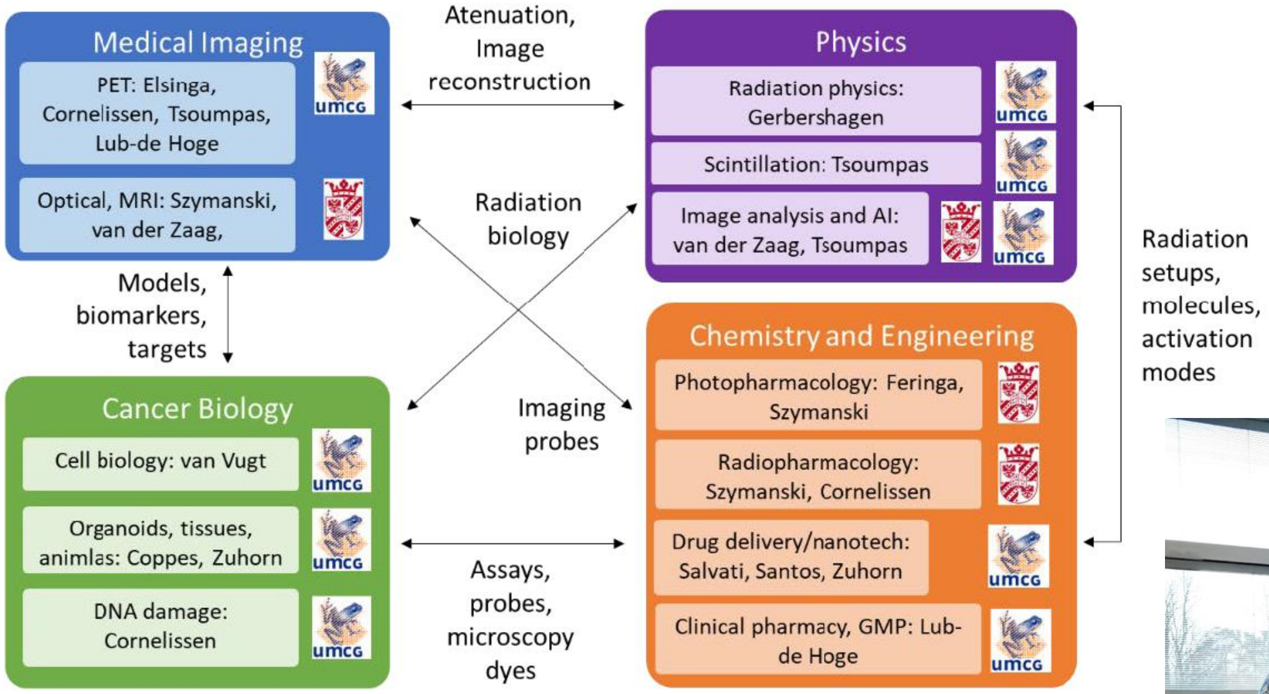
Image-Guided Pharmacotherapy

IMAGING REVEALS LOCATION



RADIATION ACTIVATES THERAPY



- 18 MEUR grant from HTRIC x UEF
- Proposal headed by Prof. Ben Feringa, Nobel prize laureate

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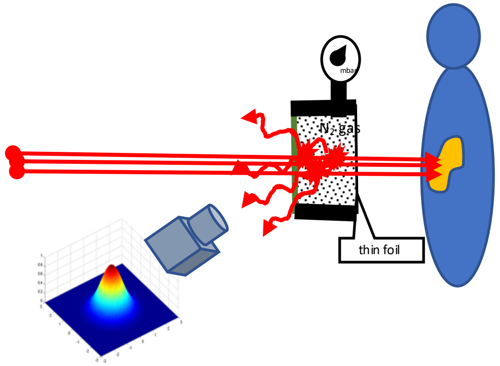

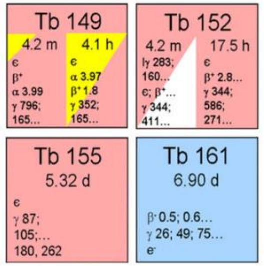

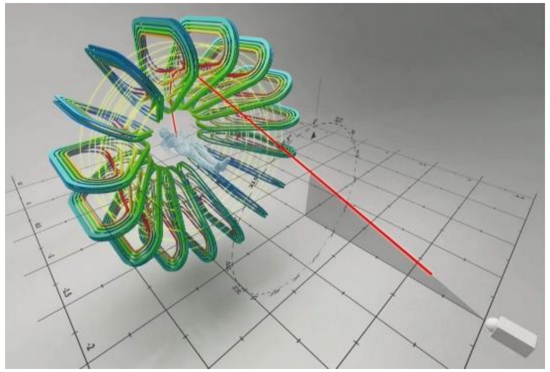

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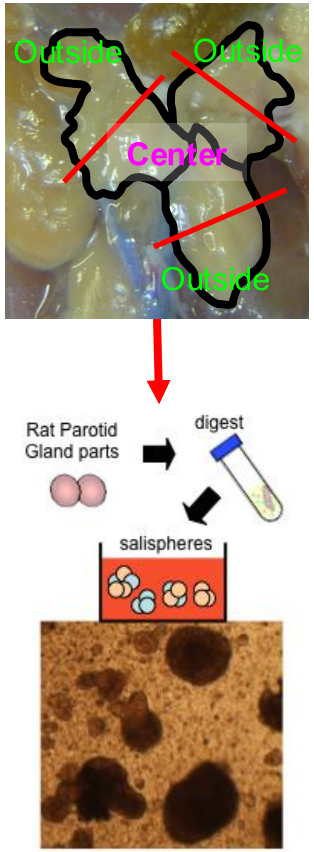
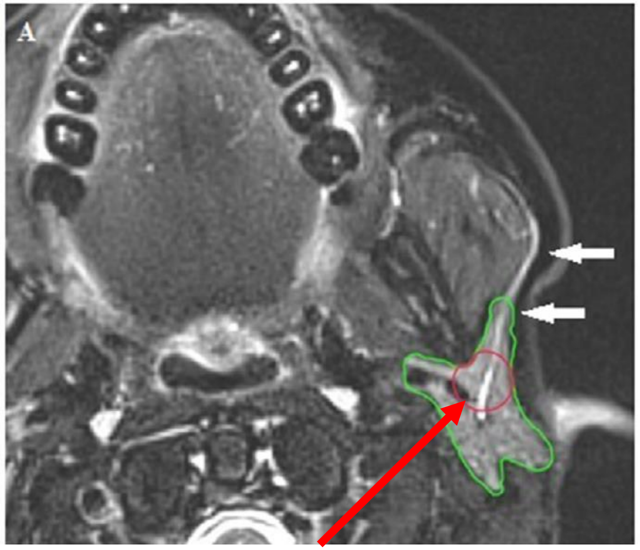
Stem cell sparing radiotherapy

Rat model



Patients



Stem cell region

- Centre of the glands is rich in organ-specific stem cells.
- Irradiation of this sub-volume results in degeneration of the entire gland.
- Irradiation of the other parts only causes local damage
- Retrospective analysis of a Canadian patient cohort
  - dose to the centre of the gland is the best predictor of post-treatment saliva production.
- Validated in a trial at UMCG.
- Currently implemented as the standard approach to minimize the risk of radiation-induced xerostomia in patients

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- van Luijk et al. Sci. Trans. Med 2015
- Steenbakkers et al. IJROB 2022

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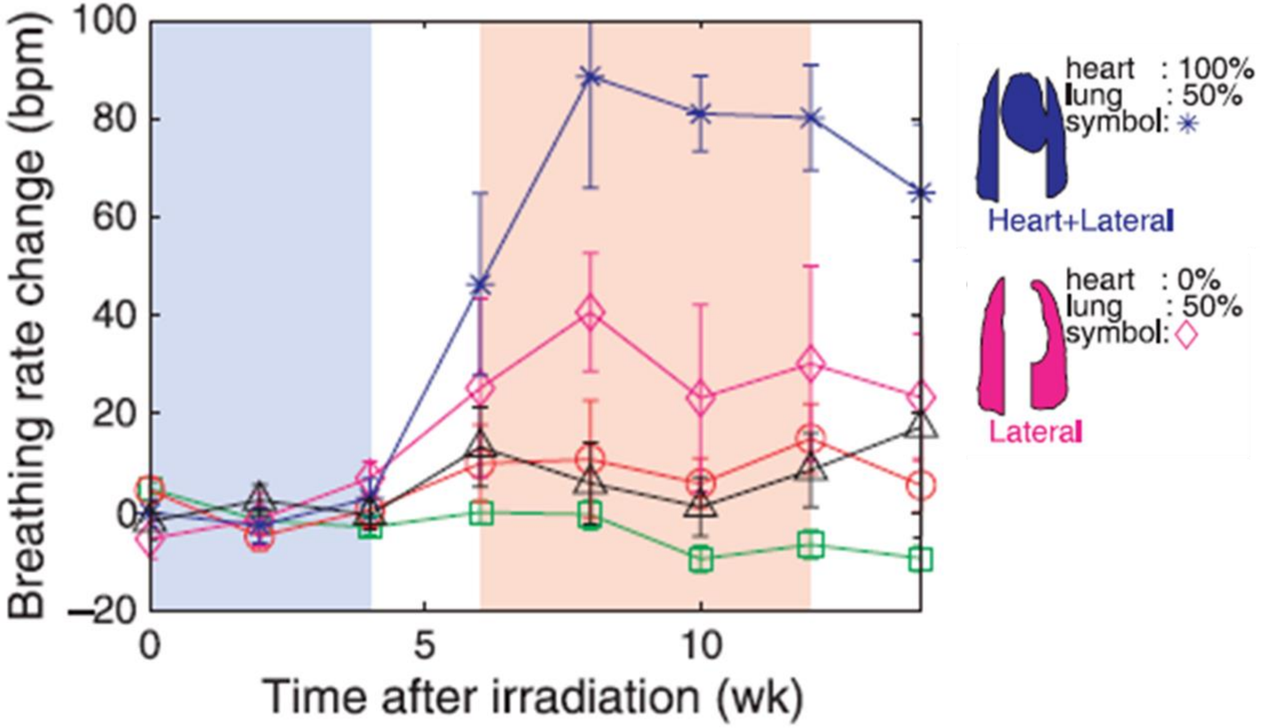
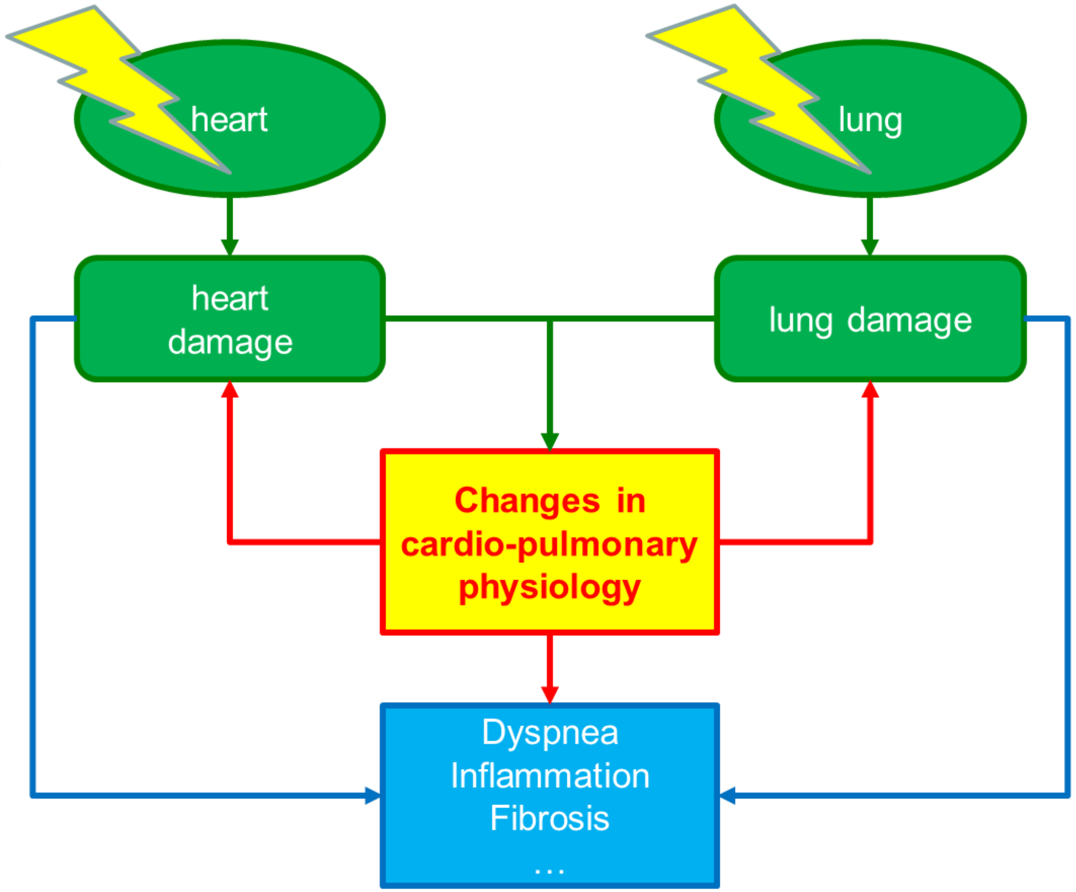
Heart/lung ➔ Cardiopulmonary





- Van Luijk et al. Canc. Res. 2005
- Ghobadi et al. IJROB 2012
- Ghobadi et al. Thorax 2012

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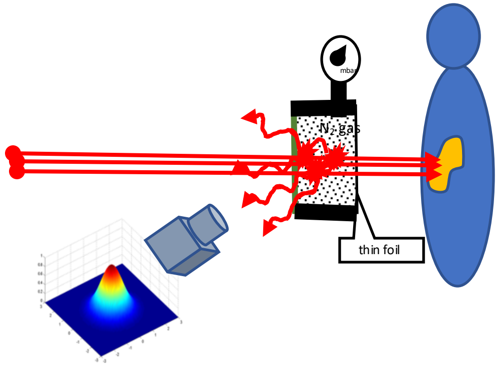
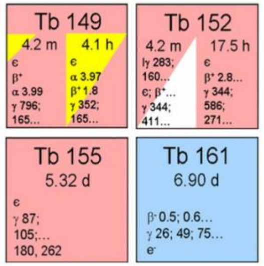
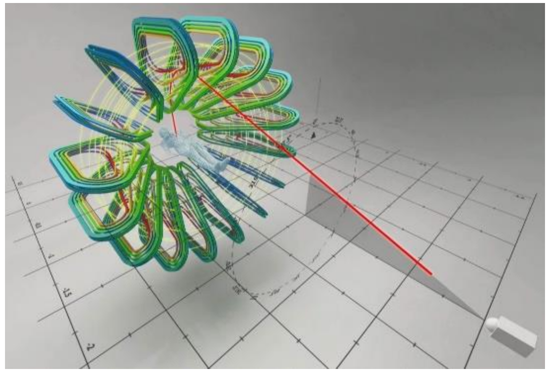
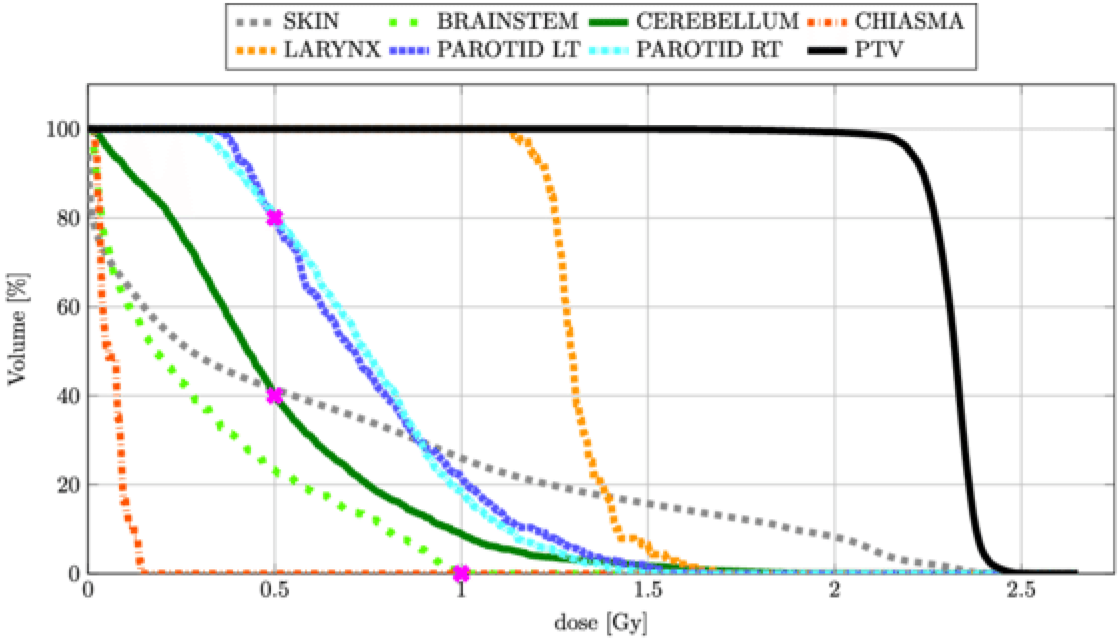






There is more than volume...

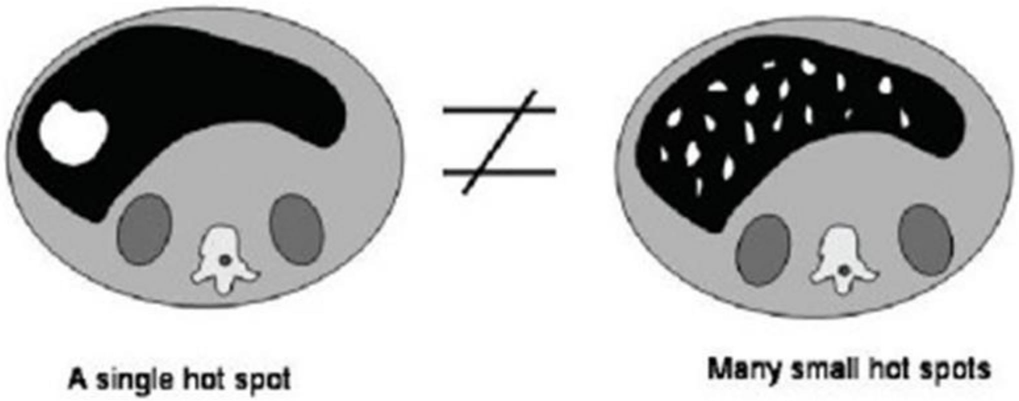


Effects of:
- Shape of dose distribution
- Regional differences
- Interaction between organs

Inherent loss of spatial data:

DVH does not tell location of a high or low dose region:

DVH does not tell how certain dose regions are distributed:



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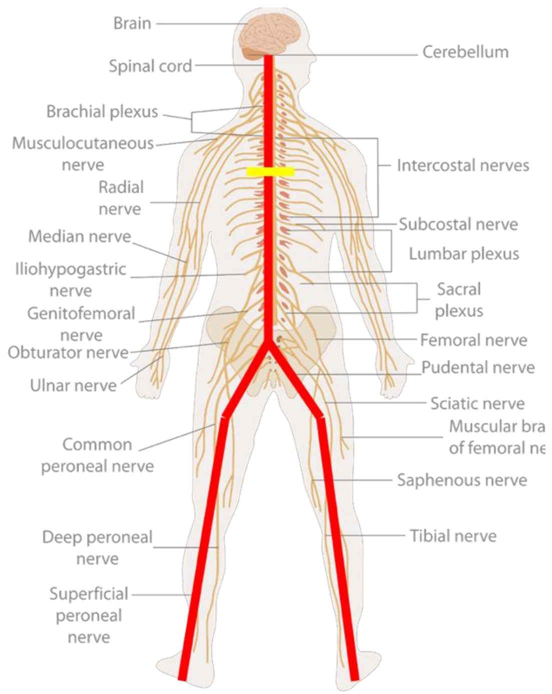
Serial and Parallel Organs

- What and how to spare?
  - Many degrees of freedom:
    - Reduce high-dose regions? (many beams)
    - Reduce low-dose volume? (fewer beams)
    - Both? (Need costly proton/ion therapy)
- Responses are tissue/organ dependent!

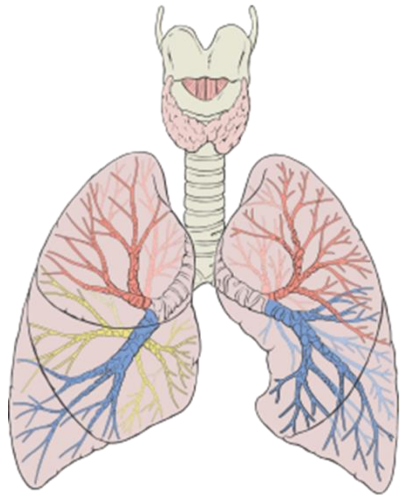
⇒ Serial vs parallel organs

- Practical approximation used clinically:
  - Serial ➔ Maximum dose as predictor
  - Parallel ➔ Mean dose as predictor

Serial

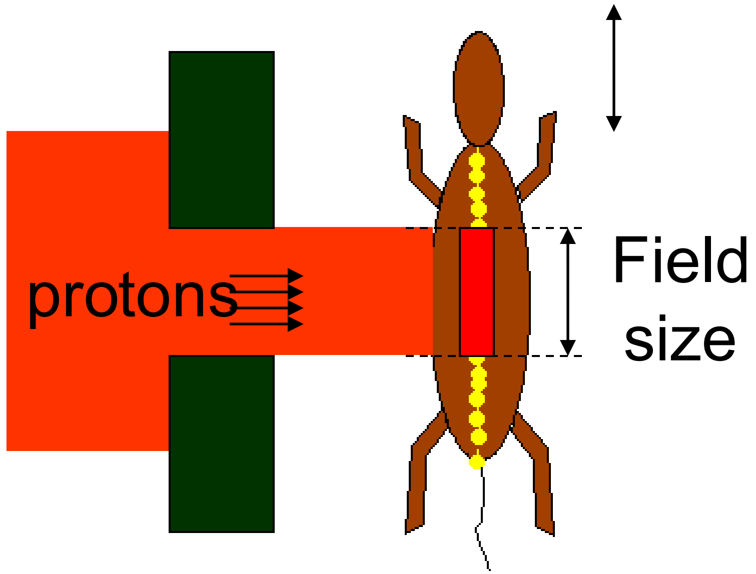


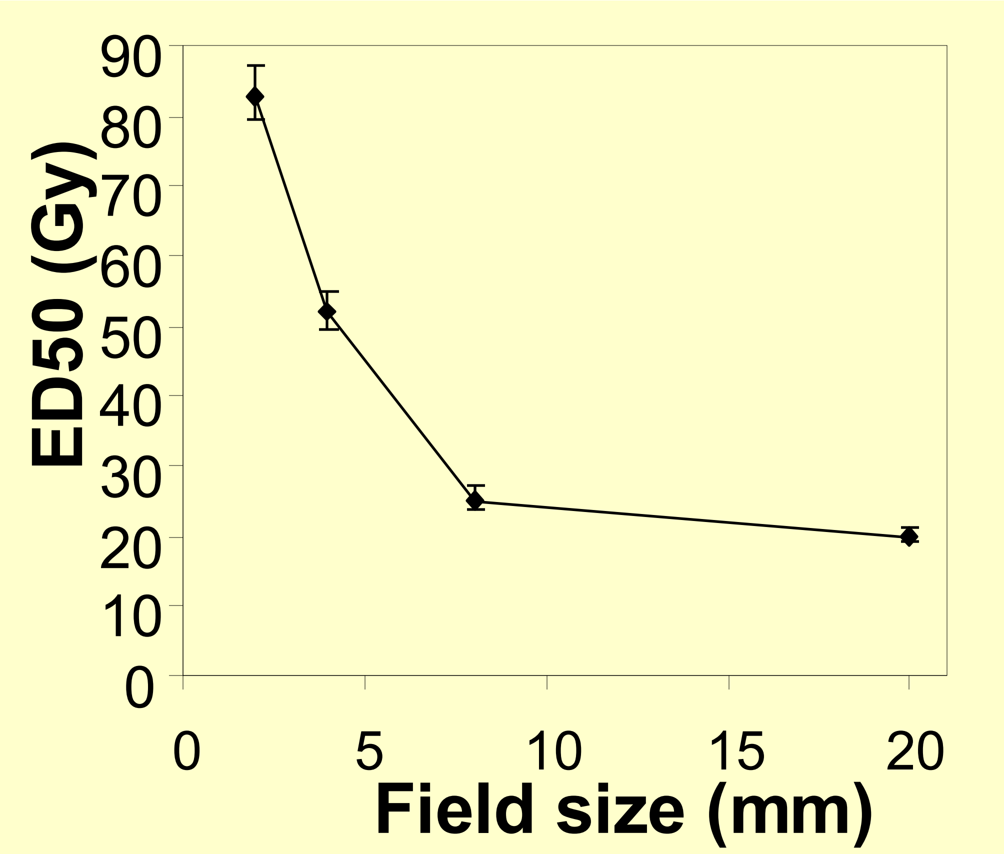
Parallel



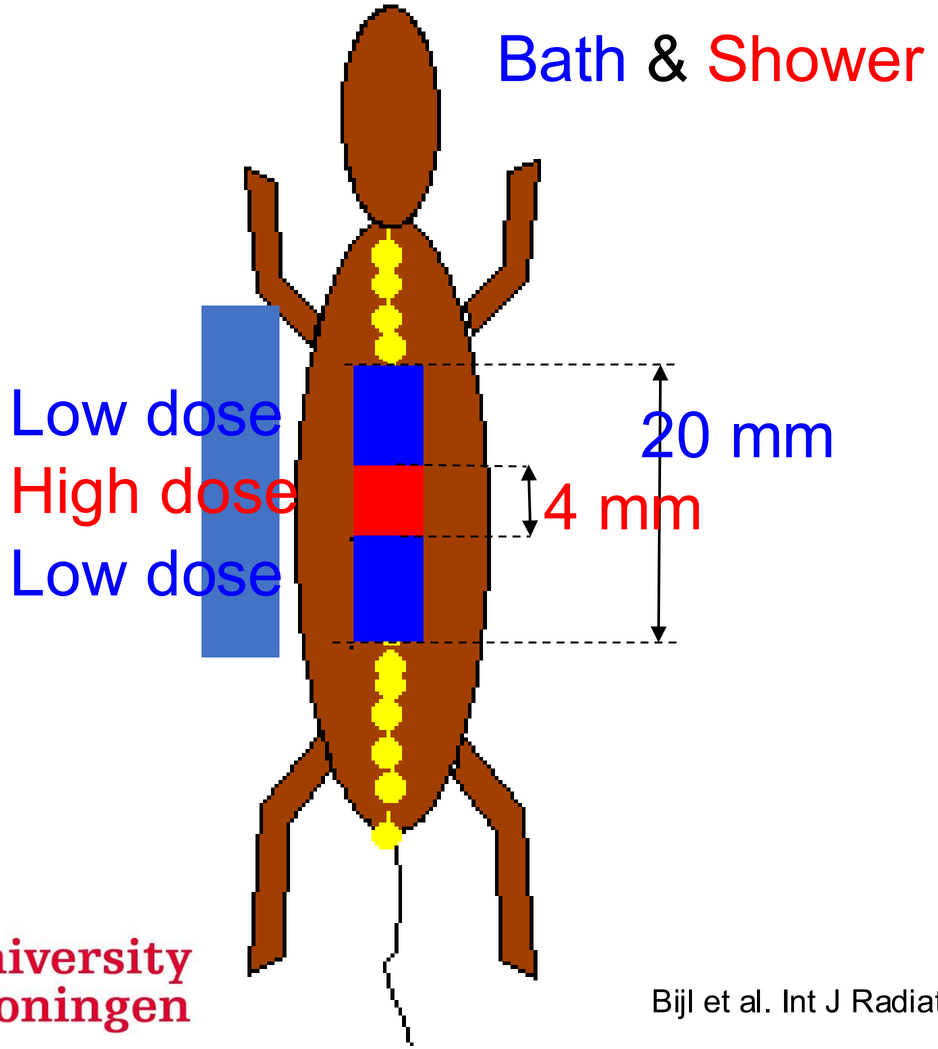
Spinal cord

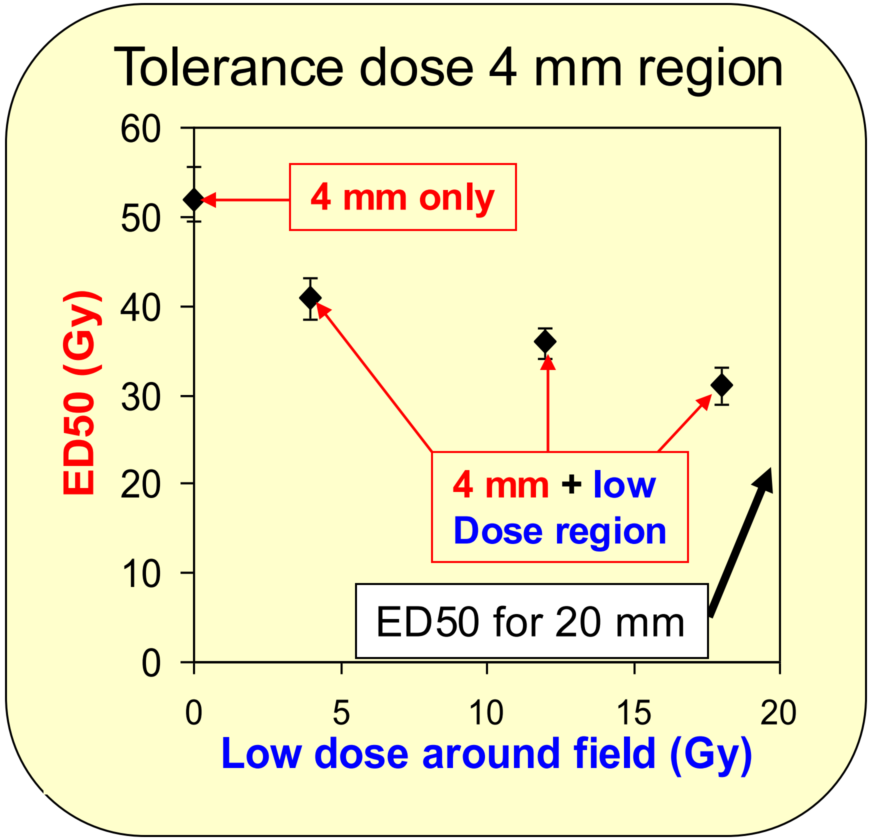
Homogeneous irradiation of different lengths of spinal cord





Spinal cord: inhomogeneous dose distribution





Bijl et al. Int J Radiat Oncol Biol Phys. 2003

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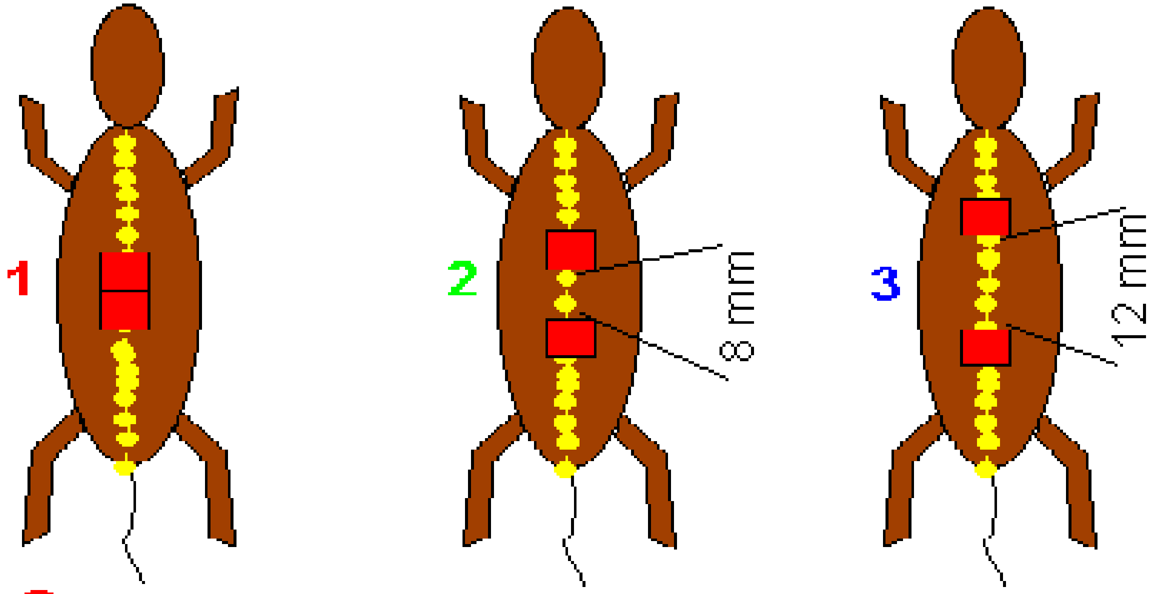
Spinal cord: inhomogeneous dose distribution



	8 mm	2x4 mm	2x4 mm	
ED50:	25 Gy	46 Gy	42 Gy	=> 2 x 4 ≠ 8

(1x 4 mm: ED50=53 Gy)

Volume-Effect ? **Configuration** determines outcome

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Bijl et al. Int J Radiat Oncol Biol Phys. 2003

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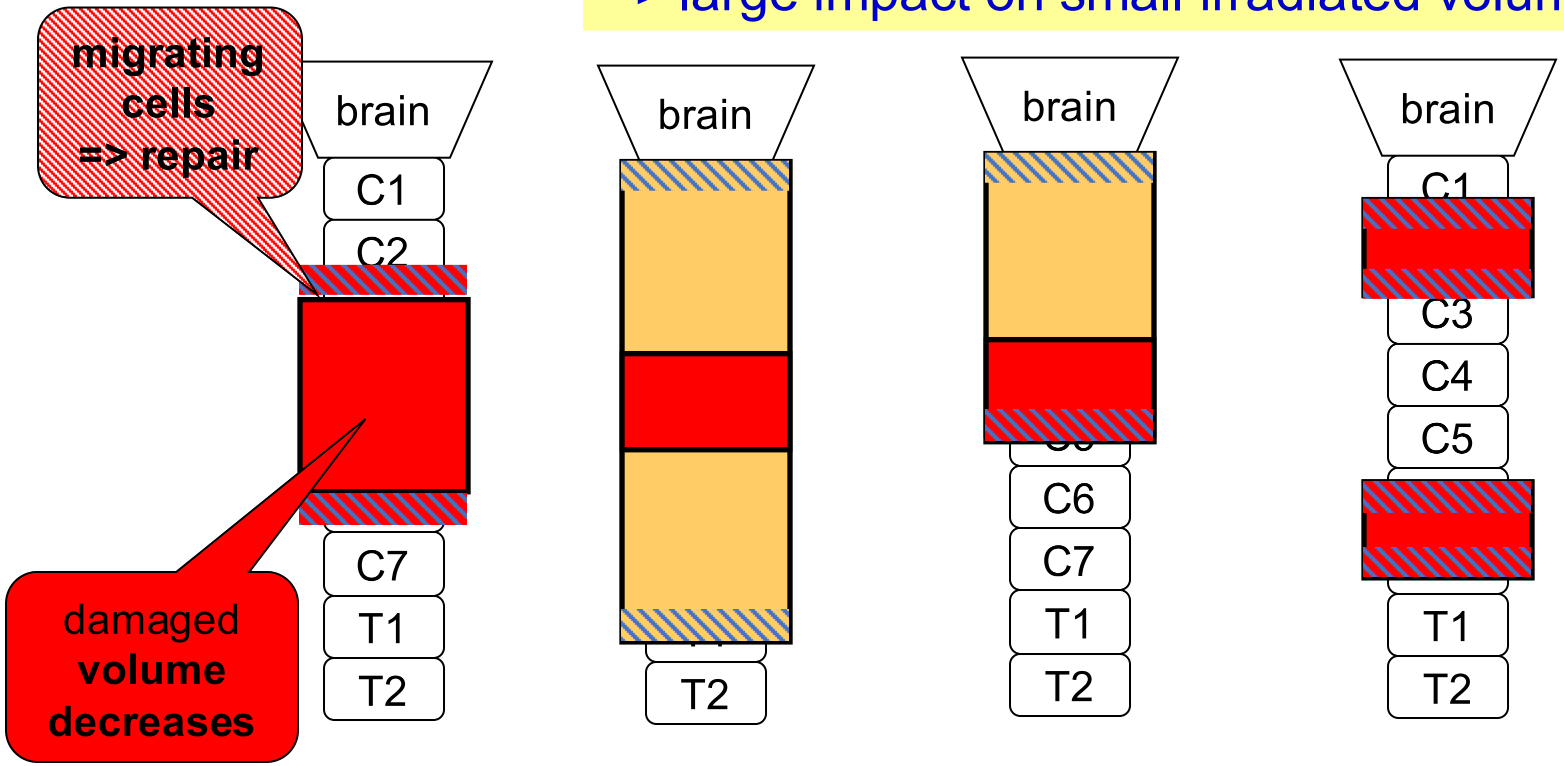
Spinal cord: include repair in model

"diffusion length"
=> large impact on small irradiated volumes



Damaging dose

Non-damaging dose, still disabling repair

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van Luijk et al. Int J Radiat Oncol Biol Phys. 2005

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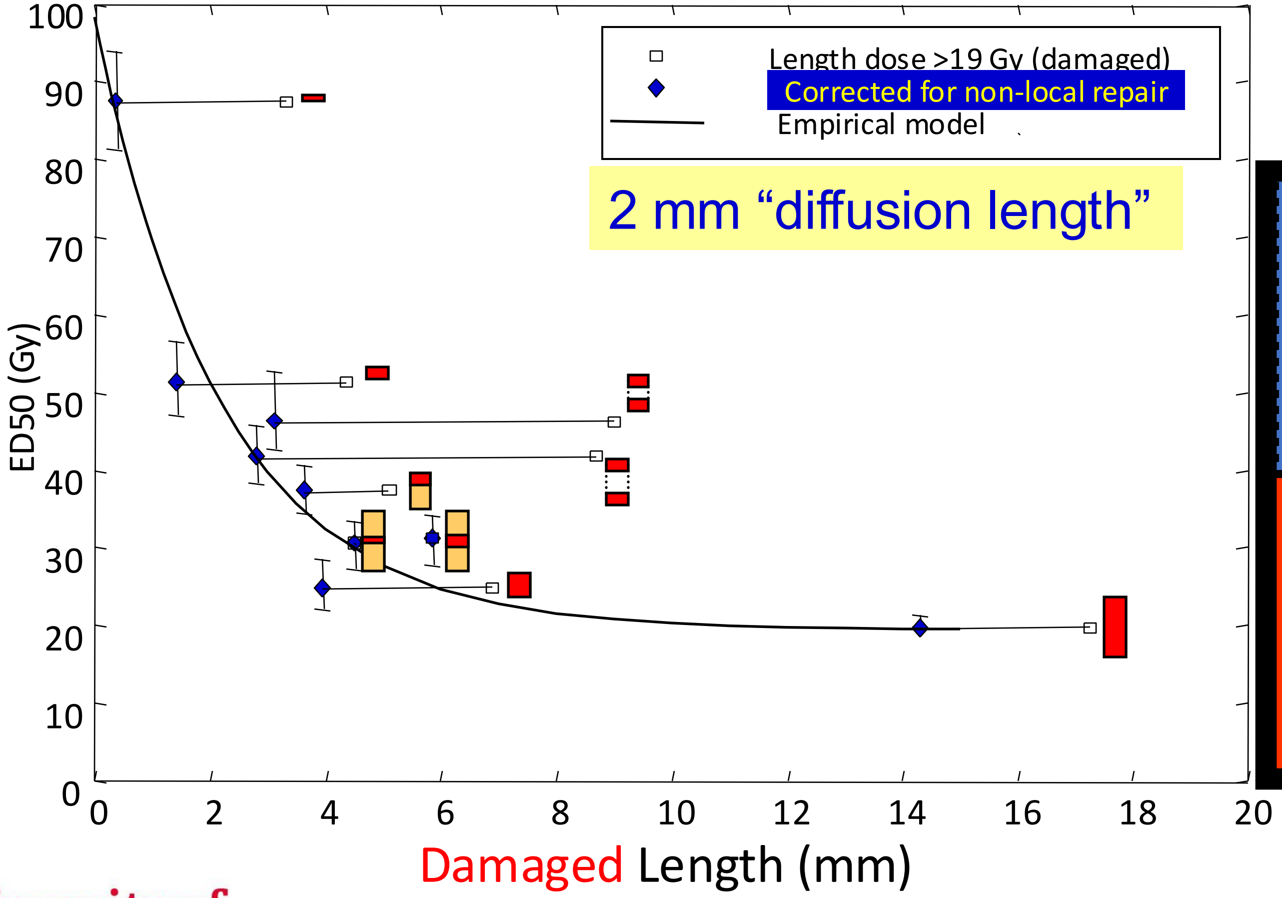
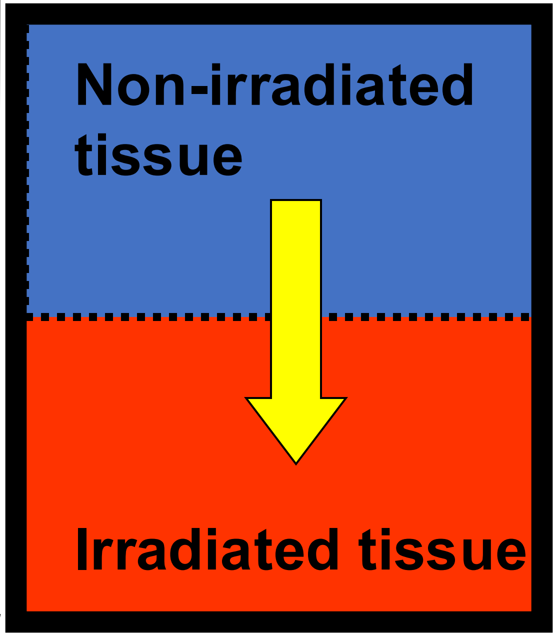
Spinal cord: include repair in model

Correct the dose distribution **for repair** from **unirradiated** tissue





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van Luijk et al. Int J Radiat Oncol Biol Phys. 2005

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  - ➡ Microdosimetry
  - Fast Irradiations
    - FLASH
    - VHEE
  - Novel Gantries
  - Patient Imaging

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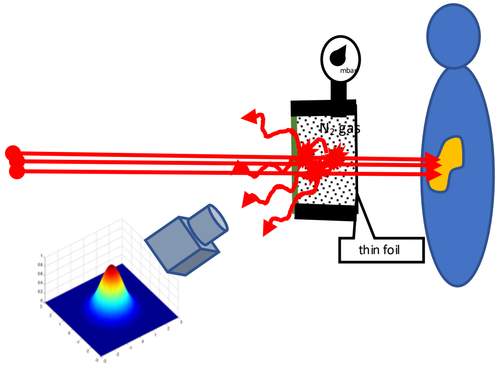

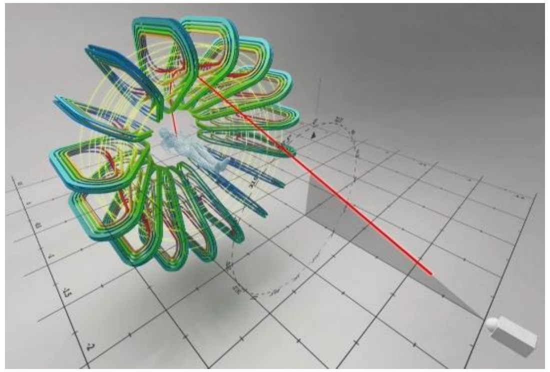

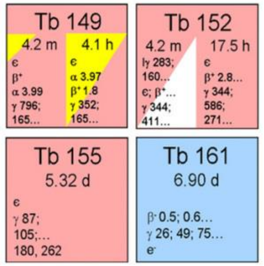

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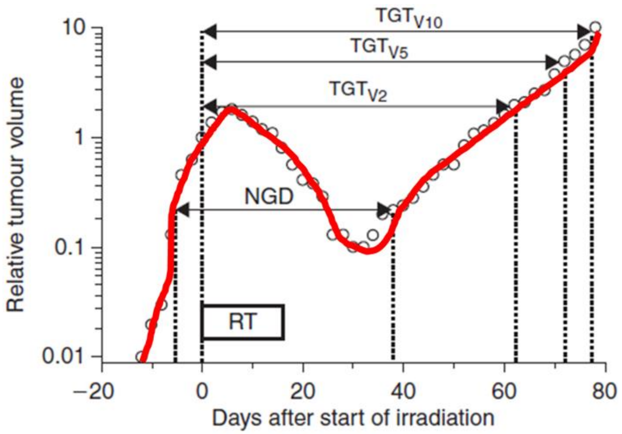
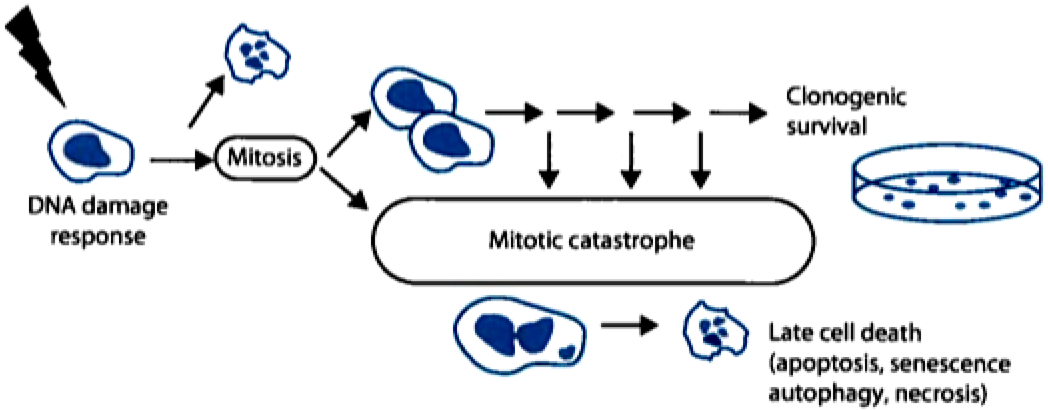
Tumour survival and cell killing



Irradiation with X-Rays

- What went wrong here?
- What's the relation between cell death and probability of curing a tumour?

- Low probability of dying from specific hit
- High number of hits
- ➔Poisson statistics!
  - $SF = e^{-m}$
    - SF: Surviving fraction
    - m: mean hits per cell (prop. to dose)



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Basic Clinical Radiobiology, 4th edition,
Basic Clinical Radiobiology, 5th edition

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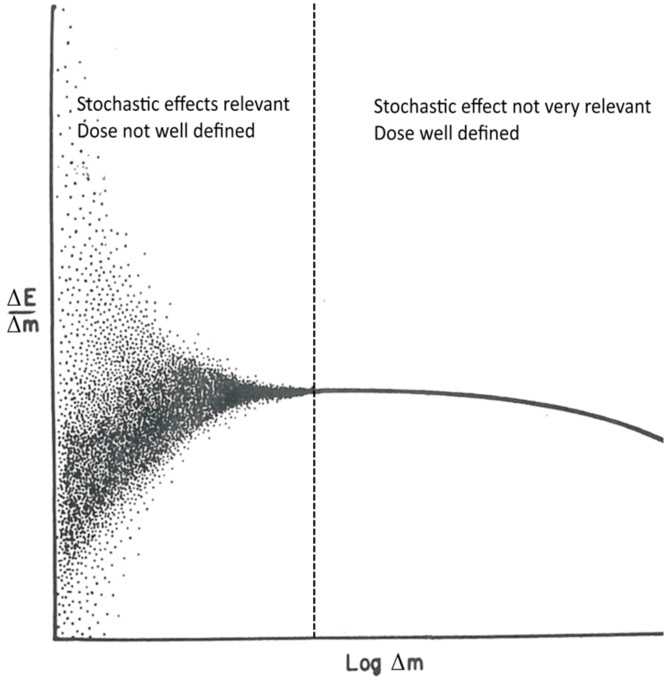
Microdosimetry vs LET

- The **Microdosimetric Kinetic model (MKM)** uses microdosimetry to describe the radiation field within each voxel and allows the RBE to be calculated.
- Useful tool to assess the energy deposited taking into account the stochastic fluctuations occurring at the nucleus scale
- Provides a more advanced description of radiation quality because:
  - Measures the **energy deposited** in a volume comparable to the **cells nucleus**
  - It takes into account **stochastic fluctuations** in energy deposition



Geant4:

+ widely validated for microdosimetry and clinical application
+ can score individual electrons' energy deposit with an arbitrary accuracy
- modelling a specific patient is *very* difficult
- illegal to use for treatment planning

Raystation:

+ easy patient modelling from CT scan
+ very fast proton, neutron, and alpha transport
- proton energy deposit modelled via tabulated stopping power
- spatial resolution ≳ mm

Rossi HH (1968)
J. Magini et.al.

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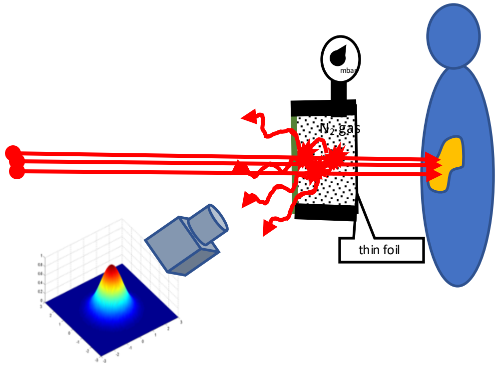

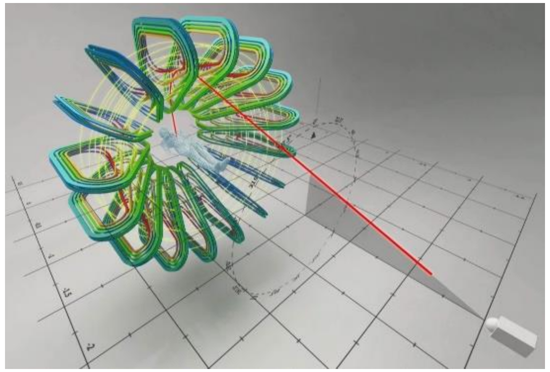

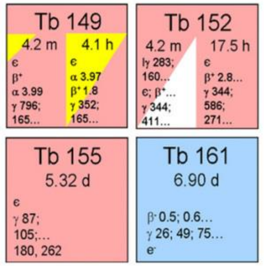

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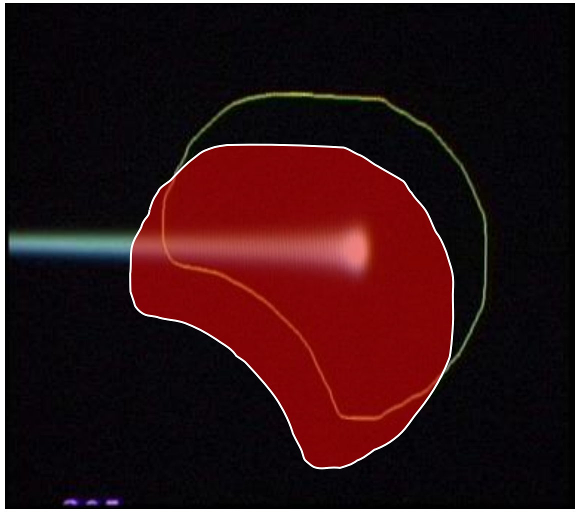
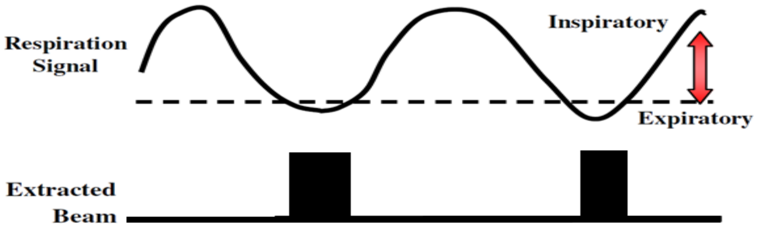
Mitigating organ / tumor motion

Possible solutions:

Organ motion

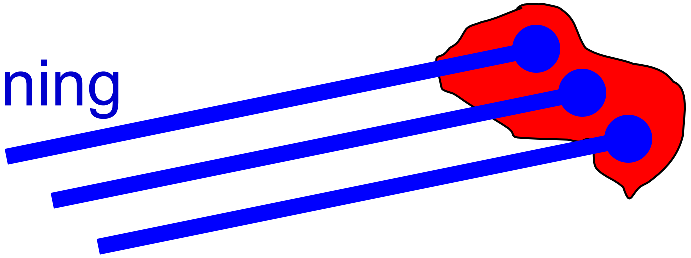


- Gating

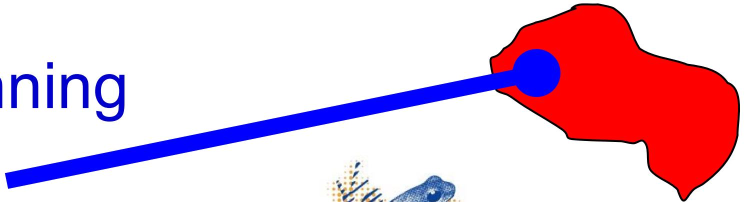


- Adaptive scanning

  (tumor tracking)



- Fast rescanning



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FLASH Therapy

- FLASH is a biological phenomenon and not defined via specific physical beam parameters
- Healthy tissue effect (not tumour tissue!)
- What have been the experimental conditions to observe a FLASH effect ?
    - Small volumes of normal tissues (a few cc)
    - Mainly with single dose (> 7-8 Gy)
    - Generally with Overall Treatment Time (OTT) < 200 ms

Conventional **FLASH**

25 Gy no necrosis

28 Gy

31 Gy

34 Gy

28 Gy

31 Gy

34 Gy, no necrosis

Source: J. Bourhis, Clinical perspectives for FLASH Therapy

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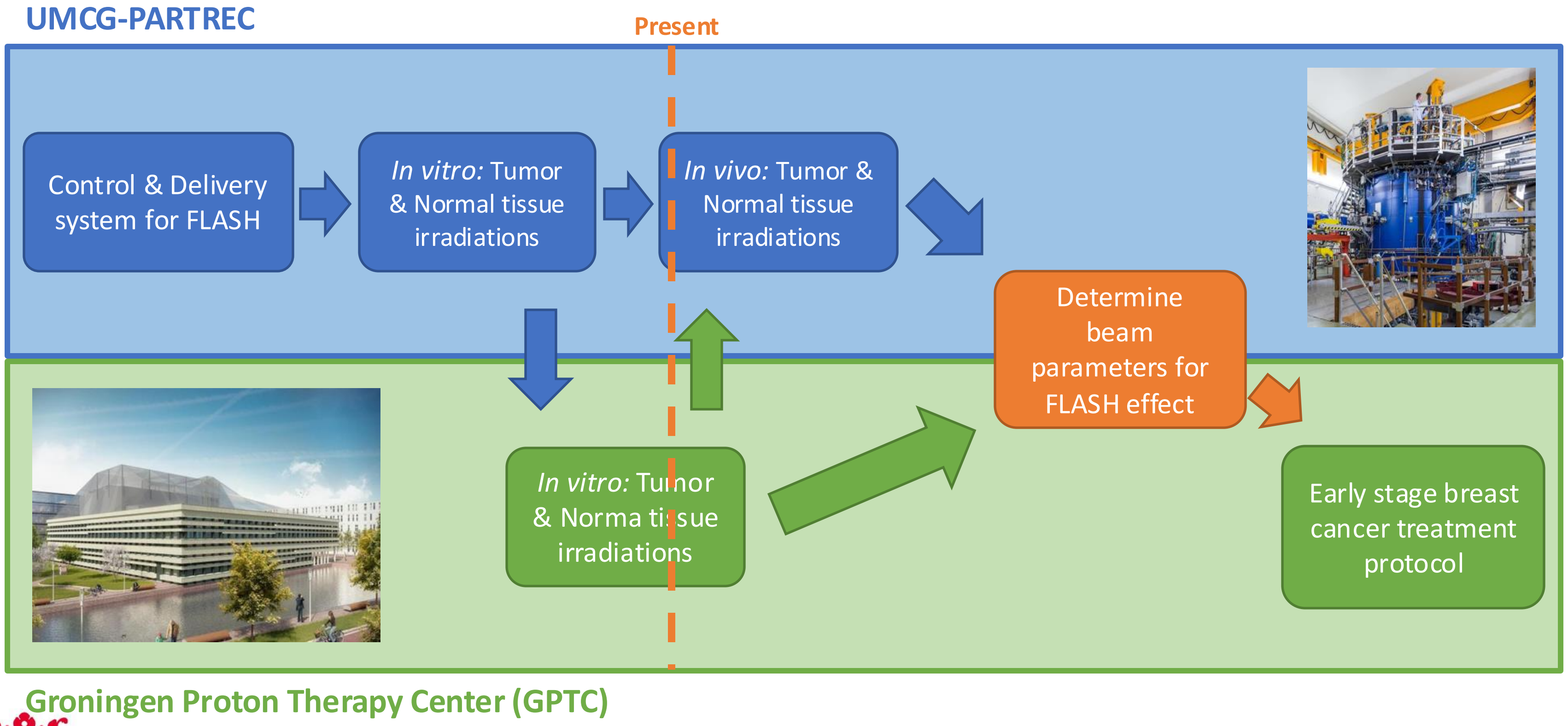
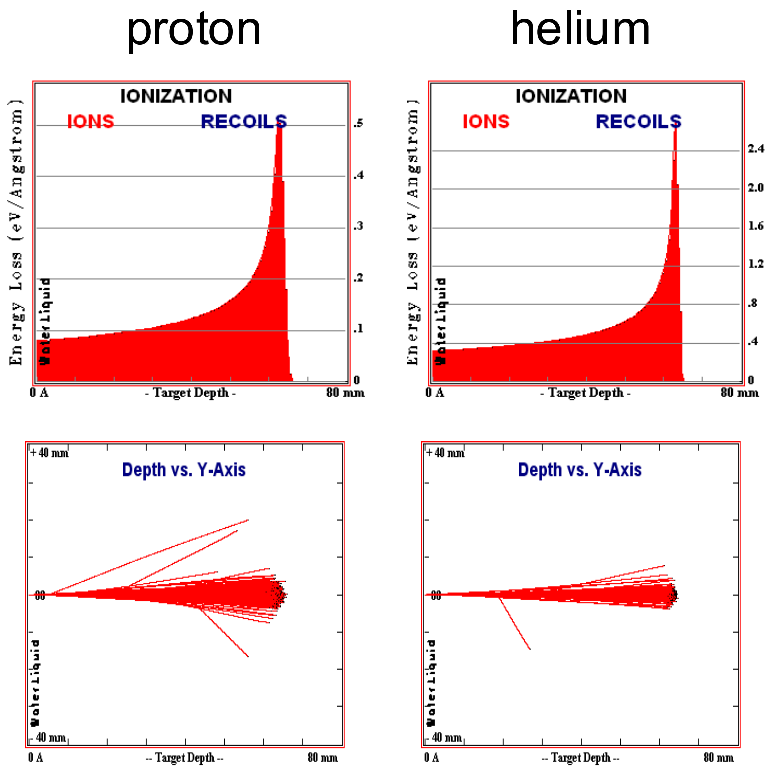
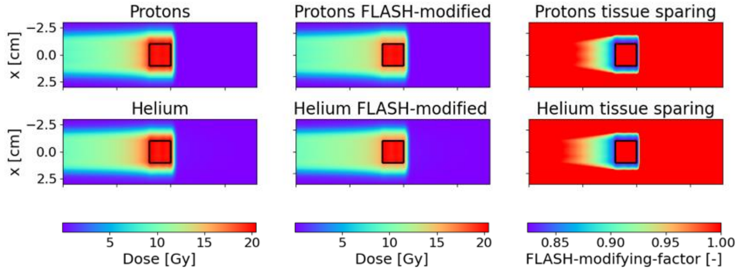
FLASH Irradiations

- Can deliver proton and helium beams with FLASH intensity
- Establish Twin Beams, replicating dose delivery parameters and control methods in conformity with clinical facilities







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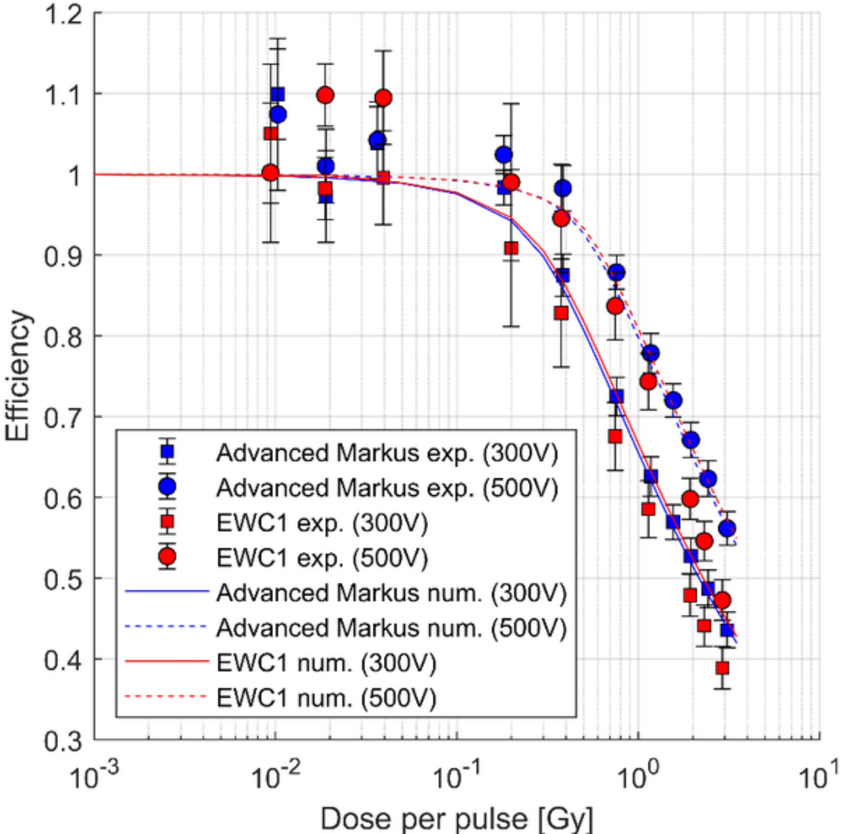
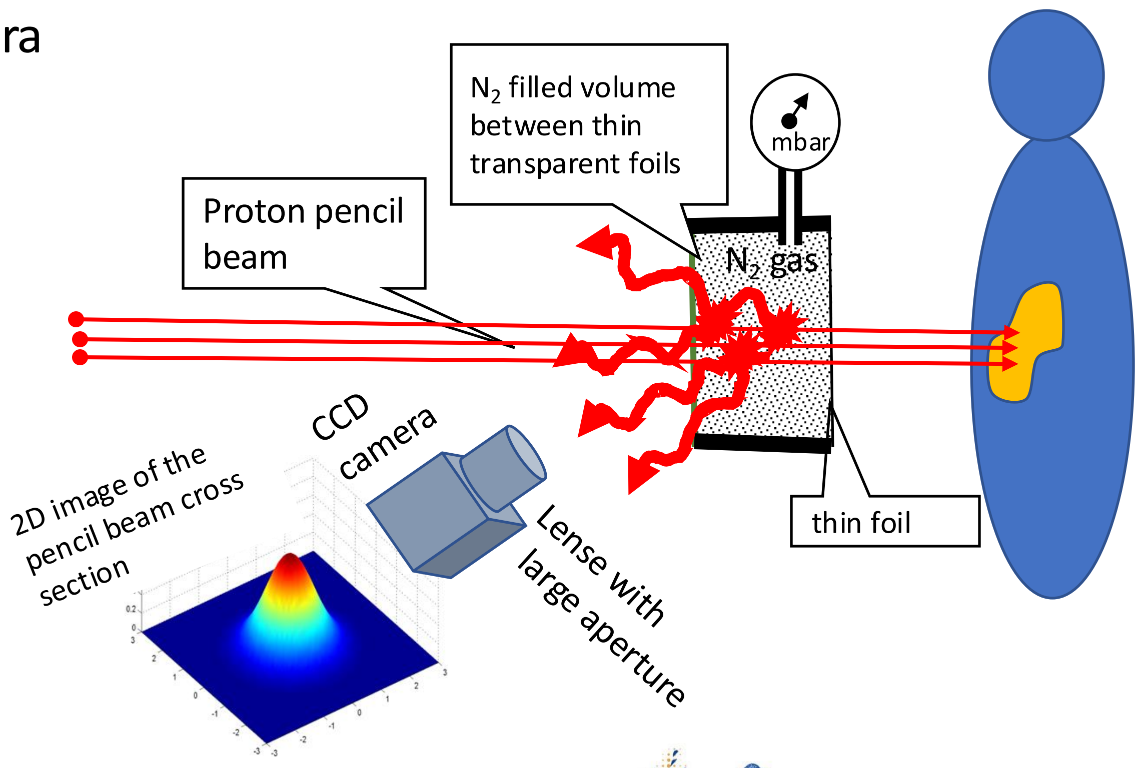
Beam Dosimetry at FLASH Dose Rates

- FLASH therapy requires >40 Gy/s
- For human tumours (~1 liter) that means 100s nA of current
- Standard solution: ionization chambers - saturate
- Proposed solution: Scintillating gas and camera



2D dose-monitor



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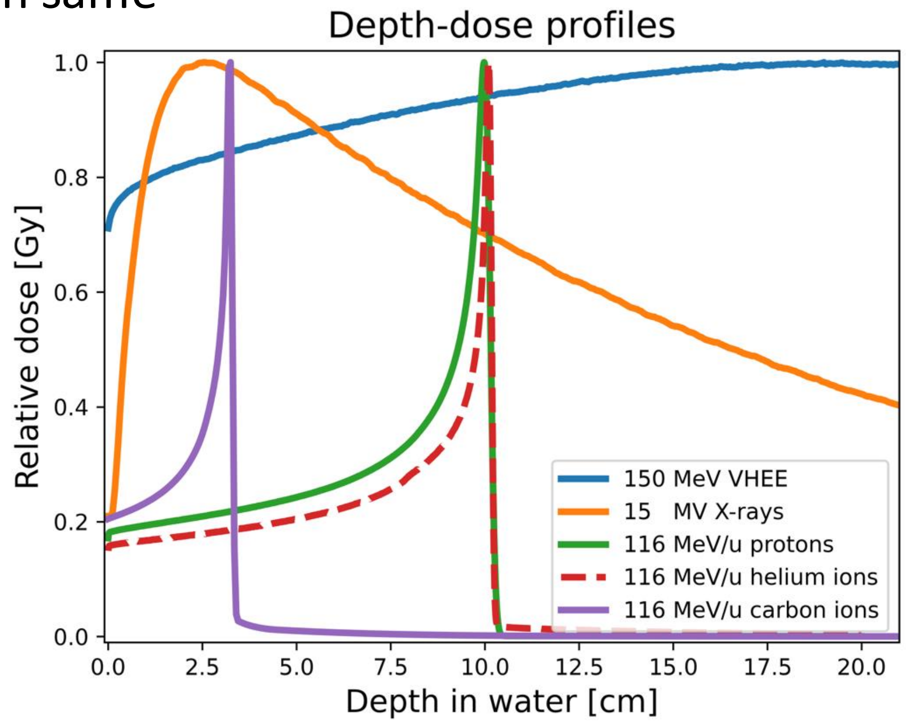
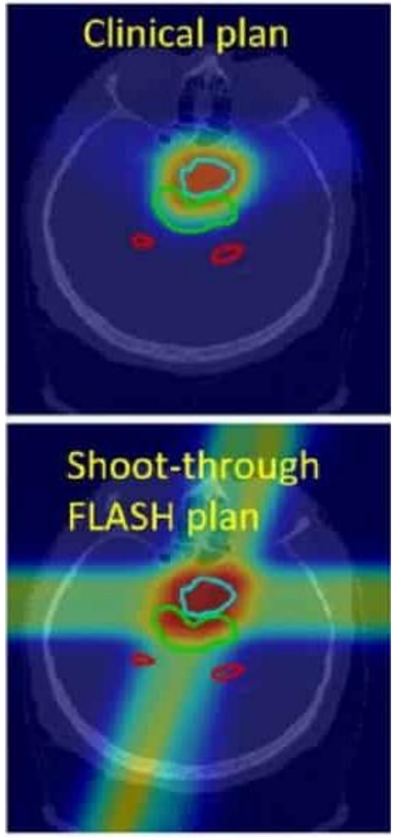
Very High Energy Electrons

- Conventional proton or ion irradiations are performed with Spread-Out-Bragg-Peak (SOBP)
- No technical solution to generating SOBP with same dose conformity at FLASH time scale

  => Applied in "transmission mode"
- Possible solution: electrons with > 100 MeV
- VHEE are less expensive
- VHEE are more sustainable
  - lower energy consumption
  - less material needed (iron, steel, concrete)
  - less activated materials

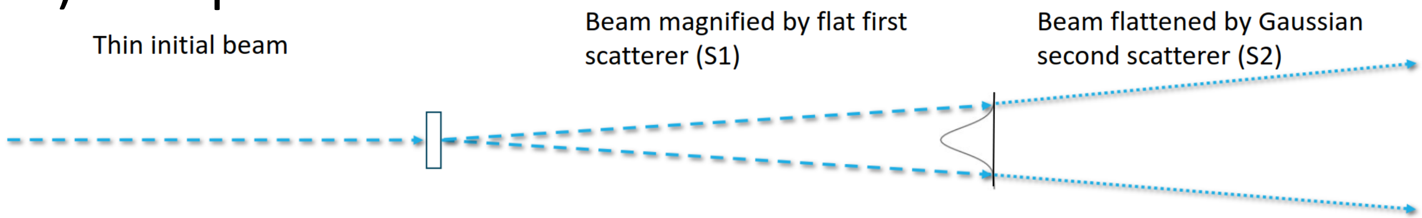


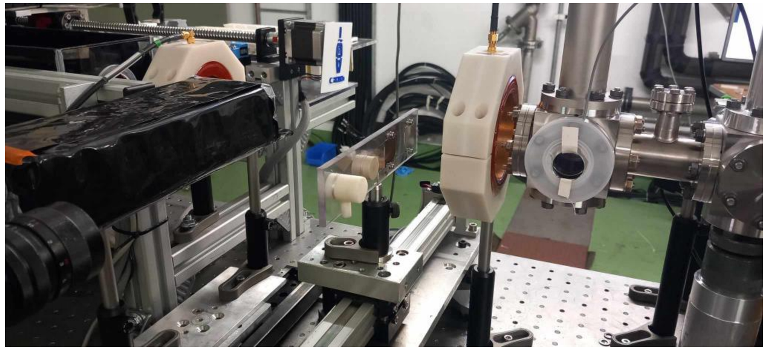


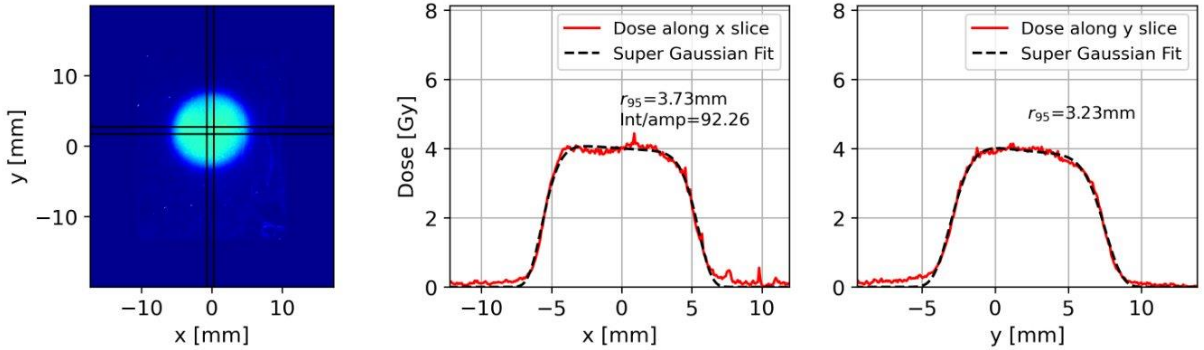
Dose Delivery for VHEE

- Scanning at FLASH time scale (100 ms) is impractical
- Solution: Scattering
- Tests at CLEAR successful

  => Now a standard tool for dose distribution for radiobiological experiments at CLEAR







- In collaboration with
  - M. Dosanjh, C. Robertson (Oxford)
  - R. Corsini, A. Latina (CERN)

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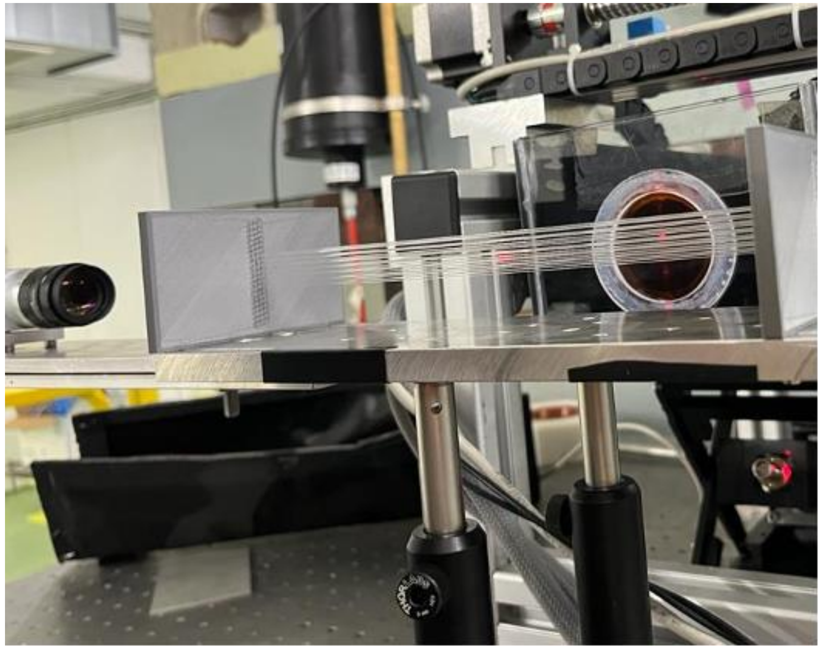
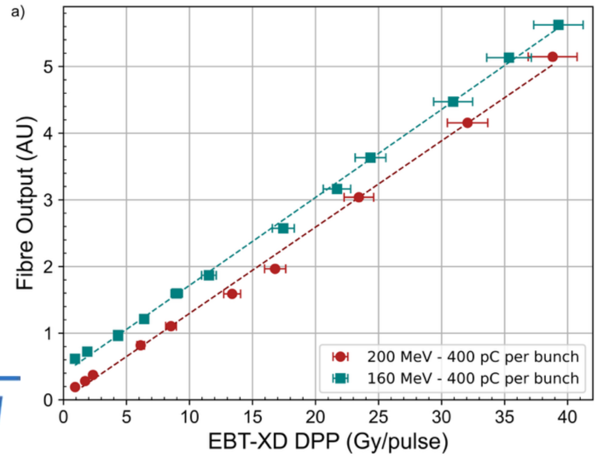
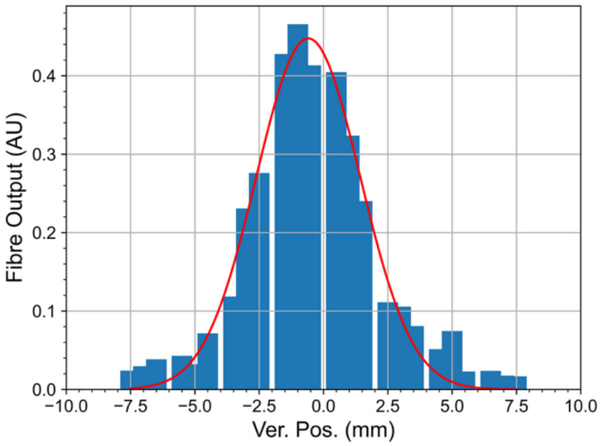
Beam Monitor for VHEE

- Two arrays of silicon fibre sensors
- Measure Cherenkov radiation (not scintillation)
- Readout: CMOS camera
- Measurements at CLEAR
  - Profile measurements
  - Linearity of response with dose rate (up to 40 Gy per 100 ns pulse)
- In collaboration with
  - M. Dosanjh, J. Bateman (Oxford)
  - R. Corsini, I. Ortega (CERN)







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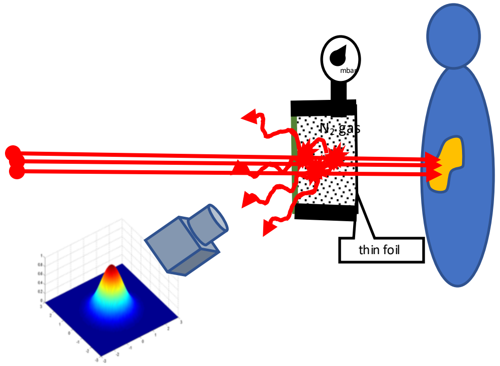

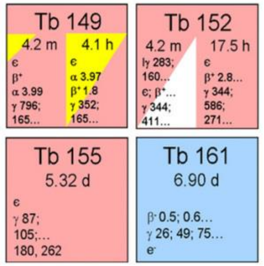

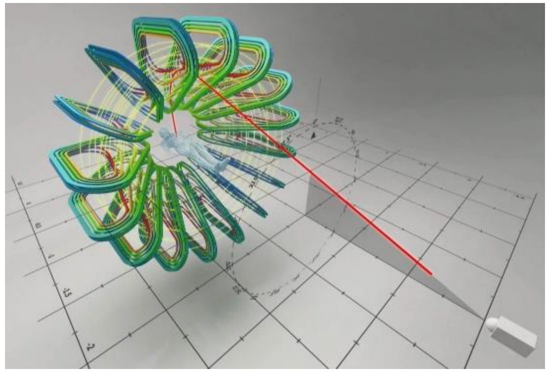

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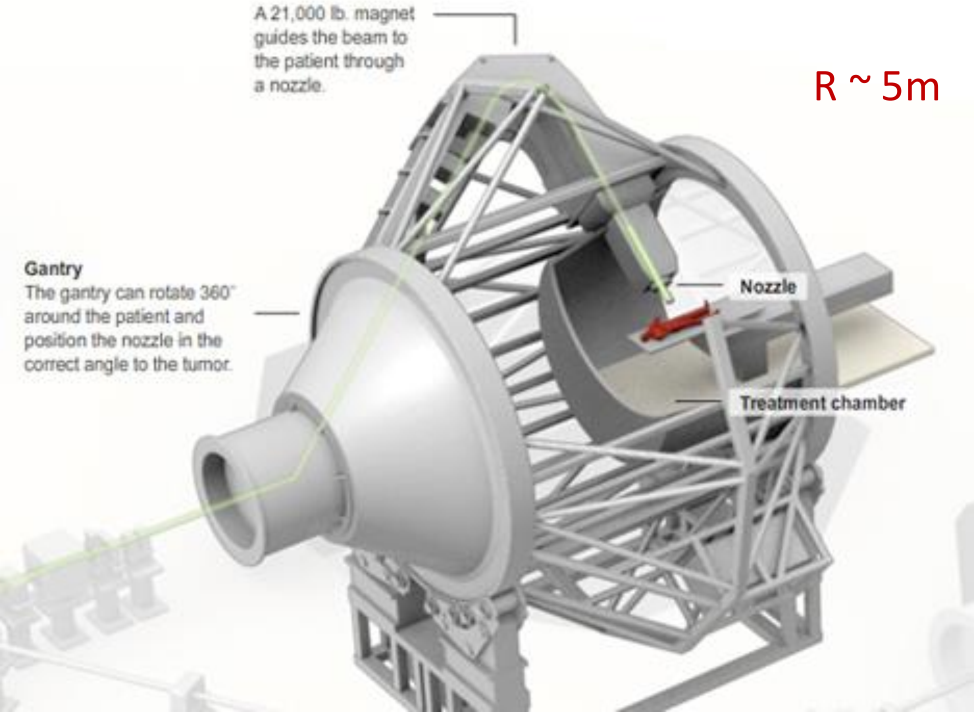
Conical gantry - Commercial standard layout



R ~ 5m

- 135° bending magnet
  - Shorter length - but larger radius
  - Cylindrical treatment cell
- Initially only for passive scattering
- Lately also for scanning

IBA
Sumitomo
Hitachi
Mitsubishi
Varian

Munich

First commercial scanning gantry of Varian in Munich

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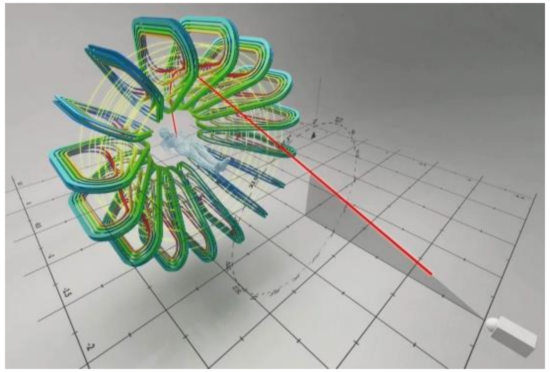
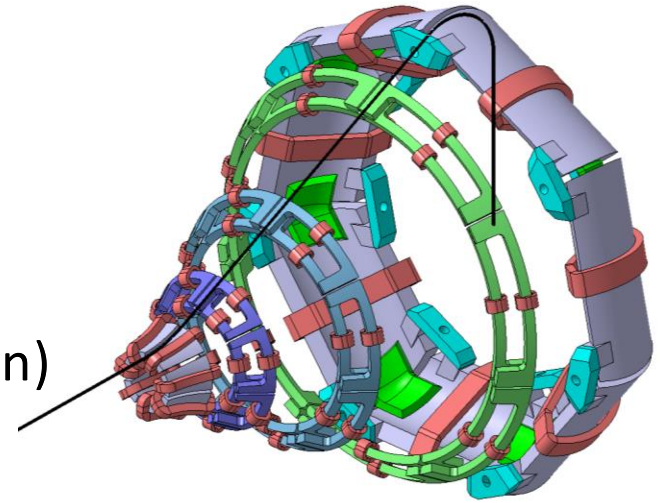
GaToroid

- Static gantry
- Irradiation angle set by vector magnet
- Beam focussed and deflected via toroidal magnets
- Advantages: extremely fast stereotactic irradiation
  => Optimal for FLASH, motion mitigation, fast-Arc therapy
- Four versions:
  - Proton, ion, VHEE and proton pre-clinical
- Applying for funding to install at PARTREC
- In collaboration with University of Oxford and CERN
  (L. Bottura, M. Dosanjh, A. Haziot, A. Latina, T. Lehtinen, C. Robertson)





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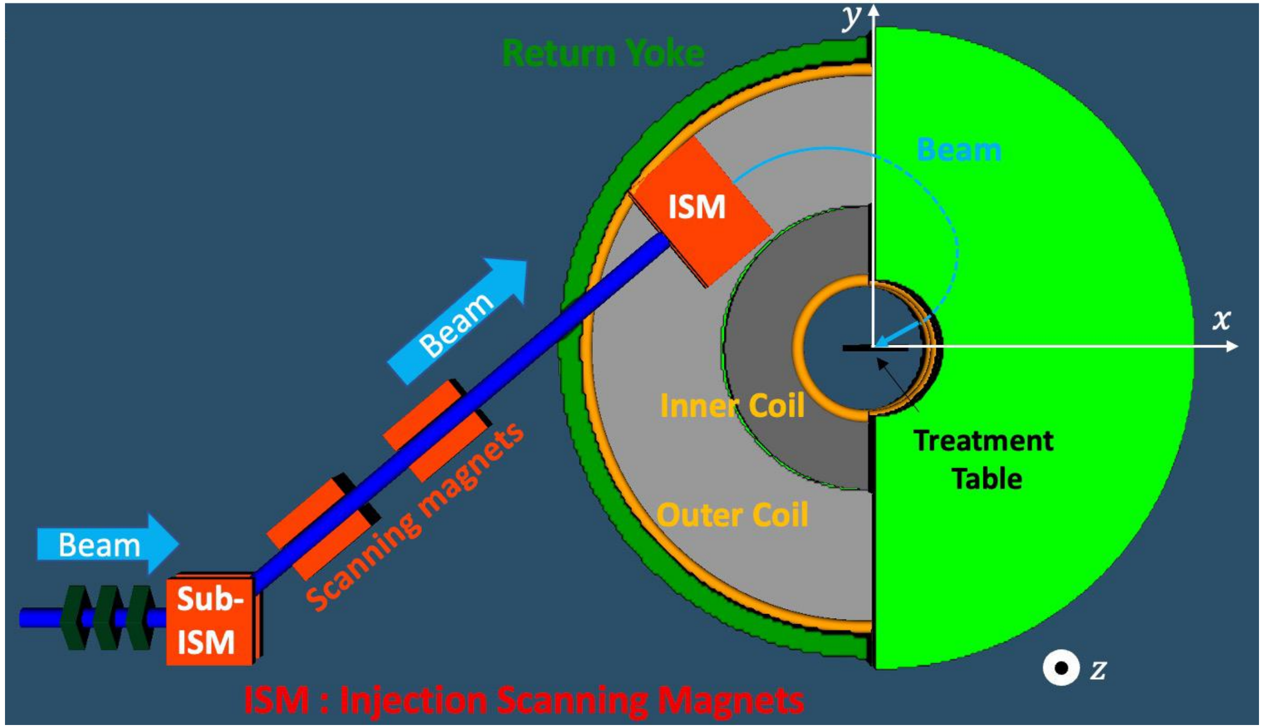
Arc gantry

- Outer Coils:
  Generate magnetic field
- Inner Coils:
  Create a magnetic free area for treatment
- ISM (Injection Scanning Magnets):
  Set the treatment angle
- Challenges:
  Beam focussing (independent of treatment angle), scanning
- In collaboration with:



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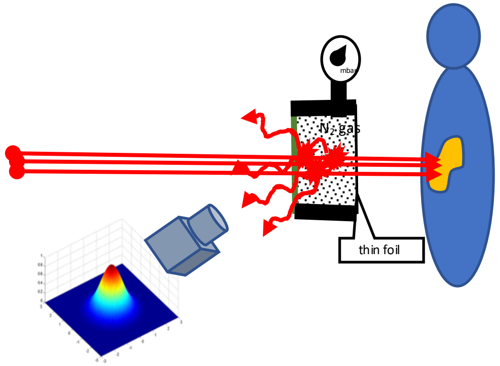

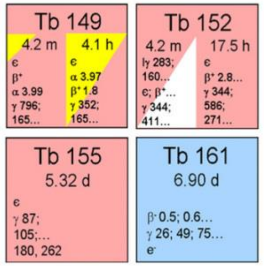

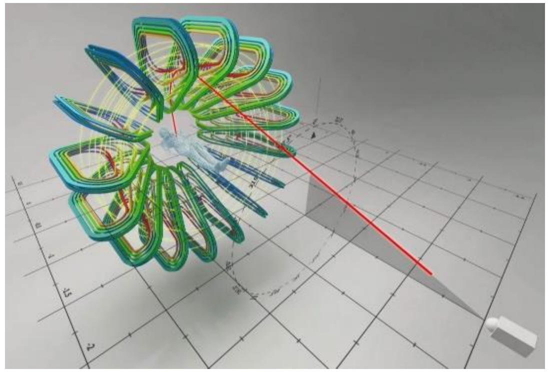

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Real-time In-vivo VERification of proton therapy (RIVER)

Aim: *“reducing treatment planning safety margins without reducing treatment safety”*

How ?

- PET imaging of the short-lived isotope N-12 ($T_{1/2}$ = 11 ms)
- Range determination per pencil beam spot

Patient benefit

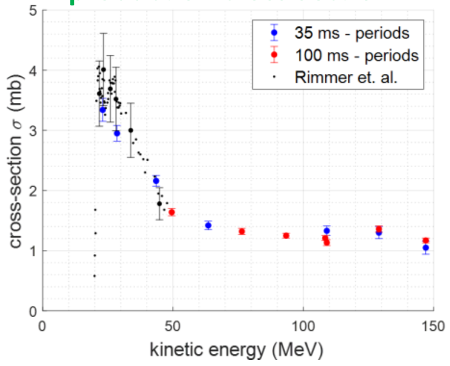
- reduced safety margins lead to
  - ➢ less dose to organs-at-risk
    - ➢ less complications
      - ➢ better quality of life

Research focus

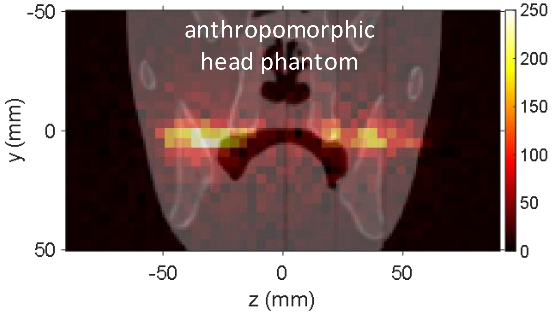
- experiments with a head phantom
- mimic clinical workflow from TPS via Monte Carlo prediction to comparison with experimental PET images

experiments at PARTREC

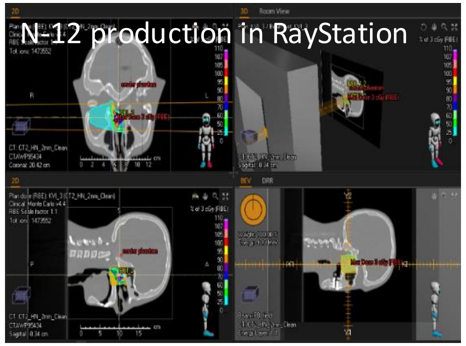
N-12 production cross section

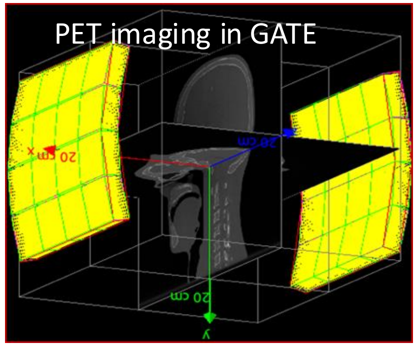


N-12 image in 10 s (10^{10} protons)



calculations/simulations





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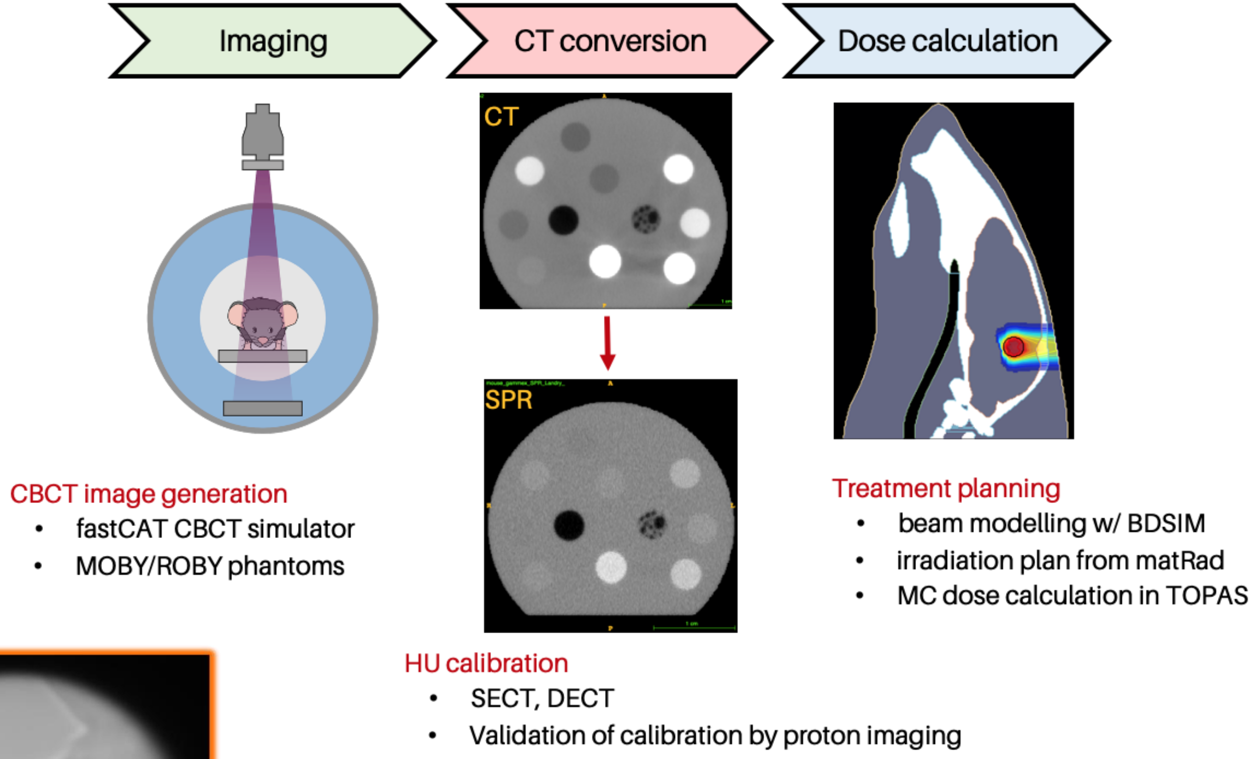
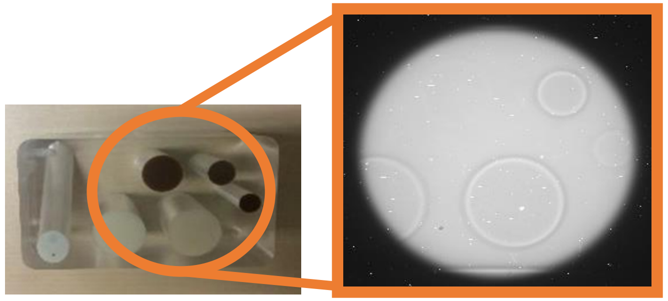
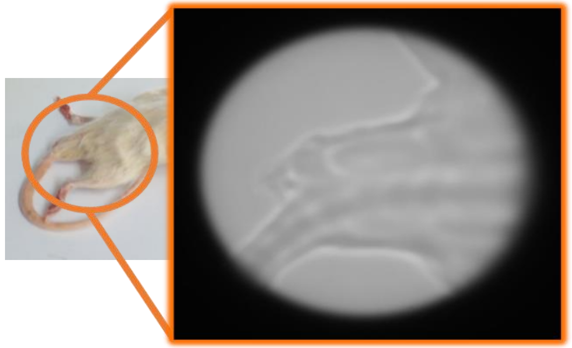
Proton Radiography

- Allows precise tissue density measurement
- Two different methods:
    1. Integral charge yield
       (at single or multiple energies)
    2. Individual particle tracking
- Irradiations of phantoms and mice performed at PARTREC
  (LANEX screen + CCD Camera, 50 mm proton field)
- Worldwide first clinical implementation at GPTC!







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Summary

- UMCG has unique combination of treatment facility (GPTC) and research center accelerator facility (PARTREC)
- PARTREC delivers protons and ions (He, C, O and others)
- PARTREC has team of 40 people
- Ongoing research topics are:
    - Radiation Biology, Microdosimetry, Minibeams, Ultra-fast Irradiations, Gantries, Patient Imaging, Nuclear Medicine

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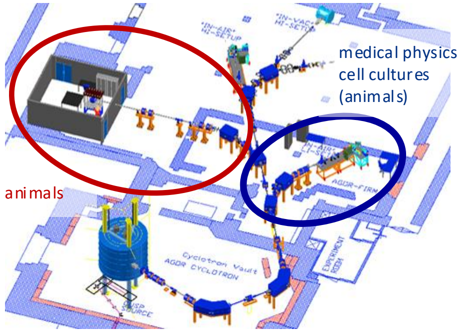

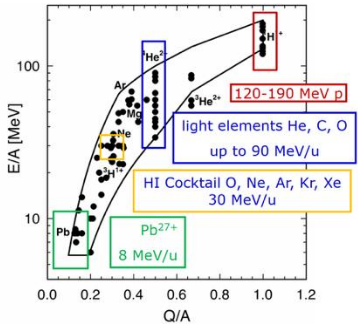

- Acknowledgement
    - Research funding
    - Access funding
    - Host institutions and all colleagues for contributing

DUTCH CANCER SOCIETY

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