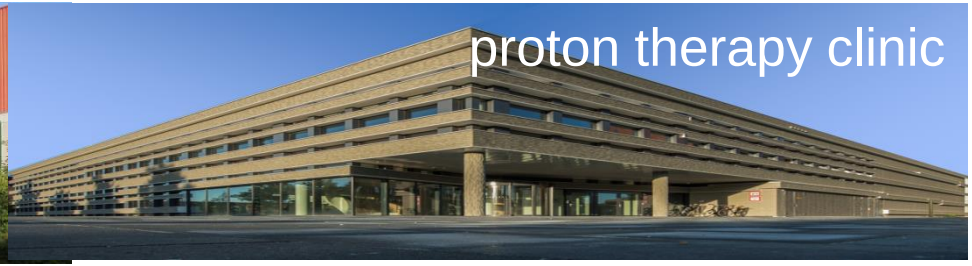
university of groningen
kvi - center for advanced radiation technology

umcg

biomedical research capabilities @ KVI-CART

S. Brandenburg[1]; L. Barazzuol[2]; S. Both[2]; R.P. Coppes[2];
M.J. van Goethem[1,2]; B.N. Jones[1]; P. van Luijk[2]

[1] KVI-CART, University of Groningen
[2] University Medical Center Groningen

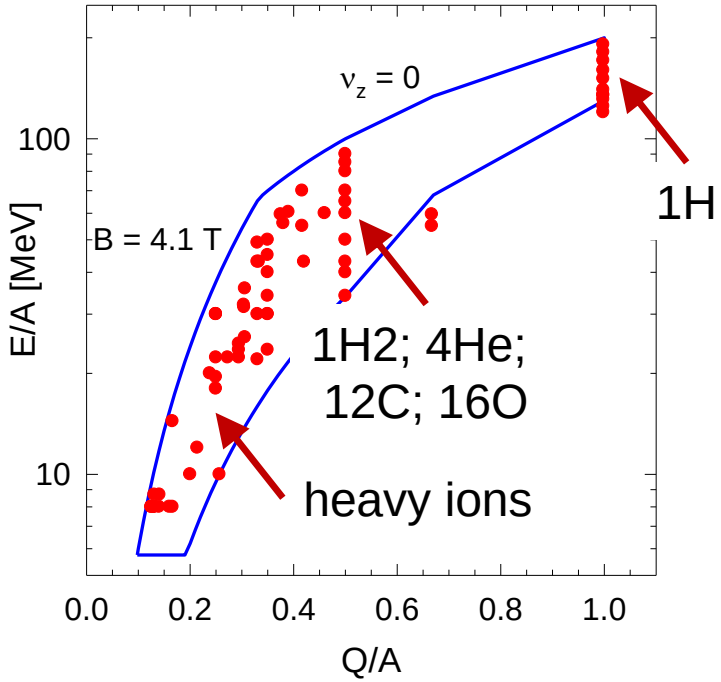


outline

- experimental facilities
- access procedures
- some examples of on-going research
  - radiation biology
  - proton therapy physics

KVI-CART accelerator facility

- superconducting cyclotron
  - multi particle; multi energy

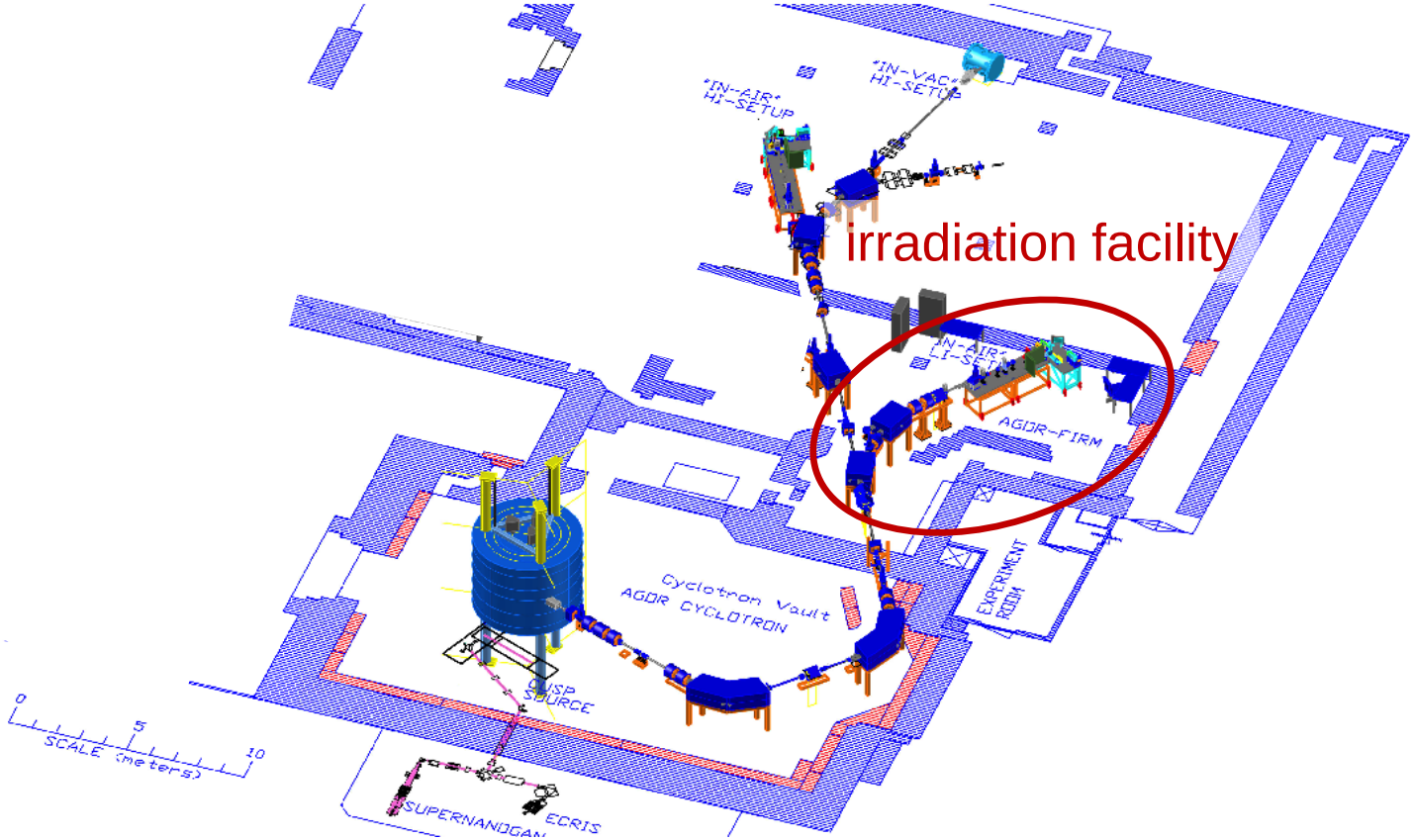


KVI-CART accelerator facility

- focus: **particle therapy research**
  - radiation biology incl. small animal research
  - radiation physics

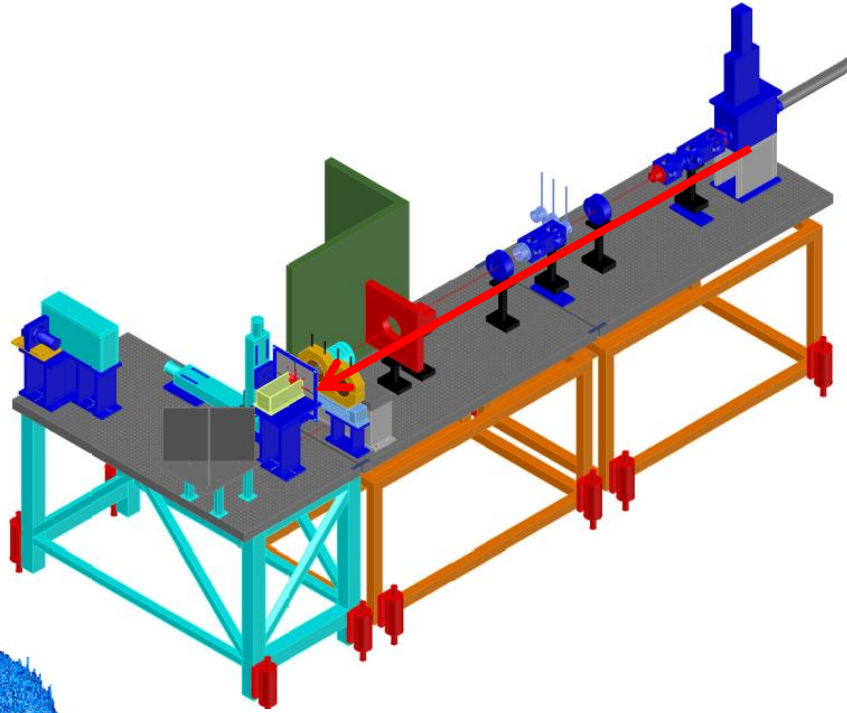
- some relevant beams
  - protons $E \leq 190$ MeV; $R_{H2O} \leq 230$ mm
  - helium $E \leq 90$ MeV/A; $R_{H2O} \leq 60$ mm
  - carbon $E \leq 90$ MeV/A; $R_{H2O} \leq 60$ mm

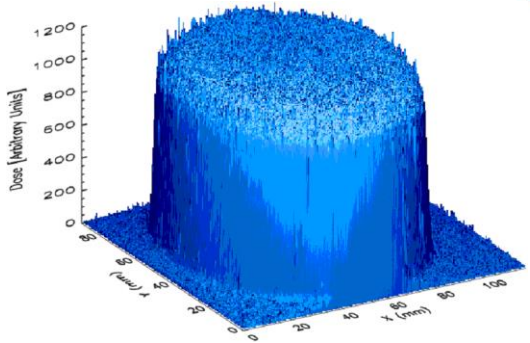
experimental facilities: current



irradiation facility

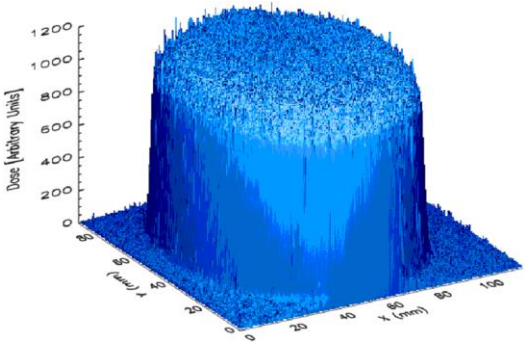
- irradiation in air
- passive scattering: up to 80 mm
  - carbon: up to 30 mm
- scanning: up to 100 mm
  - arbitrary pattern pencil beam
  - uniform
- optical tables
  ➡ flexible, reproducible
- homogeneity ± 2 %

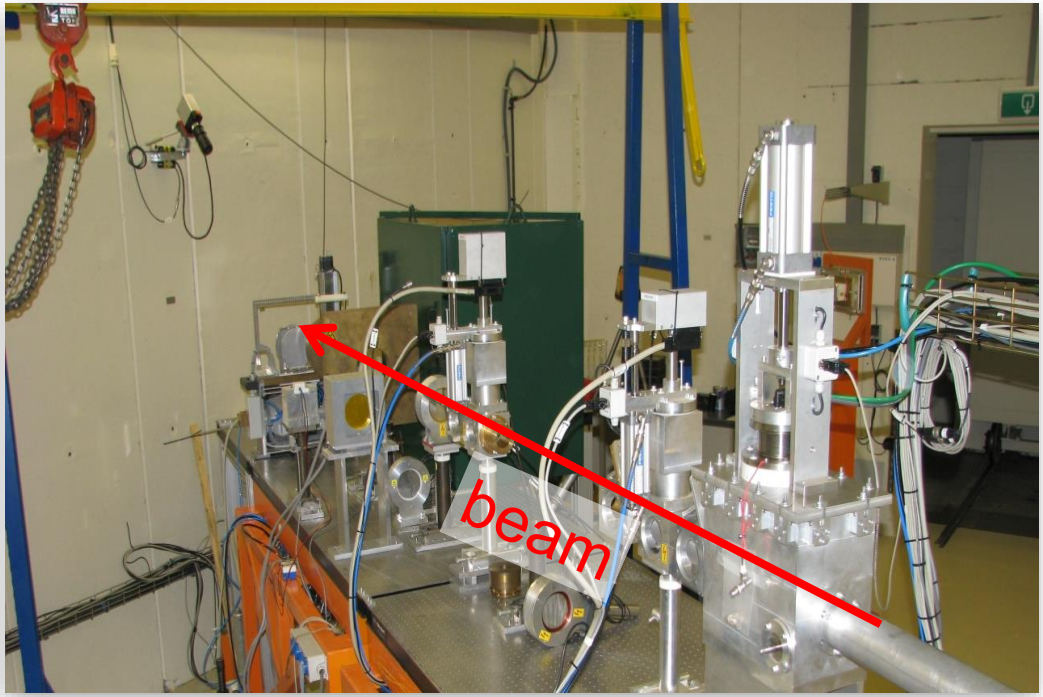




irradiation facility

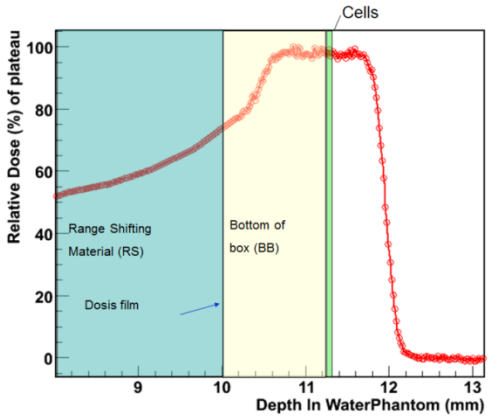
- irradiation in air
- passive scattering: up to 80 mm
  - carbon: up to 30 mm
- scanning: up to 100 mm
  - arbitrary pattern PBS
  - uniform
- homogeneity ± 2 %





irradiation facility

- longitudinal distribution
  - pristine Bragg peak
  - spread-out Bragg peak
- CW or pulsed
  - frequency $\leq$ 2 kHz
  - pulse duration $\geq$ 50 μs



beam intensity/dose rate

- beam intensity
  - protons few – 10^{13} pps
  - helium few – 10^{13} pps
  - carbon few – 10^{10} pps
- proton, helium dose rate up to 500 Gy/s
  - dependent on field size
- 90 MeV/A carbon SOBP dose rate up to 200 Gy/min
  - higher at lower primary energy

experimental facilities: future

- image guided preclinical research
  - funded by DUTCH CANCER SOCIETY
- project ingredients
  - new beam line
  - 3D X-ray imager
  - 3D optical imager
  - irradiation planning software
  - data management

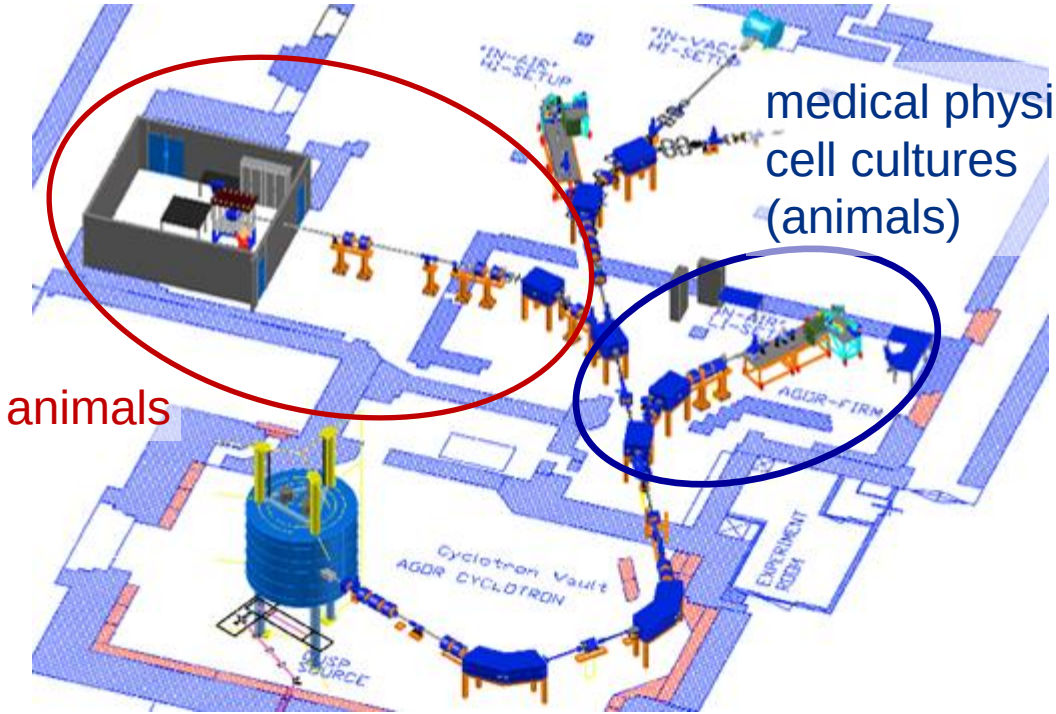


image guided preclinical research

- image guidance
  - CT + bioluminescence
- individual planning
- multiple modalities
  - PBS/scattering
  - shoot through/SOBP
  - minibeams
  - FLASH
  - protons, helium

source: Eric Ford, Seattle

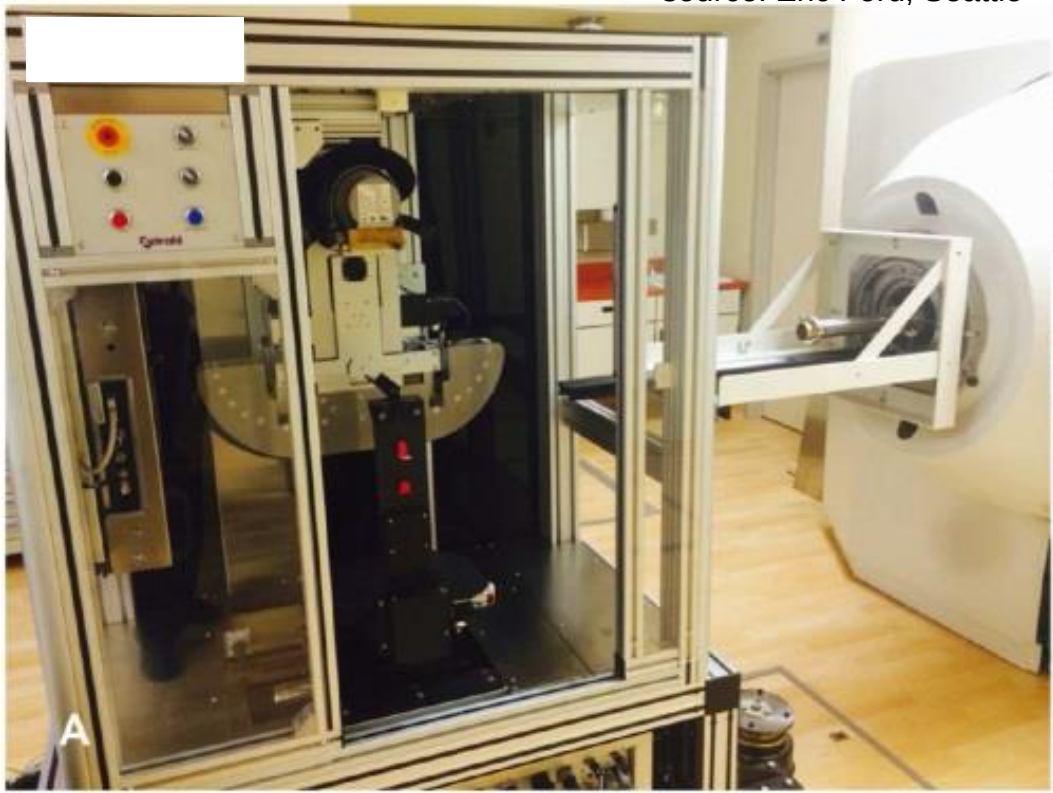


image guided preclinical research

- physics/technology challenges
  - dimensional scaling
    - beam shaping; range; positioning
  - irradiation planning
    - @ irradiation time
    - automated segmentation
    - Monte Carlo essential
  - dosimetry
    - very small fields; very high dose rates
- synergy with clinic (on-line adaptive planning)?

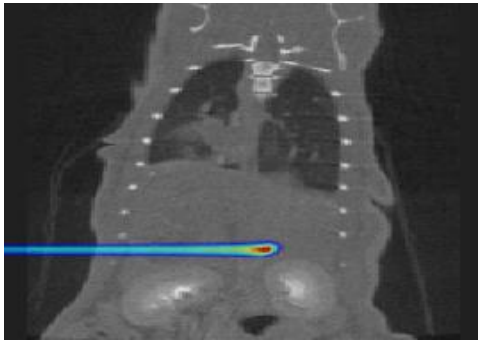
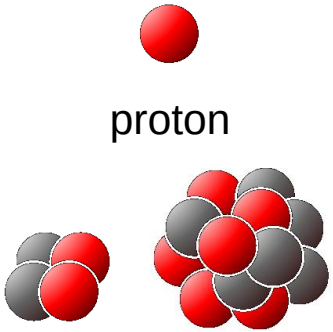
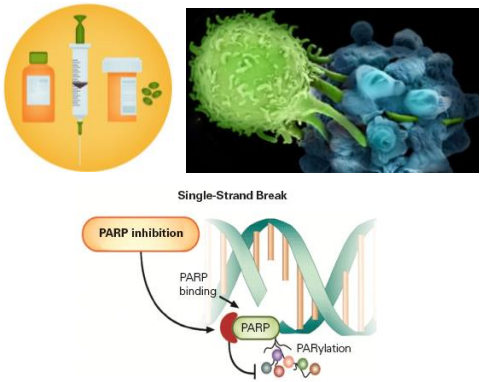


image guided preclinical research

biological effectiveness



interaction particles with systemic therapies



biological optimisation treatment response at organ level

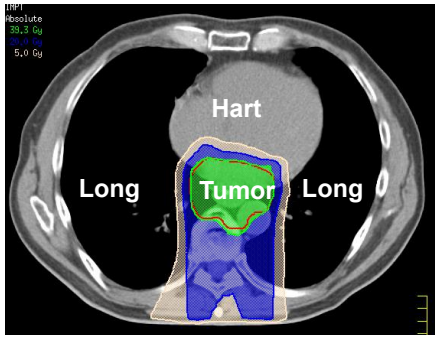
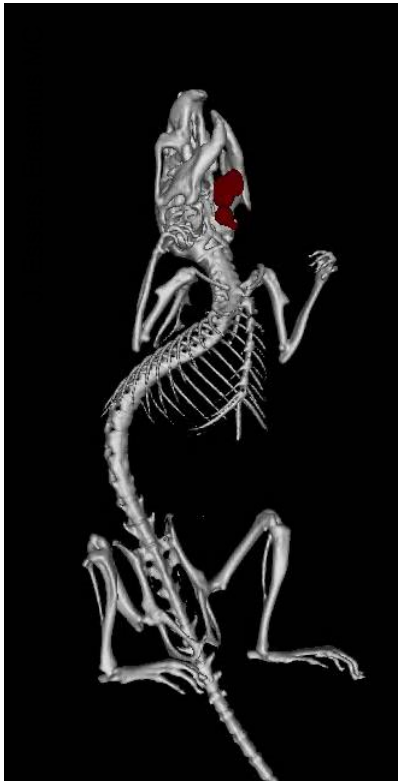


image guided preclinical research

- targets
  - orthotopic tumor models
  - organ at risk sub-structures
- individual imaging
  - anatomical variations between animals
  - individually optimized irradiation plan
- new irradiation modalities: grid, FLASH
  - effect on therapeutic window



animal facilities

- single on site animal accomodation with IVCs
  - capacity 200 rats
  - no long term stay
  - two additional accomodations planned
- laboratory for animal handling prior and post irradiation
  - two additional labs planned
- workflow not breaking containment under development
  - mitigate issues with animal returning to origin

support for animal experiments

- provide one stop shop
  - experiment development
  - ethics authorisation process
  - animal procurement logistics
  - irradiation + follow-up
  - GronSAI imaging center
    - optical
    - molecular
    - CT
    - MRI
  - data management facilities

Open Access facility

- access based on scientific quality
  - evaluated by independent PAC
- user support by
  - EU-funded transnational access
    - ENSAR2 until March 2020
    - INSPIRE until March 2022
    - new proposal under evaluation for period until mid-2024

  - ESA: Biological Effects of Space Radiation

esa
European Space Agency

- information: https://www.rug.nl/kvi-cart/research/facilities/agor/

radiation biology

- small animals: normal tissue damage
  - spinal cord
  - radiation - drug interaction
  - salivary gland
  - heart – lung interaction
  - brain
  - dose delivery technique
    - scattering
    - shoot through 150 MeV protons
- cell cultures and organoids
  - carbon < 90 MeV/amu
  - oxygen < 90 MeV/amu

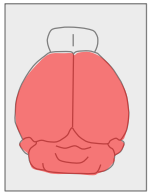
radiation induced cognition defects

Rat brain

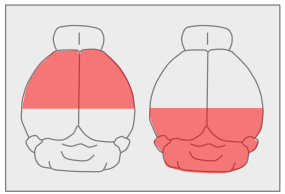
Sagittal view Dorsal view

= irradiated
= non-irradiated

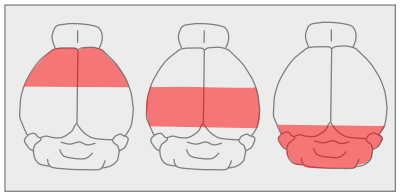
100% whole brain



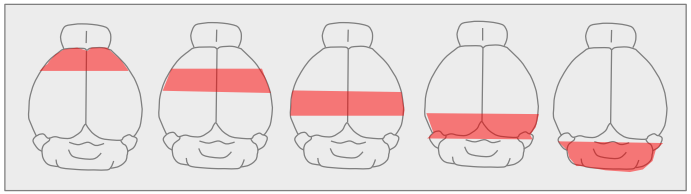
50% anterior-posterior



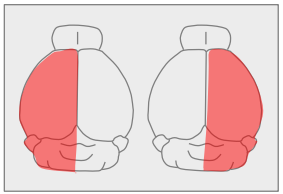
33% anterior-central-posterior



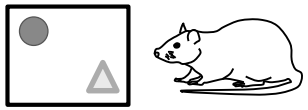
25% anterior-central anterior-central posterior-posterior



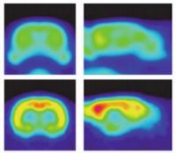
Left-right hemisphere



Behavioral tests



PET/MRI imaging



Brain tissue histology

CSF proteomics

Funding grants:

ZonMw KWF KANKER BESTRIJDING Alpe d'HuZes opgevenisgeenoptie.nl

L. Barazzuol, UMCG

radiation induced cognition defects

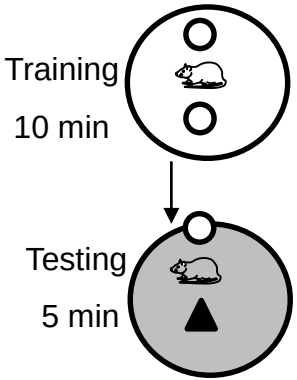
100% whole brain

50% anterior

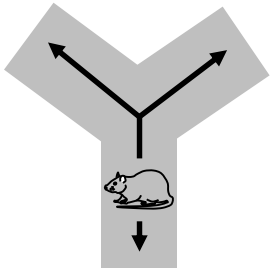
50% posterior

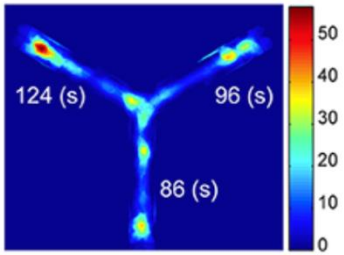
radiation induced cognition defects

Object recognition

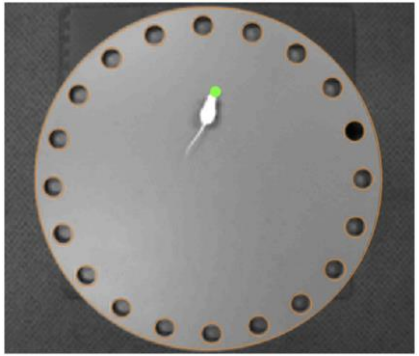


Y-maze test

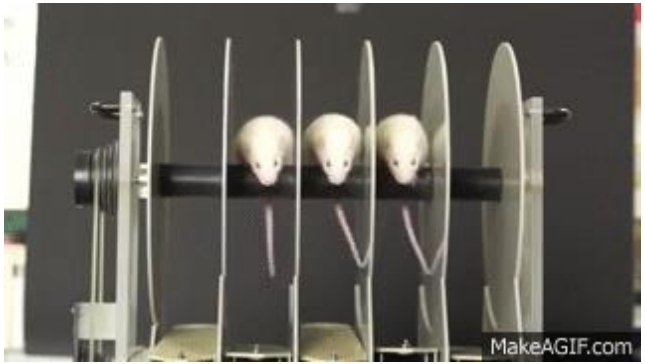




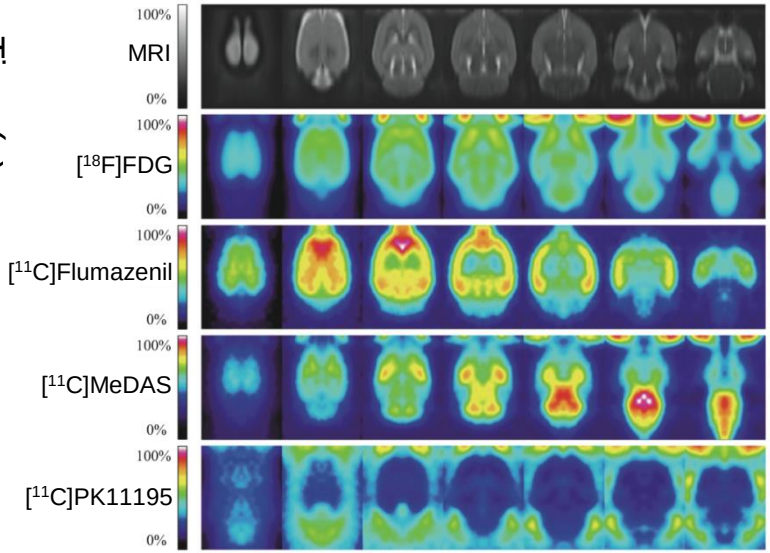
Barnes maze



Rotarod test



Horizontal view

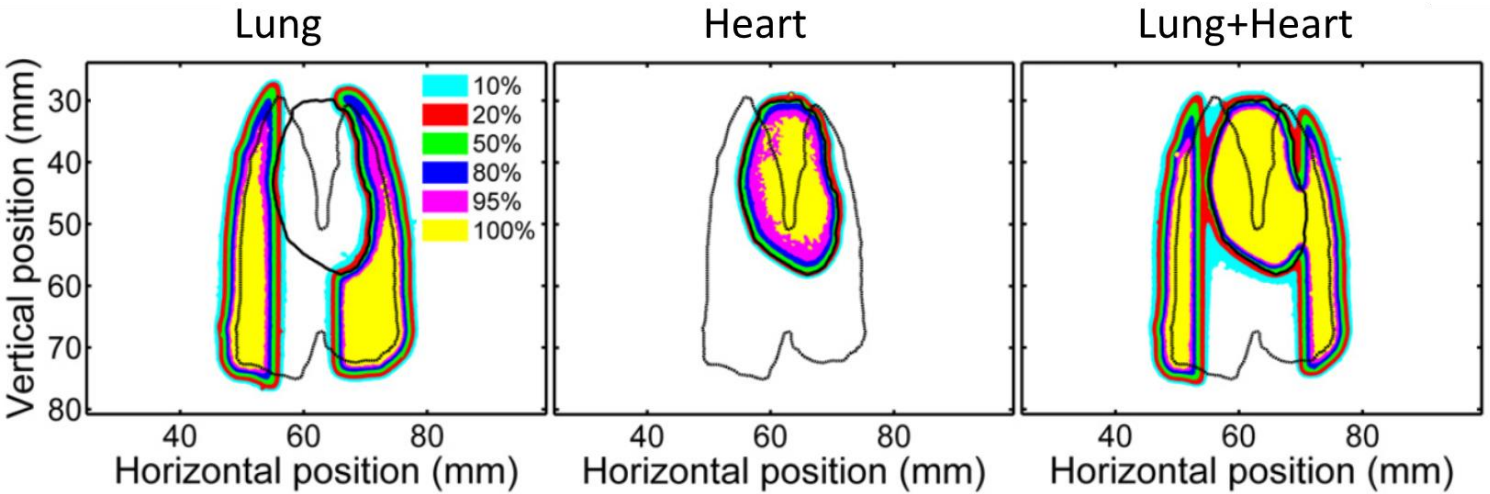


*courtesy of J. Doorduin, UMCG

L. Barazzuol, UMCG

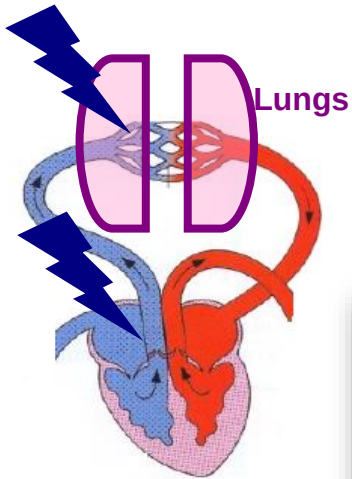
radiation induced lung toxicity

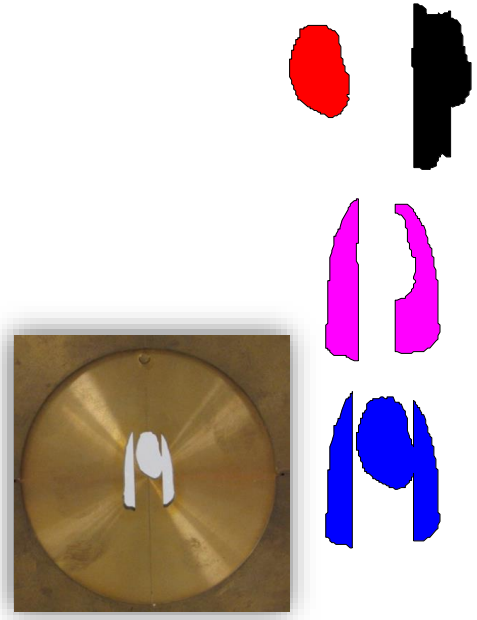
- test hypothesis: heart irradiation affects respiratory system
- unravel mechanism: pulmonary hypertension
- search for clinical evidence: retrospective study
- develop mitigation: prospective study + preclinical

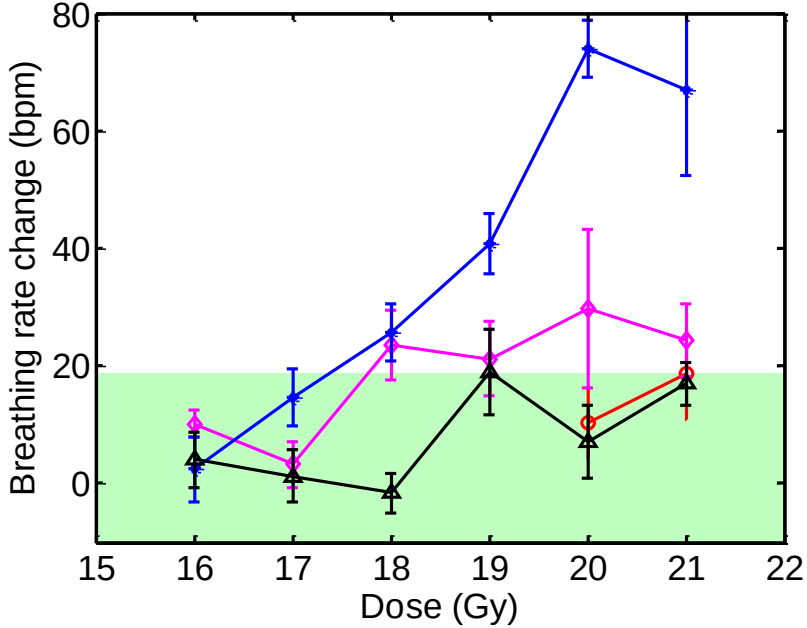


radiation induced lung toxicity

- 50 % lung with/without heart
- heart (+ small part lung)
- observable: long term respiratory capacity







P. van Luijk, UMCG

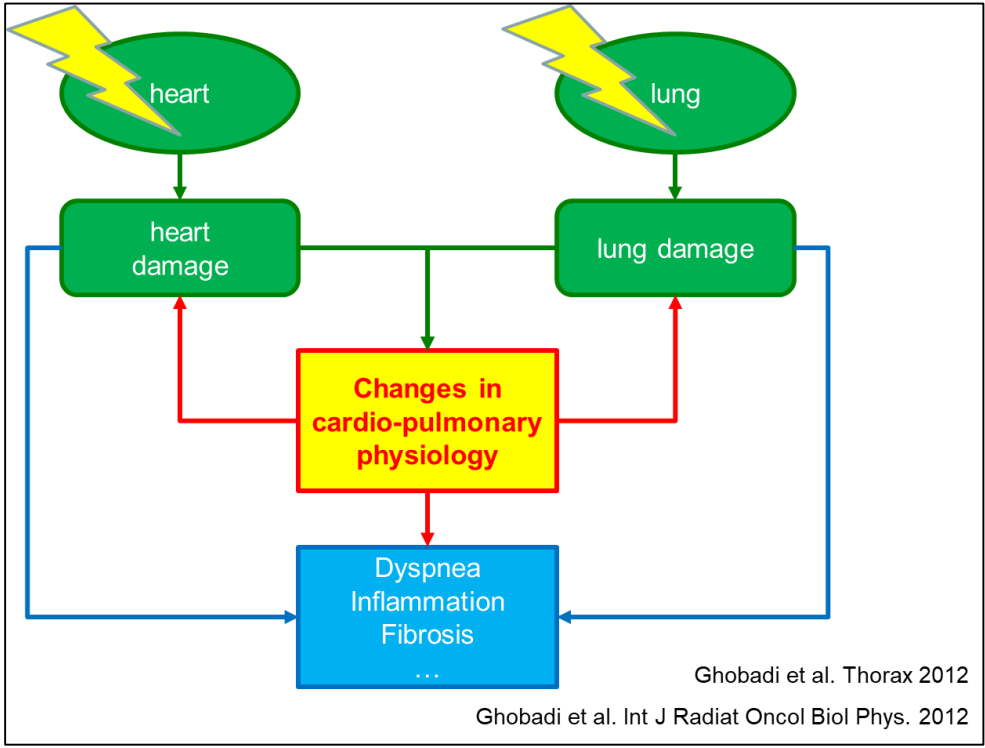
radiation induced lung toxicity

- radiation induced heart damage
  - increased pressure lung circulation
  - vascular damage

➡ impact respiratory capacity

- also observed in patients symptoms ~ heart failure

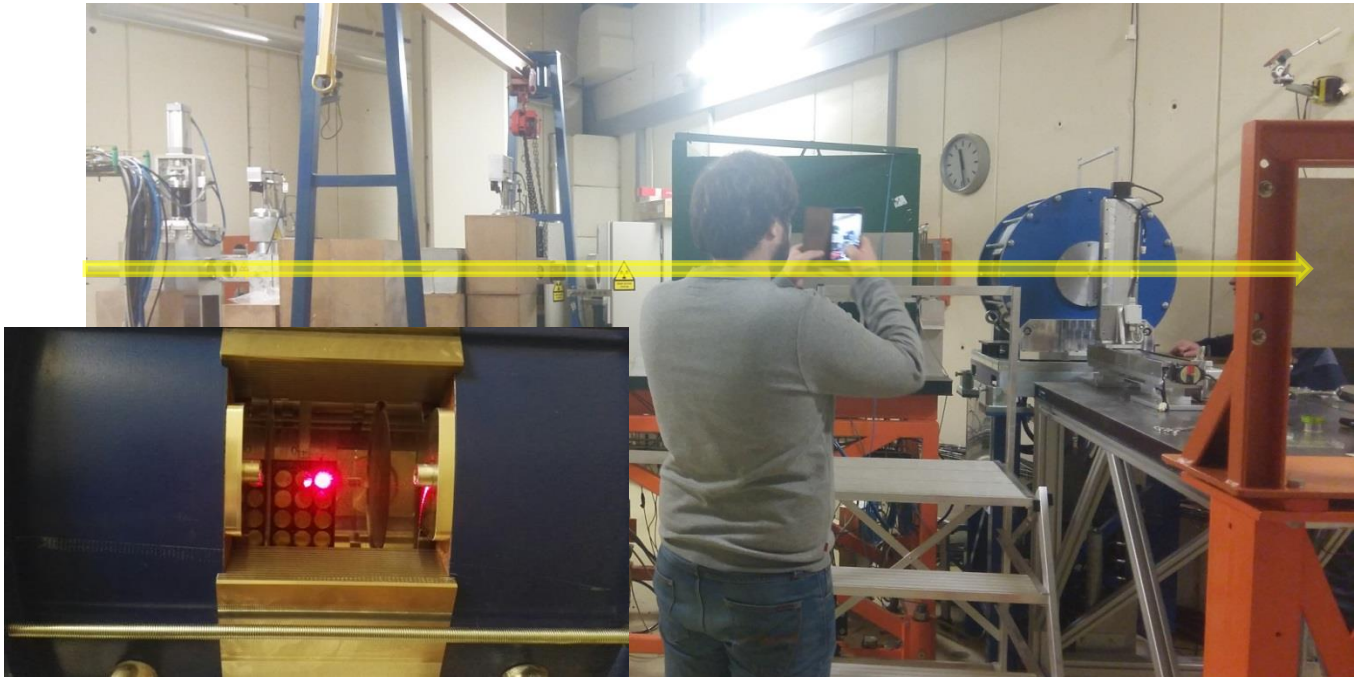
➡ preclinical study with drug



P. van Luijk, UMCG

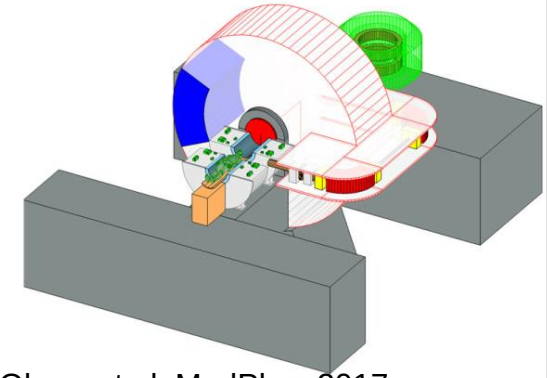
MRI-guided proton therapy

- effect magnetic field on radiation response cell cultures
- up to 1 T no effects observed
- future (2020 – 2021): measurements up to 3 T

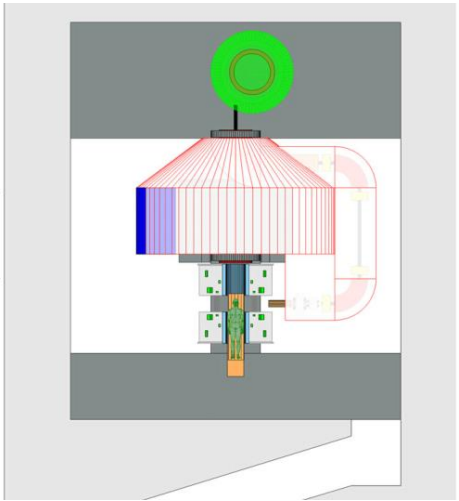


MRI-guided therapy

- interference MRI magnet – dose delivery
- impact MRI magnet on dose delivery “easily” calculable
  - required accuracy level 10^{-4}
- MRI imaging:
  - required accuracy level 10^{-6}
  - image distortion
  - dynamics scanmagnet

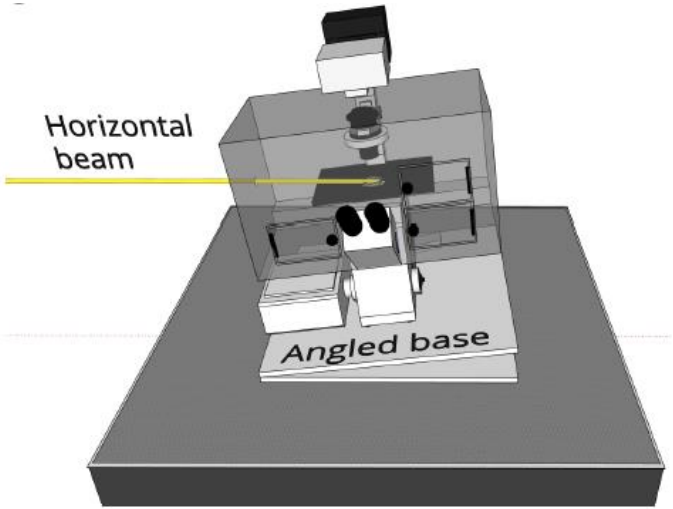


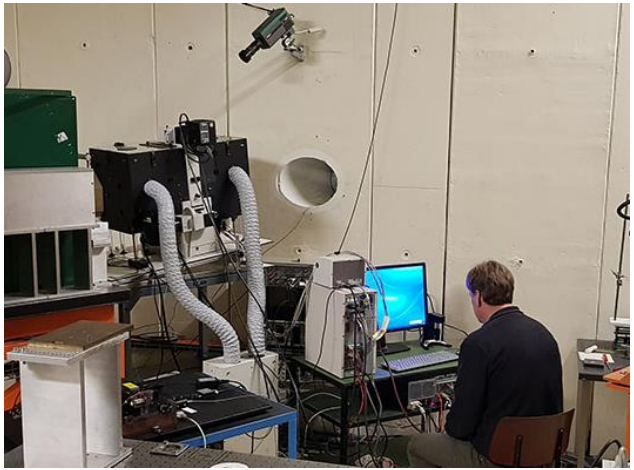
Oborn et al, MedPhys 2017

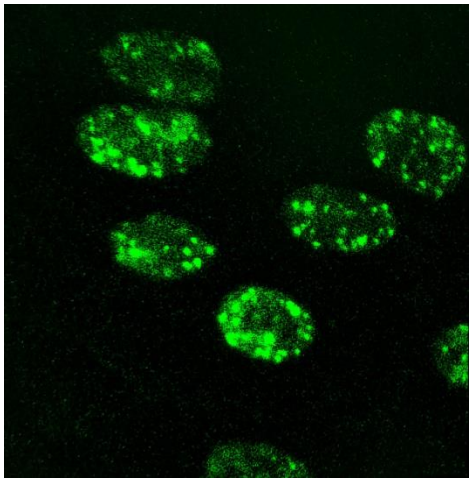


live cell confocal microscopy

- test experiment successfully performed
- first full experiments autumn 2019
- grant application state-of-the art system in preparation







P. Krawczyk, AMC

in vivo verification proton therapy

university of groningen
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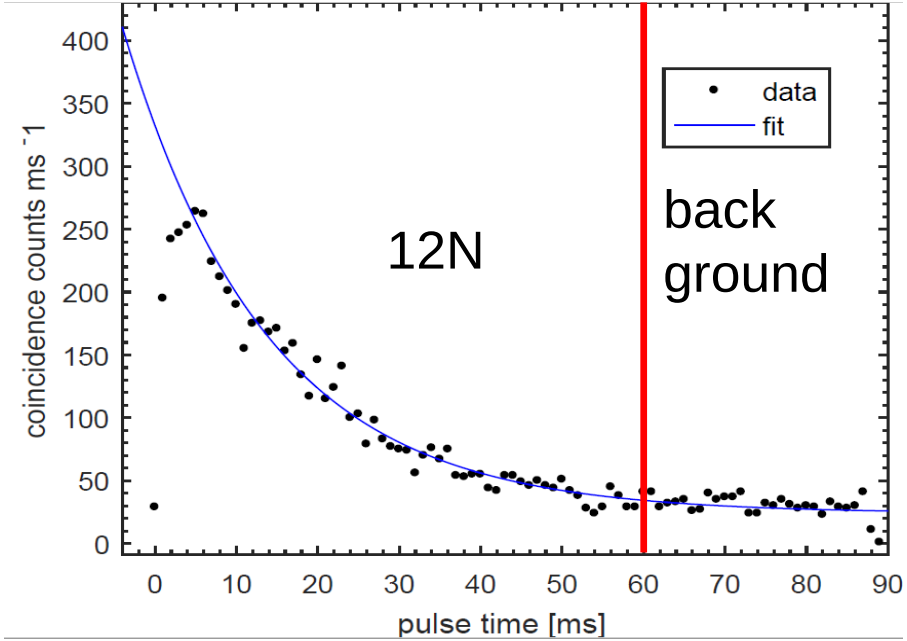
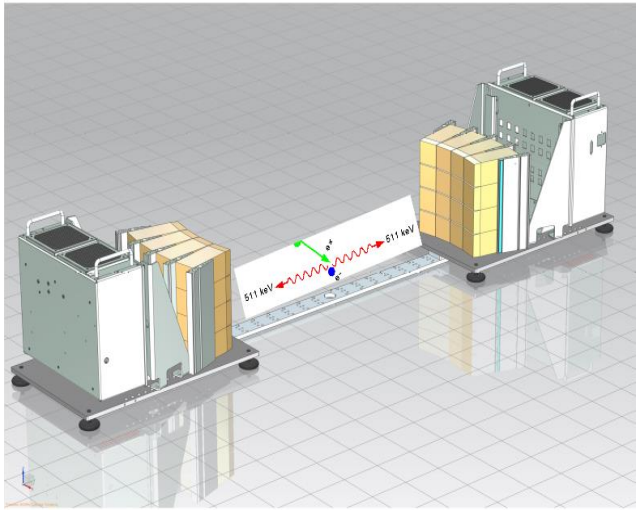
- near real-time PET imaging of 12N ($T_{1/2}$ = 11 ms)
  - produced on 12C



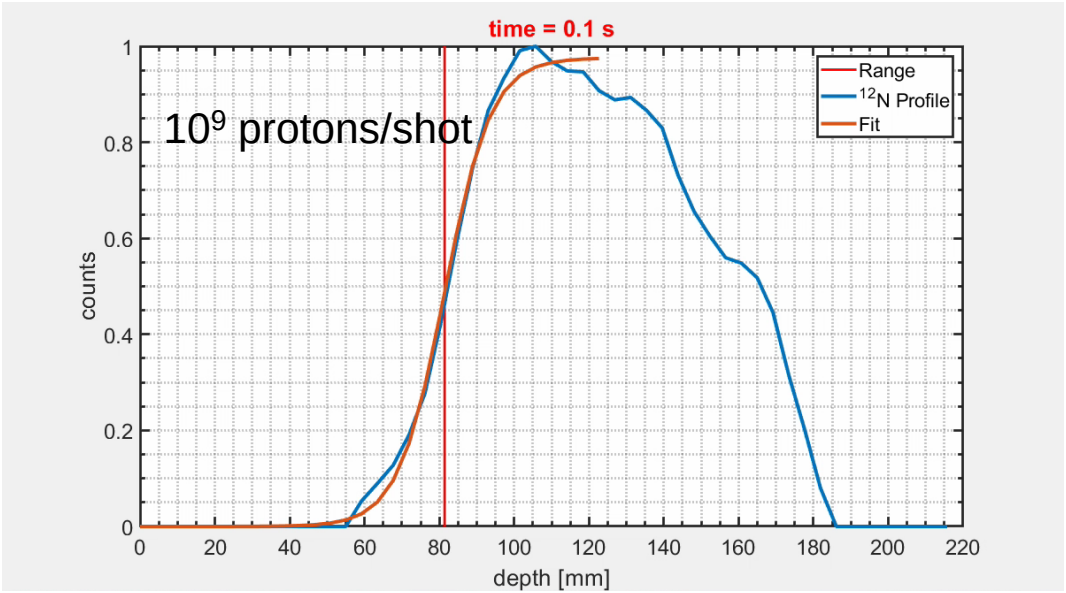


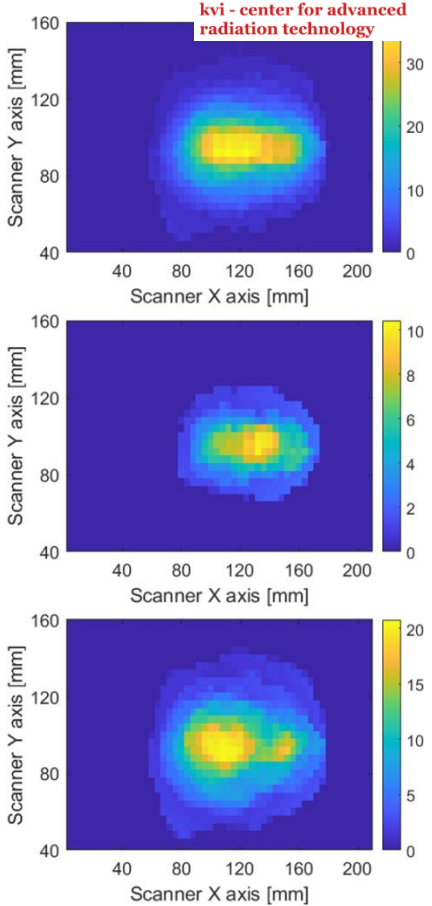
1/6 of a full-ring Siemens Biograph mCT clinical scanner.
4x4 array of block detectors.

in vivo verification proton therapy

university of groningen
kvi - center for advanced radiation technology

- near real-time PET imaging of 12N ($T_{1/2}$ = 11 ms)
  - produced on 12C
  - image long-lived background substracted
  - σ = 1.1 mm @ 10^9 protons





P. Dendooven, KVI-CART

acknowledgement

- research funding

- access funding

- host institutions

- all colleagues for contributing