An Open Access Facility for Heavy Ion Radiobiology

Why do we need it?

What do we need it for?

What do we need?

Who can provide it?

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Two Examples

Tumor Hypoxia

- Tumor hypoxia is one of the limiting factors in obtaining tumor control in radiotherapy

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LET-Painting

- at the frontier of particle therapy and radiobiology

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AARHUS PARTICLE THERAPY GROUP

Tumor Hypoxia

- Tumors with compartments containing hypoxic cells are well known to have reduced radiosensitivity compared to normoxic cells => lower control rates in radiotherapy (see e.g. Nordsmark et al. R&O 2000;57 and R&O 2005;77)

- Several treatment strategies:
  - **Hypoxia modifier** (Nitromidazole)

  - Functional imaging (PET + hypoxic markers) and
  - highly conformal RT (photons or ions) suggests heterogeneous application of dose within tumour
  - => **boost hypoxic areas** with dose ("dose painting; LET painting")

Bassler N, Jäkel O, Søndergaard CS, Petersen JB; Acta Oncol. 2010 Oct;49(7):1170-6.

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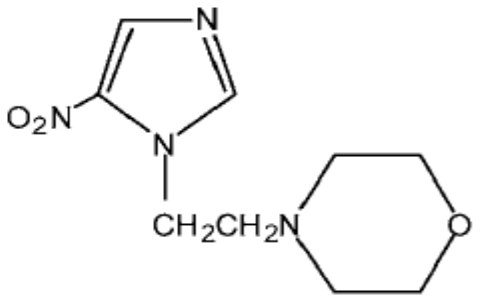
Hypoxic Cell Radiosensitizers

- **Fixing radiation induced damage under hypoxic conditions substituting oxygen**
  - Nimorazole
  - Misonidazole
  - Doranidazole



Nimorazole

- **Few, early in vivo experiments at Berkeley:**

  Misonidazole → Higher growth delay

- **High-LET radiation is less dependent on oxygen levels**

  LET > 100 - 200 keV/µm → OER close to 1

  Clinical situation: LET around 50-80 keV/µm

- **Radiosensitizers in high-LET radiation**
  - **the future in treatment of radio-resistant tumors?**

- **Hypoxia still has an impact on cell survival**
  - **clinical OER is still > 1**

Need for systematic in vitro tests of LET and oxygen dependency on the effect of radiosensitizers

In vitro studies:
How can we make a difference

Clinical relevant studies

1. **Selection of patients**
2. **Optimizing treatment**

- Radiosensitizers
- HPV and radiosensitivity
- Cancer Stem Cells (CSC)
- Induction of secondary cancer

→ Develop ideas and guidelines for in vivo experiments
……..and ultimately for clinical trials

What do we need for Painting ?

OER has strong LET dependence:

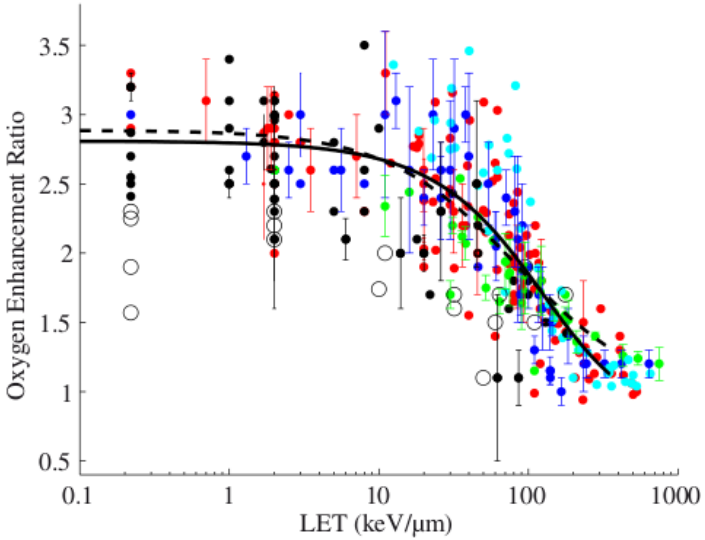
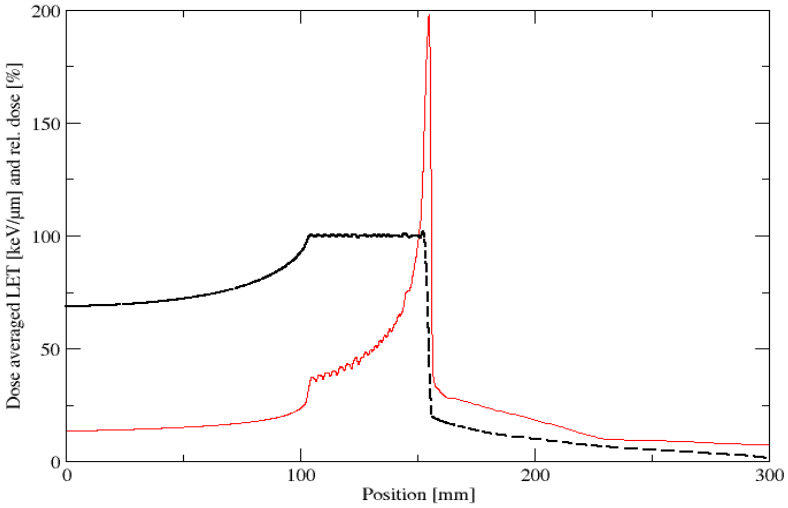


Figure 1. Experimental data from the literature (see tables 1 and 2) for the OER dependence on LET *in vitro* (filled circles) and *in vivo* (open circles) at 10% cell survival. The error bars are shown according to the original publications (if provided). Different colours (online only) correspond to different cell lines: red: V79; blue: T1; green: R1; cyan: HSG; black: other. The solid line represents the OER calculated *in vitro* for 10% cell survival at $p_a = 160$ mmHg and $p_h = 0.01$ mmHg according to equation (12). The dashed line shows results for the same survival level and pO_2 values but now with an LET dependent β parameter according to equation (13).

Wenzl and Wilkens, PMB 2011

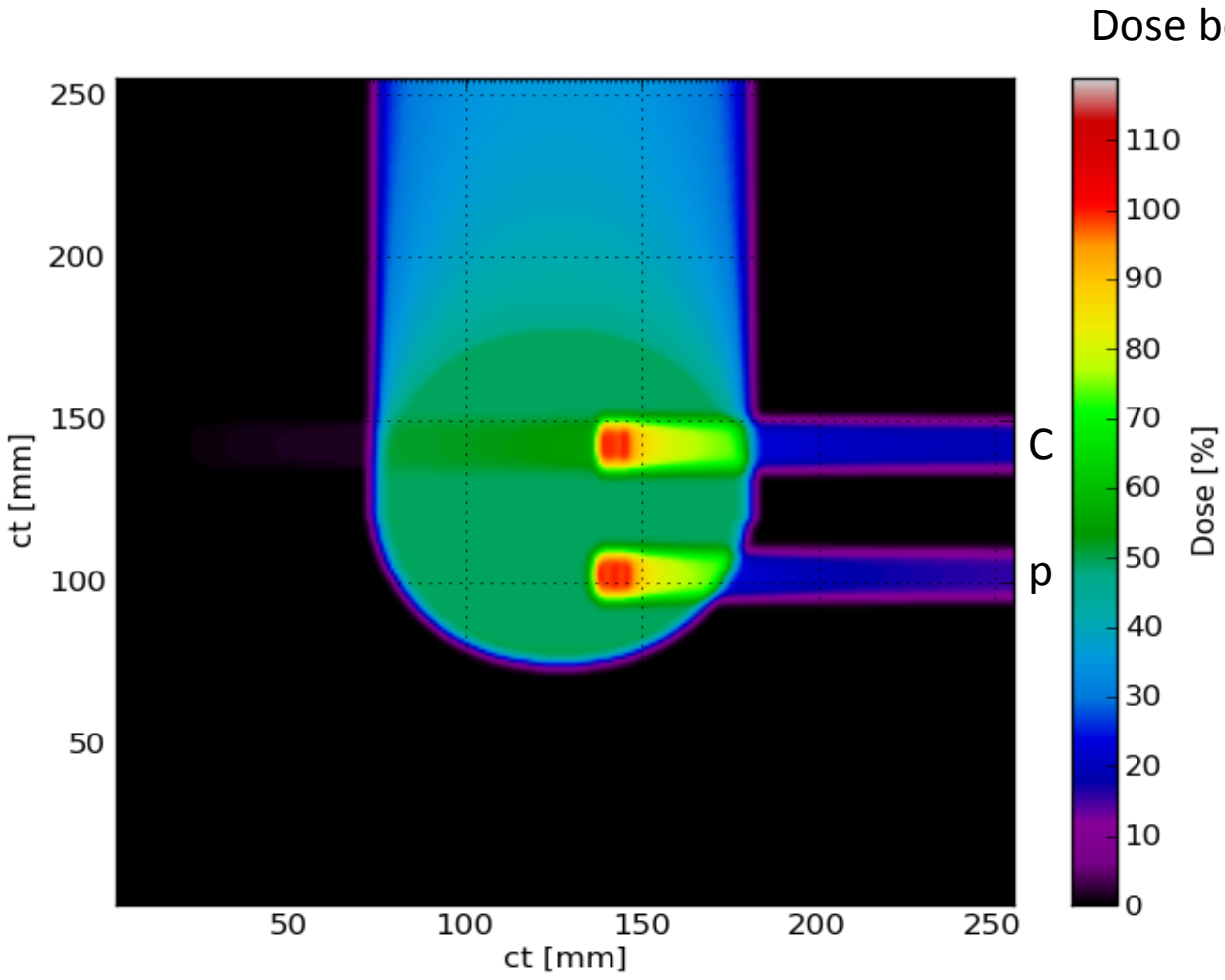
Need LET > 100 keV/µm



Dose averaged LET for 12C beam with 5 cm SOBP
Niels Bassler, Aarhus

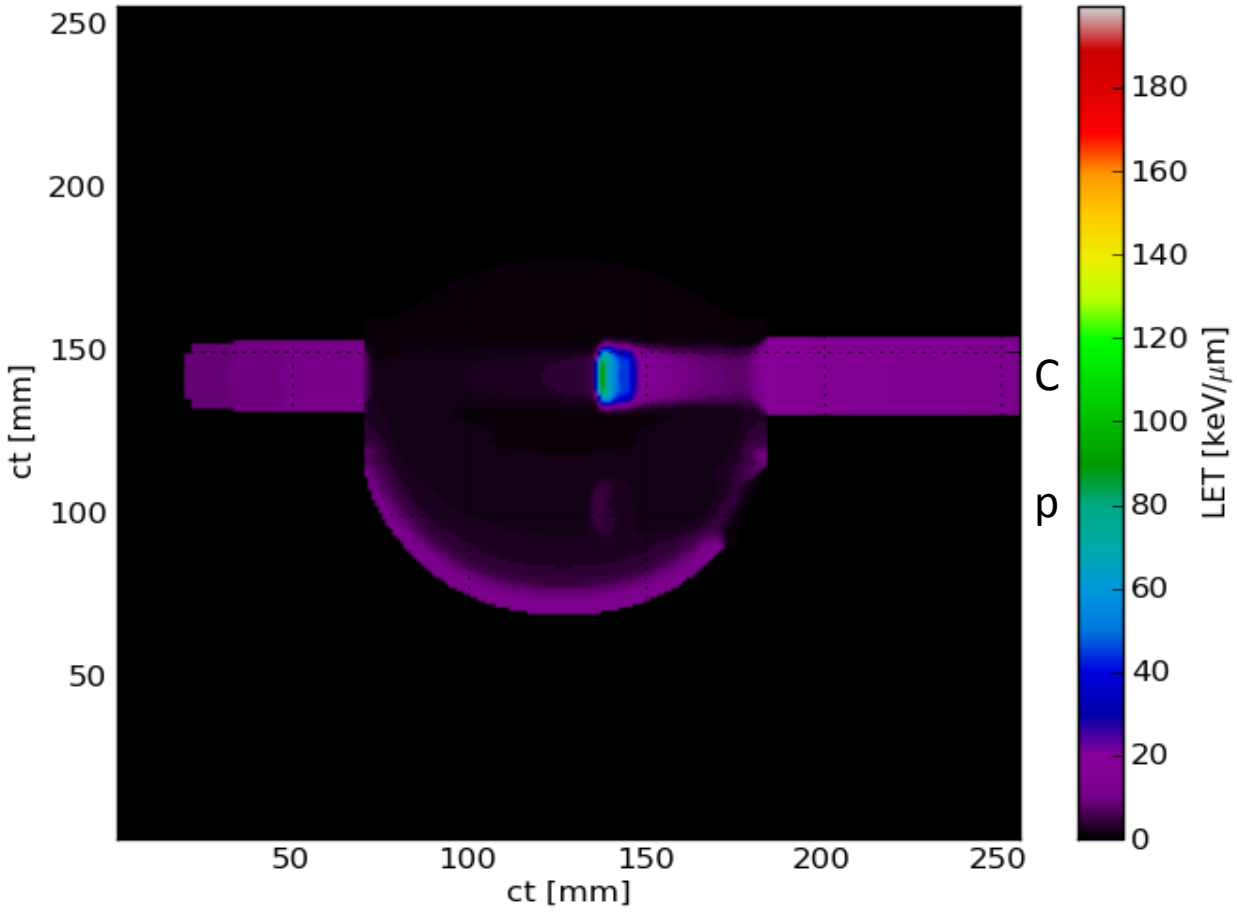
➔**Need higher LET ions (O, N, ….??)**

Proton + proton and carbon ion boost

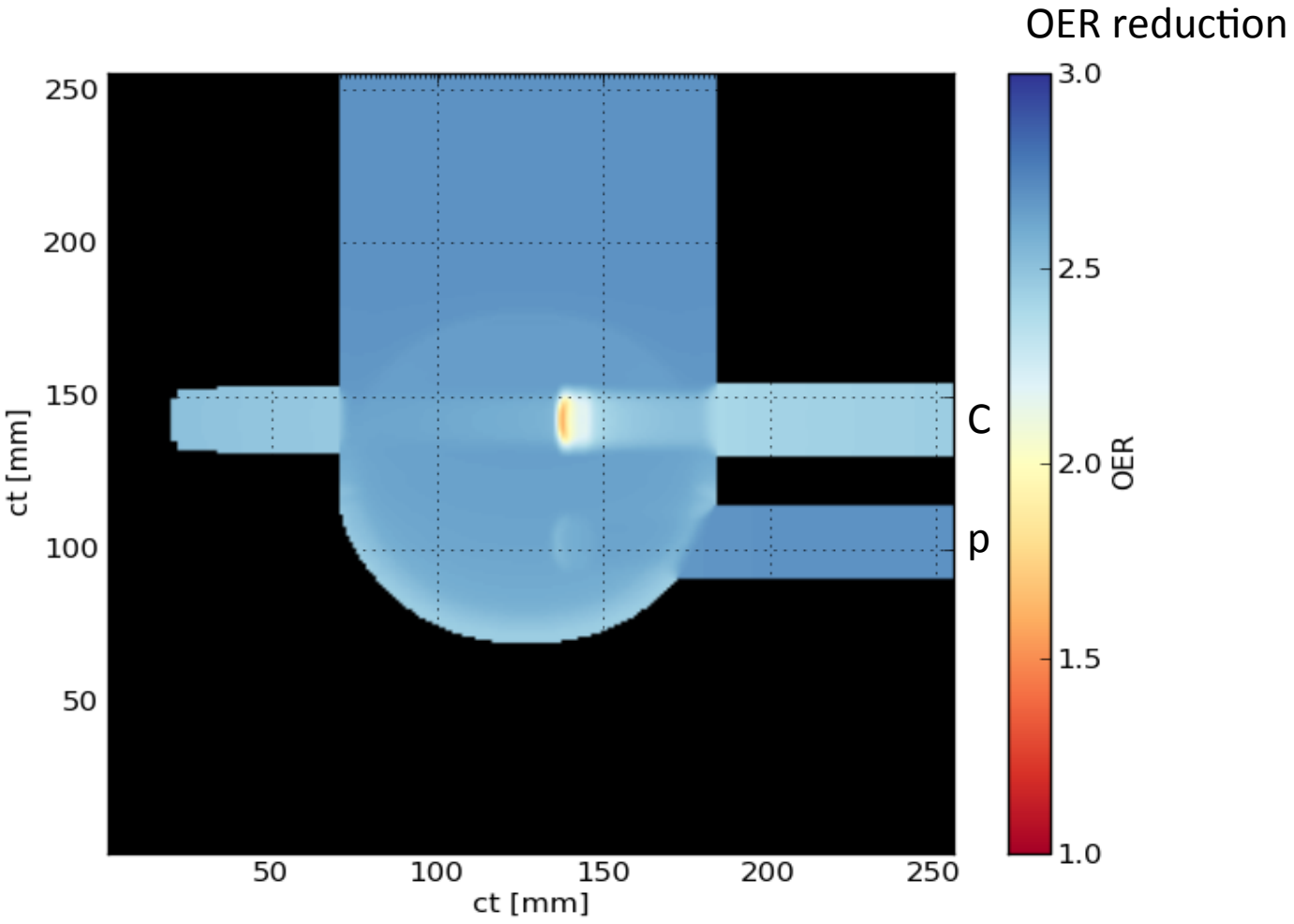


Proton + proton and carbon ion boost

LET and dose boost

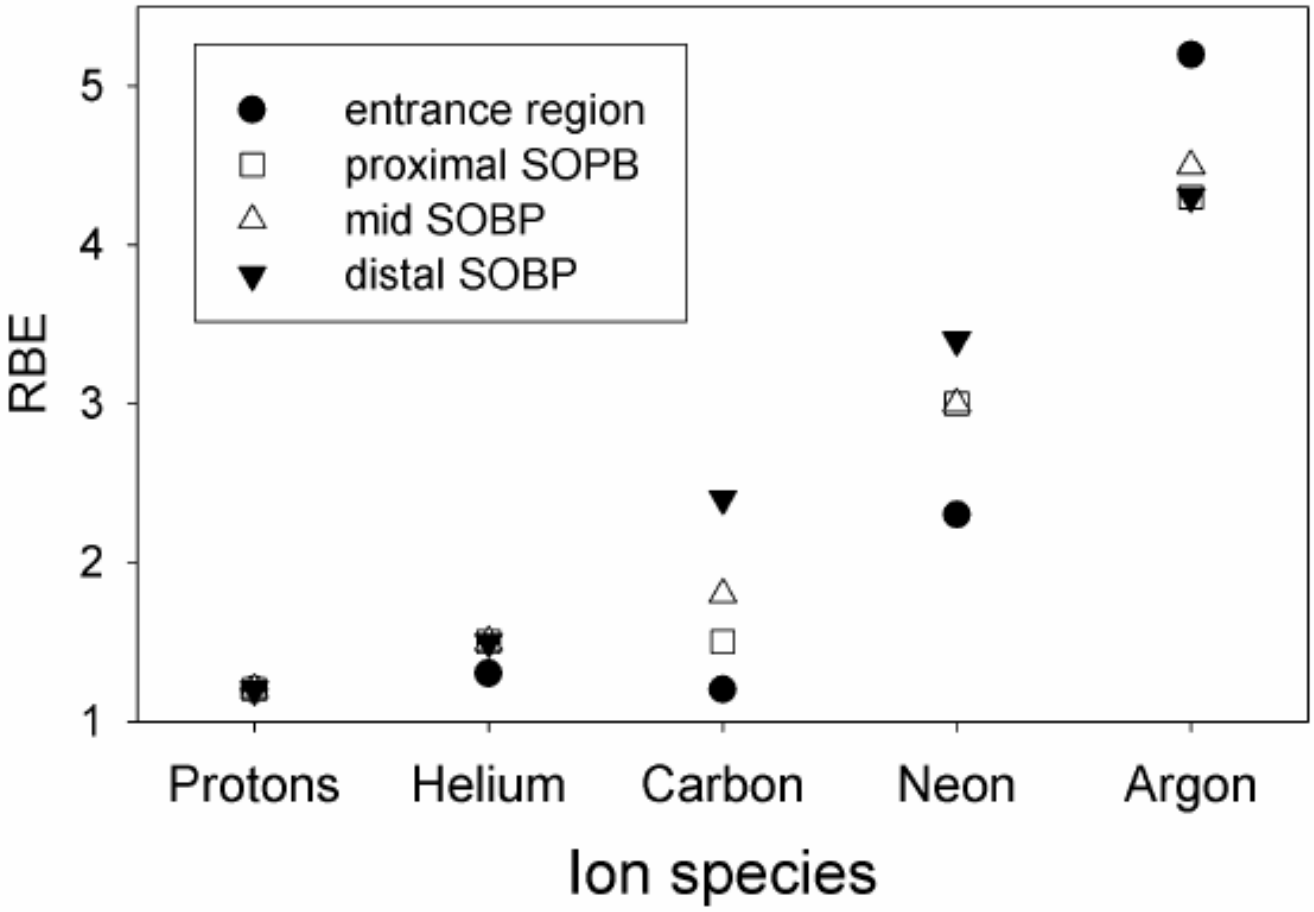


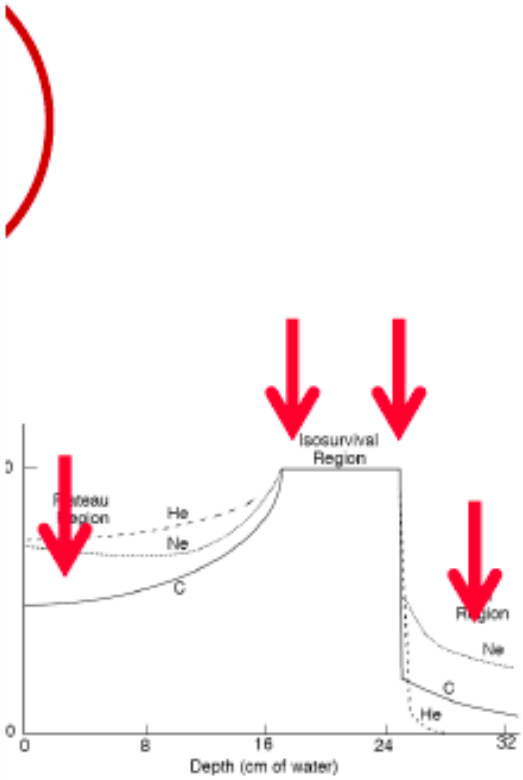
Proton + proton and carbon ion boost



Which is the best ion for RT ?

RBE for a fractionated irradiation of jejunal crypt cells of mice (SOBP of 8 cm)





Proton data: Tepper et al 1977,
Ion data: Goldstein et al. 1981.

The differential RBE peak/plateau is optimal for Li…O

THINK BIG

THINK BIG

THINK BIG

Accelerator requirements

Different ions

Up to Fe , but does not need to be complete range of Z

Energy Range

Low energy (< 70 MeV/u) desirable, up to 400 MeV/amu for ^{12}C

Fast uncomplicated energy switching (spill by spill)

either directly in synchrotron, or by a range shifter

Two beamlines

vertical for low energies up to 50 or 70 MeV/u

horizontal for all energies

shared experimental stations (no permanent installations)

Slow extraction

Irradiation field

at least 5x5 cm2 at isocenter, 1-2 % homogeneity over entire field,

pencil beams, with good knowledge of FWHM, divergence, and focal point,

could be achieved by passive scattering or wobbling

Dosimetry and fluence monitoring

we need to know to good precision the fluence at isocenter, 2% or better

basic dosimetry support, equipment (ionization chambers, dose meters)

Experimental infrastructure

At the isocenter

- XYZ translator, with sub mm precision
- water phantom (PTW MP3 or similar)
- laser guides (complete)
- Video surveillance

Access to machine shop facilities

- building custom sample holders
- custom phantoms

Reference units

- Co-60 reference unit (2 Gy/min)
- X-ray reference unit (e.g. 220 kV, variable dose rate, 0.5 Gy/min - app. 5 Gy/min)

Tissue culture lab

a dedicated room which is clean for biology setup which contains

4 or more incubators (bottle neck)
3 flow benches for handling of sterile samples
1 fume hood
refrigerators for growth media
freezer -20^{0}C and -80^{0}C for cell cultures
Centrifuges, cell counter, autoclave, special glassware dish washer
2x standard microscopes, 1x UV microscope (nice to have)
Biohazard disposal?
Gas supply (CO2 for incubators), Water-sterilizer
~10 meters of bench space

Dedicated office space for visiting groups

Counting hut

with ample cabling possibilities to exp. room (BNC, RS232, Ethernet...)

Resident Personnel

primary responsible for Bio-Lab
physicist/technician responsible for beam line

Any facility built will immediately turn out too small

Together
we can make this dream come true
- here at CERN

Thanks to all my collaborators at the different institutions
hosting me over the years

AARHUS PARTICLE THERAPY GROUP

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dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT