Activities in Experimental Room at Danish Centre of Particle Therapy

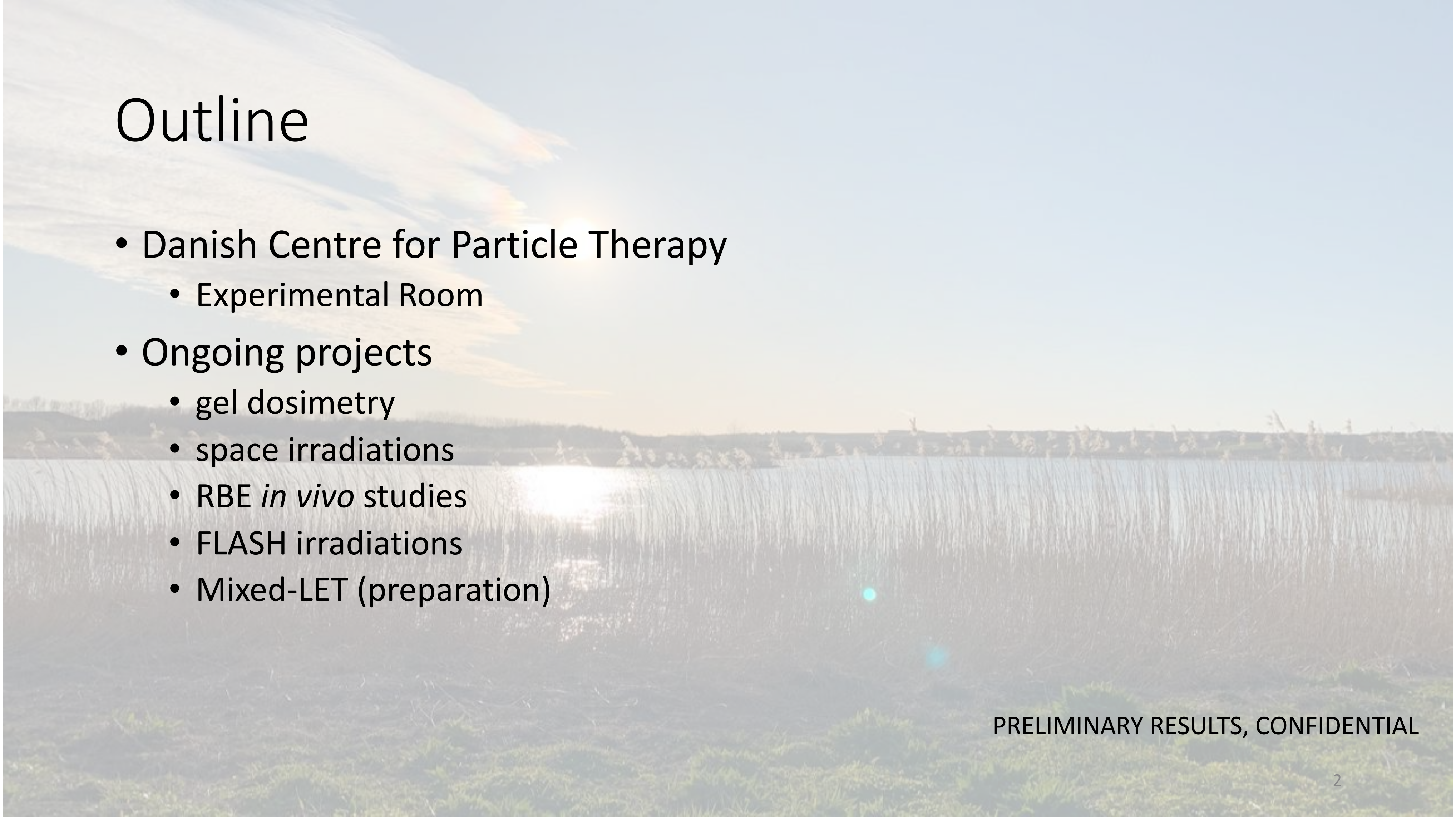
Mateusz Sitarz

FUW webinar, 08.04.2021

Outline

- Danish Centre for Particle Therapy
  - Experimental Room
- Ongoing projects
  - gel dosimetry
  - space irradiations
  - RBE *in vivo* studies
  - FLASH irradiations
  - Mixed-LET (preparation)

PRELIMINARY RESULTS, CONFIDENTIAL



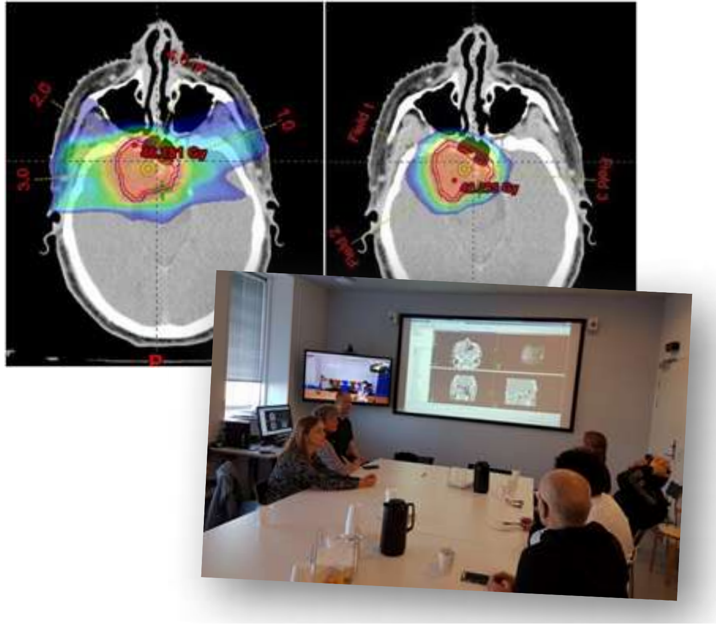
courtesy of Morten Høyer

Danish Centre of Particle Therapy at Aarhus University Hospital

Opened 28.02.2019

- About 1200 patients a year are expected to benefit from proton therapy in Denmark
- It is approx. 10% of the patients who are treated with radiation

photon vs proton



courtesy of Morten Høyer

Danish Centre of Particle Therapy at Aarhus University Hospital

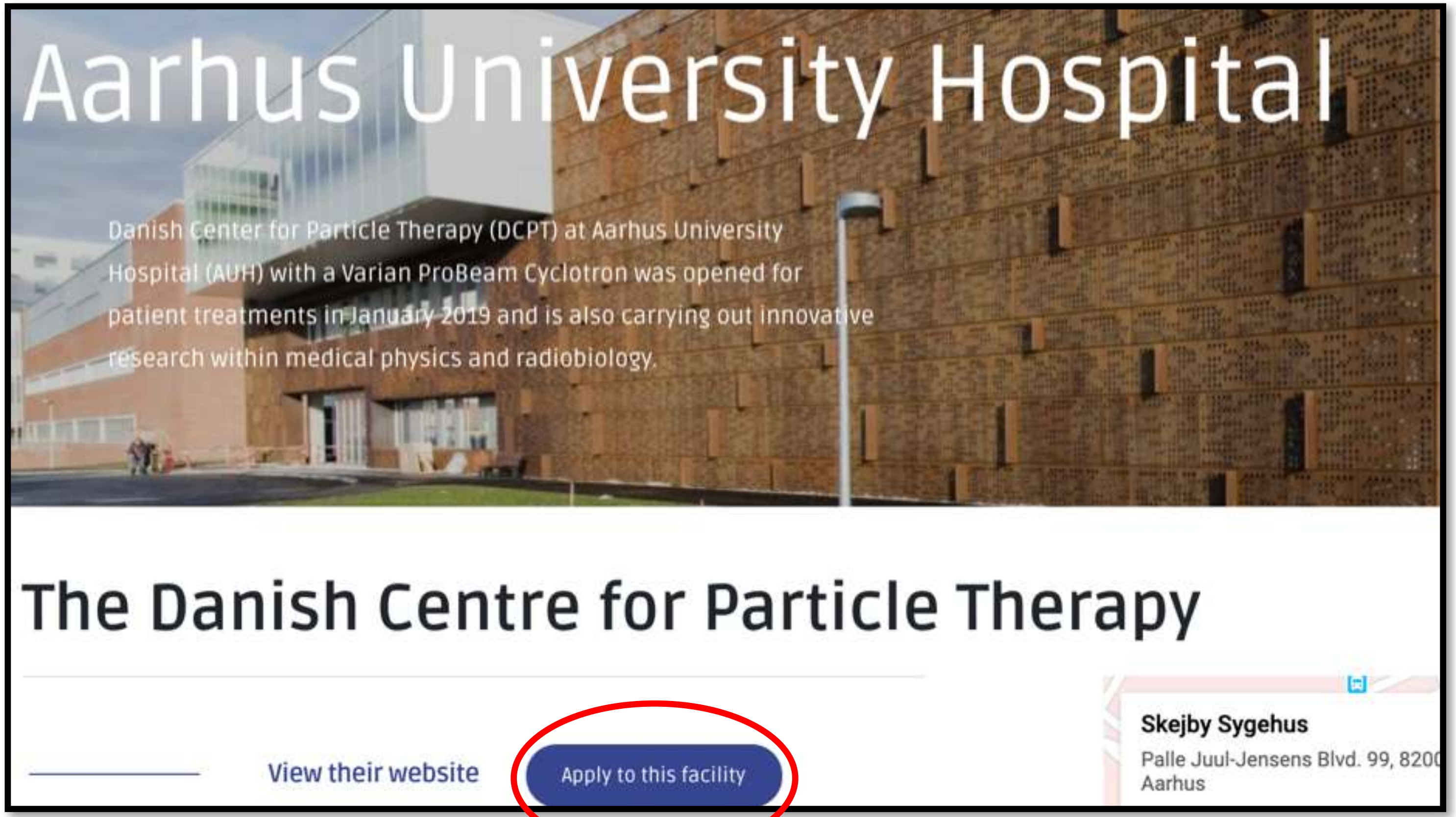
Varian cyclotron

pencil scanning proton beam
energy: 70-244 MeV
beam current on target: 0.5-15 nA
max. field: 30x40 cm^2
max dose rate: 10^6 MU/min
SAD: 228 cm

Experimental Room
(October 2019)

Treatment Rooms
(Gantries)

Transnational Access application



Aarhus University Hospital

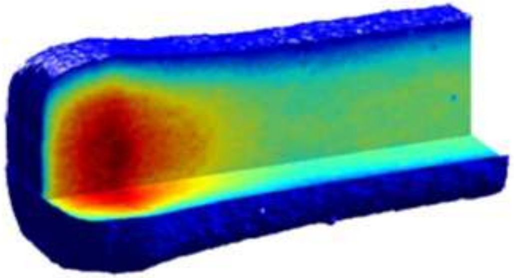
Danish Center for Particle Therapy (DCPT) at Aarhus University Hospital (AUH) with a Varian ProBeam Cyclotron was opened for patient treatments in January 2019 and is also carrying out innovative research within medical physics and radiobiology.

The Danish Centre for Particle Therapy

Projects in physics

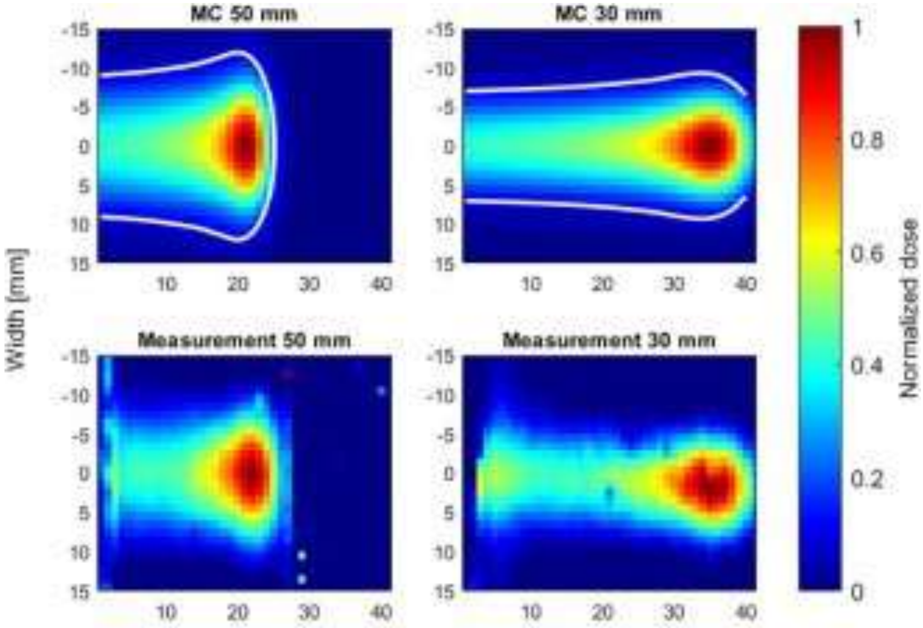
Radiochromic gels

A deformable three-dimensional radiochromic dosimeter has been produced, where the dose distribution can be read-out by using high resolution optical computed tomography.



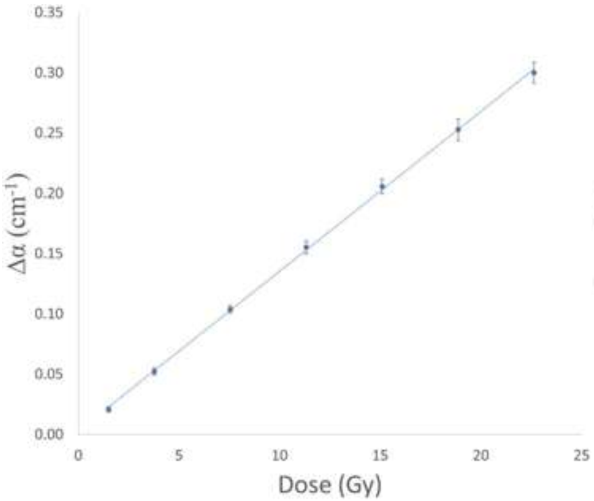
The difference in optical density measured using a spectrophotometer (Spectroquant Pharo 100) at approx. 625 nm (absorption peak for the present chemical composition). Pre-scan approx. 20 h before irradiation and post-scan approx. 6 h after.

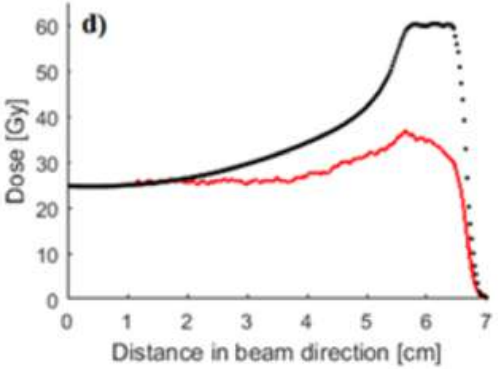
projects.au.dk/3d-dosimetry/



Radiochromic gels

- **Material development:** Optically-stimulated luminescence (OSL).
- **Read-out techniques:** calibration and quenching correction.
- **Magnetic resonance guided radiotherapy:** dosimeters are meant to help investigate the effects of radiotherapy treatments in the presence of a magnetic field.
- **Influence of motion and deformation:** the deformable silicone-based dosimeters opens a realm for investigating how the dose deposition is affected when the irradiated material is deformed.
- **Clinical integration:** dosimeters can be cast into anthropomorphic shapes, which would make them ideal to use for patient specific quality assurance.





Space radiation

1. Radiation tolerance of LIDARs
2. Detectors for GeoSatelites

- low fluence rate (max. 10^7 p/s/cm^2)
- translation of Treatment Planning System from *dose* to *fluence* regime

$$D = \phi \frac{1}{\rho}\left(\frac{dE}{dx}\right)$$

Benedikt Bergmann, Thomas Billoud, Adam Smetana, Maroš Petro
Institute of Experiment and Applied Physics, Czech Technical university in Prague

Space radiation – **MIRAM project**

MIRAM (*MIniaturized RAdiation Monitor*) is developed for the real-time measurement of the total ionizing dose, electron, proton and ion fluxes in space.

hybrid semiconductor pixel detector technology Timepix3

14 x 14 mm^2
256 × 256 pixels
55 µm per pixel

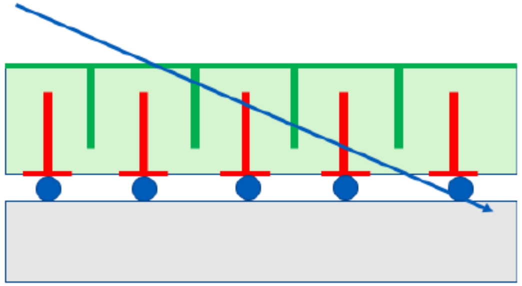
Timepix3 detectors with 500 µm thick silicon sensors are installed in High Energy Physics Experiments at CERN (ATLAS and MoEDAL) where they measure the composition and directionality of the radiation fields.

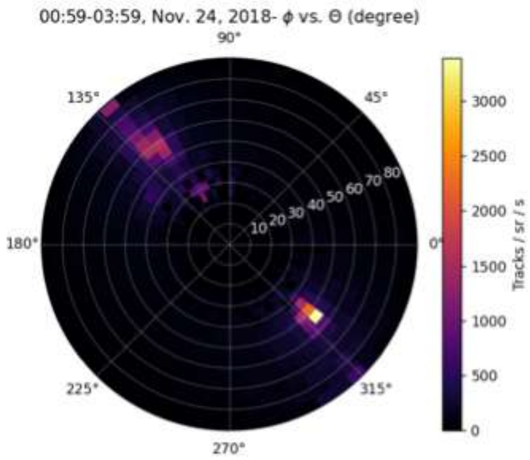
MIRAM detector

82 x 60 x 49 mm^3
weight = 140g
price < 50 kEUR
power consumption: < 1 W

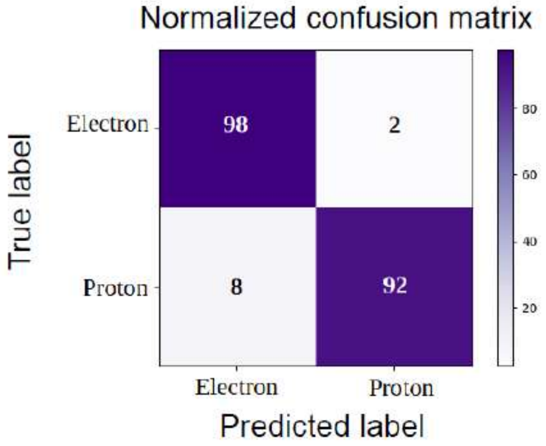
Benedikt Bergmann, Thomas Billoud, Adam Smetana, Maroš Petro
Institute of Experiment and Applied Physics, Czech Technical university in Prague

Space radiation – **MIRAM project**





Directionality map of tracks in MoEDAL



Measurement in each pixel:

- energy (keV)
- time (ns)

Track registration
(particle-by-particle)

Algorithm for species recognition.

Confusion matrix for CNN trained with simulated proton and electron data

Benedikt Bergmann, Thomas Billoud, Adam Smetana, Maroš Petro
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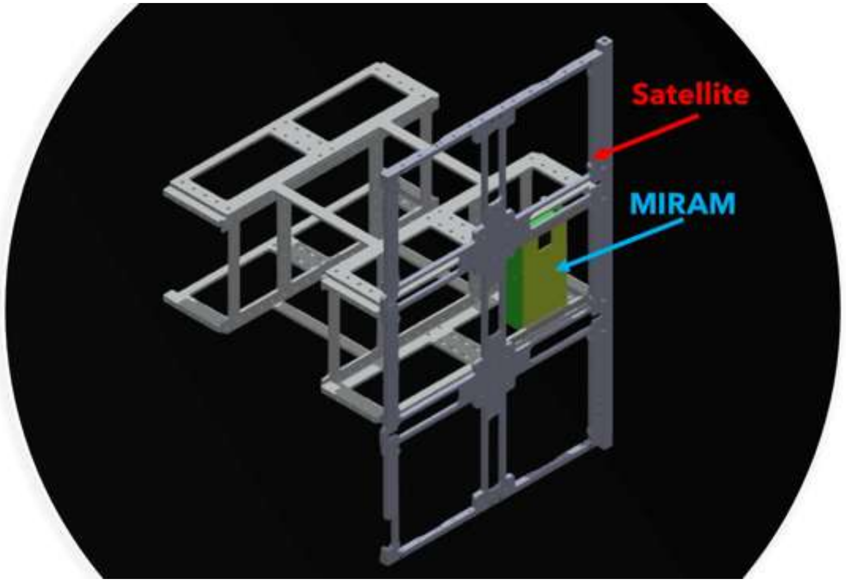
Space radiation – **MIRAM project**



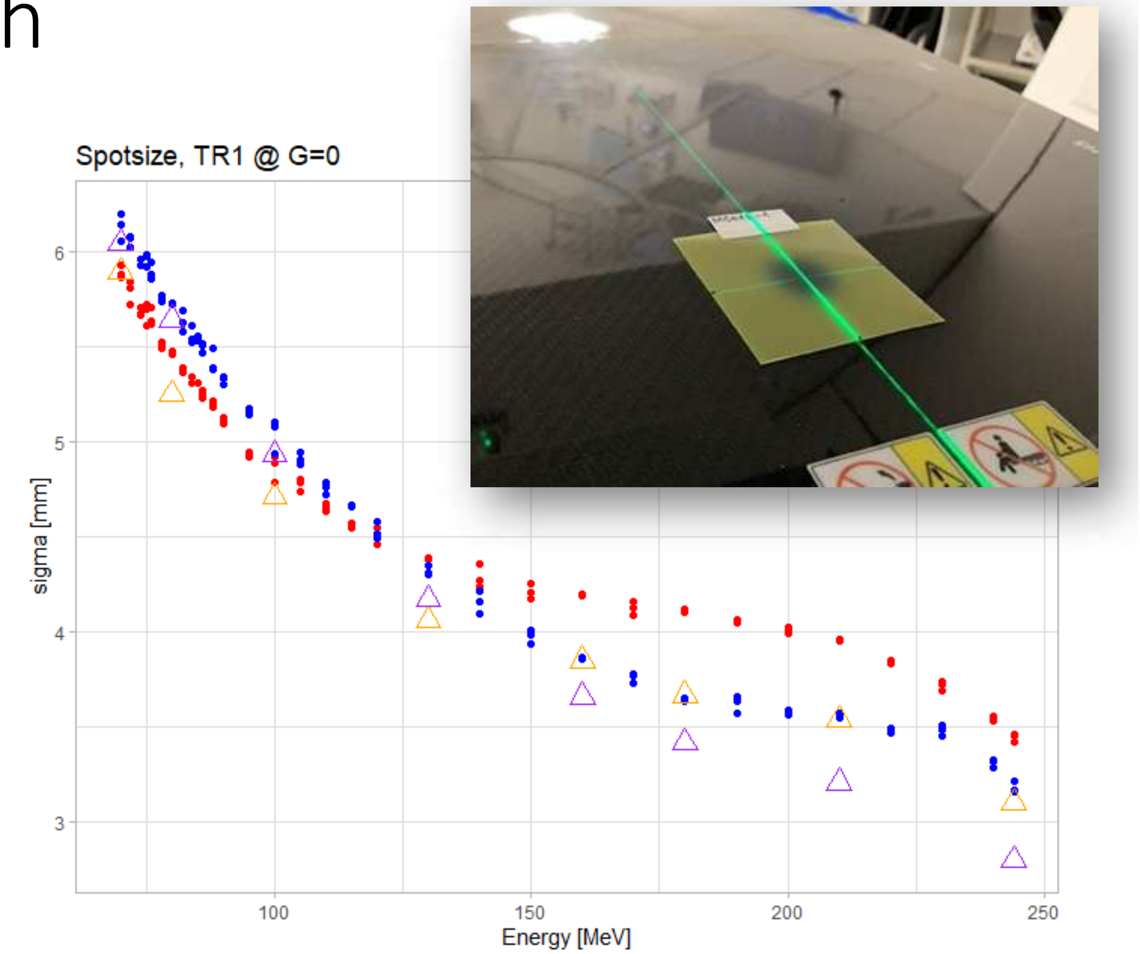
1. **Calibration of the detector parameters (charge collection efficiency, …)**
2. **Validation of particle-recognition algorithm**
3. **Input for simulations (ground truth for ML approaches improving the particle separation and tracking capability)**
4. **Verification of the detector response**
5. **Validation of the detector survivability in radiation intensive environments**

- GOMX-5 mission
- Space Polar Ice Explorer mission
- NSPO Lunar Orbiter
- ESA European Large Logistic Lander

courtesy of Christian Søndergaard

Clinics QA + research

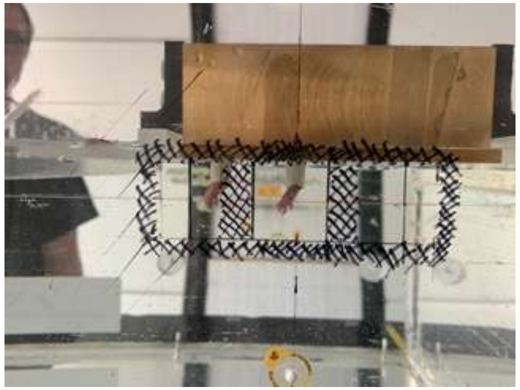
- Spot size measurements with gafchromic films
- Absolute dosimetry with ionization chambers
- Testing of prototype matrix array for FLASH
- Influence of pacemaker wires for dose distribution

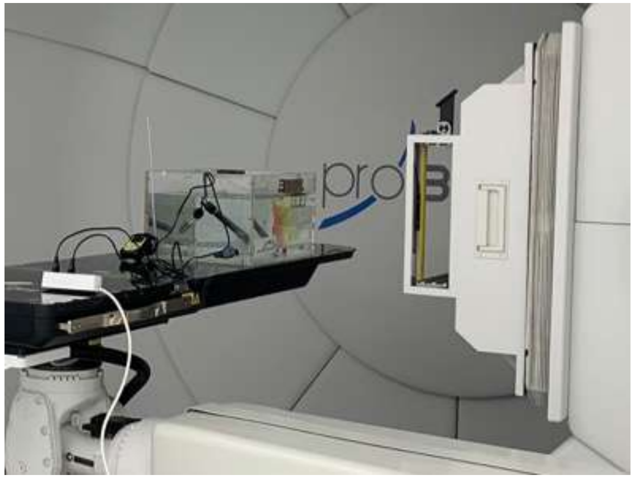


Radiobiology studies

In vivo research

CDF1 mice set-up





Acute and late effects after RT

courtesy of Cathrine Overgaard

Acute skin damage
(Moist desquamation)
→ analysed 7 to 30 days after RT


Control
Score 0


Score 2.5

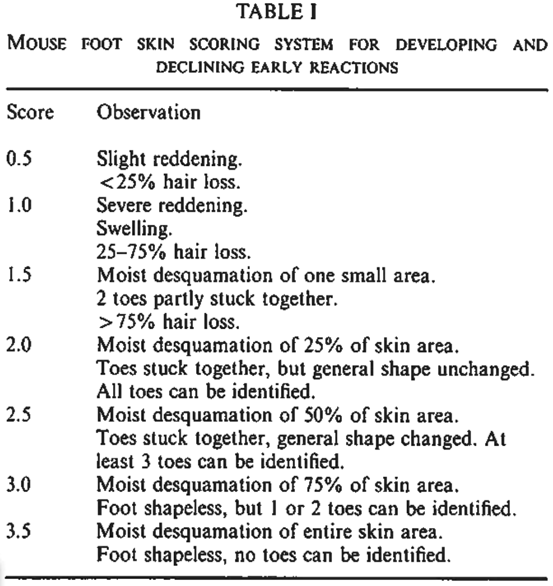


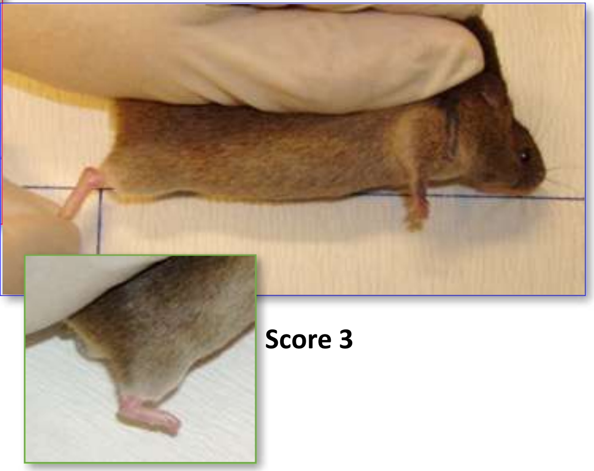
TABLE I

MOUSE FOOT SKIN SCORING SYSTEM FOR DEVELOPING AND DECLINING EARLY REACTIONS

Score	Observation
0.5	Slight reddening. <25% hair loss.
1.0	Severe reddening. Swelling. 25–75% hair loss.
1.5	Moist desquamation of one small area. 2 toes partly stuck together. >75% hair loss.
2.0	Moist desquamation of 25% of skin area. Toes stuck together, but general shape unchanged. All toes can be identified.
2.5	Moist desquamation of 50% of skin area. Toes stuck together, general shape changed. At least 3 toes can be identified.
3.0	Moist desquamation of 75% of skin area. Foot shapeless, but 1 or 2 toes can be identified.
3.5	Moist desquamation of entire skin area. Foot shapeless, no toes can be identified.

Radiation induced fibrosis
→ analysed 2 to 12 months after RT


Control
Score 0

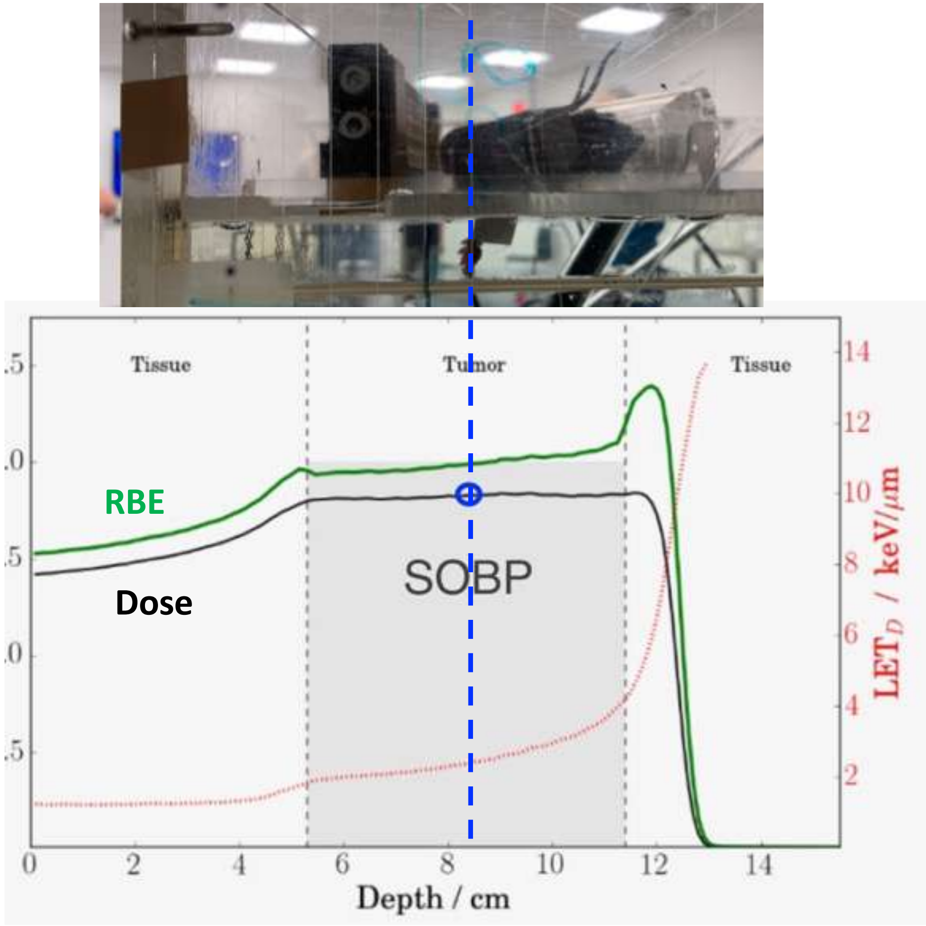

Score 3

Four legs good,
two legs ~~bad~~ better

courtesy of Cathrine Overgaard

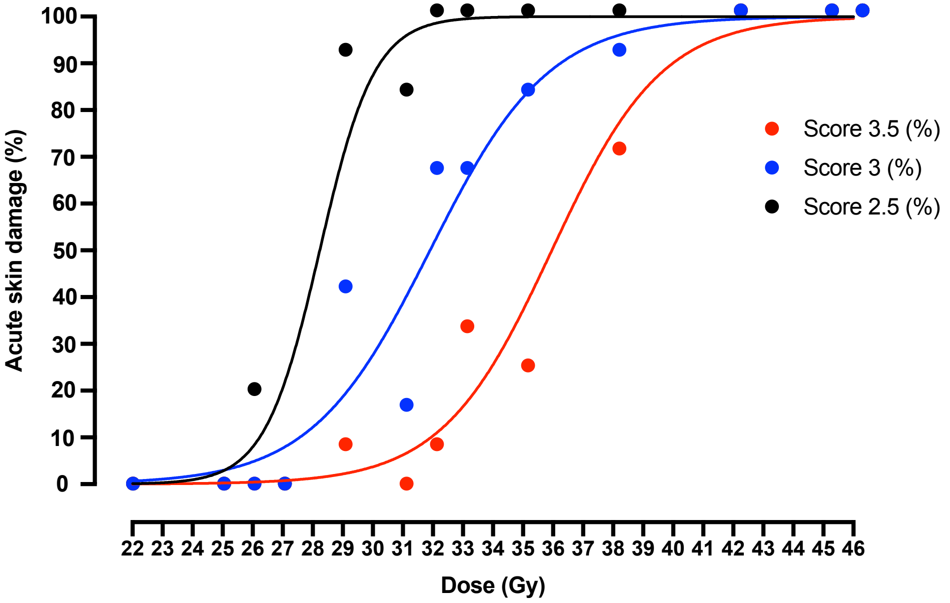
Dose response curves

PRELIMINARY RESULTS, CONFIDENTIAL



Dose response curves for middle SOBP irradiations

Three different acute skin score severities



10-12 mice per dose point

courtesy of Steffen Nielsen

In vivo research

Other research:

- influence of leg fixation methods (hypoxia)
- influence of fractionation
- RBE changes with LET
- tumour regrowth rate with immunotheraphy

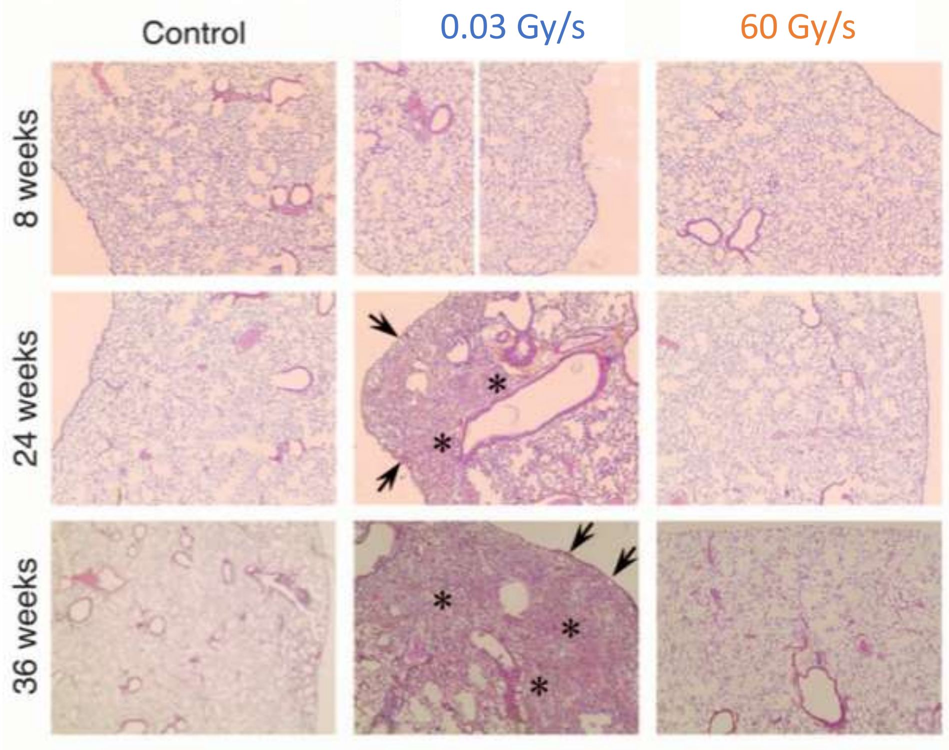
FLASH studies

FLASH effect **remarkable sparing of normal tissue after irradiation at ultra-high dose rate (>40 Gy/s)**

lung samples taken *x* weeks after bilateral thorax exposure

17 Gy CONV
0.03 Gy/s

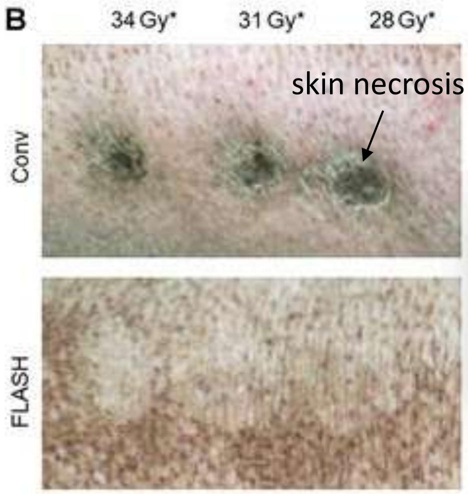
17 Gy FLASH
60 Gy/s



➔ patches of subpleural fibrosis   * intraparenchymal fibrosis

Favaudon et al., 2014

for LINAC → electron beam



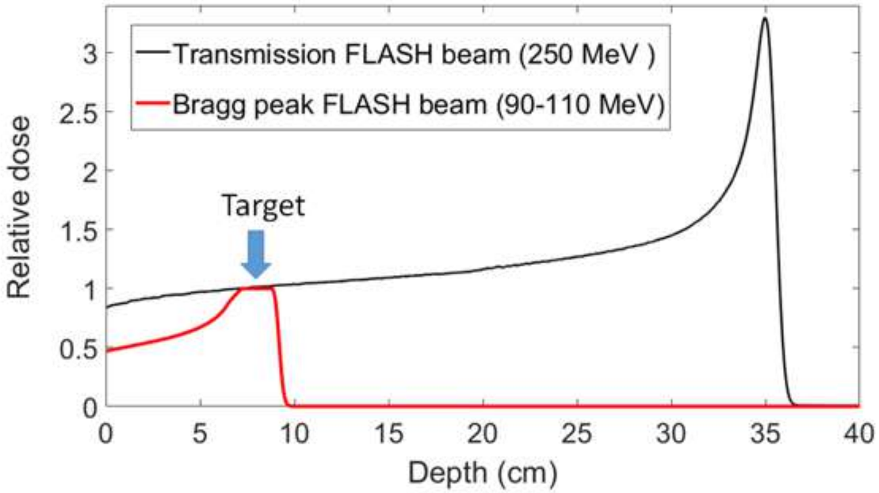
skin necrosis

Vozenin et al., 2019

courtesy of Per Poulsen

FLASH at DCPT

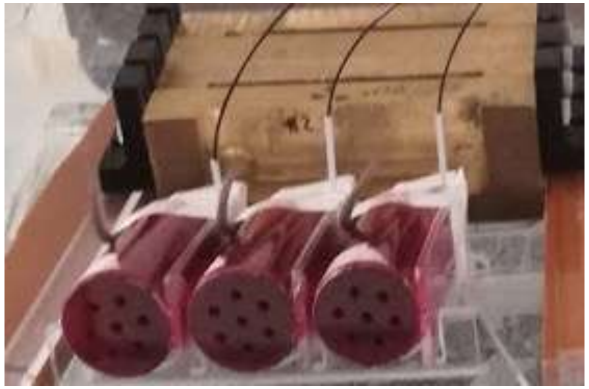
- Highest available energy (250 MeV) for **highest transmission**
- Highest available stable beam current (215 nA)

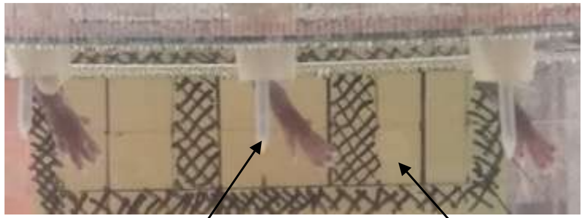


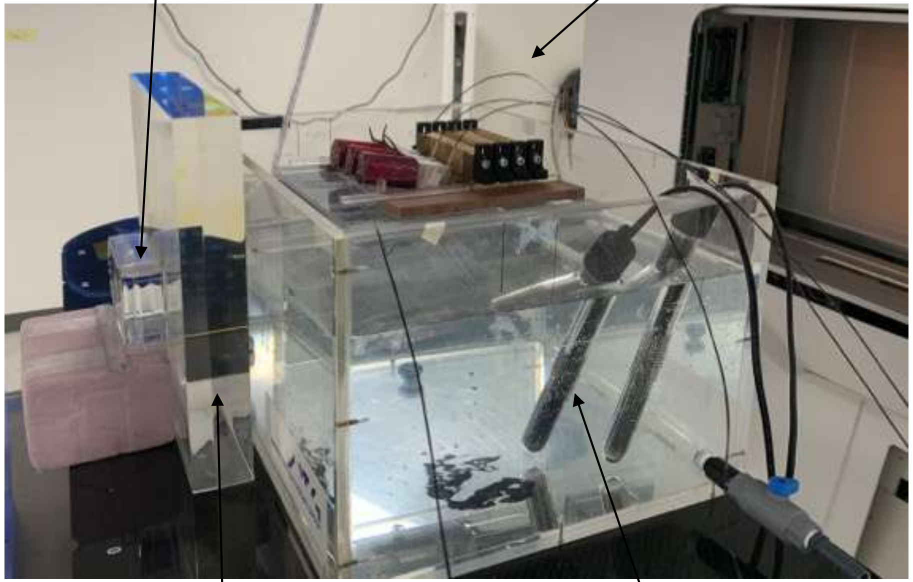
Transmission beams with treatment in entrance plateau:

- Fast 2D pencil beam scanning over small area
- No energy shifts
    - Simpler physics (“no” dose variation with depth)
    - Simpler biology (“no” RBE variation with depth)

FLASH at DCPT – set-up



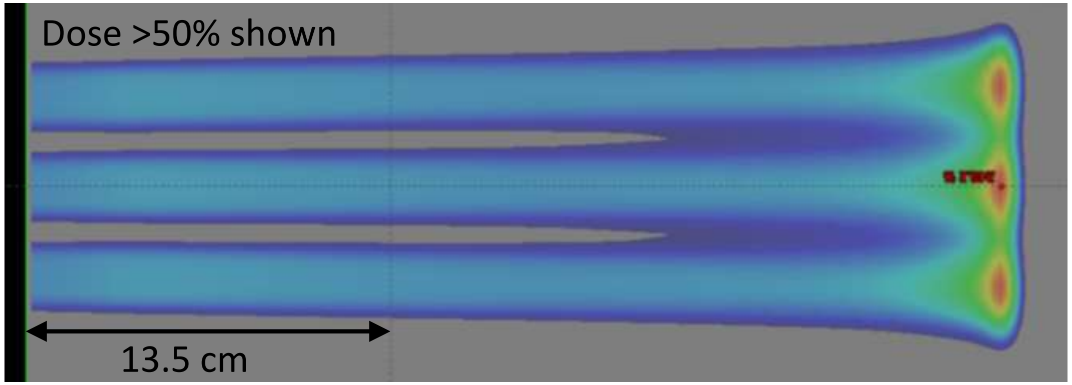


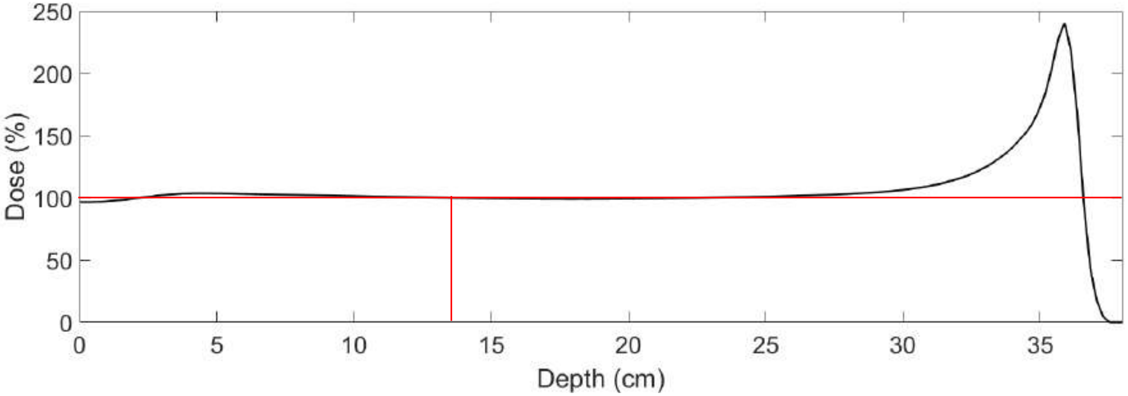


courtesy of Per Poulsen

FLASH at DCPT – treatment planning

- Forward planning in Matlab
- Dose calculation in Eclipse (only for 244 MeV)





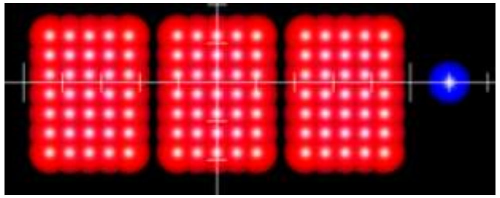
courtesy of Per Poulsen

FLASH vs CONV at DCPT

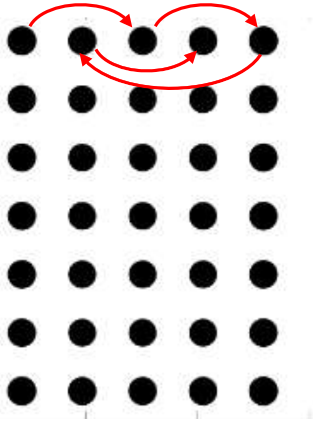
CONV irradiations

244 MeV (clinical mode)

1. low-MU spot



2. repainting

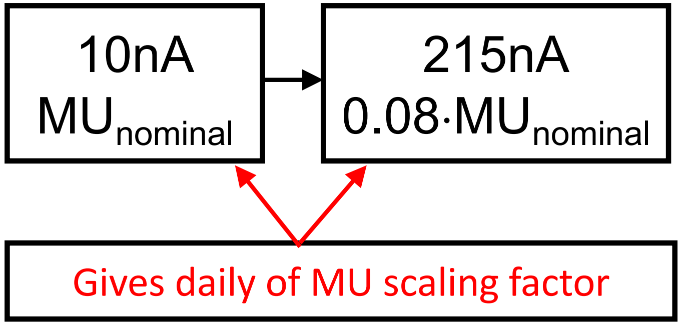


=~ 0.4 Gy/s (mean field dose rate)

FLASH irradiations

250 MeV (service mode)

The beam monitor chamber in the nozzle only measures 7-10% of the dose. MU must be scaled down accordingly.



10nA $MU_{nominal}$ → 215nA $0.08 \cdot MU_{nominal}$

Gives daily of MU scaling factor

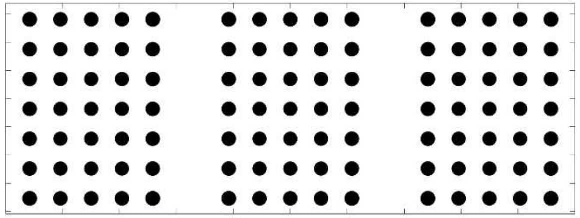
QA with Advanced Markus chamber (verified with graphite calorimeter).

=~ 100 Gy/s (mean field dose rate)

courtesy of Per Poulsen

FLASH at DCPT – set-up

Spot pattern

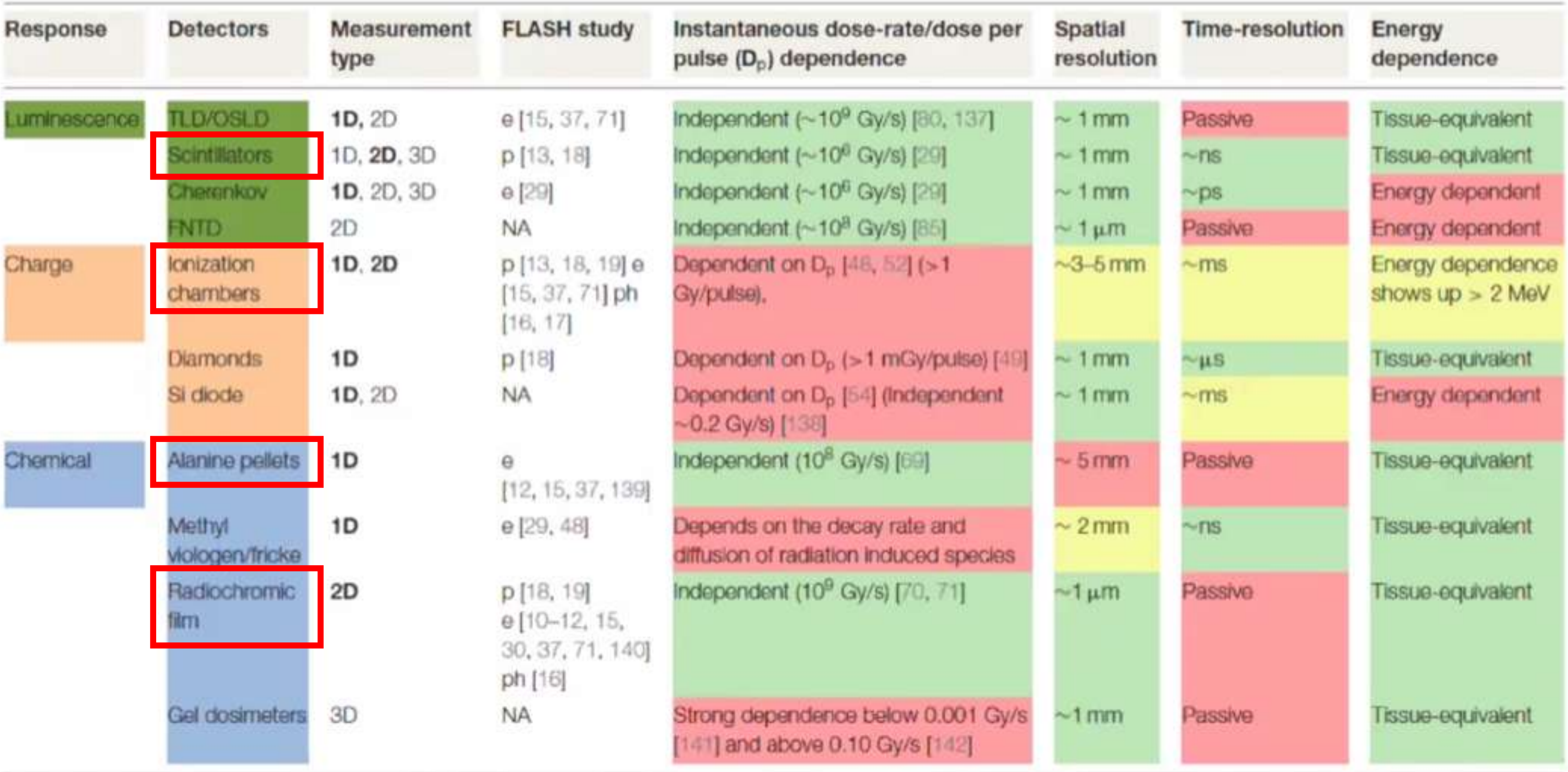


Irradiation of 3 mice at a time in CONV mode (/w repainting)

"All mice are equal"

FLASH dosimetry – at DCPT

Ashraf et al., Frontiers in Physics 2020

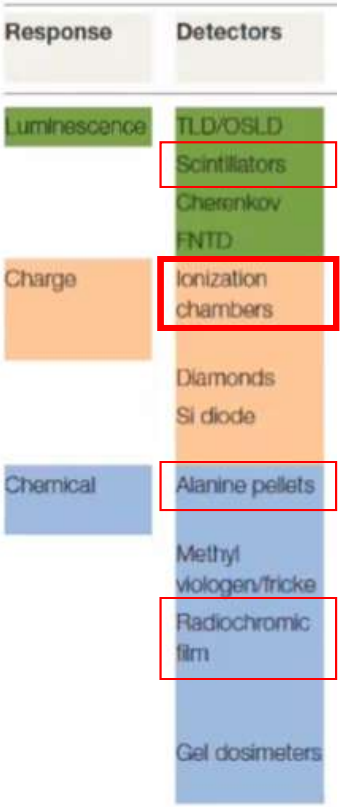


Response	Detectors	Measurement type	FLASH study	Instantaneous dose-rate/dose per pulse (D_p) dependence	Spatial resolution	Time-resolution	Energy dependence
Luminescence	TLD/OSLD	**1D**, 2D	e [15, 37, 71]	Independent (~10^9 Gy/s) [80, 137]	~ 1 mm	Passive	Tissue-equivalent
	Scintillators	1D, **2D**, 3D	p [13, 18]	Independent (~10^6 Gy/s) [29]	~ 1 mm	~ns	Tissue-equivalent
	Cherenkov	**1D**, 2D, 3D	e [29]	Independent (~10^6 Gy/s) [29]	~ 1 mm	~ps	Energy dependent
	FNTD	2D	NA	Independent (~10^8 Gy/s) [85]	~ 1 µm	Passive	Energy dependent
Charge	Ionization chambers	**1D**, **2D**	p [13, 18, 19] e [15, 37, 71] ph [16, 17]	Dependent on D_p [48, 52] (>1 Gy/pulse).	~3–5 mm	~ms	Energy dependence shows up > 2 MeV
	Diamonds	**1D**	p [18]	Dependent on D_p (>1 mGy/pulse) [49]	~ 1 mm	~µs	Tissue-equivalent
	Si diode	**1D**, 2D	NA	Dependent on D_p [54] (Independent ~0.2 Gy/s) [138]	~ 1 mm	~ms	Energy dependent
Chemical	Alanine pellets	**1D**	e [12, 15, 37, 139]	Independent (10^8 Gy/s) [69]	~ 5 mm	Passive	Tissue-equivalent
	Methyl viologen/fricke	**1D**	e [29, 48]	Depends on the decay rate and diffusion of radiation induced species	~ 2 mm	~ns	Tissue-equivalent
	Radiochromic film	**2D**	p [18, 19] e [10–12, 15, 30, 37, 71, 140] ph [16]	Independent (10^9 Gy/s) [70, 71]	~1 µm	Passive	Tissue-equivalent
	Gel dosimeters	3D	NA	Strong dependence below 0.001 Gy/s [141] and above 0.10 Gy/s [142]	~1 mm	Passive	Tissue-equivalent

*The color scheme of the "Response" and "Detectors" panel matches the spider plots in **Figure 14**. Performance of each dosimeter for a specific parameter is color coded: green (good), yellow (moderate), and red (poor).*

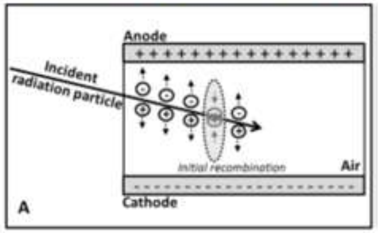
courtesy of Per Poulsen

FLASH dosimetry – at DCPT

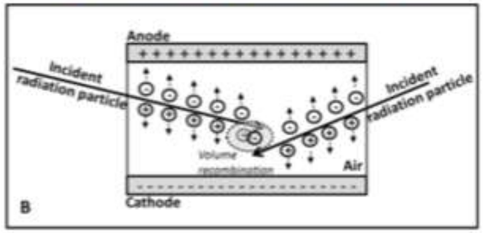


Response	Detectors
Luminescence	TLD/OSLD
	Scintillators
	Cherenkov
	FNTD
Charge	Ionization chambers
	Diamonds
	Si diode
Chemical	Alanine pellets
	Methyl viologen/fricke
	Radiochromic film
	Gel dosimeters

Initial recombination

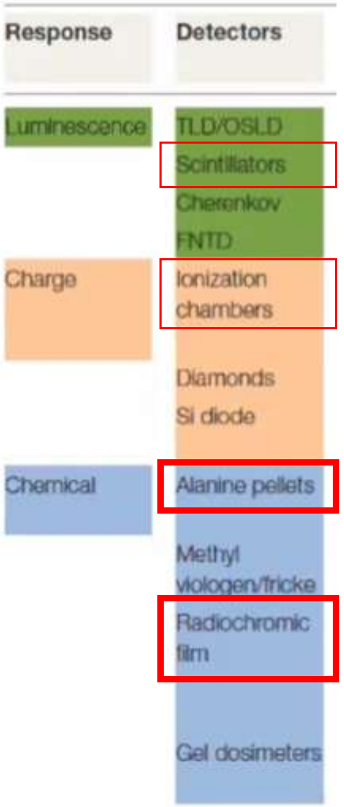


Volume recombination

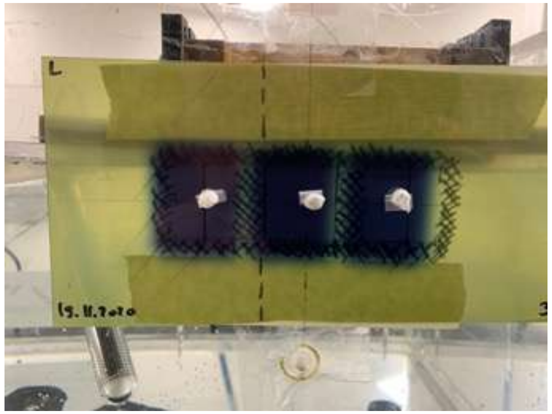


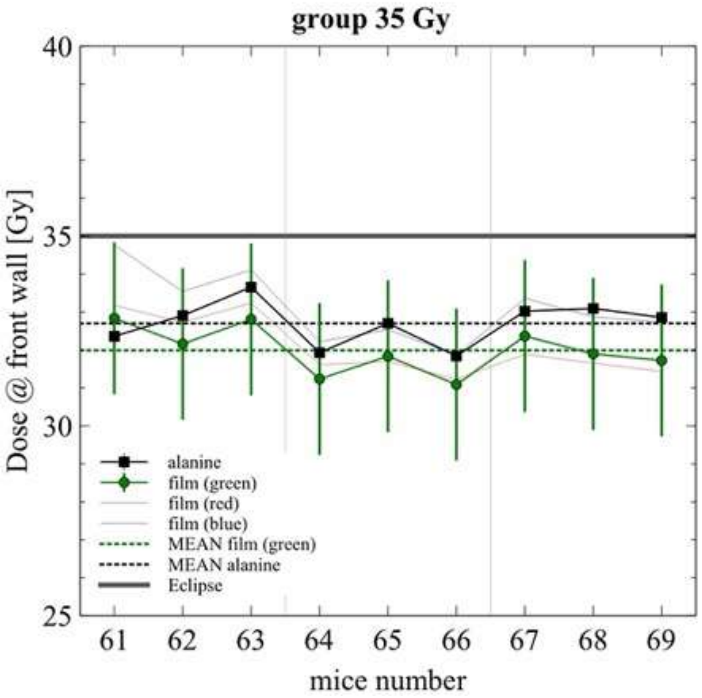
- Used to find daily MU scaling factor for FLASH
- Daily ion recombination correction factor (2-voltage method):
    - $k_S = 1.0008 \pm 0.0004$ (for 10nA)
    - $k_S = 1.0072 \pm 0.0035$ (for 215nA)

FLASH dosimetry – at DCPT



Response	Detectors
Luminescence	TLD/OSLD Scintillators Cherenkov FNTD
Charge	Ionization chambers Diamonds Si diode
Chemical	Alanine pellets Methyl viologen/fricke Radiochromic film Gel dosimeters



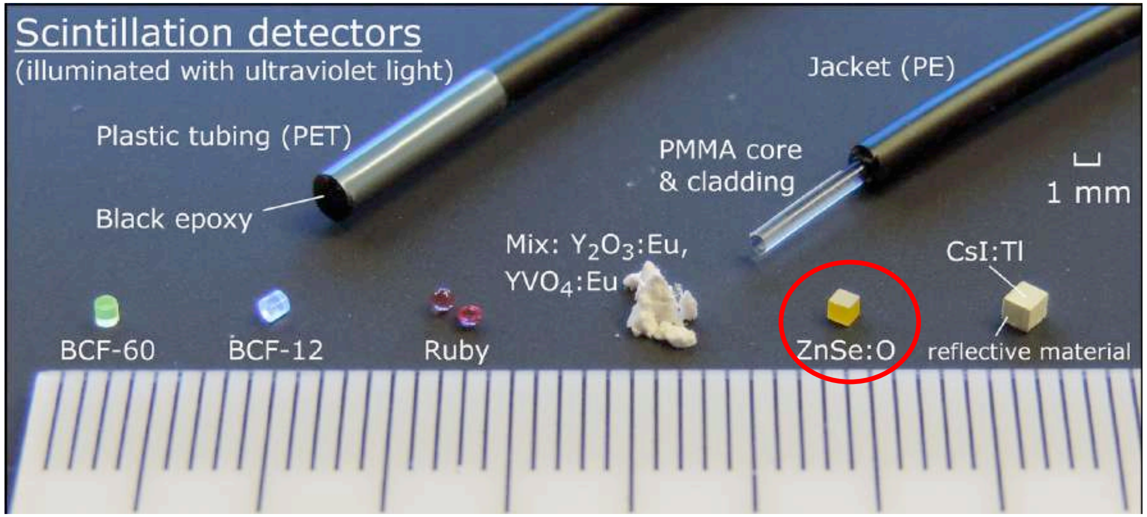


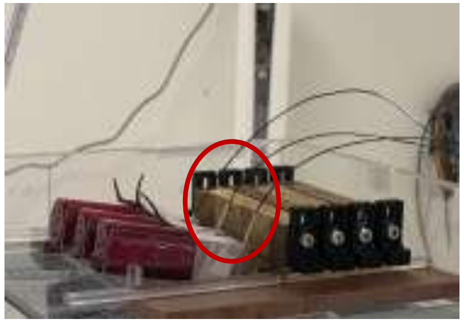
Alanine	Films
Very sensitive to humidity.	Can be submerged in water.
Dose rate independent.	Dose rate independent.
Range up to ~kGy.	Not recommended above 10 Gy.
Very high precision.	High uncertainty.

courtesy of Eleni Kanouta and Jacob Johansen

FLASH dosimetry – at DCPT

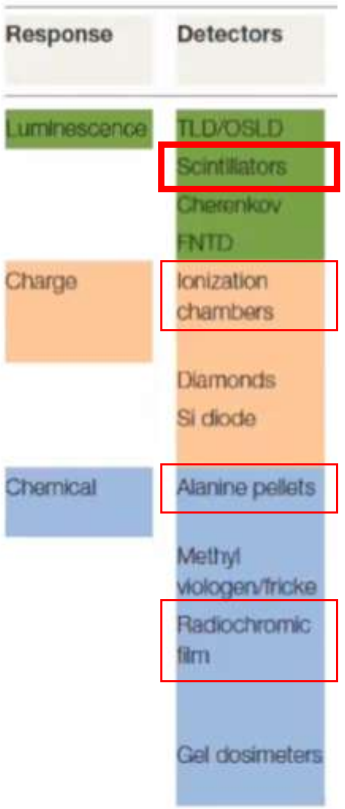
Response	Detectors
Luminescence	TLD/OSLD Scintillators Cherenkov FNTD
Charge	Ionization chambers Diamonds Si diode
Chemical	Alanine pellets Methyl viologen/fricke Radiochromic film Gel dosimeters


Scintillation detectors
(illuminated with ultraviolet light)



courtesy of Eleni Kanouta and Jacob Johansen

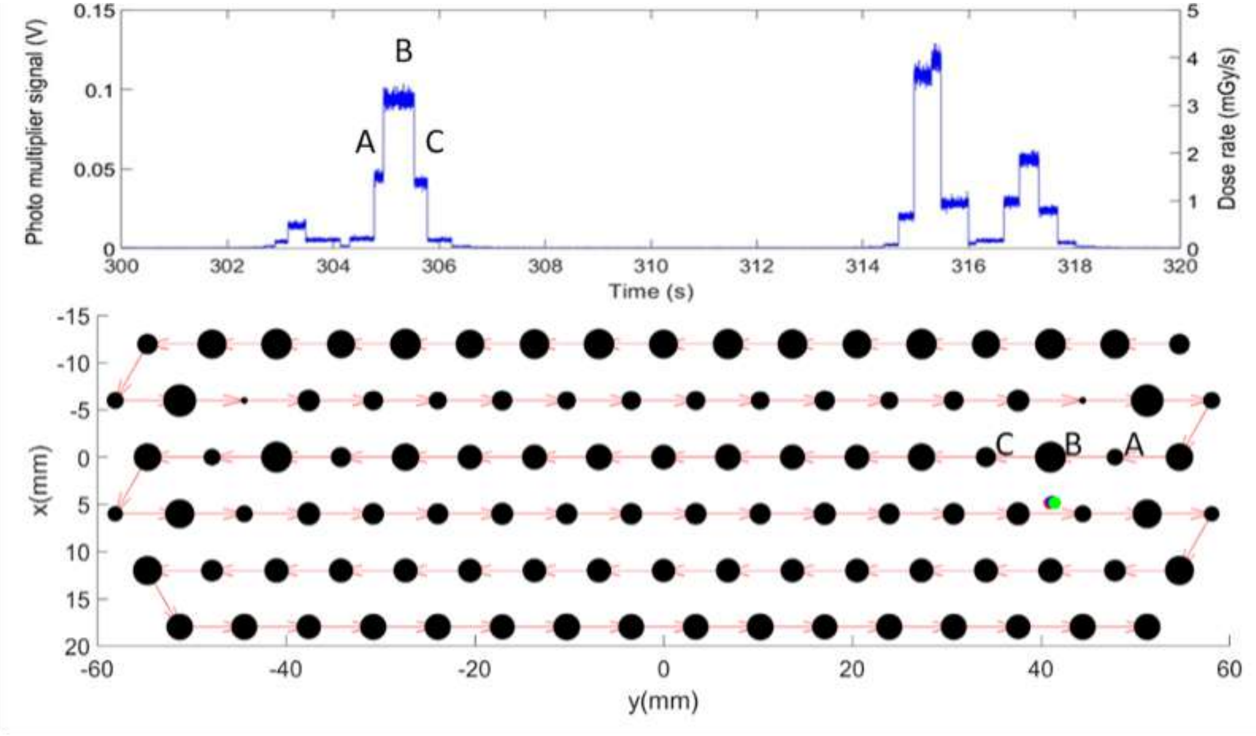
FLASH dosimetry – at DCPT



Response	Detectors
Luminescence	TLD/OSLD Scintillators Cherenkov FNTD
Charge	Ionization chambers Diamonds Si diode
Chemical	Alanine pellets Methyl viologen/fricke Radiochromic film Gel dosimeters

In vivo dosimetry with crystal scintillators and fiber-optic cables:

- position of the crystal within the spot pattern
- online monitoring of beam delivery



courtesy of Brita Sørensen

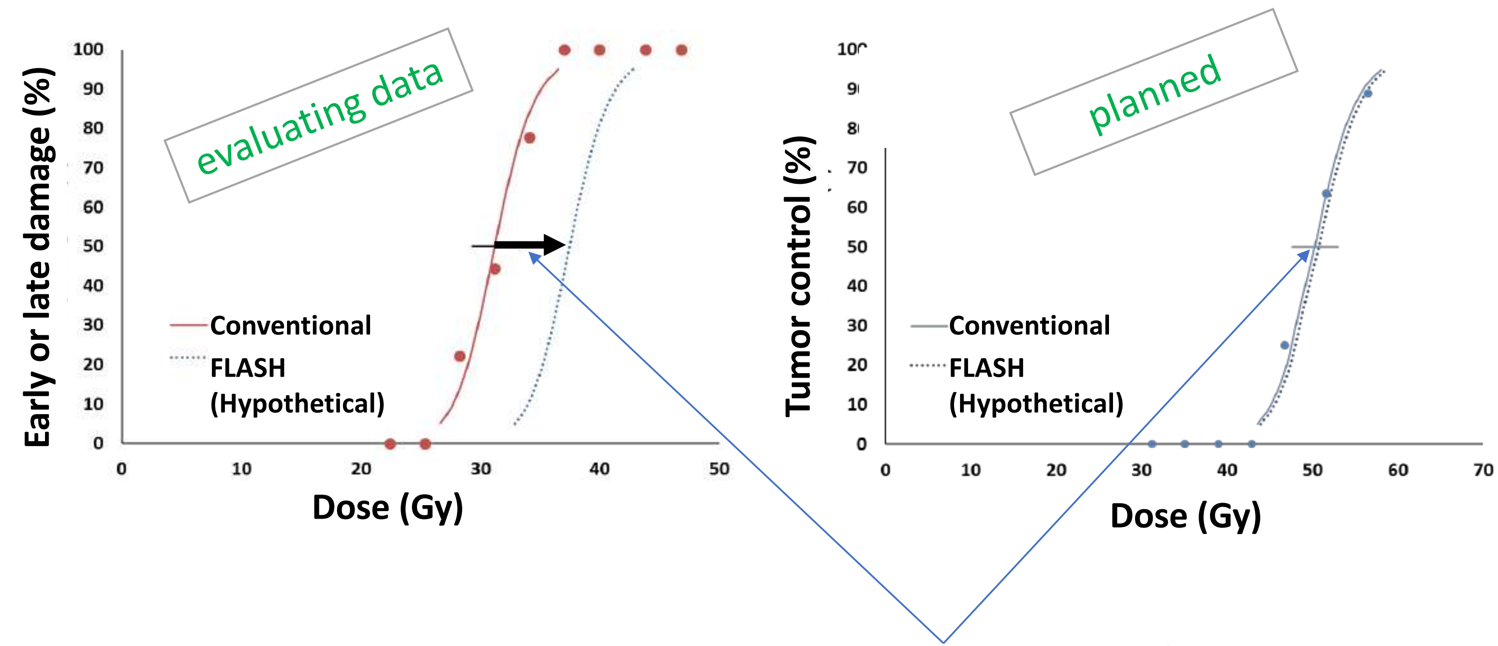
collaboration with Varian

Hypothetical FLASH response curves

PRELIMINARY RESULTS,
CONFIDENTIAL

Normal tissue response

Tumor response

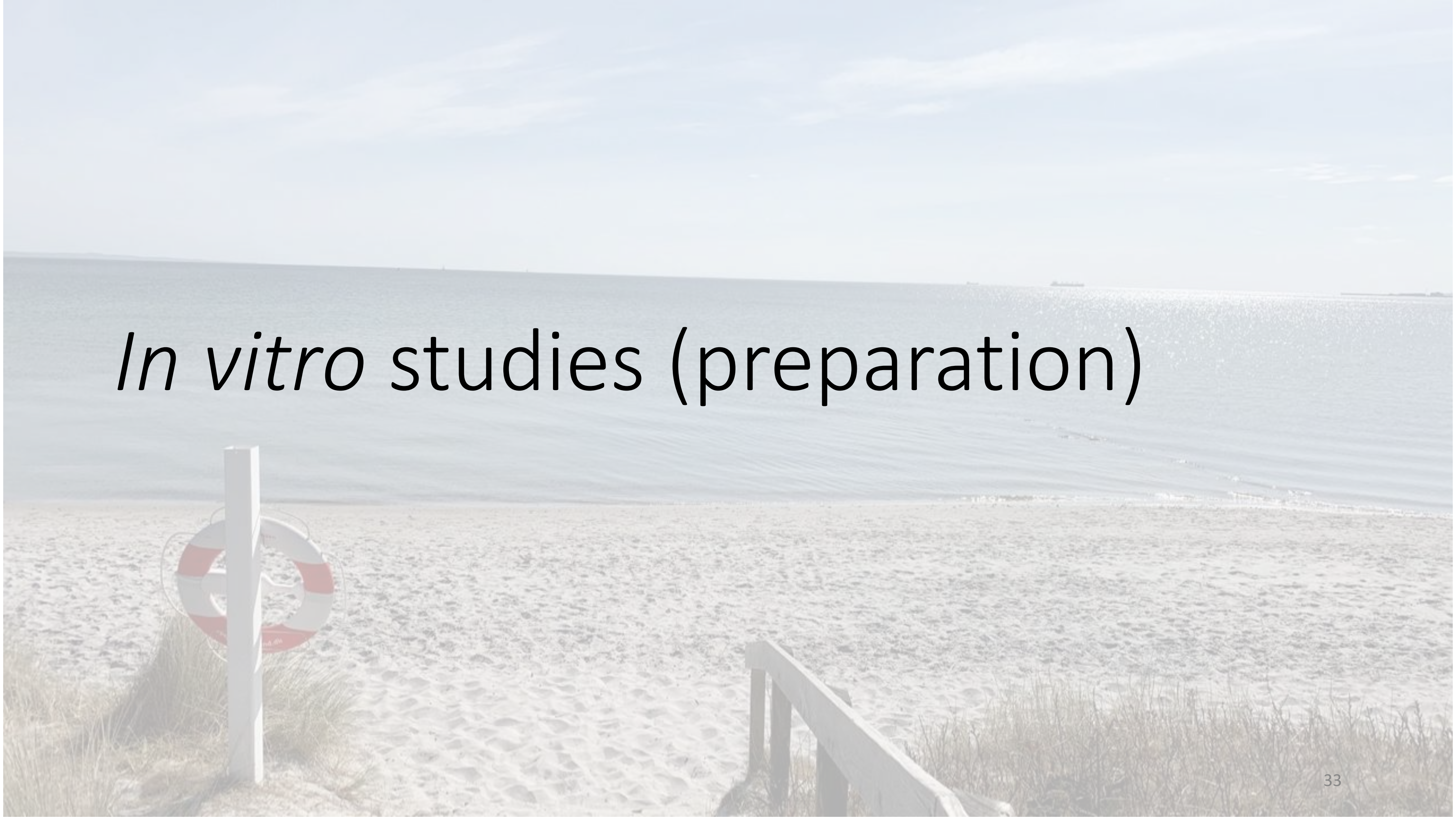


Enhancement Ratio of
FLASH

Next steps in FLASH

- Data evaluation for healthy tissue
- Dose response curve for tumor mice
- Test of new monitor chamber [Varian] – no daily scaling factor, stable beam delivery
- Film dosimetry with EBT-XD model (extended dose range)
- Monte Carlo simulations of mice set-up

In vitro studies (preparation)



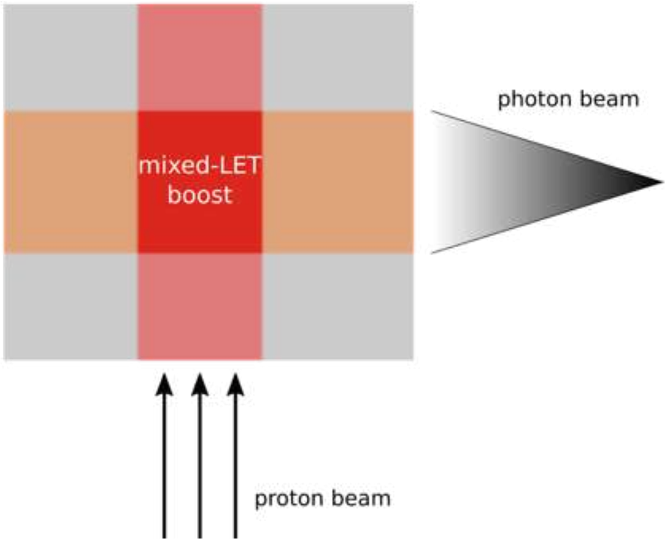
Mixed-LET effect

Clinical motivation

Simultaneous high and low LET radiations interact to produce more DNA damage than expected from an additive action.

Sollazzo et al., 2016, 2017

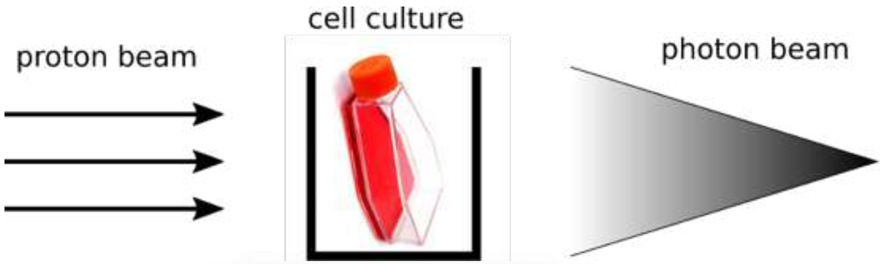
1. Lack of relevant data for mixed-LET effect with **proton + X-ray** fields.
2. Possible clinical application: mixed-LET **increase of tumor control.**



collaboration with FUW

Mixed-LET effect **Experimental verification**

clinical proton beam



x-ray tube

pencil scanning clinical proton beam

energy: 70-244 MeV
beam current on target: 0.5-15 nA
max. field: 30x40 cm^2
max dose rate: 10^6 MU/min
SAD: 228 cm

V79 cell line

(collaboration with Department of Experimental Clinical Oncology at Aarhus University Hospital) *courtesy of Jacob Johansen and Peter Georgi*

Experimental plan at DCPT

x-ray field

Papillon 50 x-ray tube

(collaboration with Department of Oncology,
Aarhus University Hospital)

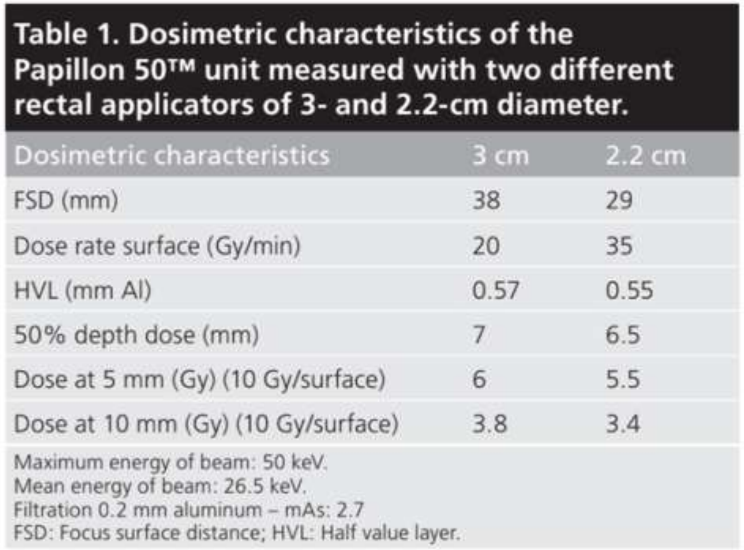
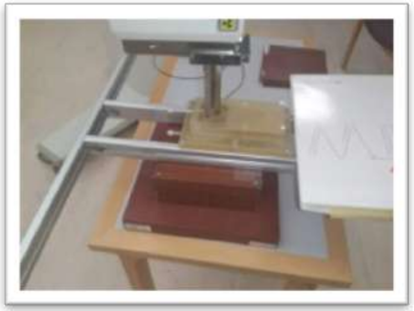


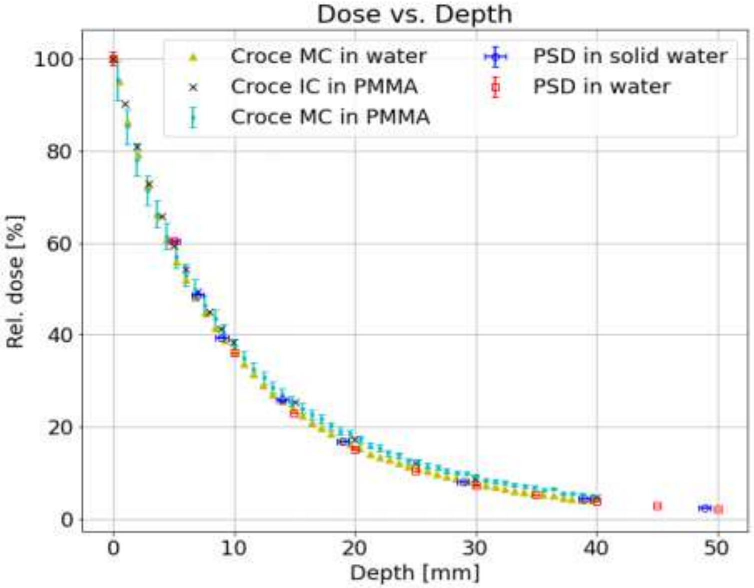
Table 1. Dosimetric characteristics of the Papillon 50™ unit measured with two different rectal applicators of 3- and 2.2-cm diameter.

Dosimetric characteristics	3 cm	2.2 cm
FSD (mm)	38	29
Dose rate surface (Gy/min)	20	35
HVL (mm Al)	0.57	0.55
50% depth dose (mm)	7	6.5
Dose at 5 mm (Gy) (10 Gy/surface)	6	5.5
Dose at 10 mm (Gy) (10 Gy/surface)	3.8	3.4

Maximum energy of beam: 50 keV.
Mean energy of beam: 26.5 keV.
Filtration 0.2 mm aluminum – mAs: 2.7
FSD: Focus surface distance; HVL: Half value layer.

first QA measurements at DCPT





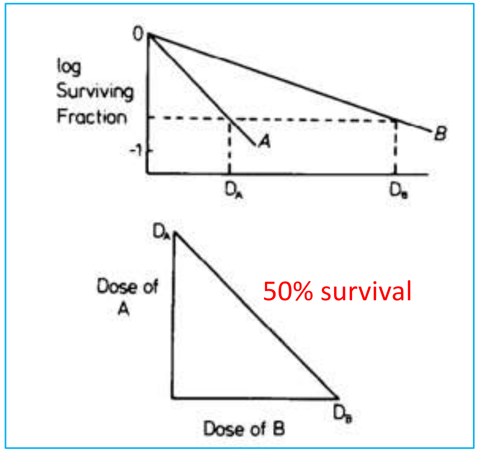
Quantification of synergism

protons irradiation → endpoint
x-ray irradiation → endpoint
protons + x-ray → endpoint

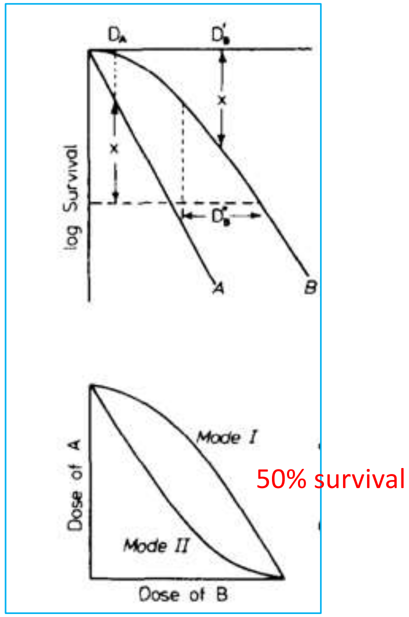
micronucleus test, γ-H2AX, gene expression, survival assay, ...

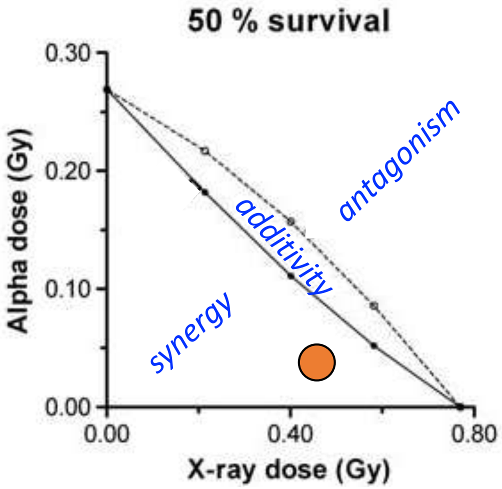
PARTRAC

- SSB and DSB
- foci kinetics



Gordon Steel et al., 1979
Staaf et al., 2012

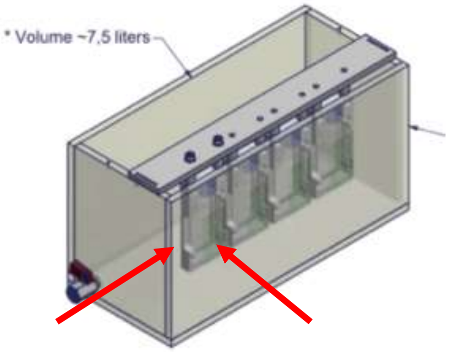


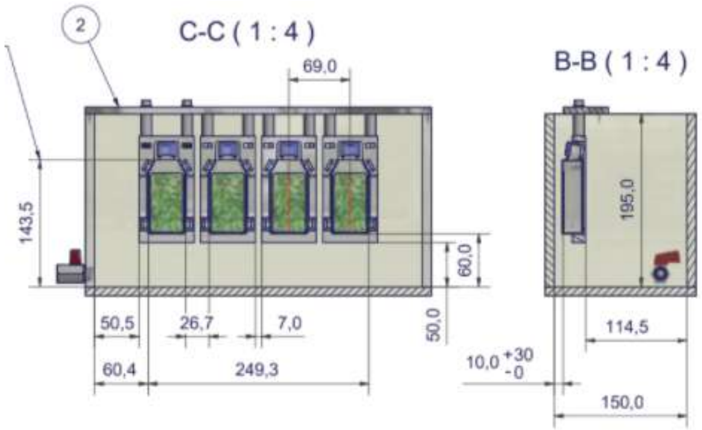


Water phantom designs

- conventional set-up for cell irradiations

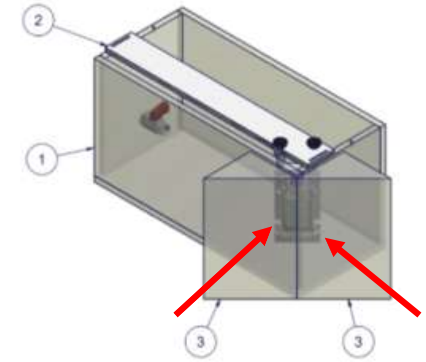
  d_{min} = 2 cm

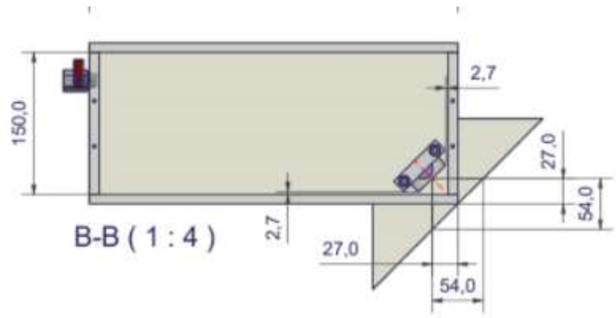


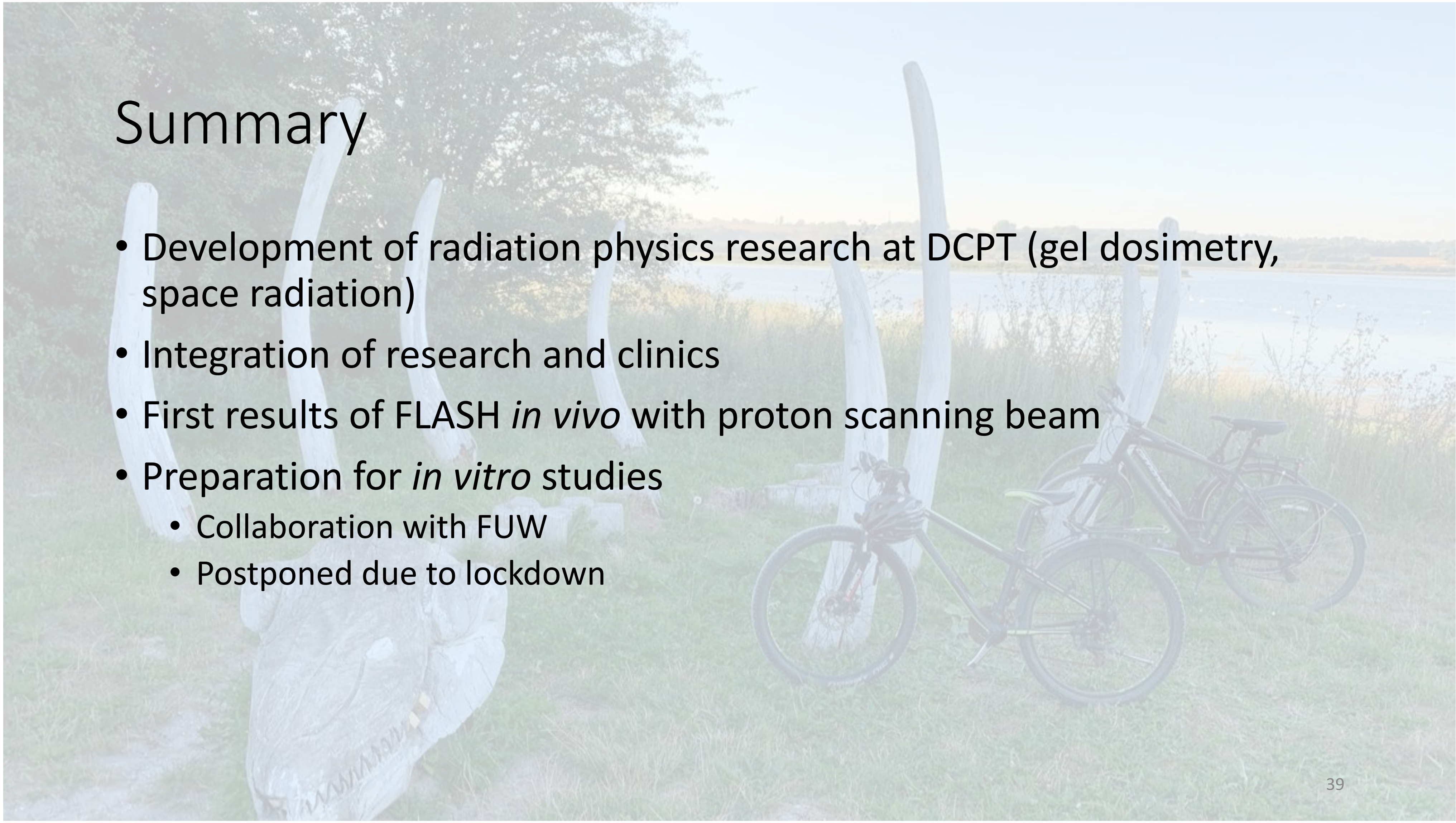


- tilted cell flask with 45° wedges

  d_{min} = 5 cm

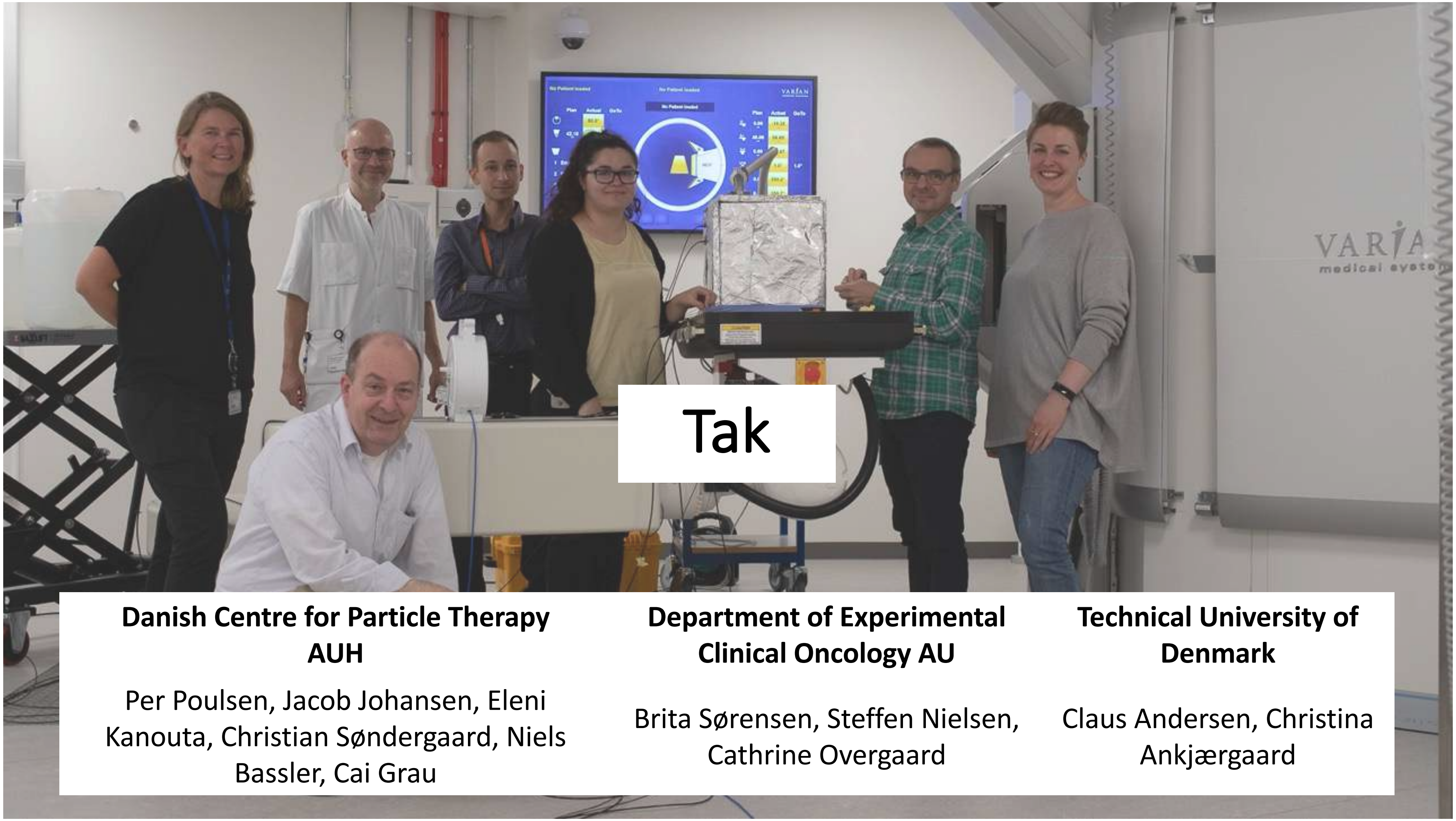






Summary

- Development of radiation physics research at DCPT (gel dosimetry, space radiation)
- Integration of research and clinics
- First results of FLASH *in vivo* with proton scanning beam
- Preparation for *in vitro* studies
  - Collaboration with FUW
  - Postponed due to lockdown



Tak

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