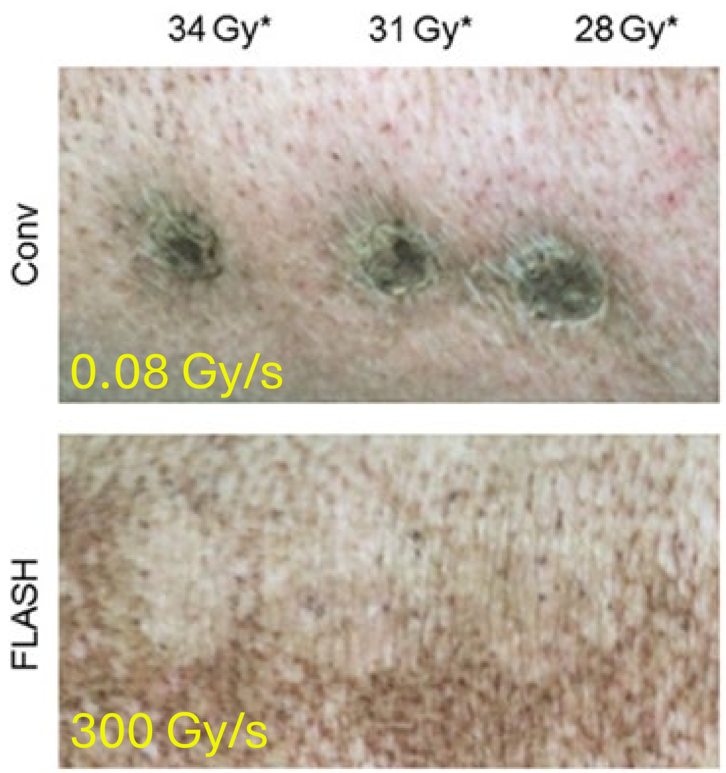
# FLASH therapy

## Upgrading a proton beamline for preclinical studies

David Meer
SPS Annual Meeting 2024, 11 September 2024

# FLASH effect in a nutshell

- Protective effect on healthy tissue while maintaining tumour killing efficiency compared to conventional RT
- Irradiation parameters for FLASH effect
  - Ultra-high dose rates $\gtrsim$ 40 Gy/s (conventional dose rate $\sim$ 0.1 Gy/s)
  - Threshold dose $\sim$10 – 20 Gy
- Experimental *in-vivo* evidence for photons / electrons / protons / heavy-ion
- Underlying mechanism not fully understood

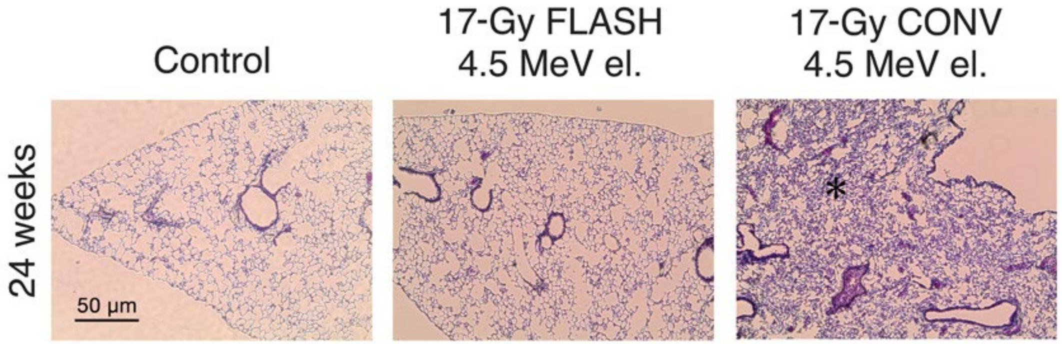



*Vozenin et al., Clin. Cancer Res. 25 (1) 2019, 10.1158/1078-0432.CCR-17-3375*

Skin of a minipig, 36 weeks post-irradiation

# (Re-)discovery FLASH effect

- Already in the 1960's, radiobiology experiments revealed dose rate dependency
- In 2014, Favaudon et al. showed a protective effect in mice lung under FLASH conditions:




Pulmonary fibrosis after electron irradiation conventional (0.03) and FLASH (60 Gy/s)

Favadon, Sci Transl Med 16;6(245):245ra93 (2014), 10.1126/scitranslmed.3008973

- Since then, the FLASH effect gained a lot of attention, many *in-vivo* studies
  ⇨ "*The next revolution in RT?*"
- Hypotheses for underlying FLASH mechanism:
  - Oxygen effect, hypoxic condition
  - Reactive oxygen species (ROS) / free radical suppression
  - Immune system
  - Inflammatory response

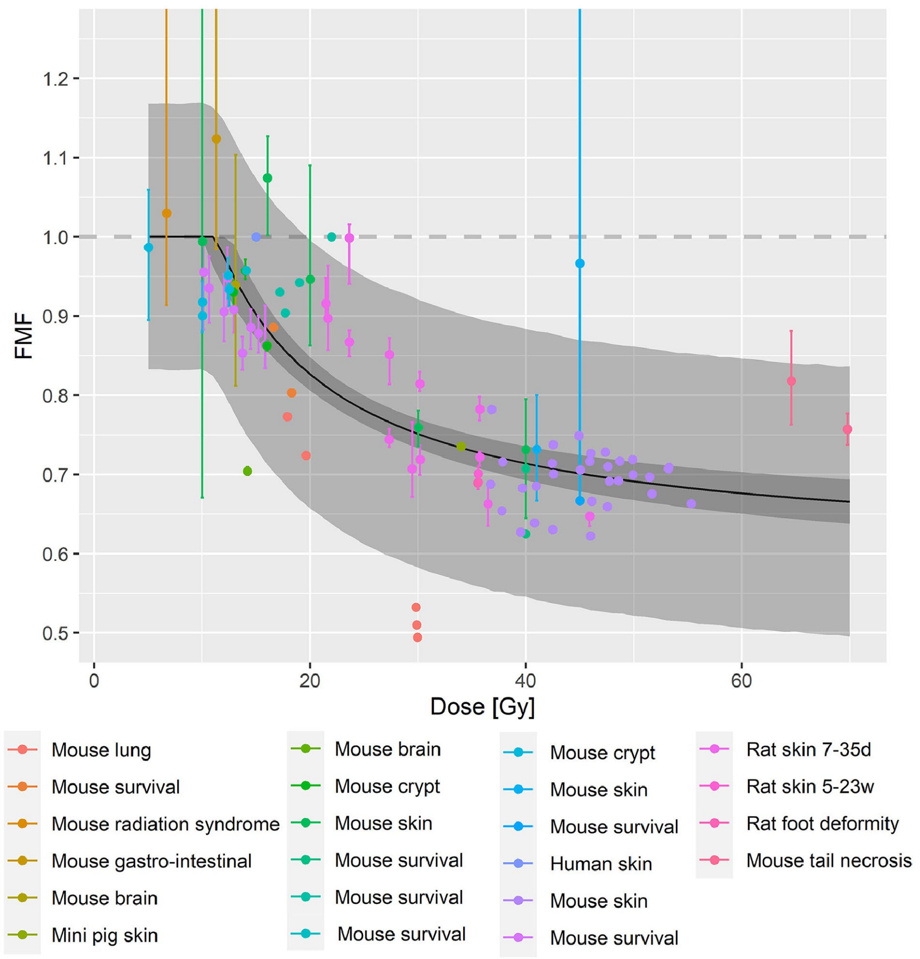
# Normal tissue sparing by FLASH: A quantification

- Systematic literature study of *in-vivo* data (FLASH/conv) by Böhlen et al.
- Clinically relevant endpoint with iso-effect
- FLASH modifying factor for normal tissue sparing

$$\mathrm{FMF} = \left.\frac{D_{\mathrm{CONV}}}{D_{\mathrm{UHDR}}}\right|_{\mathrm{iso-effect}}$$

- Single fraction, time average dose rate > 40 Gy/s

- Normal tissue sparing >20% for single dose >25Gy
- FMF saturates around 0.65
  ⇨ Normal tissue sparing ≤35%




Böhlen et al., Int. J. Radiat. Oncol. Biol. Phys. 114 **5** 103 (2022) 10.1016/j.ijrobp.2022.05.038

# Opportunity in 2019 to initiate proton FLASH studies at PSI

- End clinical operation on Gantry 1 in 2018
- First spot-scanning system but with limitations:
  - Only 1-d scanning (2$^{nd}$ lateral direction with patient table $\rightarrow$ slow scanning)
  - Local energy modulation with range shifter (fast, but scattering of beam $\rightarrow$ spot size)

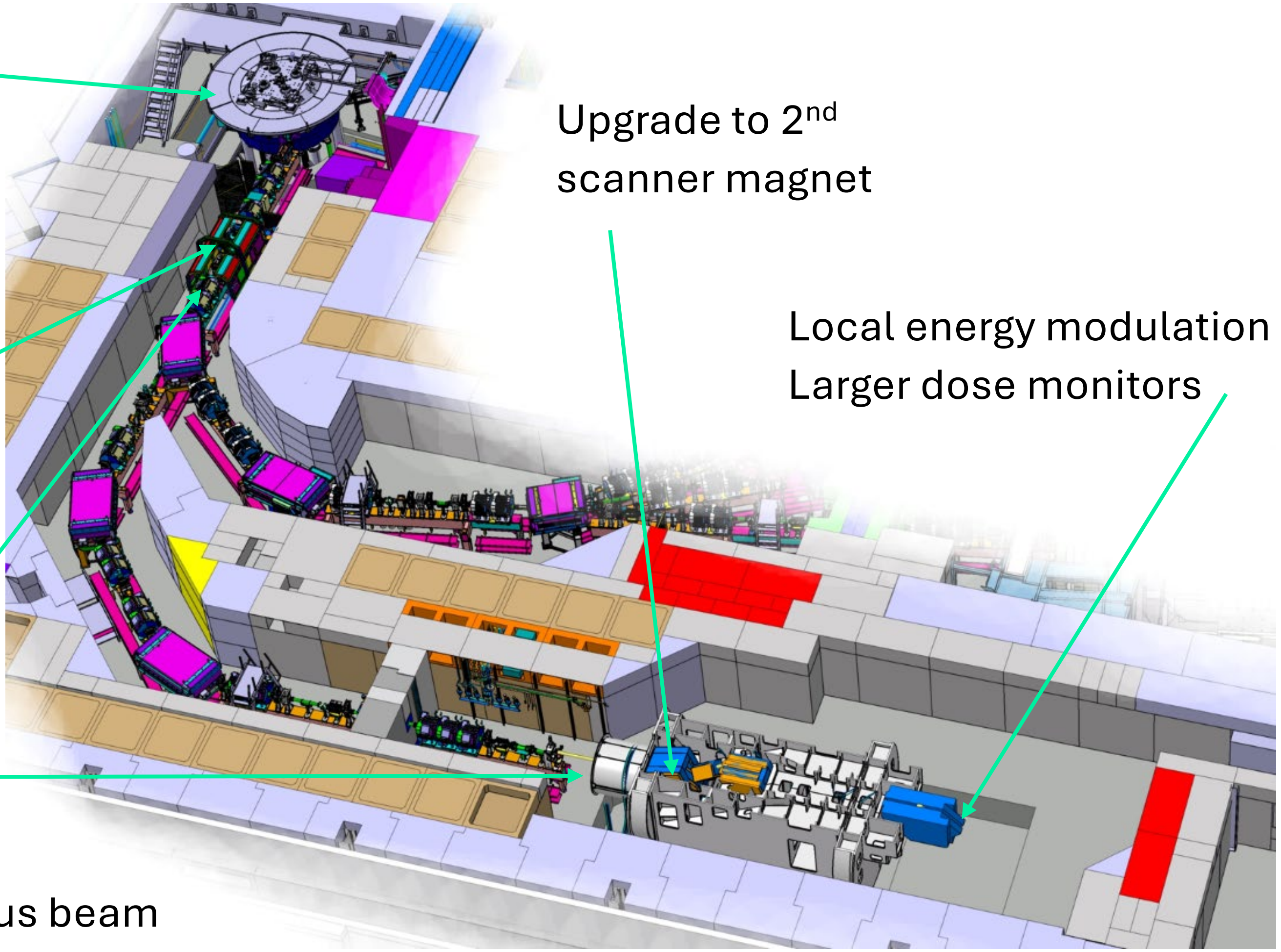
- Control system, dosimetry and safety system fully in-house developed, expertise available
- Separate access to treatment room (separation from clinics)
- Almost no proton FLASH experience at the time, most experiments with electrons

⇨ Unique opportunity to launch a proton FLASH program in 2019

# Modification / Upgrades for Gantry 1

Cyclotron (quasi-DC beam)
700+ nA beam current, 72 MHz

No energy degradation,
no beam losses

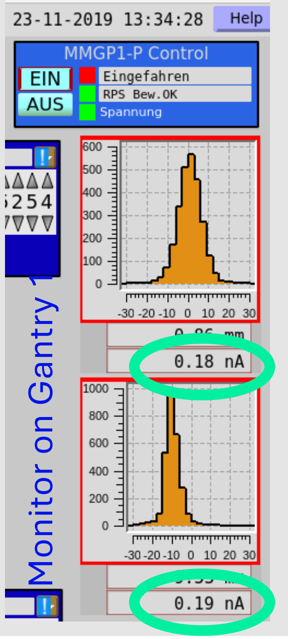


Upgrade to 2nd
scanner magnet

Local energy modulation
Larger dose monitors

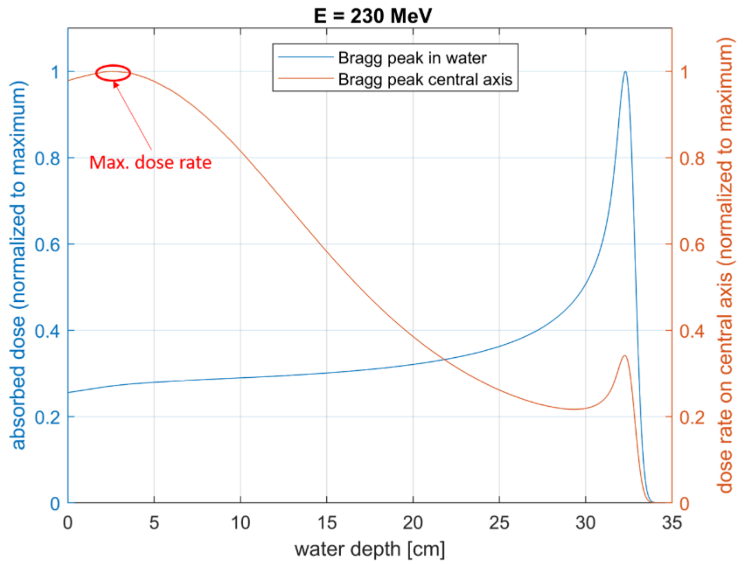
Charge integral system
Hourly limit, 1 nA → 1000 nA
⇨ interlock after 3.6s continuous beam
Authorities (BAG) very supportive

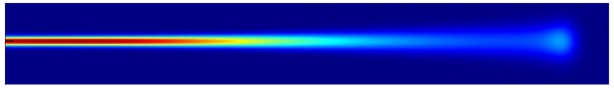
First beam tests
COMET: 0.20 nA

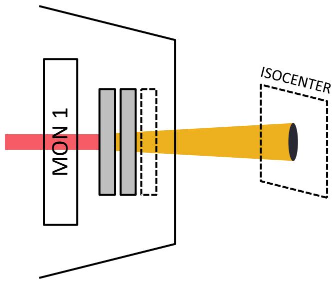


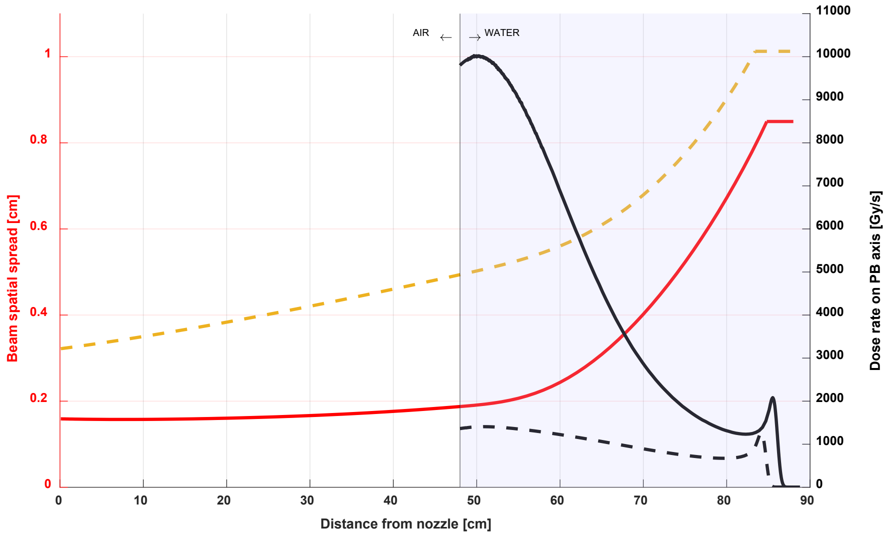
# Maximal achievable dose rate

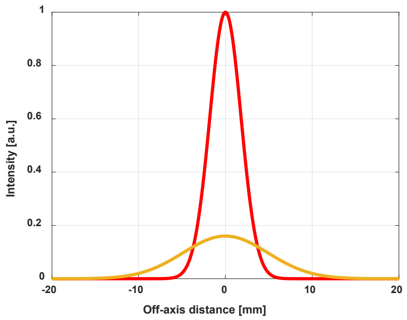
- Integral depth dose curve: Bragg peak
- Highest on-axis dose (rate) at entrance due to scattering
- Max dose rate depends on initial spot size:
  Smallest spot: 9000 Gy/s for a 1x1 $mm^2$ field (95% homogeneity)
- Range shifter to achieve different "field" sizes
  2x2 $mm^2$ -> 1400 Gy/s





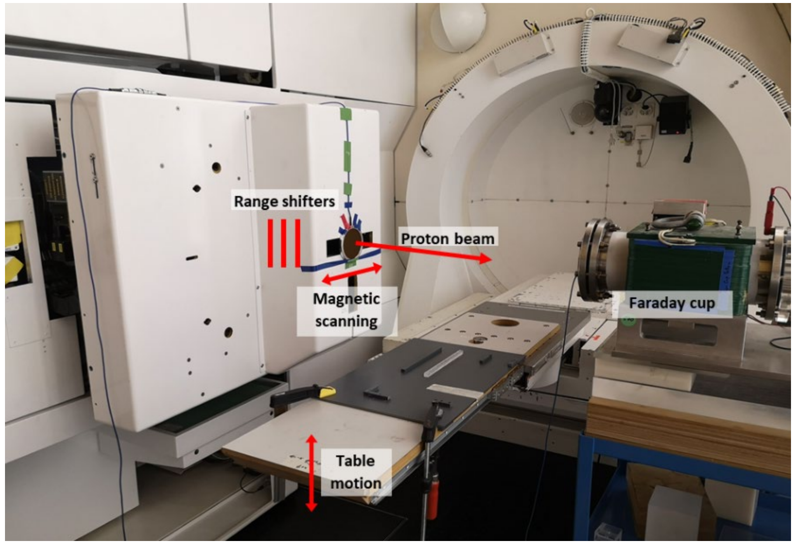



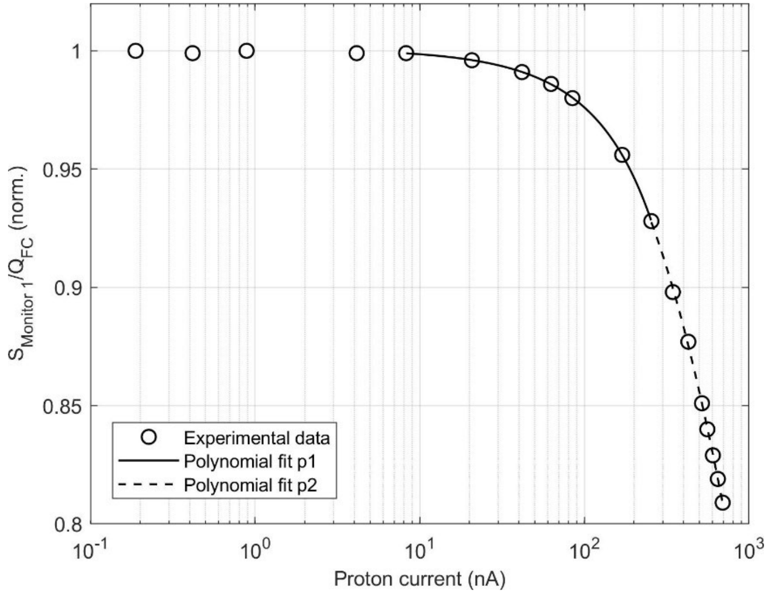




Togno, M. et al., Physica Medica 104 (2022),
10.1016/j.ejmp.2022.10.019

# Dosimetry at ultra-high dose rate

- Delivered dose determined by ionisation chambers on gantry
- Recombination effects at high ionisation density
  ⇨ drop of signal
- Faraday cup as dose rate independent measurement (collected charge)
- Empirical characterisation of primary dose monitor



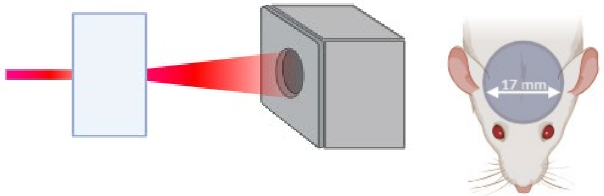

Dose validated and inter-comparison study with
Alanine, TLDs, EBT3 , µDiamond, adv. Markus chamber, OSLDs

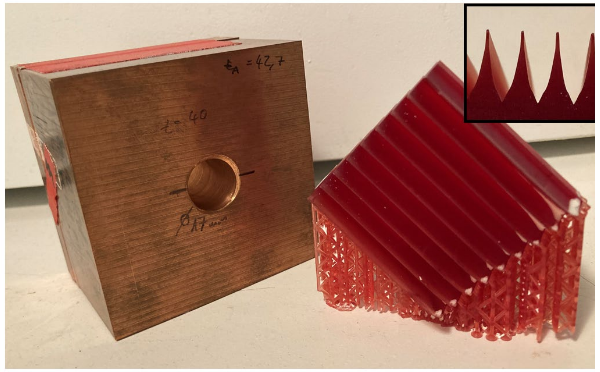
*Almeida et al., Radiother. Oncol. 190 (2024), 10.1016/j.radonc.2023.109953*

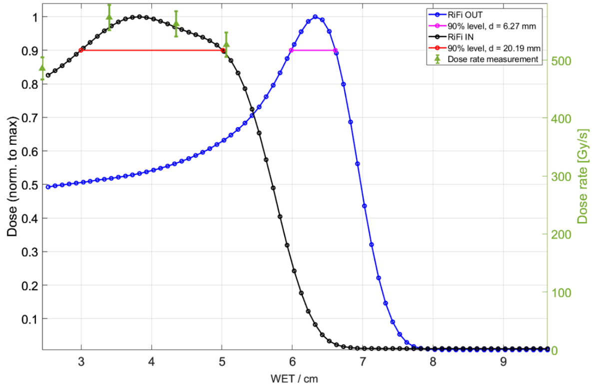
# Different beam delivery technics

## Scattering

- Collimation of scattered beam with aperture
- Target is irradiated simultaneously, well-defined dose rate
- Optional: Ripple filter to generate spread-out Bragg peak
- Only small fields

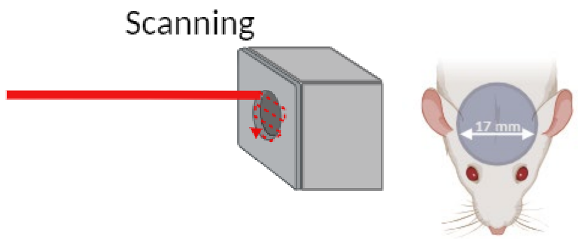





## Scanning

- Magnetic scanning of unscattered beam
- Fast energy modulation difficult:
  mainly shoot-through or with ripple filter
- Collimator is optional (to enhance penumbra)

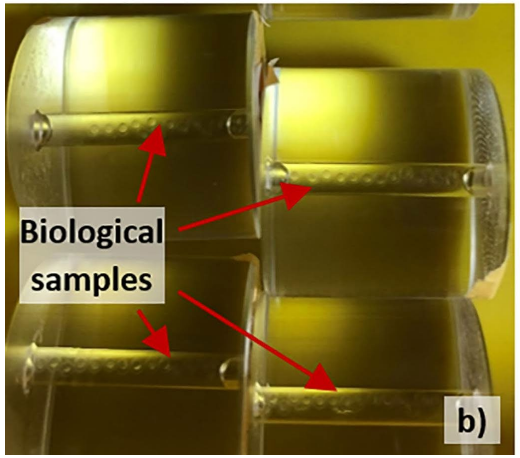


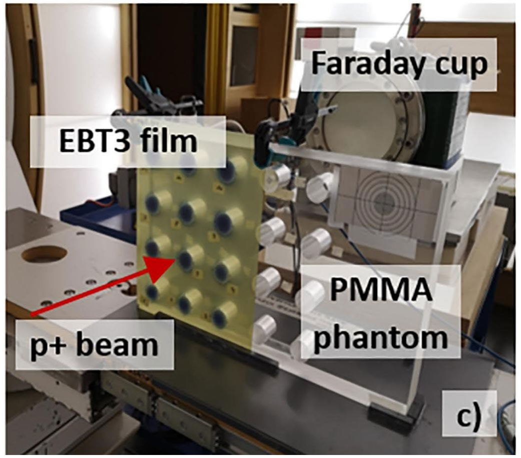

For Gantry 1 at PSI:

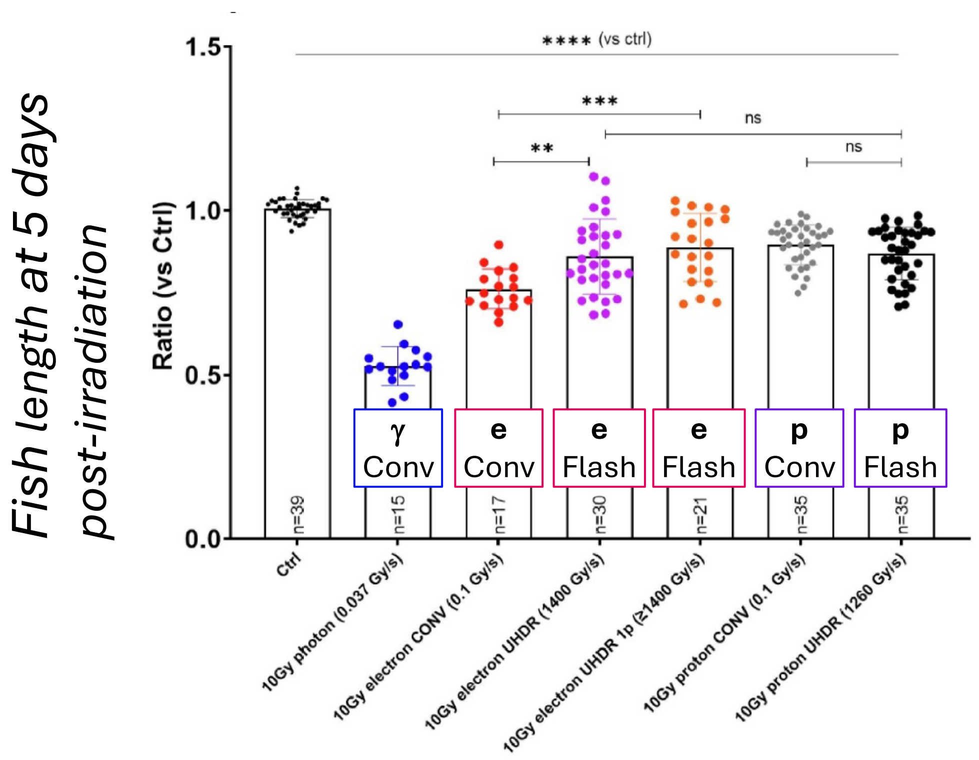
- Upgrade to 2d scanning;
  'Misuse' steering magnet as scanner
- Increase gap of dose monitors

# First in-vivo experiments: Zebra fish embryos

- Zebra fish: Fast responding in-vivo model
- Fish eggs irradiated with 9/10/11 Gy in transmission mode
- Small target, minimal scattering → high dose rate: (Flash 1260 Gy/s, Conv 0.1 Gy/s)
- Collaboration with our radiobiology partner from CHUV (Lausanne)
- Survival / developmental alterations (length)



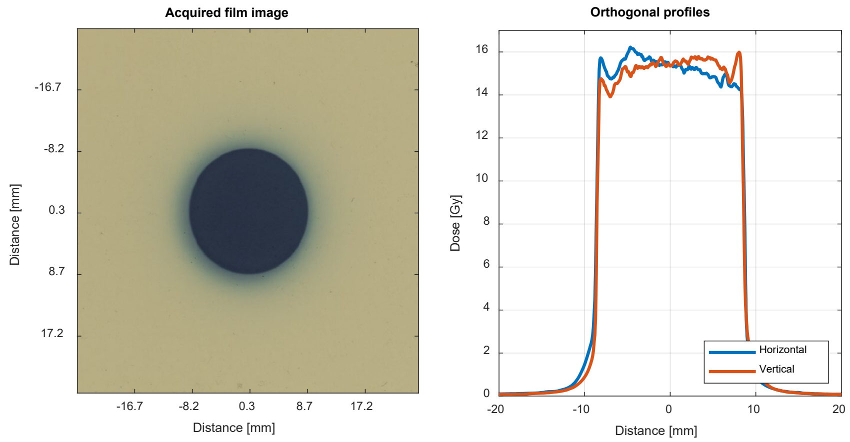



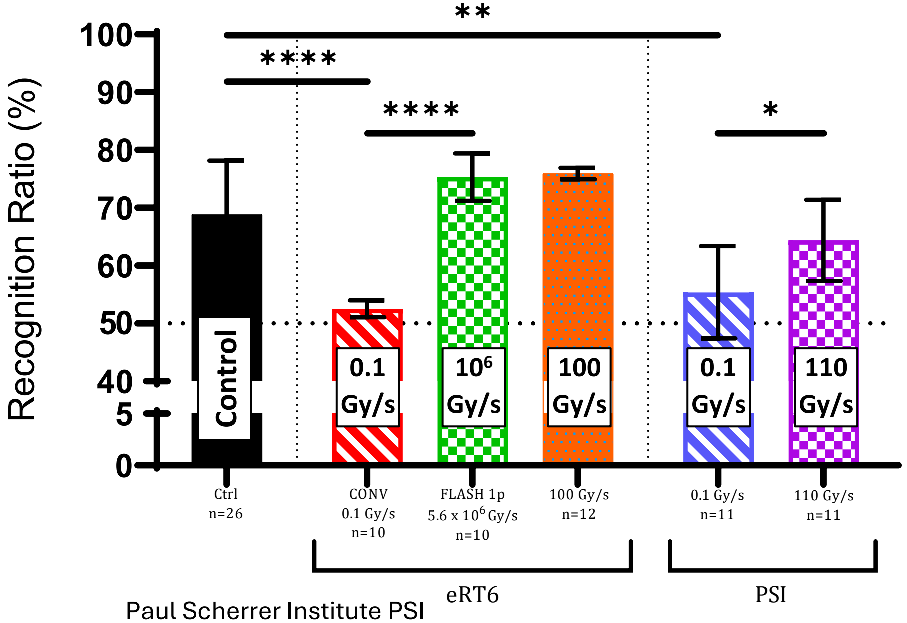

- Proton results compared to photons and electrons (irradiated at CHUV)
- Protons have minimal impact on growth and survival Conv vs. Flash

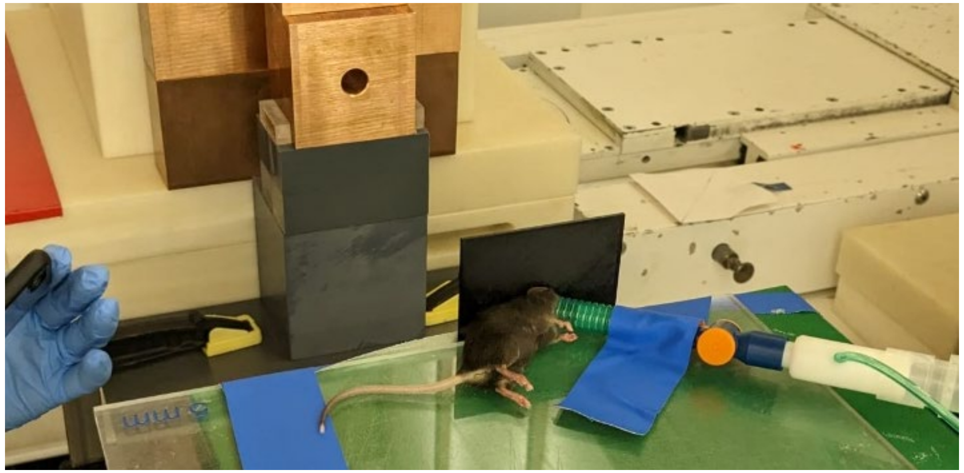
*Kacem et al., Rad. Onc., 175 (2022), 197-202*
*https://doi.org/10.1016/j.radonc.2022.07.011*

# Proton FLASH in murine model

- Full brain irradiation of mice, scattering, collimator Ø17mm
- Evaluation of novel object recognition 2/6/9 months post-IR
- 10 Gy dose in CONV (0.1 Gy/s) and FLASH (110 Gy/s)
- Sparing effect for electrons and protons after 2 month:



*Almeida et al., Radiother. Oncol. 190 (2024), 10.1016/j.radonc.2023.109953*

# FEATHER trial: Randomized phase 2/3 trial, FLASH vs. CONV

Comparison FLASH vs conventional dose rate in feline model

- Oral Squamous Cell Carcinoma OSCC of cats
- Spontaneous tumor
- Randomized with two arms CONV / FLASH
- 3 fraction of 11 Gy
- Transmission beams with scanning

Hypotheses:

- Proton FLASH is safe and effective
- FLASH halves high-grade toxicity

Endpoints:

- Acute toxicity and FLASH sparing
- Anti-tumor efficacy

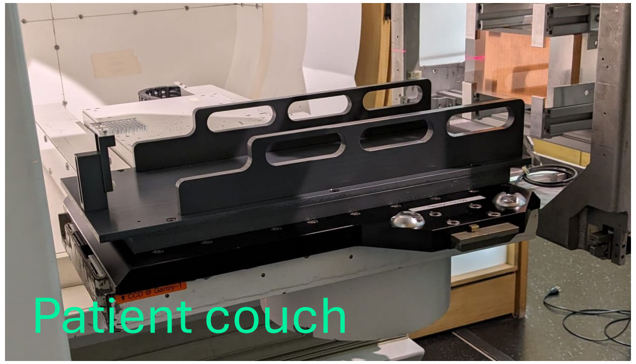
doi.org/10.3390/biology11010054

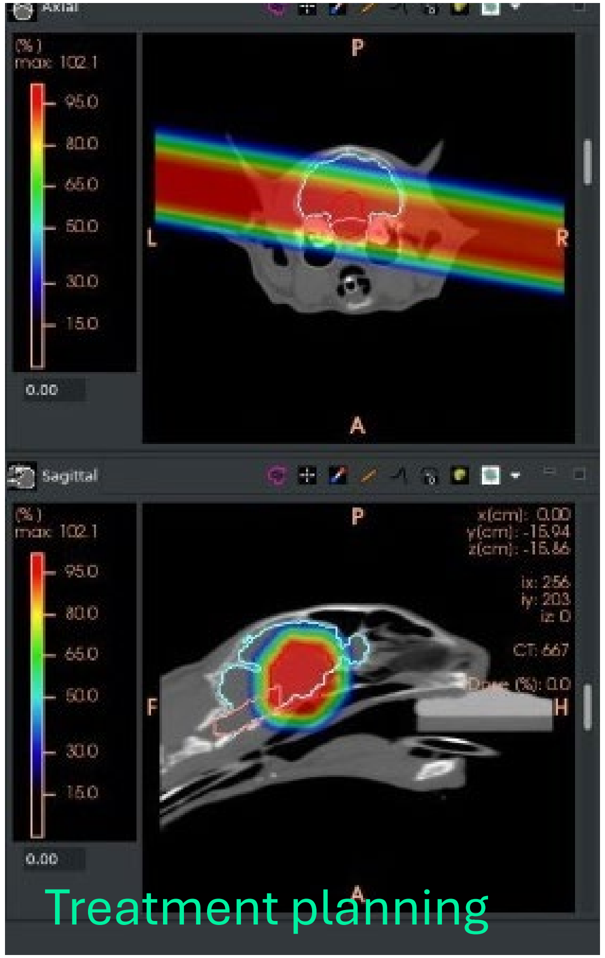
# Preparation and start of FEATHER trial

Development of

- Protocols
- Safety aspects
- Treatment planning
- Positioning
- QA procedure
- Verification measurements

Close collaboration with Vetsuisse Faculty, Zürich

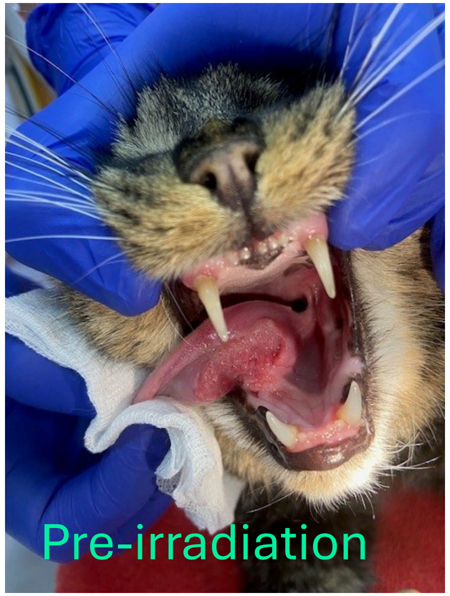

Patient couch



Treatment planning

2 patients treated so far:

- Start in Mai/June 2024
- No severer acute toxicities
- Good regression of the tumor
- Late toxicity to be evaluated


Pre-irradiation


1 week post-IR

# Conclusion

- 10-year investigation of FLASH effect
- FLASH effect is reproduced in different in-vivo models for $\gamma$ / e / p / C
- Underlying mechanism nor the required parameters not fully understood

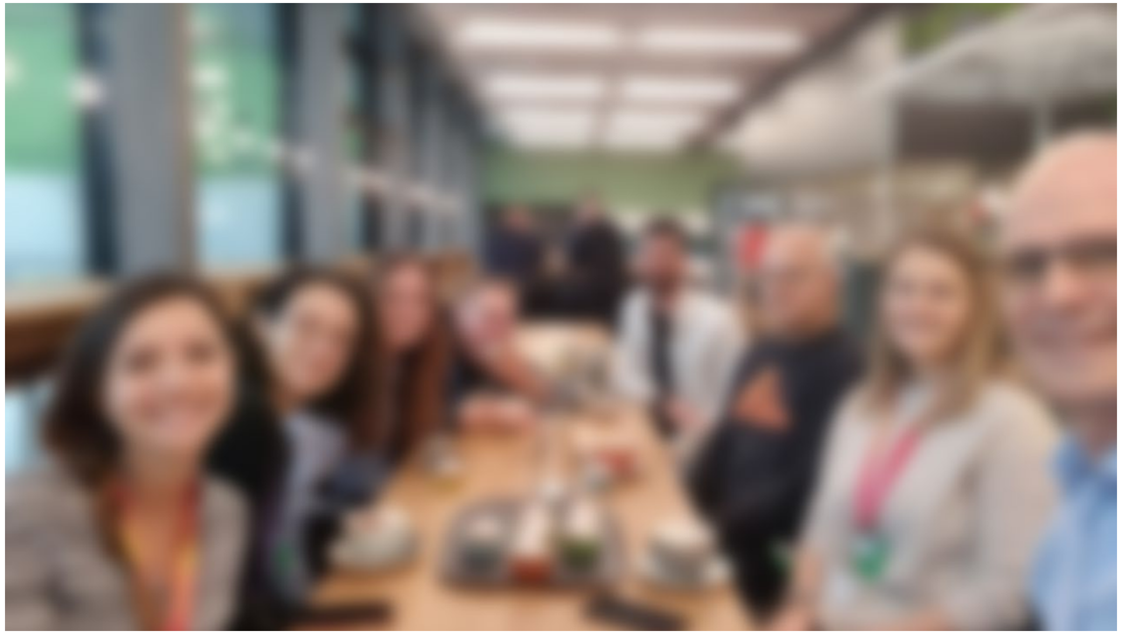
- Upgraded former clinical unit Gantry 1 to proton FLASH testbench
  - Successful proton FLASH research
  - Fostering collaboration with radiobiological expert

- Translation to clinical application very challenging

- R. Amara "*We tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run.*"

# Acknowledgments

PSI



PSI – Center for Proton Therapy

Geneva University Hospitals – M.C. Vozenin and team

Vetsuisse Faculty, Zürich – C. Rohrer and team

Works supported by

Schweizerischer Nationalfonds

varian
A Siemens Healthineers Company

krebsliga schweiz
ligue suisse contre le cancer
lega svizzera contro il cancro

Strategic Focus Area
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