Electron dose rate and oxygen depletion protect zebrafish embryo from radiation damage

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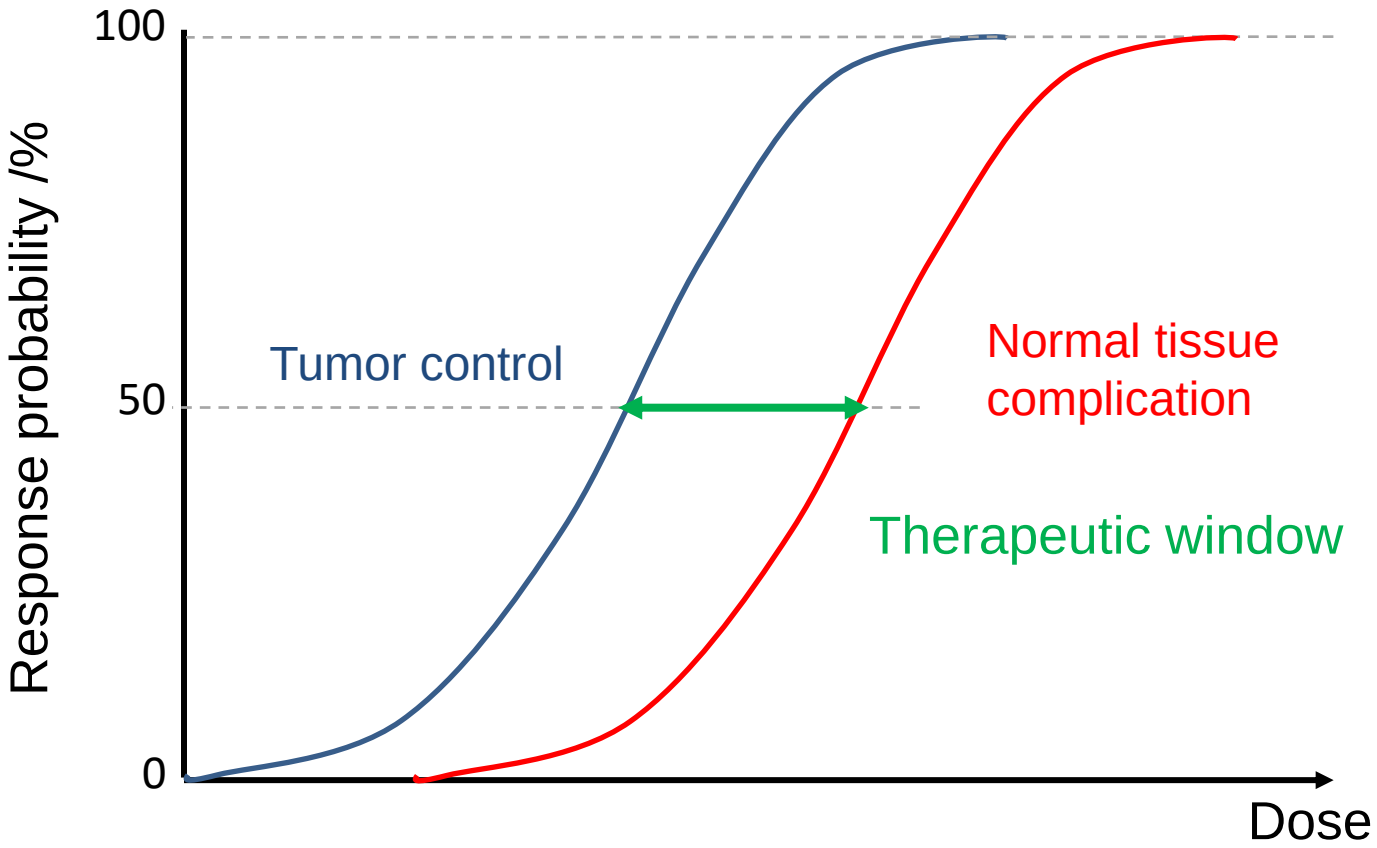
Adding up the benefits to broaden the therapeutic window



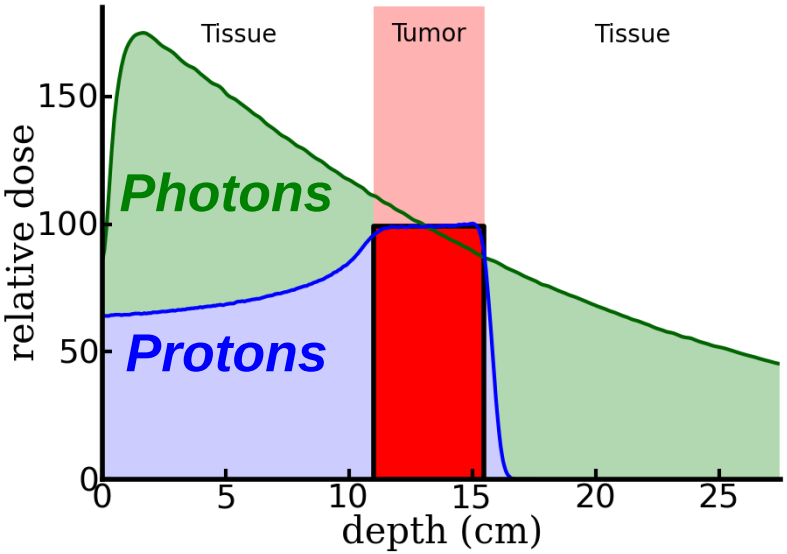
Sparring the normal tissue to broaden the window

- Tumor conform irradiation
- Differential tissue radiosensitivity

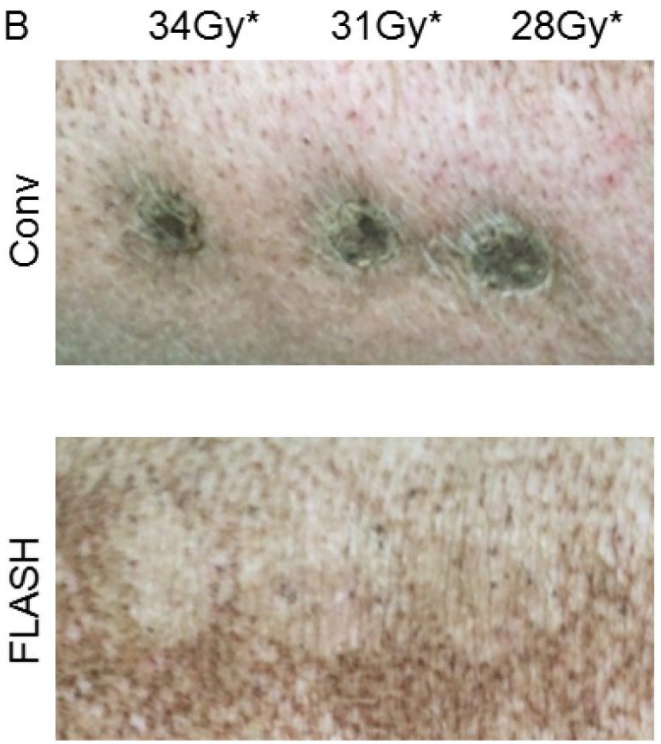
Holthusen 1928

Adding up the benefits to broaden the therapeutic window

Tumor conform irradiation
Beneficial depth-dose distribution of protons spares normal tissue



Differential tissue radiosensitivity
High dose rate (Flash) beam delivery protects normal tissue, but treats tumours efficiently

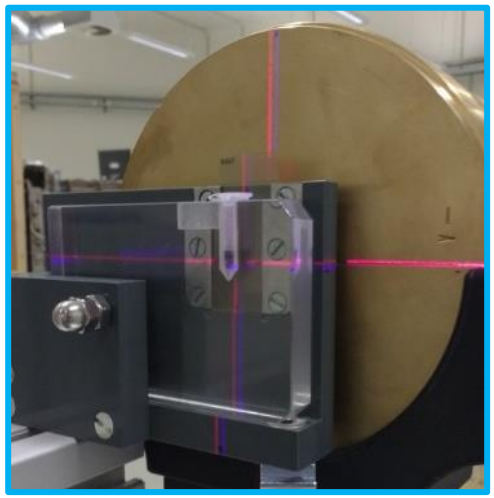


Vozenin et al. Clin Cancer Res 2019

Proton Flash experiment in Dresden - Setup

- University Proton Therapy Dresden, E_p = 70-230 MeV
- Flash: 228 MeV, 95 nA → 100 Gy/s
- Continuous: 228 MeV, 0.3 nA → 0.08 Gy/s

Irradiation geometry

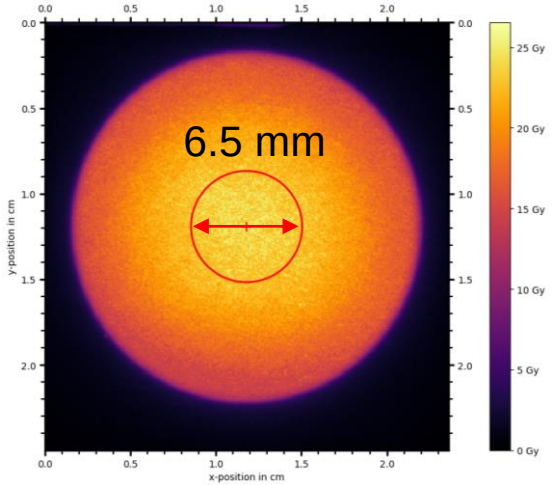


Transmission proton beam @entrance plateau

Online dose control: Two Transmission ionisation chambers

Absolute dose: Markus chamber and radiochromic EBT3 films

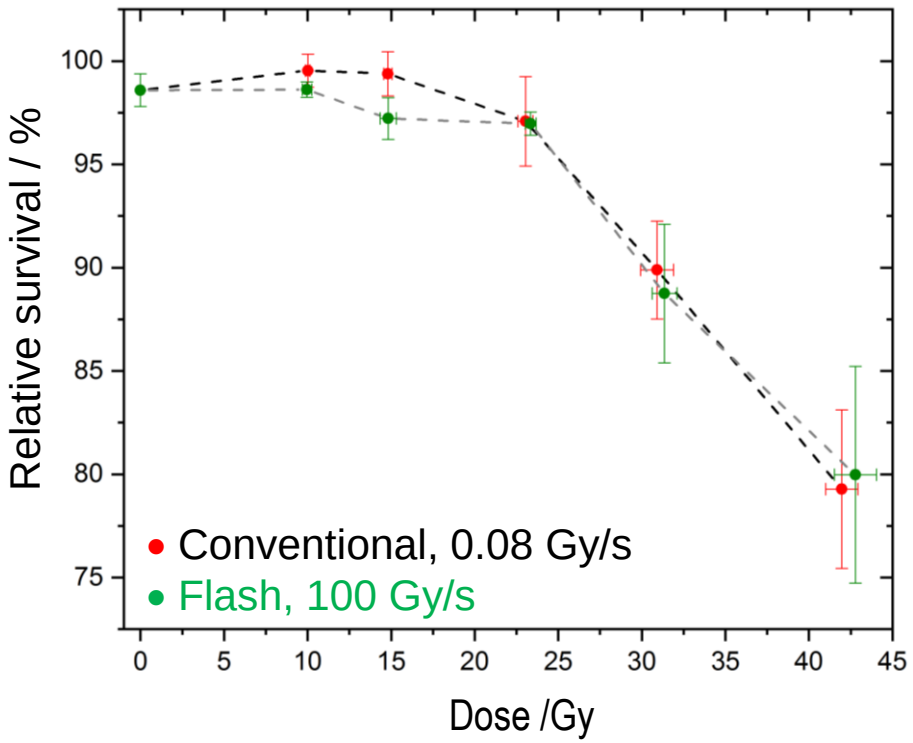
Dose homogeneity within beam spot



Zebrafish embryo, wildtype AB

- Doses ≤ 43 Gy, treatment time ~420 ms (Flash)
- Survival and morphological malformations up to four days post irradiation

Proton Flash experiment in Dresden - results

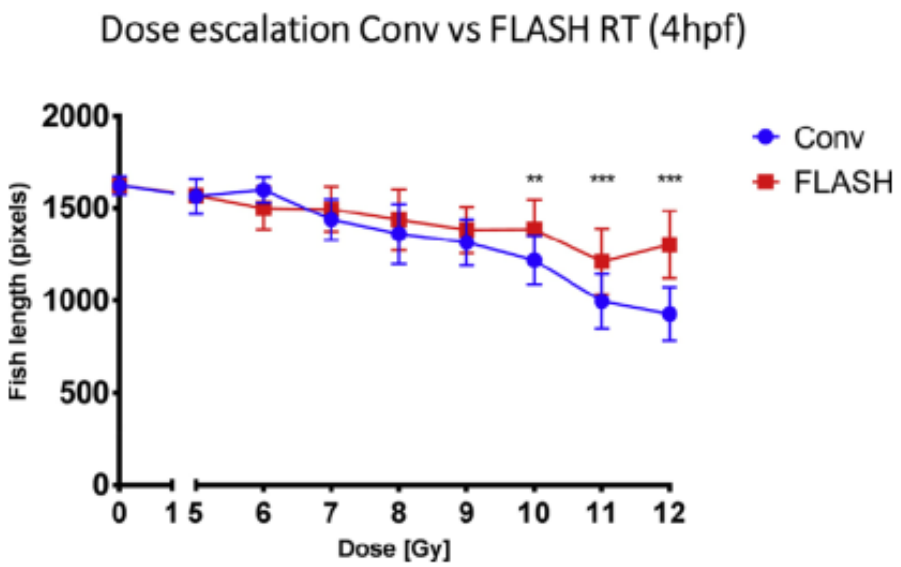


No significant protecting proton Flash effect for zebrafish embryo

Why? What are the differences to other electron/proton Flash experiments?

Proton No-Flash: Biological model and endpoint?

- Majority of Flash experiments performed with mice or other higher vertebrates
- **Zebrafish embryo model** successfully applied, but
  - 4 hpf vs. 24 hpf → defines radiosensitivity (dose)

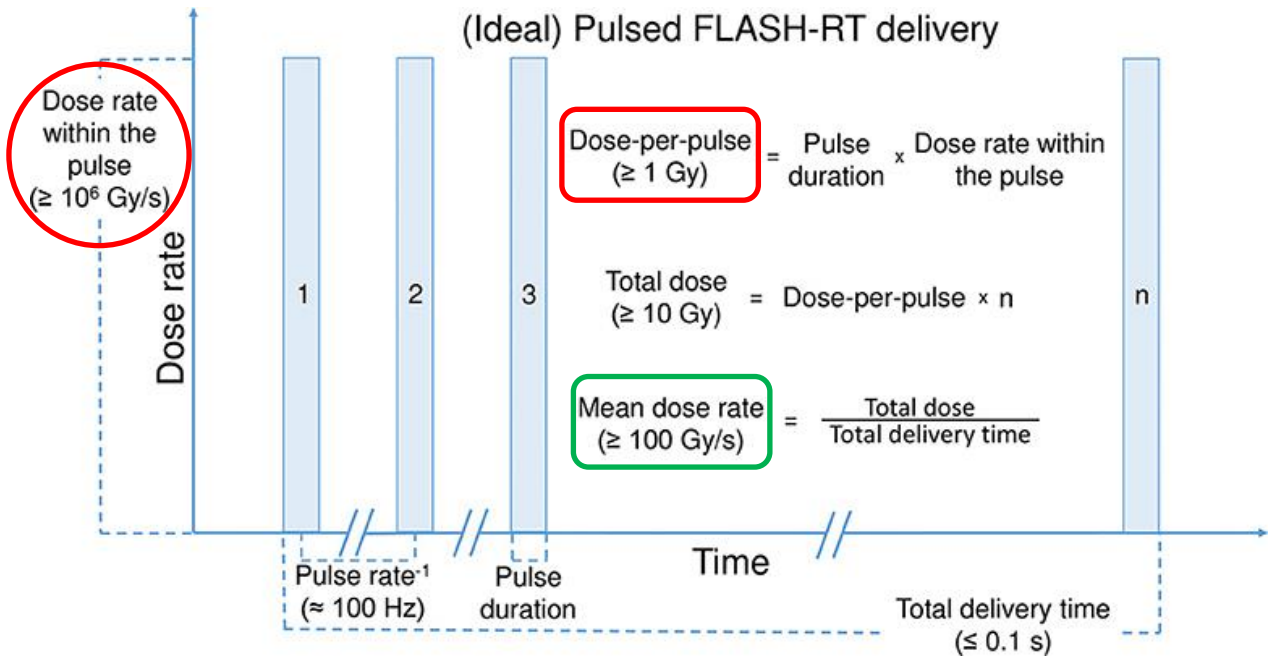


- Morphological malformations in general vs. embryo length

Vozenin et al. Clin Oncol 2019

Proton No-Flash: Beam and pulse parameters?

Recipe for electron Flash-RT published in Wilson et al. (Frontiers in Oncology, 2020):

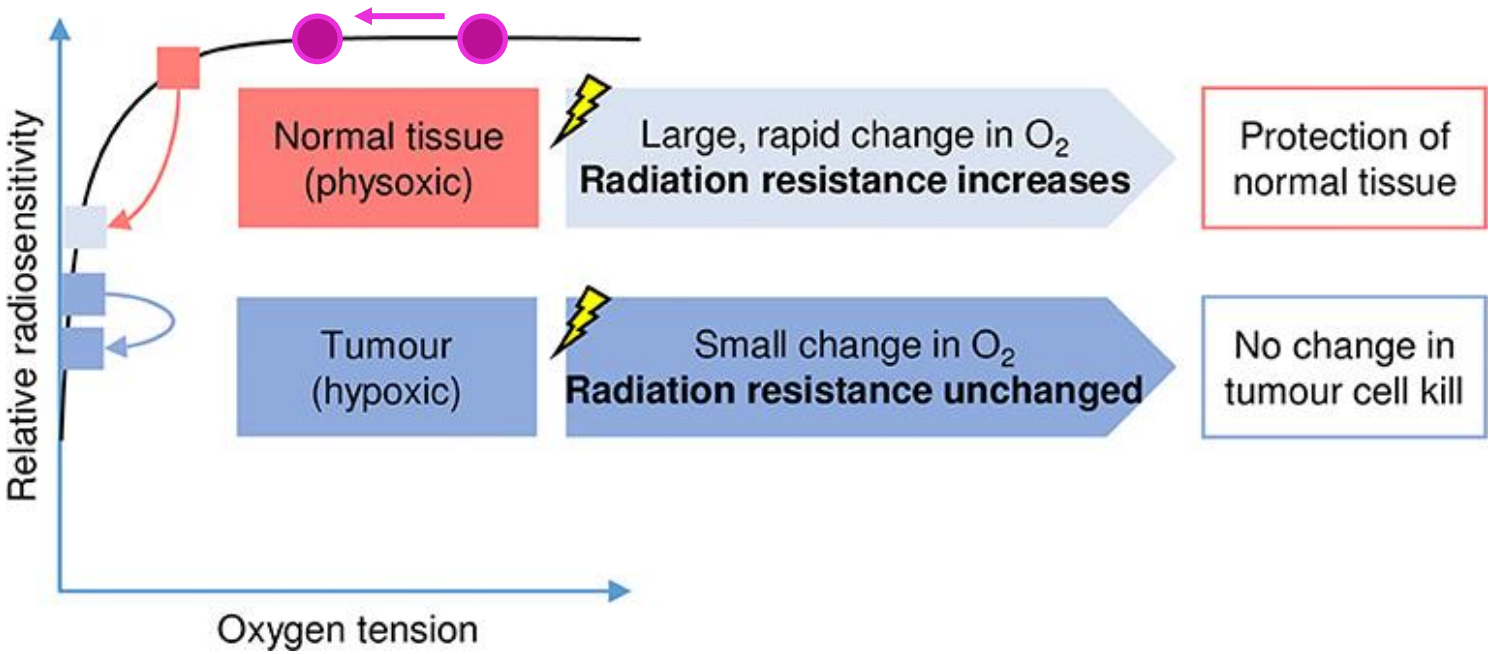


Proton Flash

- Mean dose rate: 100 Gy/s ✓
- Pulse dose rate: 10^3 Gy/s ✗
- Total delivery time: ~400 ms ✓
- Pulse length: 2 ns (✓) relevance?

Proton No-Flash: No control of partial oxygen pressure

- Oxygen depletion theory of Flash effect:
  - Physoxia in tissue vs. uncontrolled partial oxygen pressure in zebrafish embryo (in medium)
- Zebrafish embryos irradiated in Eppendorf tube
  → Accidentally too much / less oxygen?



We need to control the oxygen partial pressure somehow!?

Wilson et al. Frontiers in Oncology, 2020; modified

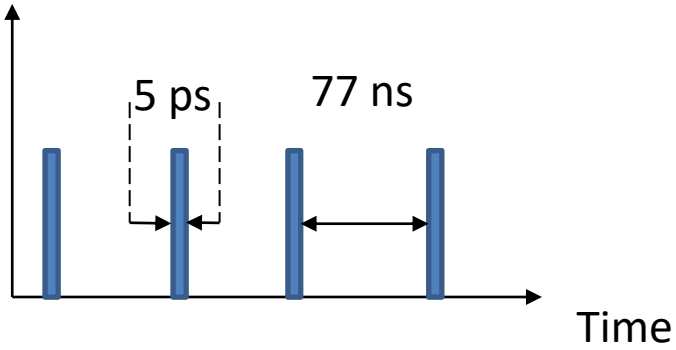
Electron Flash experiment @ELBE

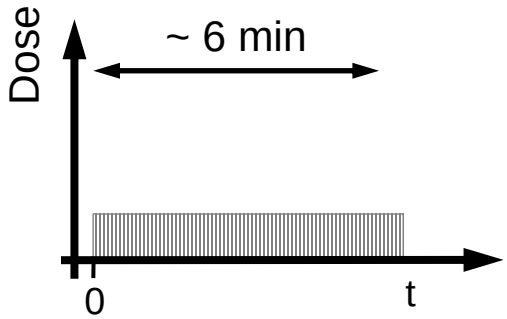
Research electron accelerator with highly variable pulse structure

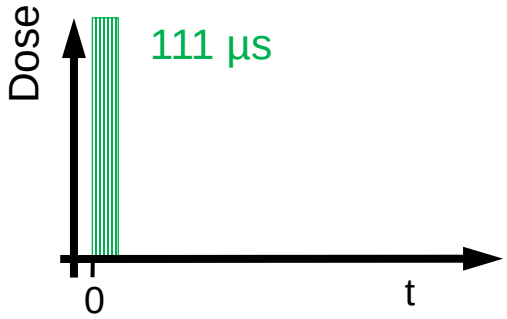
Pulse structure @ELBE:

- Basic frequency: 13 MHz
- Bunch length: 5 ps
- Bunch interval: 77 ns

See Talk of U. Schramm@06.10.2020







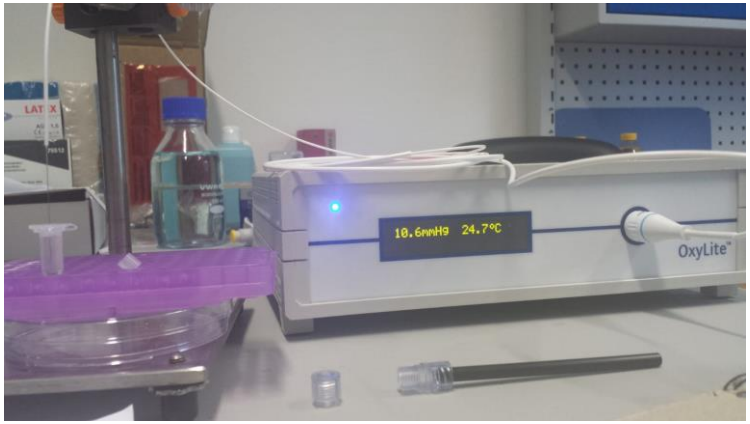
Reference

- Quasi-continuous bunches at 13 MHz
- Mean dose rate: 7 Gy/min
- Pulse dose rate: 10^3 Gy/s

Flash irradiation

- One pulse of 1441 bunches
- Mean dose rate: 2.6 x 10^5 Gy/s
- Pulse dose rate: 10^9 Gy/s

Electron Flash experiment @ELBE – oxygen pressure



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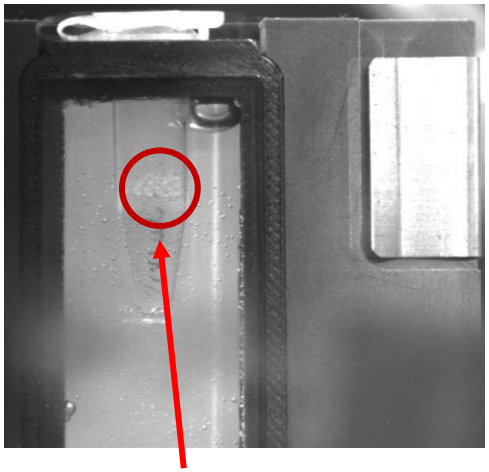
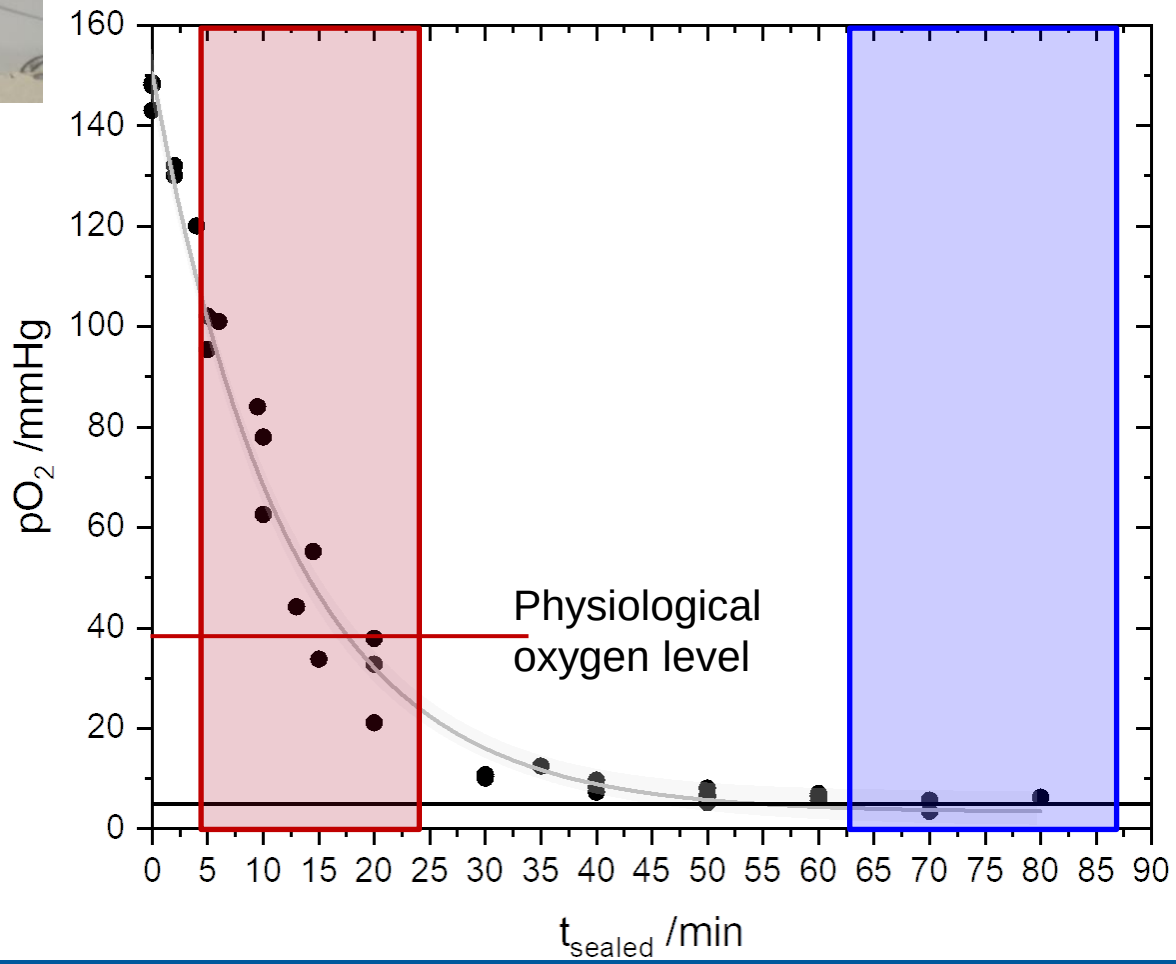


Zebrafish embryo

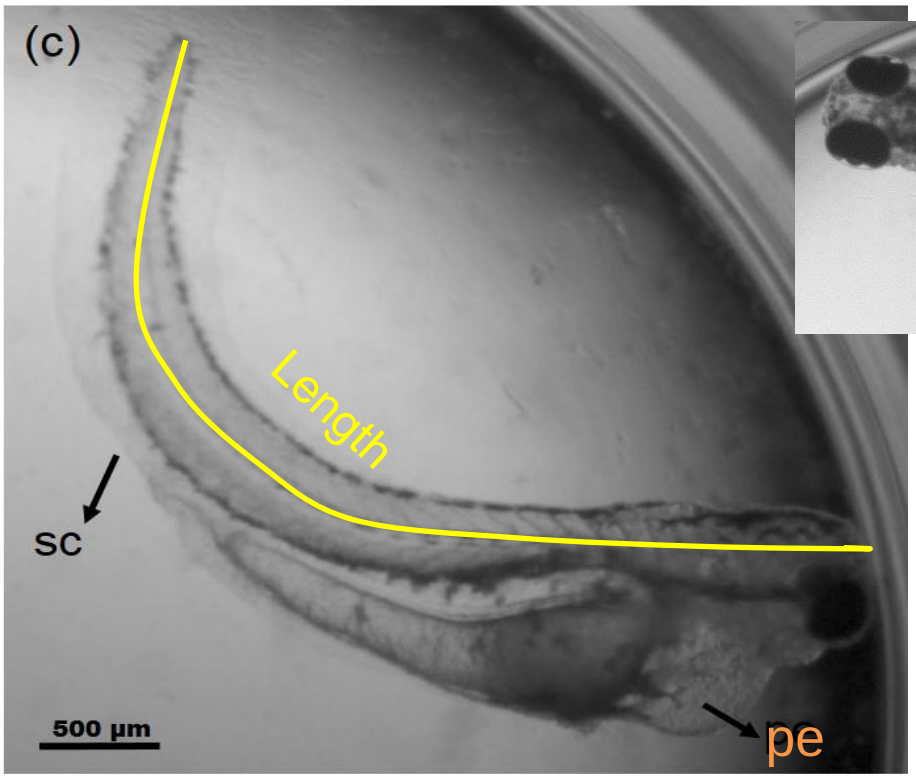
- Daily measurement under experiment conditions
- High pO2: 25-100 mmHg
- Low pO_2: Radiobiological hypoxia (<5 mmHg)

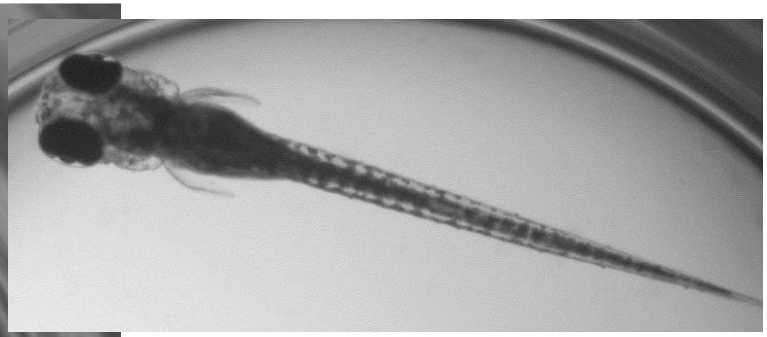


Electron Flash experiment @ELBE – results

- No significant influence on survival by electron dose rate

4 days post irradiation: radiation effects





normal

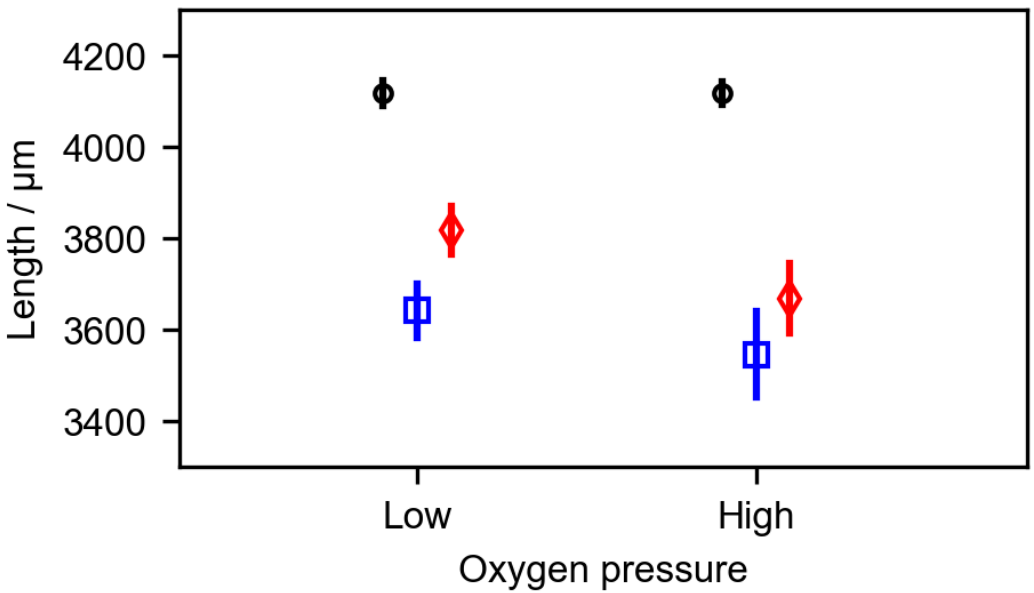
Flash vs. cw:

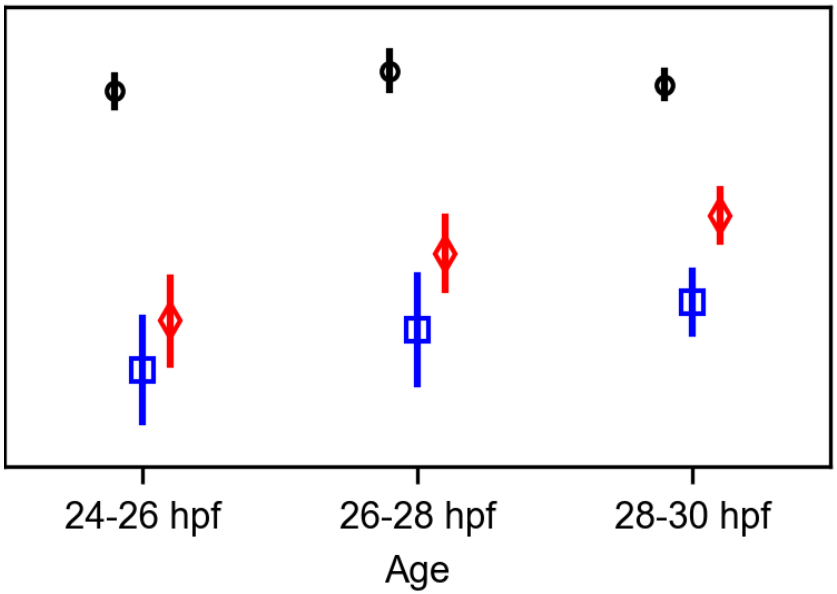
- 20% less pericardial edema
- 25% less embryo with curved spine
+ 4 % longer embryos (p<0.001) with larger eyes

Electron Flash experiment @ELBE – results

General outcome:

Embryos are significant longer after Flash irradiation ($p<0.001$)





The lower the oxygen pressure, the more pronounced is the Flash effect

The older the embryos the more pronounced is the Flash effect

Electron Flash experiment @ELBE – Summary & Outlook

Radiation response of zebrafish embryo depend on electron dose rate

- Very high doses required for ≥ 24 hpf embryos
- Very high pulse dose rate of 10^9 Gy/s
- Average dose rate of 10^5 Gy/s
- Whole organism response, individual organs hard to investigate
- Are these dose rates required to induce the Flash effect in zebrafish embryo?

Control of partial oxygen pressure intensifies the Flash effect

- Protecting effect measured for oxygen levels below atmospheric levels, but most pronounced at radiobiological hypoxia
- Partial oxygen pressure inside embryo?

Electron Flash experiment @ELBE – Summary & Outlook

Repetition of proton Flash experiment under controlled oxygen conditions,
@ University Proton Therapy Dresden, in preparation

Proton Flash experiment at very high pulse dose rates
@ Laser proton accelerator Draco (cf. Talk U. Schramm)

- Controlled oxygen conditions
- Single, ns-long laser pulse of 10^9 Gy/s
- In preparation

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