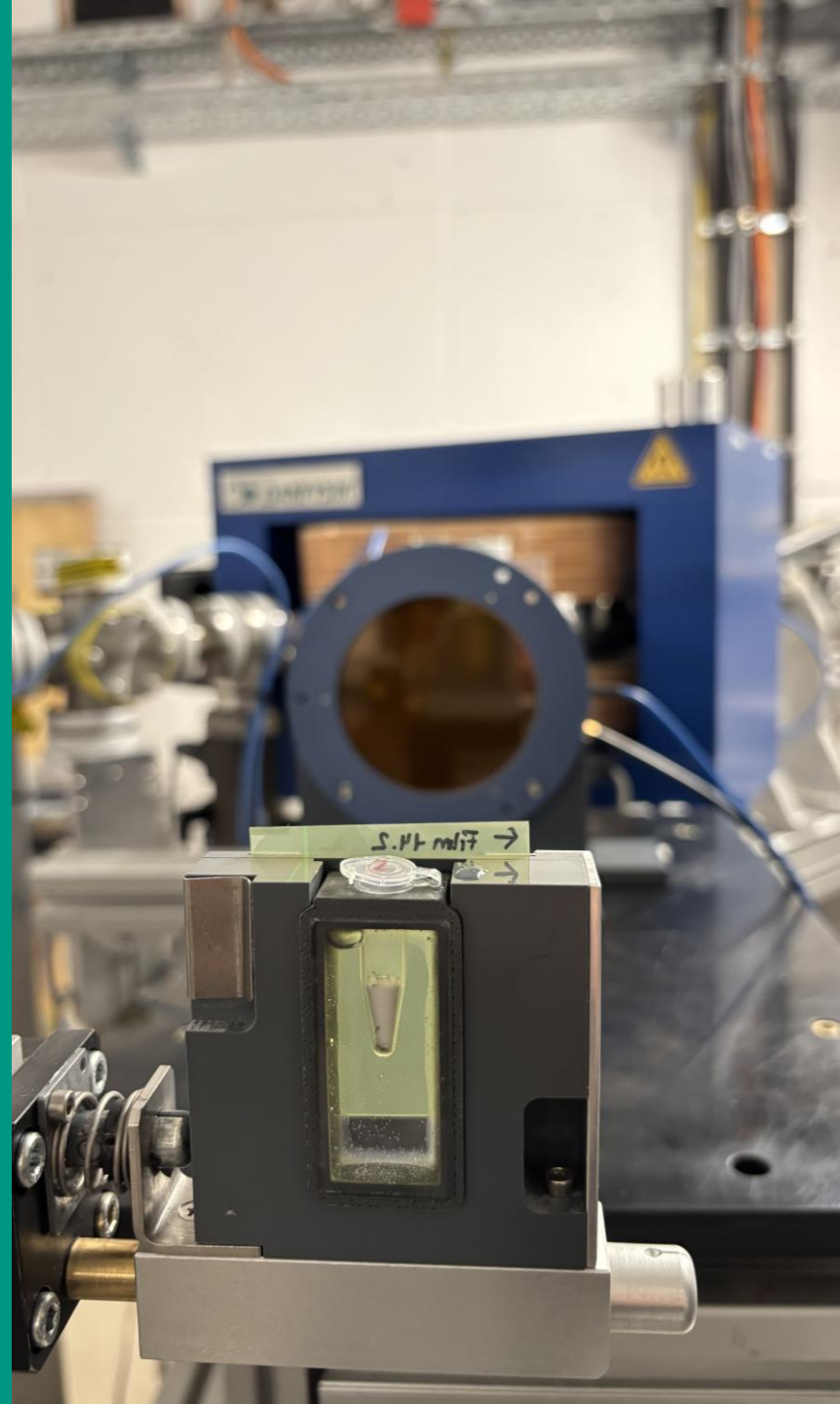


EPR study of dose-rate dependent radiolytic radical formation during ultra-high dose-rate irradiation *in vitro* and *in vivo*

Johanna Pehlivan

Karlsruhe Institute of Technology

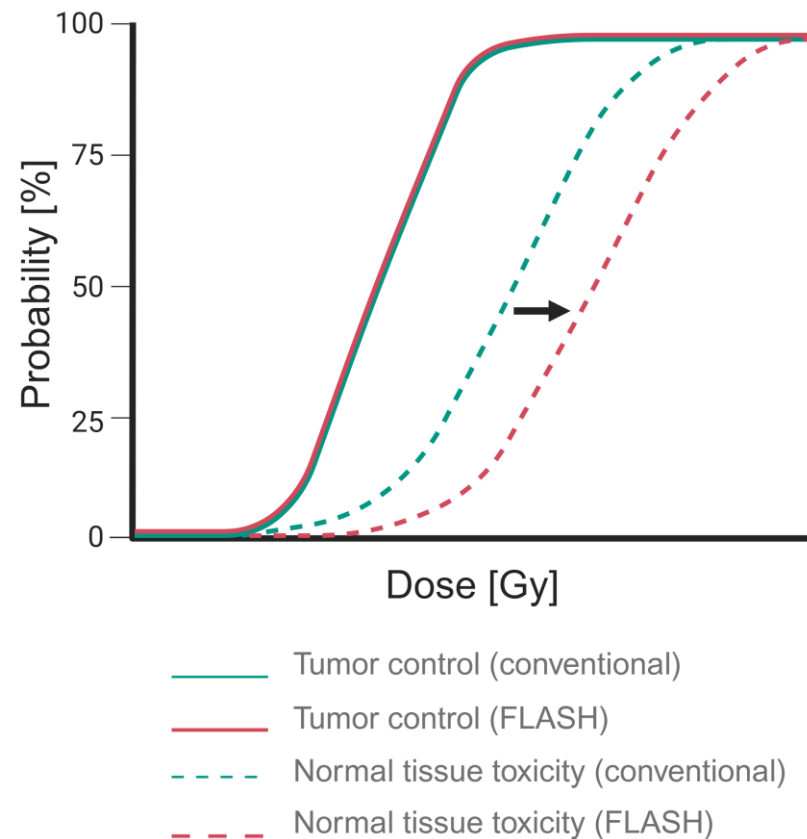
Institute of Neutron Physics and Reactor Technology



FLASH Effect: A Potential Shift in the Therapeutic Window

The FLASH effect emerges at ultra-high dose rates (UHDR), typically above ~ 40 Gy/s.

- Comparable tumor control
- Reduced normal tissue toxicity



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RESEARCH ARTICLE | RADIATION TOXICITY



Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

VINCENT FAVAUDON, LAURA CAPLIER, VIRGINIE MONCEAU, FRÉDÉRIC POUZOLET, MANO SAYARATH, CHARLES FOUILLADE, MARIE-FRANCE POUPON, ISABEL BRITO,

PHILIPPE HUPÉ, JEAN BOURHIS, JANET HALL, JEAN-JACQUES FONTAINE, AND MARIE-CATHERINE VOZENIN

fewer

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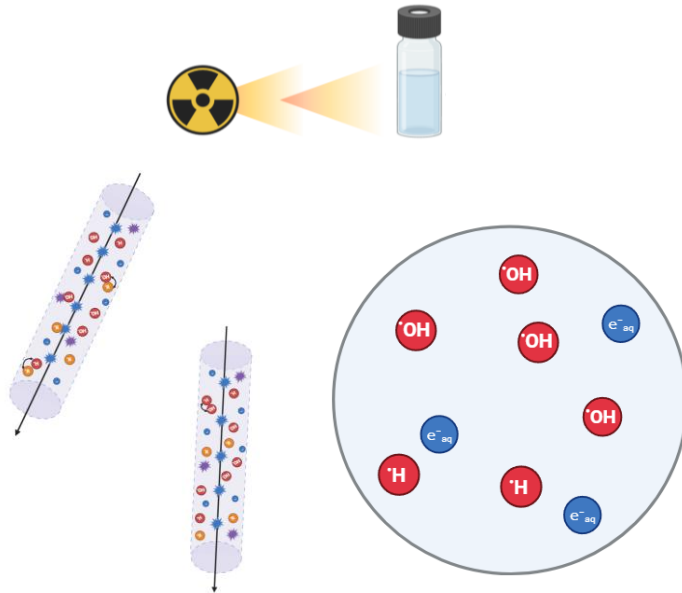


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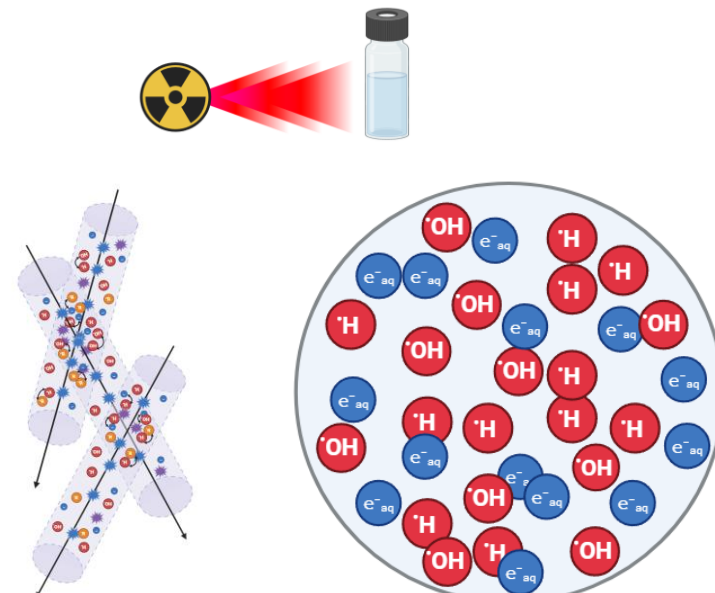
Radical-Radical Recombination Hypothesis

- Extremely high transient radical concentrations → enhanced radical-radical recombination
- Fewer free radicals available for reactions with O_2 and biological targets → altered early radiation chemistry
- Potential consequence: reduced oxidative damage in normal tissue

Conventional Irradiation

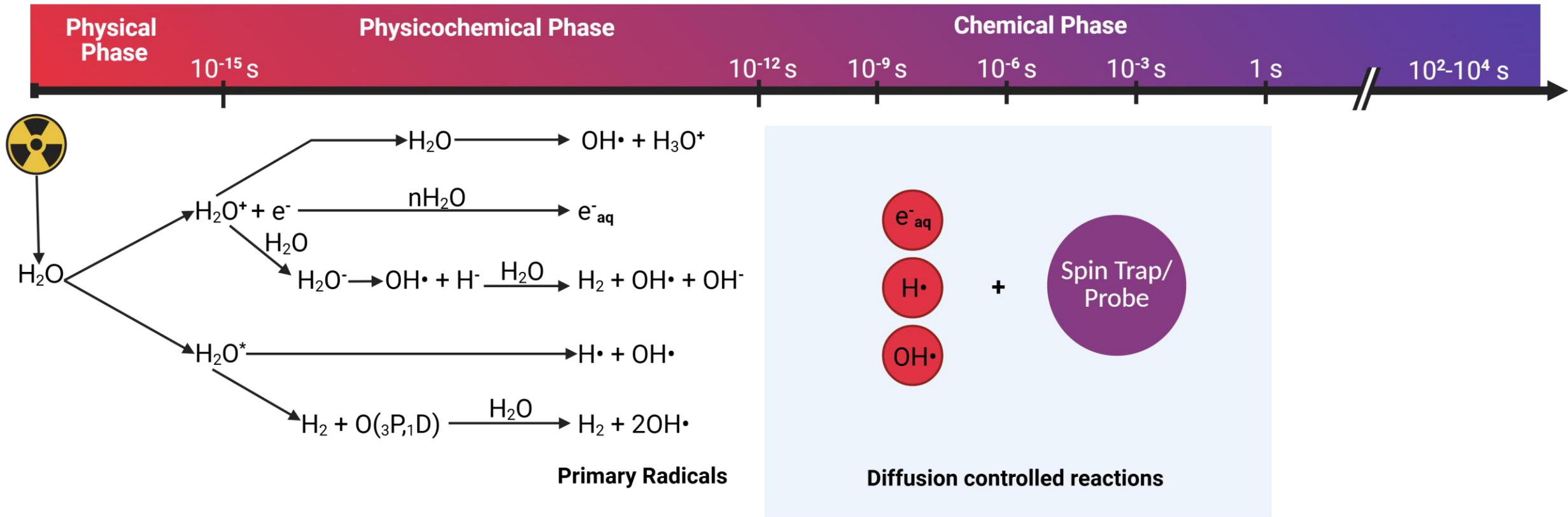


UHDR Irradiation



” Can EPR provide direct evidence for dose-rate dependent changes in radiation-induced radical chemistry?

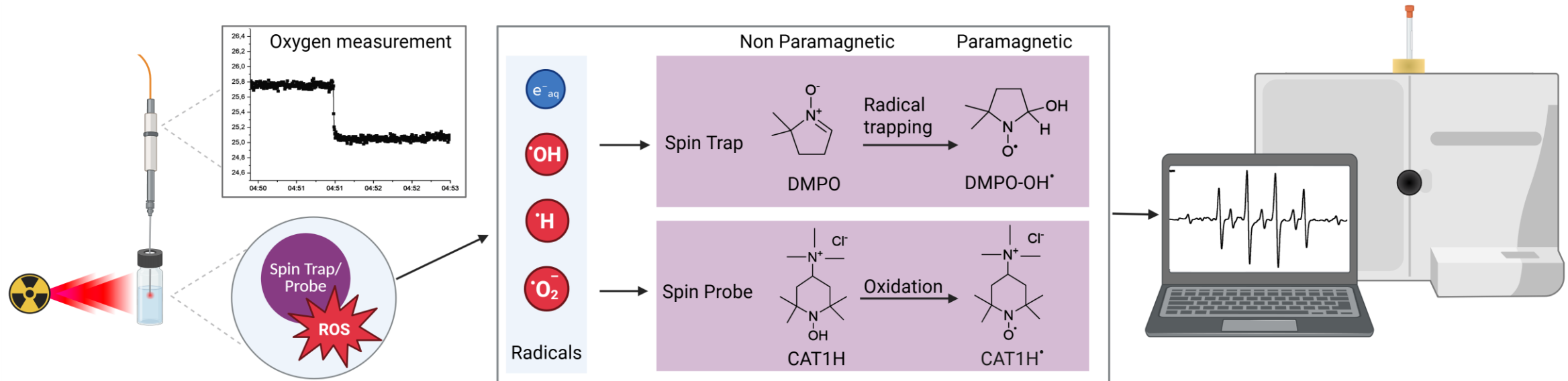
Water Radiolysis and Radical Detection by EPR



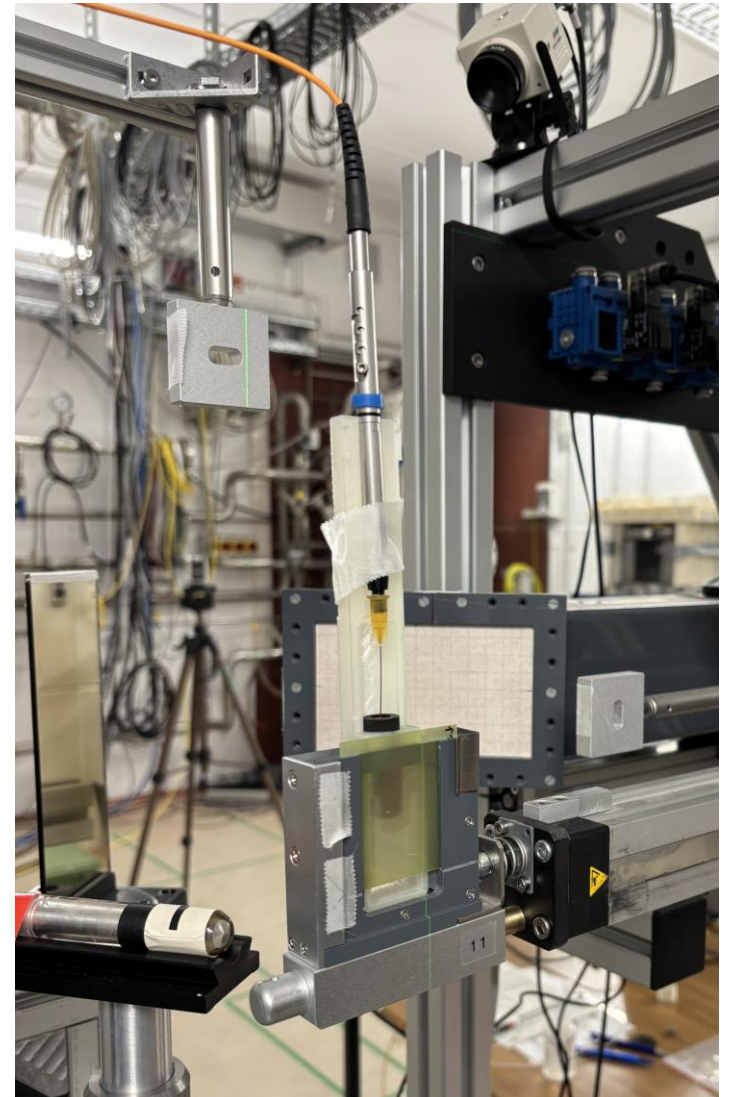
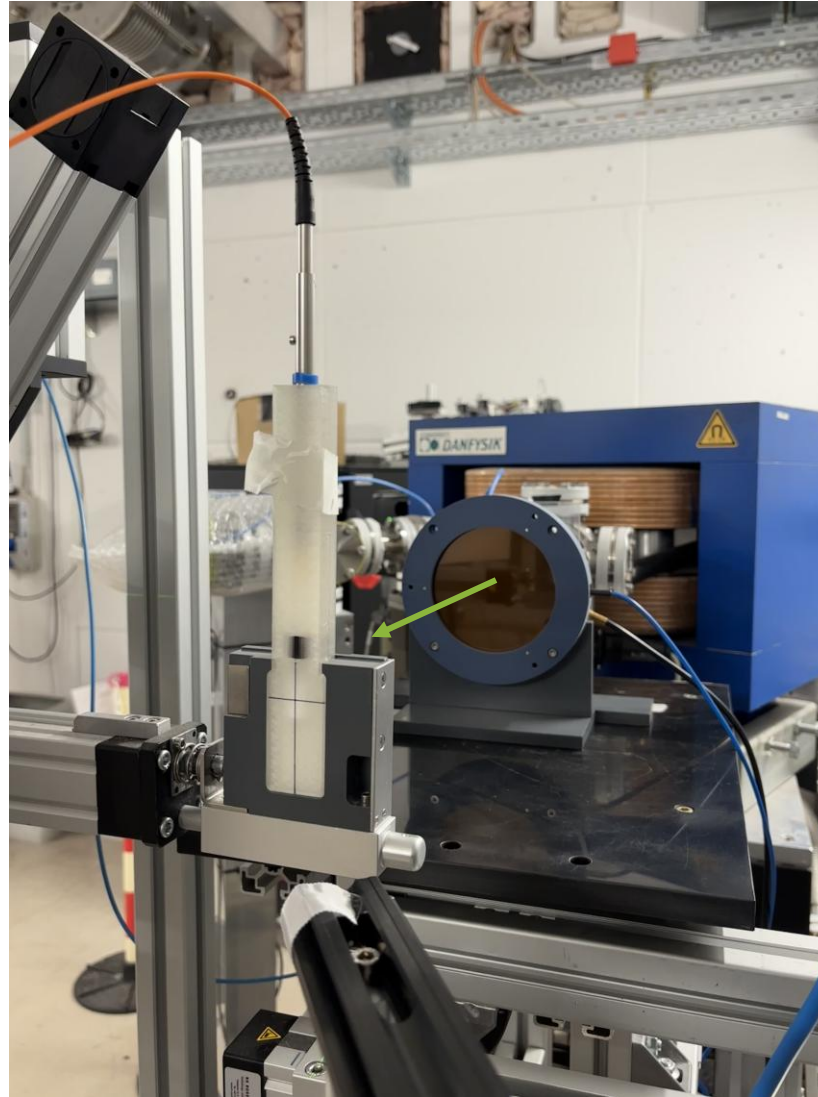
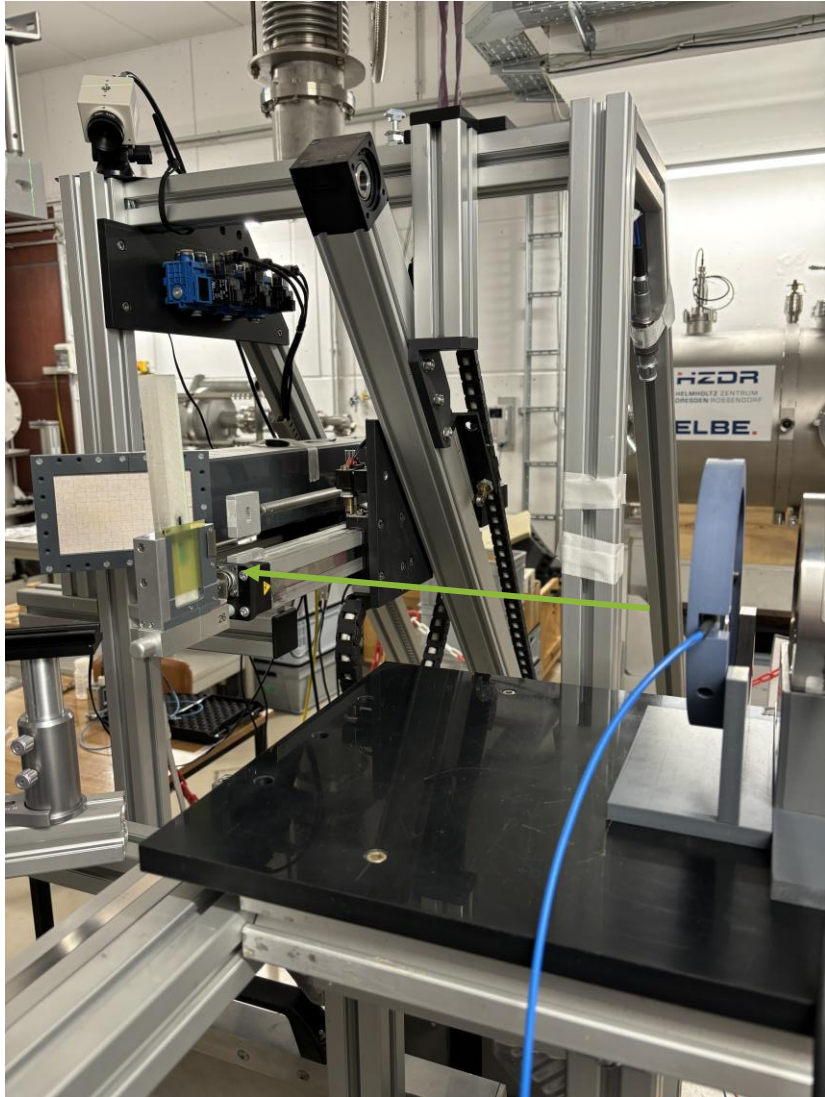
In Vitro Experimental Workflow

- ELBE accelerator · 30 MeV electrons · matched dose ≈ 30 Gy

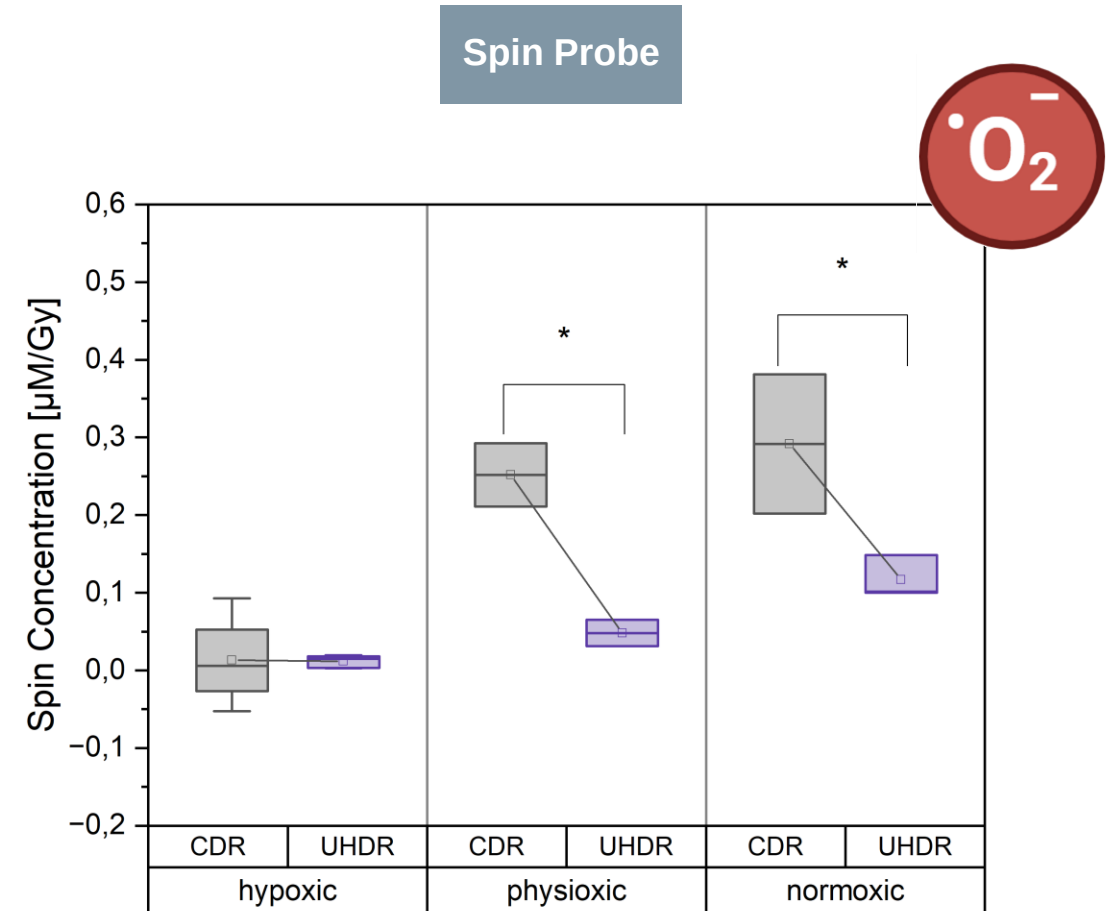
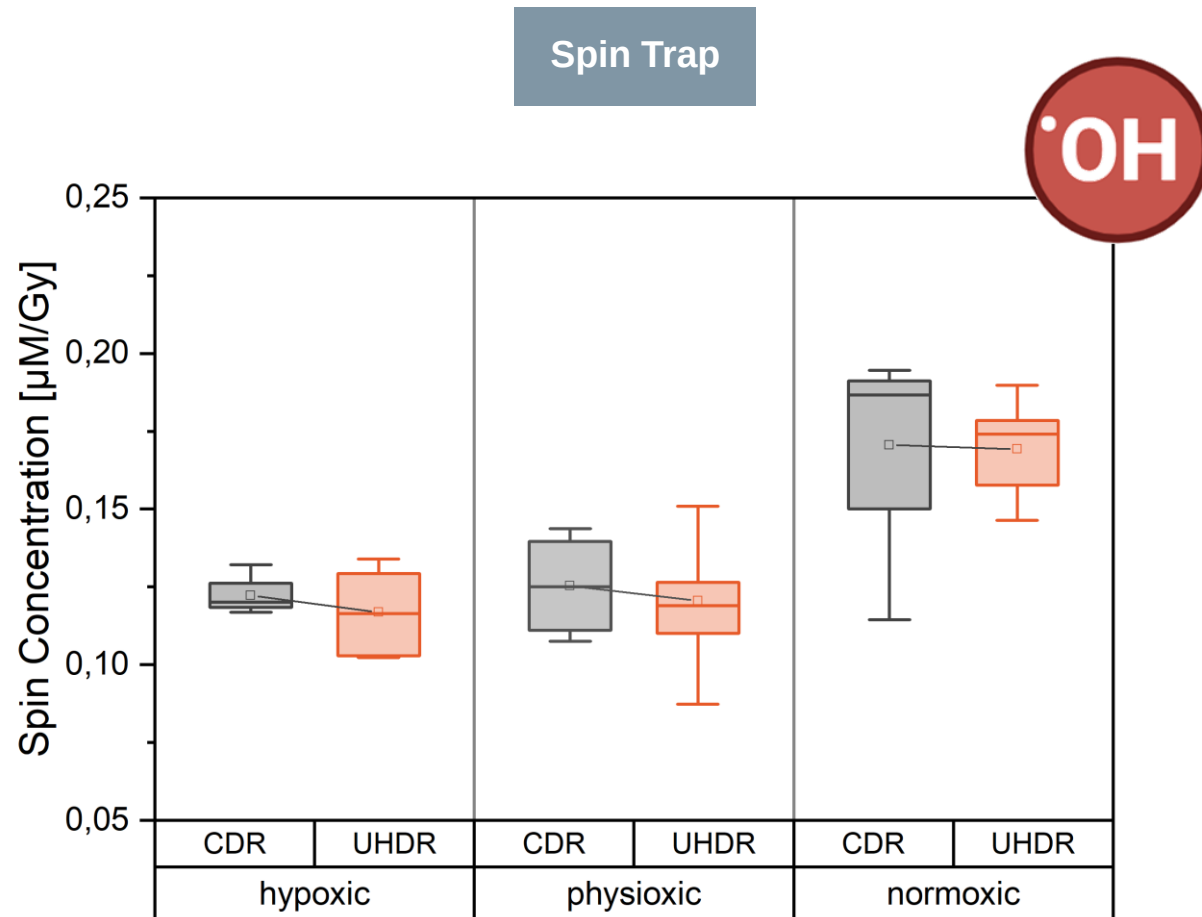
Regime	Mean Dose Rate	Bunch Dose Rate
Conventional Dose Rate (CDR)	~ 0.1 Gy/s	$\sim 10^3$ Gy/s
Ultra-High Dose Rate (UHDR)	$\sim 10^5$ Gy/s	$\sim 10^9$ Gy/s



Irradiation Setup and Beam Parameters



Results – *in vitro* – EPR Measurements



Pehlivan et al., Phys. Med. Biol. (2026)

Conclusion - *in vitro*

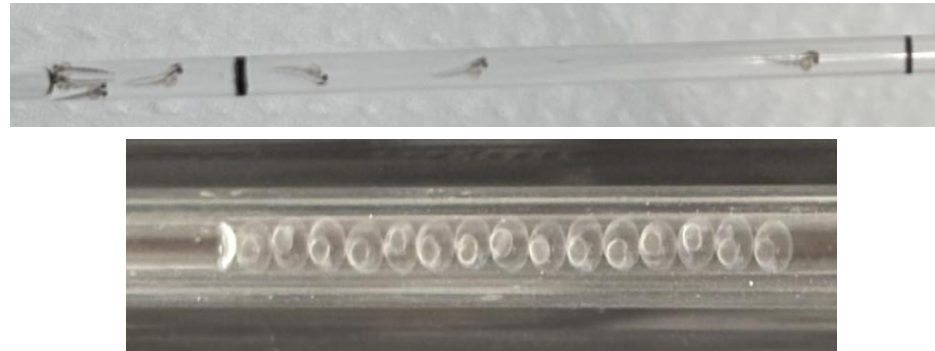
- UHDR irradiation reduced spin-probe signal intensity and oxygen consumption
- Spin-trap measurements showed no consistent dose-rate dependence, highlighting methodological limitations
- Observed effects indicate altered radical chemistry at UHDR

- FLASH is ultimately a biological phenomenon
 - Radical chemistry must be investigated under physiological conditions

- **Can we detect these changes also in vivo?**

Challenges of *in vivo* EPR

Zebrafish embryos



EPR sensitivity

Limited sample volume
Low signal intensity

Measurement Conditions

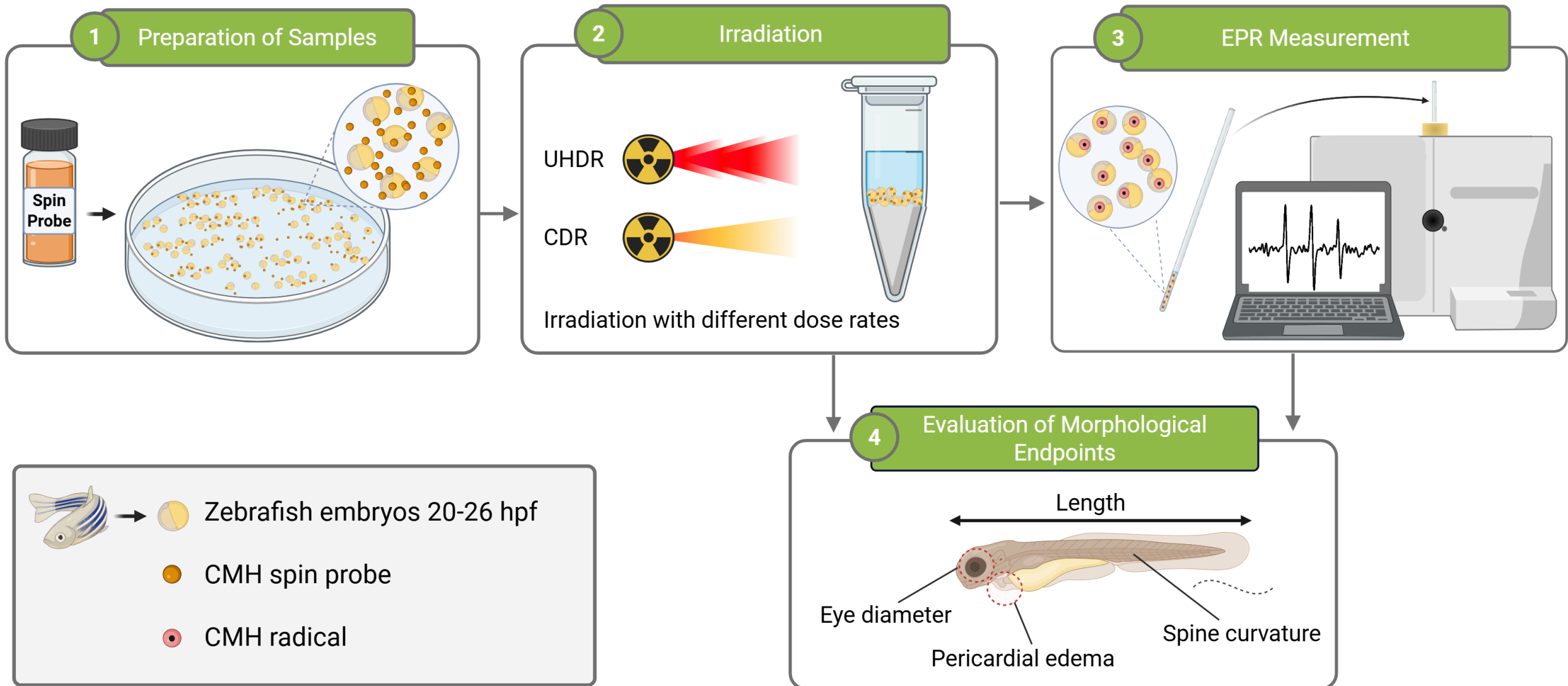
Microwave-induced heating
Movement

Biological Complexity

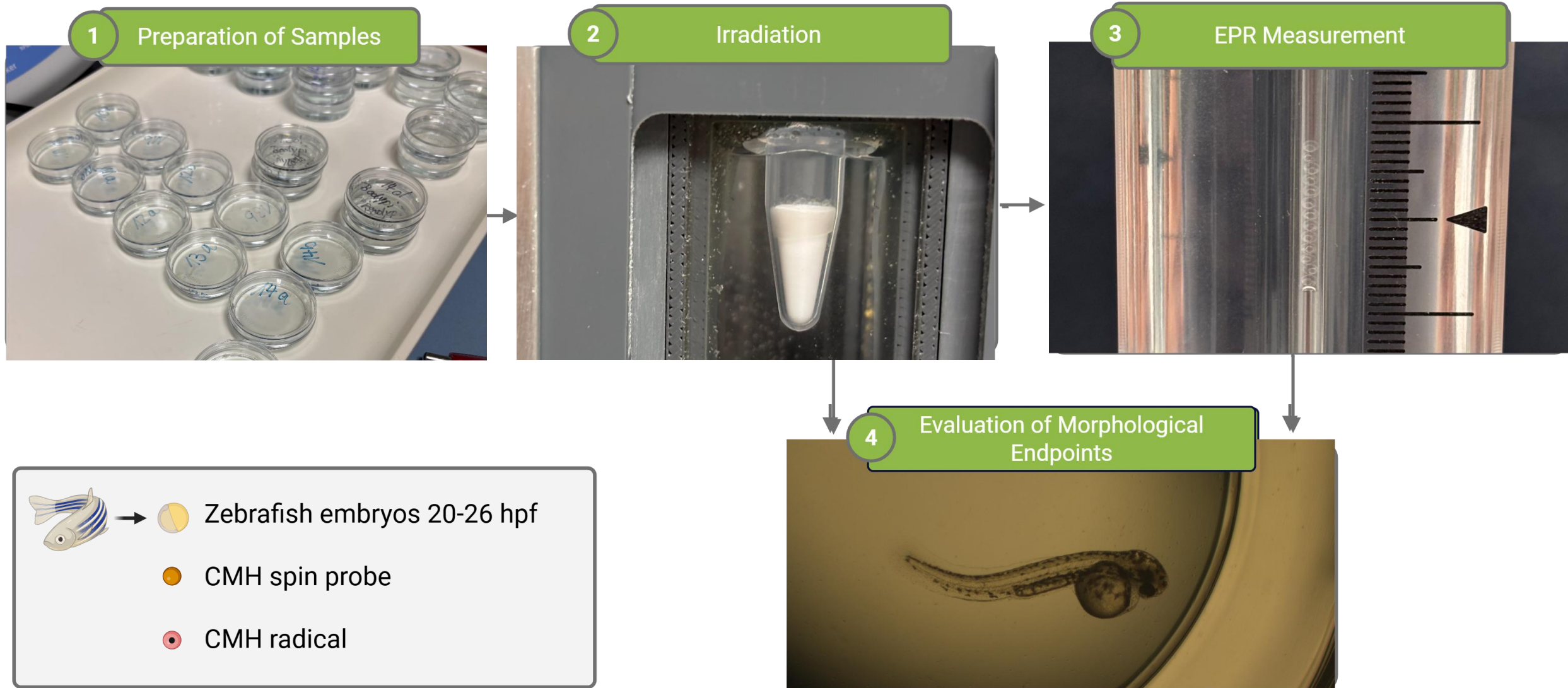
Biological variability
Spin-probe uptake
Limited O₂ control

→ **Need for an optimized and validated *in vivo* EPR workflow**

Experimental workflow *in vivo*

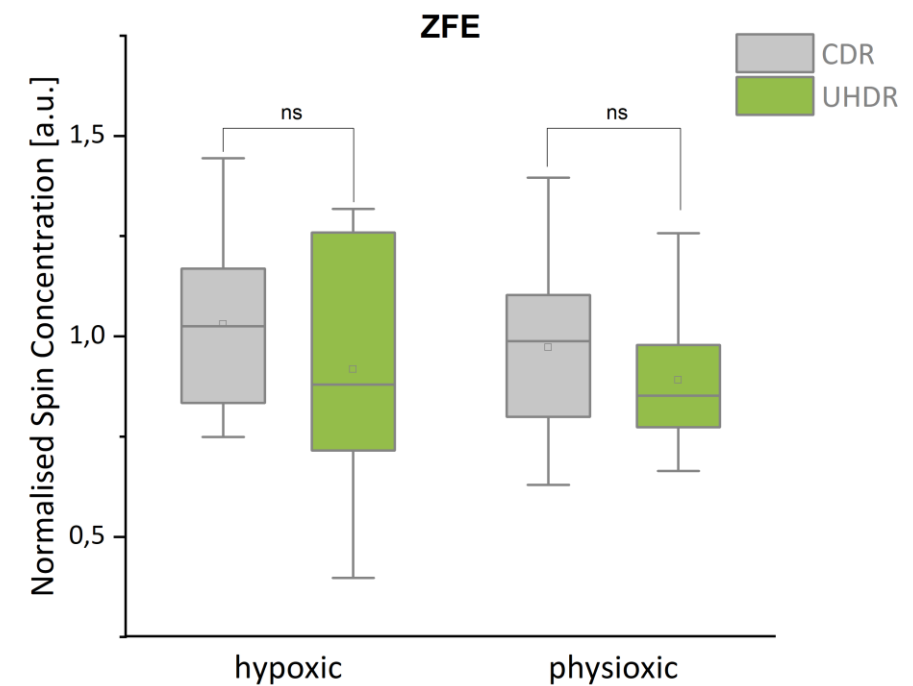
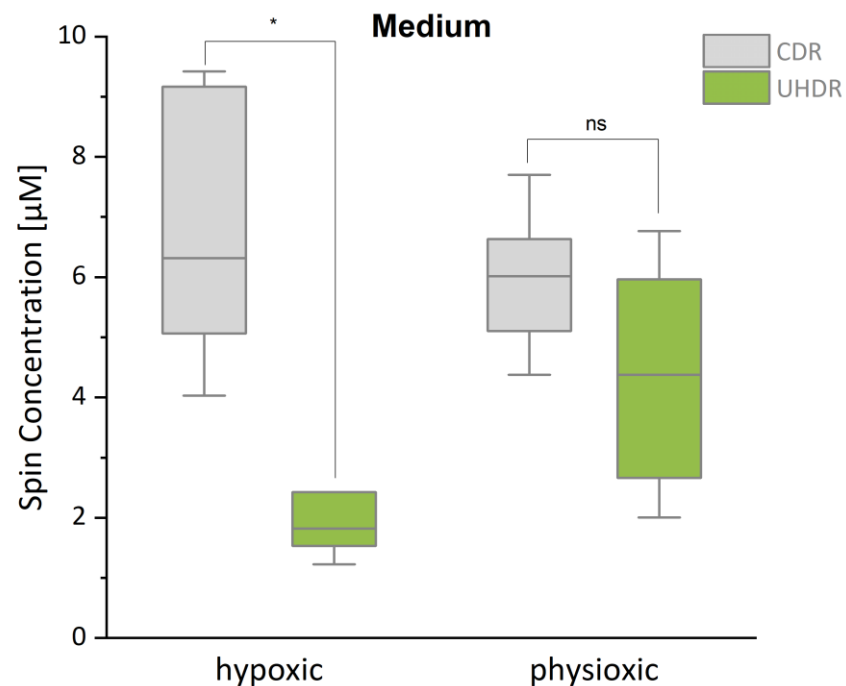


Experimental workflow *in vivo*



Results – *in vivo*

- No detectable effect of CMH/EPR workflow on morphological endpoints
- Trend toward lower EPR signals under UHDR
- No significant CDR–UHDR difference in zebrafish embryos



Take-home Message

- 1. UHDR alters radiation-induced radical chemistry**
Reduced oxygen consumption and spin-probe oxidation in vitro
- 2. EPR can probe these dose-rate-dependent processes**
but the result strongly depends on the experimental approach
- 3. In vivo EPR is feasible, but challenging**
Trends observed in zebrafish embryos require further validation

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