Beam temporal structure of laser-driven VHEE beams affects biological response

Camilla Giaccaglia
PhD Student

Laboratoire d'Optique Appliquée
ENSTA, École Polytechnique, CNRS-UMR7639, Palaiseau, France

Outline

Motivation
- Very High Energy Electrons (VHEE)
- Laser Plasma Accelerator (LPA)

Preclinical studies
- Assessing VHEE-LPA beam toxicity
- Impact of LPA pulse structure on biological response

Very High Energy Electrons (VHEE)

Very High Energy Electrons (>50 MeV) have been proposed as a potential radiotherapy modality in the 2000s.

Advantages:

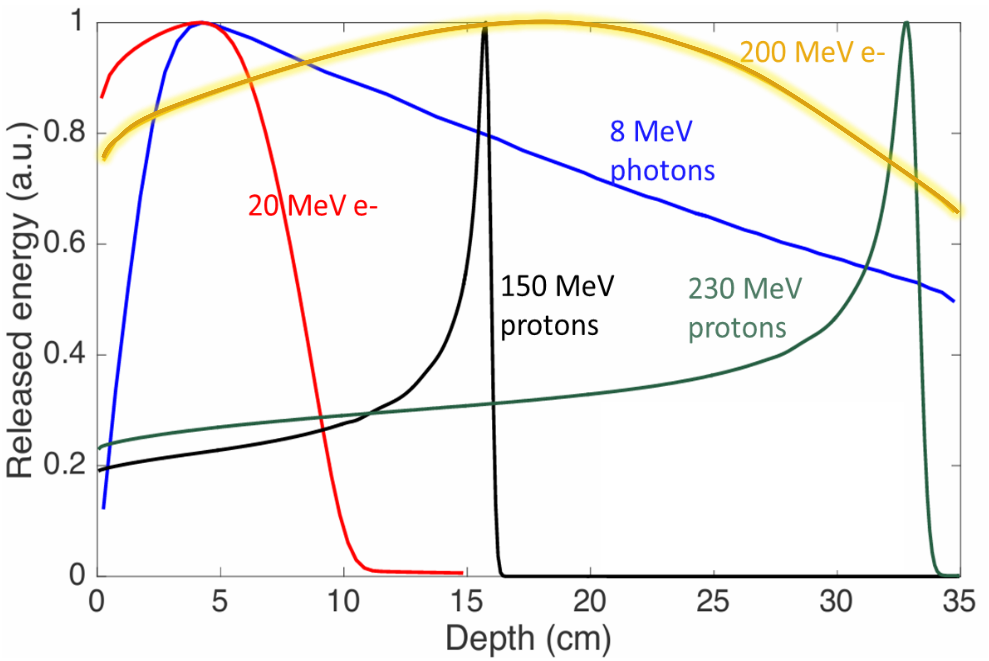
- Deeper tissue penetration
- Reduced sensitivity to tissue inhomogeneities
- Beam steering

Very High Energy Electrons (VHEE)

Very High Energy Electrons (>50 MeV) have been proposed as a potential radiotherapy modality in the 2000s.

Advantages:

- Deeper tissue penetration
- Reduced sensitivity to tissue inhomogeneities
- Beam steering



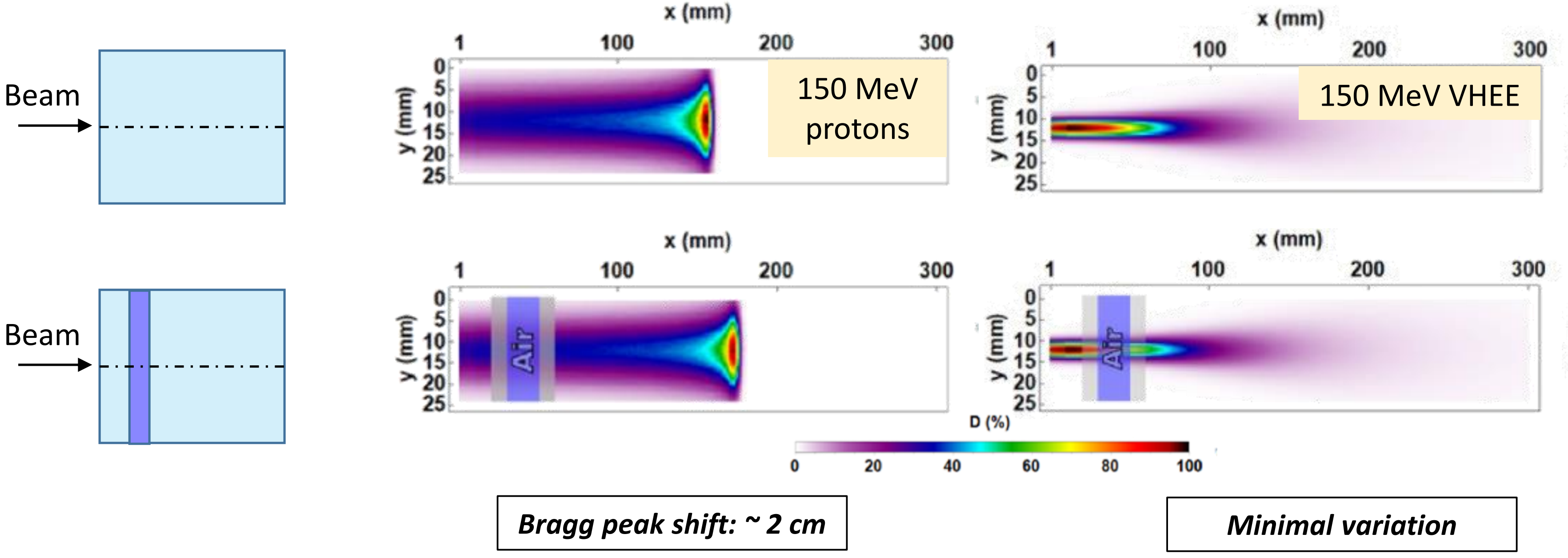
M. Cavallone, Application of laser-plasma accelerated beams to high dose-rate radiation biology, 2020.

Very High Energy Electrons (VHEE)

Very High Energy Electrons (>50 MeV) have been proposed as a potential radiotherapy modality in the 2000s.

Advantages:

- Deeper tissue penetration
- Reduced sensitivity to tissue inhomogeneities
- Beam steering



A. Lagzda et al. Nuclear Inst. and Methods in Physics Research

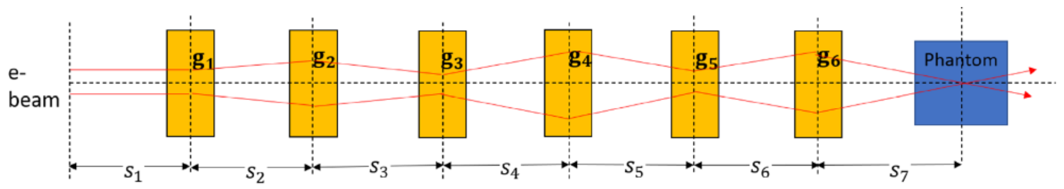
Very High Energy Electrons (VHEE)

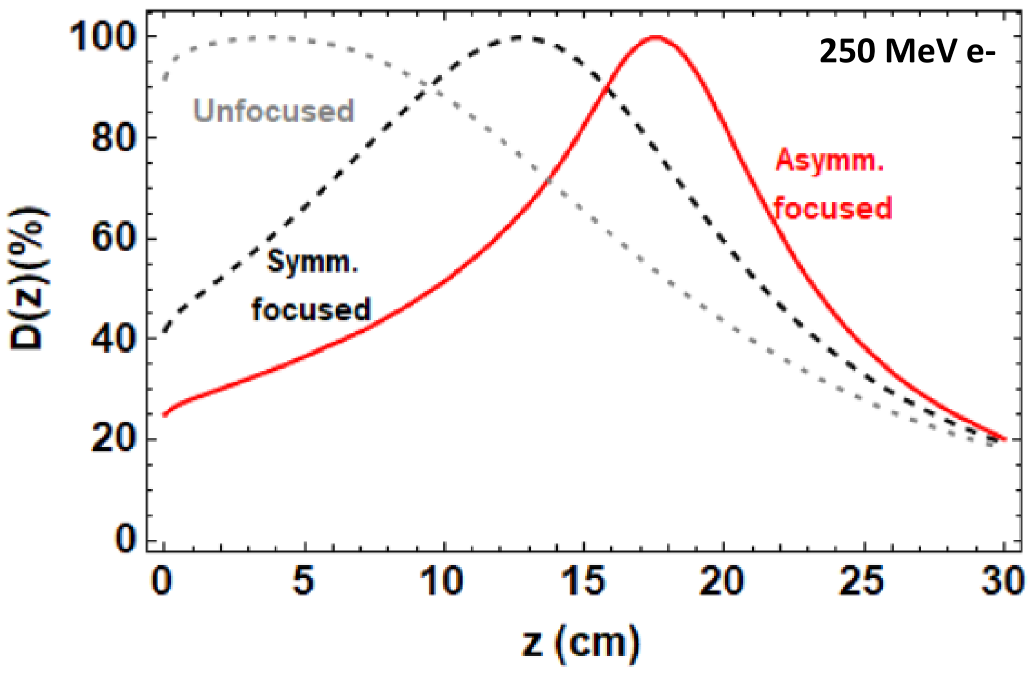
Very High Energy Electrons (>50 MeV) have been proposed as a potential radiotherapy modality in the 2000s.

Advantages:

- Deeper tissue penetration
- Reduced sensitivity to tissue inhomogeneities
- <u>Beam steering</u>

TOPAS-based Monte Carlo simulation





L. Whitmore et al. Scientific Reports | (2021)

Very High Energy Electrons (VHEE)

Very High Energy Electrons (>50 MeV) have been proposed as a potential radiotherapy modality in the 2000s.

Advantages:

- Deeper tissue penetration
- Reduced sensitivity to tissue inhomogeneities
- Beam steering

Clinical advantages

Limitations:

- Few VHEE radiobiology studies → In vitro

Small et al., Sci Rep (2021)
Wanstall et al., Sci Rep (2024)
Wanstall et al., Sci Rep (2024)

Very High Energy Electrons (VHEE)

Very High Energy Electrons (>50 MeV) have been proposed as a potential radiotherapy modality in the 2000s.

Advantages:

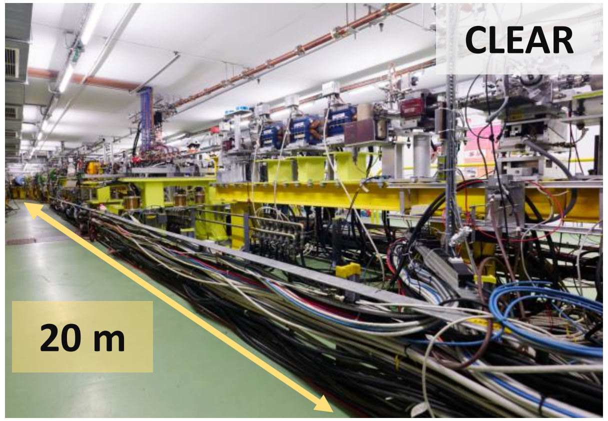
- Deeper tissue penetration
- Reduced sensitivity to tissue inhomogeneities
- Beam steering

Clinical advantages

Limitations:

- Few VHEE radiobiology studies → In vitro

Small et al., Sci Rep (2021)
Wanstall et al., Sci Rep (2024)
Wanstall et al., Sci Rep (2024)



R. Corsini CLEAR Review 2024

Very High Energy Electrons (VHEE)

Very High Energy Electrons (>50 MeV) have been proposed as a potential radiotherapy modality in the 2000s.

Advantages:

- Deeper tissue penetration
- Reduced sensitivity to tissue inhomogeneities
- Beam steering

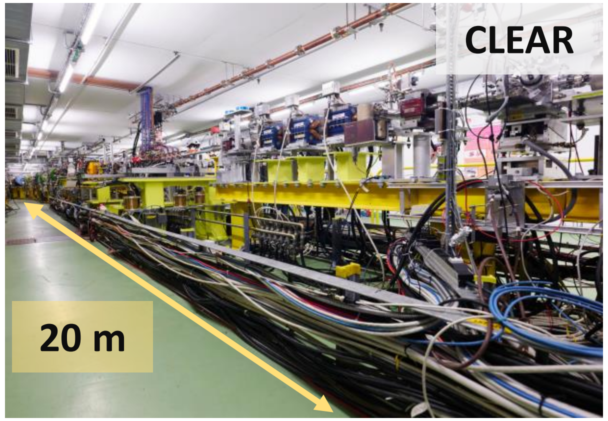
Clinical advantages

Limitations:

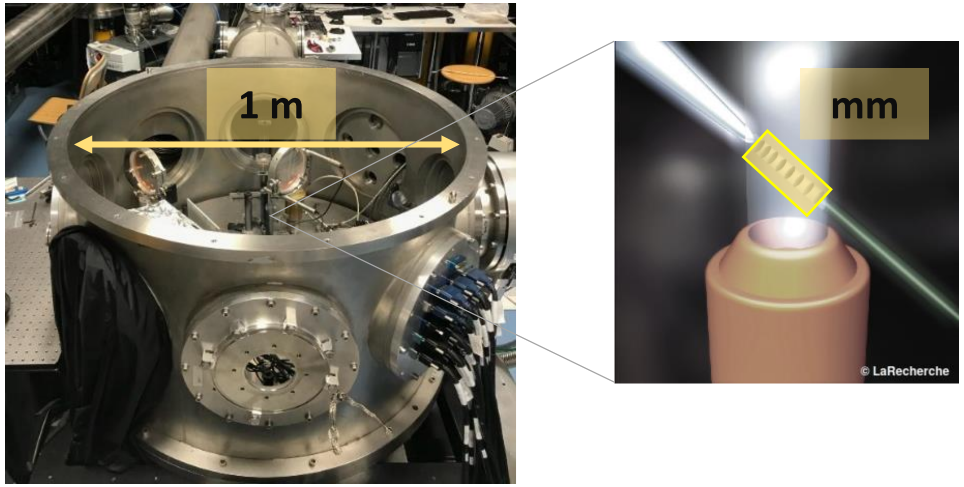
- Few VHEE radiobiology studies → In vitro

Small et al., Sci Rep (2021)
Wanstall et al., Sci Rep (2024)
Wanstall et al., Sci Rep (2024)

Laser-plasma accelerator

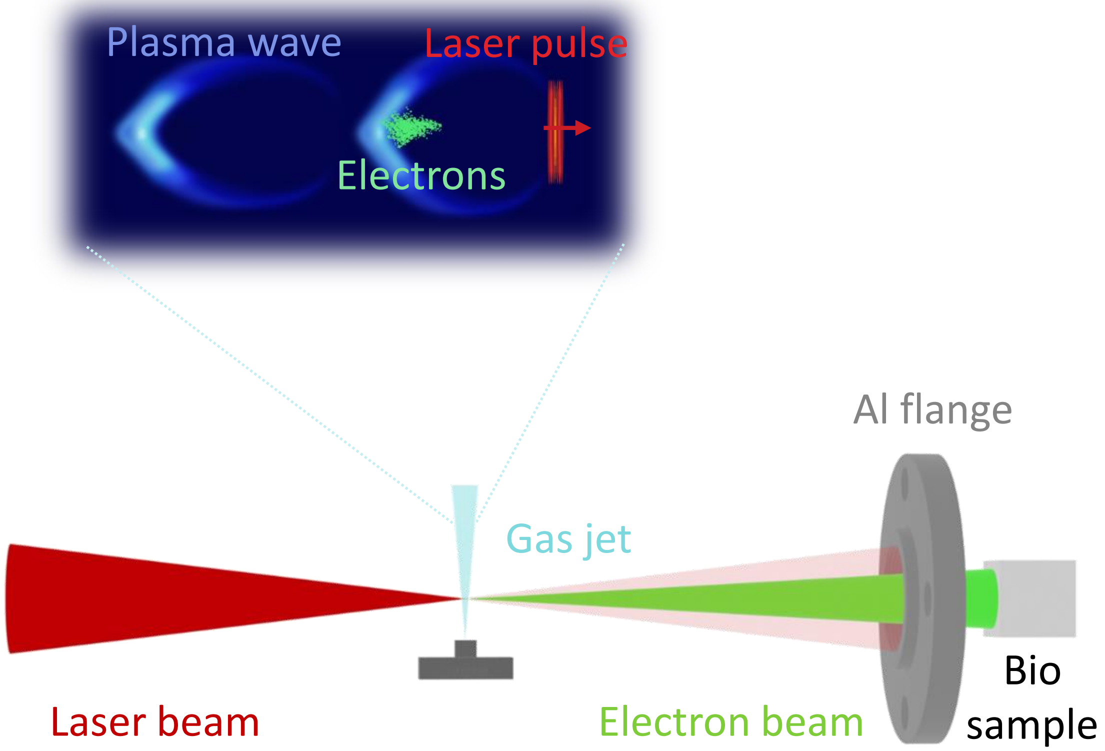


R. Corsini CLEAR Review 2024



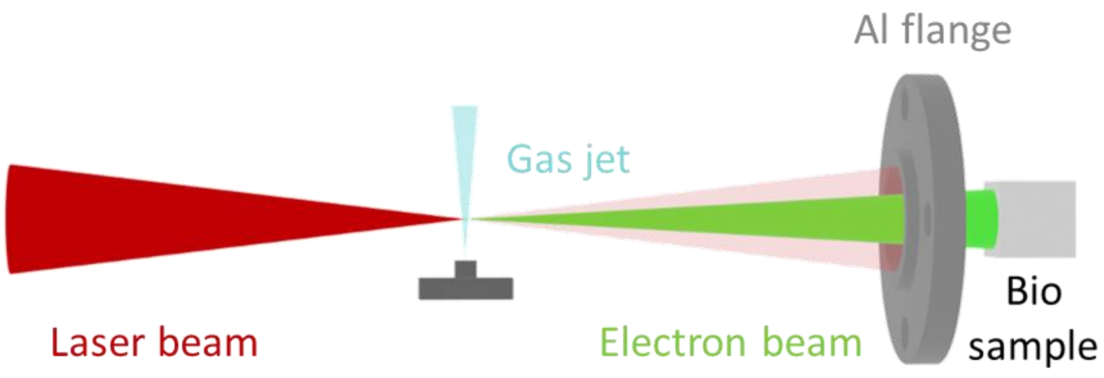
Laser-plasma accelerator (LPA)

Working principle

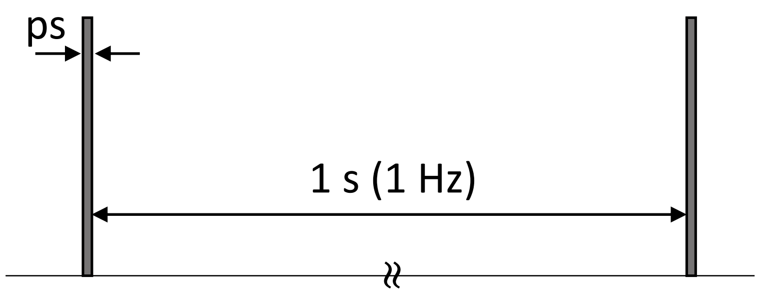


Laser-plasma accelerator (LPA)

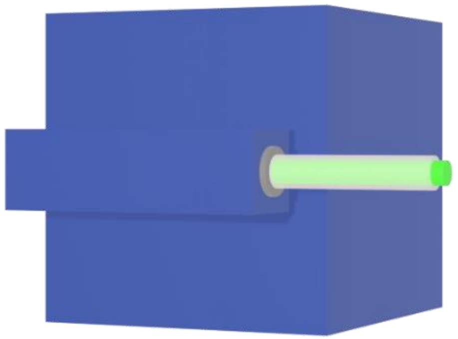
LOA- LPA

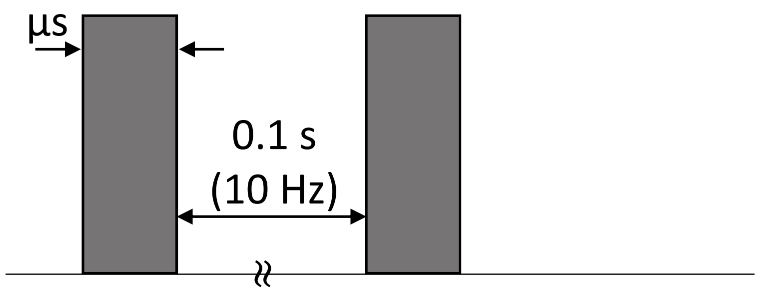


Temporal Structure



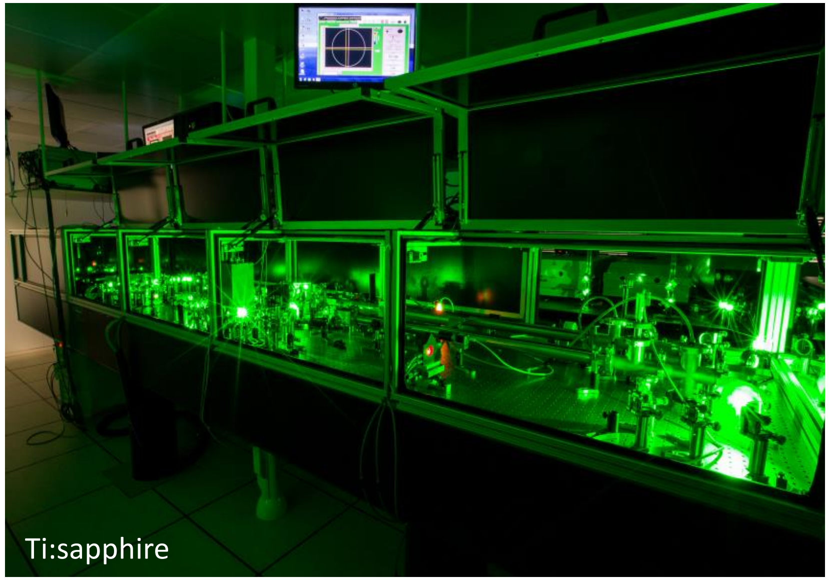
CURIE - LINAC





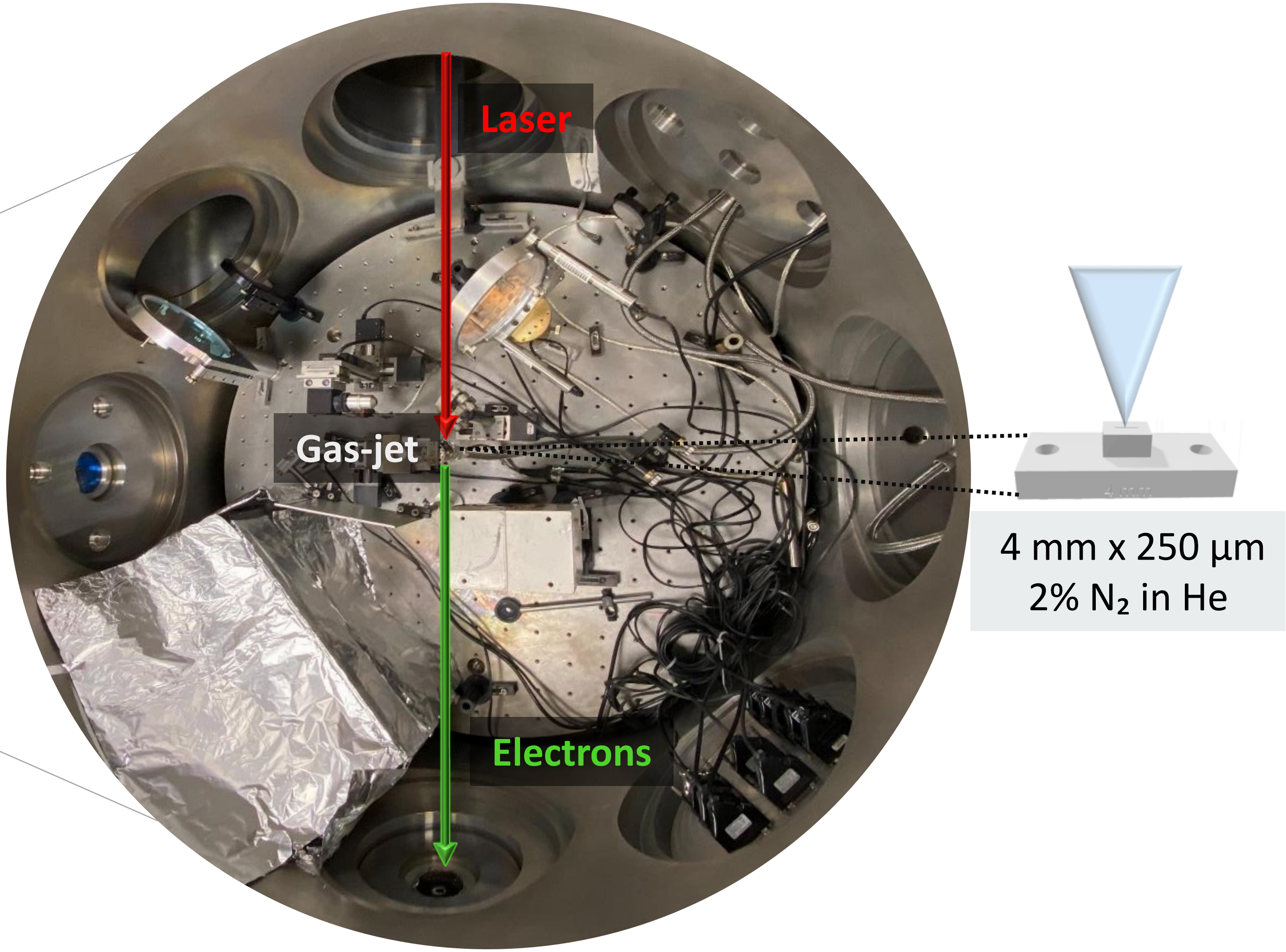
Salle Jaune Laser System

Parameters at target:
- Peak Power: 80 TW
- Peak Energy: 2.4 J
- Pulse duration : 30 fs
- Repetition rate: up to 1 Hz



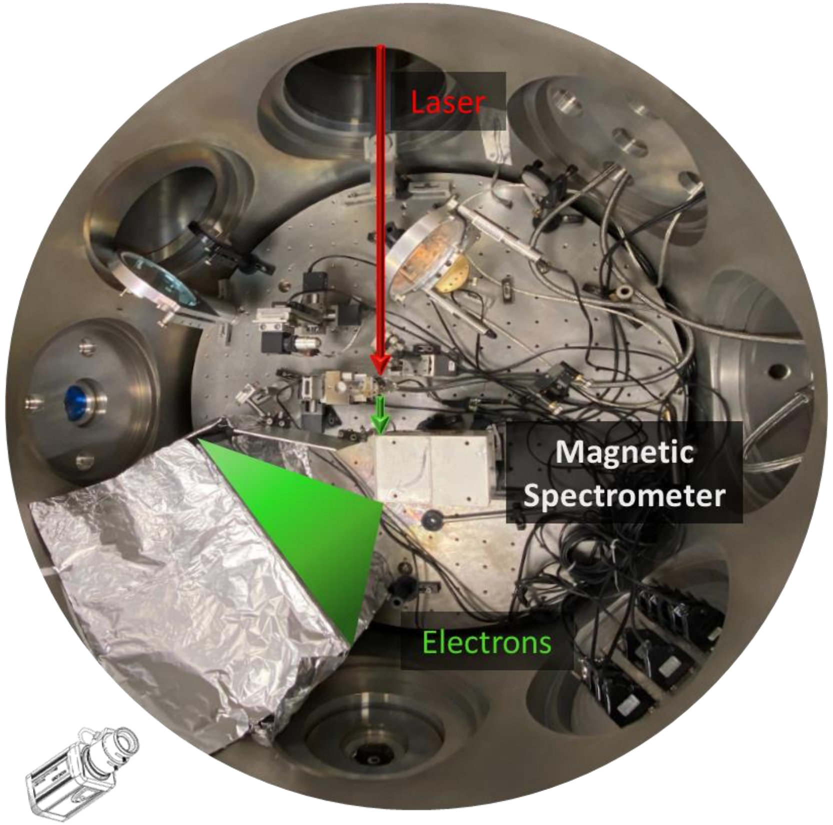
Salle Jaune Laser System

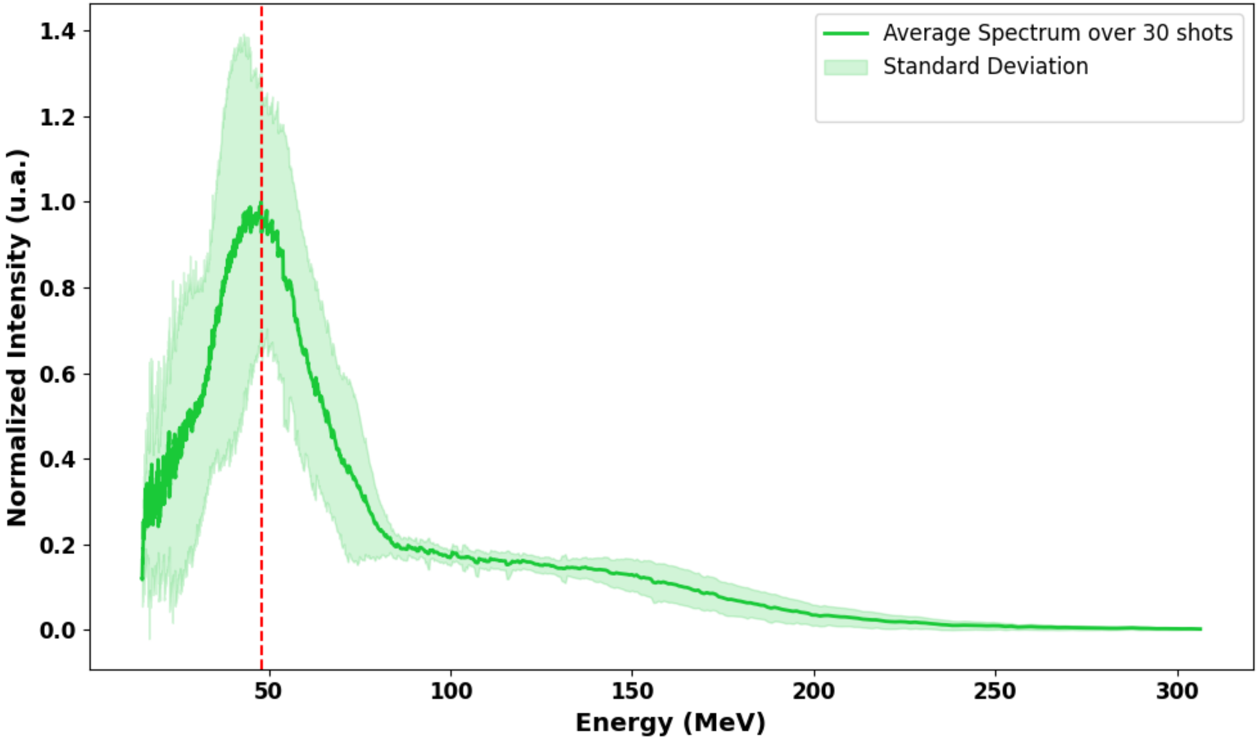
Experimental chamber



Salle Jaune Laser System

Experimental chamber

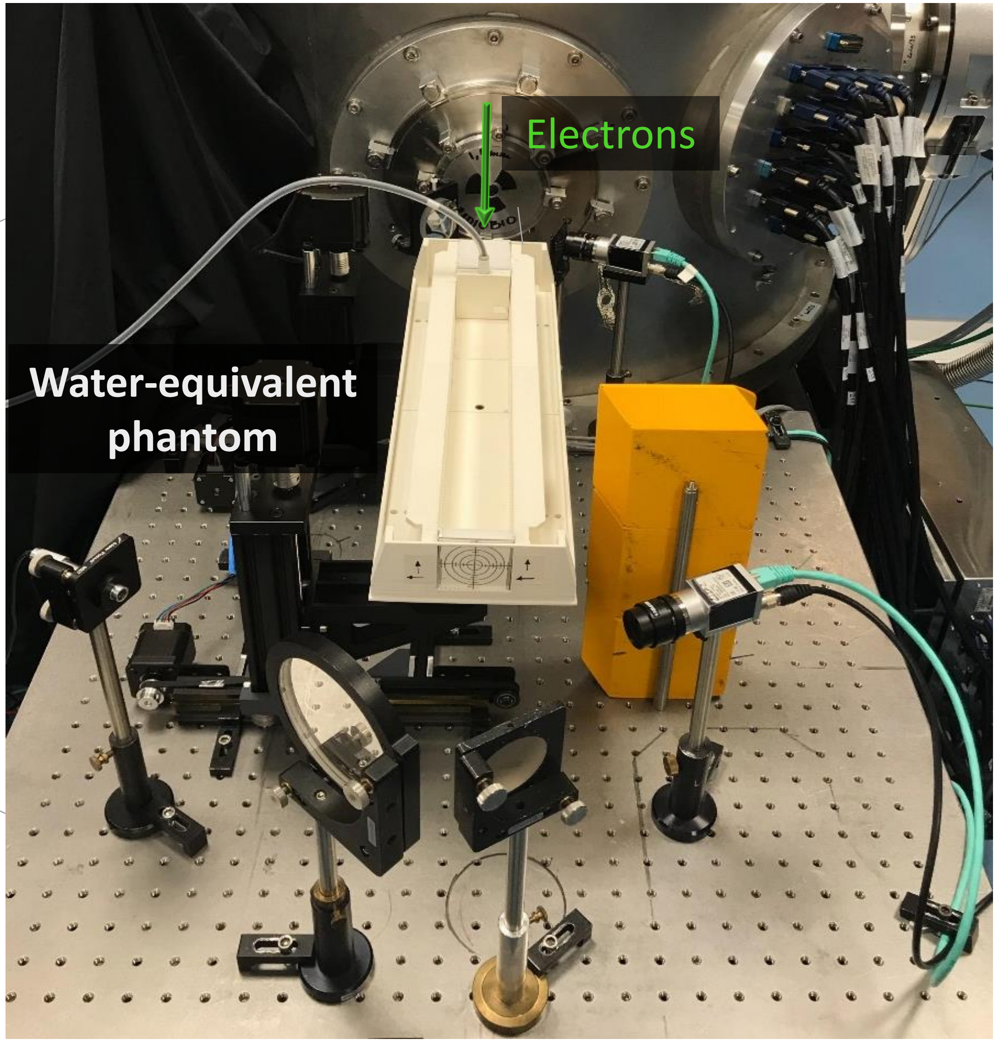




Charge	~500 pC /shot (<10% variance over 30 shots)
Divergence	~mrad

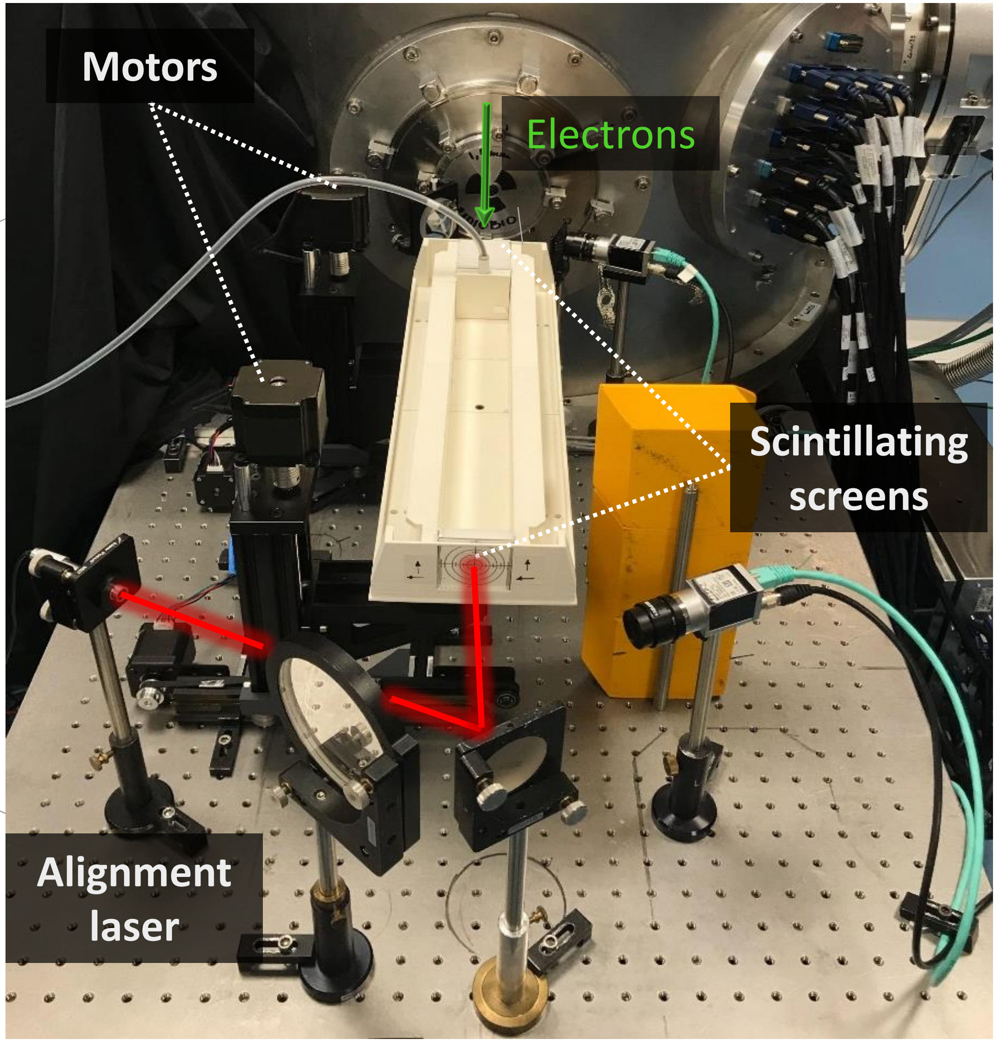
Salle Jaune Laser System

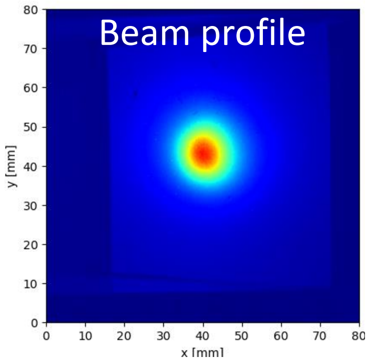
Radiobiology



Salle Jaune Laser System

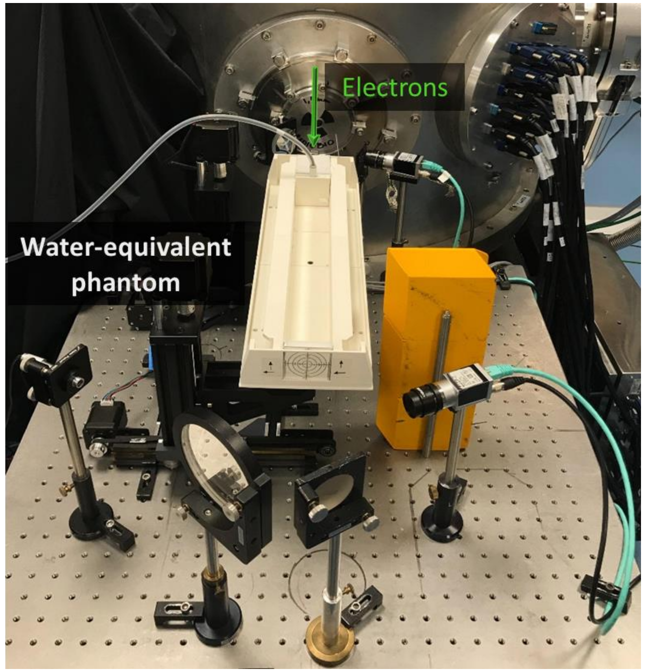
Radiobiology

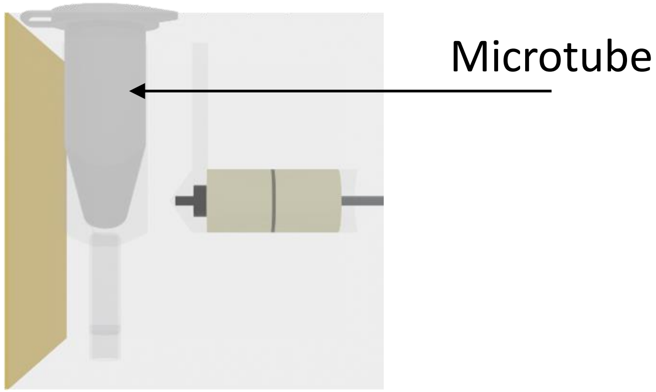


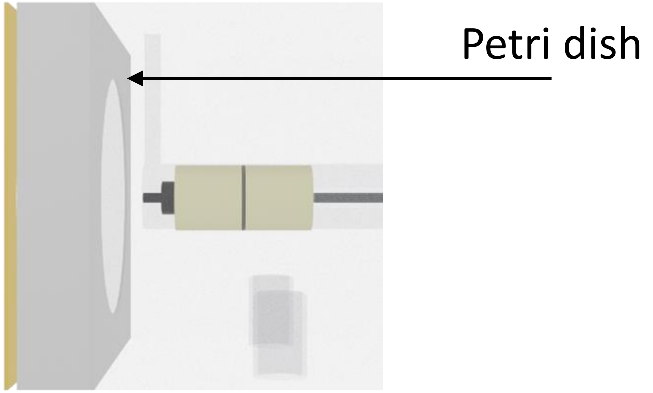


Salle Jaune Laser System

Radiobiology

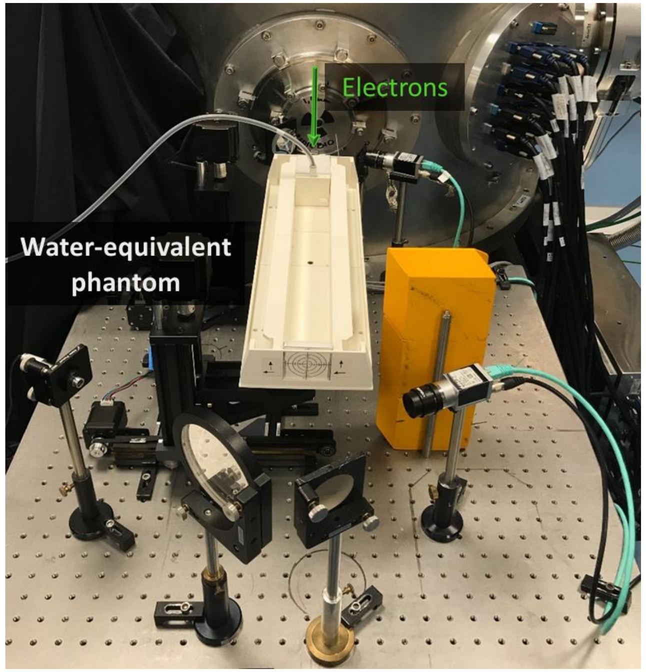






Salle Jaune Laser System

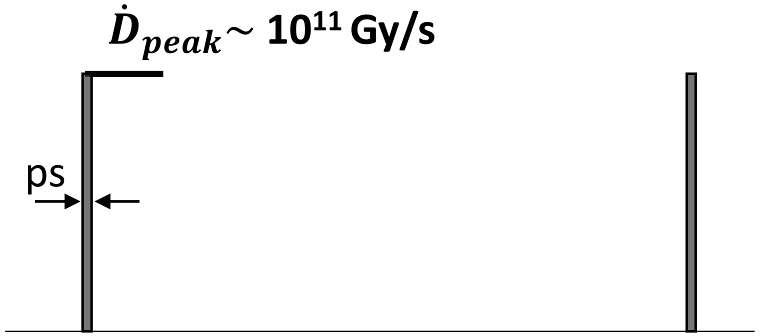
Dosimetry



Dose

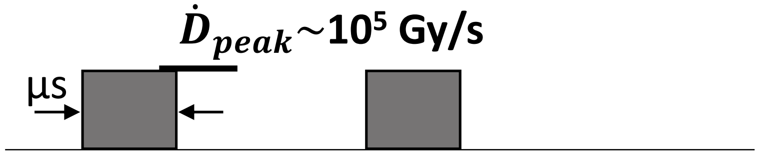
$$1\ Gy = \frac{1\ J}{Kg}$$

LPA - LOA



$\bar{D} \sim 15$ **Gy/min**
0.5 Hz

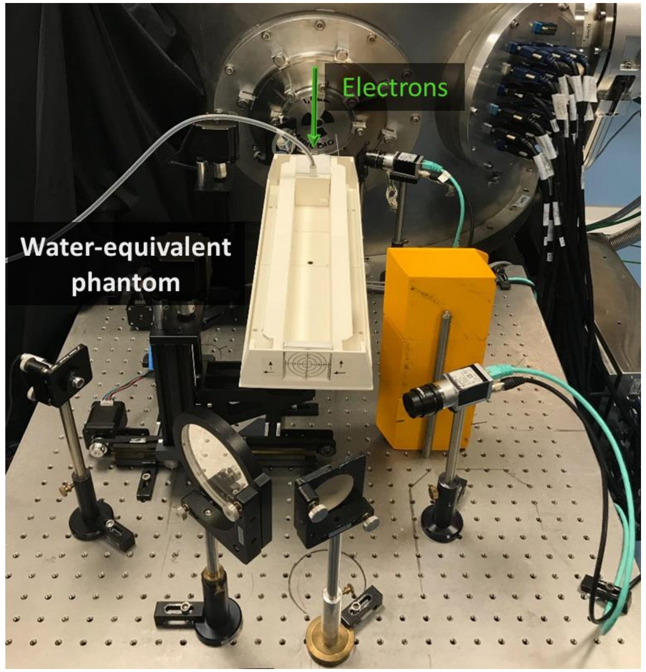
LINAC - CURIE



$\bar{D} \sim 30$ **Gy/min**
10 Hz

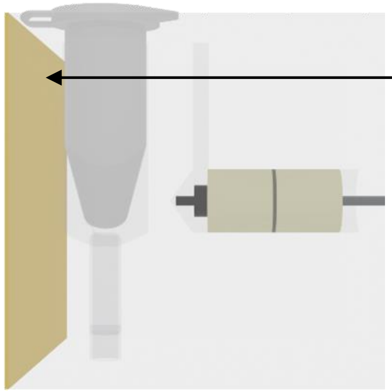
Salle Jaune Laser System

Dosimetry

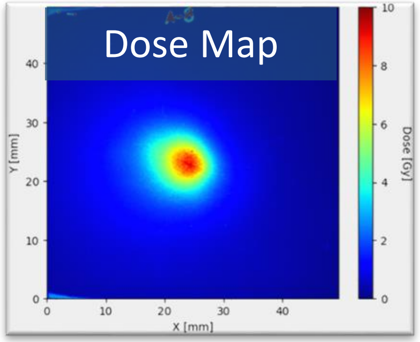


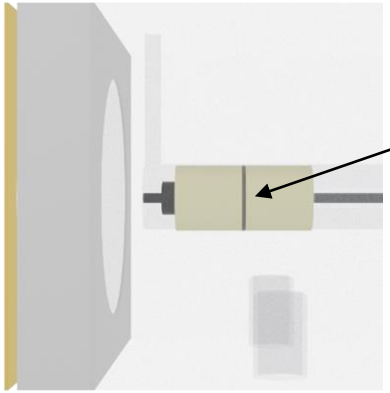
Dose

$$1\ Gy = \frac{1\ J}{Kg}$$



Radiochromic film (RCF)

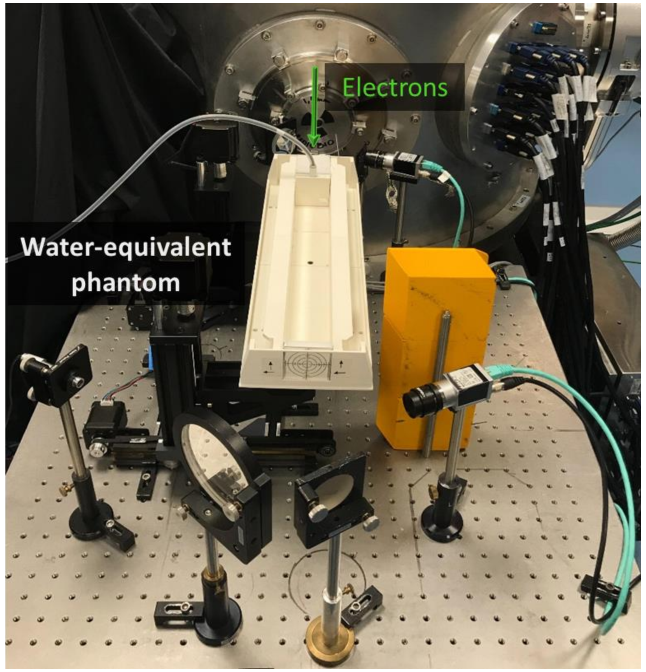




Ionization chamber (IC)

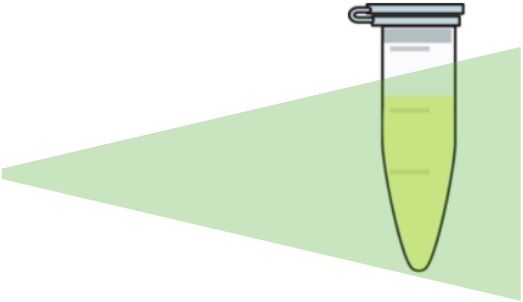
Salle Jaune Laser System

Dosimetry



Dose

$$1\ Gy = \frac{1\ J}{Kg}$$

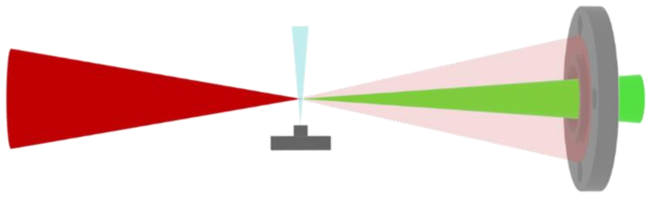


- Dose target
- Irradiation time
- Dose uniformity

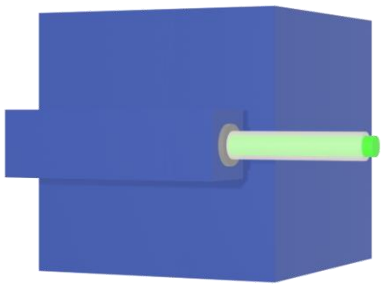
↓

3
Independent datasets

Pre-clinical studies



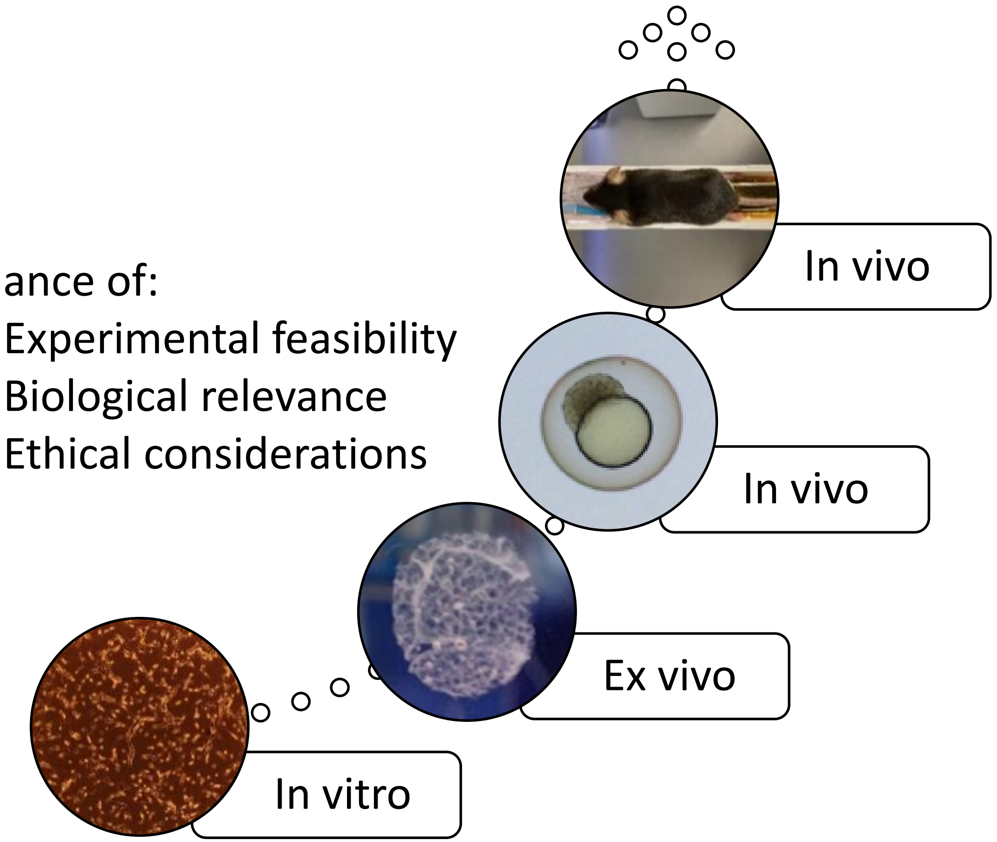
VHEE
50-300 MeV
$\bar{D} = 15\ \mathrm{Gy/min}$
$\dot{D} = 10^{13}\ \mathrm{Gy/s}$
$f = 0.5\ \mathrm{Hz}$



Conventional Intermediate Energy Electrons (CIEE)
7 MeV
$\bar{D} = 30\ \mathrm{Gy/min}$
$\dot{D} = 10^{4}\ \mathrm{Gy/s}$
$f = 10\ \mathrm{Hz}$

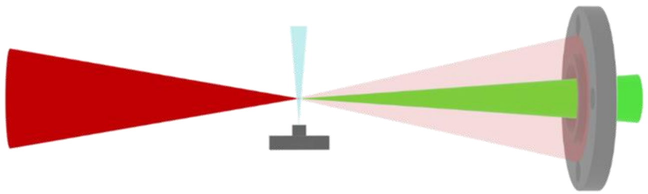
Balance of:

- Experimental feasibility
- Biological relevance
- Ethical considerations

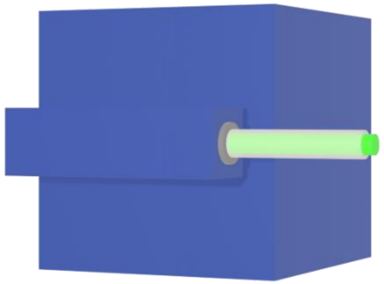


Giaccaglia et al., **Multiscale radiobiological assessment of laser-driven very high energy electrons versus conventional electrons**, https://doi.org/10.1101/2025.05.27.656200

Pre-clinical studies

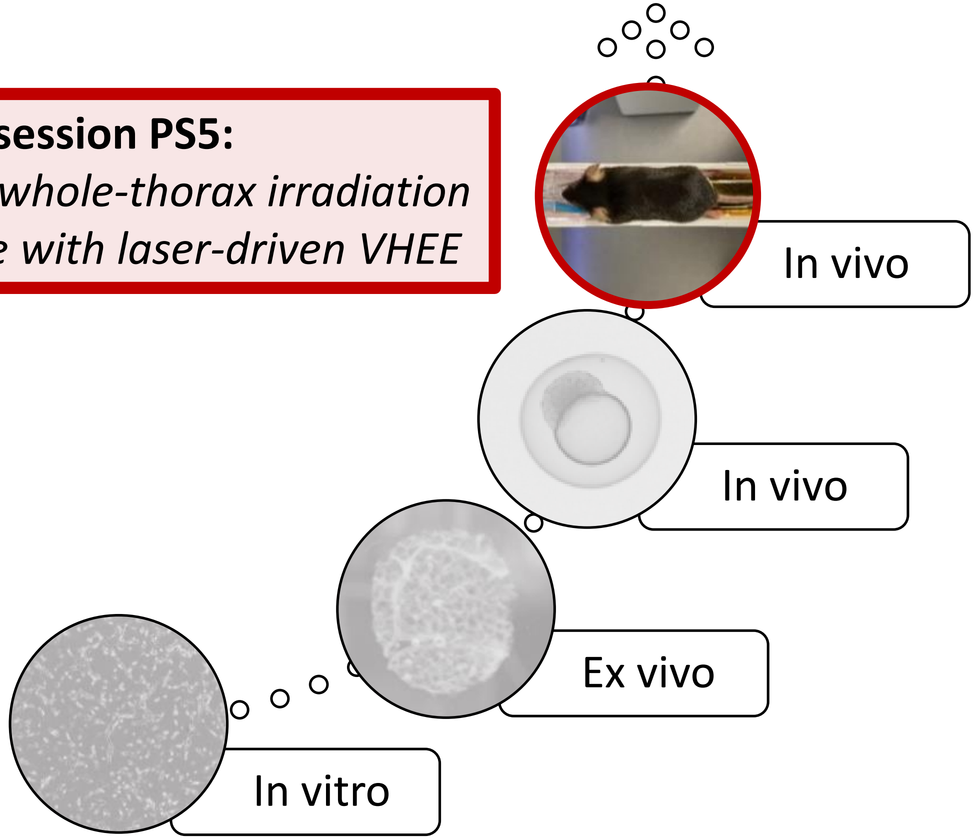


VHEE
50-300 MeV
$\bar{D} = 15\ \mathrm{Gy/min}$
$\dot{D} = 10^{13}\ \mathrm{Gy/s}$
$f = 0.5\ \mathrm{Hz}$



Conventional Intermediate Energy Electrons (CIEE)
7 MeV
$\bar{D} = 30\ \mathrm{Gy/min}$
$\dot{D} = 10^{4}\ \mathrm{Gy/s}$
$f = 10\ \mathrm{Hz}$

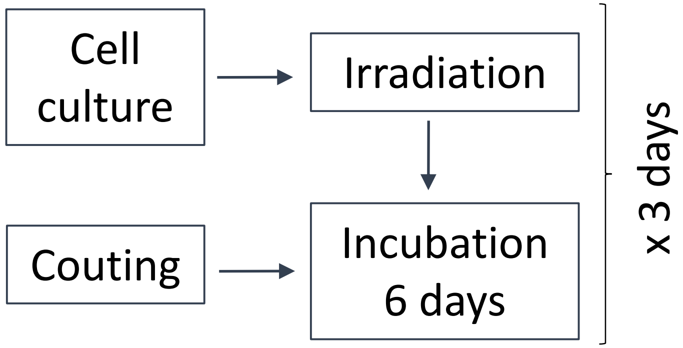
Poster session PS5:
In vivo whole-thorax irradiation in mice with laser-driven VHEE

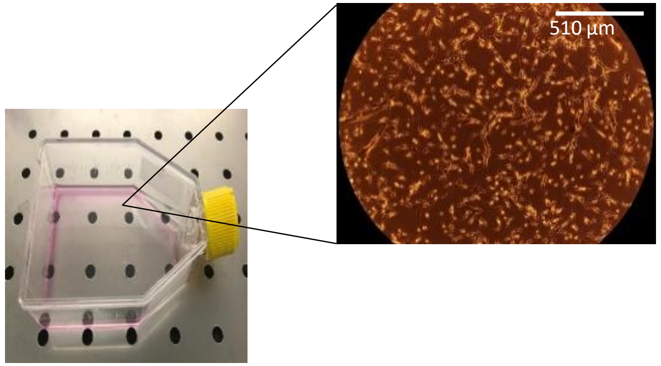


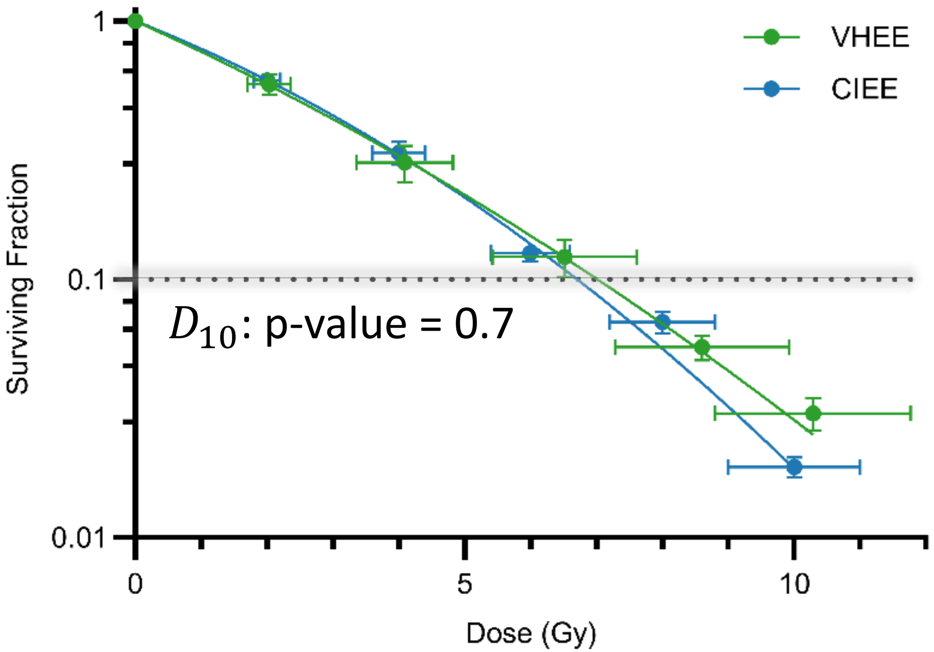
Giaccaglia et al., **Multiscale radiobiological assessment of laser-driven very high energy electrons versus conventional electrons**, https://doi.org/10.1101/2025.05.27.656200

In vitro assay

MRC5-hTert – Human fetal lung fibroblasts







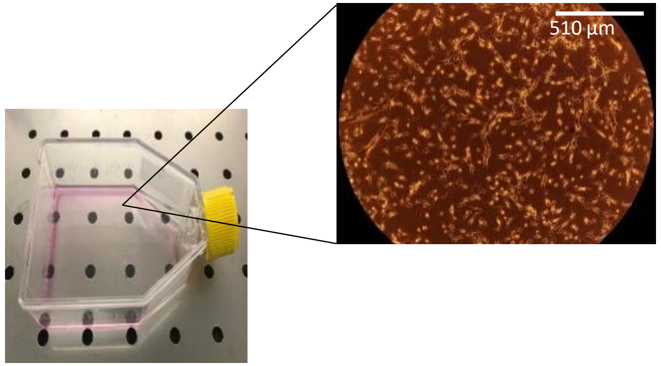
In vitro assay

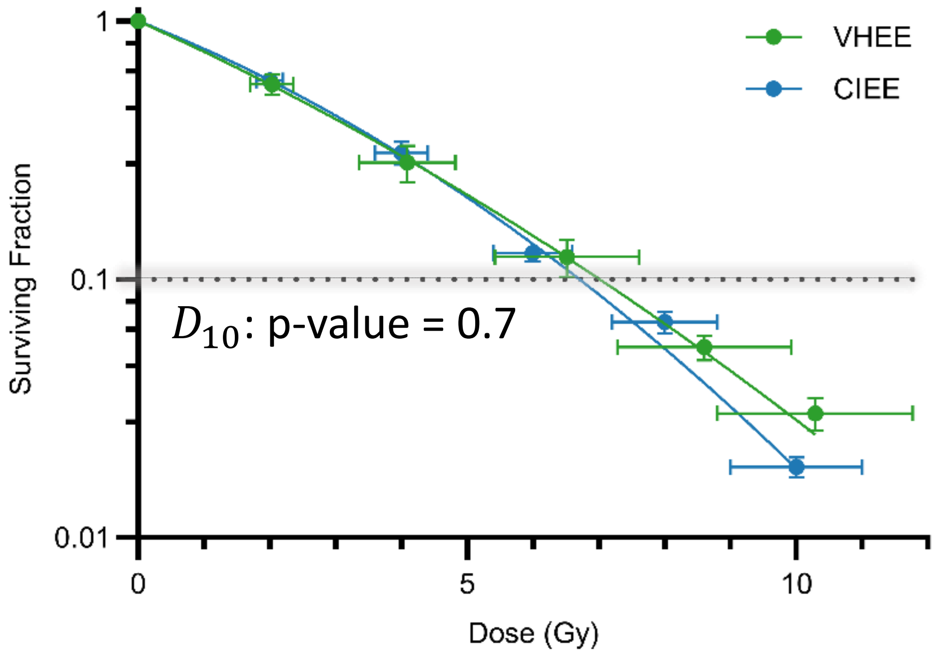
MRC5-hTert – Human fetal lung fibroblasts

Cell culture → Irradiation → Incubation 6 days

Couting →

x 3 days

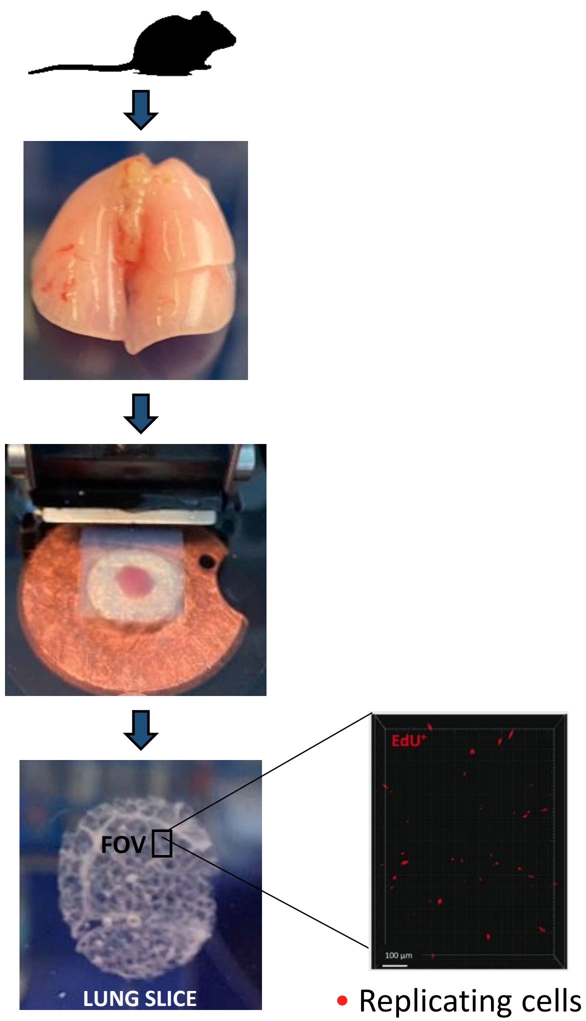




Comparable toxicity of VHEE - CIEE

Ex vivo assay

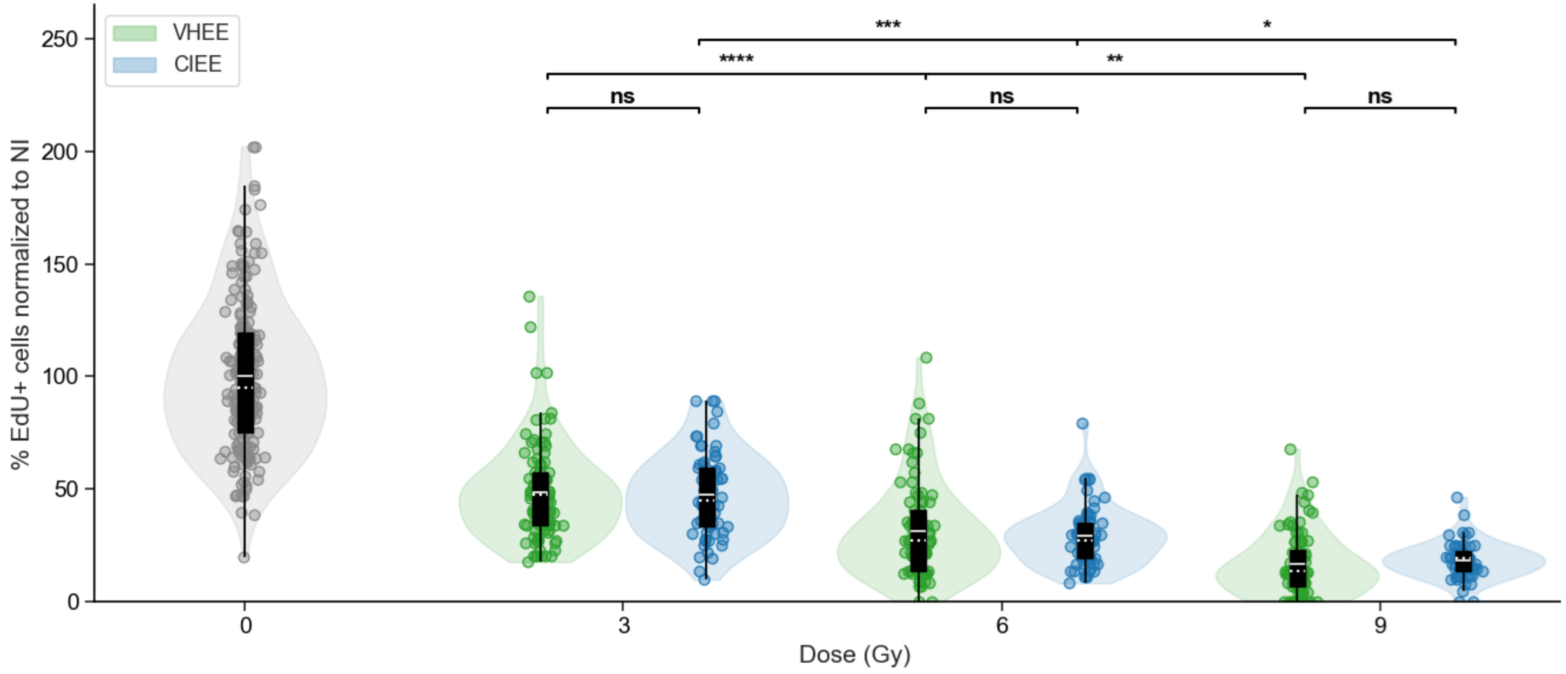
Mouse lung slices (C57BL/6J)



• Replicating cells

M. Dubail et al., 2023

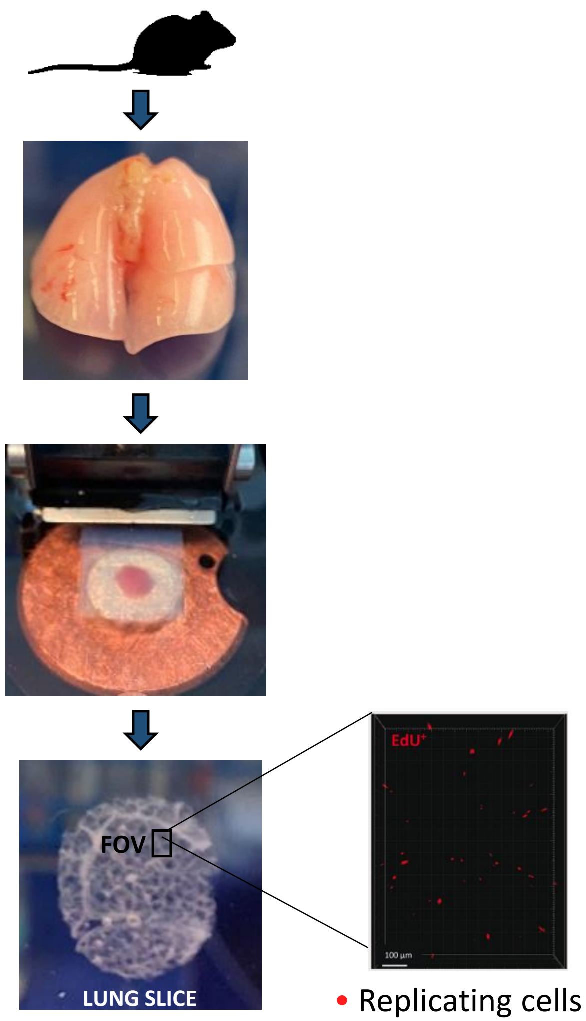
n = 5 slices/group (3, 6, 9 Gy)
5–7 fields of view (FOVs)/slice



Kruskal–Wallis test + Dunn–Holm
ns: non significant, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

Ex vivo assay

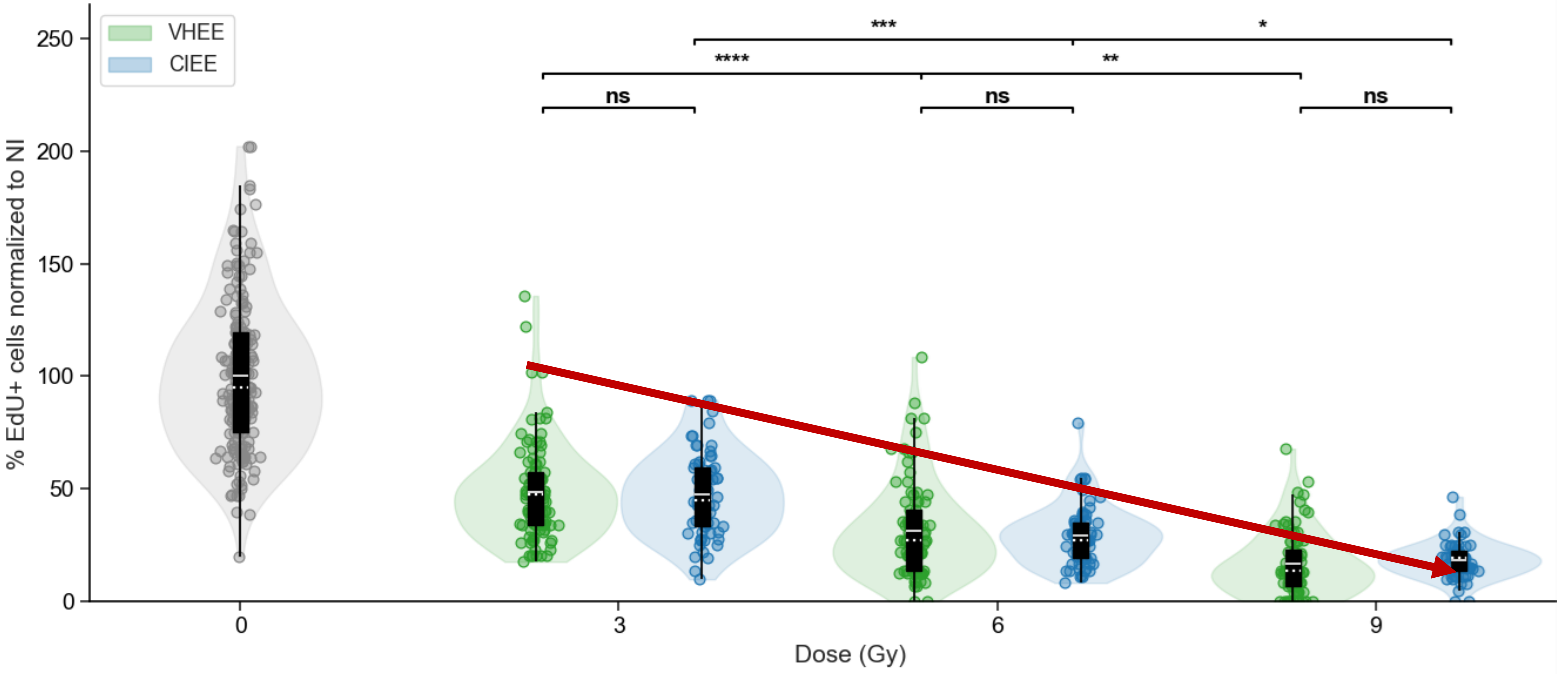
Mouse lung slices (C57BL/6J)



• Replicating cells

M. Dubail et al., 2023

Dose-dependent decrease

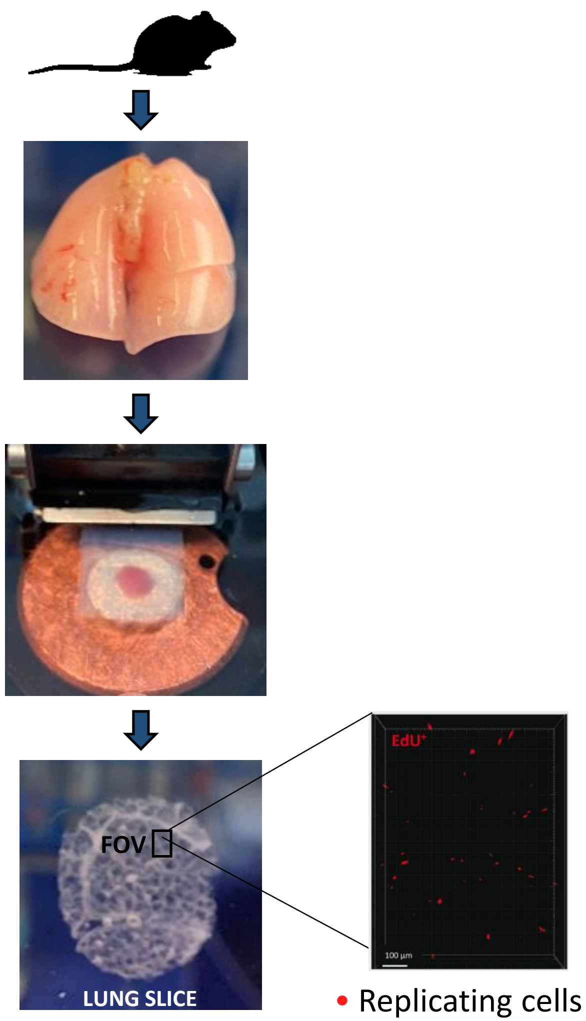


Kruskal–Wallis test + Dunn–Holm

ns: non significant, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

Ex vivo assay

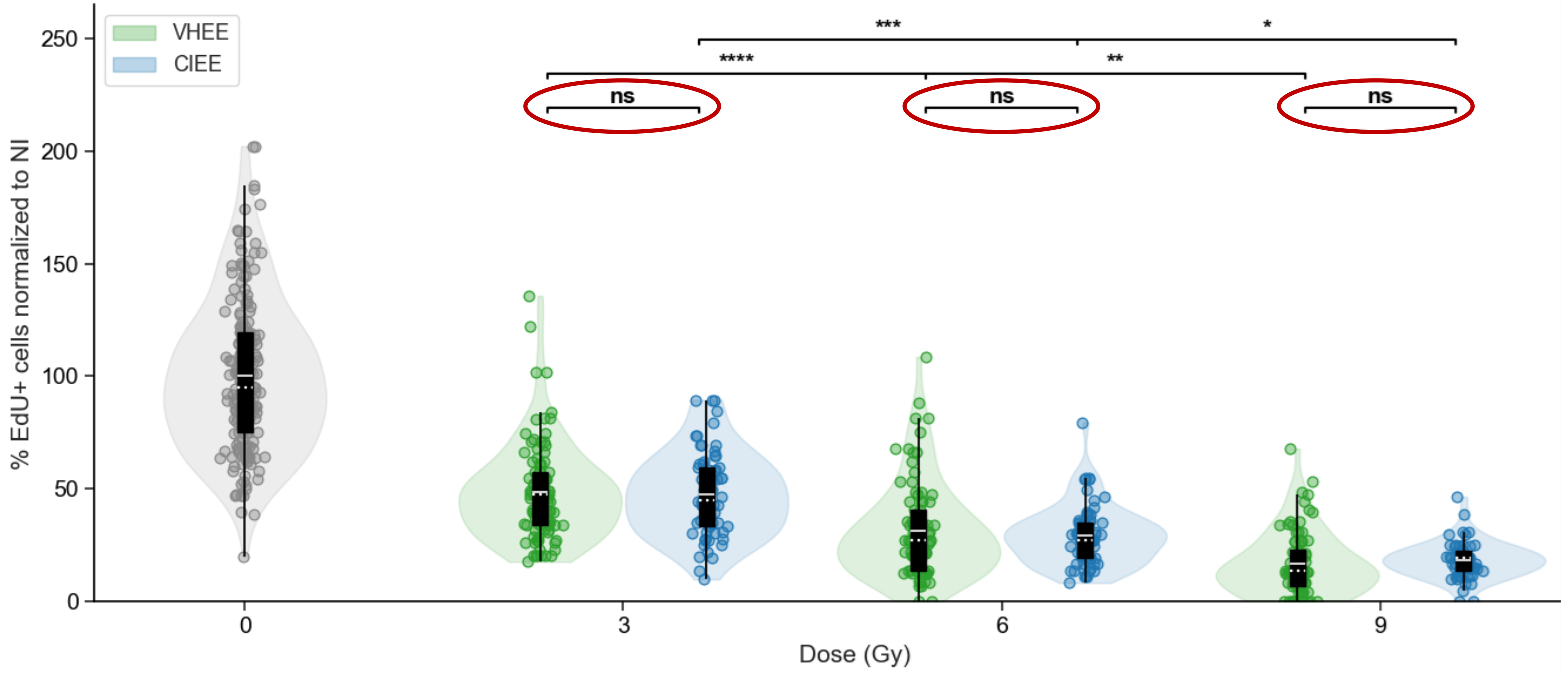
Mouse lung slices (C57BL/6J)



• Replicating cells

M. Dubail et al., 2023

Comparable toxicity of VHEE - CIEE



Kruskal–Wallis test + Dunn–Holm

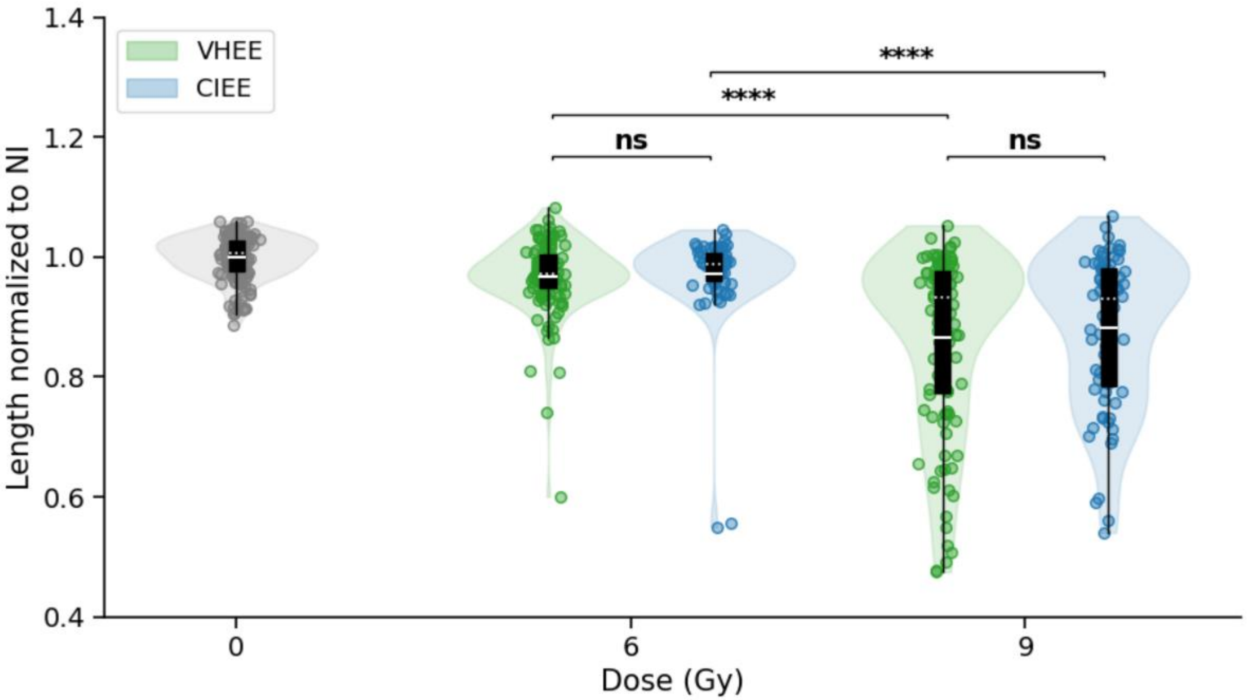
ns: non significant, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

In vivo assay

Zebrafish (*Danio rerio -WT*)

Embryos/group: VHEE n=37, CIEE n=24 (6 & 9 Gy)

Irradiation 5 hpf → Incubation 5 days → Fixation (x 3 days)

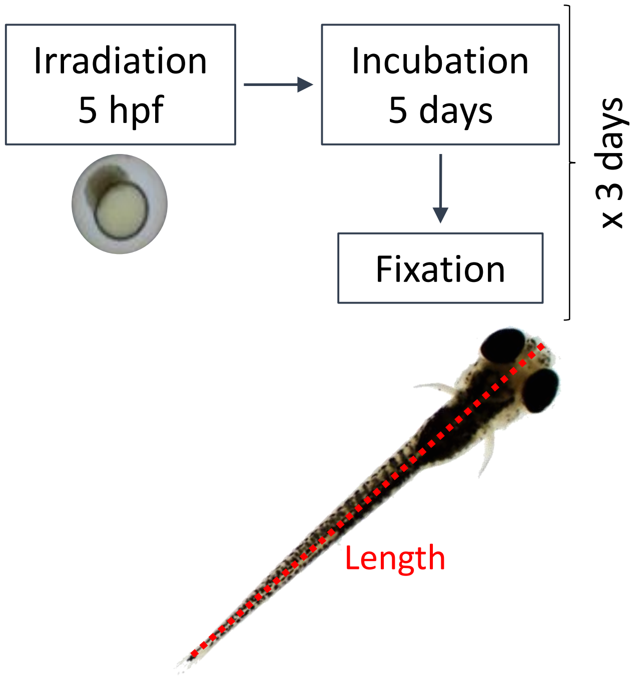


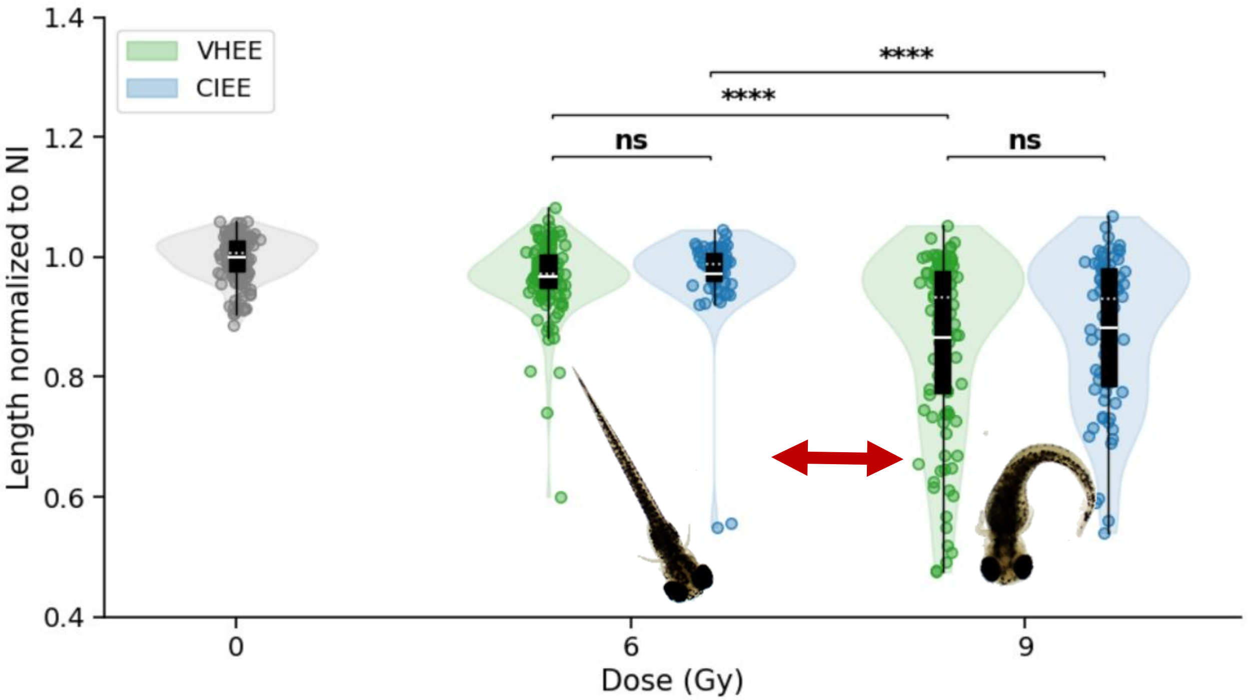
Kruskal–Wallis test + Dunn–Holm
ns: non significant, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

In vivo assay

Zebrafish (*Danio rerio -WT*)

Threshold effect





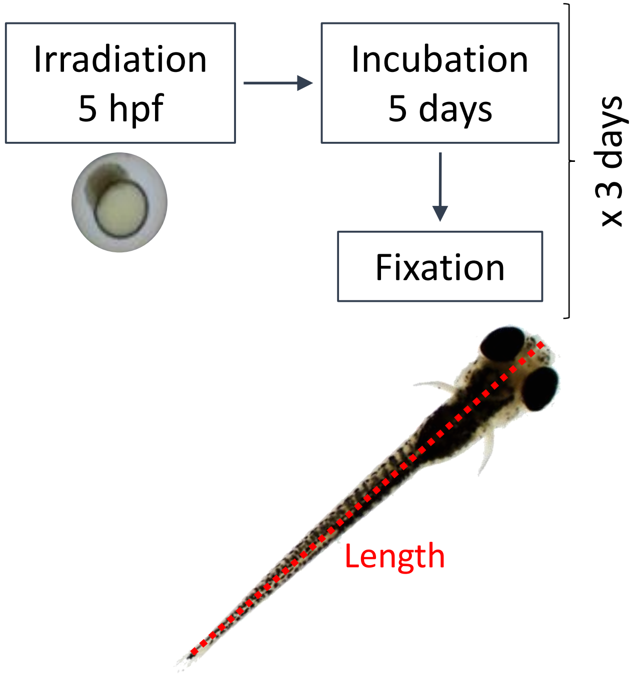
Kruskal–Wallis test + Dunn–Holm

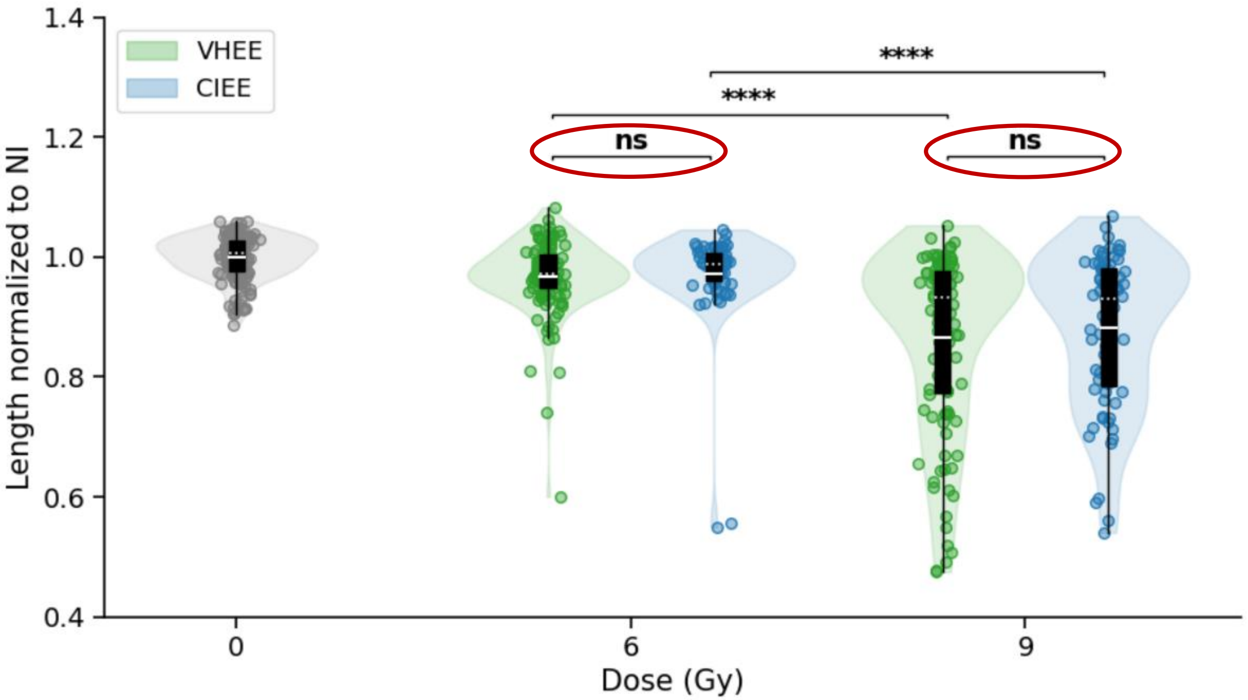
ns: non significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$

In vivo assay

Zebrafish (*Danio rerio -WT*)

Comparable toxicity of VHEE - CIEE



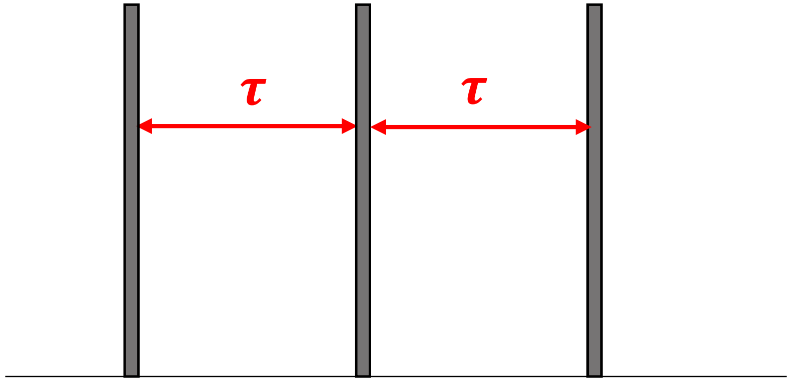


Kruskal–Wallis test + Dunn–Holm
ns: non significant, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

Pre-clinical – Temporal Modality Impact

Does the time interval between electron bunches in a LPA affect the biological response?

$\boldsymbol{\tau} = \mathbf{1 - 2 - 5 - 10\ s}$



$$\dot{D}_{av} = D_{pulse} * f$$

Giaccaglia et al., **In vivo and in vitro differential toxicity in laser driven VHEE beam fast-fractionation**, preprint ongoing

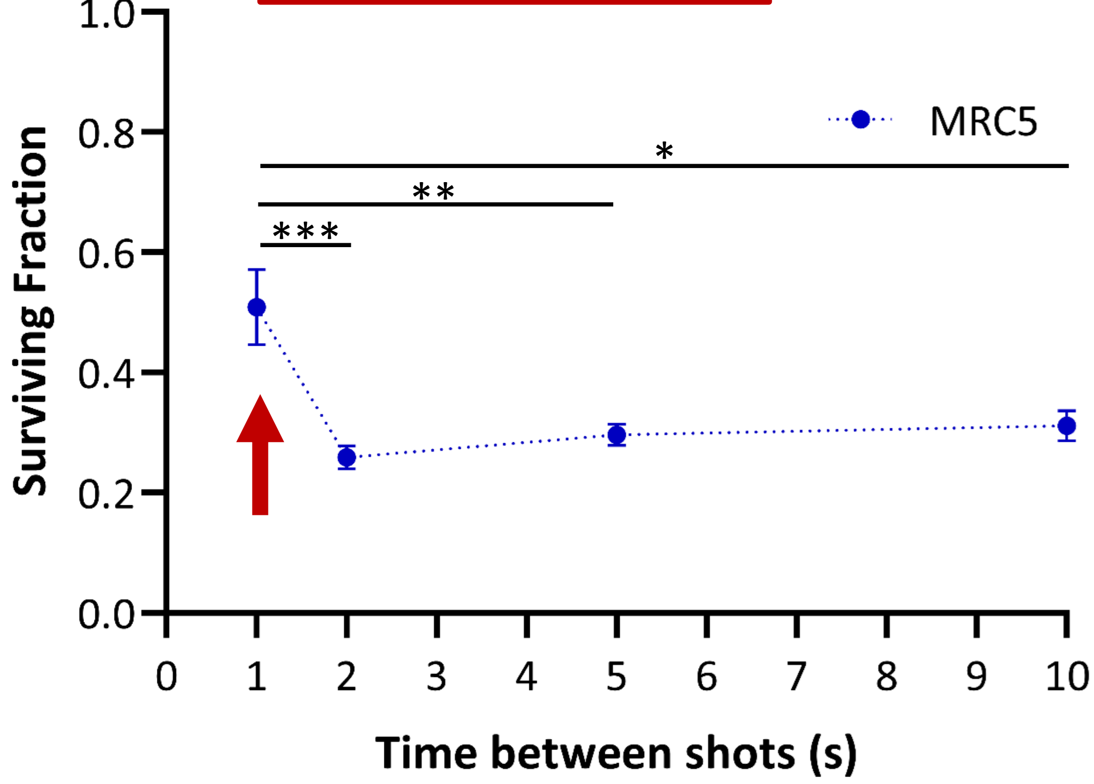
Pre-clinical – Temporal Modality Impact

In vitro

MRC5: 4.5 Gy ← Healthy cell line

Kruskal–Wallis test + Dunn-Benjamini-Hochberg
ns: non significant, *p < 0.05, **p < 0.01,
***p < 0.001, ****p < 0.0001

Higher survival at 1s



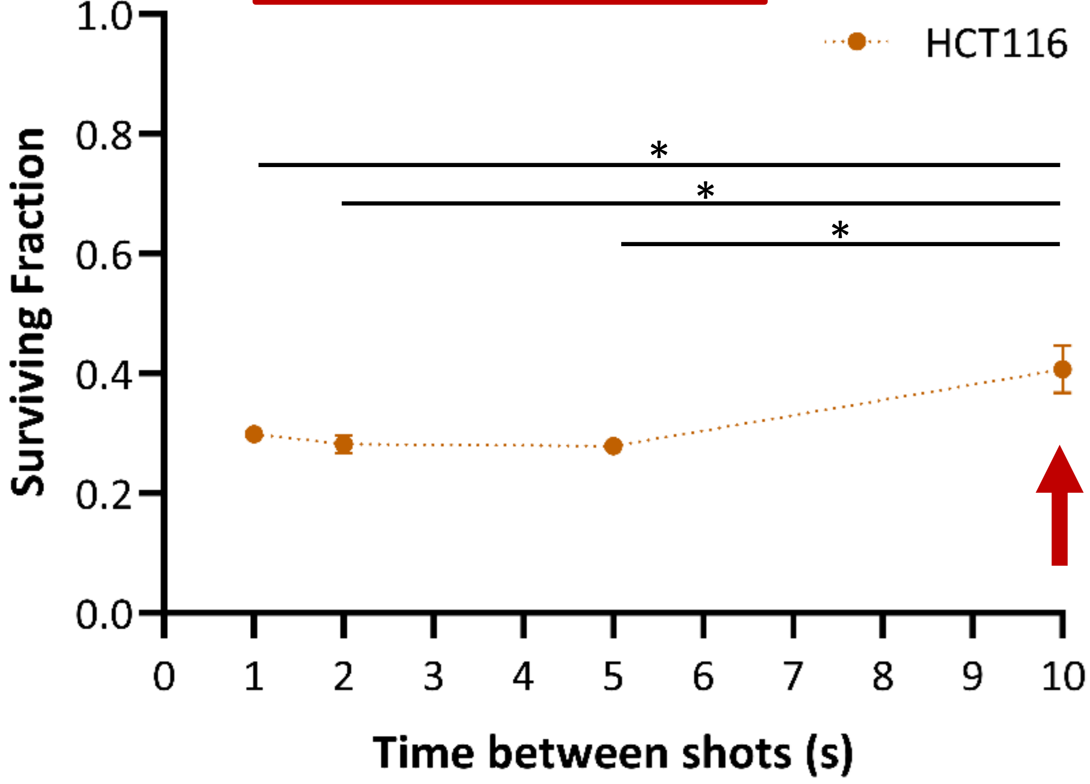
Pre-clinical – Temporal Modality Impact

In vitro

HCT116: 4.5 Gy ← Cancer cell line

Kruskal–Wallis test + Dunn-Benjamini-Hochberg
ns: non significant, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

Higher survival at 10s

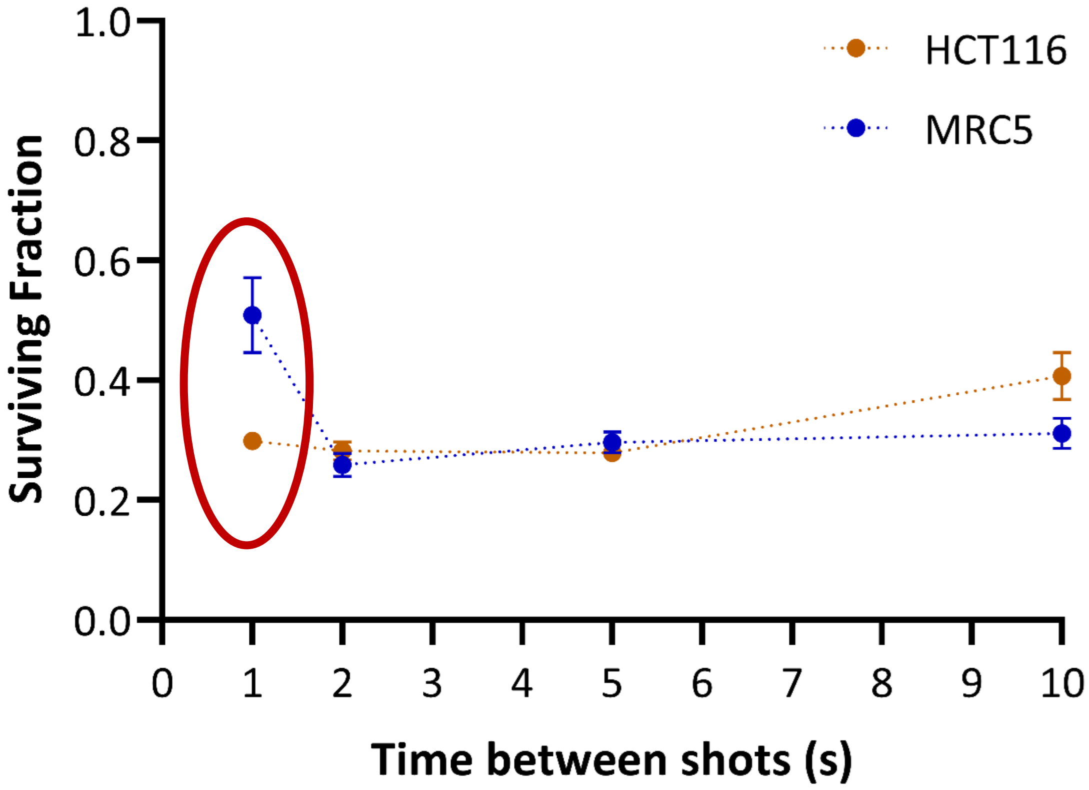


Pre-clinical – Temporal Modality Impact

In vitro

MRC5: 4.5 Gy ← Healthy cell line
HCT116: 4.5 Gy ← Cancer cell line

Kruskal–Wallis test + Dunn-Benjamini-Hochberg
ns: non significant, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001



Healthy tissue sparing
Improved tumor control

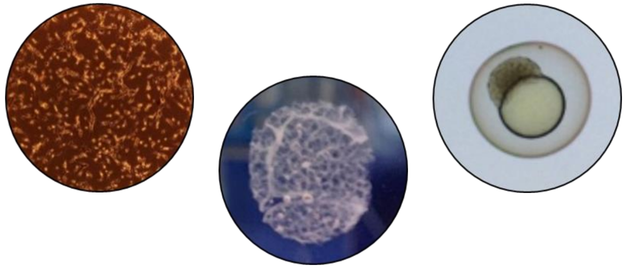
Conclusions

Laser-driven VHEE beam suitable for radiation biology experiments

VHEE - LPA

Comparable biological toxicity

CIEE - LINAC



A change in the repetition rate of the electron bunch has a biological impact?

Higher repetition rate (1Hz): spares healthy tissue while enhancing tumor control

Thank you

Alessandro Flacco
Emilie Bayart
Chaitanya Varma

Charles Fouillade
Sophie Heinriech
Maxime Dubail

Isabelle Lamarre-Jouenne

U1030 - Deutsch Eric