Review of Medical Application Studies in CLEAR

P. Korysko*,
on behalf of the CLEAR team.

CLEAR Scientific Board Meeting

February 16th 2024

*pierre.korysko@cern.ch

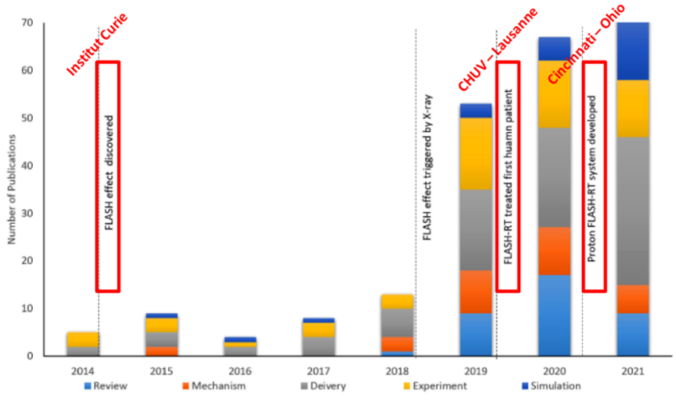
Outline

- Context: the FLASH effect.
- Tools and Methods used.
- Selected Medical Applications performed at CLEAR in 2023.
- Medical Applications planned at CLEAR in 2024.
- Conclusions.

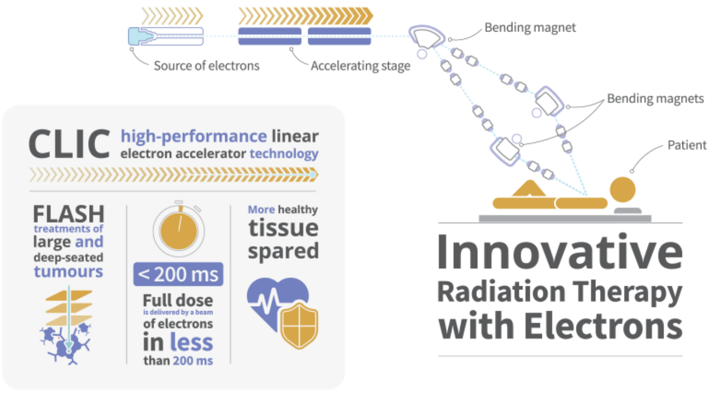
The FLASH Effect

The FLASH Effect

- The Flash effect is a **biological effect** that **destroys cancerous cells** while **sparing healthy surrounding tissues**.
- Observed for the **first time** in 2014: mice tumors were irradiated with short pulses (≤500 ms) at Ultra High Dose Rate, UHDR (≥40 Gy/s).
- The FLASH effect has been seen with **protons**, **gamma** and **low energy electrons**.
- Very High Energy Electrons (**VHEE**) would be used to treat **deep seated tumors**.
- The **FLASH** effect is **extensively studied** including in **CLEAR**.



[Gao et al. J Appl Clin Med Phys.2022]



Treatment of a first patient with FLASH-radiotherapy

ELSEVIER
Radiotherapy and Oncology
Volume 139, October 2019, Pages 18-22

First in Human

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a b], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a b c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c 1], Marie-Catherine Vozenin [a b 1]

1a : Day 0 1b : 3 weeks 1c : 5 months

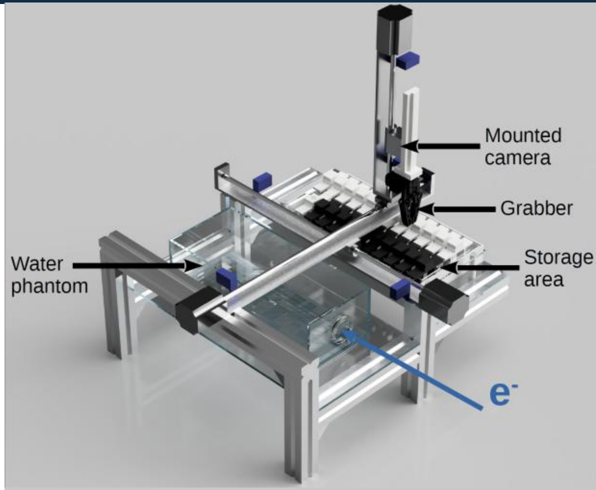
- **In 2019, 15 Gy** delivered in **90 ms**, using a **5.6-MeV electron linac**, to a 75-years old patient with a multi-resistant cutaneous lymphoma:
  - **On healthy tissues**: no decrease of the thickness of the epidermis and no disruption at the basal membrane with limited increase of the vascularization.
  - **On Tumor**: Tumor response was rapid, complete, and durable with a short follow-up of 5 months.

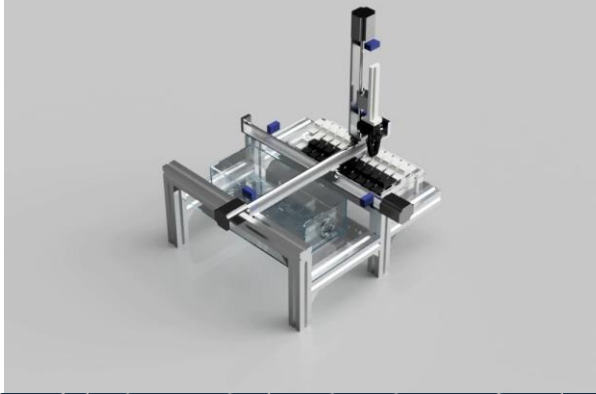
Conclusions: This first FLASH-RT treatment was feasible and safe with a favorable outcome both on normal skin and the tumor.

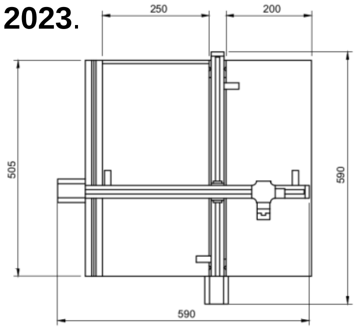
Tools and Methods

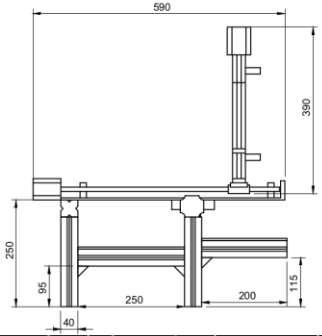
The C-Robot

- In order to **facilitate** the **precise control** of **samples** for **multiple irradiations**, the CLEAR-Robot (**C-Robot**) was designed and built by members of the CLEAR Operation Team.
- It consists of **3 linear stages**, **6 limit switches**, a **3D-printed grabber**, **two water tanks** and an **Arduino board**.
- It has a **precision in position** in 3 axis of **50 µm**.
- It is **fully remotely controllable** from the **CERN Technical Network**.
- Thanks to a **mounted camera**, it can also measure the **beam sizes** and **transverse positions** at the longitudinal position of the sample.
- It is an **open-source project**: **pictures**, **3D renders**, **drawings** and all the **codes** for the **Arduino** and the **Graphical User Interface** can be found on: https://pkorysko.web.cern.ch/C-Robot.html
- Used for **100% of Medical Applications** in CLEAR in **2023**.





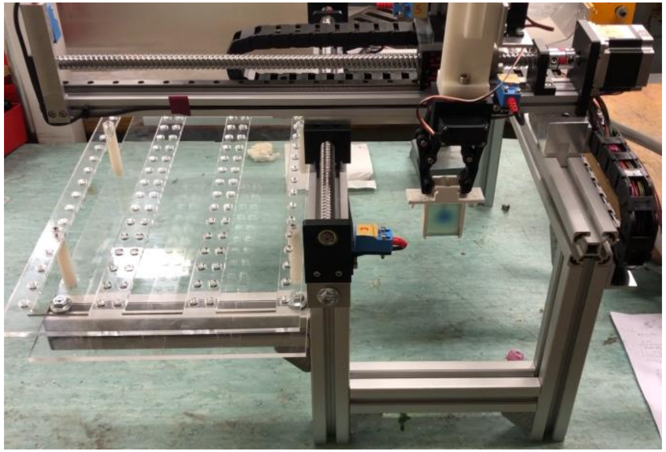


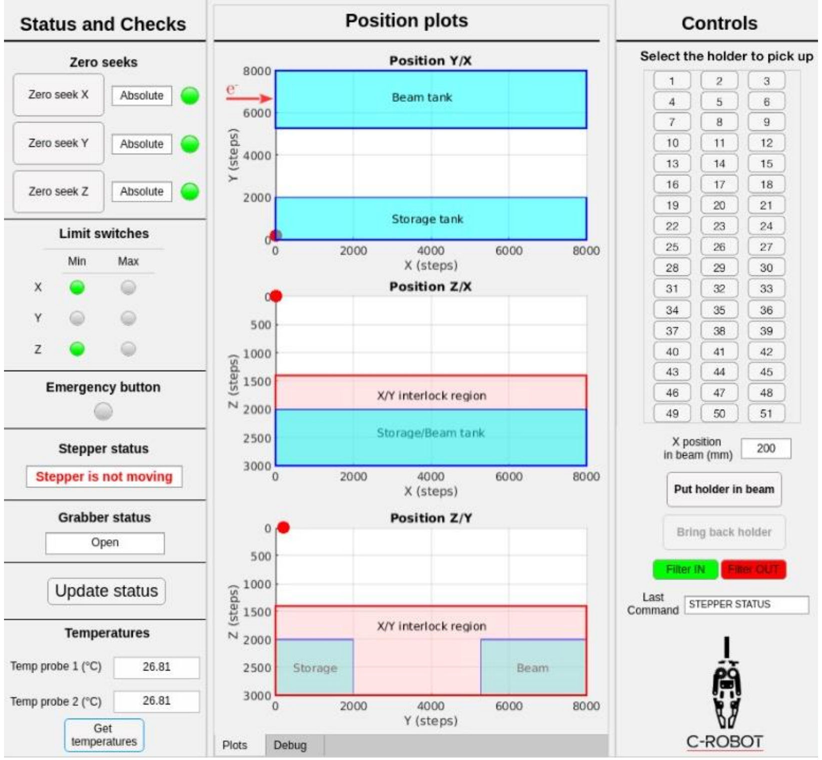


C-ROBOT

The C-Robot 2.0

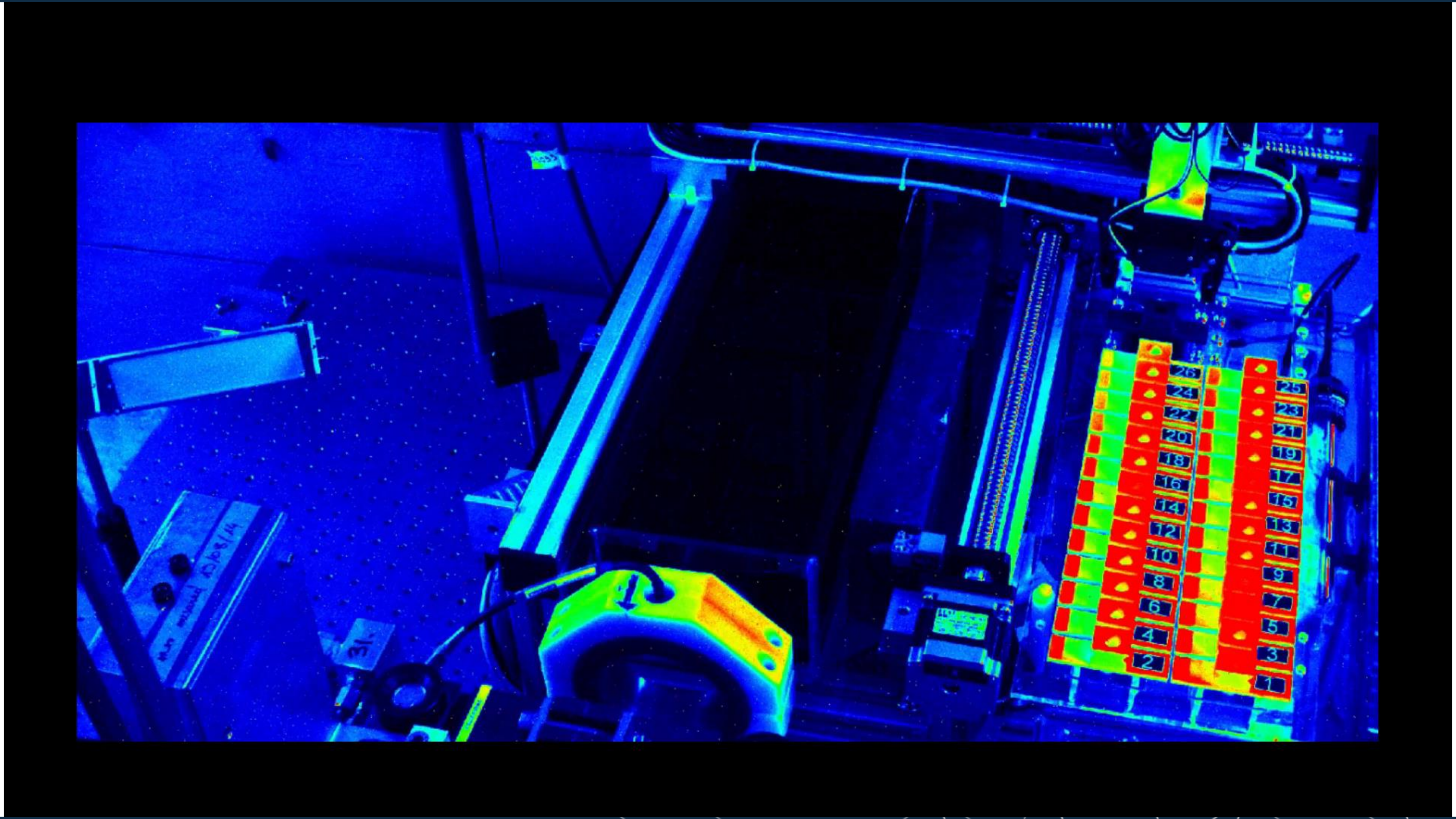
- A new robot was built for the **new CLEAR beamline**:
  - **Mirrored**, to adapt to the new in-air test area.
  - **51** available **slots**.
  - With **temperature probes**, **mounted camera**, **optical filters**.
  - This robot will be sent to PITZ (DESY Berlin) for them to reverse-engineer it and build a copy locally.





I. Najmudin

The C-Robot in action with beam

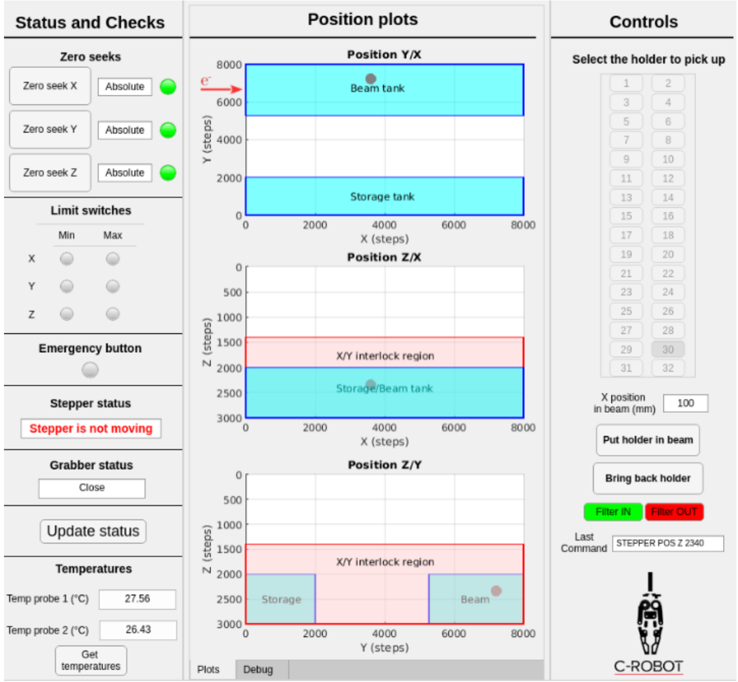


Selected Medical Applications performed at CLEAR in 2023:

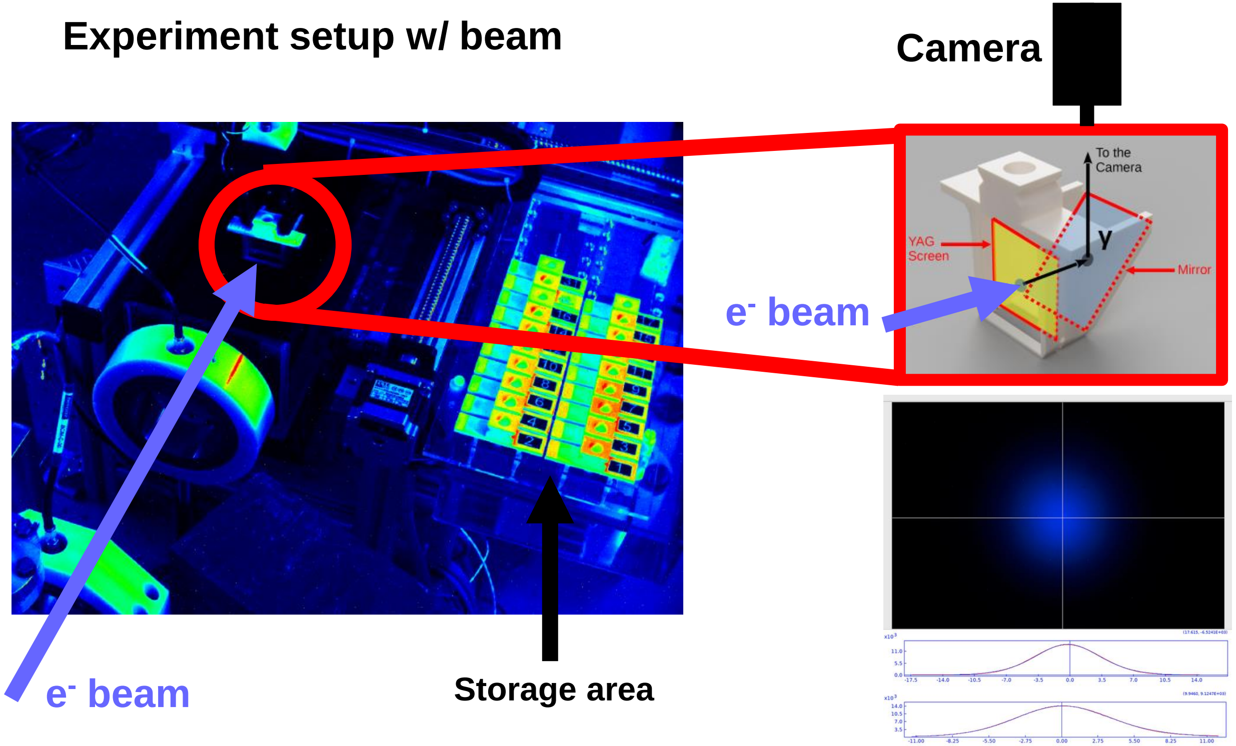
Dosimetry Studies

What can the C-Robot do?

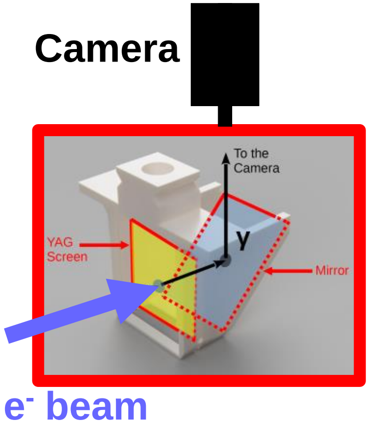
Graphical User Interface

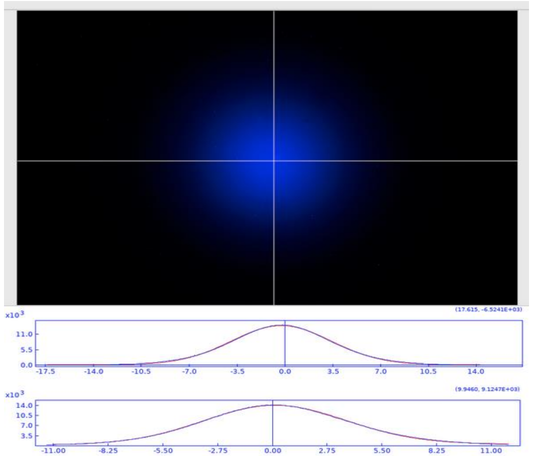


Experiment setup w/ beam

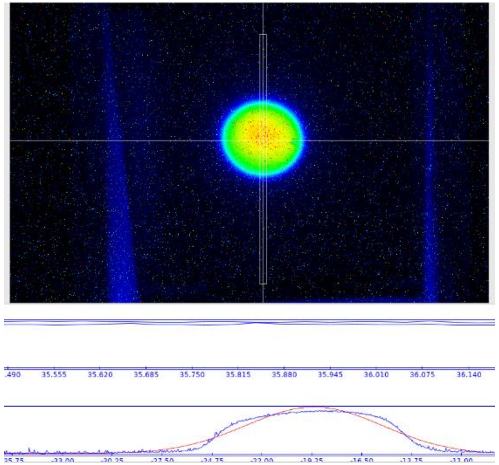


Real-Time Dosimetry

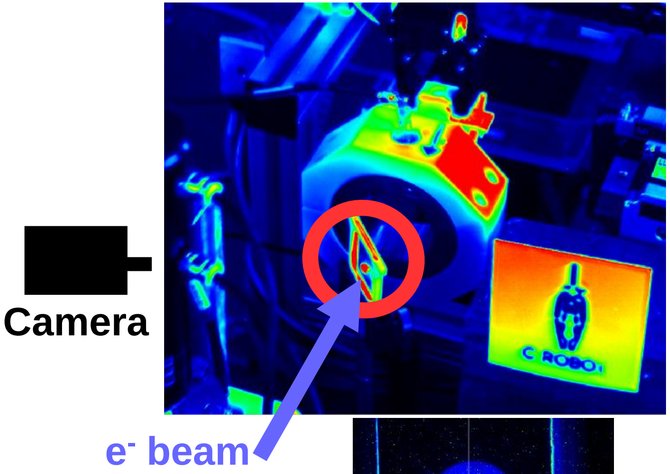


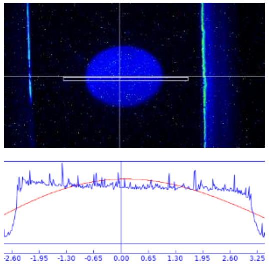


Gaussian Beam



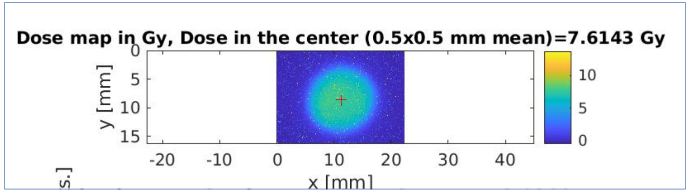
Uniform Beam





- A real-time dosimetry measurement is done using the **charge** and the **beam size** measurement with the scintillating screen (in air or in water).
- The samples are then irradiated at the same exact location.

- A similar method is being developed using a **thin scintillating screen** in air in front of the water phantom for real-time dose measurement using charge density methods.

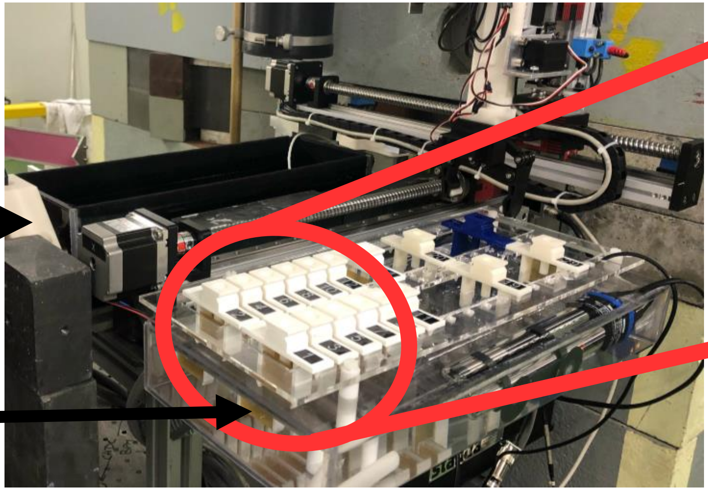


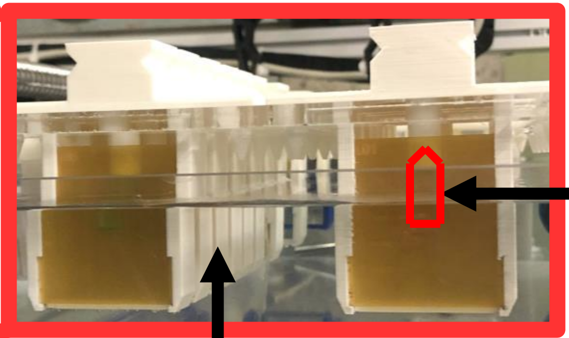
Experimental Setup & Dosimetry for VHEE at UHDR irradiations

V. Rieker

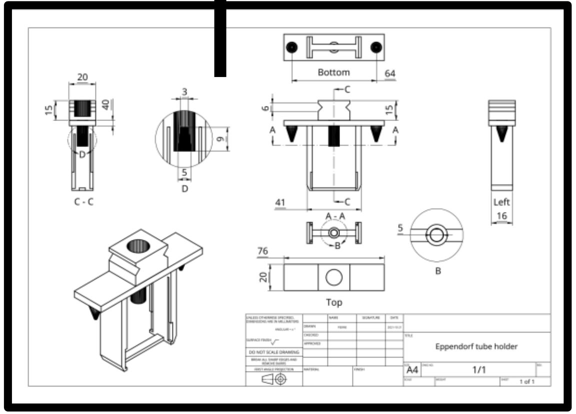
Beam water tank

Heated storage water tank





Eppendorf tube with sample to irradiate



3D printed
holder with 2 films: one before and one after the sample

Laser cut
Radiochromic films to measure the delivered dose

Dose range:
1 – 100 Gy

Before irradiation

After irradiation

This is the **passive** standard way to measure the delivered dose, but **real-time** dosimetry is crucial for clinical treatments.

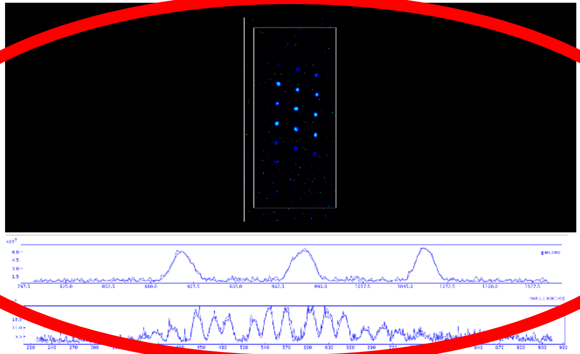
Optical Fibre Dosimetry

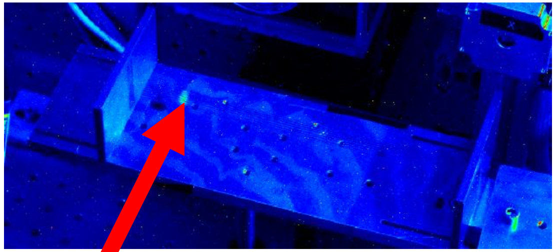
Goal :

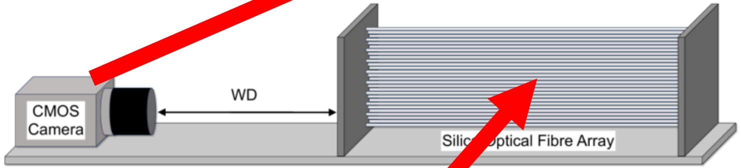
Measure in real time the doses delivered by VHEE at UHDR and CDR with two arrays of optical fibers.

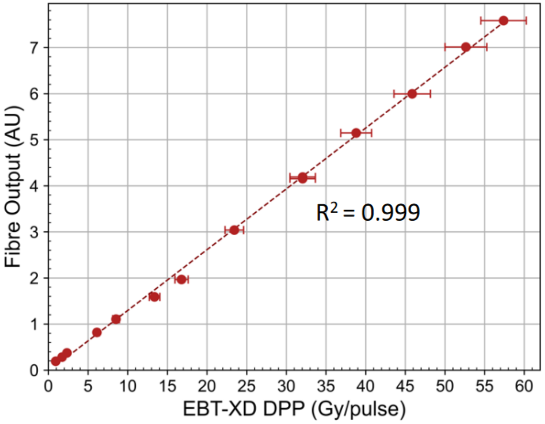
Experiment :

Recontruct the transverse profile of the VHEE beam to measure the dose in real time and compare with radiochromic films.









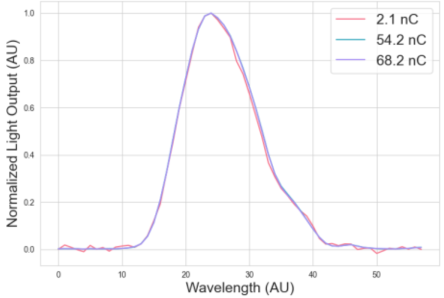
Paper under review

J. Bateman

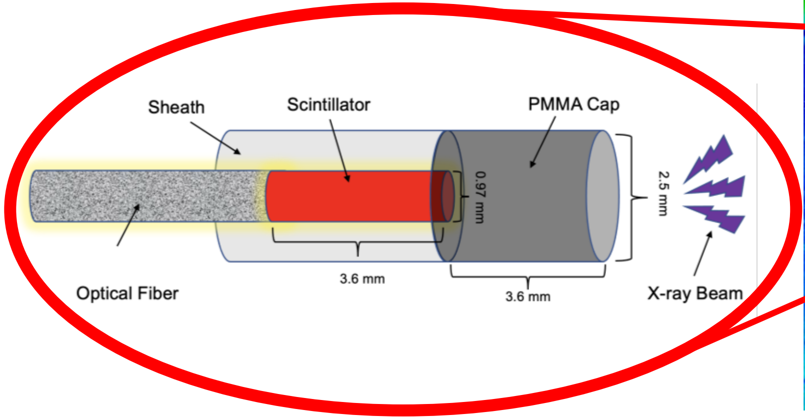
Scintillator Dosimetry

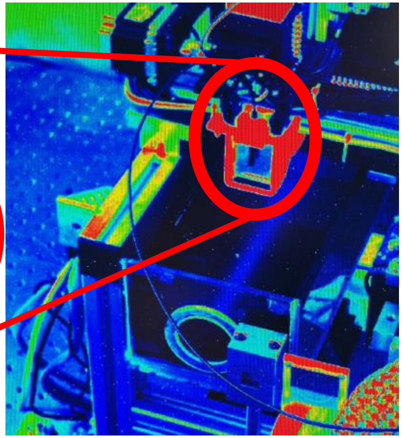
Goal:
Measure the dose at UHDR with a real-time readout and a high spatial resolution thanks to a scintillator and an optical fiber.

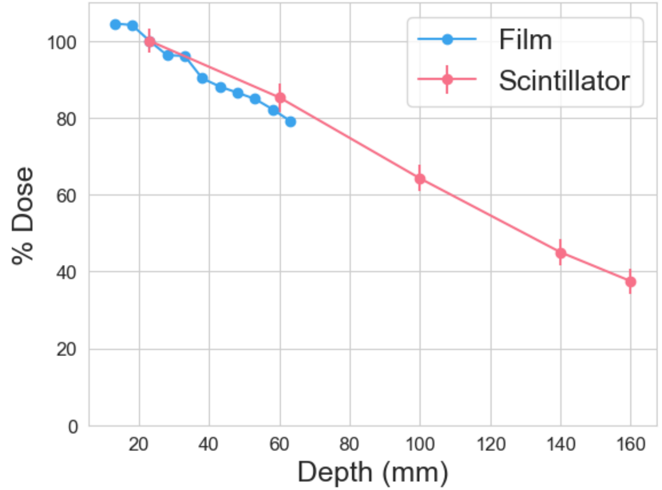
Experiment:
Measure the responses of the scintillator for different doses and water depths and compare them with the doses measured on films.



A. Hart & C. Giguère







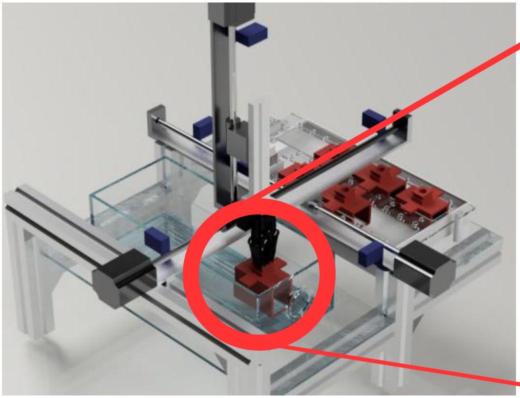
Published in IEEE Sensors Journal

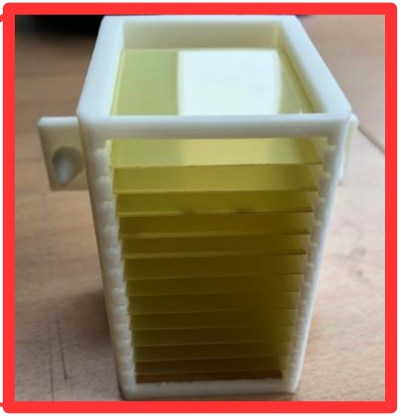
Selected Medical Applications performed at CLEAR in 2023:

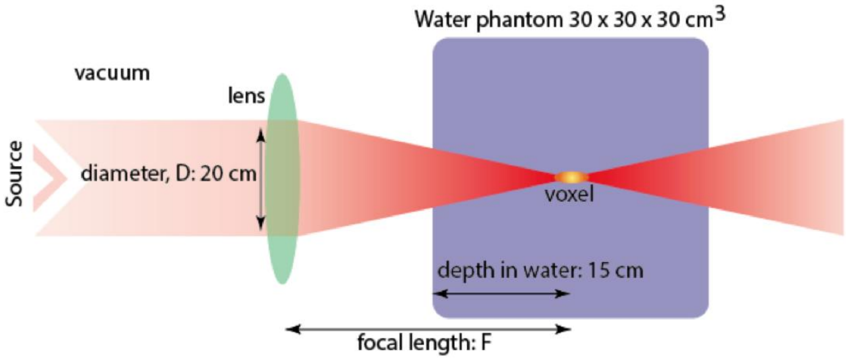
Irradiation Methods

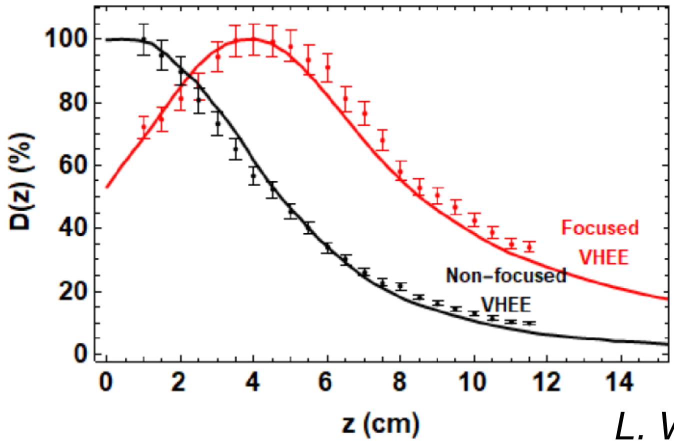
VHEE Strong Focusing

Goal:
Focus the beam on the tumor in order to minimize the dose and damage on the nearby healthy tissues.
Experiment:
Measure the beam sizes on a YAG screen in the water phantom (good model of the human body) and perform irradiations on long dosimetry films holders placed at different longitudinal positions.









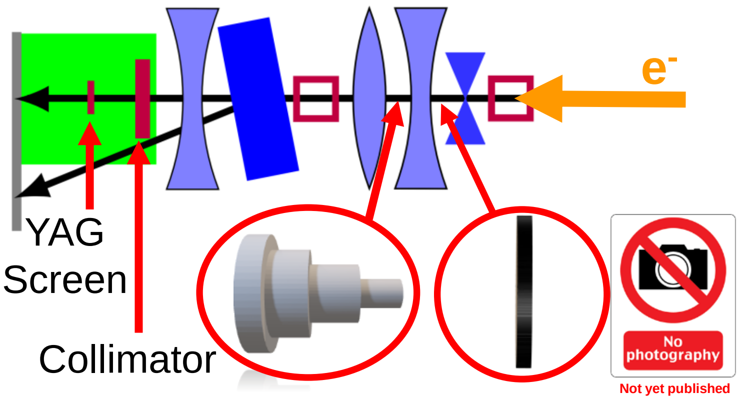
Paper under review

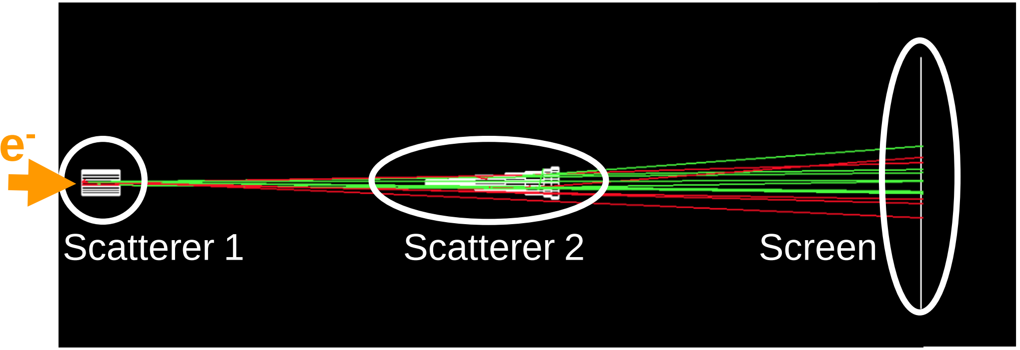
L. Whitmore

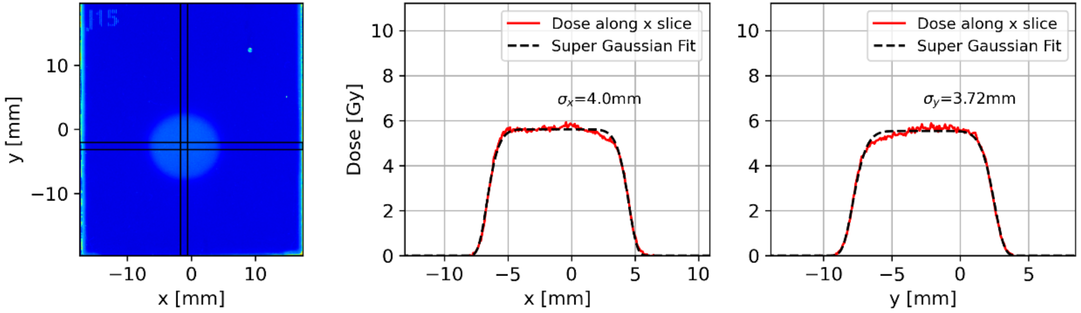
VHEE Scatterers

Goal:
Obtain a flat beam that has a constant transverse distribution at patient's tumor in order to minimize the dose and damage on the nearby healthy tissues.

Experiment:
Measure beam profiles, sizes and intensity on a YAG screen and films after carefully inserting two scatterers with the beam with the C-Robot.







X and Y beam profile

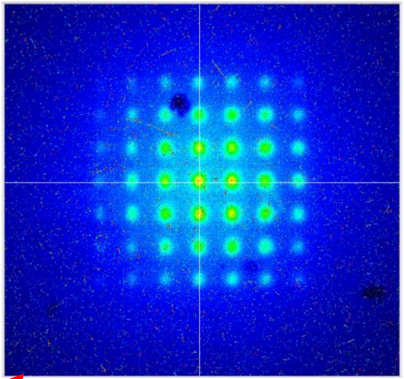
Now used by CLEAR Operation.

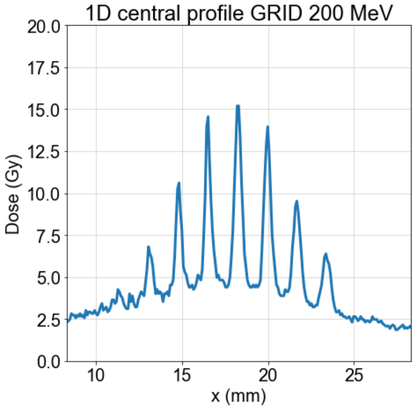
C. Robertson

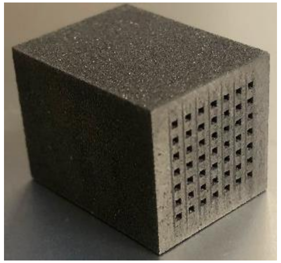
VHEE GRID

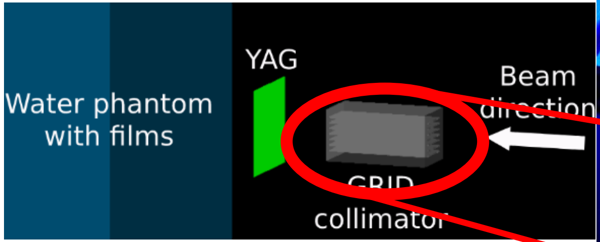
Goal:
Study the dose at UHDR for highly non-uniform dose distributions using a GRID Collimator (Spatially-fractionated RT, known for normal tissue sparing).
Experiment:
Compare the dose values and profiles with and without the GRID collimator inserted for different water depths, with the YAG screen and films.

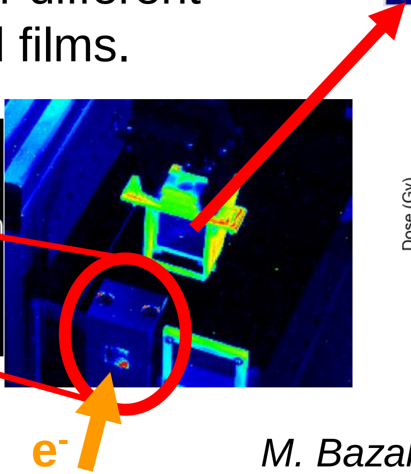
No photography
Paper under review

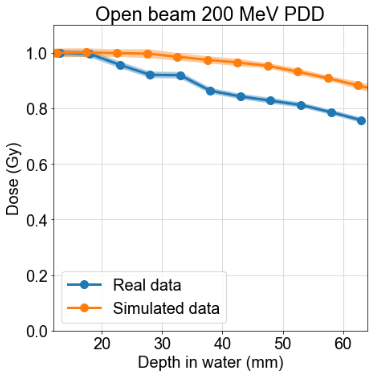


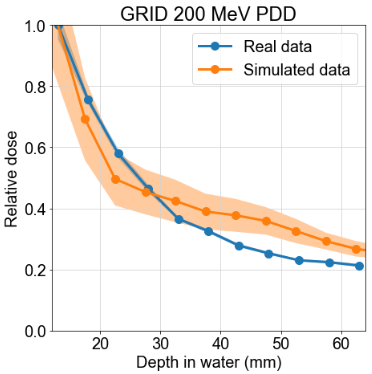












M. Bazalova-Carter, N. Clements, N. Esplen & A. Hart

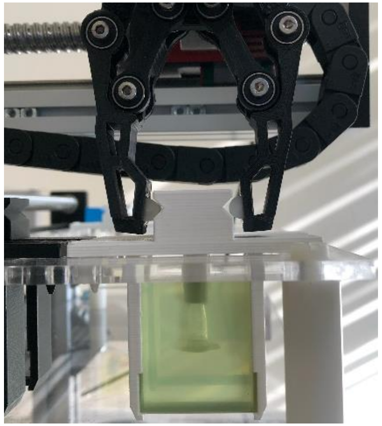
Selected Medical Applications performed at CLEAR in 2023:

Looking for the FLASH effect

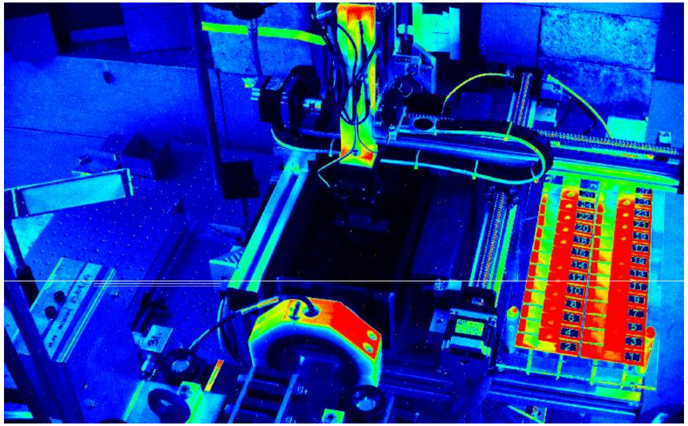
VHEE Chemistry Studies

Experiment:
Measure and compare the production of Reactive Oxygen Species (ROS) in water at Conventional Dose Rate (CDR) and Ultra High Dose Rate (UHDR).

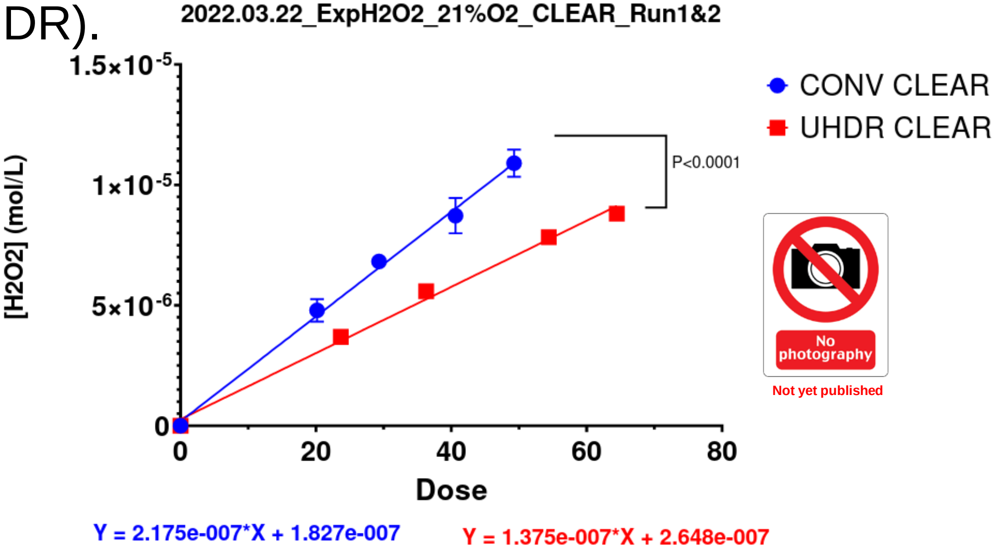
UHDR=1.2 10^9 Gy/s   CONV=0.15-0.41 Gy/s



Holder with films and Eppendorf tube



C-Robot view when performing irradiations for chemistry studies



M-C. Vozenin & H. Kacem

VHEE Plasmids irradiation

Goal:

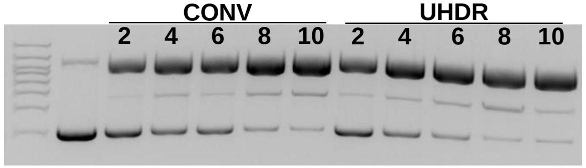
M-C Vozenin & L. Kunz

Measure the DNA damage with VHEE at UHDR and CDR.

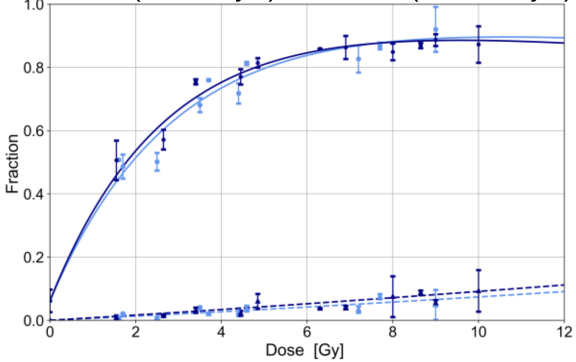
No photography

Not yet published

DNA damage in atmospheric condition (21% O_2)

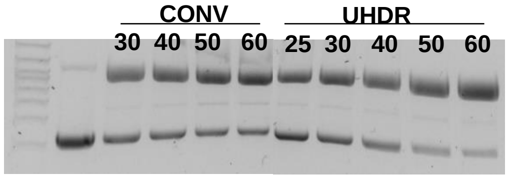


21% O2 – electron (CLEAR)
CONV ● (0.125 Gy/s) - UHDR ● (4.55E8 Gy/s)

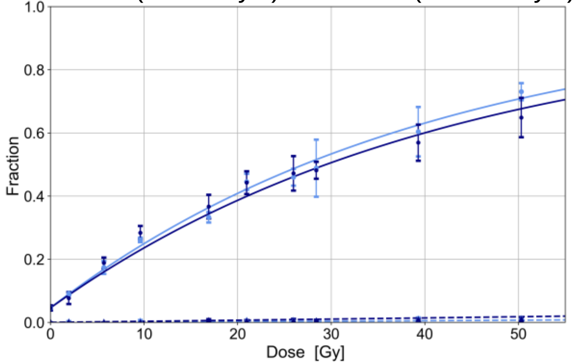


DNA damage pattern is Dose dependent <u>but</u> Dose-rate independent

DNA damage in the presence of scavengers (DMSO 14mM)

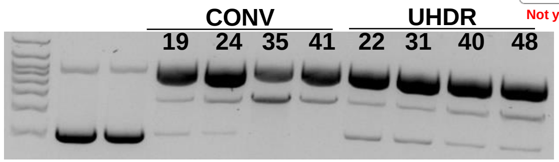


21%O2, DMSO 14mM – electron (CLEAR)
CONV ● (0.125 Gy/s) - UHDR ● (4.55E8 Gy/s)

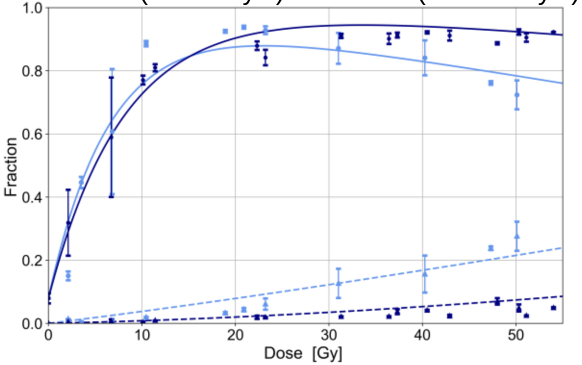


No difference on the DNA damage pattern at 21% oxygen

DNA damage in hypoxia (1% O2)



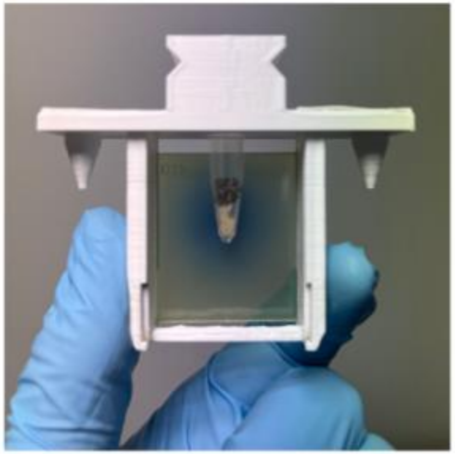
1% O2 – electron (CLEAR)
CONV ● (0.125 Gy/s) - UHDR ● (4.55E8 Gy/s)



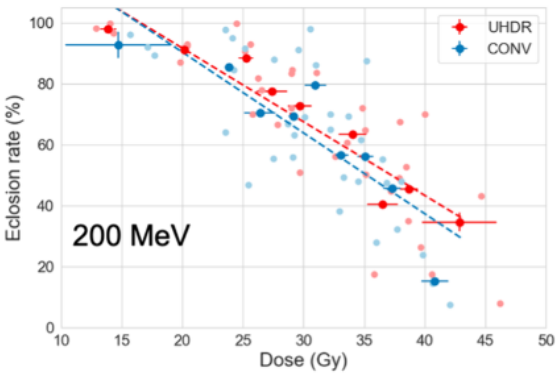
Low oxygen induces sparing effect at UHDR

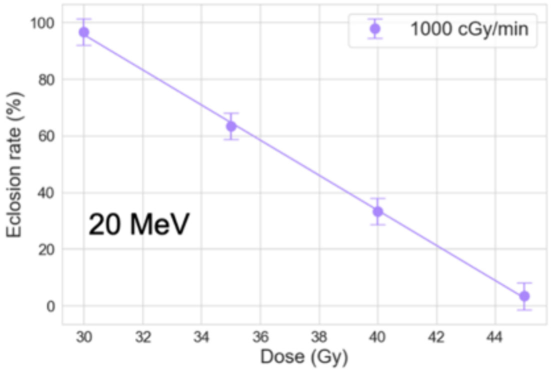
In vivo radiobiology at UHDR

Goal:
Compare the impact of 200 MeV VHEE irradiations at UHDR and CDR on *Drosophila melanogaster larvae*.
Experiment:
Deliver 15 to 45 Gy at UHDR and CDR to larvae with VHEE and measure the eclosion rate.



Preliminary results





Not yet published

A. Hart & T. Esmangart de Bournonville

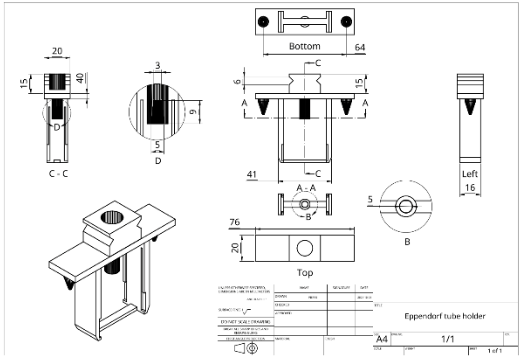
Biodosimeter Irradiations

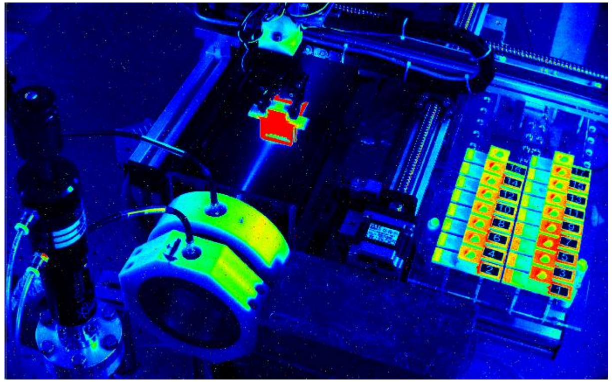
Goal :

Measure the response effect of the dose and the dose rate on biodosimeters with VHEE.

Experiment :

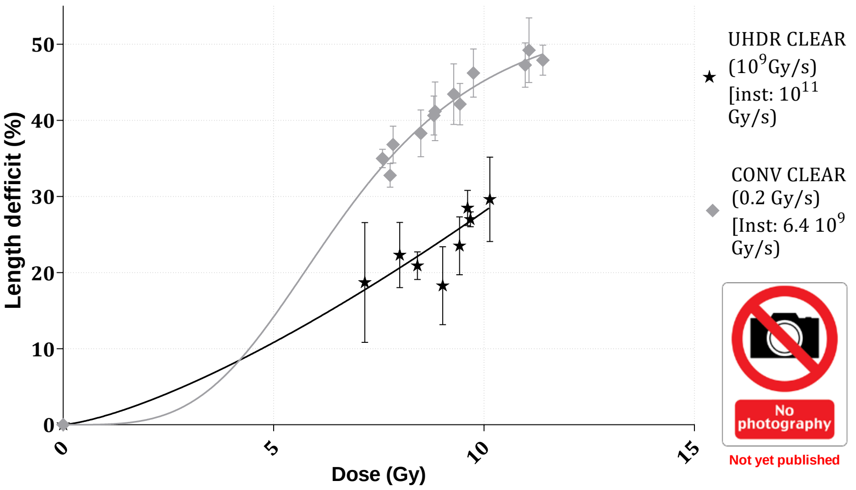
Irradiate biodosimeters with numerous doses and dose rates: UHDR (Ultra High Dose Rate) and CDR (Conventional Dose Rate) and measure the length defficit.





Preliminary results

% Deffect_ CERN-May-July2023_8,10 Gy_CONV-UHDR



M-C Vozenin & J. Ollivier

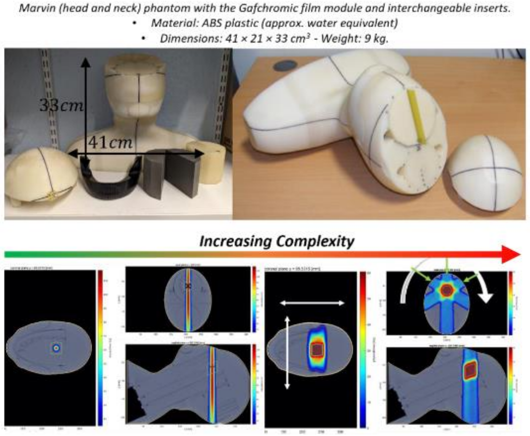
Selected Medical Applications planned at CLEAR in 2024:

Selected Medical Applications in 2024

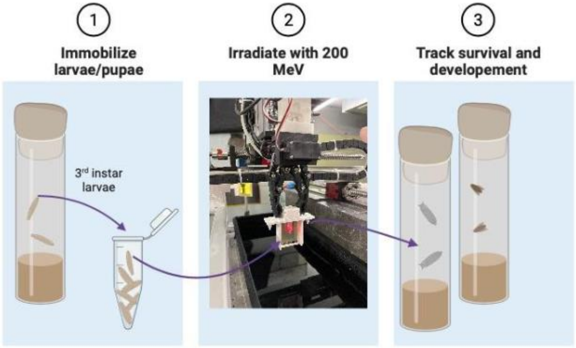
VHEE at UHDR Studies with Liposomes
VHEE at UHDR Studies with Biodosimeters
VHEE at UHDR Studies with Short Peptides & LCMS
VHEE at UHDR Studies with Cells

Goal: explore dose and dose rate parameters for both healthy and cancerous cells.

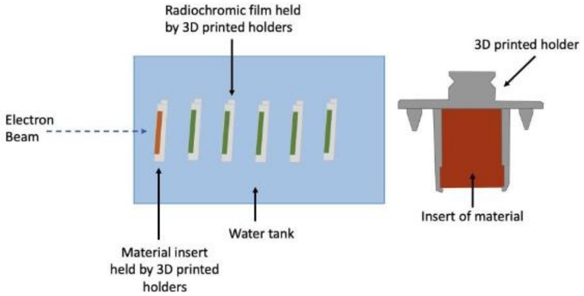
Plan Delivery to an Anatomical Phantom



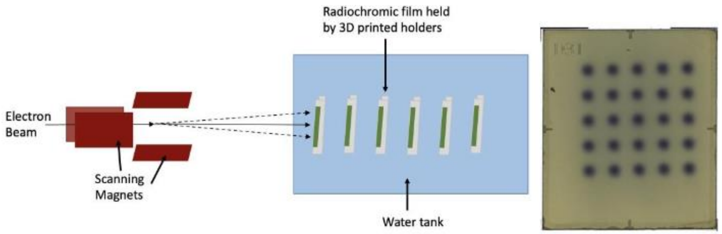
VHEE at UHDR Studies with Drosophilae



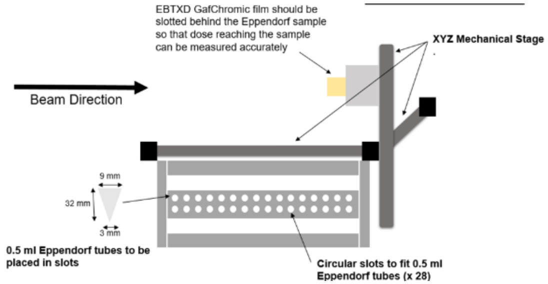
VHEE Material Irradiation Studies



Beam Scanning Spatially Fractionated RT Studies



Radio-enhancement effect of Nanoparticles in VHEE beams & Gold Nanoparticles Plasmid Studies



Directions for VHEE/FLASH Experiments

- Studying the impact of the **beam time structure** on the **FLASH effect** (average dose rate, instantaneous dose rate, etc.)
- Studying the **FLASH effect** on both **healthy** and **cancerous** cells (first experiment done on cancerous cells in Nov. 2023).
- Studying the **FLASH effect** on several **biodosimeters** (Zebra Fish Embryos & Drosophila Larvae).

Conclusions

- More and more **users** are studying the **FLASH effect, Irradiation Methods and Dosimetry** in CLEAR, leading to:
  - **14 weeks** of beam dedicated to **medical applications** in **2023.**
  - More than **10 conference proceedings** and **8 journal papers** (published or being reviewed) for medical applications, see the full list on: https://clear.cern/content/publications
  - **11 Medical Application Experiments** planned for **2024** (so far), see the full list on: https://pkorysko.web.cern.ch/CLEAR/Table/CLEAR_experiments_2024.html
  - A new robot, the **C-Robot 2.0**. 3 similar robots are being built in **Germany**, **Australia** and **China**.
  - **New beam** line with flexible optics, particularly suited for **medical applications**.
  - New collaborations with **HUG** and **Gustave Roussy**.

Thank you