Medical applications in CLEAR

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

CLEAR Review 2024

May 29th 2024

*pierre.korysko@cern.ch

Outline

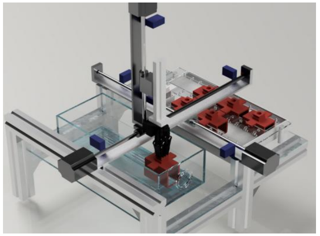
- Context: VHEE beams and the FLASH effect.
- Tools and Methods used.
- Selected Medical Applications performed at CLEAR in 2022/2023.
- Medical Applications planned at CLEAR in 2024/2025.
- Conclusions.

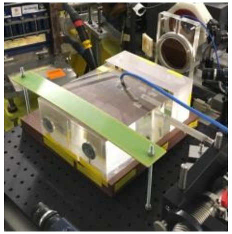
Very High Energy Electrons

Very High Energy Electrons

- The potential use of very high-energy electron (VHEE) beams (50-250 MeV) for Radio Therapy (RT) recently gained interest, since electrons at these energies can travel deep into the patient.
- Potential advantages of VHEE RT:
  - Depth – dose profile for electrons better than X-rays.
  - Charged particles can be focused and steered (not possible with X-rays) .
  - Electron beams rather unsensitive to tissue inhomogeneities .
  - Electron accelerators comparatively more compact, simpler and cheaper than proton/ion machines .
- This last advantage is now especially true given the recent advancements on high-gradient acceleration (e.g. X-band CLIC technology) .
- Ultra-high dose rate (above 100 Gy/s) radiation delivery, also known as FLASH RT, showed normal tissue sparing capabilities, without compromising tumor control.
  Most electron linacs can easily reach high beam currents needed for FLASH treatment of large fields.
- More and more existing electron linac facilities are now being intensively used to investigate VHEE/FLASH RT.

VHEE/FLASH RT studies at the CLEAR facility (CERN)



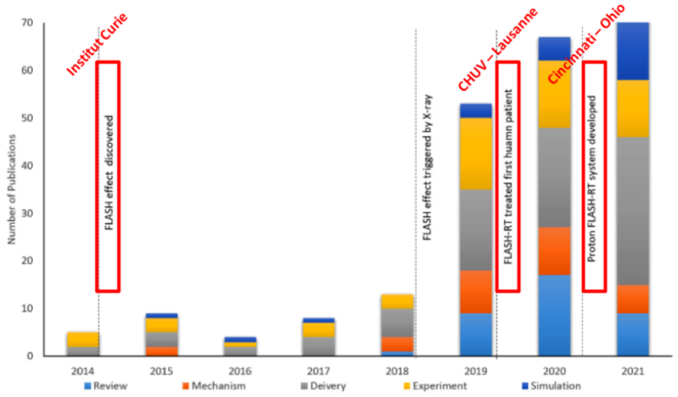


Facility	Applications
ARES	Accel. components, Diagnostics R&D Medical: VHEE RT, Electron CT Acceleration: ACHIP [29]
CLARA	Accel. components, Diagnostics R&D Medical: VHEE RT Acceleration: DWA, (P/L)WFA, THz
CLEAR	High gradient acceleration, plasma lens Radiation damage, Diagnostics R&D Medical: VHEE & FLASH RT
FLUTE	Diagnostics R&D, THz Experiments Medical: FLASH RT, Detectors Machine Learning
PITZ	Min. beam emittance developments THz source development Medical: FLASH RT & dosimetry
SPARC_LAB	Acceleration: PWFA, LWFA Radiation sources: FEL, THz, betatron

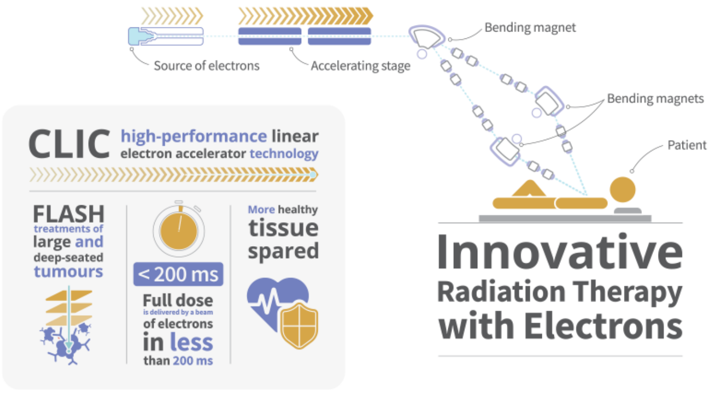
The FLASH Effect

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.

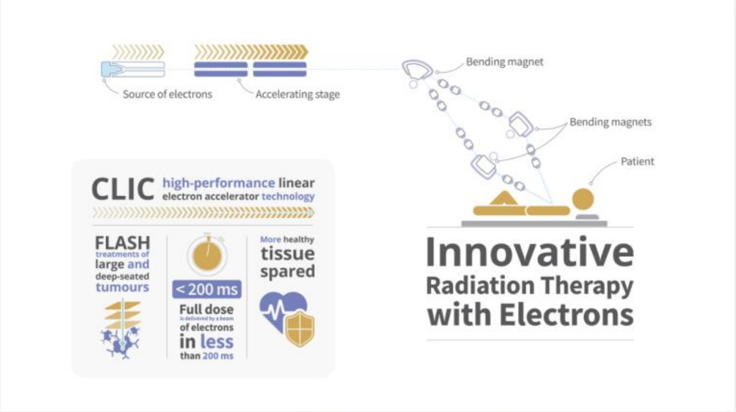
Conclusions: This first FLASH-RT treatment was feasible and safe with a favorable outcome both on normal skin and the tumor.

CERN/CHUV/THERYQ Collaboration

CERN, CHUV and THERYQ join forces for a world first in cancer radiotherapy

CERN, CHUV and THERYQ have signed an agreement for the development of a revolutionary FLASH radiotherapy device

25 NOVEMBER, 2022



https://home.cern/news/news/knowledge-sharing/cern-chuv-and-theryq-join-forces-world-first-cancer-radiotherapy

CHUV, CERN and now THERYQ are actively collaborating on the realization of a clinical facility for the treatment of large, deep-seated tumors by a VHEE beam in FLASH conditions.

The target is a facility that:

- Uses 100 MeV-range electrons and optimized dose delivery.
- Is compact enough to fit on a typical hospital campus.

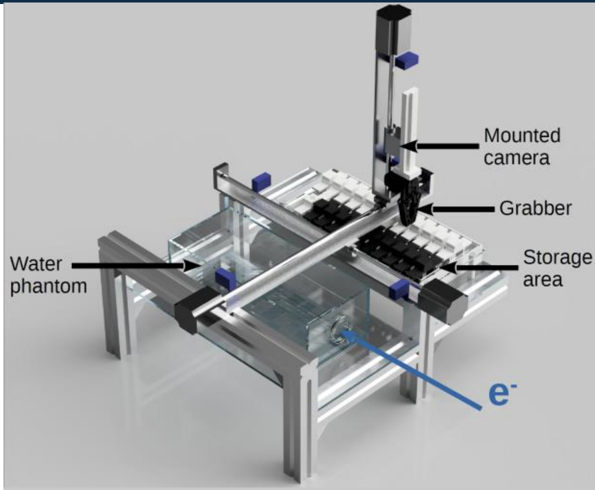
The collaboration demonstrated that the facility is feasible and are now finalizing the details of its technical implementation aiming at first clinical tests in 1-2 years.

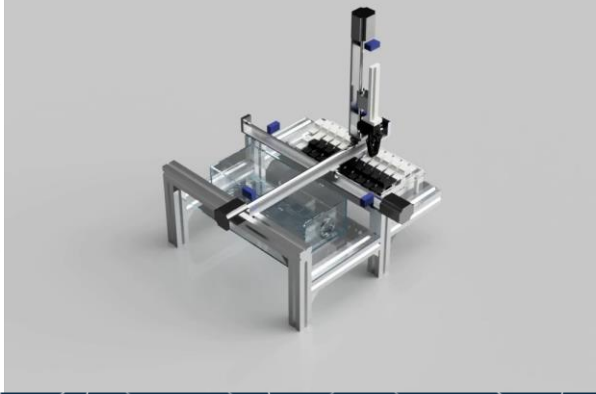
If successful, the facility may open the way for many future VHEE/FLASH facilities.

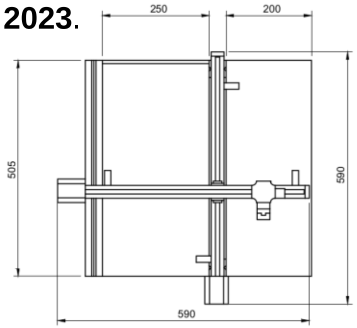
CLEAR
Tools and Methods

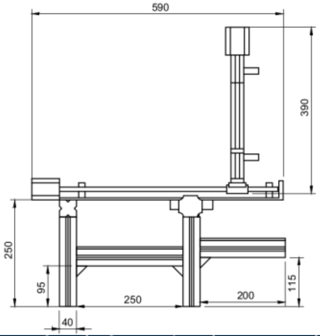
The C-Robot

- 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**.



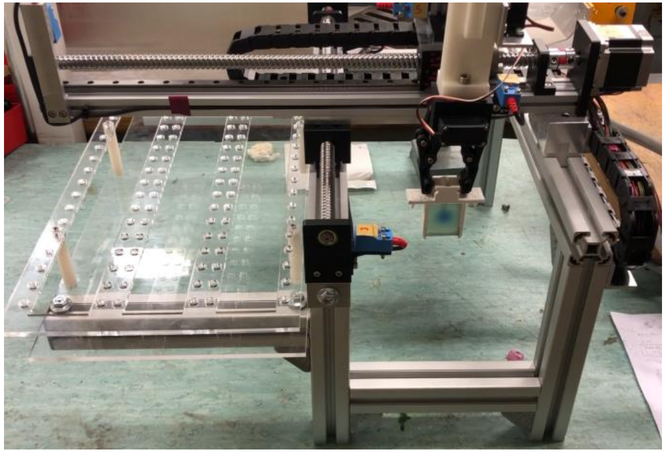


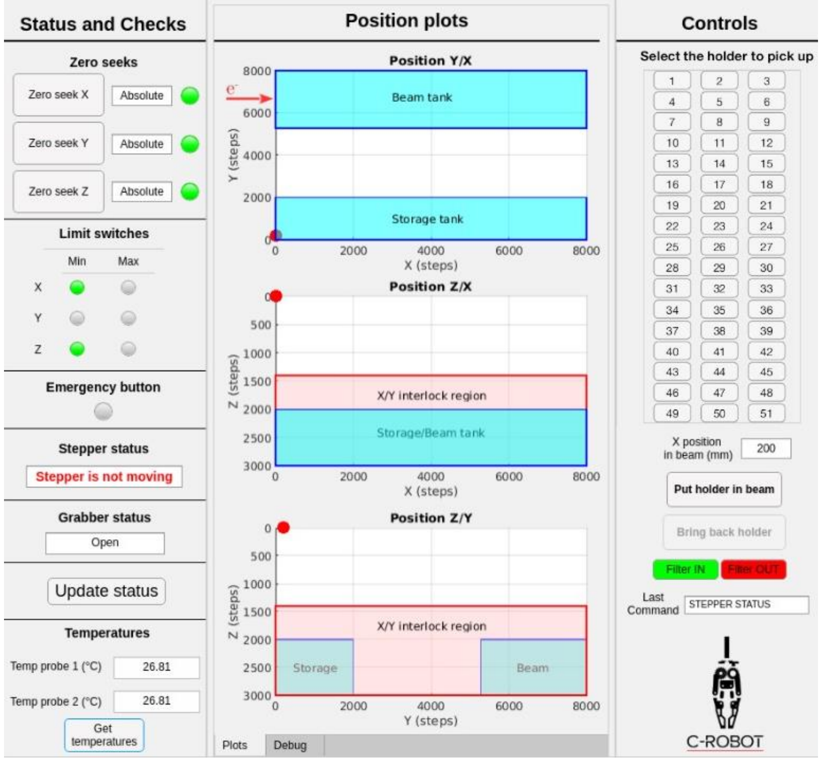




The C-Robot 2.0

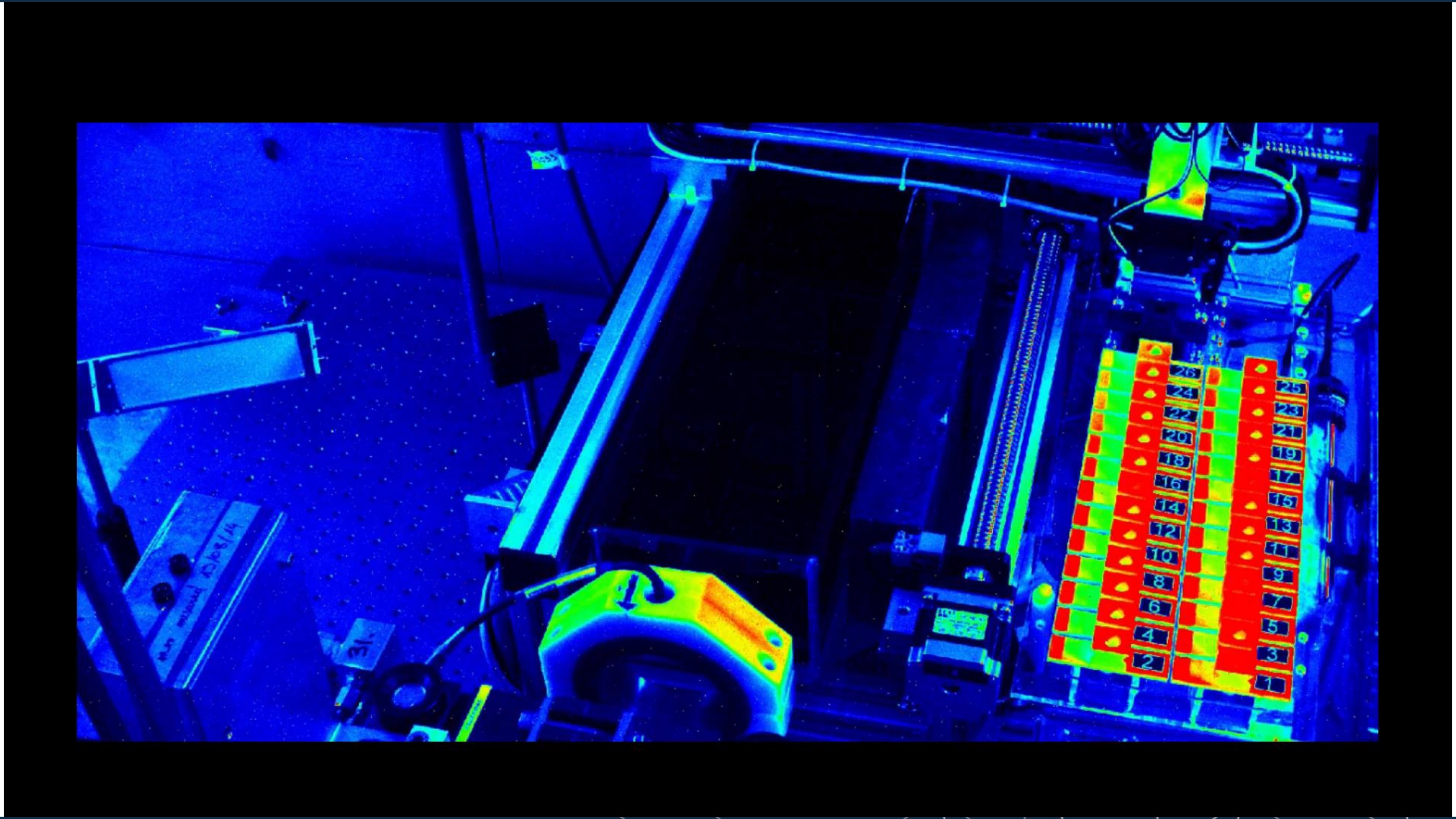
- A new robot was built for the **new CLEAR beamline**:
  - **Mirrored**, to adapt to the new in-air test area.
  - **51** available **slots**.
  - With **temperature probes**, **mounted camera**, **optical filters**.
  - This robot was sent to PITZ (DESY Berlin) for them to build a copy.





I. Najmudin

The C-Robot in action with beam

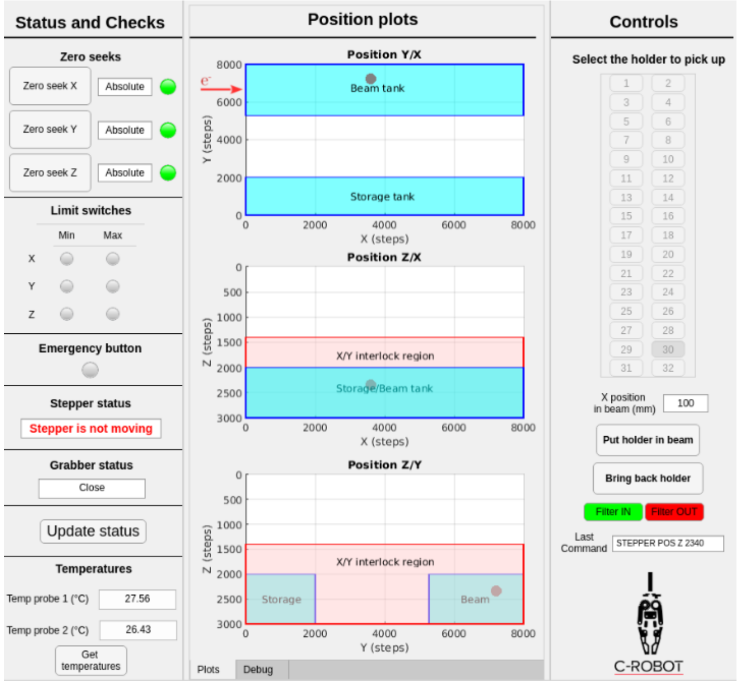


Selected Medical Applications performed at CLEAR in 2023:

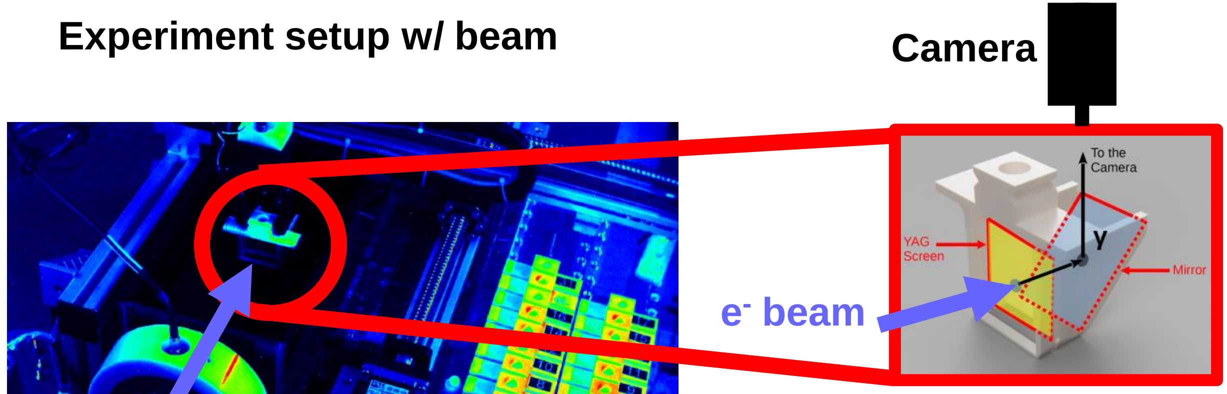
Dosimetry Studies

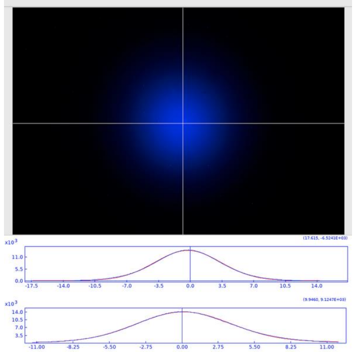
What can the C-Robot do?

Graphical User Interface

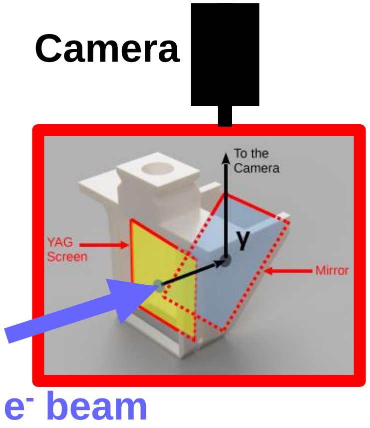


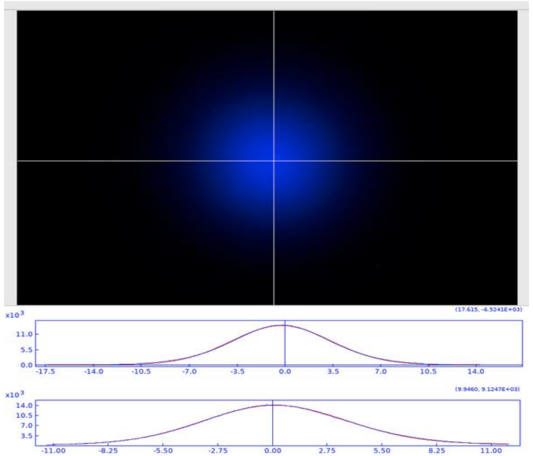
Experiment setup w/ beam



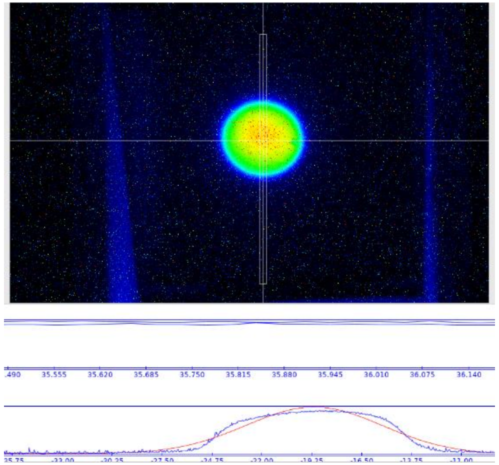


Real-Time Dosimetry

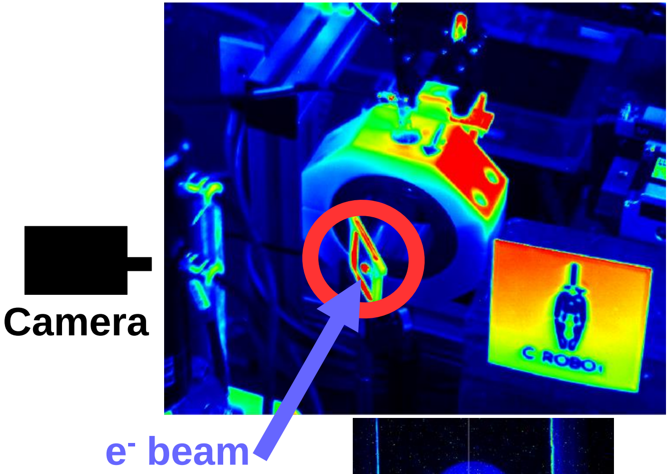


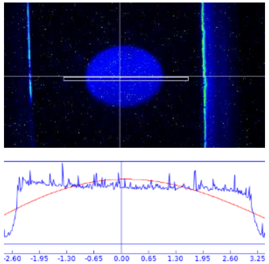


Gaussian Beam



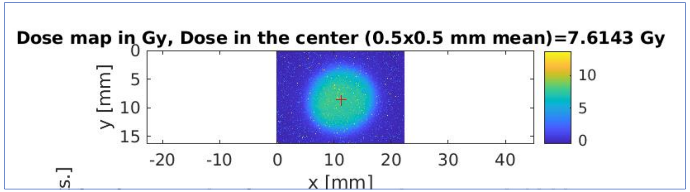
Uniform Beam





- 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.

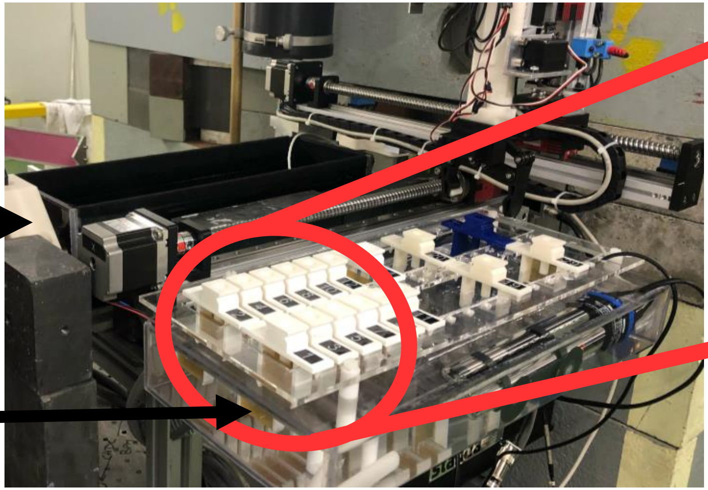


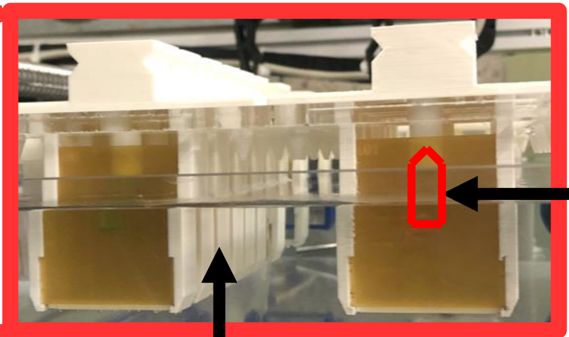
Experimental Setup & Dosimetry for VHEE at UHDR irradiations

V. Rieker

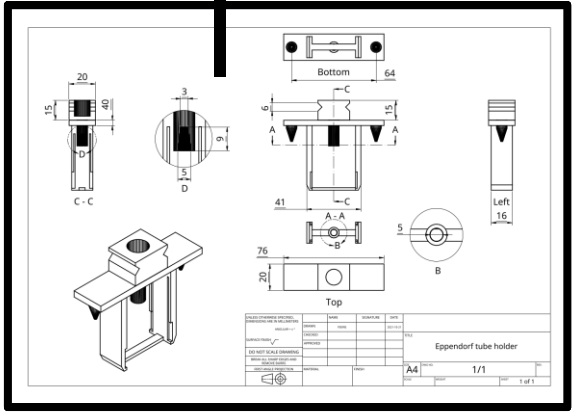
Beam water tank

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

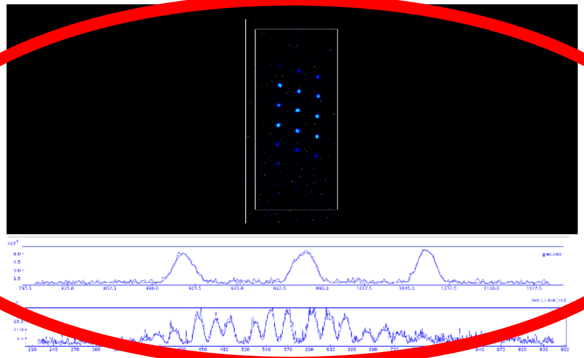
After irradiation

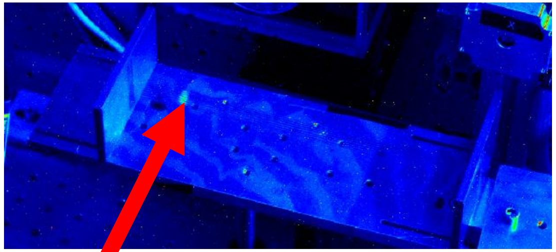
This is the **passive** standard way to measure the delivered dose, but **real-time** dosimetry is crucial for clinical treatments.

Optical Fibre Dosimetry

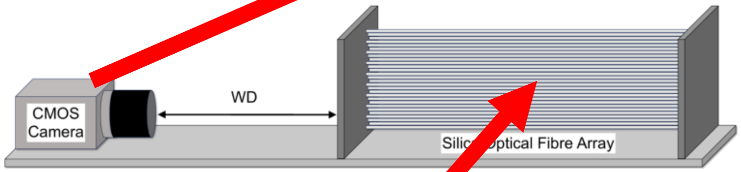
Goal :
Measure in real time the doses delivered by VHEE at UHDR and CDR with two arrays of optical fibers.

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

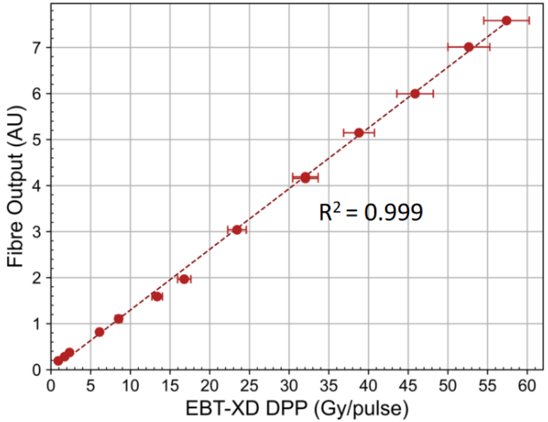




e^-



e^-

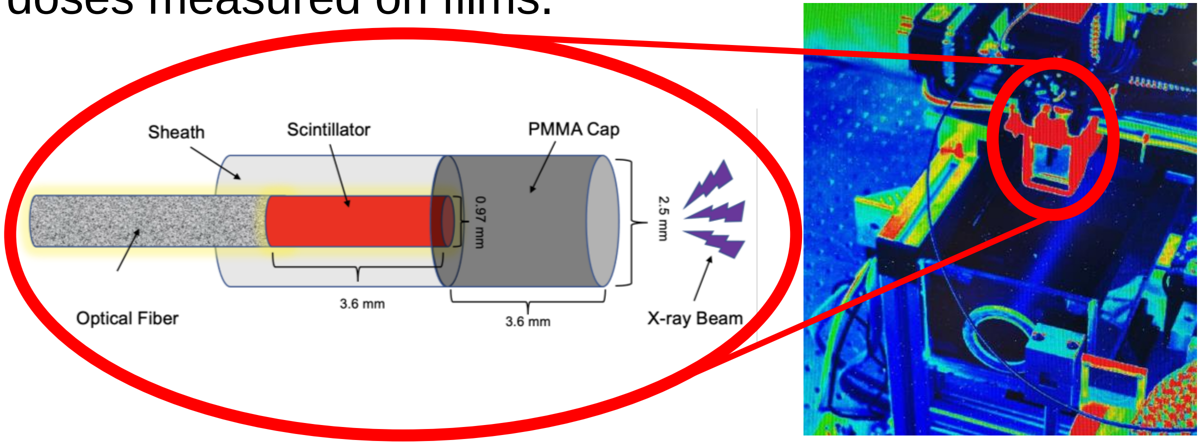


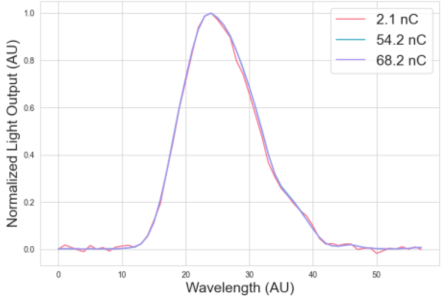
Published in [Physics in Medicine & Biology]   *J. Bateman*

Scintillator Dosimetry

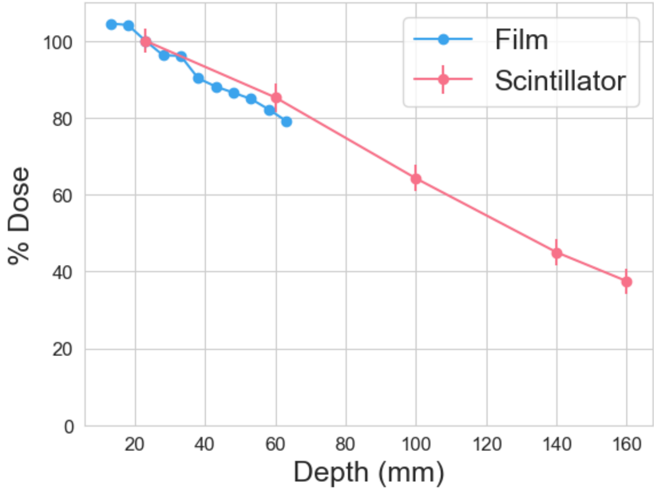
Goal:
Measure the dose at UHDR with a real-time readout and a high spatial resolution thanks to a scintillator and an optical fiber.

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



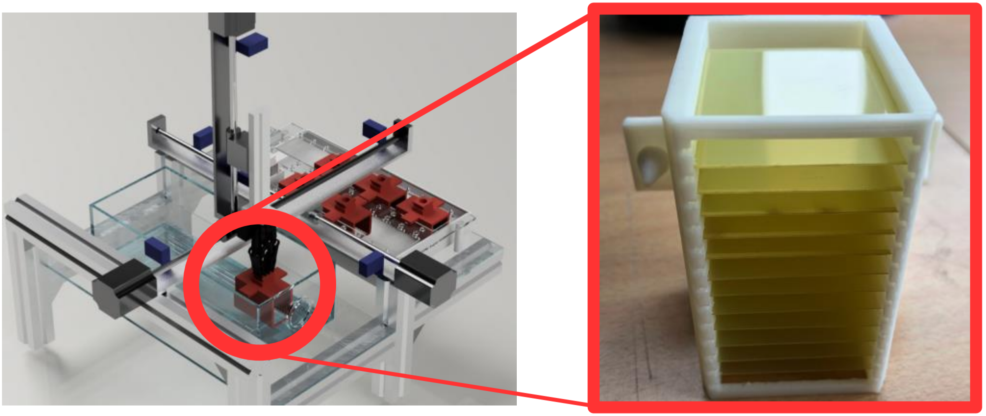
Published in IEEE Sensors Journal

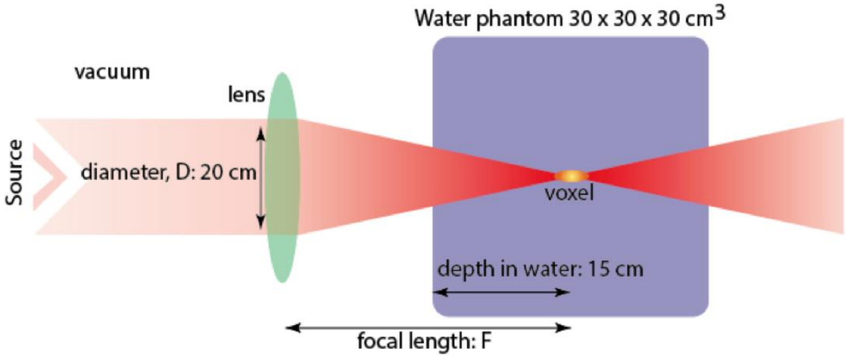
Selected Medical Applications performed at CLEAR in 2023:

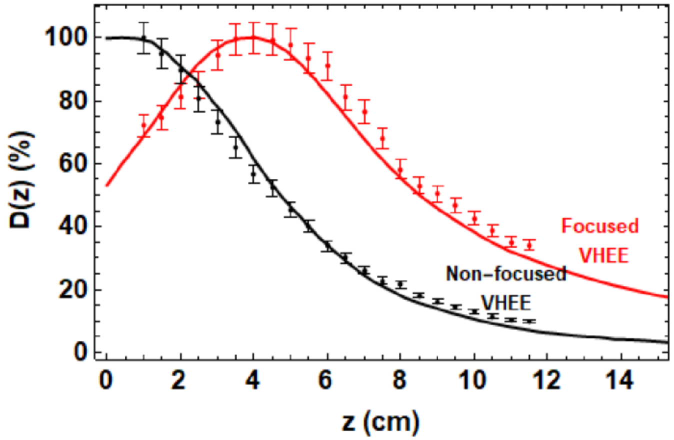
Irradiation Methods

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.





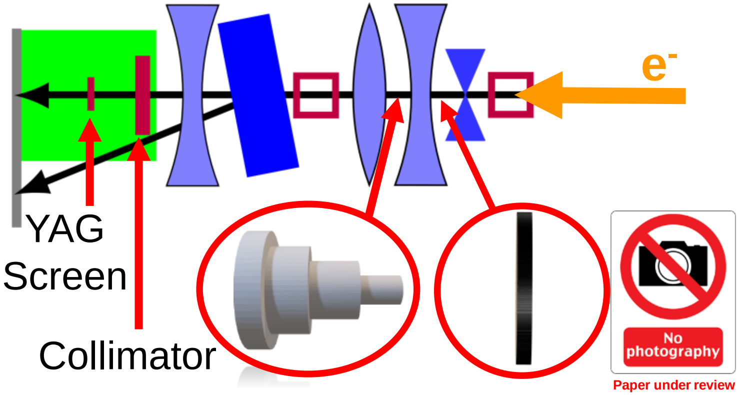


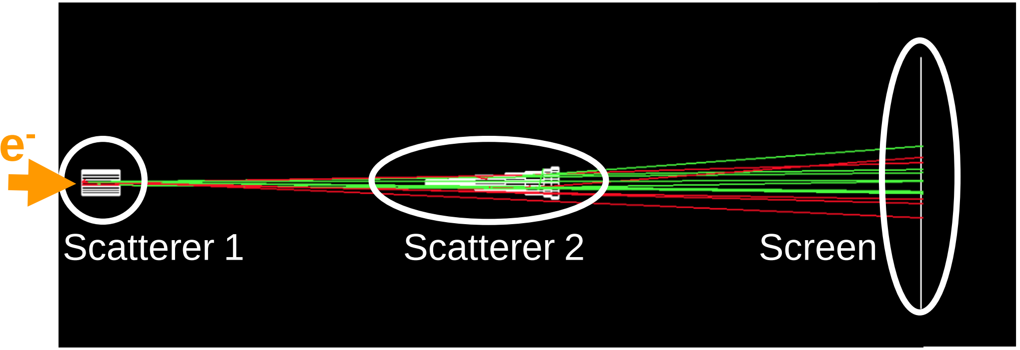
Published in [Nature Scientific Reports]

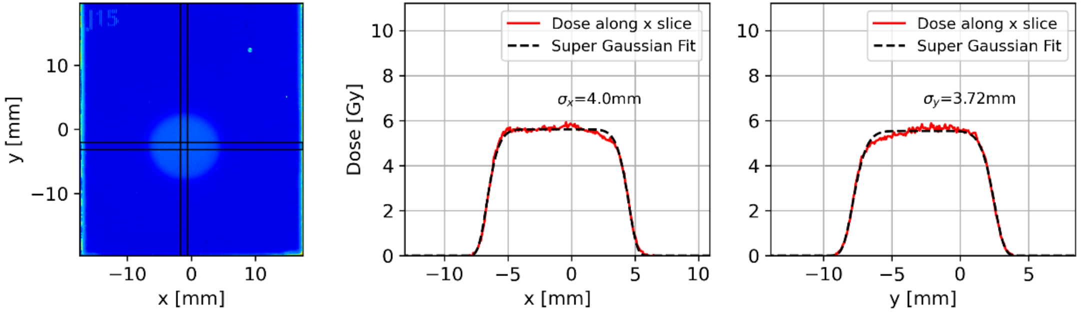
L. Whitmore

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

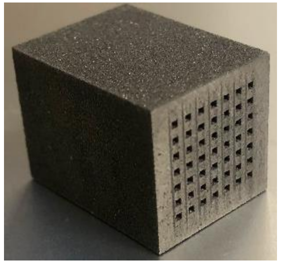
Now used by CLEAR Operation.

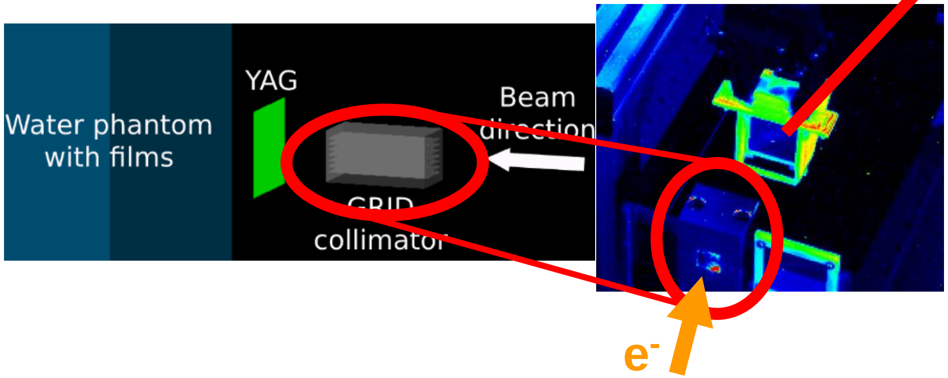
C. Robertson

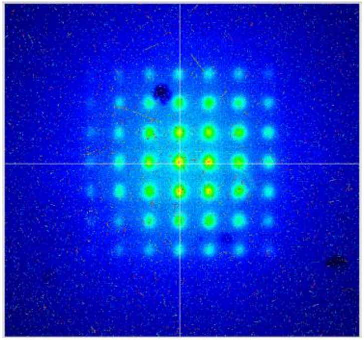
VHEE GRID

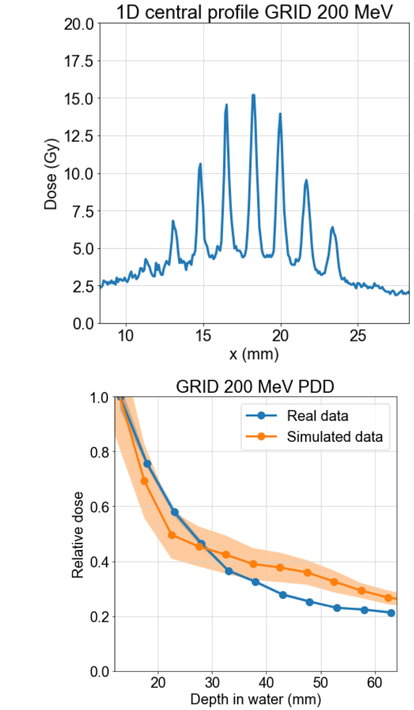
M. Bazalova-Carter, N. Clements, N. Esplen & A. Hart

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.









Published in [Physics in Medicine & Biology]

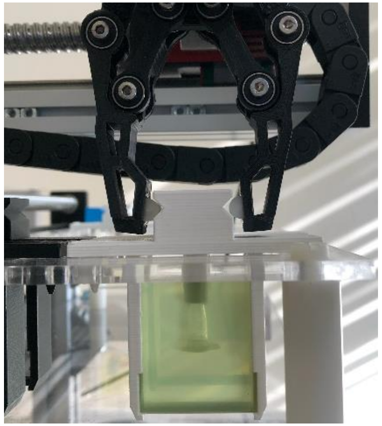
Selected Medical Applications performed at CLEAR in 2023:

Looking for the FLASH effect

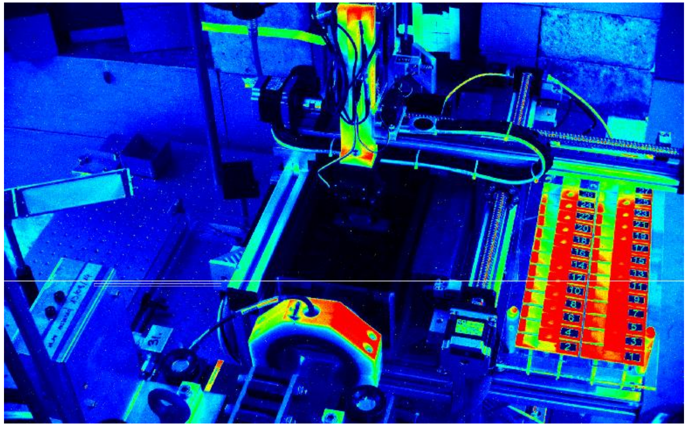
VHEE Chemistry Studies

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

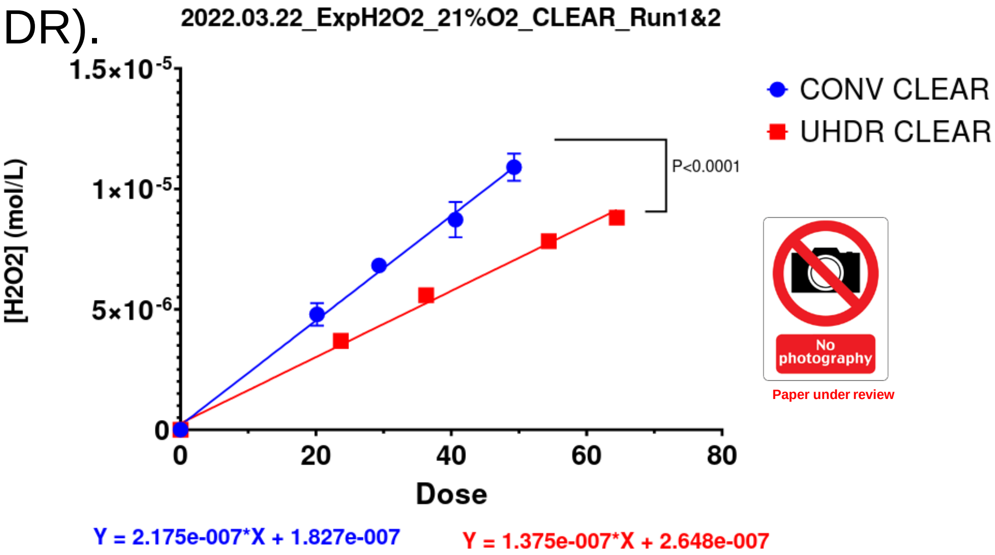
UHDR=1.2 10^9 Gy/s   CONV=0.15-0.41 Gy/s



Holder with films and Eppendorf tube



C-Robot view when performing irradiations for chemistry studies

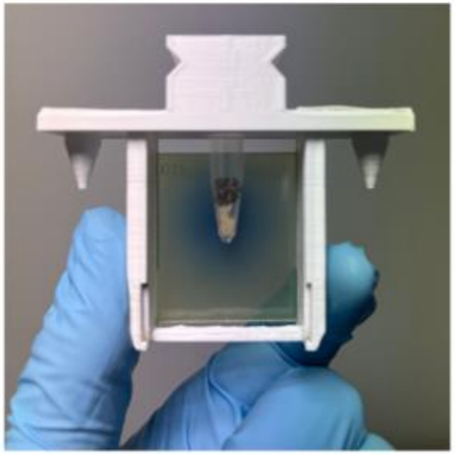


M-C. Vozenin & H. Kacem

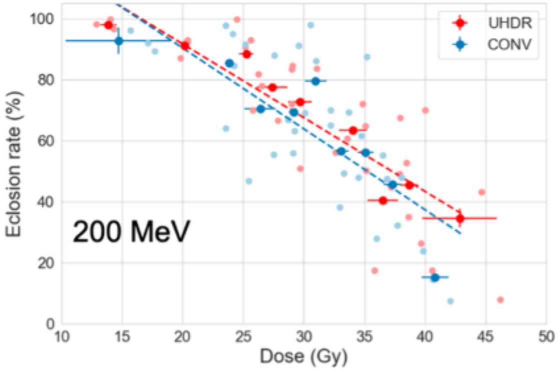
In vivo radiobiology at UHDR

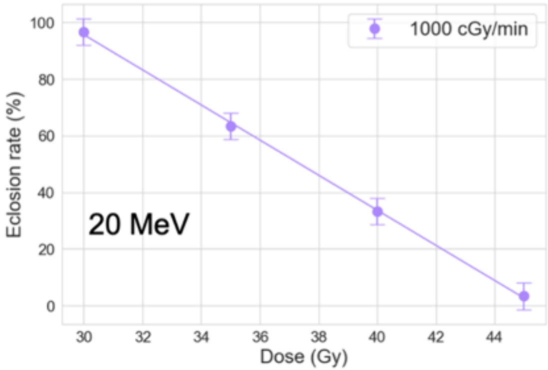
Goal:
Compare the impact of 200 MeV VHEE irradiations at UHDR and CDR on *Drosophila melanogaster larvae*.

Experiment:
Deliver 15 to 45 Gy at UHDR and CDR to larvae with VHEE and measure the eclosion rate.



Preliminary results





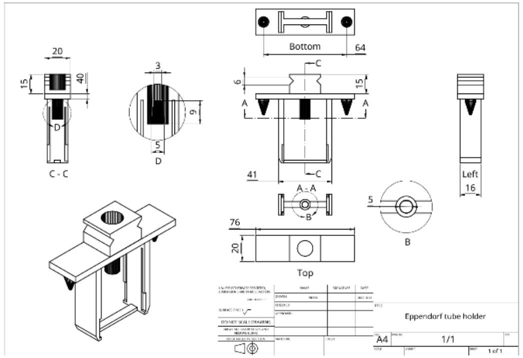
Not yet published

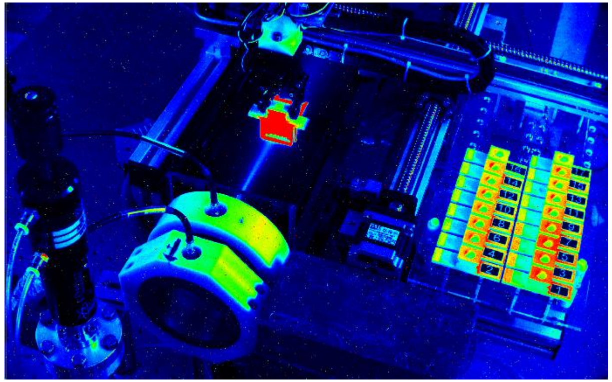
A. Hart & T. Esmangart de Bournonville

Biodosimeter Irradiations

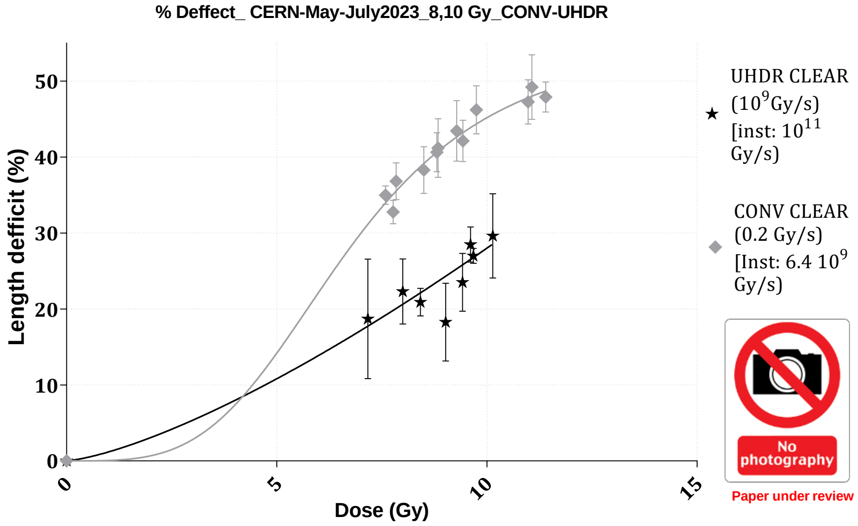
Goal :
Measure the response effect of the dose and the dose rate on biodosimeters with VHEE.

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



Paper under review

M-C Vozenin & J. Ollivier

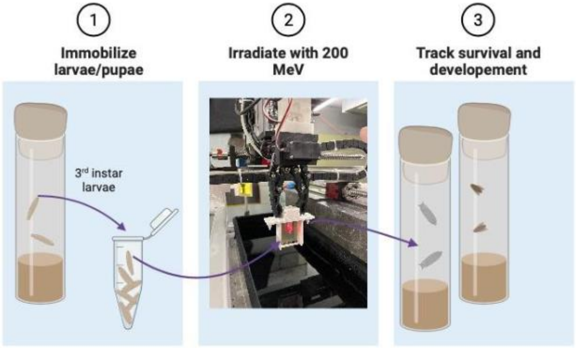
Selected Medical Applications planned at CLEAR in 2024:

Selected Medical Applications in 2024

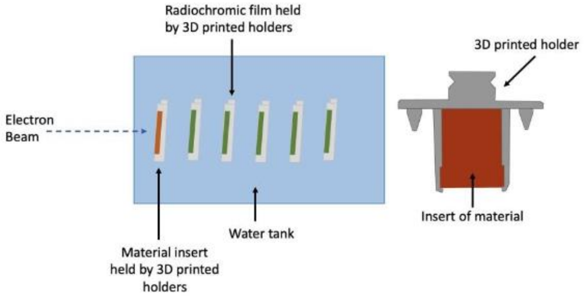
VHEE at UHDR Studies with Liposomes
VHEE at UHDR Studies with Biodosimeters
VHEE at UHDR Studies with Short Peptides & LCMS
VHEE at UHDR Studies with Cells

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

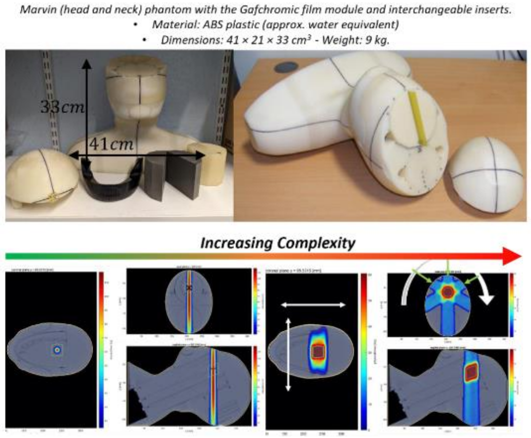
VHEE at UHDR Studies with Drosophilae



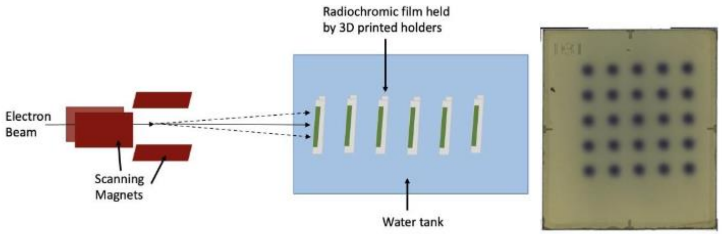
VHEE Material Irradiation Studies



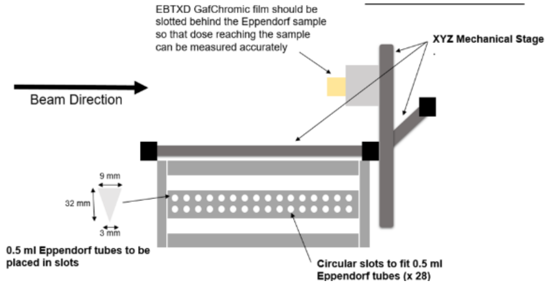
Plan Delivery to an Anatomical Phantom



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).

Comments from the CLEAR Scientfic Board

Finding 3: CLEAR is a unique facility for addressing the FLASH effect in radiotherapy with VHEE, which has brought an increase in requests in this field. The selection of experiments in 2023 (and those proposed for 2024) are strategically chosen to help progress studies of the FLASH effect towards clinical use. The new tools, C-Robot v2 and the new beamline with flexible optics, which will become available in 2025, demonstrate the degree of effort put into the facility to better serve the medical user community.

Medical applications are notably important and prominent. The next four to five years are crucial for fully establishing VHEE/FLASH therapy techniques, covering fundamental studies, time structure dependence, and optimization of parameters, as well as its supporting technologies, including beam delivery, dosimetry, and beam control. If extended, CLEAR will uniquely serve the VHEE/FLASH community for a number of years, playing a pivotal role in the field, including facilitating knowledge transfer to other laboratories equipped for animal testing.

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 **12 conference proceedings** and **9 journal papers** (published or being reviewed) for medical applications, see the full list on: https://clear.cern/content/publications
  - **13 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 was built**. 3 similar robots are being built in **Germany** (PITZ), **Australia (**Australian Synchrotron) and **China** (IHEP)**.**
  - **New beam** line with flexible optics, particularly suited for **medical applications**.
  - New collaborations in 2024 with **HUG** and **Gustave Roussy**.

Thank you