ARIES

2nd Annual Meeting

New e- linac therapies and accelerator designs

Dr. A. Faus-Golfe

LABORATOIRE DE L'ACCÉLÉRATEUR LINÉAIRE

OUTLINE

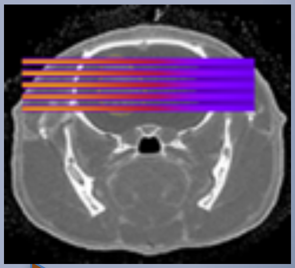
- ➢ *The Challenges of Radiotherapy*
  - ➢ *New RT approaches*
- ➢ *VHEE therapy*
  - ➢ *State of the art*
  - ➢ *Milestones*
  - ➢ *New delivery doses modalities*
    - ➢ *Grid mini-beams*
    - ➢ *FLASH*
- ➢ *Accelerators for VHEEE: linacs*
  - ➢ *Low-energy e^-*
  - ➢ *High-energy e^-*
- ➢ *Summary and Future perspectives*

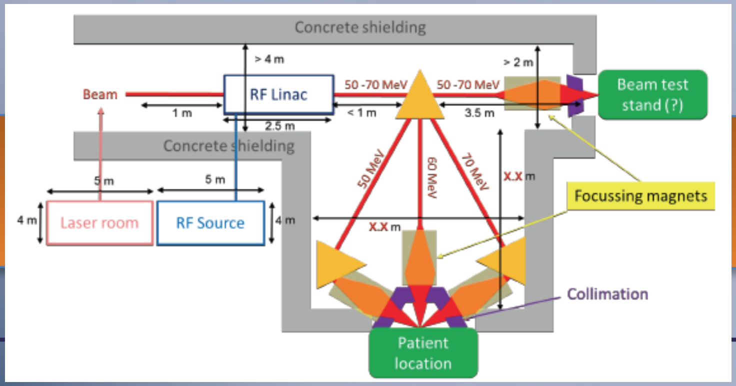
CHALLENGES IN RADIOTHERAPY

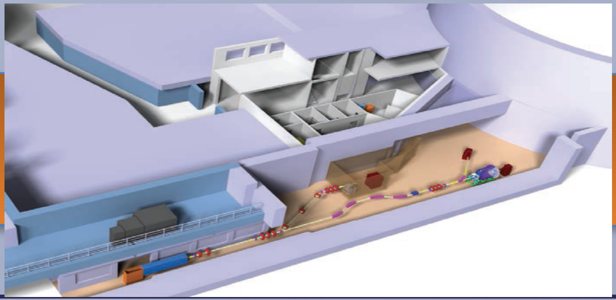
New RT approaches

- *RT treatment of some radio resistant tumours, paediatric cancers and tumours close to a delicate structure (i.e. spinal cord) is currently limited*
- One of the main challenges is to find approaches to increase the normal tissue resistance
- Standard RT is restricted to the few temporal and spatial schemes, dose rates, broad field sizes: mainly photons, 2 Gy/session, 1 session/day, 5 days/week, dose rates ~ 2 Gy/min, field sizes > cm^2, homogeneous dose distributions

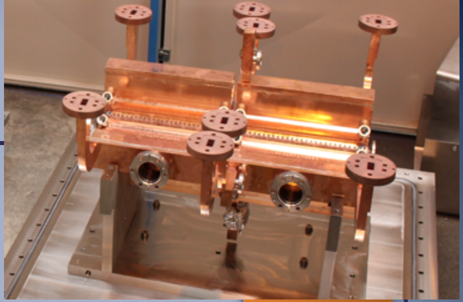
- *Possible strategies to spare normal tissue*
- Different particle types: Very High Energy Electrons (VHEE)
- Different dose delivery methods: Grid Mini-beam or FLASH RT





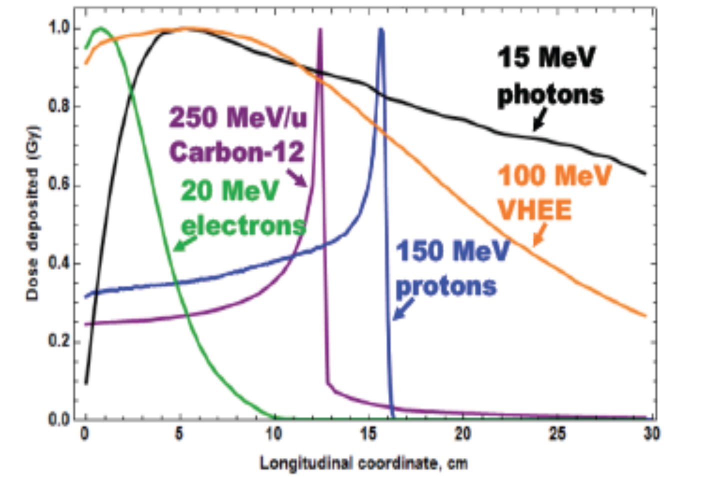


VHEE THERAPY

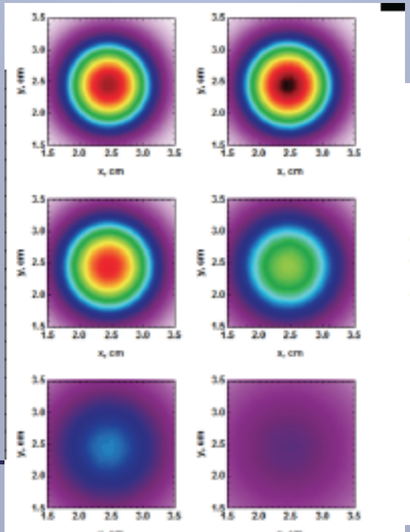


State of the Art

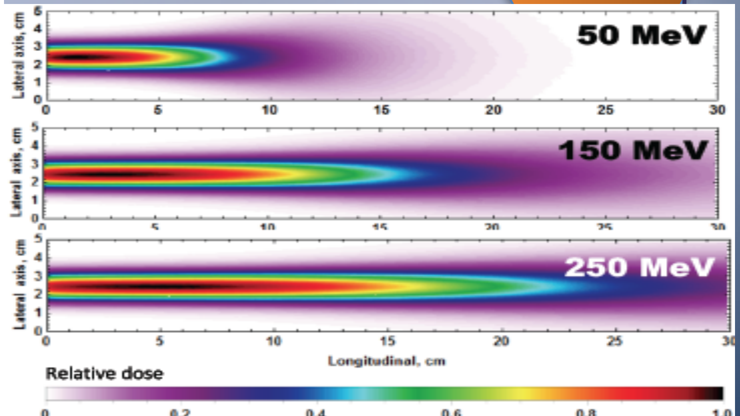
- With recent High-Gradient linac technology developments, Very High Energy Electrons (VHEE) in the range 100–250 MeV offer the promise to be a cost-effective option in anticancer RT and open up innovative treatment modalities (Grid mini-beam, FLASH,..)
- Their ballistic and dosimetric properties can surpass those of photons, which are currently the most commonly used in RT
- Their position compared to protons need to be evaluated, but they can be produced at a reduced cost



Dose profiles for various particle beams in water (beam widths $r = 0.5$ cm)



Transverse dose maps at 0.5 – 25 cm depths

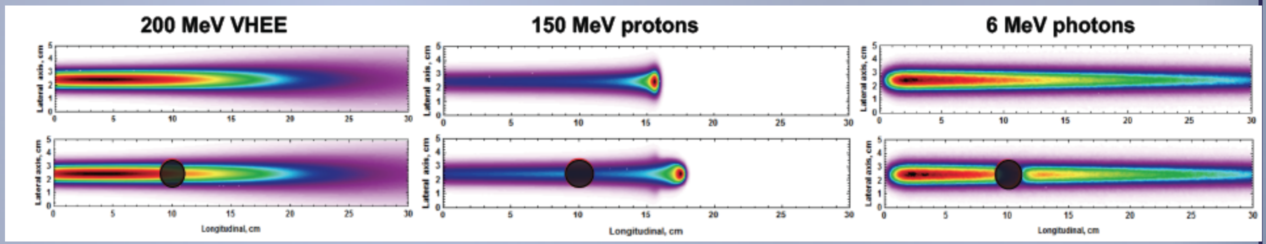


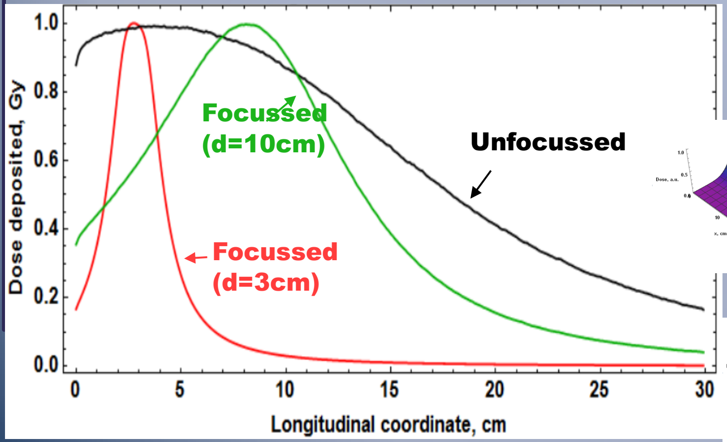
Dose maps of 50, 150 and 250 MeV VHEE beams in water

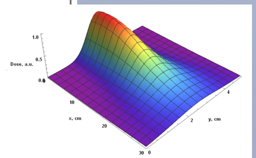
VHEE THERAPY

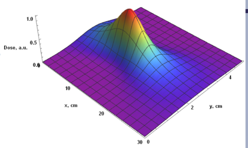
State of the Art

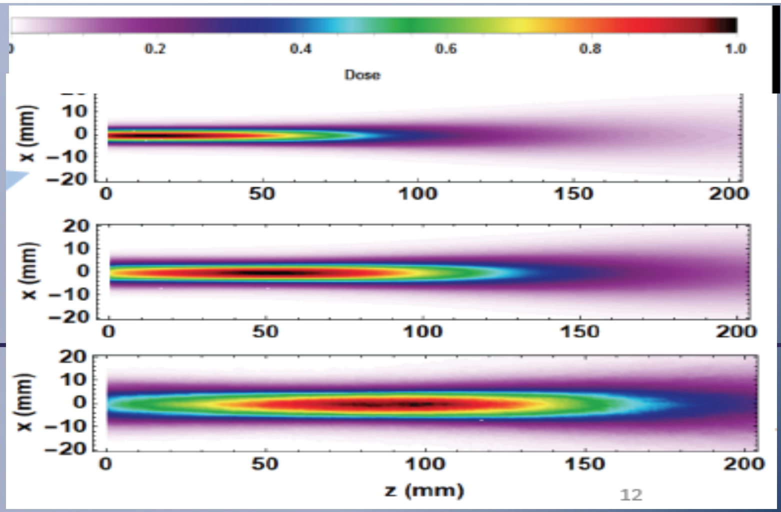
- ***Pros***
  - + Conformity ?
  - + Decrease of the integral dose rate
  - + High-dose rate
  - + Scanned beams
  - + Compact,Cheap
  - + Focused
  - +...
- ***Cons***
  - - Skin dose ?
  - - Bone dose ?
  - - Penumbra?
  - - Effect of inhomogeneities?
  - - Neutrons ?
  - -.....







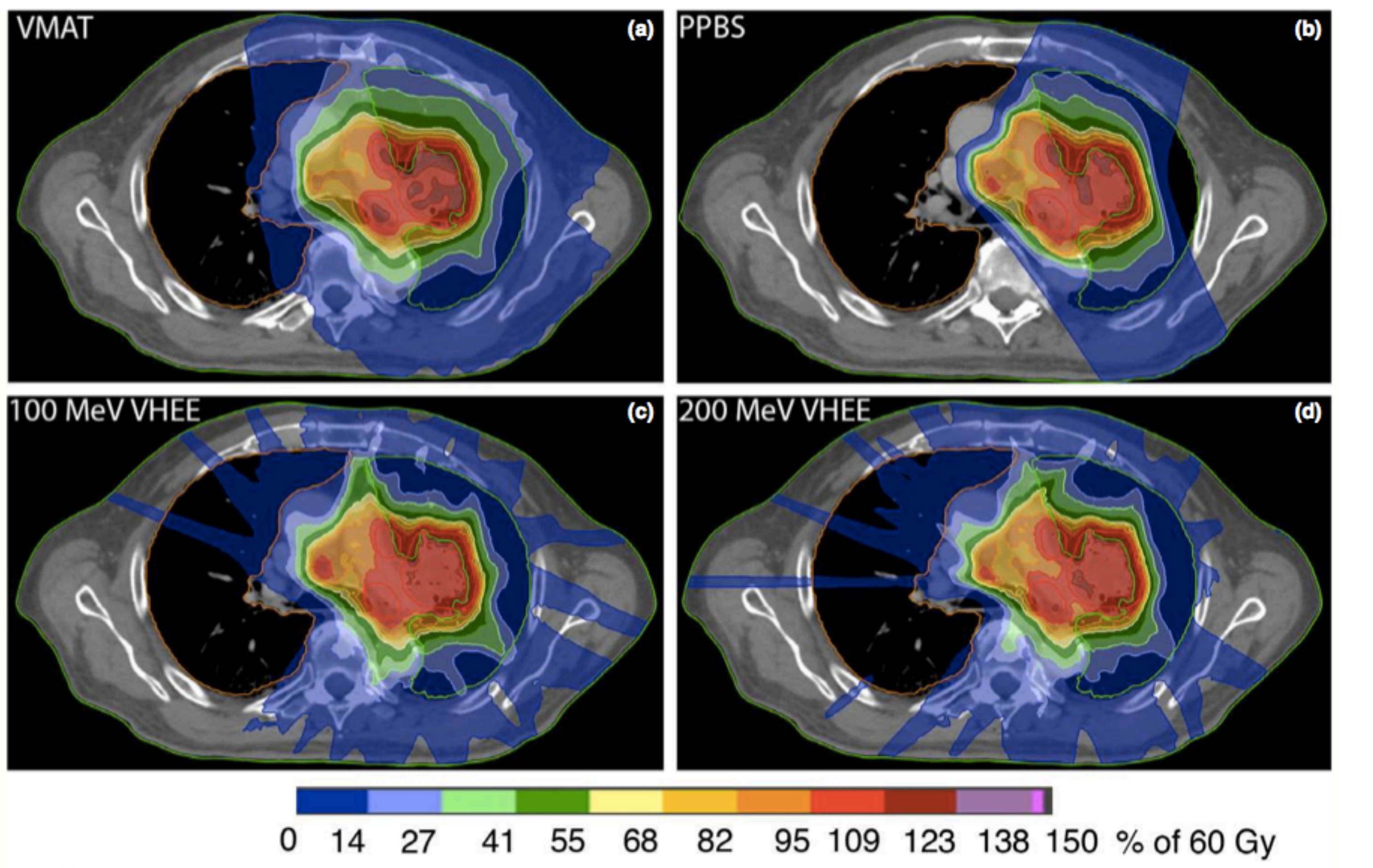




VHEE THERAPY

Milestones: Treatment Planning

➢ **Treatment plan comparison between VHEE, VMAT and PBS**

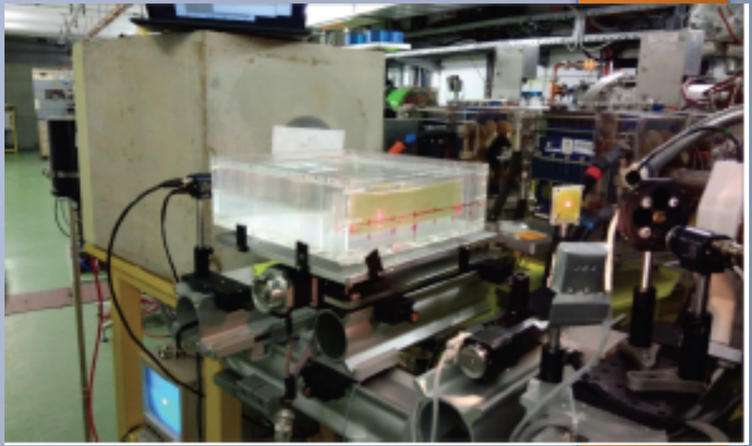


Schüler *et al.*: VHEE in radiation therapy Med. Phys. 44 (6), June 2017

VHEE THERAPY

Milestones: Beam dosimetry

- Beam Dosimetry studies with 50 – 70 MeV (NLCTA) and 160 MeV (SPARC) VHEE beams
- Beam dosimetry experiments with a 135 MeV laser-plasma wakefield accelerator (ALPHA-X)
- Beam dosimetry in CLEAR with 200-250 MeV
  - Radiosensitive films for focusing
  - Ionisation chambers for charge
  - Alanine pellets for profile depth dose
  - Generate the total dose (~10 Gy) on biological dosimeters in a single pulse (<100 ms) for profile depth dose



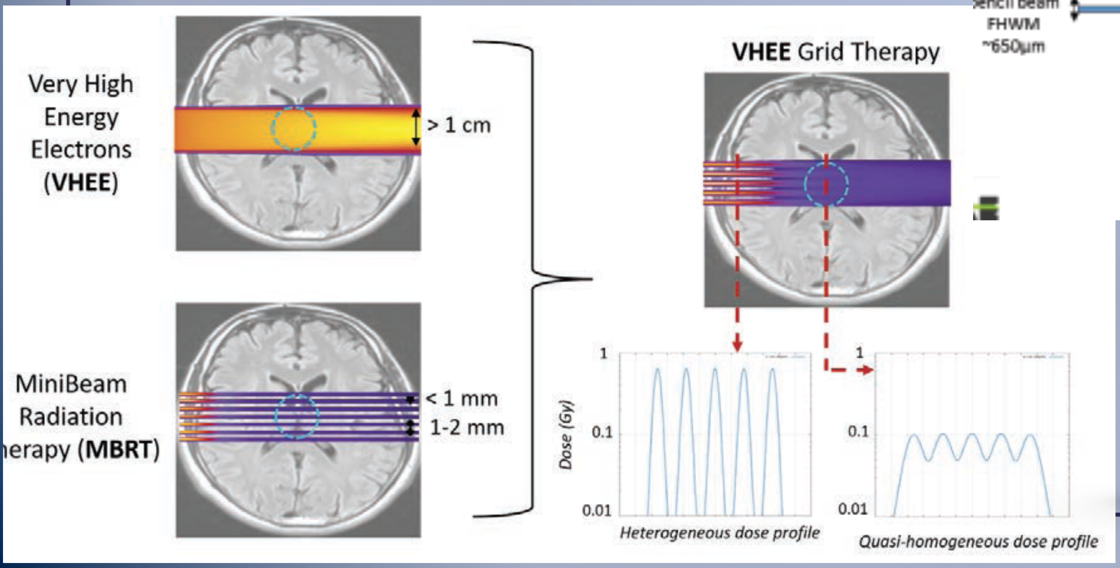
- Dosimetry for ultra-high dose rate and development of dosimeters is mandatory for a clinical application (EURAMET - EMPIR 2018)
- No experiments to date with 200 – 250 MeV beams and focused electron beams on tissue like media – essential step before patient treatment planning

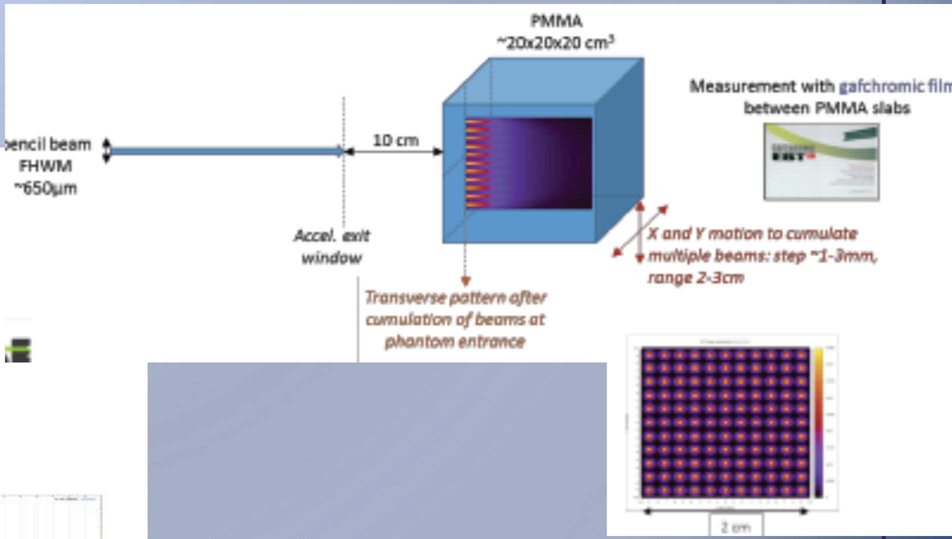
NEW DELIVERY DOSE MODALITIES

What is the Grid mini-Beams RT?

- New way of dose delivery consisting in the **combination** of **VHEE** (> 70 MeV) with **spatial fractionation** with **high-dose** healthy tissue tolerance
  - **Irradiation Grid**: spot sizes of **400-700 µm** at the sample position
  - **Small beam divergence**
  - **Grid scanning** with a translational stage or with a scanning dipole

- **First proof of concept** with **SR** and **protons**





By Y. Prezado at IMNC

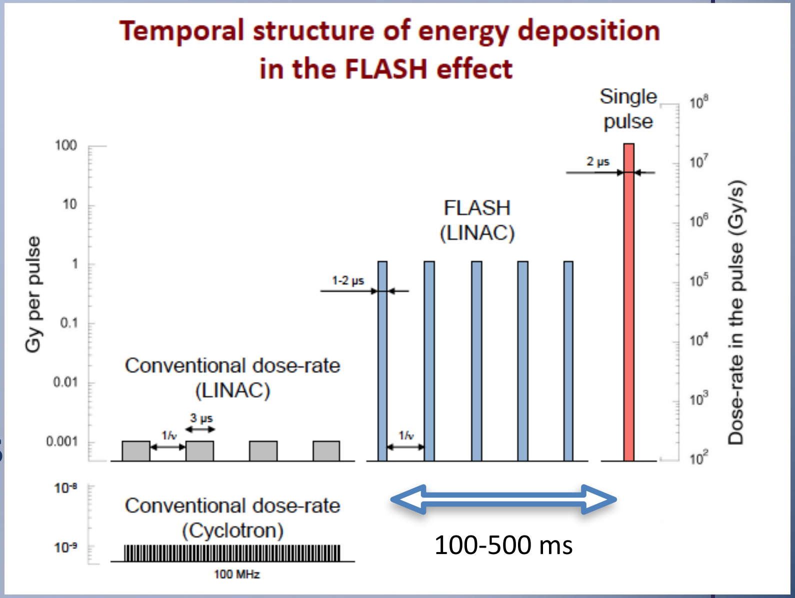
NEW DELIVERY DOSE MODALITIES
What is FLASH RT?

- New way of dose delivery consisting in ultra short irradiation time or "beam on time" (<500 ms) and very high-dose (60-200 Gy/s)

- No FLASH effect *in vitro* with clonogenic cell death as an endpoint *(Nias et al. Br J Radiol 42: 553, 1969).* The FLASH effect relates to normal, living tissue only.

- The beam-on time, not the dose-rate appears to be the major determinant of the FLASH effect

- Ultrahigh dose-rate pulses (e.g. 10^{13} Gy/s) will NOT provide a FLASH effect as long as the dose per pulse is low and the total length of radiation exposure exceeds 100-500 ms



FLASH THERAPY

First Proof-of-Concept with low-energy e^-

Radio-induced lung fibrosis in C57BL/6J mice

15 Gy in single dose (bilateral thorax irradiation)

Conventional dose-rate (CONV)	FLASH irradiation
γ-rays or 4.5 MeV electrons	4.5 MeV electrons
30 $mGy.s^{-1}$	40-200 $Gy.s^{-1}$
➤ Beam-on time 8 min	➤ Beam-on time < 500 ms

1 h - 2 h - 24 h → Apoptosis

8 - 16 - 24 - 32 - 36 weeks → Pneumonitis, Inflammation, TGF-β activation, Lung fibrosis

Hair depigmentation

Skin necrosis

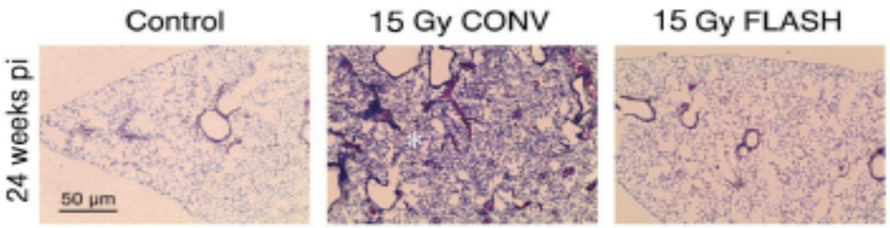
By V. Favaudon at Institute Curie

institutCurie

FLASH THERAPY
First Proof-of-Concept with low-energy e^-

Sci Transl Med 6: 245ra93, 2014

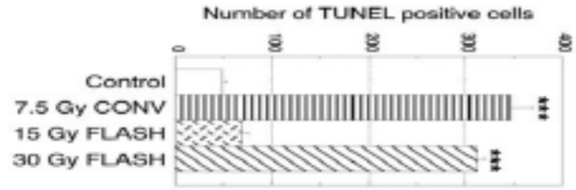
- FLASH spared normal lung tissue at doses known to induce fibrosis in mice exposed to conventional dose-rate irradiation (CONV).



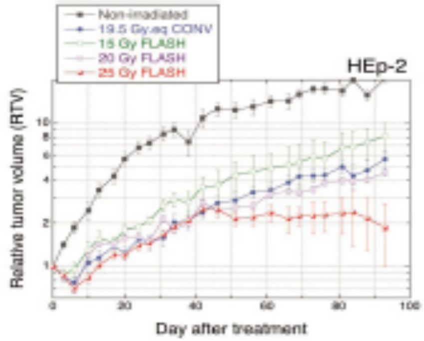
Visualisation of collagen invasion (Masson trichrome staining)

Healthy Fibrosis Healthy

- FLASH spared smooth muscle cells in arterioles from radio-induced apoptosis.



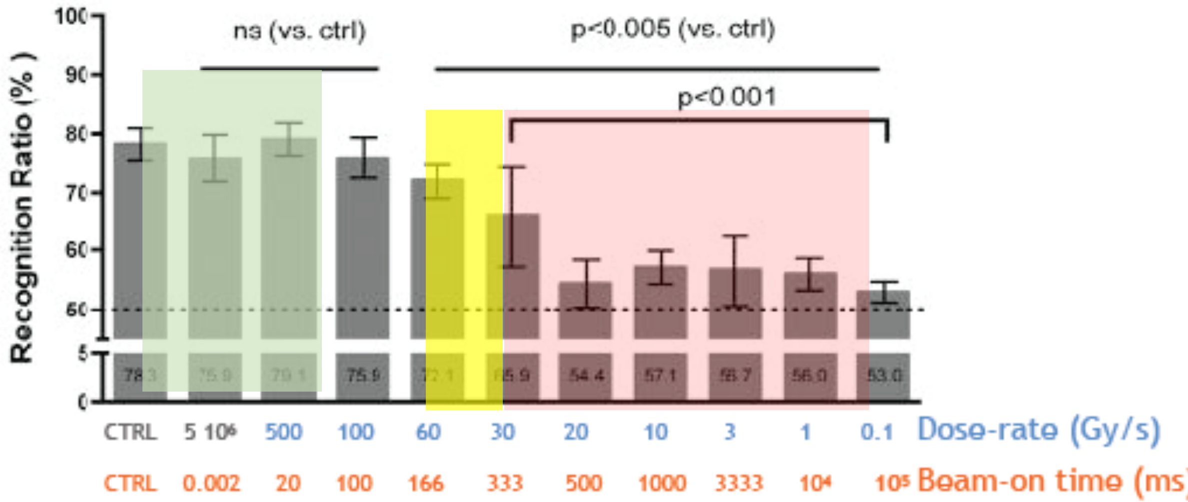
- No difference between FLASH and CONV with regard to tumor growth inhibition.
- However, normal tissue sparing by FLASH allowed dose escalation without complications, resulting in complete tumor cure in some xenograft models.

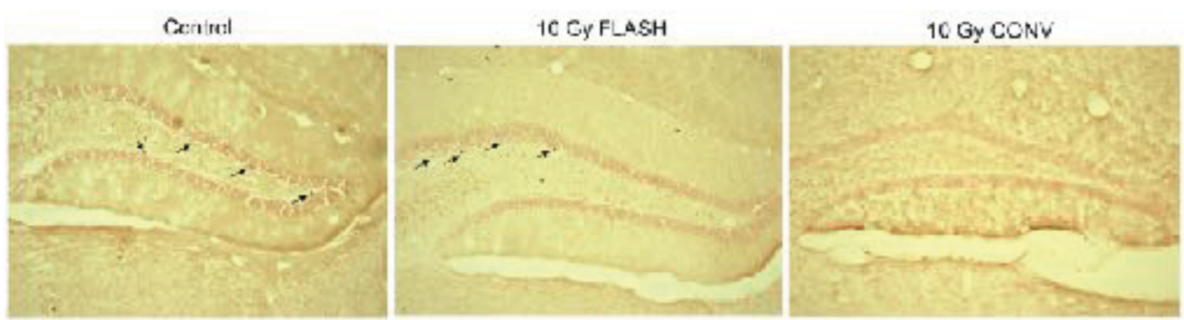


FLASH THERAPY
First Proof-of-Concept with low-energy e$^-$

Whole brain irradiatio with 10 Gy in single dose
Montay-Gruel *et al*. Radiother Oncol 124: 365-9, 2017

FLASH preserves mouse **memory** and **neurogenesis** in the hippocampus provided the beam-on time does not exceed 100 ms





BrdUrd incorporation for visualisation of replicating progenitors (stem) cells (2 months pi)

institutCurie

CHUV

FLASH THERAPY

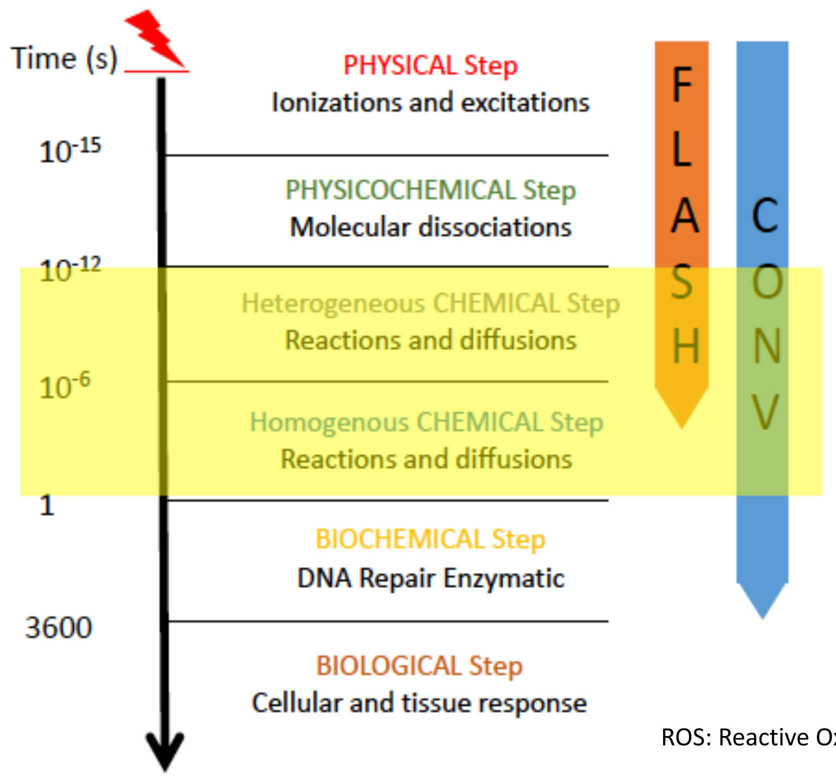
What are the underlaying mechanisms in FLASH effect?

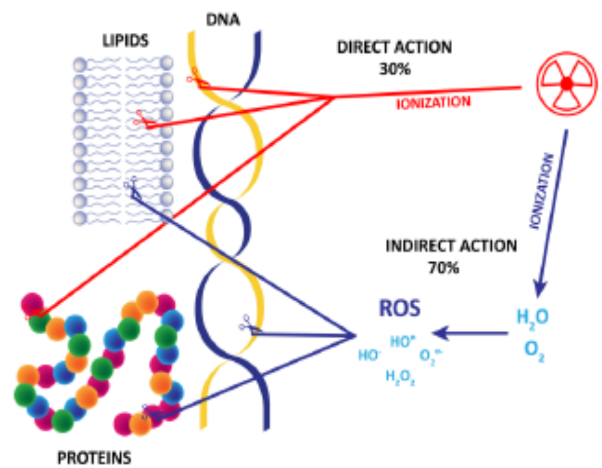
The role of the oxygen

How to explain those striking differences ?

HYP: Back to radiobiology basics: early radio-induced events can explain those differences

Chronology of post-irradiation events and FLASH irradiation





ROS: Reactive Oxygen Species

Something different might happen during the chemical steps

→ O_2 consumption and ROS production ???

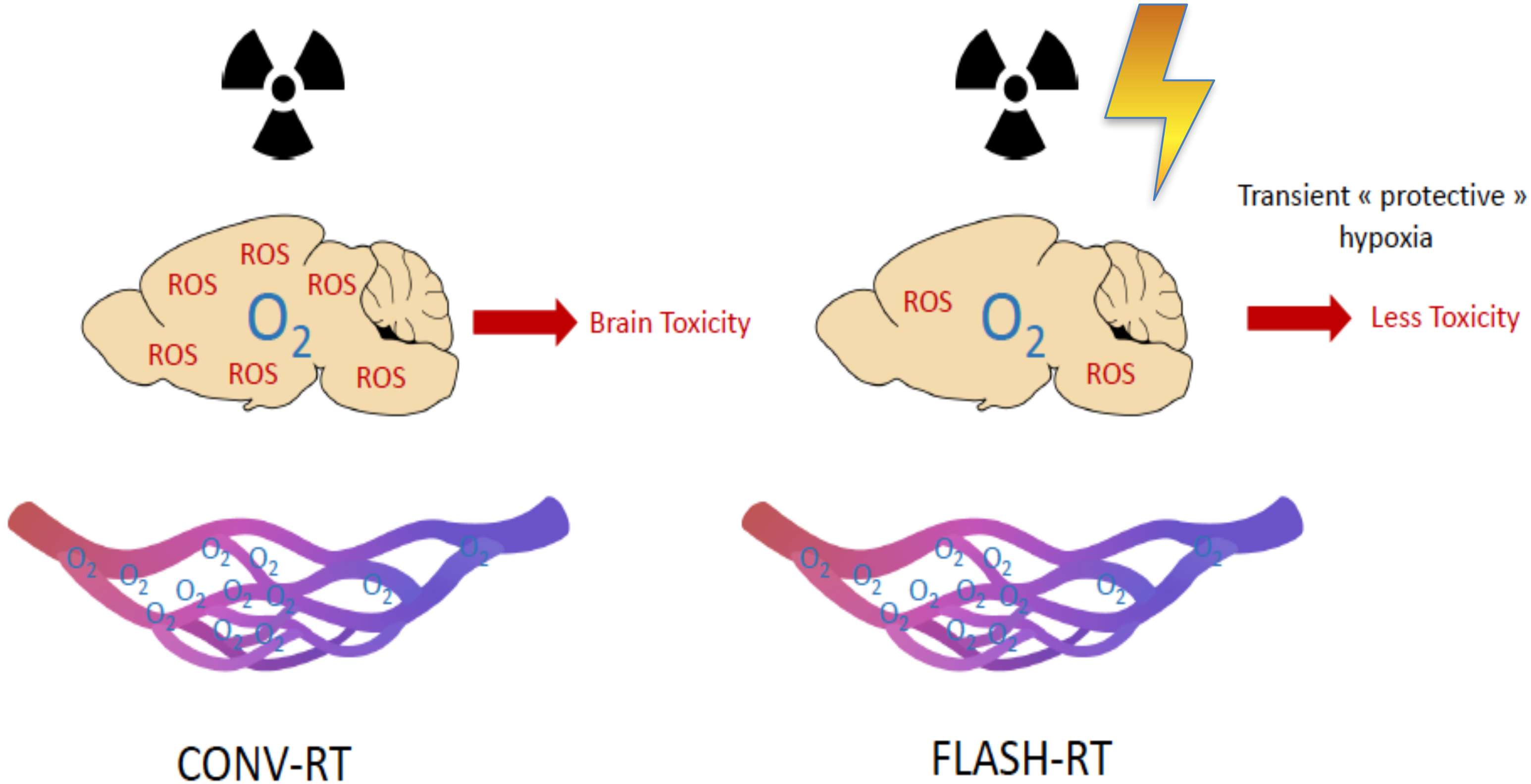
Prev. described
(Ling et al. Edward et al. Dewey et al.)
bacterian, mammalian cells, and *in-vivo*

FLASH THERAPY

What are the underlaying mechanisms in FLASH effect

The role of the oxygen

HYP: FLASH-RT induces a transient radiation-induced hypoxia that protects only the normoxic tissues



Montay-Gruel et al (in revision)

FLASH THERAPY
Towards a clinical practice

And then ?

Fish eggs
Few toxicity
Montay-Gruel et al. Sub (2)

VET CLINICAL TRIAL
Cat patients with SCC
Few toxicity
Treats the tumor
Vozenin et al. 2018

MECANISMES BIOLOGIQUES

Mouse Brain
Few toxicity
Treats the tumor
Montay-Gruel et al. 2017
Montay-Gruel et al. Sub (1)
Montay-Gruel et al. Sub (2)

Keep investigating the mechanisms in translational research

Mini pipg
Few toxicity
Vozenin et al. 2018

Mouse lung
Few toxicity
Treats the tumor
Favaudon et al. 2014

Clinical translation

- As soon as 2018
- 2020 for IORT

Induce less normal tissue toxicities
Increase the curative doses
Be more efficient to cure the tumors
Treat quickly
Increase the patient's QOL

ACCELERATORS FOR VHEE

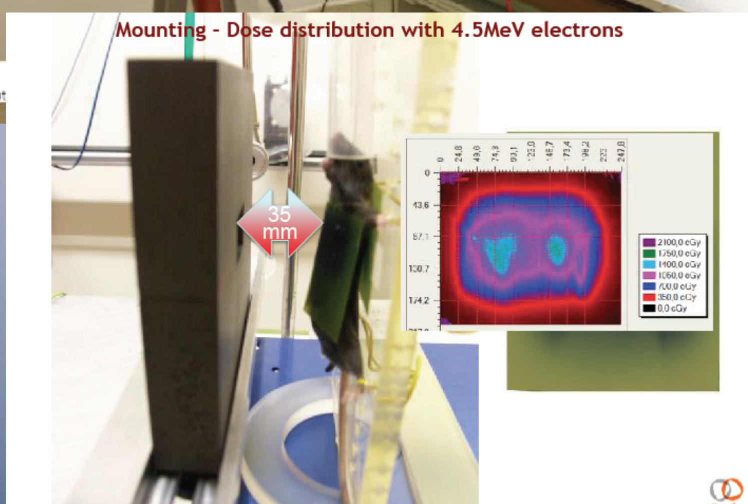
Accelerators for FLASH-RT: low-energy e^-

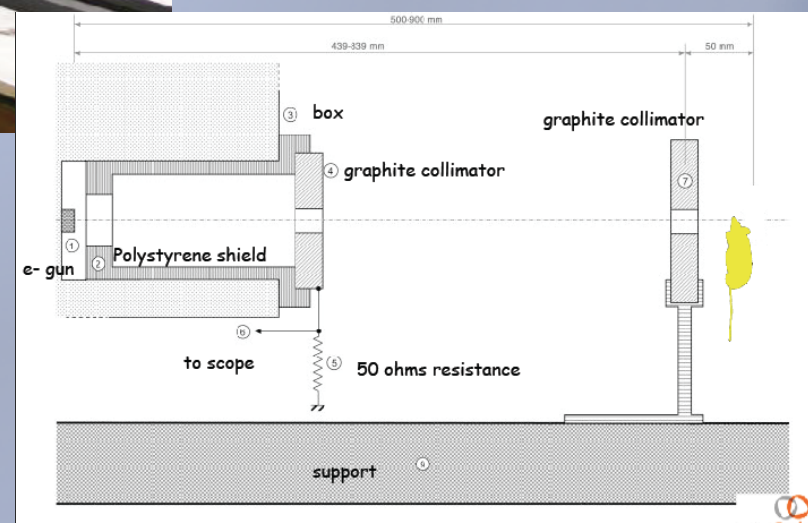
LINAC "Kinétron" (1987)
4.0-5.0 MeV electrons
Triode electron gun

LET = 0.19 keV/µm
RBE = 1.00 relative to ^{60}Co
(Compton only)

Pulse width 0.05 - 2.2 µs
Repeat frequency 0.1 - 200 Hz
Peak current 0.01 - 220 mA
Dose per pulse 0.001 - 50 Gy

Mean dose-rate 0.01 - 7000 $Gy.s^{-1}$
Maximum dose-rate during the pulse
≈ 2 10^7 $Gy.s^{-1}$





FLASH in vivo

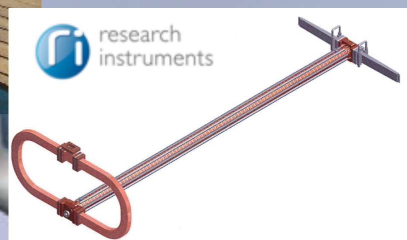
institutCurie · Institut National du Cancer · Cancéropôle Île-de-France · École Vétérinaire Alfort · Inserm · Institut de cancérologie Gustave Roussy Villejuif - www.igr.fr · CHUV

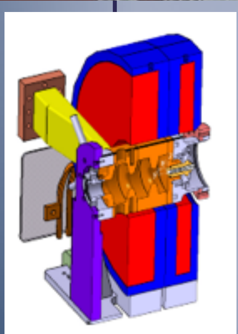
ACCELERATORS FOR VHEE

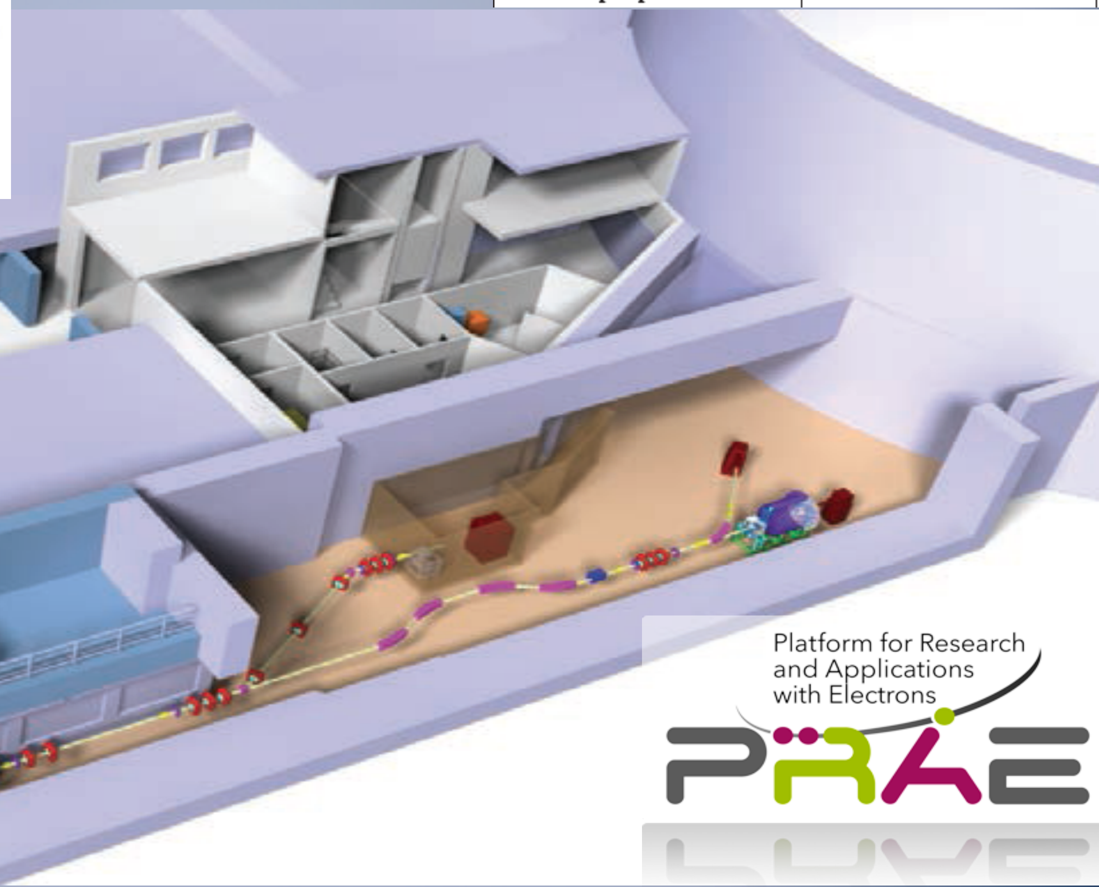
Accelerators for FLASH-RT: high-energy e⁻

- ➢ S-band: RF gun+ Linac (HG)

Parameters	
Energy	70 – 140 [MeV]
Charge (variable)	0.00005 – 2 [nC]
Normalized emittance	3-10 [mm mrad]
RF frequency	3.0 [GHz]
Repetition rate	50 [Hz]
Bunch length, rms	< 10 [psec]
Energy spread, rms	< 0.2 %
Bunches per pulse	1

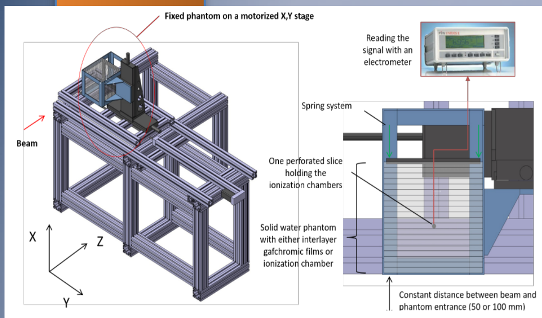






ACCELERATORS FOR VHEE

Accelerators for Grid Mini-beams: high-energy e⁻



- S-band: RF gun+ Linac (HG)

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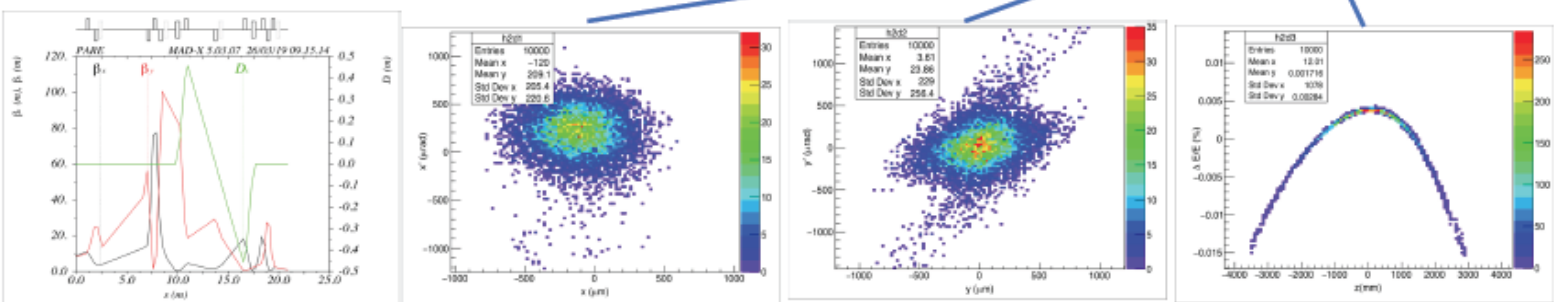
Repetition rate	50 [Hz]
Bunch length, rms	< 10 [psec]
Energy spread, rms	< 0.2 %
Bunches per pulse	1

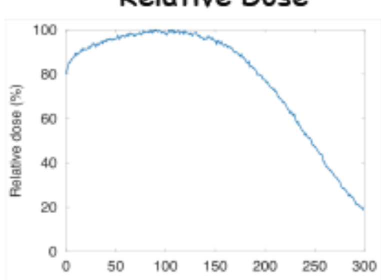
MINI beam - 70 MeV

- $\sigma_x = 207\ \mu m,\ \sigma_y = 240\ \mu m$

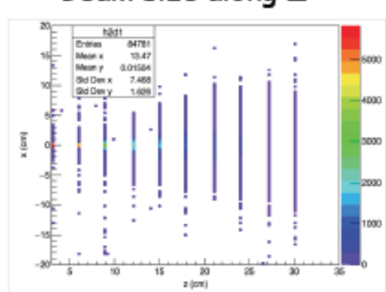
At the end of vaccum



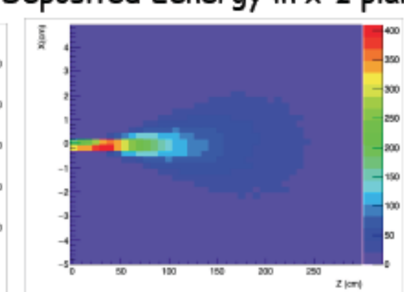
Relative Dose



Beam size along Z



Deposited Eenergy in x-z plan



In the Water

The air thick is 10 cm

	Air	Water
σ_x(mm)	0.25	35.9
σ_y(mm)	0.29	36.6

ACCELERATORS FOR VHEE

Accelerators for FLASH-RT: high-energy e⁻

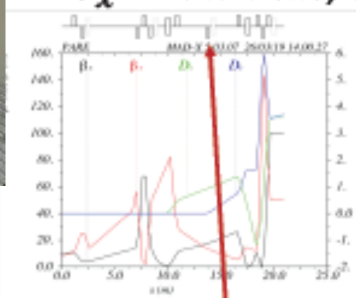
➢ S-band: RF gun+ Linac (HG)

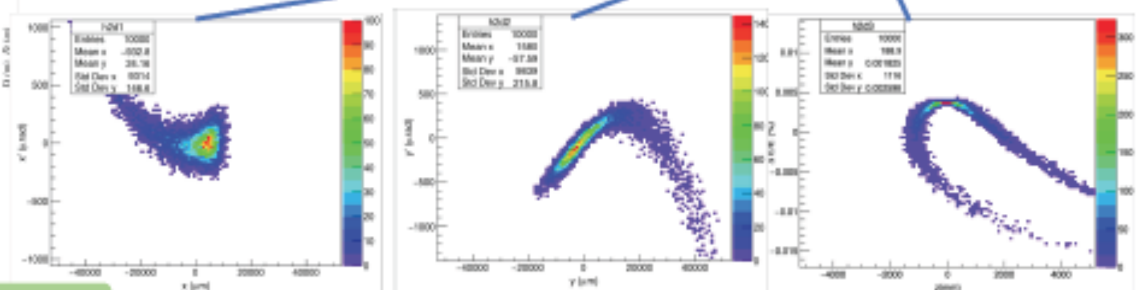
Parameters	
Energy	70 – 140 [MeV]
Charge (variable)	0.00005 – 2 [nC]
Normalized emittance	3-10 [mm mrad]
RF frequency	3.0 [GHz]
Repetition rate	50 [Hz]
Bunch length, rms	< 10 [psec]
Energy spread, rms	< 0.2 %
Bunches per pulse	1

FLASH beam - 70 MeV (1)

At the end of vaccum

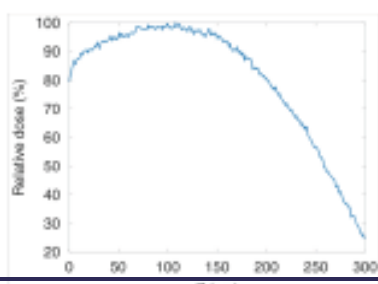
- $\sigma_x = 9.9\ mm,\ \sigma_y = 10.3\ mm$



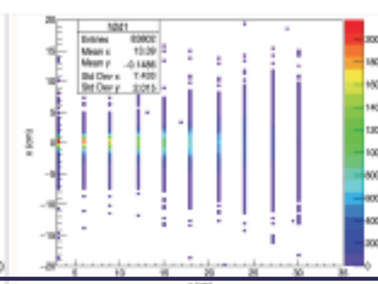


Skew Quad is used to introduce vertical dispersion

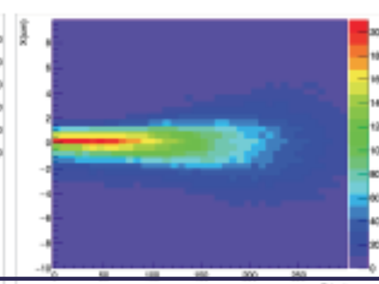
Relative Dose



Beam size along Z



Deposited Eenergy in x-z plan



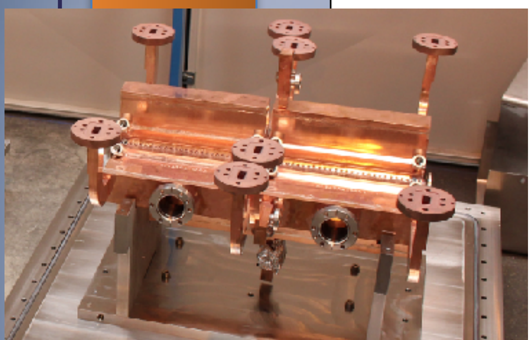
The air thick is 1 meter

In the Water

After	Air	Water
Left e^-	100%	20%
σ_x(mm)	11.4	37.3
σ_y(mm)	12.0	37.0

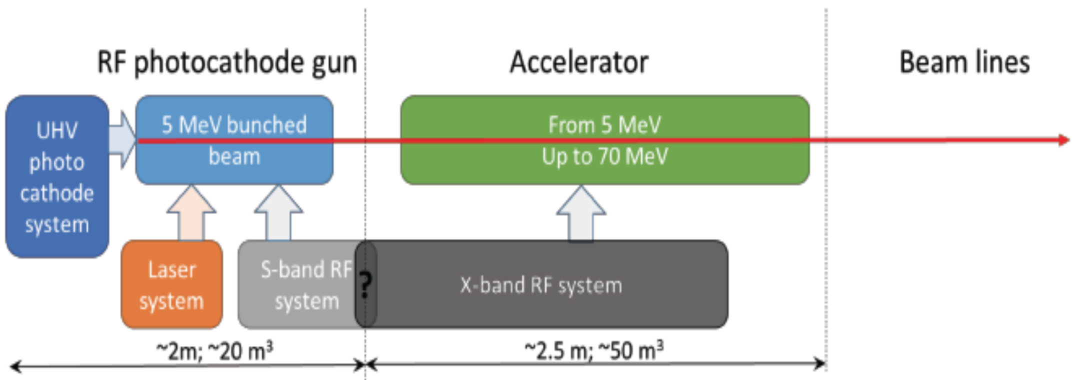
ACCELERATORS FOR VHEE

Accelerators for FLASH-RT: high-energy e⁻



Preliminary considerations

Basic schematic of a linac



<u>S-band RF unit:</u>
Standing wave cavity
1 klystrons: ~15MW x 3us
1 modulator at 400Hz

<u>X-band RF unit: Option 1</u>
4 structures => 2.5 m
4 klystrons: 4 x 7MW x 3.5us
2 modulator at 400Hz

<u>X-band RF unit: Option 2</u>
4 structures => 2.5 m
1 klystron: 50MW x 1.4us
1 modulator at 100 (200@0.1s) Hz

A. Grudiev

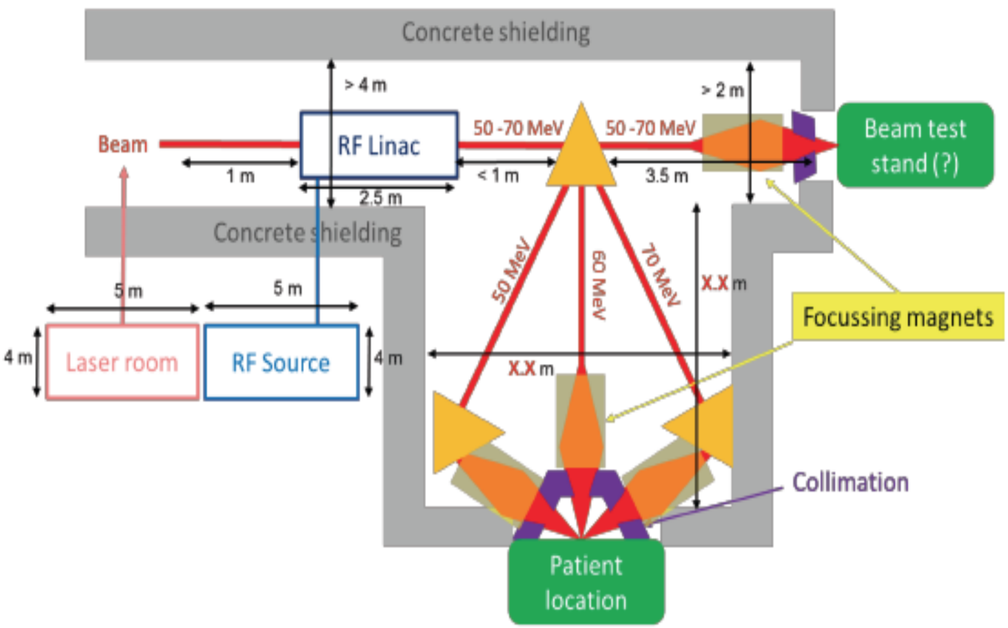
ACCELERATORS FOR VHEE

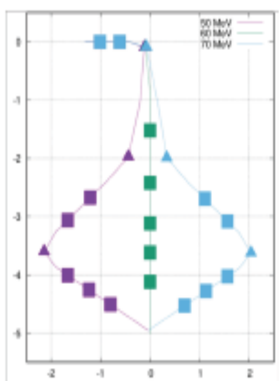
Accelerators for FLASH-RT: high-energy e⁻

Preliminary considerations

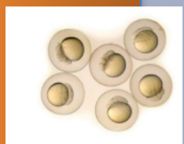
Version 1: Dimensions

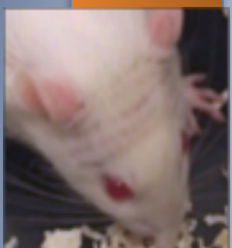
A significant aspect of a facility is the beam transport and delivery.





Andrea Latina, Alexander Gerbershagen 4





SUMMARY and FUTURE PERSPECTIVES

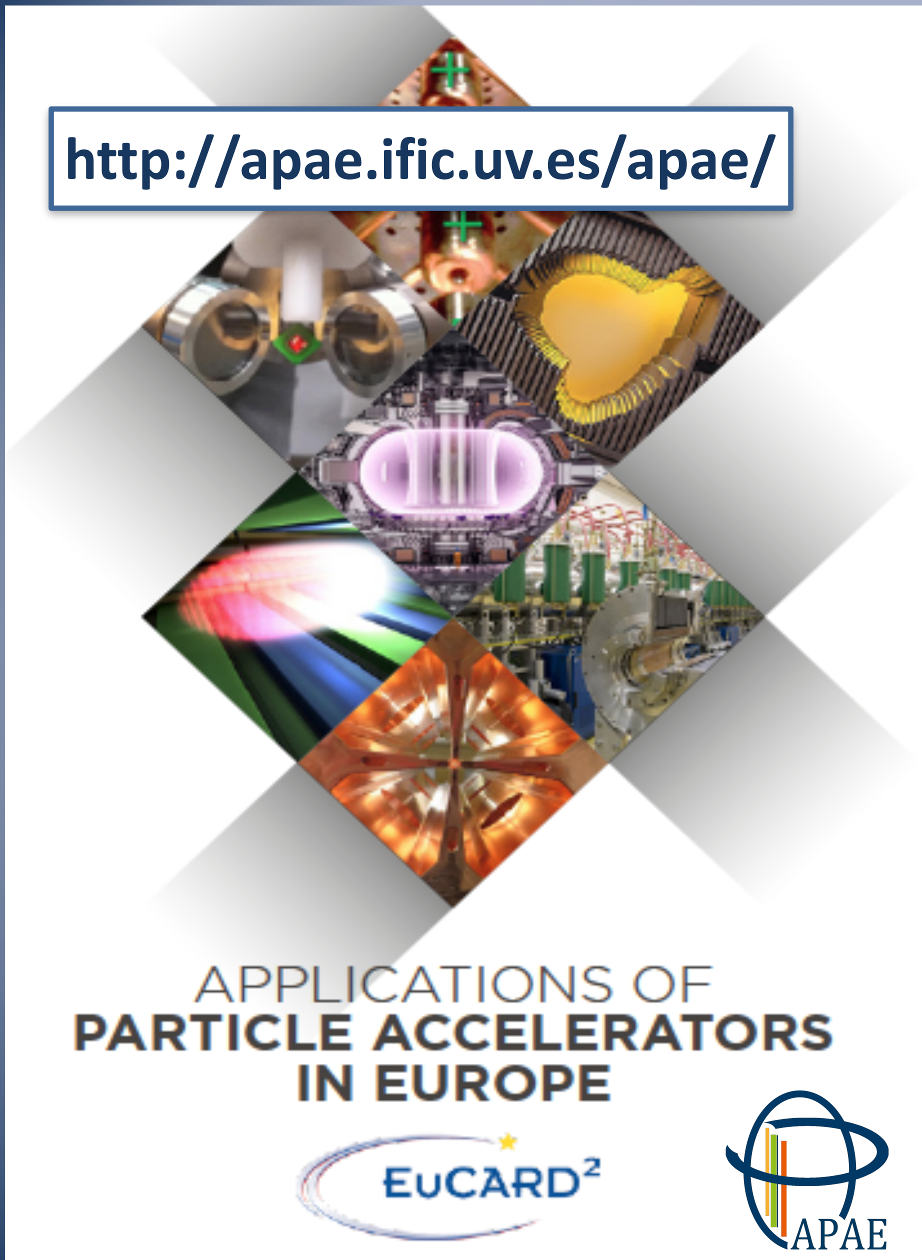
- Challenge in RT is to find possible strategies to spare normal tissue
  - Different particle types: Very High Energy Electrons (VHEE)
  - Different dose delivery methods: Grid mini-beam or FLASH RT

- Grid mini-beams consists of combination of VHEE (> 70 MeV) with spatial fractionation (400-700 µm, scanning, small divergence) with high-dose healthy tissue tolerance

- FLASH consists of ultra short irradiation time or "beam on time" (<500 ms) and very high-dose (60-200 Gy/s), that spare normal tissues from radiation-induced toxicities
  - Understanding the FLASH-RT limits (min/max dose/time)
    - Minimum beam on-time: ms => μm=> ns ? Bunching structure?
    - Maximun dose > 200 Gy/s ?
  - Understanding the FLASH-RT underlying mechanism:
    - Biological studies
    - Chemical and kinetic: role of the oxygen
  - Extending to other species: p, ^{12}C

- Dosimetry for ultra-high dose rate is a key stone, development of dosimeters is mandatory for a clinical application (EURAMET - EMPIR 2018)

- Which Accelerator is the most suitable to cope the necessary performances?



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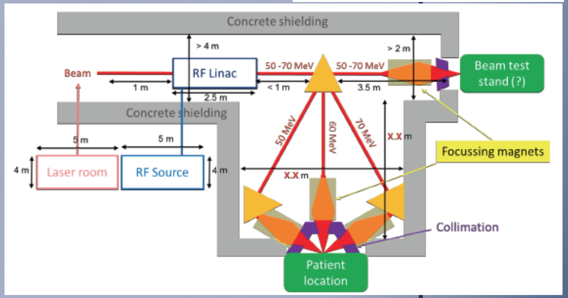
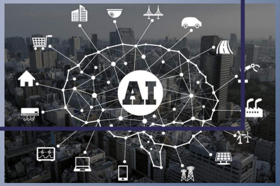
RADIOTHERAPY

What are the CHALLENGES ?

- ***Particle therapy***
  - Improved accelerator design (FFAG hybrid, linacs, dielectric wall or laser based acceleration)
  - SC technology (4T)
  - High-Intensity protons and ions
  - Beam delivery and control (gantries)
  - Combined imaging and treatment (including MRI)
  - Other particles: VHEE, BNCT, He…
  - Other beam delivery dose techniques: mini-beams, FLASH

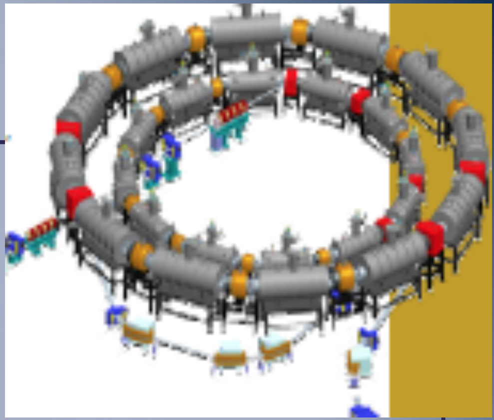


- ***Political and Societal***
  - More Research/Industry collaboration
  - Improved Computer Modelling, Control and Monitoring (Artificial Intelligence)



RADIOTHERAPY

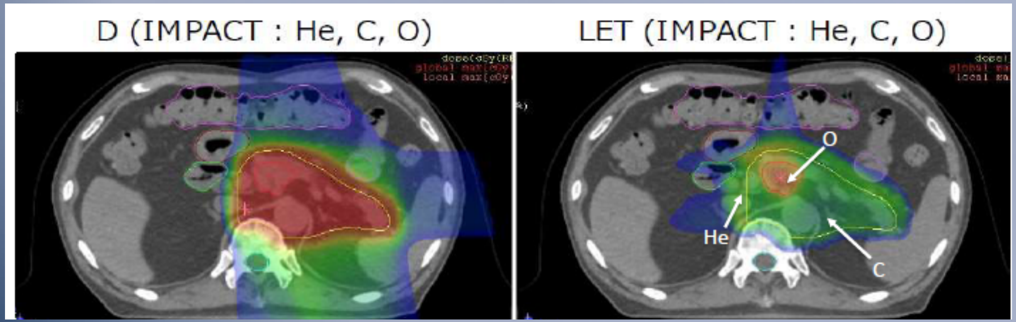
What are the needed R&D?

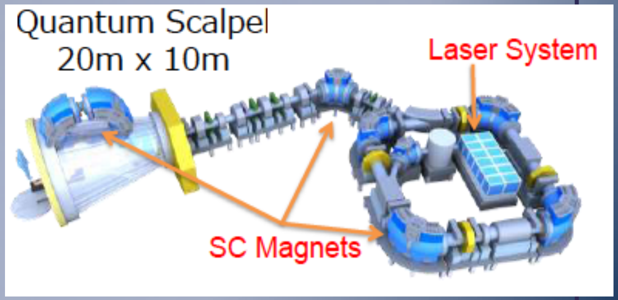


- **Multidisciplinary approach, including biological info and immunological protocols -> personalised medicine**
- **Multi-particle facility design, SC technology (gantries), high-gradient ions accelerators**

- **Systematic RBE experiments, including in-vivo animal studies and clinical studies for new therapies**

- **Reduction of initial investment and functional costs**
- **Cooperation between academics, industry, research centres and hospitals**





FLASH THERAP

What are the underlaying mechanisms in FLASH effect?

The role of the oxygen

Playing with the oxygen tension = modify ROS production

1 – Make mice breathe 95% of oxygen (before and during IR)

2 – Increase oxygen tension in the brain

3 – Deliver FLASH or conventional dose-rate irradiation

4 – Evaluate memory

CONV	CONV OXYGEN	FLASH	FLASH OXYGEN
Memory Loss	Memory Loss	Memory OK	Memory Loss

Increase in O2 tension reverses the FLASH effect

Less ROS produced by FLASH-RT ?

Montay-Gruel et al (in revision)

FLASH THERAPY

What are the underlaying mechanisms in FLASH effect?

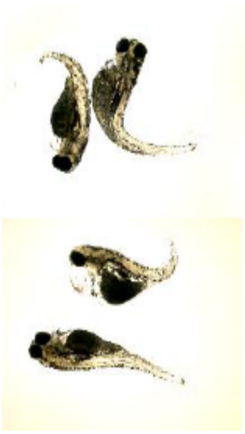
The role of the oxygen

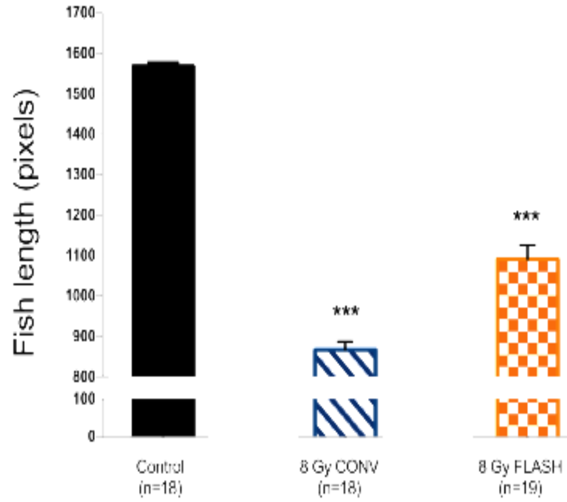
ROS Scavenging

RT of fish eggs
→ Development assessment

CONV

FLASH





→ **Antioxydant partially reverses the CONV effect**
→ **No effect of antioxydant on the FLASH-RT (still less armful)**

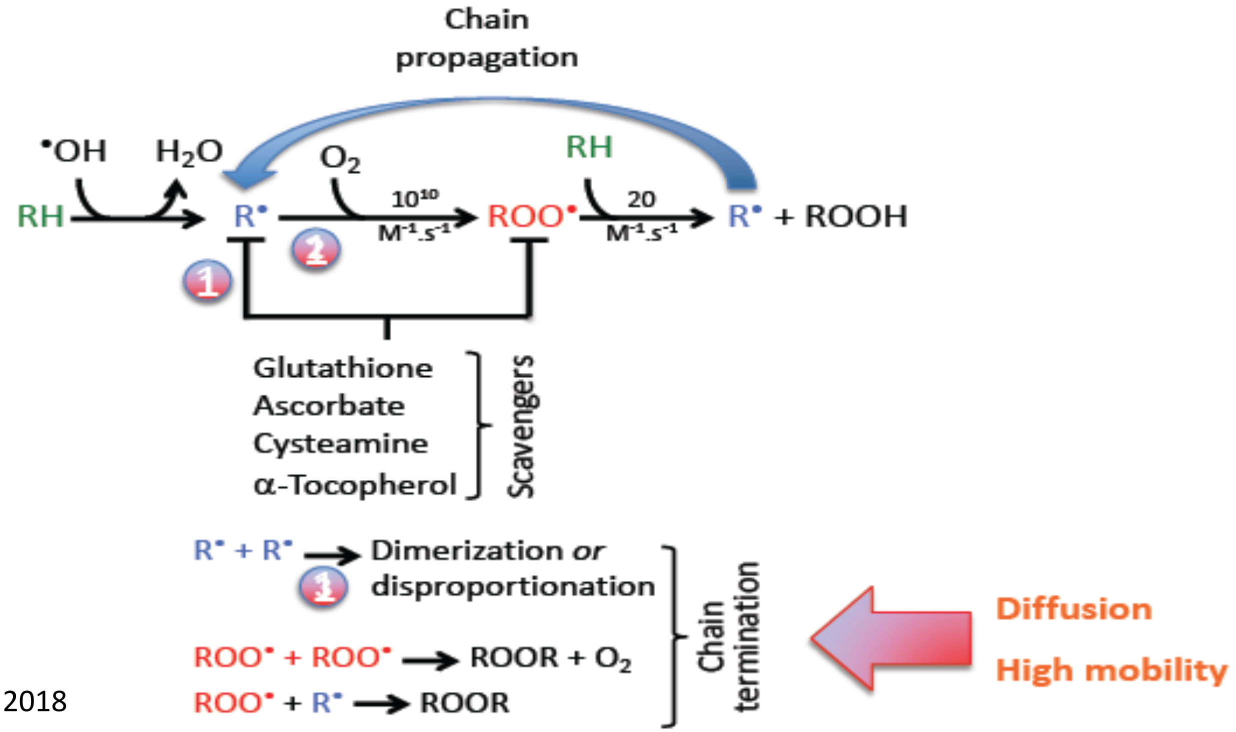
Toxicity is not mediated by ROS production with FLASH-RT

Montay-Gruel et al (in revision)

FLASH THERAPY

What are the underlaying mechanisms in FLASH effect?

Peroxyradicals formed from unsaturated lipids catalyze a chain reaction

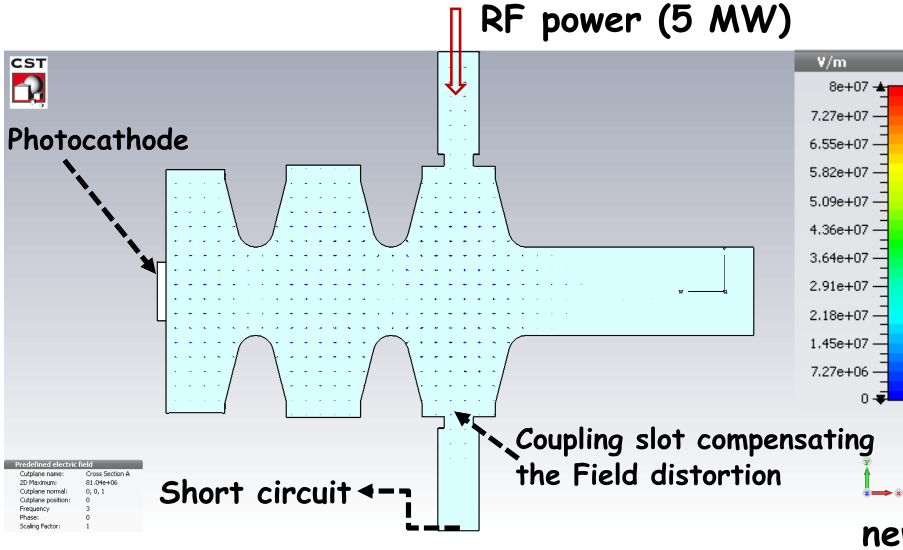


V. Fauvadon FLASH 2018

➢➢ The efficiency of the chain is maximal at low dose-rate and decreases in inverse ratio to the square root of the dose-rate.

The RF gun "revisited"

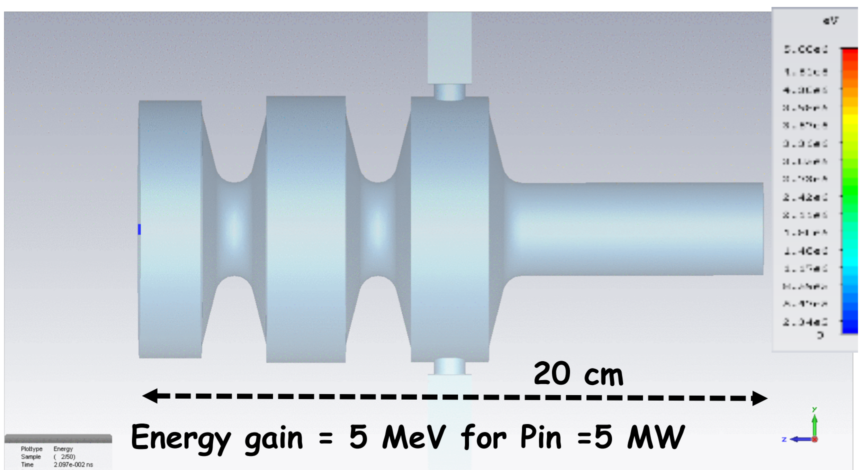
Accelerating gradient (TM_{010} _ π mode):
80 MV/m at P_{in}=5 MW



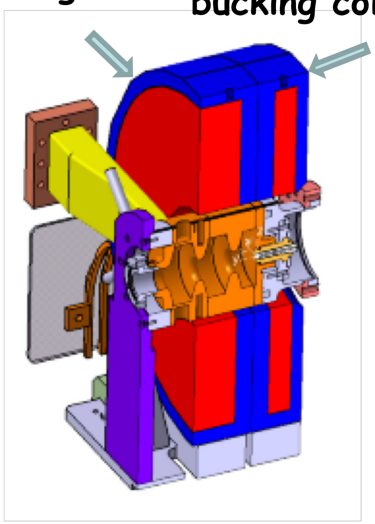
Photoinjector specification

Operation frequency	2998,55 MHz (30° C, in vacuum)
Charge	1 nC
Laser wavelength, pulse energy	266 nm, 100 µJ
RF Gun Q and Rs	14400, 49 MΩ/m
RF Gun accelerating gradient	80 MV/m @ 5 MW
Normalized emittance (rms)	4.4 π mm mrad
Energy spread	0.4 %
Bunch length (rms)	5 ps

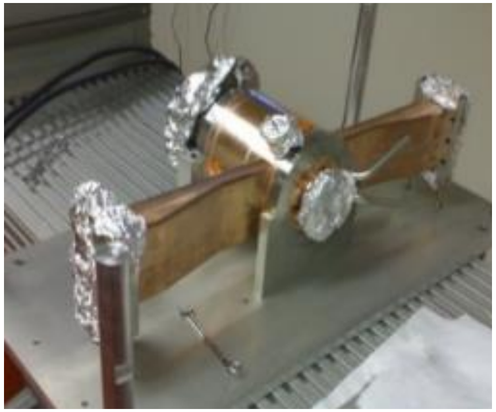
CST-Particle in cells, simulation results



new coil configurations



2.5 cells RF gun designed and produced at LAL for ThomX

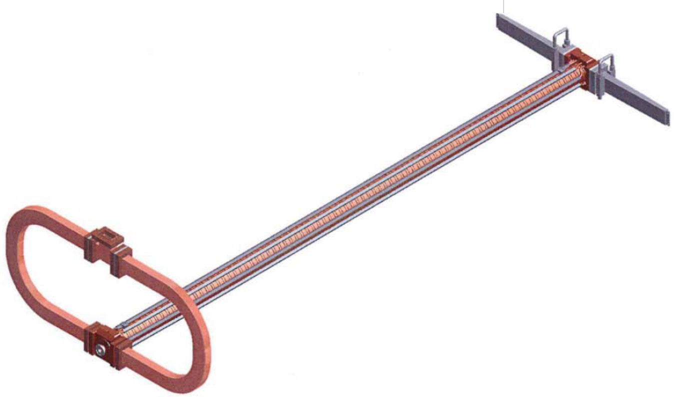


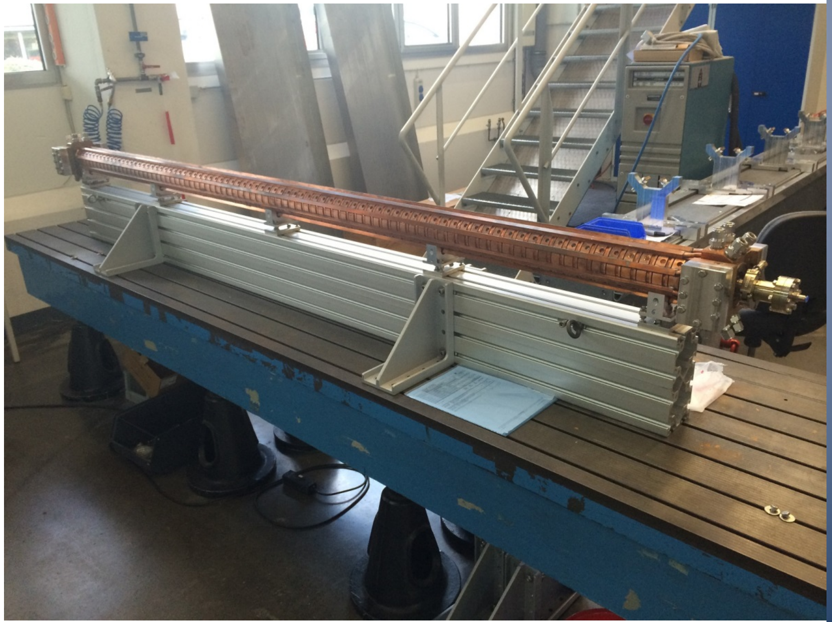
TW S-Band structures from RI

research instruments

Parameter	Value
Length	3.5m
Number of Couplers + Cells	1+96+1
Type	Constant gradient
Phase Advance	$2\pi/3$
Frequency	2998.55 @ 30° C
Pulse Width	3μs
Repetition Rate	50Hz
Max. input Power	40 MW
Max. average power	5 kW
Guaranteed unloaded energy gain	>65MeV

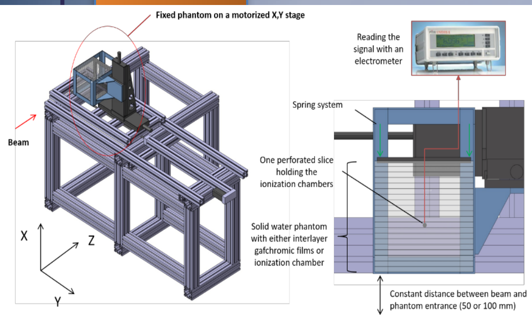
- The Structures **are SLAC-type structures**
- Constant gradient
- Race track coupler for quadrupole compensation
- BIG Splitter for dipole compensation
- 2 RF loads





ACCELERATORS FOR VHEE

Accelerators for Mini-beams: high-energy e⁻



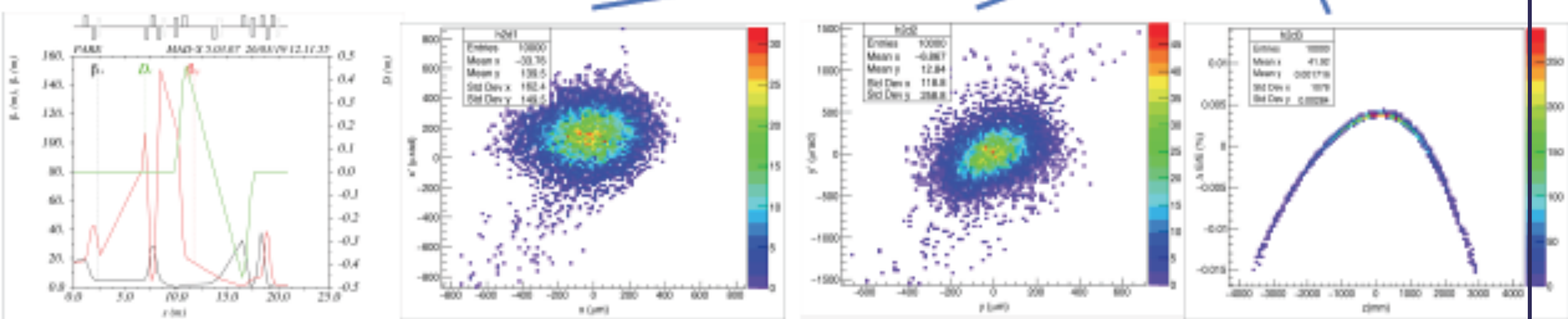
➢ S-band: RF gun+ Linac (HG)

Parameters	
Energy	70 – 140 [MeV]
Charge (variable)	0.00005 – 2 [nC]
Normalized emittance	3-10 [mm mrad]
RF frequency	3.0 [GHz]
Repetition rate	50 [Hz]
Bunch length, rms	< 10 [psec]
Energy spread, rms	< 0.2 %
Bunches per pulse	1

MINI beam - 140 MeV

- $\sigma_x = 170\ \mu m,\ \sigma_y = 142\ \mu m$

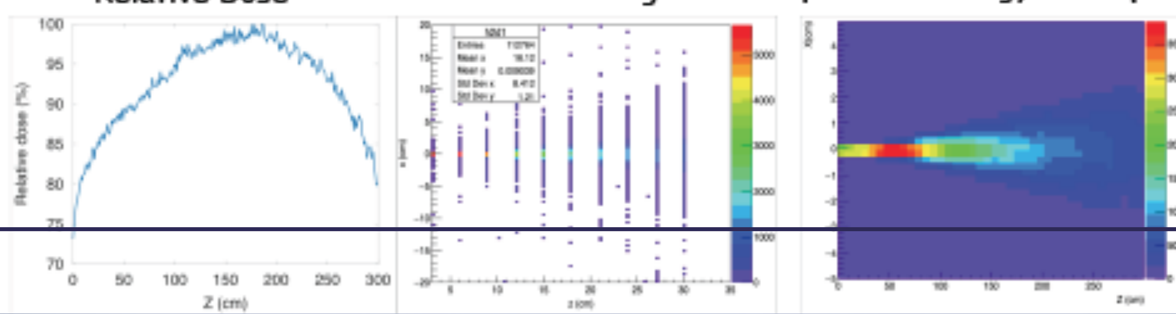
At the end of vaccum



Relative Dose

Beam size along Z

Deposited Eenergy in x-z plan



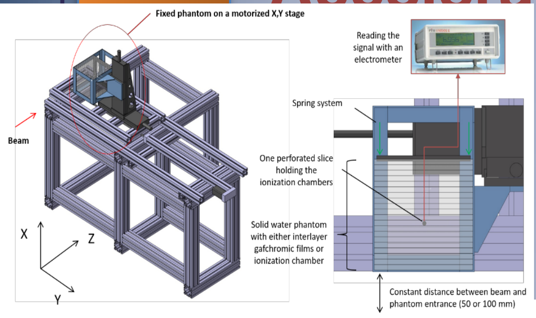
The air thick is 10 cm

In the Water

	Air	Water
σ_x(mm)	0.18	20.8
σ_y(mm)	0.15	21.2

ACCELERATORS FOR VHEE

Accelerators for Mini-beams: high-energy e-



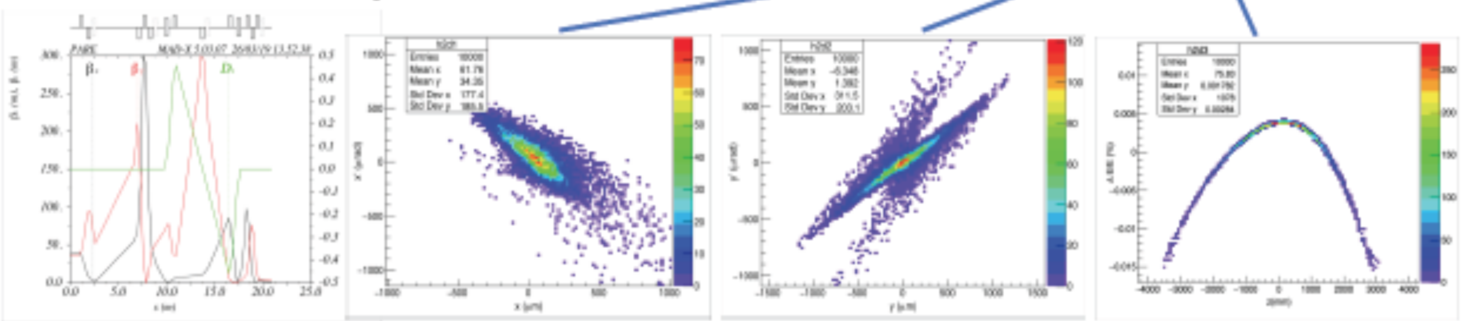
➢ S-band: RF gun+ Linac (HG)

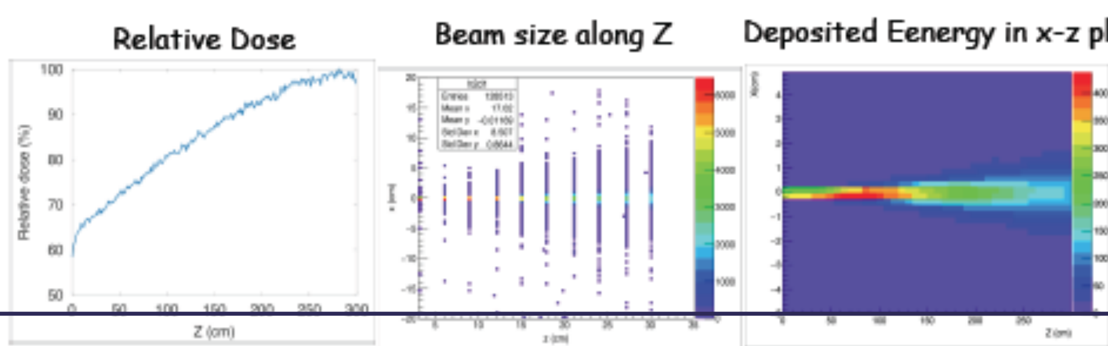
Parameters	
Energy	70 – 140 [MeV]
Charge (variable)	0.00005 – 2 [nC]
Normalized emittance	3-10 [mm mrad]
RF frequency	3.0 [GHz]
Repetition rate	50 [Hz]
Bunch length, rms	< 10 [psec]
Energy spread, rms	< 0.2 %
Bunches per pulse	1

MINI beam - 300 MeV

- $\sigma_x = 321\ \mu m, \sigma_y = 314\ \mu m$

At the end of vaccum



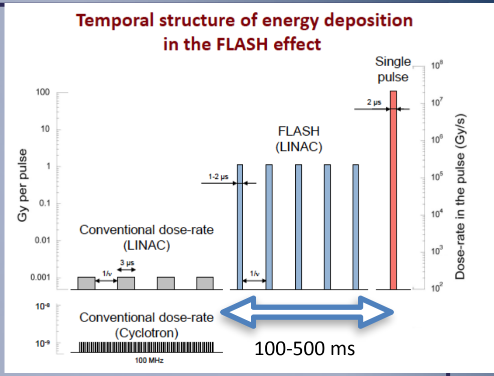


The air thick is 10 cm

In the Water

	Air	Water
σ_x(mm)	0.34	11.8
σ_y(mm)	0.33	11.7

FUTURES PERSPECTIVES



Extending FLASH RT to others species: p, ^{12}C, …

The dose rate D is defined as:

$$D = \frac{N}{dS}\frac{(dE/dx)}{\rho}$$

To deposit 1 Gy, the fluency:

- ➢ For electrons, with LET 0.2 MeV/mm :

$$1Gy = \frac{N}{dS}\frac{0.2\,10^{6}\ \times 1.6\,10^{-19}}{10^{-6}} \Rightarrow \frac{N}{dS} \approx 3.1\,10^{7}\ e^{-}/mm^{2} = 5\,10^{-3}\ nC/mm^{2}$$

- ➢ For protons, with LET 3 MeV/mm at the Bragg peak:

$$1Gy = \frac{N}{dS}\frac{3\,10^{6}\ \times 1.6\,10^{-19}}{10^{-6}} \Rightarrow \frac{N}{dS} \approx 2\,10^{6}\ p/mm^{2} = 3.2\,10^{-4}\ nC/mm^{2}$$

- ➢ For ^{12}C ions, with LET 80 MeV/mm at the Bragg peak:

$$1Gy = \frac{N}{dS}\frac{80\,10^{6}\ \times 1.6\,10^{-19}}{10^{-6}} \Rightarrow \frac{N}{dS} \approx 8\,10^{4}\ {}^{12}C/mm^{2} = 1.3\,10^{-5}\ nC/mm^{2}$$

FUTURE PERSPECTIVES
Accelerators for FLASH-RT

FLASH	Dose rate	Volume	Use
FLASH e-			
Kinetron Curie 4.4 MeV	0.1-300 Gy/s	10x10 cm^2	Preclinical studies Clinical studies for superficial tumours
Oriatron CHUV 5.5 MeV	0.1-1000 Gy/s	10x10 cm^2	Preclinical studies Clinical studies for superficial tumours
Modified linac Stanford 20 MeV	0.1-250 Gy/s	10x10 cm^2	Preclinical studies
Modified linac Lund 20 MeV	0.1-250 Gy/s	10x10 cm^2	Preclinical studies
FLASH p			
RARAF 4,5 MeV	0.05-1000 Gy/s	Round 11 mm	Biological studies
CPO-Orsay 130-198 MeV	40 Gy/s	12x12 mm^2	Preclinical studies
FLASH ^{12}C ????			
RAON 310 MeV/u	0.03-33.3 Gy/s	20x20 cm^2	Under study