



**Dose, dose-rate, beam-on time...  
what requisites for the “FLASH effect” ?**



# Radio-induced lung fibrosis in C57BL/6J mice

## 15 Gy in single dose (bilateral thorax irradiation)

**Conventional dose-rate (CONV)**

$\gamma$ -rays or 4.5 MeV electrons

30 mGy.s<sup>-1</sup>

▶ Beam-on time 8 min

**FLASH irradiation**

4.5 MeV electrons

40-200 Gy.s<sup>-1</sup>

▶ Beam-on time < 500 ms

1 h - 2 h - 24 h

8 - 16 - 24 - 32 - 36 weeks

Apoptosis



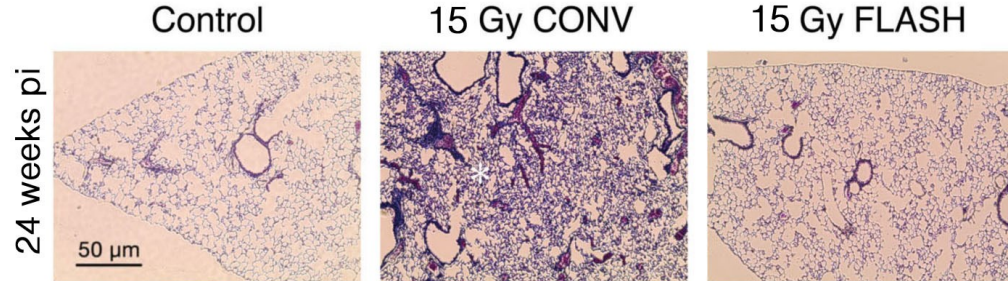
Pneumonitis  
Inflammation  
TGF- $\beta$  activation  
Lung fibrosis



Hair depigmentation  
Skin necrosis

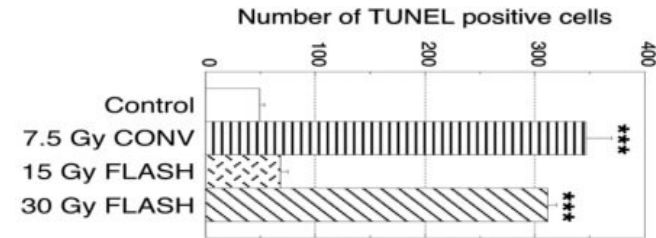
# Sci Transl Med 6: 245ra93, 2014

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

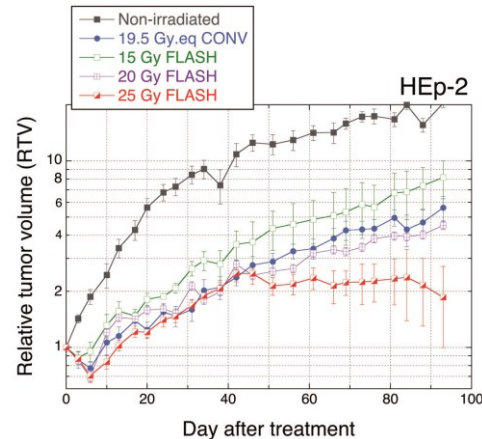


Visualisation of collagen invasion (Masson trichrome staining)

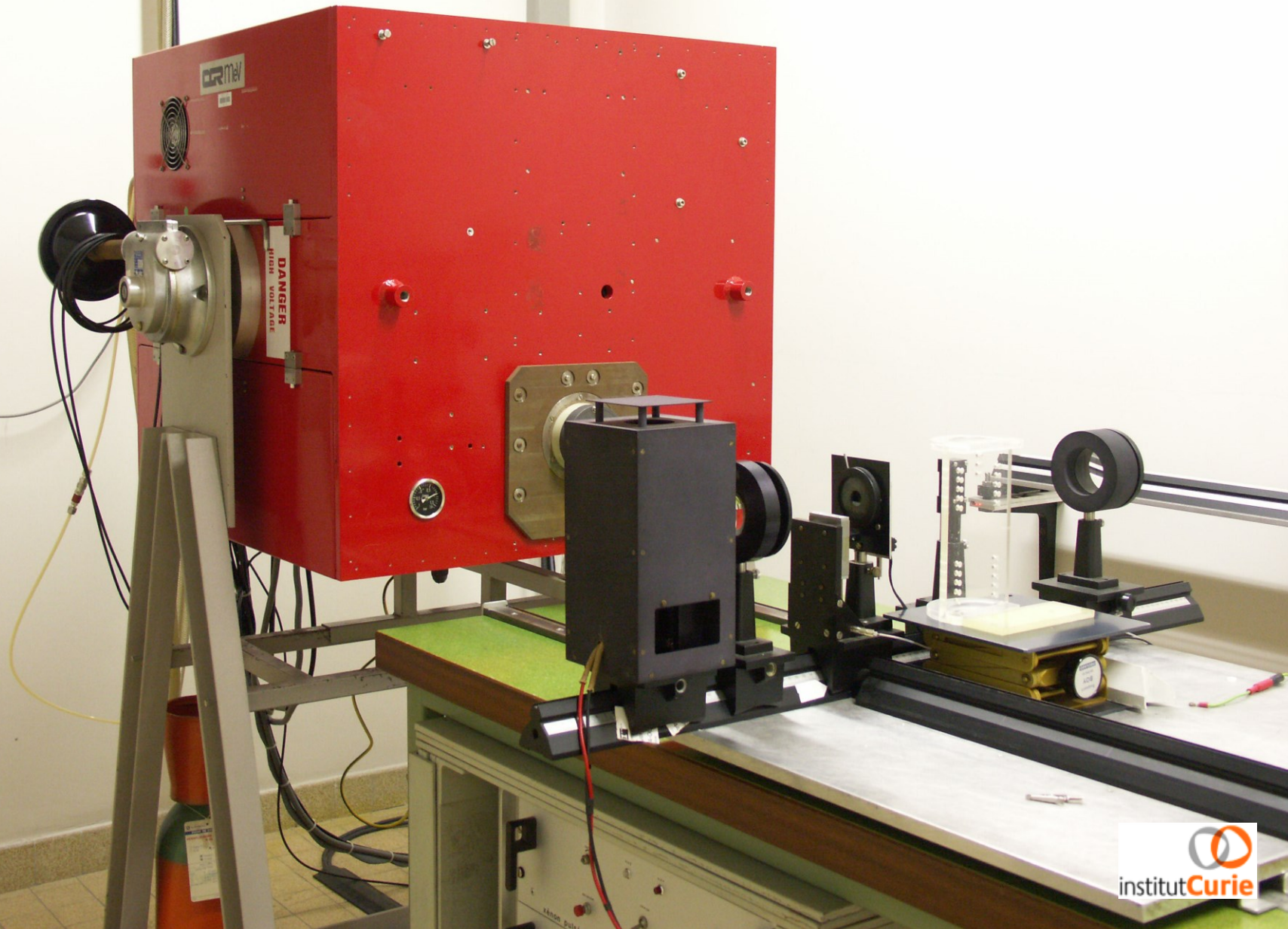
- **FLASH spared smooth muscle cells** in arterioles from radio-induced apoptosis.



- 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.



# Kinétron



# Specifications

LINAC “Kinétron” (1987)

**3.9-5.1 MeV electrons**

Triode electron gun

Thermoionic cathode

Pulse width 0.05 - 2.2  $\mu\text{s}$

Repeat frequency 0.1 - 200 Hz

**Peak current 0.01 - 200 mA (whole emission lobe)**

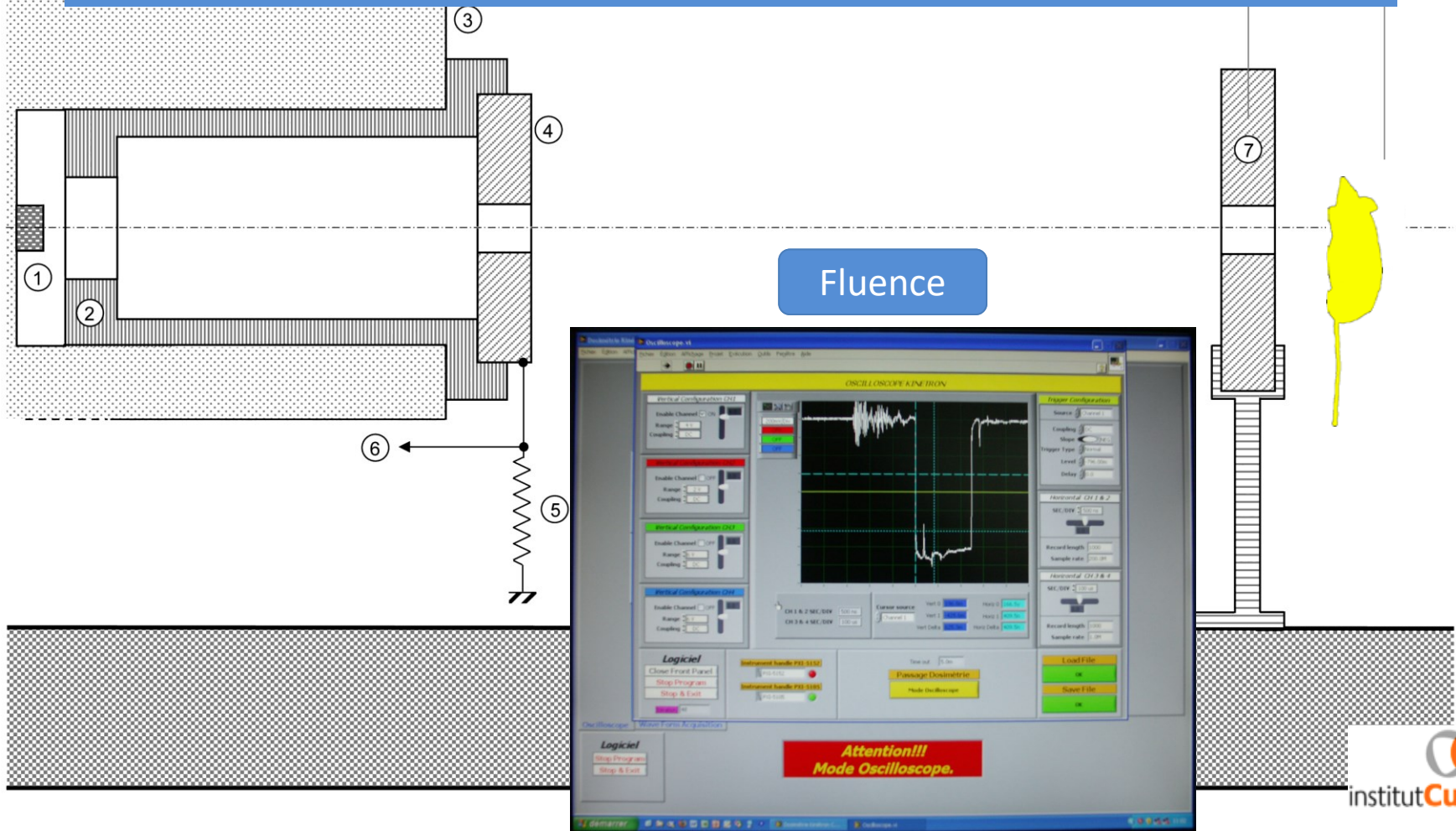
**Dose per pulse 0.001 - 50 Gy**

**Maximum dose-rate during the pulse  $\approx 3 \cdot 10^7 \text{ Gy}\cdot\text{s}^{-1}$**

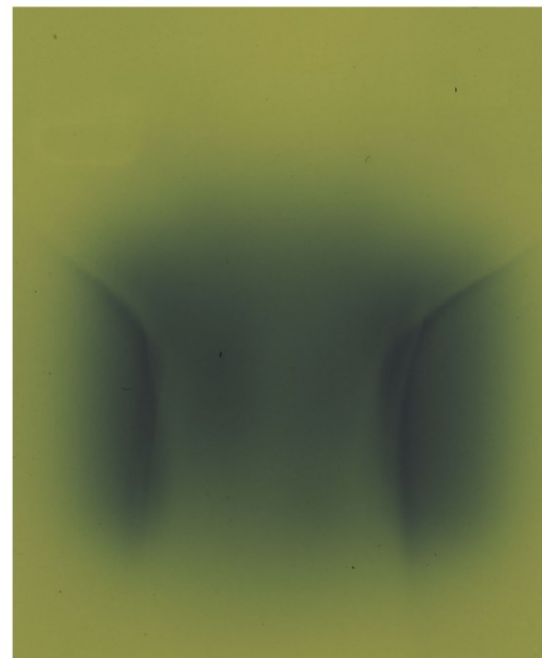
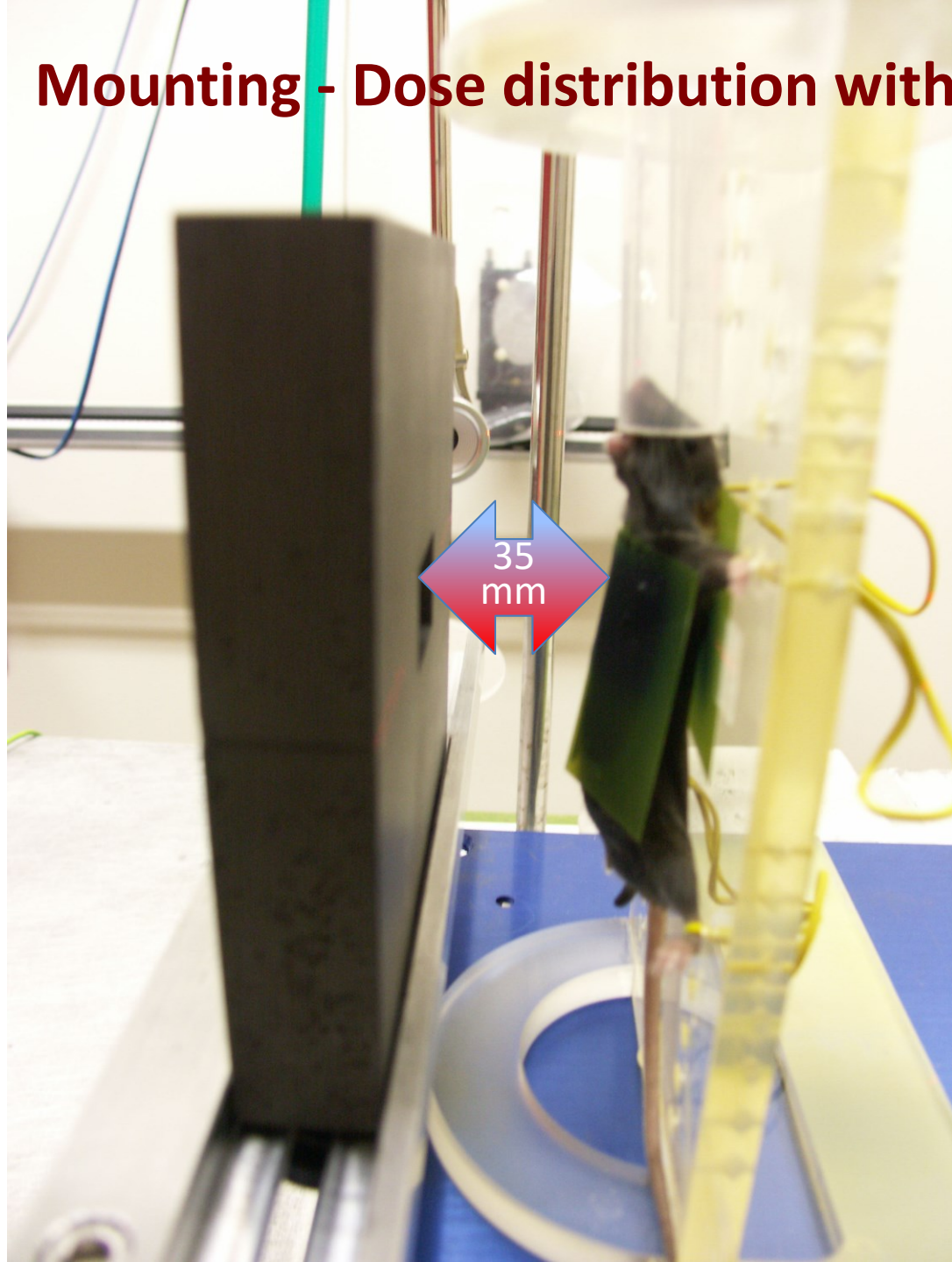
# Setup

Other available dosimetric methods:

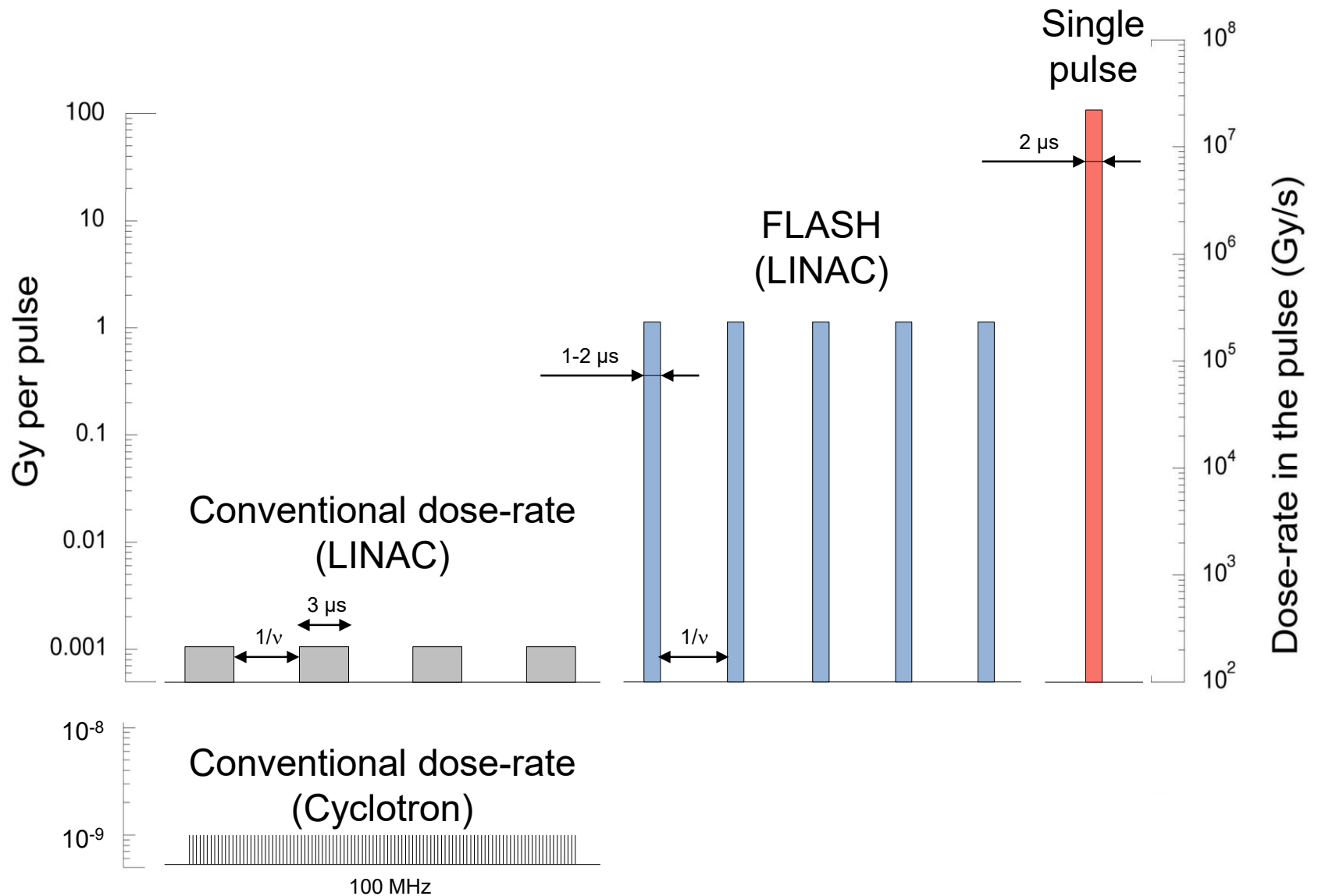
- Methyl viologen radical: submicrosecond, real-time optical detection
- Mallet-Cerenkov light : nanosecond, time-resolved dosimetry
- Gafchromic EBT3 films (leucomalachite green)
- LiF pellets (thermoluminescence)
- Low dose-rate: Markus ionisation chamber



# Mounting - Dose distribution with 4.5MeV electrons

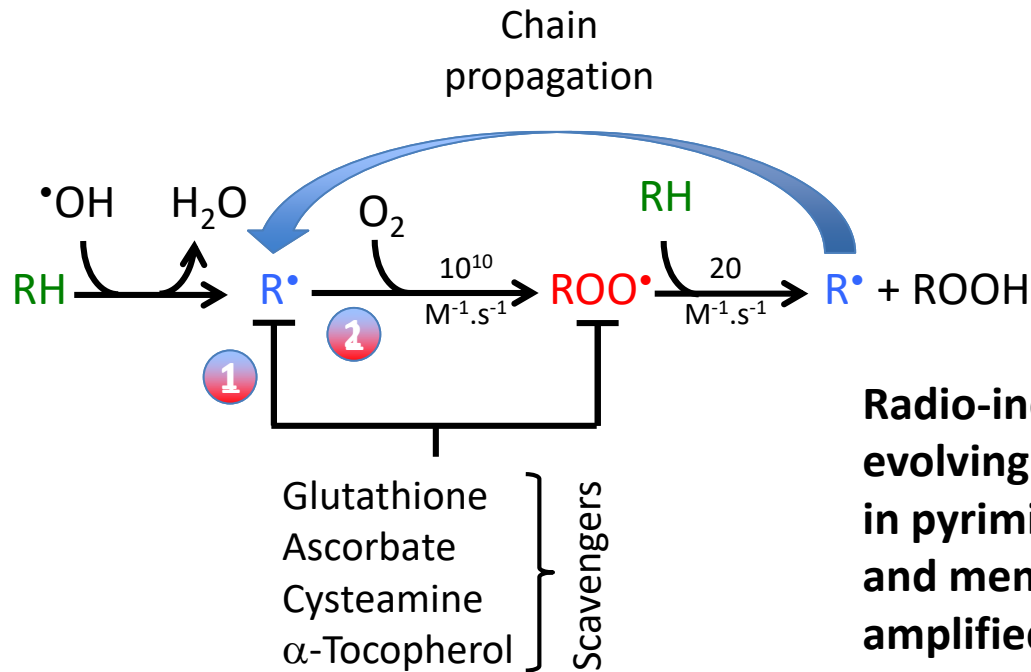


# Temporal structure of energy deposition in the FLASH effect

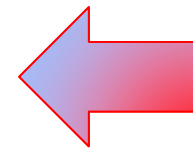
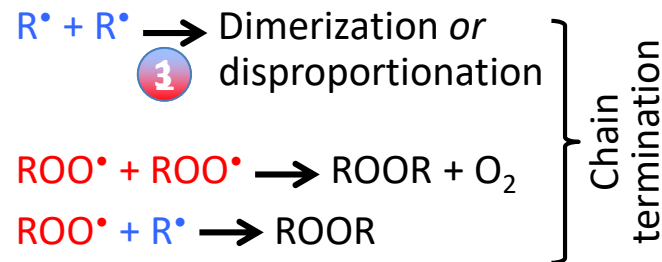




# The FLASH effect depends on the presence of oxygen



Radio-induced peroxyradicals evolving to peroxides are found in pyrimidines, deoxyribose and membrane lipids and are amplified through a chain reaction.



Diffusion

High mobility

## ACKNOWLEDGMENTS

**Inserm U 1021 – CNRS UMR 3347**

**Institut Curie, Orsay**

Charles Fouillade

Pierre-Marie Girard

Marie Dutreix

**Inserm U 1196**

**Institut Curie, Orsay**

Pierre Verrelle

**Physical Chemistry Laboratory**

**Paris-Sud University, Orsay**

Chantal Houée

**Laboratory of Radio-Oncology**

**CHUV, Lausanne**

Pierre Montay-Gruel

Marie-Catherine Vozenin

**Dept. Nucl. Med. Radiobiol.**

**University of Sherbrooke, Québec**

Jean Cadet

**INSA-Lyon**

**Platform of Functional Lipidomics**

Nathalie Bernoud-Hubac

Patricia Daira

Baptiste Fourmaux

**RadeXp**

**Institut Curie, Orsay**

Sophie Heinrich

**Animal facilities**

**Institut Curie, Orsay**

Christophe Alberti

Elodie Belloir

Virginie Dangles-Marie

Isabelle Grandjean

