

## Fact Sheet 1

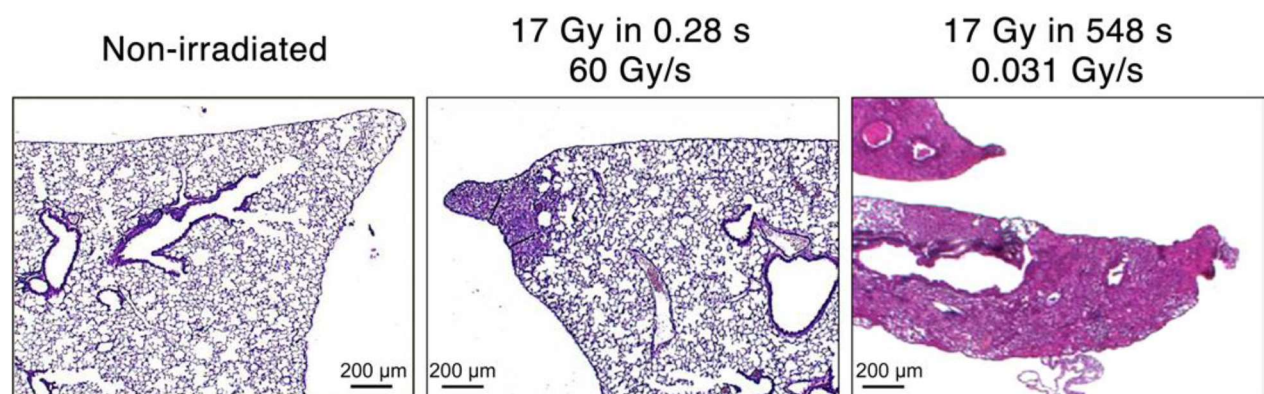
### The story of a revolutionary discovery at Institut Curie

Radiotherapy is, along with surgery, the most effective curative treatment for solid tumors, and more than half of all cancer patients require it. While considerable progress has been made in this field in terms of imaging, ballistics and dosimetry over the last few decades, dose delivery methods have not evolved much. **However, the discovery of the “Flash” effect in Institut Curie laboratories has led to a paradigm shift in radiotherapy.** Here's a look back at this discovery.

#### The breakthrough: delivering a swift and powerful attack on the tumor.

It all began in 1995: Dr. Vincent Favaudon, an Inserm radiobiology researcher at Institut Curie. He observed an unexpected effect of dose fractionation on cells *in vitro*, which he called the “W” effect. **After several years' work and the first communications in 2009, he published major results in 2014 in *Science Translational Medicine* demonstrating the “Flash effect” in a preclinical model<sup>4</sup>.** He demonstrated that very intense rays, delivered in a very short time, have the same anti-tumor effect as conventional radiotherapy, with two crucial advantages: **sparing healthy tissue and considerably reducing treatment times.** In conventional radiotherapy, the dose rate is around one Gray per second, with daily fractions of 2 Grays accumulated, whereas FLASH (ultra-high dose rate) delivers an irradiation dose of 10 Gy or more in a very short time of less than 100 ms (1,000 to 10,000 times faster than conventional radiotherapy).

In 2014, Dr. Favaudon's research on preclinical models demonstrated that a conventional 15 Gy dose used to treat lung tumors invariably resulted in pulmonary fibrosis—a significant late complication of radiotherapy—emerging between 8 weeks and 6 months post-irradiation. With FLASH irradiation, no fibrosis occurred below 20 Gy. This protective effect was also observed on apoptosis (programmed cell death produced by unrepaired DNA damage), blood capillaries and skin lesions. However, anti-tumor efficacy remained the same in all preclinical models. **FLASH irradiation therefore protects healthy tissue from side effects in a highly selective manner.**

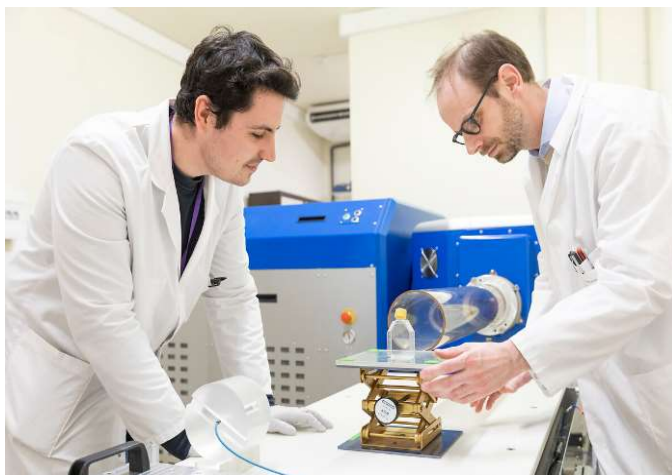


*Effect on healthy lung tissue of a 17 Gy irradiation delivered in 0.28 s, i.e. a dose rate of 60 Gy/s (center image) and in 548 s, i.e. a dose rate of 0.031 Gy/s (right image). Tissue irradiated at a very high dose rate has the same appearance as unirradiated tissue, whereas tissue irradiated at a low dose rate is totally altered.*

It took Vincent Favaudon and his team several years of basic research to accumulate sufficient data to unequivocally demonstrate this FLASH effect. Since then, numerous teams around the world have reproduced these results in different models, each time demonstrating **unchanged anti-tumor efficacy and protection against pulmonary fibrosis, memory loss, intestinal protection, etc.**

<sup>4</sup> See Fact Sheet 3 - List of publications

## A novel experimental device to validate clinical applications



**ElectronFlash 4000 installed at Orsay.** Maxime Dubail, PhD student, on the left, and Charles Fouillade on the right, radiobiologist in Institut Curie's Repair, Radiation and Innovative Anticancer Therapies team (Signaling, Radiobiology and Cancer Unit (UMR3347 / U1021)). Institut Curie / VOISIN Thibaut

The discovery of the FLASH effect in 2009 was made on a low-energy electron **accelerator installed in the laboratories of Institut Curie Research Centre in Orsay**: the kinetron (linear electron accelerator). In 2021, a new prototype device, the ElectronFlash4000, manufactured in Italy by SIT (pictured opposite), replaced the kinetron to conduct physical, physico-chemical, and radiobiological studies. These studies aim to better understand the mechanisms of FLASH irradiation compared to conventional irradiation. Such research is essential for advancing the next generation of electron accelerators, ultimately paving the way for clinical applications.

## Multidisciplinary research in radiobiology and radiophysics.

Teams at Orsay's Institut Curie focus their efforts on studying the physical, physico-chemical and biological mechanisms underlying the FLASH effect (optimal dose, dose rate, oxygenation, etc.). They analyze physiological compartments along with various molecular, cellular, and genetic pathways to unravel the mechanisms triggered by ultra-high dose-rate radiation. Their goal is to understand the key differences in how tumors and healthy tissue respond to radiation. Why do healthy tissues regenerate under the effect of FLASH radiotherapy whereas they do not under conventional treatment? There are many possible explanations, one of which lies in the role of oxygen, which is known to be a powerful radiosensitizer.

Teams at Institut Curie are involved in a number of research projects aimed at bringing the technique to the clinical trial stage (*see list of publications, FACT SHEET 3*).



## The Orsay site: ever more modern and efficient particle accelerators

Over the past 75 years, the Orsay campus has become one of the world's leading centers of scientific innovation, particularly in the field of nuclear physics. It is home to numerous research institutes, including the *Centre de Protonthérapie d'Orsay* (CPO) and Institut Curie laboratories.

### Particle accelerators

Particle accelerators use electric fields to speed up charged particles, such as electrons and protons—key components of atoms—while magnetic fields guide their trajectory. There are two types of particle accelerators: linear, where particles are accelerated in a straight line towards a target, and circular, where they follow a circular trajectory and collide. These collisions release large amounts of energy, enabling the creation of new particles or the modification of atomic nuclei.

### An annex of the Radium Institute at Orsay

**In the 1950s, the proton synchrocyclotron project initiated by Irène Joliot-Curie, then director of Institut Curie laboratory at Institut du radium, was born in Orsay.** Installation was completed in 1958. Frédéric Joliot-Curie also had a second circular accelerator moved to Orsay from the Collège de France: the historic cyclotron he had acquired in 1937, which was also used at Orsay until 1966.

### Accelerators to treat cancer

From 1991 to May 2010, Institut Curie's Centre de Protonthérapie d'Orsay (CPO) treated some 5,000 patients. In 2010, the CPO was equipped with a new, much more powerful particle accelerator to boost its clinical activity dedicated to treating patients with proton therapy (mainly ocular and pediatric tumors).

Today, the new FLASH-VHEE irradiator will be installed at the heart of the Orsay and CPO facilities, right where Frédéric Joliot Curie installed a cyclotron several decades ago...

For more information: <https://musee.curie.fr/blog/les-joliot-curie-et-la-naissance-du-campus-d-orsay>