Our team develop new antitumoral therapies associated to radio- and/or chemo-therapy to fight cancer resistance to treatment while limiting adverse effects.

New small molecules named DBAit that inhibit major DNA Repair pathways

During these last years we have:

- **Analyzed the mechanism of action of DBait** (short double-stranded DNA mimicking double-strand break).
- **Developed derived Dbait molecules with a cholesterol (AsiDNA)** to facilitate cells penetration without any transfection agent and studied the molecular mechanisms that determine the specificity of AsiDNA for tumor cells (sparing healthy tissues).
- **Demonstrated the clinical potential of the AsiDNA** in a first-in-man clinical trial (in association with radiotherapy to treat melanoma in transit).
- **Developed protocols of AsiDNA** in association with chemotherapy (mainly 5-FU, Carboplatin, Irinotecan, Doxorubicin) in solid tumors.
DNA Repair, radiations and innovative cancer therapies
UMR 3347/U1021 – Signaling, Radiobiology and Cancer

(colon cancer, hepatocarcinoma, breast cancer) and in association with radiotherapy or chemotherapy (etoposide, cyclophosphamide (4-HC), and vincristine sulfate) in hematologic malignancies

- **Tested protocols** of AsiDNA in association with poly(ADP-ribose) polymerase inhibitors and **validated** the concept of the synthetic lethality induced by targeted combined therapies.

In collaboration with ONXEO (www.onxeo.com), the team prepares next clinical trial to systemically administrate AsiDNA in patients with solids tumors (planned trial start in 2019).

**Identification of tumor sensitivity biomarkers to antitumoral treatment (i.e. AsiDNA)**

The survival of cells suffering spontaneous genetic instability, a common feature among tumor cells, depends on the efficiency of DNA repair. We have confirmed that this intrinsic characteristic of tumors and metastases is a prerequisite for the sensibility to AsiDNA to occur. We also showed that the presence of micronuclei in tumor cells from biopsies could be a good prognosis of the response to the AsiDNA treatment. The study of the feasibility and biodistribution of this biomarker in various types of tumors in clinic is in progress.

**Development of new modalities of radiotherapy**

- **The Ultrahigh dose-rate irradiation (FLASH)**

  The FLASH methodology consists in delivering the radiation dose in 0.1 second or less to target tissue, i.e, over 1000 times faster than in conventional radiation therapy. This technique relies on the use of linear electron accelerator with ultrahigh dose-rate based at the Institut Curie research center in Orsay.

  The V. Favaudon’s team at Institut Curie published in 2014 the results of a long-standing investigation carried out in vivo, demonstrating for the first time that FLASH irradiation spares normal lung tissue from radioinduced fibrosis whilst leaving the anti-tumor efficiency unchanged.

  We are currently working at decrypting and the physical, physico-chemical and biological “parameters” (optimum doses and dose-rates, oxygenation, physiological compartments, molecular and cellular pathways…) that account for normal tissue sparing from radiation toxicity. We focus our efforts to enhance our knowledge on the effects of FLASH radiation on normal tissues from both biological and technological sides and **bring FLASH radiotherapy to**
The cold plasma

Cold atmospheric pressure plasma (CAPP) is an ionized gas obtained at atmospheric pressure and room temperature and is used for biomedical applications such as healing, sterilization and decontamination. CAPP is composed of a mixture of reactive oxygen and nitrogen species (RONS), free radicals, electric field, photons, excited atoms and molecules. Part of the team, in a strong and efficient collaboration with physicists of plasma (LPGP, Orsay) who provided us a Helium-based plasma device, exploits these properties to target and eliminate in vitro and in vivo tumor cells.

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Our fundamental projects are conducted to understand the molecular effects of the treatments in cancer cells and at the preclinical level by developing animal models and setting coherent protocols of treatments in view of future clinical applications.

These projects are part of a local network organized on the Saclay University campus the AMINanoTheRad (https://www.universite-parissaclay.fr/fr/recherche/projet/nanotherad#presentation-3553) and a European network ITN-Radiate (www.radiate.eu).

Key publications

Year of publication 2021

Alexandre Leduc, Samia Chaouni, Frédéric Pouzoulet, Ludovic De Marzi, Frédérique Megnin-Chanet, Erwan Corre, Dinu Stefan, Jean-Louis Habrand, François Sichel, Carine Laurent (2021 Mar 13)  
Differential normal skin transcriptomic response in total body irradiated mice exposed to scattered versus scanned proton beams.  
Scientific reports : 11 : 5876 : DOI : 10.1038/s41598-021-85394-0

Year of publication 2019

FLASH Irradiation Spares Lung Progenitor Cells and Limits the Incidence of
**Radio-induced Senescence.**
*Clinical cancer research : an official journal of the American Association for Cancer Research : DOI : 10.1158/1078-0432.CCR-19-1440*

Wael Jdey, Maria Kozlak, Sergey Alekseev, Sylvain Thierry, Pauline Lascaux, Pierre-Marie Girard, Françoise Bono, Marie Dutreix (2019 Jul 31)

**AsiDNA Treatment Induces Cumulative Antitumor Efficacy with a Low Probability of Acquired Resistance.**
*Neoplasia (New York, N.Y.) : 863-871 : DOI : S1476-5586(19)30213-1*

**Experimental set-up for FLASH proton irradiation of small animals using a clinical system**
*International Journal of Radiation Oncology • Biology • Physics : 102 : 619-626 : DOI : 10.1016/j.ijrobp.2018.06.403*

**Predictive biomarkers of resistance to hypofractionated radiotherapy in high grade glioma**
*RADIATION ONCOLOGY : 12 : 123 : DOI : 10.1186/s13014-017-0858-0*

**Drug Driven Synthetic Lethality: bypassing tumor cell genetics with a combination of Dbait and PARP inhibitors.**
*Clinical cancer research : an official journal of the American Association for Cancer Research : DOI : clincanres.1193.2016*