Collision physics: application to ion beam therapy

Ion beam therapy has a great potential for treating radio-resistant cancers, but intensive research is needed to minimize deleterious side effects while maximizing treatment efficiency. This requires efforts in clinical and biological research, but also chemistry and physics, which is the aim of the advanced research center for hadrontherapy in Europe (ARCHADE) in Caen, in addition to state-of-the-art proton therapy that started in 2018. ARCHADE is located next to GANIL, which has been providing beamtime for hadrontherapy-related research since the LARIA radiobiology platform was launched.

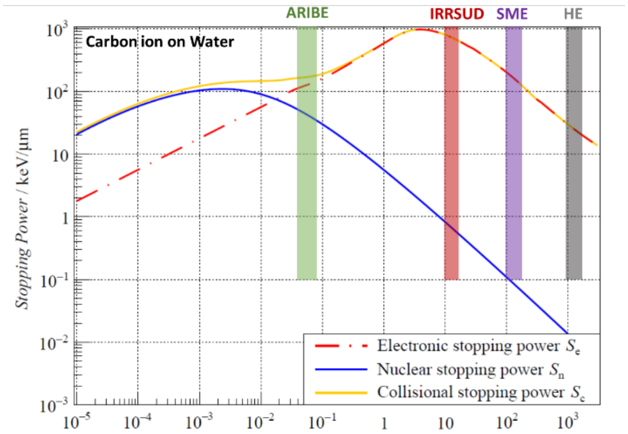

Figure 1: Stopping powers of carbon ions in water as a function of their kinetic energy. The ranges corresponding to GANIL beamlines are indicated.

Achieved and current work

At CIMAP, in recent years, we have increased the effort to better understand the biological, physical and chemical response of biological matter under irradiation, and thus the factors underlying the efficiency of hadrontherapy. Notably, we have carried out the IRHEMME project aiming at probing the consequences of a hadrontherapy of cartilage. This tissue being mostly composed of the collagen structural protein, we have applied collision physics experimental techniques coupled to mass spectrometry to unravel the molecular products of isolated collagen peptides after direct carbon ion irradiation, and found specific small molecules that might be toxic for cartilage cells and provide an explanation for the arthritis observed after cartilage radiotherapy. Furthermore, the specific triple-helix structure of collagen is damaged by carbon ions. The IRRSUD beamline has been used because the energy of the ions (about 1 MeV/u) is very close to the maximum energy transfer in biological matter (, see Figure 1) which corresponds to the Bragg peak. This has been achieved thanks to an international collaboration involving the University of Groningen. Our collaboration is also investigating radiation-effects on DNA, and in particular the role of specific duplex or G-quadruplex structures on single- and double-strand breaks. The latter have been shown to play a crucial role in the death of cancer cells in radiotherapy. Therefore, much effort is nowadays dedicated to increasing the number of double-strand breaks during radio- and hadrontherapy, notably by means of radiosensitizers such as nanoparticles (NPs). Indeed, the latter have been shown to be a source of electrons that induce double-strand breaks either directly or via the production of $HO^{\bullet}$ radicals. Recent theoretical work has demonstrated that electron emission from NPs results from different types of collective electron excitation. These processes are thought to be nanoparticle size-dependent but also to vary quite significantly with the projectile ion energy. At CIMAP, to quantify these processes, the recent IMAGERI ANR project aims to measure absolute cross-sections of electron emission from isolated metallic nanoparticles, and compare the results from different GANIL beamlines.

Perspectives and needs

These last years, due to the lack of available beamtime at GANIL, allocated beamtime by the iPAC has drastically dropped compared to the increasing of the requested beamtime**.** This is a problem for keeping the interest of external users involved in our international collaborations, and regarding the amount of data that our PhD students can obtain in three years. Besides, although only scarcely used for the moment in our field, ion beams delivered by the SME and HE beamlines (around 10 and 100 MeV/u, respectively) are also of interest, because they corresponds to the energy of ions when they interact with healthy tissues in hadrontherapy. Within the IMAGERI ANR project, measurement of absolute cross-section of electron emission from biomolecular building blocks and nanoparticles will be performed in a near future on the SME beamline. Moreover, our goal is to extend the work done at the IRRSUD beamline on proteins and DNA to these higher energy ranges. Therefore, a first need for our community is more beamtime, especially at IRRSUD, a factor of two or three compared to what was scheduled recently. Second, carbon ion beams at different charge states are required to investigate the effect of this parameter on the processes induced, especially at the IRRSUD beamline, since the charge state decreases quickly with penetration depth in tissues around the Bragg peak.

One of the most active areas of research in hadrontherapy nowadays is the investigation of the Flash effect. This is a very promising way because it has been shown that electrons and photons irradiation at very high dose rates (on the order of 100Gy/s) but usual doses induce less damage to healthy tissues than conventional treatment modalities, while being as effective on cancer cells. The first attempts to look for such a Flash effect for protons have been made only very recently, notably at the Institut Curie (Orsay, France). GANIL should be one of the leading facilities regarding the quest for a Flash effect for carbon ions, due to its high potential in sparing healthy tissues while killing tumor cells. This would imply a technical update of the existing cyclotrons to deliver such high dose rates in very short and intense ion pulses. It would be highly interesting for radiobiologists, but also for our community, because of the possibility of time-resolved pump-probe experiments with ions and/or lasers, yet to be performed. Such experiments could shed light on dynamics of ion-induced denaturation of proteins and DNA, a totally unexplored field.