CYRCé Platform

(CYclotron pour la ReCherche et l'Enseignement)

1) abstract

Molecular imaging is an essential tool to study disease development, treatments (drugs, irradiation), biological processes,… in vivo, non-invasively. Thanks to their very high sensitivities, Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) play a central role in this research domain. To perform PET and SPECT imaging we need an isotope (positron emitter or gamma emitter) combined to a molecule of interest, an animal model and a PET or SPECT system.

The history of the CYRCé platform began 15 years ago when the ImaBio group of the IReS lab developped AMISSA (A small Multi-modality Imaging System for Small Animal) combining SPECT and CT modalities on the same bench. The surrounding infrastructure has then been implemented with two Contrat de Plan Etat-Region (CPER: 2009-2014 and 2015-2020): one mostly dedicated to the production of radioisotopes with the installation of a cyclotron and the second one for the development of proton beam lines in a separate area as well as the biology laboratory. Today, the CYRCé platform can provide animal model, host them, acquire the biodistribution of an injected radiolabelled molecule and evaluate innovative treatments such as preclinical proton-therapy.

Even if the CYRCé platform is independent, it strongly benefits from the developments made by the molecular imaging team and the hadrontherapy team as well as the technical support of IPHC.

The CYRCé platform consists now in four different parts: an animal house, an imaging facility, a biology laboratory, an irradiation facility (with 2 proton beams, liquid target and solid targets). 5.7 FTE work on the different parts of the platform.
The platform is used by researchers from IPHC, Strasbourg, France and all over the world.

2) description

The CYRCé platform consists in four different parts: an animal house (headed by B. Jessel), an imaging facility (headed by L. Thomas), a biology laboratory (headed by E. Santiago) and an irradiation facility (headed by M. Pellicioli). The all platform is headed by P. Laquerriere (scientific coordinator) and M. Pellicioli (technical coordinator)

-The animal house can host 500 mice or 200 rats in two rooms. It also has a quarantine in another room.

-The imaging facility consists in 3 rooms : one with a shielded hotcells where the radioactive solution is prepared and put in syringes, one for the mice preparation (anaesthesia, injection, dissection …) and one with the imaging systems. The imaging systems are: a homemade SPECT-CT and a PET-CT from Inviscan both equipped with anaesthesia systems. The SPECT has a 0.9mm spatial resolution and 0.0004% efficiency. Its CT has 50µm spatial resolution. The PET has 1.2mm spatial resolution (in the middle of the field of view) and 9% efficiency. Its CT has 100µm spatial resolution. Mice, rats, birds, hamsters, non-human primates have already been imaged on the platform as well as ex-vivo specimen.

-The biology laboratory is equipped with two Microbiological Safety Cabinet, an incubator and a centrifuge. All these equipments are dedicated cell culture.

-The irradiation facility has two distinct rooms: the vault (funded by the CYRCé CPER) and a separate irradiation room (funded by the PRECy CPER). The vault hosts the ACSI TR 24 cyclotron (Canada). The maximum energy we can get with this cyclotron is 25MeV (500 µA max). We developed a degrader to access most of the energy we need to produce our isotopes. We produce 18-F on a homemade small volume liquid target (1mL) and 64-Cu and 89-Zr on a homemade solid target on which we added a fully automated transfer system (there are discussion with ACSI to patent and sell our system). In a room next to the vault, we recently built a new room dedicated to proton irradiation. There is a switching magnet with five exits. Currently two are used. One beam line, paid by the CMS collaboration, is more dedicated to the physics (detectors, materials…) and the other one is dedicated to biology (plants, cells, animals).

The platform has a steering committee composed of the responsible of all the four parts. This steering committee set the planning of the platform and follow the different projects. It is helped by a scientific committee to choose the projects that will be done on the platform. We organize six steering committees per year approximatively. The scientific committee is composed of five external people from all the field concerned by the platform (nuclear medicine, physics, radiobiology) :

Gilles Karcher (nuclear medicine, Nancy), Nicolas Foray (radiobiology, Lyon), Jean-Michel Chezal (radiochemistry, Clermont-Ferrand), Jean Colin (physic, Caen) and Ferid Haddad (radiochemistry, Nantes)

All the staff working on the platform are from IN2P3.

Most of the users are working on cancer (breast, prostate, hepatocellular carcinoma, glioblastoma, …) even if other users work on neurology (neurolupus), haematology (platelets),…

Over the last 3 years, a quarter of the users come from IN2P3, a quarter from CNRS (except IN2P3), a quarter from (INSERM, universities …) and a quarter from foreign countries.

There are fees to access the platform services. We have four different rates: one for IPHC, one for French public laboratories, one for foreign academic laboratories and one for private laboratories. Nine different services are offered by the platform.

3) Scientific goals

It is complicated to highlight a specific result from all the results obtained on the platform. The platform is mainly used to image mice and study the development of pathology or the effect of treatment using PET or SPECT system. The second main utilisation is the proton beam to perform proton therapy on mouse tumours, cells or plants.

I will present an important project concerning both uses.

Concerning the use of the imaging facility, it has been demonstrated that F-DOPA, a PET tracer, could be used to detect neuroendocrine tumours. In this project, the platform produced 18-F, hosted the mice and imaged them on the PET system (Journal of Nuclear Medicine 2017).

Concerning the use of the proton beam, it has been demonstrated (not yet published but submitted) that on hepatocellular carcinoma, it was possible to study the effect of proton treatment using four PET tracers. Every part of the platform was used during the project (proton beam irradiation, 18-F production, animal house and imaging facility). This project ‘rpPET) was funded by INCa

To obtain those results and others, the platform set up the production of isotopes (64-Cu and 89-Zr), mouse models, imaging protocols, proton beam. For the production of metal isotopes, we developed solid target irradiation (target, degrader, target transport to hot cells and automatic synthesizers). For the animal models, we had to choose which cell line we could inject in which kind of mouse, where to inject the cells in mice. We also determined the quantity of each radiotracers that had to be injected to mice to obtain the best image as well as the acquisition duration and the biodistribution time.

4) Platform environment

The history of the CYRCé platform began 15 years ago when the ImaBio group of the IReS lab built the AMISSA (A small Multi-modality Imaging System for Small Animal) consisted at the beginning of a homemade µSPECT and a homemade µCT (Computerized Tomography) leant to an animal house. In 2009, the lab, that became IPHC (Institut Pluridisciplinaire Hubert

Curien) obtained 5M€ to buy a cyclotron and its associated facilities (mainly building, hot cells, Good Manufacturing Practices (GMP) area, PET system). In 2012, everything was set up: the CYRCé platform was born. In 2015, IPHC obtained 1M€ to develop a proton beam line and a biology laboratory. The biology laboratory is finished since October 2019. The two proton beam lines are also finished and commissioned: one since December 2019 and the other one since January 2020)

This platform with its entire component is unique in France and very rare in Europe (not sur there are others in Europe). Most cyclotrons in France belongs to companies. There are very few cyclotrons able to reach this energy in Europe (there is on in Dresden and soon one in Bulgaria and in England). We choose this cyclotron because it has two exit ports with variable energy ranging from 16 to 25MeV and an external source: we use one for isotopes production and the other one as a proton beam. We started the project by considering that it exists more than 1 000 molecules labelled with 18-F but only 5-6 of them are FDA approved in France. In Human, probably 90% of the exams are made using FluoroDeoxyGlucose (FDG). For the preclinical research, it is very complicated to have access to another molecule than FDG. One of the first goal was to give access to those other molecules. For this purpose, we developed a database where most of the published paper on fluorine molecules can be found: http://www.iphc.cnrs.fr/dirac/

The advantage of the CYRCe platform is the variable energy of the cyclotron. It seats between ARRONAX (70MeV) and AIFIRA (4MeV) energies. One very important feature of the ACSI cyclotron is its running current. We can have a very stable current from few hundreds of aA (at the end of the beam line) to 500 µA.

The platform is in the same LabEx as ARRONAX : Innovative Radiopharmaceuticals in Oncology and Neurology. Our objective in this LabEx was to produce 64-Cu and 89-Zr. The CYRCe platform is the backup of ARRONAX for the 64-Cu production and ARRONAX is the backup for the 89-Zr production.

Nancy Hospital (Grand-Est region) hosts the most important nuclear medicine unit. Fifteen years ago, they started a GIE (Groupement d'Interet Economique) called Nancyclotep in which the partners are the university of Nancy, the Nancy Hospital and a pharmaceutical company called posifit. Nanctclotep rents the GMP area of the platform and they will buy us 18-F for their radiotracer productions.

5) futur of the platform

In 2019, the CYRCé platform obtained the IBISA label. The IBISA committee gave the platform money to buy an autoradiography system (60k€). This system will allow us to fill the gap between PET or SPECT and optical microscopy. We already explore the utility of this field through a PhD that has been defended last November.

Recently 68Ge/68Ga generator were FDA approved. The hospital saw the possibility to do PET imaging without a cyclotron. So there is an increasing interest in molecules radiolabelled with

68-Ga. In 2018 we obtained a financial support from the French Grand-Est region to develop 68-Ga production by cyclotron (215k€).

To treat a tumour using a β- isotopes, one need to know the dose deposition in the patient. The ideal case is when you can use the same molecule to treat and image. For example, the dosimetry can be calculated from the PET image. In 2019, the extension of the IRON labEx (also called IRON 2) was approved by ANR (135k€). In the extension, we will developed the production of 67-Cu. 64-Cu is a β+ emitter and 67-Cu is a β- emitter. We will have a theranostic pair 64-Cu/67-Cu.

Nuclear medicine unit of the hospital of Nancy is developing the interne radiotherapy using alpha isotopes. They need to test biological hypothesis so they need an alpha beam. So we proposed for the next CPER (2021-2027) to develop an alpha beam using the reaction ^{7}Li(p, α) in addition to the extension of our animal house.

6) human resources and funding

Eight people are working on the platform currently for a total of 5.7 FTE. All of them are from IN2P3. We regularly used all the IPHC services but especially the mechanical service as well as the accelerator service.We hired Estelle Santiago last year for the biology laboratory. Now we just need a technician in chemistry to prepare and clean the synthesizer for each production of radiotracer, syringes. IN2P3 gave a FSEP position at the end 2019 but no one from CNRS applied.

The every year costs of the platform are 100k€ in average: 50k€ for the fluids, 40k€ for the other running costs and 10k€ for the breakdowns. The other costs (mice, anaesthesia, 18-F production …) dedicated to a specific project are paid by the principal investigator of the project (most of the time ANR, INCa …).

7) SWOT

S : installation unique in France (Europe), very efficient staff (IN2P3), low current possibility

W : need more people, dependent on PI success to proposals, few proposal where to obtain >1M€

O : new challenging projects

T : big (expensive) problem on the cyclotron, TEP system. Retirement (1 x 1962, 2 x 1965)