



“**Advanced Resource Centre for HADrontherapy in Europe”**

Summary of the main ARCHADE research proposals

Coordination: Prof J. Bourhis

Writing: E Baron, A. Batalla, J. Bourhis, J. Colin, D. Cussol, M. Drouet, J.M. Fontbonne, P. Lagalle, C. Laurent, J.L. Lefaix, A. Mazal, M-H. Moscatello

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Cancer is a major public health problem and the leading cause of death worldwide. The European Union every year sees 2 800 000 new cases and 1 700 000 deaths, while in France approximately 300 000 new cases are diagnosed, only half of which can be cured with the current treatments of surgery, chemotherapy and radiotherapy. Used alone or combined with other treatments, radiotherapy is a major contributor to curing cancer. For over a century it has been based on the use of high-energy (several MeV) gamma rays or x-rays, and is currently expanding rapidly in three major areas:

- (1) improvements in precision to increase the efficacy of tumour irradiation, while minimising damage to neighbouring healthy tissues;
- (2) increasing use of multimodal and functional imaging (positron emission tomography, magnetic resonance imaging) for more accurate tumour targeting;
- (3) combination of biological modulation with irradiation to increase antitumour efficacy.

Against this backdrop, hadron therapy is a new treatment modality which uses beams of protons or carbon-12. France has two proton centres—at Orsay and Nice—which treat a total of about 800 patients a year. Hadron therapy using carbon-12 is the latest development and has a twofold advantage over x-rays:

- (1) **targeting**: like protons, carbon ions enable accurate delivery of the radiation dose to the tumour;
- (2) **biological**: carbon ions are much more effective against certain cancers highly resistant to conventional x-rays. For the same degree of safety of healthy tissues, the biological effectiveness of the dose delivered to the tumour can increase from 1- to 3.5-fold, depending on the type of tumour considered, compared with x-rays or protons.

Carbon ion therapy is one solution of the future to circumvent the problem of the radioresistance of certain cancers, notably some of those that are inoperable.

While the advantages of carbon ions are apparent in theory, analysis of the clinical benefits has started in very few clinical centres because of the use of logistically complex and costly facilities: at the end of 2009 there were just two working centres in Japan and one in Germany, and to date about 5000 patients have been treated with carbon-12. The clinical results have been particularly promising in certain radioresistant cancers: high levels of tumour control were achieved for inoperable and generally incurable cancers such as mucous melanomas, sarcomas (osteosarcomas, chondrosarcomas), salivary gland cancers, certain brain tumours, or cancers difficult to access surgically under the base of the skull. Armed with these very encouraging results, the plan is to extend carbon ion therapy to other cancers resistant to conventional x-rays, of which there are an estimated 3000 to 5000 cases per year in France. In Europe, hadron therapy is advancing apace with the forthcoming opening of treatment centres (Heidelberg, 2009; Pavia 2011) and several others under construction (Marburg, Kiel). In France, it is planned in the years to come to open two centres for carbon ion therapy, one dedicated to research in Caen (ARCHADE) and the other more to clinical applications in Lyon (ETOILE). The rapid development expected for hadrontherapy generates considerable research and development requirements in:

- particle accelerator technology.
- beam control, analysis of tissue distribution and efficacy of the dose.
- treatment planning systems (TPSs): calculations, validation and clinical research.
- preclinical and fundamental applied radiobiology.
- isocentric gantry and repositioning system.
- teaching and training.

ARCHADE: European hadron therapy resource and research centre, in industrial partnership with Ion Beam Applications (IBA)

In this context, a European resource centre for hadron therapy, ARCHADE, is being created in Caen, and will be dedicated to fundamental and applied research. This proposal of European scope is also part of a national plan, notably through a quadripartite agreement with ETOILE (Lyon), the Orsay Proton Therapy Centre (Curie), and the Centre Antoine Lacassagne (Nice).

In December 2009, the Centre National de la Recherche Scientifique, "CNRS/IN2P3" (GDR-CNRS MI2B, Modelling and Instrumentation for Biomedical Imaging) and ARCHADE signed an agreement to create a Scientific Interest Group entitled "Research and development in hadron therapy", with a view to:

- Measuring reference physical data.
- Developing instruments for beam control and dosimetry.
- Developing models and simulations for dose calculation.

The ARCHADE facility thus created will have a beam line devoted clinical research, and a line for fundamental research in biology and physics.

ARCHADE is currently a nonprofit organisation (French law of 1901) that includes the Caen University Hospital, the François Baclesse Centre, ENSICAEN and Caen University. In 2010-2011, two companies are being set up to develop the ARCHADE project: 1) SAPHYN, a public-private company to develop applications of nuclear physics to healthcare and for technology transfer to other companies, and 2) CYCLHAD, a joint venture between IBA and SAPHYN, which will invest in and run a centre housing a cyclotron and its associated equipment.

On the campus, around ARCHADE, is a scientific environment particularly favourable to the development of this proposal, divided between the following organisations:

- GANIL (CEA-DSM//CNRS-IN2P3), nuclear physics research centre.
- Caen University and in particular IFR-146 (Federative Research Institute with labs working on various biological topics, including cancer).
- Caen University Hospital and François Baclesse Centre.
- CYCERON (CEA/CNRS/INSERM), centre specialised in neuroscience and medical imaging.
- ENSICAEN, its associated laboratories, in particular the Particle Physics Laboratory.

And the following laboratories:

- CIMAP, laboratory for the nonnuclear disciplines at GANIL.
- LARIA, (CEA-DSV), radiobiology research laboratory.

ARCHADE is part of a coherent national project, through a quadripartite agreement, but is also European in scope, through key partnerships forged in the field of hadron therapy (see WP6). ARCHADE will be the only European resource centre entirely given over to hadron therapy research and innovation.

The proposal is to develop an entirely new technology to set up the first medical cyclotron able to deliver both protons (230 MeV) and carbon ions (400 MeV/nucleon), which hitherto have only been produced by synchrotrons.

The rapid developments expected of carbon ion therapy call for considerable means, given the extent of the fields of research and investigation to be explored. In the first instance, the initial programme is planned for 2011-2015 and has two main objectives:

- (1) Qualification and operation of carbon ion therapy for medical use.
- (2) Research, innovation and development.

In this perspective:

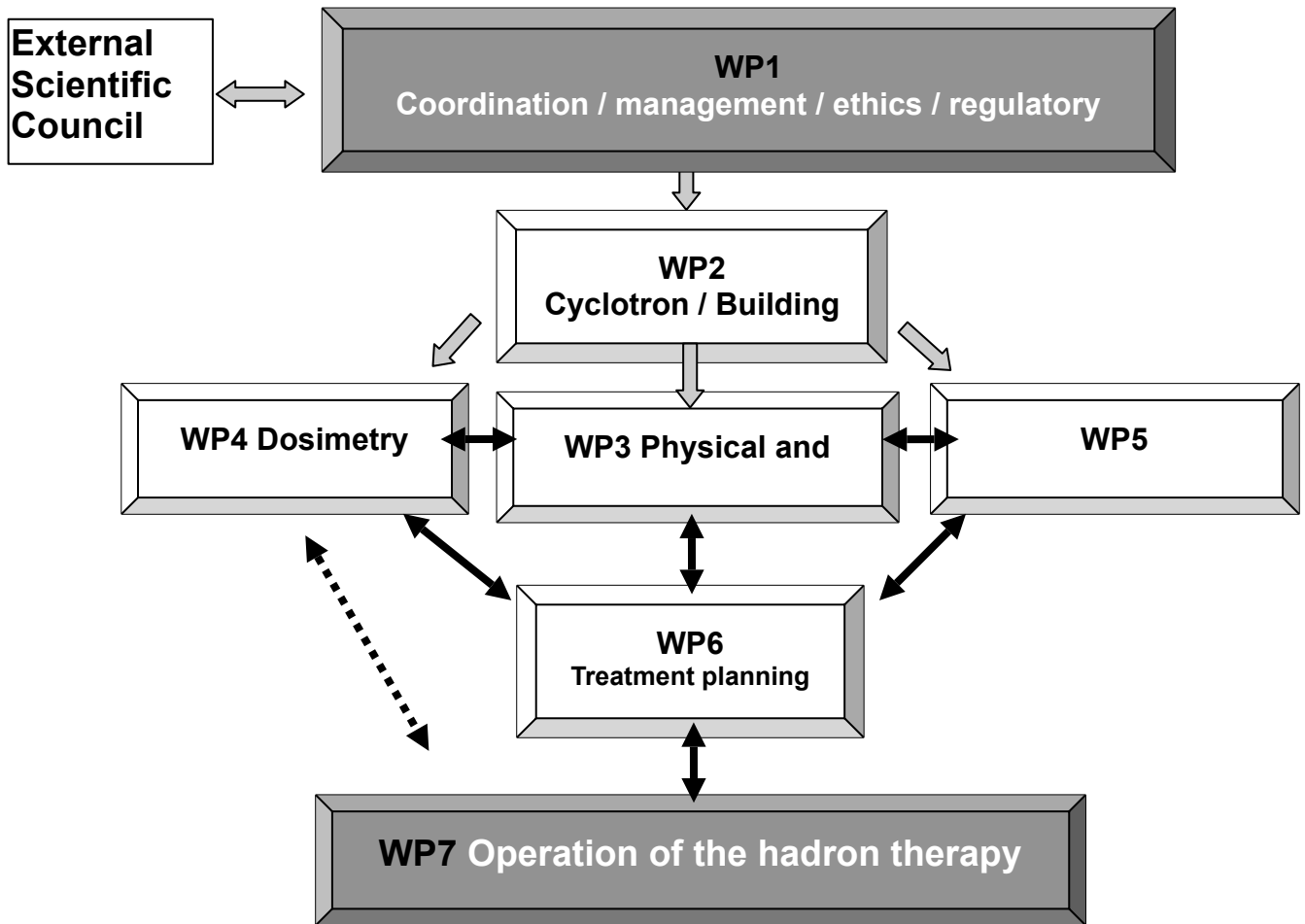
- **the first phase of the proposal** consists in anticipating and realising developments in physics and radiobiology that are needed before commissioning of the cyclotron, using existing material resources of GANIL, the François Baclesse Centre, the Particle Physics Laboratory, LARIA, etc.
- **the second phase of the proposal** is intended to validate the results of the first phase concerning the hadron therapy facility (C400 cyclotron) and to operate the cyclotron for medical use.

This second phase will enable the setting up of a centre for hadron therapy resources and training and the forging of European partnerships with existing and future hadron therapy centres.

The proposal is divided into 7 work packages (WPs), as shown in the table and diagram below. Several activities concerning notably the WP1 and WP2 started before the signing of this contract between SAPHYN and IBA.

	Work packages
WP1	Coordination /Administrative and scientific management of the project
WP2	Cyclotron /building & radiation protection
WP3	Numerical simulations
WP4	Dosimetry and beam control
WP5	Hadron biology
WP6	Treatment planning system
WP7	Commissioning of the hadron therapy facility

** The WP6 partners are: IBA, Elekta , Istituto Nazionale di Fisica Nucleare – INFN (Italy).



WP1: COORDINATION / PROJECT MANAGEMENT

Given the project's complexity and multidisciplinary character, project management and risk analysis are described in a separate document.

WP2: TECHNICAL PROJECT

Coordination : P. Lagalle/ M-H. Moscatello/ E. Baron

The ARCHADE proposal is founded on the construction and development a hadron therapy facility comprising a cyclotron, its equipment and a building (Hadron Therapy Research and Treatment Facility).

The C400 cyclotron, a prototype proposed by the Belgian company IBA, is an extrapolation of the C230 model developed over the last ten or more years for proton therapy. This new model, which is fitted with cryogenically cooled coils, will be able not only to produce proton beams (energy 230 MeV), but also 400 MeV/nucleon carbon ion beams.

The acceleration of other light ion species helium, lithium, boron, etc... is also planned.

The cyclotron will offer two beam lines, one parametrised for treating patients in clinical research protocols and the other dedicated to experimental research in physics, dosimetry and radiobiology. The whole facility, which forms the infrastructure of the ARCHADE centre, is housed in a building designed to comply with the radiation protection standards in force.

I. Description of the facilities

I.1. Cyclotron

The cyclotron is essentially a steel cylinder 6.6 m in diameter and 3.40 m long, constituting the casing of the magnet which produces the magnetic field that confines the ion beam trajectories (Figure 1). Cooling of the conductive coils by the circulation of liquid helium enables a high magnetic field to be produced, thus reducing the size of the machine.

The ions: molecular hydrogen H^{2+} , alpha particles, carbon, etc., are produced in three different sources placed under the cyclotron and injected axially into it. After acceleration by two electrodes fed by high-frequency voltage, the beam is ejected using:

- a thin sheet to strip off the H^{2+} ions, thus producing protons
- an electrostatic deflector for all other ion species

The operation requires a high vacuum:

- to minimise beam loss by charge exchange
- to avoid arc discharges in the acceleration electrodes and in the electrostatic deflector

I.2 Beam lines

The beam is then directed to degrader, a graphite target of thickness that is adjusted depending on the energy required at the point of use, be it the patient or the research experiment (Figure II). A system of magnets and slits eliminates the ion species created and the undesirable energies (energy selection system). Tubes under vacuum conduct the beam, which is directed and focused by magnetic dipoles and quadrupoles.

The clinical research beam line (room 2, Figure II) ends with a treatment head, and in particular has two magnets of variable magnetic field that allow horizontal and vertical scanning of a tumour profile. The room is equipped with a robotic bed and a positioning system.

The experimental beam line (room 1, Figure II) is also fitted with a beam scanning device, a reaction chamber and equipment for irradiation of cells or small animals.

I.3. Building

I.3.1 Cyclotron and beam rooms

The building housing the cyclotron and the beam rooms (Figure II) must be adapted to the facility and its operation and to the treatments. It must also of course comply with safety and radiation protection standards.

The sources of radiation (neutrons and gamma) are principally the electrostatic deflector of the cyclotron, the degrader and the slits that provide both angular and energy selection.

Certain elements are activated to various levels by:

- the direct beams : deflector, degrader, slits
- the neutrons: concrete used as protection against radiations ; some beam line components.

Operating precautions are taken to protect personnel and patients:

- thickness of the shielding
- device for quasi instantaneous interruption of the beam
- safety of access to rooms
- radiation monitoring instruments
- possible delayed access system
- ventilation

for both normal operation and incidents.

.2 Facilities without ionizing radiation

Requirements for components that do not generate ionizing radiation have been evaluated in terms of area:

- premises for the centre's management team
- facilities for logistics and shared utilities
- facilities for research and development in radiobiology and physics
- clinical sector for management of patients participating in clinical research protocols.

The expression of these requirements for the facilities described above is summarised in an Operational Programme, which will be forwarded to the Developer .

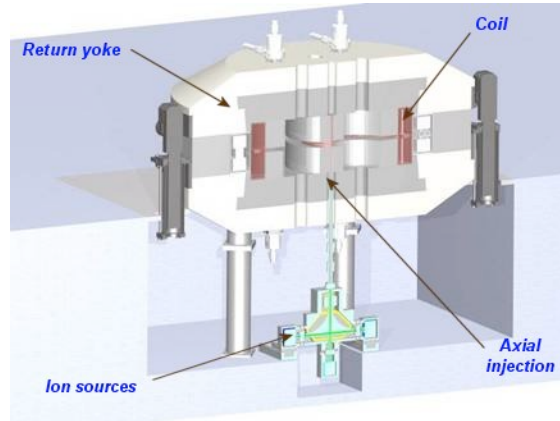


Figure I. Vertical section through the cyclotron

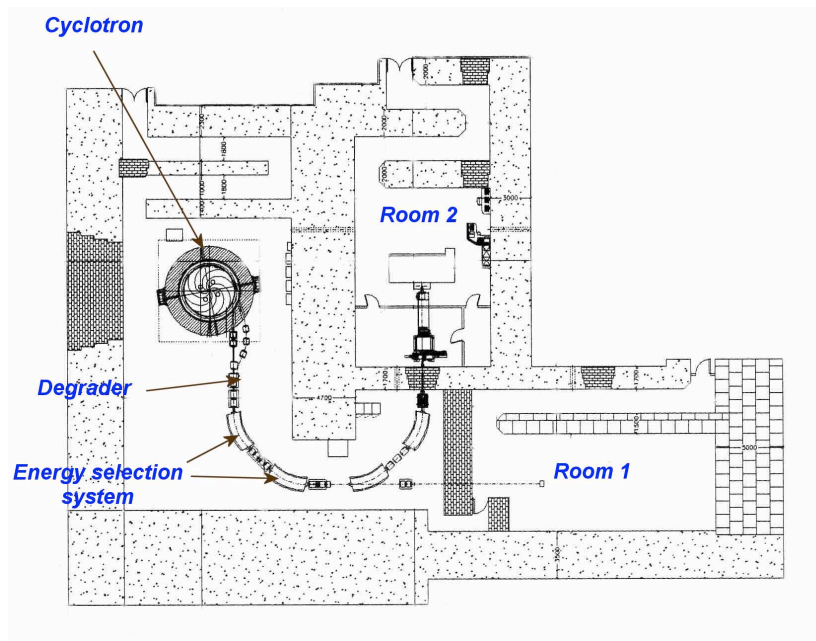


Figure II. Layout of the building housing the cyclotron and beam lines

II. Task assignment

The design, assembly and operation of the cyclotron are entirely overseen by IBA or its subcontractors. The same is true of the treatment beam line and the research beam line (apart from the experimental equipment).

The technical specifications and the acceptance tests are established jointly by ARCHADE and IBA and defined contractually.

ARCHADE and IBA have jointly produced the Operational Programme for the building requirements, and the Preliminary Safety Options File (DOSP), drawn up with the help of an engineering and innovation consultancy (ASSYSTEM). These two documents constitute information required by the Promoter chosen by ARCHADE and signatory to the contract for the design, construction and maintenance of the building.

ARCHADE is responsible for the safety of the facility.

III. Key technical characteristics of the system

As an indication, the characteristics listed below are valuable for a good understanding of the different parts of the scientific programme. The system is delivered with 3 sources for p, α and ^{12}C . The incident beam is horizontal for treatment of patients and for use in experimental work.

Beam of carbon-12 ions

- Beam intensity range at exit of energy selection system: 0.15 to 10 nA
- Energy range: 100 to 400 MeV/nucleon.

Proton beam

- Beam intensity range at exit of energy selection system: 0.6 to 300 nA
- Energy range: 70 to 230 MeV

Other ions

- all light ions with a charge/mass ratio = $\frac{1}{2}$
- $^4\text{He}^{2+}$, $^6\text{Li}^{3+}$ (enriched), $^{10}\text{B}^{5+}$ (enriched), $^{14}\text{N}^{7+}$, $^{16}\text{O}^{8+}$, $^{20}\text{Ne}^{10+}$

Common characteristics

- Maximum size of the irradiation area: 20 x 20 cm for carbons (and others $q/A=1/2$), 30 x 30 cm for protons
- Maximum continuous dose rate (without taking account of the relative biological effectiveness) in the Bragg peak: 45 Gy.l/min
- Energy variation: rapid energy adjustment at energy degrader: 1.5 sec
- Number of energy increments = 250 (predefined library)
- Variation in depth of penetration: in 1 to 1.5 mm steps
- Between-room switch time (same particle): 1 min
- Switch time between 2 types of particles (clinical): 15 min
- Beam contamination < 1%, online monitoring of beam parameters and of spectrum of the ion source.

WP3: NUMERICAL SIMULATIONS

Coordination: D. Cussol

Key features of this proposal are the development and mastery of numerical simulation of dose deposition and the use of basic physical data on dose deposition. This work will be done in parallel with that of WP4 concerning physical measurements, dosimetry and beam quality. The numerical simulations are also essential to the modelling of the biological effect of carbon ions, in collaboration with WP5 (treatment planning system). When the carbon ion beam of the hadron therapy facility is available, a reference simulation will be done using the new physical and biological data or new models.

Description of WP3:

Research aims and new developments:

- Implementation of a reference Monte Carlo simulation:
 - *Qualification/development of models of nucleus-nucleus collisions.*
 - *Qualification/development of biological models.*

Principal tasks:

WP3.1: Before the carbon ion beam is available

WP3.1.1): Numerical simulations of dose deposition

Tasks related to research activities and new developments:

- *Qualification of nuclear models used in simulations.*

We will compare the predictions of models of nucleus-nucleus collisions with available experimental data, to identify the most relevant models and their range of validity.

Ongoing collaborations: GDRMI2B....

- *Use of basic physical data on dose deposition: proton scattering, fragmentation cross sections of carbon ions.*

Data from measurements of the characteristics of particles produced by nuclear processes will be included in the Monte Carlo calculations. This could be done by using data tables, or by creating a collision model consistent with the experimental data.

Collaborations envisaged: GDRMI2B

- *Optimising calculation time and precision in dose calculation codes.*

Monte Carlo calculations are more precise than analytical calculations, but much more time-consuming and so unusable in routine clinical practice. We therefore propose to study new algorithmic approaches that ally rapidity and precision, to reduce the time of calculation of the Monte Carlo codes, ie, to increase the precision of the analytical algorithms.
Collaborations: academic partners of WP6, GDRMI2B

- Study of imaging specific to hadron therapy. Hadron tomography.

Imaging using an x-ray scanner provides information on the mean electronic density of the media crossed, but not on the nature of the nuclei encountered. This imaging cannot therefore predict the contribution of nuclear reactions to dose deposition in hadron therapy. It is therefore interesting to study the possibility of imaging using hadron beams sensitive to the nature of the nuclei encountered. If this approach proves successful, the study should also define the characteristics of the imaging device.
Collaborations envisaged: GDRMI2B....

WP3-1-2) Tasks related to numerical simulation of relative biological effectiveness (coordinated with WP6)

- Development and programming a biological model to determine (simulate) relative biological effectiveness from physical data

We plan to develop one or more reliable numerical models to determine relative biological effectiveness from the characteristics of particles contributing to dose deposition, and from the nature of the tissues crossed by these particles. This model will be designed and validated from experimental measurements done in WP5.
Collaborations envisaged: WP5

WP3-2) With the carbon ion beams of the hadron therapy facility

Research activities and new developments:

- Inclusion of new physical and biological data or of new models in the reference simulation

We will include in the reference Monte Carlo simulation physical models validated in WP3-1-1 and the numerical model for determination of relative biological effectiveness developed in WP3-1-2. The resulting numerical model will indicate the biological dose in a patient.
Collaborations envisaged: GDRMI2B

WP4: DOSIMETRY AND BEAM CONTROL

Coordination: J. Colin / J-M. Fontbonne / A. Batalla

Introduction

The use of an x-ray beam in conventional radiotherapy or of an ion beam in hadron therapy calls for precise control of beam geometry, energy, and intensity, and of the dose delivered.

X-rays interact with electrons and their use in imaging indicates the electron density of the media crossed. This electron density can be used to calculate energy deposition in tissues when high-energy x-ray beams are used in radiotherapy. Dose control measurements are done with ionisation chambers using water as reference medium, and are used to correct calculations done for patients using x-ray imaging. Detectors are calibrated with respect to the primary standard of the Gray (bolometer, for example) in the reference medium water. Extensive experience acquired in radiotherapy ensures the reliability of this approach.

Charged particles interact with electrons, but also with nuclei. The ions lose energy essentially due to interactions with electrons, but also because of the nuclear processes of scattering and fragmentation. These mechanisms underpin the use of ion beams in hadron therapy. Precise knowledge of energy deposition therefore requires knowledge of the electron density of the medium, but also of the nature and density of the nuclei composing the medium.

In hadron therapy in the presence of the patient, beam control is achieved by means of strip/pixel ionisation chambers (MOPPI) for localisation and by integral chambers for the dose. Beam quality assurance is ensured prior to treatment using a multi-layer ionisation chamber, multi-anode gas ionisation chamber, films or CR-39 detectors. At present there is no physical method for absolute calibration of these devices, and they are calibrated relative to the beams of conventional radiotherapy. The problem is that nuclear interactions of hadrons depend on the medium and results obtained with one medium cannot be extrapolated to another.

This difficulty has consequences in terms of the: 1) materials constituting the dosimeters, 2) materials in which dosimeters are placed to measure dose volume distribution, 3) TPS, 4) calculations of doses in tumour tissue and healthy tissue, and 5) extrapolation of results to another material.

The principal lines of research on physical measurements, dosimetry and beam quality control are summarised below.

Description of WP4:

Objectives

Research and development objectives:

- To set up and conduct an experimental programme for measurement of physical data.
- Research, development and installation of new experimental devices for imaging, beam control and dosimetry.
- Research, development and use of devices for online control of dose deposition.

Methodological considerations: Method:

Since 2008 certain instruments have been developed and measurements made.

- instruments: detectors, dosimeters and devices for physical measurements,
- measurements: cross sections —done or planned using existing machines at GANIL, GSI, CATANE, ...

Collaborations have been developed with IN2P3 and the CEA and with industrialists. This approach will expedite efficient use of the dedicated beams of ARCHADE as soon as they are available.

Principal tasks:

WP4-1) Tasks related to the adaptation of existing measurement instruments for carbon ion beam control and dosimetry.

- ***Beam quality control and relative dosimetry:***

Adaptation of instruments used in proton therapy to the scanning beams of carbon ions. Effects of scanning and of dose rate dynamics on the response of existing detectors.

WP4-2) Tasks related to research activities and development of new approaches and of new measurement instruments for imaging, beam control and dosimetry.

- ***Measurement of basic physical data: experimental measurements of nuclear fragmentation mechanisms (constraints for WP3 for the development and validation of a nuclear model, collaboration with WP6)***

- Measurement of the angular scattering of protons and of carbon ions on crossing different materials, to estimate lateral dose fall-off.

- Measurement of the fragmentation cross sections of carbon ions for energies below 100 MeV per nucleon to know the ionic composition of the beam in each point of the target

material, so as to determine the dose distribution, notably beyond the Bragg peak and outside the target volume.

The calculations will then be compared with these experimental data.

Definition and construction of the experimental measurement device: detectors, electronics, acquisition, targets, reaction chamber

Ongoing collaboration with GDRMI2B, INFN

- ***Beam quality control:***

Study of the different possibilities for measurement of the geometric characteristic (x, y, z) of the beam and of the number of incident ions per second dN/dt .

- Measurement of the coordinates (x, y) defines the beam envelope.
 - The coordinate z is the depth reached by the ions. For a given medium, it corresponds to the energy of the ions.
 - The measurement of ion flow dN/dt allows calibration of the monitoring devices.
- These four parameters (x, y, z, dN/dt) can be used to check that the machine parameters match the nominal characteristics.

Collaboration envisaged: GDRMI2B

- ***Imaging: Calculation of energy deposition requires knowledge of the electronic density of the media crossed, but also of the nature and density of the nuclei composing these media.***

- Development of imaging to measure the chemical composition of the media.
- Development of detectors for imaging using particles that cross the patient with carbon ion beams.

Collaborations envisaged: GDRMI2B

- ***Relative dosimetry:***

- Identification, study and measurement of parameters proportional to the dose. They must be proportional to the linear energy transfer of all the particles set in motion in the medium by the incident beam.
- Development of the apparatus.

Collaboration envisaged: GDRMI2B

- **Absolute dosimetry:** *We will study the feasibility of an apparatus to measure energy deposition (Grays) by beams of protons or carbon ions. The physical phenomena used in this device must enable avoidance of problems related to these beams, such as fragmentation, dependence on linear energy transfer and heat loss.*

A metrology instrument (based on calorimeters) will be made for calibration and qualification of the relative dosimeters.

Collaborations envisaged: GDRMI2B, CIMAP, CEA, UCL, NPL (National Physics Laboratory, UK), IBA.

- **Use of physical measurements and real-time imaging to assess dose deposition**

Three complementary approaches will be undertaken in parallel.

- Optimisation of tools to assess the dose deposited by positron emission tomography imaging. The interaction of carbon ions with matter generates β^+ emitters like ^{11}C (half-life 20 minutes). The annihilation of the β^+ in two photons of 511 keV enables offbeam imaging of the points of emission of photons. Indirectly, it is therefore possible to localise the nuclear reactions that form ^{11}C , and to simulate dose deposition.

Dose deposition can be checked after each irradiation session. It is important to study this response, its sensitivity and any improvements that could be made.

Collaborations envisaged: GDRMI2B (INNOTEP project) + FP7 project

- A second axis of research uses a gamma camera to measure the so-called prompt gammas produced at each nuclear reaction. The objective is to localise all nuclear reactions in real time and to estimate beam penetration.

Ongoing collaboration: GDRMI2B

Collaborations envisaged: European project FP7: HEALTH-2008-1.2-4

- A third approach envisaged is the development of one or more particle detectors to compare the nature and quantity of particles that cross the patient with pre-treatment calculated values. This approach ensures consistency between the planned treatment and the treatment actually administered. It can be used for simultaneous validation of the nature of the tissues encountered in the body (determined by imaging), the effective fractions taken into account in the calculations and the energy deposition in the patient.

Collaboration envisaged: GDRMI2B

WP5: HADRON BIOLOGY

Coordination: J-L. Lefaix / C. Laurent

Introduction

Since the early 1980s, much work on preclinical hadron biology has highlighted the advantages of irradiation by carbon ions. Contributions by the GSI in Darmstadt (Germany) and the NIRS in Chiba (Japan) since the mid-1990s have been essential. Research on normal cells and human tumour cell lines, *in vitro* and xenotransplanted in nude mice, have mainly related to:

- direct effects on cell / tumour growth as a function of radiosensitivity, double-strand break repair, partial oxygen pressure, normoxia/ hypoxia.
- superior relative biological effectiveness of irradiation with carbon ions *versus* photons (x-rays of 150 keV to 4-5 MV, or γ).
- induction of apoptosis as a function of linear energy transfer and/or energy, culture conditions, cellular radiosensitivity, p53 status.
- demonstration of a bystander effect on stimulation/inhibition of cell growth and involvement of NO radicals.
- modulation of the expression of certain genes by hadrons (2008).

However, limited access to beam lines dedicated to research has restricted the availability and homogeneity of biological data. Very little work has been done on direct effects *in vivo*, which have been extensively studied in conventional radiobiology. For the record, studies have been done in mice, rats, hamsters and pigs, on dose fractionation effects, the central nervous system and spinal cord, skin, lungs, liver, and gut. Few studies have compared carbon ions and photons in radiation-induced carcinogenesis in mice. No work has been done on the late clinical effects of the carbon ion irradiation, but some radiobiology studies have involved long-term monitoring of skin lesions in rodents.

Current understanding is insufficient to answer numerous questions on the biological effects of exposure of healthy tissues and tumours to carbon ions, compared with conventional radiotherapy, notably regarding:

- types of DNA damage (single- or double-strand breaks) and its repair.
- specific molecular signatures (type of cell death, cell cycle block, signalling pathways, specific expression of certain genes).
- oxidation and endogenous cellular detoxification.
- oxygen effect, anoxia – hypoxia.
- inflammatory processes involved and late effects in healthy tissues.
- role of fractionation.

Description of WP5:

Objectives

- Objectives concerning commissioning and validation of the hadron therapy facility:

- Development of *in vitro* and *in vivo* biological models for later comparison of proton and carbon ion beams of the IBA 400 MeV/nucleon cyclotron.
- Specification of relative biological effectiveness in predefined experimental conditions, using healthy and tumour cells for parameters as survival and cell death. These parameters must be usable for preplanned dosimetry and inclusion in the TPS (WP6).
- Generation of biological data on the differential effects of carbon ions *versus* protons.

- Research aims and new developments:

- The development of complementary biological models for specific and innovative research programmes to characterize and compare the different biological effects of x-rays, protons and carbon ions.

Principal tasks

WP5.1: Tasks related to commissioning and validation of the hadron therapy facility: First phase, before the availability of carbon ion beams

WP5.1.1:

- Description of the state of the art and classification by relevance of the work (in collaboration with WP6)
- Specifications and modelling of radiosensitivity to x-rays of different types of human cells and in different experimental configurations for preplanned dosimetry (in cooperation with WP6)

WP5.1.2:

Determination of relative biological effectiveness of GANIL carbon ion beam using fibroblasts, endothelial cells and human ENT carcinoma cell lines

WP5.1.3:

Development of *in vitro* and *in vivo* murine models, healthy and tumour tissues relevant to later clinical research and needed for evaluation of proton and carbon ion beams of the 400 MeV/nucleon cyclotron.

WP5.1.4:

In vitro radiosensitivity to x-rays of these models of healthy and tumour tissues

WP5.1.5:

Development of a mouse model of late radiation fibrosis relevant to subsequent clinical research.

WP5.2: Tasks related to commissioning and validation of the hadron therapy facility: Second phase, with the carbon ion beams

WP5.2.1:***In vitro measurements of relative biological effectiveness***

The reference radiosensitivity with carbon ions and protons, when the beam is calibrated and usable for biology experiments, should be established for all the human and murine cell models used in WP5.1.

In vivo measurements in mice of the relative biological effectiveness of carbon ions

The study of early and/or late effects on healthy tissues and the anti-tumour effect will be undertaken.

The comparators will be an x-ray beam and a proton beam (200 MeV)

The data will be analysed at the plateau, the Bragg peak and at the end of the peak in the penumbra of fragmentation.

These effects will be tested in normoxic and hypoxic conditions with different types of fractionation. These biological data could be used to optimise the TPS.

WP5.2.2:***Inclusion in the treatment planning system (jointly with WP6)***

Verification and optimisation of modelling: inclusion of experimental data obtained with the TPS model developed in WP6, and the local effect model (Elsässer 2008).

WP5.3: Tasks related to research activities and new developments

Setting up of complementary biological models and development of a specific innovative programme (x-rays *versus* protons and carbon ions). The models will be prepared and developed during the first phase before proton and carbon ion beams are available, and will be used in the second phase, when the beam is calibrated and ready for biological experiments:

- Complement to the study of relative biological effectiveness with human cells (fibroblasts, endothelial cells, carcinoma cells): analysis of oxidative and pro-inflammatory status, oxygen effect (normoxia and hypoxia), cell death mechanisms, DNA repair.
- Development of a similar research programme on radiosensitivity to carbon ions of human tumour cell strains ordinarily resistant to x-rays.
- Development of a research programme on *in vitro* modulation of the extracellular matrix after irradiation with x-rays / protons / carbon ions.
- Depending on the results obtained, development of a model mouse of late radiation fibrosis relevant to the clinical research to be scheduled later, using two genetic backgrounds of different radiosensitivity with specific gene knock-out .
- Development of a model of radiation-induced carcinogenesis in rodents for analysis of the late effects of irradiation of healthy tissues.
- Use of an “optimised” comparator [protons + targeted molecular therapy] to evaluate the added value of carbon ions in radiobiological terms. The aim is to explain the curative superiority of carbon ions over protons optimised by the addition of targeted molecular therapy. This question is essential for better definition of the practical value of carbon ions therapeutically and biologically.

The principal partners needed for the project are involved in hadron therapy–hadron biology research at the Institut Régional du Cancer de Basse Normandie.

- **LARIA:** Laboratoire Accueil de Radiobiologie avec les Ions Accélérés, Commissariat à l’Energie Atomique, Direction des Sciences du Vivant, Institut de Radiobiologie Cellulaire et Moléculaire (J-L. Lefaix and collaborators)
- **EA 3919:** Biologie Cellulaire et Moléculaire de la Signalisation UFR - Médecine CHU Caen (B. Sola and collaborators)
- **EA 3214:** Matrice Extracellulaire Normale et Pathologique, UFR - Médecine CHU Caen (K. Boumédiène & P. Galéra and collaborators)
- **UMR 6232 CI-NAPS,** Centre d’Imagerie-Neurosciences et Applications aux Pathologies, CNRS, CEA, Université de Caen Basse-Normandie Université Paris Descartes, CYCERON (Myriam Bernaudin and collaborators)

WP6: CONTRIBUTION TO THE EVALUATION AND VALIDATION OF A PLANNING SYSTEM FOR CARBON ION RADIOTHERAPY

Coordination: A. Batalla / A Mazal

Introduction:

The TPS is used to plan and prepare a patient's treatments dosimetrically and to determine all the irradiation parameters, taking into account the beam characteristics (energy, geometry, etc.) and the patient's anatomy. The TPS thus enables an individual treatment plan to be drawn up for each patient, and validated before starting therapy.

There are various software packages (Dosisoft, XiO-CMS, Eclipse-Varian) that calculate physical dose distribution for radiotherapy beams (photons or protons), based on different models (Monte Carlo, pencil beam, ray-tracing).

On the other hand there is currently no TPS for carbon ion beams that satisfactorily include the biological constraints, which are related to the biological effect of the carbon ions on healthy tissues and tumour tissues. In the context of carbon ion radiotherapy, certain TPSs have been developed locally and used for the treatment of patients despite their imperfections (eg, TRIP system in Germany). The German TPS is based on modelling of a scanning beam and models the biological effect using the local effect model, the latest version of which (No. 3) has just been published (Elsässer et al. IJROBP, 2008; 71:866-872). However, these models are relatively imprecise and do not give a good account of the diversity of biological effects in all healthy and tumour tissues. Optimisation is necessary to limit imprecision in the use of these models.

The creation of a new TPS for carbon ion radiotherapy is, however, very complex. As part of the C400 cyclotron work, it is planned to start from an existing TPS (that used for protons) and to develop a modular approach adding step by step functionalities specific to ion beam treatment, notably an effective biological module. The complexity of the development of a new TPS demands collaboration between academic and industrial partners, which is why the INFN (Istituto Nazionale di Fisica Nucleare) has joined forces with IBA to produce this TPS for carbon ion radiotherapy. The inclusion of modules specific to carbon will be considered through a partnership with the company Elekta, which markets the XiO TPS (CMS) and is working on the development of the Mosaic-RTP modular platform. The contribution of ARCHADE-IBA to this WP6 will follow when the TPS for carbon ion radiotherapy is operational and must be tested and validated. The utilisation of the TPS for patients undergoing carbon ion radiotherapy can only be effective after validation in clinical conditions. The tests must scan all configurations in terms of calculation of dose distribution, taking into account angles and heterogeneities, etc. In addition, the TPS for carbon ion radiotherapy must be incorporated into the preparation and administration of radiotherapy: use of Dicom medical imaging (computed tomography, magnetic resonance imaging, PET-CT, etc.), data transfer to specific information systems (R&V), production of data enabling dosimetric evaluation (dose-volume histograms, 3D ...), control of patient positioning (digitally reconstructed radiograph), drawing up of treatment plans using both photons and carbon ions.

Even if the modular structure of the TPS for carbon ion radiotherapy can be based on approved imaging modules, incorporation in a complete process should be thoroughly tested and validated. The ARCHADE facility will be the preferred site for validation of this TPS, for

defining quality control protocols, and for validation of new versions incorporating improvements inherent to a continuous process of development and for the implementation of future developments (respiratory gating, tumour tracking, etc.).

WP7: COMMISSIONING OF HADRON THERAPY FACILITY FOR CLINICAL RESEARCH

Coordination:

ARCHADE: J. Bourhis, A Batalla

Partners: François Baclesse Centre, Cancéropole Ouest, Grand Ouest and Ile de France, ETOILE

Introduction

The ARCHADE Centre is not planning to engage in carbon ion radiotherapy of patients in the framework of state health cover, as this activity is reserved in France to ETOILE in Lyon. ARCHADE's clinical contribution will be strictly limited to research activity. Treatment of patients at the hadron therapy facility will be done as part of a clinical research protocol, with the initial aim of treating patients with an inoperable cancer resistant to radiotherapy.

Description of WP7:

Objectives:

WP 7.1: Objectives concerning commissioning and validation of the hadron therapy facility:

- Definition of the specifications and criteria for authorisation of treatment of a patient in a clinical research protocol, with the hadron therapy facility delivering a carbon-12 ion beam.

- Obtaining administrative authorisations to treat patients (ASN).
 - Inclusion of all tools developed in WP3, WP4, WP5 and WP6, for commissioning of the hadron therapy facility for treatment of patients participating in research protocols.
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 - Acquisition of databases for the TPS and as reference for quality assurance systems of the facility (ARCHADE).

WP 7.2: Clinical research objectives

The clinical research proposal of ARCHADE takes account of the considerable research needs in this field. At present, it is not known with precision what are the relevant therapeutic indications for carbon ion radiotherapy and what is the added value of carbon ions clinically, compared with conventional radiotherapy (H. Suit, Radiother Oncol 2010 and 2009 report of the French National Health Authority).

It is necessary to set up an ambitious research programme to demonstrate the advantage of carbon ion radiotherapy compared with more conventional radiotherapy based on protons or photons and to help optimise the clinical use of carbon ion radiotherapy. This clinical research programme should take into account the technical specifications of the Hadron Therapy Research and Treatment Facility, which obliges us initially to favour a certain number of clinical situations. Certain technical specifications are imposed by the Hadron Therapy Research and Treatment Facility, such as energy, maximum range, the use of a fixed horizontal beam and spot scanning beam.

The number of patients treated will be very limited and they will be strictly treated as part of a clinical research protocols.

The priority for this clinical research will be inoperable, radiation-resistant tumours of the base of the skull (sarcomas, cylindromas...) which will be the initial model. A research proposal closely related to biology and functional imaging (WP5) will be implemented concerning head and neck carcinomas and glioblastomas. These two clinical models are adapted to the Hadron Therapy Research and Treatment Facility, notably the lack of isocentric gantry which is not limiting in treating this type of tumour location (manageable with patients in seated position/robotic chair). Beam field and path sizes are also compatible with the technical specifications imposed by the Hadron Therapy Research and Treatment Facility. Lastly, movements during irradiation are very limited and facilitate the use of a scanning beam. A randomised clinical study will be initiated in these two clinical models to evaluate whether carbon ions are superior to protons and to photons.

In due course, other clinical settings will potentially be included in the ARCHADE project, notably inoperable pelvic tumours (sarcomas) and/or recurrent gastrointestinal, urogenital or gynaecological tumours. The absence of an isocentric gantry and the limitation in treating patients in certain seated positions requires a combination of photons with a boost by carbon ions (horizontal arm) in these clinical situations. Other situations are even more complex and will be addressed later, notably inoperable liver and lung carcinomas for which an additional constraint is related to the movement of tumour and healthy tissues during irradiation.

Certain clinical questions will not be addressed in the carbon ion project: paediatric tumours (for which there is a major interest in protons, but not carbon ions), breast carcinomas, prostate carcinoma, metastases, ocular melanoma, etc.

- The clinical research will be conducted to include patients in protocols that comply with the Huriet Law (concerning biomedical research involving human subjects). The work as part of WP7 will involve the writing and submission of this clinical research protocol (N° Eudract, AFSSAPS and Ethical Review Committee) and then its implementation and follow-up.

Writing / Coordination of WPs:

Eric Baron, Physicist specialised in cyclotrons, ARCHADE

Alain Batalla, Head of Physics Department, CLCC François Baclesse

Jean Bourhis, Professor of Radiotherapy, Head of Department of Radiotherapy, Institut Gustave Roussy, scientific coordinator of the proposal

Jean Colin, Professor at Caen University, head of the Medical Applications Group at the Particle Physics Laboratory

Daniel Cussol, Research Associate, IN2P3, ENSICAEN

Michel Drouet, Administrative Director of the ARCHADE proposal

Jean-Marc Fontbonne, Research engineer, IN2P3

Philippe Lagalle, ARCHADE Project Manager

Carine Laurent, Research Associate, LARIA (CEA)

Jean-Louis Lefaix, Director of Research, DR1 LARIA (CEA)

Alejandro Mazal, Head of the Physics Department, Institut Curie

Marie-Hélène Moscatello, Physicist specialised in accelerators, CEA/DSM/ARCHADE