**RESEARCH AND DEVELOPMENT: THE NEXT THREE-YEARS PROGRAMME (2015-2017)**

CNAO has acquired in these few years of activity outstanding profile and visibility on the international community of hadrontherapy and radiotherapy.
In the EU 7$^{th}$ framework programme CNAO has been at the forefront of the research programmes. The project ULICE (Union of Light Ion Centre in Europe) has been concluded on July 2014 and CNAO was the coordinator of 20 European institutions working on three main domains: Joint-Reasearch Activities, Networking Activities, Trans-National Access (i.e. opening of the existing hadrontherapy facility HIT and CNAO to the research community). From 2010 to 2013 was held the project named PARTNER (Particle Training Network for European Radiotherapy) with the aim to form the young generation of users of hadrontherapy facilities in the world. Also important has been the project ENVISION (European NoVel Imaging Systems for ION therapy) for in-vivo monitoring of delivered dose and quality assurance of beams.
In order to enable the consolidation of this position of CNAO and its further increase it is necessary that investments in research and development are assured, so to make it a benchmark of absolute value in a global landscape of growth of interest in hadrontherapy in general and ion therapy in particular. The ongoing construction, in collaboration with INFN, of a beam line dedicated to research is a key-point in this advancement, because it ensures the possibility to perform preclinical research in multiple sectors, in a completely dedicated area with laboratories, independent access and available beam time.
The construction of the new beam line, shown in Fig. 1, started in summer 2014 and is going to be completed in two years.

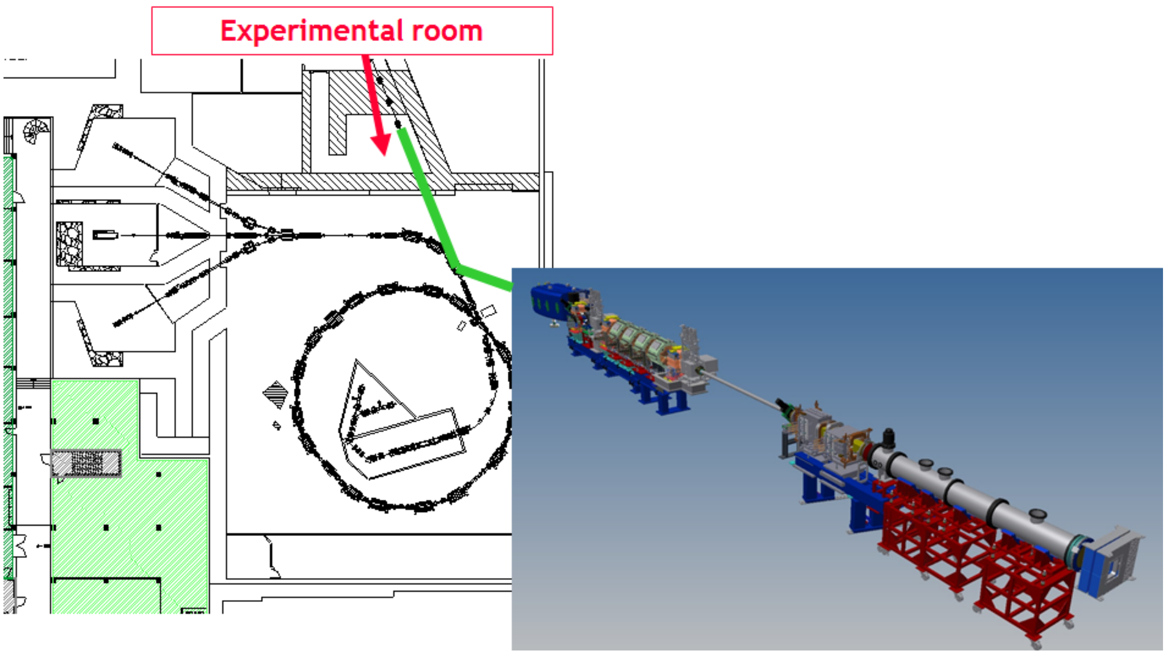


*Fig. 1 – Layout of the experimental line in construction at CNAO.*

In the first phase of the realization the beam characteristics are very similar to those available in the treatment rooms. The isocentre inside the experimental room will be movable in order to improve the flexibility and adapt the space to special experimental setups. The beam line will be later

upgraded with the addition of a third source devoted to test new ion species. A new low energy beam line will allow the insertion of a third source within the present layout of CNAO as illustrated in Fig. 2.
Besides the experimental line project, R&D programmes are involving also the present accelerator layout. The ongoing studies aim at improving the beam intensities in the treatment room. The main goal is to increase the dose rate at the patient and minimise the treatment time, of course keeping utmost attention to beam quality and safety. Another key development will be represented by the implementation of a multi-energy-extraction within a single spill [52], since this is going to exploit at best the beam intensity, reduce the beam losses and consequently minimise the radioprotection impact and above all shorten the patient treatment duration.
The main streamlines of the next three years research plan are summarised hereunder.

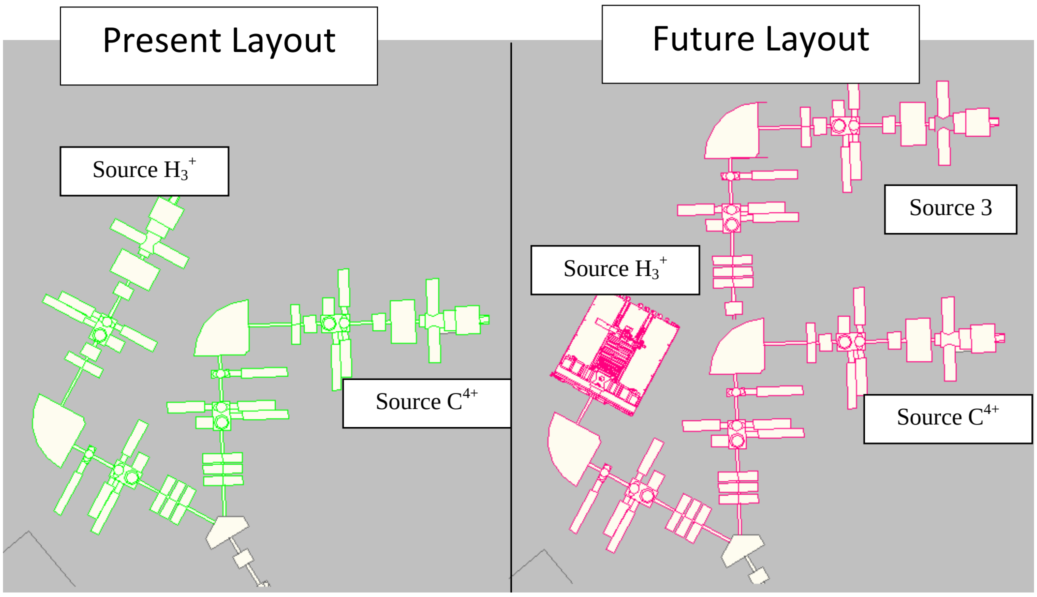


*Fig. 2 – Comparison of the present layout with two sources and the future layout with insertion of a new source and a portion of LEBT.*

***Radiobiology***. The radiobiology activity has to be strongly reinforced, in particular in the context of high-LET particles where there is great need for knowledge. This objective can only be achieved by creating a large critical mass with other research groups interested in developing shared projects. The possible activities include experimental tissue, cell and molecule research, mainly addressing the study of the response mechanisms of the cell of healthy and tumoral tissues following irradiation with protons and carbon ions. Several topics of particular interest for CNAO have been identified: radio-resistance mechanisms, the response of healthy tissues and tumor microenvironment, the analysis of the role of mRNA in response to radiation, the effects of high-LET radiations on gene expression, the interactions between hadrons and radio-sensitising drugs, the effects of low doses. An important development in the customization of therapy will also be the prediction of genetic tests made on neoplastic tissue biopsies, or, more likely, through the examination of the peripheral blood. There are international groups working in this field, with which collaborations may be established.

***Medical Physics.*** Medical Physics activities play a vital role in the general research plan and it is expected that they are carried out in three coordinated lines.
The first concerns the quality control procedures for particle beams scanning and, in particular, the design and development of 2-D dosimetry systems based on gaseous scintillation detectors and on

an array of artificial microdiamonds, as well as the dosimetry featuring the development of new solid state and photoluminescence (PL, pure crystals of LiF) detectors. The second refers to optimizing the ocular treatments with scanning beams including validation of dose calculation algorithms and the development of methods of accurate delineation of the volumes of interest during treatment planning. The third line of research aims at optimising and verifying hadrontherapy treatments, including pre-clinical validation in phantom of the in-beam PET method, the study of robustness of treatment plans to the various sources of uncertainty, the optimization and verification of mobile target treatments, the modality of biological dose prescription for treatments with carbon ions and furthermore, the study of indicators of early response to treatment with advanced protocols of diffusion-MRI for selected categories of patients undergoing treatment.

***Bioengineering.*** In bioengineering very important research topics are related to the possibility to treat tumours located in moving organs. The activities target the transfer in clinical practice of respiratory gating techniques and online tracking based on internal/external correlation models. These models are based on the integration between optical tracking surface surrogate and in-room imaging and require a set of development activities, integration and clinical transfer of techniques for the dynamic control of patient position both during imaging for treatment planning and during administration of the dose.

***Clinical research***. The objectives of clinical research can be summarized in two points:

1) drawing innovative clinical studies, able to respond to the questions that today the hadrontherapy poses, preferably through the stimulation and/or participation in multicenter projects and
2) validating, through appropriately designed cooperative clinical studies, the most extensive application of hypo-fractionated schemes.

Clinical research is the coordination and orientation motor to all areas previously reviewed, in order to ensure, on the basis of the need for applicability to patients, rapid translation of technical, physical and biological results in current practice. The most important issue is to demonstrate, through the rules of evidence based medicine, the greater effectiveness of hadrontherapy compared to previously used techniques in the treatment of “difficult” cancers, not only because these are rare or located in particular regions, but mainly because the results obtained so far are unsatisfactory. Typical examples are cancers of the pancreas, lung and brain.