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COMMENTARY

# ENLIGHT and other EU-funded projects in hadron therapy

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**ABSTRACT.** Following impressive results from early phase trials in Japan and Germany, there is a current expansion in European hadron therapy. This article summarises present European Union-funded projects for research and co-ordination of hadron therapy across Europe. Our primary focus will be on the research questions associated with carbon ion treatment of cancer, but these considerations are also applicable to treatments using proton beams and other light ions. The challenges inherent in this new form of radiotherapy require maximum interdisciplinary co-ordination. On the basis of its successful track record in particle and accelerator physics, the internationally funded CERN laboratories (otherwise known as the European Organisation for Nuclear Research) have been instrumental in promoting collaborations for research purposes in this area of radiation oncology. There will soon be increased opportunities for referral of patients across Europe for hadron therapy. Oncologists should be aware of these developments, which confer enhanced prospects for better cancer cure rates as well as improved quality of life in many cancer patients.

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Cancer is a major issue in modern society and radiation therapy has a vital role in its treatment. The main aim of radical radiation therapy is to achieve local tumour control, which can result in cure; other applications are in palliative situations for the relief of symptoms. In the radical case, the largest effective dose of radiation is delivered to a designated tumour site while sparing the surrounding healthy tissue as much as possible. Conventional radiation therapy uses penetrating megavoltage X-rays that pass through the entire thickness of irradiated tissue. Multiple overlapping beams can deliver higher doses to the tumour rather than to normal tissues; however, such techniques inevitably deposit some radiation dose unnecessarily to a wide range of normal tissues. In some instances this radiation can cause unpleasant and occasionally permanent side effects.

By contrast, modern hadron therapy uses beams of protons or light ions, which have unique physical and radiobiological properties and offer several advantages over X-rays. In particular, protons or light ions penetrate the body with little initial energy loss but deposit their maximum energy abruptly at the end of their range; little or no dose is deposited beyond the tumour. The beams can easily be formed as narrow focused ''pencil'' beams of variable penetration depth in order to cover the tumour volume. Therefore, in contrast to the situation with X-ray beams, any part of the tumour can be irradiated while sparing much of the healthy tissues. A beam of protons or light ions thus allows a highly tailored tumour therapy ranging from 1–2 cm beneath the skin to very deep-seated tumours with millimetre accuracy, while reducing doses to surrounding tissues by a factor of 2–10 depending on the precise situation.

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Such a sophisticated treatment will include some uncertainties that need to be researched; for example, the distortion of beam ranges in non-homogeneous tissues, the problem of cancers that move with respiration and how best to take advantage of the higher biological cell killing efficiency within the Bragg peaks. To make the treatment more cost-effective, rationalisation of dose schedules and a shift towards fewer treatments will be necessary.

Hadron therapy is consequently the most promising form of radiotherapy. Epidemiological studies based on cancer incidence and indications have been performed in several countries and have clearly shown the need for hadron therapy centres in Europe [1–3]. Following very encouraging reports from Japan and Germany [4–8] on carbon ion therapy, in the future European centres will be established in Germany, Italy, France and Austria that are capable of delivering light ions and protons in the same centre. There is ample scope for optimisation of many aspects of hadron therapy, as well as a need to find how best to integrate this approach with other forms of cancer therapy. Consequently, the potential research portfolio is extensive.

## EU-funded projects

In view of the immense potential of hadron therapy, and the need for further research and development in this area, the European Union has funded several projects for the research and co-ordination of hadron therapy across Europe.

### *ENLIGHT*

The European Network for Light Ion Hadron Therapy (ENLIGHT) [9] was established in 2002 to co-ordinate European efforts in hadron therapy. The ENLIGHT network is formed by the European Hadron Therapy Community and comprises more than 200 participants from 16 European countries [10]. A major achievement of ENLIGHT has been the blending of traditionally separate communities so that clinicians, physicists, biologists and engineers with experience and interest in particle therapy work together. The project has been a successful initiative in forming a common European platform and bringing together people from diverse disciplines and countries.

ENLIGHT demonstrates the advantages of regular and organised exchanges of data, information and best practices, as well as determining and following strategies for future needs in research and technological development in the hadron therapy field. In 2006, the ENLIGHT community agreed that the goals of the network could be best met by two complementary approaches: the research in areas needed for highly effective hadron therapy and the networking needed for establishing and implementing common standards and protocols for treating patients. The primary mandate of ENLIGHT is to develop strategies for securing the funding necessary for continuation of the initiative in its two fundamental aspects — research and networking.

Under the umbrella of ENLIGHT, there are now three European Commission (EC)-funded projects: PARTNER (Particle Training Network for European Radiotherapy), ULICE (Union of Light Ion Centres in Europe) and ENVISION (European NoVel Imaging Systems for Ion Therapy). The total funding for these three projects is 20 million euros. In addition, a fourth project, ENTERVISION, was submitted to the EC in December 2009. Further details can be obtained on all these projects on the following CERN website: enlight.web.cern.ch.

### *PARTNER*

Training of personnel for the emerging European facilities was a clear necessity and the Seventh Framework Programme (FP7) call for proposals in May 2007 was well timed for ENLIGHT to submit a proposal. In 2008, PARTNER [11] was established in this rapidly emerging field. This is an interdisciplinary, multinational initiative that has the primary goal of training researchers who will help to improve the overall efficiency of light ion therapy in cancer treatment. PARTNER also aims to promote clinical, biological and technical developments at a pan-European level for the benefit of all European inhabitants. The project will bring together key academic institutes and research centres of excellence as well as the two leading European companies in particle therapy (IBA and Siemens). All partners are known worldwide in the diverse, but complementary, fields associated with particle therapy: clinical, radiobiological and technological. Thus, the network covers a unique set of competencies, expertise, infrastructures and outstanding training possibilities for young researchers. CERN is the co-ordinator of the 4-year PARTNER project, which is funded by the EC to train 25 researchers in member states throughout Europe, with a total funding of 5.6 million euros.

### *ULICE*

ULICE [12] is a 4-year research project that started on 1 September 2009. It receives funding of 8.4 million euros from the EC. This project is co-ordinated by Centro Nazionale di Adroterapia Oncologica (CNAO) (the Italian hadron therapy facility) and involves 21 European institutions. All the existing and planned light ion facilities participate, together with two physics research centres (CERN and Gesellschaft für Schwerionenforschung Biophysik (GSI)) and two industrial companies (Siemens and Ion Beam Application (IBA)). The project is built around three pillars. The first of these, ''joint research activities'', is focused on improving the performances of the facilities. It will deal with technical issues such as the design of a lower cost light ion rotating gantry, development of the optimal strategy to cope with organ motion and anatomy changes and the creation of a ''clinical research infrastructure'' (*i.e.* a framework to produce scientifically sound evidence on the efficacy of heavy ion therapy). The second pillar, ''networking activities'', deals with the dissemination of the project results to the wider community of people involved in cancer care. Finally, the third pillar, ''transnational access'', is led by the Heidelberg Ion-Beam Therapy (HIT) Center in Germany [13] and will provide access for external researchers to the existing ion therapy facilities in order to perform their own pre-clinical research. It will also produce agreed protocols for multicentric clinical trials and will allow external clinical researchers to participate in those trials. This pillar is intended to maximise availability of a scarce resource to all European researchers and will utilise advanced e-science grid technology. E-science denotes the systematic development of research methods that exploit advanced computational thinking.

### *ENVISION*

ENVISION is a 4-year project set up by 17 leading European research organisations, including two leading European industrial partners (Siemens and IBA). The project started on 1 February 2010 and is funded by the EC for 6 million euros; CERN is the project co-ordinator. ENVISION simultaneously tackles the problems of real-time dose monitoring and of performing accurate quality assurance tests. To achieve this, ENVISION aims to develop novel imaging modalities and dose calculation engines that can study the very sharp changes in dose deposition. These tools will enable a better assessment of the treated volume and will allow reliable indicators of the actual delivered dose to be established.

The project also focuses on the detection of nuclear reaction products resulting from the interaction of the light ion beam with atomic nuclei of the tissue. The methods are applicable to all relevant ion species. The application of new time-of-flight (TOF) techniques to give superior temporospatial resolution to beam delivery integrated with double-headed in-beam positron emission tomography (PET) scanners has the potential for improving PET image resolution, possibly by more than one order of magnitude. Furthermore, real-time observation of the dose delivery process will become feasible for the first time. This capability will substantially reduce intervention times and allow better correction procedures where there is deviation between the planned and delivered dose.

## Summary

The projects described here exemplify the trend of international co-operation. The successful centre of excellence model already used in particle physics by CERN is applied here, although in this case it provides support to the emerging treatment centres situated elsewhere.

It is anticipated that the next decade will produce better outcomes from radiation techniques used in cancer therapy. There will be many challenges along the way to achieve this for the largest number of suitable patients, as well as in the integration of these techniques into the multimodality management of cancer. The generous contributions of the EU to this multidisciplinary effort – sharing training, education, research and development – is both exemplary and necessary to achieve progress as efficiently and rapidly as possible, and at the lowest overall cost. These activities will also address some of the criticisms made of past hadron therapy pilot studies performed on rare tumours in physics laboratories under suboptimal clinical conditions [14].

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