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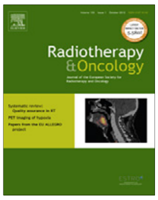

Editorial

A community call for a dedicated radiobiological research facility to support particle beam cancer therapy

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Recently more than one hundred researchers followed an invitation to a brainstorming meeting at CERN on the topic of a future dedicated radio-biological and radio-physical research center. Many more joined the meeting via webcast. After a day of presentations and discussions it was clear, that an urgent need for such a development exists, resulting in a community call for the construction of a dedicated laboratory. Below we comment on the essential points.

Why is it needed?

Over the last decade particle beam cancer therapy has developed into a major treatment option. Many new centers have been built, and more are under construction. Currently 35 proton therapy centers and six carbon ion centers are in operation and 24 and 4, respectively are in construction or in the planning stage [1]. Many of these centers are driven by financial considerations and are heavily concentrating on treating large patient numbers. It was actually financial considerations, and not technical or medical ones, which led to the premature closure of two new carbon ion facilities in Germany. This situation encourages neither large-scale fundamental research nor clinical use for complicated and high-risk cases. Following the positive experiences of the initial research at GSI, Darmstadt [2] and the recent start-up of the Heidelberg Ion Therapy Centre (HIT) [3–5] this situation is expected to change.

Particle therapy is believed to have a physical advantage over even the most modern X-ray delivery methods (IMRT) based on the physical properties of particles depositing the main portion of the dose to tissue in the Bragg peak, minimizing the dose to the entrance channel, and delivering virtually no dose beyond the distal edge of the Bragg peak. Heavier ions (i.e. carbon), in addition, due to the higher density of ionization events along the particle track, exhibit a higher relative biological effectiveness than X-rays or protons, especially in the Bragg peak region, making them prime candidates for the treatment of radio-resistant tumors [6,7].

Still, all these advantages are mere speculations based on a scatter of physical and biological studies, spread over many years, and performed in multiple centers under different conditions, resulting in significant uncertainties [8]. The criticism that no large-scale clinical or pre-clinical studies are available to support these perceptions seems justified. Consequently, to fully utilize the benefits of particle therapy, a concerted research effort is called for to provide the biological and physical data set to help clinicians in their decision on which the most appropriate cancer incidences for this advanced therapy are, and to give guidance to the biologists and physicists on how to improve the potential capabilities of particle therapy.

This need is widely recognized in the community [9] but existing centers do not have the beam time available for the basic research efforts needed. Their focus is on clinical use, and research time is often limited to a few hours at a time, not adequate for well-organized data campaigns. Obviously a dedicated center for physics and radiobiology research, offering extended blocks of beam time, with a variety of ions and energies provided, is desperately needed.

What is it needed for?

Particle irradiation and the impact in vitro have been reported in a number of publications, resulting in a large range of RBE data from a number of different cell lines and endpoints [8]. These studies have been very useful in confirming to a large extent the hypotheses of the effect of particle irradiation. Nonetheless, the heterogeneity between the different studies makes it hard to combine the obtained data and to draw any definite final conclusions.

At this point, for further use in clinical research, there is a need for a large range of systematically obtained in vitro data, using identical cell lines in the same setup and under identical conditions, enlightening the effects and side effects of particle irradiation. This will require a broad panel of different cell lines, representing cancer cells from a range of different tissues, cancer stem cells, and virus infected cells (e.g. Human Papillomavirus, which has been demonstrated in head and neck cancer to have an effect on outcome of radiotherapy [10]), irradiated with different particle types and LET-values.

A similar systematic approach must be used to test the effect of cytostatica or radiosensitizers, as for example Nimorazole, in context with particle irradiation [11–14].

Ultimately, to be able to study the impact on both tumor and normal tissue in the more complex situations presented in a living

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organism, a range of systematic in vivo experiments in suitable models are required. Studies like these are absolutely necessary to uncover the risk of morbidity and secondary cancers. Furthermore, in vivo experiments are necessary to fully clarify the interconnection of high LET irradiation and tumor microenvironmental factors, such as hypoxia.

Along with the availability of new treatment modalities, new opportunities for novel treatment strategies emerge. The concept of targeting high-LET radiation toward radio resistant areas and low-LET radiation elsewhere within the tumor entity has been demonstrated by Bassler et al. [15] to retain the beneficial radiobiological properties in the normal tissue by minimizing the amount of heavy ions delivered to only those areas where needed. The same article points out that in order to effectively overcome the hypoxia problem ions heavier than carbon ions may be desirable. However their effect, especially in a mixed modality regime, is vastly unproved. A dedicated radiobiology facility is needed to provide the answers to essential questions on this topic.

Only one radiobiological model exists that is routinely applied for patient carbon ion treatment in Europe [16–18]. It is based on track structure theory, a field that has been researched for decades. Track structure theory uses the same formalism for describing in a phenomenological way the response of solid-state detectors and biological systems alike. However, the field suffers from the same issues as mentioned earlier, acquired experimental data are scattered across a multitude of experimental facilities and data acquisition protocols, complicating the inter comparison of datasets. The resulting detector and radiobiology response models heavily rely on such data, due to the free parameters within the models. This presents a major bottleneck for improving them. A concerted effort by different research groups working together at a dedicated facility, systematically assembling a complete data set of the particle energy spectrum and the spectrum of absorbed energy for a range of detectors and in different biological systems (i.e. cell cultures) would provide the much needed database with acceptable small error bars.

A more visionary idea would be to expand the facility with a mass spectrometry unit for studying the fragmentation of bio-molecules in heavy ion beams. This is of fundamental interest for understanding the nature of ion interactions in biological systems. Such facilities exist hitherto only for low energetic particle beams, and a source which directly simulates the interaction of protons and high-LET ions with molecules at clinically relevant energies would open a new field of research, significantly contributing to our understanding of these processes [19–22]. Outcome can be linked to more fundamental modeling attempts such as those pursued by the Geant4-DNA collaboration [23] or improve existing radiological models for particle therapy [24].

What do we need?

The discussions during the one-day brainstorming made clear that a broad agreement exists on the technical needs of such a dedicated research facility. The core of the facility, the accelerator, should be able to provide a range of particles from protons up to at least neon (but not all ions in this range would be necessary) at energies from a few MeV up to energies appropriate for therapeutic use (at least for ions up to oxygen). Including space research questions and research in fundamental dosimetry and radiobiology topics such as track structure theory would call for extending the mass range up to and beyond iron. RBE is known to depend on track structure and different RBE-LET dependences are expected for different ion species. Hence, the range of available ions should span from protons through lead or uranium and the available energy should cover a large part of the therapeutically relevant range.

For studies on LET painting, switching rapidly from one ion to another species would be desirable. To allow studies on modern beam delivery mechanism it should be possible to change the energy rapidly, preferably from one spill to the next. And these energy changes should be accommodated in the accelerator and not be achieved by passive scattering systems that would introduce the new variable of changing fragmentation spectra due to the degrading process.

The beam delivered to the experimental stations should be well characterized in terms of intensity, energy spread, and beam profile to allow absolute dosimetry at a level of accuracy needed to discriminate between different models. Pencil beams are the first choice for most researchers, and to cover target volumes of sizes comparable to typical tumors, active beam steering would be preferred over passive scattering. A majority of studies can be performed with a horizontal beam, but some experiments on cell cultures, especially at lower energies, would highly benefit from the availability of a vertical beam line.

Having two separate beam lines, shielded from each other in order to allow uninterrupted access for setting up experiments at one beam line while the other end station is actively collecting data, would help utilizing the accelerator at full capacity. And even with the close proximity of medical and bio-molecular research facilities a bio-laboratory for preparation and initial analysis of samples needs to be co-located with the experimental facility.

Conclusions

A dedicated center shall not only provide the necessary beam time in large time blocks, but also foster close collaborations between research teams from different countries to rapidly move the field of hadron therapy forward. We envision a scenario similar to the large collaborations found in high-energy physics, where many teams from different institutions and many countries work side by side on specific pieces of a puzzle, pursuing one common goal. Such a facility will serve the improvement of current and future hadron therapy centers worldwide.

Building upon existing structures CERN can provide the community at a minimum of cost with the much-needed opportunity to perform fundamental research to support the application of particle beams to the health sector. CERN has a strong tradition in hosting international collaborations, a scientific and technical support infrastructure, and an excellence in science achieved over the many years of operation, making it the ideal place where such a project could be initiated and propagated. But CERN does not only mean physical infrastructures; it is mainly a crossroad of competences and expertise of people. Working side by side with researchers from many other areas of physical sciences, computer science, and mathematics is expected to spark new ideas that will lead to new approaches to the existing problems.

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