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COMMENTARY

A possible biomedical facility at the European Organization for Nuclear Research (CERN)

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ABSTRACT

A well-attended meeting, called "Brainstorming discussion for a possible biomedical facility at CERN", was held by the European Organization for Nuclear Research (CERN) at the European Laboratory for Particle Physics on 25 June 2012. This was concerned with adapting an existing, but little used, 78-m circumference CERN synchrotron to deliver a wide range of ion species, preferably from protons to at least neon ions, with beam specifications that match existing clinical facilities. The potential extensive research portfolio discussed included beam ballistics in humanoid phantoms, advanced dosimetry, remote imaging techniques and technical developments in beam delivery, including gantry design. In addition, a modern laboratory for biomedical characterisation of these beams would allow important radiobiological studies, such as relative biological effectiveness, in a dedicated facility with standardisation of experimental conditions and biological end points. A control photon and electron beam would be required nearby for relative biological effectiveness comparisons. Research beam time availability would far exceed that at other facilities throughout the world. This would allow more rapid progress in several biomedical areas, such as in charged hadron therapy of cancer, radioisotope production and radioprotection. The ethos of CERN, in terms of open access, peer-reviewed projects and governance has been so successful for High Energy Physics that application of the same to biomedicine would attract high-quality research, with possible contributions from Europe and beyond, along with potential new funding streams.

This meeting, called "Brainstorming discussion for a possible biomedical facility at CERN", was held by the European Organization for Nuclear Research (CERN) at the European Laboratory for Particle Physics near Geneva on 25 June 2012. There were 214 registrants from 26 countries, not only from the European Union (EU) but also from Australia, Canada, Colombia, India, Mexico, Russia and the USA. 17 short oral communications, from 8 countries, were given, with the intent of fostering open discussion, with generous discussion time allotted. The speaker list is available at https://indico.cern.ch/conferenceTimeTable.py?confId=193910#20120625

The following account is a summary of the presentations, detailed discussions and final summaries given at the meeting; however, first, for readers who may be unfamiliar with the topic of charged particle therapy, a brief introduction is provided.

Charged particle therapy (hadron therapy) uses protons or other heavy and charged particles, such as carbon ions, instead of X-rays to much more precisely target cancerous tumours. Hadrons overcome some limitations of X-ray beams by depositing most of their energy at the end of their range, in the target, while X-rays pass through the entire thickness of the body, with their energy loss being highest close to the entry surface of the body. The aim of hadron therapy is to improve human cancer therapy outcomes, by safer dose escalation where necessary or by reduction of integral dose to normal tissues without dose escalation [1]. There can be no complacency about cancer therapy since side effects and tissue injury risks do cause much human misery, and normal tissue dose constraints do limit success with conventional photons (X-rays). The goal is consequently tumour cure with minimised risks of treatment-related side effects, so improving overall quality of life during and after cancer therapy.

PRESENT ISSUES IN PARTICLE THERAPY

Several speakers emphasised that, although protons and carbon ions are in clinical use, there is limited clinical evidence as to their relative superiority [2]. Radiobiological studies suggest a potential for improved treatment of intrinsically radioresistant and hypoxic tumours in the case of carbon ions owing to the increased ionisation density. However, it is not known if these modalities are better than dose escalation using photons for improving tumour control. Improved patient selection based on rational biological and physics-based criteria will be required to utilise the potential of heavy ion therapy to its fullest extent. In terms of physics, this needs to include better comparative studies of three-dimensional (3D) dosimetry in heterogeneous materials that are typical of the human body (by using humanoid phantoms), real-time imaging, beam application methods, moving targets, etc. for ions and protons. Detailed studies on radiation chemistry and biology are indicated to improve and update the understanding of cellular damage and molecular responses. Many of the classical experiments in hadron radiobiology were performed before the advent of modern molecular biology, with its emphasis on cell signalling and repair pathways.

Discussions included the potential role of ions, such as helium, boron and lithium, offering ballistic advantages, with reduced laterally scattered radiation compared with protons but less particle fragmentation products than would occur with carbon. Such properties would be clinically relevant in deeper situated cancers or where cancers are very close to critical structures, such as optic nerves, spinal cord and in children and young adults with cancer. Particle therapy could be improved by doing more basic research that would improve clinical trial design [3]. Better dosimetry and confirmation of beam placement by external imaging (*e.g.* positron emission tomography scanning) as well as improved prediction of relative biological effectiveness of the various ions in different tissues and at different doses are all essential in order to achieve expected outcome benefits.

THE PRESENT AND FUTURE ROLE OF CERN IN MEDICAL APPLICATIONS

The meeting started with a brief review about the many outstanding advances in particle physics, accelerator and detector technology and computing, with applications such as the web, achieved at CERN [4]. More recently, CERN has also provided co-ordination, and training, for three large EU funded projects under the European Network for Light Ion Hadron Therapy (ENLIGHT) consortium (www.enlight.cern.ch) in order to provide infrastructure and research support to the present European particle therapy expansion [5].

It was explained that two large scientific meetings entitled "Physics for Health in Europe", held in Geneva in 2010 and 2012, had provided opportunities for preliminary informal discussions between oncologists and CERN staff about the need for a dedicated CERN

biomedical beam line in order to improve knowledge, address difficulties of beam access and provide standardisation for experiments. These discussions were followed by feasibility studies on the existing low energy ion ring (LEIR) accelerator, which currently delivers lead ions for the Large Hadron Collider (LCH) and in the future Ar and Xe ions to other super proton synchrotron experiments during only a few months each year. With some technical modifications, the facility will be capable of accelerating a range of charged particles for testing dose placement, beam ballistics and their bio-effectiveness. At present, the CERN low energy ion accelerators Linac3 and LEIR are equipped with only one ion source and fast LEIR extraction towards the next larger synchrotron of the LHC ion injector chain, but not towards the "south hall", where space can be made available for biological experiments. Options for adding another ion source with a dedicated radio frequency quadrupole (RFQ) optimised for operation with lighter ions and options for a new LEIR injector are being studied. The (re-)implementation of slower extraction, using a new channel, is planned and can be implemented more easily than a second fast extraction. Beam time structures can then be similar to typical treatment facilities, with short periods of around 2 s without beam for ramp down of the magnetic field, injection and acceleration. However, longer spills with smaller particle fluxes would be possible. The energy reach of the LEIR main magnet system is about 430 MeV/nucleon for ions with a charge-over-mass ratio of one-half, for example, He^{2+}, $^{12}C^{6+}$ or $^{16}O^{8+}$. However, with the present main power supply, some small auxiliary magnets and probably limitations owing to radioprotection (presently there is no shielding above LEIR) may impose a lower limit, at least for initial operation of the facility. In principle, electron cyclotron resonance (ECR) ion sources allow generation of a variety of ions, some ions being more difficult to implement. First estimates, based on a commercial ECR source, gave slightly more than 10^9 ions per cycle for operation with C or O; the intensity for He^{2+} is limited by LEIR to a few 10^{10} ions per spill.

An important outcome of the meeting was the need of proton beams for comparative studies. Since LEIR operation with low-energy protons from CERN's Linac3 is challenging owing to low magnetic fields, an alternative option of acceleration of H_2^+ with stripping in the extraction channel was suggested.

The proposed CERN facility would allow at least 6–8 months of beam time per year for radiation biology and oncology research, rather than the typical 1–10% of total beam time access, often fragmented to short periods of time, permitted in other laboratories and hospital-based facilities elsewhere in the world. This would allow standardisation of experimental conditions for studying beam ballistics combined with better prediction of bioeffectiveness using modern molecular, cellular and tissue biology. The ethos of CERN, in terms of open access, peer-reviewed projects and governance has been so successful for high energy physics that application of the same to biomedicine would attract high-quality research with contributions from Europe and beyond. The pattern of organisation envisaged would involve committees, with international membership, similar to the existing CERN structure.

FURTHER TECHNICAL REQUIREMENTS PRESENTED

A new facility could be developed with the following technical specifications, suggested by the meeting participants:

- Modify the 78-m circumference LEIR facility by (re-) implementing a slow extraction and a new extraction channel. A second ion source for the LEIR injector Linac3 or new injector is envisaged to improve the flexibility and availability of the facility.
- A horizontal beam line for particle energies of up to 400 MeV per nucleon, with up to 30 cm range in tissues for testing comparative particle ballistics for different ions, their dosimetry and radiobiology in humanoid phantoms, along with beam scanning capabilities. A vertical beam could be considered as a later option: it would only deliver particles of lower energies.
- An optional vertical beam line could provide lower particle energies, as low as 10 MeV, for *in vitro* work using larger cell numbers for radio-sensitising and protective drug experiments.
- A biological end station would be installed, with efficient throughput by remote control of cell placement (as presently used in Oxford, UK), microscopic/video facilities and hypoxic chambers, all at body temperatures.
- Imaging facilities would include high-quality gamma cameras, MRI and X-ray tomography; these are necessary to study dose positions in humanoid phantoms. Cellular imaging techniques (post-radiation exposure) would also be useful.

- Control X-ray irradiation for relative biological effectiveness (RBE) studies would require installation of a nearby small linear accelerator or orthovoltage X-ray set in the Compton scattering energy range with adequate filtration of lower energies.

Adjacent to the LEIR hall, there is sufficient ground space of around 500 m^2 (with 3–4 potential floors)—for a well-equipped biological laboratory for cell culture, bioassays and analysis. This would need to be built to the best standards available elsewhere.

RELATIONSHIP WITH OTHER FACILITIES AND AGENCIES

A biomedical facility at CERN would allow participating countries to perform longer and more difficult experiments and to test a wider range of cells and possibly tissues. CERN-based research would be complimentary to work done with more limited beam time in other countries and could help to standardise experimental conditions, dosimetry, etc. Free access to the CERN beams, with a wide range of particles and energies, with rapid switching between particles, should stimulate demand for more complex experiments and would be essential for detailed dosimetry studies. New funding streams were anticipated.

BIOMEDICAL EXPERIMENTAL AIMS

There was agreement for the establishment of an open access database of around 20–30 human cell lines (malignant and normal) exposed to different linear energy transfer conditions using, as far as possible, mono-energetic particles. The latter would range from protons to heavier isotopes of hydrogen, helium, boron, lithium, carbon and neon. Using diverse cell systems with known molecular profiles, end points such as radiosensitivities (assessed by both molecular and clonogenic assays), with detailed RBE estimation at predetermined levels of survival, and at the extreme limits of low and high dose [6] in order to predict RBE at any dose. Such data can then be used to test the validities of existing microdosimetry track structure models and provide definitive studies for how far RBE may vary in cells with different radiobiological properties. Testing of drug/nanoparticle or other biomodifiers of radiation responses could also be achieved. The required complex bioanalysis, such as proteomic studies, can be performed at the participating universities.

Proof of principle experiments could be done at CERN, with a view to collaborative experiments with clinical ion beam facilities as part of an overall international network.

APPLIED PHYSICS RESEARCH

The participants listed the scope for testing better beam delivery systems, improved dosimetry, radiation detectors designed specifically for this purpose, Monte Carlo simulation techniques, remote monitoring of dose deposition, proton radiography and tomography, pencilled and collimated beams at variable dose rates, advanced quality assurance and meeting the most demanding national standards for reference dose. Prototype development would also be possible. Fusion of the bioeffect research with the 3D dose distributions can be obtained in virtual systems and in humanoid phantoms for confirmatory purposes.

TRAINING AND EDUCATION

Participants involved with training of medical physicists, now governed by European directives, stated an increasing need to include training in particulate radiation owing to the growth of particle therapy centres. The CERN campus could be used for residential training in dosimetry, particle beam accelerator dynamics and high-level computing, while also offering more research opportunities during training.

FUNDING

Resource issues and potential funding through EU Framework Programme 8 (Horizon 2020) and other sources were discussed. The fact that the basic infrastructure exists at CERN means that costs over and above the necessary modifications will be limited to those for adapting the existing structure for future biomedical use, which is outside the scope of CERN's core mandate. It is anticipated that such a facility would attract new funding streams from a variety of charitable and other benevolent foundations.

JUSTIFICATION AND AIMS OF RADIOBIOLOGICAL STUDIES

There were considerable discussions of radiobiology, summarised here. Modern hadron therapy, although increasing rapidly, is based on empirical clinical data and research carried out before the advent of modern molecular biology (some being up to 50 years old). Groundbreaking biological studies of neutrons, protons

and heavier ion beams were performed at different times in many physics laboratories throughout the world, and the data sets show considerable variation. There is a real need to study the various phenomena in a more systematic way by using a dedicated facility with standardisation of experimental conditions and biological end points. Present clinical practice would probably benefit considerably from further studies to provide better predictive information [2,3,6].

To improve RBE prediction accuracy, ideally approaching —as far as possible—the 2% level (the present legal requirement for dose delivery in many countries) would be a major advance for clinical applications, although some participants doubted whether the same accuracy as that achieved for dose is feasible. Certainly, improved accuracy is urgently required since RBE is used within the treatment prescription process: the dose of particles given to a patient is obtained by dividing the intended photon dose—for a specific clinical end point—by the RBE. At present, RBE estimations contain potential errors of 5–20% or more. There needs to be allocation of tissue-specific RBE values, but knowledge of human and animal tissue RBEs remains sparse. A co-ordinated international approach is indicated. The urgent need for more animal tissue RBE research should be met at the existing—and soon to be commissioned—proton and ion beam centres by using special research beam lines away from patient treatment areas. It was suggested that a CERN facility would not do such work in the first instance, but this could follow at a later time. It was agreed that extra beam time created at CERN would eventually take the pressure away from other centres that should be concentrating on this supportive aspect of hadron therapy in the meantime.

DISCUSSION

The creation of a radiobiology database using a range of particles and ionisation densities would allow analysis and optimisation techniques to be pursued remotely in the participating national universities. The previous accumulation of fast neutron *in vitro* and *in vivo* data in the UK (between 1970 and 1990) serves as a good example because publications continue to be based on these results and are being extrapolated to proton therapy, with RBE values similar to carbon ion therapy [6]; although a carbon ion data set is being collated in Germany, it could and should be extended. Much more could be done with specific experiments using a more focused approach, which would complement the already important work emerging from carbon ion facilities [1,2,5], including verification of microdosimetry-based RBE predictions in a wider range of biological end points.

A truly international co-operative approach to these problems should allow clinicians and scientists to optimise what can be achieved. Although CERN is not a clinical site, clinicians and medical physicists with a special interest in hadron therapy would be encouraged to participate in experimental design and be part of the overall decision-making process. Clinical leadership will be essential to investigate and interpret the present uncertainties in accurate dose placement and predictions of bioeffectiveness in different tissues and tumours, at different doses, for different combinations of radiation qualities within beams, along with other modifying drugs. All these aspects need to be understood and modelled sufficiently to allow treatment optimisation. The alternative would be to allow present uncertainties to continue influencing clinical outcomes, each country attempting their own incremental improvements.

Those involved in the radiological sciences, from radioprotection to cancer therapy, particularly in the academic units, will be interested in these potential developments and should start thinking of how to become involved at CERN. The local advantages of a Geneva-based operation are numerous: it is in many respects an international city, with the World Health Organization, United Nations and Union International Contre le Cancer presence, but more so there is the expertise of CERN in beam production, detector development, advanced computing and analysis. The absence of clinical activity may also be an advantage since all efforts would be concentrated on research, although it would need to be relevant to biomedical problems and work in close liaison with the existing and future hadron therapy centres, especially in Europe.

At a time when so many national budgets are squeezed, it is sensible to share costs not only to reduce the total expenditure but also to increase the rate of progress and its scope by collaboration at the highest level possible. Also, many cancer and scientific charities, philanthropists and non-profit seeking organisations could contribute to this new proposal, allowing grant awarded

bioscientists from many universities and nations to work at CERN.

SUMMARY AND CONCLUSIONS

The essential requirements would be for an accelerator capable of producing beams of clinical quality, ranging in mass from protons to neon ions, at clinically relevant depths, with cutting edge dosimetry and imaging capabilities and nearby X-ray irradiation facilities for RBE studies. The biotargets would need to include a representative range of human cell cultures (and facilities for their preparation, storage and analysis). Humanoid phantoms could be used to simulate 3D distributions, physically and for cell placement. The question of necessary *in vivo* tissue experiments can be approached later in collaboration with nearby university medical schools or done in collaboration with existing beam facilities worldwide. The model for implementation would be that for scientific studies at CERN, with truly international cooperation.

There is, consequently, a large potential role for biomedical research at CERN. Cancer treatment requires further research in so many aspects, and is potentially one of the greatest intellectual challenges to mankind, and the disease itself the cause of much human suffering. For radioprotection, there is also the question of safer air and space travel, important for the survival of the human race if planetary conditions become sufficiently adverse.

Improvements in biotechnology, resulting in more personalised medicine, molecular imaging etc. will almost certainly produce earlier diagnosis of cancer and lead to better "short-term" measures for tumour control. Some newer molecular approaches influence only a proportion of tumour cells, often resulting in cancer progression within 1 year. Even so, these advances create a demand for "smart" applications of atomic and medical physics, such as cyclotron/synchrocyclotron and laser produced particle therapy, along with the modern surgery, chemotherapy in its widest sense and other physical methods such as highly focused sound waves. To integrate all these approaches represents a considerable intellectual challenge, perhaps commensurate with recent advances in particle physics, such as finding the Higgs boson. It is time to start.

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