

A large graphic of a globe composed of a network of white dots and lines, overlaid on a 3D anatomical image of a human head and neck in shades of red and orange. The text "THE EUROPEAN NETWORK FOR LIGHT ION HADRONS THERAPY" is superimposed in large, white, sans-serif, all-caps letters across the center of the globe.

THE EUROPEAN
NETWORK FOR
LIGHT ION
HADRONS
THERAPY

HIGHLIGHTS

December 2017

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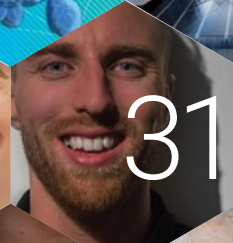


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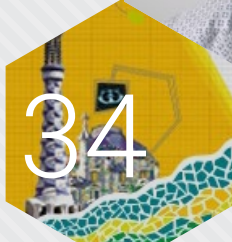


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Petya Georgieva
Manjit Dosanjh
Antonella Del Rosso

ENLIGHT COORDINATOR

Manjit Dosanjh

COVER:

A dying cancer cell.

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BRIDGING THE GAP



FROM THE ENLIGHT COORDINATOR

Manjit Dosanjh

Two recent initiatives which I am involved with are worth a special mention in this issue's Editorial: the signature of a collaboration agreement between the South-East European States to build two particle accelerators and the progress made to design an affordable linac for treating cancer in developing countries. Both initiatives remind us of the CERN model of "science for peace" that has inspired successful endeavours such as the SESAME facility in Jordan.

Indeed, inspired by CERN's example, the *International Institute for Sustainable Technologies in South East Europe* has "Science for Peace" as its primary mission. Officially launched by the Government of Montenegro, the project aims to build a Synchrotron Light Source and a Hadron Cancer Treatment and Bio-medical Research Centre (read page 21). With over 1,000 collaborating researchers, the project would not only strengthen the infrastructure in the region, but also enable research in various scientific fields such as biology, chemistry, pharmacology, ecology, geology and engineering as well as having wide application in various industries.

The second project, initiated by the *International Cancer Expert Corps (ICEC)*, and now actively supported by the *UK Science and Technology Financing Council (STFC)*, aims to provide an affordable solution to the severe shortfall in linacs for cancer treatment in low-and middle-income countries (LMICs). It is estimated that, out of the 25 million cases of cancer expected globally in 2035, 65-70% will occur in LMICs. Although the first linac in the western hemisphere was built and used clinically at London (England)

and Stanford (US) in 1956, only a few African countries have access to such treatment even today. Factors limiting the development and implementation of radiotherapy include the cost of equipment, inadequate infrastructure, a shortage of trained personnel to properly calibrate and maintain the equipment and to deliver high quality treatment. Therefore, the challenge is to design a linac and associated instrumentation that will operate reliably in regions where general infrastructures are poor, or where power outages and water supply fluctuations can occur and where climatic conditions might be harsh (more on page 35).

The goal of both projects is to reduce the technology divide that slows down the development potential and creates barriers to healthcare access and equity. This will be obtained also through a massive programme of training of local experts. Fifteen years ago, before the birth of ENLIGHT, Europe was lacking such experts in HT. Today, we can proudly say that our network has played a major role in addressing this issue and we can look positively to the future. Now it's time for us to take on a bigger challenge and work to make sure that no one is left behind.

Talking about being inclusive, I would like to thank our contributors for their continuing collaboration and support without whom the Highlights would not be possible. I would like to encourage more of you to share your work with the community and look forward to seeing you in London for the 2018 ENLIGHT Meeting. ■

Manjit Dosanjh



PROGNOSIS FOR
DCPT PERFORMANCE IN 2018

 **71-TON**
PARTICLE
ACCELERATOR

 **30,000**
TREATMENTS

 **1,200**
PATIENTS
PER YEAR

The 15th annual ENLIGHT meeting was held at the Aarhus University Hospital (AUH) in Denmark on 12-13 June 2017. The meeting was opened by Professor Cai Grau from AUH and by Charlotte Lindberg Warakulle, CERN's Director for International Relations and coincidentally a native of Aarhus who warmly welcomed the participants.

Manjit Dosanjh, ENLIGHT Coordinator, first gave a brief history of ENLIGHT and its role over the 15 years since it was launched. In her speech, Dosanjh emphasised how delighted she was to see so many of the familiar ENLIGHT participants as well as many new faces. She also explained that it was highly appropriate that this key event for the ENLIGHT community was held in one of the 2017 European Capitals of Culture, often referred to as the "city of smiles" as this is where the Danish Centre for Particle Therapy (DCPT) is coming to life.

The week before the ENLIGHT meeting, the 71-ton particle accelerator was lifted into place. It is expected that in 2018 the Centre will provide particle radiation to patients from all over Denmark. The centre will also have a capacity to perform around 30,000 treatments equivalent to approximately 1,200 patients per year.

This year's meeting focussed on three hot topics that are currently under a lot of discussion in order to deliver particle therapy more effectively so that the patients can benefit maximally: clinical trials, imaging for hadrontherapy, questions around RBE and how to accurately deliver, and measure dose in real time.

CLINICAL TRIALS: A KEY ISSUE

The session started with an overview of the current status of particle therapy in Europe and beyond by Roberto Orecchia (CNAO, Italy) who reported the increasing number of particle therapy centres that are emerging and the growing number of patients being treated. This illustrates the huge momentum that particle therapy is having globally. There are now 60 proton centres and 10 carbon centres, which have been able to treat, respectively, over 130,000 and 20,000 patients. The very first patient was as far back as 1954 in Berkeley until 1990, all patients were treated in particle physics research laboratories.

He then discussed the current on-going Proton and Carbon trials and emphasised that there is much discussion and demand for clinical trials in order to provide evidence for the efficacy and possible superiority of particles over conventional radiation therapy.

NEW IMAGING FOR PARTICLE THERAPY

The **INSIDE (INnovative Solutions for In-beam DosimEtry in Hadrontherapy)** project was presented by Giuseppina Bisogni (Pisa, Italy). Rationale for in vivo range monitoring is motivated by the fact that ion therapy is highly sensitive to range uncertainties and treatment is impacted by anatomical changes, patient positioning and inter/intra-fractional motion. The INSIDE goals for an in-beam PET are to be close to the nozzle, operated during beam-on and on-the-fly reconstruction and treatment verification. A first clinical test was successfully carried out at CNAO in December 2016. The performance was successfully assessed with protons and first measurement made during patient treatment. In the future, this will be tested with carbon beams integrated with PET profiles and CNAO clinical work-flow.

Christian Richter (Dresden, Germany) presented the latest data on **Prompt-gamma based range verification with a slit camera: sensitivity and first clinical experiences**. This is the first clinical application in double scattered particle therapy and measurement of shift detection sensitivity in the clinic.

Prompt gammas resulting directly from the nuclear interactions of a beam with the tissues leads to:

- Strong spatial correlation of gamma emissions with dose
- Emission spectrum depends on the proton energy (penetration depth)
- Detection time of prompt-gammas decodes penetration depth

Richter presented results from the evaluation of the first prototype Prompt Gamma Imaging (PGI) slit camera developed in the framework of the ENVISION project under clinical conditions. The very first clinical PGI based range verification was carried out in August 2015 on a Head and Neck tumour patient and the measurements were confirmed using an in-room control CT.



Group photo during the ENLIGHT training in Aarhus, June 2017.

The current comparisons against “treatment plan” provide valuable accuracy and high sensitivity and PGI looks very promising but needs further work.

The on-going evaluation will provide new insights on these prototypes and their clinical value.

Both the INSIDE and PGI collaborations are building upon innovative research, partly performed in the framework of the ENLIGHT-promoted EU FP7 project ENVISION and ENTERVISION.

RADIOBIOLOGY: THE HOLY GRAIL

It is becoming evident that there are major gaps in our knowledge of the biological characteristics of ions. The relative biological effectiveness (RBE, relative to photons) of ions is a complex function of multiple variables, including dose, depth of penetration, linear energy transfer (LET), cell or tissue type, oxygenation, etc. It is essential that this functional dependence is fully quantified and taken into consideration, both to understand the response to ion therapy and in treatment planning to maximize the effectiveness of ion treatments.

Kevin Prise (Belfast, UK) gave an overview of the **Present status of Radiobiology: pre-clinical data, implications for therapy**. He pointed out that currently an RBE of 1.1 is generically used for proton therapy clinically even though it is now known that it is an oversimplification since, in reality, RBE is influenced by a number of factors such as dose and dose rate, Cell line radiosensitivity, ion mass, ion energy, SOBP (Spread Out Bragg Peak), shape and size. There are increasing concerns since the dose accuracy required in

radiation therapy is in the region of 3.5 % and any uncertainty in the RBE will translate to the same uncertainty for biological effective dose, which has some clear implications for therapy that need to be addressed.

In addressing the issue of dose, LET and RBE, it is known that:

- Cellular response is determined by the level and quality of DNA damage, which reflects the energy deposition pattern.
- The severity of DNA damage depends on lesion proximity and reparability, hence it is not a constant value but depends on physical (particle type, LET, dose) and biological (cell type, oxygenation status, repair capacity) parameters.
- RBE varies with the particle energy and the change of the beam composition (SOBP and nuclear fragmentations): its distribution is not homogenous across a treatment field.
- Estimates of the RBE of each specific irradiation scenario and position along the ion path could be important inputs for the development of radiation treatment plans.

So a key requirement is to have a combined assessment of early and late cellular response including DNA damage in a range of relevant cell lines to provide systematic high-resolution information to develop a rigorous theory of ion radiation action at the cellular and molecular level. This needs to be extended to animal studies.

Julia-Maria Osinga (DKFZ, Germany) spoke about **LET: measurements for dosimetry** and showed that, although more experimental data are needed, the present data show a threefold reduction of the uncertainty compared to calcu-



A fitting venue for the cocktail of ENLIGHT and BigART coming together for multidisciplinary collaboration.



Cancer and Global warming sharing the status of modern global challenges.



Food for Thought during the training.

lated values, demonstrating that precision water calorimetry allows to significantly reduce the uncertainty related to ionization-based dosimetry of clinical carbon ion beams.

Martina Fuss (GSI, Germany) spoke about **LET: measurements for radiobiology** and specifically focussed on biological treatment planning and verification with oxygen beams which have some clear advantages over carbon. The goal is to analyse differences and advantages of oxygen compared to lighter ions since oxygen has advantages both in the physical dose profile (higher LET, very low lateral scattering) as well as biological advantages due to dense dose deposition pattern leading to a higher RBE particularly in the Bragg peak region before ions stop. This should make it possible to compensate for oxygenation effects and treat otherwise radio-resistant targets.

Brita Singers Sørensen (Aarhus, Denmark) addressed **What is needed in the future for radiobiology**. The issue is how does this higher LET translates into biological effects. She emphasised that dose and fractionation, as well as tissue types and position in the beam, are all equally important factors and one needs to determine to what extent is RBE influenced and what is the influence on the clinical outcome.

In vitro data clearly shows an increased RBE in the distal edge, but the in vivo data here is very limited so much needs to be done to establish the RBE of normal tissue damage, acute effects and late effects. Singers Sørensen's team has started to study mice using the Krakow facility.

They are finding that both ions and protons show unique molecular and cellular responses compared to photon radiation



Hard work during the training, Aarhus, June 2017.

in terms of: complexity of the DNA damage, differential gene expression, epigenetic modulation, effects on cell cycle.

Much remains to be done and further experimental studies are urgently needed, which have to include a range of in vivo models and end points.

YOUNG EXPERTS

Participants, especially young researchers were encouraged to prepare posters, which were on display during the meeting and winners of the three best posters (announced and presented by Brita Singers Sørensen and Kari Tanderup) were given the opportunity to give an oral presentation of their work in the penultimate session of the meeting. The prize winners were Lars Frederik Fjera (University of Bergen, Norway) for **a spatial analysis of biological dose distributions in the brainstem and its substructures in proton therapy of paediatric brain tumours**, Nigel Allinson (University of Lincoln, UK) for **PRaVDA: a solid-state proton imaging system** and Ikechi Ozoemelan (University of Groningen, Netherlands) with **beam-on imaging of short-lived positron emitters during proton therapy** (for further details see page 13-15).

ENLIGHT 2018

There was a lively talk by Simon Jolly (UCL, UK) on the location of the next ENLIGHT meeting, which will be held in London. He highlighted the joys and challenges of having a particle therapy facility right in the centre of a city as large as London. He invited the ENLIGHT community to the 2018 meeting, which he will host along with his colleagues. ■



Poster winners and session chairs from left to right Lars Frederik Fjera (University of Bergen, Norway), Nigel Allinson (University of Lincoln, UK), Ikechi Ozoemelan (University of Groningen, Netherlands) with presenters Brita Singers Sørensen and Kari Tanderup (Aarhus University Hospital).

A TRAINING DAY WORTH THE DETOUR

By Lars Fredrik Fjæra





Aarhus Street Food Festival, June 2017 – reflecting the multicultural approach.

Chaired by Manjit Dosanjh and locally organised by Brita Singers Sørensen, Kari Tanderup and Cai Grau, this year's annual meeting of ENLIGHT was really eventful. It was conducted back to back with the BiGART conference and included a training day with hands on work and interactions.

The training programme was organised around three lectures. The subjects were covering physics principles for proton therapy planning, comparative treatment planning and hot topics in proton therapy. The lectures were given by Jörgen Olofsson, Petra Witt and Håkan Nyström, respectively. The speakers presented interesting insight on diverse topics in proton therapy, covering aspects relevant for both physicians, clinicians and physicists. Being a physicist myself, I particularly enjoyed the clinical parts of the lectures as these are subjects I am less familiar with.

The participants also attended hands-on activities on dose planning on patient cases and visited various workshops held by researchers within different fields of proton therapy.

For the dose planning session, I must acknowledge the local organisers as they had arranged no less than 40 simultaneous accounts to access the Varian Eclipse treatment planning system. A task which I can imagine was no easy feat. The dose planning session began with a short introduction of the three patient cases we were to plan. The first patient was a male (born 1963) with an ependymoma tumour, the second; a male (born 1987) with a pituitary adenoma while the last was a male (born 2000) diagnosed with Ewing's sarcoma. The purpose behind these specific patients was to present planning cases with varying difficulty concerning limitation of doses to organs at risk as well as treatment field angle selection and optimisation criteria. In all three cases, we were also supposed to assess the robustness of the treatment plans considering both range and setup uncertainties, aspects which are highly relevant in proton therapy clinics. In order to distribute treatment planning knowledge most effectively, participants unfamiliar with Eclipse were encouraged to pair up with a person having previous experience with the treatment planning system. This was a great idea as it also advocated cooperation with persons from different work backgrounds. We also had excellent instructors available to help us with problems and answer questions.

The research workshop was divided into eight stations covering a variety of topics such as radiobiology, motion



Dinner at Street Food: the diversity of the flavours matched the diversity of the ideas and cultures coming together.

management, 3D dosimetry, imaging for stopping power calculation, treatment planning, preclinical imaging, building of a proton facility, and inter-fractional challenges in proton therapy. The researchers at each station presented their topic and opened up for both questions and discussions. Consisting of four rounds of 25 minutes each, we could choose four of the eight stations to attend. We had in advance received information about the different topics which made it easier to select the workshop stations that one considered to be the most tempting. For me personally, the most interesting topic was definitely the one concerning how to build a proton therapy centre. We are still waiting for our beloved, hopefully soon-to-come, proton facility in Norway. Therefore, to get an insight to paramount challenges of building the Danish Centre for Particle Therapy and how they were solved was quite intriguing.

The day was rounded off with an informal visit to Aarhus Street Food. Here one can eat street food from all over the world. If you are hungry for tasty Mexican tacos, Vietnamese Bahn-mi's, American soul-food, a Duck It burger or just traditional Danish sandwiches, Aarhus Street Food is the place to visit. We were kindly given Street credits (the official currency at Aarhus Street Food) by the ENLIGHT organisers, and could choose meals and drinks from the many kitchens. Let us just say that I had more than one dinner that day.

All in all, the training day provided an overview of different topics and challenges in proton therapy. Furthermore, the hands-on experience with treatment planning was an excellent way to give insight to one of the most important aspects of patient treatment in radiotherapy. If you are attending the ENLIGHT meeting in 2018 I highly recommend you to join the training day as well. ■



“The hands-on experience with treatment planning was an excellent way to give insight to one of the most important aspects of patient treatment in radiotherapy.”

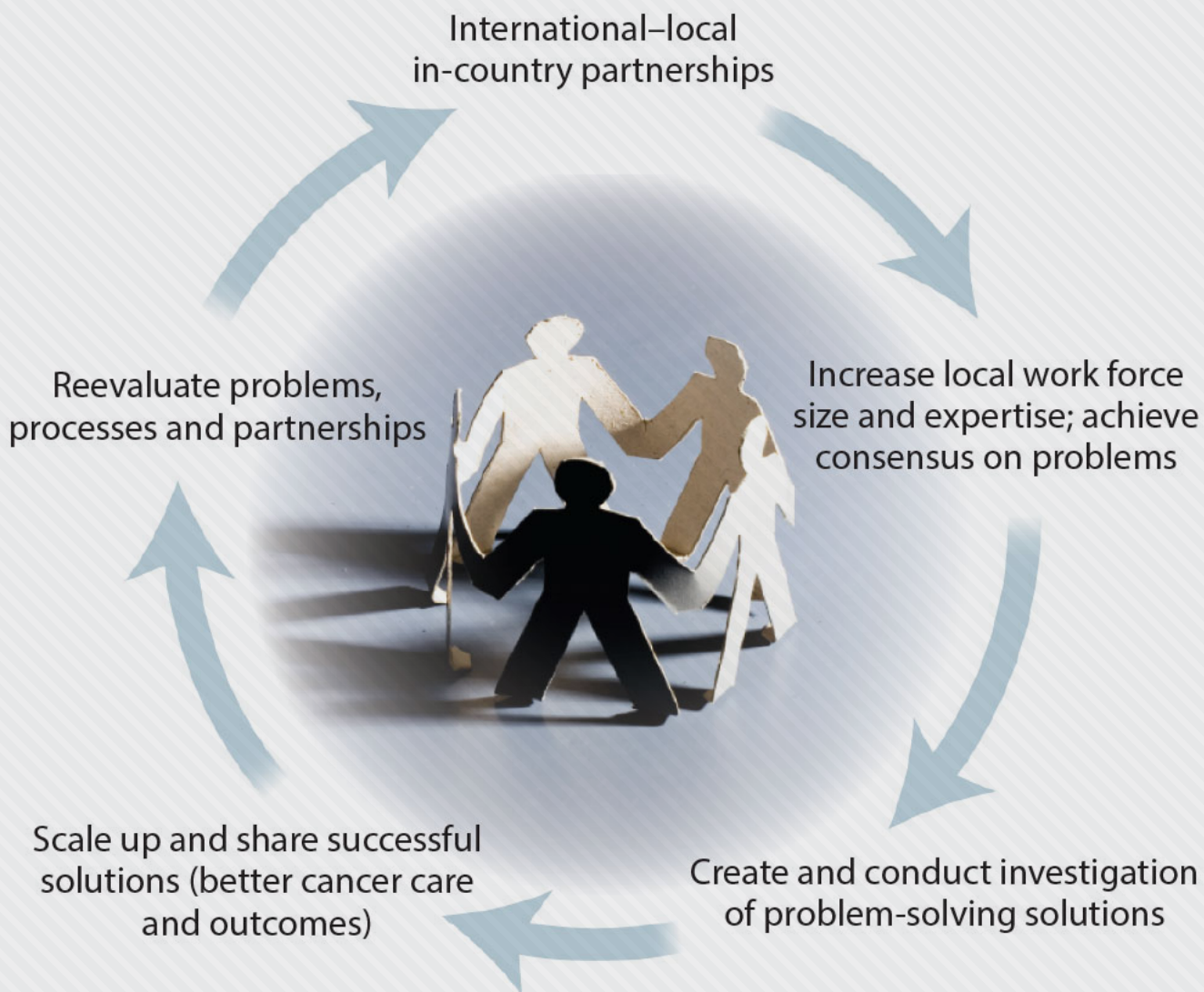
Lars Fredrik Fjæra

“SHADES OF GY”:

how can radiation be better used
in cancer treatment

*By C. Norman Coleman and David Pistenmaa
(representing the efforts of many)*

Think globally, mentor locally.



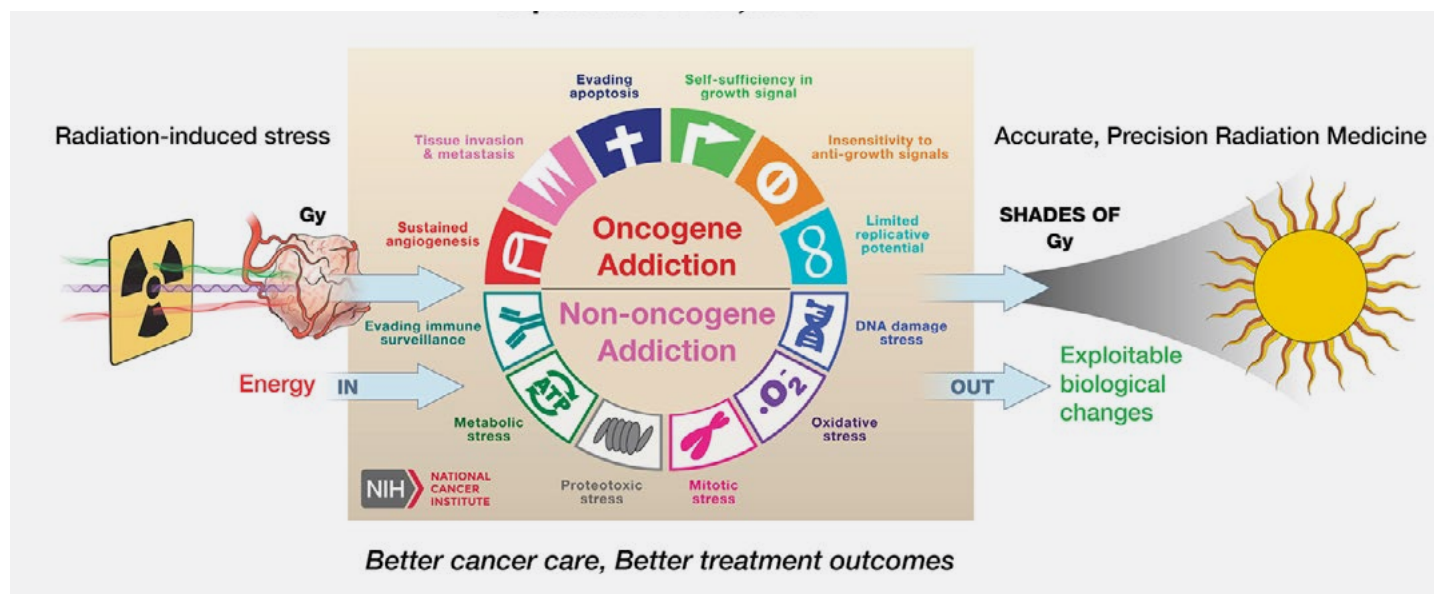


Figure 1

To best realise the breadth of potential contributions of the radiation sciences we tap into the expertise from CERN and the physics community. Their philosophy and experience with the establishment of effective global collaborations to address major challenges can help us identify new opportunities in the cancer field. In particular, we would like to address the “leading edge” of the radiation sciences in understanding how radiation interacts with tissue and the “trailing edge” in access to cancer treatment resources and how the innovation in linear accelerator design and the establishment of mentorship and educational programs can have global impact on the dire shortage in cancer care globally.

The “leading edge” issue was addressed in September 2017 at the US National Cancer Institute (NCI), “Shades of Gy” workshop. We know that, in order to understand the interaction between radiation and the biological tissue, the quantity of energy deposited in matter must be accurately described, measured and reported. The gray (Gy), (one joule of radiation energy deposited per kilogram of matter) is the unit of measurement. However, tissue, cells, and molecules do not “see” Gy but rather they absorb the energy and respond to it. At the workshop, several experts discussed the various aspects related to this issue and in particular: the dose-effect models (what do they tell us about biology and what do they allow us to do safely? Does comfort with them dissuade us from considering mechanisms and result in missed opportunities?); biophysics (why track structure from various forms of radiation and the various tissues, cells, organelles and molecules that are hit strongly suggest that simple RBE measurements will have limitations); the Relative Biological Effectiveness (RBE) and the range of endpoints used from organism down to molecular level and impact of biological perturbations as assessed in terms of dose size, dose rate and radiation quality; biomarkers and response predictors (how can one measure “radiation effect”?). The workshop was also an opportunity for clinicians to share their perspective on “dose” and desired outcome and to discuss the biological consequences of clinical relevance. Two more

sessions were dedicated to discussions about whether we can consider partial tumour volume radiotherapy in the clinic that has the proposed potential to protect normal tissue & cells and elicit intra-tumoural & distal immune attack; and what conventional accepted wisdom of radiobiology that needs re-validation using modern tools for proper use in the clinic.

The final discussions focused on the famous the ratio (level of damage produced by one beam, for example X-rays, compared to the same level of damage produced by another beam for example a proton beam) used to determine the prescribed proton dose based on the experience with a defined photon dose. An RBE of 1.1 has been used for protons. However, at previous NCI workshops (reports to be published soon), it has been recognised that a simple ratio is not the optimal way to determine dose. The “Shades of Gy” was chosen for the title of the workshop because there needs to be a new major effort to determine dose in cancer treatment both by the energy absorbed and also by the biological changes induced by a specified dose. As discussed in the workshop, the consequences of radiation exposure, especially following adaptation of multi-fraction radiation therapy, has opened up potentially unique uses of radiation.

Figure 1 is the conceptual illustration of the innumerable physical and biological interactions of ionising radiations (re-printed with permission). A detailed publication will be forthcoming in the next year. What was clear at the workshop and subsequent meetings of American Society of Radiation Oncology (ASTRO) in September and the Radiation Research Society meeting in October is that the new “Shade of Gy” paradigm will be pursued as research and development in the radiation sciences broaden its scope to meet the opportunities, challenges and possibilities of having a substantial impact on improving human health. This applies to both the treatment of cancer and normal tissue injury.

The “trailing edge” issue was addressed at the CERN-ICEC-STFC Workshop held in October 26-27, 2017 at CERN.



International Cancer Expert Corps

Partnering to transform global cancer care

The International Cancer Expert Corps (www.iceccancer.org, ICEC) is a global organisation with members in Europe and Asia as well as in North America and is in the process of establishing offices in a number of countries. It has a dual effort to improve cancer care globally, including but by no means limited to radiation therapy, through 2 major efforts: a global mentoring and education network and improving the technology.


To follow up on the recommendations emanating from the first CERN-hosted workshop in November 2016, three task forces were created and began their work in 2017. The task forces are as follows:

- Task Force 1 – Technical (“Bury the complexity”)
- Task Force 2 – Education, Training and Mentoring.
- Task Force 3 – Global Connectivity and Development

At an ICEC meeting during the International Conference on Advances in Radiation Oncology (ICARO2) in Vienna, in June 2017, it was agreed that a technology-only workshop should be the next step. Fortunately, the STFC (Science and Technology Facilities Council) agreed to co-sponsor with ICEC and CERN another workshop at CERN on October 26-27, 2017. The highlights of this meeting included pre-

sentations by radiation oncologists from Ghana, Tanzania, Zambia, Botswana describing the shortfalls in cancer care in those countries and their efforts to develop cancer care programs. A presentation by a physician from Jordan reported on the successful development of the King Hussein Cancer Center in Amman.

While outreach and development are necessary to implement mentoring programs, there are at least 20 existing potential ICEC mentoring programs that will build on ongoing established twinning relationships between experts in cancer centres in upper-income countries and associates in cancer facilities in developing nations. Interested parties are encouraged to register at the ICEC website (iceccancer.org). During the year between the workshops hosted by CERN in November 2016 and October 2017, ICEC has developed pathways for program building and recruitment. Particularly important for the enhancement of global health has been the commitment of “early career” individuals to the mission of improving cancer care globally. Thus, challenges at both the “leading” edge and the “trailing” edge of the radiation sciences and of oncology care are leading to unique programs, new partnerships and career opportunities with extraordinary potential to improve cancer care globally. ■



“We would like to address the “leading edge” of the radiation sciences in understanding how radiation interacts with tissue.”

Norman Coleman



“Trailing edge is access to cancer treatment resources and how the innovation in linear accelerator design and the establishment of mentorship and educational programs can have global impact on the dire shortage in cancer care globally.”

David Pistenmaa



ENLIGHT Annual meeting
June 25-27, 2018
Cruciform building, UCL, London



Organisers:
Richard Amos, Manjit Dosanjh,
Simon Jolly, Gary Royle,
Ricky Sharma

Please register on:
<http://enlight.web.cern.ch>

PARTICLES IN THE CITY

By Richard Amos, Simon Jolly, Gary Royle and Ricky Sharma

Artists impression of the new UCL Hospital building sitting above the proton therapy centre on Grafton Way (courtesy UCLH/Edward Williams Architects).





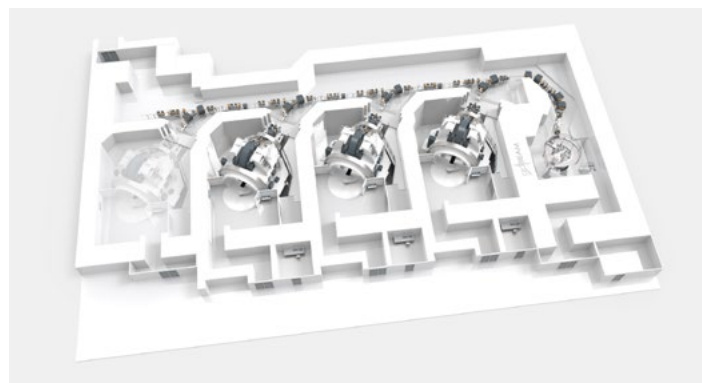
University College London (courtesy UCL).

June 2018 will see the annual ENLIGHT meeting head to the capital of the United Kingdom and hosted by University College London. The location has been chosen because of the on-going construction of the UCL Hospital Proton Beam Therapy Centre. In summer 2018 the building project will be nearing completion, before the installation of the major equipment, with first beam in 2019 and the first patients treated in 2020. It is a project that has brought particles to the city in the most real sense.

Located about 1 km from the geographic centre of a major city in a heavily developed urban area, making the design and the building particularly complex and challenging. The proton clinic, manufactured by Varian and featuring a **250 MeV cyclotron**, active spot scanning technology and four full rotating gantries, will be entirely underground. Whilst this opens up previously unoccupied space, it has the added complexity of nestling closely in between three London Underground train lines and shares the site with a number of existing buildings. Excavating the site has required the removal of the largest volume of earth from a single building in central London: the resulting pit is larger than the Royal Albert Hall.

UCL is a multifaculty, research-focused university with a strong commitment to cancer research and a track record of clinical trials. The proton therapy programme has attracted involvement from a wide variety of disciplines across three faculties, including physics, medical imaging, cancer biology, immunology, computer science and engineering.

UCL's sister institute, **UCL Hospital**, provides acute and professional healthcare to **700,000 outpatients** and **120,000**



Architectural rendering of the proton beam therapy complex at the new UCLH facility (courtesy UCLH/Varian).

inpatients every year. It operates a specialist radiotherapy service with unusually large numbers of paediatric, brain and sarcoma patients. These sites mirror the proton therapy indications list selected by the UK National Health Service.

The ENLIGHT meeting will see a training day on Monday 25th June focussing on "How to Design a Proton Therapy Facility". This will be followed on Tuesday 26th and Wednesday 27th June by the two-day ENLIGHT meeting. The ESTRO Particle Therapy Network will host their annual meeting immediately after on Thursday 28th June at the same venue. Alignment of the meetings presents an excellent opportunity to bring fundamental science and clinical development, along with other applied disciplines, in direct contact.

The training day will present topics of general proton therapy interest as well as areas in line with the Particles in the City theme, exploring the complexities of the urban environment.

The two meeting days will include fundamental topics for proton and ion therapy such as medical imaging, dosimetry and radiobiology, and will explore specific clinical aspects, such as complex cancer sites and patient selection. The topics will reflect a balanced combination of local expertise and timely topics for debate. We are particularly keen to stimulate active and progressive discussion and will ensure the schedule facilitates plenty of opportunity to share views.

The UCL organising team are excited to welcome the ENLIGHT community to London and look forward to an informative and productive discussion. ■



The UCL Cruciform Building: the original home of University College Hospital (courtesy UCL Wolfson Institute).

MANCHESTER CHRISTIE FACILITY

By Karen Kirkby, Ranald Mackay, Ed Smith and Nick Slevin



In Manchester, in 1917, Rutherford, Geiger and Marsden published their momentous discovery that allowed the structure of the atom and the proton to be identified. It therefore seems fitting that the National Health Service's (NHS) first high energy proton therapy centre will open just over 100 years after this discovery, at The Christie in Manchester, and treat its first patient in August 2018. Proton therapy is already well established in the North West of England where the Clatterbridge proton centre, was the world's first hospital based proton centre and has been treating ocular tumours for over 20 years and has now treated over 2800 patients.

The Christie is Europe's largest single site cancer hospital and traces its history back to 1890. In 1914, the Holt Radium Institute was established and Rutherford was instrumental in making the case for the purchase of the first radium sources

for clinical treatment. The Christie treats over 44,000 patients per year and has one of the world's largest radiotherapy departments and is the only site in the UK to offer both protons and MR guided radiotherapy. Radiotherapy research in Manchester is recognised as being internationally leading with research streams contributing to Manchester's NIHR Biomedical Research Centre (£28.5M) and CRUK Major Centre (£45M).

The new clinical proton therapy centre at The Christie is co-located within the hospital with full specialist multidisciplinary support services. The Christie clinical proton therapy centre is a Varian four room solution; with a Varian cyclotron and three 360° gantry rooms. The fourth room is being purpose built for research and funded by The Christie charity. All of the gantries, in the three treatment rooms are equipped to deliver 'state of the art' fast pencil beam scanning. The NHS



PTCOG comes to Manchester in 2019 bringing together experts in Particle Therapy



Gantry 2 being assembled



Artists impression of waiting areas and atrium areas



has developed a list of clinical indications for which there appears to be a clinical advantage of using protons. These are tumours in paediatric and young adult patients as well as difficult to treat sarcomas, para spinal and base of skull tumours and leaves half the capacity for evaluative studies for other tumour subtypes. Patients who have these indications are currently considered for referral overseas, and in 2018 they will start to be treated in Manchester. Conducting national clinical trials is also central to the clinical research programme with the first trial TORPEDO (for head and neck cancers) being developed through a collaboration between The Christie and The Royal Marsden Hospital in London. The first patient treatment date is the end of August 2018.

The new building which houses the clinical proton therapy centre in Manchester is co-located within the Trust grounds with full hospital multidisciplinary support services. Con-

struction is on time and on budget. Best practice has been identified from around the world to design a proton therapy centre with the patient experience at its core with discrete age appropriate zones and a focus on a light and airy environment for the patient. The cyclotron was lifted in to place in June 2017 and the construction of the gantries is nearing completion, with handover of the first gantry to the clinical team in April 2018.

Research is central to the new clinical centre and goes from basic research, through applied and translational research to clinical trials, with the aim of maximising patient outcomes and quality of life. The Christie charity is raising over £5.6m for the construction, fitting and equipment for this purpose built research room, which occupies the fourth gantry space in the clinical PBT centre. The research room will not be used for patient treatment and has two horizontal beam lines. The



“Research is central to the new clinical centre and goes from basic research, through applied and translational research to clinical trials, with the aim of maximising patient outcomes and quality of life. The Christie charity is raising over £5.6m for the construction, fit out and equipment for this purpose built research room, which occupies the fourth gantry space in the clinical PBT centre.”

Karen Kirkby



Construction of the clinical proton centre at the Christie (picture taken on Feb 14th 2017)

first beam line is fitted with an engineering nozzle, which is capable of emulating the spot scanning nozzle used in clinical treatment. The second beam line delivers an unscanned beam. At the end of these beamlines, purpose built research modules designed for individual experiments, can be placed. The first of these, funded by CRUK, allows high throughput radiobiology experiments to be undertaken in a controlled environment (from hypoxic to normoxic) with a robotic arm to facilitate rapid transfer of samples and online microscopy. It is envisaged that the research room at The Christie will form part of a national / European capability and discussions are ongoing with a number of groups on the designs of different research modules for a range of different experiments.

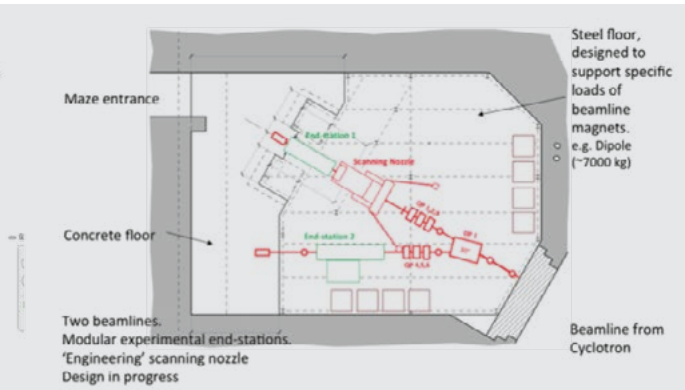
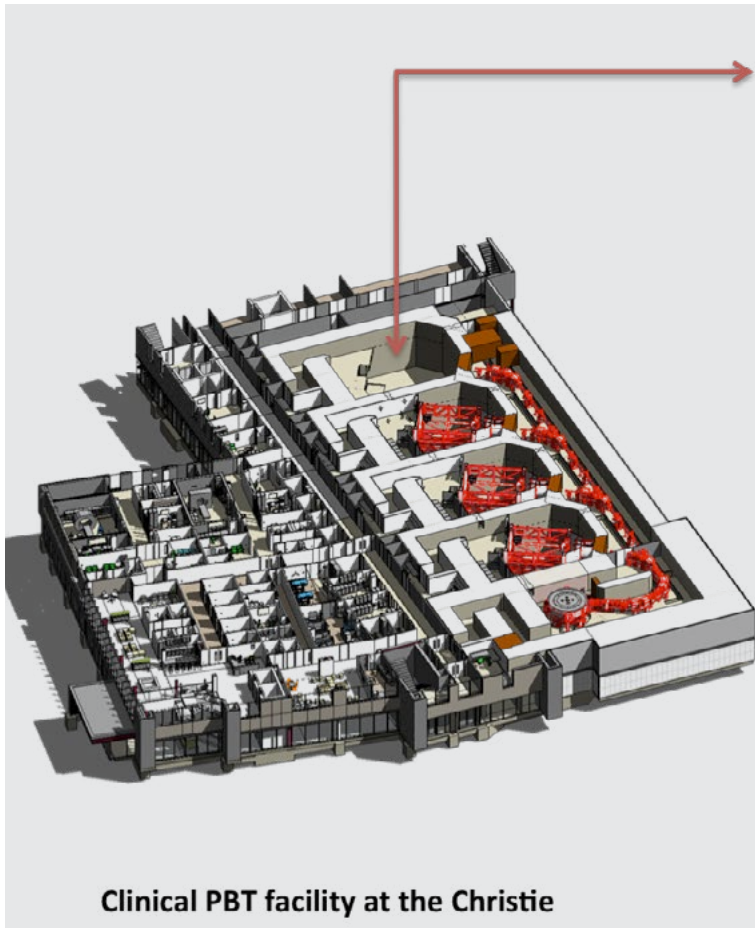
The research group brings together research at The Christie, The University of Manchester and the CRUK Major Centre. They have been successful in gaining a number of funding awards from UK Research Councils to bring the clinical and scientific and engineering communities together to work on PBT. They have also been working with colleagues across Europe and linking in to the ESTRO Particle therapy Network and will host PTCOG with colleagues from University College London Hospitals NHS Foundation Trust in 2019. ■



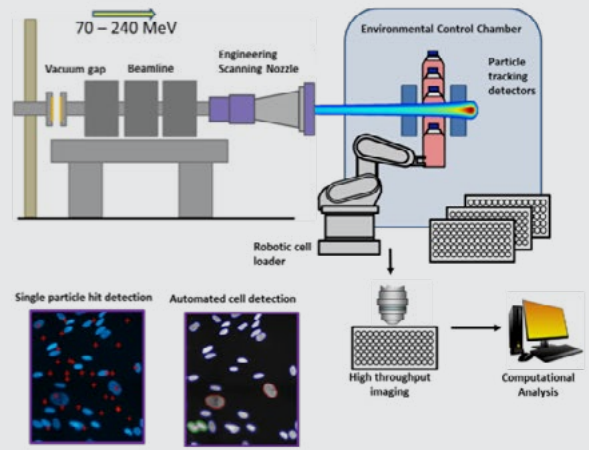
Cyclotron being lifted



Ready, steady, go! Lucy and Emma (former proton patients) press the button to start lifting the Varian cyclotron in to its position in the clinical proton therapy centre at the Christie.



Research room: schematic of beam lines



Research room: schematic of radiobiology end station



ProBeam Therapy Facility
Image courtesy of Varian Medical Systems, Inc. All rights reserved.

DANISH CENTRE FOR PARTICLE THERAPY

The Danish Center for Particle Therapy, DCPT, is currently under construction in Aarhus, Denmark.

*By Cai Grau, Ole Nørrevang,
Morten Høyer,
Brita Singers Sørensen*



DCPT

Danish Centre for
Particle Therapy
Aarhus, Denmark



The cyclotron was installed in June 2017

DCPT is a national centre, being built to serve patients from all of Denmark. There will be three gantries and a fixed beam room for research, equipped with ProBeam proton therapy equipment from Varian Medical Systems.

The ProBeam system has been delivered, and most of the hardware has been installed. The cyclotron has a superconducting magnet, and it has been cooled down. Next step is to commission the RF-system, and first beam out of the cyclotron is expected late December 2017.

The 9000 m² building was designed by Link Arkitektur¹ and built by Hoffmann². The design focusses on easy accessibility, high patient comfort and efficient workflow for the staff.

By January 2018 the building will be ready to have MRI and CT scanners installed. Clinical commissioning of scanners will start in March. By June 2018 the proton therapy system will be handed over, and first patient is planned for in October 2018.

Education of staff is a major task for the centre before the opening in 2018. We have defined learning objectives and educational plans for physicians, physicists and radiotherapy technologists in treatment planning and delivery with protons. Along with this, the first staff members will receive training at proton centres abroad. Vertual (Hull, UK) and Varian are producing a virtual ProBeam gantry for training in delivery of proton therapy, and AUH will be the first centre to use this facility in training of staff.

In addition to the in-house training, we are preparing an educational program for colleagues in the seven Danish radiotherapy centres who will be responsible for producing plans for comparison of proton and photon treatment plans, used to select patients with an indication for proton therapy at the DCPT. The external personnel are offered a teaching course in treatment planning, a workshop with dry runs and live demonstrations and a continuous series of meetings on treatment planning of cases reflecting the cancer types that will be treated at the DCPT.

Established indications will account for a relatively small proportion of the patients. The majority will be selected by the model-based approach, which means comparisons of proton and photon treatment plans for the individual patients. To minimise the operator dependency of this procedure, we are standardising the workflow of the treatment plan comparison



DCPT Staff and leaders - January 2017

with creation of generalised maps of standard tissue structures for the various sites, common solutions for treatment planning with predefined field arrangements, normal tissue constraints and optimisation process that shall be used at all the Danish centres. This work is the responsibility of the Danish Multidisciplinary Cancer Groups.

The workflow for referral of patients for proton therapy at the DCPT, which includes the duties and responsibilities of the parties, has been clearly defined. The seven radiotherapy centres all wish to take an active part in the model-based selection of patients, and most of the follow-up after treatment will be at the patients' home centre. This requires a close collaboration between DCPT and the radiotherapy centres. Therefore, a video-based national proton conference with contribution of the radiotherapy centres has been established. Currently, case presentation of all Danish patients for proton therapy are done outside and in the future, all patients considered for proton therapy at DCPT will be discussed at the conferences.

Research is an essential part of this national project. About 85% of all patients are expected to be enrolled in prospective clinical trials, either national studies conducted in collaboration with the Danish Multidisciplinary Cancer Groups, or multicenter international studies performed within the European Particle Therapy Network. In addition to the large capacity for clinical studies, DCPT will have a research room with a fixed scanning beam for physics and biology experimental work. In connection to this, the centre will have an in-house biology laboratory for cell culture work, as well as an animal room for animal preparation and short-term animal housing. The biology facilities are intended for both in-house scientists, as well as for visiting scientists, who can conduct biology experiments at DCPT. For visiting scientists, DCPT provides support for project design, sample irradiation, and animal experiments. The experimental beam room is expected to be ready for use in early 2019. More details about the research at DCPT can be found on www.dcpt.en.auh.dk. ■

¹ <https://linkarkitektur.com/en/Projects/Danish-Centre-for-Proton-Therapy>

² <http://hoffmann.dk/projekter/article21768.ece>

AN INTERNATIONAL INSTITUTE FOR SUSTAINABLE TECHNOLOGIES IN SOUTH EAST EUROPE



¹ Signed after a referendum

² Participated as an observer



The collaborating ministries who signed the "Declaration of Intent" (from left to right): Prof. Blazenka Divjak, Minister of Science and Education, Republic of Croatia - Ministry of Science and Education; Prof. Vladimir Popovic, State Secretary, Republic of Serbia - Ministry of Education, Science and Technological Development; Dr. Tomaz Boh, State Secretary, Republic of Slovenia - Ministry of Education, Science and Sport; Mr. Ervin Demo, Vice Minister of Education and Sports, Republic of Albania - Ministry of Education, Sports and Youth; Mr. Shyqiri Bytyqi, Minister of Education, Science and Technology, Kosovo - Ministry of Education, Science and Technology; Dr. Sanja Damjanovic, Minister of Science, Montenegro - Ministry of Science; Prof. Herwig Schopper, Former Director of CERN; Prof. Renata Deskoska, Minister of Education and Science, The FYR of Macedonia - Ministry of Education and Science; Mr. Andrija Pejovic, Minister of European Affairs, Montenegro - Ministry of European Affairs; Dr. Adil Osmanovic, Minister of Civil Affairs, Bosnia and Herzegovina - Ministry of Civil Affairs; Prof. Kostadin Kostadinov, Advisor to the Minister of Education and Science, Republic of Bulgaria - Ministry of Education and Science; Prof. Costas Fountas, Scientist, Hellenic Republic

On 25 October 2017 at a meeting organised at the CERN, eight Science Ministers signed a Declaration of Intent to create in the South-East Europe (SEE) region an international laboratory with the aim of promoting science and technology and improving the relations between countries in the spirit of CERN. The meeting of Science Ministers was organised at the initiative of the Montenegrin Minister of Science, Sanja Damjanovic, following a proposal by Herwig Schopper, former Director General of CERN and first Council President of SESAME to establish such an organisation.

The eight signatories were Albania, Bosnia and Herzegovina, Bulgaria, Kosovo*, The FYR Macedonia, Montenegro, Serbia and Slovenia. Croatia has also agreed to sign but for formal reasons had to delay the signature after a referendum. Greece participated as an observer. Thus, this initiative to establish a 'SEE Institute for sustainable technologies' has become a regional project.

Two options are being considered for the institute - a synchrotron radiation facility and/or a hadron beam facility for the treatment of tumours and the associated research.

To demonstrate that all signatory parties are treated on an equal level and have the same rights the meeting took place at the neutral CERN and was chaired by Herwig Schopper. During the discussion, the delegates expressed their appreciation for the work already done and supported the initiative. It was decided to set up a Steering Committee whose first session will take place in Bulgaria (which will chair next year the European Union) and will be chaired by Minister Damjanovic.

The ministries also had an opportunity to visit of the laboratory, meet with scientists from the SEE region and even have lunch with CERN's Director General Fabiola Gianotti. This contributed to create a relaxed atmosphere of the whole

meeting and 'infused' the participants with the CERN spirit, a good omen for the future cooperation.

The Concept Designs for the two options are being prepared by two international expert committees and will be presented at a Forum at ICTP on 25/26 January 2018 at Trieste both to the potential users of the region and to representatives of the EU, the IAEA, the UNESCO, the EPS, and others. ■

FORUM on New International Research Facilities in South East Europe

develop a research excellence nucleus in SEE
benefit for science and technology, training, investment in young people,
job creation, reverse of brain drain, knowledge based economy

Two options for the Institute:
**4th Generation Synchrotron Light Source
Facility for Tumour Therapy and Biomedical
Research with protons and heavier ions**

SCIENCE FOR SOCIETY

Organizing Committee:
Herwig Schopper (Chairman, former DG of CERN)
Fernando Ferroni (President of INFN)
Christoph Quitmann (Director of MAXIV, Sweden)
Nicholas Sammut (Deputy Dean, University of Malta)
Hans J. Specht (Heidelberg Univ, former DG of GSI)
Ruediger Voss (President of EPS)

Local Organizers:
Nadia Biaggini (ICTP)
Saša Ivanović (MNA)

ICTP and Ministry of Science Montenegro

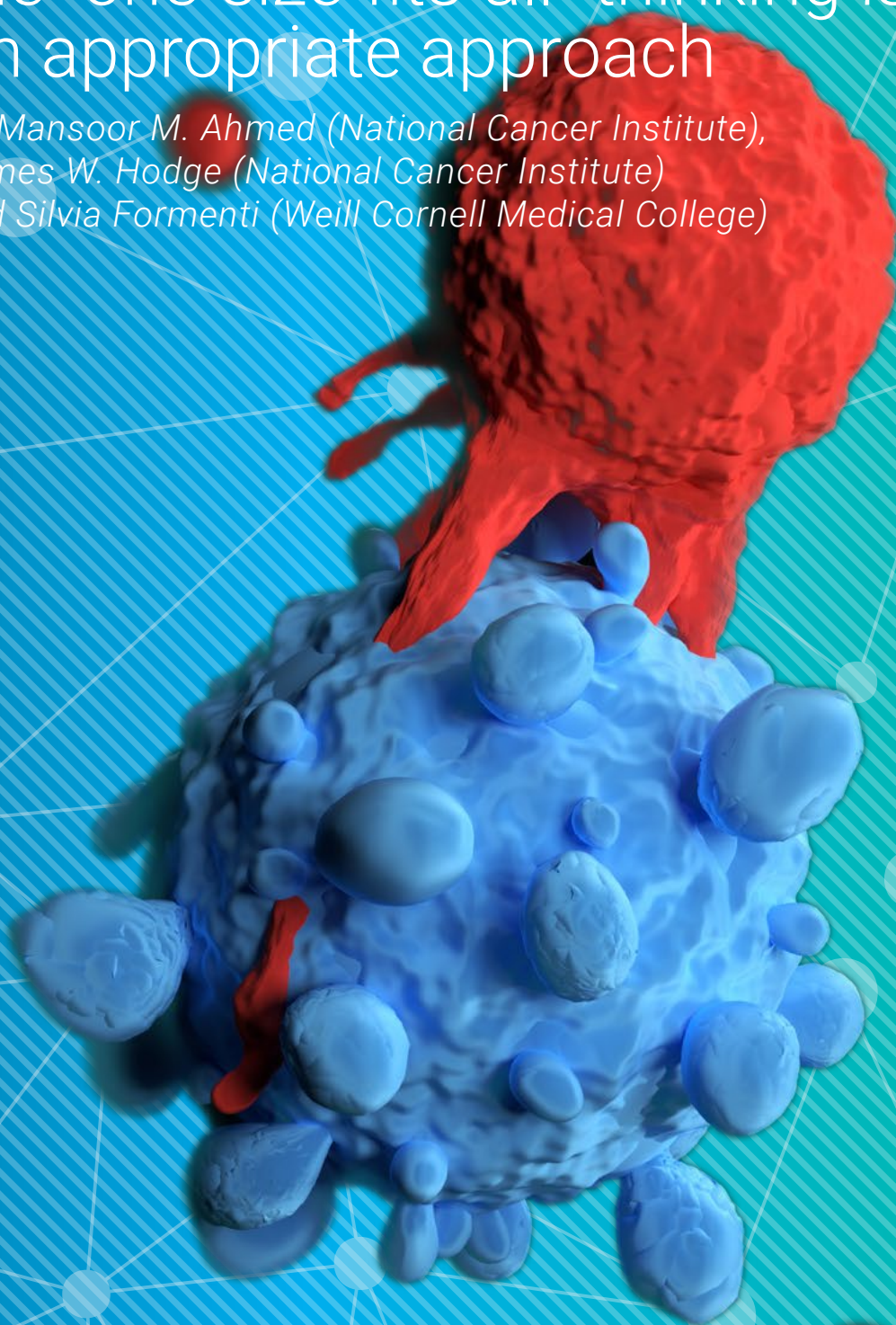
25 & 26 January 2018 ICTP, Trieste, Italy

Registration to the Forum is free. For a restricted number of participants from the region travel subsistence would be possible. Please register at <http://indico.ictp.it/event/8408/>

RADIATION ENHANCED IMMUNOTHERAPY:

the “one-size-fits-all” thinking is not an appropriate approach

*By Mansoor M. Ahmed (National Cancer Institute),
James W. Hodge (National Cancer Institute)
and Silvia Formenti (Weill Cornell Medical College)*



An immune system T cell killing a cancer cell

Radiation therapy is standard-of-care treatment for multiple malignancies, generally being employed for direct tumour cell destruction. Depending on the stage and site of disease, radiation therapy can have either a curative or palliative intent. Ionising radiation can induce cancer cell death through irreparable DNA damage, resulting in apoptosis or failure to progress through the cell cycle.

The current surge in interest in immunotherapy for cancer offers an opportunity for the fields of radiation oncology and biology to play a central role in precision medicine. Radiation therapy has a wide impact on the tumour cells, micro-environment and systemic immune response. The ability to tactically focus the radiation treatment temporally and spatially requires the establishment of scientifically with rationale based regimens rather than “one-size-fits-all” concept will not optimise the role of radiation therapy.

The tumour micro-environment harbors immune-resistant clones that escape from immune editing and surveillance processes that are regulated by several cytokines and checkpoint proteins that eventually dictate the immunogenicity of the tumour. Ionising radiation (RT) causes changes in the tumour microenvironment that can lead to intra-tumoural as well as distal immune modulation (so-called abscopal phenomenon). Tumour-associated antigens (TAAs) are released by irradiated dying cancer cells triggering danger signals such as heat-shock protein (Hsp), HMGB1, and calreticulin (“eat-me” signal for phagocytes). At the same time, RT can induce increased expression of tumour antigens and MHC class I molecules on tumour cells. Consequently, activated antigen presenting cells (APCs) migrate to the draining lymph node, further mature upon encountering T helper cells, and release interferons (IFNs) and IL-12/18 to stimulate Th1 responses that support the differentiation and proliferation of antigen-specific CTLs. Activated antigen-specific CTLs traffic systemically from the draining lymph node to infiltrate and lyse in primary as well as distal tumours. Concomitantly, tumour irradiation can also recruit immunosuppressive cells into the tumour microenvironment. Further, expression of certain negative stimulatory molecules on T-cells and tumour cells (CTLA-4, PD-1, PDL1) are induced by RT that can curtail the activation of T-cells leading to an immune suppressive environment. Other immune suppressive function of radiation can occur through induction IL-10 and TGF- β (Figure 1). These immune modulation events can also impact tumour growth at a distance from the irradiated tumour site, the “abscopal effect”, that is mostly immune and in certain instances it can be non-immune mediated through ceramide signaling.

PHOTON RADIOTHERAPY: CANCER IMMUNOTHERAPY COMBINATION OPPORTUNITIES IN HARNESSING THE RADIO-IMMUNE MODULATION EVENTS

Radiation therapy’s demonstrated ability to drive immunogenic modulation and promote immune-mediated killing of tumour cells in a variety of human carcinomas of distinct origin and genotype gives it broad clinical applicability for cancer therapy. Photon and heavy-particle radiation modalities capably increase CTL lysis of prostate, breast, and lung

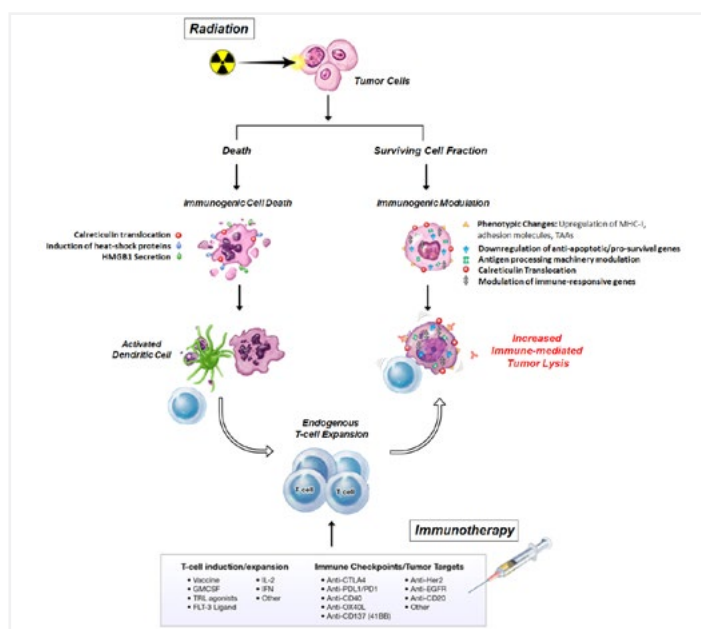


Figure 1. Radiation-induced immunogenic modulation may synergise with immunotherapy to effectively treat cancer. Photon and heavy-particle radiation modalities can induce a myriad of phenotypic changes in tumour cells that make them more susceptible to CTL-mediated lysis.

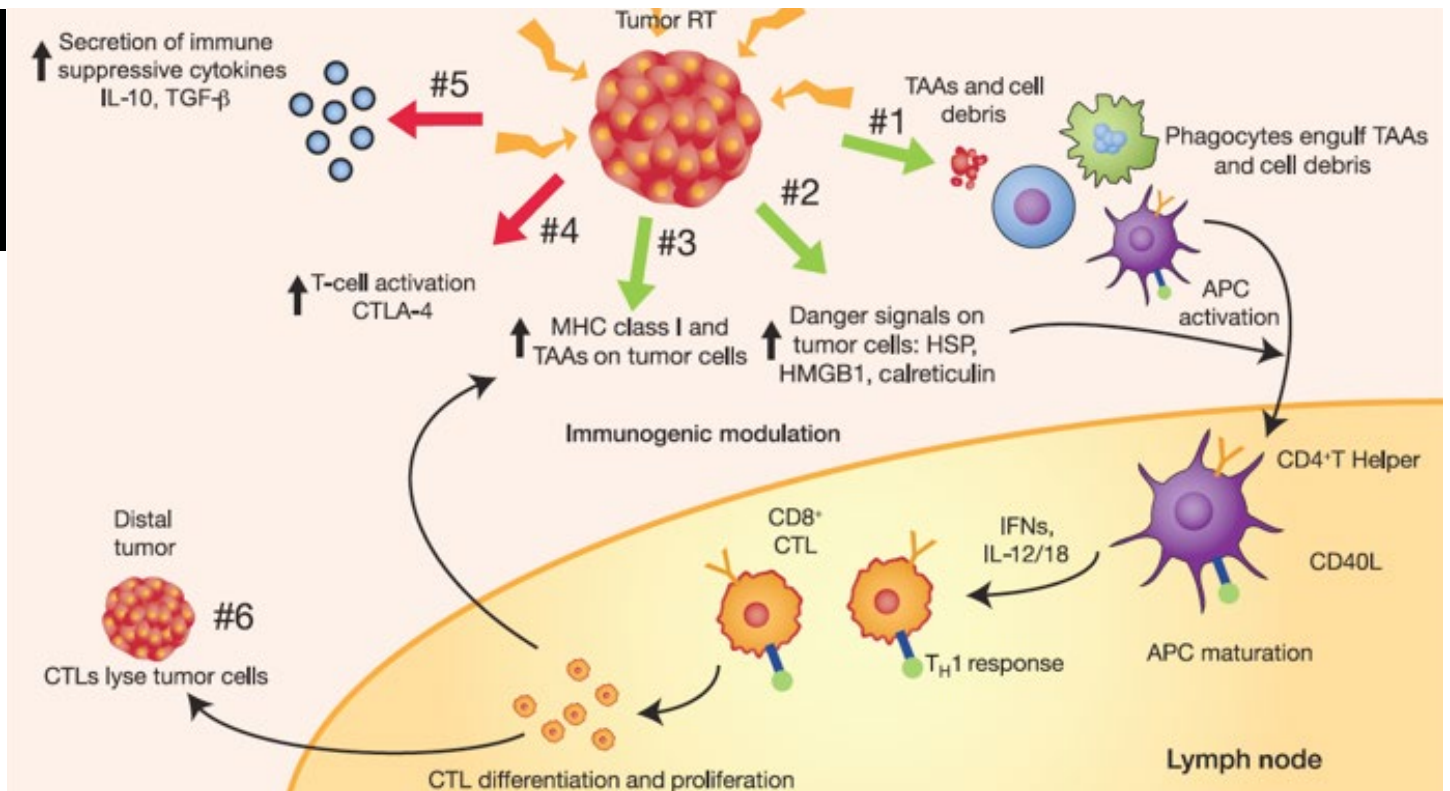
tumour cells regardless of their p53, triple-negative, or K-Ras mutational status, respectively. As a result, despite its lack of direct cytotoxic effects, sublethal radiation may still be an effective cancer therapy, especially if it can maximise the clinical benefit of other immune-activating agents as part of a combination regimen. Radiation therapy can be combined with several different types of immunotherapy, including the use of costimulatory agonists and checkpoint inhibitors that aim to boost and unleash T-cell effector function and memory formation in the development of adaptive immune responses. Cancer vaccines may also be promising candidates in combination strategies by generating robust antigen-specific T-cell populations that can ultimately exploit the immunomodulatory changes created by radiation therapy that make tumour cells more amenable to immune recognition and attack.

Several factors can influence the ability of radiation to enhance immunotherapy, including (a) the dose of radiation per fraction and the number of fractions (b) the volume of the irradiated tumour tissue and target location. However, the impact of these variables is not well understood.

Historical evidence and recent literature points out that radiation dose at opposite ends of the dose spectrum constitute robust immune activation up to 1 Gy), high-dose RT including ablation (8 Gy and above) and clinically relevant dose (1.8 to 2.2 Gy) to define immune modulation events and how these events can be harnessed with cancer immunotherapy.

Low-dose radiation

At low doses of radiation from 0.1 Gy – 1 Gy, immune activation is achieved by increased Th1 response that attracts naïve T-cells and promotes its differentiation and activation. Low dose radiation at 0.5 Gy is associated with highest number of infiltrating T-cells with a decline at > 1 Gy, and this is accompanied with redirecting macrophage differentiation from a “tumour-promoting/immunosuppressive state” to one that



A schematic view of radiotherapy-induced immune modulations, you can see radiotherapy induces increased expression of tumor antigens and MHC class I molecules on tumor cells.

enables cytotoxic T lymphocytes to infiltrate tumours and kill cancer cells. Moreover, low-dose RT causes an increase in homing of activated T-cell in tumour milieu unlocking the barriers of cancer immunotherapy. Furthermore, tumour cells when irradiated with 1 Gy fractions can robustly activate immune gene programme that can be conducive for trafficking and homing of T-cells that is similar to antimicrobial/inflammatory response. All these immune modulation conditions can be harnessed with drugs that augment dendritic cell maturation. Kinetics of immune gene activation in tumour cells treated with 1 Gy multi-fraction demonstrates that the opportunistic window to exploit the maximal immune function for adjuvant immunotherapy is around 6-10 Gy total dose.

Cancer vaccines and adoptive T-cell therapy could boost radiation-induced in-situ vaccination. Furthermore, agonistic antibodies directed against co-stimulatory/co-inhibitory molecules on T cells can synergise an increase in T-cell function⁵. Even though there are many pre-clinical studies to support the above low-dose RT combinations with immunotherapy, there is currently only one clinical trial that is opened by NCI CTEP utilising 0.5 Gy bid fractions with dual checkpoint inhibitor in NSCLC and metastatic colorectal cancer (NCT02888743).

High-dose radiation

With radiation doses of 8 Gy and above in single or multiple fractions, TAAs initiate DAMPs to release IFNs to help mature T-cells differentiation and activation leading to immunogenic cell death and anti-tumour immunity with a potential to significantly increase the incidence of distal (so-called abscopal) effects. These events lead to T-cell priming, trafficking, infiltration, in-situ vaccination and immunogenic killing.

The immune modulation events by high dose RT can be exploited to enhance immunotherapeutic efficacy by activating T-cells using antibodies targeted against co-inhibitory T-cell receptors. In several pre-clinical tumour models, efficacy of immune checkpoint targeted therapies improved when combined with high-dose radiation. Significant downregulation of PDL-1 was observed in tumour cells treated with single fraction of 10 Gy but not with multi-fraction, and hence anti-PDL1 combination can be effective with only one high-dose treatment. Similarly, vaccines or adoptively transferred CD8+ T-cells combined with high-dose radiation demonstrated complete regression or significant growth delay.

Based on these promising pre-clinical data, there are nearly 50 clinical trials testing explicitly targeting checkpoint inhibitor proteins with high radiation dose, mostly in phase 1 and 2 settings and two open trials in phase 3 setting¹⁵.

Clinically relevant dose with conventional fractionation

Doses at 1.8 to 2 Gy in fractionated settings is standard-of-care for several solid tumours. Such fractionation extends several weeks to minimise toxicity to normal tissue, while lymphocytes are rapidly cleared from the irradiated field diminishing tumour antigen-specific T cell populations through persistent site-specific cytotoxicity. Such tolerogenic immunosuppressive events of radiation can be exploited by repletion of T-cells in T-cell deficient environment that can lead to proliferative expansion of T-cells with activated phenotype and thus increase cytolytic activity to self and to tumour antigens. Other immunotherapy combinations with 2 Gy fractions that can potentially partner for synergy include TLR & CD40 agonist, IFN- β and cancer vaccines. There are several open phase 1 and 2 clinical trials with EBRT plus checkpoint blockade therapy.

TUMOUR VOLUME AND TARGET LOCATION

The size of the treatment field and radiation target can affect the exploiting potential of radio-immunomodulation. Larger treatment field tends to expose circulating lymphocytes that can impact proliferating T-cells and T-cell priming in draining lymph nodes. This is similar to protracted RT regimens that are lymphotoxic which may lead to T-cells clearance and lymphopenia. To protect lymphocytes and T-cells and reduce lymphopenia, one can adopt strategies such as reducing the treatment field size, shortening beam-on treatment times, hypofractionation and lattice radiotherapy.

Another important facet to consider when it comes to combining RT with immunotherapy is the site of radiation. As abscopal responses have been observed during irradiation of bone metastasis, there are reports to demonstrate that such abscopal events can result more from irradiation of visceral metastases. This is supported by a recently failed phase 3 trial when single fraction of 8 Gy with anti-CTLA-4 to osseous metastasis.

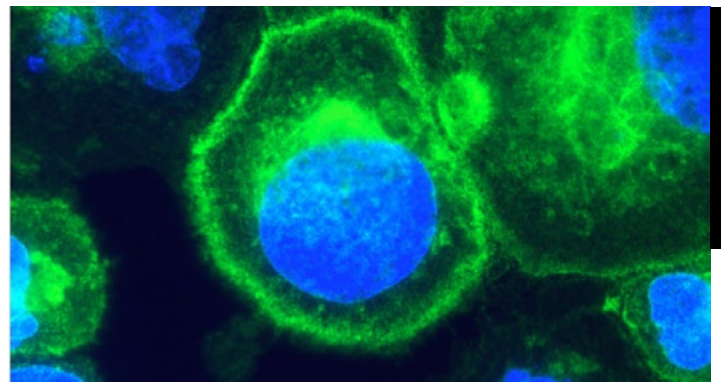
Novel radiotherapy in context of immune modulation and immunotherapy

Activated T-cell homing, Th1 cytokine milieu in tumour, CTL infiltration in tumour, DAMP mediated activated APCs for distal effects, and interferon response are key radio-immune modulator effectors of cancer immunotherapy. Furthermore, radiation can enhance expression of immune markers on tumour cell surface and endothelial cells. Literature evidence indicates that low-dose radiation and high-dose ablative radiotherapy can elicit such immune modulation robustly than clinically relevant fractionated radiotherapy.

Based on this, an optimal novel radiotherapy schema in context of immune modulation events can be a pre-boost high-dose or ablative dose with single or less than three fractions directed towards partial treatment volume. This will trigger in-situ vaccination, T-cell priming, trafficking, infiltration and immunogenic killing. Followed by boost dose, low-dose radiotherapy with 0.5 – 1 Gy fraction directed towards gross tumour volume can increase Th1 type response to facilitate the homing of activated T-cells. At this juncture, dual checkpoint blockade immunotherapy can be useful in differentiation and proliferation of CTLs and eliminate T-cells exhaustion phenotype.

Perhaps the most crucial point is that radiotherapy will best be used as a “drug” which may mean varying the dose, fractionation and target during a course of treatment to achieve the desired effect. The “one-size-fits-all” thinking is not an appropriate approach as it could lead to a lack of success by virtue of the wrong choice and not allow for the thoughtful development of the field. Biomarkers of response, including circulating molecules or cells, imaging and tumour sampling may be critical along the course of treatment to adapt to the changes in the tumour.

This novel radiotherapy approach will require validation in appropriate pre-clinical models and clinical trials prior to adopting as a standard of care for both highly and weakly immunogenic solid tumours.



Carcinoma cells recovering from exposure to photon or proton radiation show increased calreticulin expression on the cell surface, resulting in heightened sensitivity to CTL-mediated killing. In human cells after a single dose of 8 Gy proton radiation. (from Gameiro, S.R., et al., Int J Radiat Oncol Biol Phys, 2016. 95(1): p. 120-30).

IMMUNE MODULATION IN RESPONSE TO HEAVY PARTICLE RADIOTHERAPY

Radiopharmaceuticals are another class of heavy-particle radiation therapy for cancer treatment. Radium-223 dichloride (^{223}Ra) has recently received approval from the U.S. Food and Drug Administration for the treatment of bone metastases in metastatic castration-resistant prostate cancer (mCRPC), and is now being studied in other forms of cancer that metastasise to bone. For cancer therapy, ^{223}Ra radionuclide is now considered preferable to the beta-emitters strontium-89 (^{89}Sr) and samarium-153-EDTMP (Quadramet; ^{153}Sm), which fail to extend overall survival of patients with multifocal bone metastases. Alpha particles are heavily charged, while beta particles are much smaller and take the form of either electrons or positrons. As a result, ^{223}Ra can deliver a greater dose of radiation in a more localised manner.

Preclinical murine studies have supported this approach, demonstrating that radiation therapy acts synergistically with therapeutic vaccines to enhance antitumour responses. In these studies, the combination of poxviral-based cancer vaccines that express the transgene for CEA with either photon or radiopharmaceutical therapy not only effectively impaired tumour growth compared to monotherapy, but also initiated antigen cascade, developing T-cell responses to CEA and other tumour antigens not encoded in the vaccine. A recent phase II clinical trial also demonstrated the clinical benefit of combining cancer vaccines with radiation therapy.

An increase in the immunogenic cell death markers expression for charged particle irradiation was detected when compared with photon irradiation. Initial results also demonstrated a decrease in marker levels at LET higher than 110 keV/ μm , suggesting a possible plateau effect. Further investigation is warranted to study the effects of LET and types of charged particle irradiation in vitro.

Taken together, current data provide a rationale for using photon or heavy-particle radiation therapy in combination with T cell-mediated immunotherapy, particularly for patients who have failed radiation therapy alone or who have limited treatment options. ■

COULD "BLENDING" BE THE NEXT FRONTIER IN RADIOONCOLOGY?

*Interview with Jeff Buchsbaum, Medical Officer and Program Director,
Radiation Research Program, NCI, NIH, USA*

*National Cancer Institute, Bethesda, US
Credit: The JBG Companies / Jim Tetro
From cancer.gov*



ENLIGHT Highlights (EH): From the point of view of the physics process involved in it, proton therapy is definitely better than conventional photon (X-rays) therapy. However, seen from the perspective of a radiooncologist, the situation is not so sharply defined. What is your opinion?

Jeff Buchsbaum (JB): We “experts” think that there is really great need to better understand the science behind the use of protons. It is more complicated than what most people initially understood, in particular, regarding the RBE and the biological effects of such a treatment. Today, most university hospitals in the US can afford to build a proton centre if they want to. Everybody thinks that it’s an extremely promising technology, no one thinks it lacks promise; but we are having a greater appreciation for the complexity that is required to be better understood before we invoke that promise in the clinic. The real question is: when is it needed? When is it best used? How do protons interact with drugs? What are the side effects?

EH: Are you calling for more clinical trials or for something totally different?

JB: The first thing will be to do clinical trials. And we also need to carry out a lot of research in biology to evaluate the toxicity of protons, in other words, the particle beam’s side effects: how it affects heart, nerves, etc. How different drugs affect particle therapy.

EH: Why do you think doctors find it more difficult to deal with proton rather than photon beams?

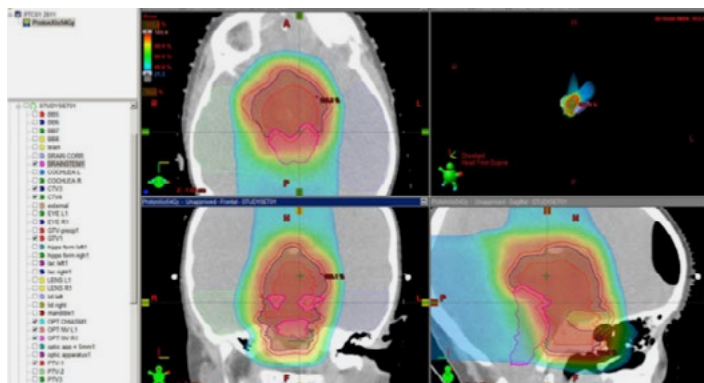
JB: A photon treatment plan is intrinsically much more robust and tolerates imprecisions much more than a treatment plan with protons. When the edges of proton beams overlap with each other they can have very high toxicity. A person doing a proton therapy treatment plan has to think in RBE dimensions, something that a photon treatment plan does not require. The limitation of the tumour is vital but the technology required to “see” the exact boundaries of the cancerous cells isn’t available yet.

EH: So, what would you suggest to improve the current situation? What will the future look like?

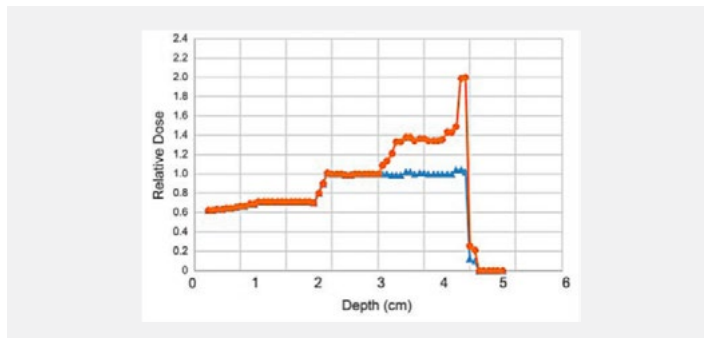
JB: I would invest all my energy and money in building a test facility to understand the biological effects of various beams on various tumours. How such treatment causes a secondary cancer or other side effects. However, this requires a lot of time and patients are, understandably, not patient. They face the limitations of science and the difficulties that the scientific process encounters. This is the long-term problem that we need to address.

Personalised medicine is the solution we are looking at in radiooncology. Every radiation (type) works as a different drug.¹ When you treat a patient you mix 3-4 drugs. It is quite possible that in the future we will find that to optimize a case 30% might be photons, 30% protons, etc, these percentages can depend on DNA and the repair processes can be different.

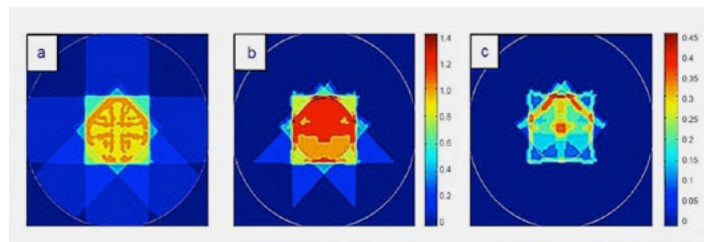
¹An idea first formulated by Norm Coleman about 15 years ago to which I arrived independently later (JB note). ■



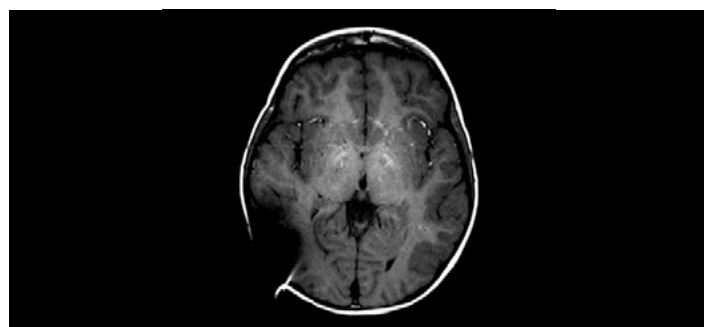
Aplplan for a large craniopharyngioma that was treated to 45 Gy.



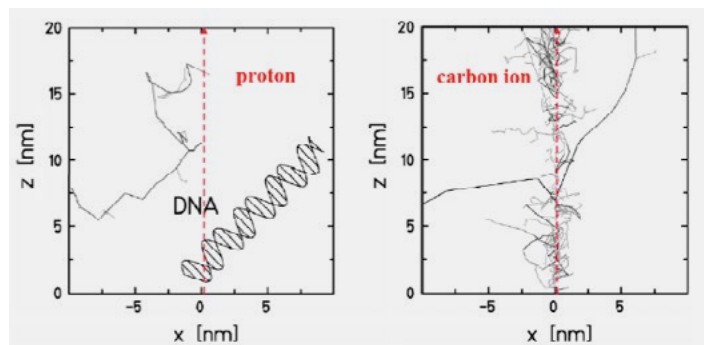
The IU RBE curve measured by clonogeni survival (Radiat Res. 2013 Jan;179(1):21-8.).



A 2D idealized model of planning with physical dose (a), RBE dose (b) and the difference. (Technol Cancer Res Treat. 2016 Oct;15(5):NP1-7.).



MRI showing multifocal calcifications the globus pallidi causing complications for the patient



Carbon beam biology is likely even more complex (Rep. Prog. Phys. 68 (2005): 1861-82.).



KATIA'S TEAM COMING FROM ENLIGHT



KATIA PARODI

Chair of Medical Physics at Ludwig-
Maximilians-Universität München
www.med.physik.uni-muenchen.de



We are a young team of around 60 researchers carrying out a broad interdisciplinary program around the usage of established and novel sources of radiotherapy beams, with special focus on ion therapy. We believe in the ENLIGHT basic values of sharing knowledge and collaborating on a wide range of complementary or synergistic subjects. This becomes a key motivation for all the young researchers at the LMU Medical Physics Chair who aim at fostering improvements of modern image-guided radiotherapy.

Set up in 2012 by Prof. Dr. Katia Parodi, Chair of Medical Physics at Ludwig-Maximilians-Universität München and member of ENLIGHT since its inception in 2002, the group relies on the contributions of several young experts coming from a variety of fields:



Georgios Dedes

Moved from the field of high-energy particle physics to the field of ion beam therapy in the framework of ENLIGHT-related initiatives in Lyon, France, including the ENVISION project. In 2013 he joined the LMU Department of Medical Physics to pursue research and teaching in this field. Since then his primary research focus is on proton therapy range monitoring, especially in relation to prompt gamma and proton imaging. Moreover, he contributes his vast knowledge in Monte Carlo methods to a large variety of projects, including novel applications of laser-driven ion beams.



Guillaume Landry

He is specialised in the use of dual-energy computed tomography in radiation therapy while completing his PhD at Maastricht University/MAASTRO Clinic. Since joining the LMU Department in 2013, he expanded his research to encompass a wide range of imaging modalities with specific application to proton therapy, starting from cone-beam CT for adaptive therapy. Together with Dr Dedes he now leads a project funded from the German Research Foundation (DFG) on the realisation of intensity modulated proton computed tomography, in close cooperation with an international collaboration lead by Loma Linda University.



Christopher Kurz

He joined the team after receiving his PhD in 2014 for work performed at the Heidelberg University Hospital, Germany, in the context of the ENVISION project. His current main research goal is to foster external beam proton therapy by improved image-guidance, with focus on pre-treatment imaging using cone-beam CT and related intensity corrections for accurate daily dose calculation and treatment adaptation. Recently, he secured funding from the German Cancer Aid to start investigations on the integration of MRI in proton therapy, in collaboration with the University of Utrecht. In the future, MRI might enable not only pre-treatment but also online image-guidance and adaptation, thus allowing full exploitation of the promised advantages of proton therapy. Now at Uni Hosp Munich.



Chiara Gianoli

Also moved to Munich in 2014, after having contributed to the ENVISION project in her PhD studies at Politecnico di Milano in Italy and her postdoctoral fellowship at the Heidelberg University Hospital in Germany. In particular, her research interest shifted from time-resolved X-ray computed tomography and positron emission tomography to transmission imaging with protons and even heavier ions. In this context, she secured a national DFG research grant to finance her position of Principal Investigator. In her project "HIGH ART" (Hybrid Imaging framework in Hadrontherapy for Adaptive Radiation Therapy) she investigates state-of-the-art and innovative radiographic and tomographic imaging methodologies to promote simple and cost-effective "integration-mode" detector configuration with scanned beams as an alternative to widely investigated "list-mode" detector configurations with broad beams.

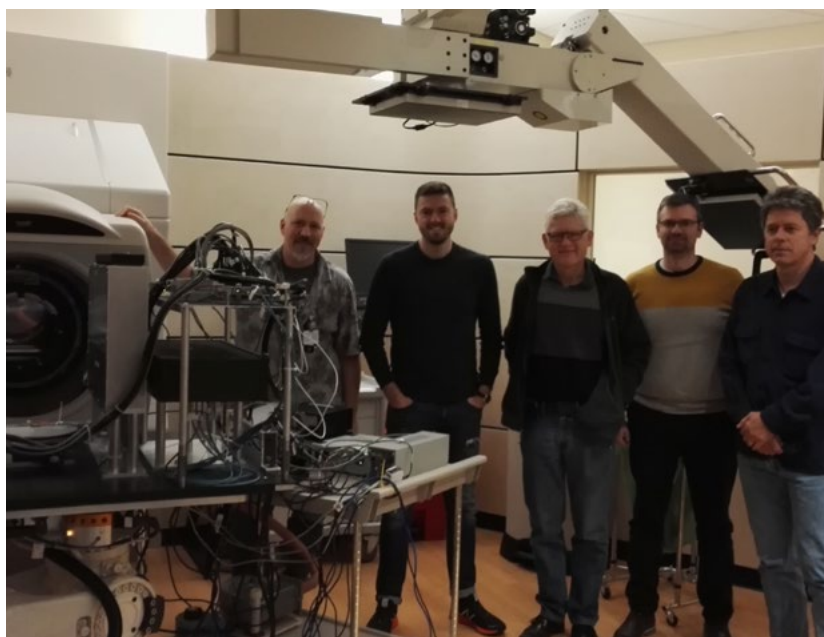


Marco Pinto

Joined the LMU team in 2015, after having received his PhD in Lyon, France, in the framework of the ENLIGHT-coordinated project ENTERVISION. His current primary research activities feature the implementation of a Monte Carlo-based platform for carbon ion dose calculation and optimisation on graphics processing units (GPUs), and the development of analytical methods for fast estimation of positron emission tomography and prompt gamma distributions for proton and carbon ion therapy. In this endeavour, he is actively involved in several collaborations with the University of Texas Southwestern Medical Center (Dallas, USA), the company RaySearch Laboratory (Sweden, Stockholm), the National Institute of Radiological Sciences (NIRS, Japan), the University of Wollongong and the Australian Nuclear and Science Technology Organization (ANSTO, Australia).



Dr. Dedes and Dr. Landry performing collaborative experimental campaigns at the proton therapy centers in Munich.



In Chicago using the proton computed tomography prototype developed by Dr. Reinhard Schulte (in the middle).

A SPATIAL ANALYSIS OF BIOLOGICAL DOSE DISTRIBUTIONS IN THE BRAINSTEM AND ITS SUBSTRUCTURES IN PROTON THERAPY OF PAEDIATRIC BRAIN TUMOURS



LARS FREDRIK FJÆRA

PhD student at University of Bergen
Department of Physics and Technology

I was first introduced to proton therapy (PT) in a lecture back in 2013 during the last year of my physics B. Sc. and I decided to pursue a master's degree in medical physics focusing on PT. I have always had a great interest in the topic of medicine, however physics remains my favourite subject. Therefore, medical physics was just the perfect combination for me. During my M.Sc., I developed a software that could recalculate (clinically) radiotherapy treatment plans using FLUKA Monte Carlo code. Use of Monte Carlo allows for better accuracy of calculated dose distributions, in addition to enabling studies of quantities such as linear energy transfer (LET) and secondary particle production.

A Norwegian particle therapy centre is scheduled to treat patients by the year 2022 and there is ongoing discussion on the location of the centre (Bergen or Oslo), but it is necessary to start developing expertise among both clinicians and physicists at an early stage. As a result, there has been an increased focus on PT research in Bergen in recent years. This has opened up research positions, and I was given the opportunity to do a PhD at the University of Bergen involving radiobiological modelling in PT.

So far clinically a constant relative biological effectiveness (RBE) of 1.1 to describe the increased biological effect compared to is photon radiotherapy is used. Although the RBE varies depending on factors such as dose, dose rate, endpoint, cell type and LET. A better understanding of the biological effect of protons is therefore important to increase accuracy of dose delivery and further to enable exploiting the full potential of proton therapy. Several biological dose

models have therefore been developed to describe these RBE variations, which have been a focus of our research group at the University of Bergen/Haukeland University Hospital^{1,2}. Since starting my PhD in early 2017, my main focus has been on proton therapy for paediatric brain cancer patients, and how the LET will affect the biological dose to organs at risk (OARs) depending on the applied RBE model (as well as depending on tumour location relative to OARs³).

The primary focus for the PhD is the correlation between LET distributions and brainstem toxicity in a paediatric brain cancer patient cohort previously treated with proton therapy at the University of Florida Health Proton Therapy Institute. By implementing the proton beamline into the Monte Carlo code, we can obtain the LET distributions for these patients, and this will hopefully give a better understanding of the clinical consequences of the elevated LET that occurs at the end of treatment fields.

Working on projects that may contribute to improving radiation treatment for cancer patients is a great motivation to keep me focussed and engaged during my studies. I will definitely pursue a career within proton therapy after my PhD, and I can not wait to see how cancer treatment will evolve in the future. ■

¹ Rørvik, E. et al., *Med. Phys.* 44, 2586 (2017)

² Dahle, T.J. et al., *Acta Oncol.* 56, 779 (2017)

³ Fjæra, L.F. et al., *Acta Oncol.* 56, 763 (2017)

BEAM-ON IMAGING OF SHORT-LIVED POSITRON EMITTERS DURING PROTON THERAPY



IKECHI OZOEMELAM

PhD student at KVI - Centre for Advanced Radiation Technology, division of the University of Groningen

Throughout my studies I have been driven by a desire to be an active player in the field of radiation therapy and this has led to varied experiences in medical imaging and radiation therapy. During my master's studies in Nuclear Application, I had an introduction to radioisotopes production and hadron therapy. After my master's degree, I decided to pursue an exciting PhD program at the KVI-Centre for Advanced Radiation Technology (KVI-CART) at the University of Groningen, which combines two fascinating aspects of nuclear science – nuclear imaging and hadron therapy, thus allowing me to advance my expertise in these areas.

The KVI-CART, is one of the city with a Dutch proton centre, is involved in research at improving the quality of particle therapy. One project is the in-vivo verification of dose delivery during particle therapy and is my PhD thesis. topic. My colleagues and I are involved in the development and advancement of techniques, which are based on the imaging of secondary particles, to monitor the dose delivery and reduce the range uncertainties of particle beams. Considering that range uncertainties constitute a significant limitation to the full exploitation of the dosimetric superiority of charged particle beams, the inclusion of imaging feedback goes a long way in boosting confidence in the treatment quality. Although other imaging techniques are being explored for this purpose, Positron Emission Tomography (PET) imaging of the beam-induced positron emitters represents an advanced method which is currently available for routine application. Some clinical implementations of PET verification have been recommended. The beam-on technique is attractive as it offers advantages including the reducing biological washout,

enhanced PET counts and provision of faster feedback on the monitoring of dose delivery. For the provision of valuable input on a short timescale within typical irradiation duration of a few minutes, the contributions of short-lived positron emitters is increasingly important.

At the ENLIGHT 2017 meeting, I presented the results from a test of principle experiment in which I, along with my colleagues, imaged the short-lived positron emitters created during proton irradiation with a dual head TOF-PET scanner. We adopted an approach based on a selective windowing into the pauses of a pulsed beam delivery, which permits the imaging of the short-lived positron emitters with minimal contribution of longer-lived ones. A part of the presented results highlights the application of our approach to bone tissue. To simulate bone tissue, a calcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$) insert, sandwiched in between two PMMA blocks was used. By imaging $^{38\text{m}}\text{K}$ ($T_{1/2} = 0.9\text{s}$), a short-lived positron emitter, which is created during irradiation, millimetric accuracy in target shifts was realised.

I am impressed by the progress I have made since the beginning of my PhD work and filled with a renewed sense of curiosity to advance In-Beam PET for particle therapy. ■

A SOLID-STATE PROTON IMAGING SYSTEM



NIGEL M ALLINSON, MBE

Distinguished Professor of Image Engineering, University of Lincoln

So how did an electronics engineer find himself leading a project on imaging for Proton Beam Therapy?

I have always been involved with imaging, both in hardware and software. Realising no one would fund me to play with electronics or computers, it was quite clear to me that I would receive financial support to solve other people's problems. In fact, I love solving other people's problems. In 2004, I started a large project to develop monolithic active pixel sensors with a team of over 50 people. Some of our end-users in the project were medical physicists who had the clearest idea of what they wanted. So we set about designing wafer-scale radiation-hard CMOS sensors for medical imaging. We produced the world's largest monolithic imaging chip at over 13 cm square and spun-off a CMOS design house dedicated to making such devices for healthcare equipment manufacturers. It was a chance encounter with Stuart Green, Director of Medical Physics, University Hospital Birmingham, that got me involved with Proton CT.

We pulled together a group of people, – medical physicists, high energy physicists, electronic engineers, etc. with a background in developing and using solid-state sensors, we decided to build a system that would use silicon sensors solely. After an unsuccessful funding application submitted to the Engineering and Physical Science Research Council (EPSRC), we thus turned our efforts to obtain some financial support from The Wellcome Trust. They agreed to help us even if the area was far from what they would require usually.

Although as a group, we followed standard project protocols, starting with a user requirements document and then

producing a functional specification document. A comprehensive Geant4 simulation platform, GEANT4-based Super Simulation (SuSi), was started and this guided our design and implementation. SuSi managed to develop and grow in its capabilities as we modelled two complete delivery systems and included accurate models of our sensors.

In UK, we used Clatterbridge Cancer Centre with up to 60 MeV protons, and the University of Birmingham MC40 Cyclotron with up to 36 MeV for testing the component parts of our system but for full clinical energies, we flew our system to the iThemba LABS near Cape Town, SA. This turned out to be an ideal site for our experiments.

Along with our brilliant small group of young researchers, we managed to achieve remarkable results in just four years – relative stopping power errors down to the order of 1%, first comparative proton and X-ray CTs for biological samples, first demonstration of scattering power proton CT and more, much more. After four decades of imaging research, this project has been my high point in terms of commitment and actions – not bad for someone, who is well past his “use-by-date”. ■

AGENDA 2018

NAME OF THE EVENT	DATE	PLACE OF THE EVENT
Forum on New International Research Facilities in South East Europe	25-26 January 2018	Trieste, Italy
1st Russian Scientific and Educational Congress with International Participation "Oncoradiology, Radiology and Radiotherapy"	16-17 February 2018	Moscow, Russia
XIV Workshop on Resistive Plate Chambers and related detectors	19-23 February 2018	Puerto Vallarta, Jalisco State, Mexico
ESTRO 37 Annual Meeting	20-24 April 2018	Barcelona, Spain
X International Congress "Nevsky Radiology Forum 2018"	26-28 April 2018	Saint-Petersburg, Russia
PTCOG 57 Annual Meeting & PTCOG-NA 5th Annual Conference	21-26 May 2018	Cincinnati, Ohio, US
ENLIGHT 2018	25-27 June 2018	London, UK
ASTRO's 60th Annual Meeting	21-24 October 2018	San Antonio, Texas, US
2018 IEEE Nuclear Science Symposium and Medical Imaging Conference	09-17 November 2018	Sydney, Australia

1ST RUSSIAN SCIENTIFIC AND EDUCATIONAL CONGRESS WITH INTERNATIONAL PARTICIPATION "Oncoradiology, Radiology and Radiotherapy"
 16-17 February, 2018, Moscow, Russia.
 (Holiday Inn Moscow – Sokolniki, Rusakovskaya Ulitsa, 24)
www.oncoradiology.ru



X INTERNATIONAL CONGRESS "NEVSKY RADIOLOGY FORUM 2018"
 26-28 April 2018, Saint-Petersburg, Russia.
 (Venue: EXPOFORUM, Peterburgskoye Shosse, 64)

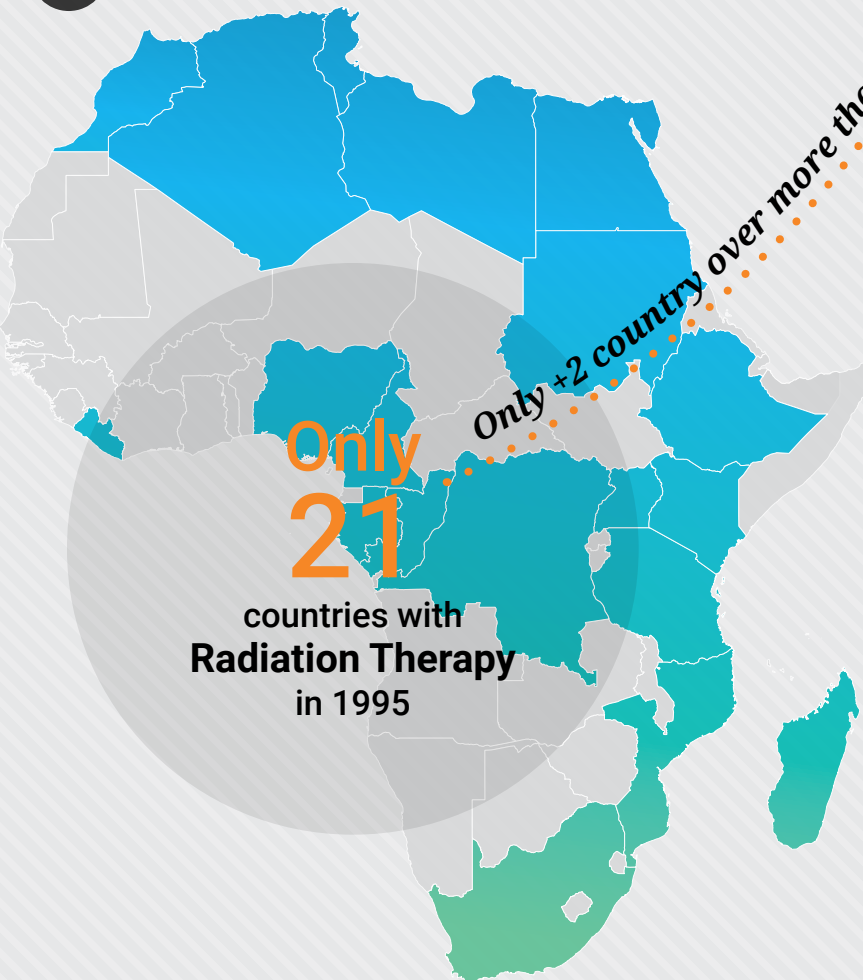
www.spbra.ru



ESTRO 37
 20-24 April 2018
 Barcelona, Spain
 Innovation for Value and Access

DEVELOPING MEDICAL LINACs FOR CHALLENGING ENVIRONMENTS

By Petya Georgieva





Participants to the Workshop on Innovative, Robust and Affordable Medical Linear Accelerators for Challenging Environments held at CERN, 25-27 October 2017

About 50 experts in accelerator technologies, medical physics and oncology from Botswana, Ghana, Jordan, Nigeria, Tanzania, ICEC, the UK and CERN met at CERN in October 2017 to discuss the goal of developing innovative, robust and affordable medical linear accelerators for challenging environments. This was the follow-up of a first workshop, hosted by CERN in November 2016 and co-organised with the International Cancer Experts Corps (ICEC). Last year's workshop resulted in the creation of three task forces by: 1. Technical, 2. Education, mentoring and training and 3. Global Connectivity and development) to address the treatment of cancer in challenging environments and to explore new possible emerging directions in the radiotherapy treatment of cancer.

At the follow up workshop, entitled "Innovative, robust and affordable medical linear accelerators for challenging environments", the participants, which included representatives from the Official Development Assistance (ODA) countries on the Development Assistance Committee (DAC) list, shared their grass-roots perspectives and the needs and struggles in order to build a strategy for increasing access to radiotherapy to a larger number of patients. The event¹ was organised in collaboration between CERN, ICEC and the Science and Technology Facilities Council (STFC).

Funded through the UK's Global Challenges Research Fund, the workshop became a constructive dialogue among experts in accelerator technologies, medical physics and oncology who pledged to identify resources and practices to enhance the effectiveness of the machines to be deployed. There was significant interest in this brainstorming event and presentations from Botswana and Ghana were given using video conference platform. The extreme difficulty in establishing these connections once again illustrated how challenging are these environments.

In terms of time and priorities, all the participants agreed that improving and enhancing the operating machines is needed urgently as the current ones are technically complex and require frequent and expert maintenance. As a second step, in the next 3 to 7 years, we have to find solutions for a better linac and associated instrumentation which is adapted for such challenges. An important aspect that was strongly stressed throughout the open discussions was to make the linac components and system as a whole more robust and easily

¹For more information, please visit <http://indico.cern.ch/event/661597/overview>

maintainable in regions where experienced technical staff are limited.

Simplicity of operation is another significant factor in using linacs in clinical settings. On one hand, the radiation technologist should be able to do the setups under the direction of the radiation oncologist and follow the treatment plan. And on the other hand, maintenance should also be as easy as possible – from remote upgrades and monitoring to anticipating failure of components. These centres and their machines should be able to provide treatment on a 24/7 basis, as needed, and, at the same time, deliver exclusive first-class treatment comparable with the state of the art in developed countries.

A frequent challenge for reliable radiotherapy delivery is the environment in which the advanced linacs must function continuously. Harsh factors such as high temperatures, inadequate cooling, extensive dust and the high humidity in developing countries are only few of the factors that can impact both the robustness of the machines and the general infrastructure.

This workshop, as outlined above, established many of the challenges for the future of this joint collaboration for delivering radiotherapy for difficult environments. The immediate objective is to develop 4-5 projects in collaboration with participants from ODA countries that will address the points raised in the technical sessions, which will be presented in the next workshop in March 2018.

The eventual goal is to embed the individual projects and develop an umbrella proposal in collaboration with ODA countries, CERN, ICEC, STFC institutes which is going to address the needs and develop the medical linac for treating cancer. STFC will lead the proposal to the Global Challenges Research Fund Foundation Awards 2018. ■



Animated discussion during one of the presentations.

ENLIGHT

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Radiation Oncologist,
Oxford



Manjit Dosanjh
Biologist, CERN
ENLIGHT Coordinator,
Geneva



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THE EUROPEAN NETWORK FOR LIGHT ION HADRON THERAPY

A multidisciplinary platform aimed at a coordinated effort towards ion beam research in Europe.

The European Network for Light Ion Hadron Therapy (ENLIGHT), which had its inaugural meeting at the European Organization for Nuclear Research (CERN) in February 2002, today has more than 600 participants from nearly 25 European countries. Harnessing the full potential of particle therapy requires the expertise and ability of physicists, physicians, radiobiologists, engineers, and information technology experts, as well as collaboration between academic, research, and industrial partners.

The ENLIGHT network has been instrumental in bringing together different European centres to promote hadron therapy and to help establish international discussions comparing the respective advantages of intensity modulated radiation proton and carbon therapies. A major success of ENLIGHT has been the creation of a multidisciplinary platform bringing together communities that were traditionally separated, so that clinicians, physicists, biologists, and engineers work side-by-side. Special attention is also given to the training of young researchers and professionals of oncologic radiotherapy.

For more information and contact details please visit the ENLIGHT website at cern.ch/enlight (or scan the QR code).

Join the ENLIGHT network. Register to become a member here:

<https://indico.cern.ch/event/180036/registrations/495/>

