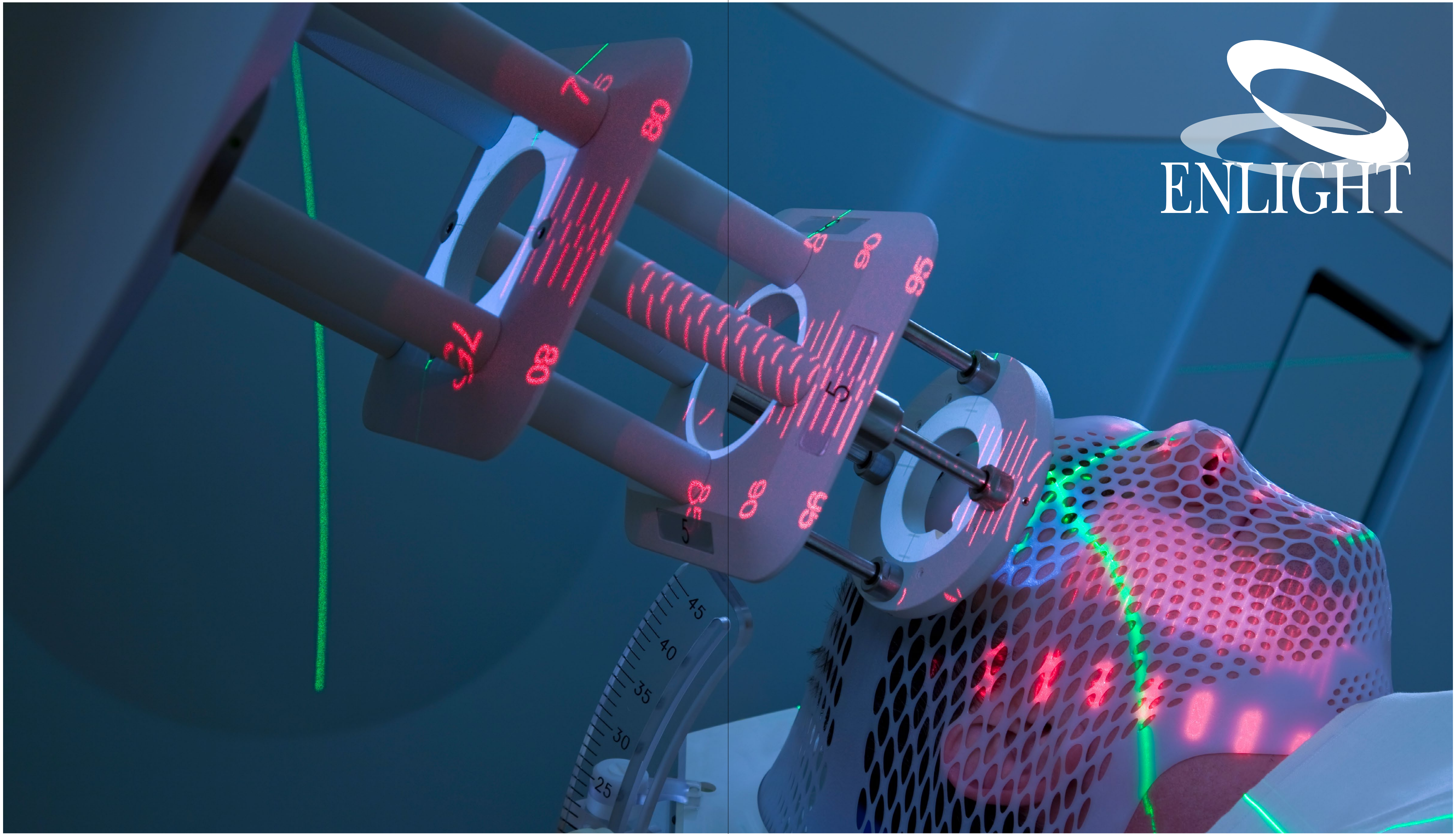
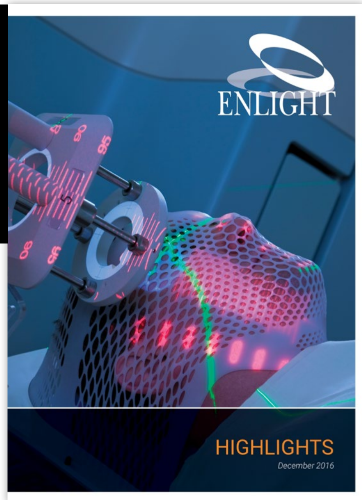


ENLIGHT

HIGHLIGHTS

December 2016



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Cover: Head mask for radiotherapy, used to aid correct and optimal positioning during the treatment.

ENLIGHT

THE EUROPEAN NETWORK FOR LIGHT ION HADRON THERAPY

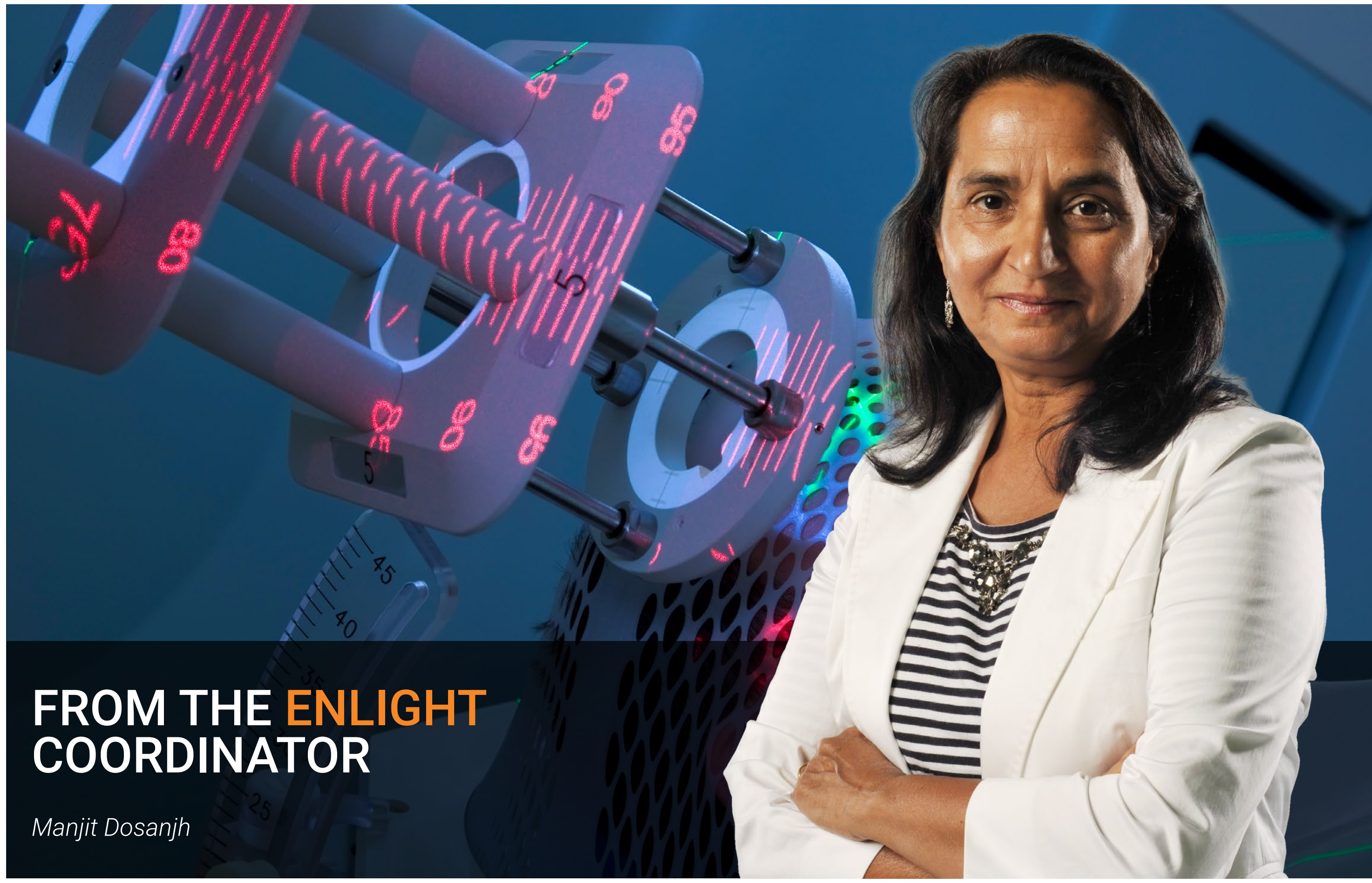
A multidisciplinary platform aimed at a coordinated effort towards ion beam research in Europe.

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 centers 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 working in the field.

For more information and contact details please visit the ENLIGHT website at cern.ch/enlight

Join the ENLIGHT network. Register to become a member here. https://indico.cern.ch/confRegistrationFormDisplay.py/display?confId=180036



FROM THE ENLIGHT COORDINATOR

Manjit Dosanjh

Phase 2 has started

In almost 15 years since its creation in 2002, ENLIGHT has witnessed a large increase of dedicated centres that use proton and carbon ions to treat cancer. In addition, despite their continuing cost, innovative medical imaging techniques are starting to make their way into routine diagnostic methods. Adapting and evolving is an intrinsic feature of the ENLIGHT network and in 2015 the network decided to gear up and start a new phase to meet the fast-changing environment for improving cancer outcomes. I am proud to say that the change has already begun.

At our annual meeting last year in Krakow, after reflections and discussion we had outlined some ideas, including the establishment of an advisory committee to help the coordinator, the need for lobbying for funding and the addition of training as one of the main scopes of the network's activity. Following up on those ideas, a project within the CERN in Society frame has been presented. Although we are still waiting for evaluation, this is the first, important step to make ENLIGHT self-sustaining. For the same reasons, we also plan to establish ENLIGHT as a foundation or a non-profit organization and possibly charge for institutional membership.

At our recent gathering in Utrecht, we already implemented the idea of including training in the programme of ENLIGHT annual meetings. Indeed, the construction of more and more facilities providing particle therapy across Europe makes it necessary to deliver more dedicated training to nurture experts in such a complex and multidisciplinary field. Our members are among the best trainers the world needs to meet this requirement.

Thanks to the highly collaborative spirit existing in our network and with the help of the newly appointed members of the advisory board, we are committed to work in identifying and prioritizing our challenges, those that will shape the future of ENLIGHT. The advisory committee and the coordinator will have to work on defining strategies to secure funds for the network. We also need to make sure that our actions and impact are appropriately covered in the media and in the press as much as possible.

Our main communication and outreach means are the very pages you are reading. ENLIGHT Highlights is distributed for free in over 100 institutes in about 25 countries. It helps us share information about the network and its achievements. We are committed to improve it further and make it an even more valuable resource for you ENLIGHT members to share it as much as you can and for everybody to keep up-to-date with the latest news in cancer treatment based on cutting-edge solutions and the research needed to make it happen.

Manjit Dosanjh

PAGE INDEX

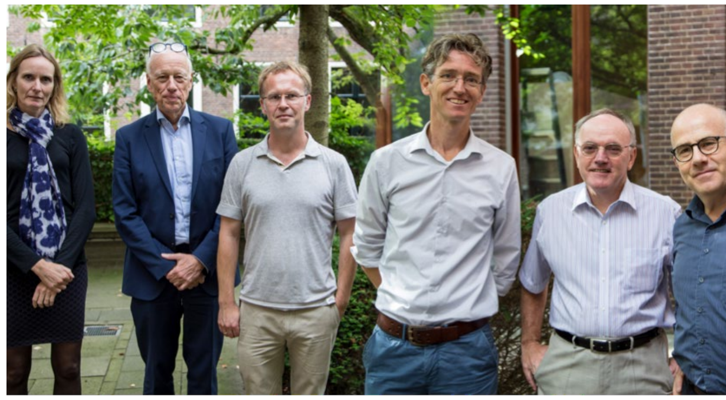
Photos by Hanne Nijhuis

ENLIGHT
Annual Meeting 2016

By Manjit Dosanjh (CERN), Virginia Greco (CERN) and Bleddyn Jones (University of Oxford and CERN)

ENLIGHT 2016

The Organizing Committee and collaborators. From left to right: Jan Visser (Nikhef), Manjit Dosanjh (CERN), Els Koffeman (Nikhef), Virginia Greco (CERN), Christos Papasimos (CERN), Giovanni Porcellana (CERN).



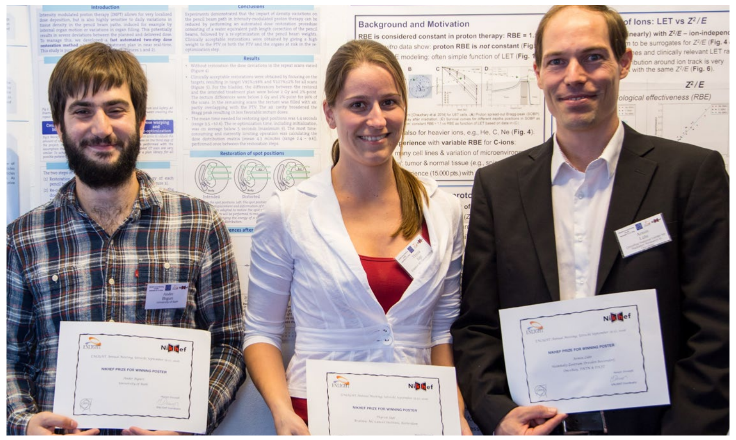
Faculty members of the first training course organised during the ENLIGHT meeting. From left to right: Kari Tanderup, Richard Poetter, Machiel Jansen, Bas Raaymakers, Bleddyn Jones and Martin Pruschy.

The ENLIGHT Annual Meeting this year was held in Utrecht, the Netherlands, on 15 and 16 September. For the first time, ENLIGHT has brought training in the core programme of its network meetings, dedicating a full day (17 September) to lectures on keys aspects of particle therapy.

The annual meeting of the ENLIGHT network gathers experts and delegates from most of the European centres and research institutions working on particle therapy for cancer treatment. This year the meeting was hosted by the University of Utrecht, in the Netherlands, on 15 and 16 September. Chaired by the ENLIGHT co-coordinator, Manjit Dosanjh, and the local organizers, Els Koffeman and Jan Visser from Nikhef, the conference was attended by almost 100 participants from 15 countries.

The location was carefully selected as one of the key topics of discussion of the meeting was the design and realisation of four brand new centres for proton therapy in the Netherlands, - Groningen, Maastricht, Delft and Amsterdam – that followed the recent approval by the Dutch Government of a plan for making proton therapy available nation-wide.

In addition to the collaborative model of the new Dutch centres for treatment with proton and heavier ions, many other hot topics were discussed, including the recent progress and technological break-throughs in medical imaging, the importance of using a standard NCTP model for selecting patients for different types of treatments, and the need for access and sharing of clinical data.



The poster session was one of the highlights of the annual meeting of the ENLIGHT network. From left to right: Ander Biguri (University of Bath), Thyrza Jagt (Erasmus MC Cancer Institute, Rotterdam) and Armin Luhr (Oncoray, Dresden).

Time was also given to young researchers, who had the possibility of exhibiting posters summarizing their research activity. The second day of meeting was closed with the awarding of the authors of the best three posters the chance to give oral presentations of their work to the ENLIGHT meeting participants. The prizes were presented by Els Koffman and Jan Visser from Nikhef to the winners Ander Biguri (University of Bath), Thyrza Jagt (Erasmus MC Cancer Institute, Rotterdam) and Armin Luhr (Oncoray, Dresden).

PROTON THERAPY BOOSTED IN THE NETHERLANDS

Leading medical experts of the new Dutch centres for proton therapy (Hans Langendijk, Marco van Vulpen, Bart Vanhauten, Geert Bosmans) presented the national programme and the current state of the facilities, which are distributed over the country: in Delft, Groningen, Maastricht, and Amsterdam. The ambitious and extensive programme was launched in 2013 by the Dutch government and it is being implemented in a relatively short time. The Holland Proton Therapy Centre (Holland PTC) of Delft and the UMC Groningen PTC are already under construction and they foresee to start treating patients at the end of 2017 (August for Delft and December for Groningen). The proton therapy centre in Maastricht is heading towards the construction phase and plans to integrate the proton facility in the existing radiotherapy centre, so that hospital structures and experts can be shared. They should be able to treat the first patient in 2018. Finally, the fourth centre, which will be established in Amsterdam, is going through the phase of choosing the company that will provide the technical equipment for the facility.

All of these centres will have one or two treatment rooms equipped with gantries, which allow a complete rotation of the beam axis around the patient to better target the tumour. Given the paramount importance of medical imaging for treatment planning and adaptation, MRI and PET scan machines will be available in the same centres, while CT scan will be performed in-room. When the four centres are operative, the Netherlands will be able to treat more than 1000 patients per year with protons.

In order to be run, particle centres need highly specialized staff,

Participants to the ENLIGHT annual meeting in Utrecht, 15-16 September 2016.

composed of medical doctors, physicists, radiobiologists, and technicians, who have to be specifically trained. At the moment there are only few experts in this emerging field, thus an important role will be given to the training of young professionals, as well as to research. Indeed, each centre also presented a research programme, aiming at improving proton therapy and developing more precise, effective treatment procedures with fewer side-effects.

The status of particle facilities Europe-wide was summarized by Beate Timmermann, of the West German Proton Therapy Centre Essen (WPE), and Karin Haustermann, of the Academic Hospital (UZ) of Leuven, Belgium, who also talked about the challenging path that has to be followed to move from the project design of a new centre to the implementation and then the clinical practice. It is a tough and time consuming process, which never completely reaches an end, since the rapid evolution of technologies and discoveries has to be followed and implemented.

NEW PERSPECTIVES IN MEDICAL IMAGING

Large space for talks and discussions was also given to medical imaging since it is a key to accurate and effective treatment, the recent developments of which were presented in two dedicated sections. In order to deliver a really effective treatment and, at the same time, avoid side effects - such as healthy cells killing, damage to critical organs, secondary tumour caused by irradiation-, it is important to localize at the best of possibilities the position of the cancerous mass and be aware of its modification along the treatment period. Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI) and Computed Tomography scan (CT) are used alone or in combination between them (multi-modal imaging) to assess the volume and the position of the tumour before, after and during treatment whenever possible.

The ENLIGHT network organised the very first multidisciplinary training session open to all participants.

A session of the training course on the last day of meeting in Utrecht.

Particularly complicated is the case of moving organs, such as the lungs, which has to be addressed by using in-room multi-modal imaging, associated with an adaptive treatment workflow. Theoretically, tracking would be the best solution, which require online, real-time 3D information, as highlighted by Antje-Christin Knopf, of the Institute of Cancer Research (ICR) of London.

The advantages of having simultaneous MRI and treatment irradiation were discussed by Bas Raaymakers, of the University Medical Centre (UMC) of Utrecht. The integration of MR imaging with Linac can provide image-guidance concurrent with treatment minimising the patient exposure to the additional ionizing radiation of CT scans. It can also offer a real-time view of what happens in a patient's body during each treatment, taking advantage of MRI's strength in imaging soft tissue and thus enable adjustment of the targeted radiation treatments.

TAILOR-MADE TREATMENTS

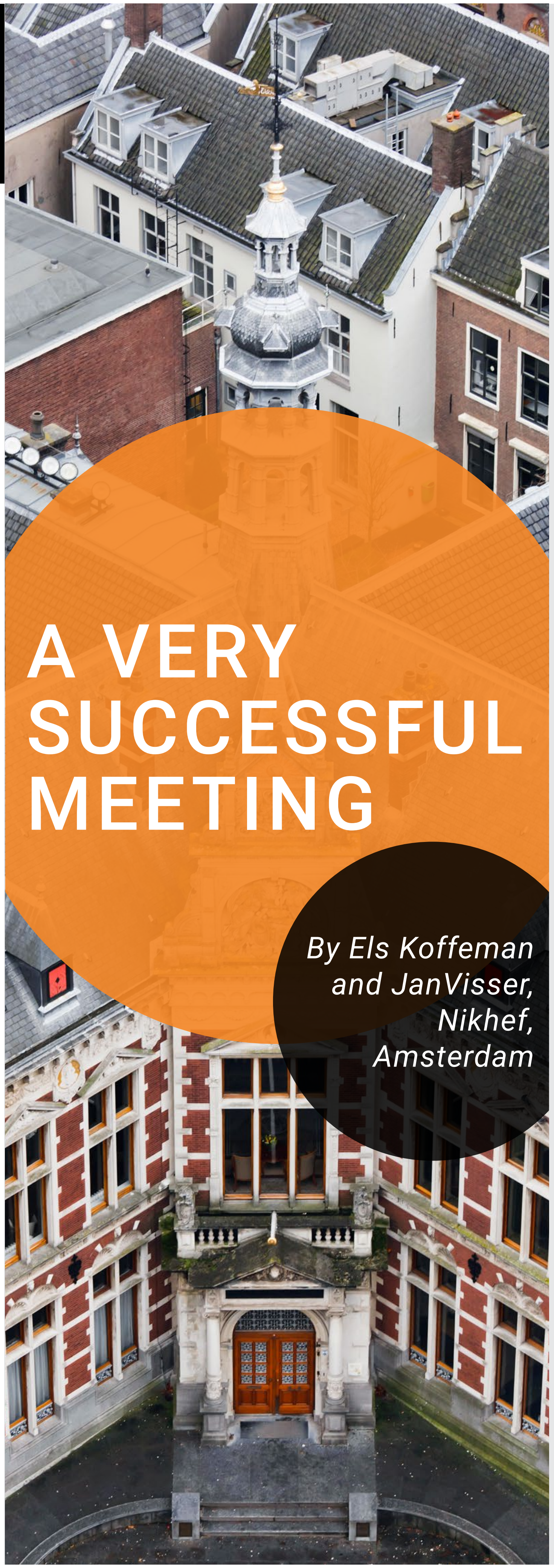
The image-guided proton therapy (IGPT) is one of the applications of the new paradigm that is emerging in oncology: the shift to a personalized and precise medicine, where the treatment is tailor-made for the single patient.

In the same direction the perspective goes of developing a proton therapy decision support system that would assist the medical doctors in the choice of the best combination of treatments for their patients. In order to take an informed decision, the practitioner has to be able to rely on as much data from previous cases as possible. Here is where the emerging big data systems come into play, since it would allow the doctor to analyse the single patient condition in comparison with some model extracted by the analysis of past cases information. Of course this system can be built only if clinical data are accessible, which is still a controversial issue, because of privacy concerns. Nevertheless, as Philippe Lambin of the University Hospital of Maastricht highlighted, this is strongly needed and actions have to be taken in this direction. An important change in culture is actually ongoing, since society is quickly moving towards massive data gathering and sharing.

TRAINING AT ENLIGHT

For the first time since the establishment of the network in 2002, this year the annual ENLIGHT meeting was followed by one-day training on keys aspects of particle therapy, including radiobiology, medical imaging, and data sharing. The network was very fortunate that high profile scientists and medical doctors (see photograph at page 8, top right) made their expertise available to colleagues and young researchers through a number of lectures, given in the fantastic setting of a historic building of the University of Utrecht.

The training was highly appreciated by the members of the community, so a similar course will be organised in the next annual meeting, which will be held in June 2017 in Aarhus. This is the city that will be the home of the first particle therapy in centre in Denmark and the convention will actually coincide with the installation of the cyclotron.



A VERY SUCCESSFUL MEETING

By Els Koffeman and JanVisser, Nikhef, Amsterdam

It was our pleasure to host the annual meeting of the ENLIGHT network and share with the participants our excitement for the new perspectives of particle therapy in the Netherlands.

The rich agenda of interesting talks caught the attention of the attendees, who got involved in very stimulating discussions with the speakers and among themselves. In addition, the poster session and the prize for the three best posters showed the engagement of many young researchers.

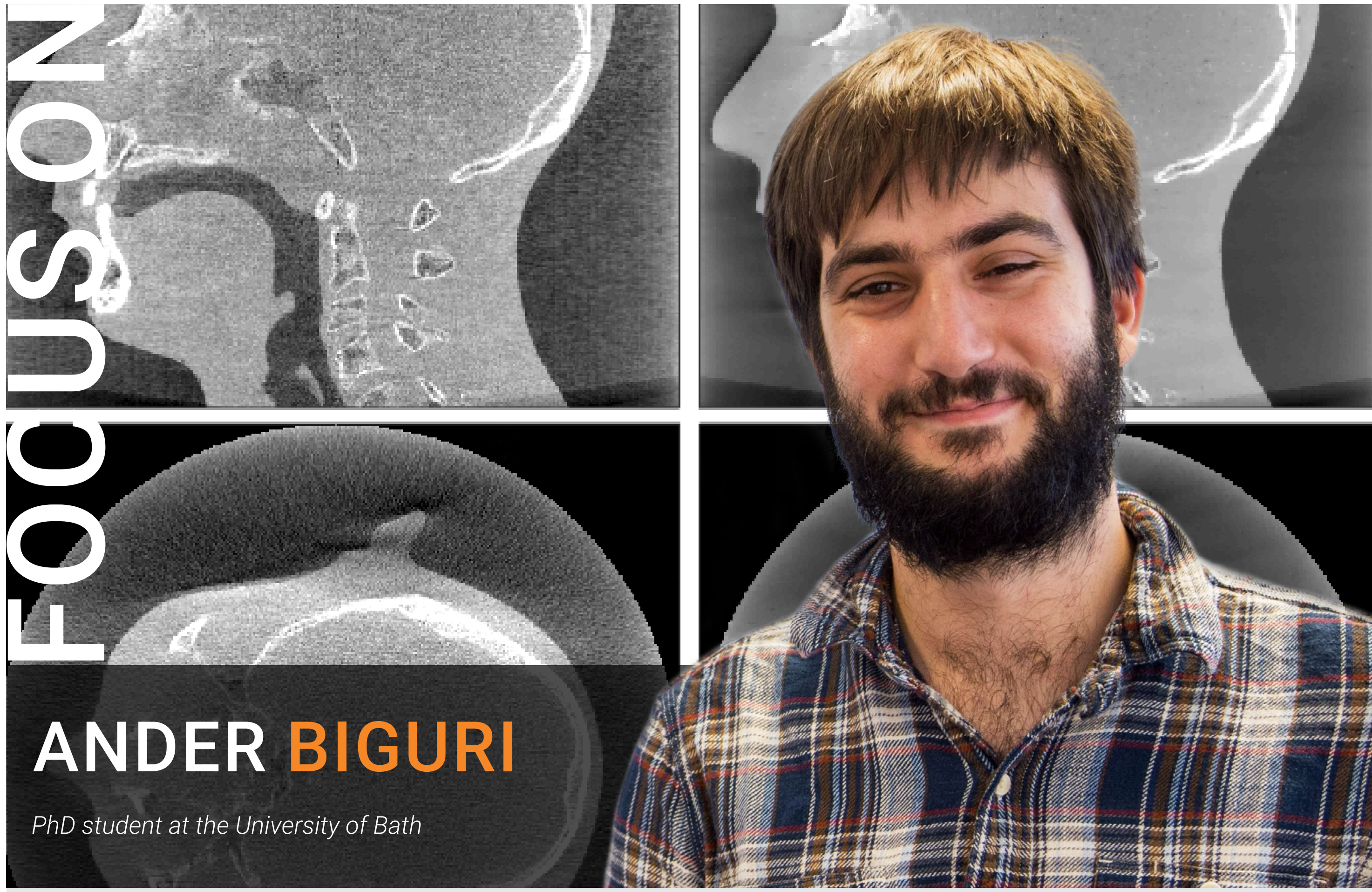
We also invited the industrial sponsors to share their view on the development of equipment for hadron therapy – diagnostic, imaging, and treatment. After their short presentations, a lively discussion arose with them in which experts from the medical field and from the technical field shared ideas on the complex domain of technology transfer, on advantages for patients and cost-effective implementation.

We are also glad that for the first time this year a training day was organised in the context of an ENLIGHT annual meeting. The main idea was to give an overview of a number of topics from different viewpoints, as perceived by physicists and professionals from the medical world. In this edition, we had lectures on Magnetic Resonance Imaging, Multi-Modal Imaging, Radiobiology and Big Data. These talks of 45 minutes each provided the opportunity to treat these subjects in depth and have discussions between the excellent speakers and the audience. The attendees commented that it was really useful since they learned a lot. We are already looking forward to the training event the organisers of next year's convention in Denmark will put together and we hope it will become a regular feature in the ENLIGHT meeting agenda.

> *"It was our pleasure to host the annual meeting of the ENLIGHT network and share with the participants our excitement for the new perspectives of particle therapy in the Netherlands."*
>
> *Els Koffeman and Jan Visser, Nikhef, Amsterdam*

Els Koffeman

Jan Visser



ANDER BIGURI

PhD student at the University of Bath

I started my PhD at the University of Bath almost three years ago with little knowledge of the medical field but with a strong motivation for trying to improve the current technologies. I have been studying tomography together with computational mathematics within the framework of a joint project which sees the Engineering Tomography Laboratory at Bath collaborating with CERN. At the moment I am working on motion correction in X-ray tomography and at the Annual ENLIGHT meeting in Utrecht I presented my research on iterative reconstruction methods and motion compensation.

Clinical X-ray tomographic imaging is dominated by cone-beam computerized tomography (CBCT). And, although new, improved CBCT algorithms are developed every year, just one prevails in clinical reconstructions: Feldkamp-Davis-Kress (FDK). This is a single-pass algorithm whose resultant speed is an important factor in its widespread use. However, I have succeeded to make a range of iterative CBCT algorithms run on graphical processor (GPU) architectures with such a dramatic gain in execution speed that the advantage of single-pass is no longer such a persuasive argument to shun iterative routines [1,2]. But it isn't just about raw speed. Some of these alternative algorithms can even match the image quality of FDK using fewer projections as input, which means a potential reduction in radiation dose for the patient being imaged. In addition, iterative methods open the door to a motion compensation scheme pioneered to image the particle beams circulating in the accelerators at CERN.

I have made a proof of principle of motion compensation in a Simultaneous Algebraic Reconstruction Technique (SART) algorithm by incorporating the same ideas behind CERN's so-called phase space tomography [3]. I created a simple in silico thorax-like phantom based on a collection of spheres. The figure below shows three reconstructions through its mid-plane. All elements of the phantom are completely static for the first reconstruction, while the second shows the obvious degradation when the data are generated on the basis that the left lung is moving (without deformation) during the CBCT scan. The motion was sinusoidal and in the z-direction only with an amplitude of the diameter of the tumour (of course lung, tumour and scan are simulated). The third image was produced from the same dynamic dataset as the second using the same SART algorithm, but the geometry of the reconstructed field of view is modified as a function of time during the data record in order to compensate for the known movement. This effectively freezes the third reconstruction at the starting point of the cyclic motion without any recourse to phase binning. Indeed, the entire dataset is used in each reconstruction and it is a feature of the CERN compensation method that the motion is not even constrained to be cyclic.

The emphatic success of the motion compensation is evident. Furthermore, because the mathematics of the reconstruction remains untouched and only the geometry of its operators are modified, the same approach can in principle be rolled out to any iterative algorithm. The caveat, of course, is that an accurate model is required to describe the motion during data taking. We would like our colleagues to share with us such models and real patient data. Future work will include exploring the limits imposed on the accuracy of these models.

[1] https://github.com/CERN/TIGRE

[2] Biomedical Physics and Engineering Express 2, 055010 (2016)

[3] Physical Review Special Topics - Accelerators and Beams 3, 124202 (2000)

FOCUS ON

ARMIN LÜHR

Researcher at OncoRay, Dresden

I pursued my PhD studies in theoretical atomic physics in Berlin, working on low-energy collisions of antiprotons and protons with hydrogen molecules. It provided me with a solid background in the physics of ion collisions. I came in contact with particle therapy when I was hired as a post doc in Aarhus to join and to help establish the Aarhus Particle Therapy Group (APTG). There, I worked on the development of a Monte Carlo code optimized for ion therapy, on dosimetry questions, and on biologically individualized particle therapy. Shortly before leaving, one of APTG's main aims became reality: Aarhus won the competition to host the Danish national center for particle therapy.

During a long transition phase (more than a year) from Aarhus to the OncoRay in Dresden, I dealt with the important issue of how patients who would benefit most from particle therapy should be selected. This was a ULICE project and this gave me my first contact with ENLIGHT.

After three years in Aarhus, I joined the Translational Radiation Oncology group in Dresden, where I was the only physicist, surrounded mainly by clinician scientists and biologists, but also computer scientists and lawyers. This experience helped me to widen my horizon beyond a typical physicist's view on radiotherapy. I also learned how important it is to find a common language in a truly interdisciplinary team and that it requires patience and openness from all involved partners.

My research in the Translational Radiation Oncology group in Dresden currently focuses on two main topics: magnetic resonance integrated proton therapy (MRiPT) and the effect of radiation on cells and patient outcome. Additionally, I am responsible for the large proton experimental hall at OncoRay.

At the 2016 ENLIGHT meeting in Utrecht I presented the latest results of my research, which show that the relative biological effectiveness (RBE) of radiation therapy does not depend on the type of particles used.

A characteristic of my personality that has surely influenced my research and my career is the fact that I like to choose different paths, rather than taking the same common straight route from one place to another. The reason for this is that I am attracted by perspectives that complement each other and driven by a desire to reveal correlations between different observations.

For more than five years, and despite being engaged in so many different projects, I have being trying to understand better RBE by studying scientific literature, discussing with biologists, doctors and physicists, performing Monte Carlo simulations as well as RBE experiments, and even trying to reconsider some quantum mechanics calculations performed during my PhD. When asked whether it was worth the effort, I say "yes". Putting together all these little pieces, it was possible for me to go beyond standard textbook knowledge. I hope that in the future RBE will no longer be plotted as a function of LET. But the real challenge for me is still ahead: translating such basic understanding into patient treatment.

FOCUS ON

THYRZA JAGT

PhD student Erasmus MC - Cancer Institute, Department of Radiation Oncology, Rotterdam

I have always been interested in the combination of mathematics and medicine. Consequently, once I had completed my Master's education in Applied Mathematics, I eagerly started my PhD studies at the Department of Radiation Oncology at the Erasmus MC Cancer Institute in the Netherlands. I am currently in the second year of my studies and at this point I am one of few researchers working in the field of proton therapy in this department.

Currently, the Netherlands does not have any operational proton therapy treatment centres. Two facilities are under construction and they are about to start building another. One of the two under construction is the HollandPTC, which is a collaboration between the Erasmus Medical Centre, the Leiden University Medical Centre and the Delft University of Technology. Within this collaboration, the ADAPTNOW (High-Precision Cancer Treatment by Online Adaptive Proton Therapy) project has been initiated and I am working on this during my PhD studies. In this project researchers of the three institutes involved collaborate to move towards a more accurate proton therapy cancer treatment. Combining the strengths of each department, we are aiming at developing a workflow in which we can adapt for geometric variations just seconds before treatment while also performing quality assurance during treatment.

At the ENLIGHT 2016 meeting I presented results of the first part of my research, in which, together with my colleagues, I developed a fast dose restoration method that adapts for density variations on the pencil beam path in near real-time. The dose restoration method consists of two steps: (1) restoration of spot positions (Bragg peaks) by adapting the energy of each pencil beam to the new radiological depth; and (2) re-optimization of pencil beam weights by minimizing the dosimetric difference with the planned dose distribution using a fast and exact quadratic solver. So far we have demonstrated that the impact of density variations on the pencil beam path in intensity-modulated proton therapy can be reduced by applying our restoration method. In the future we would like to combine this method with the use of a plan library, allowing us to also adapt for geometric changes of the target structures.

I am really enjoying my PhD work. Knowing that good results might lead to more efficient (proton therapy) cancer treatments is a very strong motivator to keep on looking for new methods and better ideas. These ideas often originate from discussions with co-workers. Besides this, as our department also focuses on conventional photon therapy, there are often discussions in which certain aspects of the two treatment modalities are compared. These exchanges have inspired several new research ideas for both modalities.

A fascinating aspect of my project is that, since it is developed within the activities of the HollandPTC collaboration, my research position allows me to get a front-row seat in the introduction of proton therapy treatments in the Netherlands. Being able to witness up close this effective synergy between applied sciences and medicine is, for me, extremely exciting.

The next ENLIGHT Annual Meeting will be held in Aarhus, Denmark, from 13 to 16 June 2017, in conjunction with the 16th Acta Oncologica conference on biology-guided adaptive radiotherapy (BiGART2017).

The key topics of the conference will be biology of tumours and normal tissue for selecting appropriate patients for treatment, functional imaging techniques, treatment planning and delivery, clinical outcome of biology-guided and adaptive radiotherapy including particle therapy.

Aarhus, with its public university new University Hospital, will become home to the first particle therapy centre in Denmark. The ENLIGHT meeting will, in fact, coincide with the installation of the cyclotron and the participants will have the opportunity to visit the facility under construction.

"It is our pleasure to welcome the members of the ENLIGHT collaboration to Aarhus for a special meeting," comments Cai Grau, University of Aarhus, Department of Oncology. "The participants will be hosted in a very nice venue and will be given the chance to have a tour of the construction site of the Danish Center for Particle Therapy (DCPT) and participate in BiGART2017."

Further information and subscriptions at the link **http://www.bigart2017.dk/**

Agenda 2017

NAME OF THE EVENT	DATE	PLACE OF THE EVENT
PTCOG 56 Annual Conference	8-13 May 2017	Kanagawa, Japan
ESTRO 36	5-9 May 2017	Vienna, Austria
ENLIGHT 2017	13-16 June 2017	Aarhus, Denmark
IEEE Nuclear Science Symposium and Medical Imaging	21-28 October 2017	Atlanta, USA

Photos by Salvatore Flore

ICTR-PHE 2016:

a successful intersection between medicine and physics

By Virginia Greco, Anaïs Schaffer and Manjit Dosanjh, CERN

Last February, physicists, biologists and medical doctors met in Geneva for the third edition of the International Conference on Translational Research in Radio-Oncology and Physics for Health to discuss advances and perspectives in cancer treatment.

The third edition of ICTR-PHE www.cern.ch/ictr-phe16 was held in Geneva, from 15 to 19 February 2016. More than 400 physicists, biologists and healthcare professionals from across the world interacted during the five days of the conference. Once again, this unique event proved to be the ideal place for experts to share their knowledge and expertise and leave with a wealth of new ideas, collaboration opportunities, and optimistic visions for the future of cancer therapy with innovative techniques. The plenary and parallel sessions covered a large spectrum of topics, spanning from radiobiology, nuclear medicine, to detectors and accelerators, imaging techniques, data processing and innovative medical treatments.

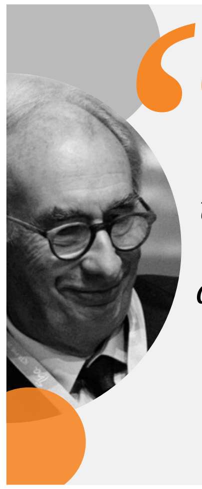
Eckhard Elsen, CERN's Director for Research and Computing, and the conference chairs, CERN's Manjit Dosanjh and Jacques Bernier from Clinique de Genolier (Geneva), opened the conference and presented the goals of the 2016 edition. "The primary mission of the ICTR-PHE conference", Bernier commented, "is to bridge gaps between all disciplines involved in translational research, in order to boost advances in biophysics and enhance the quality of their transfer into clinical practice." Indeed, already on that first day, experts in detector technologies, particle accelerators and nuclear medicine, as well as radiochemists, biologists and IT professionals were exchanging ideas and sharing their knowledge.

The conference was in full swing immediately after the opening addresses, with its first session on radiobiology. Among the various topics discussed, the presentation by Michael Story, from the University of Texas Southwestern Medical Center, intrigued the audience. He discussed novel potential biomarkers and in particular miR 551a and 551b-3p, two micro RNA (small non-coding RNA molecules) that were found statistically associated with disease phenotype. The talk by Ahmed Mansoor, from the US National Cancer Institute, confirmed how important it is for radiation biology to partner with immunology. New clinical trials have recently proven that when radiation therapy is combined with immune modulating agents it is possible to obtain a higher progression survival with respect to just immunotherapy.

Among the topics covered during the session on nuclear medicine, focus was given to "theranostics", which is the use of short-lived tracers for predicting the absorbed doses in molecular radiotherapy. This is a very active field of research and nowadays many new radiopharmaceuticals are available. Nevertheless, it is still a challenge to establish reliable dose-response relationships.

Detectors and imaging technologies play an important role in delivering an effective treatment, thus many experts came on stage to discuss key aspects of this topic. Among them, Thomas Bortfeld, from the Massachusetts General Hospital and Harvard Medical School, gave an overview on beam spatial control, an issue that is very critical for hadron-therapy effectiveness. Big effort is being put in to developing imaging techniques for beam range assessment and a number of possibilities are on the table.But according to Bortfeld, prompt gamma imaging appears to be the most promising at present, since it would allow real time detection of the position of the beam in the body of the patient (during treatment) with an accuracy of about 1mm. The development and the clinical use of prompt gamma camera were then presented in detail by Christian Richter from Oncoray, Dresden.

New technologies are key potential weapons in the fight against cancer and several sessions of the conference covered this field with high-level presentations and speakers. The use of magnetic resonance imaging for external beam radiotherapy guidance, one of the latest key technology developed in



"The primary mission of the ICTR-PHE conference is to bridge gaps between all disciplines involved in translational research, in order to boost advances in biophysics and enhance the quality of their transfer into clinical practice."

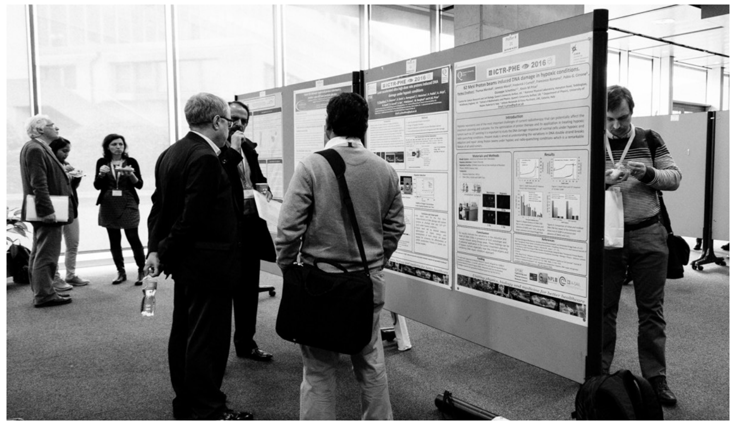
Jacques Bernier,
Clinique de Genolier (Geneva)

An area of the conference venue was dedicated to the industrial exhibition and a special space was reserved for start-ups

Participants to the ICTR-PHE 2016

the field was presented by Jan Lagendijk, from the Universitair Medisch Centrum Utrecht. Lagendijk explained that although for certain tumours it is possible to have a good visualization of the cancerous structures with cone beam CT-linac radiotherapy systems, that's not the case for all the tumours. Indeed, for most other tumour locations, such as rectum, oesophagus, pancreas, kidney or individual lymph nodes, the limited visualization using cone beam CT and the lack of dynamic information hinder a better targeting.

Various speakers highlighted the importance of gathering clinical data and processing them to create predictive models. In particular, Klaus Maier-Hein, from the University of Heidelberg, talked about radiomics and presented a method developed with his colleagues that can foresee the development and progression of tumours.



More than 100 young researchers contributed to the conference with a poster presenting their latest results.

Philippe Lambin, from the University Medical Centre of Maastricht, came on stage to show how distributed learning can be the solution for rapid learning health care. Lambin described "rapid learning" as the use of data routinely generated through patient care and clinical research to feed an ever-growing database. Thanks to this database, Lambin hopes to be able to develop mathematical models – following the example of weather models – capable of "predicting the future". But to achieve that, computing scientists need huge amounts of data – data they are eager to collect all over the world through the Euregional Computer Assisted Theragnostics project (EuroCAT).

Personalised medicine is the "holy grail" for today's doctors. In his GHF award lecture, Søren Bentzen, of the University of Maryland, discussed the need to combine precise medicine with multimodality treatment (surgery, radiotherapy, chemotherapy, etc.) to offer tailored therapy to the patient. The award was testimony to Bentzen's lifelong dedication to this field and to his commitment to providing the best possible outcome for patients.

Many other important topics, including clinical trials, immunology, radioresistance of tumours and multimodal treatment, were discussed in dedicated parallel sessions.

Room was given also to a presentation by the OPENMED project, which aims at establishing an open-access facility for biomedical research at CERN; and the MEDICIS-PROMED programme, launched to promote the use of radioactive ion beams at CERN's ISOLDE facility to produce specific ions for radiopharmaceuticals and hadron therapy.

In addition, Norman Coleman, senior scientific advisor to the International Cancer Expert Corps (ICEC) and a member of the US National Cancer Institute, presented the history and mission of the non-governmental organization ICEC. The organization committed to designing a radiotherapy system affordable to countries having low or medium income with challenging environments (see article on the ICEC workshop).

On the very last afternoon, the youngest researchers of the 2016 ICTR-PHE conference took the floor. Indeed, on the first day of the conference, more than 100 of them arrived with posters presenting their latest research carefully rolled in their bag. Pinned one by one on to the main conference hall panels, the posters raised a lot of interest and triggered many discussions during the whole week of the conference. Among them, six were chosen by a jury of experts to give a talk and awarded a special prize; one of the highlights of the conference.

An area of the conference venue was also dedicated to the industrial exhibition; this year included a special innovation corner, where new SMEs could show their products and interact with attendees. They also had the opportunity to give short presentations in a dedicated session.

The social event featured a special talk "Sound for Health", which was open to the general public. The talk focused on the application of sounds and music to research in biomedical sciences. Domenico Vicinanza and Genevieve Williams, of the Anglia Ruskin University in Cambridge (UK), presented a project in which data sonification (translation of data into sounds) is used as a tool for studying the corporal coordination mechanisms affected by diseases.

"We can say we've met the objective of this conference, which is to create interactions between physics, biology and medicine; from the first to the last day, we saw constructive exchanges not only in the conference rooms, but also in the corridors, where discussions are often more open"

concluded Jacques Bernier and Manjit Dosanjh

PARTICLE THERAPY in the Netherlands

Information on Geographic distribution of Proton therapy facilities in The Netherlands was provided by Johannes A. Langendijk

HOLLAND PARTICLE THERAPY CENTRE IN DELFT

View of the gantry. © Ernst van Hoek

By Mischa Hoogeman, Erasmus University, Rotterdam

Holland Particle Therapy Centre (HollandPTC) is the independent clinic and research centre in which Delft University of Technology (TU Delft), Leiden University Medical Centre (LUMC), and Erasmus Medical Centre (Erasmus MC) of Rotterdam collaborate in providing excellent care and cutting-edge research. Scheduled to start treating patients in autumn 2017, HollandPTC has the ambition to become one of the worldwide leading institutes in the field of proton therapy.

The Netherlands is a worldwide leader in research oriented towards improving the treatment of cancer with radiotherapy. Erasmus MC and LUMC are important players in this field.

With the TU Delft as a third partner, a strong research partnership has been created to apply research-driven proton therapy and to contribute to the development of the next generation of proton therapy. The aims are to increase the cure rate, reduce the risk of side effects from the irradiation, and provide evidence of the benefits of proton therapy. In preparation for the arrival of the proton centre HollandPTC, a joint research program has been launched in Delft, Leiden and Rotterdam.

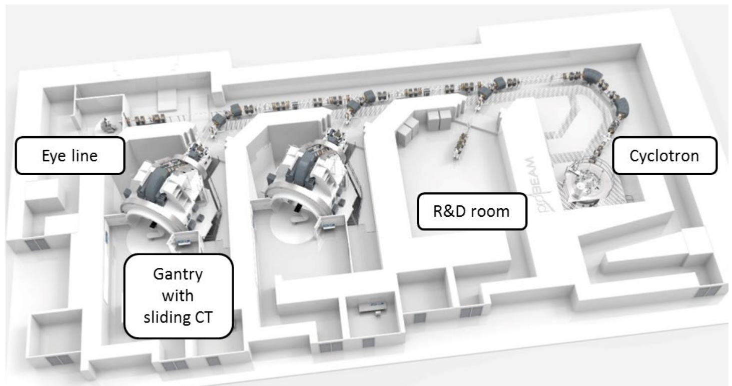
The treatment in HollandPTC will take place through the affiliated medical centres (Erasmus MC and LUMC). Patients will visit the facility in Delft for preparation and daily treatment sessions. To support high-level patient care and research, HollandPTC will be equipped with two gantries, each with an in-room sliding CT scanner. A Dual-energy CT, a 3-Tesla MRI, and a PET-CT scanner will be available for imaging for treatment planning and follow up. In addition to the two gantries, the centre will have a dedicated station to treat ocular tumours. The multi-room set-up of HollandPTC also features a separate R&D beamline, allowing research to be carried out without disrupting the clinical treatment of patients.

For HollandPTC and the partners, their objective is to contribute to ground-breaking research that is focussing on improving the treatment precision, by developing and applying advanced imaging and treatment adaptation techniques, and as well as carrying out clinical studies. The research programme, which also aims to enhance the biological effectiveness of proton therapy by the development of biology-guided proton therapy, has been structured on six pillars (see inset).

TREATMENT PRECISION

One of the priorities of both the clinical and the research programme of HollandPTC is the application of advanced imaging and treatment adaptation to enable more precise treatment with protons and to improve sparing of the surrounding healthy tissue. The strength of proton therapy is that the protons can be precisely directed so that there is minimal dose delivered behind the tumour – this is in contrast to radiotherapy with X-rays. However, this treatment is particularly sensitive to anatomical changes during irradiation. Such changes may occur at different time scales within a few weeks, a few days or even a few seconds. Major lines of research are therefore:

- Online and offline compensation for anatomical changes using high-quality imaging and automated treatment plan adaptations.
- Design of irradiation plans that are robust against anatomical changes.
- Development of detectors and methodologies to evaluate the quality of dose delivery during the irradiation.
- Inclusion of biological information in the optimization and adjustment of the irradiation plans (for example, to adjust for variations in the radiation sensitivity of the tumour).



Artist's impression of the interior structure of the centre

HOLLAND PTC TIMELINE

2013

The Dutch Minister of Health, Welfare and Sport granted a treatment permit to HollandPTC, within the framework of the Special Medical Procedures Law in December 2013.

2014

The European Investment Bank (EIB) guaranteed a loan of **90 million Euros** for the construction of HollandPTC in May 2014.

After a European tendering procedure, **Varian Medical Systems** was selected to supply, install and maintain the proton therapy equipment for the planned centre, as well as to participate in a joint research program.

2015

Construction of the building in Delft started in May 2015 with '**Ready for Equipment**' status reached **one year later: this represents a world record for this type of building**.

2016

O**n 10 May 2016 the cyclotron was installed.** It is planned that the first patients will be treated in the autumn of 2017.

CLINICAL STUDIES

A second priority is conducting of clinical studies with the aim to learn more about the effect of the treatment on the tumour and the surrounding healthy tissue. This also includes research on predictive modelling of clinical outcomes used for patient selection, including big data analytics, development of decision support systems, and cost-effectiveness studies of photon and proton therapy. For the latter - apart from the actual treatment costs - the societal costs will be also estimated, by means of prospectively collected questionnaires on long-term side effects and quality of life, and used for final cost effectiveness analysis. Finally, clinical outcomes will be made available as input for the decision Support Systems (physician facing) and Shared Decision Making systems (joint physician-patient facing), which can be used to support the choice between proton and conventional photon therapy. In addition, we will be testing in a randomized setting whether dose escalation made possible by the use of proton therapy, improves the clinical outcome for selected indications.

EDUCATION

HollandPTC will provide education and training in the field of proton therapy for clinicians (radiation oncologists), medical physicists, radiotherapy technicians and technical staff. In addition, graduate and PhD students will be trained within the research team of the centre.

A team of experienced radiation oncologists and medical physicists specialized and trained in the use of protons is currently being put together.

The consortium is open to the participation of additional centres willing to contribute to research, education and patient care. For more information please **contact info@hollandptc.nl**

THE RESEARCH PROGRAM AT HOLLAND PTC IS DIVIDED INTO THE FOLLOWING PILLARS:

1 Technology for the next generation of proton therapy: To increase the geometric, dosimetric and biologic precision of proton therapy by developing technology for high-precision image-guided and biology-guided online adaptive proton therapy.

2 Imaging for biology-guided adaptive proton therapy: To develop and clinically and pre-clinically validate quantitative imaging biomarkers for pre-treatment characterization and response assessment of the tumour and healthy tissues.

3 Implementation and evaluation of new technology: To implement and evaluate innovations in clinical practice in HollandPTC realizing the next generation of proton therapy.

4 Radiobiology: To improve mechanistic understanding of DNA damage repair and to exploit this understanding to enhance the effectiveness of proton irradiation.

5 Predictive modelling, big data analytics, decision making, economics: To develop knowledge on the optimal clinical indication of proton therapy, integrating patient's characteristics and preferences, cost-effectiveness analysis and predictive modelling of complications for photon and proton therapy.

6 Clinical trials: To provide level-1 clinical evidence of the currently theoretical benefit of proton therapy compared to the best possible photon treatment available at the moment.

Installation of the cyclotron. © Levien Willemse

Installation of the cyclotron. © Levien Willemse

DEVELOPMENT OF THE GRONINGEN PROTON THERAPY CENTER

By Hans Langendijk and Sytze Brandenburg, University of Groningen.

The very first plans for proton therapy in Groningen date back to the early 1990s when the superconducting AGOR cyclotron, delivering 190 MeV protons, became operational at the Kernfysisch Versneller Instituut (KVI) in University of Groningen.

The publication of an evaluation of proton therapy by the Dutch Health Council in 2009 marked the vigorous revival of the project to establish a clinical proton therapy facility at the University Medical Center Groningen (UMCG). A decision-making process at national level culminated in a plan for making this cancer treatment accessible to the whole Dutch population. In particular, in 2012 proton therapy was integrated in the basic healthcare package in the Netherlands and UMCG was given a license to deliver this treatment at the end of 2013.

In the meantime, the development of the specifications for the proton therapy facility had also been completed, so that the selection of the manufacturer for the proton therapy equipment (cyclotron and two gantries with pencil beam scanning) and of the company that would construct the building could be completed before the summer of 2014. After extensive preparation, which also had to take into account new building regulations related to the risk of significant earthquakes caused by the exploitation of the large gas reserves in Groningen, construction activities started at the beginning of 2015.

After completion of the building and factory acceptance of the cyclotron in July 2016, the installation of all the equipment is progressing according to the planned schedule. The arrival of the cyclotron on 5 October 2016 was a major and spectacular milestone on the route towards the commissioning of the facility, which will start operation with beams before the end of the year. The treatment of the first patients is scheduled for the last quarter of 2017.

On the clinical side the preparations are also well underway. Additional staff with substantial proton therapy experience has been recruited to strengthen in particular the medical physics team, an integrated treatment planning platform for both photons and protons (the proton therapy center will be an integral part of the UMCG Radiation Oncology department that annually treats more than 4500 patients with state-of-the-art photon therapy) has been acquired and all the quality assurance (QA) tools put in place.

The selection of patients to be treated with protons instead of photons will be based on an assessment of the benefit for the

PROJECT TIMELINE

Positive decision by board UMCG

Jan 2015

Start facility construction

May 2015

Start equipment installation

Sept 2016

First patient treatment

Dec 2017

GRONINGEN PTC

After extensive preparation, the construction of the proton therapy centre of Groningen started at the beginning of 2015.

PARTREC DIAGRAM

PARTEC THEMES	**PARTEC Technology**	**PARTEC Imaging**	**PARTEC Clinics**	**PARTEC Biology**	**PARTEC Economics**
	Prediction, prevention and treatment of normal tissue damage				
PARTEC PROGRAMS	Motion mitigation	Toxicity imaging	Model-based clinical validation	Organoids	HTA
	Adaptive proton therapy	Target imaging	NTCP models	Mechanisms of RT damage	
	MR Protons	Prognostic imaging	Clinical studies (Phase I, II and III)	RBE normal tissues	
		Recurrence analysis			

individual patient, based on photon and proton therapy planning comparison, the so-called model-based approach. This is accepted as an alternative evidence-based methodology in which patients are selected for proton therapy on the basis of the expected difference in toxicity profiles between protons and photons, which can be estimated by translating differences "in dose" distribution (delta-dose) to differences "in toxicity risk" (delta-NTCP) by using Normal Tissue Complication Probability (NTCP) models. The protocol for this selection procedure has been developed by UMCG and will be used in all proton therapy centers in the Netherlands. In addition, all patients will enter a long-term follow-up programme that will allow experts to evaluate the benefit of proton therapy in terms of long-term radiation-induced side effects.

On the research side, the UMCG Radiation Oncology department established together with several other UMCG departments (Radiology, Molecular Imaging, Radiobiology and Medical technology assessment) and the KVI-Center for Advanced Radiation Technology (KVI-CART) of the University of Groningen the Particle Therapy Research Center (PARTREC), which has a coordinated comprehensive research programme to further improve the quality and effectiveness of proton therapy. The joint expertise of the PARTREC partners covers essentially all domains relevant to proton therapy and the centre can count on the access to a large range of facilities, including an experimental room at KVI-CART where high-energy beams of protons, alpha-particles and carbon ions are available.

ZON-PTC IN MAASTRICHT

By Frank Verhaegen

The most recently fully-approved proton radiotherapy centre in the Netherlands will be built in the Brightlands Maastricht Health Campus in Maastricht, which sits at the very south of the country, close to Belgium, Germany and Luxemburg. Called ZON-PTC (Zuid Oost Nederland Protonen Therapie Center) the centre is affiliated with MAASTRO Clinic and Maastricht University Medical Center (MUMC).

It will complement the larger proton radiotherapy centres of Groningen, in the north, and Delft, on the coast, but will be smaller, equipped with only one gantry and no fixed beamline. Its aim is to treat about 400 patients per year after ramping up during the first few years. Construction of the facility will start this year and the first cancer patients are expected to be treated in 2018. Besides following the already approved standard criteria (base of skull tumours and pediatric cancers), patients will be selected for treatment using the government approved Dutch model-based selection approach (e.g. for lung, breast, head & neck and prostate cancer).

The single-gantry of ZON-PTC will consist of a Mevion device in which a 230 MeV proton cyclotron is mounted on a gantry. The facility will be one of the first Mevion centres to be equipped with an ultra-fast scanning proton beam, the Hyperscan system with adaptive aperture technology, including a micro-multileaf collimator, to reduce the lateral penumbra. A 3-D imaging apparatus, either a diagnostic CT or a cone-beam CT scanner, will be available in the treatment room. The treatment planning systems are still to be chosen. For contouring and dose calculation, ZON-PTC will have easy access to the imaging equipment of MAASTRO Clinic and MUMC, which consists of several MRI scanners (up to 9.4T), 2xPET/CT, PET/MRI, dual-energy CT scanners, etc.

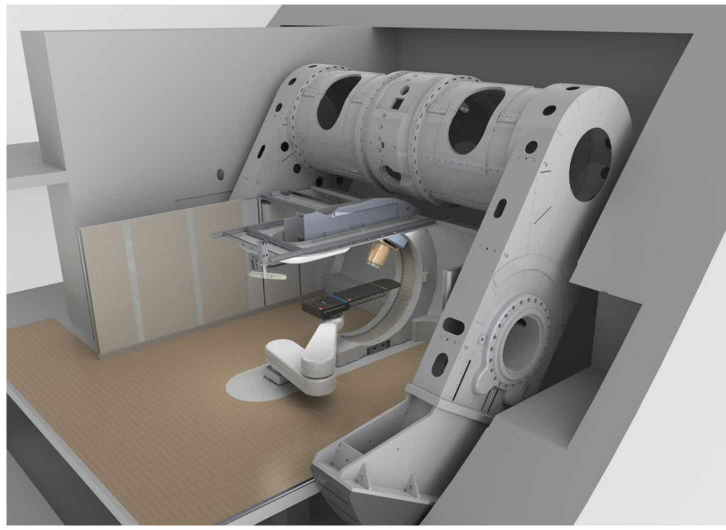
The new proton irradiation equipment will be installed in the existing facilities of MAASTRO Clinic so no extra budget will be needed for building a new expensive surrounding structure. For the new proton facility , one and a half of the presently existing photon bunkers will be demolished and some existing machinery will be relocated. In this way proton therapy will be fully integrated in a 'classical' photon-based radiotherapy department, which has not been the common practice in the past.

Besides performing clinical trials for the tumour sites mentioned above, Maastricht University in collaboration with ZON-PTC will start research on imaging methods for range verification and treatment planning comparisons of radiotherapy with photons, protons and carbon ions (an extension of the ROCOCO study running at MAASTRO Clinic). Research activities are also ongoing to develop a large-scale system for rapid learning health-care and decision support systems, which will be used nation-wide. Extensive preclinical studies with proton beam using novel cancer models are also being planned, in analogy with the ongoing work with precision photon beams.

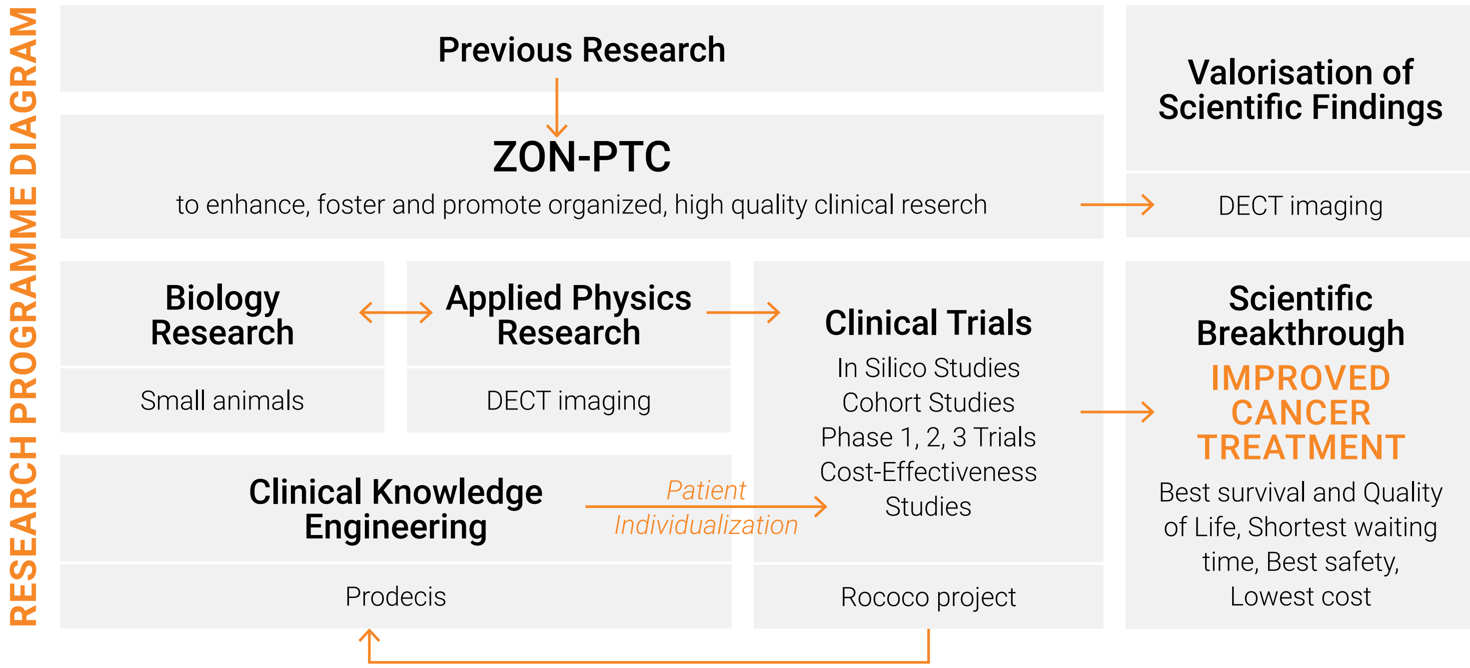
This project has been under consideration for more than ten years and at MAASTRO Clinic we are delighted that finally it is now starting to become reality.

The single-gantry of ZON-PTC will consist of a Mevion device in which a 230 MeV proton cyclotron is mounted on a gantry.

The new proton irradiation equipment will be installed in the existing facilities of MAASTRO Clinic. One and a half of the presently existing photon bunkers will be demolished and some existing machinery will be relocated.



The facility will be one of the first Mevion centres to be equipped with an ultra-fast scanning proton beam.



PROJECT TIMELINE

> “Radiation quality is the parameter that takes into account the way energy is delivered: for some types of radiation the energy release is very dense and concentrated along the track of the particle, while for others the ionization is more sparsely distributed. These characteristics produce different biological effects.”

THE MEDINET PROJECT

and the role of radiation quality in ion-beam therapy

by Giulio Magrin, EBG MedAustron, Ion-beam therapy centre, Wiener Neustadt

The members of MediNet network during the kick-off meeting in Munich, in May 2016

MediNet is a Networking Activity financed by the EU Horizon 2020 program in the framework of the ENSAR2 project, which focuses on nuclear-physics fundamental and applied research. Starting in March this year and continuing until February 2020, MediNet activities are dedicated to the optimization of diagnostic and radiation therapy, and in particular to ion-beam therapy.

Under the umbrella of MediNet, two distinct and complementary pillars have been defined. The first deals with instrumentation research for radiation therapy focusing on large-area transmission detectors, non-destructive beam intensity measurements, beam-delivery methods, imaging technology for proton and ion radiography and tomography, in-situ PET systems, prompt-gamma imaging detectors, vertex imaging, and reliable online dosimetry.

The activities of the second pillar focus on radiation quality for ion-beam therapy, including software and hardware tools such as MonteCarlo codes, tissue equivalent proportional counters, and solid-state microdosimeters. It also covers studies on cell signalling, biological dosimetry, and bio-compatibility for new insights on biological effectiveness.

WHAT IS RADIATION QUALITY?

Radiation quality is the parameter that takes into account the way energy is delivered: for some types of radiation the energy release is very dense and concentrated along the track of the particle, while for others the ionization is more sparsely distributed. These characteristics produce different biological effects.

To describe radiation quality we can use its original definition, according to which it is the type and energy spectrum of each radiation component in a specific irradiation point. Simple in its expression, this definition is indeed very problematic in its use. For instance, to describe the radiation quality in a small volume of a tumour treated with carbon ions, we should be able to measure the energy spectra of carbon ions, each of the ions resulting by the fragmentation of carbon, neutrons, and gamma rays crossing that volume. These measurements are extremely challenging and practically unfeasible, also taking into account that the radiation quality should be assessed in many different points for each tumour target.

The more usual ways in which the radiation quality is “specified” is via linear energy transfer or LET values, or via microdosimetric quantities. The use of the verb “specify” was introduced 60 years ago by Harald Rossi, when he described his newly invented microdosimeters, and it remains today to define the radiation quality in terms of LET or microdosimetric quantities. In the most commonly applied fashion, a single number, indicating the mean value of LET or the lineal energy, can be used to specify the radiation quality in each point: this simplifies the description but also omits important information contained in the spectra.

Within the spirit of the EU networks, MediNet’s second pillar is joining forces, first to establish the state of the art of hardware and software for radiation quality in ion-beam therapy, and second to design a roadmap for the implementation of radiation quality to different phases of clinical practice.

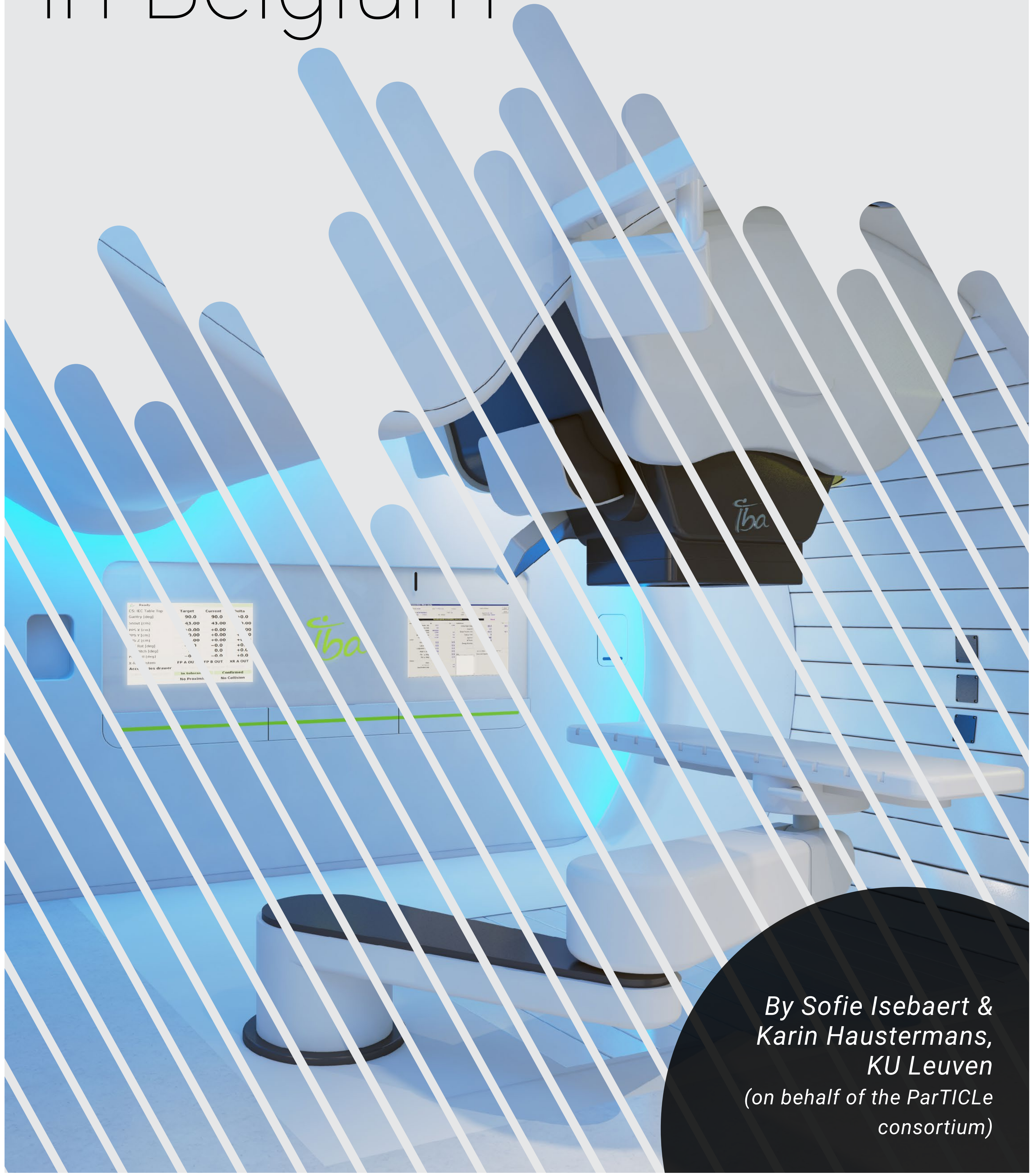
One criticism we frequently receive concerning the research in radiation quality or microdosimetry is that the concepts, the instrumentation, and the computational means we use are all consolidated tools, developed several years ago. This is, in general, not the case. Novel instrumentation must be studied specifically to operate at the intensity of therapeutic ion beams (solid-state diodes were recently developed for this reason and now they can complement, and in many cases substitute, the traditional tissue equivalent chambers). Fundamental concepts as the definition of the “most significant size” have not reached universal consensus (nanometric sites instead of micrometric sites are frequently indicated as fundamental for the investigation). The simulations tools of nuclear physics do not completely cover the characteristics of the therapeutic ion beam (the cross sections of the nuclear reactions are limited for compounds and for low energy).

During the next three and a half years, with the help of the ion-beam therapy communitywe will address these topics and some key questions,.. Among the others, these are the questions we will try to answer:

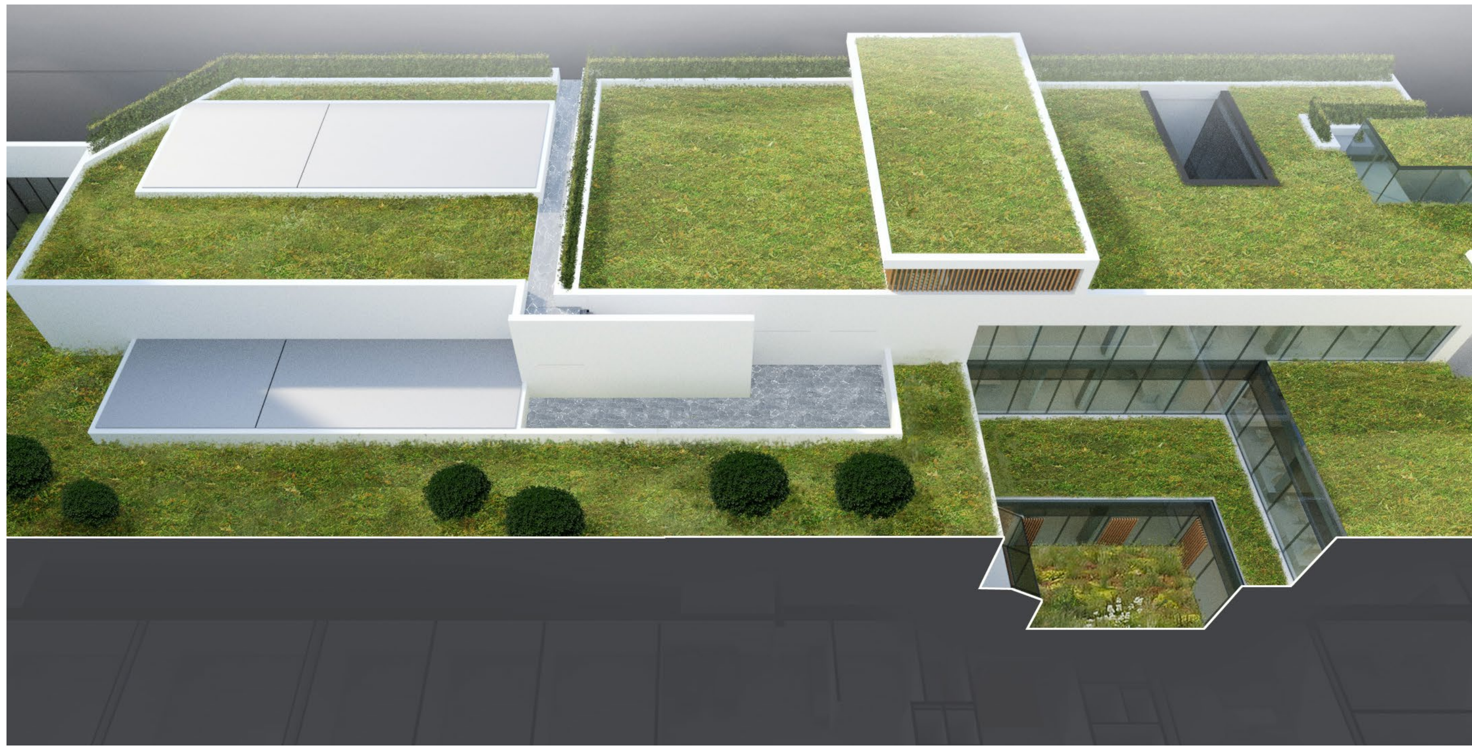
- Is it feasible to think at a specification of the radiation quality using spectra instead of simple mean values?
- Should we aim to specify the radiation quality with direct measures during treatment or should we consider a less challenging scenario in which the tools are used during the treatment preparation with the help of phantoms?
- In order to correlate LET to biological effectiveness how important is the recognition of the particle types that produce that LET?

The ENLIGHT network is the obvious place to have these discussions as knowledgeable feedback can be provided for the optimization and the prompt implementation to the medical practice of the instruments and the methodologies investigated by MediNet.

THE INTRODUCTION OF ParTICLe in Belgium



By Sofie Isebaert & Karin Haustermans, KU Leuven
(on behalf of the ParTICLe consortium)



Artist's impression of the exterior of ParTICLe

Proton therapy, the most common form of charged particle therapy, is on the march in Europe. The recent rapid growth of centres equipped to deliver this treatment is allowing an increasing number of patients to take advantage of this technology. Such a huge interest in proton radiation therapy is motivated by the increased clinical experience and availability of clinical data that support the use of proton therapy, as well as extensive research in physics, biology, and clinical aspects of proton therapy, which leads to new technological developments. In addition, proton therapy is becoming more in reach thanks to the development of compact systems with a smaller footprint and available at a lower cost.

In Belgium, however, this treatment is not yet available and patients with clear indications for proton therapy - such as uveal melanoma, tumours of the skull base, paraspinal tumours and certain tumours in children - are still being referred to centres in neighboring countries which can deliver this treatment.

A consortium of UZ Leuven/KU Leuven and Saint-Luc/UCL, strongly supported by UZ Ghent, UZA and UZ Brussels and their respective universities, decided to join forces to build the first proton therapy centre in Belgium, within the context of a solid medical, scientific and strategic alliance with all interested centres and partners. This interuniversity, multi-institutional collaboration is called ParTICLe, i.e. Particle Therapy Interuniversitary Centre Leuven.

The proton centre will be located in the city of Leuven, at the Health Sciences Campus Gasthuisberg of the University Hospitals Leuven. This location at the centre of the country will ensure easy accessibility to the facility both to patients and to collaborators coming from Belgium or abroad.

It also allows the proton centre to be fully integrated within the existing clinical and research environment of an academic hospital. In particular, it is situated in close proximity to the existing Radiation Oncology Department, Radiology Department, Medical Imaging Research Centre and Nuclear Medicine Department. The location also allows for experts in the relevant disciplines to share their expertise and to make available their research infrastructures (e.g. the PET-MRI scanner).

The centre itself will encompass two main areas: one for patients' treatment and one dedicated to research purposes. In the clinical area a Proteus®ONE system capable of pencil beam scanning – the latest technological leap in proton beam delivery techniques – will be installed to provide the full scope of imaging modalities (kV-kV, CBCT), including an in-room dual energy CT on-rails. The research bunker will host a horizontal beam line consisting of a modular set-up in order to accommodate different experiments.

The two sections will each have its own accelerator, i.e. a superconducting synchrocyclotron (S2C2). This implies that the research room will be able to function independently from the clinical treatment one. This unique set-up offers several important advantages: there will be no need to perform the experiments outside treatment hours (evening, night or weekends) to avoid interference with the clinical workflow. Conversely, beam ramp-up and ramp-down time in the clinical gantry room will not affect experiments to be performed in the research area. Furthermore, it will be possible to leave complex experimental apparatus in position for an extended period of time.

Construction work is currently ongoing and clinical activity is foreseen to start mid-2019. Besides treatment of patients and development of a proton-specific research program, the centre will also be used for educational purposes (academic and non-academic).

IMAGE GUIDED AND ADAPTIVE PROTON RADIOTHERAPY for Moving Targets

By Antje-Christin Knopf, Groningen

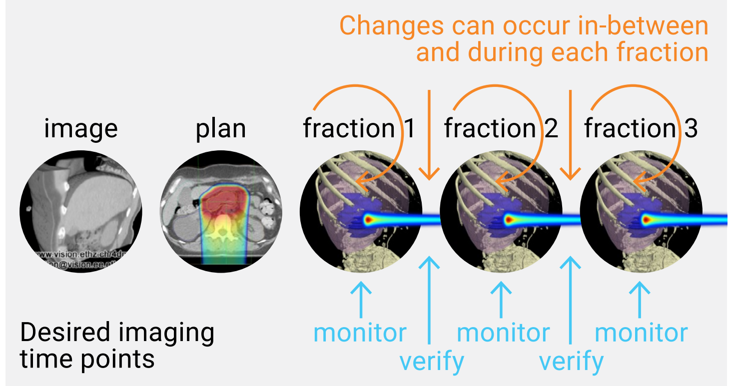


Figure 1: When treating moving targets with scanned proton beams, imaging is desired before and during each fraction.

Thanks to some key technological advancements, radiotherapy treatments have become more and more precise over the last years. In particular, intensity-modulated proton therapy (IMPT) allows for highly conformal target dose delivery while minimizing the dose to the surrounding normal tissue. However, highly conformal dose distributions are particularly prone to uncertainties. Therefore, especially in proton therapy, very precise images are required for treatment planning and image guidance during treatment delivery.

Conventionally, computed tomography (CT) images acquired a few days before starting the therapy are used for treatment planning. In the treatment room itself, image capabilities are usually limited. To verify the patient geometry and control changes occurring over time (e.g., weight loss or tumour shrinkage), it is desirable to perform imaging just prior to dose delivery, preferably for each fraction of the treatment.

Anatomical changes can also occur during each fraction (e.g., due to bowel gas movement, heartbeat or respiration). Scanned proton beam delivery is especially sensitive to these intra-fraction changes as they can result in interplay effects (highly inhomogeneous dose distributions in the target region). Therefore, imaging is not only desired before each fraction, but ideally it should also be performed during treatment delivery in order to monitor the patient geometry, as illustrated in Figure 1.

The treatment of moving tumours is a key objective at the new proton therapy facility at the University Medical Center Groningen (UMCG), which will start clinical operation in 2017. The center will be equipped with an IBA ProteusPLUS two-gantry room configuration, including next-generation Pencil Beam Scanning (PBS) and Cone Beam CT (CBCT) capabilities.

For the treatment of moving targets, an image-guided and adaptive work flow, as sketched in Figure 2, is foreseen. Treatment planning will be based on 4DCTs, considering the patient specific motion during 4D robust optimization. Before delivery of each fraction, 4DCBCT imaging could be performed to verify robustness settings. During each fraction, the dose delivery can be recorded in a log-file and patient movements monitored with the help of an ANZAI belt. This time-resolved information will then be used to perform subsequent 4D dose accumulation. Treatment plan adaptation can be introduced either if the assumed robustness limits are no longer valid or when the 4D accumulated dose exceeds predefined limits.

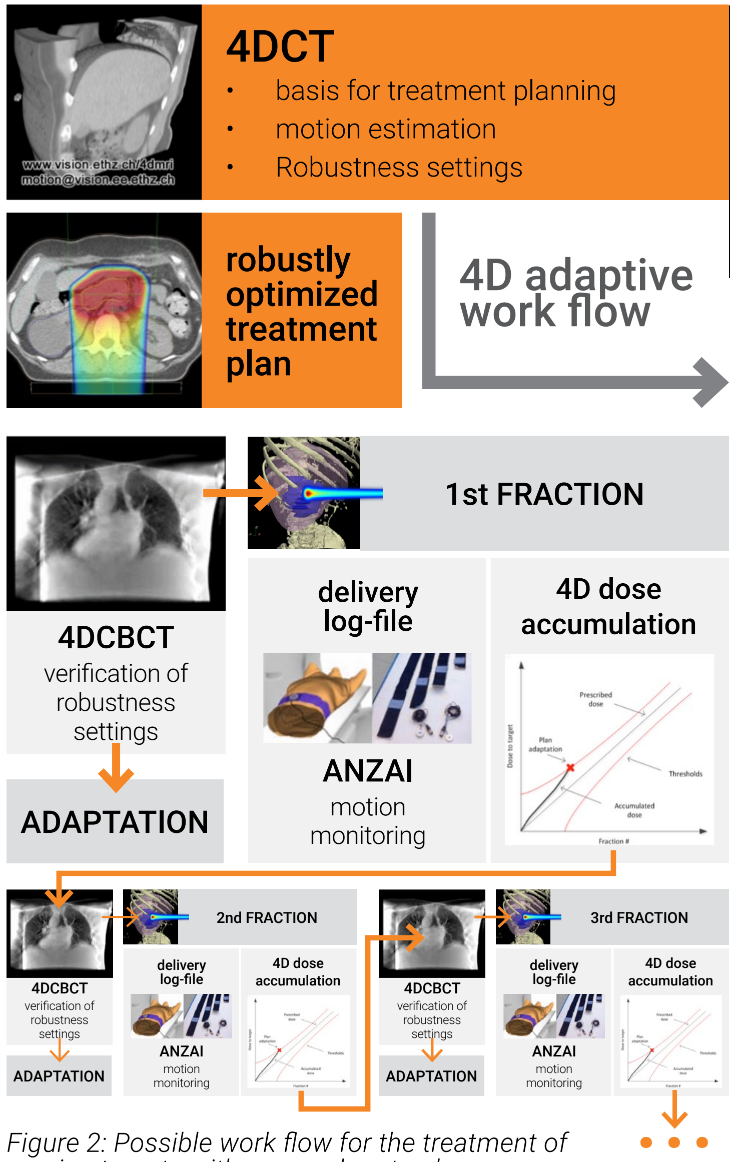


Figure 2: Possible work flow for the treatment of moving targets with scanned proton beams.

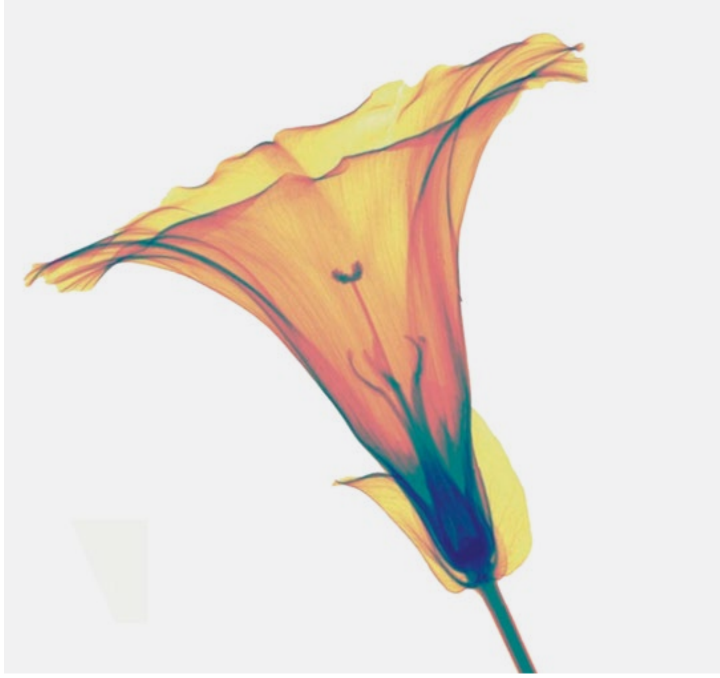
In general, current online imaging and monitoring options for proton therapy facilities encompass 1D surrogate monitoring (e.g., ANZAI, RPM, calypso or fluoroscopy), 2D surrogate monitoring (e.g., VisionRT) and CBCT imaging. None of these options allows for real-time 3D imaging of the whole region of interest. The best modality would be magnetic resonance (MR) as it provides images with excellent soft-tissue contrast at no cost in imaging dose.

In conventional photon radiotherapy, the first MR-radiotherapy-hybrid-machines that enable 3D imaging and dose delivery in close temporal proximity (or even simultaneously) are being developed. These machines are believed to be particular beneficial for treating moving targets, as they provide a 3D-motion-feedback, enabling real-time-target tracking. Currently, the first MRI-Linac machines combining a 1.5T MR and a conventional Linac have been installed.

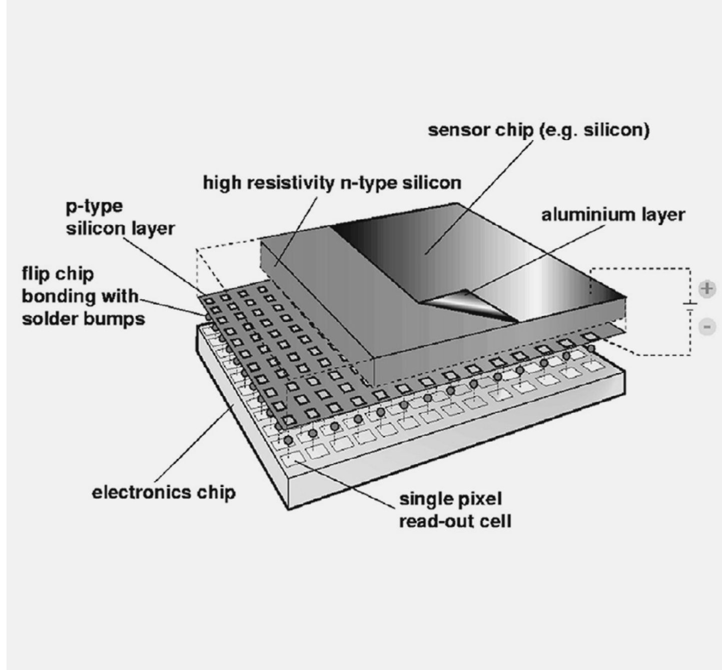
A hybrid MRI-proton therapy system is not available yet. There are many technical hurdles to be taken to realize such a machine. MR-guided proton therapy will be one research focus at the new proton center at UMCG in the upcoming years. We will look into the potential and challenges of an integrated MR-proton machine in order to lead the way toward an even more advanced image-guided and adaptive treatment approach for moving targets.

MEDIPIX BASED IMAGING DEVICES at Nikhef

By Jan Visser and Els Koffeman, Nikhef, Amsterdam



X-ray CT of a flower

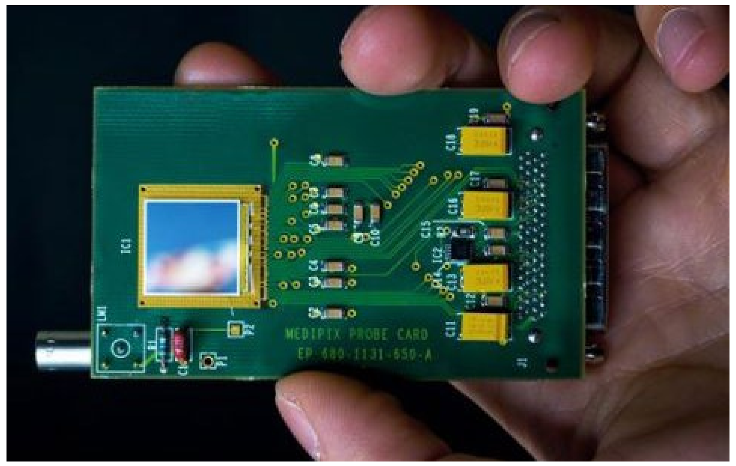


Medipix 2 chip diagram

With a strong expertise in detector R&D and chip design, Nikhef has been and still is one of the key institutes of the Medipix collaboration. Over the last decade, researchers at Nikhef have investigated a number of medical imaging applications with Medipix devices. One of the most recent highlights, especially relevant to the ENLIGHT community, is the development of a proton radiography detector.

In a small time projection chamber (TPC), the individual protons are tracked both in front of and behind the object under study. The trajectory of the protons in the gas of the TPC is relatively unhindered and can be accurately reconstructed. The actual energy loss of the protons in the object under study is determined using a calorimeter.

The time projection chambers developed for this purpose are based on Timepix chips with Gridpix technology. Gridpix consists on an amplification grid mounted on top of the dedicated front-end chip. This technology was first proposed and tested at Nikhef. The Timepix3 chip originates from the Medipix design and stands out with its time resolution of 1.6 ns. This fast time stamping allows the reconstruction of 3D proton tracks from the entrance to the exit points of the protons in a phantom.



The Medipix chip installed on a Probe Card.

By knowing the trajectories of the protons and the deposited energy, we can produce a radiograph that provides intrinsically relevant information on the stopping power distribution within the phantom. This method is a priori more precise than calculations with X-ray computed tomography data. The extra precision should result in treatment plans with smaller error margins and, thus, in a reduced volume of healthy tissue being irradiated.

Another imaging modality that is being developed at Nikhef is energy-resolving X-ray imaging with the Medipix3 chip. The research conducted on this topic is divided into two branches: mammography and computed tomography reconstruction algorithms. In mammography, researchers at Nikhef have shown that, using the energy information in addition to the number of detected photons, more micro-calcifications can be identified than with the current state-of-the-art systems used in hospitals. This should reduce the number of false negatives where potential breast tumours are not found in the screening process. As a result, tumours should be identified at an earlier stage and require less drastic treatment procedures, making it possible to improve the survival rate.

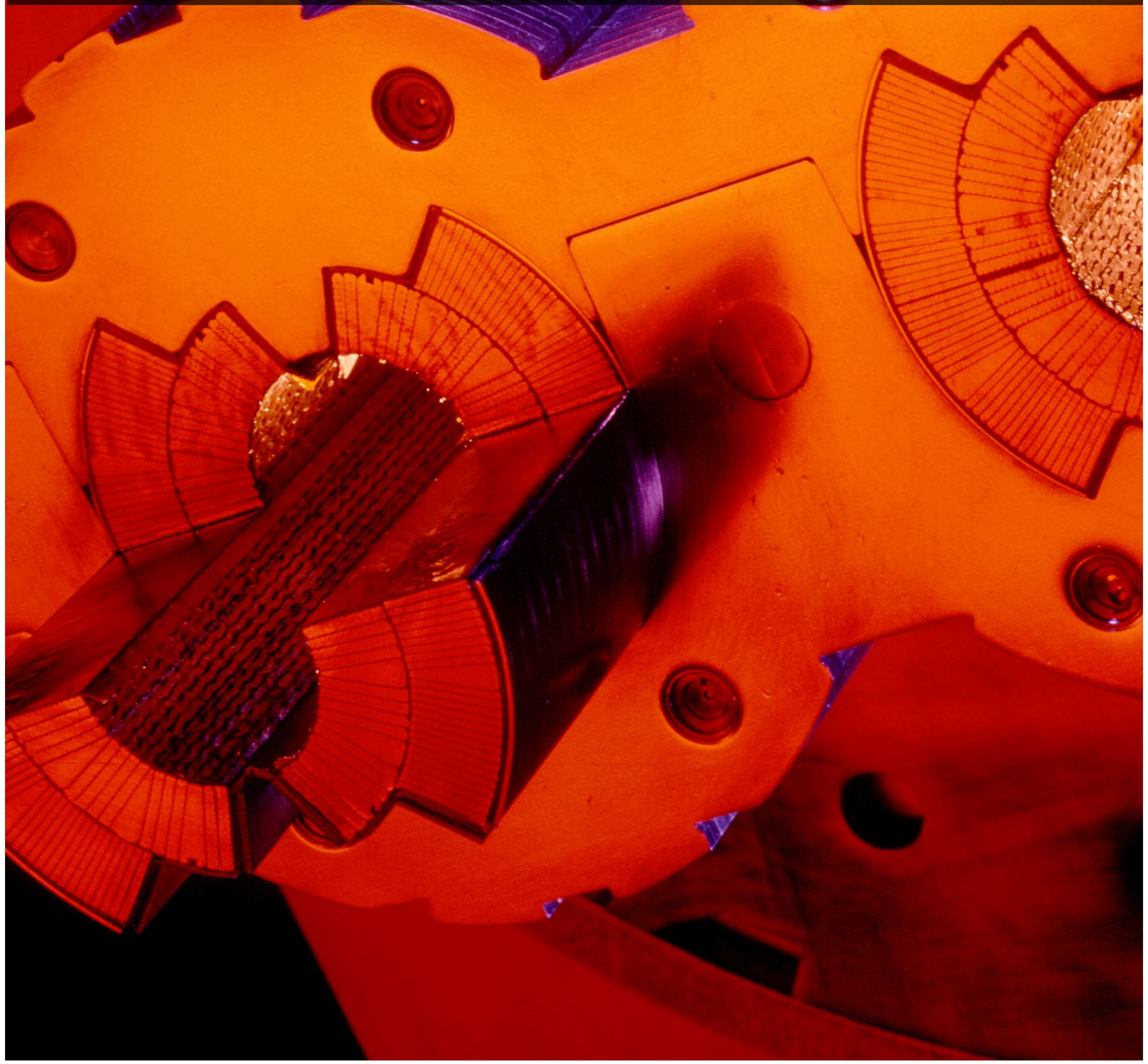
The work on computed tomography reconstruction algorithms was started a few years ago and aims to implement the energy information in the initial phase of the algorithm. This spectral CT can be used in a number of industrial applications where it is required to identify different materials. For medical imaging, the technique should enhance tissue contrast and reduce the effects of beam-hardening. Beam-hardening artefacts may obscure regions and thus potential tumours close to dense materials, like bone or dental implants. Providing the true image without artefacts will allow doctors more accurately to diagnose the tumours, which should reduce treatment procedures.

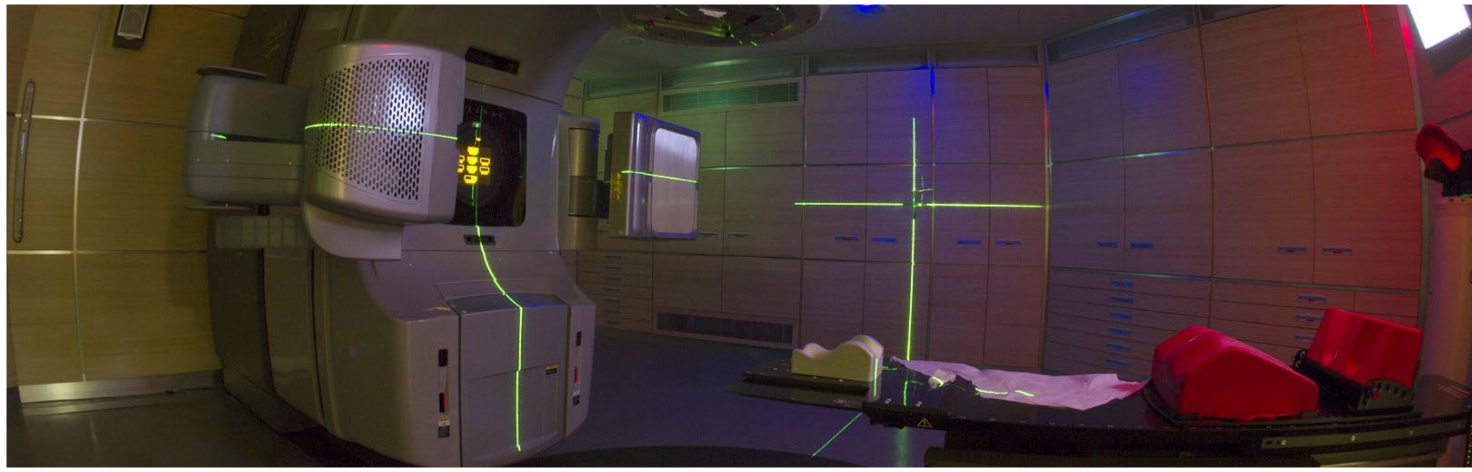
ADVANCES IN IMAGING

DIVONNE BRAINSTORMING

What are the needs of the medical field?

By Antonella Del Rosso, CERN





Treatment room, Genolier Cancer Centre, Geneva. © CERN

At the second brainstorming meeting on CERN medical applications, which took place last February, leading experts in medical physics, oncology, imaging and data processing discussed the future of this multidisciplinary field and the role that CERN can play in it.

The goal of the series of brainstorming meetings on CERN medical applications, the second edition of which was held in Divonne, France, from 19 to 21 February 2016, is to give input to the centre's management on what the medical community would need in terms of imaging for diagnostics, accelerator-based facilities and big data.

Four expert groups on particle therapy, imaging, radioisotopes and nuclear medicine, and medical data, were asked to outline the top priorities, challenges and needs from physics, radiobiology and information sciences in the coming years.

PARTICLE THERAPY

CERN has the unique capacity to produce a large range of ions from protons to higher z values, at clinically relevant energies, with a control megavoltage photon beam and with long durations of beam-time access.

The clinical priority was stated as studies on relative biological effectiveness (RBE), which would ultimately influence the precise ranges of dose compensation used in clinics when energy-transfer conditions change.

The Bio-LEIR/OpenMed project (https://cds.cern.ch/journal/CERNBulletin/2012/30/News%20Articles/1462262) was also discussed. The members of the expert group see it as an ideal facility to generate new data on RBE on a wide range of cells with different radiosensitivities. Bio-LEIR would also be a test bed for the R&D of compact and sophisticated dosimeters, linear-energy-transfer (LET) detectors, and the remote detection of positron emissions, prompt gamma emissions, and neutrons.

Besides Bio-LEIR, the experts emphasised the strong need for the community to have a common place for sharing experience, ideas, and results. CERN, with its great experience in knowledge exchange and international collaboration, could be the host place for a network, and would be part of a collaboration as member.

IMAGING

Medical imaging is a fast-developing field, and predicting the needs for the coming years is an almost impossible task. One of the main points discussed by the experts in Divonne was the new EXPLORER project and the perspectives that it opens. The EXPLORER project, funded by the US, seeks to reduce scanning times, improve sensitivity and spatial resolution, and enable the whole body to be imaged simultaneously with high temporal resolution, by constructing a whole-body PET scanner. It is anticipated that the next generation of EXPLORER will incorporate more advanced detector technology such as that being developed at CERN.

Indeed, electronics and detectors with ~10 ps resolution are under development in various collaborations around the world, including the Crystal Clear collaboration.

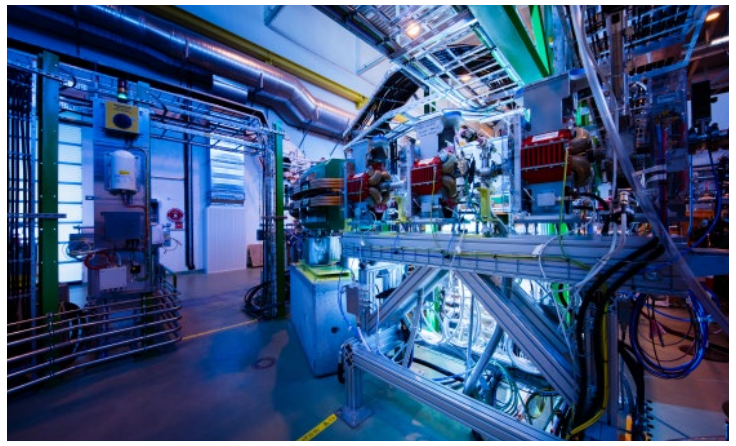
Another CERN collaboration, Medipix3, contributed to the development of the "Spectral CT", which offers the possibility of imaging several contrast agents simultaneously. In future, if combined with biomarkers using metal nanoparticles, this technique may even introduce functional imaging to CT.

Accurate dose-range determination during hadron therapy continues to be a key concern. Work continues on various techniques and, in particular, on Compton cameras. Developments in 3-gamma detection may help to improve the efficiency of Compton cameras, leading to improvements in range detection for hadron therapy. A promising approach is the tracking and tagging of charged fragments leaving the patient during ion therapy. Feasibility studies have been carried out at HIT, Germany, using Timepix as the tracking and particle identification detector.

RADIOISOTOPES AND NUCLEAR MEDICINE

CERN is constructing MEDICIS (CERN Courier November 2013 p37), a dedicated facility for the production of innovative isotopes, which are of potentially high relevance to the medical field. The members of the expert group identified the construction of MEDICIS as a high-priority project that would significantly boost the research on new isotopes. Thanks to MEDICIS, it would be possible to increase the supply of R&D isotopes such as 152Tb and 155Tb. This α emitter is often referred to as the Swiss army knife of nuclear medicine, allowing at the same

Crystal Clear is an international collaboration working on the development of inorganic scintillators, which are widely used in medical imaging.



MEDICIS will use the ISOLDE facility (portrayed in the photo) at CERN to produce specific ions to be used in innovative radiopharmaceuticals or to perform hadron therapy treatments.

time imaging by PET and SPECT and treatment of the cancerous cells.

The experts stressed the fact that the best results in this promising field would be achieved through effective collaborations with the European Spallation Source (ESS) currently under construction in Sweden, as well as with the Belgian ISOL@Myrrha. These should also be pursued in view of seeking EU funding from existing schemes.

MEDICAL DATA

This new topic was introduced this year and immediately became a main focus, first of the ICTR-PHE conference (CERN Courier April 2016 p29) and then of the Divonne brainstorming meeting.

Modern medicine increasingly relies for research, diagnoses and treatment on the use of large multifactorial preclinical and clinical data sets of heterogeneous data such as, but not limited to, images, patient history, genomics, metabolomics, proteomics, simulations, standard lab tests, and microbiome and environmental data.

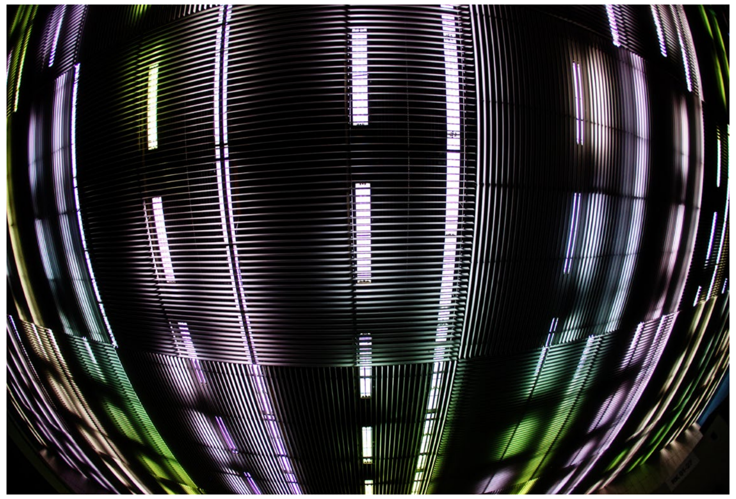
The use and combination of such data sets is an active area of research, which is anticipated to enable breakthroughs in various medical disciplines and open up entirely new interdisciplinary research fields such as personalised medicine – a medical model that stratifies patients based on all available personal data to inform patient-tailored medical decisions. Indeed, looking at a patient on an individual basis allows for a more accurate diagnostic and specific treatment plan.

CERN's contribution to these efforts could be threefold. First, it can provide the necessary computing infrastructure. Second, it can help in the development and tailoring of data-analytics software tools for the management and analysis of large preclinical and clinical data sets, for biophysical simulations and for the development of decision-support systems. And third, the open culture at CERN can be harnessed to accelerate the development of new tools for data analysis, and to promote the development of new research angles and questions.

In addition, CERN attracts numerous talented students and personnel who constitute an invaluable reservoir of skills and interest that could be harnessed for medical-data projects directly, or via hackathons or competitions of the type organised in the machine-learning community.

The two days of the meeting saw focussed and fruitful discussions. The four reports will be compiled into a single document that will be submitted to CERN's management for discussion and evaluation in the coming months.

Engineers and technicians working in one of the CERN's workshops.



CERN Computing Centre. © Andrew Strickland

DIVONNE 2016

The series of brainstorming meetings on CERN medical applications, the second edition of which was held in Divonne Les Bains (France), 19-21 February 2016, aims to give input to the centre's management on the needs in terms of technologies of the medical community.

Four working groups of experts outlined the top priorities and challenges to be addressed in the fields of particle therapy, medical imaging, radioisotopes and nuclear medicine, and medical data.

A PARTNERSHIP-MENTORSHIP APPROACH

for global access to radiation therapy

By Virginia Greco, CERN

Experts in all aspects of radiation treatment met at CERN in November 2016 to discuss possible solutions to develop affordable instrumentation and sustainable infrastructure for radiotherapy and thus increase worldwide availability of effective cancer treatment.

Participants to the Workshop on Design Characteristics of a Novel Linear Accelerator for Challenging Environments, held a CERN, 7-8 November 2016.

On 7-8 November 2016, CERN hosted a Workshop on Design Characteristics of a Novel Linear Accelerator for Challenging Environments, organized by Norman Coleman and David Pistenmaa from the International Cancer Experts Corps (ICEC) in collaboration with Manjit Dosanjh, from CERN. The participation to the event was by invitation only and reserved to about 70 internationally-recognized experts in various fields correlated to radiotherapy for cancer treatment. They met to define a strategy for increasing access to radiotherapy to a larger number of people and to discuss possible solutions for geographical areas that present economic and technological challenges as well as a quickly changing political situation.

The idea of designing affordable equipment and developing sustainable infrastructures for delivering radiation treatment for cancer in countries that lack resources and expertise is a core mission of ICEC. Established in 2013 as a non-governmental organization, ICEC has set itself as an international sustainable mentoring network of cancer professionals, whose aim is to establish partnership projects in low- and medium-income countries, as well as in isolated indigenous communities of all countries, oriented at facilitating access to radiotherapy and improving the quality of the treatment offered. This will be achieved by encouraging and supporting initiatives of local groups, providing mentorship and training, and guiding them through a number of steps to be completed in order to be recognized as high standard cancer care centres.

Leading experts coming from key international organisations, research institutes, universities, medical hospitals, and companies producing equipment for conventional x-ray and particle therapy took the stage in turns at the workshop to share their knowledge and expertise and to discuss needs, goals and possible solutions. The key topics of discussion were the technology to be employed, sustainability of the centres, and training.

An essential step that ICEC and collaborating experts have to accomplish is designing a linear accelerator and associated instrumentation needed to deliver radiotherapy that would have to be operated in places where general infrastructures are poor or lacking, power outages and water supply fluctuations can occur, and whose climatic conditions might be harsh. The ideal facility should have a modular structure, in order to be easily shipped, assembled in-situ, upgraded and repaired. The equipment also needs to have an intuitive and simple interface, such as that of a smartphone, even though it is highly technologically advanced.

A critical issue that was also discussed at the meeting at CERN was the treatment system sustainability after its installation. Technical staff is required to maintain the equipment and promptly repair it, if needed, relying on availability of standard spare parts and quick and easy replacement procedures that will be developed in order to make maintenance as easy as possible. Difficulties of displacement and communication are also to be taken into account. As a consequence, these centres could be designed following the philosophy of a space station, where astronauts have spare components available and can easily replace faulty parts as pieces of lego, with remote guidance.

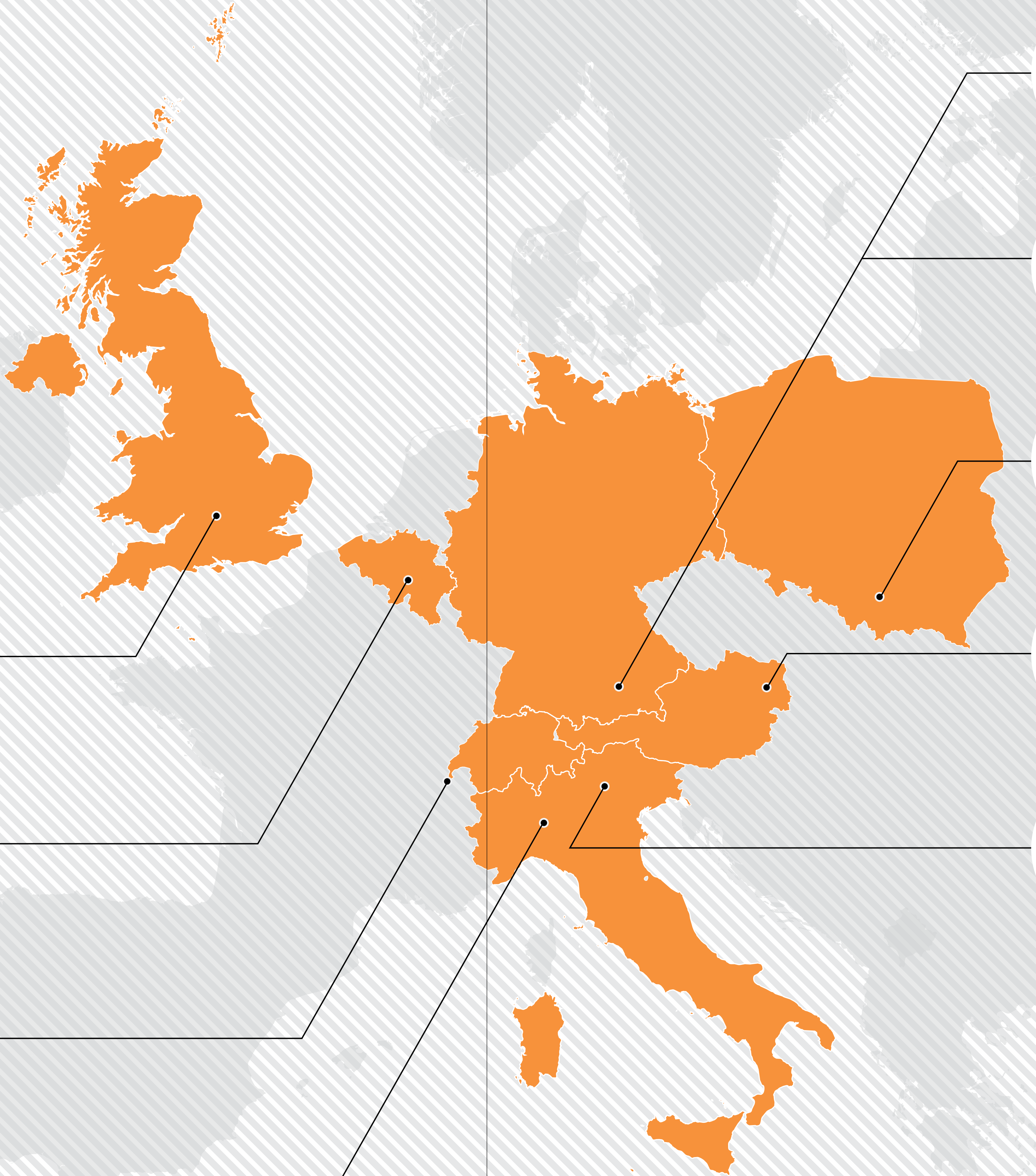
The participants to the workshop agreed that training is fundamental to make such ambitious projects possible. ICEC's strategy consists of setting up a team of mentors to guide local groups throughout the various phases of the programme. In this way, each centre located in a region with cancer treatment disparities and insufficient resources that is aiming at implementing radiotherapy would be associated with a centre in a resource-rich country, and eventually become a reference centre for other local groups willing to follow a similar path.

Professionals in oncology, radiotherapy, radiobiology, and medical physics, as well as nurses and ancillary staff, will have to be identified in order to ensure assistance to remote locations. After completion of regular academic training, the personnel of the remote centre would be mentored and trained by ICEC's experts through face-to-face lectures, periodic on-site visits and consultations via video-connection. This would ensure that, at a later stage, they would be able in turn to train future staff.

At the end of two intense days of debate and exchange of ideas, the participants have obtained a more precise picture of needs, limits and priorities, as well as a lot of input for further reflection. As a follow up, working groups will be established to address different aspects of the problem and the date for another global meeting fixed. The report emerging from the workshop will be published in various media and journals in order to highlight the initiative, extend collaboration and continue the momentum.

ENLIGHT Advisory Committee

At the 2015 ENLIGHT meeting in Krakow there was an agreement on the necessity of a core group, composed of representatives of the various technological and clinical disciplines, who will help the ENLIGHT Co-ordinator, Manjit Dosanjh, set the scientific policy of the network. The annual meeting of this year in Utrecht closed with the announcement of the members of this committee that were voted by the network members.



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