HIGHLIGHTS

June 2017

COVER
Synchrotron of the MedAustron particle therapy centre.

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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.

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FROM THE ENLIGHT COORDINATOR

Manjit Dosanjh

Did you say “issue”?

This issue of the ENLIGHT Highlights goes to press a few days before our 15th annual meeting, which will be held in Aarhus, Denmark. It is only fitting that this key event for the ENLIGHT community will be held in one of the 2017 European Capitals of Culture, as this is where a new proton therapy centre will soon come to life.

While Denmark is making its first steps in this field, the MedAustron facility in Austria has started to treat its first patients (our well-deserved cover image), the TIFPA centre in Trento (Italy) has opened a new research line and the TERA Foundation (Italy) celebrates its 25th anniversary.

Radio and hadrontherapy have made impressive progress over the last 15 years and the ENLIGHT community has played a crucial role in it. Not only have new centres been built but new topics have come under the spotlight of the scientific community. I am deliberately avoiding using the word “issue” here as I strongly believe that these are challenges that are actually nurturing the whole community. Indeed, the currently open questions about how big data are going to help our field or how our knowledge of the Relative Biological Effectiveness (RBE) of protons is evolving for the benefit of the patients, should not be seen as issues but, rather, as new opportunities and *raisons d’être* of our network. This is where we and our multidisciplinary approach to problem solving can contribute best. We will pursue this important objective also at the upcoming meeting, which will include discussions about clinical trials as well as LET and radiobiology.

This issue of Highlights also reminds us of another important aspect of our network, which is training. Onyine Belogun (a member of the International Cancer Experts Corps, ICEC) emphasises the importance of training experts who will be able to offer the best radiation-based treatments to fight cancer also in countries with a relatively low national income. This is part of a global effort which scientists worldwide are making to offer the same high standards to an increasingly large population. ENLIGHT is playing a role there too and we can proudly say that we have been emphasising the importance of sharing as widely as possible the knowledge and the best practices acquired in this complex field.

Let me take this opportunity to thank all the contributors, hoping that many more of you will be willing to share your work on these pages in the future. I hope you will enjoy this edition and look forward to seeing you in Aarhus! ■

Manjit Dosanjh

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15TH ANNIVERSARY OF ENLIGHT

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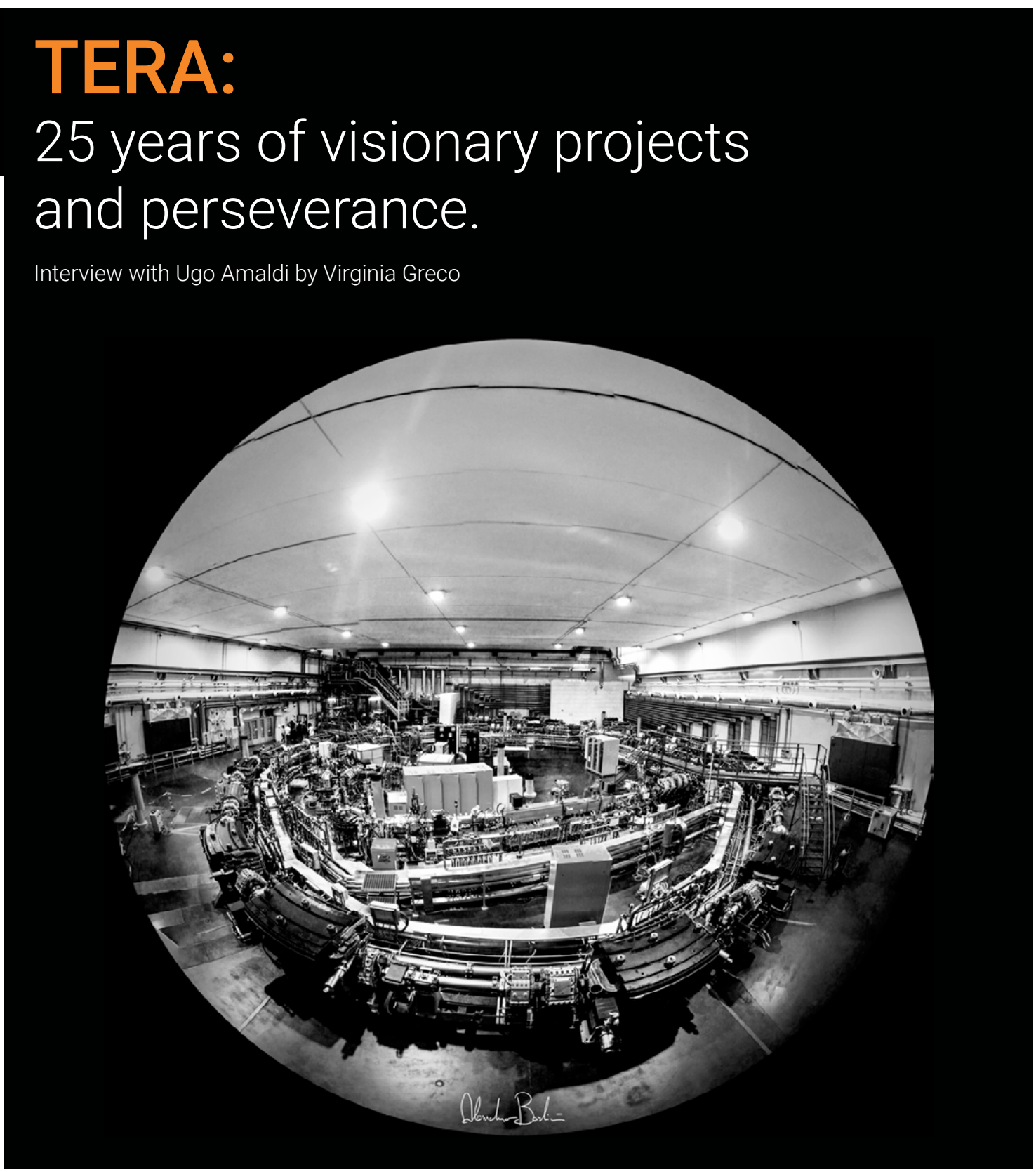
TERA:
25 years of visionary projects and perseverance.

Interview with Ugo Amaldi by Virginia Greco



The syncrotron of the CNAO facility in Pavia, Italy.
Credits: Alessandro Barbaria

In September this year the TERA Foundation, a research group dedicated to the study and development of accelerators for particle therapy, will celebrate its 25th anniversary. Its main achievement has been the design of the first carbon-ion centre for hadron-therapy in Italy, which led to the construction of CNAO in Pavia. We talked about TERA and its history with Ugo Amaldi, the mind and heart behind this great endeavour.

Professor Amaldi, over the last 25 years the TERA Foundation has played an important role in the development and diffusion of hadron therapy in Italy and in Europe in general. Could you tell us how it was born and which are the main milestones it reached?

The TERA Foundation was established in 1992 with the aim of raising money to finance research activities and the design of a centre for hadron therapy to be built in Italy and, in general, to promote hadron therapy in Europe. At that time, I had reduced

In only few months I managed to put together a large collaboration of about one hundred physicists, medical doctors, engineers and radiobiologists. We focused on the design of a synchrotron for particle therapy and the needed beam lines and monitoring systems "

Ugo Amaldi

my involvement in particle physics and I was following a project on particle therapy for cancer treatment.

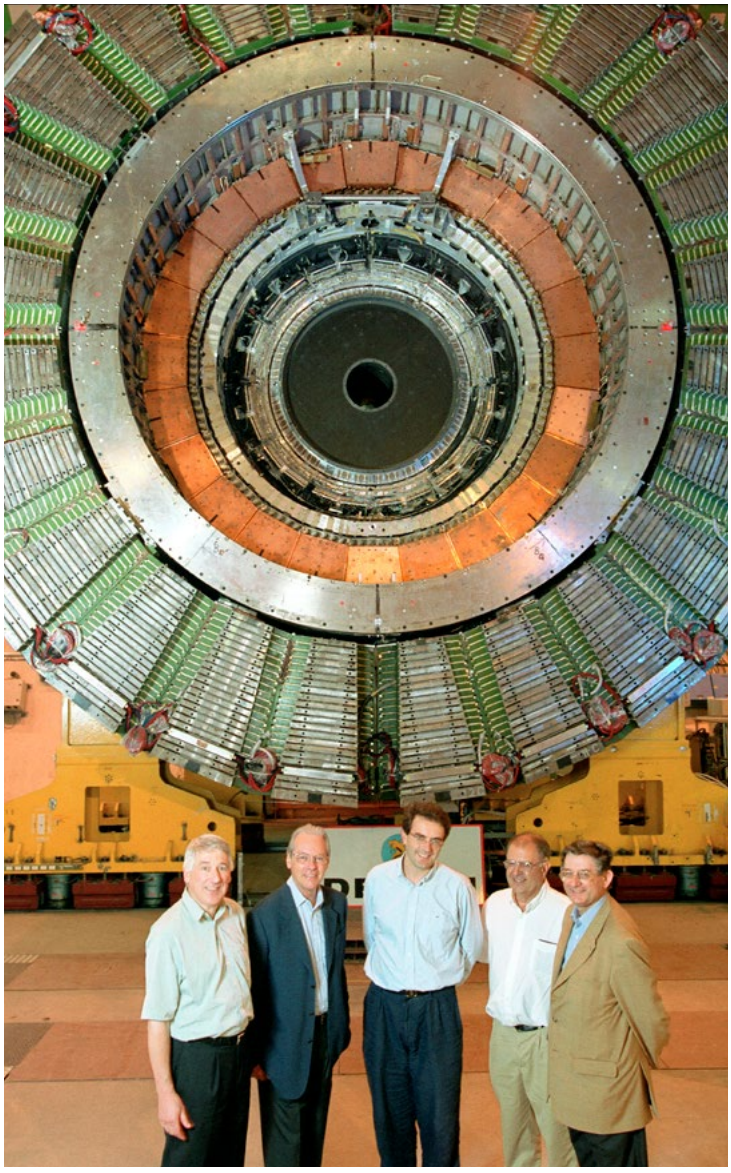
This change of direction in my career had been a consequence of various causes. In August 1990, while I was spokesperson of the DELPHI experiment at CERN's LEP accelerator, I participated in an international conference in Singapore. In a session dedicated to LEP, the spokespersons of the other three experiments – ALEPH, L3, OPAL – and myself presented our latest results on behalf of our collaborations. There I learnt with great satisfaction that DELPHI had been the first to measure the three-gluon coupling, an important result to which I had directly contributed.

At the beginning of 1991, using new LEP data my friend Wim De Boer and I published a paper on the unification of the electroweak and strong fundamental forces. Being the first scientific article on this topic, it has become a milestone in the field, as demonstrated by the fact that it has reached about 2600 citations (it's one of the most quoted articles produced at CERN).

It was clearly the time to move on to another field and face other challenges. The choice of resigning from spokesperson of DELPHI and dedicating myself to cancer therapy was in some way natural. Medical physics had been my first love, since in the early stage of my career I had worked for 15 years in the Italian National Health Institute (ISS - Rome), in particular on the effects of radiation on human beings.

In addition, in the previous years I had taught a postgraduate course on radiation physics at the Specialization School of Medicine of the University of Milan. There I became good friends with a colleague, Giampiero Tosi, a very renowned Italian medical physicist. As a consequence of various exciting discussions, we decided to write a report entitled "For a future hadron teletherapy centre", in which we proposed the design of a hospital facility for therapy with light ions and protons to be built in Italy. In the summer of 1991 I had the occasion to discuss the proposal with Nicola Cabibbo, a great Italian theoretician and President of the Italian National Institute for Nuclear Physics (INFN) back then, who liked the idea and encouraged me to go ahead with a request for funding. So we received from the INFN an initial grant, which we used for meetings, and we started working on a project called ATER (from AdroTERapia, the word I coined for this new type of radiation therapy, soon translated into "hadrontherapy" or "hadron therapy").

We needed more funding, though, to be able to pay students and researchers to design the accelerator and it was immediately clear that INFN couldn't provide any manpower. At that point Gaudenzio Vanolo, a brilliant youngster working in Novara in science communication, who I had met some years before and involved in this activity, suggested to create a foundation to raise money and build a permanent staff. Hence, in September 1992 – almost 25 years ago – TERA was born and we immediately received funding from the "Banca Popolare di Novara".



Ugo Amaldi with a group of collaborators in front of the detector of the DELPHI experiment at the LEP (CERN). From left to right: Jan Timmermans, Ugo Amaldi, Tiziano Camporesi, Wilbur Venus, Jean Eudes Augustin.

Credits: Laurent Guiraud and Patrice Loïez

Once the Foundation was established, what did you do next?
We tried to create a group of engineers and physicists who could develop our project of designing the future centre for hadron therapy in Italy: among them there were Guido Petrucci, Marco Silari, and Gianluigi Arduini, our first research fellow.

Inauguration at CERN of the first unit of the Linac for Image-Guided Hadron Therapy (LIGHT) designed by A.D.A.M. From left to right: Sergio Bertolucci (CERN), Rolf Heuer (CERN), Alberto Colussi (A.D.A.M.), Carlo Lamprecht (A.D.A.M.), Domenico Campi (A.D.A.M.), Ugo Amaldi (TERA Foundation).
Credits: CERN

In only few months I managed to put together a large collaboration of about one hundred physicists, medical doctors, engineers and radiobiologists. We focused on the design of a synchrotron for particle therapy and the necessary beam lines and monitoring systems. In 1994 we published a technical design report (the so-called "Blue Book") of such a facility, which I called CNAO (National Centre for Oncological Hadrontherapy), meant to be built in Novara. Unfortunately in 1995 the just-elected local government of the city rejected the project.

I didn't give up though and, with the help of Umberto Veronesi, a world-renowned surgeon and oncologist, we identified another place, outside Milan, where the centre could be built: the outskirts of the Mirasole Abbey. In 1996, TERA and five hospitals and oncological centers of the Lombardy Region (including the famous public National Tumour Institute and the private European Institute of Oncology directed by Veronesi) signed an agreement and –about one year later – the bylaws of a foundation. Called "Mirasole Foundation", it would have been responsible for implementing the project and building the facility.

In the meanwhile, in 1995, I thought of redesigning the accelerator for the centre.

Why? Wasn't the project published in 1994 good enough?
Well, I realized that we could make it better. First, a bit more compact; second, a machine meant for carbon ions from the beginning, while the first one had been designed for protons with the possibility to update it for carbon ions.

Thus, my collaborator Gianluigi Arduini – under the guidance of Petrucci, Silari and Pierre Lefèvre (who had designed the LEAR accelerator at CERN) took many ideas from LEAR and designed this second machine. At the end of 1996 the project (described in the so-called "Red Book") was presented to the Lombardy and National authorities, with the purpose of building the centre on the Mirasole Abbey site. Unfortunately, in March 1997, the Italian Health Minister declared that public institutions were not allowed to enter a foundation, so the plan of building this centre in the land close to the Abbey faded away. Those were very hard times.

But you didn't lose hope, did you?
No, we didn't. First of all, we kept ourselves busy with improving the project of the accelerator.

Indeed, back in 1995, while we were working on the design of the second machine, I discussed the project with Meinhard Regler, who was the coordinator of the Austrian group in DELPHI. An experimental physicist, Regler had launched the project "Austron", a sort of precursor of the European Spallation Source, to which he had dedicated a lot of time and energy. The English CERN engineer Phil Bryant was the head designer of Austron. At a certain point they decided to add to this complex a ring that would be used for particle therapy, so the name was changed to "MedAustron". They presented the project for this centre in 1995, at the time when I was looking for a place to build CNAO.

Regler and I decided to work on a common project, asking Phil Bryant to design a synchrotron dedicated to hadron therapy. That is how the idea of the Proton-Ion Medical Machine Study (PIMMS), carried out at CERN between 1996 and 2000, was born. It means that the heart of CNAO was redesigned for the third time. TERA and MedAustron contributed with 25 and 10 person-years respectively.

The National Centre of Oncological Hadrontherapy (CNAO), in Pavia.

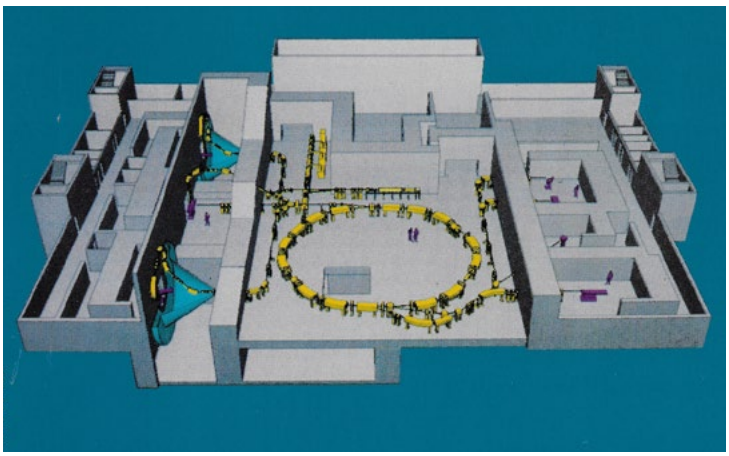
The synchrotron of CNAO.

Towards the end of this period the Government in Italy changed again and Umberto Veronesi was appointed Health Minister: this was finally a stroke of luck for us. He was absolutely supportive and in 2000, using the bylaws written for Mirasole, the Ministry created a foundation, which we called "CNAO Foundation" as the centre we wanted to build. Twenty million euros of public money were made available during the next two years for starting the construction of this nehadron therapy facility, as well as ten million for the acquisition of new linear accelerators (linacs) for conventional radiotherapy, which thanks to this could reach high quality and diffusion throughout the Italian territory, particularly in the South.

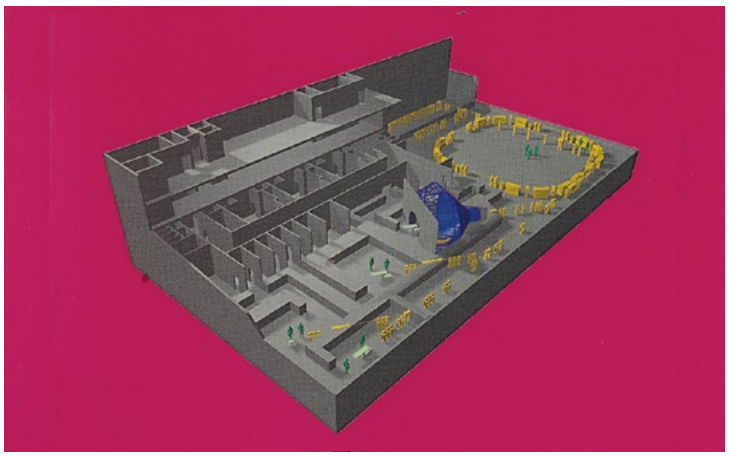
At that point, the knowledge of TERA and 80% of its manpower - i.e. 15 employees and 9 consultants, were transferred to the CNAO foundation, together with 2000 pages of drawings and technical specifications. The "White Book" - titled "The Path to the Italian National Centre for Ion Therapy" - describes the history I just told and contains part of this material.

But the story still hadn't reached a happy ending, right?
Exactly. In 2001 a new government team took power and the new Health Minister gave a hard time to CNAO again. The project was blocked and a Committee established to judge the opportunity to go on with it. Luckily Umberto Veronesi, Elio Borgonovi, Jacques Bernier and myself were in the Committee, together with many opponents. Tough discussions took place, but we were good enough to convince the Committee, which eventually voted positively. Hence, in November 2001 the Health Minister appointed Erminio Borloni as the first President of CNAO. Shortly after Sandro Rossi, who had been TERA Technical Director from 1996 to 2004, became initially Technical Director and finally Director General.
In 2005 Pavia, a town close to Milan, was chosen by the Government as the new place to set the centre and the construction started.

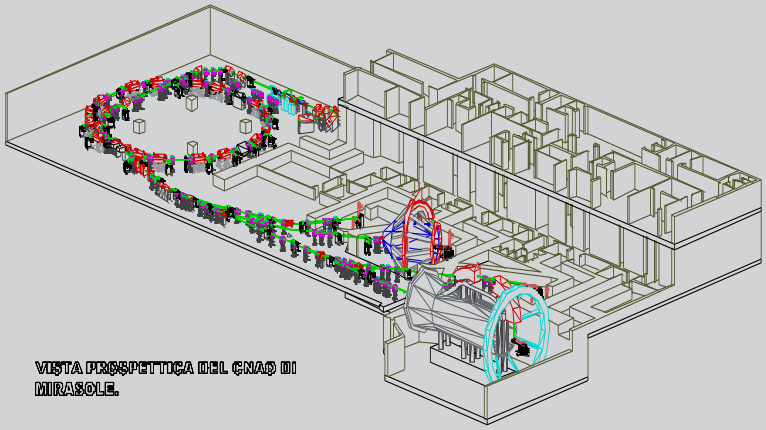
Was the project of the CNAO centre based on the PIMMS study?
Yes, but actually my group had never stopped researching and improving the design, so that the CNAO is based on a PIMMS/TERA project, which is to some extent an update of PIMMS. This is the project of which, years later, MedAustron bought the detailed designs for 3.2 million euros. For the realization we have been very lucky because the CNAO core group knew the project very well, having participated to all its successive designs, and INFN and CERN gave great contributions to the construction.



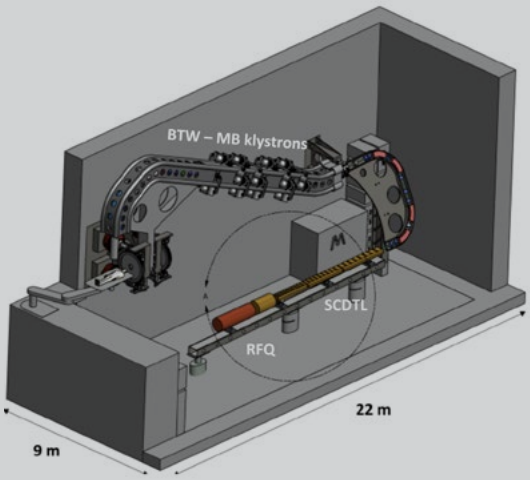
First design of the Italian National Centre for Oncological Hadrontherapy (CNAO), realized by the TERA Foundation and published in 1994 ("Blue Book").
Credits: TERA



Second design of the Italian National Centre for Oncological Hadrontherapy (CNAO), realized by the TERA Foundation and published in 1997 ("Red Book).
Credits: TERA



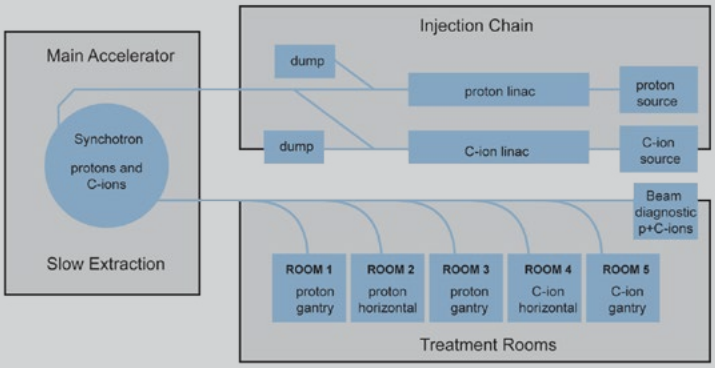
Third CNAO project for Mirasole (PIMMS/TERA – 1999)



Design of TULIP

Fourth design of the Italian National Centre for Oncological Hadrontherapy (CNAO), realized by the TERA Foundation.

Credits: TERA



PIMMS design study from 1996-2000 co-ordinated by CERN.

Ugo Amaldi and Roberto Orecchia (Scientific Director of CNAO) in front of the synchrotron of CNAO, Pavia (Italy).

Meeting of ENLIGHT held in June 2005 in Oropa, in the Italian Alps. Organized by TERA, it was chaired by Ugo Amaldi.

So the project for building CNAO had been finally approved: it was an excellent achievement. It is impressive that you didn't give up before all these difficulties…

I really believed in the project and I kept pushing for it and looking for ways to achieve our goal. One sure advantage was that we never defined the site but always said that TERA would accept any site chosen by the National and Regional authorities.

With the construction of the Italian Centre for Carbon Ion Therapy, the primary purpose of TERA had been reached. What new goal did you set for TERA then?

Although we were focused on building this centre in Italy, TERA has always been a foundation dedicated to research: that is why the Mirasole and CNAO Foundations had been conceived. I wanted to keep separated the research and development part from the implementation and construction.

Thus, the existence of TERA was not necessarily tied down to the fate of the synchrotron centre for carbon ion therapy, as demonstrated by the fact that the development activities had never paused. In 1993 I had already started another project, dedicated to the development of a linear accelerator for protons running at the same high frequency (3 GHz) and being hence transversally small, like the electron linacs used for conventional radiotherapy. I set up a study group in collaboration with the Italian Institution for New Technology, Energy and Environment (ENEA), INFN and many other institutes and universities; a first design of this proton linear accelerator at high frequency was included in the "Green Book" report published in 1995 by the Frascati Laboratories of INFN.

In 2001 a 1.2-meter long 3 GHz linac — built by a TERA-CERN-INFN collaboration and led by Mario Weiss, a retired CERN engineer – was connected to the cyclotron of the INFN South Laboratories in Catania and used to accelerate protons from 62 MeV to 74 MeV, as designed. From the success of this LInac BOoster (LIBO) another project blossomed: building a centre based on ten similar modules, which would accelerate protons up to the maximum energy needed to treat deep - seated tumours: 230 MeV.

The construction of such a facility struggled to start. But at the end of 2007, a friend of mine - who is a generous and open-minded entrepreneur - Alberto Colussi, founded A.D.A.M., an engineering company for "Applications of Detectors and Accelerators to Medicine". A.D.A.M. built the first commercial unit of a machine based on TERA's design of the high frequency linac.

In 2013 the London Company Advanced Oncotherapy (AVO) bought A.D.A.M., signed an agreement with CERN and is now constructing, in a bunker located on CERN premises, the first prototype of the Linac for Image Guided Hadron Therapy (LIGHT). CERN has built and recently commissioned the 750 MHz RadioFrequency Quadrupole (RFQ) that injects 5 MeV protons in the 3 GHz linac.

In the recent years TERA has worked - and is still working - with its two "sons", CNAO and AVO-A.D.A.M., on various research and development projects.

The contribution of TERA to the particle therapy field has been crucial not only for the design of the CNAO centre and its accelerator, but also for the key role played in training and nurturing young talents. I think you can be very proud of this…

Yes, absolutely. TERA has seen more than 200 talented physicists and engineers developing their competencies and expertise and then leave towards the next step of their career. Many of them now have important positions in research centres, in particular at CERN. Moreover I was one of the originators of the ENLIGHT network, which – under the guidance of Manjit Dosanjh – has promoted many training projects, to which TERA has also participated.

> *"TERA has seen more than 200 talented physicists and engineers developing their competencies and expertise and then leave towards the next step of their career. Many of them have now important positions in research centres, in particular at CERN."*
>
> *Ugo Amaldi*

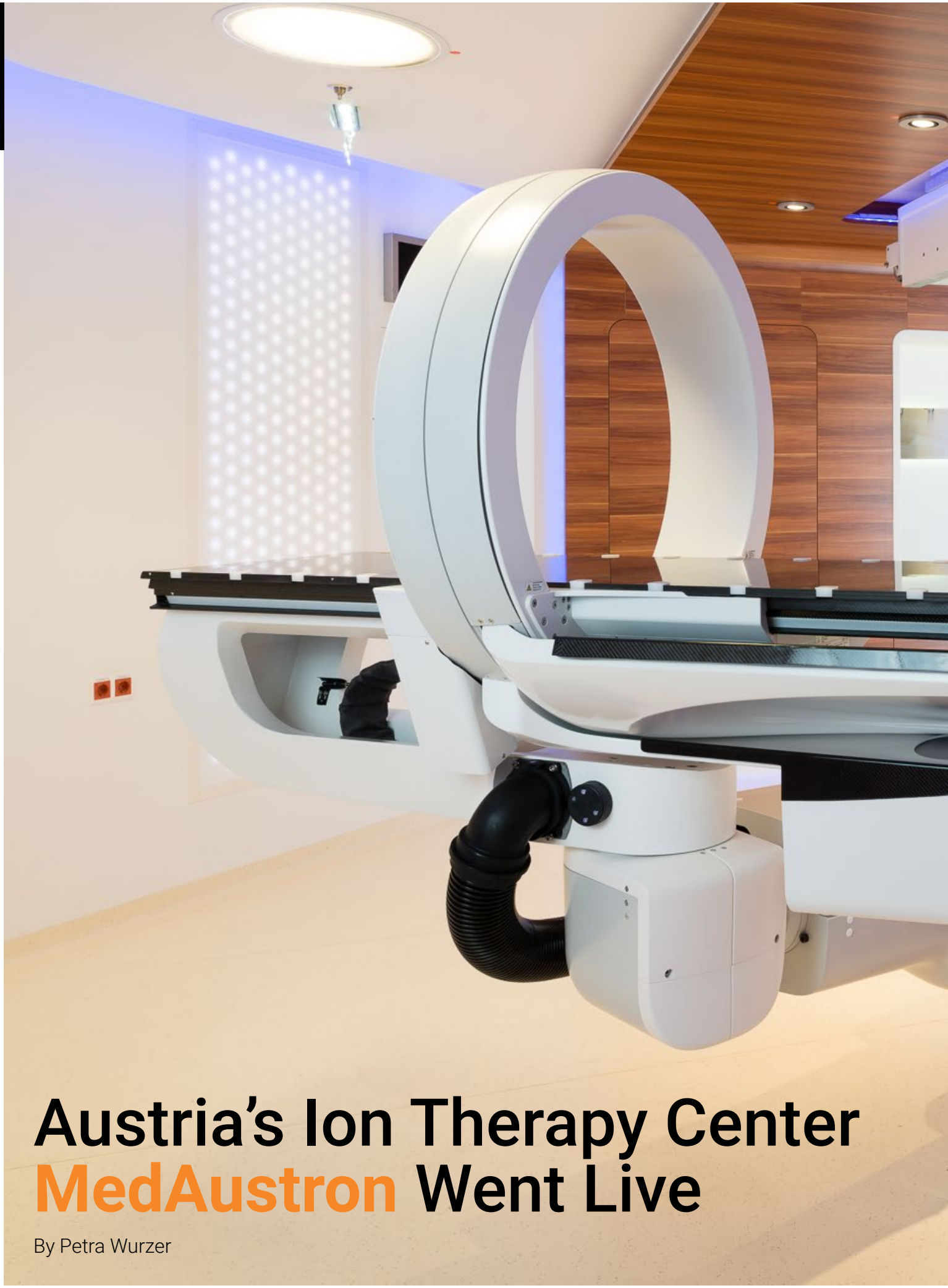
Are you developing new projects at TERA?

In the past years, we have designed a linac for carbon ions (CABOTO) and a compact single-room facility (TULIP) in which a 7-meter long proton linac is mounted on a rotating gantry. These are developments, done in collaboration with the CERN CLIC group, of the LIBO accelerator that we have built and tested with protons.

At present, we are working on a new accelerator for helium ions. In my opinion, helium can bring great benefit to medical treatments. It is lighter than carbon, thus requires a smaller accelerator, but it has much lesser lateral scattering compared to protons, resulting in sharper lateral fall-offs next to organs at risk. We are in contact with eminent researchers in the USA on this topic: Dr. Joe Minervini from MIT and Professor Douglas Packer of the Mayo Clinic. The former has designed a very innovative and interesting superconducting synchrocyclotron ('ironless'), which could be the ideal injector for our second-generation 3 GHz helium ion linac. The latter is studying the treatment of cardiac arrhythmias with hadron beams.

The most deadly one of these diseases is Ventricular Tachycardia (VT), while the most widespread is Atrial Fibrillation (AF), characterized by the presence of anomalous electrical circuits that put in communication the heart with the lungs, through the lung vessels and send stray signals that affect the cardiac contraction rhythm. These vessels can be ablated in order to stop the propagation of the electric pulses: nowadays it is done in an invasive way using a catheter. The idea is to use an external beam instead. ■

Ugo Amaldi and Umberto Veronesi.



Austria’s Ion Therapy Center MedAustron Went Live

By Petra Wurzer

© Thomas Kästenbauer - Roboter Irradiation Room 2

On 14 December 2016, at the end of a very busy and exciting year paved with accomplishments, MedAustron reached its most important milestone since its inception: the treatment of its first patient.

Designed in the early years 2000, the facility was built between 2011 and 2013 and the first beam extracted by the synchrotron in the autumn of 2014. Last year the centre went through the validation tests necessary for the European Community labeling - following the European Medical Device Directive - and performed the commissioning for clinical use of the MedAustron Particle Therapy Accelerator (MAPTA).

A few days after the facility received the official certification, the first patient entered the treatment room, and many others have already followed. While it takes time and regular medical check-ups to speak of a success – meaning that the therapy has fully destroyed the tumors – physicians at MedAustron report that all patients have tolerated their proton treatments very well and that no unexpected side effects have occurred.
At the moment, about seven patients per day receive treatment, with plans to continuously increase the throughput to 12. The typologies of cancer treated include mainly tumors of the brain, of the skull base, of head and neck and of the pelvic region. In April this year, yet another milestone has been achieved with the start of pediatric patient treatment.

Currently the center has only one room with a horizontal fixed beam available for treating patients with protons. By mid-year, commissioning of the second horizontal beamline will be finished, giving the medical team the capability to use two treatment rooms. It is expected that MedAustron will be able to deliver proton therapy to roughly 150 patients in 2017.

The facility also includes an irradiation room dedicated exclusively to non-clinical research activities, which earlier in 2016 was handed over to research teams working on projects in the fields of Radiobiology, Medical Radiation Physics, and Radiation Physics.

Beam time is still limited and thus the most valuable resource, since various groups at MedAustron have to push their competing agendas in order to reach full operation. It is very challenging to ensure sufficient time for patient treatments, commissioning, quality assurance, and research and development with only 24 hours a day.

Besides guaranteeing proton beam delivery at 255 different energies and 4 intensities (which equals a total of 1,020 treatment options), MedAustron's accelerator experts are working hard to provide also carbon ions. They actually managed to send the first carbon ion beam into an irradiation room in March. While the first beam had an energy of only 69 MeV, the second one already achieved the minimum clinical energy of 120 MeV.

More development and exciting results are bound to be achieved in the following months and years, when MedAustron will proceed with the technical commissioning of carbon ions beam and the installation and commissioning of the other two beam lines. This will allow increasing the number of patients and the spectrum of cancer typologies.
The center is expected to reach full operation by 2020, with three rooms for patient treatment – including two horizontal and one vertical fixed beamlines and a gantry -, as well as the room with a horizontal fixed beamline for non-clinical research. At that point, MedAustron will be able to treat up to 1,000 patients per year. ■

TIMELINE

1989 – Initial idea for a spallation neutron source "Austron"

2000 – 2004 – Design study for "MedAustron" facility

2007 – EBG MedAustron GmbH company founded to deploy and operate the center; Cooperation agreement with CERN; Design of the accelerator started

2011 – Groundbreaking of the center in Wiener Neustadt

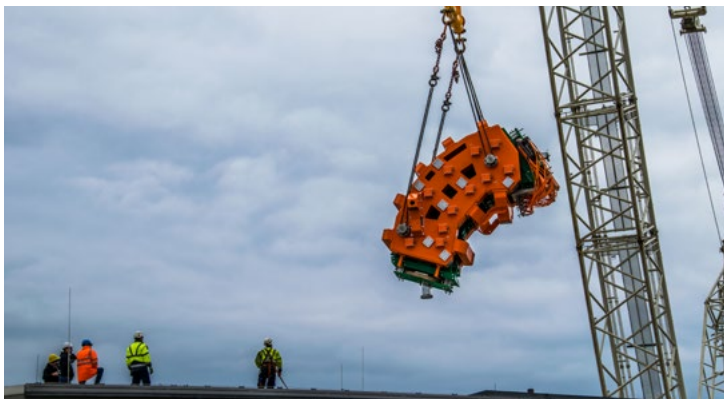
2012 – Construction of the building completed; installation of the particle accelerator started

2014 – Extraction of the first beam from the synchrotron and delivering to irradiation room

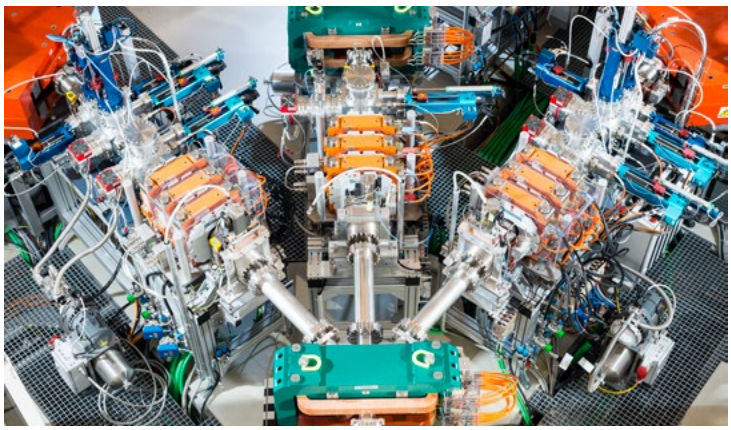
2016 – Particle accelerator system certified according to the European Medical Device Directive

2016 – On December 14th, first patient treatment with protons

Power Converter
© Thomas Kästenbauer



MVB-F lifted through to roof into IR 2
© MedAustron



Injectorhall at MedAustron - Ion Sources
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Synchrotron at MedAustron
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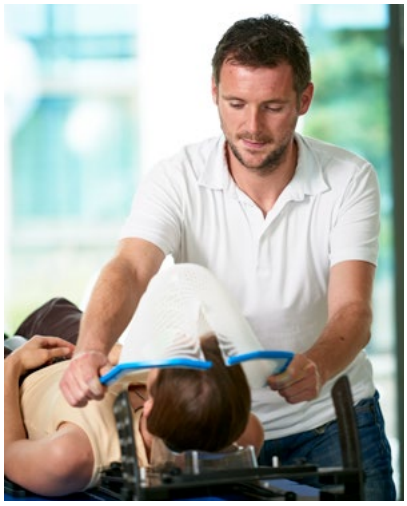
Finished immobilization mask
© Thomas Kästenbauer



RT putting on immobilization mask
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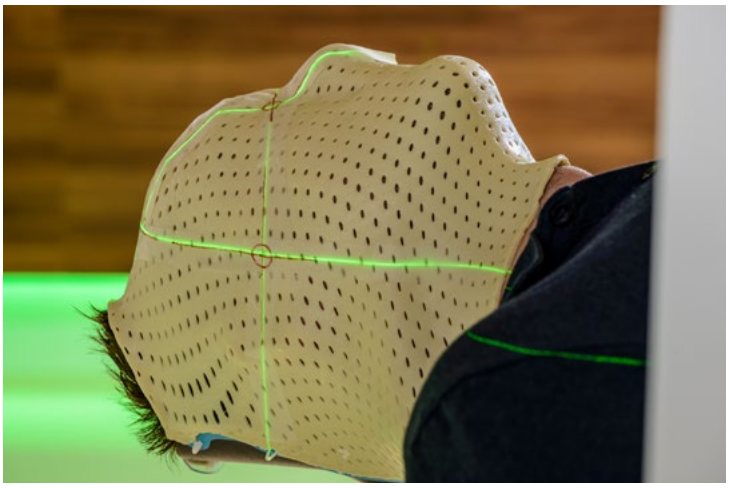
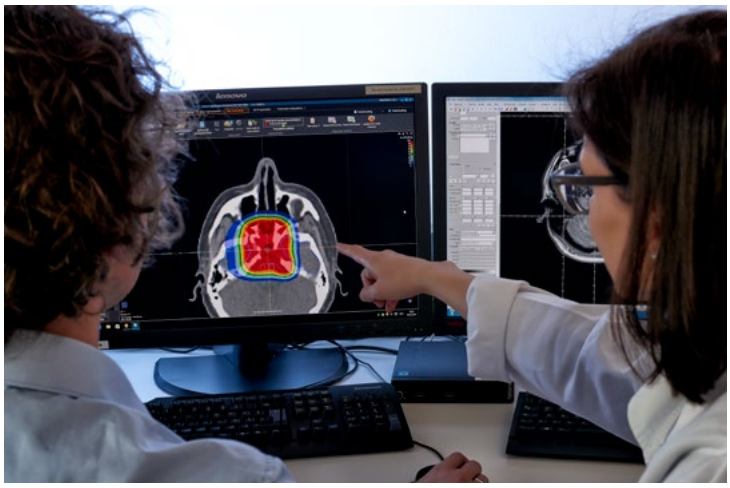
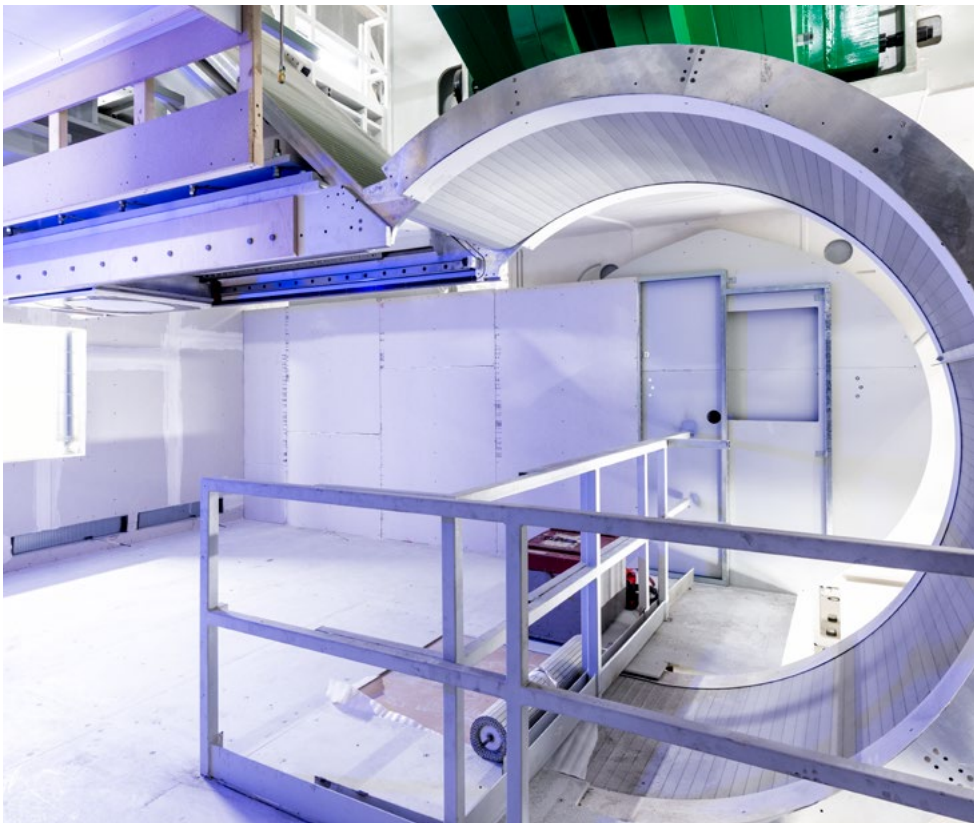
Patient lying on treatment table
© Thomas Kästenbauer



Patient in immobilization mask
© Thomas Kästenbauer



CT examination is used for the base of the irradiation plan
© Thomas Kästenbauer



Irradiation Room 3 with Gantry unfinished
© Thomas Kästenbauer

Gantry
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A new research facility at the proton therapy clinical centre in Trento

By Francesco Tommasino, Chiara La Tessa and Marco Durante

Figure 1: The proton therapy center in Trento

After a start-up period of about three years, the new Proton Therapy Centre of Trento (Fig.1) is now taking off, thanks to the opening of the second treatment room and the introduction of proton therapy - for some typologies of cancer - in the list of treatments covered by the Italian Health System. The experimental area has also been completed and is offering precious beamtime and resources for research.

Property of the Trentino Healthcare Agency (APSS), the facility was built by IBA (following the Proteus®PLUS design), which completed it by the end of 2013. The first treatment was delivered in October of the following year and since June 2015 also pediatric patients are admitted.

Built around a cyclotron that can produce proton beams of energies between 70 and 226 MeV, the facility comprises two treatment rooms and one experimental area. It is the first proton centre in Italy equipped with a 360-degree isocentric gantry, which – together with the six degrees of freedom of the patient positioning system – allows directing the beam onto the target from different directions. In addition, the proton beam can be controlled in 'pencil beam scanning' mode, as to shape at best the dose distribution in the tumour.

By the end of 2016, more than 200 patients were treated, of whom 30% were children and 30% re-irradiation cases. At full operation, the centre is expected to treat 1000 patients per year. If the economical effort required for building this kind of facilities is motivated by the clinical aspects, the potential relevance for the research community shouldn't be underestimated. Experiments with high-energy protons are needed for both therapy-related (medical physics, biology) and non-medical (detector development, space research, radiation hardness tests, nuclear physics) research. Not surprisingly, many of the new proton therapy centers include an experimental room, where pre-clinical and non-clinical studies can be performed.

At the beginning of 2016 the experimental area of the Trento Proton Therapy Centre was completed. The research room is run by the Trento Institute for Fundamental Physics and Applications (TIFPA), a National Centre of the Italian Institute for Nuclear Physics (INFN) in association with APSS, the University of Trento, and the Bruno Kessler Foundation (FBK). TIFPA is an innovative research centre dedicated to applied sciences; it's one of a kind, which covers the full path from fundamental research to knowledge transfer on the territory. The accelerator of the Trento Proton Therapy Centre is a key infrastructure for TIFPA. The research room (Figure 2) has two beamlines, one at 0 and one at 30 degrees, dedicated to radiobiology and proton physics, respectively. The beam has been characterized in air and energies between 70 and 230 MeV at intensities from 10^2 to 10^9 protons/s. The experimental vault is designed as a user facility, and a Program Advisory Committee (PAC) regulates the access for research institutes and companies. Based on the results of the proton beam characterization, it was possible to host already in 2016 several external groups, involved in both national and international collaborations. The activities performed by the guest groups spanned from radiation hardness (ALICE), to space detectors and shielding applications (ALTEA, Limadou, Rossini2), and detector testing (PRIMA-RDH, QBeRT). At the same time, preliminary studies dedicated to the irradiation of plant seeds (SHIELD) started. This demonstrates the large spectrum of research lines that might benefit from accessing the experimental area of this facility. in In April 2017 the PAC approved twelve new applications in the first selection round. The experiments cover proton radiography, range verification, detector calibration, radiobiology, and tests of single event effects in microelectronics. TIFPA welcomes new beamtime applications from excellent research groups. All technical information on the new facility and forms for beamtime applications are available online at http://www.tifpa.infn.it ■

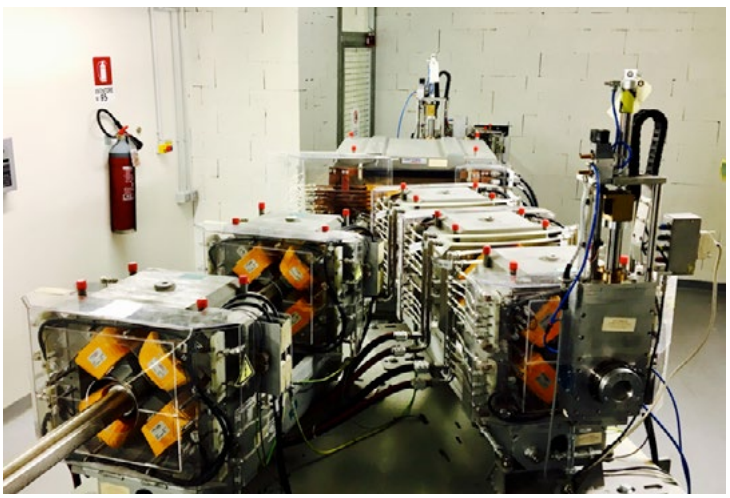
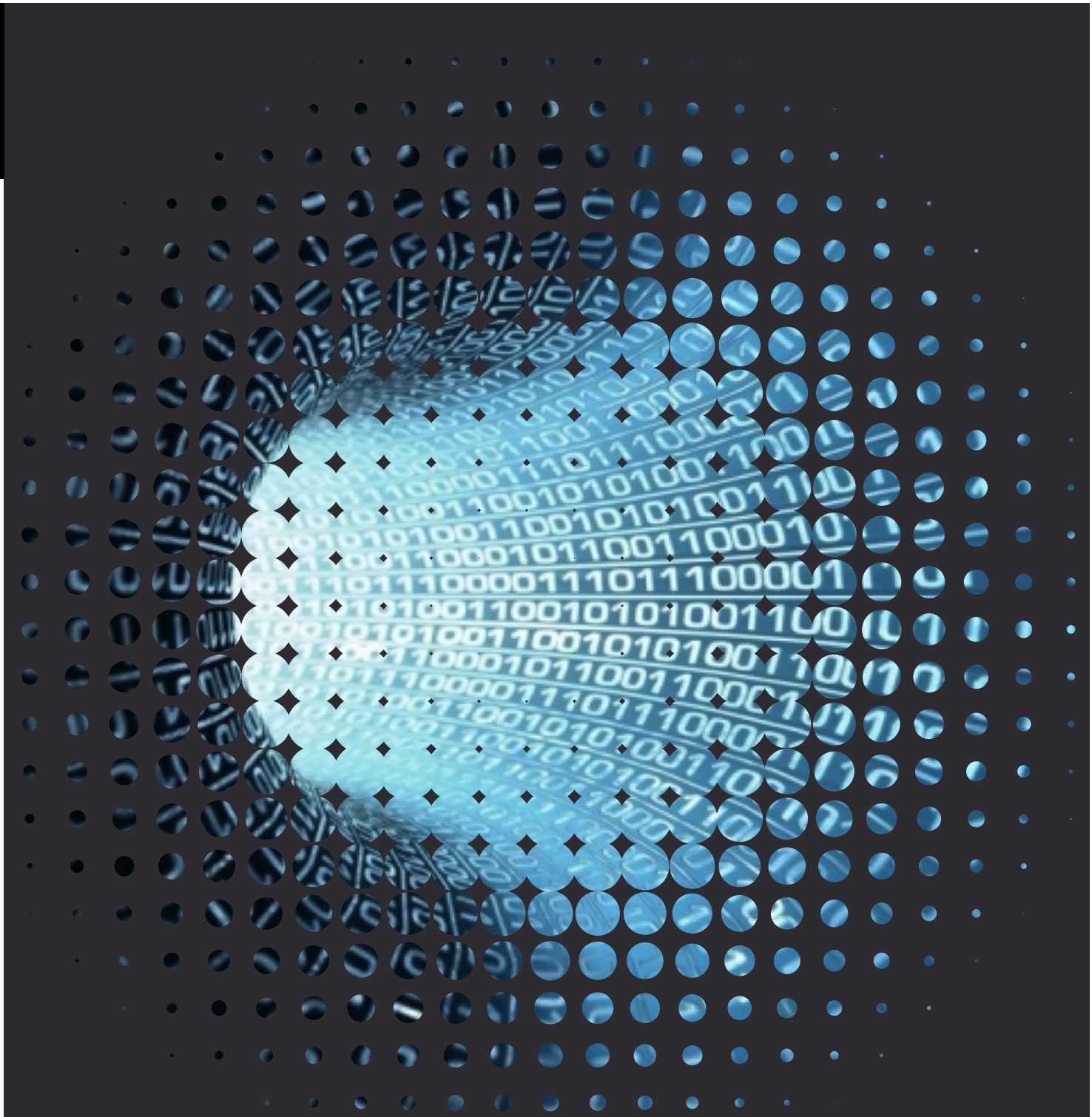


Figure 2. The two beamlines in the experimental vault in Trento.



In the e-Health era:
new informatics tools for radiation therapy

By Alberto Di Meglio, Stephanie Combs, Kerstin A. Kessel, Philippe Lambin and Virginia Greco

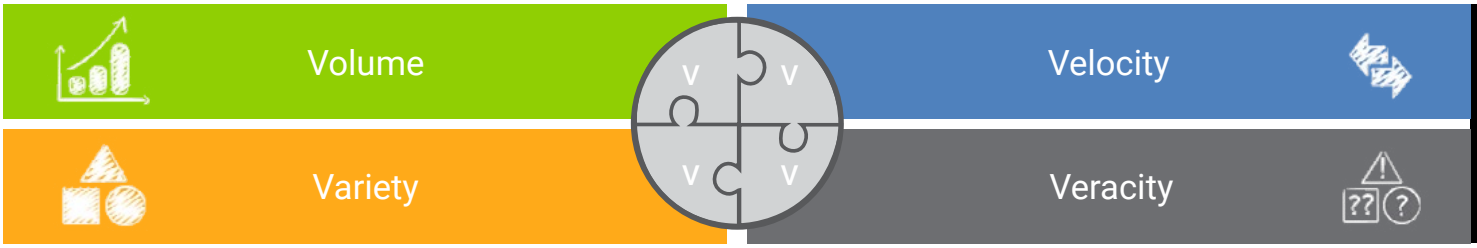


Figure 1: The V's model of Big Data:

The huge variety of tumours and patient physiological characteristics, together with the increasing number of treatment options now available, are driving modern oncology towards tailored cancer therapies. A dedicated treatment plan, which includes the combination of various techniques, can dramatically increase the rate of success in terms of survival expectations.

Physicians, though, have the responsibility of choosing the best therapy among many possibilities taking into consideration the literature and their experience. Classic randomized clinical trials to compare all the treatment options are considered the "gold standard", which nowadays is not readily reachable because of the current fast speed of innovation in this field. In addition, matching the characteristics of each single patient to those of the subjects in clinical trials is not straightforward.
Medical doctors need to be supported in the decision making process by a reliable system that could check and match the many variables involved thus providing indications based on existing literature. They should also be put in condition to easily store the results of their treatment within a system that allows sharing data and increasing common knowledge.
This support can be provided by information technologies, specifically, by data storage platforms and software able to analyze a large amount of data and extract useful information. Of course, when health-related information is involved, privacy and security are important concerns and requirements, which need to be properly addressed.
A number of projects are being explored and established to investigate the application of IT systems and tools developed for sorting, storing and analyzing huge quantities of data (what is referred to as "big data") to the specific needs of the medical community. In addition to systems designed to support the decision-making process, other possible applications of new technologies are being considered, such as the development of applications for mobile phones and tablets to accompany clinical trials. This user-friendly-interfaced software should allow the patient to measure and document on a daily basis fundamental health parameters, so that the evolution of the disease and of the therapy could be constantly monitored and a much clearer picture of the situation could be produced than only through periodical visits.

Rapid learning software to support medical doctors

In routine practice, medical doctors collect a large amount of data that, if stored and analyzed in the right way, can complement those coming from clinical trials and –in some way- enlarge the scope of the trials. Relevant information can be extracted from all this data and analysed by dedicated software. Thanks to distributed machine learning algorithms, it is possible to mine data, and thus learn from them, without data having to leave their institution: thus, privacy issues are overcome. Models are then built to fit the data. When applied to a new patient (in other words, to a defined set of data describing the characteristic of the new patient and its disease), these models can make predictions on the possible outcomes - including survival, quality of life, toxicity, etc. – of different therapies.
Decision Support Systems (DSS), i.e. software tools elaborating data and assisting healthcare professionals, are already used in radiotherapy. They are built around physics- or radiobiology-based models, while the approach of rapid learning

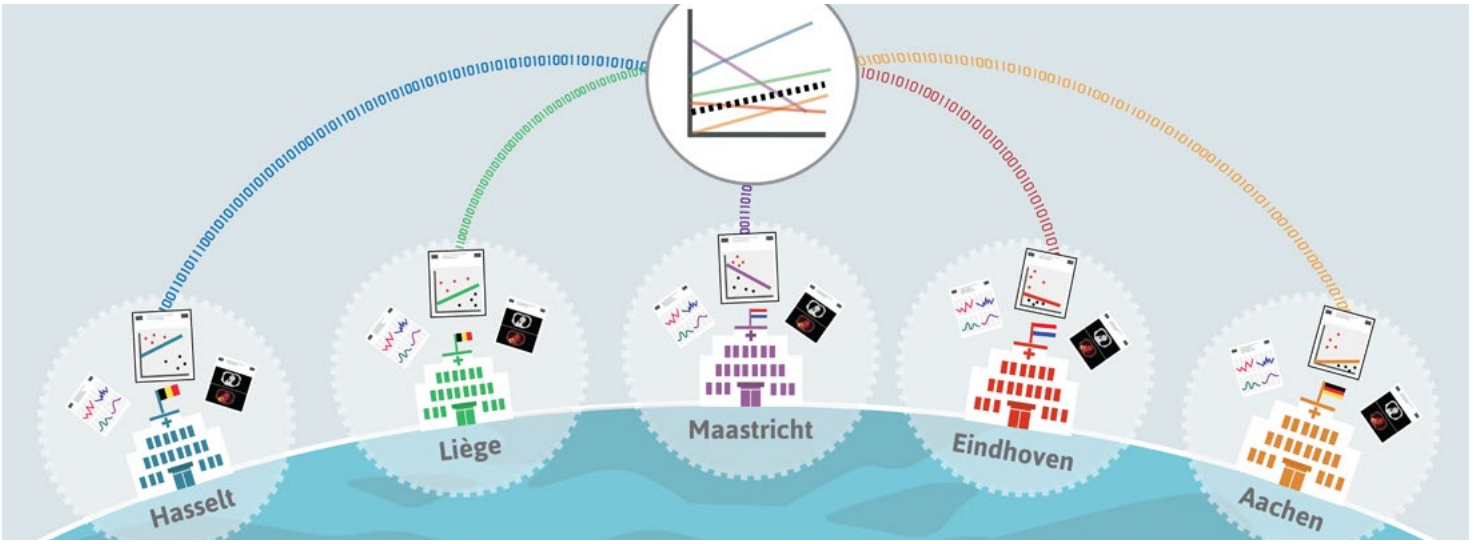


Figure 2: EuroCAT is an IT infrastructure for systematic data sharing among research institutes.
(From: Deist T. M. et al. "Infrastructure and distributed learning methodology for privacy-preserving multi-centric rapid learning health care: euroCAT." Clinical and Translational Radiation Oncology 4 (2017))

Figure 3: IT systems and tools developed within the environment of physics experiments for sorting, storing and analyzing huge quantities of data can be applied to the specific needs of the medical community.

Figure 4: The amount of oncology data, as well as genomics and general omics data, is increasing rapidly and can already be classified as "Big Data".

from distributed data allows for more holistic and multifactorial models, which take into account the physiology of the patient and the specific tumour, as well as other factors that could be relevant. As a proof of concept, the euroCAT project (www.eurocat.info) was launched in September 2010 to create, at several cancer centres, data stores in which information is extracted and mapped into standard concepts (watch the animation at https://youtu.be/ZDJFOxpwqEA). Data processed this way are then made available to external users, who can analyse them but do not have direct access to the personal details of the patients.

Big Data from particle physics to cancer therapy

Until recently, medical data have represented a small fraction of the scientific information generated every year, in particular if compared to the mountain of information stored and analyzed in high-energy physics experiments (50 Petabytes only in 2016, almost an Exabyte in total, 1.5 ExaBytes/year in 2015 – Figure 5). However, oncology data, as well as genomics and general omics data, can be classified as "Big Data", as they are increasingly characterized by the traditional V's model (Figure 1): volume, velocity and variety, to which we can also add variability and value. The total amount of cancer patient data produced in the world today is estimated to have already exceeded the Exabyte level. Storage requirements for human genome sequence data is expected to grow to as much as 40 Exabytes by 2025 (Figure 6).

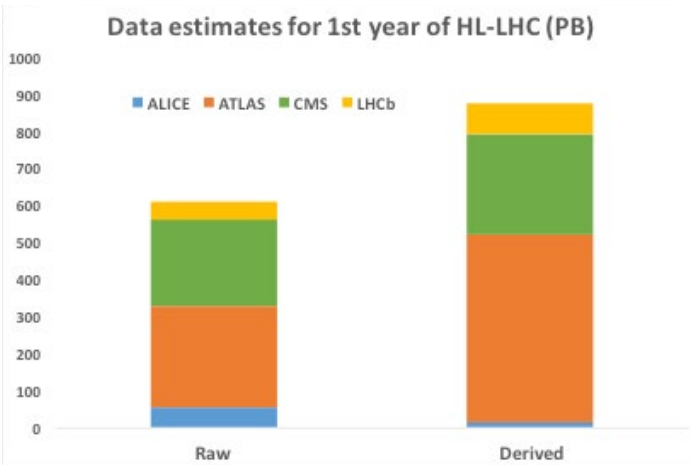


Figure 5: HEP data production estimate in 2025 (High-Luminosity LHC): 1.5 Exabyte/year.

Consequently, the collaboration between the Life Sciences, Medical Research and the High-Energy Physics (HEP) communities is becoming even more important than in the past. Some of the tools and methods developed in the context of physics experiments to select, store, and analyze very large amounts of complex data can be adapted or generalized for multi-disciplinary applications. Since the beginning of 2000, there are examples of such partnership: a number of projects, such as Mammogrid and Health-e-Child, explored the possible applications to medical research of the worldwide computing grid.

New ideas about use of emerging technologies like machine learning and new accelerated platforms would benefit both communities. Therefore, new projects and initiatives are being defined to develop distributed computing and data platforms able to take into account the specific needs of medical data processing, while at the same time adopting some of the data sharing and open collaboration principles used in HEP.

These platforms will provide an entry point for generalized access to data analysis and machine learning tools, libraries of community-moderated software, integrated access to open data and publication repositories (like Zenodo), and ways of sharing information and best practices.

The path towards an effective implementation of such systems is not without challenges. Effort is needed to improve semantic definitions to integrate and validate the quality of heterogeneous data, address the need for confidentiality, while still support increased prediction abilities of the models generated. A fundamental aspect is also the development of friendly end-user interfaces to simply describe workflows, submit and retrieve data, and share information, in order to make these new informatics tools easily usable with minimal training.
These platforms could also be used to improve the reproducibility of experiments by linking publications, software, data and workflows from reputable, community-curated repositories.

Mobile applications in cancer treatment and research

The large diffusion and increasing use of smartphones opens up new possibilities of integrating tools in medical practice and research. Applications (apps) will take the medical practice to the era of "mHealth" or "eHealth", as labeled by the WHO.

With the help of dedicated apps, in fact, patients could record vital parameters and other information on a daily basis, so that they are monitored along the whole therapy, not only in the routine visits. Therefore, patients are continually linked to the treating department and thus communication and compliance is enhanced. Further, the information could be registered in a data base and made available to the physicians. Patient involvement and, in particular, patient reported outcome (PRO) is increasingly developing into an important tool to measure side effects, symptoms and toxicity. Health-related quality of life (HRQoL) data of cancer patients can be used to adjust the individuals' treatment or to offer supportive therapy. Surveys on therapy satisfaction will help to improve the departments' workflow and the patients' contentment.

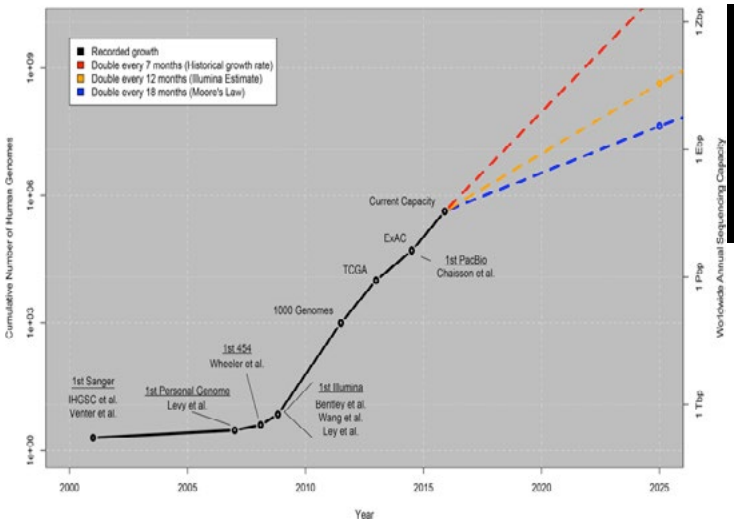


Figure 6: Growth of DNA sequencing (From: Stephens Z. at al. - https://doi.org/10.1371/journal.pbio.1002195).

Researchers go even one step further by already thinking of smartRCTs (app-accompanied randomized clinical trials, Figure 7). The use of apps and the direct involvement of the patients in the monitoring process would allow the recruitment of more people in trials and would reduce the time spent by hospital professionals in data storing, production of documentation and reports. On the other hand, the use of apps for smartphones present also some challenges, the first of which is related to privacy and data safety: the information transmitted has to be encrypted and anonymised. Legal limitations and constraints in this field may differ in various countries. Another issue to take into account is the fact that not all patients may have an adequate device to use the app. This could be overcome by providing the patients involved in the trial with a mobile device – with a specific operating system - to be given back at the end of the trial. This solution requires funding to purchase devices, but avoids costs for developing apps for various operating systems. Moreover, patients and medical staff need to be trained and keen to use such an app, as otherwise failure is unavoidable.

Efforts still have to be made in developing these tools. There are a number of challenges to be faced. Nevertheless, in the information era we are living in, medical doctors can certainly find new solutions and answers to their needs in the fast-moving field of information technology and (big) data processing. The future is all about personalised medicine, resulting improved outcome and cost effective treatment, in which these new tools will play a fundamental role.

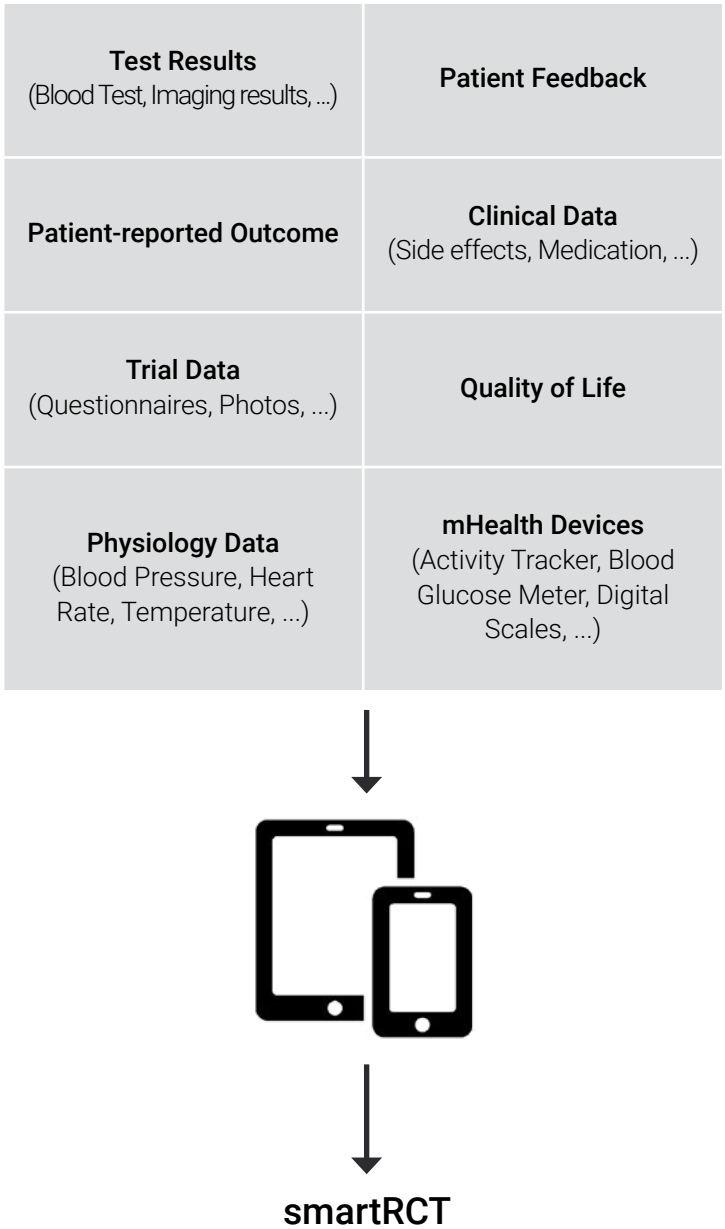
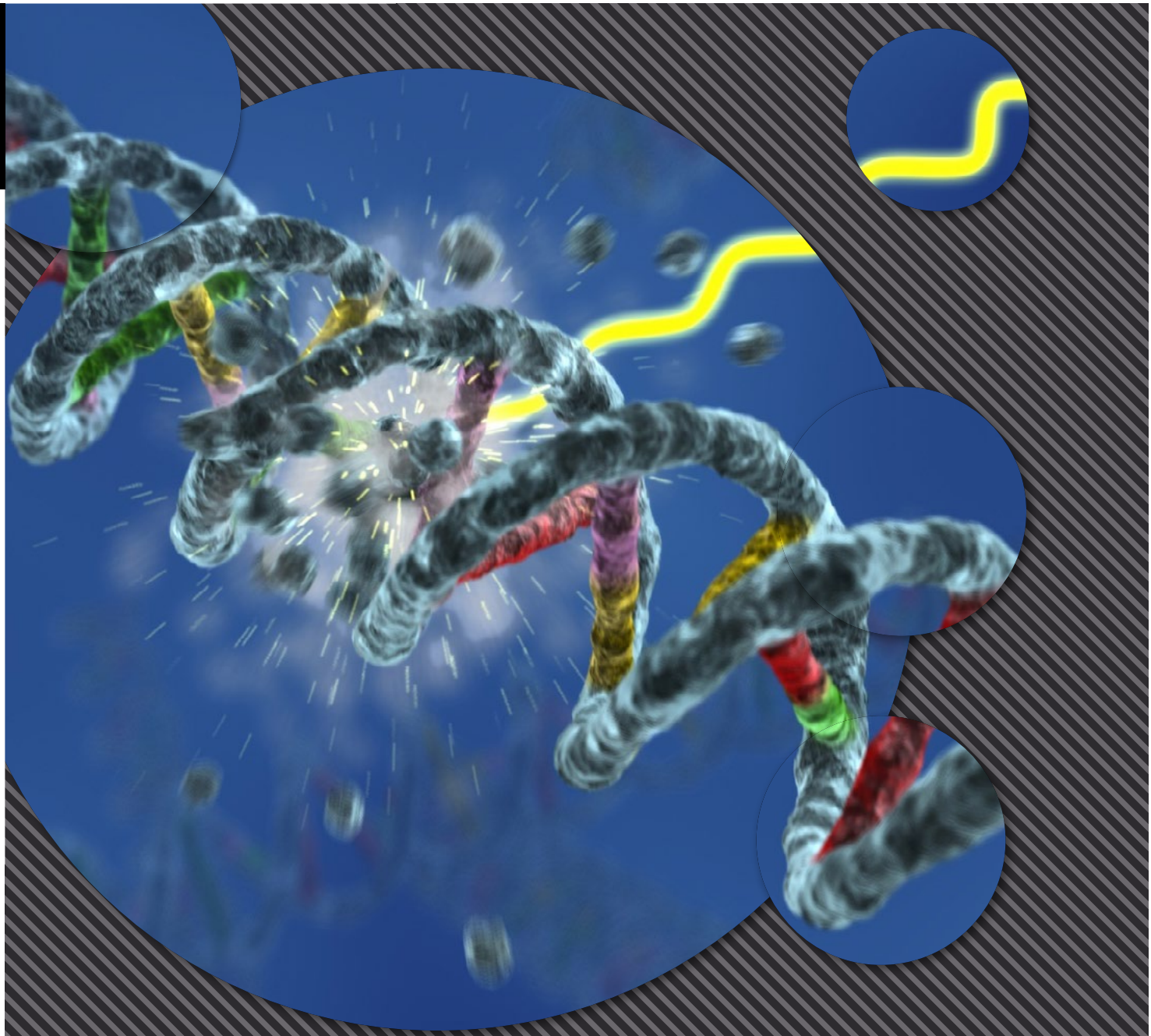


Figure 7: Data Collection by mobile applications for smartRCTs.
Credit: Technical University of Munich.

> *"New information technologies can support medical doctors in choosing the best therapy for each patient, by implementing a system able to check and match the many variables involved and provide indications based on literature."*



Proton RBE:
time to move beyond the constant 1.1 value?

Relative biological effectiveness (RBE) is a value used to account for differences in radiobiological effect between photons and other particles employed for radiation treatments. For protons, a generic value of 1.1 is commonly used at proton therapy centres worldwide, however the validity of using a fixed value is under increasing discussion in many recent reviews and has been a key topic of discussion in a number of conference and dedicated workshops (NCI Washington, Dresden).

Therefore, we have asked three prominent scientists in the field to give us their point of view and future directions of how to best benefit from particle therapy and the Bragg peak.

The Dilemma of Dose Selection in Proton Therapy

By Bleddyn Jones, University of Oxford, UK

Proton therapy offers delivery of lethal doses of radiation to the cancerous tissue, while limiting exposition of the rest of the body, thanks to the specific way in which the energy is released by the particles when passing through matter and, thus, the dose delivered. This characteristic of the ionizing radiation associated with protons and heavier ions is represented by the so-called Bragg peak effect.

However, there are two potential disadvantages that have to be taken into account and overcome. First of all, heterogeneous tissue densities, patient movement, daily positioning, as well as beam delivery related factors, can lead to peak placement inaccuracy. In addition, within peaks, energy is deposited in clusters rather than through sparse ionisation events. This causes DNA damage which is more difficult or impossible for enzymatic DNA repair mechanisms to restore, resulting in enhanced biological effects: these may be advantageous within the tumour, but possibly deleterious for normal tissues surrounding it.
Currently, the medical prescription of proton therapy dose includes a 10% reduction in dose to all tumours and tissues to compensate for enhanced bio-effectiveness. This figure is currently under dispute. To understand this issue, it is necessary to be familiar with the physics and biology terms associated with enhanced bio-effectiveness. It is also important to consider that normal tissues beyond a cancer are included in the treated area, in order to eradicate the cells within its spreading edge - which is not as well-delineated by present imaging techniques. This results in the fact that the volume of healthy tissue treated to high dose is often larger than the tumour volume itself.

Some essential physics and radiobiology

An important parameter to take into account is the linear energy transfer (LET), which basically averages the energy that the ionizing particle transfers to the material traversed per unit distance. Essential as well is the relative biological effectiveness (RBE). It is formally defined as a ratio and, in the context of proton therapy, it is given by the ratio between the absorbed dose of (megavoltage) photon radiation and the absorbed dose of proton radiation necessary to achieve a same specified bio-effect. Given this definition, the actual physical dose of protons (the Cobalt Equivalent Gy or RBE-Gy) given to the patient is the intended photon dose divided by the RBE. Presently the value of RBE universally used is 1.1. It follows that if this value is incorrect in some tissues, the dose delivered will be incorrect.

The relationship between LET and RBE is generally linear, with RBE increasing up to a maximum value after which RBE falls, due to energy 'wasting'. The magnitude of the RBE is inversely related to the dose and is also related non-linearly to the intrinsic cellular radiosensitivities (α and β parameters explained below).

In proton therapy Bragg peaks are 'spread out': tissues receive a mixture of radiations in the Bragg peak (high LET) and non-Bragg peak (low LET) regions, often resulting in average LET`s around 1-2 keV.µm-1 in the tumour region, although it can be higher and up to 8-10 keV.µm-1, depending on field arrangements and technique used. Pencil beam delivery can result in higher LETs, with perhaps additional bio-effects due to closer inter-track distances compared with passively scattered (wider) beams. fin
The average LET of conventional megavoltage radiotherapy is around 0.2 keV.µm-1, which has the immediate implication that the LET corresponding to the middle of the spread-out Bragg peak (SOBP) may be around 6-9 times higher. Another complicating factor is that much of the research on LET and RBE (for protons and other forms of radiation) used low voltage x-ray beams, whose LET was already around 1-1.5 keVµ m-1. Frequently used to estimate proton RBE, it inevitably led to underestimating it by 5-10%.

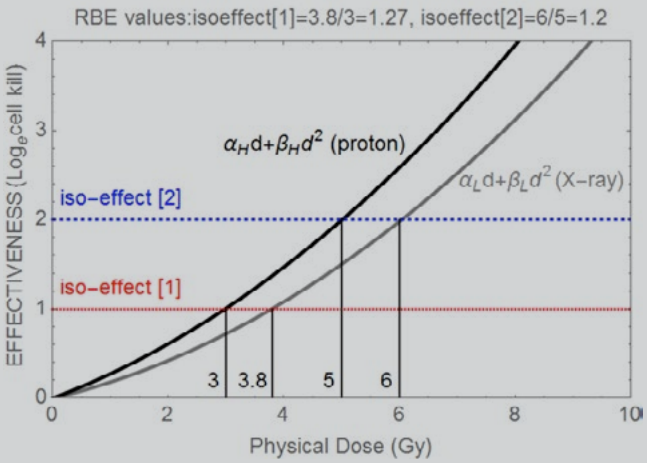


Figure 1: Demonstration of the RBE principle for two dose effectiveness curves produced by x-rays (photons) and protons (assuming αL=0.15 Gy-1, αH=0.24 Gy-1, βL=0.03 Gy-2, βH=0.032 Gy-2) and where two different iso-effect levels (lines corresponding to a specific value of bio-effectiveness) [1] and [2] are considered and their corresponding RBEs are shown. The numbers 3, 3.8, 5 and 6 refer to the physical doses where each iso-effect line meets each curve and so are respectively dH followed by dL for isoeffect [1] and dH and dL for isoeffect [2]; the RBE is given by dL/dH in each case and is shown on top of the frame.

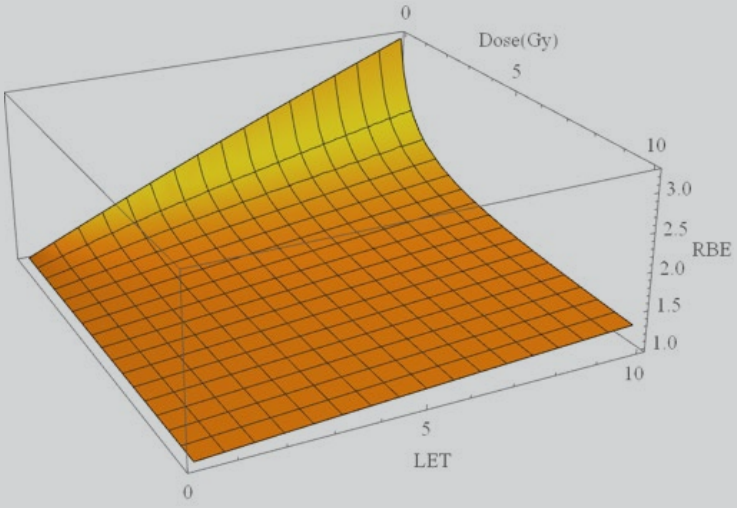


Figure 2 (a)

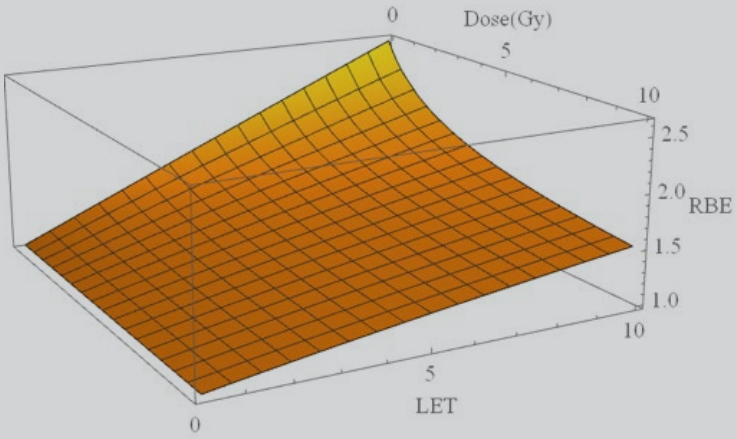


Figure 2 (b)

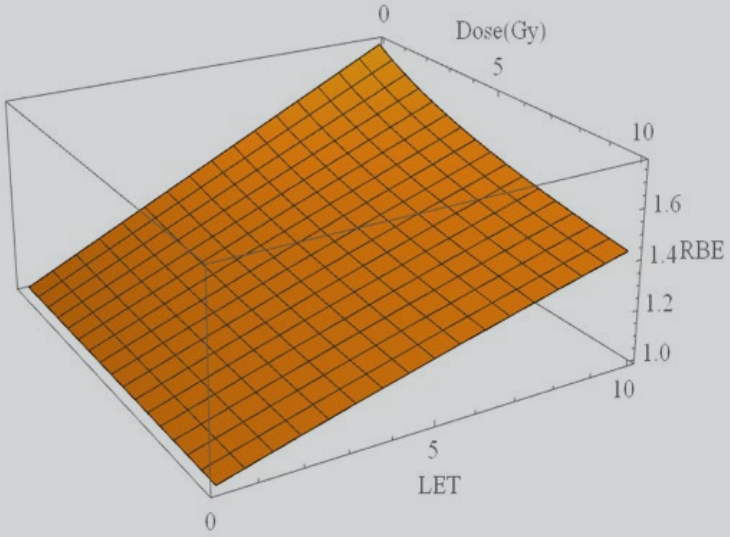


Figure 2 (c)

Figure 2 (a, b, c): Three-dimensional plots of LET, dose per fraction and RBE for three different α/β values: 2a: α/β=2Gy (representing highly fraction sensitive late reacting tissue such as spinal cord and brain), 2b: α/β=10 Gy (acute normal tissue effects and most rapidly growing moderately radio-sensitive tumours), and 2c: α/β=25 Gy (highly radiosensitive tumours).

A major challenge faces every proton therapy clinician: should they adopt different RBE values to limit toxicity and ensure better effectiveness in some situations?"

Bleddyn Jones

For further understanding it is necessary to introduce the simple, but elegant mathematical relationship between radiation dose (d) and bio-effectiveness (E). It is described by the linear-quadratic (LQ) model, with the expression: $E=\alpha d+\beta d2$, where α and β are radio-sensitivity (or cell killing) coefficients, α predominating at low dose and β at high dose [see also box on 'Linear-quadratic model of cell survival'].
If we consider a same bio-effect for protons and conventional megavoltage x-rays (photons) we can write EH=EL, or:

$$\alpha_H d_H+\beta_H d_H^2=\alpha_L d_L+\beta_L d_L^2,$$

where subscripts H and L refer to the high LET (protons) and low LET (photons) states of each radiation. The RBE is then the dose ratio dL/dH, which should always exceed 1. These relationships can be seen in figure 1, where it can also be noted that the RBE is larger at lower dose and effectiveness levels (this is due to the linear quadratic shapes of each curve).

Some general trends have been confirmed from LET-RBE experimental studies that have used a variety of radiation modalities, including fast neutrons (that mainly produce recoil protons), low energy x-rays, alpha particles, carbon, and other light ions. These include the fact that the α parameter increases by more than the β parameter with LET, which leads to the inverse relationship between RBE and dose.

Modelling the RBE

RBE changes with LET can be modelled using phenomenological or theoretical models or a combination of each. They either relate RBE inversely to the α/β ratio of the control radiation, or involve separate treatment of α, or α and β, coupled with saturation effects that limit the maximum possible increases. The latter assumption is used to generate figures 2(a-c) for three α/β values (characteristic α/β values are: 2 Gy are characteristic for the central nervous system, 10 Gy for many cancers and 25 Gy for highly radiosensitive tumours such as lymphomas and childhood cancers). The baseline LET value is set to 0.22 keV.µm-1, being representative of clinical megavoltage photons. It can be seen that this model shows changing values of RBE, which could modify treatment outcomes considerably.

Disappointing clinical outcomes

Higher than expected proton brainstem toxicity, assessed by radiological changes, has been reported in ependymoma and meningioma. Switzerland`s famous PSI laboratory have observed a serious neurological toxicity (blindness and brain necrosis) of around 12.3% in proton therapy, a result that is considered unacceptable in photon-based therapy. Also, long-term results of children treated with protons in Japan show serious toxicities of 6%, 17% and 17% at five, ten and twenty years respectively.
Are these results due to Bragg peak placement errors or radiobiology uncertainties? Realistic assessment of both is needed. It is also logical to expect that Bragg peak positioning errors would increase normal tissue toxicity outside the target and cause reduced tumour control in the same patient: there is no evidence that this has occurred, so it is reasonable to invoke inappropriate RBE as being the main culprit of 'unexpected' toxicity.

Discussion: How can radiobiology improve proton therapy?

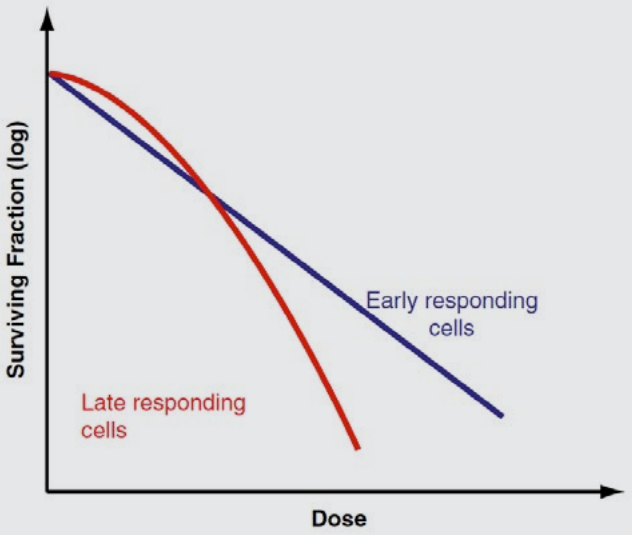
Some authorities have proposed LET×Dose as being a good predictive index, which bypasses the need for the RBE concept. However, the product does not have meaningful dimensions and RBE becomes a hidden variable (related to each parameter in a different way). Plots of the product against cell survival do not show sufficient predictive accuracy.
The invariant 1.1 RBE value used currently has been extensively criticised on the basis of LQ model theory, use of inappropriate short-term bio-assays and use of non-megavoltage control irradiation. When will the constant RBE be replaced? Will this be left to individual institutions to decide, or will international bodies (e.g. ICRU and ICRP) intervene?
A major challenge faces every proton therapy clinician: should they adopt different RBE values to limit toxicity and ensure better effectiveness in some situations? Should randomised control studies be done to test RBE allocations? For example, they could be performed by allowing randomisation of patients to either the standard RBE or to an RBE of 1.2 in the normal tissues exposed to LET of 1-2 keV.µm-1. Very radiosensitive tumours (with very small RBEs) could be tested by using an RBE reduction of only 1.03, or not using an RBE at all, provided that critical structures are not overdosed.
It remains to be seen if clinicians adopt these cautious suggestions to improve safety and clinical effectiveness. ■

Linear-quadratic model of cell survival

A cell survival curve describes the relationship between the surviving fraction of cells, i.e., the fraction of irradiated cells that maintain their reproductive integrity, and the absorbed dose.
Several mathematical methods of varying degrees of complexity have been developed to define the shape of cell survival curves.
The linear-quadratic (LQ) model is now most often used to describe the cell survival curve assuming that there are two components to cell kill by radiation:

$$SF(D) = \exp(-\alpha D - \beta D2) ,$$

where SF(D) is the fraction of cells surviving a dose D, α is a constant describing the initial slope of the cell survival curve, and β is a smaller constant describing the quadratic component of cell killing. The ratio α / β gives the dose at which the linear and quadratic components of cell killing are equal.
There is a clear distinction in radiation response between tissues that are early responding (skin, mucosa, intestinal epithelium) and those that are late responding (spinal cord).
The cell survival curves for the late responding tissues are more curved than those for the early responding tissues. For early effects the ratio α /β is large and α dominates at low doses. For late effects α /β is small and β has an influence even at low doses.



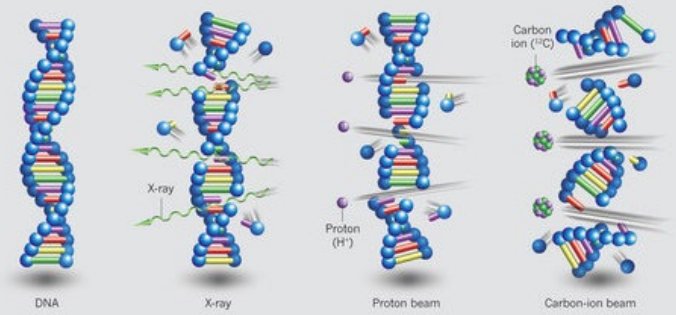
Cell survival curves for late responding tissues (small α /β) and for early responding tissues (large α /β).

> *"The question of changing current clinical practice despite uncertainties can only be answered by clinical evidence that RBE variations indeed matter in patients. However, such evidence is scarce."*
>
> *Harald Paganetti*

Endpoint

In clinical trials, it is called an endpoint an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. The endpoints of a clinical trial are usually included in the study objectives. Some examples of endpoints are survival, improvements in quality of life, relief of symptoms, and disappearance of the tumor.

Radiation-induced DNA damage



Credits: T. Nomiya, NIRS Japan

Radiation can kill cancer cells by damaging their DNA. X-rays can hit or miss the DNA. Protons are slightly more lethal to cancer cells than X-rays.
Carbon ions are around 2-3 times as damaging as X-rays.

Clinical challenges with respect to proton RB

By Harald Paganetti, Harvard Medical School, Boston

Even though a constant RBE is currently being used in proton therapy, it is well known that the RBE varies among cell lines, tissues, endpoints, as well as with beam-quality. What prevent the incorporation of these variations clinically are uncertainties, especially in vivo.

Experimental data are obtained predominantly in vitro. They do show a trend towards an increase in RBE as shoulder of the x-ray dose-response curve increases (as parameterized by α/β of the linear-quadratic model). Furthermore, one would also expect the RBE to increase as dose diminishes, although very few data exist for doses relevant in classical radiation oncology. Higher RBE also corresponds to higher linear energy transfer (LET), thus mainly at the end of range of proton beams.
None of these effects is currently take into account quantitatively in proton therapy although some consideration is given towards variable RBE values by, for instance, avoiding specific beam angles or reducing the dose to critical structure for a limited number of fractions.

Various phenomenological models are capable of predicting the RBE as a function of the parameters mentioned above. However, input parameters for these models are solely based on cell survival data obtained in vitro. It is unclear if in vitro relationships can be translated to in vivo endpoints, even for tumor control, which is related to cell survival. To define normal tissue complications, the endpoint of cell survival may not be appropriate at all. Most importantly, patient specific radiosensitivity is poorly understood and response biomarkers, indicating for example DNA damage repair deficiencies in patients, are not yet defined. Thus, incorporating RBE values in treatment planning might even be counterproductive at this point due to uncertainties in relative effects between tumors and healthy tissues. On the other hand, photon therapy faces the same issue in that patient specific radiosenitivities are not well known. The question of changing current clinical practice despite these uncertainties can only be answered by clinical evidence that RBE variations indeed matter in patients. However, such evidence is scarce. Toxicities in proton therapy are mostly in line of what one would expect based on a constant RBE and their scarcity hinders establishing statistically significant findings. Nevertheless, it may not be warranted to wait until such evidence becomes statistically proven, in particular when it comes to pediatric patients.

Thus, the focus should be on mitigating potential impacts of proton RBE uncertainties, while building improved datasets and models in the longer term. One strategy is to focus on physics, i.e. LET, a parameter that can be calculated on a CT voxel grid with high accuracy. As RBE is increasing with increasing LET, one can improve a treatment plan by redistributing the LET away from critical structures without significantly changing the dose distribution (see Fig. 3). This improvement thus holds for any patient even though it can not be quantified in terms of RBE.

Moving forward, additional in vivo experiments are required and clinical data need to be analyzed with respect to RBE effects. The quest for patient specific biomarkers in the context of therapies such as immunotherapy will most likely also improve our knowledge on patient specific radiosensitivity. ■

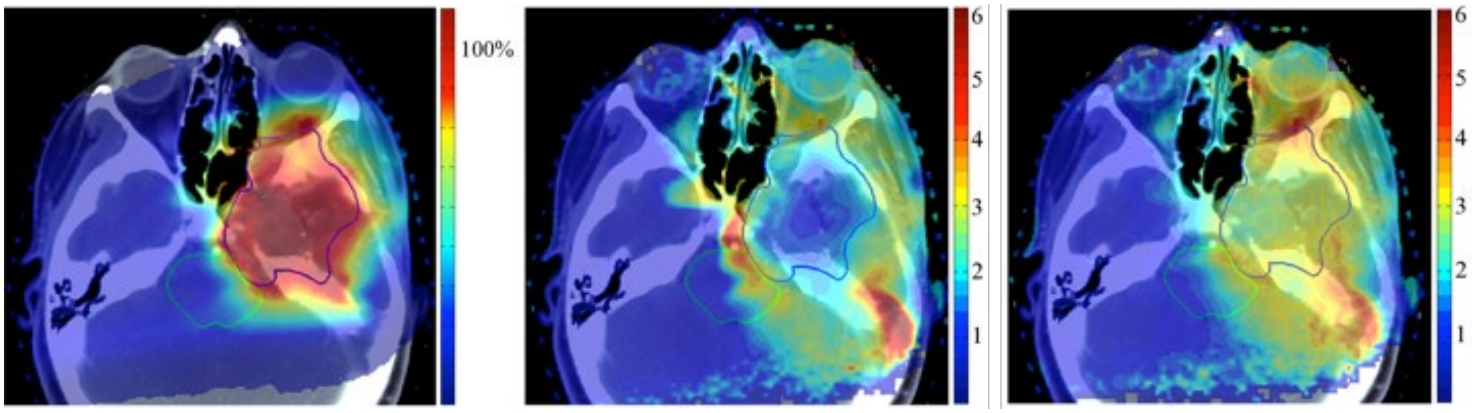


Figure 3: Dose distribution in a patient (left) and two dose-averaged LET distributions from two different treatment plans that result in this dose distribution while differing significantly in LET and thus RBE.

Relative Biological Effectiveness Issues in Particle Therapy

By Radhe Mohan, Anderson Cancer Center, Houston, US

In principle, positively charged particles (ions) have enormous potential in the treatment of wide range of cancers, particularly in the form of intensity-modulated particle therapy (IMPT) as illustrated in Fig.4. To maximize this potential, there is a great need to improve our understanding of physical and biological properties of particles and their effect on the human body. Owing to their unique scattering and ionization characteristics, charged particles interact very differently than photons with cells and tissues. Depending on the ion species and the particle energy, the biological effect of particles traversing the body is almost always greater and substantially more complex than for photons. While such differences are quite apparent for ions heavier than for protons, and models have been developed to take these differences into account, the relative biological effectiveness (RBE) of protons relative to photons is simplistically assumed to be a constant of 1.1 for all situations. This choice is based on average of data derived from historical experiments performed under limited conditions. Recent experiments show that RBE may vary significantly along the proton beam path. As a consequence, the biologically effective dose distributions actually delivered may lead to unforeseen toxicities and/or failure to control the disease.

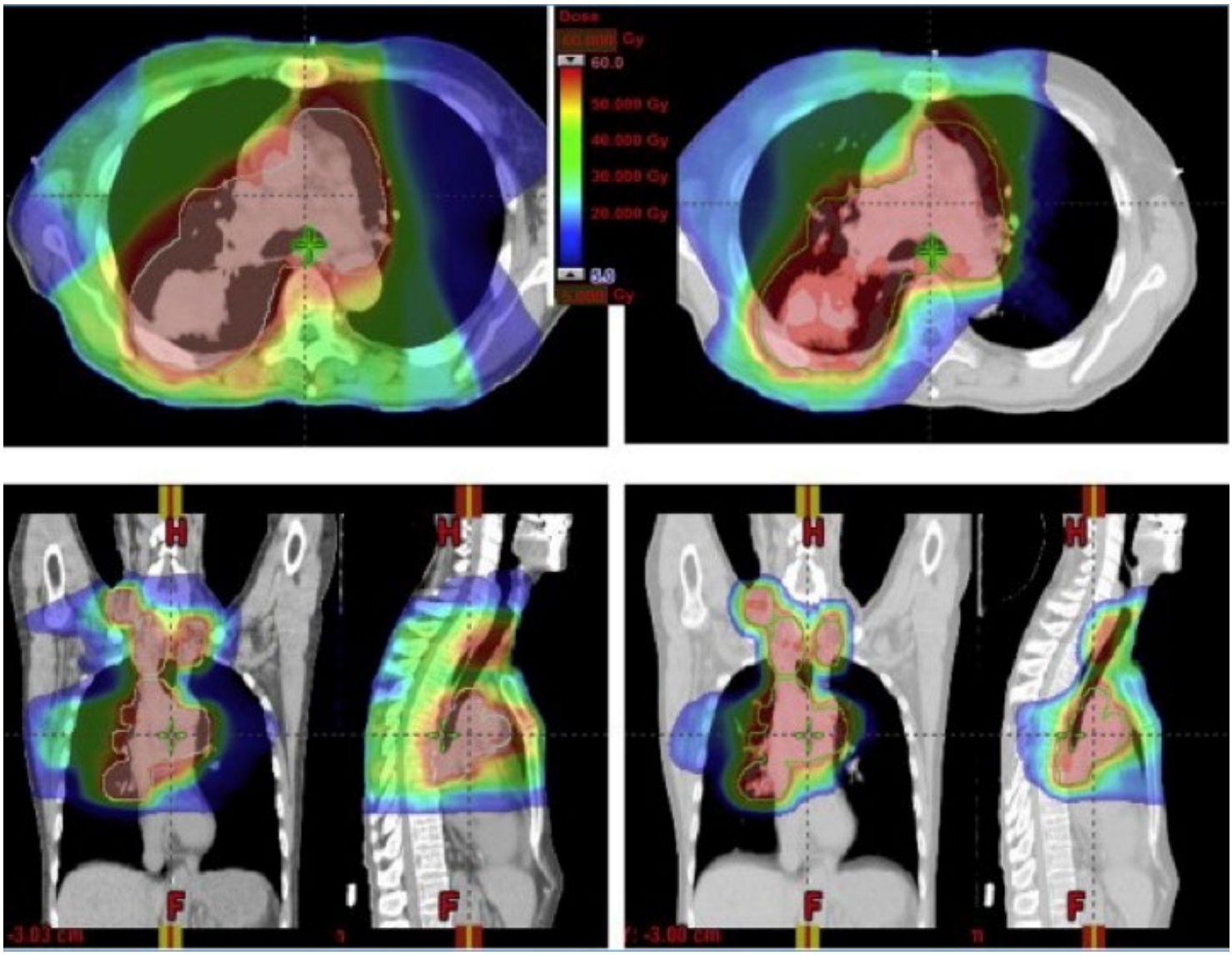


Figure 4:. A typical lung case comparison between IMRT (photons) and IMPT (protons) illustrating the significant potential of IMPT to produce compact dose distribution patterns to spare healthy tissues while irradiating tumors to high doses.

From J.Y. Chang et al., Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer, Cancer, 117 (2011).

> *This ongoing debate indicates the need for considerable further research to fill gaps in our knowledge of RBE based on the existing in vitro and in vivo experiments. There is also a need to refine existing models, or develop new ones, for predicting RBE.n"*
>
> *Radhe Mohan*

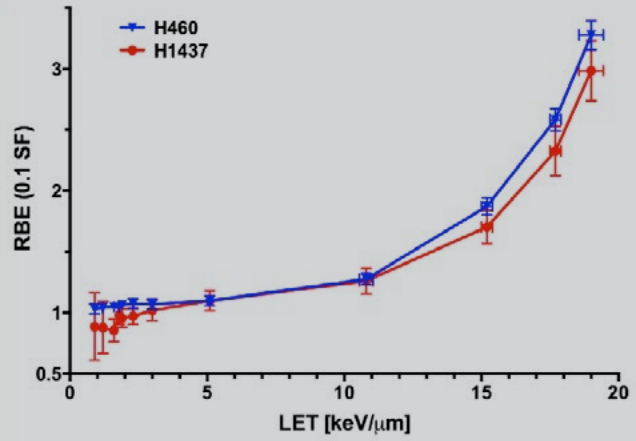


Figure 5: RBE vs. LET at 10% surviving fractions for H460 and H1437 lung cancer cells irradiated with an 80 MeV mono-energetic proton beam. A nonlinear trend between biological effect and LET was observed for both cell lines at higher LET values at points in the distal fall off region.

From: Guan F. et al., Spatial mapping of the biologic effectiveness of scanned particle beams: towards biologically optimized particle therapy, Sci Rep 2015.

There is ongoing debate about the need for the development and implementation of advanced approaches to account for RBE variability. The rationale for continued use of the proton RBE of 1.1 in the current practice of proton therapy is that: there is large interpatient sensitivity variability that makes variability in RBE irrelevant; the higher RBE affects only a small region near the distal edge; there is no clinical evidence of harm to-date necessitating a change. However, proton RBE is variable, increasing from approximately 1.0 at the entrance into tissue to a value of the order of 1.4 at the Bragg peak of a monoenergetic beam and to considerably higher values (of the order of 4) in the distal fall-off region. Although the Bragg peak region is rather narrow in water, it is degraded in tissue, particularly when the proton beam passes through a complex heterogeneity, and may spread over a larger volume in human tissues, especially in a low-density medium such as lung. With regard to the argument about the lack of clinical evidence, it is plausible that such evidence is obscured by uncertainties related anatomy variations, approximations in dose calculations, anatomy delineation and patient-specific factors.

In order to unequivocally demonstrate the value of protons, it is essential to improve our understanding of the effect of RBE variability on treatment response. This, in turn, requires that - to the extent possible - other sources of uncertainties be mitigated and residual uncertainties be incorporated into computed radiation dose distributions. Correlation of more accurate estimates of dose distributions actually delivered with treatment response indices may reveal quantitative information about RBE variability. Such research is currently in progress [4]. The resulting improvements in our understanding should lead to either confirmation of the validity of existing RBE models or their further development. Current models are simplistic and inconsistent with recent high precision experiments showing a supra-linear behavior for points close to and beyond the Bragg peak (Figure 5).

Robust RBE models are important not only for evaluating the potential clinical impact of particle dose distributions produced by a treatment planning system but also for optimizing IMPT dose distributions to maximize the biological effect within the tumour target and to minimize it outside. One approach to achieve this differential may be to perform IMPT optimization based on criteria defined in terms of RBE-weighted dose computed using a variable RBE model. The optimization process would preferentially direct higher biologically effective protons into the tumour and away from normal tissues. Alternative strategies are to base the optimization criteria on LET or dose*LET (assumed to be a surrogate for biological effect) to minimize LET in normal tissues and/or maximize it in the tumor. Strengths and weaknesses of each approach continue to be argued.

This ongoing debate indicates the need for considerable further research to fill gaps in our knowledge of RBE based on the existing in vitro and in vivo experiments, and from correlations of various clinical and imaging response markers with accurate estimates of dose distributions actually delivered. There is also a need to refine existing models, or develop new ones, for predicting RBE. Such research is critical to exploit and demonstrate the true clinical value of proton therapy.
While most of the discussion above is focused on protons, it is important to note that variable RBE models and RBE-weighted optimization of IMPT are already in use for carbon therapy although the models are in need of improvement. ■

Future outlook

As highlighted by the three experts, RBE values are dependent upon a large number of known and unknowns including tissue α/β, organ sensitivity, and tissue architecture and response, among others. The ongoing debate indicates the need for considerable further research to fill large gaps in our knowledge of RBE, based on in vitro and in vivo experiments as well as on correlations of various clinical and imaging response markers with accurate estimates of dose distributions actually delivered. This should permit the formulation of enhanced mathematical models, giving greater insight into the effects of proton radiation. ■

Focus on Onyinye Balogun

By Virginia Greco (CERN)

A graduate of Harvard University and Yale University School of Medicine, Onyinye Balogun is an attending Radiation Oncologist at Cornell University. In addition to her clinical duties, she is engaged in global health projects focused on cancer care. She is a member of the International Cancer Expert Corps (ICEC), whose main aim is to reduce mortality and improve the quality of life of people suffering cancer in low- and middle-income countries (LMIC), and in particular she is involved in various educational projects oriented at training radiotherapy professionals in those countries. We talked with her about her interest in this cause and her experience in the field.

Why and when did you decide to invest time and energy in contributing to the diffusion of radiation therapy for cancer treatment in low and middle-income countries?

My paternal aunt/godmother died of breast cancer when I was about 12 or 13 years old. Before she died, I visited her in Nigeria and she showed me her scars. (Due to my lack of medical knowledge, I thought her scars were due to surgery but when I came across the pictures I'd taken of my aunt many decades later, I realized her scars were due to radiotherapy side effects!) Shortly after her death, I developed a vendetta against cancer which led me to pursue medicine. After college, I spent a year in Ibadan, Nigeria, working with a breast cancer advocacy group and working to start a clinical trial. During my time there, I helped to run a weekly Q&A session within the radiotherapy clinic in Ibadan. I had no medical experience so I had to read a great deal about cancer and radiotherapy to try and answer the patients' questions. I guess my time with my aunt and my year in Nigeria laid the seeds subconsciously for my decision to get involved in radiotherapy for LMICs.

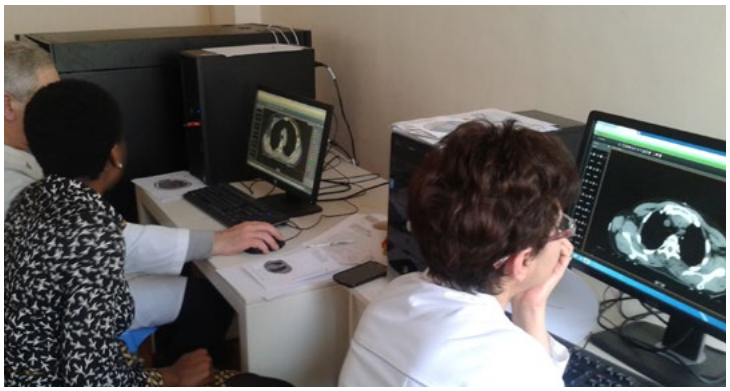
How did you get involved in ICEC?

I first met Norman Coleman in the fall of 2014 when my chair, Dr. Silvia Formenti, introduced us to one another. ICEC sounded like a promising venture so over time I became more involved. Mentors like Dr. Formenti and Dr. Brereton have taken me under their wing and the organization has truly encouraged my passion for improving healthcare in LMICs. I feel very fortunate to have ICEC's support.

You focus mainly on education and training of medical doctors, radiologists and nurses living and practicing in resource-poor countries. Could you explain what kind of activities you are carrying out and their goal?

Radiation therapy is an important component of cancer care globally. Until the mid-1980s, radiation therapy plans were designed using two-dimensional X-rays with bony anatomy landmarks serving as guides for field definition, reference points set at specified depths and dose calculated by hand. Access to computerized tomography (CT) and magnetic resonance imaging (MRI) has enabled the design of plans using three-dimensional images and computer algorithms. Three-dimensional conformal radiation therapy (3-DCRT) has been in widespread use in developed nations since the 1990s. In contrast, radiation therapy centers in developing nations are just beginning to

Onyinye Balogun is involved in various educational projects oriented at training radiotherapy professionals in low- and middle-income countries.



Onyinye Balogun designed a 2-week pilot curriculum for implementing 3-DCRT for breast cancer. The National Center of Oncology in Yerevan, Armenia was the pilot site in 2015.

Balogun (in the centre) with her colleagues at the National Center of Oncology in Yerevan, Armenia.

Balogun in front of the National Center of Oncology in Yerevan, Armenia.

adopt this technology. Standardized means for assisting radiation therapy professionals as they transition from 2-D planning to 3-DCRT are lacking. In response to this need, I designed a 2-week pilot curriculum for implementing 3-DCRT for breast cancer. The National Center of Oncology in Yerevan, Armenia was the pilot site in 2015. Ten RT professionals participated in the pilot curriculum (6 ROs, 2 MPs, and 2 RTTs), which was designed to provide them with the basic foundations of 3-DCRT and confirmed the feasibility of the model for wider application. As a result, we received a grant from the Cornell Institute of African Studies to implement the breast curriculum in Libreville, Gabon. We hope that this will aid centers in delivering radiotherapy safely to patients.

What was the outcome of this project in Armenia and what did you learn from this experience?

It confirmed the feasibility of implementing in a LMIC setting a curriculum that would improve physicians' level of comfort and familiarity with 3-DCRT. The physicians found the exercises that were provided via an online module, Educase, particularly helpful. The experience also highlighted potential areas of improvement i.e. running the curriculum while balancing the physicians' need to tend to busy clinics. It also highlighted the need for more training geared toward radiation therapists who are responsible for the day-to-day positioning of patients on the machine and treatment.

What are the next projects you are going to work on?

One project is to test the pilot curriculum for breast 3-DCRT in Libreville, Gabon.

In addition, we plan to expand the curriculum in Armenia to gynecologic tumours, since they pose a serious threat to the health of Armenian women. Studies of cervical cancer patients have demonstrated that survival is improved when 3-DCRT is used rather than 2-D techniques, most likely because of a better ability to visualize the tissue of interest and deliver dose to this region. In addition, healthy surrounding organs receive a lower dose.

At present, the gynecological patients in Yerevan are treated using 2-D techniques but there is a strong desire to take advantage of the CT scanner and pass to 3-DCRT. This project aims at pilot testing a two-week long curriculum to train radiation oncology professionals in the key processes associated with 3-DCRT implementation for gynecological cancers, in particular: patient positioning for CT scans; delineation of tumor target volumes and organs at risk for radiation damage; design of beam shapes and positions to spare normal tissues. We also seek to expand the training component for radiation therapists, the workers who position and treat the patients each day. Finally, we will pilot test the use of a teleconferencing platform that will connect Weill Cornell Medicine and the National Center of Oncology, with the goal of facilitating feedback on 3D plans. Telemedicine has been posited as a potential means of bolstering radiation therapy delivery in developing nations. This effort will be led by Dr Matteo Botteghi, who designed and successfully piloted "Share and Meet" - a novel intercontinental teleconferencing platform oriented to oncology specialties - in Mwanza, Tanzania in 2015. Among its many functions, this platform conveys the ability to share radiology images and patient medical records for diagnostic and care purposes. The National Center of Oncology in Yerevan, Armenia acquired a CT simulator and a new Elekta linear accelerator in 2015. This is the first center to implement 3-DCRT in a nation of 3.3 million people.

We know that money is a crucial barrier, which prevents these countries from improving their health system and, specifically, from making radiotherapy available to a large fraction of their population. What kind of solutions can we envisage to overcome this problem and reduce the cancer divide between countries?

One goal is to work with manufacturers to innovate machines that are better suited to function in LMIC settings (i.e. machines that take into account an unsteady electricity source) and that are more affordable. Another is to work with governments to determine how resources can be shared amongst countries. For instance, there are ~27 African countries with no radiotherapy machines. For each country to build its own radiotherapy units may be cost-prohibitive. Perhaps there is a way for neighboring countries to pool their resources so that at least in the immediate period they can jointly create radiotherapy services and finance their citizens travel to the agreed upon site of the jointly shared radiotherapy machine. ■

Ion Therapy in the US:
Texas calls Italy

By Marco Durante, Hak Choy and Roberto Orecchia

Table – Hot topics and panelists of round tables at ISIT 2016

Moving targets: problem solved? (Panelists: C. Bert, C. Graeff and K. Noda)	What can we learn from photon and proton physics research? (Panelists: H. Paganetti, S. Schwarz, S. Jiang)
Radiobiology: beyond RBE (Panelists: M. Story, S. Bailey, M. Durante)	Hypofractionation: better with ions? (Panelists: R. Timmermann, I. Toma-Dasu,M. Krengli)
Monitoring in hadrontherapy (Panelists: K. Parodi, D. Dauvergne, G. Battistoni)	Are heavy ions more immunogenic than photons? (Panelists: S. Formenti, W. Tinganelli, T. Shimokawa).
The best phase III comparative trial to compare C-ions to photons (Panelists: S. Combs, P. Fossati, S. Yamada)	Protons or C-ions or else? (Panelists: E.A. Blakely, F. Tommasino, E. Scifoni).

The 3rd International Symposium on Ion Therapy (ISIT) was held in November 2016 in Milan, Italy. A venue for interesting discussions between heavy-ion therapy experts, ISIT was also the occasion for signing a Memorandum of Understanding between US and Italian research institutions.

Heavy ion therapy started in the 70's at the Lawrence Berkeley Laboratory in California, with a pilot project led by Cornelius Tobias. This programme was terminated in the early 90's and, since then, the US have only built proton therapy centres (24 currently in operation; see www.ptcog.ch/), while in Asia and Europe many heavy ion therapy facilities have been established – focusing in particular on carbon ions.

Initiatives are now under way in the US to bring heavy-ion therapy back. The National Cancer Institute (NCI) has awarded 2 planning grants to establish the research components of a future US heavy-ion therapy facility. To promote these activities, the University of Texas (UT) Southwestern School of Medicine in Dallas, one of the recipients of the NCI grant, started in 2014 the International Symposium on Ion Therapy (ISIT), which was held in Dallas in 2015 as well.

This meeting gathers renowned experts in heavy-ion clinical research as well as leaders of ion therapy facilities in Europe and Asia, who bring their knowledge and experience to support the project of building the first national heavy-ion therapy and research centre in the US.

Following a proposal by Hak Choy, ISIT President and chairman of Radiation Oncology at UT Southwestern, the 3rd edition of the Symposium took place in Milan, on 3-4 November 2016, and included a visit to the Italian carbon-ion therapy centre (CNAO) located in the nearby city of Pavia. On that occasion, a Memorandum of Understanding (MoU) between UT Southwestern and the Italian Institute for Nuclear Physics (INFN) was also signed, setting an international collaboration for the R&D in different areas (from medical physics to detectors and dosimetry) in the new US centre (Fig. 2).

ISIT 2016 attracted about 100 participants from the US, Europe and Asia. After a status report from active C-ion therapy centers, the meeting moved on to round tables on different hot topics. For each of them, a panel of three experts gave their vision and hosted a discussion with the attendees. The topics covered spanned radiobiology, dose fractionation, immunology, moving targets, clinical trials, and comparison between protons and different ions (see table for more details on subjects and speakers).

Clinical experience from Europe and Japan was discussed and US researchers presented their future programmes. Among various relevant issues, the importance of designing new comparative, randomized trials comparing X-rays to C-ions and protons was highlighted. In particular, it emerged from the discussion that the future of particle therapy heavily relies on the results of well-defined, comparative, phase-III trials, to be performed on tumors with high incidence and mortality, such as pancreatic cancer, for which the Japanese results are particularly encouraging.

Many students and young researchers attended the workshop. The discussion with them was especially heated and extraordinary interesting, and showed clearly the enormous interest of the radiotherapy community for heavy ions. The meeting also included presentations from companies providing equipment for particle therapy facilities, a session on new initiatives, and a special lecture – held at CNAO - on the clinical activities carried out at the Italian centre.

The 4th ISIT meeting will be held once again in Dallas, on November 2-3, 2017. More information on past and future ISIT events can be found on their website (www.iwptr.org). ■

Figure 1. Group photo of ISIT 2016 in the synchrotron room at CNAO, Pavia.

Figure 2. Signature of a MoU between UT Southwestern and INFN at the opening of ISIT 2016 in Milan.

PhD Scholarship opportunities at the University of Groningen (NL)

The University of Groningen offers 3 scholarship PhD positions for the most talented and motivated national and international students, starting between 1 July 2017 until 31 December 2017. All PhD positions are part of larger research programs, often spanning across different expertise groups and being strengthened by complementary PhD projects already in progress and in preparation. Successful candidates will have completed a Master's degree (or equivalent) in physics or another field of science relevant for the position. They have good command of English (oral and written).

All relevant information is available at
www.rug.nl/education/phd-programmes/phd-scholarship-programme/phd-scholarships?details=00347-02S0005JSPv

Future Events - 2017

DATE	NAME OF EVENT	LOCATION OF EVENT
20-23 June	International Conference on Advances in Radiation Oncology	Vienna, Austria
24-27 September	ASTRO's 59th Annual Meeting	San Diego, California, US
21-28 October	2017 IEEE Nuclear Science Symposium and Medical Imaging Conference	Atlanta, Georgia, US
23-25 October	PTCOG-NA 4th Annual Conference	Chicago, Illinois, US