ENLIGHT

HIGHLIGHTS

June 2018

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DESIGN & LAYOUT
Media Frontier

CALL FOR ACTION

FROM THE ENLIGHT COORDINATOR

Manjit Dosanjh

After having announced it in previous Editorials, in this issue we are including a short article on the launch of the fundraising initiative to support the ENLIGHT Training. Training the next generations of experts in our field has always been an important pillar of our Network, it's certainly one of our founding values. With the ever-growing interest in the field and the increasing number of centres, the need for trained personnel becomes urgent and yet at the same time, it becomes increasingly difficult to secure the necessary support for the students, in particular the young ones coming from challenging financial situations. The inclusion of ENLIGHT in the CERN & Society initiatives, provides us with the necessary framework to allow us to obtain funding in order to make this training possible for which as always, we need and rely on your collaboration and support. Obviously, this calls for an action by each and everyone in ENLIGHT to share this opportunity within your private networks and help us to raise funds for this vital activity. Feel free to distribute copies of this issue and share the link as widely as you can to people who are interested in the field and could become potential donors and sponsors.

Indeed, this issue is particularly suitable for a wide distribution as the topics we touch on are really among some of the hottest ones for the community and span across several countries: Nanoparticles but also Theragnostics, the Focus on Brita Singers Sørensen in Denmark and Surbhi Grover in Botswana, the efforts being carried out to make hadron therapy available in India, and finally the progress made by the UK with the completion of their first National Health Service Hadron therapy centre. The articles are testimony to our members' hard work in several fields and the nice thing about all this is that, thanks to our Network, we can work all in synergy and join forces to move the field forward.

To continue with the good news, in this issue we also report on the Forum of the South-East Europe International Institute for Sustainable Technologies (SEEIIST) held in ICTP Trieste, Italy as well as the Intergovernmental Steering Committee meetings, which took place in Sofia, Bulgaria and Tirana, Albania.

As usual, I would like to thank all the contributors and people in my team for their continued support to make this journal grow in quality issue after issue. I wish all our readers an interesting time spent with us! ■

Manjit Dosanjh

PROTON BEAM THERAPY IN THE UK: THE WAIT IS OVER.

*Raj Jena**

" 2018 will be a landmark year for clinical radiation therapy in the UK.

Raj Jena

*Cambridge

2018 will be a landmark year for clinical radiation therapy in the UK. We look forward to the beginning of clinical proton beam therapy both in the content of our National Health Service (NHS), and from independent providers. We also of course look forward to hosting the ENLIGHT meeting in our glorious capital! However, in spite of long standing clinical and pre-clinical interests in particle therapy, the only clinical treatment capacity in existence in the UK has been the 60 MeV National Eye Proton Therapy Centre at Clatterbridge which started clinical service in the early 1990's. The new NHS Proton Beam Therapy service is implemented across two treatment centres based in London and Manchester, to minimise travel times and link to high quality cancer centres to provide an integrated treatment path with specialist surgery and systemic anti-cancer therapies. The two sites will offer six treatment rooms to NHS patients, each room offering gantry-based pencil beam therapy with in-room cone-beam CT imaging. The Christie Hospital in Manchester is on track to commence clinical services in August-September 2018, whilst services at UCLH (University College Hospitals NHS Foundation Trust) are on track to commence in 2020 due to the scale of the build in a central London location, which also includes short stay surgery facilities and Europe's largest centre for the treatment of blood disorders. In the meantime, there has been significant interest in the provision of proton beam therapy in the private sector, using a simpler single treatment room design. The Rutherford Cancer Centre in Newport, South Wales treated their first patient on 11th April 2018. Even when all of the planned centres are up and running, the combined capacity for PBT treatments will equate to 3% of all radiotherapy activity for the 54 million population of England. As such the capacity for PBT remains conservative when compared to other European nations, where it is envisaged that PBT will represent up to 15% of all radiotherapy activity. However, for the wider U.K. community with clinical and research interests in proton beam therapy, this is a good starting point, and the Christie Hospital will offer the first high energy clinical grade research beam line in the U.K.

Over the last ten years, NHS patients suitable for proton beam therapy have been referred for treatment overseas. The number of indications for overseas treatment remains very small, restricted mainly to paediatric indications and those adult indications where there is evidence of survival benefit for PBT. As a result, most adult patients receiving treatment have para-spinal chordomas or chondrosarcomas, and we have accrued little clinical experience of any other treatment indications. We have also had no experience of re-irradiation using proton beam therapy, which remains a contentious but important use case in many other health systems.

Table 1
Proton Overseas Programme - Diagnosis and age casemix

Diagnosis	Adult	Teenage and young adult	Paediactric
Chordoma	147	18	15
Chondrosarcoma	86	12	5
Low grade giloma	__	16	138
Ependymoma	__	11	140
Craniopharyngioma	__	11	87
Rhabdomyosarcoma	__	8	176
Peripheral primitive neuroectodermal tumours	6	8	105
Soft tissue sarcoma	11	10	15
Other	17	40	62
Total	267	134	743

Cambridge University

As a member of the ENLIGHT community, it has been frustrating to witness the press reaction to PBT as a new technology, when we know that this is not the case. Proton Beam therapy commenced 64 years ago in Berkeley, in the same month that CERN was established. Proton beam therapy in Europe started 61 years ago in Uppsala. One might argue that these early laboratory-based treatments are not reflective of a clinical grade service, but even taking this into account, it is 28 years since the first hospital-based treatment at Loma Linda University Medical Centre in California. Our own efforts in the ENLIGHT consortium to perform research in accelerator physics, radiation biology, imaging, dosimetry and informatics now have a 16-year pedigree. So, whilst it is clear that PBT is not conceptually new, it's clinical evidence base remains in an early state, and it is this aspect where perhaps the U.K. can focus. In radiation therapy we have a strong history of undertaking practice-shaping clinical trials. We have a strong infrastructure for clinical trials in the form of the National Clinical and Translational Radiotherapy Research Group (CTRAD) and we can draw from a large population of patients all treated and followed up in a single healthcare system. As indications for the common adult tumours are explored, we can start to build a clinical trial evidence base and contribute a useful resource to the international radiation oncology community. However, for the rarer tumours, including many of the paediatric indications, we cannot accrue patients at a sufficient rate to make a national clinical trial feasible. The only way to gather enough patients in a reasonable timescale is to establish trans-national clinical trial. As a clinician member of ENLIGHT, I hope that the wider clinical community can learn from our own experiences of working together in a productive research consortium. ■

Authors note: *This commentary was written following the publication of a special issue on the topic of proton beam and particle therapy in Clinical Oncology May 2018, Volume 30, Issue 5.* ***http://www.clinicaloncologyonline.net/***

X-RAY TO PARTICLE THERAPY IN INDIA: NEEDS, CHALLENGES, AND OPPORTUNITIES

*Siddhartha Laskar, Sanjeev Sood, Rajendra Badwe**

Total Area
3,287,263 Sq. km

Total Population (X1000)
1,21,01,93,422

Literacy Rate
59%

Infant Mort. Rate
54.6 deaths /1000 Live Births

New Cancer Cases/ Yr
1 million (approx)

**Tata Memorial Centre, Mumbai*

THE CURRENT SCENARIO

With a population of over 1.2 billion people, a literacy rate of 59%, 14 official languages and an irregular distribution of resources with many contrasts and cultural gaps, India faces many challenges in health care, including the delivery of affordable and equitable cancer care. Given the rate at which the Indian population will grow in the coming years and other factors, the International Agency for Research on Cancer GLOBOCAN project has predicted India's cancer burden to nearly double in the next 20 years, from slightly over a million new cases in 2012 to more than 1.7 million by 2035.

Radiation therapy forms an integral component of treatment for most solid tumours. It plays an important part in the treatment regimens for common cancers in India, including breast, head and neck, cervical cancers. In almost 70% of cases, radiotherapy is used with a curative intent as either a definitive treatment or as an adjuvant along with surgery and/or chemotherapy. It is also used extensively as an effective and inexpensive modality for palliation of symptoms in advanced or incurable diseases.

The use of radiotherapy in India dates back to the late 50s. The first Cobalt 60 Teletherapy unit and Linear Accelerator were installed in 1956 and 1976 respectively at the Tata Memorial Hospital, in Mumbai and the Adyar Cancer Institute in Chennai. According to data from the Atomic Energy Regulatory Board and from IAEA-Directory of Radiotherapy Centers, approximately 438 centres (till December 2017) are currently licensed to use ionizing radiation for treatment of cancers in India (see Table 1).

Although a large proportion of cancers requiring radiotherapy can be treated using Cobalt 60 machines, as we know, linear accelerators are required for delivery of more complex techniques. Unfortunately, although the number of Linacs available in India has increased over the years there still remains a large shortfall. Indeed, the World Health Organization and the International Atomic Energy Agency (IAEA) norms recommend one teletherapy machine per million population. In India, the current status is 0.41 machines per million population. With a population of 1.3 Billion (1300 Million), India would ideally require 1300 teletherapy units. With the present machine strength of 642, the shortfall is of approximately 650 machines.

The very good news is that proton beam therapy will soon be available in India. The first proton therapy facility in the public sector is being built at the Tata Memorial Centre, in Mumbai. It is expected to be commissioned in 2020.

National Hadron Beam Therapy Facility Tata Memorial Centre, Mumbai

Table 1: Status of Tele-therapy & Brachytherapy Machines in India (2017)	
Cobalt 60 Teletherapy	220
Linear Accelerators	398
Cyber Knife	7
Gamma Knife	7
Tomotherapy	10
Total Number of Teletherapy Machines	**642**
Brachytherapy (LDR + HDR)	**313 (40 + 273)**

Over the coming years and besides the shortfall of modern equipment, India will also experience an acute shortfall of trained human resources required for delivery of optimal cancer care in the whole country.

THE BIG GAP

If compared with high-income countries, public expenditure on cancer is 10 times smaller in India, and overall public expenditure on health care is still only slightly above 1% of gross domestic product. Although cancer incidence is less in India than in the US (1014 cases per 100000 people in India, to be compared with 1603 per 100000 in the US), the cancer deaths are more numerous (682 to be compared with 617 every 100000). More importantly, the 5year survival rate of all cancers is less than 30% in India and over 60% in the US. Finally, in the US the ratio of simpler to sophisticated treatment is 25:75, while in India it is 70:30.

THE OPPORTUNITIES

Given the current accessibility to state-of-the-art technology, technically speaking, the situation in India could rapidly improve, in particular via the introduction of particle therapy. However, this calls for additional clinical research to develop robust data to support or refute the use of particle therapy with respect to more classical treatments.

Indeed, in spite of its high potential, charged particle therapy has not witnessed rapid developments even in higher-income countries (see Table 2). This relatively slow progress in the development and clinical use of particle therapy can be attributed to four main reasons: 1) Very high cost 2) Large size of equipment/facility and the need for refinements in technology i.e. dosimetry/ gantry/ patient positioning systems/ image verification etc. 3) Higher levels of expertise required compared to conventional radiotherapy and 4) Rapid developments happening in the field of radiation therapy using photons (IMRT, IGRT, SRT, Helical Tomotherapy etc.)

THE TATA MEMORIAL CENTRE

The Tata Memorial Centre (TMC), Mumbai is a Grant-in-Aid institution under the Dept. of Atomic Energy, Govt. of India. The Tata Memorial Centre was conceptualised and built by the house of Tata's in 1941 as a comprehensive cancer care centre. Since its inception the motto of the institution has

Table 2

Statistics from Proton Therapy Co-operative Oncology Group (PTCOG) Updated July 2017

Functional Facilities:

Proton: 62 (Japan - 8, China – 1, S. Korea – 1)

Carbon: 11 (Japan – 4, China – 2)

Facilities Under Construction:

Proton: 29 (Japan – 4, China – 1, S. Arabia – 1, S. Korea – 1, Taiwan – 1, India – 2)

Carbon: 4 (Japan – 1, China – 2)

For more information about the current status of particle therapy centres worldwide, please go to page 18 - 19

been Service, Research and Education.

TMC currently registers approximately 65,000 new cancer patients every year, with patients from all across the country and the subcontinent. Patients are investigated and treated under one roof with specialised treatments delivered within specific disease management groups. With rapid increase in the number of patients and with the focus at making quality cancer care accessible and affordable across the country, TMC has established multiple satellite centres across the country under a hub and spoke model to ensure uniformity in delivery of quality care. The commissioning of the Proton Therapy Facility in 2020 will make this advanced treatment modality accessible to patients from across the country and abroad at an affordable cost.

The Tata Memorial Centre (TMC), proton therapy facility will be a state of the art facility with 3 patient treatment rooms having 3600 rotation gantries incorporated with the latest Pencil Beam Scanning (PBS) technology capable of delivering Intensity Modulated Proton Therapy (IMPT) using a cyclotron producing protons with energies ranging from 60 - 230 MeV. All treatment rooms will be equipped with robotic treatment couches enabling 6 degrees range of motion with image guidance, planning and quality assurance tools allowing maximal flexibility in treatment delivery with high precision. The treatment rooms will also have facilities for delivery of anaesthesia during treatment for very young children requiring sedation for treatment. In India approx. 50,000 children are diagnosed with cancer every year. Approx. 2000 of them would potentially benefit with proton beams. Similarly, a much larger number of patients in the adult age group would also benefit from proton beam therapy.

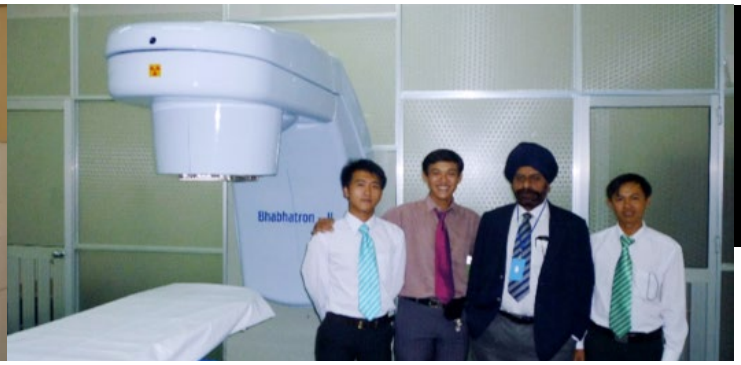
The facility at TMC would benefit patients in both paying and non-paying categories (40:60 in TMH). Currently the cost of one course of proton beam therapy treatment in the US is approx. 100-250,000 USD (1-1.5 Crore INR). The commissioning of the proton therapy facility in 2020 at TMC will make this state of the art treatment facility accessible to a large number of deserving patients from within the country and also cater to patients from neighboring countries. The TMC facility will be able to treat approx. 800 patients every year. It will be India's national facility for hadron therapy.

RESEARCH AND DEVELOPMENT

With the available expertise and research infrastructure at TMC and the growing use of particle therapy for treatment of cancers globally, there is a definite need to conduct focused research to critically review the impact of this technology in the outcomes of cancer therapy. With the large numbers of patients that we expect to treat in the proton therapy facility at TMC, there will be an opportunity to embark on relevant research directed at generating robust high quality scientific evidence to support or refute the use of particle therapy for

Tata Memorial Hospital (TMH)

Advanced Center for Treatment. Research and Education in Cancer (ACTREC)



Indigenous Technology - *Top left:* ***Nigeria,*** *top right:* ***Vietnam,*** *bottom left:* ***Zambia ,*** *bottom right:* ***Mongolia***

various indications both in adults and paediatric populations.

Towards this we propose not only to initiate in-house research projects but also collaborate with our global counterparts like the Radiotherapy and Oncology Group (RTOG), Childrens Oncology Group (COG), European Organisation for Research and Treatment of Cancer (EORTC), Proton Therapy Cooperative Oncology Group (PTCOG), National Cancer Institute (NCI), and International Atomic Energy Agency (IAEA) etc.

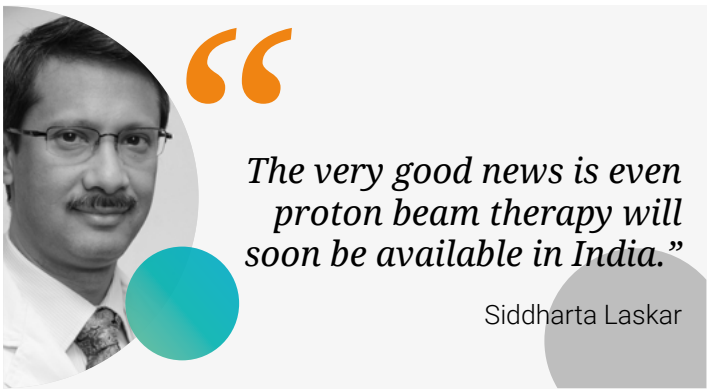
It will be an opportunity for undertaking research related to high and low LET radiation biology. Scientists/physicists from TMC, Bhabha Atomic Research Centre (BARC), Centre for Development of Advanced Computing (C-DAC), and Society for Applied Microwave Electronics Engineering and Research (SAMEER) and other affiliated institutions will have an opportunity to work in tandem with institutions like IIT, CERN, NCI and Industry partners involved in the development of hadron facilities and undertake research activities related to heavy particle accelerator technology. The TMC's interest in developing a multiple-ion compact accelerator for clinical particle therapy is in sync with the Proton-Ion Medical Machine Study (PIMMS II) initiative of CERN.

In keeping with the current efforts of the government of India to encourage indigenous development of technology, 20% of the proton therapy equipment being installed at TMC is manufactured in India. Further, this could pave way to indigenous development of advanced and low-cost technologies with wider applicability in the future. TMC in collaboration with BARC (DAE) has successfully developed indigenous cobalt teletherapy machine (Bhabhatron) and radiation therapy simulator (Imagine). This locally manufactured equipment is in use within the country as well as abroad.

EDUCATION

Training and human resource development in particle therapy and related areas of technology and biology will be areas of thrust for the TMC PTC. ■

IAEA Technical meeting in Particle Therapy, Vienna, Austria.

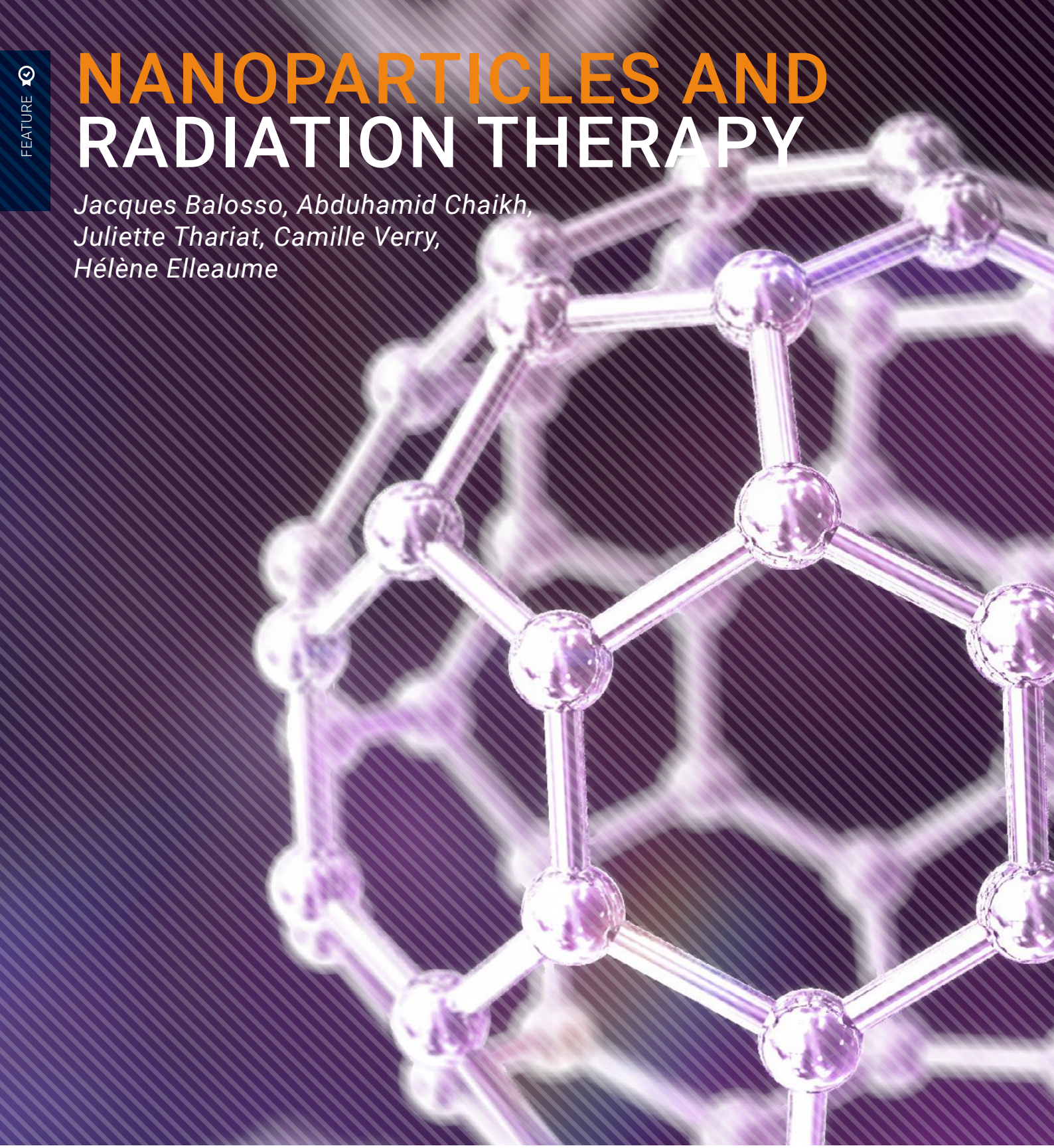


"The very good news is even proton beam therapy will soon be available in India."

Siddharta Laskar

NANOPARTICLES AND RADIATION THERAPY

Jacques Balosso, Abduhamid Chaikh, Juliette Thariat, Camille Verry, Hélène Elleaume



NANOPARTICLES, WHAT ARE THEY

Nanoparticles used in medicine are nanostructures having dimensions ranging from 1 to 100 nm. They are built from a core, possibly with little reactivity, surrounded by different layers or coated with functional structures designed to give them several particular properties, such as enhanced selectivity for their targeted tissues. Small nanoparticles, less than about 10 nm are usually eliminated by the urinary tract and have little tendency to accumulate in the body after treatment; large nanoparticles are potentially more toxic and may be responsible for long-term effects. The synthesis of nanoparticles is based on the combination of physical and chemical methods that sometimes results in a certain variability, so the exact reproducibility of nanoparticles is a real difficulty. Firstly, the remarkable properties of nanoparticles, not only in pharmacology but also in chemical and industrial terms, are primarily due to the extraordinary interacting surface offered per unit mass, so that a material with little or no reactivity in massive form can become very reactive in the state of activated nanoparticles. Secondly, come the potentialities offered by the multiple layers and functional structures that

can be added and which are not yet, by far, neither mastered nor well explored. The possible combinations of functions are literally infinite and we can consider that the nanoparticles, as currently conceived, are molecular toolboxes with multiple interchangeable functions (see Figure 1), some even speak about nanobots, for which possibilities are certainly very wide.

WHY USE NANOPARTICLES IN RADIATION THERAPY?

The principle of a combined modality

Nanoparticles may be associated with radiation therapy for several purposes. In particular, they aim at increasing the differential effect between healthy tissues and tumours. In fact, adding a medical treatment, currently still known as "chemotherapy", to irradiation for combined modality (chemo-radiotherapy) is a widespread and standardized practice for most radiation therapies with curative intent, or even as complement to surgery. Common belief is that chemotherapy modifies the radiosensitivity of tumour cells and not of healthy cells. In fact, the standard chemotherapies used in radiotherapy have no discriminating character between healthy and tumour cells, and, fortunately enough, they do not modify the cells' radiosensitivity but act to reduce the kinetics of tumour repopulation during the protraction of the treatment, which is already a very considerable effect. To improve the limited effectiveness of radiotherapy on radioresistant tumours (because of their intrinsic radioresistance and/or the sensitivity of the surrounding healthy tissues), radiation oncologists continue to search for agents capable of specifically sensitizing tumour cells to irradiation. The potentialities of nanoparticles make them candidates for this purpose and many are therefore developed and are being developed and tested for this aim. nanoparticles may act as chemotherapy but in a more selective way, the treatment being therefore less toxic and more effective on tumour cells (without necessarily interacting with the physico-chemical phenomena of irradiation) or may interact directly with irradiation and dose deposition. The latter effect of nanoparticles has been studied for several years with synchrotron radiation, and can now, thanks to nanoparticles, enter the field of radiotherapy in general. Finally, in a more indirect way, nanoparticles devoted to medical imaging can help to specify the targets of irradiation, or even participate in both imaging and treatment, which is precisely the case of theranostic nanoparticles.

Increase the local dose at the cellular level

Increasing direct interactions of irradiation with nanoparticles, requires doping the tumour tissue (not necessarily by penetrating the tumour cells) with particles containing heavy chemical elements (^{14}Si, ^{26}Fe, ^{53}I, ^{64}Gd, ^{72}Hf, ^{79}Au, ^{78}Pt, ^{82}Pb ...). Most of these elements are absent from the human body or in very low quantity and are generally not constituents of anticancer drugs. These elements are either part of the core of the nanoparticles or attached to it by chelating molecules. The nanoparticles present in the tissues physically intercept the radiation that interacts with these heavy elements according to various effects: photoelectric, Compton, etc. The result

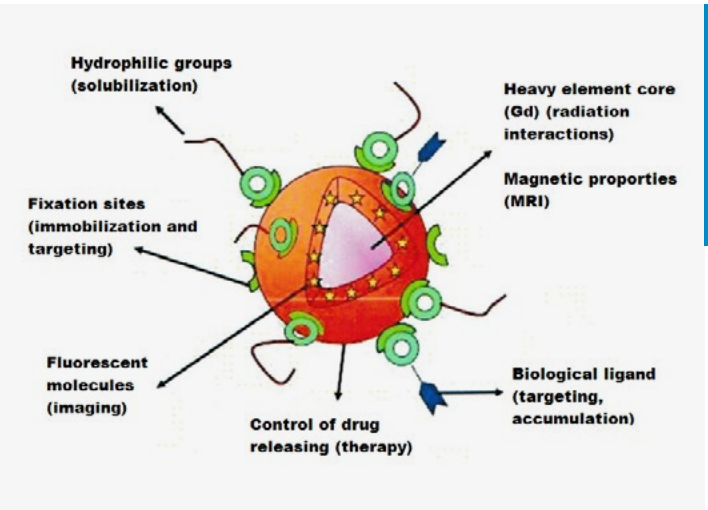


Figure 1: *The principle of a multilayer and multifunctional nanoparticle (redraw from I. Miladi, PhD thesis 2012)*

is a dense sheaf of secondary electrons (photoelectrons and Auger electrons) producing a local dose, which is huge at the micrometric scale. Radiation oncologists may have experienced unexpected severe mucositis in contact with metal dental implants in patients due to similar phenomenon. At the subcellular level, dose peaks are created (see Figure 2), which can be assumed to be deleterious to the affected cells even if they are outside the nuclei. The diffusion and retention of these nanoparticles in the tumour often rely on a passive phenomenon (Enhanced Permeability and Retention, EPR) related to the tumour microenvironment and nanoparticles' characteristics. Some nanoparticles remain out of cells; others penetrate the cells and accumulate like some iron and gold nanoparticles. These phenomena are not yet sufficiently understood to be predictable and designed, but the possibility of real targeting is expected.

While the majority of nanoparticles used rely on passive targeting via the EPR effect, there is a clear trend towards active targeting to further increase drug accumulation and efficacy in the tumour, while reducing toxicity in other organs. Nanoparticles can also be used both for imaging and treatment, they are then called "theranostic nanoparticles". In a very simple way, as for example with gadolinium, this heavy atom (Z = 64) makes the nanoparticle radiotoxic but also makes the tumour visible in MRI. Moreover, we can also substitute a Gd atom with a radioisotope and make the nanoparticle therapeutic and visible in SPECT or PET; use of different versions of the same nanoparticle with different radioisotopes suitable for imaging (photon emission) or treatment (beta or alpha emission); can also use fluorescent functions, etc. In addition, providing the nanoparticles molecular patterns of specific recognition of tumour cells or other structures (vessels by cRGD peptide for example) could allow their entry and retention in cells, etc. (see Figure 1). At this stage, the transport of cytotoxic elements will transform these nanoparticle, from radiotherapy adjuvant nanoparticles, into a perfectly autonomous anti-tumour treatment, which is the main objective of nanoparticle research in oncology. Ultimately, this will enhance radiotherapy effects using cytotoxic chemotherapy-like effects and dose enhancement.

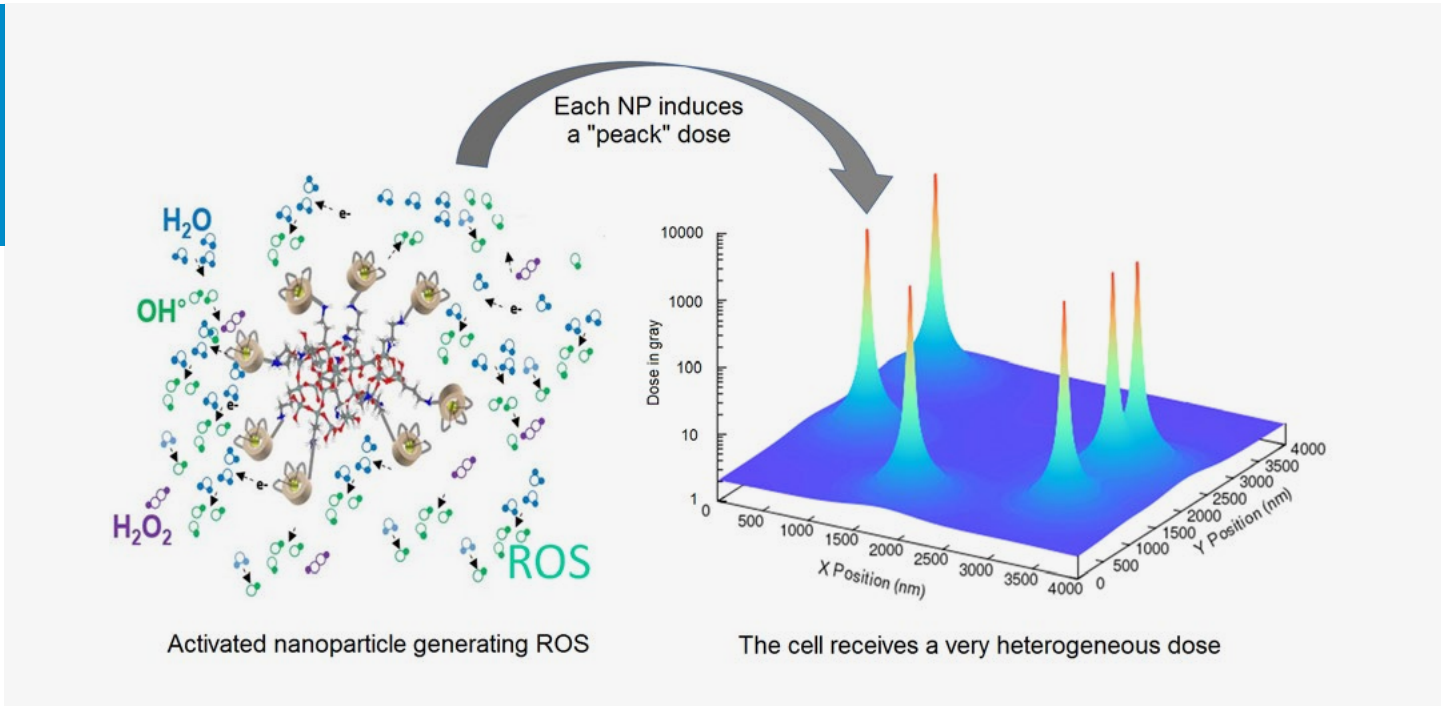


Figure 2: *Representation of the huge dose enhancement at location of nanoparticles, or cluster of nanoparticles, present in the cell and generating under irradiation a very important cluster of ROS (draw from L. Sancey, 2014 and SJ. McMahon simulation, 2010).*

Increasingly complex nanoparticle radiation interactions

Beyond this still rather simplistic use (physical sensitization), other photon-material interaction mechanisms could be further exploited. The efficiency of the photon-electron interaction with the heavy elements of the nanoparticles could be considerably increased by irradiating at the energy levels of the photoelectric effects (a few tens of keV) using quasi-monochromatic radiation, which is possible with synchrotron radiation as experienced in the first clinical trial performed at the European Synchrotron Light Source (ESRF). We could trigger extremely destructive phenomena such as the Mössbauer effect by interacting with ^{57}Fe nanoparticles that have a cross section 450 times larger than that of the photoelectric effect. Alternatively, photodynamic therapy could also be triggered by irradiation during radiotherapy by using nanoparticles containing both a radioluminescent element and a phototoxic element, the former activating the second during irradiation and producing an additional toxic effect. The combination of ferromagnetic nanoparticle with magnetic stirring, or ultrasound, can create local hyperthermia that will enhance the effect of radiotherapy by slowing down the DNA repair of malignant cells, etc.

Toxicity and routes of administration

These approaches, which are much more complex, also raise the question of the route of administration. The simplicity of a general administration by intravenous (i.v.) route could then favour the very small nanoparticle because they can be excreted by the urinary route and can thus present an outstanding good tolerance. However, even the larger nanoparticles initially administered by transcutaneous direct route by multi-puncture tumour, much like mesotherapy, may find an interesting use by intra-arterial injection into the tumour vessels by interventional radiology as is common practice for hepatic tumours and metastases. With respect to radioactive or chemotoxic microparticles, this technique would have the advantage of dissociating the anatomical distribution (which may sometimes inadvertently exceed the limits of the organ) of the toxicity (focused by the ballistics of the irradiation). These large nanoparticles could then offer more specific functionalization possibilities.

THE SPECIFIC AND SURPRISING CASE OF HADRONTHERAPY

Can hadrontherapy, the ultimate frontier of radiotherapy, mastering physical and radiobiological complexity, also benefit of nanoparticles? Hadrontherapy does not cure everything, it is one more step for radiotherapy but it also has limits and failures. Thus, the same way of thinking applies to particle therapy and research on the interactions between heavy elements and protons or ions have been conducted for a long time even before the concept of nanoparticle encompasses this field. Proton-nanoparticle clinical trials are being prepared. Some studies also take unexpected paths such as using protons without the spread-out Bragg peak (SOBP), as the dose-increasing factor can be very high. The types of possible interactions in particle therapy with nanoparticle are different from those of photons and could be triggered by projectile induced x-rays emission (PIXE), itself being the origin of intra-atomic cascades of electron emissions.

Nanoparticles could eventually transform hadrontherapy even more than photon therapy. However, combined chemotherapy is only just beginning to appear in hadrontherapy, so it may take some time for radical changes to hadrontherapy by nanoparticles. For the moment, this remains a rather long-term experimental prospect.

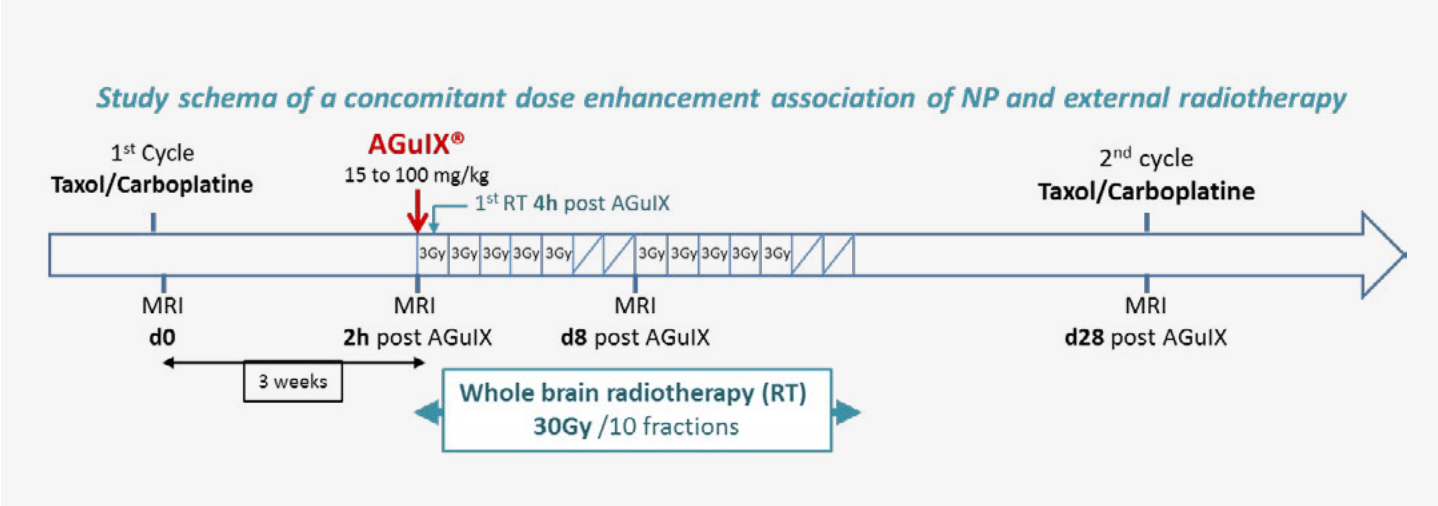


Figure 3: *The experimental schema of i.v. route administration of a Gd based theranostic nanoparticle in association with external beam radiotherapy for multiple brain metastasis in a phase I, first in man trial (PI C.Verry, Sponsor Grenoble University Hospital).*

WHAT IS THE BEST ROLE CASTING FOR A NANOPARTICLE?

Small to use via general i.v. route; a rather diffuse effect than solely at the level of the targeted cells to overcome tumour heterogeneity; multifunctional to provide biological and physical sensitization; theranostic to guide dosimetry and ballistics; vectorized toward areas of greater tumour radioresistance; inexpensive (therefore easy and reliable to produce); low toxicity for repeated use, even daily during radiotherapy; and ancillary functions of targeting, intracellular retention, transport of anti-tumour drugs or molecules activated by the oxidant stress produced by irradiation around the nanoparticles, etc.

MACRO PERSPECTIVES FOR NANOPARTICLES

Given the structural potential of nanoparticles we could say that today we just know how to use the subframe of these extraordinary pharmacological vehicles. We certainly do not have enough imagination to think of anything that can appear and be experienced in the future, so it is difficult to guess what will happen in the routine, but one thing is certain, the radiotherapy tomorrow, RX or particle therapy, will be accompanied by nanoparticles and some surprising advances can be expected. In addition, it is not excluded that nanoparticles also do other things in radiotherapy that help kill tumour cells, we can imagine very sophisticated diagnostic functions as at last true molecular imaging, but also functions that are not yet feasible (information on evolution and tumour response, real-time in-vivo dosimetry information, etc.).

Given the structural variations, the structure-function relationships are extremely complex and provide an obvious place for a huge amount of in vitro and pre-clinical experimentation for decades to come.

Do the first clinical trials meet their promises? Could a substantial and selective increase in tumour radiosensitivity avoid the use of much more expensive and rare treatments such as proton and ion radiotherapy? Will nanoparticles open today unimaginable curative indications and not only "improve" difficult situations such as, for example, brain multimetastatic conditions treated with pan-encephalic external irradiation with very little differential effect and no definite success? The first marketing authorizations are coming, but there are still very few prospective clinical studies that really combine nanoparticles and radiotherapy. One can count, on the site Clinicaltrial.gov, 82 active studies in the World, recruiting or not, of the application of nanoparticles in oncology, in 8 of these, the nanoparticles are associated concomitantly with radiotherapy and only 6 under the concept of dose enhancement (see Figure 3). For the moment these questions are unanswered but the development of studies is very fast and this question will undoubtedly be at the centre of the onco-radiotherapy practice of tomorrow. ■

Acknowledgments: The authors are grateful to the following scientists for information sharing, experimental and results discussions: Imen Miladi, Claire Billotey, Pr Marc Janier, Laure Bobyk, Jean-luc Ravanat, Rachel Delorme, Pr Christophe Champion, Mathieu Angelon, Florence Taupin, Lucie Sancey and Pr Claire Rodriguez-Lafrasse.

"We can consider nanoparticles as molecular toolboxes with multiple interchangeable functions."

Jacques Balosso

FEATURE

THERAGNOSTICS: THE TROJAN HORSE FOR BATTLING CANCER

Stefano Buono, the founder and, after its acquisition by Novartis in 2018, current Advisor of the international radiopharmaceutical company Advanced Accelerator Applications (AAA); seems to have learned how to trick cancer. The principle behind such a weapon is the typical Trojan horse: bringing the weapon, disguised as a friendly molecule, inside cancer cell to kill it.

"Although the idea of theragnostics is not young – some reference it back more than 50 years – the very first registrations of gallium 68- and Lutetium 177- based radiopharmaceuticals that could be used as a theragnostic pairing were achieved by AAA in 2016 and 2017," confirms Buono. The theragnostic concept in nuclear medicine is based on using a single targeting molecule to deliver either a diagnostic or therapeutic radioisotope to a tumour cell, providing a more complete approach to patient management. Gallium 68 is a short-lived and PET compatible positron emitter, which, once trapped in the tumour's cells, allows for a very precise localization of the lesion and is quickly cleared from the body. As reported by R.Levine and E. Krenning, the first 12 patients were imaged with ^{67}Ga-dotatoc as a surrogate for ^{68}Ga-dotatoc PET in 1995 and early 1996. A decade later, in 2016, the first theragnostic drug based on Gallium 68 was registered in the US. Regarding ^{177}Lu, we have to go back to 1998 when ^{177}Lu dotatate was being investigated by S.P.I.R.I.T (Specific Peptides for Imaging and Radio Isotope Therapy), the scientific collaboration whose goal was to develop marketable radiopharmaceuticals using targeting peptides and peptide-like molecules to deliver diagnostic or therapeutic medical doses to specific sites within the body. Over the next 16 years, over 3,000 patients were treated with ^{177}Lu-dotatate on an investigative and compassionate use basis prior to approvalby regulatory authorities. After acquiring BioSynthema Inc., the spinoff of the S.P.I.R.I.T. collaboration, AAA set up a commercial manufacturing process and negotiated with the FDA and the European Medicines Agency to run the multinational phase 3 study (NETTER-1) at 41 global sites. "Physics teaches us that ^{177}Lu is a potentially perfect isotope," says Buono. "Its beta particles have just the right energy to kill cancerous cells and, in addition, it emits gamma rays that can be used to monitor drug penetration into the tumour mass during the treatment".

From September 2012 through mid-January 2016, a total of 229 patients with progressive midgut neuroendocrine tumours underwent randomization at 41 sites (27 sites in Europe and 14 in the United States). According to the "Phase 3 Trial of 177Lu-dotatate for Midgut Neuroendocrine

Manufacturing at AAA

Tumours" (N Engl J Med 2017; 376:125-135 DOI: 10.1056/NEJMoa1607427) study published in January 2017, treatment with ^{177}Lu-Dotatate resulted in a risk of progression or death that was 79% lower than the risk associated with high-dose octreotide long-acting repeatable (LAR), the best supportive care. The estimated rate of progression-free survival at month 20 was 65.2% (95% CI, 50.0 to 76.8) in the ^{177}Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The median progression-free survival was 8.4 months in the control group and had not yet been reached in the ^{177}Lu-Dotatate group. ^{177}Lu-Dotatate, when administered concomitantly with a renal-protective agent, was associated with low rates of grade 3 or 4 hematologic toxic effects and showed no evidence of renal toxic effects over the trial time frame (median duration of follow-up, 14 months).

"Thanks to the industrial platform and the logistics provided by AAA, 177Lu-based therapeutic drug is now being made available to all eligible patients in the US and Europe," explains Buono. "On the other hand, the situation with our 68Ga-based drug for PET diagnostics is more complex, because, given its very short half-life, it needs to be produced really locally. In the US, we have equipped over 50 radiopharmacies with Gallium generators, devices that produce gallium from germanium three times a day. In Europe, radiopharmacies do not exist everywhere and therefore hospitals need to buy such devices and produce the radiopharmaceutical in situ as they do with technetium-99 (99Tc) used in SPECT. Unlike 99Tc generators, which need to be bought once a week, the gallium generators last about 6 months, but are more expensive."

The penetration and distribution of drugs happen with very different modalities in the US and in Europe, but this is just a bureaucratic detail that won't prevent these drugs from making their way to patients and replacing the "one size fits all" approach used historically. "However, these AAA theragnostic drugs can only be used for those malignancies that express high levels of targetable receptors," clarifies Buono. "Unlike fluorine-18, gallium-68 cannot be bonded with simple molecules like sugar and therefore cannot be used to perform an accurate diagnostic of general tumours."

In other words, the current theragnostic drugs are exploiting a certain type of "Trojan horse" but more research is needed in order to find other targetable receptors in tumour cells that will let the horse in. "This is where the research becomes very specific," explains Buono. "We now have the industrial platform that allows us to produce gallium 68 for imaging and lutetium 177 for treatment but we need to develop good molecular targeting molecules which also need to quickly leave the body after use. Those molecules will get the isotopes into the cancer cells. "Currently we are working on developing drugs to target a variety of malignancies, such as metastatic prostate and breast cancer, colorectal cancer, lung cancer and other GI cancers.," says Buono. "Our next two theragnostic drugs are starting clinical trials now. Each time we target a new type of tumour we foresee a research and development phase of 5 to 10 years."

During Buono's tenure, the AAA company he founded expanded its presence to 13 countries and reached €150M in sales prior to the launch of its first therapeutic. However, since a few months, Stefano Buono's professional path has moved away from AAA. Educated as a research physicist with a number of scientific publications, grown up as a business man operating in the pharma industry, Buono is now turning his attention to the biotech field, as well as social and other fields of innovation that have the potential to produce a real-life impact on people. ■

"Theragnostics brings the weapon, disguised as a friendly molecule, directly inside the cancer cells and kill them."

Stefano Buono
interviewed by
Antonella del Rosso

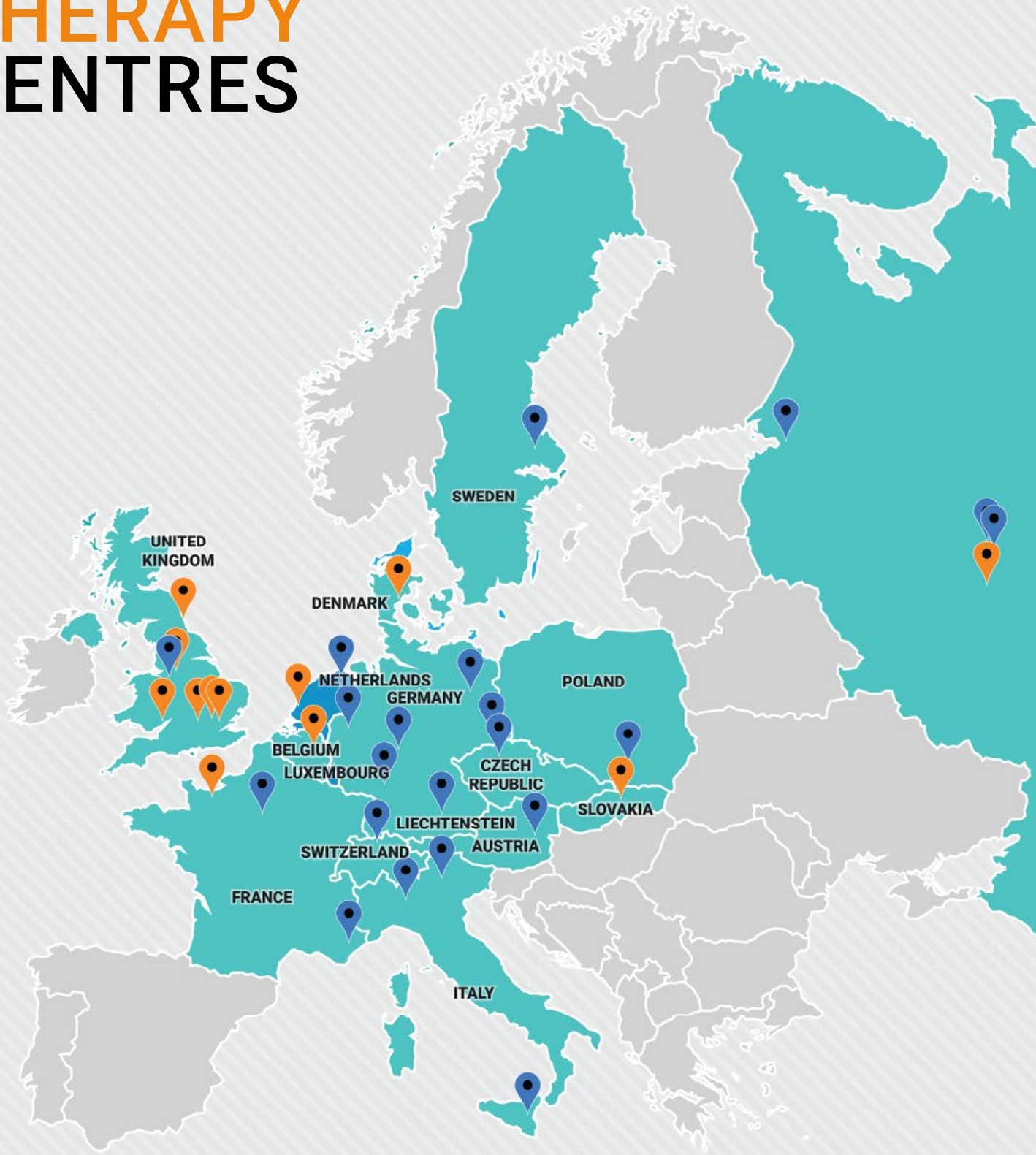
Disclaimer: *Lutathera is approved in the US to treat adults with a type of cancer known as gastroenteropancreatic tumours (GEP-NETs) that are positive for the hormone receptor sandostatin, including GEP-NETs in the foregut, midgut and hindgut. Lutathera is approved in the EU to treat unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive GEP-NETs in adults. Lutathera can cause serious side effects including: decreased blood cells, increased liver enzymes, vomiting, nausea, increased blood glucose and decreased blood potassium. If patients experience any of these side effects, they should discuss with their doctor. Netspot, after labeling with Gallium 68, is a diagnostic radioactive agent used to image and localize neuroendocrine tumours, that are positive for the hormone receptor somatostatin, in adults and children. Netspot contributes to long-term exposure to radiation, which is associated with increased risk of cancer. SomaKit is indicated for PET imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated GEP-NETs for localizing primary tumours and their metastases.*

AGENDA

NAME OF THE EVENT	DATE	PLACE OF THE EVENT
Ideas and technologies for a next-generation facility for medical research and therapy with ions	19 - 21 June 2018	*Archamp, France*
ENLIGHT 2018	25 - 27 June 2018	*London, UK*
ASTRO's 60th Annual Meeting	21 - 24 October 2018	*San Antonio, Texas, US*
2nd Estro Physics Workshop - Science In Development	26 - 27 October 2018	*Malaga, Spain*
2018 IEEE Nuclear Science Symposium and Medical Imaging Conference	10 - 17 November 2018	*Sydney, Australia*
ESTRO 38 Annual Meeting	26 - 30 April 2019	*Milan, Italy*
PTCOG 58 Annual Meeting	10 - 15 June 2019	*Manchester, UK*

2018 IEEE Nuclear Science Symposium and Medical Imaging Conference
25th International Symposium on Room-Temperature Semiconductor X-Ray & Gamma-Ray Detectors
10 - 17 November 2018, International Convention Centre Sydney, Australia

PARTICLE THERAPY CENTRES



ENLIGHT

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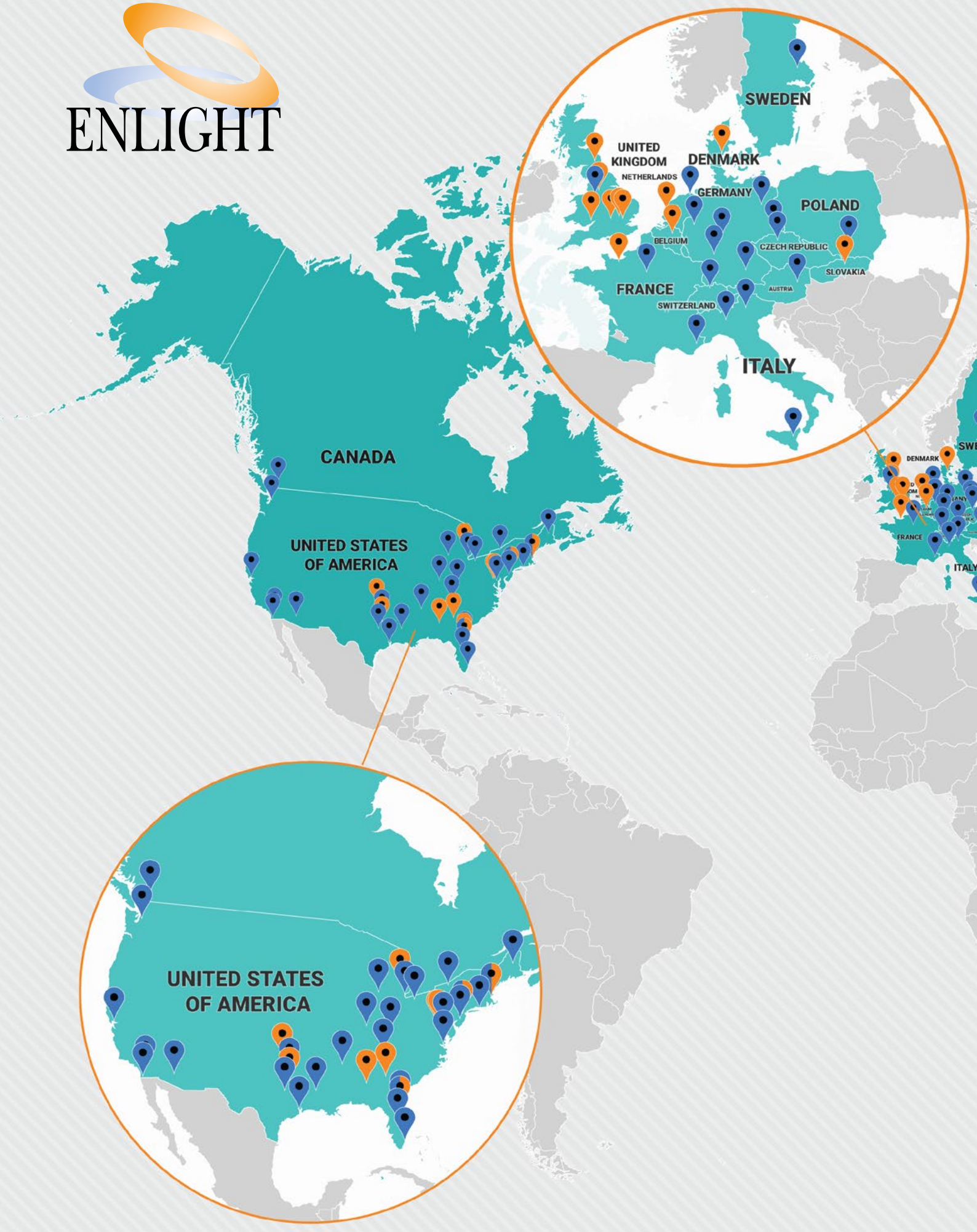
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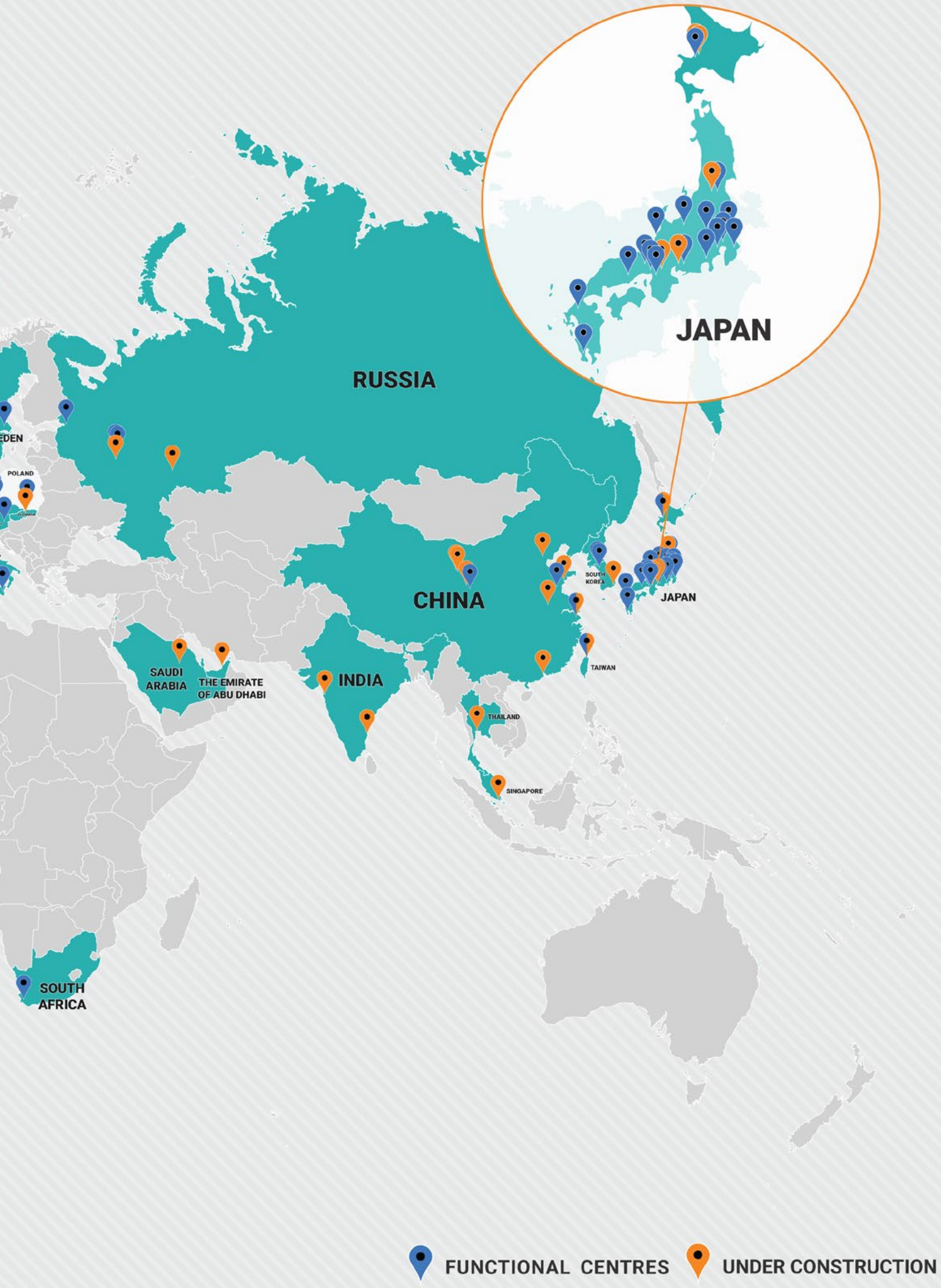
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FUNCTIONAL CENTRES
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CERN & SOCIETY FOUNDATION IS PROUD TO SUPPORT ENLIGHT TRAINING

cern.ch/giving

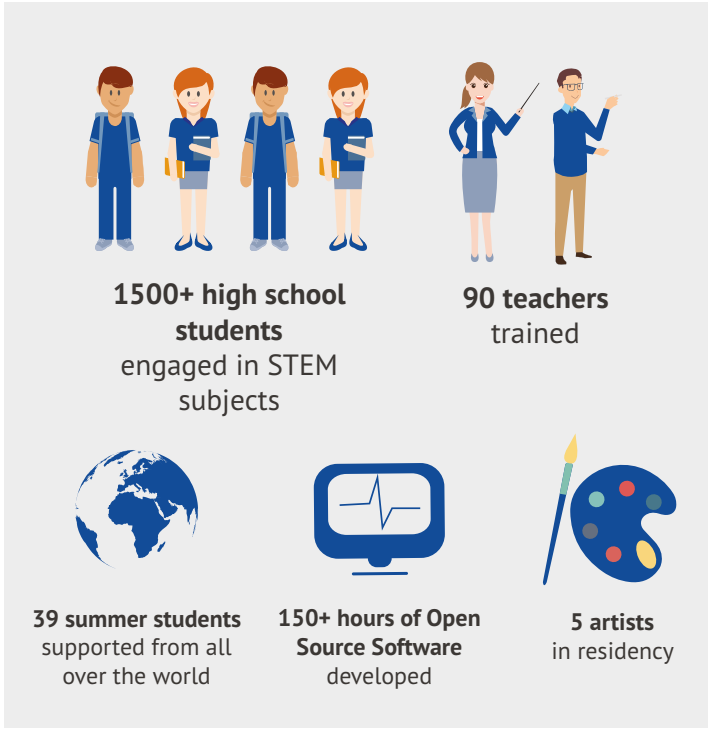
CERN & SOCIETY INTRODUCES ENLIGHT TRAINING:

The CERN & Society Foundation was established in 2014 to raise awareness of the pivotal role of science in society. CERN's impact reaches far beyond fundamental research, and it is the Foundation's goal to support and promote how CERN's mission impacts society. This vision requires more resources than are available for such activities in the CERN budget, provided by CERN's Member States.

The CERN & Society Foundation focuses on the key areas involving *Scientific Education & Outreach, Innovation & Knowledge Exchange and Culture & Creativity*. The objective is to pursue this ambition to increase the positive public engagement of CERN, in particular, by:

- promoting public understanding of science and the various ways it affects our daily life;
- encouraging and supporting young talent in STEM (Sciences, Technology, Engineering and Maths) in countries from all around the world;
- trying to help in alleviating the STEM crisis, which, according to the European Commission, will lead to a shortage of 850,000 STEM professionals by 2020;
- building capacity in developing countries by providing young researchers and individuals from different backgrounds with scientific knowledge and tools;
- fostering creative synergies between science and culture, inspiring and enriching the cultural landscape; and
- sharing scientific knowledge and innovative technologies to find solutions for a better world.

Although our foundation is still young, we have already achieved some important results to benefit young people from all over the globe. Some of our achievements in 2017 were:



The foundation has accomplished a lot, but we know that much more is needed.

This year, we are enhancing the CERN & Society programme of activities with the addition of ENLIGHT Training in cancer therapy. The training organised by ENLIGHT will be offered to students in late-stage undergraduate or postgraduate education from all over the world, with a focus on low and middle-income countries (LMICs) and from challenging environments.

Three types of training opportunities will be offered (initial, advanced and internship) dependent on the student's experience.

This project is extremely valuable, as it provides training to a new generation of much-needed experts working in hadron therapy for cancer care so they may fulfil the needs of radiation therapy. We are also aware of the immeasurable value that comes with joining the ENLIGHT network of experts and experienced practitioners, allowing the students to network, learn and collaborate across institutes and countries for both personal and professional growth.

The particular objectives and benefits of the ENLIGHT Training are:

- students acquire multidisciplinary, state-of-the-art knowledge and techniques for cancer care from experts in the field;
- students will join ENLIGHT and contribute to building up a worldwide network of young scientists, importantly in LMICs that do not have many RT and research facilities;
- students can transfer their newly acquired knowledge and network back to their home countries to contribute to improved cancer care around the world; and
- the creation, and encouragement, of links between fundamental research and efforts to find viable solutions to critical issues, particularly cancer, for the benefit of society.

We hope that with the trainingfrom cancer will have the opportunity to benefit from this advanced cancer treatment modality.

If you wish to learn more about the CERN & Society Foundation and ENLIGHT Training, and how you can help us deliver this worthwhile project, we invite you to visit our website at cern.ch/giving or to contact us at partnerships.fundraising@cern.ch.

We are grateful for your support. ■

Hilary Nathan & Petya Georgieva

Spreading the CERN spirit of scientific curiosity, for the inspiration and benefit to society.

CERN & Society

FOCUS ON THE NEEDS FOR RADIOBIOLOGY ESPECIALLY FOR ANIMAL STUDIES

FOCUS ON

BRITA SINGERS SØRENSEN

BACKGROUND: TELL US SOMETHING ABOUT YOUR SELF

I am molecular biologist, and I am an associate professor at Aarhus University, Denmark. I have been working in the field of radiobiology since 2004, and I have been involved in experimental studies in particle radiobiology since 2006, when I joined the work of ACE (The Antiproton Cell Experiment) at CERN, working on the RBE of antiprotons. Currently I am working on preparing and setting up the radiobiology program at the Danish Centre for Particle Therapy (DCPT), which will be ready for operation in October 2018.

1. Which research are you involved in? Where? Who else is involved?

A large part of the radiobiology program at DCPT will be focused on the biological effect of proton radiation on the normal tissue. This is both on in vitro and in vivo models. The major part of the in vivo work is aiming at determining the RBE for both acute and late normal tissue damage in a mouse model in different positions in the beam. We are also interested in the effect of proton irradiation on cytokine expression, and we have studies concerning this topic currently running both in vitro and in vivo models.

While are waiting for our research facility to become operational at DCPT, we have carried out experimental work at other institutions. A large part of our research has been performed at IFJ in Krakow, in collaboration with Professor Pawel Olko and his group.

Dr Niels Bassler is the physicist responsible for majority of the radiation experiments – we have had very close collaboration for many years since we were both involved in the ACE work carried out at CERN. When we are doing experimental work at other institutions, a team of people are involved from my group as well from the host laboratory. These also include technicians and an animal care-taker, so we can work as efficiently as possible during the allocated beam time.

How animal studies can be useful for optimising particle therapy? How long have you been working with animals?

A very large part of the current knowledge on biological effects of particle radiation is obtained from in vitro studies. In vitro studies are a great tool for studying mechanisms and biological pathways, however animal models are necessary and essential for providing evidence and links for translating to the clinic, as the situation in vivo is complex and involves many factors which cannot be mimicked in cell cultures. I have worked with animals since I did my masters, which was focusing on animal models for hearing impairment. In connection to radiation effects and to biomarker studies, I have worked with animals for the last ten years.

3. Current status of the research?

For the studies on in vivo normal tissue effects, we are currently working on the follow up of a large experiment, where 300 animals where irradiated in October in Krakow. In this particular experiment, we are both evaluating the effect of proton irradiation on acute skin damage, late radiation-induced fibrosis and the levels of circulating cytokines at different time points following irradiation. We have simultaneous follow up of a large cohort of x-ray irradiated animals, which will serve as the control arm.

We also have an ongoing data analysis of gene expression levels of in vitro proton irradiated patient derived fibroblasts. This is a quite comprehensive study, involving 30 fibroblast cultures, irradiated in different positions of the proton beam, with co60 irradiated cells as reference radiation.

4. Can you give us some details on what kind of results do you identify from the animal studies for preclinical and clinical studies?

One of our major aims is to investigate the effect of the high LET range in the distal edge of the SOBP on normal tissue effect in in vivo models. Our first data in this regard shows an

For experimental work, there is a whole team of people involved.

increased effect in the very distal edge on acute skin damage in a mouse model, which is confirming the in vitro data that has previously been reported. In vivo data on the RBE in different parts of the SOBP is lacking and is very much needed for addressing the current discussion on whether a RBE of 1.1 in clinical use is still appropriate.

5. Which are the challenges linked to animal studies?

There is a range of challenges linked to animal studies in general. First of all, compared to most in vitro systems, animal studies are slow and expensive. There is a long follow up time, especially on the late effects, and the follow up can require a lot of work from skilled personnel. There is of course also an ethical site to carrying out animal experiments, and a lot of considerations have to go into minimizing the number of animals required, while still obtaining statistical valid data.

Specifically, for animal studies of biological effects of particle radiation, a very high precision is required, as we are looking for effects occurring within millimeters. This also means, that compared to cell studies, where the effect can be studied in one cell layer, there is a possible dilution of the effect when looking at in vivo models.

6. How much data do you need and how much have you collected? Is some this already published?

To fully enlighten the effect of particle radiation on the normal tissue, RBE data for a large panel of in vivo normal tissue models should be obtained, covering a range of endpoints. This should be done in different positions of the beam and taking clinical considerations such as fractionation into account. This is not a task that can be covered by one research group but should rather be the aim of a consortium. It is tasks as this the Radiobiology group in EPTN (The European Particle Therapy Network, a Taskforce under ESTRO) are aiming to coordinate.

We have published data on the effect of particle irradiation on normal tissue damage in vivo, both for carbon ions (Sorensen et al, Acta Oncol, 2015) and for protons (Sorensen et al, Acta Oncol,2017). The first data on the effect of proton irradiation on cytokine expression in fibroblasts irradiated vitro is also published (Nielsen et al, Acta Oncol, 2017).

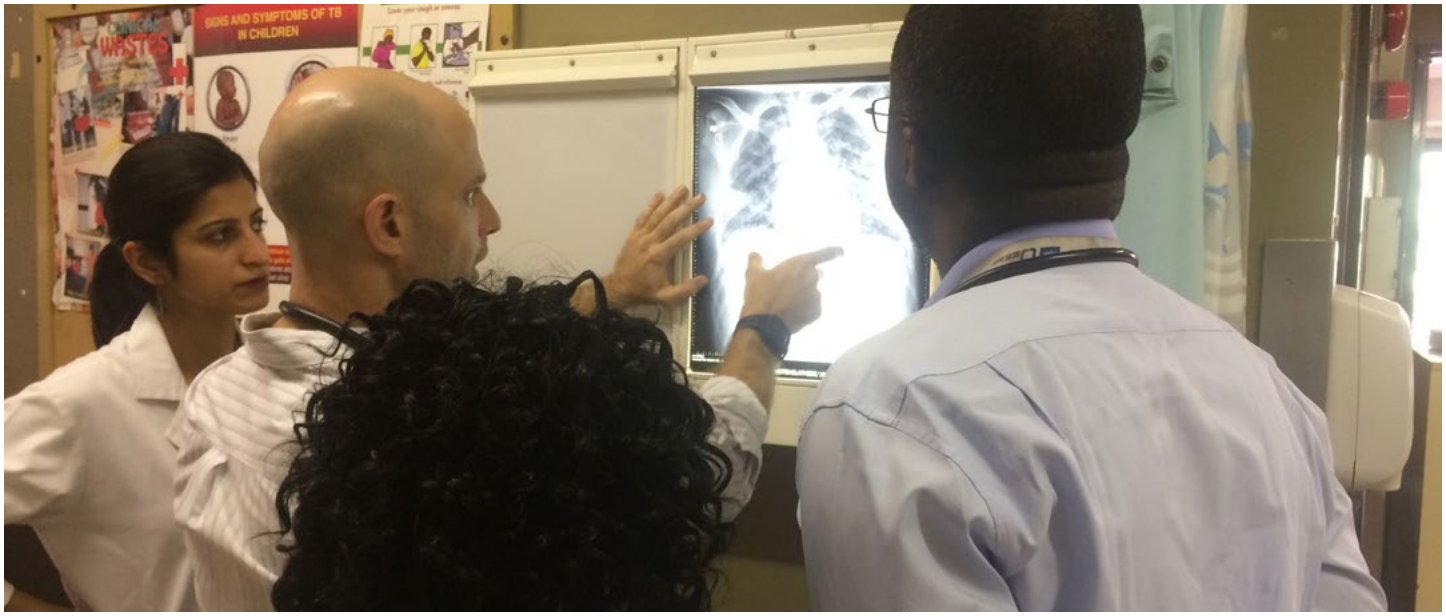
7. What are your thoughts for research in the future? Which is your dream(s) for future research?

My hope for future research is to provide radiobiological data needed for optimizing particle treatment and I believe this will be very much helped if we can succeed in establishing a functioning European-wide network (EPTN) and a concerted collaboration consisting of all the people involved in research on these topics at various irradiation facilities and sites. This is a rapidly expanding research area, and we now have the opportunity to coordinate and standardize the research and experimental setups in order to ensure the needed data, and that it is both comparable and clinically usable and try to make a real difference for optimizing treatment and improving patient outcome. ■

A large part of the experimental work has been performed at IFJ in Krakow, in collaboration with Professor Pawel Olko and his group. This is from setup of an experiment in the clinical gantry.

I grew up in India and moved to NYC during high school. My interest in public health developed during college in NYC at Columbia University and medical school at Harvard. Today, I am Assistant Professor of Radiation Oncology at University of Pennsylvania (US) and Adjunct Senior Lecturer at University of Botswana. In my work, I focus on public health endeavors and cost-effective clinical initiatives to improve access to cancer care and outcomes of care in developing countries. After College, I took some time off to work in India where I was exposed to issues in oncology care. I worked with Professor Jeffrey Sachs at the Earth Institute and the Gates Foundation on advising the Ministry of Health of India on the National Rural Health Mission, a rural health initiative to strengthen basic and preventive healthcare in rural India. I didn't know much about radiation oncology at that time but I had a great mentor that convinced me that my focus should have been to improve access to radiation oncology globally. As I was graduating from residency, Penn wanted to expand their ongoing program in Botswana from HIV care/medicine to oncology. I was very keen and we carved out a position for me to be based in Botswana starting 2014, when I graduated. I was initially supposed to be there for 1 year. It has been 3.5 year at this point and likely another 4-5!

My current activity in Botswana develops around four main pillars: **clinical care** at PMH (largest tertiary public hospital with the largest public department in the country) for 50% of my time; **research** in the framework of a collaboration of UPENN department of radiation oncology with University of Botswana; **education** through U54 (a mentoring core collaborative grant between UPenn and UB grant aimed to develop research capacity in HIV and cervical cancer among junior faculty at UB); **technical Assistance to Ministry of Health (MOH)** to develop cancer guidelines for top 10 cancers in Botswana.



Ward teaching with an invited expert in Imaging Detection

Cervical cancer clinic and Cervical cancer research team

CLINICAL CARE:

Working in collaboration with Princess Marina Hospital, Botswana (PMH), we established a new patient clinic for teaching and established an evidence-based care for all patients seen in clinic. Due to the high volume of gynecological and head and neck cancer patients, we also established a gynecological and head and neck multi-disciplinary clinic to streamline care for these patients. Most recently, we established a follow up clinic for gynecological cancer patients to help manage toxicities post oncological treatment.

In addition to direct clinical care, UPENN oncology and pathology teams are working with collaborators at PMH and University of Botswana on programmatic initiatives to eliminate chemotherapy stockouts and improve delays in pathological diagnosis of cancers through collaboration with American Society of Clinical Pathology.

RESEARCH:

The UPENN department of radiation oncology and University of Botswana have been awarded an NCI funded U54 consortia grant focusing on a natural history of cervical cancer and research capacity building in Botswana. This grant is a five-year award and involves 3 sub-projects. In addition, there are several centres for AIDS and UICC funded grants in oncology lead by me and other UPENN and UB collaborators. I have also lead and developed the first research working group in the oncology department at University of Botswana to support young investigators in oncology and help them link with mentors for their specific projects.

EDUCATION:

Through U54, UPENN faculty are involved in research methods training for junior faculty at University of Botswana. As an adjunct professor at the UB School of medicine, I am involved with oncology teaching for medical students. In this role I also established a month radiation oncology rotation in Botswana for residents to get training and exposure to US radiation oncology. This allows for senior residents to provide clinical care in Botswana and explore opportunities to be involved in global health as their career in the future.

Research mentoring session with the research time and junior faculty

Cervical cancer clinic

TECHNICAL ASSISTANCE TO MINISTRY OF HEALTH:

Working closely with the head of department of oncology at PMH and MOH, we developed cancer guidelines for top 10 cancers in Botswana and we are working on the establishment of the new radiation oncology facility at the University of Botswana. I also had the opportunity to support MOH in development of the cancer symposium held in Botswana in 2014 and 2016 to establish goals for Botswana in regards to cancer screening and treatment.

For me, it is important to work on developing a cohesive partnership in the region so we can share expertise given the limited human resources on the African continent. This also implies establishing partnerships with other LMICs outside of Africa that have come up with more creative ways to get around similar challenges we have. For example, India. It is a huge country and lower GDP per capita than Botswana. India has figured out models to deliver quality care in rural/semi-urban setups and we have a lot to learn from that.

Towards this goal, I am working closely with African Organisation for Research and Training in Cancer (AORTIC) to develop a Radiation Oncology Special Interest Group (Rad Onc SIG) that will bring together radiation oncologists and physicists together from all over the African continent to share expertise, challenges and solutions. We have initiated Chartrounds Africa, similar to Chartrounds USA and Chartrounds India that hopes to bring all the physicians and physicists on the continent together once a month to share cases and learn from each other. We also hope that Rad Onc SIG will become the platform for collaboration between African centres and centres from high-resource settings, which will allow us to make linkages to tie up a center in Africa that has a specific need with specific collaborators from high income country that can offer support for the specific challenge. This will help us use in the best way possible resources available and hopefully develop healthy collaborative relationships. ■

Bedside teaching for medical officers

Bedside teaching for medical officers

Research analysis meeting

Case discussion with pathology and oncology colleagues in cervical cancer clinic.

Bedside/ward teaching for medical officers

ASTRO'S 60TH ANNUAL MEETING

Translating Discovery to Cure

MIDTERM MEETING OF THE NETWORKING INITIATIVE 'MEDINET'

Peter Thirolf and Giulio Magrin

Manjit Dosanjh presenting the talk "From physics to Medical Application" at the Serbian Academy of Science after the conclusion of MediNet Midterm Meeting.

Impressions from the poster session.

Opportunity to meet and discuss in relaxed atmosphere with exquisite Serbian food.

Left: snapshot during one of the topical sessions

Right: impression from the social dinner, held, in a typical Serbian restaurant.

Participants of the Midterm Meeting of the EU-funded networking initiative MediNet (within the H2020 consortium ENSAR2), held on March 12-14 in Belgrade, hosted and organized by the team of the VINCA Institute for Nuclear Sciences.

The Networking Initiative 'MediNet' (https://medinet.medaustron.at) is part of the overarching EU-funded (H2020) Integrating Initiative ENSAR2, which brings together nuclear physics, astrophysics and applications of nuclear science in Europe. MediNet focuses on the development of tools to be used for medical applications and specifically for radiation therapy with emphasis on applications for ion-beam therapy. Two distinct and complementary pillars are forming MediNet under a common topical umbrella: Research on detector instrumentation for radiation therapy (Task 1 with 15 institutions from 7 countries, coordinated by P. Thirolf from LMU Munich) and development of nuclear tools for the radiation quality characterization in ion-beam therapy (Task 2 with 18 institutions from 7 countries, amongst them ENLIGHT, coordinated by G. Magrin from MedAustron). Besides knowledge exchange in various working groups, MediNet (co-)funds participation in topically relevant workshops, schools and seminars and promotes exchange visits of young researchers between MediNet institutions. As part of the contractual deliverables within ENSAR2, reports on "Specific need and proposed solutions of nuclear tools for medicine" and "Clarifying and adapting nuclear concepts to the medical field" have been compiled with emphasis to be on the level of a scientifically interested general public. With a project duration of 4 years, starting in March 2016, recently the Midterm Meeting of MediNet was held in Belgrade from March 12-14, hosted and organized by our colleagues from the Vinča Institute of Nuclear Sciences. Thirty-three participants enjoyed presentations on the network-related scientific activities ongoing in the various member institutions. Keynote lectures presented by T. Yamaya (NIRS-QST, Chiba/Japan: 'Development of the OpenPET for in-beam carbon ion therapy imaging') and G. Cuttone (INFN-LNS Catania/Italy: 'Nuclear Physics and Medicine: a challenging collaboration') provided a broader perspective, while a lively poster session served as platform for young researchers to present their work and get into personal contact with more experienced colleagues.

A number of young researcher actively participated to the meeting presenting, in some cases, the activities of their group and, in particular, taking part to the poster session. Before the session started the poster authors were asked to give an 'elevator speech': they had exactly 60 seconds to present the topic of their work and to try to capture the interest to their poster. The experiment of the elevator speech was certainly successful transforming a session that frequently risks to be isolated and detached to a very animated and well integrated event.

The intense scientific atmosphere with fruitful discussions on present activities and envisaged further perspectives was ideally balanced by the accompanying social program prepared by the local hosts. Belgrade with its rich history and architectural treasures could be discovered with competent guidance, while the culinary diversity of Serbian cuisine could be digested during a social dinner that provided further opportunities to deepen existing connections and to form new ones. Concluding discussions within the two pillars of MediNet on future activities (both scientifically as well as outreach-oriented) led to an immediate action to strengthen the internal communication within MediNet: soon after a twitter account was created (@MediNet_ENSAR2) and from now on (in addition to the MediNet Wiki website) #MediNet can be used for a fast exchange of scientific information as well as, e.g., for posting of job opportunities within the network.

It is the foremost merit of our local hosts from the Vinča Institute of Nuclear Sciences, Aleksandra Ristic Fira and Ivan Petrovic (together with their colleagues) to make this MediNet midterm meeting a success for all participants. The second half of the MediNet project promises further exciting science, supported and strengthened by the network between the MediNet member groups. ■

"The meeting featured an intense scientific atmosphere balanced by a social program that allowed to deepen existing connections and to form new ones."

Peter Thirolf
and Giulio Magrin

ABDUS SALAM, FOUNDER OF ICTP TRIESTE

HADRON RADIATION THERAPY AND BIOMEDICAL RESEARCH: SHAPING SCIENCE IN SOUTH EAST EUROPE

Participants of the Forum on New International Research Facilities in South East Europe, held at ICTP Trieste, Italy.

The Forum on New International Research Facilities in South East Europe held on 25-26 January 2018 at the Abdus Salam ICTP in Trieste turned out to be a really great event, attracting more than 100 participants. The main purpose of this event was to present for the first time to the scientific and science-policy communities the concept designs for the two options for the core of the Institute, prepared by two international expert committees. The Forum was organized by the Ministry of Science of Montenegro and the ICTP, under the auspices of the IAEA, the UNESCO and the EPS. Among the participants were representatived from the European Commissions (DG for Research and Innovation at that time, Robert Jan Smits), the Chair of the ESFRI Giorgio Rossi, representatives of the IAEA, the EPS, RCC, representatives of the SEEIIST Intergovernmental Steering Committee, a representative from the BMWFW Austria, but also high-level representatives from the science community, the Medical and Technical Directors of HIT Heidelberg, Juergen Debus and Thomas Haberer, and the Director of CNAO, Sandro Rossi, representatives from CERN, including the Director of the Accelerator department Fredry Bordry, the deputy directories of DESY and GSI-FAIR. Thanks to the financial help of the IAEA and some help from the EPS, more than 40 Users from the region also attended the Forum.

The first meeting of the SEEIIST Intergovernmantal Steering Committee (SC) took place in Sofia, Republic of Bulgaria, a few days after the Forum, on 30 March 2018. The meeting was preceded by a reception at the President of the Republic of Bulgaria, Mr. Rumen Radev. The President declared his full personal support and that of the Bulgarian Government for the realization of the proposed SEEIIST project in the region of South-East Europe.

The second SEEIIST Steering Committee meeting took place in Tirana, Republic of Albania, on 30 March 2018. As the main outcome of the meeting, the participants unanimously agreed to establish as the core of SEEIIST a Regional Institute for Tumour Therapy and Biomedical Research with Protons and Heavier ions. The institute will allow the treatment of patients with the most advanced scientific and technical achievements, but about half of the beam team time foreseen will be used for biomedical research which will even make the facility unique in the world.

The mission of the SEEIIST Project, centered around a large-scale internationally competitive facility, would be to promote scientific and technical cooperation within the region, to address common challenges of economic development and social cohesion, as well as to enhance and to improve cooperation between the countries of the region. Capacity building and the reversal of brain drain would become immediate benefits. It thus fully meets the objectives of the current new European-Balkan initiative of the EU. ■

Second SEEIIST Steering Committee meeting in Tirana, Albania

First SEEIIST Intergovernmental Steering Committee meeting in Sofia, preceded by a reception at the President of the Republic of Bulgaria.

THIRD CERN-ICEC-STFC WORKSHOP – MARCH 2018 MANCHESTER, UK

David Brown

International Cancer Expert Corps

Partnering to transform global cancer care

Science & Technology Facilities Council

10 Years of Impact and Inspiration

Burying the Complexity: Re-engineering for the Next Generation of Medical Linear Accelerators for Use in Challenging Environments.

This workshop, jointly organised by STFC, the International Cancer Expert Corps (ICEC) and CERN, was funded through the UK's Global Challenges Research Fund (GCRF). It continued to develop the work that arose from two previous meetings held at CERN in November 2016 and October 2017. Its focus was to hear the outcome of five STFC seed-corn funded projects developed at the October 2017 workshop, and further refine the specification for a novel medical linear accelerator radiotherapy machine.

- Study of Accelerator Technology Options
- Robust Permanent Magnet Beam Delivery Systems for Medical Radiotherapy Linacs
- RF Power Systems and Optimized RF Structures for Electron Beam Acceleration
- Linear Accelerator Simulations for Stable and Sustainable Operation of Developing Country Radiotherapy Linear Accelerators
- Cloud-based Electronic Infrastructure in Support of Linac-based Radiotherapy in Challenging Environments

At the March 2018 workshop the work package leaders presented the outcome of their initial studies for review and discussion by the experts in the room. The expertise of the participants had been expanded to include additional accelerator and medical physicists, oncologists, engineers, representation from the UK's National Physical Laboratory, and additional LMIC participants from Kenya, Nepal and Ukraine. This and the previous two workshops have had involvement also from the IAEA, and LMIC representatives from Botswana, Ghana, Jordan, Nigeria and Tanzania. The LMIC representatives again contributed to the discussions of considerations in their countries to ensure that potential solutions of any future machine addressed in-country needs and challenges.

The participants examined the key parameters of a future machine, identifying specifications that could be fixed, those that had more flexibility and those where further work was needed. Thought was also given to identifying gaps in research to ensure that the whole system is covered, including imaging and treatment planning. There had been significant progress in each of the five areas that successfully moved the project forward and it was apparent from the workshop discussions that there was significant interdependency between parameters and components and that no single modification would have a dramatic impact. It was also recognised that modularity, which would provide cheaper routes to maintenance and repair, was a goal in itself.

Each of the five work areas above has received additional support that will enable them to continue their research and to network and take forward ideas generated by the series of workshops. The main goal of the wider collaboration has been identified as refining specifications for a complete radiotherapy treatment system as well as working towards a conceptual design report for a modular medical linac for challenging environments. ■

ST PETERSBURG X INTERNATIONAL CONGRESS NEVSKY RADIOLOGY FORUM 2018 (NRF-2018)

Photo credits: St Petersburg University

Hallway in the Twelve Collegia building, St. Petersburg State University: one of the longest academic hallways in the world founded in 1724 by Peter the Great, Ivan Petrovich Pavlov, a graduate of the Natural Department of the University's Faculty of Physics and Mathematics, became the first Russian Nobel Prize winner.

On April 27th and 28th, 2018, the X International Congress Nevsky Radiology Forum 2018* (NRF-2018) *took place at the EXPO-forum in Saint Petersburg, Russian Federation. The organizer of this international congress is the "St. Petersburg Radiological Society". The latter is the oldest one in Russia (it was formed more than 100 years ago) and unites the regional radiologists, researchers and specialists in the field of beam diagnostics, radio-oncology and radiobiology. The very first forum of Russian radiologists was held in Saint-Petersburg in 2003. A low-profile conference after years of effort has turned into a popular scientific and practical event.

Under the motto "Strive for the new, keeping the old!" the jubilee forum brought together more than 2000 leading specialists from Russia, CIS (Commonwealth of Independent States) countries, Europe, Asia and the USA. Doctors and scientists, discussed during the two-day program of this Forum the latest technologies and innovations for cancer treatment, the key topics were modern technologies for diagnostics and therapy of oncological diseases, advanced achievements in radiology, safety in radiology, application of biomarkers in radio-diagnosis and principles of patient-driven personalised medicine, new methods of radiation diagnosis of non-oncological brain diseases, metastatic lesions in breast cancer, pathologies of the musculoskeletal system. The Forum included more than 100 scientific and educational events: thematic schools, scientific sections, round tables, symposiums, contests, the "Nevsky Stars" Olympiad, visit to the new Centre for Proton Therapy. There was also a technical exhibition of equipment manufacturers and pharmaceutical companies. Part of the official plenary session was devoted to the celebration of 100 years of the State Roentgen and Radiology Institute, the world's first, that was established in 1918 in Saint-Petersburg as a medical-biological department of the State Institute of X-ray Technology and Radiology. (Today it is known as the "Russian Scientific Centre of Radiology and Surgical Technologies named after A.M.Granov" -- the RSCRST).

For the very first time at this Forum, there was also a Special Session organized which was devoted to hadron therapy. The session was initiated, and moderated by Grigory Feofilov, the physicist from the Saint-Petersburg State University, and it was supposed to support the increasing interest in hadron

therapy by Russian colleagues from the medical disciplines. Grigory, born and raised in Saint Petersburg is the Head of the Laboratory of Ultra-High Energy Physics at the Saint Petersburg State University (SPbSU) and is involved in ALICE at the LHC at CERN since 1992 as one of the experiment development project leaders and as the university team-leader. He joined also the European Network for Light Ion Hadron Therapy (ENLIGHT) community at CERN in 2006.

The session started with a talk given by Manjit Dosanjh (CERN) who gave a comprehensive overview of the medical applications, resulting from physics research which has been and continues to be instrumental in the development of technologies in the biomedical domain especially the use of ionizing radiation for medical imaging and therapy ever since the discovery of X-rays. She also discussed the European Network for Light Ion Hadron Therapy (ENLIGHT) network that has been essential in catalysing the efforts for collaboration between physicists, physicians, radiobiologists, engineers, and information technology experts, as well as between academic, research and industrial partners to meet the challenges of the hadron therapy.

Ramona Mayer (former Medical Director of MedAustron, Austria) tried to answer in the her talk the very important question: "Do we need hadron therapy? A medical doctor's point of view". Ramona Mayer showed that in recent years, there has been increasing evidence that radiation oncology with hadron therapy has the potential to increase the local control rate and survival in many types of tumours while improving the quality of life in cured patients.

Furthermore, she pointed out that hadron therapy can be seen as one part, as one pillar of modern multimodality cancer treatment; it should be understood that the potential of hadron therapy can only be exploited if a full integration of hadron therapy into clinical environments is given and if new medical and technologic advances are properly incorporated into the total treatment process.

Monument to Dmitriy Mendeleev (chemist) on Moskovskiy Prospekt in St Petersburg, Russia

Ramona Mayer, Manjit Dosanjh and Grigory Feofilov: contributors to the Special Session on hadron therapy at the Xth International Congress Nevsky Radiology Forum 2018 © photo by V.Zherebchevsky.

This talk was followed by another presentation of by Manjit Dosanjh covering the future needs of hadron therapy developments.

Aleksey Mikhailov from the newly opened Proton centre at the St. Petersburg Centre of Nuclear Medicine of the Dr. Sergey Berezin Medical Institute (Russia) gave an overview on the role and experience of proton therapy in the complex treatment of breast cancer. It was followed by Oleg Korytov from the RSCRST (Russia) who discussed their experience in proton therapy with 1000 MeV pencil beam (the so-called Gatchina method). The last speaker of this session, Dr. Vladimir Zherebchevsky from SPbSU gave a comprehensive insight in Theranostics: new methods for radionuclide therapy and diagnostic. The report included the basics of the combination of imaging and therapy and highlighted the important role of novel radionuclides used both for diagnostics purposes (in Positron Emission Tomography and Single Photon Emission Computed Tomography) and for therapy of oncology diseases. Practical information on studies of the nuclear reactions needed for development of novel radionuclides used in theranostic was also provided.

The questions and comments of the audience showed that there is a great deal of interest in the topics discussed at this special session of the NRF-2018 and pointed that further actions in development of this multidisciplinary scientific and educational platform for hadron therapy in Saint-Petersburg region are urgently needed. ■

Manjit Dosanjh, Grigory Feofilov and Ramona Mayer

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THE EUROPEAN NETWORK FOR LIGHT ION HADRON THERAPY

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

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

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

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

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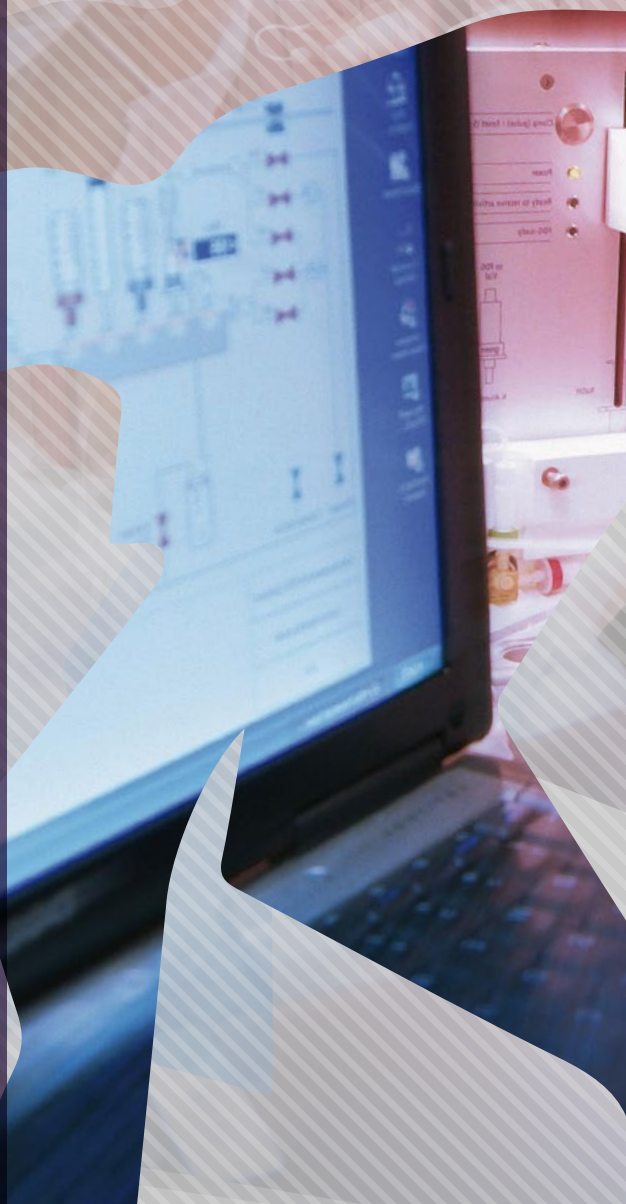

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