FLASH Therapy

ENLIGHT

Highlights *July 2019*

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Reading the amazing contributions featured in this issue of the ENLIGHT Highlights makes me even more aware of the high power of our network. The field is in constant evolution but sometimes we all have that special feeling, the sensation that we are indeed experiencing a turning point.

And that is indeed the feeling you get when you read the interview with Marie-Catherine Vozenin **(page 26)**, the scientist who awakened the "sleeping beauty" bringing it back to the present, a technology that had been almost forgotten until very recently. This is the first of the "turning points" that are clearly shaping these recent months of activity of our field, something that will certainly move the radiation therapy field forward and that could even change forever the way it is delivered.

Another turning point or, rather, a true paradigm change, is certainly the way we have decided to approach the issue of radiation therapy in challenging environments. We have gone there, seen with our own eyes and listened to the local experts to understand what it means to create modern RT centres in the African continent. On **page 20** you will be able to read the inspiring quotes that the local medical community sent to us as a testimony of the success of our first ICEC, STFC and CERN joint meeting for Radiation Therapy in Botswana.

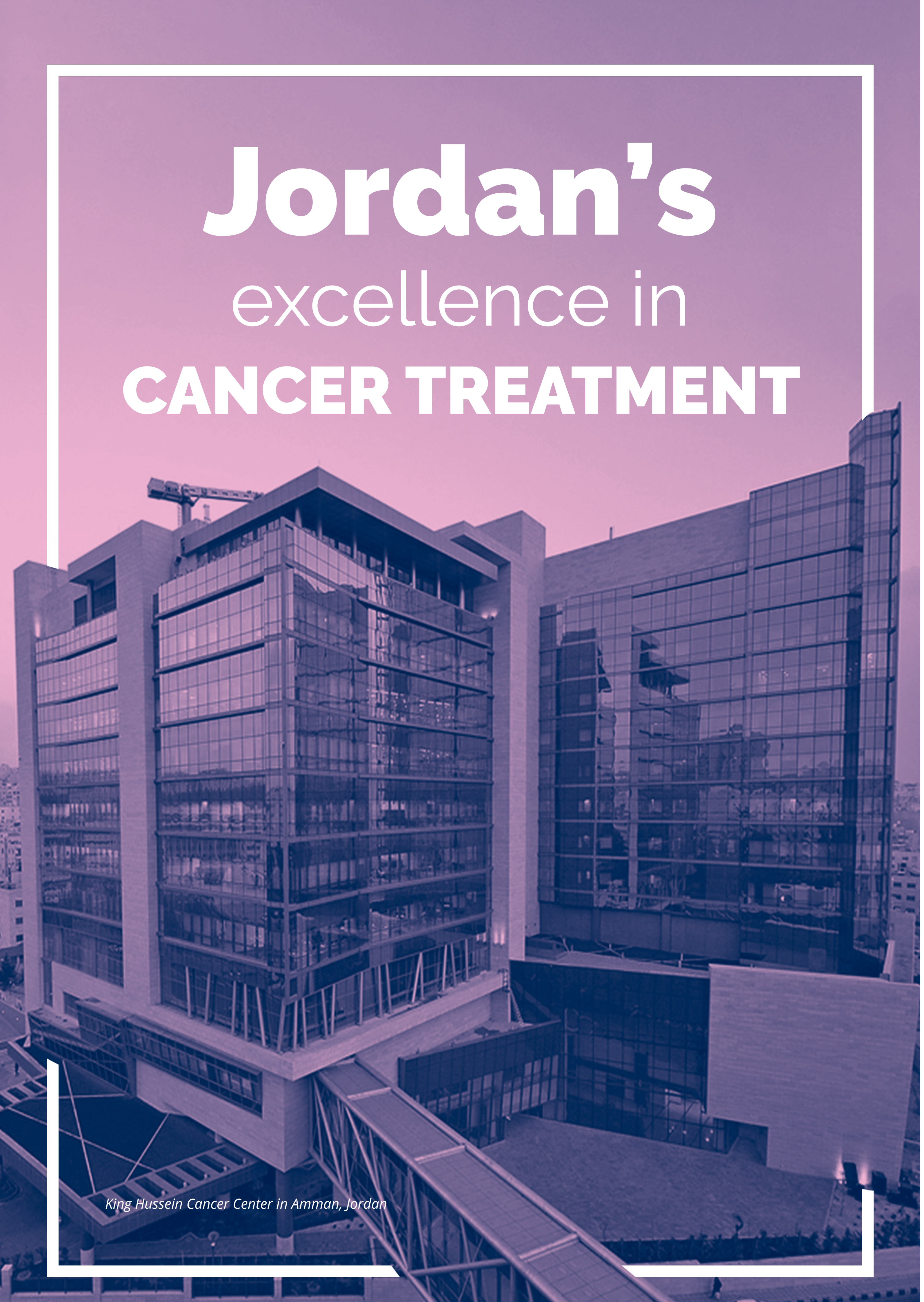
And if the globe still presents a non-homogenous distribution of resources dedicated to advanced cancer treatment, we do have reasons for hope as the young Rami from Nepal recalls **(page 46)**. Rami's story reminds us of the importance of listening to the views of the young generation who will be delivering the RT in the future.

In all of this, we are talking about big endeavours for which cost is key. One way to keep costs under control is using big data techniques to quickly identify the best, most personalised, and most cost-effective treatment for each specific patient. An approach that is good for the patient and for the health systems **(page 32)**.

Our usual meeting reports complete this issue **(from page 32)**. You might wonder why we ask our colleagues to send us their reports from meetings that have happened around the world. The reason is that this allows us to see what is being done in various places and show us the trends that will shape the future of the field. The reports are a collaborative tool that captures where the field is moving years ahead.

It goes without saying that nothing would be possible without the work of all the contributors and their generosity and willingness to spend their precious time to share their achievements, ideas and latest news. We, the editors like the readers, are already looking forward to the next issue!

Jordan's excellence in CANCER TREATMENT



King Hussein Cancer Center in Amman, Jordan

Linear Accelerator with advanced technology

Jordan's King Hussein Cancer Center (KHCC) is one of the best comprehensive cancer centers in the Middle East which treats both adult and pediatric patients. The Center was initially named Al-Amal center (hope center) founded in 1997 by the late King Hussein. In 2002, the center was renamed to the King Hussein Cancer Center in honour of the late King who died from cancer.

> **KHCC treats over 7000 new cancer patients each year, from Jordan and the region.**

KHCC treats over 7000 new cancer patients each year, from Jordan and the region. It is equipped with state-of-the-art medical equipment and services, including 12 operating rooms and 352 beds. It houses 36 intensive care units, including 6 ICU specialized for pediatric care. Highly-qualified oncologists and healthcare professionals (over 300 oncologists and consultants) and 1000 nurses, trained specifically in oncology nursing, work tirelessly to ensure that patients receive the latest in comprehensive cancer care.

KHCC delivers comprehensive cancer care by treating patients as a "whole", focusing on their physical, emotional and social well-being. In that regard, KHCC has established programs which focus on all stages of comprehensive cancer care: from prevention and early detection, through diagnosis and treatment, to palliative care. KHCC offers many services to ensure that patients are supported throughout their difficult treatment, including survivor groups, a physical rehabilitation program, a nutrition clinic, a psycho-oncology clinic, and a pediatric pain management clinic among many others.

KHCC treats all cancers and performs approximately 300 bone marrow transplants (BMT) a year. The KHCC BMT program is one of the largest and most successful programs in the Middle East, achieving cure rates compatible with international standards.

KHCC earned many prestigious international accreditations like Joint Commission International Accreditation (JCI), JCI Disease Specific Certification (DSC) - First cancer center outside of the United States, Hazard analysis and critical control points (HACCP) Systems and Guidelines for its Application, College of American Pathologists Accreditation (CAP), Health Care Accreditation Council of Jordan.

On April 24th, 2019 KHCC added another accomplishment to their journey of remarkable achievements by attaining the (MAGNET) Recognition Certificate (certificate of excellence) from the American Nurses Credentialing Center (ANCC). This accreditation provides an opportunity for the KHCC Nursing staff to advance their nursing career as well as prove their ability to provide high- quality patient care. KHCC is the first cancer center in the world, outside the USA, to achieve this high prestigious accreditation.

Beside, KHCC is becoming the hub in the region for cancer capacity building by establishing many well-structured competency-based residency & fellowship programs in collaboration with renowned cancer centers in the Western countries.

KHCC staff celebrating Colon Cancer Awareness Month

Jamal Khader,
KHCC

KHCC staff celebrating Breast Cancer Awareness Month

> “ KHCC is equipped with state-of-the-art medical equipment and services, including **12 OPERATING rooms** and 352 beds. It houses 36 intensive care units, including 6 ICU specialized for pediatric care.

KHCC staff celebrating Breast Awareness Month

Figure 1. Picture of equipment at one of the public institutions that support training of medical physicists: DMX Linear accelerator

ZIMBABWE MEDICAL PHYSICS PROGRAM PREPARES FOR THE FUTURE

Zimbabwe has a population of about 15 million people. Based on the input data to the Lancet Oncology Commission Report, the estimated cancer incidence in Zimbabwe was 15,520 cases in 2012. This is expected to increase to 27,720 by 2035, i.e., an 80% increase. It was estimated that 41% of these cases will benefit from having radiation therapy thus at the present time at least 6,400 patients should be receiving radiation therapy. As outlined in the Lancet Oncology Commission Report, developing countries including Zimbabwe should expect a growing incidence of cancer in the coming years.

Currently, Zimbabwe has three radiotherapy centres: two public and one private. One public institution is in Bulawayo while the other two centres are in Harare. The two public centres have four linear accelerators in clinical use with installation of the fifth one expected to be completed later this year. The private centre has one linear accelerator. **Figure 1** is a photograph showing some of the equipment available at one of the public institutions. The centre also has a computerised treatment planning system, a record and verify system and a comprehensive information management system.

For any expansion to take place and meet the growing needs to fight against cancer, trained professionals including medical physicists will be required. In order to address the shortage of medical physicists, the National University of Science and Technology (NUST) introduced a Master's degree in Medical Physics to fulfil the academic requirements for training medical physicists. Enrolment to the program is also open to candidates from neighbouring countries and other regions.

The MSc Medical Physics degree at NUST has been running since 2015. It was developed with support from the International Atomic Energy Agency (IAEA) who provided funding for experts to come and teach specialist modules. The program has been approved by the Zimbabwe Council for Higher Education (ZIMCHE) and Allied Health Practitioners Council of Zimbabwe (AHPCZ). The MSc

Figure 3. Pictures of the first graduates from the MSc Medical Physics Degree.

Medical Physics degree is aimed at addressing the urgent need for building sufficient human capacity of Medical Physicists in Radiation Therapy, Diagnostic Radiology, Nuclear Medicine, and Health Physics especially recognizing the enormous increase in the number of cancer patients needing treatment in Zimbabwe. The initial enrolment to the program was 13 students in September 2015. Enrolment for the following years has been restricted to a maximum of 10 students to ensure adequate supervision for their projects and clinical placements. The program is structured to take two years with the second year dedicated to a research project and clinical placements. The taught modules include: radiotherapy physics, medical imaging physics, nuclear medicine physics, physics of non-ionising radiations, anatomy and physiology, basic physics and biology of radiation, medical electronic and instrumentation and safety and quality management. **Figure 2** shows a photograph of one of the IAEA supported expert lecturers conducting a practical session with the students for one of the specialist modules.

Challenges that faced the program included lack of lecturers to cover teaching of all modules, limited funding to set up a medical physics laboratory, limited computing infrastructure to support computer simulations and image processing. The country had no capacity to bring in external lecturers to support the teaching. This was coupled with a government freeze on recruitment. We were able to get assistance from the IAEA through a National Project which was aimed at capacity building for medical physicists and other professionals involved in cancer management.

The Zimbabwean government is fully supportive of the initiative to train medical physicists locally. When the program started, there were only three experienced Medical Physicists who had completed an MSc degree in medical physics and undergone supervised clinical training, working in the two cancer centres and could teach at the university. The program has now enrolled three intakes, the first intake graduated in 2017. The fourth intake is expected to commence studies in September 2019. A photograph of the first graduates is shown in **Figure 3**.

The future of the program looks bright as the government plans to recruit more lecturers to teach on the program and is also investing in service contracts for equipment in the public institutions to ensure minimal downtime and reliable provision of clinical service as well as a good training environment for the students enrolled in the program. At the moment program still relies on experts to teach on some modules but it should be self-sustaining in the next year or two. The next challenge will be to develop some of the younger medical physicists to enrol of PhD degrees so that we improve on the research component. There is an urgent need to establish a medical physics laboratory for students to conduct experiments related to radiation physics.

Figure 2. *Professor Fraxedes Mayor with the first cohort of students during one of the practical sessions for the Nuclear Medicine Physics Module.*

Author:
Professor Godfrey Azangwe

Professor Godfrey Azangwe obtained an MSc degree in Medical Physics in 1997 at the University of Aberdeen in Scotland and obtained a PhD in Bio-Medical Physics in 2001. He has worked as a Radiation Oncology Physicist in a number of centres in the United Kingdom and is currently the Chair of the Applied Physics Department at the National University of Science and Technology (NUST, Zimbabwe) and Chief Medical Physicist at Mpilo Central Hospital (Zimbabwe). He spent 6 years at the International Atomic Energy Agency (IAEA, Vienna) working as a Dosimetrist and Quality Manager. He was instrumental in setting up the MSc programme in Medical Physics in Zimbabwe. Since his stay at IAEA, Prof Azangwe has dedicated his time to training of medical physicists in the region and was instrumental in starting the MSc Medical Physics program at NUST.

News

Accelerating the Future: Designing a Robust and Affordable Radiation Therapy TREATMENT SYSTEM for Challenging Environments

The 4th Conference to coordinate efforts to design and develop an affordable and robust yet technically sophisticated linear accelerator-based radiation therapy treatment (RTT) system was held in Gaborone, Botswana on March 20-22, 2019. The conference was sponsored by STFC with funding from the UK Global Challenges Research Fund (GCRF) and supported by CERN and ICEC.

All too often, conferences related to creating a new program or technology to improve the care of patients with cancer or other conditions in LMIC's and underserved regions of UIC countries are held in major world cities; New York, Geneva, London. Convening this conference in Gaborone enabled a significant number (over one half of the attendees) of physicians, physicists and staff from Sub-Sahara Africa and other LMICs to attend, present their reports and interact with the scientists working with them in their own region of the world thereby generating a sense of a global community working toward a common goal. It also allowed participants to visit hospitals, both private and public, in Gaborone to see the conditions under which the robust and modular RTT system will be used. The visiting participants left Gaborone with a much better understanding of the challenges faced by those treating patients with cancer in LMICs and a much stronger commitment to work with their colleagues to develop the new RTT systems that they need.

This workshop, built upon two prior workshops held at CERN in November 2016 and October 2017, and one in Manchester UK in March 2018. LMIC countries with participating representatives included: Botswana, Ghana, Jordan, Kenya, Nepal, Nigeria, Tanzania, Zambia, and Zimbabwe. Expertise included accelerator and medical physicists, engineers, oncologists, and healthcare management representatives.

Fourth CERN-ICEC-STFC workshop held in Gaborone, Botswana March 2019.

Linnet Nhari, the radiographer at Life Gaborone Private Hospital

State-of-the art linac facility at Life Gaborone Private Hospital

Medical staff from Botswana

Mokolodi Nature Reserve in Botswana

The meeting was organized with presentations and discussions encompassing five areas:

1. Local LMIC perspective on healthcare, cancer care, and technology challenges

2. Current radiation therapy systems and challenges

3. Project reports on the STFC funded work packages

4. Education, training and technical support needs

5. Discussion on priorities and next steps

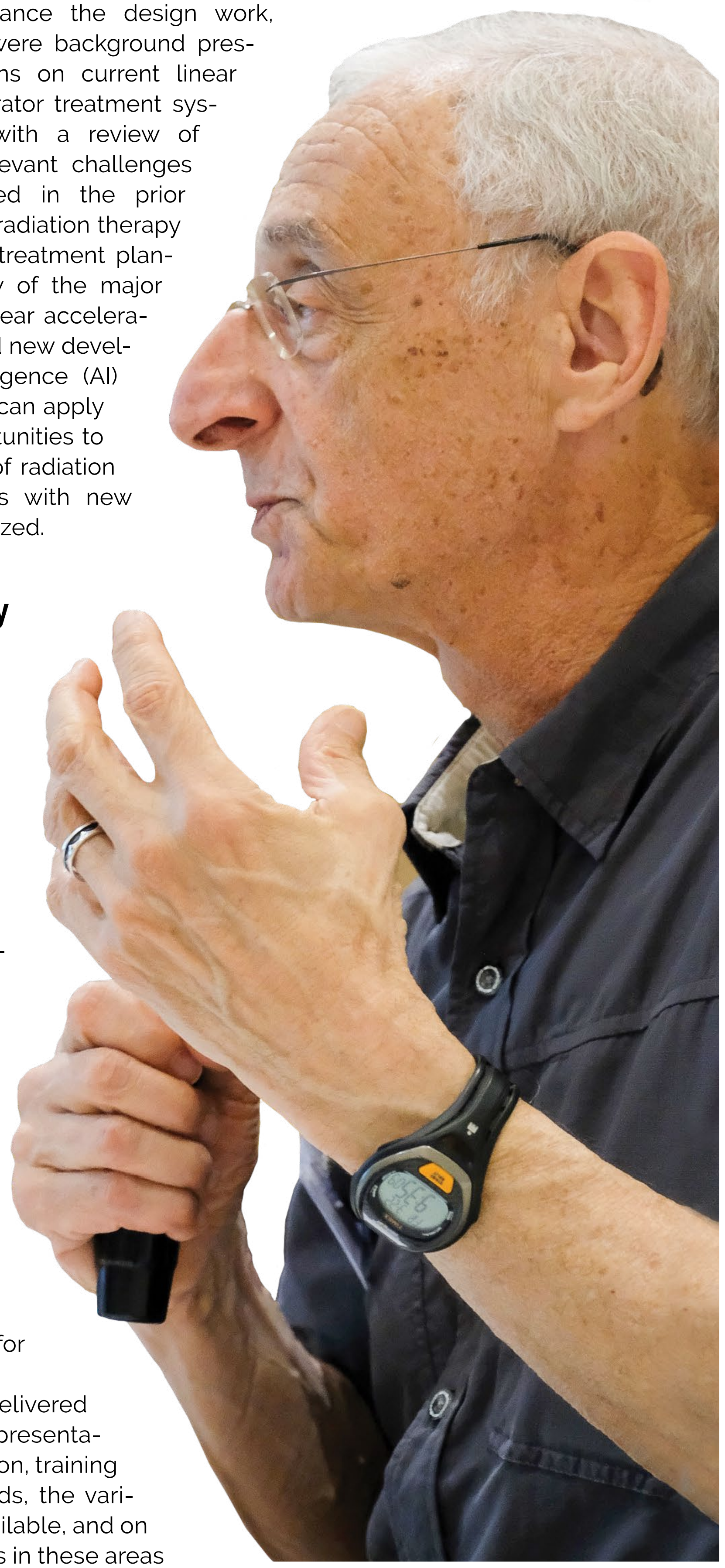
Manjit Dosanjh (CERN), Norman Coleman (ICEC), Charlotte Jamieson (STFC) with Memory Bvochora-Nsingo, radio oncologist in Botswana.

To set the stage for the discussion to advance the design work, there were background presentations on current linear accelerator treatment systems with a review of the relevant challenges identified in the prior workshops; an overview of radiation therapy treatment techniques and treatment planning systems; an overview of the major sub-systems of medical linear accelerators and their shortfalls, and new developments in artificial intelligence (AI) and machine learning as it can apply to radiation therapy. Opportunities to improve the performance of radiation therapy treatment systems with new technologies were summarized.

“The sense of community that this group of world class scientists and oncologists have achieved in pursuit of a technology to improve access to cancer care in challenging environments was inspiring.

Reports were presented on five work packages funded by STFC covering: linear accelerator technology design, accelerator operations and subsystems; power supply options; and cloud technology. Preliminary results from a failure mode study survey for radiation therapy technology experienced in LMICs were also presented. Recommendations were offered on additional areas for R & D.

With radiation therapy delivered within a system of care, presentations were given on education, training and technical support needs, the various programs that were available, and on the continuing unmet needs in these areas with several sessions focusing on medi-



International Cancer Expert Corps

News

cal physics. Technological solutions to support long-distance mentoring and technical support to compensate for shortages of staff and expertise were discussed.

To learn more about cancer care in Botswana, in addition to meeting with cancer program staff and hospital tours, the group met with the Acting Dean of the Medical School, hospital management, and health ministry representatives and to learn about their priorities, resource commitments and challenges. The WHO Botswana Country Office representative was able to join the group for dinner and talk about WHO's priorities.

The workshop concluded with a summary of progress, priorities to be addressed, and next steps. The meeting sponsors and participants were most grateful to Princess Marina Hospital, the Life Private Hospital, Sir Ketumile Masire Teaching Hospital and University of Botswana for their time, graciousness, and hospitality.

Donna O'Brien

"Seeing the clinical settings and hearing directly from front line staff on the challenges of providing cancer care was invaluable."

Larry Roth

"The sense of community that this group of world-class scientists and oncologists have achieved in pursuit of a technology to improve access to cancer care in challenging environments was inspiring."

Dr Surbhi Grover at the Princess Marina Public Hospital.

Group photo in front of Avani Gaborone Hotel where the workshop took place.

> There is need to save many of LMICs from the scourge of cancer which ENLIGHT is promoting.

Bridge this gap

Platform to exchange ideas

Training the oncologists in Africa

Eye opener

Tackle this global health challenge

> The cancer scourge can be "tamed" with concerted commitments and efforts from all the role players and stakeholders.

> Universal access to comprehensive cancer care can be made possible through collaborations and scientific innovations

True picture of the need

> Design concept to the challenging environment to better capture the needs

Improve access to radiotherapy

Heavy patient burden, challenges with shared equipment

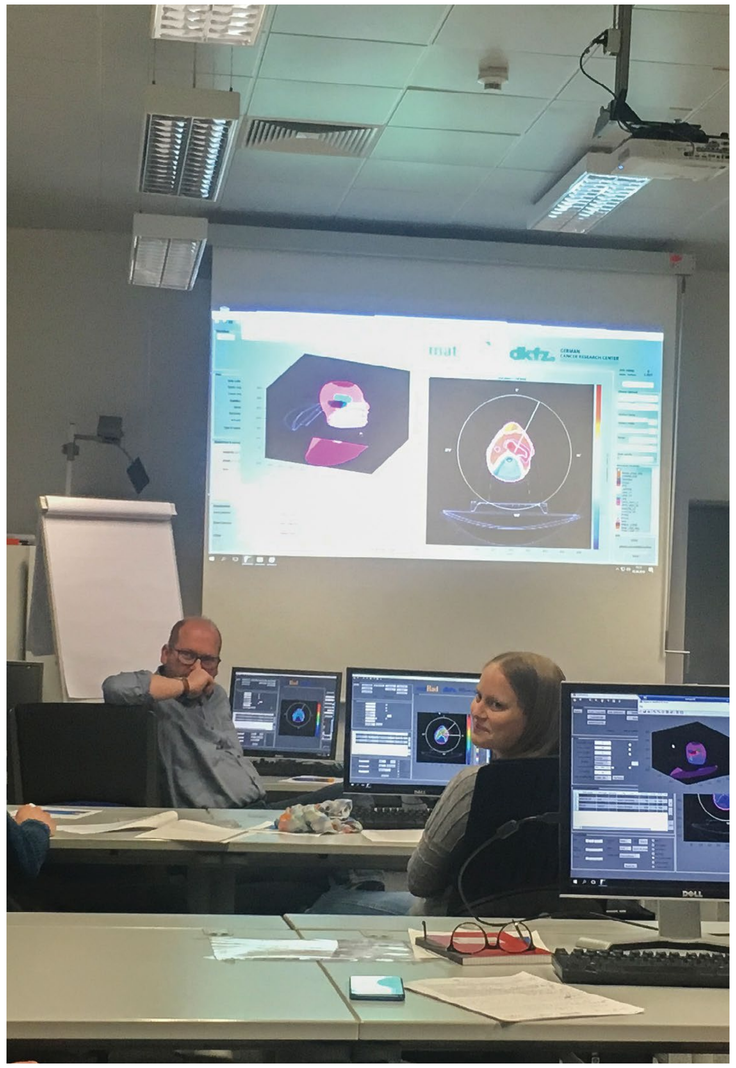
> URGENCY, COMMITMENT AND PASSION

Particle Therapy goes to school

Introduction to particle therapy at CERN.

The first pilot Particle Therapy Masterclass took place on April 5th with the simultaneous participation of CERN, GSI Darmstadt and DKFZ Heidelberg. High-school pupils were invited in each one of the institutes for a full day event, following the same agenda. At CERN, more than 30 school children aged 12-17 participated from neighbouring French and Swiss schools accompanied by their school teachers. After inspiring lectures and the ENLIGHT animations they could visit the unique Antimatter factory. After lunch, tutored by CERN colleagues, they immersed in the hands-on experience. The event culminated with a common video-conference where they could share their experiences and discuss their own results with their colleagues at the other participating institutes, as international scientific collaborations do.

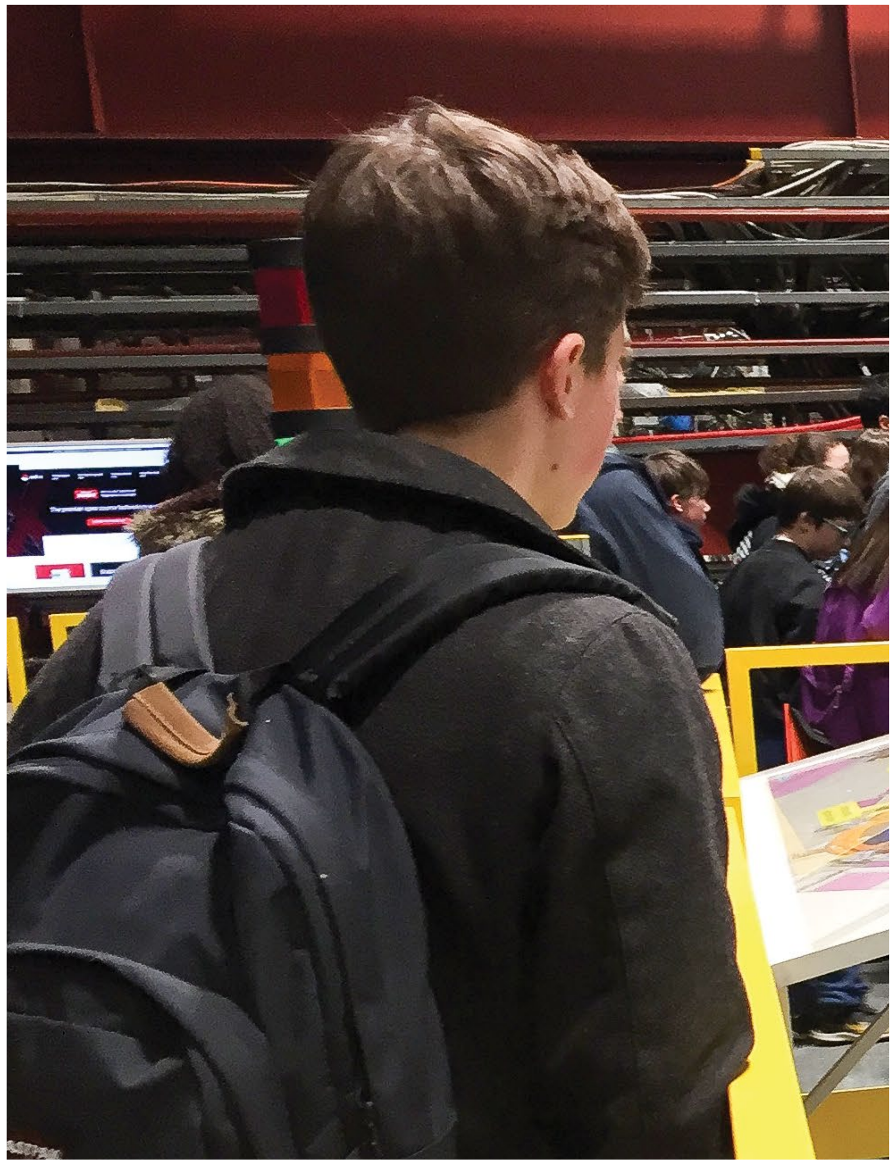
This new masterclass was proposed with the aim of enriching the programme of the well-established International Physics MasterClasses, IMC, (https://physics-masterclasses.org/) an educational outreach activity and flagship project of the International Particle Physics Outreach Group, IPPOG (http://ippog.org). The aim of the pilot Particle Therapy session was to explore the student's interest in this very important subject of particle therapy, and also, to get feedback from participants before presenting the new package to the IMC steering group during the spring IPPOG meeting on 23-25 May at FAIR-GSI. More specifically, the theme of this new masterclass was chosen with the aim to highlight benefits for society from fundamental research, focusing on medical applications, and addressing related questions of the public. The Particle Therapy MC aims at making the young participants aware of the actual techniques employed by researchers to study innovative treatment of cancer using x-rays, protons or carbon ions, in a realistic way. The professional research software toolkit "matRad", (www.matrad.org), developed by the German Cancer Research Centre DKFZ in Heidelberg was used during this masterclass.

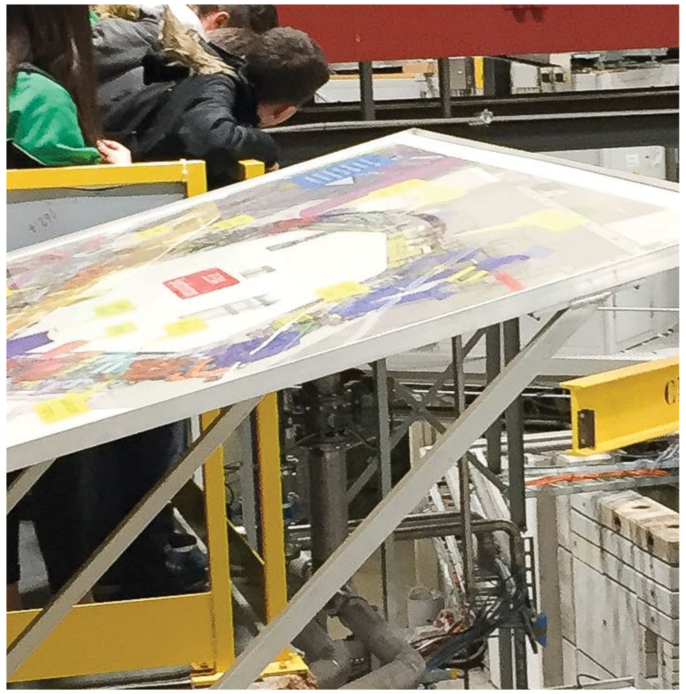


Hands-on session of the 5th April pilot Particle Therapy MasterClass at GSI. The obtained results were then discussed with CERN and DKFZ participants during the common video-conference.

The "alpha testing" phase of the program was done at GSI on February 2019 and comments from the students were implemented in the program's next version. Subsequently, following the pattern of any typical masterclass day, the involved institutes organised the local details of the event with schools of their area. They also worked out a plan for the presentation of results and discussion during the common video-conference at the end of the hands-on session. Each institute tailored the exact program of the masterclasses on the local needs, i.e. language, program details etc, in order to make it as attractive as possible by the participants. Comments from the participants, as well as from observer PhD students and scientists, were recorded and will be taken into consideration as the project moves to its next phase.

During the common video-conference discussion of results, a lot of enthusiasm and interest was shown by the school-children. They all wanted to interact with the other schools involved in the call. Their understanding of





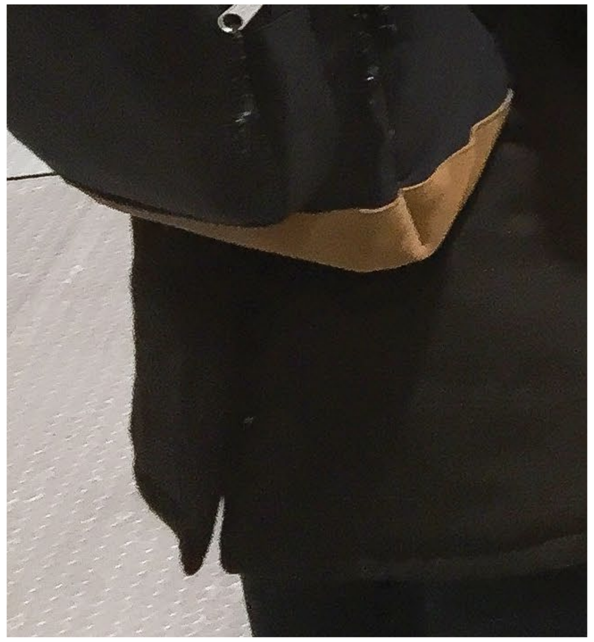
the presented topics was highly recognised in the questions they were asking and answers they were giving. The local organisers that contributed in preparing and performing the event in all three institutes expressed their deep satisfaction but also their motivation and commitment to continue and improve the initiative so that the MasterClass become more accessible to the targeted group of students.

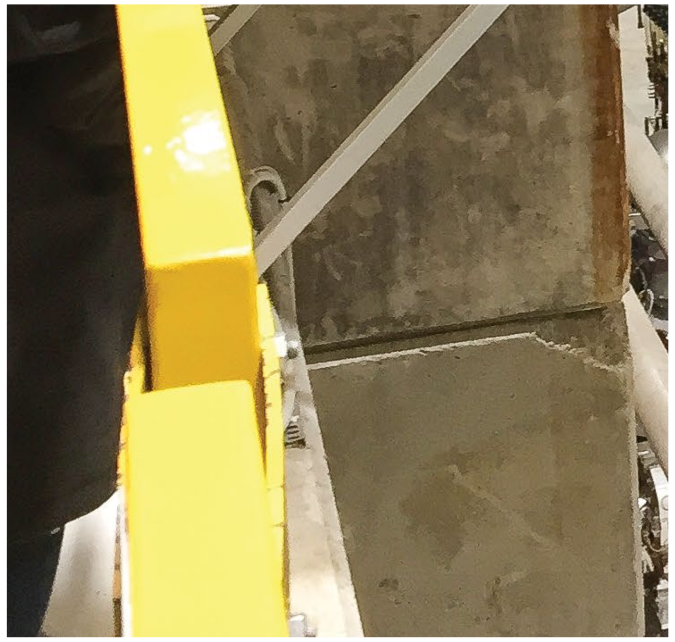
> **“This extremely fulfilling teamwork among colleagues of all three institutes contributes in preparing the next generation of scientists**

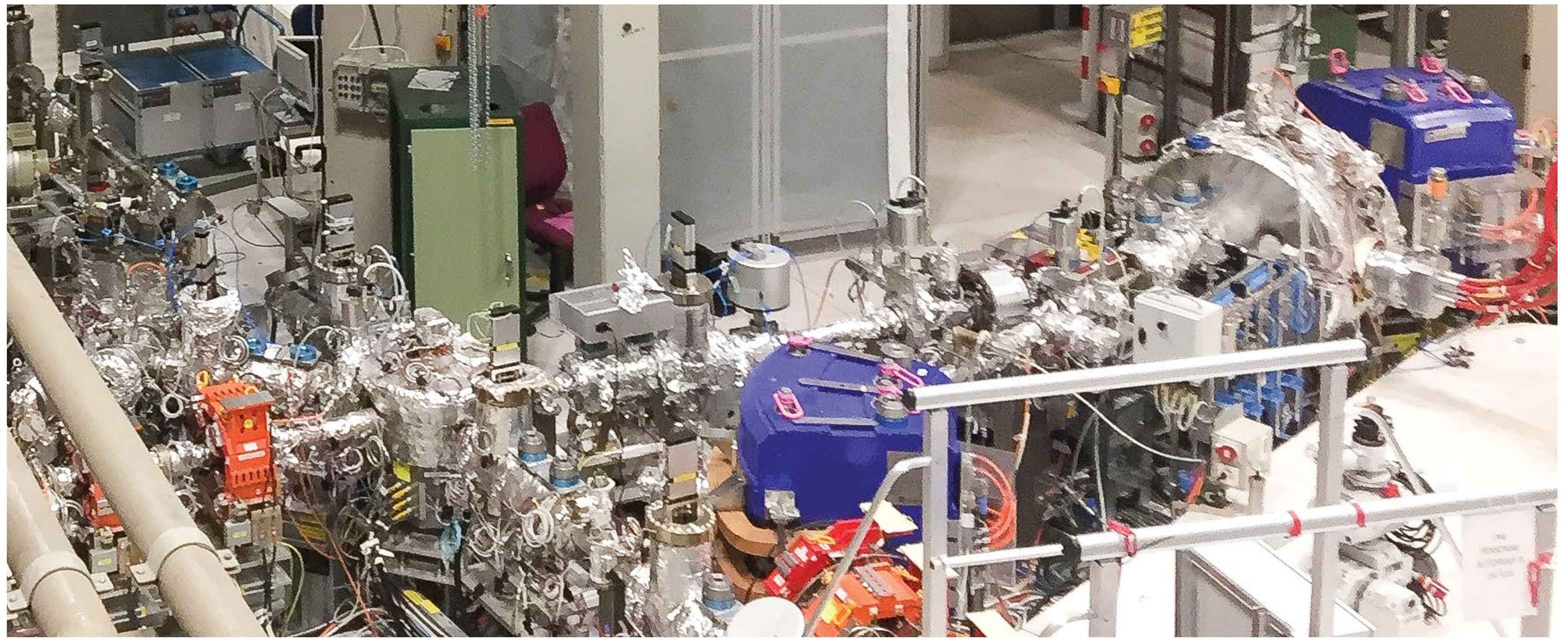
This extremely fulfilling teamwork among colleagues of all three institutes contributes in preparing the next generation of scientists but also in strengthening bonds among the involved institutes developing this project.

This successful pilot session has set the basis and already several other institutes have shown interest to join. In addition to its impact in the framework of IMC, it has a great potential that can be explored and applied in many different ways to enhance awareness of public, trigger interest and engage the next generation of scientists, promote education and training in related fields, make clear the benefits of science and international collaborative spirit for society.

Authors:
Yiota Foka,
Petya Georgieva







Saint-Genis-Pouilly (France) college visiting the Antimatter factory at CERN

FLASH RADIOTHERAPY:

when ultra-high dose-rate improves the biological response

Modern radiation therapy based upon high-precision image-guided irradiation is today one of the cornerstones for efficient cancer treatment, combined with chemo, targeted and bio-therapies. The complexity of these combined medical treatments contrasts with the fact that the technology of radiotherapy itself has essentially been focused on tumour conformation. However, real opportunities to improve the biological effectiveness of radiation therapy exist and recent research explored such an option by investigating the impact of duration of radiation exposure on biological responses.

Working at the interface of physics, chemistry and biology **(Figure 1)**, the FLASH technology integrates the fourth dimension: beam time delivery

Group photo of the radio oncology team at Lausanne, CHUV

(Figure 2). "At CHUV, we had the opportunity to use an experimental electron beam linac **(Figure 3)**[1], which is able to deliver electrons beams at ultra-high dose rate," explains Marie-Catherine Vozenin, who co-discovered the potential of FLASH and is Principal Investigator (PI) of the FLASH project in the Department of Radiation Oncology at the Lausanne University Hospital. "We developed a multidisciplinary research program to investigate the biological response to ultra-high dose rate FLASH irradiation with the aim to enhance radiotherapy efficacy and safety."

FLASH-radiotherapy (FLASH-RT) is based on the ultra-fast delivery of radiotherapeutic doses at dose-rates several orders of magnitude higher than those currently used in routine clinical practice. "We have found that the very short time of exposure leads to a relative protection of various normal tissues when they are exposed to single doses of FLASH-RT, as compared to conventional dose-rate-RT," confirms Vozenin. "This effect can be observed even when FLASH-RT is administered in a single fraction." Another advantage of FLASH-RT results from the very short "beam-on time" that literally freezes organ motion thus ensuring a good control during targeting.

"We have named this reduced toxicity induced in normal tissues, the FLASH effect" **(Figure 4)**. The effect has been reported on various experimental animal models (mice, zebrafish, pig, cats), various organs (lung, gut, HS, brain, skin) and various groups across 40 years of research but had never really attracted the attention of the community until very recently. Nowadays, a few devices are able to deliver ultra-high dose rate irradiation on large volumes of tissue. "At CHUV, we have defined some of the physical and biological parameters required to produce the FLASH effect using the experimental linac, which delivers electrons at 6 MeV," says Vozenin. "For instance, the critical role of

[1] *The Oriatron, an electron linac Built by PMB-Alcen.*

Figure 1:

Features

physiological oxygenation has been recently demonstrated in the brain of mice in vivo."

In spite of these very promising results, the FLASH story is still in its infancy and new exciting areas of investigation in the field of radio-physics, chemistry, biology and medicine are now open. "More work is clearly needed to narrow and understand the parameters relevant for the production of the FLASH effect," confirms Vozenin. "In the meantime, a first patient has been treated and there is no doubt that the FLASH-RT application will be extended and will be especially relevant if able to treat refractory tumours."

Significant technological shift is still required and a strong and positive influx is internationally occurring with several important collaboration ongoing and starting between the main actors of FLASH field such as the one started between CHUV and CERN teams. Many groups are beginning to be equipped with preclinical devices in Europe and the USA. These experimental devices will enable the studies required to enhance our understanding of the FLASH effect. In addition, proton therapy facilities are being optimized to deliver FLASH-dose rate. New generation of linacs will also be able to readily deliver FLASH dose rate with photons and very-high-energy electrons. Advances include magnetic focusing of electron beams on the target providing highly improved conformality, and the construction of more efficient and cheaper linacs for FLASH-RT.

"We are entering a novel and exciting era for the radiation community with fundamental physics, chemistry and biology questions to be investigated and possible major improvement in the radiotherapeutic management of cancer," concludes Vozenin.

Author:
Marie-Catherine Vozenin

Figure 2: eRT6 Oriatron

Figure 3:

FLASH RT time scale

Time (s) between initial physical interactions and organism

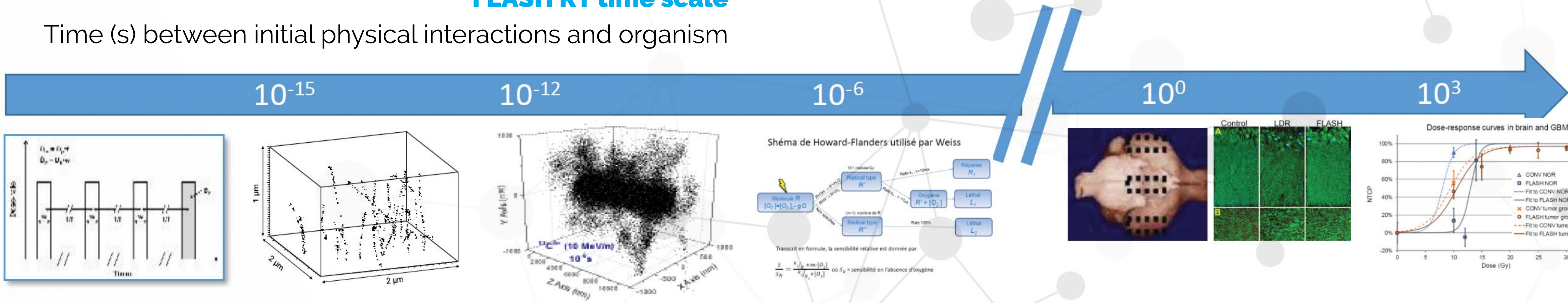
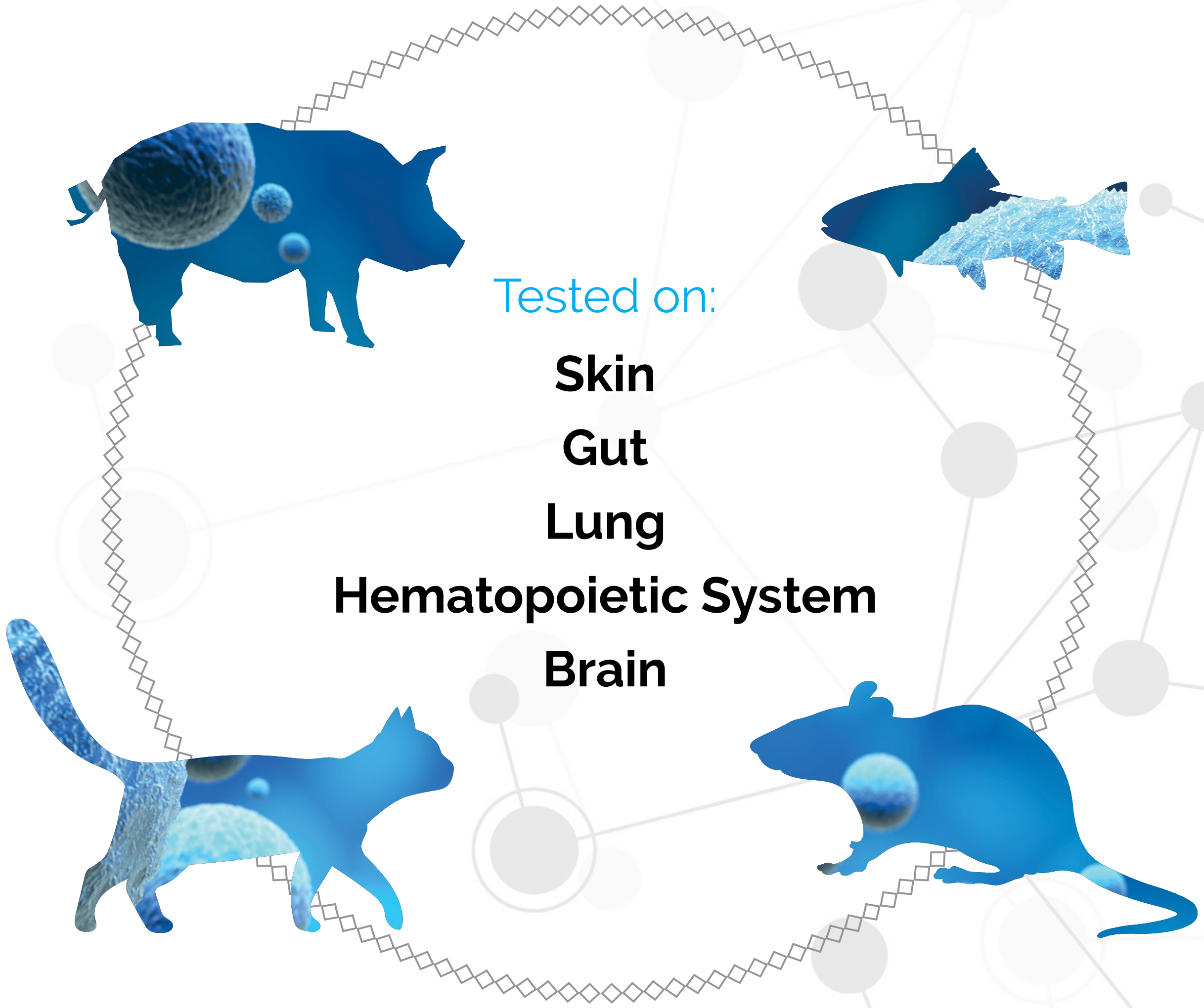


Figure 4:

THE FLASH EFFECT

FLASH-RT does not Induce damages at the normal tissue level



Past Events

SHARING CERN'S EXPERTISE IN BIG DATA WITH the biomedical community

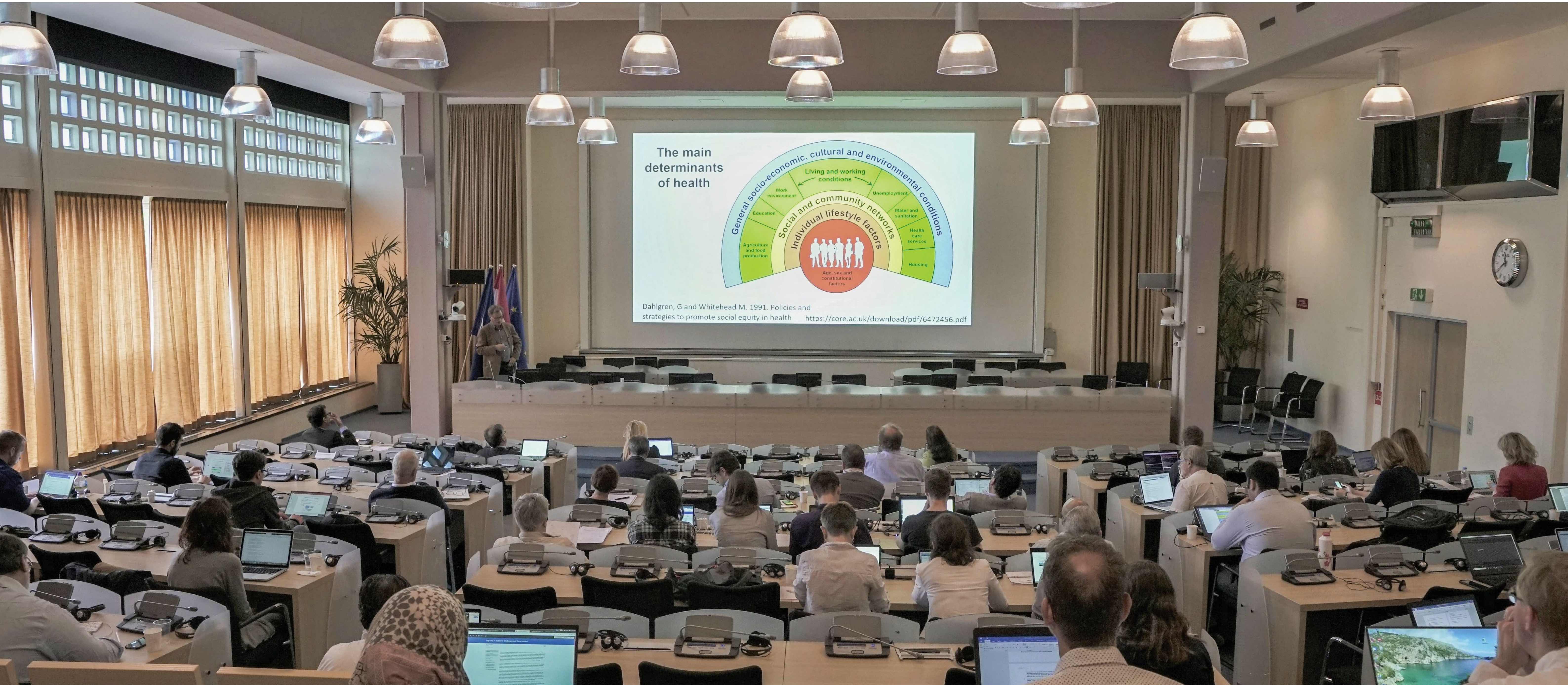
On 6-7 June, CERN hosted a first-of-its-kind workshop on big data in medicine. The event marked the conclusion of a two-year pilot investigation into how CERN-developed technologies and techniques related to computing and big data could potentially be used to address challenges faced in biomedicine. The main goal of the workshop was to establish the terms for broader collaboration with the medical and healthcare research communities in future and was organised by Philippe Lambin (who leads 'The D-Lab' at Maastricht University in the Netherlands) and Alberto Di Meglio and Manjit Dosanjh from CERN.

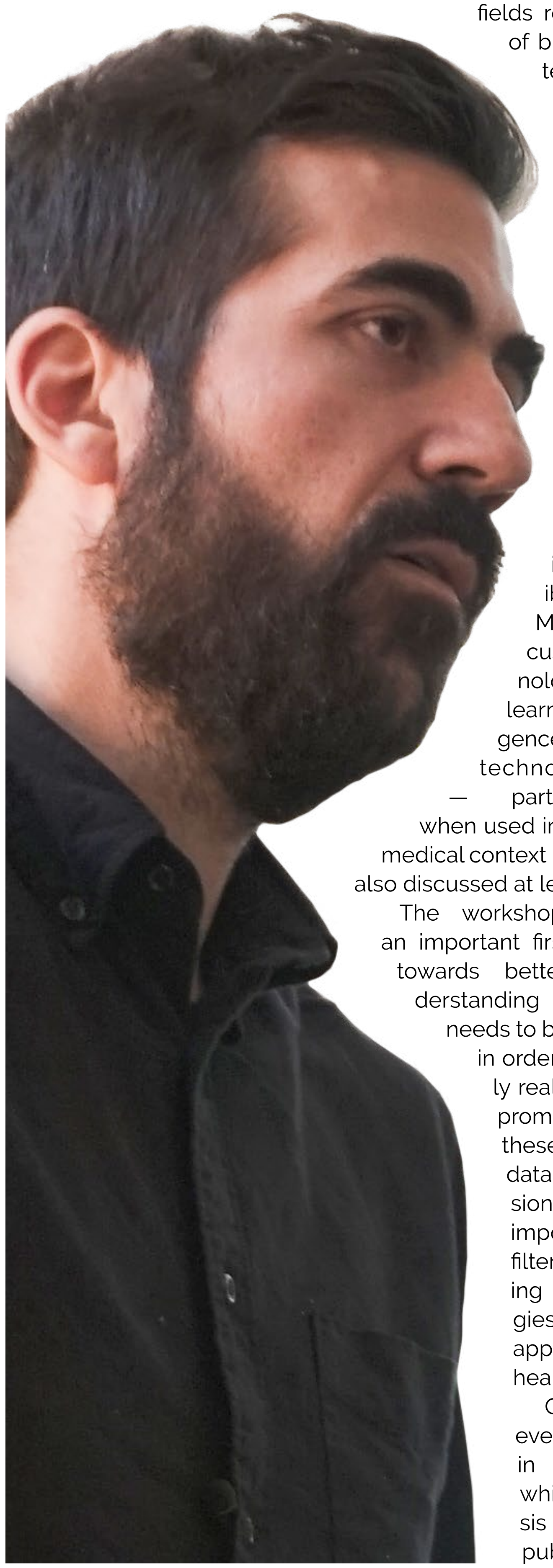
CERN and the high-energy physics community have pioneered the use of large-scale, distributed, data-driven research models. Over recent years, other scientific fields have begun to collect and process ever more data, meaning that they now face similar challenges in terms of data infrastructures, computing technologies, and software applications.

In 2017, CERN adopted a specific knowledge-transfer strategy for medical applications. This strategy focuses on maximising the impact of CERN's engagement through sharing knowledge and ideas with the medical and healthcare communities, in order to identify the most relevant applications for these user communities.

The workshop brought together leaders from a variety of

"Big data in Medicine: Challenges and Opportunities" Workshop in CERN, Council Chamber





fields related to the application of big-data technologies and techniques in biomedicine. The World Health Organization and the European Commission were both represented at the event, as well as a number of leading universities. Participants discussed topics such as personalised medicine, in silico trials, digital health ecosystems, blockchain, and more. Several talks centred on data, addressing various aspects related to its handling — including data privacy, compatibility, and preservation. Many discussions also focused on emerging technologies, such as machine learning and artificial intelligence (AI). The ethics of these technologies — particularly when used in a biomedical context — were also discussed at length.

The workshop was an important first step towards better understanding what needs to be done in order to fully realise the promise of these big-data technologies. The sessions at the event played an important role in helping to filter out the hype surrounding many of these technologies with regards to their application in medicine and healthcare.

“Through the workshop, we tried to separate the hype from the reality when it comes to big-data technologies and AI for personalised medicine.

On the second day of the event, participants took part in an in-depth discussion, which will serve as the basis for a white paper to be published later this year.

This document will set out the main societal and economic challenges in medical research and healthcare systems that emerged from the discussion, describe how collaborative platforms and big-data technologies can help addressing such challenges, and provide recommendations on how such multidisciplinary efforts could be organised.

During these in-depth discussions, it became clear that the participants from the biomedical community were not only keen on learning about technologies developed at CERN, but were also eager to understand more about the intricacies of CERN's model for collaboration across countries and research communities, as well as how technological innovation and adoption is driven within our community.

Author:
Andrew Purcell,

International experts met at CERN to discuss big data technologies.

THE LINAC BASIC RESEARCH NEEDS WORKSHOP

The US Department of Energy (DOE), National Institutes of Health (NIH), Department of Defense and the Department of Homeland Security held the thirteenth basic research needs (BRN) workshop with a focus on the complete LINAC ecosystem in the context of medical and security needs. One hundred and eight invited panellists and observers attended the meeting.

LINAC physicists, education experts, materials scientists, system engineers, computer experts, futurists, and other subject matter experts explored the entire scope of these areas in the intense 3-day, dawn to beyond dusk, interactive workshop to define the current state of the science, define the gaps to address in the near term, and define the medium to long term science and needs of the medical and security spaces.

The explicit goal of the workshop was to generate a formal report to be published alongside prior reports in an open fashion on the web. The nature of these reports is to review and focus the efforts of the scientific community over the next 5 to 15 years.

The nature of the workshop differed dramatically from all other types of normal and even unusual scientific workshops. Group leaders met for months prior to the workshop and prepared preliminary documents and made attendee selections. Charge questions were focused upon by the two application working groups, medicine and security, in the first half of the meeting and technology crosscut groups focused on the gaps and specifications presented to them by the applications groups over the last day of the meeting. Themes, goals, and common needs and problems were focused upon. Synergy was found, expanded upon, and used to create themes.

Past Events

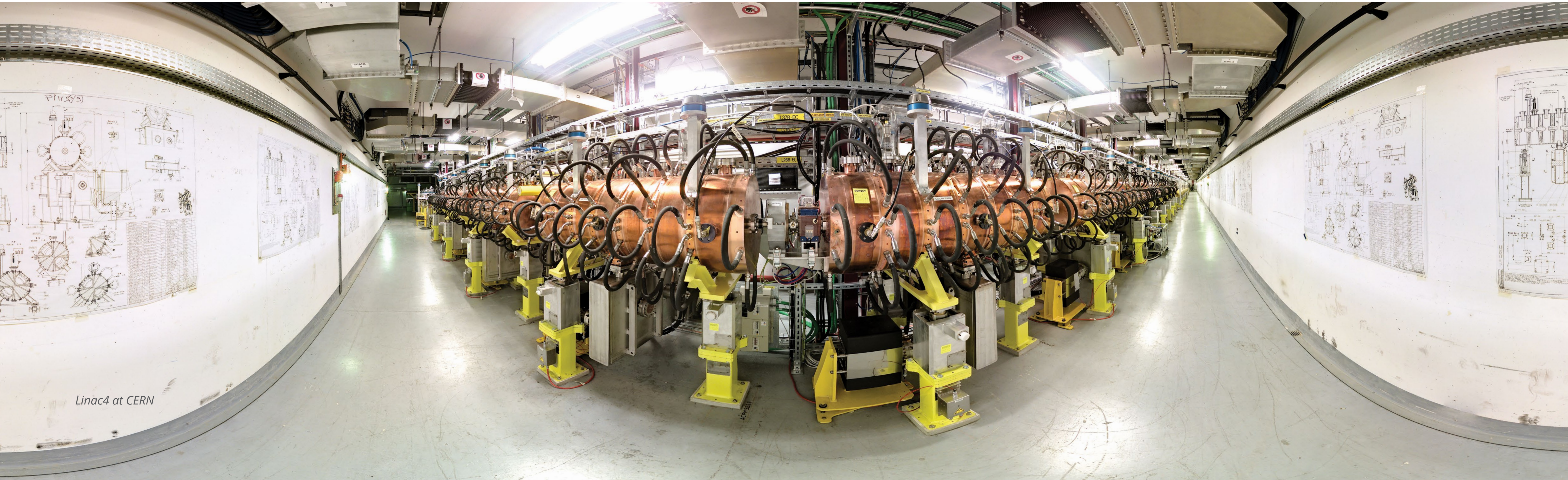
Linac4 tunnel at CERN

In the context of the meeting, hadron LINAC systems were discussed with leaders of CERN present to discuss the capacities of such devices and their application sets. Education and workforce interfaces were also focused upon and the ENLIGHT system was acknowledged to be a leading model for the bidirectional movement of high technology into the user environment and users into the environment that creates high technology.

The tools and ecosystem of LINACs are common and so work in this space will only help to move other aspects of LINAC capacities forward. Every attendee asked (by the author) universally felt the meeting was helpful to them in their space because they gained insights into how their work impacted and was needed by other areas of science in new ways.

The workshop report is expected in the Fall of 2019.

Author:
Jeff Buchsbaum



Linac4 at CERN

THE INTERNATIONAL **Biophysics Collaboration** AT FAIR

Figure 1. *The GSI Helmholtz Center in Darmstadt, and the FAIR construction site in September 2018. Photo: T. Middelhauve/GSI/FAIR*

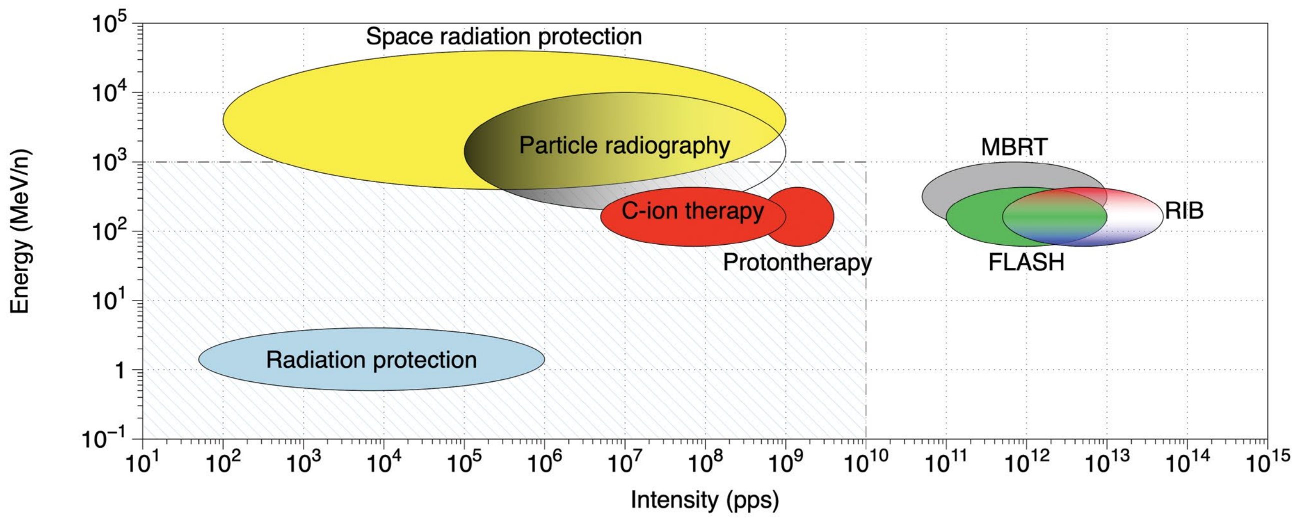


Figure 2. *Biomedical applications at new accelerators. The shaded rectangle includes the (E, I) region covered by particle accelerators. FAIR will provide higher energy and intensity, thus allowing experiments in space radiation protection and particle therapy not possible at current heavy ion accelerators. MBRT= minibeam radiotherapy; FLASH = ultra-high dose-rate therapy; RIB = radioactive ion beams for therapy and beam visualization. Image from: M. Durante, R. Pleskac and C. Graeff, The Biophysics Collaboration: biomedical research at new accelerators. GSI Rep. 2019-3, May 2019, p.1 DOI: 10.15120/GSI-2019-00596*

The Facility for Antiprotons and Ion Research (FAIR) is the new international accelerator facility presently under construction at the site of the GSI (Helmholtzzentrum für Schwerionenforschung) in Darmstadt, Germany **(Figure 1)**. With its numerous physics programs that can be operated in parallel, the new facility will offer outstanding research opportunities and discovery potential for about 3000 scientists from about 50 countries. International collaborations in hadronic physics, nuclear structure etc. are already actively working to prepare the experiments for the opening of FAIR (https://fair-center.eu/).

FAIR will also host an intense and innovative program in applied nuclear physics (APPA), and in particular in biophysics. In fact, FAIR can offer unique opportunities for biomedical research. The production of very high energy (10 GeV/n) heavy ions is very important for studies in space radiation protection, both in biology and microelectronics. The high energy can also be used for particle radiography and theragnostics, whereas the high intensity of the FAIR beams gives opportunities for using high-energy radioactive ion beams and ultra-high dose rates in particle therapy, and for the production of new radioisotopes **(Figure 2)**.

Similarly, to the other FAIR collaborations, the Biophysics Collaboration held a meeting at GSI/FAIR on May 20-22, 2019. With 250 participants from 27 countries in the 5 continents, the meeting demonstrated the enormous interest of the scientific community for the biomedical applications at FAIR **(Figure 3)**.

Several new ideas for experiments at FAIR have been proposed. For the ENLIGHT community, particularly interesting are the experiments on particle therapy. The high energy makes possible particle radiography in every tumour site, with unprecedented spatial and temporal resolution. The PaNTERA experiment at FAIR will indeed explore the possibility to use 4.5 GeV protons for radiography and tomography with sub-mm resolution.

This will enable image-guided proton radiosurgery.

The high-intensity offers even more opportunities for particle therapy. FLASH needs ultra-high dose rates (>40 Gy/s) that so far have been achieved with electrons in modified linacs and protons at cyclotrons, but at FAIR can be tested with heavy ions. Very high dose rates will also open new possibilities in minibeam radiation therapy (MBRT): moving targets could start being considered without jeopardizing the spatial fractionation of the dose. The access to high energy heavy ions will allow exploring new avenues in hadron MBRT. Radioactive ion beams provide a very high signal/noise ratio for online PET imaging and can be produced at therapeutic intensities at FAIR. With the start of FAIR-phase-0 in February 2019, these high-intensity experiments are already feasible at the SIS18 synchrotron of GSI.

Unlike other detector-centred collaborations, the International Biophysics Collaborations goes beyond FAIR. In fact, there are many new accelerator facilities under construction all over the world (e.g. NICA in Russia, RAON in Korea, FRIB in USA, ELI, SPIRAL2 and SPES in Europe, etc.) where applied nuclear physics programs are planned and biomedical research will be possible. The International Collaboration will serve all these facilities and will develop research programs and specific devices for use at various accelerators. Accelerators currently operating for biomedical research (KVI, LNS, etc.) are also part of the collaboration and contribute with their local research program and with hardware to be built with the other facilities.

Vincenzo Patera (University of Rome "la Sapienza", Italy) and Yolanda Prezado (CNRS, Orsay, France) have been elected spokesperson and deputy spokesperson of the collaboration respectively. The collaboration webpage is:

www.gsi.de/bio-coll

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Figure 3. *Group photo at the Biophysics Collaboration Meeting at GSI, May 20, 2019. Photo by Gabi Otto, GSI.*

European Particle Therapy Network (EPTN) WP6: Radiobiology and RBE

Protons and heavier particles have differential biology compared to photon irradiation. Part of this is accounted for in the concept of RBE – Relative Biological Effectiveness. The current use of an RBE of 1.1 for proton irradiation is under debate and there is a need for pre-clinical data on the radiobiology of particle irradiation to support the clinic. The aim of WP6 in the European Particle Therapy Network (EPTN) is to form a network of clinical facilities with radiobiological research in order to facilitate research collaborations, standardization of radiobiological experiments and to coordinate the research in order to obtain the needed data.

As part of the networking activity, WP6 has been arranging yearly workshops, which are open meetings, where everybody with interest in the radiobiology of particles can participate. The aim of the workshops is to bring together the experimental scientist, the modelling people, and the people with the knowledge on the clinical issues, and to create a roadmap on where to take the research. An important theme is to identify the topics of interest, which data are missing for the different aspects and method on how to obtain these data.

This year's workshop was in February in Groningen with Peter van Luijk as the local organizer for the first day. Once again it was organised as an open meeting for all with an interest in experimental particle radiobiology; there were 43 participants from 11 countries and 23 centres were represented. The aim of the meeting was to get people together to network and to discuss primary points of interest, methodological issues and future directions for WP6 – what can we do to facilitate the necessary research. The sessions were centred around the topics identified to be of primary interest at the first workshop at GSI: Differential RBE, Dose-Volume Effects, Normal Tissue Response, Combination Therapy, Modelling, Basic Mechanisms, and New Techniques. The program included both presentations from the participants, as well as discussions on which data are needed and future directions to fill the gaps in the current knowledge.

In the session on dose-volume effects, which was chaired by Peter van Luijk from Groningen, Marc Vooijs from Maastricht talked about biomarkers and targets for tumour and normal tissue response to proton combination therapy, Lara Barazzuol from Groningen presented work on radiotherapy-induced neurocognitive decline from animal models to human brain organoids, while Peter van Luijk discussed the UMCG models for heart/lung and parotid gland.

The second session on Normal Tissue Response was chaired by Christian Karger from Heidelberg who presented a small survey from participants on the existing projects on normal tissue response and which models and endpoints are currently used. There were presentations from Rob Coppes, Groningen, on using organoids to reflect normal tissue radiation response, and from Marc Vooijs, Maastricht, on lung fibrosis and CT monitoring, where after Christian Karger presented the Heidelberg data on RBE of ions in the rat spinal cord. This led to a discussion on the differential RBE of tumour and normal tissue, Chaired by Armin Lühr and Jörg Pawelke from Dresden.

One main point of discussion was, is there a differential RBE originating from biology and/or physics. It was argued that that RBE for tumour response depends on biological factors such as differentiation of the tumour cell and this, for example, has already been demonstrated for carbon ions. Here, the dose response to photon reference radiation varies more strongly than the response to high LET carbon ions. From a clinical perspective, the physical LET variation within the clinical target volume is minor for proton treatments. Therefore, LET related RBE increase is expected at the distal edge of the proton treatment field, i.e. this falls in the normal tissue.

The session on Combination Therapy was chaired by Martin Pruschy from Zurich, who gave a short update on the current status. Thomas Friedrich from GSI and Michael Horsman from Aarhus both presented their view on combining immunotherapy with radiation, and Karen Kirkby from Manchester presented the Manchester experience, while Peter van Luijk and Rob Coppes from Groningen discussed models for testing combined treatment modalities.

In the session on Basic mechanisms, Brita Singers Sørensen from Aarhus gave a short introduction, and Klaudia Szymonowicz, Essen talked about DNA repair foci´s, Justyna Miszczyk from Krakow about the effect of proton irradiation on human peripheral blood lymphocytes and Felicitas Rapp from GSI on Cardiac AV node ablation by carbon ions

There was a presentation on the current status of Modelling by Michael Scholz from GSI, which led to a discussion on which experimental data is currently needed to support the modelling. Michael Merchant from Manchester presented their

Group visiting the facility.

Brita Singer Sørensen in an animated discussion

Armin Lühr is explaining the different RBE in tumour vs. normal tissue

Group photo of EPTN participants in Groningen, The Netherlands

modelling work on the radiobiological effects.

In the session on New techniques, the chair Manjit Dosanjh pointed out that there was a lot of current attention on Flash irradiation and introduced Marie Catherine Vozenin (who published groundbreaking paper with Vincent Favaudon in 2014) from Lausanne, gave a very exciting presentation on the current knowledge on FLASH irradiation, and Yolanda Prezado, Paris, and Thomas Schmid, Munich, both presented their work on microbeams and also touched on grids. In the evening, the participants could enjoy a tour of the clinical facilities at UMCG including the proton facility.

On the second day, that was organised by Sytze Brandenburg at KVI-CART, there was an introduction of the European INSPIRE project by Karen Kirkby, and the ENLIGHT Network and current activities by Manjit Dosanjh. This was followed by the recent developments in the Dutch particle community, with the establishment of a Dutch consortium for particle radiobiology research, INTO-PROT, and a European facility for particle radiobiology research, IMPACT. After lunch, there was a tour of the experimental facilities at KVI-CART. It was agreed that the meeting in 2020 will be in Manchester.

Authors:
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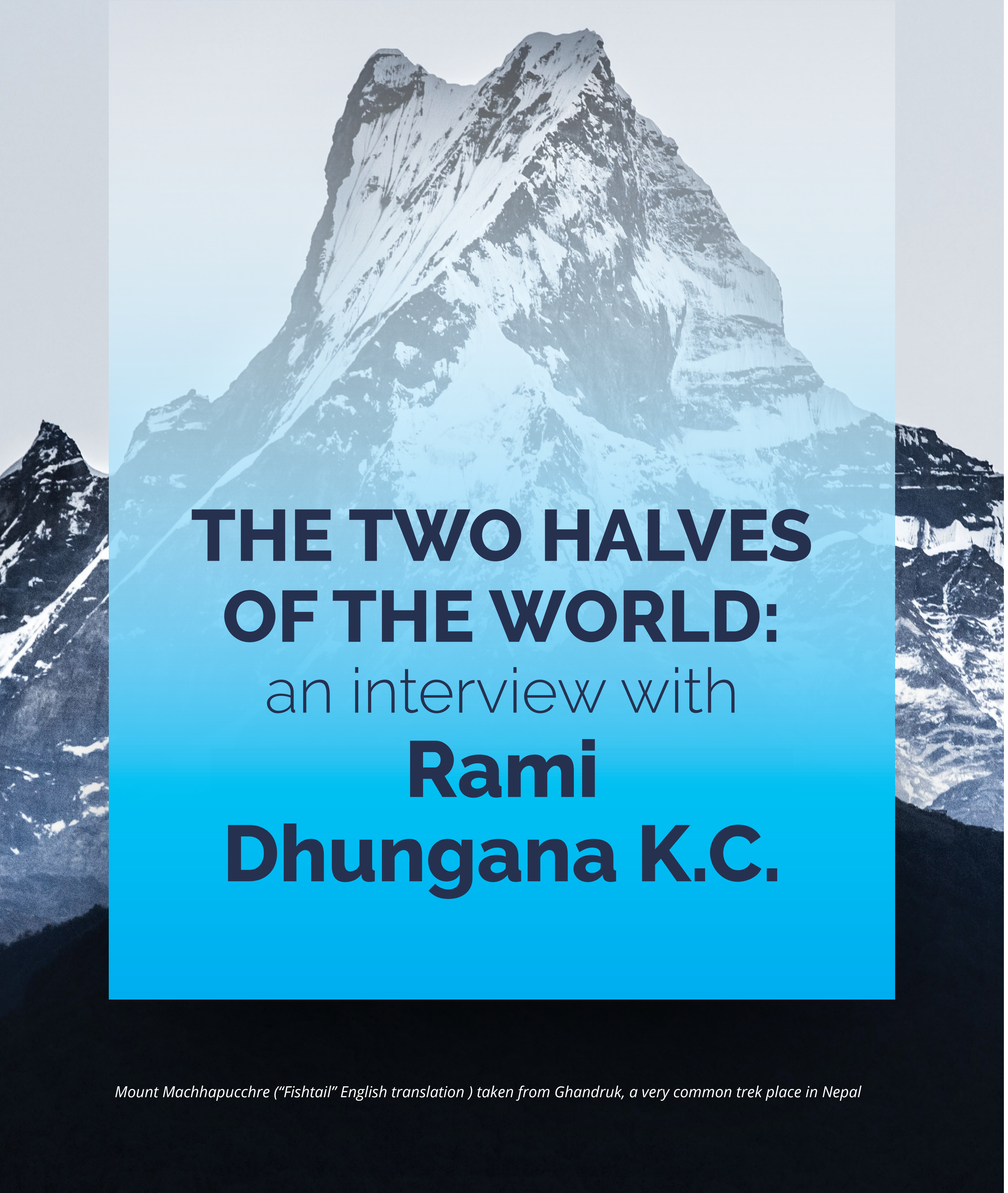
Jörg Pawelke,
Martin Pruschy



THE TWO HALVES OF THE WORLD: an interview with Rami Dhungana K.C.

Mount Machhapucchre ("Fishtail" English translation) taken from Ghandruk, a very common trek place in Nepal

Focus On

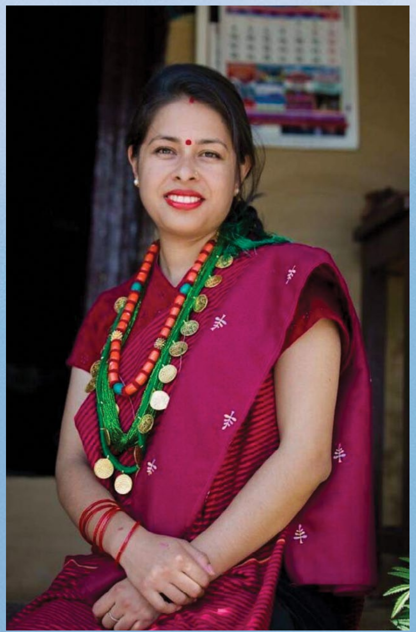
Rami hiking in Pokhara, Nepal

Rami is a Master student in physical sciences at St. Xavier's College, Kathmandu, Nepal. As a student, she is working on a thesis that covers two main areas of research: the systematic review of breast imaging in the context of Nepal, covering also the cost-effectiveness, accuracy, efficacy and methodology; and the evaluation of the accuracy of 2 phase model based on deep neural network for the detection of breast cancer using mammographic data set. "Thanks to my thesis, I am learning new skills, which is much needed in Nepal," explains Rami. "I am doing my master's thesis with the NepAl Applied Mathematics and Informatics Institute for Research (NAAMII) with the aim of identifying the imaging modalities feasible in Nepal where the cost-effectiveness is key."

Rami is determined to become a medical physicist because in her words "it's physics for a good cause". Dr Abish Adhikhari is playing a key role in her career development who she met when she attended the meeting in Botswana **(see page 12)**. "This has been an overwhelming experience for me," she enthuses. "For the first time, I had the opportunity to meet many experts in the field of medical physics and they were all discussing about radiation therapy in challenging environments...it was just perfect for me!" And she goes on to say: "Half of the world is talking about precision, personalized medicine and hadron therapy while the other half is struggling with even just having access to a conventional radiation therapy facility. I was positively impressed by what I saw in Botswana. The government hospitals are so clean, so organised and there is not so

Rami in front of St. Xavier college in Kathmandu

Rami with her supervisor Dr. Abish Adhikari



Rami in Gurung ethnic dress

much difference between government and private hospitals. It's very different from Nepal where hospitals do not have enough public funds. It's very frustrating to see that a lot of activities are compromised because of cost."

Rami was born in a very rural place but her family quickly moved from there to Dolakha, a small city in the mountains near the capital city. She has always loved physics and maths. "My parents were very sceptical about me studying physics because they thought that engineering was better for the job market," she recalls. "During my masters' first year, I heard that there is a field called "Medical Physics" and since then I never thought of a second option." Rami's research journey began when she attended a winter School organized by the ICTP during which she got to know about the CERN summer school for which she applied and was indeed selected. "This turned out to be the most important thing that gave me confidence."

"After Botswana, I realised that it is not only the technology that matters but there is something that we can actually do to help countries like ours. And I just want to be in a place where I can use the technologies, the latest advances for challenging environments," she concludes.

Rami in Mustang, Nepal

Camping in Kalinchowk, Nepal

Rami is doing research under the supervision of the oncologist Dr. Abish Adhikari for GRANDE International Hospital.

Mount Annapurna, taken from the Ghandruk

Start of the SEEIIST Design Phase

A Large-scale Competitive Research Facility

South East European International Institute for Sustainable Technologies (SEEIIST)

Core of SEEIIST:

'Facility for Tumour Therapy and Biomedical Research with Protons and Heavier Ions'

Advisory Committee:

Ugo Amaldi (TERA Foundation)
Frederick Bordry (Director of Accelerators, CERN)
Juergen Debus (Medical Director, HIT Heidelberg)
Marco Durante (Director of Biophysics, GSI)
Herwig Schopper (Chairman, former DG of CERN)
Hans J. Specht (Heidelberg University, former DG of GSI)
Horst Wenninger (Coordinator of the SEEIIST Preparatory Phase)

Organizer

Montenegro
Ministry of Science

18 September 2019, Budva, Montenegro

Registration to the Forum is free. Please register at https://indico.cern.ch/event/807172/

DATA-DRIVEN MEDICINE: the challenges and opportunities of **electronic health records** for research and care

Figure 7. The Denaxas Lab (http://denaxaslab.org) at University College London Institute of Health Informatics (from left to right): Muhhamad Arfeen, Maxine Mackintosh, Arturo Gonzalez-Izquierdo, Natalie Fitzpatrick, Maria Pikoula, Michalis Katsoulis, Albert Henry, Vaclav Papez, Kenan Direk. (not pictured: Nonie Alexander, Ghazaleh Fatemifar)

It's fair to say that a significant proportion of the evidence base driving clinical decisions and therapies in modern healthcare has been derived from data which were historically limited in terms of sample size, breadth, and depth. This has led to the creation of many "one size fits all" treatments which only work for less than half of the patients they are prescribed to while potentially causing adverse events in others **(Figure 1)**. Over the recent years, the widespread adoption of clinical information systems combined with advancements in biomedical technology has led to an explosion of electronic data which are generated and captured during routine interactions of patients with the healthcare system. These electronic health records (EHR) are highly relevant to the understanding of human diseases and are driving forward a new era of data-driven medicine.

EHR are not created for use in research but for other reasons (i.e. reimbursement, audit) and, as such, require a significant amount of preprocessing before they can be statistically analyzed. Structured (e.g. recorded using controlled clinical terminologies), unstructured (e.g. free text) and binary (e.g. medical imaging) data for the same individual are often generated and stored across different information systems and vary in terms of schema, quality and depth of information. Researchers create and validate complex rule-based or probabilistic algorithms **(Figure 2)** which link, normalize and combine data from these multiple sources to identify disease or disease-related information (a process referred to as phenotyping, **Figure 3**). As well as considerable technical challenges, significant challenges around security, confidentiality and information governance exist due to the sensitive nature of health data which must be taken into consideration.

Despite these challenges, however, EHR are increasingly used for translational research at scale. In the CALIBER resource at UCL (http://www.caliberresearch.org), the increased sample size offered by EHR enables researchers to study diseases with rare symptoms and outcomes, to improve early detection for diseases difficult to diagnose, to capture detailed disease progression over time **(Figure 4)** or to disaggregate conditions which were traditionally lumped together and study them in higher resolution such as cardiovascular diseases. Using supervised learning approaches, EHR can be utilized for creating accurate risk prediction models which can be used to predict the risk of a patient developing a disease (e.g. type 2 diabetes) or not responding to a particular treatment. The richness of EHR data allow scientists to identify and characterize disease subtypes for diseases which are highly heterogeneous (e.g. COPD, **Figure 5**.) which in turn can enable the discovery of new drug targets or better diagnostic tools. In interventional research, EHR offer the ability to undertake randomized interventions embedded in routine clinical care pathways thereby lowering the cost associated with these studies and offering a more pragmatic approach to evaluation.

In summary, EHR are a disruptive force which can potentially lead to significant improvements to human health and healthcare through the creation of a data-driven **(Figure 6)** healthcare system. Health data however pose significant chal-

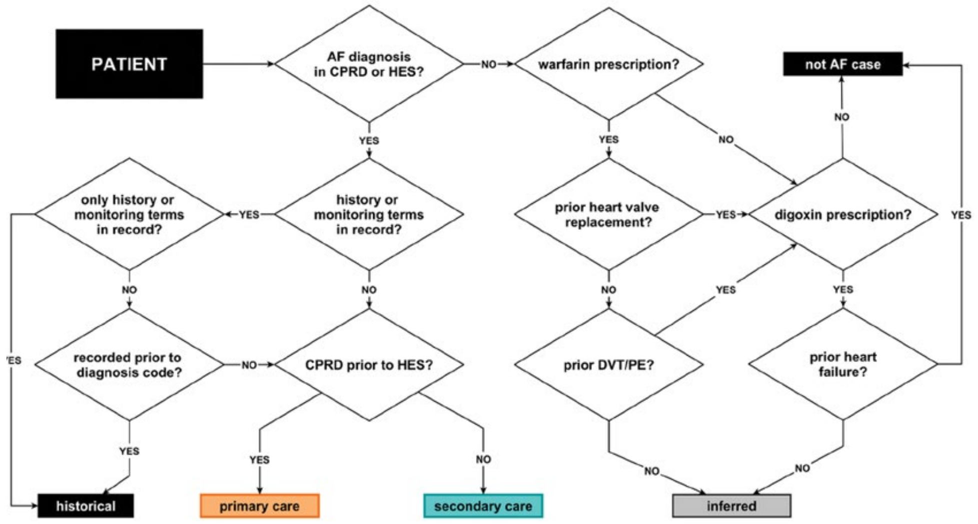


Figure 3. Rule-based phenotyping algorithm from the CALIBER resource utilizing diagnosis and prescription information from structured EHR to identify patients with atrial fibrillation. Source: 10.1371/journal.pone.0110900

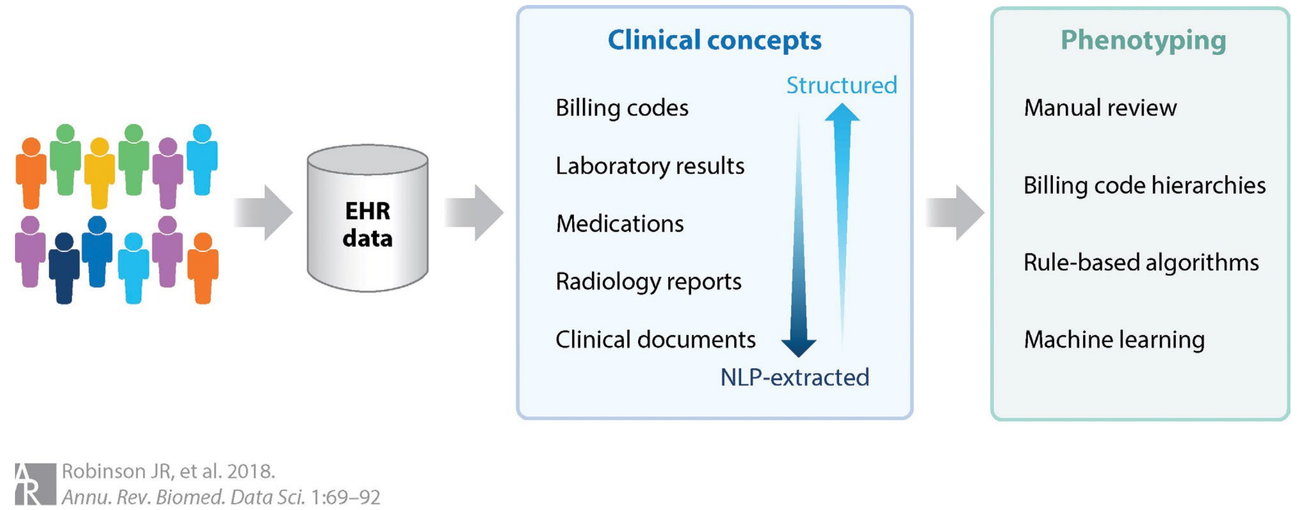


Figure 2. Clinical concepts such as laboratory measurements or diagnoses can be stored in structured or unstructured data and researchers must create phenotyping algorithms to extract information from these heterogeneous data sources. Source: 10.1146/annurev-biodatasci-080917-013335

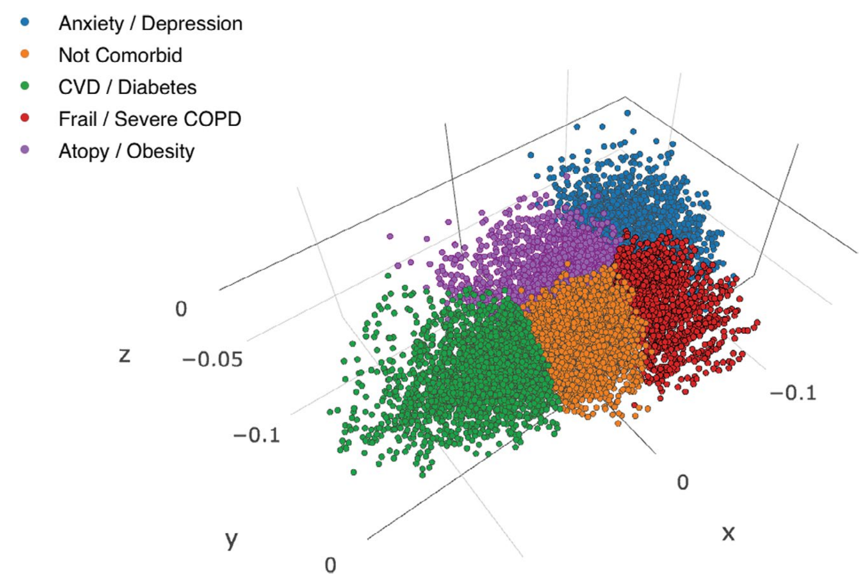


Figure 5. Using unsupervised learning approaches to identify five distinct and clinically-meaningful clusters of patients from a group of 30,961 Chronic Pulmonary Obstructive Disease (COPD) patients defined in EHR from the CALIBER resource. Figure is a 3D scatter plot of the three Multiple Correspondence Analysis (MCA) components colour-coded by cluster assignment. Source: 10.1186/s12911-019-0805-0

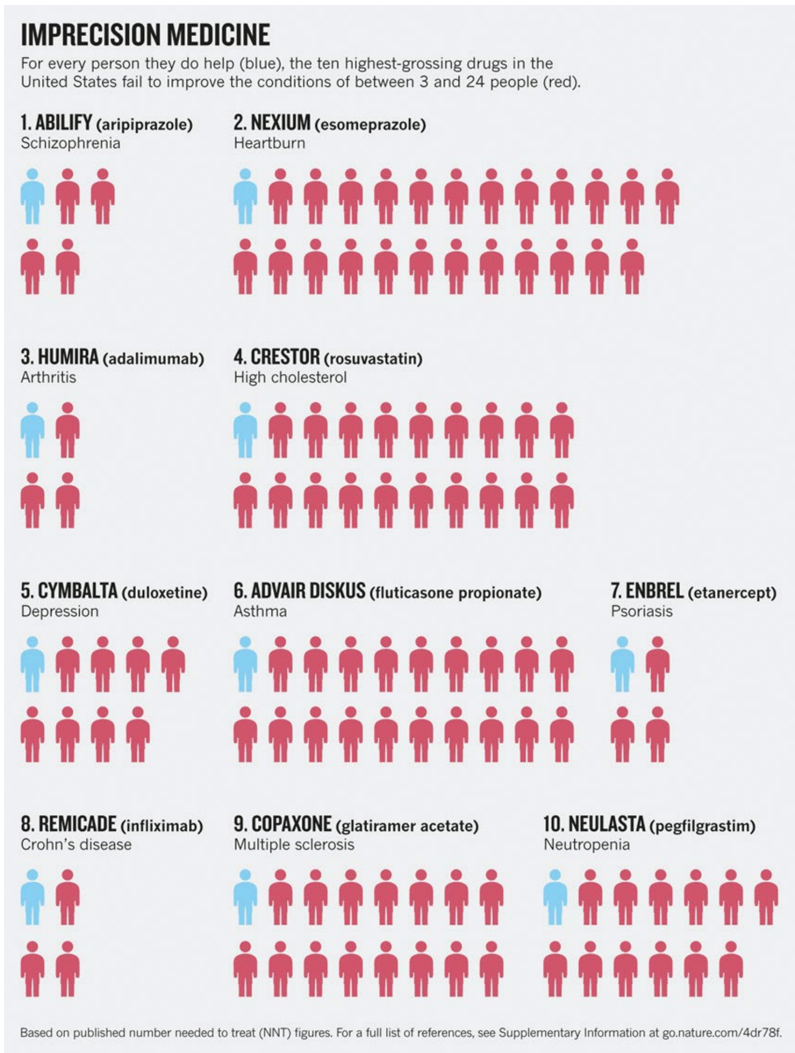


Figure 1. The top ten highest-grossing drugs in the United States help between 1 in 25 and 1 in 4 of the people who take them. Source: 10.1038/520609a.

> **In summary, EHR are a disruptive force which can potentially lead to significant improvements to human health and healthcare through the creation of a data-driven healthcare system**

lenges and multidisciplinary teams **(Figure 7)** spanning computer science, clinical research, public health, law and epidemiology are required to fully capitalize on the opportunities of EHR. In the UK, the newly-established Health Data Research UK (HDR-UK, http://www.hdr.ac.uk) National Institute for health data science aims to act as a catalyst for research using such rich data and train the next generation of health data scientists.

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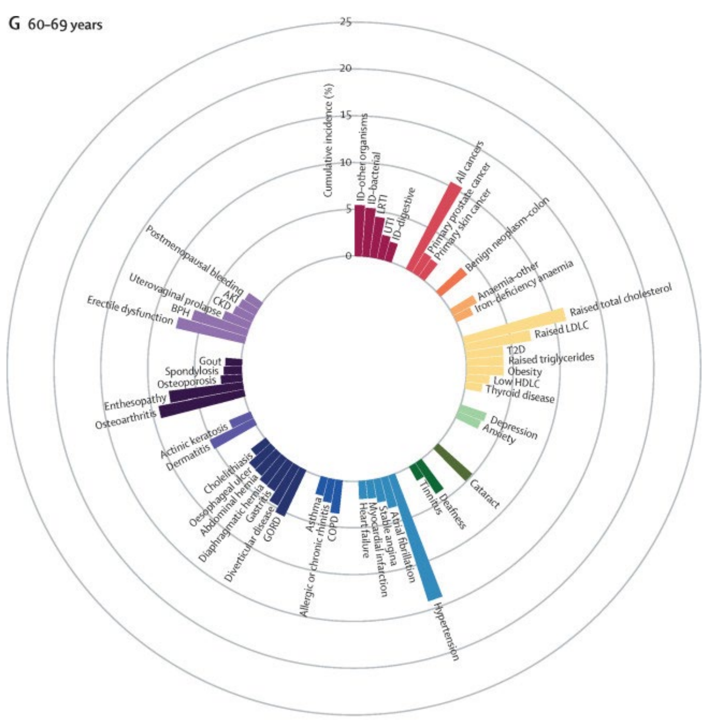


Figure 4. *Cumulative incidence (%) of the top 50 diseases and all cancers between April 1, 2010, and March 31, 2015, for individuals aged 60-69 years old, adjusted for sex. Using EHR from the CALIBER resource, researchers tracked more than 300 physical and mental health conditions and constructed the first-ever chronological map of human disease. Source: 10.1016/S2589-7500(19)30012-3*

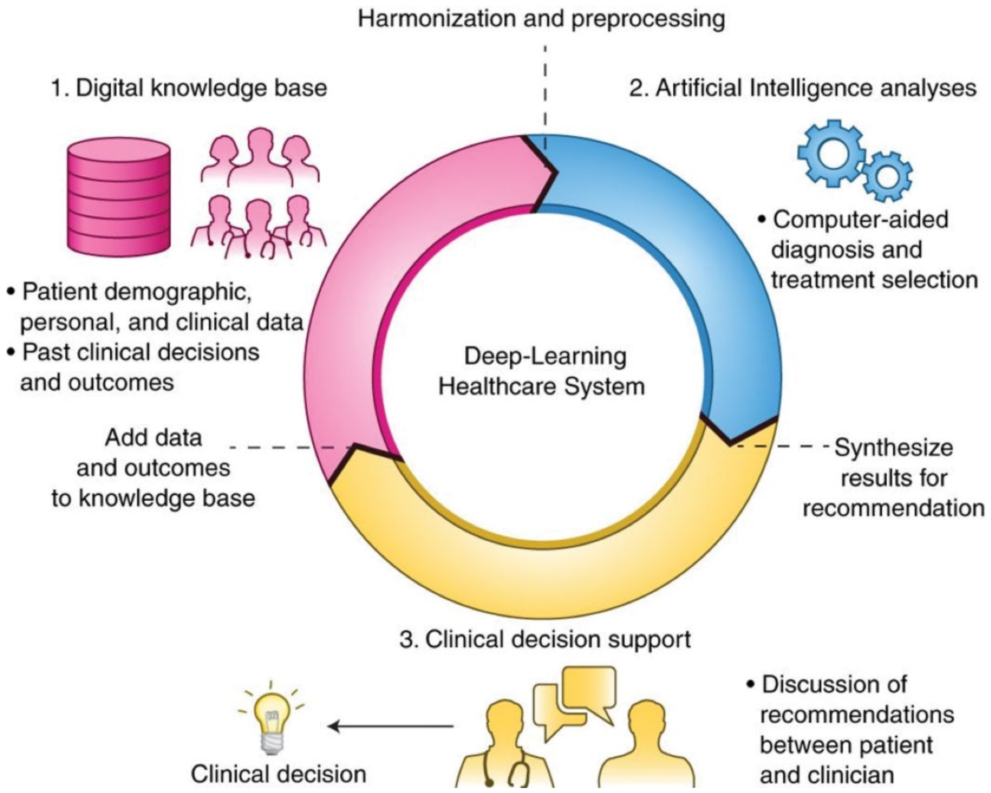
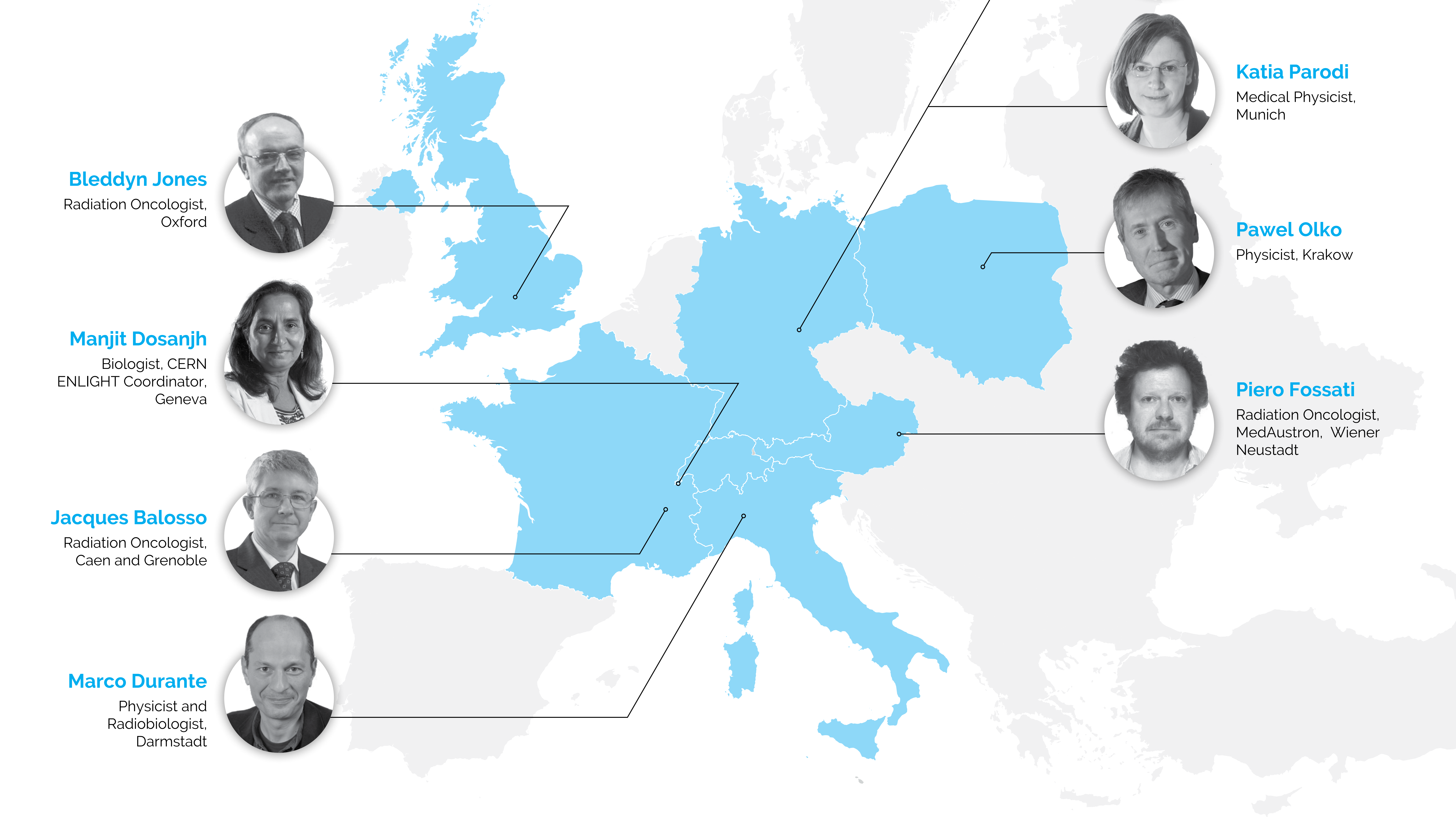


Figure 6. *Schematic representation of a "deep learning healthcare system" which leverages data from EHR combined with deep learning methods to rapidly improve clinical decision support and patient outcomes. Source: Nature Medicine 25, 14–15 (2019)*

Future Events

NAME OF THE EVENT	DATE OF EVENT	PLACE OF EVENT
15-18 September 2019	ASTRO's 61st Annual Meeting	Chicago, IL, USA
18 September 2019	Start of the SEEIIST Design Phase	Budva, Montenegro
27 October- 03 November 2019	2019 IEEE Nuclear Science Symposium and Medical Imaging Conference	Manchester, UK
03-07 April 2020	ESTRO 39 Annual Meeting	Vienna, Austria
9-14 May 2020	PTCOG 59 Annual Meeting	Taipei, Taiwan
22-24 June 2020	ENLIGHT 2020	Bergen, Norway

ENLIGHT advisory COMMITTEE



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
Join the ENLIGHT network.
Register to become a member here.
https://indico.cern.ch/event/180036/registrations/495/

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