WELCOME

CERN Courier – digital edition

Welcome to the digital edition of the 2021 medical technology focus issue of *CERN Courier*.

This issue showcases the impact of high-energy physics in the medical arena. Ever since the discovery of X-rays, developments in fundamental physics have found their way into medical applications. From advanced imaging technologies to dedicated accelerators for cancer therapy and nuclear medicine, simulations, and data analytics, state-of-the-art techniques derived from particle accelerators, detectors, and physics computing are routinely used in clinical practice and medical research centres.

This issue opens with a new CERN project to expand the use of hadron therapy (p5), from which upwards of 170,000 cancer patients have already benefitted at almost 100 centres worldwide, and describes how technology developed for a linear electron–positron collider at CERN is enabling a paradigm-shifting radiotherapy technique called FLASH (p9 and 12).

Accelerators are also rapidly growing in importance for the production of radioisotopes (p25), as demonstrated by CERN's MEDICIS facility (p23), while recent articles from the Courier's archive demonstrate the role of particle accelerator (p27) and detector (p15) expertise in the fight against COVID-19. We hope you enjoy this "med-tech" snapshot, which demonstrates the broad societal impact of fundamental research.

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FLASH THERAPY

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CERN's next step for hadron therapy
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IN FOCUS MEDICAL TECHNOLOGY

From the Editor

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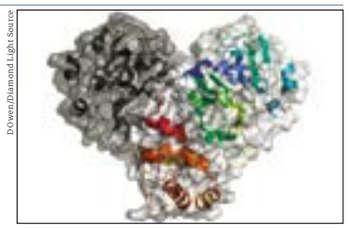

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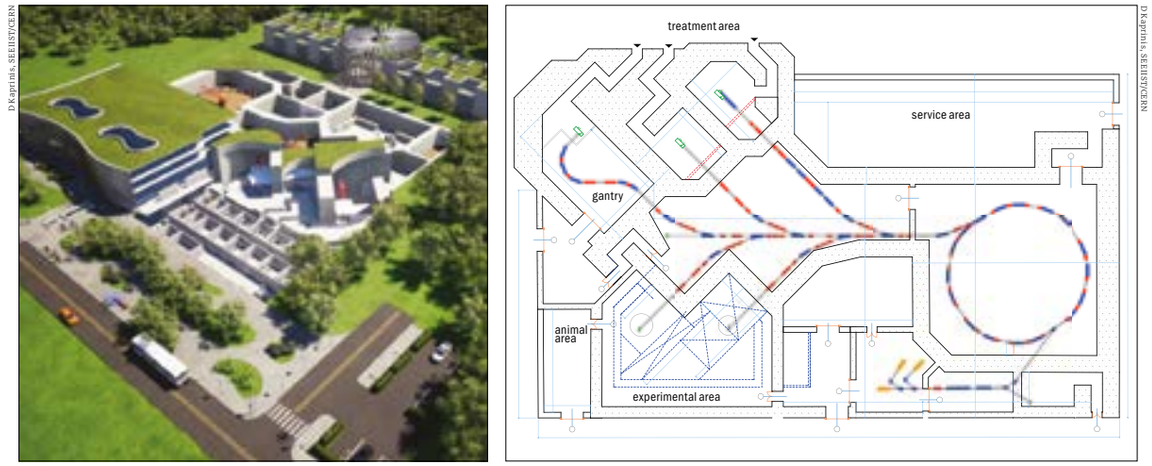
CERN TAKES NEXT STEP FOR HADRON THERAPY

The Next Ion Medical Machine Study (NIMMS) aims to leverage CERN technologies and expertise in accelerators to design a new generation of light-ion accelerators for medicine.



Ions for therapy *How the SEEIIST Ion Therapy Research Infrastructure (left) in South East Europe might look, where the open roof shows the synchrotron and the treatment rooms with the gantry, and detail of the accelerator layout (right).*

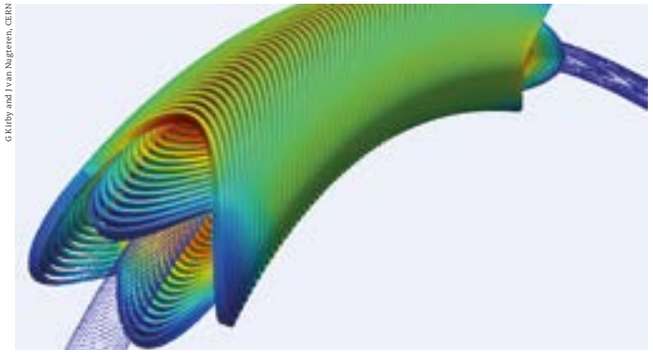
Twenty years ago, pioneering work at CERN helped propel Europe to the forefront of cancer treatment with hadron beams. The Proton Ion Medical Machine Study (PIMMS), founded in 1996 by a CERN–TERA Foundation–MedAustron–Oncology2000 collaboration, paved the way (see p18) to the construction of two hadron-therapy centres: CNAO in Pavia (Italy) and MedAustron in Wiener Neustadt (Austria). A parallel pioneering development at GSI produced two similar centres in Germany (HIT in Heidelberg and MIT in Marburg). Since the commissioning of the first facility in 2009, the four European hadron-therapy centres have treated more than 10,000 patients with protons or carbon ions. The improved health and life expectancy of these individuals is the best reward to the vision of all those at CERN and GSI who laid the foundations for this new type of cancer treatment.

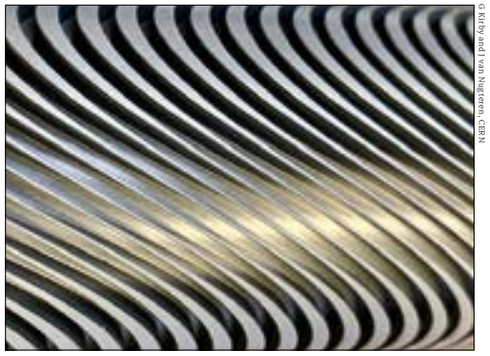
Almost four million new cancer cases are diagnosed per year in Europe, around half of which can be effectively treated with X-rays at relatively low cost. Where hadrons are advantageous is in the treatment of deep tumours close to critical organs or of paediatric tumours. For these cancers, the "Bragg peak" energy-deposition characteristic of charged particles reduces the radiation dose to organs surrounding the tumour, increasing survival rates and reducing negative side effects and the risk of recurrency. With respect to protons, carbon ions have the additional advantages of hitting the target more precisely with higher biological effect, and of being effective against radioresistant hypoxic tumours, which constitute between 1 and 3% of all radiation-therapy cases. Present facilities treat only a small fraction of all patients who could take advantage of hadron therapy, however. The diffusion of this relatively novel cancer treatment is primarily limited by its cost, and by the need for more pre-clinical and clinical research to fully exploit its potential.

Given these limitations, how can the scientific community contribute to extending the benefits of hadron therapy to a larger number of cancer patients? To review this and similar questions, CERN has recently given a new boost to its medical accelerator activities, after a long interruption corresponding to the time when CERN resources where directed mainly towards LHC construction. The framework for this renewed effort was provided by the CERN Council in 2017 when it approved a strategy concerning knowledge-

THE AUTHOR

Maurizio Vretenar *is the leader of the NIMMS study at CERN.*





G Kirby and J van Nugteren, CERN

Combined windings *Solution for curved and straight "canted-cosine-theta" coils combining dipole and quadrupole in the same winding.*

transfer for the benefit of medical applications. This strategy specifically encouraged new initiatives to leverage existing and upcoming CERN technologies and expertise in accelerator technologies towards the design of a new generation of light-ion accelerators for medicine.

The hadron-therapy landscape in 2020 is very different from what it was 20 years ago. The principal reason is that industry has entered the field and developed a new generation of compact cyclotrons for proton therapy. Beyond the four hadron (proton and ion) centres there are now 23 industry-built facilities in Europe providing only proton therapy to about 4000 patients per year. Thanks to this new set of facilities, proton therapy is now highly developed and is progressively extending its reach in competition with more conventional X-ray radiation therapy.

Despite its many advantages over X-rays and protons, therapy with ions (mainly carbon, but other ions like helium or oxygen are under study) is still administered in Europe only by the four large hadron-therapy facilities. In comparison, eight ion-therapy accelerators are in operation in Asia, most of them in Japan, and four others are under construction. The development of new specific instruments for cancer therapy with ions is an ideal application for CERN technologies, in line with CERN's role of promoting the adoption of cutting-edge technologies that might result in innovative products and open new markets.

Next-generation accelerators

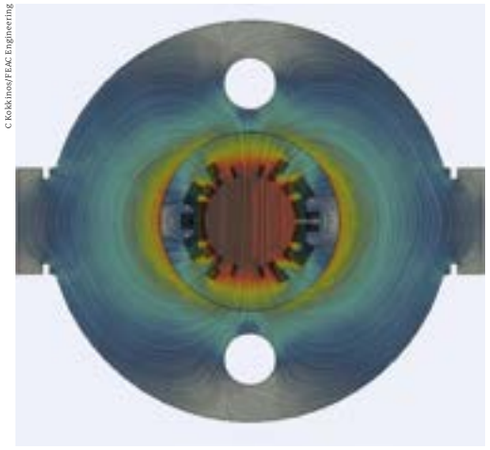
To propel the use of cancer therapy with ions we need a next-generation accelerator, capable of bringing beams of carbon ions to the 430 MeV/u energy required to cover the full body, with smaller dimensions and cost compared to the PIMMS-type machines. A new accelerator design with improved intensity and operational flexibility would also enable a wide research programme to optimise ion species and treatment modalities, in line with what was foreseen by the cancelled BioLEIR programme at CERN. This would allow the exploration of innovative paths to the treatment of cancer such as ultra-short FLASH therapy (see p9) or the promising combination of ion therapy with immunotherapy, which is expected to trigger an immune response against diffused cancers and metastasis. Moreover, a more compact accelerator could be installed in, or very close to, existing hospitals to fully integrate ion therapy in cancer-treatment protocols while minimising the need to transport patients over long distances.

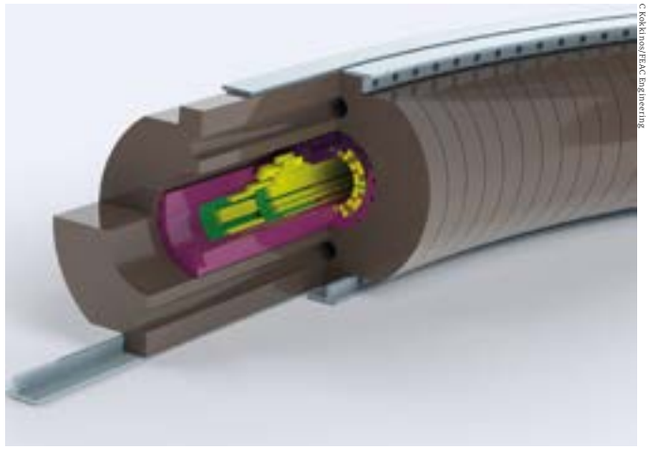
These considerations are the foundation for the Next Ion Medical Machine Study (NIMMS), a new CERN initiative that aims to develop specific accelerator technologies for the next generation of ion-therapy facilities and help catalyse a new European collective action for therapy with ion beams. The NIMMS activities were launched in 2019, following a workshop at ESI Archamps in 2018 where the medical and accelerator communities agreed on basic specifications for a new-generation machine. In addition to smaller dimensions and cost, these include a higher beam current for faster treatment, operation with multiple ions, and irradiation from different angles using a gantry system.

In addressing the challenges of new designs with reduced dimensions, CERN is building on the development work promoted in the last decade by the TERA Foundation. Reducing the accelerator dimensions from the conventional synchrotrons used so far can take different directions, out of which two are particularly promising. The first is the classic approach of using superconductivity to increase the magnetic field and decrease the radius of the synchrotron, and the second consists of replacing the synchrotron with a high-gradient linear accelerator with a new design – in line with the proton therapy linac being developed by ADAM, a spin-off company of CERN and TERA now part of the AVO group. The goal in both designs is to reduce the surface occupied by the accelerator by more than a factor of two, from about 1200 to 500 m^2. With these considerations in mind, the NIMMS study has been structured in four work packages.

The main avenue to reduced dimensions is superconductivity, and the goal of the first work package is to develop new superconducting magnet designs for pulsed operation, with large apertures and curvatures – suitable for an ideal "square" synchrotron layout with only four 90 degree magnets. Different concepts are being explored, with some attention to the so-called canted cosine-theta design (see "Combined windings") used for example in orbit correctors for the high-luminosity LHC, of which a team at Lawrence Berkeley National Laboratory has recently developed a curved prototype for medical applications. Other options under study are based on more traditional cosine-theta designs (see "Split yoke"), and on exploiting the potential of modern high-temperature superconductors.

The development of new specific instruments for cancer therapy with ions is an ideal application for CERN technologies





C Kokkinos/FEAC Engineering

Split yoke *Model of a curved cosine-theta dipole and vertical split yoke with assembly clamps.*

The second work package covers the design of a compact linear accelerator optimised for installation in hospitals. Operating at 3 GHz with high field gradients, this linac design profits from the expertise gained with accelerating structures developed for the proposed Compact Linear Collider (CLIC), and uses as an injector a novel source for fully-stripped carbon based on the REX-ISOLDE design. The source is followed by a 750 MHz radio-frequency quadrupole using the design recently developed at CERN for medical and industrial applications.

The third NIMMS work package focuses on compact superconducting designs for the gantry, the large element required to precisely deliver ion beams to the patient that is critical for the cost and performance of an ion-therapy facility. The problem of integrating a large-acceptance beam optics with a compact superconducting magnetic system within a robust mechanical structure is an ideal challenge for the expertise of the CERN accelerator groups. Two designs are being considered: a lightweight rotational gantry covering only 180 degrees originally proposed by TERA, and the GaToroid toroidal gantry being developed at CERN.

The fourth work package is dedicated to the development of new high-current synchrotron designs, and to their integration in future cancer research and therapy facilities. To reduce treatment time, the goal is to accelerate more than an order of magnitude higher current than in the present European facilities. This requires careful multi-turn injection into the ring and strict control of beam optics, which add to other specific features of the new design, including a fast extraction that will make tests with the new ultra-fast FLASH treatment modality possible. Two synchrotron layouts are being considered, a more conventional one with room-temperature magnets (see "Ions for therapy"), and a very compact superconducting one of only 27 m circumference. The latter, equipped with a gantry of new design, would allow a single-room carbon-therapy facility to be realised in an area of about 1000 m^2. Additionally, NIMMS will consider new designs for the injector linac, with reduced cost and dimensions and including the option of being used for production of medical radioisotopes – for imaging and therapy – during the otherwise idle time between two synchrotron injections.

Ambitious work plan

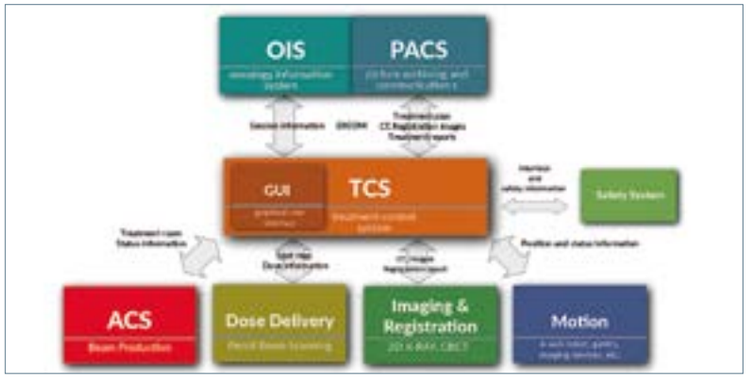
This ambitious work plan exceeds the resources that CERN can allocate to this study, and its development requires collaborations at different levels. The first enthusiastic partner is the new SEEIIST (South East European International Institute for Sustainable Technologies) organisation, which aims at building a pan-European facility for cancer research and therapy with ions (see "Ions for therapy"). SEEIIST is already joining forces with NIMMS by supporting staff working at CERN on synchrotron and gantry design. The second partnership is with the ion therapy centres CNAO and MedAustron, which are evaluating the proposed superconducting gantry design in view of extending the treatment capabilities of their facilities. A third critical partner is CIEMAT, which will build the high-frequency linac pre-injector and validate it with beam. Other partners participating in the study at different levels are GSI, PSI, HIT, INFN, Melbourne University, Imperial College, and of course TERA which remains one of the driving forces behind medical-accelerator developments. This wide collaboration has been successful in attracting additional support from the European Commission via two recently approved projects beginning in 2021. The multidisciplinary HITRIplus project on ion therapy includes work packages dedicated to accelerator, gantry and superconducting magnet design, while the IFAST project for cutting-edge accelerator R&D contains an ambitious programme focusing on the optimisation and prototyping of superconducting magnets for ion therapy with industry.

Every technology starts from a dream, and particle accelerators are there to fulfil one of the oldest: looking inside the human body and curing it without bloodshed. It is up to us to further develop the tools to realise this dream. ●

NIMMS will consider new designs for the injector linac, with reduced cost and dimensions

Trends in control technology for particle-therapy machines

Particle-therapy (PT) systems are one of the most complex medical devices. Their complexity represents a significant engineering challenge, especially for the control-system (CS) software, which needs to enable each separate subsystem – including the accelerator, patient positioning subsystem, gantry, imaging solution and safety system – to work on their own. Additionally, the CS software must integrate the subsystems into a full-featured PT system that is nevertheless easy to use. But there is an even bigger challenge for PT control software. If a PT machine does not work correctly, it can cause serious, even fatal, harm to patients and PT personnel, and the burden of preventing such disastrous mistakes falls squarely upon the control system itself.



A high-level representation of the main subsystems that form a typical PT control system.

Researchers have been working on accelerator CSs for decades, and a handful of CS platforms, frameworks and tool suites have emerged as widely used and community-approved, battle-hardened and industrial-strength, and battle-proven, such as EPICS, TANGO and TINE. Typically, these are flexible and open, and allow developers many options in how to use them and how to implement the required functionality. On the other hand, for medical devices, flexibility is less important than safety, reliability and ease of guaranteeing regulatory compliance (focused towards certification). The latter is essential, especially in commercial systems, so some of the other control technologies typically found in industry are sometimes used, such as SCADA systems or National Instrument's LabVIEW platform.

The auxiliary systems for the medical accelerators used in PT are typically implemented using programmable logic controllers (PLCs) following the same concept as that used in the scientific research domain. The number of risks that come with a PT system are so significant that it makes sense to cover the majority of these in a separate subsystem explicitly dedicated to safety. As most required logic caters to monitoring and conditional triggering interlocks, PLC systems are typically chosen as the preferred technology in PT systems.

Some safety mechanisms, as well as the actual delivery of the particle beam to the patient, require real-time processing. The technology of choice here is typically field-programmable gate array (FPGA), but engineers also implement parts of logic using real-time operating systems.

Patient positioning involves couch and imaging systems, which are typically developed independently. Additional motion-control logic needs to be implemented, first to integrate both systems and second to implement the overall workflow combining the functionality of both systems to quickly, correctly and securely position the patient. Both couch and imaging systems also require specific expertise. Positioning is typically achieved using a robot with six degrees of freedom, so knowledge of robotics is necessary to be able to implement kinematics calculations, path planning and collision avoidance. The imaging system must also encompass image processing based on "image registration", which is the determination of a common coordinate system.

The treatment control system (TCS), shown above, is most prominent because it represents a central subsystem that has to integrate all other subsystems and combine them in a functional and safe final system. Because it implements business logic and typically doesn't have tight timing requirements, higher level programming languages like C++, C# or JAVA can be used. Besides compensating for complications in the rest of the subsystems and ensuring that the treatment workflow is efficient and safe, the TCS has to be flexible to support different workflows – the ones that are typically needed today, as well as those being readied for the future. The expected lifetime of PT machines is 20+ years, and during this period new technology and treatment protocols will evolve.

Currently, each manufacturer will invest a considerable amount of effort and time – also delaying time-to-market – in developing, debugging and certifying custom controls. And with the limited install base at present, the cost of the development effort contributes significantly to the overall higher cost of PT systems. But is the PT CS a competitive advantage? Are hospitals deciding on which system to buy based on the CS? Cosylab believes the answer is no and has developed a suite of PT-specific and medically certifiable CS platforms and products that most PT manufacturers can use. These are C-ACS – an accelerator control system, C-MSS – a medical safety system, C-TCS – a treatment control system, and C-DDS – a dose delivery system for pencil beam scanning.

All of the products are integrated and provide open interfaces to connect to existing systems or build additional functionality on top. The latter could be the future vision for PT – to focus on the real advantages of specific systems and, for the rest, to rely on available, field-tested and open solutions to control the PT machines.

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Dr Rok Gajsek is the head of products at Cosylab d.d., a company providing state-of-the-art software and electronics for cancer-therapy systems, high-tech startups and complex big-physics machines, i.e. particle accelerators, optical and radio telescopes, and nuclear-fusion reactors. In his free time, he likes blowing off steam with various sports, a good book or by spending time with family and friends.

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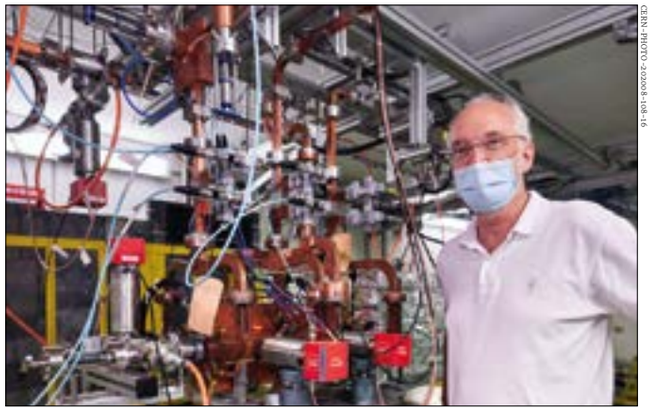
ADAPTING CLIC TECH FOR FLASH THERAPY

A collaboration between CERN and Lausanne University Hospital will see technology developed for the proposed Compact Linear Collider (CLIC) drive a novel cancer radiotherapy facility.



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Technology transfer *CERN FLASH study-leader Walter Wuensch in CERN's high-accelerating gradient test area with CLIC accelerating structures, specially adapted versions of which will drive a high-performance accelerator for a future clinical facility.*

About 30–40% of people will develop cancer during their lifetimes. Surgery, chemotherapy, immunotherapy and radiotherapy (RT) are used to cure or manage the disease. But around a third of cancers are multi-resistant to all forms of therapies, defining a need for more efficient and better tolerated treatments. Technological advances in the past decade or so have transformed RT into a precise and powerful treatment for cancer patients. Nevertheless, the treatment of radiation-resistant tumours is complicated by the need to limit doses to surrounding normal tissue.

A paradigm-shifting technique called FLASH therapy, which is able to deliver doses of radiation in milliseconds instead of minutes as for conventional RT, is opening new avenues for more effective and less toxic RT. Pre-clinical studies have shown that the extremely short exposure time of FLASH therapy spares healthy tissue from the hazardous effect of radiation without reducing its efficacy on tumours.

First studied in the 1970s, it is only during the past few years that FLASH therapy has caught the attention of oncologists. The catalyst was a 2014 study carried out by researchers from Lausanne University Hospital (CHUV), Switzerland, and from the Institute Curie in Paris, which showed an outstanding differential FLASH effect between tumours and normal tissues in mice. The results were later confirmed by several other leading institutes. Then, in 2019, CHUV used FLASH to treat a multi-resistant skin cancer in a human patient, causing the tumour to completely disappear with nearly no side effects.

The consistency of pre-clinical data showing a striking protection of normal tissues with FLASH compared to conventional RT offers a new opportunity to improve cancer treatment, especially for multi-resistant tumours. The very short "radiation beam-on-time" of FLASH therapy could also eliminate the need for motion management, which is currently necessary when irradiating tumours that move with respiration. Furthermore, since FLASH therapy operates best with high single doses, it requires only one or two RT sessions as opposed to multiple sessions over a period of several weeks in the case of conventional RT. This promises to reduce oncology workloads and patient waiting lists, while improving treatment access in low-population density environments. Altogether, these advantages could turn FLASH therapy into a powerful new tool for cancer treatment, providing a better quality of life for patients.

CERN and CHUV join forces

CHUV is undertaking a comprehensive research program to translate FLASH therapy to a clinical environment. No clinical prototype is currently available for treating patients with FLASH therapy, especially for deep-seated tumours. Such treatments require very high-energy beams (see p12) and face technological challenges that can currently be solved only by a very limited number of institutions worldwide. As the world's largest particle-physics laboratory, CERN is one of them. In 2019, CHUV and CERN joined forces with the aim of building a high-energy, clinical FLASH facility.

The need to deliver a full treatment dose over a large area in a short period of time demands an accelerator that can produce a high-intensity beam. Amongst the current radiation tools available for RT – X-rays, electrons, protons and ions – electrons stand out for their unique combination of attributes. Electrons with an energy of around 100 MeV penetrate many tens of centimetres in tissue so have the potential to reach tumours deep inside the body. This is also

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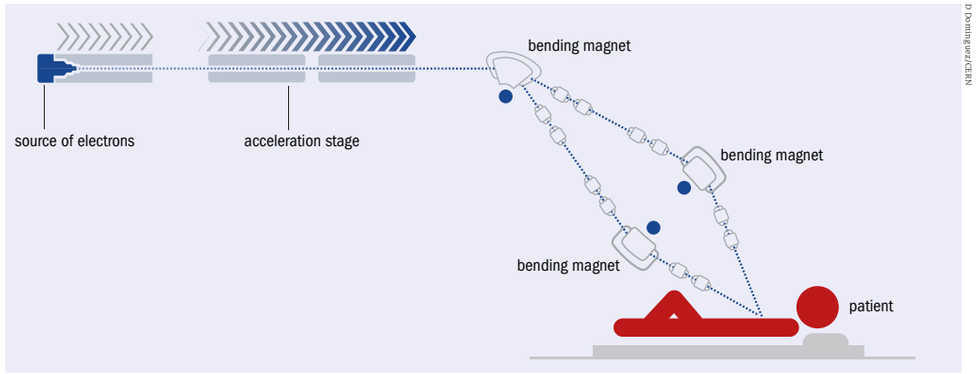


D Dominguez/CERN

FLASH therapy
Schematic layout of a FLASH radiotherapy facility.

true for the other radiation modalities but it is technically simpler to produce intense beams of electrons. For example, electron beams are routinely used to produce X-rays in imaging systems such as CT scanners and in industrial applications such as electron beam-welding machines. In addition, it is comparatively simple to accelerate electrons in linear accelerators and guide them using modest magnets. A FLASH-therapy facility based on 100 MeV-range electrons is therefore a highly compelling option.

Demonstrating the unexpected practical benefits of fundamental research, the emergence of FLASH therapy as a potentially major clinical advance coincides with the maturing of accelerator technology developed for the CLIC electron–positron collider. In a further coincidence, the focus of FLASH development has been at CHUV, in Lausanne, and CLIC development at CERN, in Geneva, just 60 km away. CLIC is one of the potential options for a post-LHC collider and the design of the facility, as well as the development of key technologies, has been underway for more than 20 years. A recent update of the design, now optimized for a 380 GeV initial-energy stage, and updated prototype testing were completed in 2018.

Despite the differences in scale and application, the key requirements for CLIC correspond astonishingly well with the requirements for a FLASH facility. First, CLIC requires high-luminosity collisions, for example to allow the study of rare interaction processes. This is achieved by colliding very high-intensity and precisely controlled beams: the average current during a pulse of CLIC is 1 A and the linac hardware is designed to allow two beams less than 1 nm in diameter to collide at the interaction point. High levels of current that are superbly controlled are also needed for FLASH to cover large tumours in short times. Second, CLIC requires a high accelerating gradient (72 MV/m in the initial stage) to achieve its required collision energy in a reasonably sized facility (11 km for a 380 GeV first stage). A FLASH facility using 100 MeV electrons based on an optimised implementation of the same technology requires an accelerator of just a couple of metres long. Other system elements such as diagnostics, beam shaping and delivery as well as radiation shielding make the footprint of the full facility somewhat larger. Overall, however, the compact accelerator technology developed for CLIC gives the possibility of clinical facilities built within the confines of typical hospital campus and integrated with existing oncology departments.

The key requirements for CLIC correspond astonishingly well with the requirements for a FLASH facility

Over the decades, CLIC has invested significant resources into developing its high-current and high-gradient technology. Numerous high-power radio-frequency test stands have been built and operated, serving as prototypes for the radio-frequency system units that make up a linear accelerator. The high-current-beam test accelerator "CTF3" enabled beam dynamic simulation codes to be benchmarked and the formation, manipulation and control of very intense electron beams to be demonstrated. Further beam-dynamics validations and relevant experiments have been carried out at different laboratories including ATF2 at KEK, FACET at SLAC and ATF at Argonne. CERN also operates the Linear Electron Accelerator for Research (CLEAR) facility, where it can accelerate electrons up to 250 MeV, thus matching the energy requirements of FLASH radiotherapy. For the past several years, and beyond the collaboration between CERN and CHUV, the CLEAR facility has been involved in dosimetry studies for FLASH radiotherapy.

Towards a clinical facility

All of this accumulated experience and expertise is now being used to design and construct a FLASH facility. The collaboration between CERN and CHUV is a shining example of knowledge transfer, where technology developed for fundamental research is used to develop a therapeutic facility. While the technical aspects of the project have been defined via exchanges between medical researchers and accelerator experts, the CERN knowledge-transfer group and CHUV's management have addressed contractual aspects and identified a strategy for intellectual property ownership. This global approach provides a clear roadmap for transforming the conceptual facility into a clinical reality. From the perspective of high-energy physics, the adoption of CLIC technology in commercially supplied medical facilities would significantly reduce technological risk and increase the industrial supplier base.

The collaboration between CHUV and CERN was catalysed by a workshop on FLASH therapy hosted by CHUV in September 2018, when it was realised that an electron-beam facility based on CLIC technology offers the possibility for a high-performance clinical FLASH facility. An interdisciplinary team comprising medical doctors, medical physicists, radiation biologists and accelerator physicists and engineers was formed to study the possibilities in greater depth. In an intense exchange during the months following the workshop, where requirements and capabilities were brought together and balanced, a clear picture of the parameters of a clinical FLASH facility emerged. Subsequently, the team studied critical issues in detail, validating that such a facility is in fact feasible. It is now working towards the details of a baseline design, with parameters specified at the system level, and the implementation of entirely new perspectives that were triggered by the study. A conceptual design report for the facility will be finished by the end of 2020. CHUV is actively seeking funding for the facility, which would require approximately three years for construction through beam commissioning.

Basic elements

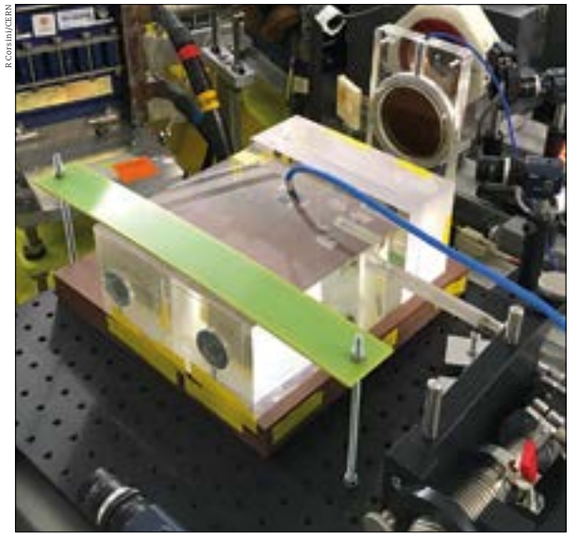
The basic accelerator elements of the 100 MeV-range FLASH facility that emerged from this design process consist of: a photo-injector electron source; a linac optimised for high-current transport and maximum radio-frequency-power to beam-energy-transfer efficiency; and a beam-delivery system which forms the beam shape for individual treatment and directs it towards the patient. In addition, accelerator and clinical instrumentation are being designed which must work together to provide the necessary level of precision and repeatability required for patient treatment. This latter issue is of particular criticality in FLASH treatment, which must be administered with all feedback and correction of delivered dose to clinical levels completed in substantially less than a second. The radiation field is one area where the requirements of CLIC and FLASH are quite different. In CLIC the beam is focused to a very small spot (roughly 150 nm wide and 3 nm high) for maximum luminosity, whereas in FLASH the beam must be expanded to cover a large area (up to 10 cm) of irregular cross section and with high levels of dose uniformity. Although this requires a very different implementation of the beam-delivery systems, both CLIC and FLASH are designed using the same beam-dynamics tools and design methodologies.

An interdisciplinary team comprising medical doctors, medical physicists, radiation biologists and accelerator physicists and engineers was formed

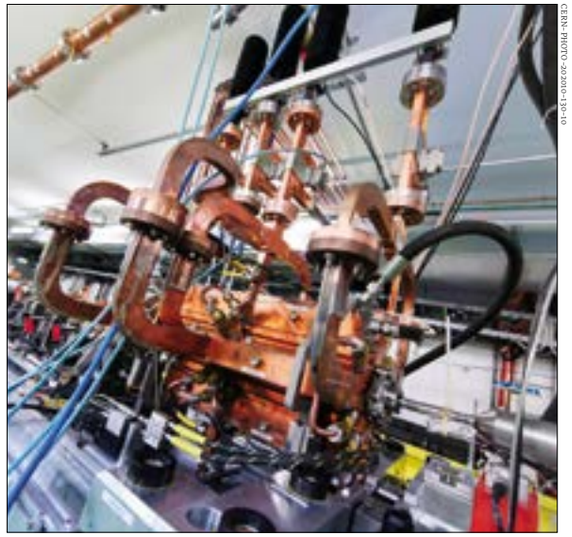
Many challenges will have to be overcome, not least obtaining regulatory approval for such a novel system, but we are convinced that the fundamental ideas are sound and that the goal is within reach. A clinical FLASH facility based on CLIC technology is set to be an excellent example of the impact of developments made in the pursuit of fundamental science can have in society. ●

VERY HIGH-ENERGY ELECTRONS FOR CANCER THERAPY

The VHEE 2020 International Workshop saw more than 400 scientists gather virtually to evaluate the production of very high-energy electrons for radiotherapy.



R Corsini/CERN



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High-tech *A dosimetry experiment for VHEE studies in collaboration with NPL (left) and a CLIC RF X-band cavity prototype (right) in CERN's CLEAR user facility.*

Radiotherapy (RT) is a fundamental component of effective cancer treatment and control. More than 10,000 electron linear accelerators are currently used worldwide to treat patients with RT, most operating in the low beam-energy range of 5–15 MeV. Usually the electrons are directed at high-density targets to generate bremsstrahlung, and it is the resulting photon beams that are used for therapy. While low-energy electrons have been used to treat cancer for more than five decades, their very low penetration depth tends to limit their application to superficial tumours. The use of high-energy electrons (up to 50 MeV) was studied in the 1980s, but not clinically implemented.

More recently, the idea of using very high-energy (50–250 MeV) electron beams for RT has gained interest. For higher energy electrons, the penetration becomes deeper and the transverse penumbra sharper, potentially enabling the treatment of deep-seated tumours. While the longitudinal dose deposition is also distributed over a larger area, this can be controlled by focusing the electron beam.

The production of very high-energy electrons (VHEE) for RT was the subject of the VHEE 2020 International Workshop, organised by CERN and held remotely from 5–7 October. More than 400 scientists, ranging from clinicians to biologists, and from accelerator physicists to dosimetry experts, gathered virtually to evaluate the perspectives of this novel technique.

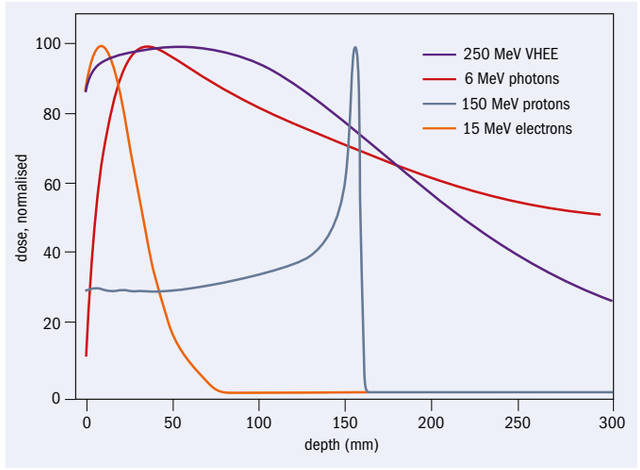
FLASH effect

VHEE beams offer several benefits. First, small-diameter high-energy beams can be scanned and focused easily, enabling finer resolution for intensity-modulated treatments than is possible for photon beams. Second, electron accelerators are more compact and significantly cheaper than current installations required for proton therapy. Third, VHEE beams can operate at very high dose rates, possibly compatible with the generation of the "FLASH effect".

FLASH-RT is a paradigm-shifting method for delivering ultra-high doses within an extremely short irradiation time (tenths of a second). The technique has recently been shown to preserve normal tissue in various species and organs while still maintaining anti-tumour efficacy equivalent to conventional RT at the same dose level, in part due to decreased production of toxic reactive oxygen species.

THE AUTHORS

Manjit Dosanjh *CERN and the University of Oxford,* **Roberto Corsini** *CERN,* **Angeles Faus-Golfe** *IJClab–IN2P3 and* **Marie-Catherine Vozenin** *CHUV.*



In deep *Dose profile for various particle beams in water (for beam widths of 0.5 cm).*

The FLASH effect has been shown to take place with electron, photon and more recently proton beams. However, electron beams promise to deliver an intrinsically higher dose compared to protons and photons, especially over large areas as would be needed for large tumours. Most of the preclinical data demonstrating the increased therapeutic index of FLASH are based on a single fraction and hypofractionated regimen of RT and 4–6 MeV beams, which do not allow treatments of deep-seated tumours and trigger large lateral penumbra. This problem can be solved by increasing the electron energy to values higher than 50 MeV, where the penetration depth is larger.

Today, after three decades of research into linear colliders, it is possible to build compact high-gradient (~100 MV/m) linacs, making a compact and cost effective VHEE RT accelerator a reality. Furthermore, the use of novel accelerator techniques such as laser-plasma acceleration is also starting to be applied in the VHEE field. These are currently the subject of a wide international study, as was presented at the VHEE workshop.

At the same time pioneering preliminary work on FLASH was being carried out by researchers at Lausanne University Hospital (CHUV) in Switzerland and the Curie Institute in France, high-gradient linac technology advances for VHEE were being made at CERN for the proposed Compact Linear Collider (CLIC). An extensive R&D program on normal-conducting radio-frequency accelerating structures has been carried out to obtain the demanding performances of the CLIC linac: an accelerating gradient of 100 MV/m, low breakdown rate, micron-tolerance alignment and a high RF-to-beam efficiency (around 30%). All this is now being applied in the conceptual designs of new RT facilities, such as one jointly being developed by CHUV and CERN (see p9).

High-energy challenges

Many challenges, both technological and biological, have to be addressed and overcome for the ultimate goal of using VHEE and VHEE-FLASH as an innovative modality for effective cancer treatment with minimal damage to healthy tissues. All of these were extensively covered and discussed in the different sessions of VHEE 2020.

From the accelerator-technology point of view an important point is to assess the possibility of focusing and transversely scanning the beam, thereby overcoming the disadvantages associated in the past with low-energy-electron- and photon-beam irradiation. In particular, in the case of VHEE–FLASH it has to be ensured that the biological effect is maintained. Stability, reliability and repeatability are other mandatory ingredients for accelerators to be operated in a medical environment.

The major challenge for VHEE–FLASH is the delivery of a very high dose-rate, possibly over a large area, providing a uniform dose distribution throughout the target. Also the parameter window in which the FLASH effect takes place has still to be thoroughly defined, as does its effectiveness as a function of the physical parameters of the electron beam. This, together with a clear understanding of the underlying biological processes, will likely prove essential in order to fully optimise the FLASH RT technique. Of particular importance, as was repeatedly pointed out during the workshop, is the development of reliable online dosimetry for very high dose rates, a regime not adapted to the current standard dosimetry techniques for RT. Ionisation chambers, routinely used in medical linacs, suffer from nonlinear effects at very high dose rates. To obtain reliable measurements, R&D is needed to develop novel ion chambers or explore alternative possibilities such as solid-state detectors or the use of calibrated beam diagnostics.

All this demands a large test activity across different laboratories to experimentally characterise VHEE beams and their ability to produce the FLASH effect, and to provide a testbed for the associated technologies. It is also important to compare the properties of the electron beams depending on the way they are produced (radio-frequency or laser-plasma accelerator technologies).

A number of experimental test facilities are already available to perform these ambitious objectives: the CERN Linear Electron Accelerator for Research (CLEAR), so far rather unique in being able to provide both high-energy (50–250 MeV) and high-charge beams; VELA–CLARA at Daresbury Laboratory; PITZ at DESY and finally ELBE–HZDR using the superconducting radio-frequency technology at Dresden. Further radiobiology studies with laser-plasma accelerated electron beams are currently being performed at the DRACO PetaWatt laser facility at the ELBE Center at HZDR-Dresden and at the Laboratoire d'Optique Appliqué in the Institute Polytechnique de Paris. Future facilities, as exemplified by the previously mentioned CERN–CHUV facility or the PHASER proposal at SLAC, are also on the horizon.

Establishing innovative treatment modalities for cancer is a major 21st century health challenge. By 2040, cancer is predicted to be the leading cause of death, with approximatively 27.5 million newly diagnosed patients and 16.3 million related deaths per year. The October VHEE workshop demonstrated the continuing potential of accelerator physics to drive new RT treatments, and also included a lively session dedicated to industrial partners. The large increase in attendance since the first workshop in 2017 in Daresbury, UK, shows the vitality and increasing interest in this field. ●

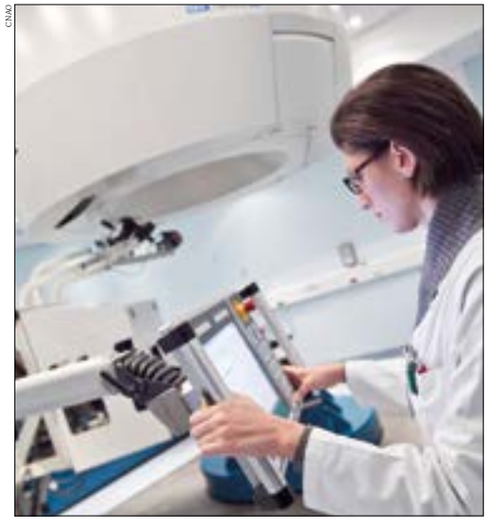
NEWS HIGHLIGHTS

Cardiac arrhythmia

Protons herald new cardiac treatment

On 13 December 2019, in a clinical world-first, a proton beam was used to treat a patient with a ventricular tachycardia, which causes unsynchronised electrical impulses that prevent the heart from pumping blood. The feat saw a 150 MeV beam of protons be directed at a portion of tissue in the heart of a 73 year-old male patient at the National Center of Oncological Hadrontherapy (CNAO) in Italy – a facility set out 25 years ago by the TERA Foundation and rooted in accelerator technologies developed in conjunction with CERN via the Proton Ion Medical Machine Study (PIMMS). The successful procedure had a minimal impact on the delicate surrounding tissues, and marks a new path in the rapidly evolving field of hadron therapy.

The choice by clinicians in Italy to use protons to treat a cardiac pathology was born out of necessity to fight an aggressive form of ventricular tachycardia that had not responded effectively to traditional treatments. The idea is that the Bragg peak typical of light charged ions (by which a beam can deposit a large amount of energy in a small region) can produce small scars in the heart tissues similar to the ones caused by the standard invasive technique of RF cardiac ablation. "To date, the use of heavy particles (protons, carbon ions) in this area has been documented in the international scientific literature only on animal models," said Roberto Rordorf, head of arrhythmology at San Matteo Hospital, in a press release on 22 January. "The Pavia procedure appears to be the first in the world to be performed on humans and the first results are truly encouraging. For this reason, together with CNAO we are evaluating the feasibility of an experimental clinical study."


CNAO

Heart of the matter
Treatment room of the CNAO hadron therapy centre in Italy.

CNAO is one of just six next-generation particle-therapy centres in the world capable of generating beams of protons and carbon ions, which are biologically more effective than protons in the treatment of radioresistant tumours. The PIMMS programme from which the accelerator design emerged, carried out at CERN from 1996 to 2000, aimed to design a synchrotron optimised for ion therapy.

"The proton treatment recently announced, proposed to CNAO by cardiologists of the close-by San Matteo Hospital to save the life of a seriously ill patient, is a turning point," says TERA founder Ugo Amaldi. "Since light-ion ablation is non-invasive and less expensive than the standard catheter ablation, I think that in 20 years' time cardiac arrhythmias will be mostly treated with light-ion accelerators. For this reason, TERA has secured a patent on the use of ion linacs for heart treatments."

- *This article was adapted from* CERN Courier *March/April 2020 p11: cerncourier.com/a/protons-herald-new-cardiac-treatment.*

Imaging

First human 3D X-ray in colour

In July 2018, New-Zealand company MARS Bioimaging Ltd used technology developed at CERN to perform the first colour 3D X-ray of a human body, offering more accurate medical diagnoses. Father and son researchers Phil and Anthony Butler from Canterbury and Otago universities in New Zealand spent a decade building their product using Medipix read-out chips, which were initially developed to address the needs of particle tracking in experiments at the Large Hadron Collider.

The CMOS-based Medipix read-out chip works like a camera, detecting and counting each individual particle hitting the pixels when its shutter is open. The resulting high-resolution, high-contrast images make it unique for medical-imaging applications. Successive generations of chips have been developed during the past 20 years with many applications outside high-energy physics. The latest, Medipix3, is the third generation of the technology, developed by a collaboration of more than 20 research institutes – including the University of Canterbury.

MARS Bioimaging Ltd was established in 2007 to commercialise Medipix3 technology. The firm's product combines spectroscopic information generated by a Medipix3-enabled X-ray detector with powerful algorithms to generate 3D images. The colours represent different energy levels of the X-ray photons as recorded by the detector, hence identifying different components of body parts such as fat, water, calcium and disease markers.


MARS Bioimaging Ltd

New view
A 3D colour image of a wrist with a watch on, showing part of the finger bones in white and soft tissue in red.

"In all of these studies, promising early results suggest that when spectral imaging is routinely used in clinics it will enable more accurate diagnosis and personalisation of treatment," said Butler.

- *This article was adapted from* CERN Courier *September 2018 p11: cerncourier.com/a/first-human-3d-x-ray-in-colour.*

Covid-19

Physicists develop stripped-down ventilator

As part of the global response to the COVID-19 pandemic, a team led by physicists and engineers from the LHCb collaboration proposed a design for a novel ventilator in March 2020. The High Energy Ventilator (HEV) is based on components that are simple and cheap to source and, although the system needs to be verified by medical experts before it can enter use, in the interests of rapid development the HEV team presented the design in March to generate feedback. The proposal is one of several recent and rapidly developing efforts launched by high-energy physicists to help combat COVID-19.

Most people infected with COVID-19 recover without requiring special treatment, but in some cases the disease can cause severe breathing difficulties and pneumonia. For such patients, the availability of ventilators that deliver oxygen to the lungs while removing carbon dioxide could be the difference between life and death. Even with existing suppliers ramping up production, the rapid rise in COVID-19 infections is causing a global shortage of ventilators.

HEV was born out of discussions in the LHCb VELO group when lead designer Jan Buytaert of CERN realised that the systems which are routinely used to supply and control gas at desired temperatures and pressures in particle-physics detectors are well matched to the techniques required to build and operate a ventilator.

As the HEV team comprises physicists, rather than medics, it was vital to get the relevant input from the very start, explains HEV collaborator Paula Collins of CERN. "Here we have benefited enormously from the experience and knowledge of CERN's HSE [Occupational Health & Safety and Environmental Protection] group for medical advice, conformity with applicable legislation and health-and-safety requirements, and the working relationship with local hospitals. The team is also greatly supported from other CERN departments, in particular for electronic design and the selection of the best components for gas manipulation. We were also very encouraged to find that it was possible in a short space of time to set up an online chat group of experienced anaesthesiologists and respiratory experts from Australia, Belgium, Switzerland and Germany, which sped up the design considerably."


J Fischer/CERN

Rapid development
Jan Buytaert and Paula Collins with the HEV prototype in the LHCb VELO lab at CERN on 6 April 2020.

The HEV concept comprises electro-valves, a 10 litre buffer container, a pressure regulator and several pressure and flow sensors. Embedded components – currently Arduino and Rasbperry Pi – are being used to meet portability requirements. The first stage of prototyping, which was achieved at CERN on 27 March, demonstrated that the HEV principle is sound and allows the ventilator to operate within the required ranges of pressure and time. The support of clinicians and international organisations is now being harnessed for further prototyping and deployment stages.

The HEV ventilator complements another recent proposal initiated by physicists in the Global Argon Dark Matter Collaboration: the Mechanical Ventilator Milano (MVM), which regulates the flow of the incoming mixture of oxygen and air via electrically controlled valves.

Sharing several common ideas with the MVM principle, another ventilator design called Project Open Air has been proposed by particle physicists at the Laboratory of Instrumentation and Experimental Particles Physics in Portugal. All designs are evolving quickly and require further development before they can be deployed in hospitals.

"It is difficult to conceive a project that goes all the way and includes all the bells and whistles needed to get it into the hospital, but this is our firm goal," says Collins. "After one week we had a functioning demonstrator, after two weeks we tested on a medical mechanical lung, and we are now prototyping under clinical supervision. We find ourselves in a unique and urgent situation where there are many proposals on the market, but we don't know now which ones will in the end make a difference, so everything that could be viable should be pursued."

- *This article was adapted from* CERN Courier *May/June 2020 p8: cerncourier.com/a/particle-physicists-propose-stripped-down-ventilator-to-help-combat-covid-19.*

Nuclear medicine

Novartis acquires CERN spin-off

In January 2018, global Global healthcare company Novartis announced plans to acquire Advanced Accelerator Applications (AAA), a spin-off radiopharmaceutical firm established by former CERN physicist Stefano Buono in 2002. With an expected price of $3.9B, said the firm in a statement, the acquisition will strengthen Novartis' oncology portfolio by introducing a new therapy platform for tackling neuroendocrine tumours. Trademarked Lutathera, and based on the isotope lutetium-177, the technology was approved in Europe in September 2017 for the treatment of certain neuroendocrine tumours and is under review in the US.

With its roots in nuclear-physics expertise acquired at CERN, AAA started its commercial activity with the production of radiotracers for medical imaging. The successful model made it possible for AAA to invest in nuclear research to produce innovative radiopharmaceuticals. "We believe that the combination of our expertise in radiopharmaceuticals and theragnostic strategy together with the global oncology experience and infrastructure of Novartis, provide the best prospects for our patients, physicians and employees, as well as the broader nuclear medicine community," said Buono, who is CEO of AAA.


AAA

Spin-off
AAA's headquarters in Saint-Genis-Pouilly, France, just across the border from CERN.

- *This article was adapted from* CERN Courier *January/February 2018 p9: cerncourier.com/a/novartis-acquires-cern-spin-off.*

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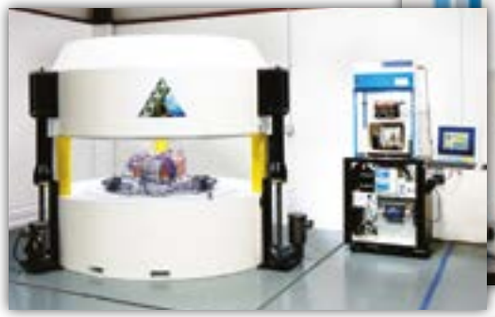

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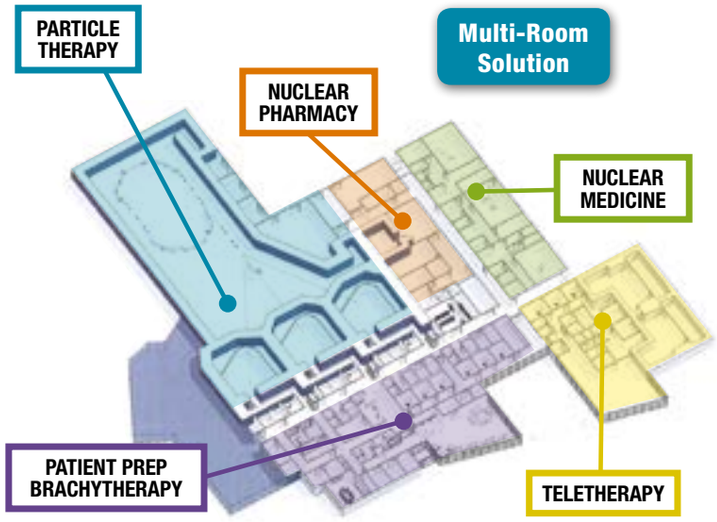

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THERAPEUTIC PARTICLES

The accelerator technology underpinning Europe's first particle-therapy facilities was driven by the TERA Foundation during the past 25 years.

Last September the TERA Foundation – dedicated to the study and development of accelerators for particle therapy – celebrated its 25th anniversary. Led by visionary Italian physicist Ugo Amaldi, TERA gathered and trained hundreds of brilliant scientists who carried out research on accelerator physics. This culminated in the first carbon-ion facility for hadron therapy in Italy, and the second in Europe: the National Centre for Cancer Hadron Therapy (CNAO), located in Pavia, which treated its first patient in 2011.

The forerunner to CNAO was the Heidelberg Ion-Beam Therapy Centre (HIT) in Germany, which treated its first patient in 2009 following experience accumulated over 12 years in a pilot project at GSI near Darmstadt. After CNAO came the Marburg Ion-Beam Therapy Centre (MIT) in Germany, which has been operational since 2015, and MedAustron in Wiener Neustadt, Austria, which delivered its first treatment in December 2016.

While conventional radiotherapy based on beams of X-rays or electrons is already widespread worldwide, the treatment of cancer with charged particles has seen significant growth in recent years. The use of proton beams in radiation oncology was first proposed in 1946 by Robert Wilson, a student of Ernest Lawrence and founding director of Fermilab. The key advantage of proton beams over X-rays is that the absorption profile of protons in matter exhibits a sharp peak towards the end of their path, concentrating the dose on the tumour target while sparing healthy tissues. Following the first treatment of patients with protons at Lawrence Berkeley Laboratory in the US in 1954, treatment centres in the US, the former USSR and Japan gradually appeared. At the same time, interest arose around the idea of using heavier ions, which offer a higher radio-biological effectiveness and, causing more severe damage to DNA, can control the 3% of all tumours that are radioresistant both to X-rays and protons. It is expected that by 2020 there will be almost 100 centres delivering particle therapy around the world, with more than 30 of them in Europe.

Europe entered the hadron-therapy field in 1987, when the European Commission launched the European Light Ion Medical Accelerator (EULIMA) project to realise a particle-therapy centre. The facility was not built in the end, but interest in the topic continued to grow. In 1991, together with Italian medical physicist Giampiero Tosi, Amaldi wrote a report outlining the design of a hospital facility for therapy with light ions and protons to be built in Italy. One year later, the pair established the TERA Foundation to raise the necessary funding to employ students and researchers to work on the project. Within months, TERA could count on the work of about 100 physicists, engineers, medical doctors and radiobiologists, who joined forces to design a synchrotron for particle therapy and the beamlines and monitoring systems necessary for its operation.


MedAustron

Patient care
A treatment room at the MedAustron centre in Austria, behind which lies a 25 m diameter synchrotron that precisely directs high-energy protons and light ions at tumours.

Ten years of ups and downs followed, during which TERA scientists developed three designs for a proton-therapy facility initially to be built in Novara, then in the outskirts of Milan and finally in Pavia. Political, legislative and economic issues delayed the project until 2001 when, thanks to the support of Italian health minister and oncologist Umberto Veronesi, the CNAO Foundation was created. The construction of the actual facility began four years later.

"We passed through hard times and we had to struggle, but we never gave up," says Amaldi. "Besides, we kept ourselves busy with improving the design of our accelerator."

Introducing PIMMS

Meanwhile, in Austria, experimental physicist Meinhard Regler had launched a project called Austron – a sort of precursor to the European Spallation Source. In 1995, together with the head designer – accelerator physicist Phil Bryant – he proposed the addition of a ring to the facility that would be used for particle therapy (and led to the name of the project being changed to MedAustron). Amaldi, Regler and Bryant then decided to work on a common project, and the "Proton-Ion Medical Machine Study" (PIMMS) was created. Developed at CERN between 1996 and 2000 under the leadership of Bryant and with the collaboration of several CERN physicists and engineers, PIMMS aimed to be a toolkit for any European country interested in building a proton–ion facility for hadron therapy. Rather than being a blueprint for a final facility on a specific site, it was an open study from which different parts could be included in any hadron-therapy centre according to its specific needs.

THE AUTHOR
Virginia Greco
CERN.

Heavy machinery
The 25 m diameter synchrotron of CNAO in Italy.


CNAO

The design of CNAO itself is based on the PIMMS project, with some modifications introduced by TERA to reduce the footprint of the structure. The MedAustron centre, designed in the early 2000s, also drew upon the PIMMS report. Built between 2011 and 2013, with the first beam extracted by the synchrotron in autumn 2014, MedAustron received official certification as a centre for cancer therapy in December 2016 and, a few days after, treated its first patient. "In the past few years we have worked hard to provide the MedAustron trainees with a unique opportunity to acquire CERN's know-how in the diverse fields of accelerator design, construction and operation," says Michael Benedikt of CERN, who led the MedAustron accelerator project. Synergies with other CERN projects were also created, he explains. "The vacuum control system built for MedAustron was successfully used in the Linac4 test set-up, while in the synchrotron a novel radiofrequency system that was jointly developed for the CERN PS Booster and MedAustron is used. The synchrotron's power converter control uses the same top-notch technology as CERN's accelerators, while its control system and several of its core components are derived from technologies developed for the CMS experiment."

All the existing facilities using hadrons for cancer therapy are based on circular cyclotrons and synchrotrons. For some years, however, the TERA Foundation has been working on the design of a linear accelerator for hadron therapy. As early as 1993, Amaldi set up a study group, in collaboration with the Italian institutions ENEA and INFN, dedicated to the design of a linac for protons that would run at the same frequency (3 GHz) as the electron linacs used for conventional radiotherapy. The linac could use a cyclotron as an injector, making it a hybrid solution called a cyclinac, which reduces the sizes of both accelerators while allowing the beam energy to be rapidly changed from pulse to pulse by acting on the radiofrequency system of the linac. In 1998 a 3 GHz 1.2 metre-long linac booster (LIBO) was built by a TERA–CERN–INFN collaboration led by retired CERN engineer Mario Weiss, and in 2001 it was connected to the cyclotron of the INFN South Laboratories in Catania where it accelerated protons from 62 MeV to 74 MeV. This was meant to be the first of 10 modules that would kick protons to 230 MeV.

We passed through hard times and we had to struggle, but we never gave up

Linear ambition

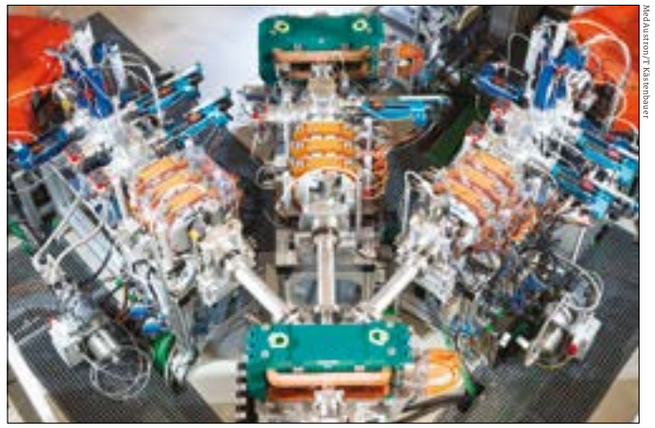
In 2007 a CERN spin-off company called ADAM (Applications of Detectors and Accelerators to Medicine) was founded by businessman Alberto Colussi to build a commercial high-frequency linac based on the TERA design. Under the leadership of Stephen Myers, a former CERN director for accelerators and technology and initiator of the CERN medical applications office, ADAM is now completing the first prototype. It is called Linac for Image Guided Hadron Therapy (LIGHT), and the full accelerator comprises: a proton source; a novel 750 MHz RF quadrupole (RFQ) – designed by CERN – which takes the particles up to 5 MeV; four side-coupled drift-tube linacs (SCDTL) – designed by ENEA – to accelerate the beam from 5–37.5 MeV; and a different type of accelerating module, called coupled-cavity linac (CCL) – the LIBO designed by TERA – which gives the final kick to the beam from 37.5 to 230 MeV. The complex will be 24 m long, similar to the circumference of a proton synchrotron.

Compared to cyclotrons and synchrotrons, linear accelerators are lighter and potentially less costly because they are modular. Most importantly, they produce a beam much more suited to treat patients, in particular when the tumour is moving, as in the lungs. The machine developed by ADAM is modular in structure to make it easier to maintain and more flexible when it comes to upgrading or customising the system. In addition, thanks to an active longitudinal modulation system, the beam energy can be varied during therapy and thus the treatment depth changed. LIGHT also has a dynamic transversal modulation system, allowing the beam to be rapidly and precisely modulated to "paint the tumour" many times in a short time – in other words, delivering a homogeneous dose to the whole cancerous tissue while minimising the irradiation of healthy organs. The energy variation of cyclotrons and synchrotrons is 20–100 times slower.

"The beauty of the linac is that you can electronically modulate its output energy," Myers explains. "Since our accelerator is modular, the energy can be changed either by

switching off some of the units or by reducing the power in all of them, or by re-phasing the units. Another big advantage of the linac is that it has a small emittance, i.e. beam size, which translates into smaller, lighter and cheaper magnets and allows to have a simpler and lighter gantry as well." In the last decade, LIBO has inspired other TERA projects. Its scientists have designed a linac booster for carbon ions (while LIBO was only for protons) and a compact single-room facility called TULIP, in which a 7 m-long proton linac is mounted on a rotating gantry.

The new frontier of hadron therapy, however, could be helium ion treatment. Some tests with these ions were done in the past, but the technique still has to be proven. TERA scientists are currently working on a new accelerator for helium ions, says Amaldi. "Helium can bring great benefit to medical treatments: it is lighter than carbon, thus requiring a smaller accelerator, and it has much less lateral scattering than protons, resulting in sharper lateral fall-offs next to organs at risk." In order to accelerate helium ions with a linac, we need either a longer linac compared to the one used for protons or higher gradients, as demonstrated by high-energy physics research at CERN and elsewhere in Europe. The need for future, compact and cost-effective ion-therapy accelerators is being addressed by a new collaborative design study coordinated by Maurizio Vretenar and Alessandra Lombardi of CERN, dubbed "PIMMS2".



MedAustron/T Kästenbauer

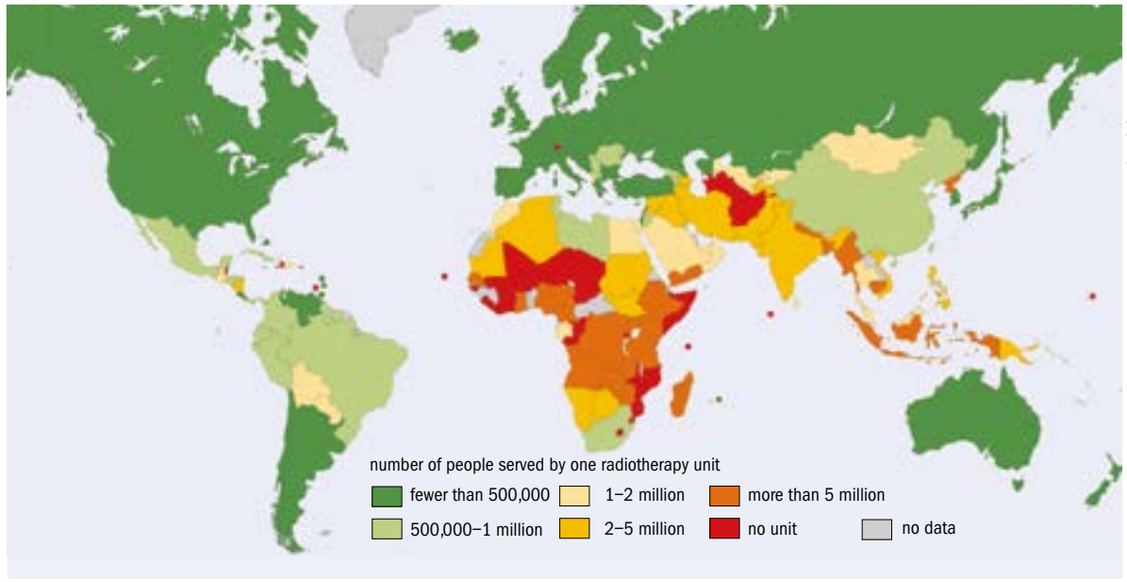
Particle injection *The ion-beam injectors of the MedAustron facility in Austria.*

A proposal, which includes a carbon linac, is being prepared for submission to the CERN Medical Application group, potentially opening the next phase of TERA's impressive journey (see p5). ●

● *This article was adapted from* CERN Courier *January/February 2018 p25: cerncourier.com/a/therapeutic-particles/.*

DEVELOPING MEDICAL LINACS FOR CHALLENGING REGIONS

Physicists, oncologists and industry experts are defining the design characteristics of a novel linear accelerator that will make radiotherapy more readily available in lower-resourced countries.



IAEA, AGaRT: caterct.iaea.org/agart.asp

Shortfall *There is a shortfall of more than 5000 radiotherapy machines in low-to-middle income countries, with patients in some countries in Africa and Asia having almost no access to radiation therapy.*

The annual global incidence of cancer is expected to rise from 15 million cases in 2015 to as many as 25 million cases in 2035. Of these, it is estimated that 65–70% will occur in low-and middle-income countries (LMICs) where there is a severe shortfall in radiation-treatment capacity. The growing burden of cancer and other non-communicable diseases in these countries has been recognised by the United Nations General Assembly and the World Health Organization.

Radiation therapy is an essential component of effective cancer control, and approximately half of all cancer patients – regardless of geographic location – would benefit from such treatment. The vast majority of modern radiotherapy facilities rely on linear accelerators (linacs) to accelerate electrons, which are either used directly to treat superficial tumours or are directed at targets such as tungsten to produce X-rays for treating deep-seated tumours.

Electron linacs were first used clinically in the 1950s, in the UK and the US. Since then, great advances in photon treatment have been made. These are due to improved imaging, real-time beam shaping and intensity modulation of the beam with multileaf collimators, and knowledge of the radiation doses to kill tumours alone and in combination with drugs. In addition, the use of particle beams means that radiotherapy directly benefits from knowledge and technology gained in high-energy-physics research.

In September 2015, the Global Task Force on Radiotherapy for Cancer Control (GTFRCC) released a comprehensive study of the global demand for radiation therapy. It highlighted the inadequacy of current equipment coverage (image above) and the resources required, as well as the costs and economic and societal benefits of improving coverage.

Limiting factors to the development and implementation of radiotherapy in lower-resourced nations include the cost of equipment and infrastructure, and the shortage of trained personnel to properly calibrate and maintain the equipment and to deliver high-quality treatment. The GTFRCC report estimated that as many as 12,600 megavolt-class treatment

THE AUTHORS

David Pistenmaa *and* **Norman Coleman** *International Cancer Expert Corps, Inc., and* **Manjit Dosanjh** *CERN.*

Major savings would also result from developing new advanced software to expand the capability of the hardware

machines will be needed to meet radiotherapy demands in LMICs by 2035. Based on current staffing models, it was estimated that an additional 30,000 radiation oncologists, more than 22,000 medical physicists and almost 80,000 radiation technologists will be required.

Approximately three years ago, with the aim of making cancer treatments accessible to underserved populations, initial discussions took place between CERN and representatives of the US National Cancer Institute and an emerging non-government organisation, the International Cancer Expert Corps (ICEC), whose aim is to help LMICs establish in-country cancer-care expertise. The focus of discussions was on an "out-of-the-box" concept for global health, specifically the design of a novel, possibly modular, linear accelerator for use in challenging environments (defined as those in which the general infrastructure is poor or lacking, where power outages and water-supply fluctuations can occur, and where climatic conditions might be harsh). Following further activities, CERN hosted a workshop in November 2016 convened by the ICEC, which brought together invited experts from many disciplines including industry.

In addition to improving the quality of care for cancer patients globally, linac-based radiotherapy systems also reduce the reliance on less expensive and simpler systems that provide treatment with photons from radionuclide sources such as ^{60}Co and ^{137}Cs. While some of the ^{60}Co units have multileaf collimators for improved beam delivery, they do not have the advanced features of modern linacs. Eliminating radionuclides also reduces the risk of malicious use of medical radioactive materials.

It is important that the newly designed linac retains the advanced capability of the machines now in use, and that through software advances, resource sharing and sustainable partnerships, the treatments in LMICs are of comparable quality to those in upper-income countries. This not only avoids substandard care but is also an incentive for experts to go to and remain in LMICs.

The ideal radiation-therapy treatment system for LMICs is thought to be as modular as possible, so that it can be easily shipped, assembled in situ, repaired and upgraded as local expertise in patient treatment develops. Another critical issue concerns the sustainability of treatment systems after installation. To minimise the need for local specialised technical staff to maintain and promptly repair facilities, procedures and economic models need to be developed to ensure regional technical expertise and also a regional supply of standard spare parts and simpler (modular) replacement procedures. Difficulties due to remoteness and poor communication also need to be considered.

There are several design considerations when developing a linear accelerator for operation in challenging environments. In addition to ease of operation, repair and upgradability, key factors include reliability, self-diagnostics, insensitivity to power interruptions, low power requirements and reduced heat production. To achieve most of these design considerations relatively quickly requires a system based on current hardware technology and software that fully exploits automation. The latter should include auto-planning and operator monitoring and training, even to the point of having a treatment system that depends on limited on-site human involvement, to allow high-quality treatment to be delivered by an on-site team with less technical expertise.

Current technology can be upgraded with software upgrades, but generally it requires the purchase of an entire new unit to substantially improve technology – often costing many millions of dollars. A modular design that allows major upgrades of components on the same base unit could be much less expensive. Major savings would also result from developing new advanced software to expand the capability of the hardware.

We need to develop a treatment machine that delivers state-of-the-art radiation therapy, rather than to develop a sub-standard linac in terms of the quality of the treatment it could deliver. The latter approach would not only provide lower-quality treatment but would be a disincentive for recruitment and retention of high-quality staff. As used in virtually all industries, the user interface should be developed through interaction with the users. Improved hardware such as a power generator in conjunction with energy management should also be provided to control electrical network fluctuations.

The task ahead

Successful radiotherapy programmes require secure local resources, adequate planning, local commitment and political stability. To make a highly functional radiotherapy treatment system available in the near-term, one could upgrade one or more existing linear accelerators with software optimisations. The design and development of a truly novel radiation treatment system, on the other hand, will require a task force to refine the design criteria and then begin development and production.

Following the November 2016 workshop, an oversight committee and three task forces have been established. A technology task force will focus on systems solutions and novel technology for a series of radiation-treatment systems that incorporate intelligent software and are modular, rugged and easily operated yet sufficiently sophisticated to also benefit therapy in high-income countries. A second task force will identify education and training requirements for the novel treatment systems, in addition to evaluating the impact of evolving treatment techniques, changes in cancer incidence and the population mix. Finally, a global connectivity and fundraising task force will develop strategies for securing financial support.

The overall aim of this ambitious project is to make excellent near-term and long-term radiation treatment systems, including staffing and physical infrastructure, available for the treatment of cancer patients in LMICs and other geographically underserved regions in the next 5–10 years. The high-energy physics community's broad expertise in global networking, technology innovation and open-source knowledge for the benefits of health are essential to the progress of this ambitious effort. It is anticipated that an update meeting will take place at the International Conference on Advances in Radiation Oncology (ICARO2) to be held in Vienna in June 2017. ●

● *This article was adapted from* CERN Courier *March 2017 p31: cerncourier.com/a/developing-medical-linacs-for-challenging-regions.*

MEDICIS SHOWS ITS STRENGTH

CERN's MEDICIS facility is producing novel radioisotopes for medical research.

The use of radioisotopes to treat cancer goes back to the late 19th century. Great strides have been made, and today radioisotopes are widely used by the medical community. Produced mostly in reactors and cyclotrons, radioisotopes are used both to diagnose cancers and other diseases, such as heart irregularities, as well as to deliver very small radiation doses exactly where they are needed to avoid destroying the surrounding healthy tissue.

However, many currently available isotopes do not combine the most appropriate physical and chemical properties and, in the case of certain tumours, a different type of radiation could be better suited. This is particularly true of the aggressive brain cancer glioblastoma multiforme and of pancreatic adenocarcinoma. Although external beam gamma radiation and chemotherapy can improve patient survival rates, there is a clear need for novel treatment modalities for these and other cancers.


M. Brice / CERN

Remote handling *The robot target handler at MEDICIS.*

On 12 December 2017, a new facility at CERN called MEDICIS produced its first radioisotopes for a batch of terbium (^{155}Tb), which is part of a quadruplet of Tb isotopes considered promising for both diagnosis and treatment. MEDICIS is designed to produce unconventional radioisotopes with the right properties to enhance the precision of patient imaging and treatment, and already it has expanded the range of radioisotopes available for research projects.

Initiated in 2010, MEDICIS is driven by CERN's Isotope Mass Separator Online (ISOLDE) facility. ISOLDE has been running for more than 50 years, producing 1300 different isotopes from 73 chemicals for research in many areas including fundamental nuclear research, astrophysics and life sciences. The year 2020 marks the 40th anniversary of the first biomedical imaging studies at ISOLDE with ^{167}Tm, and a record operation performance for MEDICIS of 50% mass purification yield – a number which is very rarely met.

Although ISOLDE already produces isotopes for medical research, MEDICIS is now able to regularly produce isotopes with specific types of emission or new purity grades, such as the pure beta-emitter ^{169}Er or ^{153}Sm produced in nuclear reactors. These were restricted to niche treatments before MEDICIS could physically purify them during its 2019 and 2020 harvesting campaigns to grades that make them suitable for a new form of personalised medicine: targeted radioimmunotherapy.

ISOLDE directs a high-intensity proton beam from the Proton Synchrotron Booster onto specially developed thick targets, yielding a large variety of atomic fragments. During proton-beam operation, MEDICIS works by placing a second target behind ISOLDE's: once the isotopes have been produced on the MEDICIS target, an automated conveyor belt carries them to a facility where the radioisotopes of interest are extracted via mass separation and implanted in a metallic foil. The final product is then delivered to local research facilities including the Paul Scherrer Institute, the University Hospital of Vaud, Geneva University Hospitals, or other laboratories such as the UK's National Physical Laboratory.

Clinical setting

Once in a medical-research environment, researchers dissolve the isotope and attach it to a molecule, such as a protein or sugar, which is chosen to target the tumour precisely. This makes the isotope injectable, and the molecule can then adhere to the tumour or organ that needs imaging or treating. The first isotopes selected by the MEDICIS collaboration board were first tested *in vitro*, and *in vivo* by using mouse models of cancer, opening new territories for researchers in radiopharmaceuticals and molecular oncology.

MEDICIS is not just a world-class facility for novel radioisotopes. It also marks the entrance of CERN into the growing field of theranostics, whereby physicians verify and quantify the presence of cellular and molecular targets in a given patient with a diagnostic radioisotope, before treating the disease with the therapeutic radioisotope. Together with local leading institutes in life and medical sciences and a large network of laboratories, MEDICIS's exciting scientific programme and technological breakthroughs have triggered a new project supported by the European Commission – PRISMAP, the European medical isotope programme – starting in 2021. Though still young, MEDICIS is a prime example of how accelerators are set to play an increasing role in the production of life-changing medical isotopes. ●

● *This article was updated from* CERN Courier *January/February 2018 p29: cerncourier.com/a/isotopes-for-precision-medicine.*

THE AUTHOR
Thierry Stora
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OPINION
VIEWPOINT

Reactors and accelerators join forces

Demand for medical isotopes requires reactor- and accelerator-based production methods.


SCK·CEN

Nuclear reactors are usually thought of in the context of electricity generation, whereby heat generated by nuclear fission produces steam to drive an alternator. A less well-known class of nuclear-fission reactors fulfils an entirely different societal goal. Known as research and test reactors, the heat they produce is a by-product, while the neutrons resulting from the fission reactions are used to irradiate materials or as probes for materials science. In some reactors, neutrons are used to transmute stable isotopes into radioactive ones for industrial or medical purposes.

Medical radioisotopes are a vital tool in the arsenal of oncologists in detecting and fighting cancer. In the case of ^{99m}Tc, which is a daughter product of ^{99}Mo, roughly 30 million patients per year are injected with this isotope. This accounts for 80% of all nuclear-medicine diagnostic procedures, and demand is only growing. Classically, ^{99}Mo is produced as a fission product in uranium targets: after irradiation lasting around one week, the targets are rushed off to the processing facility where the ^{99}Mo is extracted. Since its half-life is only around six days, there is no way to stock up on the isotope, and therefore a continuous chain of target production, irradiation, isotope extraction and purification – and finally supply to hospitals – is required.

The importance of a steady supply of medical radioisotopes such as ^{99}Mo cannot be overestimated, yet it is generally not possible to cover the cost of operating a large research reactor or other facility solely for the production of radioisotopes. Traditionally, the economics of constructing an accelerator facility for the sole purpose of generating ^{99}Mo have been challenging, especially since the fission yield of ^{99}Mo outweighs the possible yields from non-reactor methods by at least a factor of 10. Recently, however, a reduction in the construction costs of high-power accelerators and the increasing costs associated with operating reactors has generated interest in accelerator-based production of ^{99}Mo, for example via semi-commercial initiatives such as SHINE and NorthStar in the US.

One of the driving forces behind these developments is the ageing of existing research reactors. The global supply of ^{99}Mo mainly originates in a handful of reactors such as the BR2 in Belgium, the NRU in Canada or the HFR in the Netherlands, and most of them are more than 50 years old. The NRU, which alone is responsible for about a third of the global demand of ^{99}Mo, is scheduled to cease production this year. Some reactors are still planned to continue operation for multiple decades (such as OPAL in Australia, SAFARI in South Africa and BR2), while smaller research reactors such as MARIA in Poland and LVR-15 in the Czech Republic are getting increasingly involved in radioisotope production and new research reactors are being contemplated: MYRRHA in Belgium, PALLAS in the Netherlands and JHR in France (for which construction is ongoing), for instance. Despite these developments, it is uncertain if the rising demand can continue to be met without assistance from accelerator-based production.

Traditional approach

Belgian Reactor 2, which started operation in 1962, is among the most powerful research reactors in the world.

Neutrons are very suitable for isotope production because the cross-sections for neutron-induced nuclear reactions are often much larger than those for charged particles. As such, there is an advantage in using the neutrons already available at research reactors for isotope production. But it is clear that accelerators and reactors are highly complementary. Reactors generate neutron-rich isotopes through fission or activation, whereas accelerators typically allow the production of proton-rich isotopes. Alpha emitters are also becoming more popular in nuclear medicine, particularly in palliative care, and the role of accelerators will likely become more important in the future production of such isotopes. It is therefore healthy to maintain multiple production routes open for such vital and rare products, on which people's lives can depend. ●

This article was adapted from CERN Courier *October 2016 p5: cerncourier.com/a/viewpoint-reactors-and-accelerators-join-forces.*

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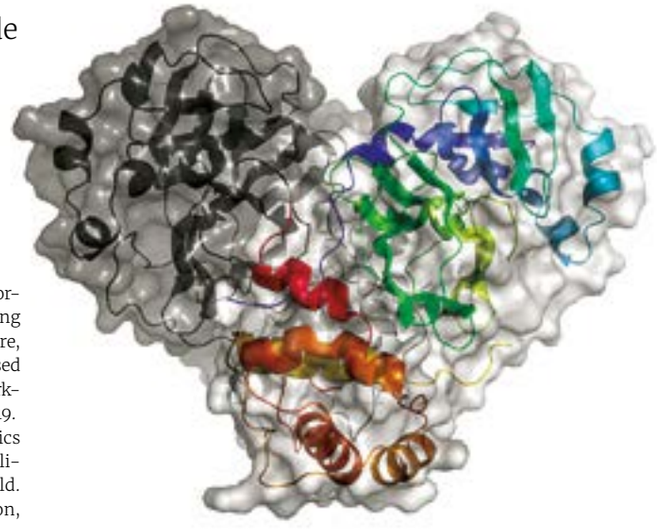
SYNCHROTRONS ON THE CORONAVIRUS FRONTLINE

Impressive progress is being made by synchrotron X-ray facilities to solve the structure of the SARS-CoV-2 virus – a first step towards the development of new drugs and vaccines.



D Owen/Diamond Light Source

Structural map *Representation of the 3D structure of the main SARS-CoV-2 protease – an enzyme much smaller than the virus, which goes on to process the viral proteins that have been made, allowing the cell's life cycle to continue.*

At a time when many countries are locking down borders, limiting public gatherings and encouraging isolation, the Diamond Light Source in Oxfordshire, UK, has been ramping up its activities, albeit in an organised and controlled manner. The reason: these scientists are working tirelessly on drug-discovery efforts to quell COVID-19.

It is a story that requires fast detectors, reliable robotics and powerful computing infrastructures, artificial intelligence, and one of the brightest X-ray sources in the world. And it is made possible by international collaboration, dedication, determination and perseverance.

Synchrotron light sources are particle accelerators capable of producing incredibly bright X-rays by forcing relativistic electrons to accelerate on curved trajectories. Around 50 facilities exist worldwide, enabling studies over a vast range of topics. Fanning out tangentially from Diamond's 562 m-circumference storage ring are more than 30 beamlines equipped with instrumentation to serve a multitude of user experiments. The intensely bright X-rays (corresponding to a flux of around 9×10^{12} photons per second) are necessary for determining the atomic structure of proteins, including the proteins that make up viruses. As such, synchrotron light sources around the world are interrupting their usual operations to work on mapping the structure of the SARS-CoV-2 virus.

Knowing the atomic structure of the virus is like knowing how the enemy thinks. A 3D visualisation of the building blocks of the structure at an atomic level would allow scientists to understand how the virus functions. Enzymes, the molecular machines that allow the virus to replicate, are key to this process. Scientists at Diamond are exploring the binding site of one enzyme, the main SARS-CoV-2 protease, which is responsible for the breakdown of proteins into smaller pieces. A drug that binds to this enzyme's active site would throw a chemical spanner in the works, blocking the virus's ability to replicate and limiting the spread of the disease. Coronavirus is the family of viruses responsible for the common cold, MERS, SARS and others. Novel coronavirus, aka SARS-CoV-2, is the newly discovered type of coronavirus and COVID-19 is the disease that it causes.

Call to arms

On 26 January 2020, Diamond's life-sciences director, Dave Stuart, received a phone call from structural biologist Zihe Rao of ShanghaiTech University in China. Rao, along with his colleague Haitao Yang, had solved the structure of the main SARS-CoV-2 protease with a covalent inhibitor using the Shanghai Synchrotron Radiation Facility (SSRF) in China. Furthermore, they had made the solution freely and publicly available on the worldwide Protein Data Bank.

During the phone call, Rao informed Stuart that their work had been halted by a scheduled shutdown of the SSRF. The Diamond team rapidly mobilised. Since shipping biological samples from Shanghai at the height of the coronavirus in China was expected to be problematic, the team at Diamond ordered the synthetic gene. A synthetic gene can be generated provided the ordering of T, A, C and G nucleotides in the DNA sequence is known. That synthetic gene can be genetically engineered into a bacterium, in this case *Escherichia coli*, which reads the sequence and generates the coronavirus protease in large enough quantities for the researchers at Diamond to determine its structure and screen for potential inhibitors.

Eleven days later on 10 February, the synthetic gene arrived. At this point, Martin Walsh, Diamond's deputy director of life sciences, and his team (consisting of Claire Strain-Damerell,

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Diamond Light Source

Intense X-rays
The transfer lines at Dimond Light Source where ultra-relativistic electrons produce intense synchrotron radiation.

Petra Lukacik and David Owen) dropped everything. With the gene in hand, the group immediately set up experimental trials to try to generate protein crystals. In order to determine the atomic structure, they needed a crystal containing millions of proteins in an ordered grid-like structure.

X-ray radiation bright enough for the rapid analysis of protein structures can only be produced by a synchrotron light source. The X-rays are directed and focused down a beamline onto a crystal and, as they pass through it, they diffract. From the diffraction pattern, researchers can work backwards to determine the 3D electron density maps and the structure of the protein. The result is a complex curled ribbon-like structure with an intricate mess of twists and turns of the protein chain.

The Diamond team set up numerous trials trying to find the optimum conditions for crystallisation of the SARS-CoV-2 protease to occur. They modified the pH, the precipitating compounds, chemical composition, protein to solution ratio… every parameter they could vary, they did. Every day they would produce a few thousand trials, of which only a few hundred would produce crystals, and even fewer would produce crystals of sufficient quality. Within a few days of receiving the gene, the first crystals were being produced. They were paltry and thin crystals but large enough to be tested on one of Diamond's macromolecular crystallography beamlines.

Watching the results come through, Diamond postdoc David Owen described it as the first moment of intense excitement. With crystals that appeared to be "flat like a car wind shield," he was dubious as to whether they would diffract at all. Nevertheless, the team placed the crystals in the beamline with a resignation that quickly turned into intense curiosity as the results started appearing before them. At that moment Owen remembers his doubts fading, as he thought, "this might just work!" And work it did. In fact, Owen recalls, "they diffracted beautifully." These first diffraction patterns of the SARS-CoV-2 virus were recorded with a resolution of 0.19 nm – high enough resolution to see the position of all of the chemical groups that allow the protease to do its work.

By 19 February, through constant adjustments and learning, the team knew they could grow good-quality crystals quickly. It was time to bring in more colleagues. The XChem team at Diamond joined the mission to set up fragment-based screening – whereby a vast library of small molecules ("fragments") are soaked into crystals of the viral protease. These fragments are significantly smaller and functionally simpler than most drug molecules and are a powerful approach to selecting candidates for early drug discovery. By 26 February, 600 crystals had been mounted and the first fragment screen launched. In parallel, the team had been making a series of samples to send to a company in Oxford called Exscientia, which has set up an AI platform designed to expedite candidates in drug discovery.

As of early March, 1500 crystals and fragments have been analysed. With huge numbers of data sets, the team could pin down the parameters of the viral protease with a high degree of confidence. The same amount of data collected with a lab-based X-ray source would have taken approximately 10 years. At Diamond, they were able to collect the data in a few days of accumulated beamtime.

Rapid access

Synchrotron light sources all over the world have been granting priority and rapid access to researchers to support their efforts in discovering more about the virus. Researchers at the Advanced Photon Source in Argonne in the US, and at Elettra Sincrotrone in Trieste, Italy, are also trying to identify molecules effective against COVID-19, in an attempt to bring us closer to an effective vaccine or treatment. Researchers at PETRA III, a synchrotron light source at DESY in Germany, are examining several thousand existing drugs to access whether they are effective against the virus. COVID-19 research is also being conducted at BESSY II at Helmholtz-Zentrum Berlin, ANSTO's Australian Synchrotron, and light sources all over the world have announced rapid-access schemes for research directly related to COVID-19. The community as a whole has a platform called www.lightsources.org where scientists can have a bird's-eye view of calls for proposals and access.

In addition to allowing the structure of tens of thousands of biological structures to be elucidated – such as that of the ribosome, which was recognised by the 2009 Nobel Prize in Chemistry – light sources have a strong pedigree in solving the structure of viruses. Development of common anti-viral medication that blocks the actions of the virus in the body, such as Tamiflu or Relenza, also relied upon synchrotrons to reveal their atomic structure.

Mapping the SARS-CoV-2 protease structures bound to small chemical fragments, the Diamond team demonstrated a crystallography- and fragmentation-screen tour de force. The resulting and ongoing work is a crucial first step in developing a drug. Forgoing the usual academic route of peer-review, the Diamond team have made all of their results openly and freely available to help inform public heath response and limit the spread of the virus, with the hope that this can fast-track effective treatment options.

This work is continuing. The researchers at Diamond are testing hundreds of compounds each week, and with each step they learn something new about the virus and how to target it. ●

● *This article was adapted from* CERN Courier *May/June 2020 p29: cerncourier.com/a/synchrotrons-on-the-coronavirus-frontline.*

The first 360° rotating carbon-ion beam-delivery system installed at HIT (Germany). Image credit: HIT

NETWORKING AGAINST CANCER WITH ENLIGHT

The European Network for Light Ion Hadron therapy (ENLIGHT) adapts to the rapidly developing hadron-therapy scene.

Since the establishment of the first hospital-based proton-treatment centres in the 1990s, hadron therapy has continued to progress in Europe and worldwide. In particular, during the last decade there has been exponential growth in the number of facilities, accompanied by a rapid increment in the number of patients treated, an expanded list of medical indications, and increasing interest in other types of ions, especially carbon. Harnessing the full potential of hadron 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. Thirteen years ago, the necessity to catalyse efforts and co-operation among these disciplines led to the establishment of the European Network for Light Ion Hadron therapy (ENLIGHT). Its annual meeting, held in Cracow in September 2015, offered an ample overview of the current status and challenges of hadron therapy, as well as stimulating discussion on the future organisation of the community.

ENLIGHT was launched in 2002 with an ambitious, visionary and multifaceted plan to steer European research efforts in using ion beams for radiation therapy. ENLIGHT was envisaged not only as a common multidisciplinary platform, where participants could share knowledge and best practice, but also as a provider of training and education, and as an instrument to lobby for funding in critical research and innovation areas. During the years, the network has evolved, adapting its structure and goals to emerging scientific needs. The annual ENLIGHT meeting has always played a defining role in this evolutionary process, and this year, new and long-time members were challenged to an open discussion on the future of the network.

Emerging topics in all forms of radiation therapy are the collection, transfer and sharing of medical data, and the implementation of big data-analytics tools to inspect them. These tools will be crucial in implementing decision support systems, allowing treatment to be tailored to each individual patient. The flow of information in healthcare, and in particular in radiation therapy, is overwhelming not only in terms of data volume but also in terms of the diversity of data types involved. Indeed, experts need to analyse patient and tumour data, as well as complex physical dose arrays, and to correlate these with clinical

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outcomes that also have genetic determinants.

Hadron therapy is facing a dilemma when it comes to designing clinical trials. In fact, from a clinical standpoint, the ever increasing number of hadron therapy patients would allow randomised trials to be performed – that is, systematic clinical studies in which patients are treated with comparative methods to determine which is the most effective curative protocol.

However, several considerations add layers of complexity to the clinical-trials landscape: the need to compare standard photon radiotherapy not only with protons but also with carbon ions; the positive results of hadron therapy treatments for main indications; and the non-negligible fact that most of the patients who contact a hadron therapy centre are well informed about the technique, and will not accept being treated with conventional radiotherapy. Nevertheless, progress on clinical trials is being made. At the ENLIGHT meeting in Cracow, the two dual-ion (proton and carbon) centres in Europe – HIT, in Heidelberg (Germany) and CNAO, in Pavia (Italy) – presented patient numbers and dose-distribution studies carried out at their facilities. The data were collected mainly in cohort studies carried out within a single institution, and the results often highlighted the need for larger statistics and a unified database. More data from patients treated with carbon ions will soon become available, with the opening in 2016 of the MedAustron hadron therapy centre in Wiener Neustadt (Austria). Clinical trials are also a major focus outside of Europe: in the US, several randomised and non-randomised trials have been set up to compare protons with photons, and to investigate either the survival improvement (for glioblastoma, non-small cell lung cancer, hepatocellular carcinoma, and oesophageal cancer) or the decrease of adverse effects (low-grade glioma, oropharyngeal cancer, nasopharyngeal cancer, prostate cancer and post-mastectomy radiotherapy in breast cancer). Recently, the National Cancer Institute in the US funded a trial comparing conventional radiation therapy and carbon ions for pancreatic cancer.

It is clear that the focus of R&D for hadron therapy has shifted since the birth of ENLIGHT

Besides clinical trials, personalised treatments are holding centre stage in the scientific debate on hadron therapy. Technology is not dormant: developments are crucial to reduce the costs, to provide treatments tailored to each specific case, and to reach the necessary level of sophistication in beam delivery to treat complex cases such as tumours inside, or close to, moving organs. In this context, imaging is key. Today, it is becoming obvious that the optimal imaging tool will necessarily have to combine different imaging modalities, for example PET and prompt photons. PET is of course a mainstay for dose imaging, but a well-known issue in its application to in-beam real-time monitoring for hadron therapy comes from having to allow room for the beam nozzle: partial-ring PET scanners cannot provide full angular sampling, therefore introducing artefacts in the reconstructed images. The time-of-flight (TOF) technique is often used to improve the image-reconstruction process. An innovative concept, called a J-PET scanner, detects back-to-back photons in plastic scintillators, and applies compressive sensing theory to obtain a better signal normalisation, and therefore improve the TOF resolution.

A subject of broad and current interest within the hadron-therapy community is radiobiology. There has been great progress in the comprehension of molecular tumour response to irradiation with both ions and photons, and of the biological consequences of the complex, less repairable DNA damage caused specifically by ions. Understanding the cell signalling mechanisms affected by hadron therapy will lead to improvements in therapeutic efficacy. A particularly thorny issue is the relative biological effectiveness (RBE) of protons and carbon with respect to photons. More extensive and systematic radiobiology studies with different ions, under standardised dosimetry and laboratory conditions, are needed to clarify this and other open issues: these could be carried out at existing and future beamlines at HIT, CNAO and MedAustron, as well as at the proposed CERN OpenMED facility.

The future of ENLIGHT

Since its annual meeting in Summer 2014, the ENLIGHT community has started to discuss the future of the network, both in terms of structure and scientific priorities. It is clear that the focus of R&D for hadron therapy has shifted since the birth of ENLIGHT, if only for the simple reason that the number of clinical centres (in particular for protons) has dramatically increased. Also, while technology developments are still needed to ensure optimal and more cost-effective treatment, proton therapy is now solidly in the hands of industry. The advent of single-room facilities will bring proton therapy, albeit with some restrictions, to smaller hospitals and clinical centres.

From a clinical standpoint, the major challenge for ENLIGHT in the coming years will be to catalyse collaborative efforts in defining a road map for randomised trials and in studying the issue of RBE in detail. Concerning technology developments, efforts will continue on quality assurance through imaging and on the design of compact accelerators and gantries for ions heavier than protons. Information technologies will take centre stage, because data sharing, data analytics, and decision support systems will be key topics.

Training will be a major focus in the coming years, as the growing number of facilities require more and more trained personnel: the aim will be to train professionals who are highly skilled in their speciality but at the same time are familiar with the multidisciplinary aspects of hadron therapy.

Over the years, the ENLIGHT community has shown a remarkable ability to reinvent itself, while maintaining its cornerstones of multidisciplinarity, integration, openness, and attention to future generations. The new list of priorities will allow the network to tackle the latest challenges of a frontier discipline such as hadron therapy in the most effective way. ●

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