ENLIGHT

HIGHLIGHTS
December 2019

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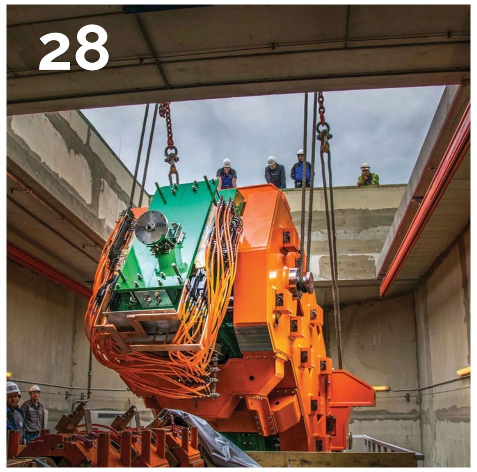

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COVER:
Organ on chip

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Farewell to 2019!

FROM THE ENLIGHT COORDINATOR

Manjit Dosanjh

Carrying on what has become a tradition for our publication, also in this issue we tackle topics that are at the forefront of research in the highly technological biomedical field. Indeed, this issue's feature article covers the highly sensitive topic of replacing animals in labs with alternative, equally or even better-performing solutions. This topic is very close to my own experience as a biologist: back in 1995, before coming to CERN, I was invited to spend two years as a visiting scientist at the JRC, Ispra (Italy) in the newly established centre called "ECVAM" - the European Centre for Validation of Alternative Methods to Replace, Reduce and Refine (the three "Rs") the use of animals in labs. So, the "Organ on the chip" feature article has come full circle for me and I am sure that it will mark a turning point on how scientific and medical tests will be conducted in the future.

This issue is printed at the end of the year, the classical moment to give in to the temptation of touching base and taking stock of what has been achieved over the past 12 months. This is, therefore, the perfect time to read **on page 20** through the lifelong recollections of Jacques Bernier, a good friend of mine and a precious collaborator in many enterprises. And if going through the past of our field undoubtedly makes us very proud of our achievements, it is absolutely inspiring to read about the present and future of the proton minibeam radiotherapy **(page 14)**, the SEEIIST project in the Balkan area and all the thinking that is going on about the radiation treatment system for challenging environments.

Since July, the MedAustron centre has joined the lucky group of 6 facilities in the world that can use also carbon ions and proton to combat cancer. This is great news for all our community and we will make sure to follow up on the new results at our future meetings. By the way, time flies and **on page 32** you will find the preliminary information about the ENLIGHT annual meeting, which, in 2020, will be held in Bergen, Norway from June 22nd to 24th.

Let me use these last lines to wish you and your loved ones all the best for a Merry Christmas and a very Happy New Year! I am sure that it will be another great year for ENLIGHT and all our community. Happy reading to all!

LEADING EXPERT gathered at the 2019 ENLIGHT MEETING

The 2019 annual meeting of the European Network for Light Ion Hadron Therapy (ENLIGHT) (cern.ch/enlight) was hosted by the University of Caen (in Normandy, France) and the centre for cancer treatment named the Centre François Baclesse of Caen, from 1-3 July 2019 (https://indico.cern.ch/event/783037/overview).

The ENLIGHT annual meetings have become a unique opportunity for experts to gather and discuss common issues. Since the meetings began 17 years ago, delegates who work on particle therapies for cancer treatment in most of the European medical and research facilities and research institutions have taken time out to attend. This year, the meeting was attended by more than 100 participants from more than 20 countries worldwide. The meeting was chaired by the ENLIGHT coordinator, Manjit Dosanjh (from the European Organisation for Nuclear Research CERN), and the local organisers, Yannick Saintigny from the French Commissariat à l'Energie Atomique (CEA, called in English the Alternative Energies and Atomic Energy Commission, a joint research unit with the Centre of Research on Ions, Materials and Photonics, CIMAP) and Jacques Balosso (of the radiotherapy department, Centre François Baclesse). Both the local organisers are work-package leaders of the ARCHADE project, a European research and clinical facility for hadrontherapy that uses proton and light ions. Caen was the per-

So many interesting topics for discussion.

fect venue for the 17th ENLIGHT meeting, not only because of the 75th anniversary celebrations of the Normandy landings, but also because the region had recently been selected to host the ARCHADE project.

The network invests in future generations

As has become usual, the first day of the meeting was devoted to the teaching and training of early-stage researchers and newcomers in the field, with a didactic session and two workshops.

The purpose of the lectures by Siamak Haghdoost, a researcher at the University of Caen and ARCHADE's leader for radiobiology, was to offer a synopsis of radiobiology and biomarkers of radio-resistance and radio-sensitivity considered in terms of the consequences of oxidative stress. Beyond fundamental reasoning in this domain, detailed experimental results demonstrated the complexity of any biological interpretation of findings. The lecturer stressed the need for closer collaboration between biologists and physicians, more radiobiological data, longer beam times and additional in-vivo studies.

The first workshop was dedicated to the principles and constraints of access to experimental platforms in Europe and beyond, including, in particular, financial aspects and beam time-sharing programmes. An emphasis was placed on reviewing currently funded European Union (EU) projects as tools to enable beam access for both in-vivo and in-vitro studies. The projects under the spotlight were: RADIATE (designed to provide easy access for researchers from academia and industry to the participating ion-beam facilities); INSPIRE (which aims to provide a world-leading integrated forum for European research into proton-beam therapy), and ERIN (the European Reintegration Network, a proposal supposed to continue the transnational access infrastructure project called the European Nuclear Science and Applications Research 2 (ENSAR2) study). In addition, specific presentations were given by the German research facility GSI, at which the Facility for Antiproton and Ion Research (FAIR) is under-

going construction, and by KVI's Centre for Advanced Radiation Technology in The Netherlands. These presentations considered access arrangements to accelerator and ion-beam study sites. A very animated general discussion, which included consideration of the Grand Accélérateur National d'Ions Lourds (GANIL, the French National Large Heavy Ion Accelerator) in Caen, concluded this workshop. The discussion underlined constraints regarding access to beams that were relevant to radiobiology projects.

The second workshop was dedicated to animal models for particle-therapy experiments. The aim was to share practical information regarding the development of the use of animal models for tumour and normal-tissue experiments in the particle-therapy field. Following an overview of European regulations on the use of animal models, which was given by Dr Cyrille Orset of the University of Caen, three examples of particle-therapy research platforms with fully integrated animal-model facilities were presented and discussed: the OncoModel platform at the Cycéron facility (Caen); the RadExp platform (Curie-Orsay) and the platform at the Istituto Nazionale di Fisica Nucleare - Laboratori Nazionali del Sud (INFN-LNS) in Catania (Sicily). Finally, a very attractive alternative to animal models, referred to as 'an organ on a chip', was presented in detail by Dr Frederic Zenhausern (University of Arizona, USA). Dr Zenhausern also described several radiobiology experiments that had been carried out using this innovative concept.

The organising team.

A unique scientific programme

The intense scientific programme of the meeting was spread across eight successive sessions. The discussions among the participants were very lively, both during the question time after each session and at the coffee breaks and luncheons. Sessions (see dedicated boxes) covered topics that ranged through quality assurance, advanced instrumentation and organ motion control, applied radiobiology, a presentation of the French ARCHADE project in preparation for a visit to the CYCLotron for HADron therapy (Cyclhad) centre, clinical results and ongoing trials in Europe and beyond, presentation of the three poster awardees, insight on facilities progress, new projects and new technology designs, and a technical presentation related to the industrial sponsors.

The social programme was enriched by a very interesting visit to the Abbaye aux Hommes, which was founded in 1063 by William, Duke of Normandy, later to become King William I of England, known as William the Conqueror. He is buried at the Abbaye, which is now the town hall. The visit was followed by a superb dinner there, during which the participants were entertained by the flute of Jean Louis Habrand, a longstanding member of the ENLIGHT network and a renowned radio-oncologist.

ENLIGHT 2019

ENLIGHT's Awards

As in previous years, all participants, especially young researchers, were encouraged to prepare posters, which were on display during the meeting. This year 30 posters were submitted, covering the full gambit of hadron-therapy topics. The winners of the three best posters were selected by a poster committee. They were announced and presented to the participants by Profs Balosso and Dosanjh. The winners were given the opportunity to give oral presentations of their work and were each awarded a travel bursary. The winners were:

Quality insurance, advanced instrumentation and organ motion control

A discussion about machine quality assurance (QA) was opened with a presentation by Dr Sairos Safai of the Paul Scherrer Institute (PSI, Switzerland). Denis Dauvergne of the Laboratory of Subatomic Physics and Cosmology, Grenoble, provided a very nice review of 20 years of research in the domain of patient quality assurance for PET and prompt gamma detectors. Organ-motion control in clinical practice was discussed by Alessandro Vai of the Italian National Centre for Oncological Hadrontherapy (CNAO, Italy). Along the same lines, Ye Zhang of PSI, gave a very didactic presentation on the global issue of motion mitigation. The discussion of 'Jet ventilation apnoea' surprised the participants for the simplicity of the idea. Jean Bourhis of Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois (CHUV, Switzerland) explained this technique.

The meeting took place in beautiful Caen where the participants could enjoy the incredible architecture of the city.

Dinner was held at the Abbaye aux Hommes, founded in 1063 by the future William the Conqueror and now the town hall of the city of Caen, France.


Group picture during the ENLIGHT welcome dinner.


At the treatment room of Normandy Proton Therapy Centre, Caen, France.

Applied radiobiology

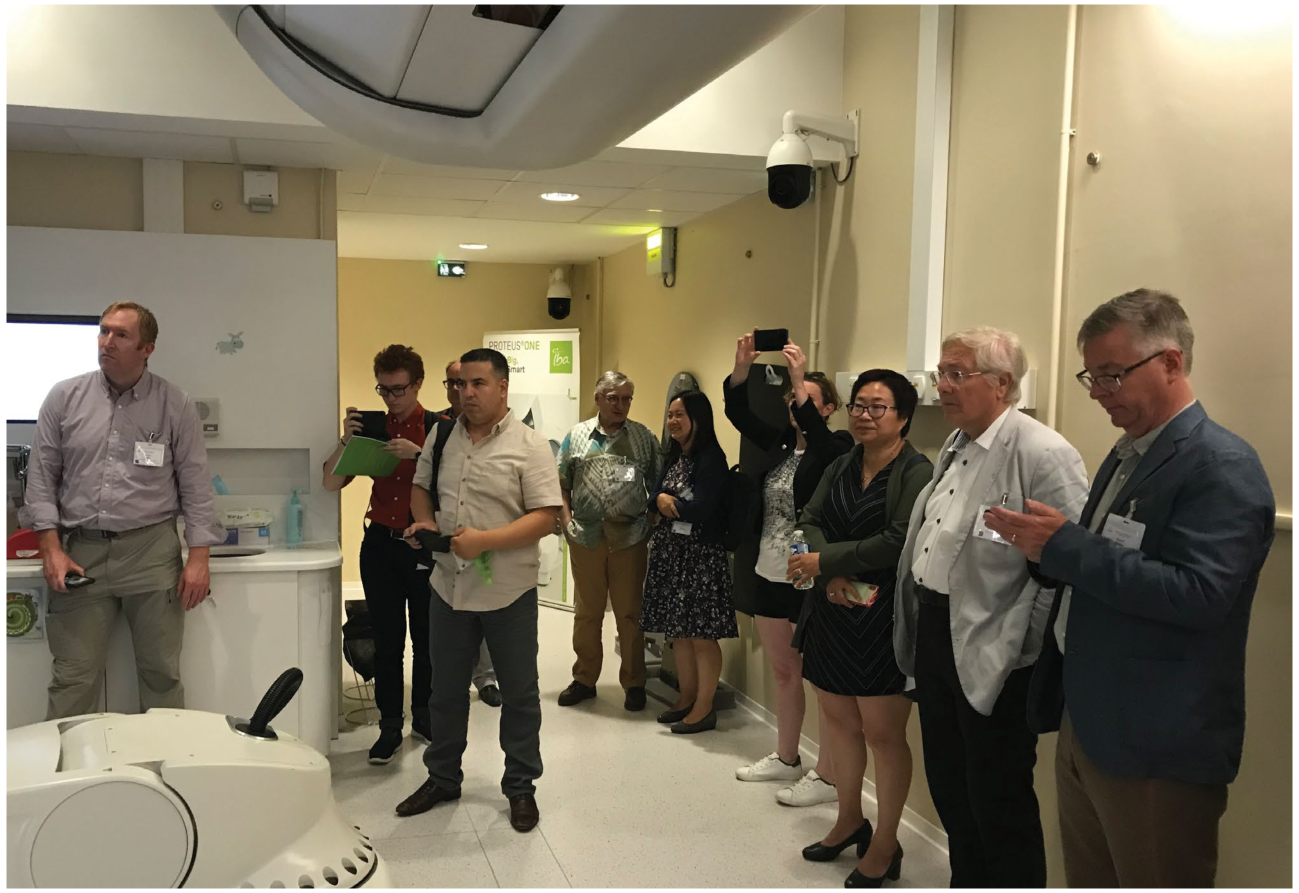
Jean Bourhis (CHUV, Lausanne) offered a very comprehensive review of the history of the FLASH effect. The discussion continued with Andrea Mairani (HIT-CNAO) who showed a comprehensive analytical dose-calculation engine based on parallel graphics processing unit (GPU) computing with pencil-beam-splitting approach. The NanOx model was presented in detail for the first time by Michael Beuve (IPN Lyon). Gerd Datzmann (Munchen) presented convincing preclinical data regarding a modern adaptation of the grid concept to protons while the entrance of the use of nanoparticles in clinical practice was confirmed by Jacques Balosso (Grenoble and Caen). Claire Rodriguez-Lafrasse of the University of Lyon, France, gave an overview of 17 years of radiobiology research devoted to heavy ions and radio-resistance. Is hypoxia sensitive to particle therapy? This question was tackled by Walter Tinganelli (GSI).

Olivier Guipaud, (researcher in radiobiology at the Institute for Radiological Protection and Nuclear Safety (IRSN), Fontenay-Aux-Roses, France), who presented a poster on Molecular profiling of human primary endothelial cells exposed to high doses of carbon ions in comparison with photon irradiation.

Sebastien Curtoni, (PhD student at Université Grenoble-Alpes, Laboratoire de Physique Subatomique et Cosmologie


The François Baclesse Centre uses Proteus One proton therapy equipment (by IBA) which has a mobile gantry system with pencilbeam scanning (PBS), allowing conformational treatment with 3D modulation of the dose delivered.


Council chamber of the city of Caen.


Visiting the facility, understanding the treatment.

(LPSC), CNRS/IN2P3) France), who presented a poster entitled Towards a beam-tagging diamond hodoscope for online ion-range monitoring.

Stewart "Mac" Mein, (PhD student at the Heidelberg Ion-beam Therapy Center (HIT) and the German Cancer Research Center (DKFZ, Heidelberg, Germany), who presented a poster on Combined ion-beam constant RBE (CICR): development and validation of a novel particle-therapy modality.

The baton is now passed to the organisers of the 2020 ENLIGHT annual meeting, which will be held from 22 to 24 June 2020 in Bergen (Norway). Again, this is a very timely choice for the venue, as Norway is scheduled to build two new proton-therapy centres, one in Bergen and one in Oslo. Construction should start in 2023. You are all invited to take part in the meeting!

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> **This year, the meeting was attended by more than 100 participants from more than 20 countries worldwide.**

The gala dinner at the historical venue.

The dinner venue was kindly offered by the city of Caen.

Lunch breaks involved networking and poster viewing.

Clinical results and ongoing trials in Europe

European results and progress were offered from studies at the Heidelberger Institut fur Radioonkologie (HIRO), Germany and at the Centro Nazionale di Adroterapia Oncologica (CNAO) or the National Centre for Oncological Hadrontherapy in Italy. Piero Fossati (MedAustron, Austria) spoke regarding MedAustron development of CIRT and the continuation of proton therapy. In the same sessions, participants could also hear from Jacques Balosso (Grenoble, Caen, Archade) the latest advances of the randomised trial called PHRC-ETOILE (France-Italy). A software application for radiotherapy hypoxia dose painting was presented by Michaël Gérard (Centre François Baclesse, Archade) while the need for randomised clinical trials in particle therapy was stressed by Enrico Clementel (European Organisation for the Research and Treatment of Cancer, EORTC).

Facilities progress, new projects and new technology design

Pawel Olko (Krakow, Poland) gave a complete and exciting review of all the projects in Europe and Russia under the title Progress report on treatment centres (MedAustron, Aarhus, Manchester, Maastricht and Groningen among others). Marco Shippers (Paul Scherrer Institute, Switzerland) gave An overview of new techniques/options/methods that are being studied/proposed at the moment while Robert Miller (US) offered a wise and pragmatic approach to proton therapy economics inspired by his new institution, the Maryland Protontherapy Center. Particle therapy status in South Korea was a review of the fast development of particle therapy in this country of 50 million inhabitants, given by Woo-Yoon Park (South Korea).

Proton minibeam radiotherapy

A BIG STEP INTO THE FUTURE of precision tumor therapy

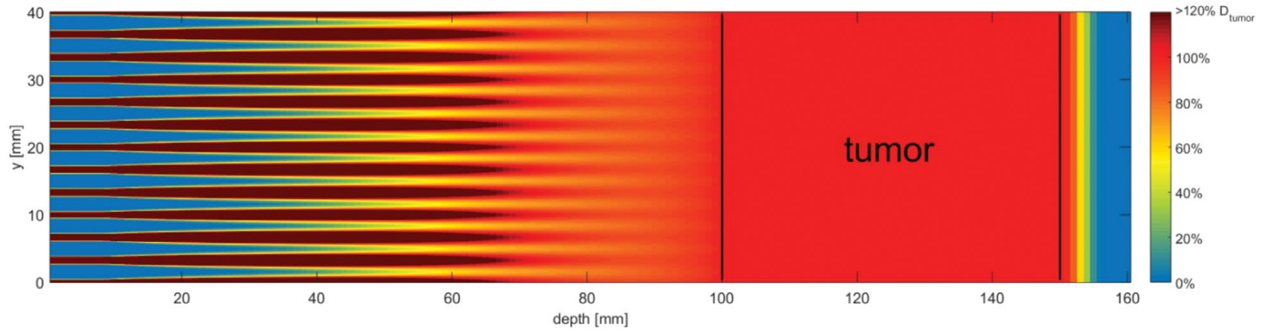

Figure 1. *Minibeam dose distribution of a 5cm wide tumor located in 10cm depth*

In the past two decades high precision proton therapy for cancer treatment has emerged and serves as an additional pillar in the field of radiotherapy. Although the number of patients being treated with particles compared to X-rays is still only about 1% (USA), more than 80 centers all over the world are offering this precise treatment option daily to patients and the number of centers is increasing rapidly. The use of particles such as protons or carbon ions enables great advances especially by sparing the healthy tissue behind the tumor. However, the healthy tissue in front of the tumour is still exposed to a significant amount of dose.

A method to reduce normal tissue damage in front of the tumor is spatial fractionation, introduced in 1909 by Alban Köhler via the use of grids in x-ray therapy sparing (large) parts of tissue by simply masking it from radiation. Recently, this idea has been revisited using the innovative power of interdisciplinary working groups in the field of biology, medicine and physics. Proton minibeam radiotherapy (pMBRT) brings together the tissue sparing effects of both conventional proton radiotherapy and spatial fractionation profiting from a superposition of both effects.

In conventional pencil beam scanning techniques, beam spots of a few mm are scanned covering the target area of the tumor. The distance between two adjacent spot positions (few mm distance) is typically chosen such that a nearly homogeneous dose distribution in the tumor is achieved, leading in consequence to homogeneous dose in the skin of the patient. In pMBRT, the beam spot size is much smaller (in the micrometer or at least sub-millimeter range) while the inter-beam distances remain in the millimeter regime. This results in a large fraction of tissue that is not exposed to radiation (see blue areas in Figure 1). Due to scattering of the protons in the tissue the minibeams spread laterally and merge together at the depth of the tumor. The inter-beam distance and number of protons per minibeam is optimized for a homogeneous dose coverage of the target with the prescribed tumor dose.

The experimental investigation of opportunities and capabilities of pMBRT is headed by two groups worldwide: the SNAKE group (Figure 2) around Judith Reindl and Günther Dollinger of the Universität der Bundeswehr München in collaboration with the Klinikum Rechts der Isar in Munich and the group of Yolanda Prezado at the CNRS in Paris.

Studies at SNAKE in human skin and in an in-vivo mouse ear model performed with that SNAKE setup (Figure 5) at the tandem accelerator lab in Munich showed less or even no acute side effects (such as inflammation) for pMBRT compared to homogeneous proton irradiation. Additionally, histologic findings 90 days after irradiation of mice ears revealed severe histopathological changes for homogeneous irradiation in contrast to none or only slight for minibeam irradiation (Figure 6).

The group of Y. Prezado demonstrated the positive effect of proton minibeams in rat brain where the minibeam irradiated healthy rats showed less clinical and neurological symptoms as well as less brain defects. In a further study, Prezado and co-workers investigated the potential of pMBRT on tumor treatment using high-grade gliomas in rats. While both homogeneous and minibeam irradiation lead to tumor control, survival after minibeam treatment was clearly enhanced (Figure 6).

Although experimental results are promising the research about the mechanisms of minibeams is still in its infancy. Nevertheless, multidisciplinary research led to first approaches of explanations. The cells in the path of the minibeams receive ultra-high doses causing high cell death rates in these regions. But migrating viable cells from the unirradiated regions adjacent to the irradiated site can infiltrate the damaged tissue and thus reduce radiation damage and toxicity. This can be attributed to two effects the so-called "dose volume effect" and the "microscopic prompt tissue repair effect" for submillimeter beam diameters. The first describes the fact that the maximum tolerable dose increases when the volume of irradiated tissue decreases. The latter describing the fast re-

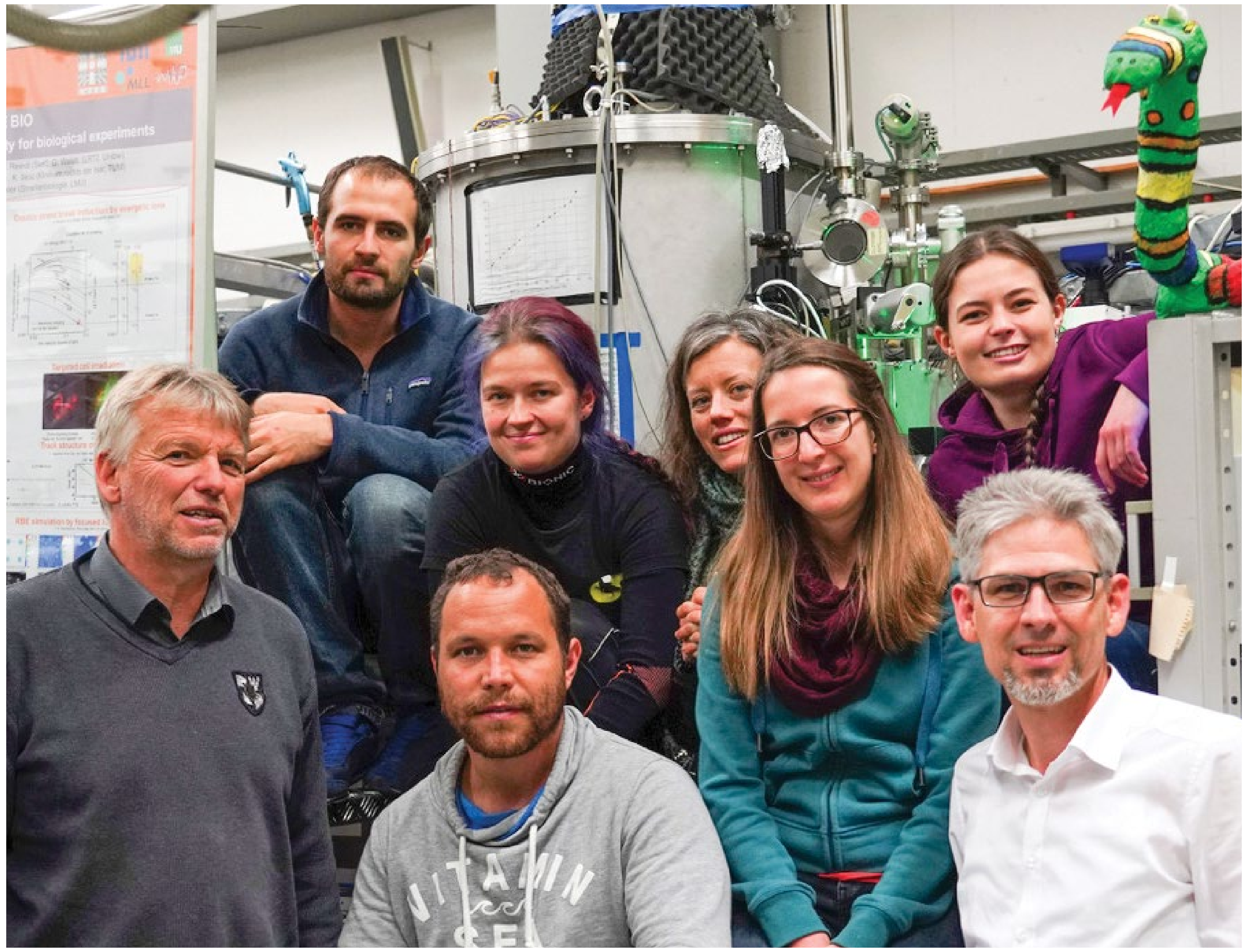

Figure 2 *SNAKE group headed by Prof. Günther Dollinger (left) and Prof. Judith Reindl (third from left).*

Perspective

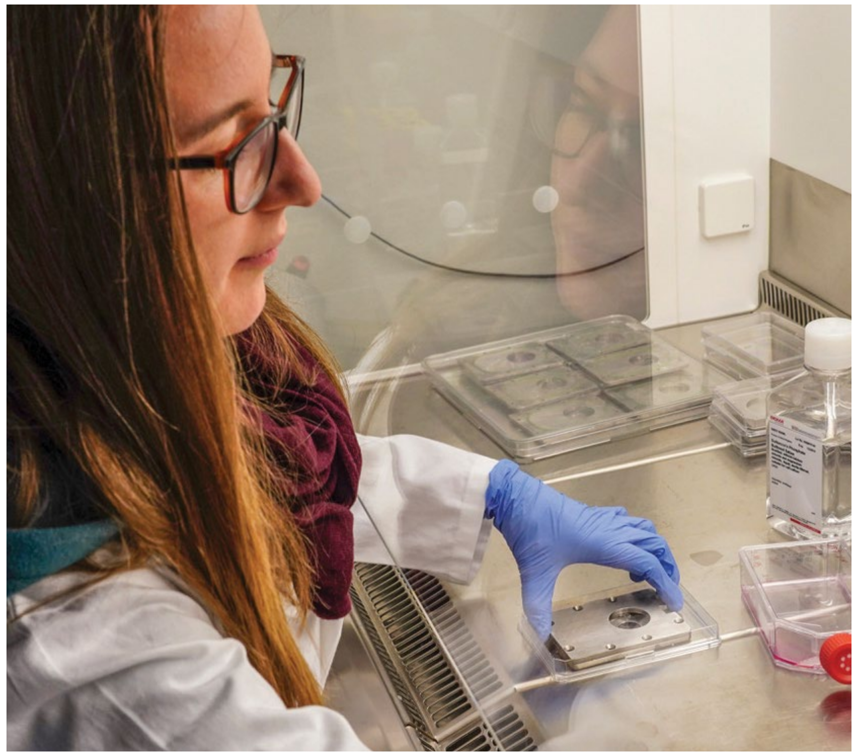

Figure 3 *Sample preparation for irradiation with proton minibeams.*

pair of capillary blood vessels via regeneration of angiogenic cells from the undamaged regions in between the minibeams within days or even hours. The repaired blood supply can then support and enhance the repair of other normal tissues in the minibeam paths.

For bringing proton minibeam therapy to the next level of maturity and applicability, new dedicated pre-clinical or even clinical minibeam irradiation setups have to be developed and set up. In order to fully exploit the advantages of pMBRT it is necessary to protect the patient from secondary radiation which would occur when proton minibeams are generated by collimators. This implies high precision beam focusing and sufficient proton flux leading to a minimum amount of secondary radiation. To achieve submillimeter spot sizes, a proton beam with a very small emittance is a must. Setting up a minibeam irradiation facility with proton energy up to 70 MeV is a challenging goal, since conventional cyclotrons or synchrotrons are not well-suited to fulfill this request.

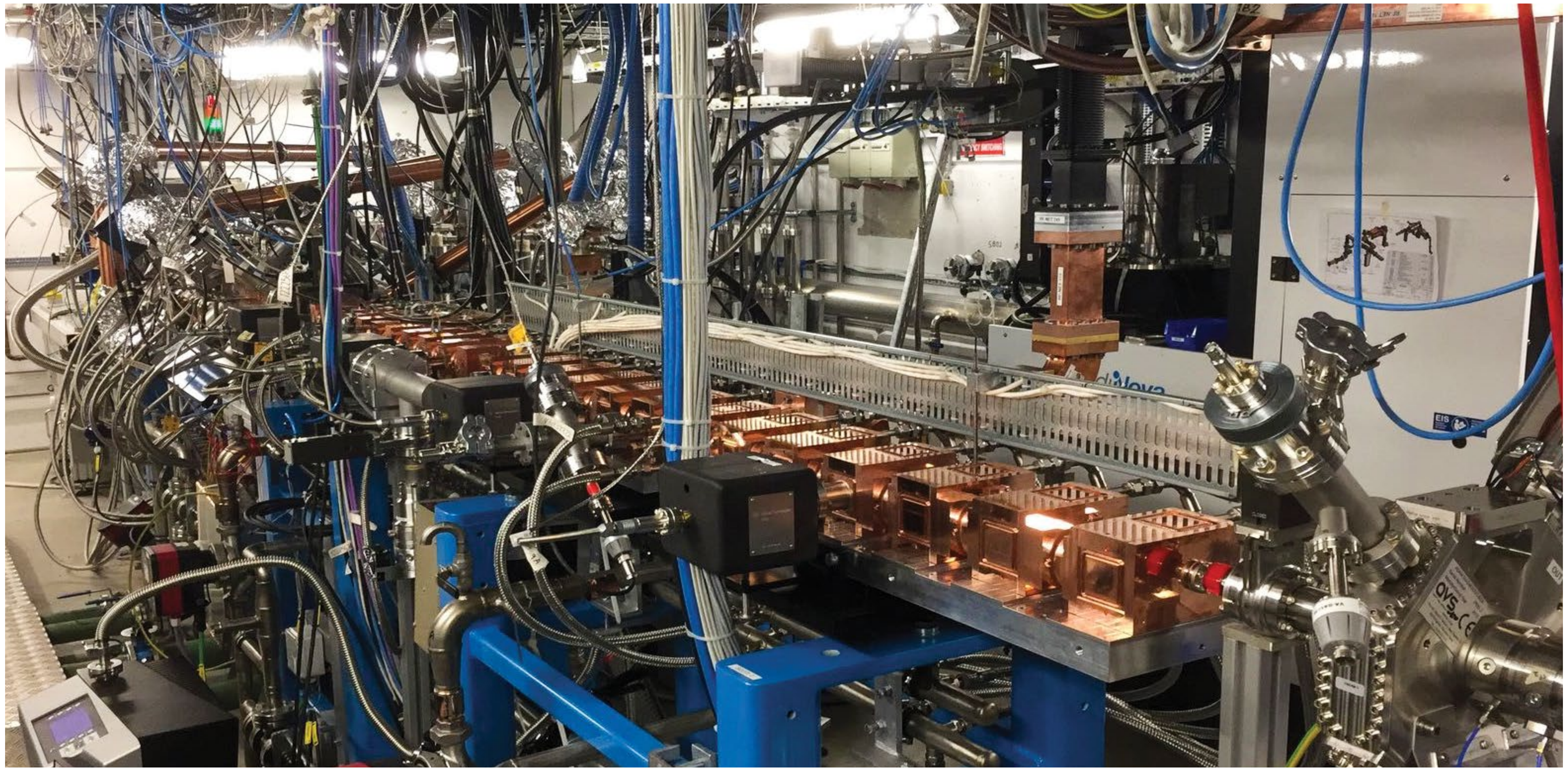

Figure 4 *The LIGHT linac prototype system installed and tested at CERN by ADAM.*

From a technological point of view, a solution to these challenges has been identified in high frequency RF-linacs. To understand the potentials of using RF-linacs for pMBRT, a collaboration between the SNAKE group and ADAM (the R&D branch of Advanced Oncotherapy) has been setup from 2017. Both partners are now in the building and testing stage for the technical equipment. Advanced Oncotherapy, with its subsidiary ADAM, has already successfully produced a high brightness beam up to 52 MeV with 3 GHz linac structures on its prototype system LIGHT installed at CERN (Figure 4), that is well-suited to produce proton minibeams.

Figure 5 *Focusing the proton beam to submillimeter dimensions at the SNAKE setup in Munich.*

The experimental evidence that pMBRT outperforms homogeneous irradiation with respect to healthy tissue protection while keeping tumor control - together with the promising technological developments in collaborations between research and industry - give cause for optimism that pMBRT can be used for treatment with less side effects. But this is not the only benefit from this method. The current status of knowledge and technology also allows to think out of the box. The pulsed time structure of the minibeams provided by RF Linacs intrinsically give the opportunity to exploit the FLASH effect in combination with pMBRT. This has the potential to further enhance normal tissue protection and give space for thinking on the opportunity of hypofractionation. This treatment scheme can be used to adapt the dose per fraction for optimal tumor treatment while keeping side effects under control.

Perspective

A dedicated preclinical irradiation facility, with the option of post acceleration given by the AVO-ADAM linac structures is being proposed, for performing further in-depth research programs with this new treatment modality and for understanding its radiobiological mechanisms in different tissues as well as living animals.

Taking all this together proton minibeam radiotherapy is a fascinating area of investigation and a big step into the future of precision tumor therapy. “Proton minibeam radiotherapy is an exciting new approach in radiation oncology that promises a substantial reduction of radiation induced side effects. I am particularly inspired by the observation that FLASH and minibeam therapy trigger immune reactions against tumors and I see their potential to revolutionize our view on radio-immunotherapy.” confirms Prof. Dr. S. E. Combs, professor and chair of the Department of Radiation Oncology, Technical University of Munich and director of the Institute of Radiation Medicine, Helmholtz Zentrum München.

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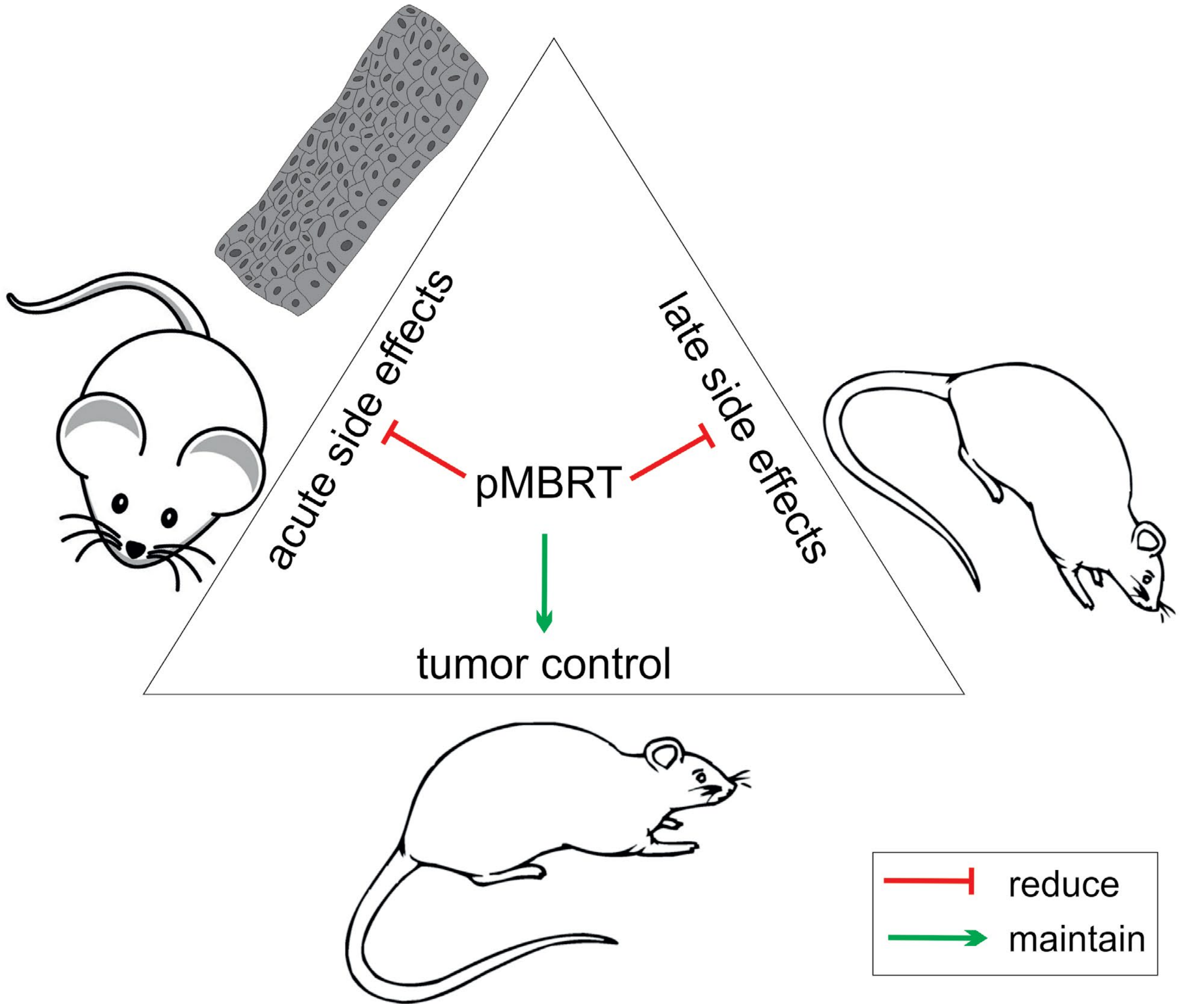


Figure 6 *Schematic representation of the results gained in studies performed with proton minibeams worldwide.*

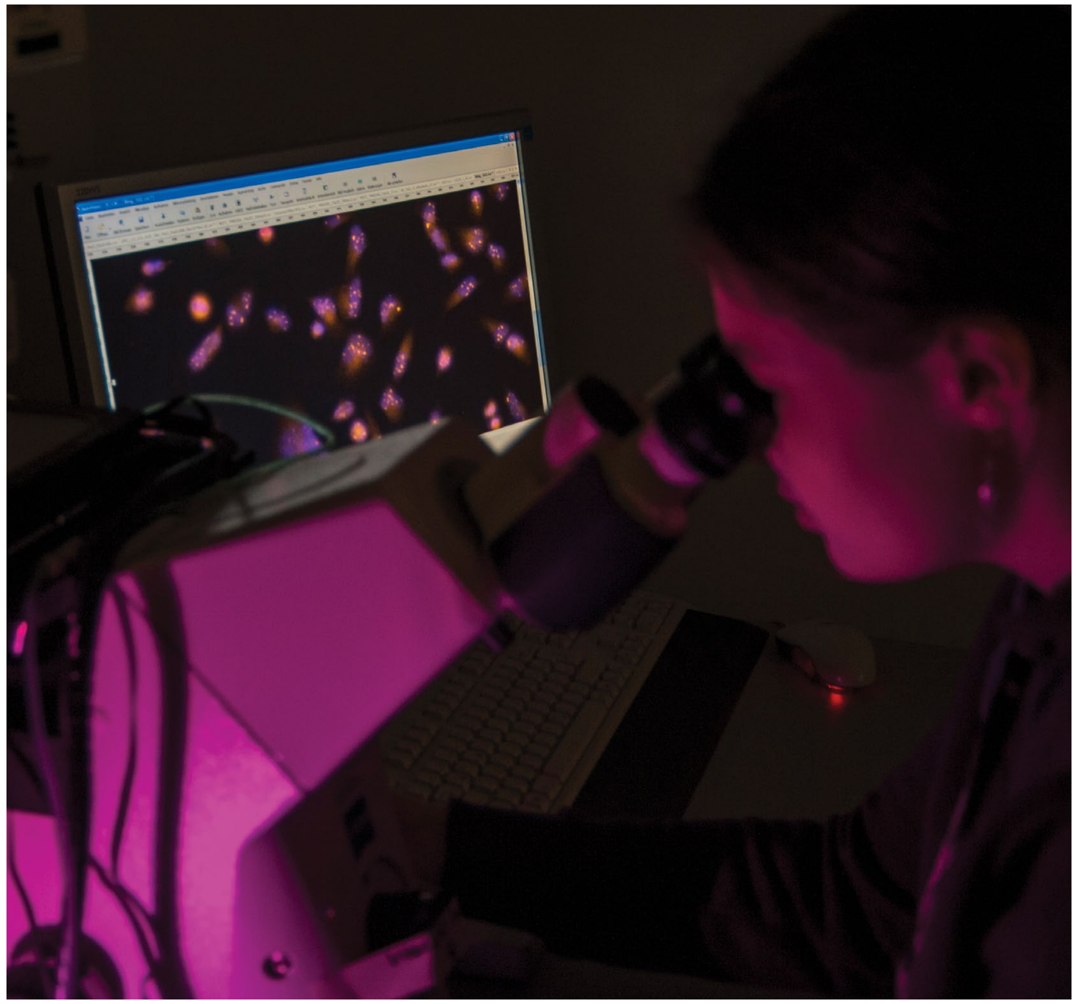


Figure 8 *Investigating DNA damage to understand the mechanistic effects of proton minibeam radiotherapy.*

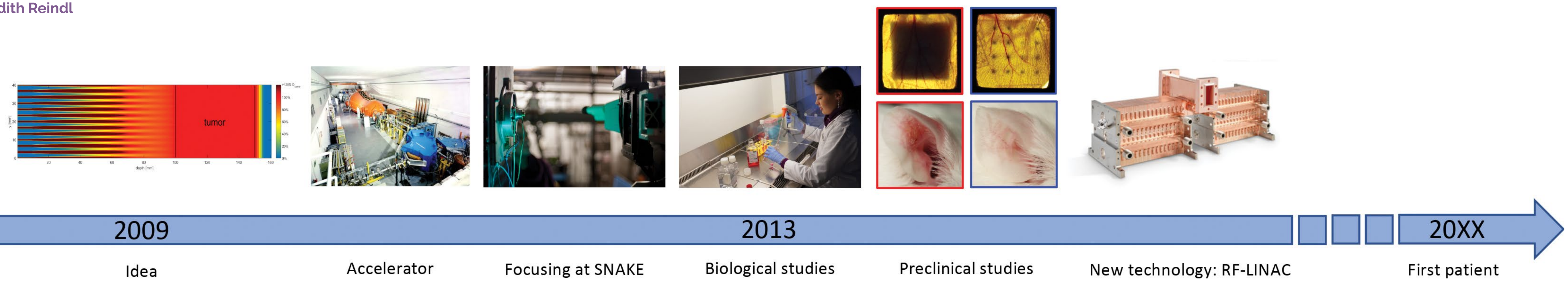


Figure 7 *Evolutionary steps for developing proton minibeam radiotherapy from the idea to the first patient.*

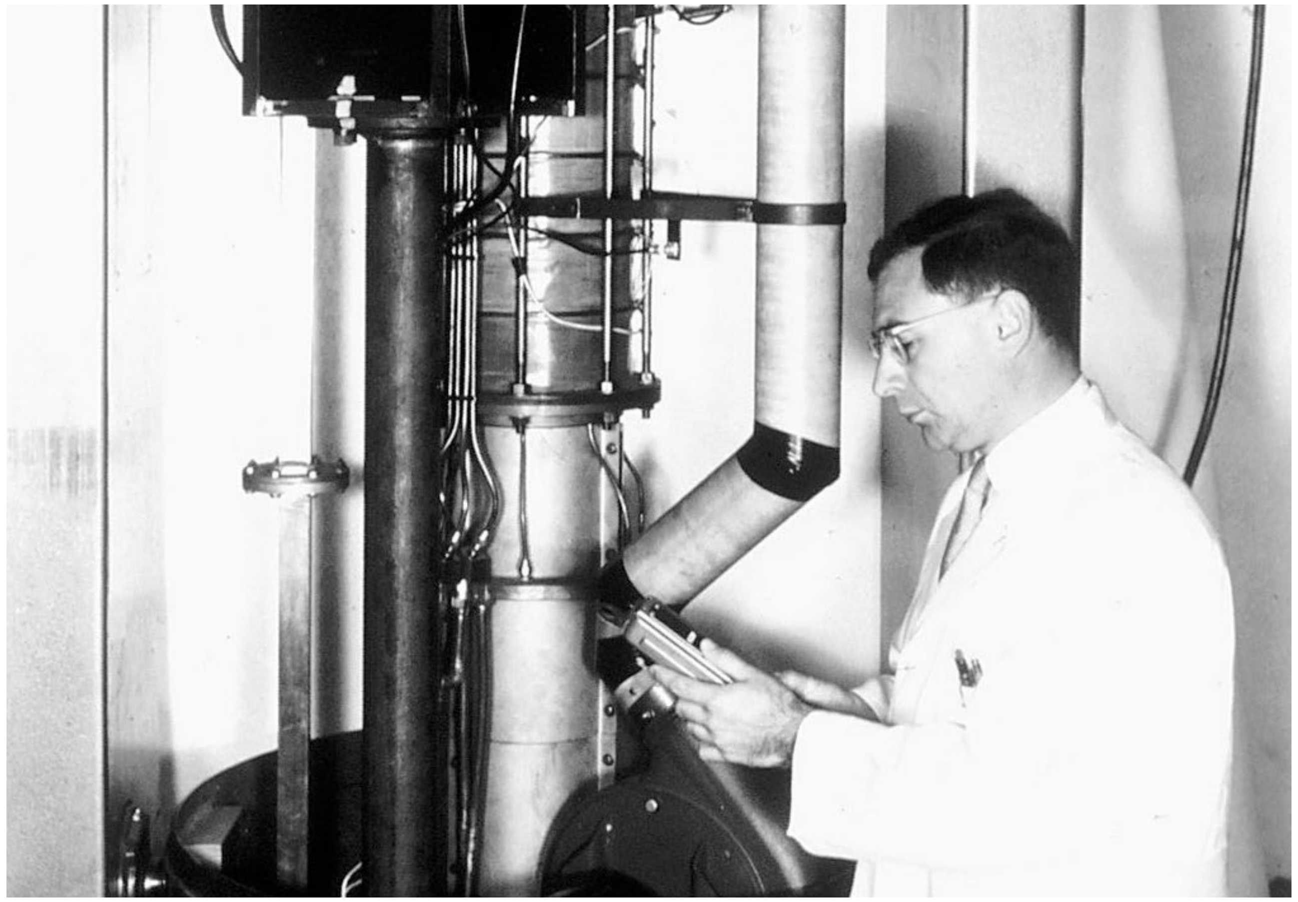
Radio-oncology: from empirical to high-tech

Seeing something inside the body without even cutting the skin is certainly one of the most significant revolutions that the medical field has gone through. Since the beginning, people realized that such a revolution was only possible thanks to breakthrough technologies, which had not been developed from the beginning for medical purposes. Today, the diagnosis, treatment and control of tumours relies on high-tech equipment that was not even imaginable just a few decades ago. If, on one hand, this allows patients to have a longer life expectancy and a better quality of life quality when they face the consequences of the disease, on the other hand it makes the cures increasingly expensive and obliges the whole medical field to rethink the processes that lead to disease diagnosis and treatment.

But, how did we go all the way from X-rays to the precision medicine that is growing and starting to be practised currently and will certainly be growing and building our future? To understand modern radiotherapy, we have to go back to the roots of radiation oncology and go through the list of actors of this discipline.

The roots of modern radiotherapy

The development of radiotherapy, alongside its most significant advances, can only be understood by looking at its “ecosystem”, which is shaped by four main disciplines: physics/technology, biology, clinics, and biomathematics/bio-informatics. These four components are part of a whole when we consider the most recent steps forward in radio-oncology. As you can see, the scenario is far from being simple and straightforward.

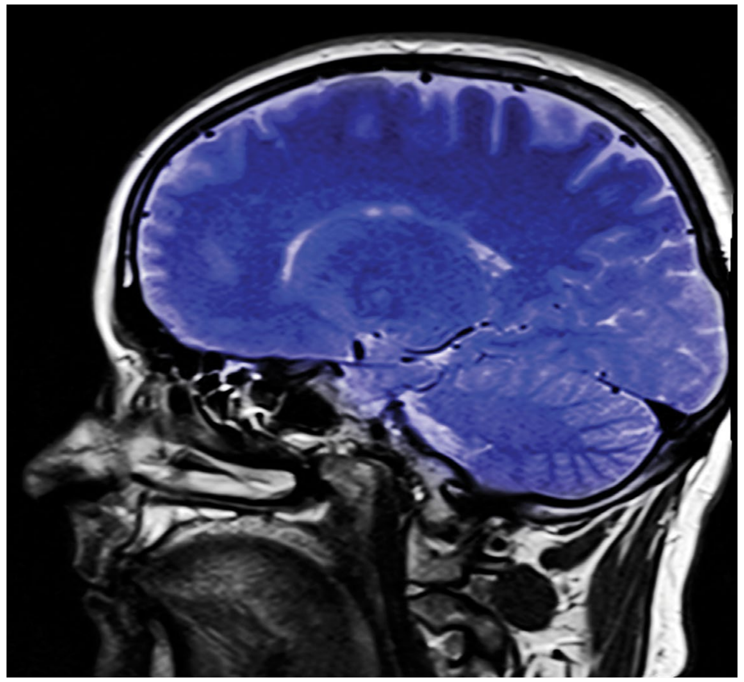


Dr. Henry Kaplan, in the 1950's, with an early model of the Linear Accelerator to treat cancer developed by the Varian brothers

The situation doesn't get any simpler when we try to define to whom do we owe the achievements of radiotherapy as one of the major pillars of cancer treatment. Together with Eric Hall and Amato Giaccia we tried, at the turn of the century, to answer this question in an article commissioned by the research journal Nature. Our analysis identified four main schools, which left their mark at different periods of the XXth century. From 1900 to ~1920, the German school dominated with the use of a few large “toxic” doses of radiation, which frequently led to impressive responses, but few long-term ‘cures’. From 1920 to ~1940, the French school offered significant contributions related to the exploitation of a differential between destruction of the tumour and unwanted damage to adjacent normal tissue. In this way, fractionated protracted radiation therapy was born. From 1940 to 1960, it was the British school which prevailed with the strong development of medical physics in the United Kingdom. This came with the advent of accurate dosimetry, more sophisticated beam arrangements and treatment planning, all of them contributing to a rapid development of radiation oncology with medical physics. And finally, from 1970 to date, the creation of the American Society for Radiation Oncology (ASTRO) in the US and of the European Society of Radiation Oncology (ESTRO) in Europe were followed by the beginning of evidence-based medicine, the proliferation of clinical trials to match the new and improved treatment machines, and the revolution in medical physics and computer-controlled technology.

Technology brings its boost

Which technologies boosted such an impressive development? To answer this question, let's modulate it by categories, starting from the evolution that technology brought to the radiation beams. After the discovery of the X-rays and natural radioactivity at the end of the 19th century, we had to wait for the 40s to have access to high-energy beams with the Betatron for electrontherapy, and the 50s for photons, with the installation of tele-gamma Cobalt-60 units. In the mid-fifties, the first linear accelerators were installed in the US and in the UK, opening a new era in the way to deliver more efficiently radiation to deep-seated tumors, especially with the use of 3-DCRT, and thereafter IMRT and volumetric modulated arc therapies.



X-rays photograph of the brain.

Combined to these technological advances, researchers were focusing on improving the treatment planning and delivery, acting on, among others, dose painting, breath-hold techniques, image-guided radiotherapy, and adaptive radiotherapy. What does “more efficiently” mean for a radio-oncologist? It refers essentially to the quest to obtain the highest differential possible between tumor cell killing and normal tissue sparing. In other words, the Holy Grail of radio-oncology is the solution to increase as much as possible the so-called “therapeutic index”.

Undoubtedly, the advent of hadrontherapy in the 80s represented a big step forward in an effort to optimize the anti-cancer therapy: proton beams first, then carbon ions, rapidly showed their physical and biological advantages over photon therapy, thanks to a sharper dose distribution and more effectiveness in radioresistant tumors with low oxygen levels. Along similar lines, intra- and extracranial stereotactic radiotherapy represented a significant progress to target relatively small tumors and reduce markedly the dose delivered to surrounding tissues. Originally delivered with tools produced by brands including Gamma Knife and CyberKnife, stereotactic techniques have now become accessible to a larger number of patients thanks to the use of LINACs. In parallel, significant progress was also observed for brachytherapy: twenty years after the advent of remote after-loading techniques in the 60s, high dose-rate units were introduced, allowing various types of endocavity, interstitial, or endoluminal applications, making short sessions of irradiation possible.

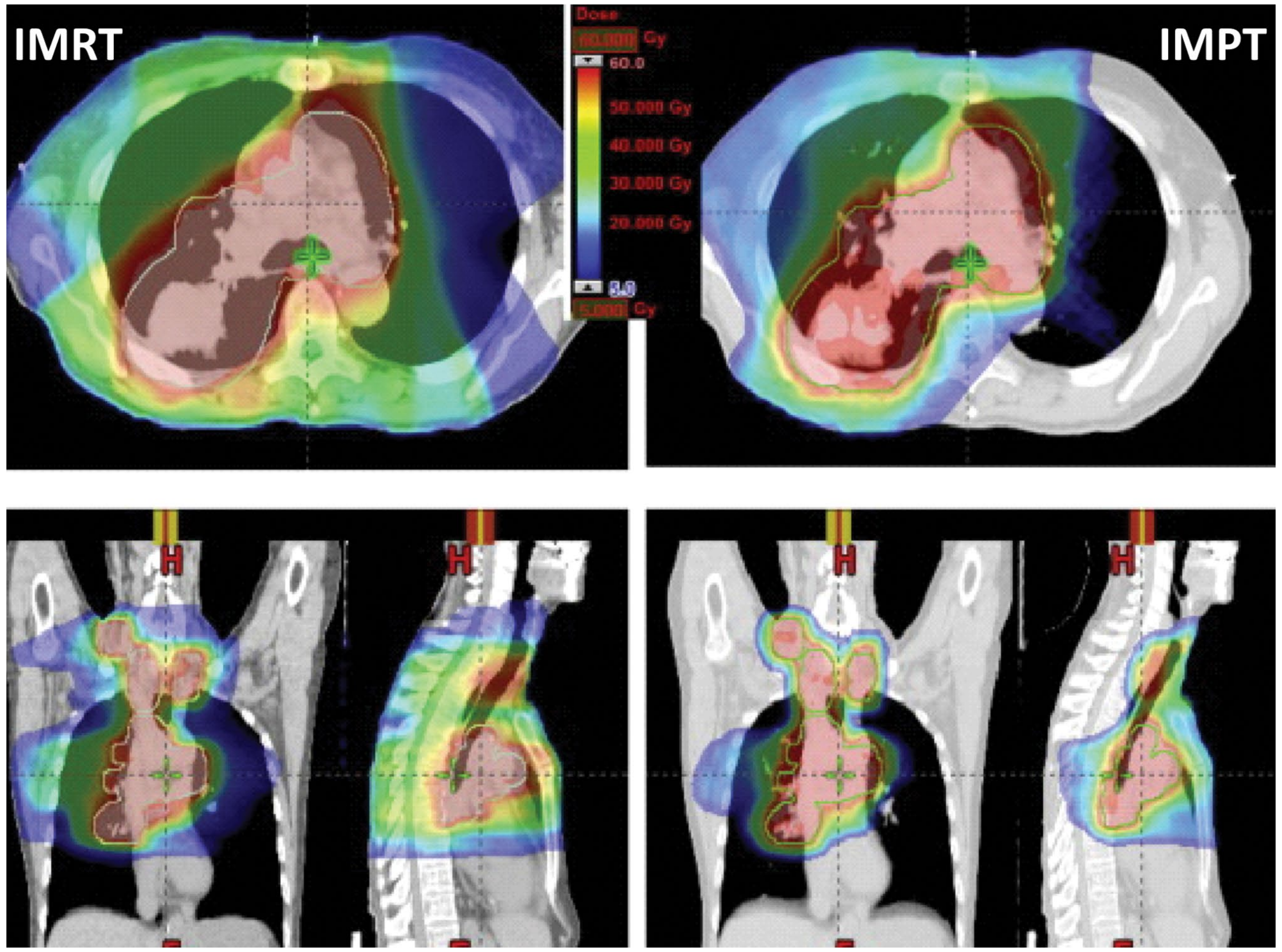
Biology: a field in motion

Progress in radiation oncology can also be analyzed through the lens of biology. There have been so many milestones in radiobiology that any selection is purely arbitrary. It's indeed impossible to pay tribute here to all teams who contributed significantly to allow us to do what we now do in our labs and clinics. One of the most important contributions of radiobiology to radiation oncology in the twentieth century was the development of assays to quantitate cell killing in vitro and in vivo for both normal and tumour tissues. In 1956, the cell-survival assay was developed by Puck and Marcus, which allowed researchers to investigate the intrinsic sensitivity of cells to genotoxic damage. In the seventies, the fundamental principles of radiobiology — repair, redistribution, reoxygenation and repopulation, known as the 'four Rs', were set out by Rodney Withers. It paved the way for the era of radiation doses fractionation to spare normal tissue toxicity and kill more tumour tissue, especially with the use of hyperfractionated and accelerated schedules of irradiation, predicted by biomathematical models developed by Howard Thames at MDACC in Houston, and applied successfully in clinical setting by numerous EORTC Cooperative Groups.

With the development of bioinformatics, significant advances in the organization and analysis of tumor-, host- and treatment-related data help clinicians identify important trends and patterns – the ultimate goal being the application of innovative diagnostic and therapeutic protocols.

From biology to multimodal approaches

Although it is very difficult to select just a few milestones in the history of radio-oncology, there is one breakthrough that would certainly find a general consensus in the community and that is the switch from cellular to molecular biology. This was really the turning point of modern oncology in general and radio-oncology in particular. For



A typical lung case comparison between IMRT (photons) and IMPT (protons) illustrating the significant potential of IMPT to produce compact dose distribution patterns to spare healthy tissues while irradiating tumors to high doses. (FromJ.Y. Chang, R. Komaki, C. Lu, H.Y. Wen, P.K. Allen, A. Tsao, M. Gillin, R. Mohan, J.D. Cox)

Image courtesy of Varian Medical Systems, Inc. All rights reserved.

the latter, this switch marks the intensification of the multimodal approaches integrating radiotherapy and another local or systemic treatments.

The first successful multimodal approach was actually the radio-surgical association and one of its seminal and most wonderful examples was the use, from the first quarter of the XXth century on, of postoperative radiotherapy in laryngectomized patients.

Combination of radiotherapy concomitantly to cytostatic agents was pioneered in the 80s by various institutional and cooperative groups. To illustrate what was achieved by concomitant chemo-radiotherapy, let's take the example of the EORTC phase III trial for which I had the privilege to be the principal investigator. This cooperative study on patients operated for locally advanced head-and-neck cancer randomized postoperative radiotherapy alone versus the same radiotherapy to which was added high-dose cisplatin. The conclusions were twofold: the first one was that chemo-radiation significantly improved treatment outcome in terms of both local control and survival index; the second one related to the higher toxicity of chemoradiation compared to radiotherapy alone, with also a poorer compliance to treatment intensity in the experimental arm, one third of the patients experiencing treatment delays or drop out.

Higher toxicity levels were confirmed in most trials conducted on chemo-radiation and this led us, through the last two decades, to consider the integration of radiotherapy into multimodal protocols based this time on the use of the so-called targeted therapies using either monoclonal antibodies or small molecules. With the combination of this biological, non-cytostatic approach, radiation oncology had jumped a bit more in the exploitation of biomolecular mechanisms to increase tumour cell killing induced by radiation, for instance by interacting with EGFR inhibitors all along the chain of membrane receptors and intracytoplasmic cascades. One of the major advantages of bio-radiation over chemo-radiation is the usually lower toxicity, which allows to maintain a good compliance to the prescribed dose values.

The future of radio-oncology

An exploding lab and clinical science throughout the last decade, immunology-based therapies are nowadays used with success in an increasing number of indications. We observe very positive results in consolidation phases for immunotherapy both as sole treatment or in combination with other types of systemic treatments. But we already know that, for us radio-oncologists, immunotherapy also opens a very promising window of opportunity to boost radiotherapy effects, especially with the use of techniques such as stereotactic radiotherapy and high-radiation doses per session. There are many clues on the promising applications of this combination. I will limit myself to the metastases example. The possibility of combining immune checkpoint blockade with radiation for the treatment of metastases represents indeed an exciting innovative strategy. This combinatorial strategy has the potential to enhance rates of tumor control, it produces less exposure of the normal tissue to radiation, and, in patients with brain metastases it improves cognitive outcomes.

Precision medicine is also bound to affect markedly radiotherapy results in the future. Indeed the addition of predictive tools to the clinical armament should prevail over the use of the sole prognostic factors, also in radiotherapy. For instance, in breast cancer, a number of predictive assays have recently elicited significant associations between molecular profiles and radio-sensitivity levels. Recent advances in predictive assays aimed at distinguishing patients with a more radioresistant tumour that necessitates radiation dose escalation or a switch to therapeutic approaches other than radiotherapy, plea in favour of an increasing role in the near future, for radiation-specific molecular signatures.

Another emerging avenue of research in radiotherapy is, undoubtedly, FLASH radiotherapy, in which the dose per pulse and the instant dose-rate during the pulses is about 100 higher than those used in conventional treatments. FLASH was shown to spare mouse lung from radio-induced fibrosis, whilst leaving unchanged the antitumour potential. Other teams also demonstrated reduced complications to normal brain and intestinal crypts with this innovative approach.

Besides the use of nanotechnology that would improve radioactive compound access into tumor tissue, I think that, in order for us to increase the role of radio-therapy in cancer treatment, we should look into the direction of innovative immunological approaches including chimeric antigen receptor T-cell therapies to which radiotherapy could be combined.

Multimodality, multidisciplinarity, multiapproaches

Cancer is not a single disease and patients cannot easily be put in a single, unified picture. What we have learned in all these years is that each patient should be treated as an individual case. This represents a paradigm shift for the whole field. Instead of relying on generalized protocols, doctors have to rely on the contribution of several other experts to better understand and tackle the disease of each single patient. This includes biologists, immunologists but also physicists for an optimal evaluation of the dose delivered, engineers for the design of the needed facilities and IT experts for the data handling. Actually, the expert contributions that scientists from fields other than the medical one can provide to the fight against cancer could be easily seen as one of the most important breakthroughs of the early 2000s.

In this framework, an important role was played by the ICTR (International Conference on Translational Research in Radio-Oncology) conference. Across its first four editions, the conference brought together experts from various schools and approaches who could exchange their views and discuss common topics. In 2010, the ICTR joined the Physics for Health in Europe (PHE) conference and the ICTR-PHE conference kicked off in 2012. Together with Manjit Dosanjh, I had the opportunity to chair the 2012, 2014 and the 2016 editions. These were undoubtedly breakthrough events for all the participants who came from all across the world and from many different scientific fields. Thanks to gatherings like ICTR-PHE we could build trust among the different communities and also provide long standing platforms where ideas and views are still exchanged today.

The future of radio-oncology is no longer imaginable without the contribution of all. This is arguably the best answer to the multifaceted cancer disease.

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Dr méd. Jacques Bernier

Chief Science Officer, Swiss Medical Network Genolier, Switzerland

Towards first-class research in SOUTH-EASTERN EUROPE

Montenegro Prime Minister Duško Marković marks the Start of the SEEIIST Design Study Phase on 18 September Credit: gov.me/B. Cupic

The South-East European International Institute for Sustainable Technologies (SEEIIST) initiative is gaining momentum and it was presented to the public at a meeting in Budva, Montenegro, on 18 September. The state-of-the-art facility for tumour therapy and biomedical research with protons and heavier ions has now moved from a conceptual to a design phase, thanks to the first financial support from the European Commission.

The idea for SEEIIST was raised three years ago at a meeting of trustees of the World Academy of Art and Science in Dubrovnik, Croatia, where the former CERN Director-General Herwig Schopper proposed such an initiative. The political support to SEEIIST has been growing since 2017 when Montenegro with the lead by its Science Minister Sanja Damjanovic became the first country of the region to promote the creation of the new facility. Two years later, in July 2019, six Prime Ministers signed a Memorandum of Understanding in Poznan.

SEEIIST will be a platform for internationally competitive state-of-the-art research, designed in the spirit of CERN and SESAME "Science for Peace" models, offering world-class research needed to reduce or even to revert the brain drain that is causing a shortage of talent and major economic losses in South-East Europe. The new facility will be used for tumour therapy and

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as a centre for biomedical research with protons and heavier ions. The aim is to create a local community of experts, provide them with powerful instruments for first-class research, thus retaining and increasing the number of specialists and doctors within the region. "Currently, our industry is not competitive, so we also aim at involving industrial partners and allow them to acquire the needed expertise," says Sanja Damjanovic, Minister of Science of Montenegro, and also a physicist working at CERN in Geneva and at GSI-FAIR in Darmstadt. "Gathering, storing and sharing medical data throughout SEE is essential for making smart patient decisions for referral, treatment and follow-up we'll need to build a digital hub preferably in a country different from the one where the centre will be located in order to have distributed knowledge and technologies expertise. We also need to to set up a clinical hub and a cancer board as well as other hubs such as for green energy and solar power which will also be spread out in the region."

No such a centre currently exists in South-East Europe, in spite of a growing number of tumours being diagnosed. The SEEIIST beam time will be shared 50:50 between treating patients and performing research with a wide spectrum of different ions beyond the presently used protons and carbon ions, making the facility unique in the world.

Montenegrin Science Minister Sanja Damjanović (right), former DG of CERN Professor Herwig Schopper (middle) and H.E. Ambassador Stefan Esterman Swiss Federal Department Foreign Affairs (left) at the Budva event. Credit: gov.me/B Ćupić

Introductory words about the start of the SEEIIST Project by Prof. Herwig Schopper, former DG of CERN. Credit: gov.me/B. Cu

Participants to the SEEIIST Kick-off event held in Budva, organized by the Ministry of Science of Montenegro. Credit: gov.me/B.Cupic

The next steps towards the realization of the new facility include: preparing a final technical design for the facility; proposing a structure and business plan for the organization and defining the conditions for the selection of the site. To carry out these tasks several working groups are being set up in collaboration with CERN and GSI-FAIR in Darmstadt, Germany. If all goes well, the construction is expected to start in 2023, with first patient treatment foreseen in 2028.

The local medical community is definitely onboard. "We are collecting declarations of support and cooperation from directors of oncological clinics in the region," confirms Damjanovic. "Oncologists from our region really like to move to something new. All the other tumour treatment centres are national, while our medical staff will be international, speaking different languages. We will have a pool of international doctors treating hundreds of international patients".

History has been tough on the communities living around this European region. SEEIIST could really help them to build trust in each other while keeping the cultural and economic development fair for all.

MedAustron enters the CARBON ION STAGE

Particle therapy has been successfully used at MedAustron for two and a half years. Whereas previously patients were treated exclusively with protons, carbon ion therapy is now also available. These particles open up new opportunities for tumours that were previously difficult or impossible to treat. MedAustron is thus finally joining the ranks of only six centres worldwide that can combat tumours with both protons and carbon ions. The first treatment with carbon ions took place on July 2, for a patient with an adenocystic carcinoma of the left ear.

The main advantage of particle therapy - reducing the risk of side effects and long-term consequences – applies to both protons and carbon ions. However, carbon ions offer additional advantages over protons because they are biologically more effective.

Not only carbon ions offer an excellent dose distribution, but their high LET also shows itself only in the last part of the path.

In the last part of their path, protons are still sparsely ionizing: i.e. this means the distance between two ionization events is much larger than the DNA diameter. Carbon ions instead become densely ionizing and can break multiple bonds in a space of 2 – 3 DNA bases. This damage is very difficult to repair. This means that the higher biological effectiveness can be focused on the tumour, thereby increasing chances of local control without increasing damage to normal tissues. Moreover, as one single particle can create a DSB, the dose-effect curve becomes linear and therefore the dose per fraction can be safely increased.

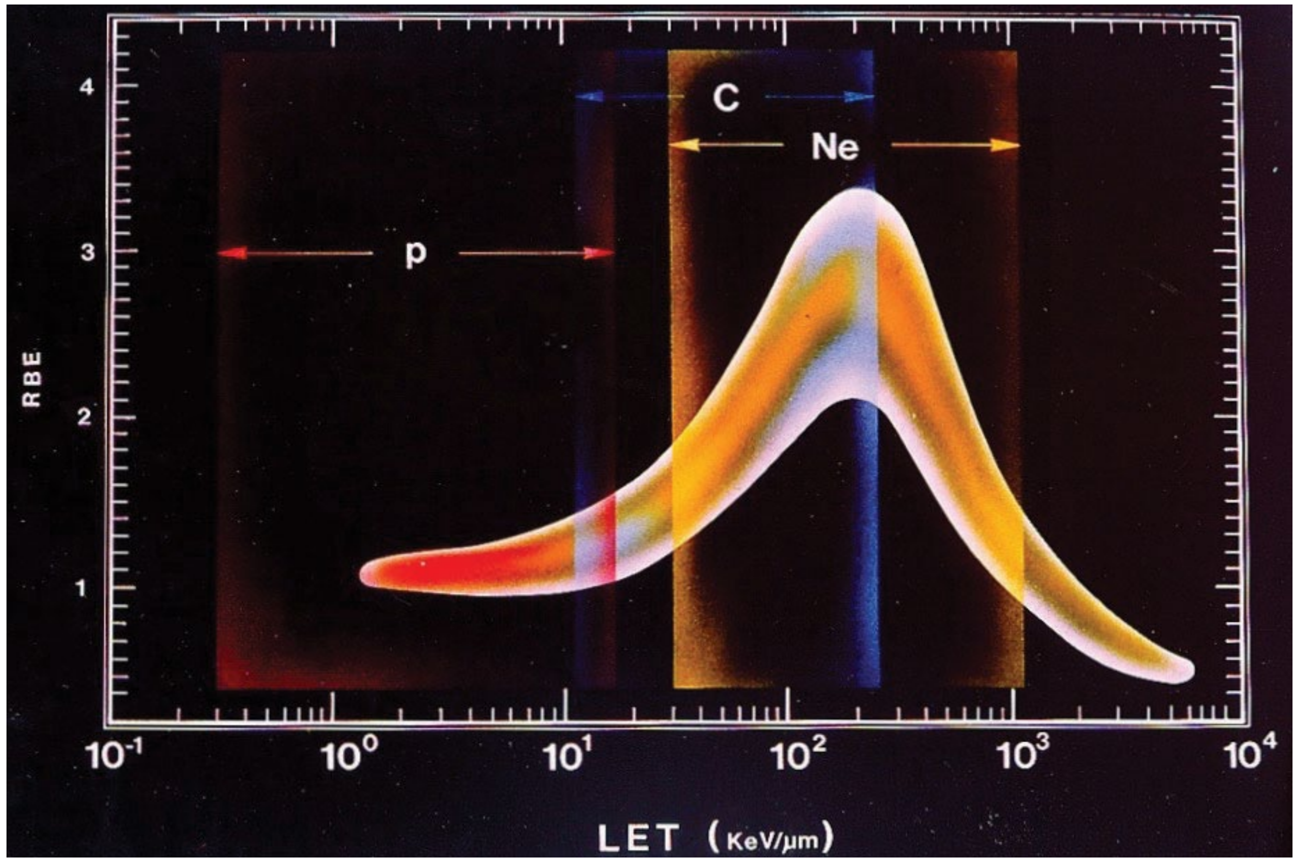
Carbon ions are used to treat patients with macroscopic diseases: unresectable or inoperable or incompletely (R2) resected or recurrent tumours. At MedAustron, treatment with carbon ions initially focuses primarily on tumours in the head and neck region and at the base of the skull. The spectrum will be continuously expanded, for example, to include gastrointestinal indications such as pancreatic or rectal carcinomas and sarcomas.

Dr Piero Fossati, MedAustron's Clinical and Scientific Director for Carbon Ions, summed up the advantages of these particles: "Irradiation with carbon ions makes it possible to maintain both the physical functions and the quality of life of patients, even with very complicated tumours".

> *"Irradiation with carbon ions makes it possible to maintain both the physical functions and the quality of life of patients, even with very complicated tumours.*

> *"The main advantage of particle therapy - reducing the risk of side effects and long-term consequences – applies to both protons and carbon ions.*

Author:
Dr Piero Fossati
Clinical and Scientific Director for Carbon Ions



"Not only offer carbon ions an excellent dose distribution, but their high LET also shows itself only in the last part of the path."

News

The deflecting magnet for protons and carbon ions on its way into the MedAustron building.

Photo credits: Fotograf Harald Valderhaug https://creativecommons.org/licenses/by-nc-nd/2.0/

ENLIGHT 2020 meeting
welcomes you to Bergen

The ENLIGHT 2020 meeting will be held from June 22nd to 24th 2020 at the campus of Haukeland University Hospital, in Bergen, Norway. The Hospital is located 10 minutes away from the Bergen city centre.

The Norwegian Government has decided to build two proton therapy facilities, one at the Radium Hospital, Oslo University Hospital, with two treatment rooms and one room for research purposes, and at Haukeland University Hospital, with one treatment room and one room for research purposes. Both the treatment rooms and research rooms will be equipped with 360 rotational gantries to prepare the research rooms for upgrading to treatment rooms if required. Clinical startup is scheduled from 2023 – 2024. Among the most visited sites is the Troldhaugen, the home of composer Edvard Grieg and a trip by cable car to the mountain Ulriken the highest of the seven mountains around the city or by foot or funicular to the Fløyen mountain.

The city of Bergen is located at the West Coast of Norway and has a mild but often rainy climate. Situated between beautiful mountains you can enjoy hikes just 20 minutes away from the city centre. The core of the city is the harbour where Bryggen, a UNESCO Heritage Centre is a central part. The harbour during summer times is crowded by coast traffic freight ships and a myriad of ships of many shapes and sizes including sailing ships. Today the city is the main port for supplies to the large offshore activity in the North Sea.

The ENLIGHT 2020 meeting will start on Monday, June 22nd with a training day program and a reception in the evening. The normal ENLIGHT meeting will follow on Tuesday, June 23rd and Wednesday, June 24th with lectures and discussions related

Staatsraad Lehmkul


Bergen Harbour

to the use of particles in cancer treatment. The ENLIGHT 2020 meeting will cover the core topics of particle therapy; improvement of our understanding of RBE and related radiobiology issues, the use of heavier ions (Helium, Carbon) in particle therapy, development of dose verification tools, mechanisms for improvement of margins applied during dose planning, novel treatment techniques, ongoing work with clinical trials and an outlook into the future of particle therapy.

Do not miss the social dinner which will be held at a special seafood restaurant reached by boat transport outside Bergen on the evening of June 23rd.

Professor Olav Dahl is the local host for ENLIGHT 2020 and the Organization Committee is chaired by medical physicist Kirsten Nygaard Bolstad, the meeting is organized in close collaboration with The University of Bergen and our colleagues from Oslo University Hospital.

The Norwegian ENLIGHT 2020 organizing team warmly welcomes all that wish to visit our beautiful country for interesting and intriguing discussions in the field of particle therapy in a friendly atmosphere in the prime time of the year at the West Coast of Norway.

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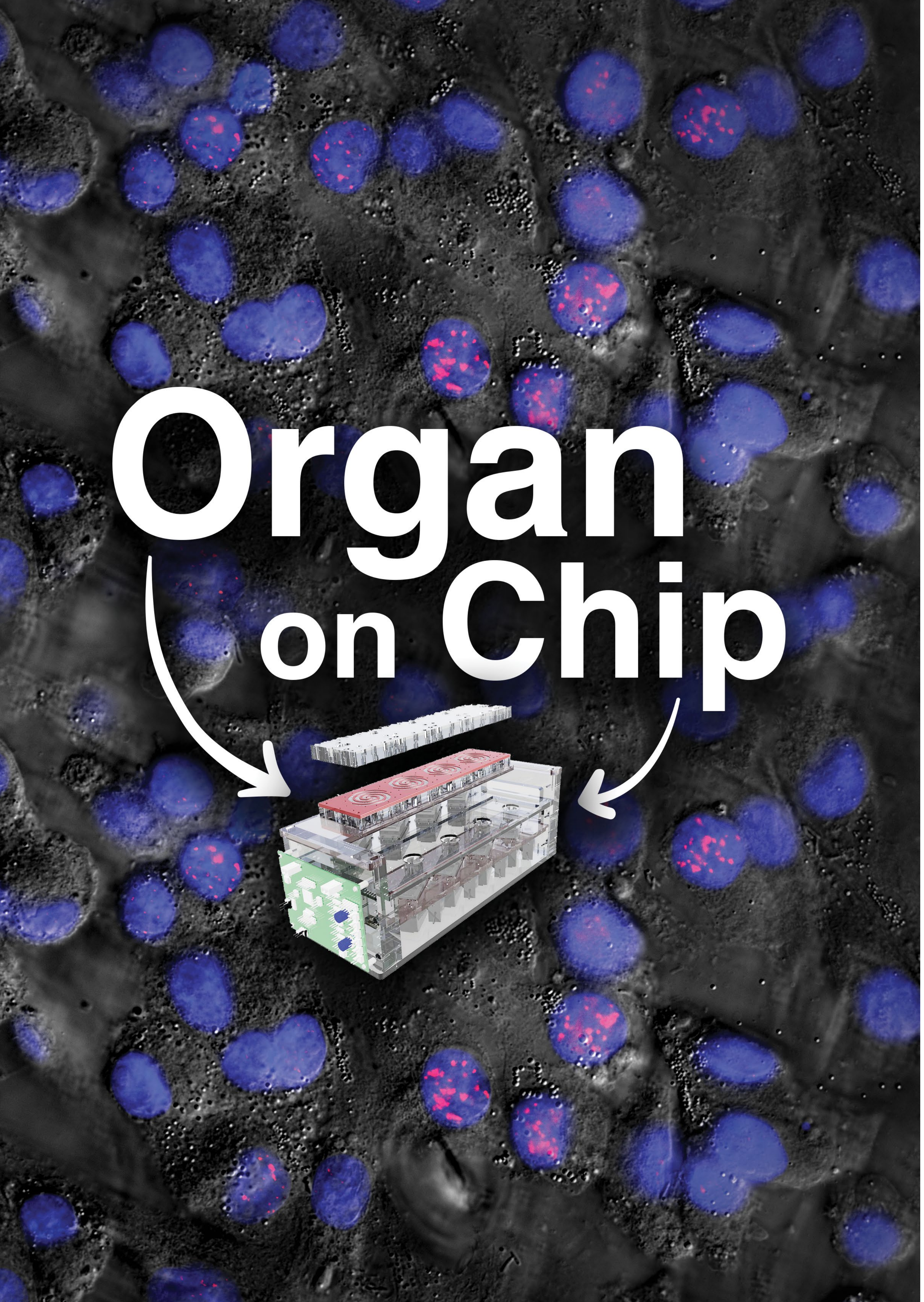
Haukeland University Hospital

Photo Nina Aldin Thune: *https://creativecommons.org/licenses/by-sa/2.5/deed.en*



ORGAN-ON-CHIP AND RADIATION:

Alternative in vitro Models to Animal Testing

The European Parliament is actively promoting the use of alternatives to animal use in research by implementing its 3Rs policy (Replacement, Reduction and Refinement) across the European Union. The status quo as it pertains to investigate radiation effects on human tissues, and to identify radiation biomarkers, is to use animal models, including non-human primates, or samples from radiotherapy patients. However, these in vivo models are currently limited by the species difference that restrict the extrapolation of results and validation to humans. Collected human samples are usually biased by the presence of many confounding factors that can modify radiation responses. The platform technology of organs-on-chip (OOC) can provide new models to better mimic in vivo human tissues by taking into account both biochemical signals and biophysical properties to investigate radiation effects while keeping the same experimental flexibility as in vitro models.

Typically, OOC are biomimetic, microfluidic, cell culture devices created with microchip manufacturing methods that contain continuously perfused hollow microchannels inhabited by living cells arranged to simulate tissue- and organ level

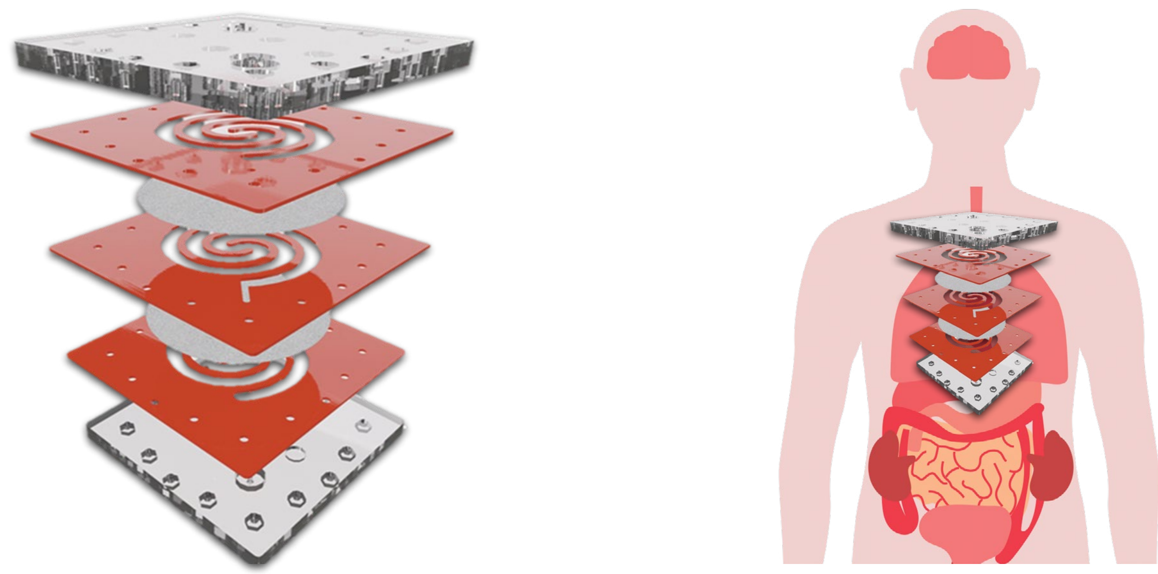
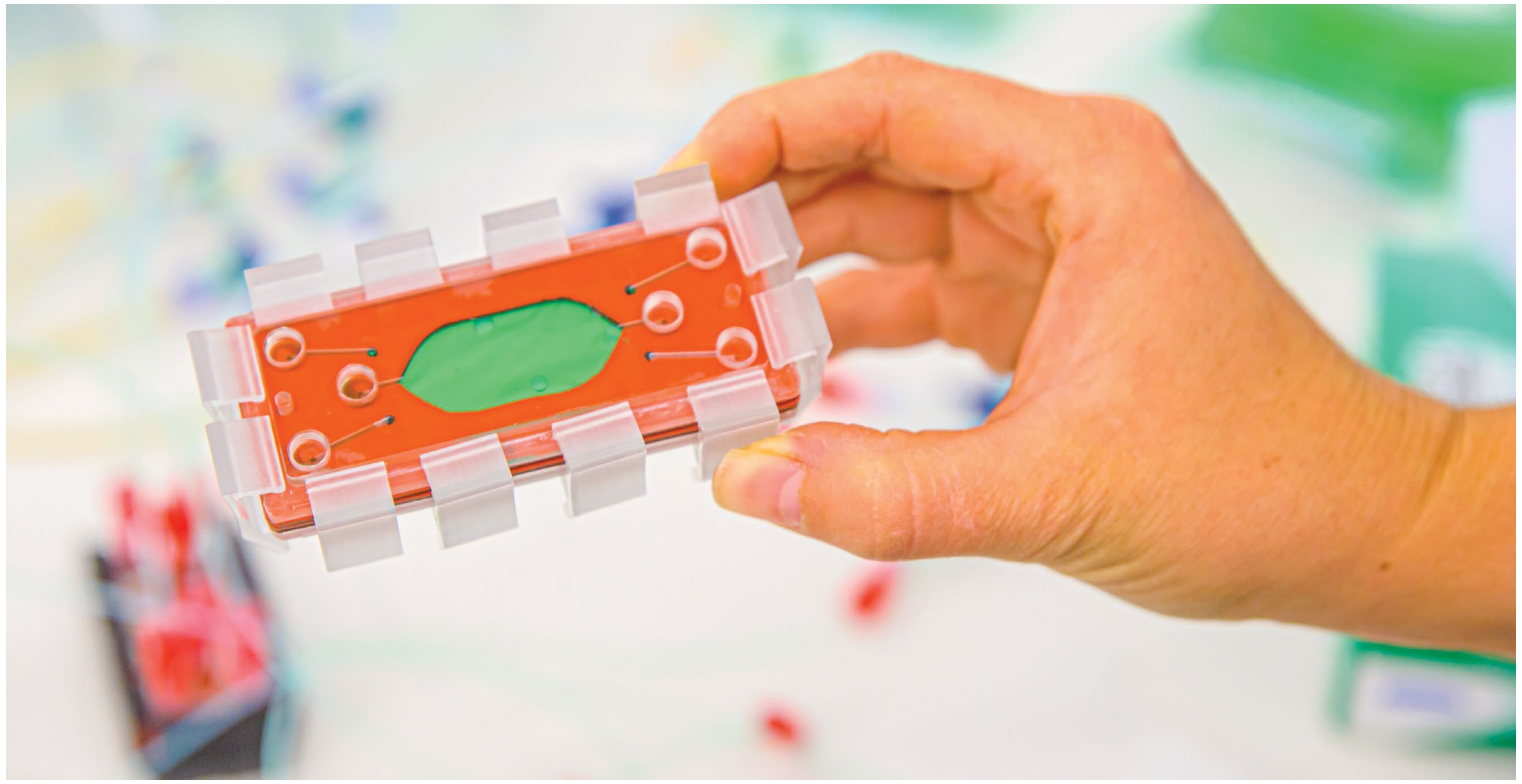


Figure 1: The details of the HumiX gut-on-chip multilayers assembly displaying plastic microfluidics and nanoporous polycarbonate membranes on elastomeric layer (orange).



physiology. By recapitulating the multicellular architectures, tissue-tissue interfaces, chemical gradients, mechanical cues, and vascular perfusion of the body, these devices produce levels of tissue and organ functionality not possible with conventional (2D) or three-dimensional (3D) culture systems.

Our team at the University of Arizona has developed a modular, microfluidics-based human "gut-on-a-chip" model (HuMiX for "human–microbial crosstalk"), which allows co-culture of human and microbial cells under conditions representative of the gastrointestinal (GI) human–microbe interface. Importantly, the use of microfluidics allows the exploitation of laminar flow profiles which facilitates the establishment of dedicated culture conditions for both human and microbial cells simulating in vivo conditions. The presence of microbiome recapitulates the gut ecosystem ideally suited for this device to be applied in radiobiology studies given the growing evidence that dysbiosis of intestinal microbiota likely plays a key role in the response to radiation exposure. Importantly, we have shown that current iterations of the HuMiX model accurately recapitulates in vivo transcriptional, metabolic, and immunological responses in human intestinal epithelial cells. More recently, the HumiX device design was adapted to explore the effects of simulated galactic cosmic radiations under a NASA-sponsored project. Such OOC device will also allow to perform seminal functional, biomarker and countermeasure studies defining the effects of low and high dose rate irradiation on the human GI tract.

The development of 3D bioengineered platforms using primary human cells can better mimic the cell-cell and cell-extracellular matrix (ECM), mechanical and biochemical interactions of in vivo tissue. This is partially driven

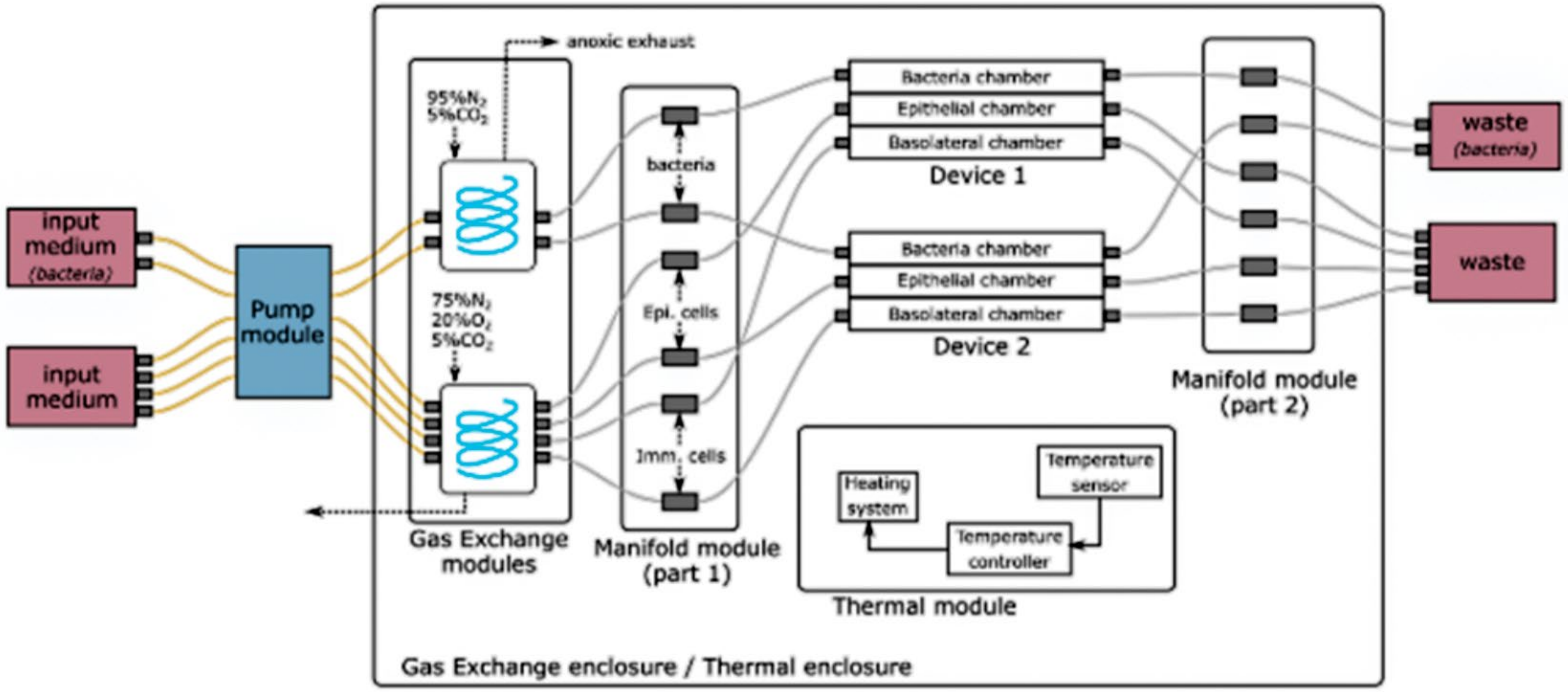
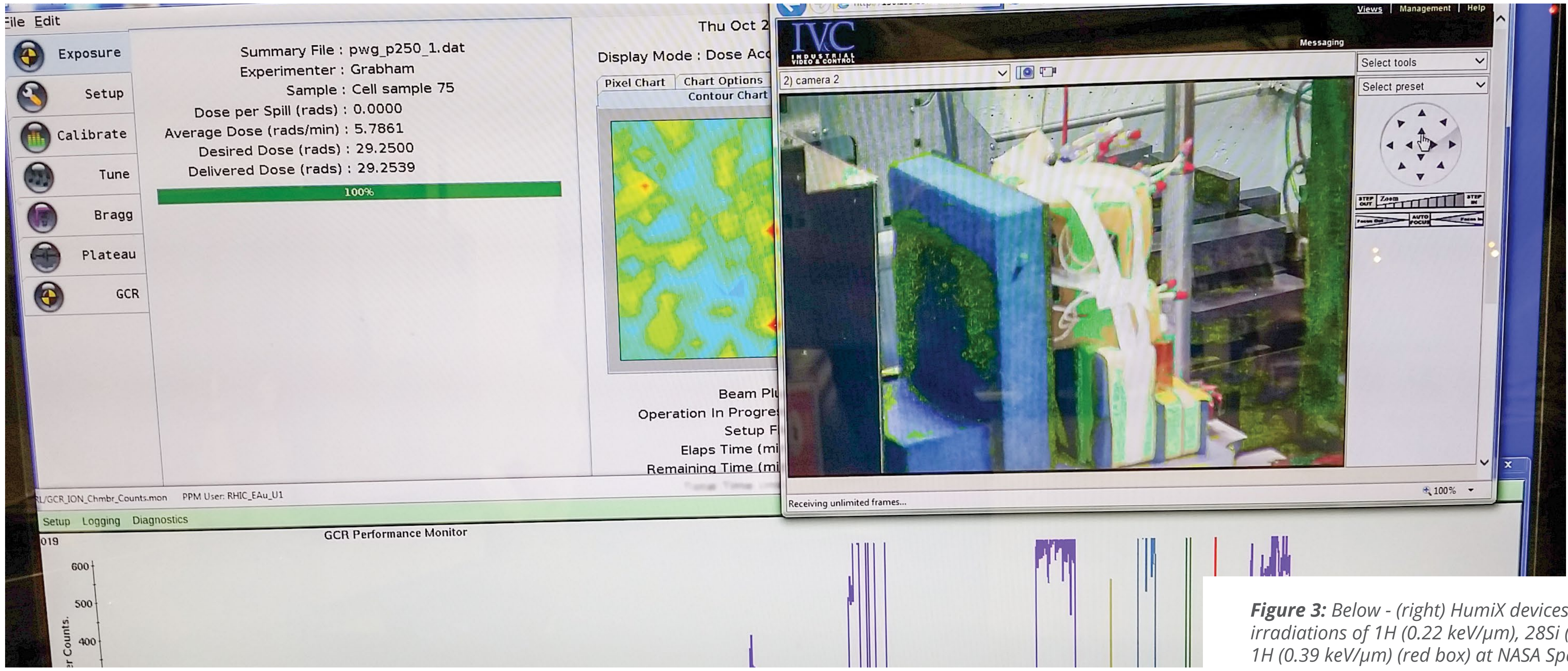


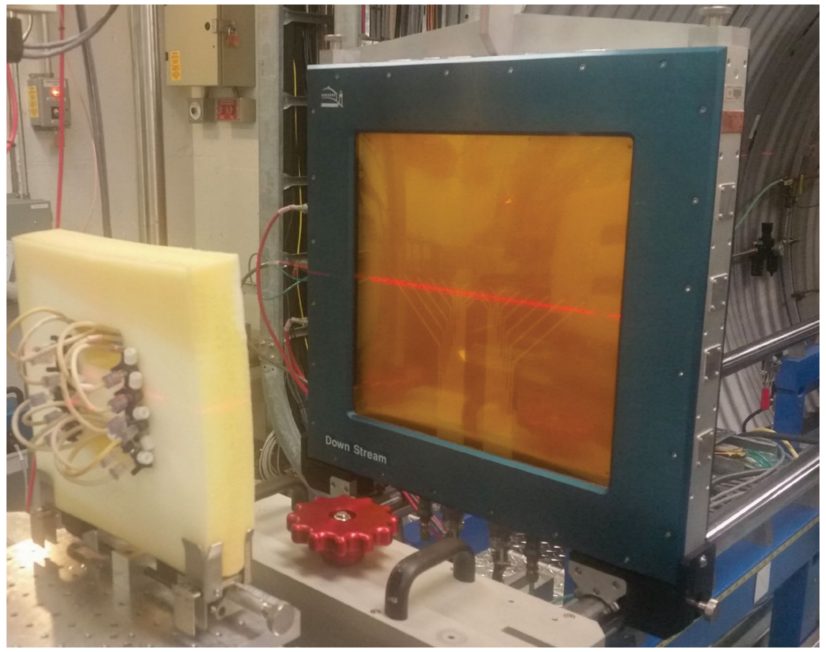
Figure 2: *(Up left) Plastic multilayered microfluidic device of HumiX gut-on-chip device; (Up right) Two HumiX devices connected with all ancillaries and placed into a CO2 incubator for running cells co-culture; (bottom) Diagram of instrumental system to run the microfluidic device.*

Figure 3: *Above - (left) Picture of the HumiX devices placed into the particles beam system at the NASA Space Radiation Laboratory (Brookhaven National Laboratory, Upton, NY, USA); (right)*



Features

by cancer research that takes advantage of organoids derived from a patient's own tumor sample to select a personalized and effective therapy. There has been a tremendous push to develop biomimetic, engineered ex vivo patient-derived cancer models that maintains a high degree of similarity (spatiotemporal architecture and heterogeneity) to the in-vivo human disease. Such systems overcome the limitations of 2D in vitro cell culture models by incorporating physiological relevant tissue architectures to build 3D models for multiple organs.



" By recapitulating the multicellular architectures, tissue-tissue interfaces, chemical gradients, mechanical cues, and vascular perfusion of the body, these devices produce levels of tissue and organ functionality not possible with conventional (2D) or three-dimensional (3D) culture systems.

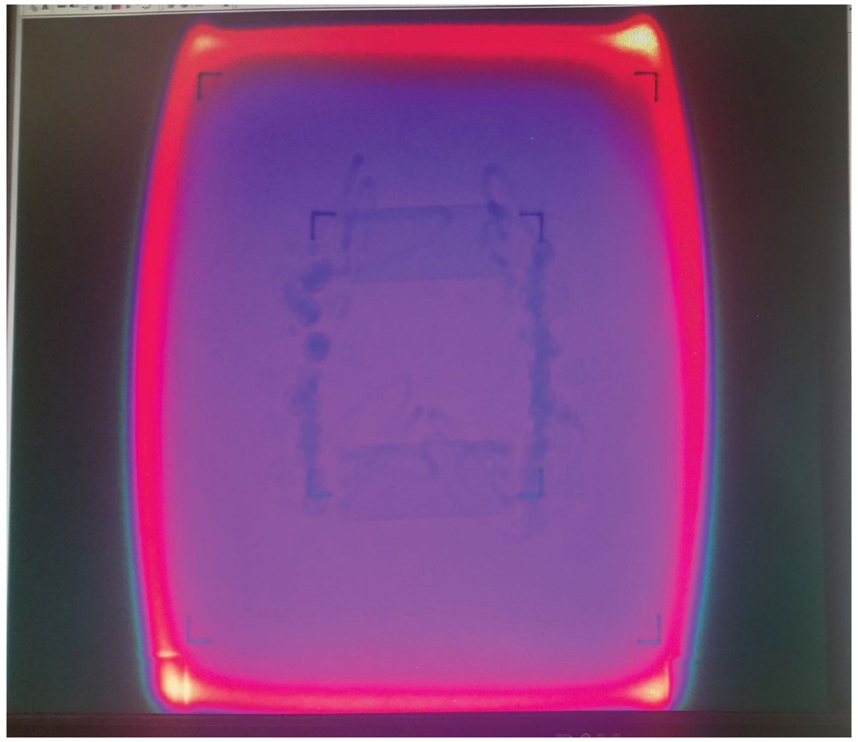


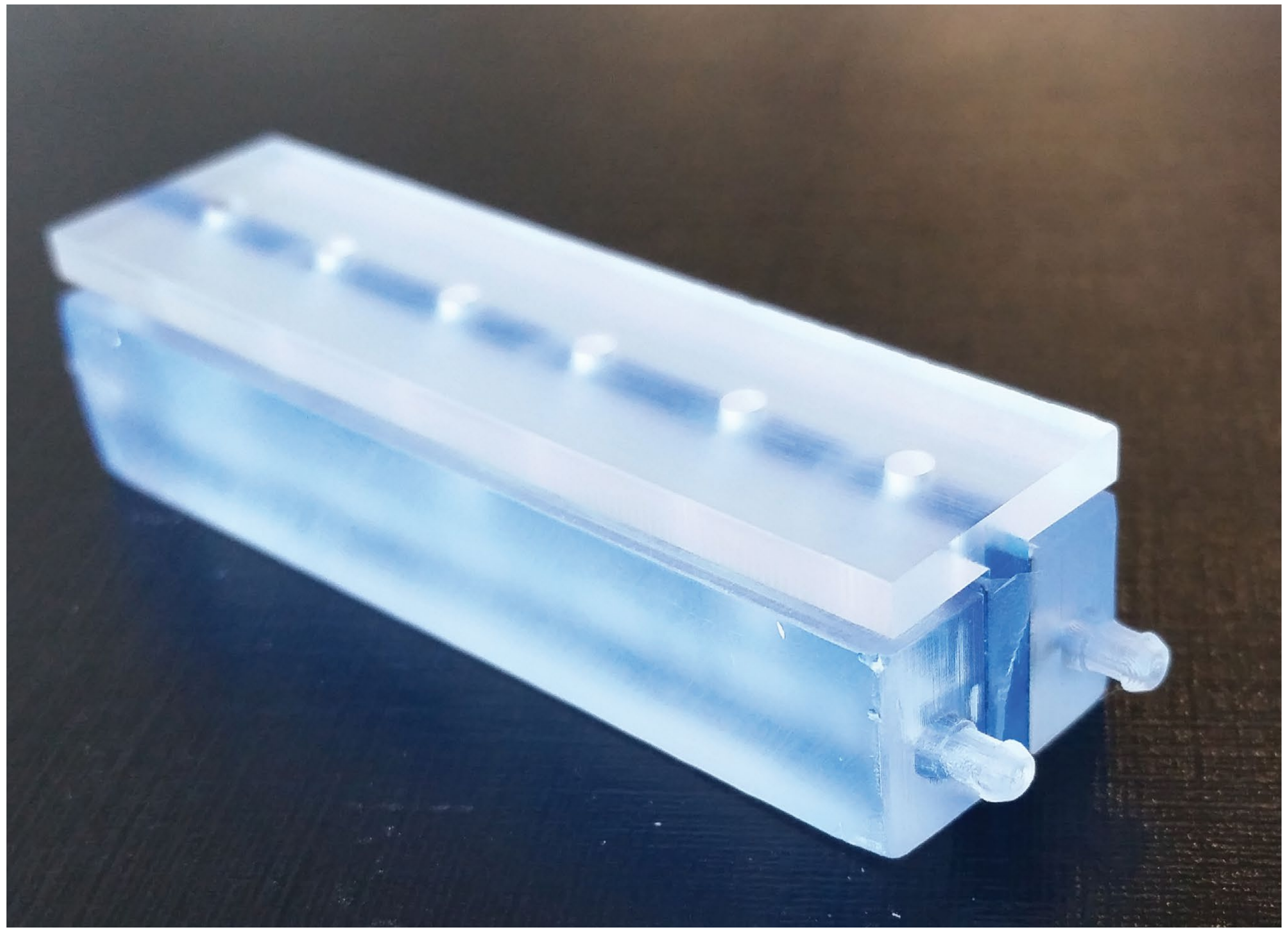
Figure 3: *Below - (right) HumiX devices being exposed to a simplified 5-ion GCR Simulator including sequential irradiations of 1H (0.22 keV/μm), 28Si (50.47 keV/μm), 4He (1.58 keV/μm), 16O (20.90 keV/μm), 56Fe (174.07 keV/μm) and 1H (0.39 keV/μm) (red box) at NASA Space Radiation Laboratory; (right) Device alignment into the beam.*

Features

The combination of these organoids systems with microfluidics can provide modular tissue platforms that can capture more salient features of the human tissues and their functions in real-time, including both their biochemical and physical cues.

The fabrication approach and biomaterials characteristics must also mimic the physical and mechanical properties of the human organs to replicate their physiology. Often, the cellular organization of major organs includes a high density of blood vessels in unique and complex 3D environment defining specific architectural properties, both of which having profound implications for physiological function. For example, the specific structure and hemodynamics of the liver sinusoid significantly slow down the intrahepatic blood flow and prolong contact between circulating molecules and liver cells. Because of the significant challenges associated with the preparation of synthetic scaffolds that recapitulate such complex environments, there has been increasing interest in the development of naturally biologic scaffolds obtained through the process of decellularization. However, this approach is currently in its infancy, and issues related to the decellularization and subsequent recellularization processes remain to be addressed. At present, currently available systems do not yet provide a complete model for biomedical research. In response to these limitations, plant-derived scaffolds (or "plantimals") have emerged as alternative systems for modeling complex organs because they retain the vascular network inherent to the plant following the decellularization process, which can be used to perfuse fluid. For example, spinach leaves have been shown to provide a matrix that mimics heart vasculature, while we have demonstrated their use for studying cancer cells response to ionizing radiation (IR).

Radiotherapy is associated with increased arterial stiffness; this effect being more evident when radiotherapy is administered after 35–40 years of age. Recent data also showed that IR could have opposite effect on ECM since clinical doses of radiation reduce an ex vivo tumor and an in vitro collagen matrix. Nevertheless, these results suggest that IR alter tissue mechanics but whether tissue mechanics alters IR response is still to be explored, in particular with the growing application of particle beam therapies. The plant scaffold vasculature network can present different elasticity and stiffness in order to reconstitute artery and heart tissue of young and old individuals and investi-



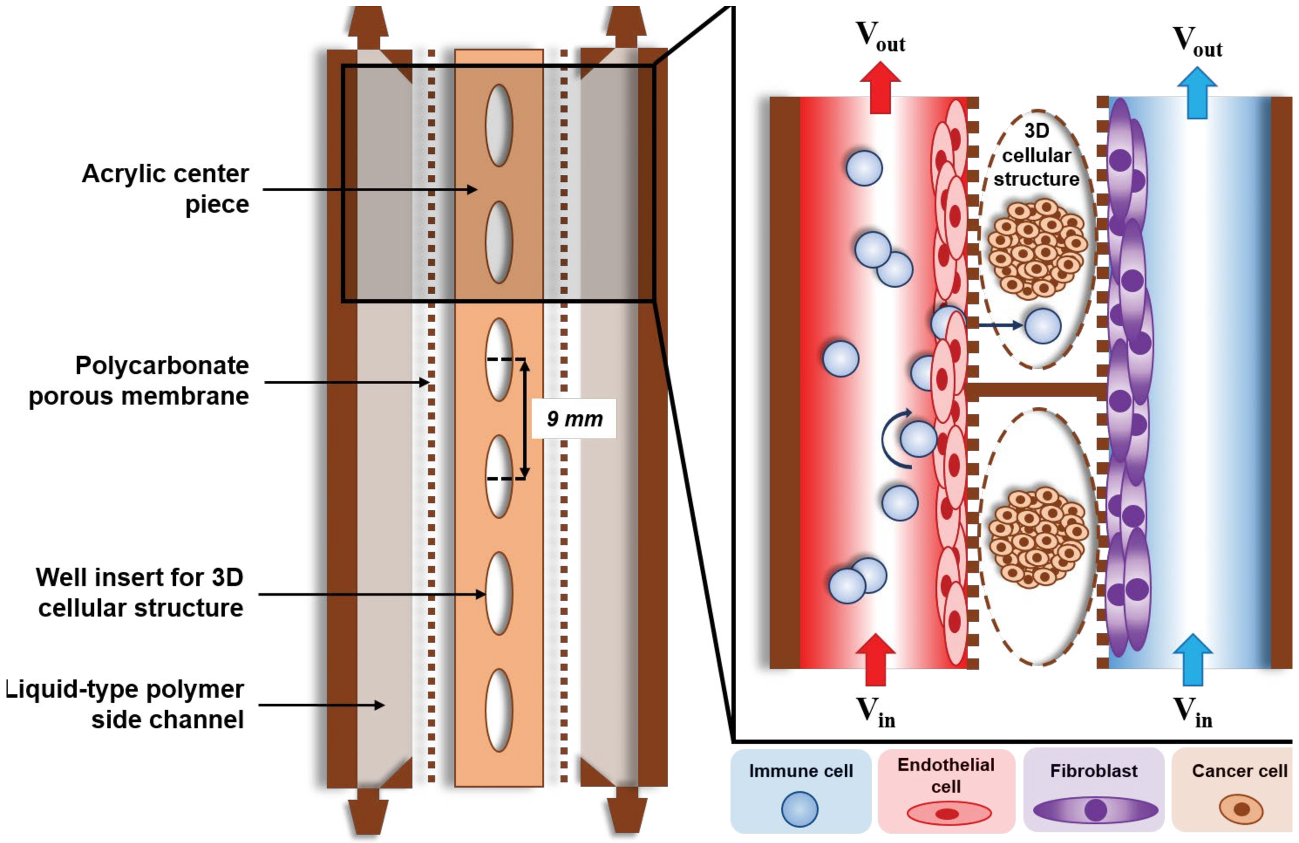


Figure 4: *Picture of an assembled device (left) and schematic concept (right) for a multiple organs platform or Apparatus to Simulate Tumor Environment and Reproduce Organs using an Interactive and Dynamic System (ASTEROIDS).*

Features

gate the role of vasculature mechanics after IR. It has also been reported that irradiated endothelial cells under physiological flow shear conditions have a different response to IR from cells under static culture conditions as demonstrated by differential transcriptomic response, activation of NF-B signaling and oxidative stress and other stem cell biology signaling pathways. Moreover, "plantimal" models could be used to identify predictive biomarkers of such tissue damage. This will bring new insights on the differential vascular radiation response between pediatric and geriatric population and will help in elaborating new medical interventions.

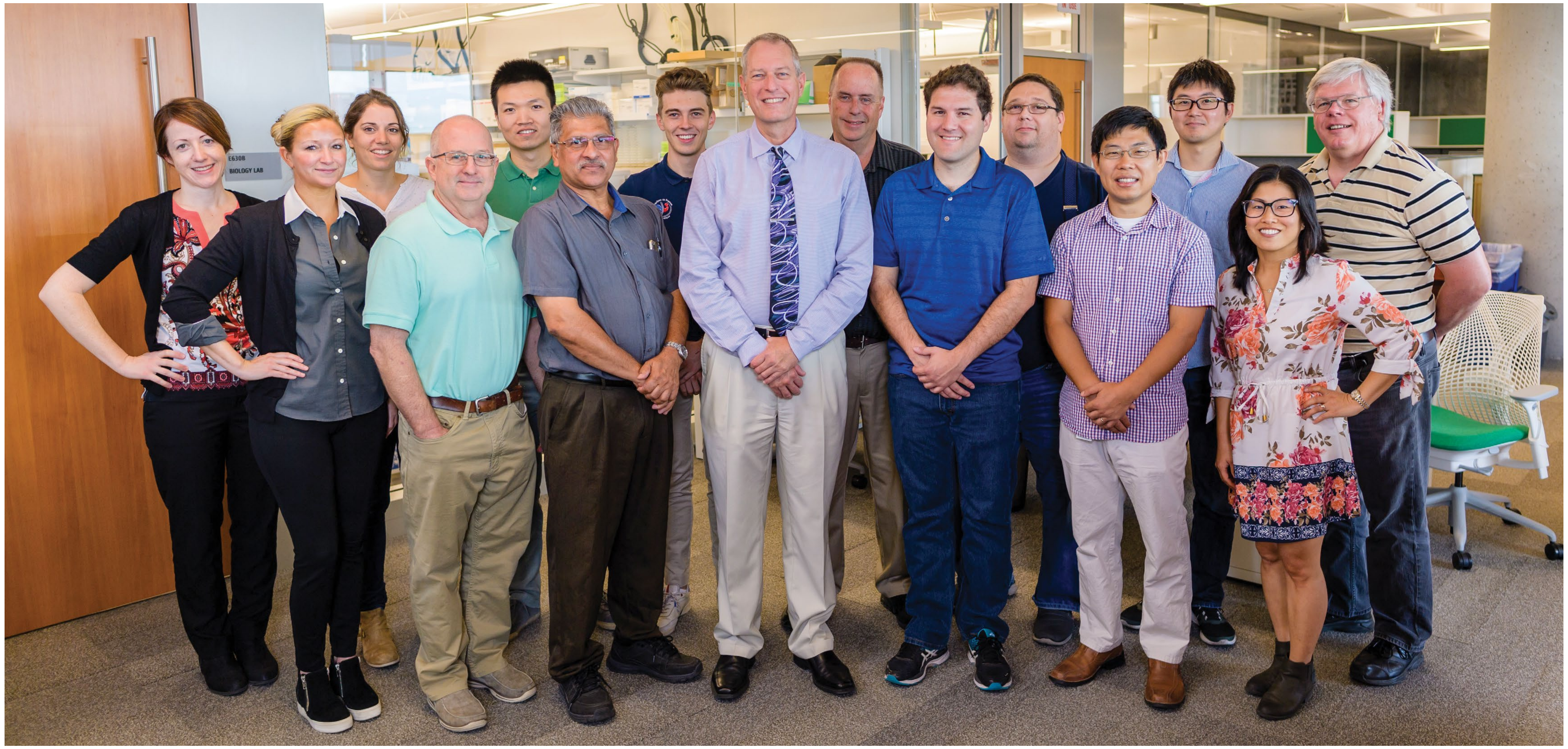


Figure 6: *Staff members at the University of Arizona's Center for Applied Nanobioscience and Medicine located in Phoenix, Arizona.*

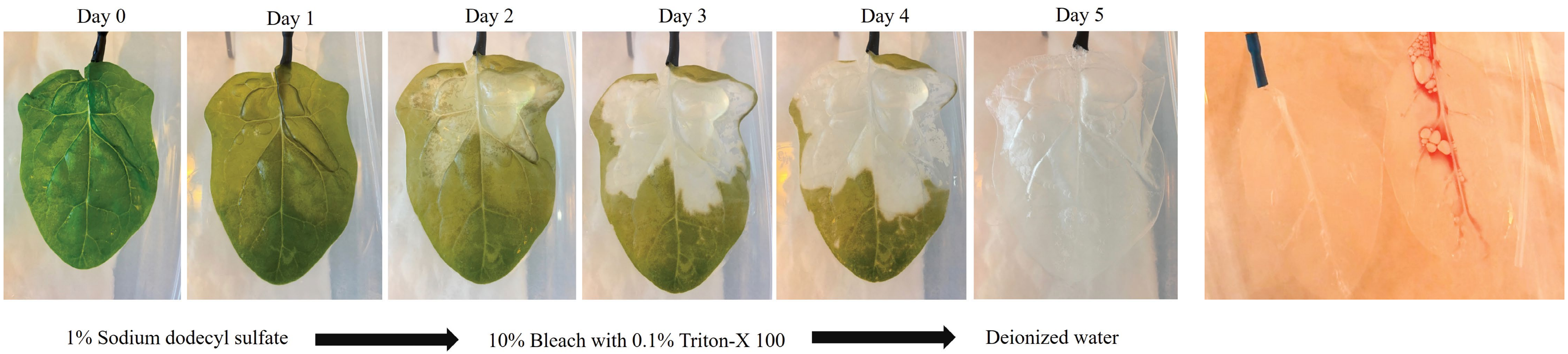


Figure 5: *(left) Chemical de-cellularization process of a plant spinach leaf to produce a tissue scaffold suitable to be recellularized with human cells and (right) blood vessels through the plant vasculature.*

Past Events

Advancing the Design of a ROBUST AND AFFORDABLE RADIATION THERAPY TREATMENT SYSTEM for Challenging Environments

Group photo of the meeting in Washington D.C.

Washington D.C. was the location of the 5th workshop to advance the design of an affordable and robust, yet technically sophisticated linear accelerator-based radiation therapy treatment (RTT) system. The meeting was hosted by the International Cancer Expert Corps (ICEC) and included participants from the STFC Daresbury Laboratory, CERN, Lancaster University (UK), Kings College London Institute of Cancer Policy, Oxford University (UK) and Melbourne University (AU), and ICEC and its Scientific Advisors.

Building on the input from prior workshops and design sessions at the recent meeting in Botswana (March 2019), a core team of physicists, radiation oncologists, and health systems experts convened to further refine design decisions and planning for a new LINAC.

The agenda had presentations and discussion on topics that included:

- ***An overview of the developing science and future implications for Radiation Therapy***
- ***A discussion on the clinical functional requirements for a radiation treatment system designed for challenging environments***
- ***Refinement of the design elements for the LINAC***
- ***A review of trends in cancer treatment and payment, and healthcare system priorities and challenges in both UICs and LMICs***
- ***Opportunities to support a sustainable skilled workforce, for both treatment applications, and service and maintenance requirements in LMICs, through the development of ongoing education and training programs***

“With only 10 % of patients in low-income countries who need radiotherapy having access to this treatment, this project is critically important for improving cancer care.

-Donna O'Brien

Key decisions on many elements of the proposed system were made amongst the group. The initiative is rooted in developing a systems solution for improving cancer treatment in LMICs, an organizing theme for all of the workshops. To ensure that the needs and barriers are understood, a survey was designed for distribution to cancer programs in LMICs to gather more specific information on servicing challenges and downtime. This survey builds on a failure mode analysis that is being conducted in parallel. Ongoing education, training and mentoring programs will be an integral component of the planning for the new LINAC, so each workshop includes a discussion on how these needs are best met and funded.

The workshop concluded with a summary of progress, priorities to be addressed, a proposed timeline, and next steps.

Author:
Donna O'Brien

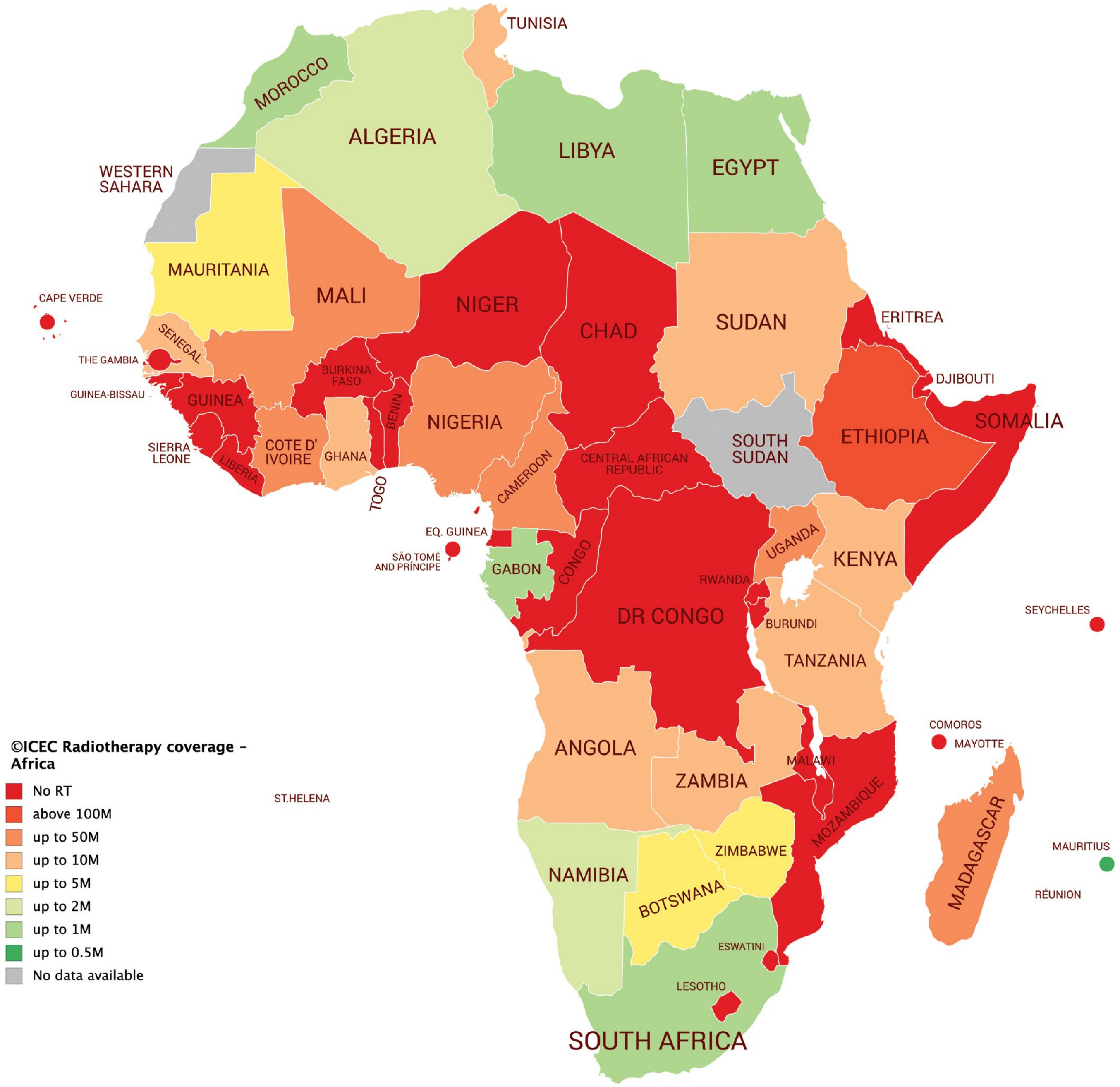
Author:
Larry Roth

Author:
Nina Wendling

> **This project continues to inspire leading physicists, physicians, and healthcare management and health policy professionals to use their expertise to expand access to radiation therapy for those most in need.**
> *-Larry Roth*

McIntosh, Spears, Dosanjh and Chin - animated discussions during the meeting.

> **As the project moves forward, the creativity, positivity and generation of new ideas to address many of the current challenges to deliver radiotherapy in LMICs and challenging environments globally never falters among this group of incredibly talented individuals**
> *-Nina Wendling*



Map showing the number of people per functioning machine in Africa.

Past Events

Final Meeting of the **EU Networking** Initiative '**MediNet**'

The group visiting the experimental irradiation room of MedAustron Facility.

The Networking Initiative 'MediNet' (https://medinet.medaustron.at) is dedicated to bringing together European scientists working on two complementary topical pillars:research on detector instrumentation for radiation therapy (Task 1, coordinated by Peter Thirolf from LMU Munich/Germany) and nuclear tools for ion beam therapy (Task 2, coordinated by Giulio Magrin from MedAustron, Wiener Neustadt/Austria). MediNet is part of the EU-funded Integrating Initiative ENSAR2 within the Horizon 2020 framework, which constitutes a platform for nuclear physics, astrophysics and applications of nuclear science in Europe. MediNet started in 2016 with 25 teams from 9 countries, in the spirit of a truly open network. Today, it has grown to involve 36 teams from 10 countries.

In view of the end of the ENSAR2 project (and thus also of MediNet) in spring 2020, the Final Meeting of MediNet was held on October 7-9 in Austria, at the premises of the Fachhochschule Wiener Neustadt and locally organized from the MedAustron Ion Therapy center. The meeting, attended by 30 scientists, started with the introductory remarks on ENSAR2 aimed particularly for the younger colleagues, combined with a status report on recent network and reporting activities by the task coordinators Peter Thirolf and Giulio Magrin. Besides the individual research activities of the member groups and the organization of the network-wide meetings, MediNet supported workshops, participation in schools and exchange of young researchers amongst the participant groups and presented its activities at international conferences and in publications

.

The following documents, targeting a scientifically interested general public, have been produced as contractual deliverables during the project duration:

1. Specific need and proposed solutions of nuclear tools for medicine

2. Clarifying and adapting nuclear concepts to the medical field

3. Nuclear physics instrumentation for Medicine

4. Use of nuclear physics tools to support biological effectiveness assessment in ion-beam therapy

Paolo Colautti presenting the activities of his institute.

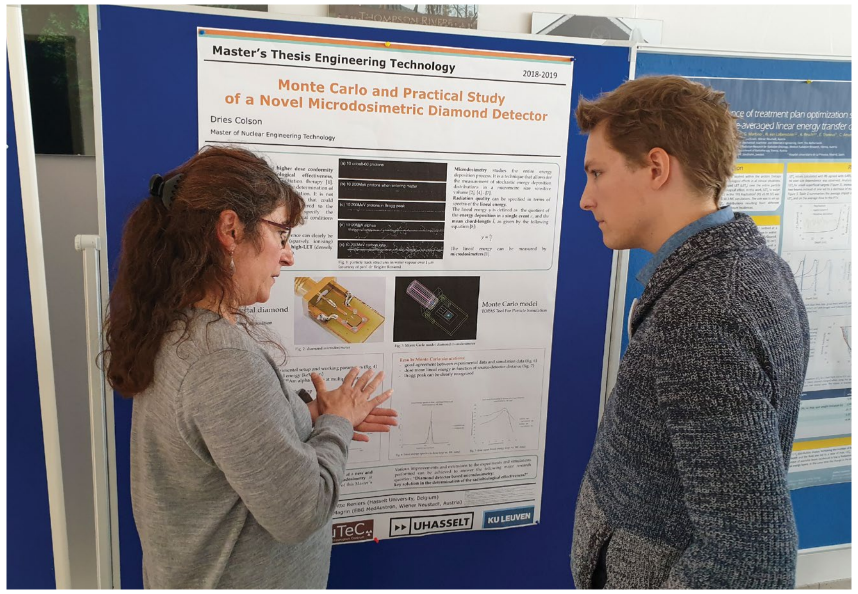
Past Events

In view of the end of the ENSAR2 project (and thus also of MediNet) in spring 2020, the Final Meeting of MediNet was held on October 7-9 in Austria, at the premises of the Fachhochschule Wiener Neustadt and locally organized from the MedAustron Ion Therapy center.

All reports can be downloaded from the MediNet website:

https://medinet.medaustron.at/index.php/Network_documents#MediNet_reports

The scientific part of the final meeting was headed by two invited keynote lectures, dedicated to the focus areas of the two MediNet pillars: for Task 1 Denis Dauvergne (LPSC Grenoble and IPNL Lyon/France) reported on "Online Control for Quality Assurance"; for Task 2 Katia Parodi (LMU Munich/Germany) presented "Opportunities and challenges in particle radiotherapy".



Sharing experiences and ideas about ion-beam detectors.

The individual MediNet member institutions provided status reports, demonstrating the broad scope and high scientific quality of ongoing activities towards the improvement of particle therapy for cancer treatment.

A strong part of MediNet's mission is to promote the career support of young researchers (PhD students and postdocs) by introducing them to the community in an early phase of their career and to provide them with first-hand information beyond the scope of their own projects by encouraging co-funded ex-

The participants of the Final Meeting of MediNet

Past Events

change visits to MediNet partner institutions working on related topics. In this spirit, also the participation of young researchers in the final meeting was promoted by inviting poster submissions and including a poster session into the program. In order to attract the attention of the audience to their posters, 'Elevator Speeches' were invited at the beginning of the poster session. Here each poster presenter was given exactly 60 seconds time to advertise his/her poster, stating why it is a must to be visited. Lively discussions in front of each of the posters followed, serving as a platform for the young researchers to present their work and get into personal contact with more experienced colleagues.

The intense scientific atmosphere with fruitful discussions on present activities was balanced by the accompanying social program. Several opportunities were offered to deepen existing connections among the groups and envisaged further perspectives of collaborations outside the scientific program. An informal "get together" was offered in the evening of the arrival day on Sunday, October 6, and a social dinner concluded the next meeting day in Wiener Neustadt. Finally, a tour of Vienna with its rich history and architectural treasures was organized with the help of a local guide in the afternoon of the second meeting day.

This day also featured a plenary discussion, stimulated by introduction remarks, on the perspectives to continue the successful and fruitful experience of the MediNet initiative beyond the scope of the ENSAR2 project, ending in March 2020. Since the envisaged successor of ENSAR2, the H2020 Integrating Initiative ERINS, was not approved in the EU reviewing procedure, alternatives were discussed, ranging from a COST action to a Marie Curie Innovative Training Network (ITN). There was consensus amongst the MediNet community that the successful path that was followed within the network should not come to an abrupt ending with the completion of the ENSAR2 framework in March 2020.

Authors:

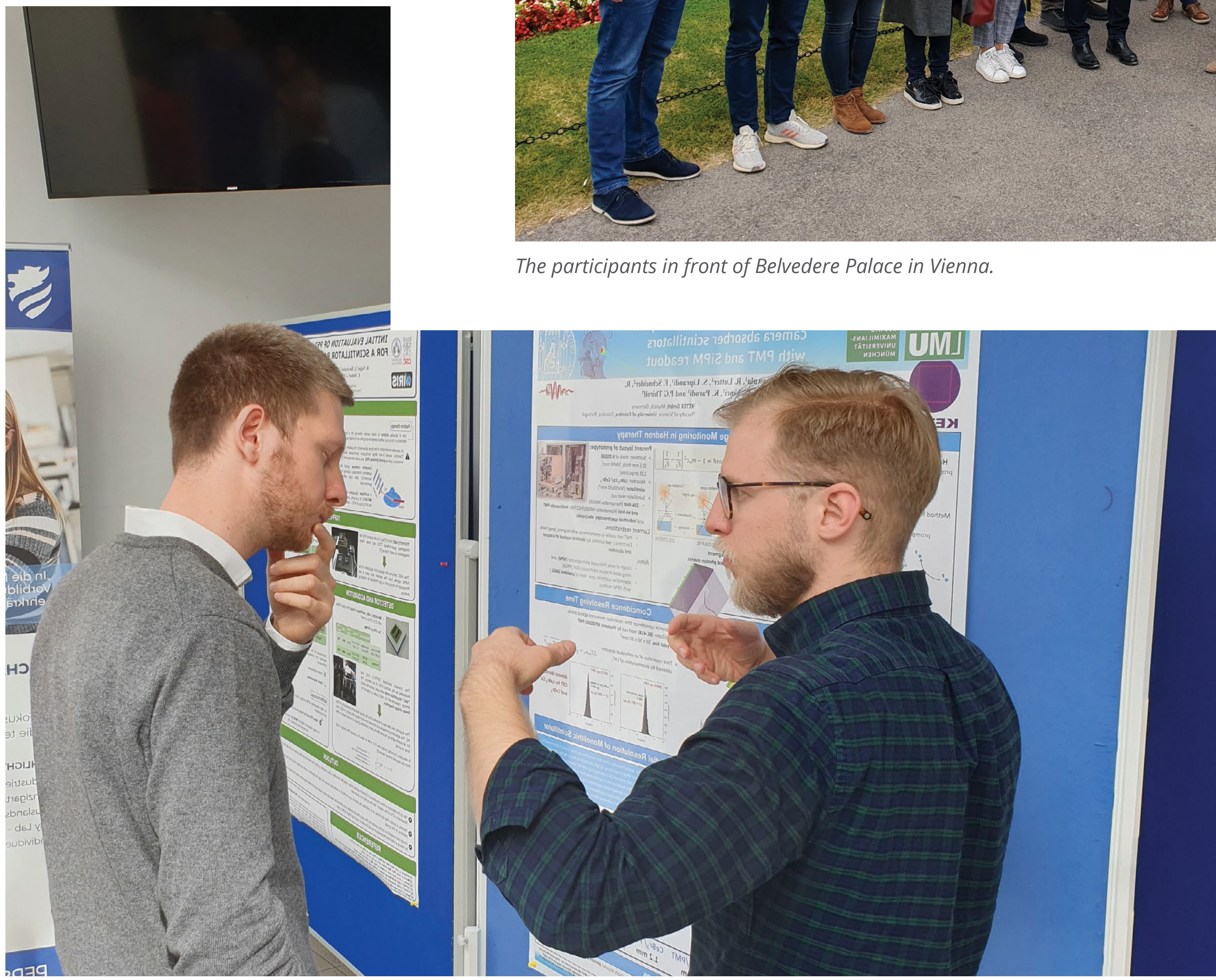
Peter Thirolf

Giulio Magrin

Presentation of the posters with 60-second 'Elevator Speeches'.

The participants in front of Belvedere Palace in Vienna.

The group of MediNet Task2 during a scientific discussion.



An intense conversation during poster session.

ENLIGHT PARTICLE THERAPY STAND

taking part in the

CERN Open Days 2019

CERN regularly opens the doors of its laboratories to the general public with event gathering thousands of visitors interested to explore the accelerators and experiments looking for the mysteries of the universe. Once again ENLIGHT had this great opportunity to demonstrate, one of the applications of CERN technologies in hadron therapy.

During an entire weekend on the 14th and 15th of September volunteers working at CERN, CERN alumni and helpers made it possible to host more than 70 000 visitors. This incredible initiative took place on all CERN sites – the two main campuses Meyrin (Switzerland) and Prevessin (France) as well as the detector points.

The ENLIGHT (European Network for Light Hadron Therapy) stand was kindly hosted by the EHN1 experiment which is one of CERN's largest experimental buildings, housing multiple experimental zones and four-particle beamlines. Visitors could first experience the real research and experimentation followed by an illustrative interactive explanation understanding the concrete application to learn the basic principles of particle therapy. Based on particle accelerators and particle detectors and as well computers and physics simulations, the hadron therapy is becoming increasingly important for the treatment of cancer and visitors could learn more about this alternative to the conventional radiotherapy treatment.

Explaining the science behind Hadron Therapy.

Group photo of all ENLIGHT volunteers.

While a lot of the visitors were rushing to find a spot for a guided tour at the building exploring the secrets of the dark matter or visiting the cloud chamber, others were instantly attracted by ENLIGHT platform where screens were showing videos of a hadron therapy facility and its interactive map. Another attractive point of the particle therapy stand was an open-source software for radiation treatment planning, a programme called matRad*. On a specially dedicated computer, the visitors could experience simulating real treatment process comparing different types of radiation with photons/electrons, protons and carbon ions.

CERN open days event was everything from expressing deep interest to science to demonstrating teamwork and collaboration. Not only that the ENLIGHT volunteers were receiving hundreds of people in groups and individually which they carefully hosted and warmly revealed important facts about what hadron therapy is and how this is related to CERN and medical applications, but they were raising awareness. Raising awareness about the importance of having OPEN science, research, network and collaboration at an international and multidisciplinary level.

*http://e0404.github.io/matRad/

Author:
Petya Georgieva

CERN Open Days ENLIGHT Particle Therapy stand in numbers:

2 days

ENLIGHT

10 ENLIGHT **volunteers**

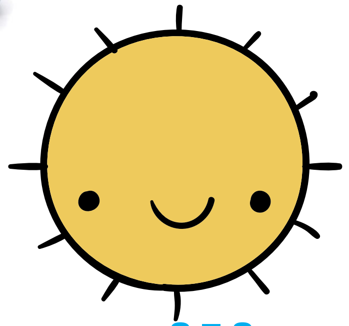
3 screens

18 litres of water

70 000 PEOPLE **visited CERN**

x12 hours of presence **nonstop on site**

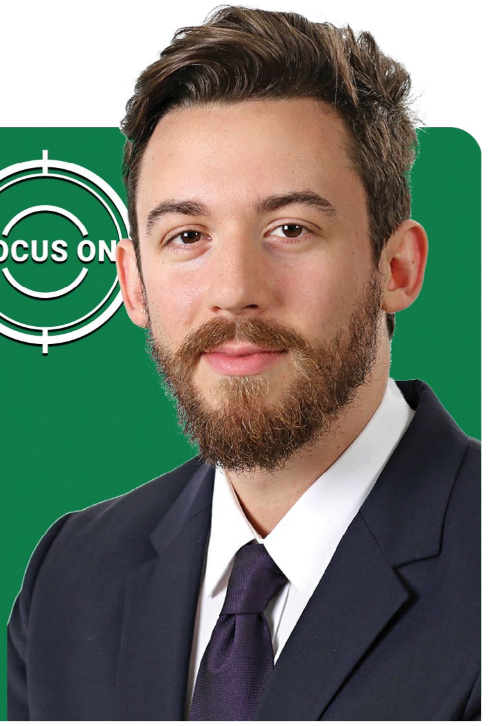
30 **croissants**



1 milion **smiles, at least!**

Stewart "Mac" Mein

PhD Student at the Heidelberg Ion-beam Therapy Center (HIT) and the German Cancer Research Center (DKFZ), Germany



"My internship in particle therapy during my master's coursework was the first time I observed medicine, physics, and engineering ally themselves outside of a textbook. My fascination with real-world applications led me to continue with doctoral studies at Heidelberg University, working with physicians and physicists at the Heidelberg Ion-beam Therapy Center (HIT) to translate novel particle therapy modalities to the clinic."

Conventionally, treatment planning in radiotherapy is dictated by and restricted to the use of commercially available software and models. So our most recent efforts in the Biophysics in Particle Therapy group (BioPT) focus on translating next-generation biophysical models and techniques into clinical practice.

In response to this year's AAPM TG-256 report calling for an immediate clinical restructuring of RBE handling for proton therapy, we developed and validated a novel dose calculation engine — FRoG (Fast Robust dose calculation on GPU). Functional with four-particle beams (p, 4He, 12C and 16O), FRoG is currently supporting clinical operation at four facilities across Europe, providing biophysical metrics beyond the capabilities of a clinical TPS, i.e., LETd and effective dose using variable RBE schemes with biophysical, mechanistic and/or phenomenological models (Sci. Rep. 10.1038/s41598-018-33194-4).

At this year's annual ENLIGHT summit, we presented our most recent aim with the FRoG system and showcased the PRECISE TPS for particle therapy treatment planning with single and combined ion-beam optimization strategies. Presently, protons and carbon ions are the leading hadron therapy modalities with numerous studies comparing their unique characteristics, benefits and tradeoffs. Neither protons nor carbon ions can be considered as the "perfect" particle and the determination of which particle is best suited for a particular treatment is circumstantial. By unifying the two clinical beams and appropriately optimizing their features, we propose combined ion-beam with constant RBE (CICR) particle therapy with the following aims:

1. **Reduce the highly variable biological uncertainty and distal LET gradients in heavy-ion therapy.**
2. **.Enhance the therapeutic ratio and target conformity of light ion fields like protons.**

Alongside my colleague Benedikt Kopp and led by PD Dr Andrea Mairani (BioPT Group Leader), we've made efforts in multi-particle optimization strategies by using overlapping forward- and inverse-wedge field configurations, with a high and low LET particle dominating the proximal and distal field, respectively. In short, this multi-ion beam approach can produce nearly uniform physical dose, RBE and, in turn, effective dose distributions.

We demonstrated both dosimetry and through in vitro clonogenic assay that CICR treatments can provide more biophysically robust plans compared to conventional carbon ion therapy, with target RBE values of ~1.5, roughly a 40% increase compared to protons alone. This work also constitutes the first verification of multi-ion particle therapy in a clinical setting. As preparations continue to bring hospital-based heavy ion therapy centres in North America, implementation of CICR-based treatment schemes can provide the motivation to establish the multi-particle facility as opposed to single modality solutions.

For more information regarding this work and related projects, visit us on our website:

https://www.klinikum.uni-heidelberg.de/radiologische-klinik/radioonkologie-und-strahlentherapie/forschung/forschungsschwerpunkte/biophysik-in-der-partikeltherapie/

Sebastien Curtoni

PhD student at Université Grenoble-Alpes

Laboratoire de Physique Subatomique et Cosmologie (LPSC), CNRS/IN2P3

Towards a beam-tagging diamond hodoscope for online ion range monitoring

Ion range uncertainties remain one of the main factors still limiting a full exploitation of ions ballistics in particle therapy. These uncertainties can arise from treatment planning but also during the treatment sessions. At present, range security margins take into account these uncertainties but this tends to lower down the highly localised dose deposition capability of the technique. An online range monitoring system would not only allow reducing the range margins but would also make it possible to detect potential discrepancies between the actual and the prescribed range during a treatment session.

Several online range verification techniques are currently under investigation. They mainly rely on the detection of secondary radiation emitted by the patient. During the treatment session, some of the ions are involved in nuclear collisions with body nuclei along their path, which leads to the emission of gamma rays. The so-called Prompt-Gamma photon (PG) emission is linked to the ion path, occurs almost instantaneously after the collision – within a picosecond - and PG propagates in straight lines with a high probability to exit the patient body without interacting. Imaging prompt-gamma emission during the session is, therefore, a key issue to obtain a piece of online actual range information.

As a PhD student in LPSC Grenoble, I am part of the CLaRyS collaboration gathering four laboratories developing Prompt-Gamma Imaging systems. The originality of the CLaRyS prototypes is the use of an additional beam-tagging hodoscope. This detector has to be set at the accelerator output. It aims to provide spatial and temporal tagging of incoming ion bunches. The transverse position information produced is used for the image reconstruction process. Besides, we can measure the time interval between the ions detected by the hodoscope and the PG detected by the gamma detector. This information enables us, at first, to discriminate the gamma signal from an important neutron-induced background. With an excellent overall time resolution (< 100 ps) and if we reduce the beam intensity to detect single protons, we can even detect range shifts on the basis of timing measurements uniquely.

In this context, my work is to develop and characterize a beam-tagging hodoscope demonstrator made of artificial diamonds. Diamond is a very interesting material for this application. It can be used as a detector, provides a low-noise and very fast response while being known for its radiation hardness. These intrinsic capabilities allow us to plan the development of a position-resolved high count-rate diamond hodoscope. We have tested various qualities of diamond crystals, both at the lab and in experiments at accelerator facilities. We have also developed a first hodoscope demonstrator made of a 1 cm^2 double-sided strip diamond detector. The characterization tests we performed with X-rays, protons and carbon ions all highlighted time resolutions better than 100 ps, with an excellent 18 ps time resolution with carbon ions. We also obtained good detection efficiencies, with both protons and X-ray bunches. The next step of our project is to build a four-diamond double-sided strip detector, covering a larger sensitive area. We will characterize its performance with proton and carbon ions beams.

Olivier Guipaud

Researcher in radiobiology at the Institute for Radiological Protection and Nuclear Safety (IRSN), Fontenay-Aux-Roses, France

Molecular profiling of human primary endothelial cells exposed to high doses of carbon ions in comparison with photon irradiation

During the almost 20 years that I have been working in the field of radiobiology, I have witnessed considerable progress in radiotherapy stemming from the development of increasingly powerful techniques and technologies designed to treat and cure patients.

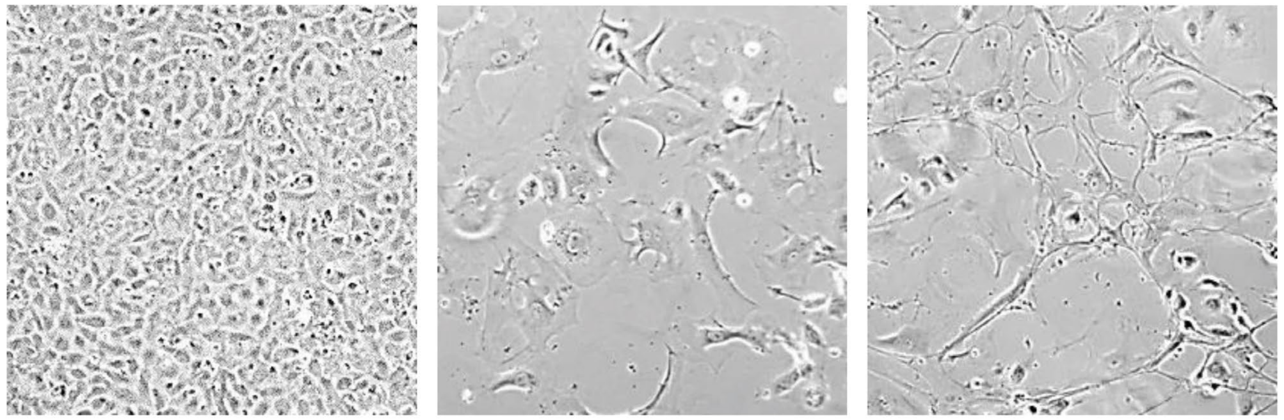
Now more than a hundred years old, radiation therapy has advanced substantially in the last two decades, driven by progress in biology, physics, technology, computer science and imaging. The accuracy of dose deposition has improved remarkably, while the possibilities of combination therapy have flourished, offering a plethora of opportunities for radiation therapists. Patients today are routinely treated with IMRT. However, new technologies like SBRT and accelerated particle therapy, which are increasingly affordable, have led to significant and rapid progress. Promising and revolutionary techniques, such as flash and minibeam radiotherapy, are emerging, and applications for associating them with accelerated ion therapy are being seriously considered. With the availability of many chemical and biological treatments, including immunotherapy and targeted therapies, the theoretical number of treatments associated with the different radiotherapy techniques is increasing incredibly.

However, in radiotherapy, the dose that can be safely delivered to organs at risk still limits the dose delivered to tumours. Since the effect of new radiotherapy modalities and combinations of treatments on normal tissues cannot be easily predicted, there is an urgent need to devise simple and rapid means to evaluate the impact of these treatments. This is what we are currently developing at IRSN's Radiobiology of Medical Exposure Laboratory.

Because of their central role in the response of tumours and surrounding normal tissue to radiation, we use vascular endothelial cells, the inner monolayer of all body vessels, as a tool in our investigations. Yet, the pathophysiological fate of irradiated endothelial cells may play a much larger role than cell death itself. The challenge of our research is to decipher and model the molecular pathways involved in this dysfunction. We plan to utilize this knowledge to understand, compare and, in the future, predict the biological impact of different radiation modalities used in radiotherapy.

The work I presented at the annual ENLIGHT meeting is a piece of the puzzle that we are completing. We exposed cells to high-energy carbon ions in the GANIL facility (Caen, France) and determined their gene expression profile. Interestingly, we found similarities after irradiation with carbon and photons at high doses, but differences at 2 Gy, a common dose in fractionated radiotherapy. Surprisingly, 5 to 10% of the seeded cells were still present and metabolically active up to three weeks after exposure to carbon ions (Figure), as for irradiation with photons, whereas we thought we would no longer observe cells at this dose considering the 2- to 3-fold greater biological effectiveness of carbon ions as compared with X-rays.

Our results show that the effect of irradiation on cells is more than death itself. Under physiological conditions, some cells surviving irradiation could persist in vivo and express a pathological phenotype involved in the adverse effects. Overall, this methodology will potentially deliver interpretable hypotheses needed to help radiobiologists provide tools to predict the adverse effects of radiotherapy.



Primary (normal) human endothelial cells three weeks post-irradiation

Focus On

Future Events

NAME OF THE EVENT	DATE OF EVENT	PLACE OF EVENT
03-07 April 2020	ESTRO 39 Annual Meeting	Vienna, Austria
9-14 May 2020	PTCOG 59 Annual Meeting	Taipei, Taiwan
26-30 May 2020	LXX International Conference «NUCLEUS – 2020. Nuclear physics and elementary particle physics. Nuclear physics technologies»	Saint-Petersburg, Russia
15-19 June 2020	Eighth International Conference on radiation in various fields of research	Herceg Novi, Montenegro
21-26 June 2020	29th international conference on atomic collisions in solids & 11th international symposium on swift heavy ions in matter	Helsinki, Finland
22-24 June 2020	ENLIGHT 2020	Bergen, France
25 -28 October 2020	ASTRO's 62nd Annual Meeting	Miami Beach, Florida
31 October – 07 November 2020	2020 IEEE Nuclear Science Symposium and Medical Imaging Conference	Boston, Massachusetts

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THE EUROPEAN NETWORK FOR LIGHT ION HADRON THERAPY

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

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

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

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