Life.
Science.

SOLUTION PAPER

ConformalFLASH®

Maximizing the benefits of proton FLASH radiotherapy

FURTHER · FASTER · GENTLER

Introduction

Cancer treatment outcomes have continuously improved with radiation therapy innovations. However, many tumors remain radioresistant to conventional radiotherapy delivered at doses tolerated by surrounding normal tissues. This underscores an unmet clinical need for innovative approaches to deliver more effective tumor doses without increasing toxicity to normal tissues. [1,2]

Proton therapy addresses this need through its unique Bragg peak depth-dose characteristics, which minimize delivery to healthy tissues around the target volume and facilitate the escalation of tumor doses, improving local control and patient quality of life. [3]

FLASH radiotherapy, an emerging cancer treatment approach, delivers radiation at ultrahigh dose rates, offering similar tumor control to conventional radiotherapy but enhanced protection of healthy tissue through the FLASH-sparing effect. Among various FLASH modalities, proton therapy is gaining particular interest due to its superior dosimetric and delivery characteristics. [4]

In line with its mission to protect, enhance and save lives, IBA is developing ConformalFLASH® - the next evolution in proton FLASH therapy. It combines FLASH dose rates irradiation with the use of highly conformal fields, benefitting from the sparing effects of the Bragg peak and intending to expand the therapeutic window for cancer treatment.

Shaping the future of Proton Therapy.

100% committed to Proton Therapy.

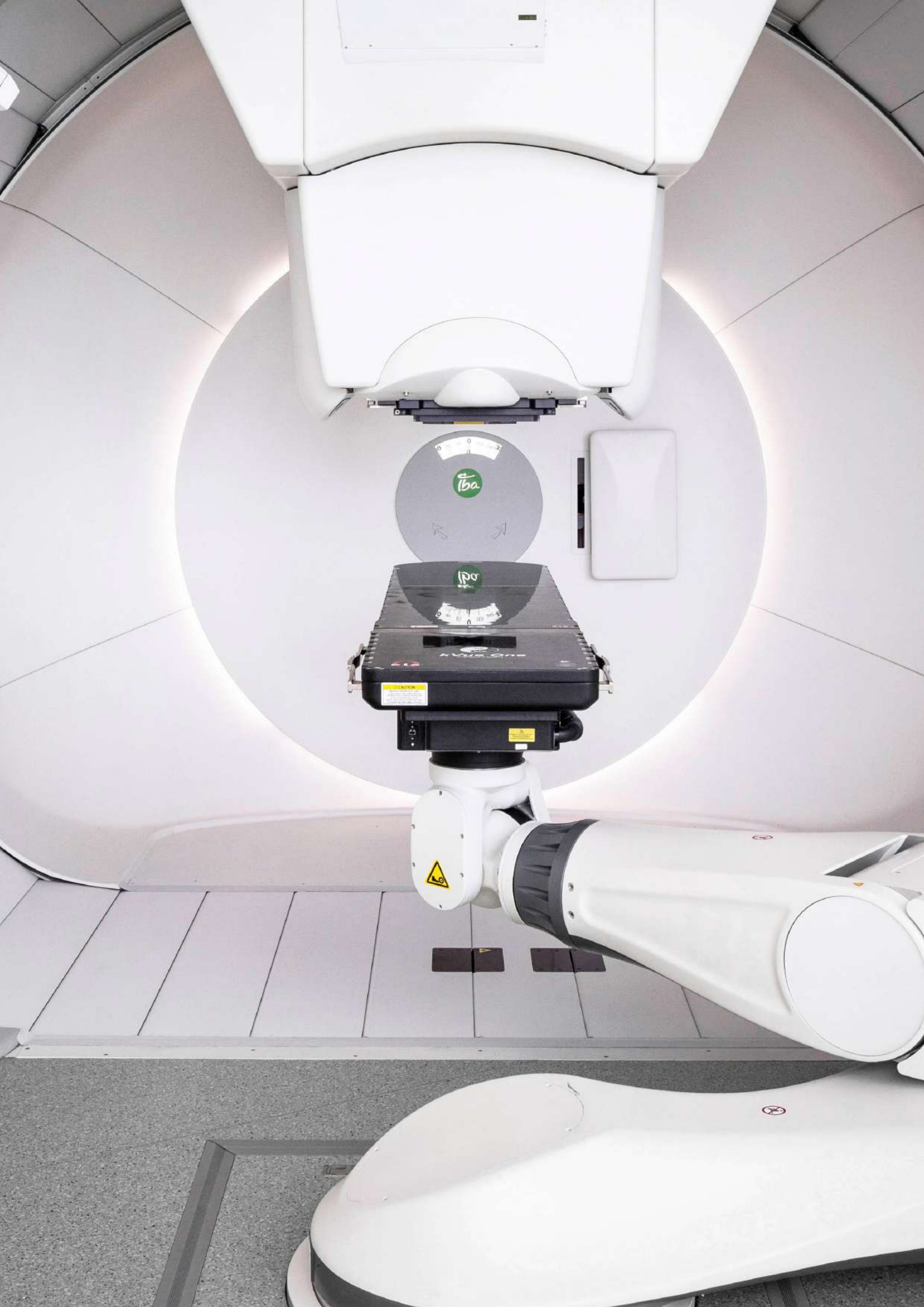
The most knowledgeable community.

IBA prioritizes ConformalFLASH® development through 3 strategic pillars:

- **Shaping the future of proton therapy –** by continuously developing high current delivery and superior beam shaping technologies.
- **Fully committed to proton therapy –** by creating a dedicated product ecosystem, in collaboration with strategic industrial partners.
- **The most knowledgeable community –** by nurturing the ConformalFLASH® Alliance with FLASH pioneers.

In this Solution Paper, we provide an overview of FLASH therapy in radiation oncology and focus on the advantages of ConformalFLASH® and IBA's commitment to FLASH research and innovation. We also discuss future research and clinical development directions and how ConformalFLASH® contributes to future-proofing a proton therapy investment.

ConformalFLASH® is the registered brand of IBA's Proton FLASH irradiation solution, which is currently under research and development. ConformalFLASH® will be available for sale when regulatory clearance is received. Due to a continuous research and development program, IBA reserves the right to make changes in design, technical descriptions, and specifications of its products without prior notice. Some features are under development and may be subject to review by competent authorities.



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FLASH therapy in radiation oncology

What is FLASH therapy?

FLASH therapy is a novel radiation treatment technique that is gaining significant interest due to its potential to revolutionize cancer treatment. FLASH therapy delivers ultra-high dose rates (UHDR) of radiation, typically exceeding 40 Gy/second, within extremely short time frames. This technique differs from conventional radiotherapy, which operates at dose rates of approximately 5 Gy/minute (2-10 Gy/minute).[4,5]

The distinguishing feature of FLASH therapy is the "FLASH effect," a phenomenon by which the ultra-high dose rate of radiation reduces the toxicity to healthy tissues, commonly associated with conventional radiotherapy, while maintaining the efficacy of tumor control. This effect has been demonstrated in numerous preclinical studies and could be particularly relevant for patients with recurrent tumors or those requiring reirradiation, where toxicity from conventional radiotherapy often limits treatment options.[2,4]
FLASH dose rates expand the therapeutic window, providing isoeffective tumor control with significantly reduced toxicity compared to conventional dose rates, offering new solutions for radioresistant tumors and expanding indications in tumors surrounded by radiosensitive tissues. Moreover, the ultra-fast delivery time of FLASH could help reduce the effect of respiration-induced tumor motion and overall treatment duration, and has been shown to reduce the depletion rate of lymphocytes compared to conventional fractionated radiotherapy.[1,2,6,7,8]

Some of the main advantages and disadvantages of FLASH compared to conventional radiotherapy are summarized in Table 1.

	FLASH radiotherapy
Strenghts	**Biological** • Reduced acute toxicity, reduced and delayed late toxicity.[9,10] • Tumor control effects similar to conventional dose rates. • Dose escalation possibility for radioresistant tumors. • Lymphocyte sparing and possible immunotherapy-radiation combinations. **Physical** • Full treatment of one fraction in milliseconds. • Reduced effect of tumor motion (respiration-induced, patient movement...). • Could enable hypofractionated treatment regimens that would reduce treatment times and potentially decrease treatment cost per patient.[11]
Weaknesses	• The optimal dose rate for clinical application is not yet known. • The effectiveness of treatments for different diseases is not yet clear. • Requires patient-specific accessories.

Table 1. Main advantages and disadvantages of FLASH compared to conventional radiotherapy. [Adapted from Yan et al, 2024]

The potential of FLASH in radiation oncology

The benefits of ultra-high dose rate radiotherapy and the FLASH effect were noted in a 1982 study, in which Hendry et al. irradiated the tails of un-anesthetized mice at different dose rates and observed an induced resistance to epithelial necrosis. Research stalled until 2014, when Favaudon and colleagues first described what we know today as the FLASH effect. Their results demonstrated that short pulses (≤500 ms) of radiation delivered at ultra-high dose rate (≥40 Gy/s, FLASH) prevented acute pneumonitis and late lung fibrosis in mice, unlike conventional dose-rate irradiation (≤0.03 Gy/s). Moreover, FLASH irradiation spared normal smooth muscle and epithelial cells from acute radiation-induced apoptosis while being as efficient as conventional dose-rate irradiation in repressing the tumor growth, thus increasing the differential response between normal tissue and tumors. [2,12]

Since then, the isoeffective tumor control and normal tissue sparing by the FLASH effect has been investigated and confirmed by different institutions and for different beam modalities (electrons, photons, protons), species (mouse, rat, cat, mini pig, zebrafish), organs (brain, gastrointestinal tract, lung, skin, bone, blood), and endpoints (lethal dose, skin and gut reactions, neurologic tests), including early and late toxic effects (Figure 1). [2,4,6,8,13]

Recent studies, particularly in proton therapy, suggest that combining precise dose deposition with ultra-high dose rate exposure may further enhance therapeutic outcomes: [6]

- The first *in vivo* proton FLASH delivery experiments demonstrated significant reduction of acute cell loss and late fibrosis, and improved survival in a mouse model of pancreatic cancer. The subjects were irradiated with protons at FLASH rates, compared to standard rates. Tumor growth inhibition was preserved between the two modalities. [9]
- More recent experiments conducted by the same team demonstrated the benefits of FLASH proton delivery in a mouse model of head and neck cancer: FLASH proton radiotherapy improved multiple pathophysiologic toxicities associated with irradiation, including salivary gland dysfunction and oral mucositis. It also significantly improved overall survival while having similar tumor-controlling efficacy as standard proton therapy rates. [14]

In parallel to the preclinical work, the first treatment of a human patient with T-cell cutaneous lymphoma with electron FLASH showed positive outcomes in both the tumor and the skin. [14] More recently, the first clinical trial evaluating the feasibility of FLASH proton therapy for symptomatic bone metastasis treatment (FAST-01) confirmed the clinical viability of proton FLASH delivery, with treatment efficacy and adverse event profiles comparable to conventional photon radiotherapy. Building on these findings, other ongoing trials continue to explore the clinical therapeutic potential of different beam modalities for different types of cancers, including chest bone metastases (FLASH-02, using protons), melanoma (Impulse trial, using electrons), basal cell carcinoma and squamous cell carcinoma of the skin (LANCE, using electrons), while aiming to elucidate optimal dosing strategies to enhance tumor control and mitigate radiation-induced adverse effects. [2,4,7,13]

While these trials highlight the potential of FLASH therapy, further research is essential to explore its application to solid tumors such as those in the brain, lung, and gastrointestinal tract. FLASH's ability to reduce side effects makes it a promising option for pediatric treatments also, but challenges remain in standardizing techniques, understanding its biological mechanisms, and optimizing its use for deep-seated tumors. [2,7]

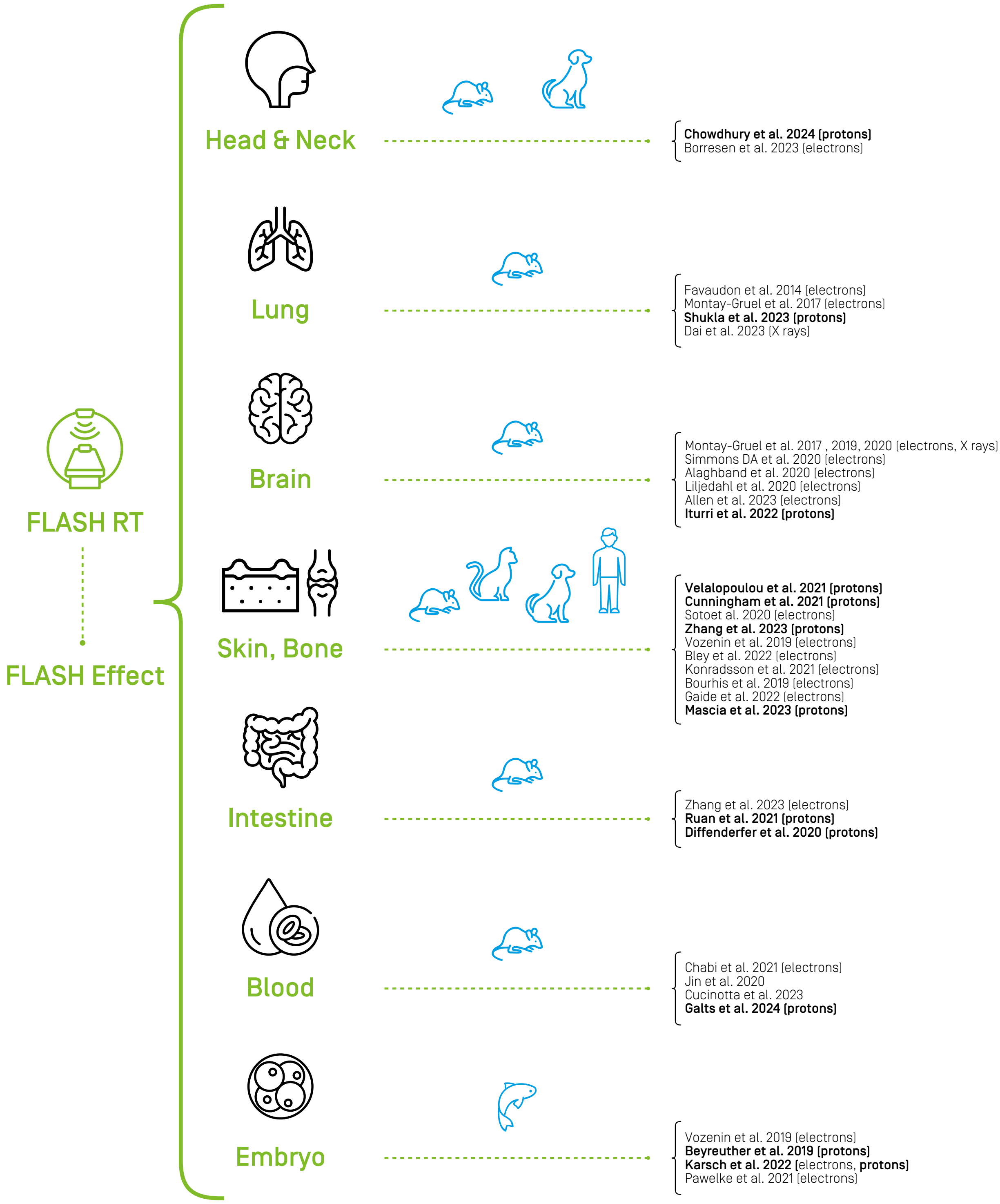


Figure 1. Overview of the preclinical and first-in-human clinical evidence about the ultra-high dose rate FLASH effect (Adapted from Borghini et al., 2024)

FLASH therapy milestones

2014 — First evidence of the normal tissue sparing FLASH effect

2019 — Treatment of a first patient with FLASH electron therapy

2020 — First *in vivo* proton FLASH delivery on an IBA Proteus® platform

The current state of FLASH research

The rise of FLASH has driven considerable research efforts to understand its radiobiological mechanisms and optimize its clinical implementation. Ongoing investigations also focus on modifying existing treatment systems, optimizing the beam and field properties, developing new hardware and software solutions, and refining biological models to better understand the therapeutic potential of FLASH in the treatment of tumors. [4]

Beyond studying its tumor control effectiveness and normal tissue sparing in preclinical and clinical studies, FLASH research has also focused on better understanding optimal physical parameters and biological implications. In recent years, studies have focused on:

1 - The radiobiological mechanisms of the FLASH effect. Several biological mechanisms have been proposed to explain the FLASH effect, including: [2,7]

- ***Oxygen depletion –*** is one of the first mechanisms proposed for the FLASH effect, and it hypothesizes that FLASH irradiation protects normal tissue by rapidly depleting intracellular oxygen, increasing its resistance to radiation. Tumors, which are already hypoxic, do not experience this protective effect, maintaining sensitivity to radiation.
- ***Free radicals –*** their transient concentration and their rate of recombination would be increased by FLASH, thereby modifying the concentration of reactive oxygen species (ROS) formation that lead to cell damage or death. Normal cells can effectively and rapidly eliminate ROS and reduce cell toxicity, while tumor cells, having weaker antioxidant defenses and higher metal ions load, suffer amplified peroxidation chain reactions.
- ***DNA damage –*** in normal cells, it seems to be reduced after FLASH irradiation, while tumor cells show comparable damage between FLASH and conventional dose-rate irradiation, which may explain the comparable tumor control effects.
- ***Immune response –*** FLASH irradiation was associated with lymphocyte sparing, stimulation of systemic immune response, and reduction in the levels of cytokines involved in radiation-induced inflammatory processes, as well as in TGF-ß expression and tumor-enhancing signaling, thereby promoting anti-tumor immunity.

2 - The beam modalities, including electrons, photons, protons and heavy ions, and their advantages and disadvantages, that are summarized in Table 2.[7]

	+ ADVANTAGES	- LIMITATIONS
LOW ENERGY ELECTRONS	• Easy to implement with existing linear accelerators • Require manageable radiation protection measures • Used in most pre-clinical studies	• Limited tissue penetration depths [1-7 cm for 4-20 MeV] • Use restricted to superficial tumors or require intraoperational irradiation • Less conformal dose distributions, with broad lateral penumbra
PHOTONS	• Potential for treating deep-seated tumors • Familiar modality for clinicians	• Lack of preclinical data • Ineffective in radioresistant cases • Inefficient electron-to-X-ray conversions
PROTONS	• Greater penetration depth [4-32 cm for 70-230 MeV] • Improved dose conformality if using the Bragg peak • Higher relative biological effectiveness [RBE] compared to electrons and photons • Accuracy in tumor targeting and energy delivery, optimized tissue protection and side-effects mitigation • Particularly advantageous for tumors near vital organs or sensitive tissues • Minimal modifications needed in current equipment to achieve FLASH conditions	• Uniform dose rates across targets are challenging to achieve • Limited biological data
HEAVY IONS	• Improved dose conformality if using the Bragg peak, as with protons • Higher relative biological effectiveness [RBE] compared to conventional modalities	• Expensive technologies and limited facilities • Fragmented dose deposition beyond the distal falloff • Insufficient preclinical data

Table 2. Different beam modalities used for FLASH, their advantages and limitations. [6,7,15,16]

3 - Dosimetry is one of the challenges of FLASH research, due to the necessity to characterize the dosimeter's response to the UHDR and as current radiotherapy dosimetry protocols are not designed for such conditions. Medical societies around the globe are currently working on recommendations and guidelines for FLASH dosimetry, while industry leaders, such as IBA Dosimetry, work on developing UHDR-compatible dosimetry products.[16]

4 - Dose conformation to the target volume is also a great challenge in FLASH and depends greatly on the beam modality. The precise beam-shaping methods, including multileaf collimators [MLCs] or pencil beam scanning [PBS] and gantry movements, may require more time and introduce complexities in maintaining UHDR.[15]

5 - Treatment planning systems (TPS) must be adapted to include dose-rate objectives and ensure compatibility with FLASH delivery. However, there are still challenges in optimizing to achieve dose conformality in large volumes while maintaining high dose rate in the volume.[15]

While FLASH therapy expands the therapeutic window, opening the possibilities for dose escalation, the compensating effect of hypofractionation in some cases, and the reduction of long-term toxicity, additional studies are needed to translate the FLASH potential advantages into routine clinical practice.

IBA stands at the forefront of these research and development efforts, pushing the boundaries of FLASH proton therapy through the development of ConformalFLASH® and the engagement in long-standing partnerships with leading academic and clinical institutions and strategic industrial partners.

These collective efforts aim to fill in the gaps in the need for specialized equipment, robust dosimetry methods, and clinical protocols defining the dose and dose rate to prescribe for successful FLASH proton therapy.

ConformalFLASH®: IBA's innovative approach in FLASH proton therapy

Definition of ConformalFLASH®

ConformalFLASH®, developed by IBA, is a proton FLASH delivery technique that integrates the tissue-sparing benefits of FLASH radiotherapy with the precise dose-shaping capabilities of the proton Bragg peak. To do so, IBA is proposing to use Pencil Beam Scanning (PBS) with a patient-specific ridge filter, called the Conformal Energy Modulator (CEM) (Figure 2) to adjust the beam energy, shape the beam, and control its proximal and distal surface as well as the flatness of the spread-out Bragg peak (SOBP). Additionally, the range shifter ensures that the distal fall-off of the SOBP matches the distal surface of the Planning Target Volume (PTV), and the collimator reduces the lateral penumbra. This innovative approach aims to widen the therapeutic window by delivering FLASH dose rates while maintaining the precision of the Bragg peak throughout the tumor volume, minimizing damage to healthy tissues and maximizing tumor

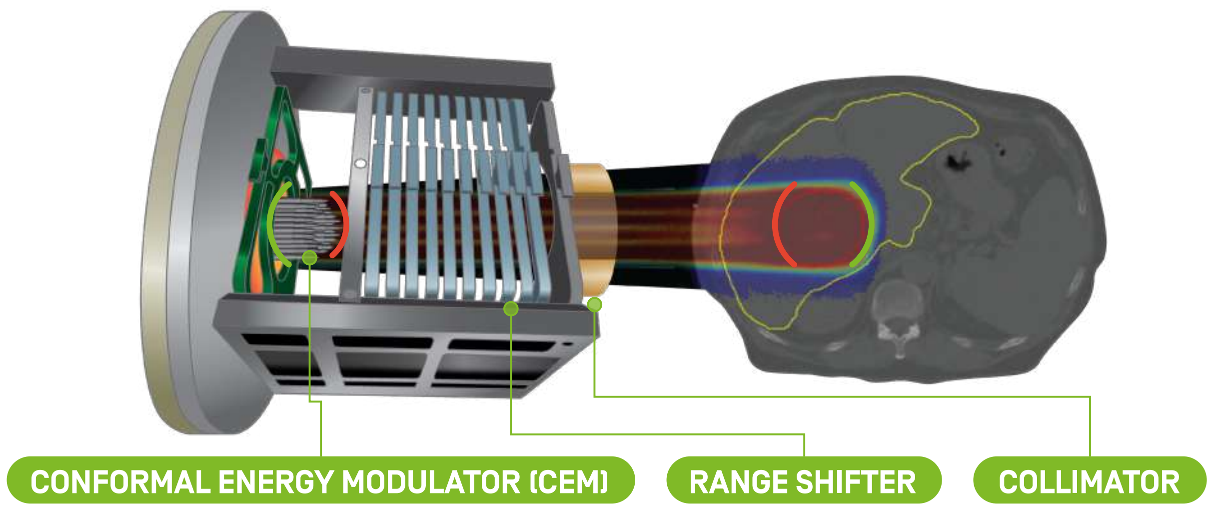


Figure 2. Schematic representation of the ConformalFLASH® CEM, range shifter and collimator.

The importance of preserving the Bragg peak

One current challenge of proton therapy technology for FLASH application is the energy-switching time of intensity-modulated proton therapy (IMPT), which slows down the delivery of overall volumetric FLASH dose rates. Two proton FLASH techniques are currently tackling this challenge: shoot-through (or transmission) FLASH and ConformalFLASH®.

Shoot-through FLASH techniques aim to use the highest beam current available to deliver high-energy single-layer plans, avoid the dead time associated with energy changes, and take advantage of the higher beam line transmission efficiency at high energy. The dose and the linear energy transfer (LET) are constant inside the PTV. However, this modality also delivers a high dose upstream and downstream of the target. In this case, the Bragg peak occurs outside the target and is not used for dose shaping (Figure 3A). [17,18]

IBA's unique ConformalFLASH® approach capitalizes on the use of the patient-specific 3D printed CEM that allows the delivery of a field-specific SOBP, composed of multiple Bragg peaks, with a single energy layer. The CEM also ensures that the distal fall-off of the SOBP matches the distal surface of the PTV and reduces the lateral penumbra (Figure 3B). [17,18,19]

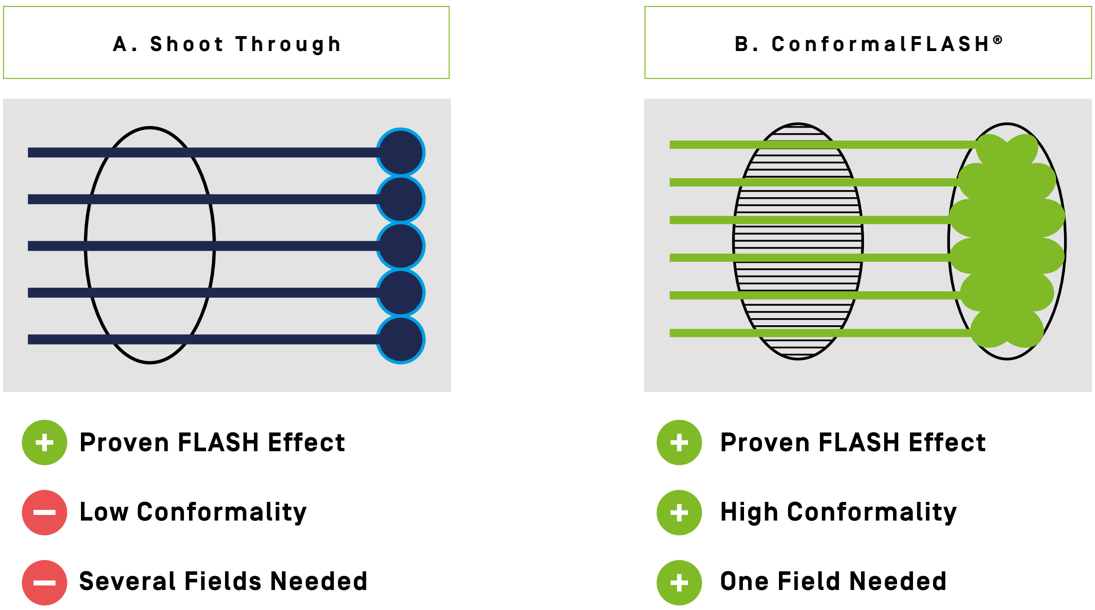


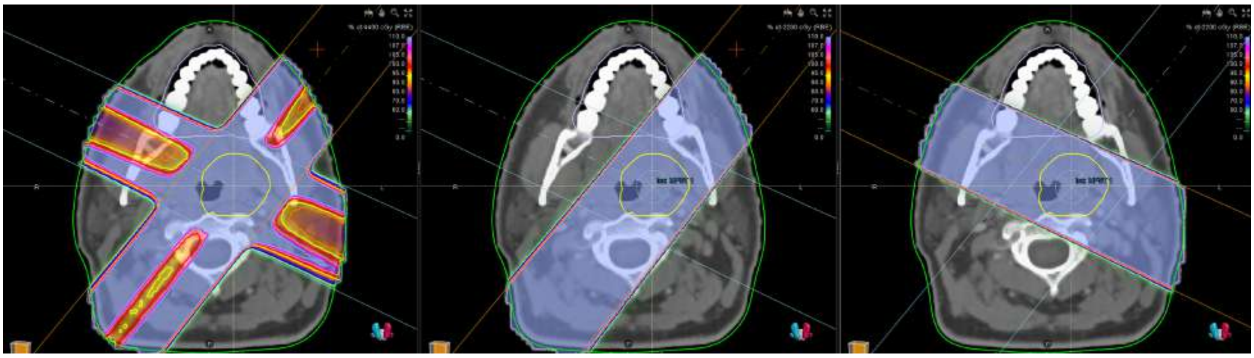
Figure 3. Schematic representation of proton FLASH delivery methods. (A) PBS proton beam in transmission mode, and (B) ConformalFLASH®.

Advantages of ConformalFLASH®

The unique approach of ConformalFLASH® has numerous advantages in comparison with the shoot-through approach:

- Improved conformality due to the reduced entrance and exit dose compared to shoot-through FLASH (Figure 4).
- Dose delivery in one or two beams, no need for multi-field delivery, dose-splitting, which could lead to potentially losing the FLASH effect.
- Potentially more patients in ConformalFLASH® than shoot-through FLASH, through more eligible indications like abdominal cancers.
- Improved safety due to no danger of Bragg peak ending inside the healthy tissue of the patient (as in shoot-through FLASH treatment - i.e., if the patient is too large, the beam won't exit and might end up depositing dose inside the patient) and reduced in-room shielding requirements.

SHOOT-THROUGH FLASH



ConformalFLASH®

Figure 4. Illustrations of dose map on a brain case presenting the reduced entrance and exit dose and the improved conformality of the ConformalFLASH® technique. Left images represent total dose, center and right represent the contribution of each beam.

CLICK OR SCAN THE QR CODE TO DISCOVER MORE ABOUT ConformalFLASH® AND ITS ADVANTAGES, ON IBA CAMPUS

IBA also works closely with its partners to ensure a smooth future integration of ConformalFLASH® treatment in the therapeutic arsenal for cancer patients.

- The treatment plan is optimized in RayStation, the commercial treatment planning system (TPS), with a specific FLASH extension for clinical studies. RayStation helps optimize the shape of the CEM and the PBS spot position based on the patient and tumor characteristics.
- IBA developed a FLASH snout to easily and accurately fix the patient-specific devices on the treatment machine.
- IBA's close partnership with 3DS allows for the easy 3D printing of the CEM based on the treatment plan, and the received CEM can be smoothly inserted in the FLASH snout.
- For research use, the proton therapy machine can seamlessly switch between conventional and FLASH modes, eliminating the need to dedicate a separate treatment room for FLASH. Patients receive conventional IMPT treatments during the day, with FLASH therapy research conducted in the evening following a straightforward mode switch.

What sets ConformalFLASH® apart from other FLASH approaches?

ConformalFLASH® represents a groundbreaking advancement in proton FLASH therapy, uniquely combining the biological tissue-sparing effects of FLASH with the physical dose-sparing properties of the proton Bragg peak. This innovative approach addresses the limitations of existing FLASH techniques, such as electron-based and photon-based methods, as well as shoot-through FLASH:

Compared to proton shoot-through FLASH:

- **Utilization of the Bragg peak** for improved dose distribution and normal tissue sparing
- **Potential for seamless integration** with existing proton therapy systems and TPS
- **Fewer beams needed** for conformal delivery (1-2) with high dose per beam

Compared to photon FLASH:

- **Reduced** integral dose to healthy tissues
- **Sharper** dose gradients
- **Potential** for better normal tissue sparing
- **More advanced** technology readiness for proton FLASH

Compared to electron FLASH:

- **Greater** penetration depth
- **Superior** dose conformality
- **Potential** for treating deep-seated tumors

IBA's commitment to FLASH research and innovation

The ConformalFLASH® Alliance

Given its close collaborations with the most knowledgeable community in proton therapy, IBA launched the ConformalFLASH® Alliance in 2022: a collaborative platform bringing together leading clinical and academic institutions and industry partners worldwide to advance the clinical application of ConformalFLASH® proton therapy.

The Alliance's primary objective is to deepen the understanding of FLASH therapy fundamentals and effectively integrate them with proton therapy's unique properties. By fostering collaboration between leading researchers and industry experts, the Alliance seeks to accelerate the translation of ConformalFLASH® into clinical settings, ultimately aiming to revolutionize cancer treatment and improve patient outcomes.

Key participants in the ConformalFLASH® Alliance include prominent academic centers such as the University of Pennsylvania (UPenn), University of Washington, UZ Leuven, University of Kansas Medical Center (KUMC), and University Medical Center Groningen (UMCG), among others, alongside industry leaders such as IBA Dosimetry and RaySearch Laboratories (Fig. 5). These collaborations are instrumental in sharing insights, developing new technologies, and establishing clinical protocols to bring ConformalFLASH® proton therapy to patients worldwide.

Industrial Partners

Clinical Partners

Figure 5. Founding members of the ConformalFLASH Alliance.

Through the ConformalFLASH® Alliance, members can gain access to advanced tools and expertise that support the development and clinical implementation of ConformalFLASH®, including innovative treatment planning systems, specialized dosimetry tools, and 3D-printed CEM tailored for precise dose delivery.

Membership in the Alliance facilitates collaborative research and fosters first-hand knowledge exchange among leading academic centers and industrial partners. By participating, members benefit from shared resources and the opportunity to contribute to impactful scientific publications, accelerating the clinical translation of FLASH therapy and enhancing their leadership in this rapidly-growing research field. Additionally, the Alliance provides a platform for institutions to advance their own research initiatives, offering support in refining treatment protocols and integrating FLASH technology into clinical practice.

> *FLASH is a very exciting opportunity, and we believe that proton therapy can be a very suitable modality to achieve the desired outcomes. We are at a stage where more research is needed to understand the mechanisms of FLASH irradiation better, and we are very excited about our current research program at Penn Medicine. Coordinating our efforts with other centers is key, and IBA's meetings offer a great forum to share our insights.*

DR. ALEXANDER LIN
Associate Professor of Radiation Oncology,
Chief of the Head & Neck Oncology Service and Medical Director
Roberts Proton Therapy Center at the University of Pennsylvania,
Philadelphia, United States

Collaborations with leading academic and clinical institutions

IBA is leveraging strategic partnerships with leading academic and clinical institutions worldwide to collaboratively ensure the advancement of FLASH therapy's clinical application. These collaborations aim to deepen the understanding of FLASH therapy's biological mechanisms, refine delivery systems, and transition from preclinical research to clinical applications, paving the way for patient treatments.

One of IBA's long-standing partners and a global leader FLASH therapy development is the **University of Pennsylvania.** Since 2010, UPenn has treated patients using IBA's Proteus®PLUS system across five treatment rooms at the Roberts Proton Therapy Center in Philadelphia and has recently acquired two Proteus®ONE systems. In 2021, IBA and UPenn signed a multi-year research agreement to develop, test and validate ConformalFLASH®, with plans to soon treat the first human patient within a clinical study with this unique technique. [20,21]

Since 2017, IBA has also been collaborating with **PARTICLE (Particle Therapy Interuniversity Center Leuven),** and in 2023 they initiated a research partnership to enable FLASH delivery for pre-clinical experiments on their clinical machine. This initiative allows researchers from UZ Leuven, KU Leuven and UCLouvain to perform preclinical experiments to evaluate the FLASH effect on normal tissue toxicity using IBA's Proteus®ONE. [22]

Other key partnerships include the research collaboration agreement with the **University of Kansas Medical Center** to advance preclinical research into the use of ConformalFLASH® on Proteus®ONE, and the four-year research partnership with the **University Medical Center Groningen** to develop a new FLASH irradiation protocol for early-stage breast cancer. [23,24]

These and other partnerships capitalize on multidisciplinary expertise and cutting-edge technologies to define the key parameters of ConformalFLASH® therapy's healthy tissue sparing effects while keeping the same tumor control. This collective effort has already yielded numerous scientific publications and congress communications, enhancing the global understanding of FLASH therapy, such as:

Penn, University of Pennsylvania	– Secondary neutron dosimetry for ConformalFLASH® proton therapy.[25] – FLASH proton radiotherapy mitigates inflammatory and fibrotic pathways and preserves cardiac function in a preclinical mouse model of radiation-induced heart disease.[26] – Design Implementation and *in vivo* validation of a novel proton FLASH radiation therapy system.[9] – FLASH proton radiotherapy spares normal epithelial and mesenchymal tissues while preserving sarcoma response.[10] – Verification of dose and dose rate for quality assurance of spread-out-Bragg-peak proton FLASH radiotherapy using machine log files.[34]
UZ Leuven	– Definition of dose rate for FLASH pencil-beam scanning proton therapy: A comparative study.[27] – First demonstration of reduced toxicity following upper abdominal FLASH proton irradiation in mice using the Proteus®ONE clinical system.[28] – Combined 1D and 2D Dosimetry using EBT-XD, OSL and Alanine for Small Field UHDR Dosimetry for a Pulsed Beam Proton Therapy System.[29]
KU Medical Center, The University of Kansas	– Experimental demonstration of 360nA FLASH proton beam current via synchrocyclotron using IBA Proteus®ONE. (Poster PTCOG 2023)
W University of Washington	– Commissioning a clinical proton pencil beam scanning beamline for pre-clinical ultra-high dose rate irradiations on a cyclotron-based system.[30]
institut Curie	– Experimental set-up for FLASH proton irradiation of small animals using a clinical system.[31] – A physicochemical model of reaction kinetics supports peroxyl radical recombination as the main determinant of the FLASH effect.[32] – Model studies of the role of oxygen in the FLASH effect.[18]

IF YOU WANT TO BECOME A MEMBER OF THE ConformalFLASH® ALLIANCE CLICK OR SCAN THE QR CODE TO CONTACT THE RESEARCH TEAM.

DOSIMETRY

A fruitful collaboration with IBA Dosimetry

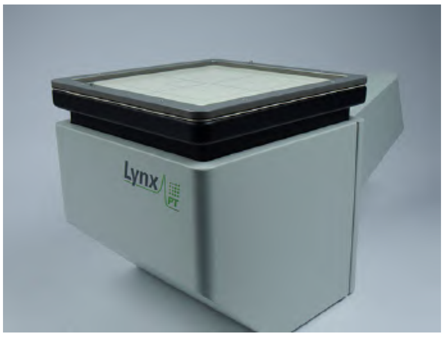
Thanks to a continuous and close collaboration with IBA Dosimetry, the FLASH program benefits from the latest developments in UHDR-compatible dosimetry products. Our long-term partners are now offering FLASH-ready electrometers and parallel chambers, such as the *DOSE-X* and *PPC05.* For accurate quality assurance (QA) of the beam positioning and geometry, the *Lynx PT Flash* is the device of choice to verify machine performance under high dose rate conditions.

In the field of patient QA, the *MatriXX AiR** is also designed to withstand the ultra-high dose rates of the new treatment modality, while keeping the accuracy and the sensitivity that this product has been known for. Additionally, the *myQA iON* software platform can be used to reconstruct the dose, and soon, the dose rate and other relevant beam parameters required for accurate and reliable dosimetry in FLASH therapy.

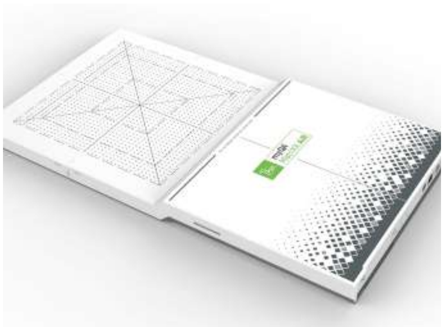
PPC05

DOSE-X

LynxPT Flash



MatriXX AiR



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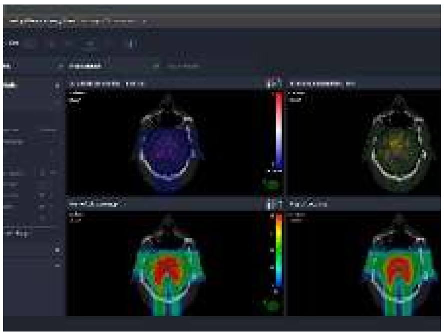


myQA iON

**For more information, contact the IBA Dosimetry team here: https://www.iba-dosimetry.com/contact*

Collaborations with other strategic industrial partners

IBA has also established strategic collaborations with leading industry partners to advance the development and clinical implementation of ConformalFLASH® technology, while remaining open to collaborations with other vendors and partners.

Since 2013, IBA and RaySearch have partnered to integrate RaySearch's treatment planning systems with IBA's proton therapy solutions. In 2021, this collaboration expanded to include FLASH radiotherapy, proton arc therapy, and the treatment of moving tumors, aiming to enhance the precision and effectiveness of proton therapy treatments. [33]

CLICK OR SCAN THE QR CODE TO LEARN MORE ABOUT RAYSERCH LABORATORIES

As experts in 3D printing, they are engaged in the production of patient-specific Conformal Energy Modulators, commonly referred to as "hedgehogs," which are essential components in modulating proton beam energies to ensure the preservation of Bragg peak for ConformalFLASH® applications.

CLICK OR SCAN THE QR CODE TO LEARN MORE ABOUT 3D SYSTEMS

Specializing in custom, patient-specific radiation therapy devices, .decimal collaborates with IBA to provide tailored apertures for proton therapy. These custom devices enhance the precision of proton beam delivery, ensuring that the radiation conforms closely to the tumor shape while sparing surrounding healthy tissue.

CLICK OR SCAN THE QR CODE TO LEARN MORE ABOUT DECIMAL

These collaborations leverage the unique expertise of each partner, fostering innovation and accelerating the clinical adoption of the ConformalFLASH® technology.

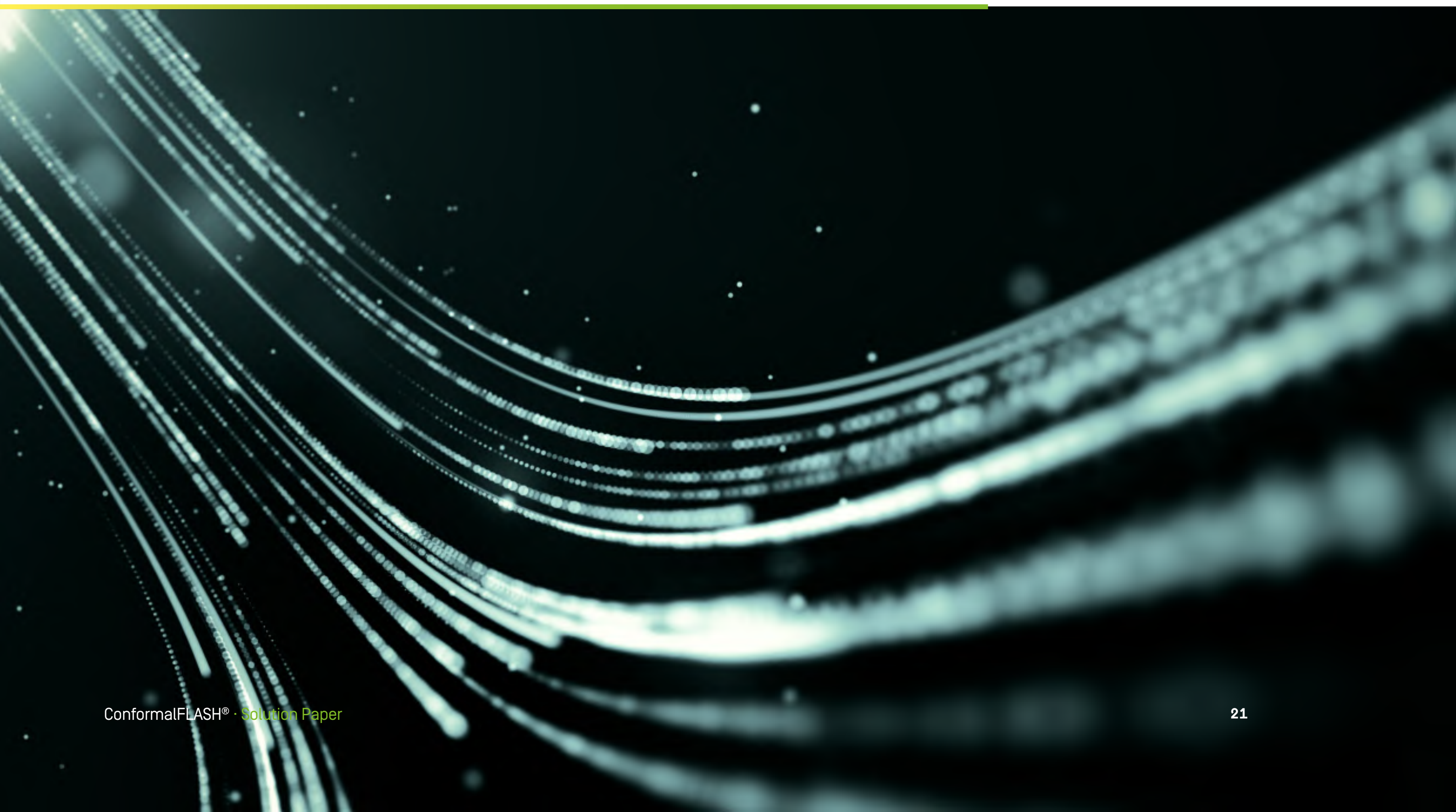
Open-source initiatives

IBA's commitment to pioneer the development and adoption of ConformalFLASH® has also enabled the development of open-source initiatives to help researchers from the community and further enhance collaboration and innovation that facilitate research and development in this exciting field. Among them, IBA has developed and made available **OpenFLASH, an open-source software** platform designed to assist in the treatment planning of FLASH-RT. It offers researchers and clinicians customizable tools to simulate and optimize FLASH treatment protocols, thereby accelerating the translation of ConformalFLASH® into clinical practice. IBA has also released the **description of its private DICOM tags** (in treatment plan) to make communication between researchers and 3D printer companies easier and facilitate the 3D printing of the CEM.

IBA and its partners also support the development of models that allow a deeper understanding of the radiobiological mechanisms underlying the FLASH effect, such as the **radio-kinetic models.** It has been involved in studies exploring the role of oxygen dynamics during irradiation, contributing to the development of frameworks to predict tissue responses under different oxygenation conditions. IBA has also released in open source the code for the radio-kinetic model, so that the research community can use it and build on it.[18,32]

Among the current research work, IBA is evaluating the utilization of **machine log files** in PBS to better understand their integration into QA workflows and allow Monte Carlo simulations to validate the accuracy of dose rate reconstructions using these data. These actions help facilitate research by providing open-source data for users.[34]

CLICK OR SCAN THE QR CODE TO ACCESS THE ConformalFLASH SOFTWARE LIBRARY AND THE OPEN-SOURCE TOOLS THAT ARE AVAILABLE TO RESEARCHERS



IBA's engagement in scientific conferences

Demonstrating its commitment to leading the path to the clinical application of FLASH proton therapy through its investment in ConformalFLASH®, IBA has been one of the most prominent sponsors of conferences such as the Flash Radiotherapy and Particle Therapy (FRPT) and organizes regular seminars, webinars and ConformalFLASH® Alliance meetings. Most presentations and discussions are made available on the IBA Campus to ensure the latest advancements are shared with the proton therapy community.

Watch some of the most recent webinars and presentations of the latest developments of FLASH proton therapy and ConformalFLASH® on IBA Campus:

FRPT FLASH Radiotherapy & Particle Therapy

The 2023 FRPT Seminar discussing advantages and applications beyond the FLASH effect, including intrafraction motion and the reduction in the volume of circulating blood irradiated during treatment, and the possible benefits this sparing might have on anti-tumor immunity.

CLICK OR SCAN THE QR CODE
TO WHATCH THE 2023 FRPT WEBINAR

The 2024 FRPT industry-led session focused on the most recent developments on Proteus®PLUS and Proteus®ONE for ConformalFLASH® treatment.

CLICK OR SCAN THE QR CODE
WHATCH THE 2023 FRPT PRESENTATION

AACR American Association for Cancer Research

The 2025 presentation at the AACR Radiation Medicine Meeting on how ConformalFLASH® can maximize the true benefits of proton FLASH.

CLICK OR SCAN THE QR CODE
TO DISCOVER THE 2025
AACR PRESENTATION

Campus your proton therapy community

The latest webinar on how ConformalFLASH® can revolutionize radiotherapy, including discussions around the first full end-to-end treatment of a canine patient with ConformalFLASH® on Proteus® technology.

CLICK OR SCAN THE QR CODE
WHATCH THE FULL WEBINAR

Future directions and potential

Ongoing research areas

FLASH radiotherapy, particularly ConformalFLASH®, currently represents a dynamic and exciting research field for biologists, medical physicists and clinicians, and different key areas are continuously being investigated: [4,11,15,35]

- **Optimizing FLASH parameters to maximize the FLASH effect:**
  The optimal dose rates, pulse structures, volumes, and the optimization of fractionation schedules are continuously being investigated to maximize the normal tissue-sparing benefits of the FLASH effect. Recent studies investigate whether the FLASH tissue-sparing capabilities could counterbalance the heightened damage from hypofractionation, which would have the potential to broaden the therapeutic window for more aggressive treatment regimens. [11]

- **Understanding biological mechanisms:**
  It is essential to further elucidate the underlying biological processes responsible for the FLASH effect and their impact on radiobiological damage, as well as other potential biological pathways that require deeper investigation, to ensure the successful application of FLASH into clinical practice.

- **Improving delivery techniques:**
  Current research and development of FLASH delivery techniques also focuses on improving the precision, efficiency and adaptability to clinical settings. Key areas include the development of optimized TPS that integrate FLASH-specific parameters such as dose rate, beam current, and spot delivery sequence to maximize the FLASH effect. [17] Innovations like single-energy Bragg peak and CEM techniques aim to enhance dose conformality and minimize exit doses, making ConformalFLASH® more suitable for deep-seated tumors. Additionally, efforts are underway to reduce energy switching times and optimize scanning paths in pencil-beam scanning systems to achieve ultra-high dose rates efficiently. [4,36] These advancements, combined with robust dosimetry tools and hardware improvements, are essential for translating FLASH therapy into broader clinical applications while maintaining its therapeutic benefits. [15]

- **Expanding treatment sites:**
  Ongoing research also focuses on expanding the potential of FLASH therapy for various cancer types and anatomical locations, including deep-seated tumors or tumors located in high-risk regions, such as the brain, or very close to organs at risk. Recent studies highlight the sparing effect of FLASH on synaptic plasticity, showing promising results for patients with brain tumors, and the ConformalFLASH® organ sparing, over transmission proton FLASH, in recurrent head and neck cancer. [35,36]

Translating the promising biological advantages of FLASH therapy observed in preclinical studies into meaningful clinical benefits requires a comprehensive and collaborative effort. This transition depends on multidisciplinary research spanning biology, physics, clinical practice, and engineering. Experts across these fields must address the technological challenges of delivering FLASH therapy with precision and safety, particularly for complex anatomical regions, to fully realize its potential in improving patient outcomes.

Preparing for clinical trials

Limited human trials have allowed to test the feasibility and safety of delivering FLASH dose-rates in a clinical setting. Industrial partners and scientific organizations are actively addressing the technical challenges to facilitate the clinical exploration of FLASH therapy. While the commercial sector is supporting these efforts by providing FLASH-capable proton systems and treatment planning software, significant gaps have only recently been closed, such as the need for robust, conformal patient plans and real-time dose monitoring systems. Early experiences with shoot-through FLASH proton therapy trials did not show overwhelming superiority due to immature technology and safety concerns related to radiobiological effects on normal tissue. These limitations delayed widespread adoption and affected trial enrollments, with insurance companies using early findings to deny coverage. ConformalFLASH® trials must design rigorous early-phase protocols to avoid similar pitfalls and build a strong foundation for larger, multi-institutional studies, ensuring robust outcomes and improved adoption. [5,37]

The successful design and implementation of FLASH clinical trials, and further advancement into clinical practice, will depend on different technology. FLASH therapy will require support for quality assurance, definition and control of safe beam delivery, standardization in treatment system analysis, patient positioning, treatment planning, and thoughtful trial design to effectively answer clinical and scientific questions. Figure 6 summarizes the key components needed to conduct FLASH clinical trials successfully, and IBA has greatly contributed to the advancement up to today. [5] IBA is continuing to work closely with its clinical and industrial partners to address these issues and ensure the safe implementation of ConformalFLASH® into clinical practice.

YESTERDAY - - - - **TODAY** - - - - → **GOAL**

UDHR Technology

ANCILLARY TOOLS
Develop Tools
Test Integration
Ensure Reproducibility

BEAM MONITORING
Develop Tools
Test Equipment
Ensure Reproducibility

DICOM TOOLS
Develop Tags
Test Function
Implement Clinically

DOSE OPTIMIZATION / RECORDING
Define Pertinent Parameters
Develop Reporting Standards
Harmonize Across Institutions

MACHINE QA
Develop Protocols
Test Equipment
Ensure Reproducibility

Preclinical & Early Clinical Feasibility Trials

COMPLEX FLASH
Multi-fraction
Multi-field
Multi-modality
Heterogeneities
Low Dose Penumbra

BIOLOGY
RBE by Disease Site
RBE by Modality
RBE with Dose Escalation
RBE Reproducibility

CORRELATIONAL STUDIES
FLASH + Comorbidities
FLASH + Other Medications
FLASH + Other Radiotherapy
FLASH Re-treatment

REGISTRY / OUTCOMES
Reproducible Human Data
Tumor Control
Normal Tissue Toxicity
Late Effects
Consistent Outcomes?

Phase II/III Human Trials

STANDARDIZED PROTOCOLS
Disease Site
Prescription
Margins
Technology Allowed

SAFETY CULTURE
Incident Reporting
Patient Registry
Peer Review

TRIAL CREDENTIALING
Develop Tools
Audit Participants
Ensure Consistency

TRIAL LOGISTICS
International Collaborations
Funding Sources
Data Management
Outcomes Analysis

Figure 6. Roadmap for successful FLASH clinical trials. (Adapted from Taylor et al., 2022)

IBA's commitment to advancing FLASH therapy

As the world leader in particle accelerator technology and the world's leading provider of proton therapy solutions for the treatment of cancer, IBA remains dedicated to pushing the boundaries of FLASH therapy, continually investing in research, development, and collaborations with clinical and industrial partners to bring ConformalFLASH® technology to patients worldwide. Figure 7 highlights IBA's involvement, from the first FLASH beam delivery in a clinical room to the desired routine patient treatment with FLASH therapy.

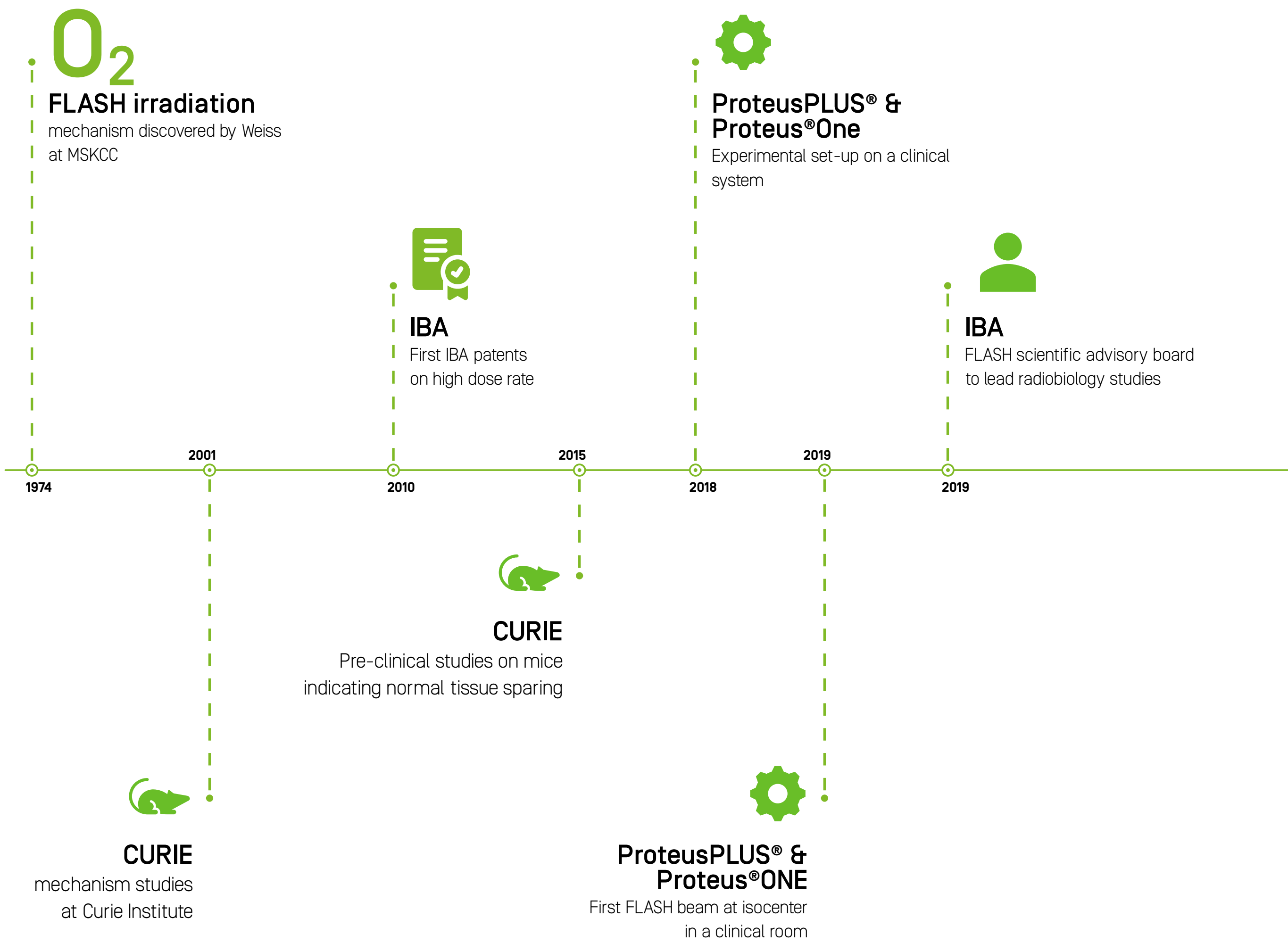


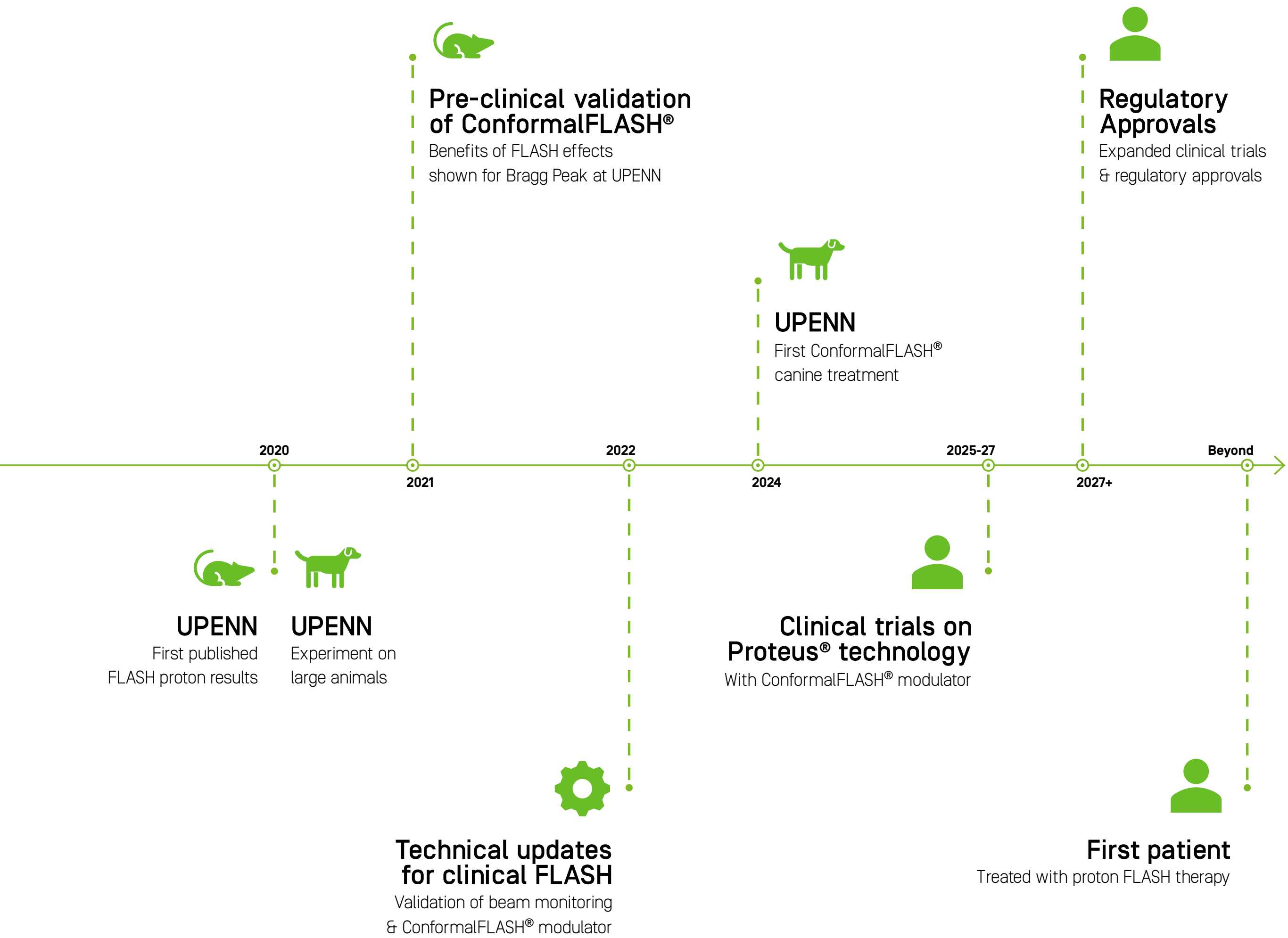
Figure 7. IBA's involvement in FLASH therapy development, from pre-clinical research to patient treatment.

The team at the Unniversity of Pennsylvania performed ConformalFLASH® delivery on canine subjects.

The second dose delivered went incredibly smoothly with full FLASH clinical software. Again, tremendous team effort.

PROF. KEITH A. CENGEL
Professor of Radiation Oncology
Hospital of the University of Pennsylvania, Philadelphia, United States

ConformalFLASH® experiments performed at IBA's partner site at the University of Pennsylvania were the first to show the biological effectiveness of combining proton SOBP and FLASH in both mice and canine subjects.[10,26] The first successful treatments of canine osteosarcoma subjects with shoot-through FLASH demonstrated the feasibility, safety, and dosimetric accuracy of this method, paving the way for human patients receiving FLASH irradiation.[10] The world's first ConformalFLASH® trial, focusing on treating canine subjects with head and neck tumors using all hardware and software developments, demonstrated the successful delivery of ConformalFLASH® therapy with dosimetric accuracy comparable to IMPT.[38]



Proteus® systems & ConformalFLASH®

Compatibility and implementation potential on Proteus® platforms

IBA's Proteus proton therapy systems are designed with the potential for ConformalFLASH® implementation. Both Proteus®ONE, our compact single-room solution, and Proteus®PLUS, our multi-room system, have been used to test and improve FLASH delivery in several pre-clinical studies. The results have been shared with the scientific community. Our collaborators utilized the Proteus® systems as follows:

On Proteus®PLUS

Researchers at UPenn measured the low level of secondary neutron production, design and dosimetry parameters for accurate beam control of ConformalFLASH® delivery in mouse models, normal epithelial and mesenchymal tissue sparing after ConformalFLASH® delivery in mice. Other studies have focused on the quality and robustness of dose distribution generated by the CEM and are soon to be published. [9, 10, 25]
At the Curie Institute, researchers characterized the dosimetric properties and monitoring systems for FLASH delivery on mouse lungs. [31]

CLICK OR SCAN THE QR CODE TO DISCOVER THE ADVANCED FLASH IRRADIATION WITH IBA'S Proteus®PLUS AND THE CYCLOTRON CAPABILITIES DEMONSTRATED AT UMCG IN THE NETHERLANDS

On Proteus®ONE

Researchers at PARTICLE Leuven recently communicated their results using the Proteus®ONE synchrocyclotron at the 2024 FRPT conference, showing good inter-dosimeter agreement and immediate post-irradiation verifications of the beam profile, and reduced toxicity following upper abdominal FLASH proton delivery in mice. [28, 29]

CLICK OR SCAN THE QR CODE TO DISCOVER THE FIRST FLASH IRRADIATION WITH COMPACT Proteus®ONE, IN BOTH CLINICAL AND RESEARCH MODES, AT THE RUTHERFORD CANCER CENTRE, THAMES VALLEY, UNITED KINGDOM

The most recent developments on Proteus®PLUS and Proteus®ONE for ConformalFLASH® treatment were also presented at the latest FRPT 2024 conference.

CLICK OR SCAN THE QR CODE TO WATCH THE FULL 2024 FRPT PRESENTATION

Current collaborations with clinical and industrial partners from the ConformalFLASH® Alliance ensure the continuous development and optimizations of the Proteus® platforms for the successful delivery of ConformalFLASH® in research and clinical modes, with relatively easy switches between the two modalities.

Pre-clinical research capabilities

Isochronous cyclotrons, like the one of Proteus®PLUS, currently used in patient treatments, have consistently demonstrated the capability of achieving dose rates compatible with FLASH delivery.[17] Several field-applicable upgrades have been identified to enable the increase of the current in the S2C2 synchrocyclotron of Proteus®ONE to ensure FLASH-compatible dose rates for clinical application.

Future-proofing your proton therapy investment

By choosing an IBA Proteus® system, institutions can future-proof their proton therapy investment. As one of the pioneers in FLASH research, IBA is building upon its expertise in accelerator systems and working closely with its partners and users to ensure Proteus® users* will be able to deploy FLASH for research in the future. IBA's fully integrated range of solutions, combined with its close relationship with major vendors, make the Proteus® platforms the ideal tool for exploring and advancing the most innovative proton therapy protocols, ensuring users remain at the forefront of cancer treatment for decades to come.

The core technology to develop FLASH irradiation is the accelerator system, IBA's area of expertise. It must be powerful enough to generate enough current and fluence to create such high dose rates. IBA started in 1986 and now has 35+ years of relevant accelerator experience. IBA has sold 500+ accelerators worldwide. Delivering ultra-high dose rate is essential but not enough to guarantee a wide clinical deployment of FLASH techniques. The modality of delivery and the ability to shape the beam play a critical role that still needs to be fully understood by the FLASH community. IBA is committed to delivering ConformalFLASH®, a method we believe to be the safest and most effective delivery of FLASH for the oncology community.

Another exciting innovation, on which IBA is actively working, is DynamicARC®, a novel dynamic treatment modality that enables simultaneous dynamic proton beam delivery at variable energies while the gantry is rotating. By precisely targeting the tumor from multiple directions, DynamicARC® helps enhance tumor coverage and healthy tissue sparing in multiple cancer types.

CLICK OR SCAN THE QR CODE TO FIND OUT MORE ABOUT DynamicARC®, ITS ADVANTAGES AND HOW IT CAN HELP SHAPE THE FUTURE OF CANCER CARE

** Please contact your IBA representative for more information about the specific technical and financial conditions.*

Conclusion

ConformalFLASH® represents a significant leap forward in radiation therapy, offering the potential to dramatically improve cancer treatment outcomes while minimizing side effects. By combining the biological advantages of FLASH irradiation with the physical precision of the Bragg peak, ConformalFLASH® has the potential to expand the therapeutic window for a wide range of cancer types, contributing to make proton therapy available to all cancer patients who could benefit from it.

IBA's commitment to advancing ConformalFLASH® technology positions it at the forefront of this revolutionary approach to cancer treatment. The ongoing research and development efforts, including preclinical studies and preparations for clinical trials, underscore the promising future of ConformalFLASH®.

As we look ahead, ConformalFLASH® offers three key advantages:

- **FURTHER:** ConformalFLASH® is being developed to treat deep-seated tumors, leveraging the high beam current and transmission efficiency of Proteus® platforms.
- **FASTER:** IBA is committed to bringing ConformalFLASH® faster to all eligible Proteus® users*, to treat cancer patients with protons.
- **GENTLER:** ConformalFLASH® expands the therapeutic window for relevant cancer indications, combining reduced normal tissue toxicity with efficient tumor control.

The integration of ConformalFLASH® capabilities into IBA's Proteus systems offers cancer centers the opportunity to future-proof their investments in proton therapy. This technology not only promises to enhance current treatment modalities but also opens new avenues for treating challenging cases and potentially improving patient outcomes.

As research progresses and clinical trials begin, ConformalFLASH® has the potential to redefine the standard of care in radiation oncology. By expanding the therapeutic window and potentially increasing the number of patients who can benefit from the FLASH effect, ConformalFLASH® brings hope to cancer patients worldwide, aiming to help more patients keep everything but cancer.

Abbreviations

UHDR: ultra-high dose rates
Gy: Gray
PBS: pencil beam scanning
TPS: treatment planning system
SOBP: spread-out Bragg peak
CEM: conformal energy modulator
IMPT: intensity-modulated proton therapy
LET: linear energy transfer
PVT: planning target volume
KUMC: Kansas University Medical Center
UMCG: University Medical Center Groningen
UPenn: University of Pennsylvania
QA: quality assurance
FRPT: Flash Radiotherapy and Particle Therapy

** Please contact your IBA representative for more information about the specific technical and financial conditions.*

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