Transformative Technology for FLASH Radiation Therapy

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Primary Frontier/Topical Group:

- Community Engagement Frontier (CommF)/ CommF1: Applications & Industry

Additional Frontiers/Topical Groups:

- Instrumentation Frontier (IF)/IF2: Photon Detectors/IF9: Cross Cutting and Systems Integration
- Accelerator Frontier (AF)/ AF6: Advanced Accelerator Concepts/ AF7: Accelerator Technology R&D
- Computational Frontier (Comp F)/CompF3: Machine Learning/ CompF5: End user analysis

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ABSTRACT

Conventional cancer therapies include a combination of surgery, radiation therapy, chemotherapy, and, more recently, immunotherapy. Unfortunately, most patients receiving radiation therapy suffer from acute and long-term side effects. In patients where the treatment dose required to cure the tumor is beyond the normal tissue tolerance, the cure cannot be achieved. Up to now, the prevailing method to increase the therapeutic index of radiation therapy has been to create a physical dose differential between tumors and normal tissues through precise dose targeting using image guidance and high dose-conformality. Recently, however, a fundamentally different paradigm for increasing the therapeutic index of radiation therapy has emerged, supported by preclinical research. This new paradigm is based on the FLASH radiation effect. FLASH radiation therapy (FLASH-RT) refers to ultra-high dose rate delivery of therapeutic radiation doses within microseconds to a fraction of a second. At these dose rates, radiation-induced toxicities to normal tissues are greatly reduced but are not reduced to tumors. There is a great opportunity, but also many challenges, for the high energy and particle physics communities to create the desired dose rates in novel compact accelerators. There is also a lack of suitable large-area monitors for FLASH-RT and suitable in vivo dose-monitoring systems. The objective of this LOI is to document our desire to develop strategic planning and engagement that will promote applications and technology transfers from the particle physics community to applications with high impact in the field of FLASH-RT.

Development of accelerator and detector technology for FLASH radiation therapy and research

Cancer is the second-largest cause of death in the US, and more than 50% of all cancer patients receive radiation therapy during their course of disease, mostly by some form of external beam radiotherapy (EBRT) with photons, electrons, protons, or heavier ions [1]. The most troublesome toxicities of EBRT typically manifest several years after treatment and get progressively worse. Reducing the long-term side effects of EBRT is, therefore, a central goal within radiation oncology. Despite the most recent technological advances in photon, proton, and ion EBRT technology to minimize normal tissue exposure to an "acceptable" level, this goal has not been reached.

FLASH radiotherapy (FLASH-RT) is attracting great interest in the radiation oncology community as it promises to reduce normal-tissue toxicities and the impact of patient motion. In FLASH-RT, doses higher than 10 Gy are typically delivered in less than 100 milliseconds at ultrahigh dose rates in the range of 100 to 1000 Gy/sec, which are orders-of-magnitude more than the commonly used dose rates of around 0.05 Gy/s.

An increasing body of evidence in the literature from studies at radiobiology laboratories has demonstrated a "**FLASH effect**," i.e., significant normal tissue sparing without compromising tumor control compared to the same doses given at conventional dose rates [2-7]. A first-in-human case has demonstrated the FLASH effect in a skin tumor [8].

While the FLASH effect has been confirmed in multiple laboratories, research into its underlying mechanisms is still immature, mostly due to a lack of suitable FLASH radiation sources. The most popular hypothesis is that radiochemical oxygen depletion achieved by sufficient doses delivered at FLASH dose rates is the reason for normal tissue sparing, perhaps especially in relatively hypoxic stem cell niches [6, 9-11]. Tumor cells are often hypoxic from the outset, and therefore, are not further protected, or enjoy higher oxygen concentrations than normal stem cells, thus preventing the FLASH effect in tumors. Besides the reduction of side effects from radiation, there is a reduction of the impact of patient and organ motion, and reducing the treatment regime from 1-2 months to a single day or a few days [8]. Such a drastic reduction could allow an order-of-magnitude more patients to be treated in a given facility, tremendously increasing facility patient utilization rates and greatly reducing patient treatment costs.

Considering the transformative potential of FLASH-RT, basic research on the accelerator and detector technologies to enable further research to advance the mechanistic understanding of FLASH through preclinical experimentation and clinical translation of FLASH to patient care is essential [12]. Translating FLASH to general clinical radiation therapy of deep-seated and large tumors in humans will require capabilities far beyond those of current commercially available radiation sources. Another major factor impeding the clinical transition of FLASH-RT is the lack of detectors capable of directly monitoring and analyzing the FLASH-RT beam in real-time and able to interact in real-time with the beam accelerator and make adjustments if needed as the patient is being irradiated. Unfortunately, dosimetry at very high dose rates and fast delivery times is inherently challenging. No single dosimetry technique exists that would give all of the information needed in real-time during the <100 ms patient treatment.

The objective of this LOI is to document our intent to develop strategic planning and engagement that will promote applications and technology transfers from the particle physics community to applications with high impact in the field of FLASH-RT. The primary significance of this initiative is to enable FLASH-RT, which could revolutionize the treatment of many types of cancer. To reach this goal, we propose the following application areas, requiring a well-coordinated effort between national laboratories, industry, academia, and medical practitioners.

Application Area 1: Development of low-cost, compact, and FLASH-capable accelerators for cancer cure

All EBRT systems consist of the medical accelerator (photons, electrons, protons, ions) plus ancillary devices, including (1) beam modifiers (collimators or pencil beam scanning systems), (2) image-guidance systems (cone-beam X-ray CT, MRI, and future proton or He radiography/CT systems), and (3) beam monitoring and accelerator control systems providing independent verification and accelerator feedback for correct treatment delivery. These ancillary needs should be considered in conjunction with accelerator design since each is equally important to achieving effective and safe treatments. Current R&D needs on the accelerator side include:

- Very high energy electron (VHEE) FLASH sources in the range from 100 to 250 MeV;
- MV FLASH photon sources provided at conventional energies, and with multiple, ultracompact sources that will eliminate the requirement for mechanical rotation;

- FLASH proton/ion sources, compact, CW or pulsed, ultra-rapid change of energy for longitudinal scanning;
- Ultra-low intensity protons or ions (He) for pencil-beam-scanned particle image-guidance and treatment planning.

Application Area 2: Expanded operational parameters for ultra-high dose rate delivery

We cannot currently deliver nor reliably verify the dose at the high rate needed for the FLASH effect. To generate the FLASH effect reliably, we need to measure and modulate the ultrafast dose delivery, for which we need quality assurance systems with tight tolerances. This challenging demand creates a broad field of interrelated needs and engineering challenges that need to be integrated. Areas 3 and 4, to follow, are particularly critical and will be addressed separately.

Application Area 3: Development of improved large-area, ultrafast radiation detectors for real-time FLASH-dose monitoring and FLASH imaging

Much time is often spent to design and optimize the radiation dose distributions delivered in EBRT in general, and FLASH-RT, in particular, to assure tumor control and avoid side effects. Recent advances in high-performance computing have enabled highly accurate dose calculations. However, there is a strong need to verify and adapt these dose distributions while they are delivered during FLASH-RT. FLASH-dose-rate capable large-area radiation detectors currently do not exist. It will require the development of an ultrafast and transmissive (UFT) beam monitor capable of monitoring large radiation fields. Also, detectors that measure the interaction of the radiation field with the patient and their underlying biology are of great scientific and practical interest. Interaction by-products such as scattered charged particles of prompt gamma photons could be measured to validate the FLASH treatment process as it progresses. Approaches include activation by-product imaging using short-pulse control and monitoring during treatment. The time-structure control would also open the door to monitoring the impact of the beam on oxygen depletion during FLASH-RT delivery.

FLASH-RT delivery, being ultra-short, freezes the motion of patient organs, e.g., due to breathing, which is a very attractive aspect for the treatment of moving tumors with protons or ions. However, the actual position of the tumor at the time of FLASH plus delivery must be known with sufficient accuracy to avoid target misses or unwanted exposure of healthy tissues. For pre-delivery image guidance in the treatment of moving targets, ultra-fast photon or particle systems for FLASH imaging have to be developed. The development of FLASH monitoring and FLASH imaging systems that are fully integrated with the control system integration is another important need.

Application Area 4: Development of improved beam-shaping and -modulating technology

With the expected achievement of very high dose rate delivery, the conventional mechanical multileaf collimator (MLC) for photon and electron EBRT has become a major roadblock to shaped and intensity-modulated FLASH-rate treatments. Similarly, magnetically scanned pencil beams need to be scanned at an order-of-magnitude higher speed than during conventional proton or ion therapy. We currently do not have fast longitudinally-scanned (energy modulated) proton or ion pencil beams that would enable fully optimized 3D particle FLASH therapy in a single FLASH treatment. To address these needs, we need outside-the-box solutions for the photon/electron MLC and particle beam scanning systems. For photons and protons/ions, the goal must be to develop a device class and surrounding technology that allows innovative ways of dose shaping and modulation.

Application Area 5: Optimization and development of treatment planning and delivery control systems to allow for real-time biologic and volumetric treatment adaptation

There are currently no first principles start-to-end simulation capabilities, codes, or models describing the transport from the accelerator source to the dose deposited to the patient, including biological relevant parameters (micro- and nano-dosimetry) that can handle the FLASH dose rate treatment. For example, if it turns out that oxygen depletion is the main mechanism of the FLASH effect in normal tissues, oxygen depletion maps will need to be provided by the treatment planning system.

Lastly, computational codes for FLASH-RT system treatment planning could be designed to employ AI and machine learning systems to better address tumor change and host/normal tissue change that will allow the data generated in treatment to be validated, stored, and optimized for research.

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