Transformative Accelerator Technologies for FLASH Radiotherapy*

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Review

Transformative Technology for FLASH Radiation Therapy

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Featured Application: We report on new accelerator technology that has applications in FLASH radiation therapy. FLASH radiation therapy may have profound implications in cancer therapy because it may significantly spare normal tissues and solve the problem of tumors in motion due to the short time interval (sub-second) during which it is delivered.

Conventional and FLASH Radiotherapy

Radiation therapy is driven by new accelerator technologies and innovation

~2/3 OF US CANCER PATIENTS UNDERGO RADIATION THERAPY; OFTEN THE PRIMARY COURSE OF TREATMENT

PHOTON AND ELECTRON BEAM THERAPY – used to treat the majority of cancer patients

- **Bremsstrahlung photons and ≤10 MeV low energy electrons**
  - Photons produced using a 10-20 MeV pulsed electron linac, from an e-beam on target
  - Sophisticated, compact and inexpensive beam delivery systems (<0.1 Gy/sec on average)
- **High integral dose to normal tissue (dose limited by early & late toxicity)**

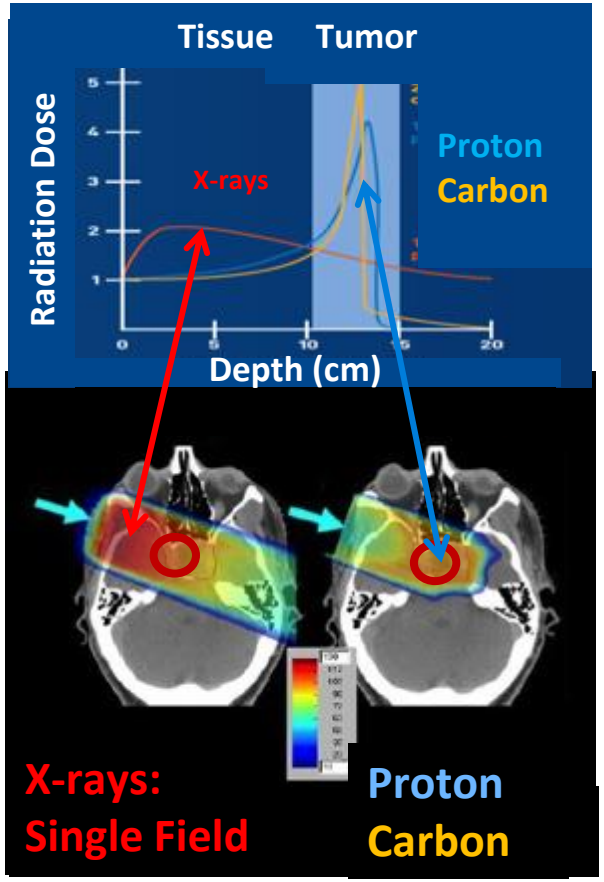
PROTON AND ION BEAM THERAPY

- **Highly conformal dose distribution; biological advantage for high LET ions**
  - enhanced local tumor control; Bragg peak maximizes energy deposition at tumor site;
  - Overall better sparing of normal tissue and organs at risk
- **Important for pediatric tumors, retreatment, organs at risk (brain, spinal cord)**
  - Delivered dose ~2 Gy/treatment < 3 Gy/min, typical is 20-40 treatment fractions
  - Reduced early and late toxicity response

FLASH THERAPY NEW!

- **Acute dose of radiation delivered in a fraction of a second**
  - Many preclinical and clinical results indicate a dramatic reduction of toxicity response
  - First patient treated (T-cell lymphoma, recurring), complete response, minimal toxicity[1]
  - Even after multiple non-FLASH skin irradiation and damage from photons and electrons!

[1] Bourhis J, et al. doi: 10.1016/j.radonc.2019.06.019



The FLASH Effect:

Dose rates far exceed conventional therapies

STRIKING TOXICITY REDUCTION AT VERY HIGH DOSE RATES WHILE MAINTAINING TUMOR RESPONSE

EARLY EVIDENCE OF SPARING AT HIGH DOSE RATES (1969)

- **In vitro mammalian cells (noncancerous) irradiated with X-rays[1]**
  - Cells irradiated with nanosecond pulses ($7x10^{10}$ rad/sec or ~10^8 Gy/sec instantaneous) remained viable; while lower rates decreased cell survival

RE-DISCOVERED IN RADIATION INDUCED LUNG FIBROSIS (2014)

- **Mice were irradiated with 4-6 MeV electron beams[2]**
  - Irradiation dose rate was ≥40 Gy/sec average in <500 ms for FLASH vs. 0.03 Gy/s Conventional
  - A 15 Gy total dose with CONV RT induced lung fibrosis, no fibrosis for 20 Gy with FLASH (other sparing effects)
  - ***HOWEVER, LUNG TUMORS SHOWED THE SAME RESPONSE TO THE TOTAL DOSE FOR FLASH AND CONVENTIONAL RT!***

PRECLINICAL FLASH STUDIES

- **Electrons: Performed using 4-6 MeV electron beams from modified clinical linacs**
  - Provides the strongest, consistent evidence for FLASH
- **Photons: Synchrotron Radiation and keV X-rays (early study)**
  - Mixed results
- **Protons: CW or iso-cyclotrons (shoot-through beams, beam is not energy degraded)**
  - Mixed results – better tumor control in one study

[1] Berry RJ, et al. doi: 10.1259/0007-1285-42-494-102, [2] Favaudon V, et al., doi: 10.1126/scitranslmed.3008973

Preclinical FLASH Studies with Electrons

LOW ENERGY (<10 MeV) ELECTRON BEAMS PRODUCED USING 100-200 Hz CLINICAL LINACS

FLASH EFFECT OBSERVED - highlights:

- **Study of pulmonary fibrosis from irradiation of the lung[1]**
  - Severe to moderate for conventional average dose rate of 0.03 Gy/sec, 17 Gy total dose
  - For an average dose rate of 40-60 Gy/sec, equivalent fibrosis occurred at 30 Gy total dose
- **Study of neurocognitive impairment from brain irradiation[2]**
  - Severe neurocognitive degeneration at an average dose rate of 0.1 Gy/sec, 10 Gy total dose
  - Improvement starts at 30 Gy/sec with no neurocognitive decline at 100 Gy/sec average dose rate for10 Gy!
- **Skin irradiation (mini-pig)[3]**
  - Fibrosis and necrotic lesions observe at and average dose rate of 0.08 Gy/sec, (22-37 Gy total dose)
  - Only mild depigmentation at an average dose rate of 300 Gy/sec, (22-37 total dose)!

INITIAL PRECLINICAL ELECTRON STUDIES have established general beam conditions for FLASH

- **FLASH: ≥40Gy/sec, ≥10 Gy delivered in 0.1-1 sec, instantaneous dose rate 10^5 - 10^6 Gy/sec (during beam pulse)**

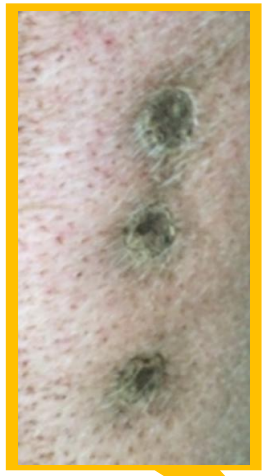
[1] Favaudon V, et al., doi: 10.1126/scitranslmed.3008973, [2] Montay-Gruel, et al., doi: 10.1016/j.radonc.2017.05.003,

[3] Harrington KJ. et al., doi: 10.1158/1078-0432.CCR-18-1796, [4] J. Wilson, et. al., doi: 10.3389/fonc.2019.01563,

FLASH Effect in Skin Irradiation with electrons

Vozenin, et al, The advantage of Flash RT confirmed in mini-pig and cat-cancer patients." Clinical Cancer Research. 2018;

	CONV	Dose	FLASH
Beam Type	Electron	28 Gy	Electron
Nominal Energy	6 MeV		6 MeV
Beam Structure	Pulsed	31 Gy	Pulsed
Pulse Rep Rate	10 Hz		200 Hz
Pulse Width	Few µs	34 Gy	1 µs
Mean Dose Rate	0.08 Gy/s		300 Gy/s



Preclinical FLASH Studies with Photons

(photon dose rates from clinical electron linacs are too low)

CREATING HIGH DOSE RATES OF PHOTONS

PHOTONS FROM LIGHT-SOURCE SYNCHROTRONS

- **Synchrotron Broad-Beam Radiation therapy (SBBR)**
  - One study did not show FLASH effect (37 – 41 Gy/sec, 4-28 Gy)[1]
  - Another, mouse-brain irradiation (37 Gy/sec, 10 Gy), significant cognitive sparing; (vertical beam size x20 smaller)[2]
- **Microbeam Radiation therapy (MRT) – grid of "pencil" photon beams[1]**
  - Parallel beam array, 25-100 μm (peak) spaced by 100-400 μm (valleys)
  - Peak average dose rate ~300 Gy/sec; valley average dose rate lower factor of ~30 and strong indicator of toxicity
  - The low dose rates, especially in valleys, conjectured to be the reason for no FLASH effect

PHOTONS FROM BREMSSTRALUNG[3]

- **FLASH dose rates produced by a high intensity 10-MeV SRF electron linac, tungsten target;**
  - Significant FLASH effect observed for lungs and tissues[3]
  - Original 1969 study and a recent Monte Carlo Study suggests FLASH with X-ray tubes may be possible[4]

[1] Smyth LML, et al., doi: 10.1038/s41598-018-30543-1), [2] Montay-Gruel, et al., doi: 10.1016/j.radonc.2018.08.016)

[3] Gao F, et al., doi: https://doi.org/10.1101/2020.11.27.401869;, [4]Bzalova-Carter M, et al., doi: 10.1002/mp.13858.2017.05.003

Preclinical FLASH Studies with Protons

(Pulsed FLASH has been proposed using large synchrotrons and fast single-turn extraction)

VERY HIGH PROTON DOSE RATES (CW) FROM ISO-CYCLOTRONS

230-250 MEV PROTON THERAPY CYCLOTRONS – very few studies

- **Requires shoot-through or non-degraded beam to achieve FLASH intensities**
  - **MIXED RESULTS** (high-energy beam placed Bragg peak beyond the targeted area)[1,2]
- **Individual RF (MHz) proton bunch structure may be important for proton FLASH**
  - Proton RF "bunches' are fractions of a microsecond; electron RF bunches are fractions of a nanosecond
  - Proton beam is "quasi-continuous" ; 100-300 Hz electron linacs produce a microsecond "macro-pulse"
  - For proton FLASH it can be hypothesized that the instantaneous dose rate of $>10^5$ Gy/sec must be achieved within the RF bunch pulse
  - For pulsed electron beams the instantaneous dose rate is integrated over microsecond macro-pulse
- **The <1 sec treatment time may not apply to quasi-continuous beams**
  - CW electron linacs , like proton cyclotrons, produce a quasi-continuous beam

[1] Rama N, Saha, et al., doi: 10.1016/j.ijrobp.2019.06.187, [2] Beyreuther E, et al., doi: 10.1016/j.radonc.2019.06.024

COMPENDIUM: FLASH IN VIVO STUDIES IN NORMAL TISSUES: Irradiation parameters with outcomes for electrons (green), protons (blue) and X-rays (grey)
J. Wilson, et. al., "Ultra-high Dose Rate (FLASH) Radiotherapy Silver Bullet or Fool's Gold", Frontiers in Oncology, Vol 9, Jan 2020.

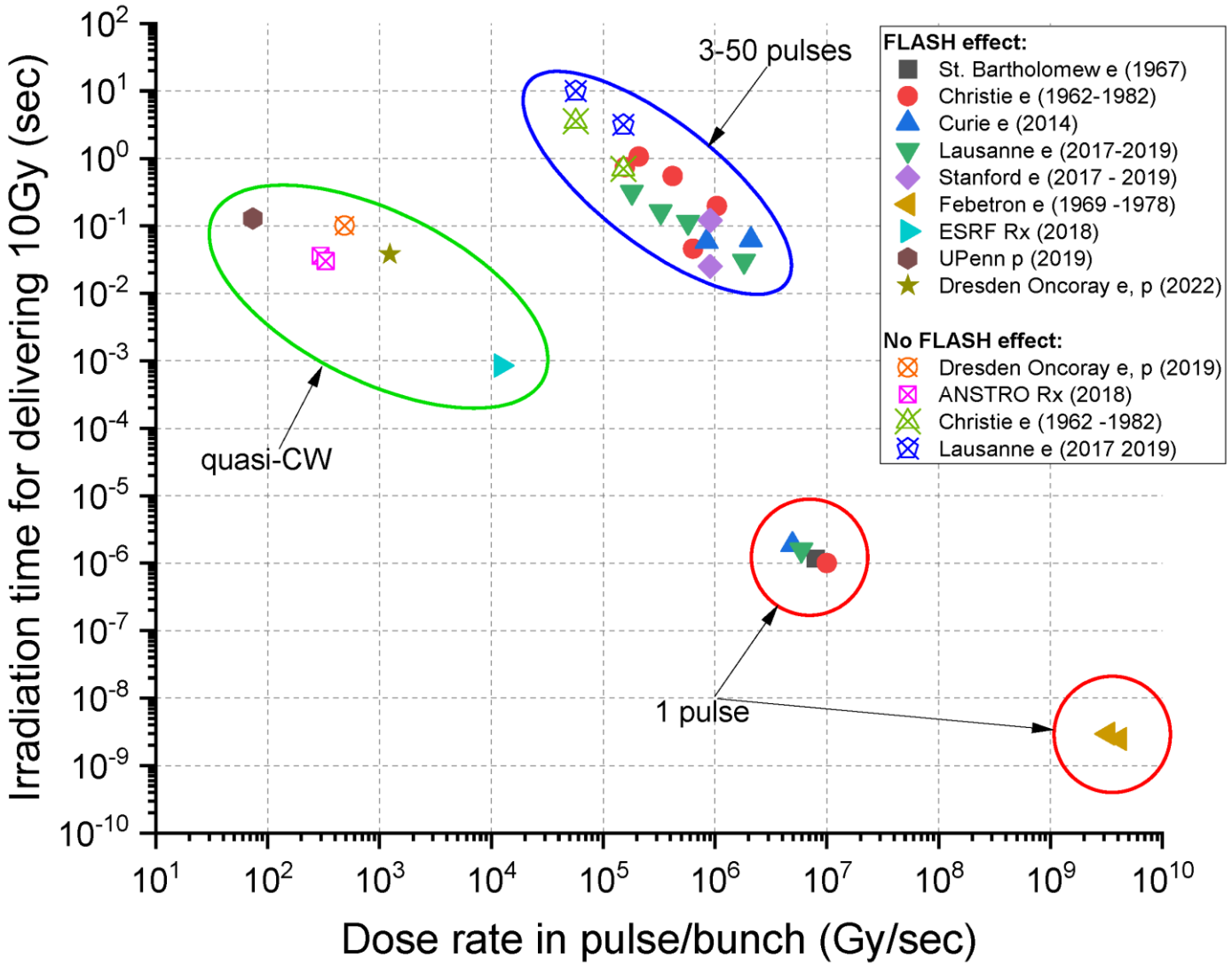
Model	Assay	FLASH dose modification factor (Bold if >1)	Total dose (Gy)	Dose rate (Gy/s)	Pulse rate (Hz)	Modality of radiation
Zebrafish embryo (16)	Fish length	**1.2–1.5**	10–12	10^6-10^7	Single pulse	Electron
Zebrafish embryo (29)	Fish length, survival, and rate of oedema	1	0–43	100	0.106 × 10^9	Proton
Whole body irradiation of mice (34)	LD50	**1.1**	8–40	17–83	400	Electron
Thoracic irradiation of mice (10)	TGFβ signaling induction	**1.8**	17	40–60	100–150	Electron
Thoracic irradiation of mice (18)	Number of proliferating cells, DNA damage, expression of inflammatory genes	**>1 Significant Differences**	17	40–60	100–150	Electron
Abdominal irradiation of mice (33)	Survival	<1 Significant Difference	16	35	Likely 300	Electron
Abdominal irradiation of mice (12)	LD50	**1.2**	22	70–210	100–300	Electron
Abdominal irradiation of mice (17)	Survival, stool formation, regeneration in crypts, apoptosis, and DNA damage in crypt cells	**>1 Significant Differences**	12–16	216	108	Electron
Whole brain irradiation of mice (25)	Novel object recognition and object location tests	**>1 Significant Differences**	30	200, 300	108, 180	Electron
Whole brain irradiation of mice (13)	Variety of neurocognitive tests	**>1 Significant Differences**	10	5.6·10^6	Single pulse	Electron
Whole brain irradiation of mice (14)	Novel object recognition test	**>1 Significant Differences**	10	30–5.6·10^6	100 or single pulse	Electron
Whole brain irradiation of mice (8)	Novel object recognition test	**≥1.4**	10	5.6–7.8·10^6	single pulse	Electron
Whole brain irradiation of mice (24)	Novel object recognition test	**>1 Significant Difference**	10	37	1,300	X-ray
Total body and partial body irradiation of mice (32)	TD50	1	3.6–28	37–41	1,388	X-ray
Thoracic irradiation of mice (11)	lung fibrosis, skin dermatitis, and survival	**>1 Significant Difference**	15, 17.5, 20	40	?	Proton
Irradiation of mouse tail skin (49)	Necrosis ND50	**1.4**	30 and 50	17–170	50	Electron
Irradiation of mouse skin (27)	Early skin reaction score	**1.1–1.6**	50–75	2.5 mean, 3 × 10^4 in the pulse	23–80	Electron
Irradiation of rat skin (26)	Early skin reaction score	**1.4–1.8**	25–35	67	400	Electron
Irradiation of mini-pig skin (15)	Skin toxicity	**≥1.4**	22–34	300	100	Electron

COMPENDIUM: FLASH IN VIVO STUDIES IN TUMOR TISSUES: Irradiation parameters with outcomes for electrons (green), protons (blue) and X-rays (grey)
J. Wilson, et. al., "Ultra-high Dose Rate (FLASH) Radiotherapy Silver Bullet or Fool's Gold", Frontiers in Oncology, Vol 9, Jan 2020.

In vivo studies			Irradiation delivery technique			
Model	**Assay**	**FLASH dose modification factor (Bold if >1)**	**Total dose (Gy)**	**Dose rate (Gy/s)**	**Pulse rate (Hz)**	**Modality of radiation**
Thoracic irradiation of orthotopic engrafted non-small cell lung cancer (Lewis lung carcinoma) in mice (36)	Tumor size and T-cell Infiltration	**>1 Differences in tumor size (significant) and T-cell infiltration**	18	40	?	Proton
Thoracic irradiation of orthotopic engrafted mouse lung carcinoma TC-1 Luc+ in mice (10)	Survival and tumor Growth Delay	1	15-28	60	100–150	Electron
Abdominal irradiation of mice (17)	Number of tumors, tumor weights	1	12–16	216	108	Electron
Whole brain irradiation of nude mice with orthotopic engrafted H454 murine glioblastoma (8)	Tumor Growth Delay	1	10–25	$2.8–5.6 \cdot 10^6$	Single pulse	Electron
Local irradiation of subcutaneous engrafted Human breast cancer HBCx-12A and head and neck carcinoma HEp-2 in nude mice (10)	Tumor Growth Delay	1	15–25	60	100–150	Electron
Local irradiation of subcutaneous engrafted U87 human glioblastoma in nude mice (8)	Tumor Growth Delay	1	0–35	$125–5.6 \cdot 10^6$	100 or single pulse	Electron
Local irradiation of subcutaneous engrafted U87 human glioblastoma in nude mice (19)	Tumor Growth Delay	1	10–30	$125–5.6 \cdot 10^6$	100 or single pulse	Electron
Local irradiation of subcutaneous engrafted Human hypopharyngeal squamous cell carcinoma ATCC HTB-43 in nude mice (35)	Tumor Growth Delay in irradiated Mice and RBE	1	20	0.008 mean, $\approx 10^9$ in pulse	<<1	Proton
Treatment of locally advanced squamous cell carcinoma (SCC) in cat patients (15)	Tumor response and survival	1 Similar response as in published studies with CONV-RT	25–41	130–390	100	Electron
Treatment of CD30+ T-cell cutaneous lymphoma T3 N0 M0 B0 in human patient (9)	Tumor response	1 Similar response as previous treatments with CONV-RT	15	167	100	Electron

FLASH STUDIES AT ACCELERATOR FACILITIES

†R. Schulte and C. Johnstone, editors, "Transformative Technology for FLASH Radiation Therapy", in Appl. Sci., 13(8), Apr, 2023, pp. 5021. https://doi.org/10.3390/app13085021



FLASH studies at accelerator facilities with different radiation types† (right panel).

The FLASH effect has been observed for a wide IDR range of repeated linac pulses and different types of quasi-CW bunch delivery with iso-cyclotrons and synchrotron radiation light sources.

*FLASH effects were also seen with single electron pulses with IDR in the range of 10^5–10^7 Gy/s and single pulse 10^9–10^{10} Gy/s, respectively.**

* Graph Modified from Montay-Gruel P et al. Clin Cancer Res. 2021 doi:10.1158/1078-0432.CCR-20-0894; data grouped according to delivery method with an added data point from Karsch et al, Radiother. Oncol. 2022, 173, 49–54.

Beam Conditions for FLASH

The FLASH effect has been observed for

- **A wide Instantaneous Dose Rate (IDR) range**
  - A train of electron linac pulses
  - quasi-CW bunch delivery with iso-cyclotrons and synchrotron radiation light sources.
  - Single electron pulses with IDR in the range of 10^6–10^7 Gy/s and 10^9–10^{10} Gy/s, respectively.

Preclinical FLASH beam properties relevant to a clinical application of FLASH

Electron Beam	Min. for Observed FLASH	Optimal for FLASH
Average dose rate	30 Gy/s **(now ~70 Gy/sec)**	100 Gy/s
Intrapulse dose rate	~10^5 Gy/s	≥10^6 Gy/s
Total dose	<10 Gy	≥10 Gy—tissue dependent
Delivery time for 10 Gy	<1 s	1 μs–10 ms

Factors that Influence the FLASH effect

mean and instantaneous dose rate, total dose, pulse structure, fractionation, and radiation type

ABSENCE OF SYSTEMATICS in MOST STUDIES:

INITIAL FLASH SYSTEMATICS (wide range of dose rates)

- **FLASH effects begin to appear at average dose rates >30 Gy/sec, apparent optimal at 100 Gy/sec[1]**
  - FLASH effect likely tissue dependence
  - Dependence on the micro-structure of beam delivery and the uniformity of dose deposition
- **Beam Delivery**
  - Maximum dose delivery time for a consistent (electron) FLASH effect is $\leq$0.1-1 second
  - ***MOST positive FLASH studies used a pulsed clinical electron linac (beam pulse length of microseconds)***
  - Instantaneous (within the pulse) FLASH dose rate is 10^6 Gy/sec (again, characteristic of clinical electron linacs)
- **Dosimetric issues**
  - Observed Volumetric dose deposition dependence
  - Low dose-rate areas not tolerated during FLASH – toxicity reappears[2]
  - Bragg peak and pencil beam scanning questions - distal edge and penumbra issues which create lower-dose rate beam "halos"?
  - ***Can a Large Gross Tumor Volume be uniformly irradiated with FLASH?***
  - ***Instantaneous FLASH dose rate and delivery time for 10 Gy - is it consistent for all radiation types***

[1] Montay-Gruel, et al., doi: 10.1016/j.radonc.2017.05.003, [2] Smyth LML, et al., doi: 10.1038/s41598-018-30543-1

FLASH intensities translated into hadron accelerator currents

Dose translated to a clinical application of ion FLASH - Derived from electron FLASH conditions

R. Schulte, et. al. https://www.mdpi.com/2076-3417/13/8/5021

U. Titte, MDAnderson, private communication

Dose Delivery Mode	Protons	Helium	Carbon
Conventional: 2.6 Gy/fraction	2×10^9 p/s	5×10^8 He/s	1.7×10^8 C/s
Delivery time: 100 s	0.4 nA	0.2 nA	0.2 nA
FLASH: $\geq$10 Gy/fraction	1×10^{13} p/s	2.5×10^{12} He/s	0.8×10^{12} C/s
Delivery Time: 100 ms	1.6 µA	0.8 µA	0.8 µA

FLASH with Pulsed Electron Accelerators

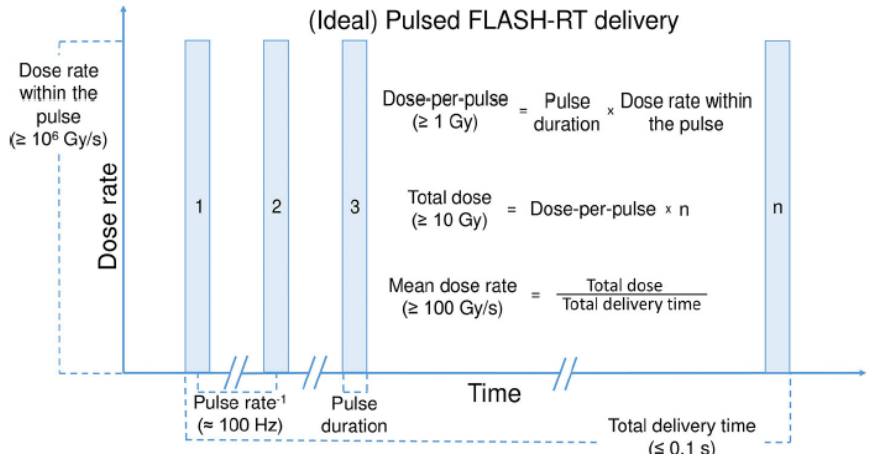
A pulsed electron accelerator is very effective for applying clinical FLASH

Example of Electron Pulsed Beam Structure for FLASH[1]

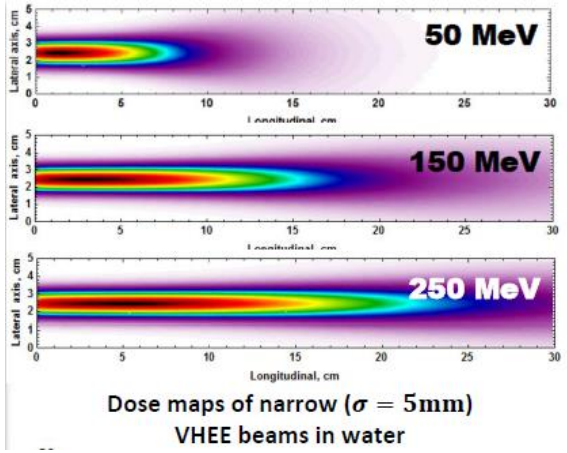
- **Schematic of typical clinic pulse structure is shown in Figure**
  - Given ≥10 Gy total dose in 100 ms, 10^6Gy/sec instantaneous
  - Dose is then calculated per single pulse and macro-pulse length

Very High Energy Electrons (VHEE) Therapy[2]

- **Tumor depths of 30 cm require 200-250 MeV electrons**

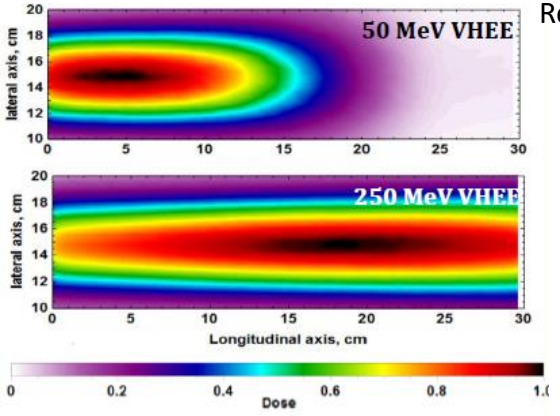


Schematic view of pulsed beam delivery inducing the FLASH effect



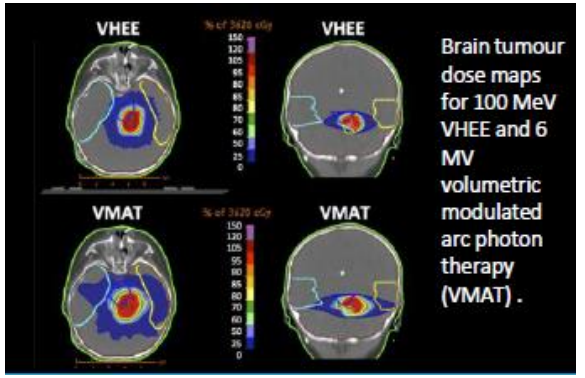
Dose maps of narrow ($\sigma = 5$mm) VHEE beams in water

Ref 3



Dose maps of wide ($\sigma = 20$mm) VHEE beams in water

Ref 4



VHEE vs arc photon treatment plans

- Higher dose rate vs photons
- ~70% lower dose to normal tissue
- Particle steering and focusing capability

[1] J. Wilson, et. al., doi: 10.3389/fonc.2019.01563, [2] D. Bartkoski, private communication, [3]A. Lazda, et al, "Applications of VHEE for Radiotherapy," CLIC workshop 2017, , [4]M. Bazalova-Carter *et al*, "Treatment planning for radiotherapy with very high-energy electron beams and comparison of VHEE and VMAT Plans," Medical Physics, vol. 42(5), 2015.

Towards Understanding FLASH Radiobiology

What do we know about the radiobiology and radiation chemistry of FLASH?

Primary mechanism of tumor kill is DNA damage from radiation induction of free radicals into the DNA structure

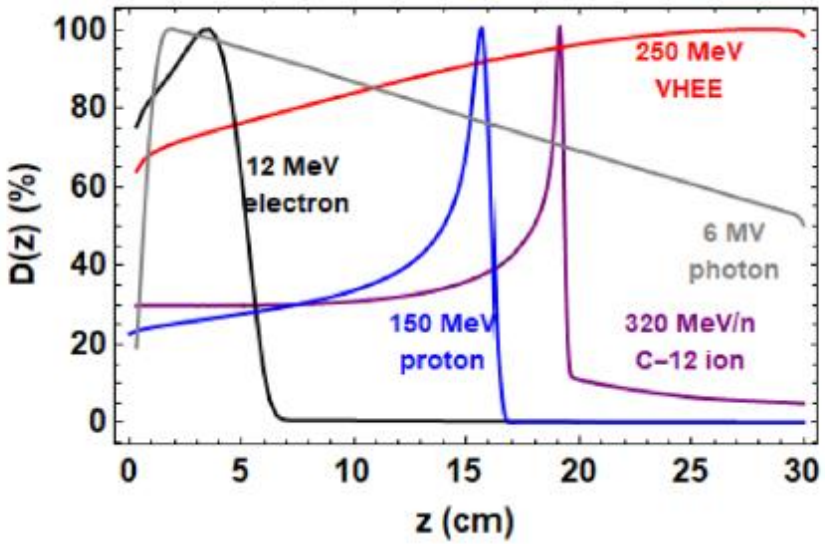
- **Depletion of oxygen**
  - Oxygen depletion is one of the most frequent hypotheses to explain the FLASH effect
  - In healthy tissues, oxygen can be depleted from a normal level by numerous radio-chemical reactions that take place during the physico-chemical and chemical stage of irradiation, cells might be transiently hypoxic and radioresistant
  - In tumors, O2 concentration is generally lower, so tumors are not as impacted by the depletion of oxygen
- **Other Explanations**
  - Mitochondrial oxygen metabolism in tumor cells is mostly due to aerobic glycolysis (Warburg effect)
  - Tumors consume large amounts of glucose a mechanism insensitive to hypoxia
  - Hypoxic cells in tumors do not become more hypoxic by FLASH and remain resistant to low radiation doses
  - Puzzling, is that they seem to be more sensitive at high radiation doses, possibly to immune-sensitization.
  - The tumor's microvasculature also appears more sensitive to high single doses than normal capillaries.
  - Tissue oxygen levels return to normal (estimate is 10^{-3} sec)– pulse structure of beam may play an important role
    - Race against oxygen replenishing – maintains hypoxia environment during a short radiation pulses
    - Tumor vessels are known to be more transparent for oxygen (leaky) and replenishing could happen faster
    - This would further explain the absence of a FLASH sparing in tumors

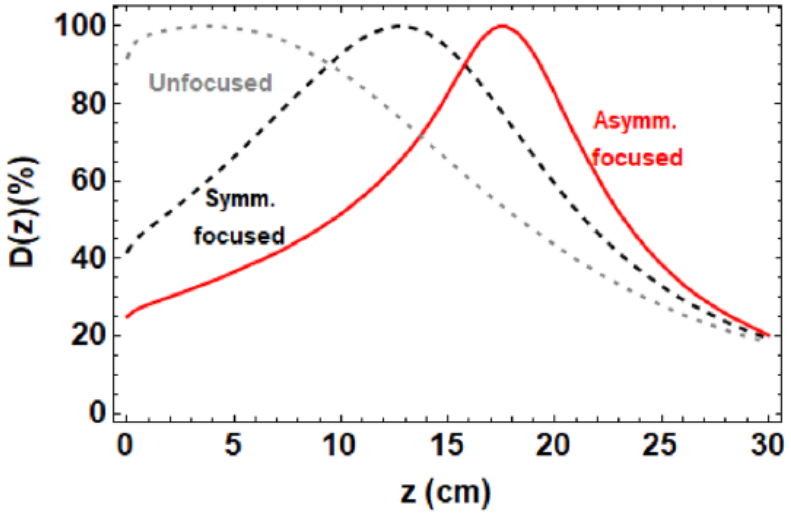
Controlling VHEE Dose Deposition

Creating a targeted preferably peaked dose deposition

The OPTICS of dose deposition with VHEE [1]

- **Comparing radiotherapy with electrons, protons, photons and unfocused/focused VHEE**
  - TOPAS-based Monte Carlo simulations for integrated normalized dose for incident Gaussian beam (σ = 4 mm)
  - TOPAS-based Monte Carlo simulations for normalised on-axis dose for 250 MeV "symmetric and asymmetric" focused beams and nominal unfocused 250 MeV VHEE.





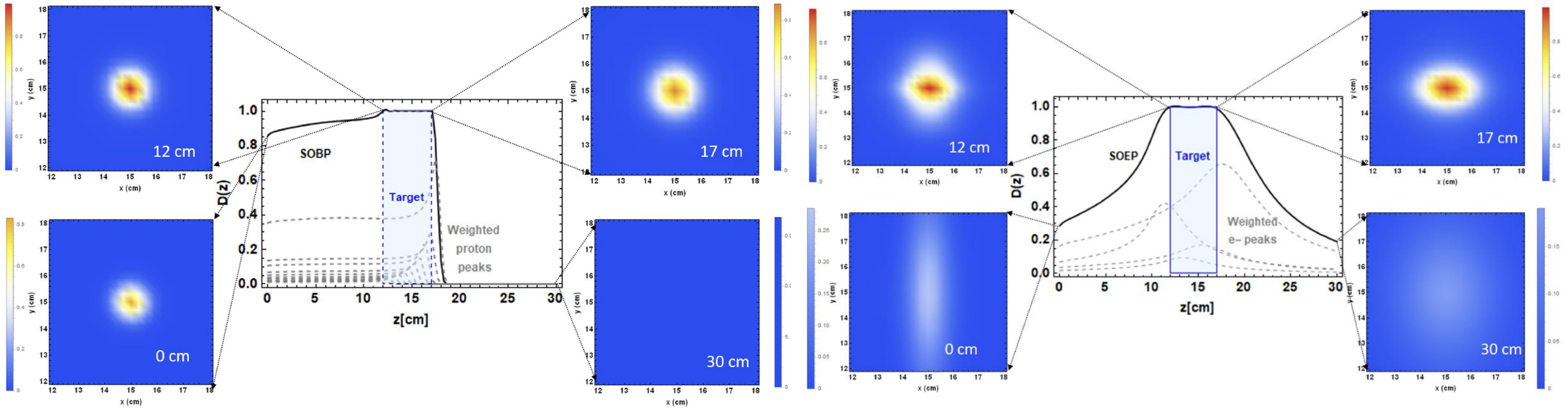
[1] L. Whitmore,. *et al.* Focused VHEE (very high energy electron) beams and dose delivery for radiotherapy applications. *Sci Rep* **11**, 14013 (2021). https://doi.org/10.1038/s41598-021-93276-8

Clinical Application of VHEE

A clinical application then requires combining doses to create a Spread-Out Dose Peak over the Tumor

Spread-Out Peaks covering and conformal to Gross Tumor Volume in depth [1]

- **Creating a Spread-Out Bragg and Electron Peak (SOBP and SOEP)**
  - SOBP requires the accelerator/beam delivery to change energy for depth
  - SOEP does not change energy but intensity and focusing for depth
    - Intensity Modulated Radiotherapy is standard in photon therapy



[1] L. Whitmore,. *et al.* Focused VHEE (very high energy electron) beams and dose delivery for radiotherapy applications. *Sci Rep* **11**, 14013 (2021). https://doi.org/10.1038/s41598-021-93276-8

Clinical Application of FLASH with Pulsed Electron Accelerators

A clinical application also requires transverse scanning over a large field

Example: 100 Hz Accelerator FOR 200 MeV VHEE [1,2]

- **Treatment models give 10 Gy/sec ≅ 10^{11} e/sec[ref 2] using a Gaussian beam (σ=1.5 mm)**
  - Average 100 Gy/sec in 100 msec = 10 Gy dose, which is ten 1-Gy pulses @100 Hz
  - 10^6 Gy/sec instantaneous dose rate requires a 1 μsec single pulse length for a 1 Gy pulse
  - This is 10^{11} electrons delivered in 100 ms, or 10^{10} e/μsec (# electrons scales with pulse length, # of pulses inversely)
- **How would you scan with a 100 Hz Linac,, 1 μsec pulse length?**
  - 15 cm x 15 cm field – 10 pulses at each 1.5 mm position x (100 x 100 positions) or 100,000 pulses; 1000 sec or 17 min
  - Scan rate – 15 cm/1000 pulses or 15 cm/10 sec or 1.5 cm/sec - isn't technically challenging
  - Clinical electron linacs are only 10-20 MeV – so here is where advanced accelerators can play a major role

[1] J. Wilson, et. al., doi: 10.3389/fonc.2019.01563, [2] D. Bartkoski, private communication

Existing FLASH-capable beams

Facilities with intense beams and high energy beams

SRF Linac

- **Lower cycling time is relevant for FLASH Radiobiology (Fermilab FAST Linac)**
  - FAST SRF Linac produces 5, 50, 150, and 300 MeV electron beams
  - FAST delivers 10^{14}e/msec-pulse @5Hz;
  - The FAST Linac can delivers $\leq 10^4$ Gy/ms pulse @instantaneous dose rate of 10^7 Gy/sec
  - 5 Hz represents a limitation for clinical scanning

Synchrotrons and Laser Accelerators (proton, ion, and electron)

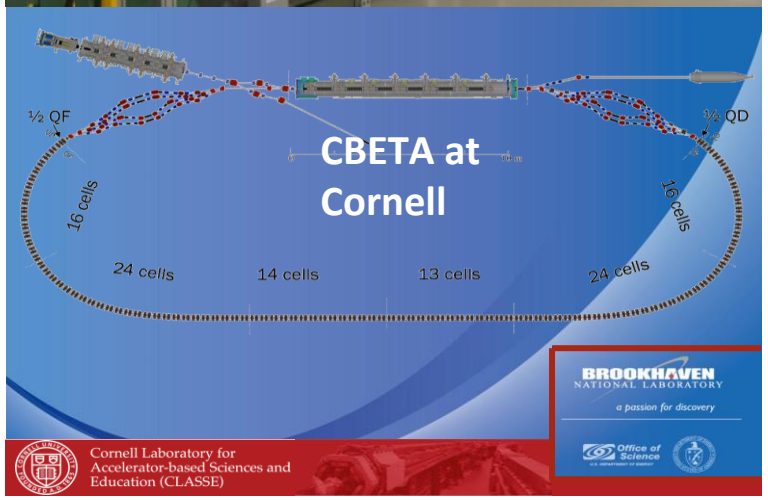
- **Single intense, low-energy nanosecond pulses @1-10 Hz**
  - Platform for understanding radiobiology – being pursued at BELLA with protons
  - Hadron synchrotrons produce "single-spill", variable energy FLASH beams

CBETA – Energy Recovery Linear Accelerator (ERL): 6-150 MeV electrons

- **CW 1.3 GHz linac, single FFA arc, 4 simultaneous acceleration turns**
  - CW VHEE beam in a recirculating format,
  - CBETA can deliver ~10^8 e/nsec-bunch @instantaneous dose rate of 10^6 Gy/sec
  - CBETA can SCAN: 10^6 Gy/sec @ 200 cm/ms at peak intensity!
  - Machine size can be dramatically reduced by replacing permanent magnets

Synchrotron Light Sources

- **Produces short pulse, high intensity broad-band X and gamma rays**
  - Photons are the most penetrating; ongoing preclinical studies



What about Dosimetry – *Monitoring FLASH delivery*

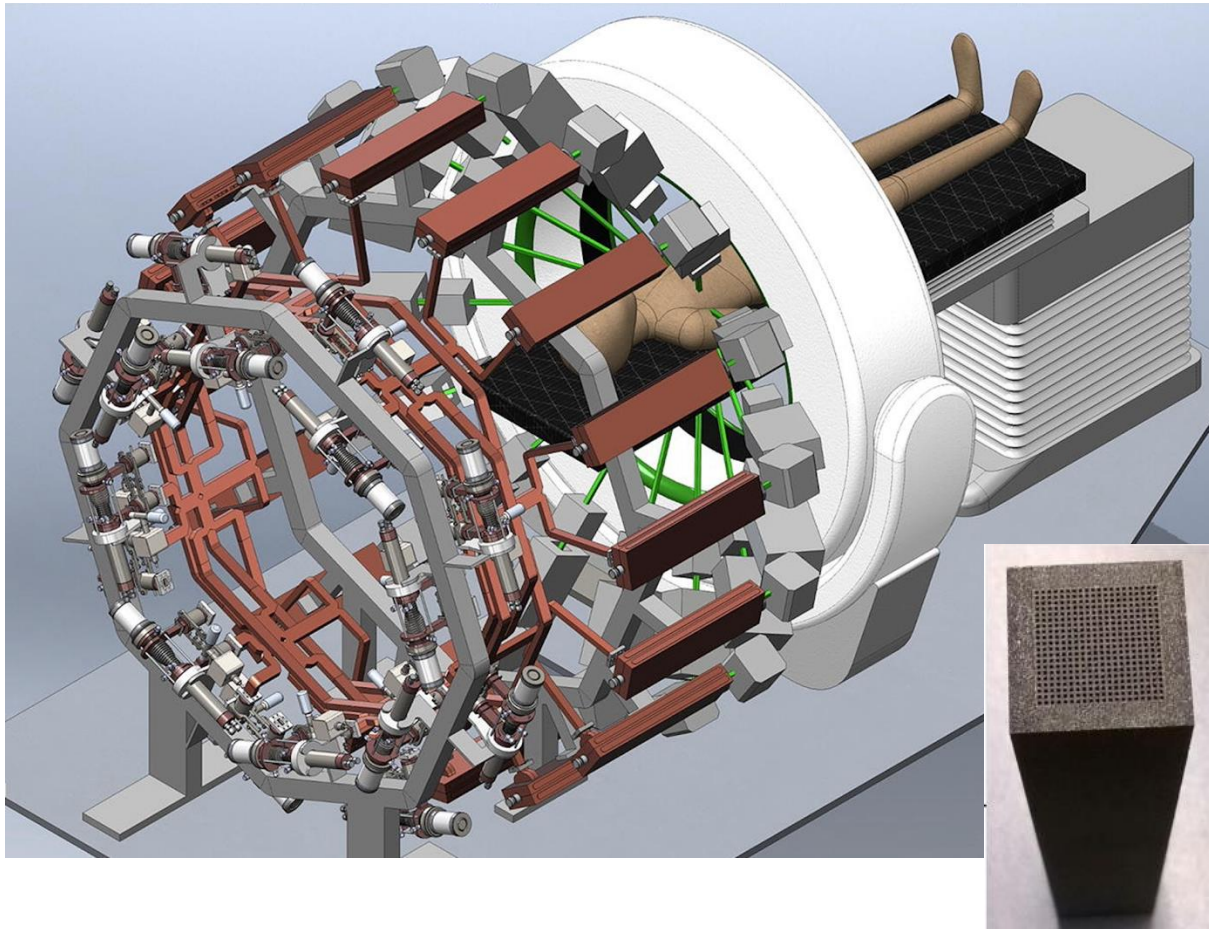
FLASH is ***~1000*** times faster

FLASH dose is delivered in **< 100 ms**. For *proton*-FLASH (@40 Gy/sec) the corresponding beam luminosity is $\sim 6.25 \times 10^{11}$ ***protons/cm²-sec***

- ***Standard dosimetry methods <u>do not work</u>*** at the radiation intensity of FLASH delivery

PHASER: multiple linac beam delivery

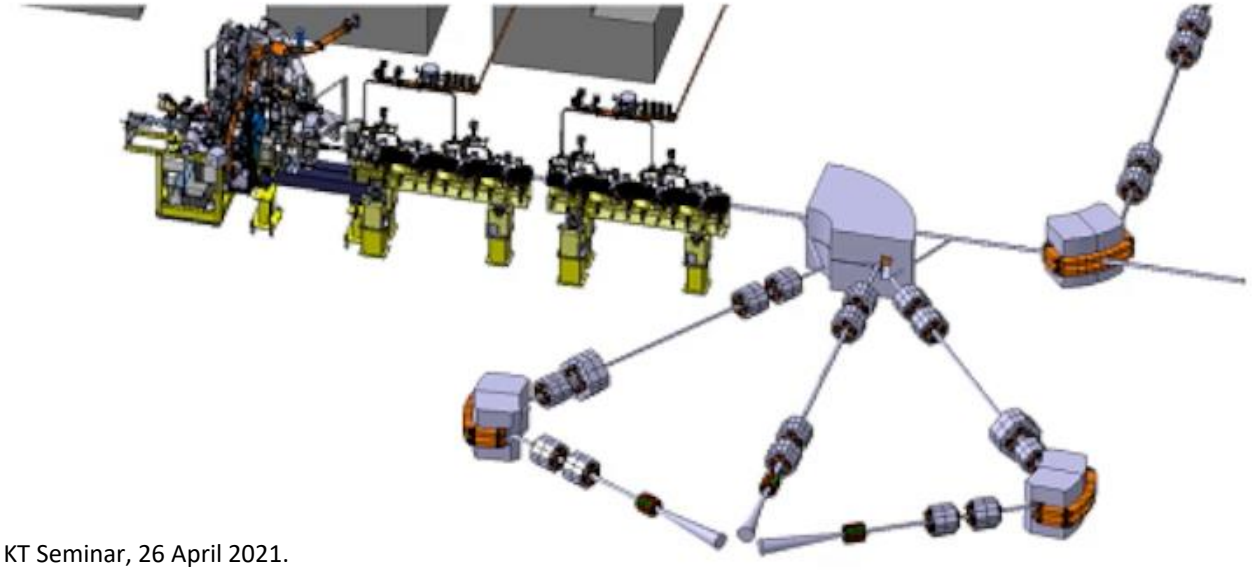
- A team from Stanford/SLAC has proposed the Pluridirectional High-energy Agile Scanning Electronic Radiotherapy (PHASER) concept
- To deliver X-rays at FLASH dose rates, 16 linacs are arranged around the patient
  - 10 MeV, 300 mA peak, 1.5 mA average
- Power from 16 klystrons are combined and transmitted to each linac in sequence with a special waveguide network
- To achieve intensity modulation, the beam is quickly scanned over an X-ray converter/collimator array
- Also considering adapting this approach for very high energy electrons (VHEE).

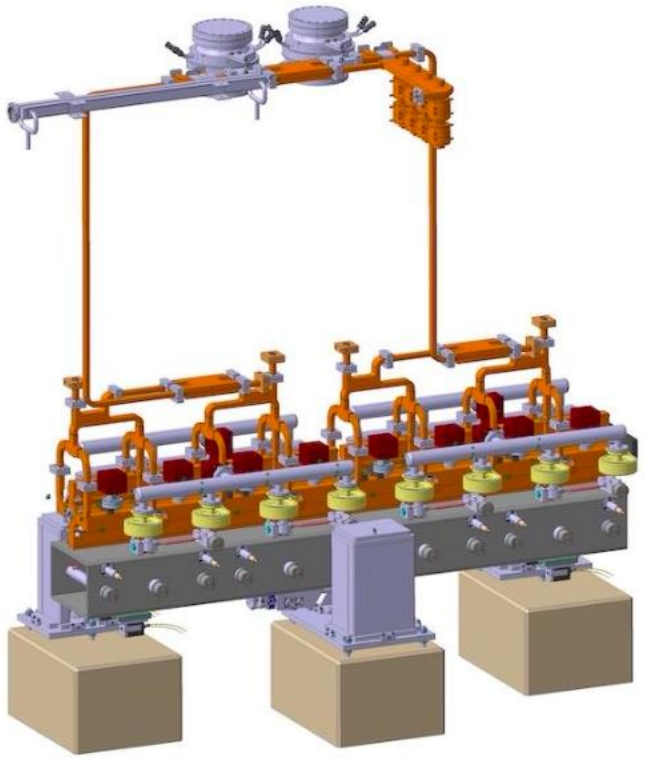


P.G. Maxim et al. / Radiotherapy and Oncology 139 (2019) 28–33

DEFT: CERN CLIC-based Accelerator Technology

- CHUV (Lausanne) and CERN have begun to develop an approach to VHEE FLASH called Deep Electron FLASH Therapy (DEFT)
- 160 MeV using 2 m of high-gradient X-band linacs, leveraging CLIC technology
- Multiple beam angles to patient provided by energy modulation + dipole ma



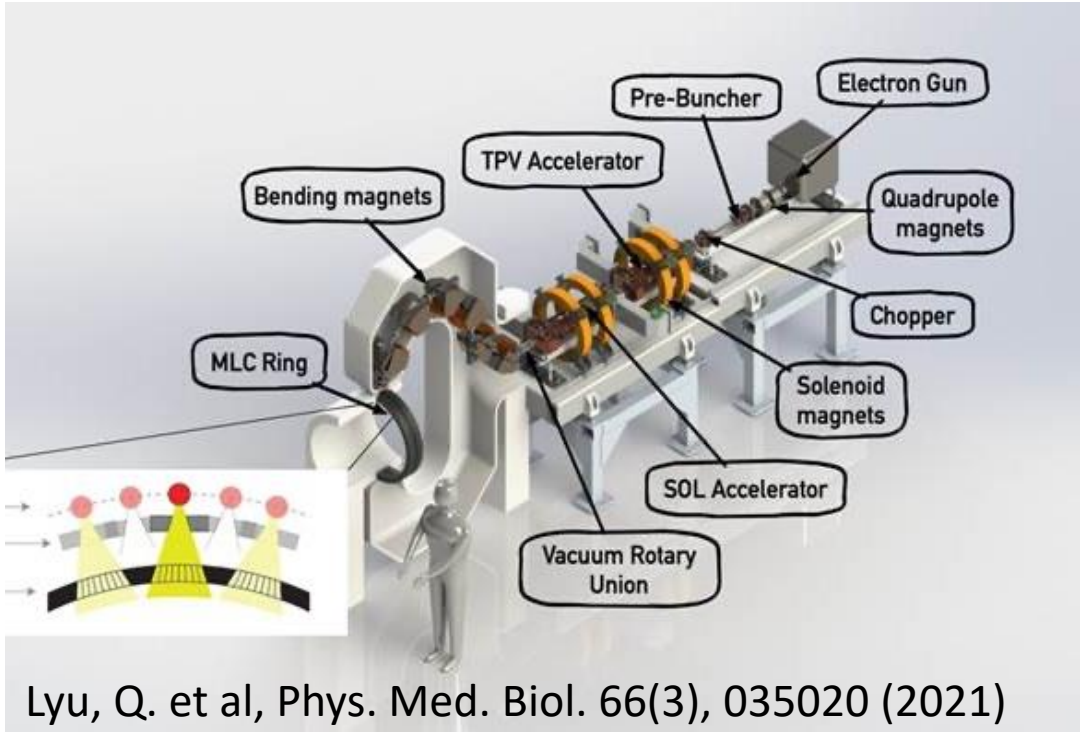


W. Wuensch, KT Seminar, 26 April 2021.
https://indico.cern.ch/event/975980/

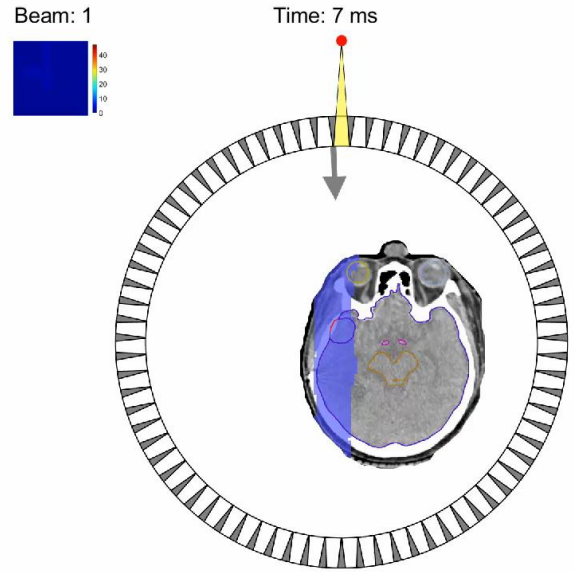
ROAD: Collaboration between Radiabeam and UCLA

- RadiaBeam with UCLA are working to design and build a single linac solution based on a ROtational direct Aperture optimization with a Decoupled (ROAD) multi-leaf collimator (MLC) ring
- The linac pulses are timed to align with a counter-rotating ring of 75 pre-shaped MLC apertures. As both the linac and MLC ring rotate in opposite directions at 60 rpm, 150 modulated beams are delivered in 1 s, with each delivering up to 0.67 Gy to the tumor*

*The goal of this project is to study the parameters for X-ray delivery that result in the best combination of FLASH effect

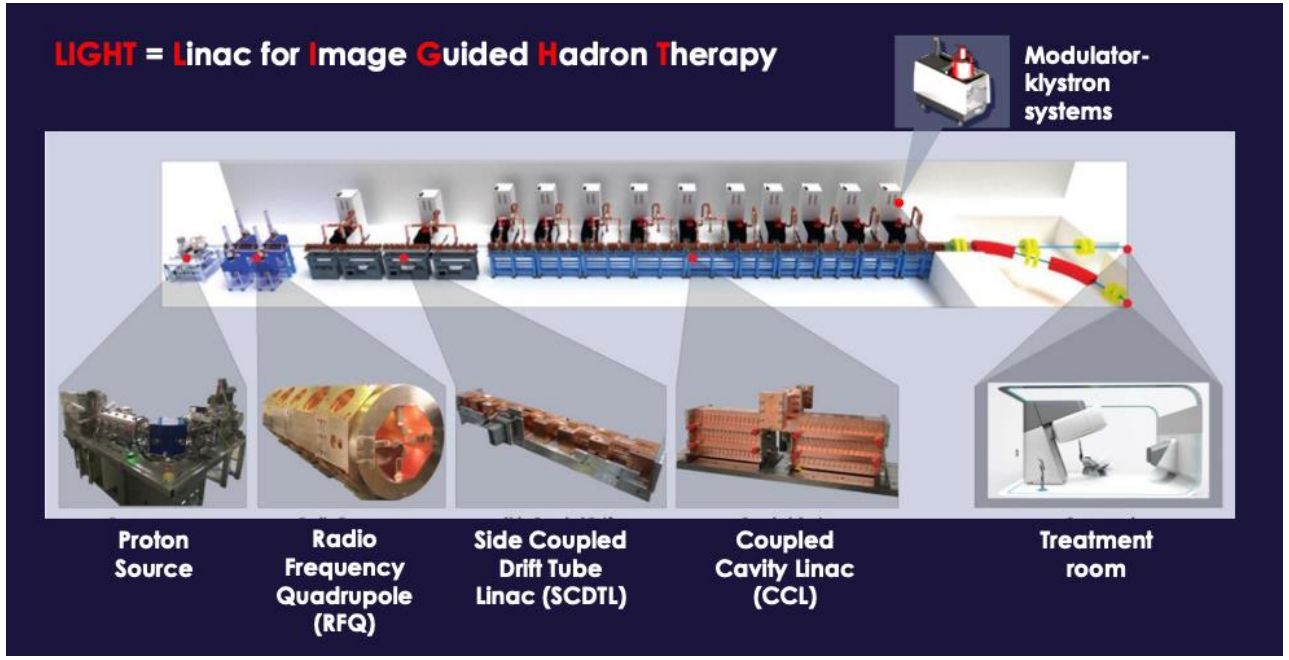


Lyu, Q. et al, Phys. Med. Biol. 66(3), 035020 (2021)

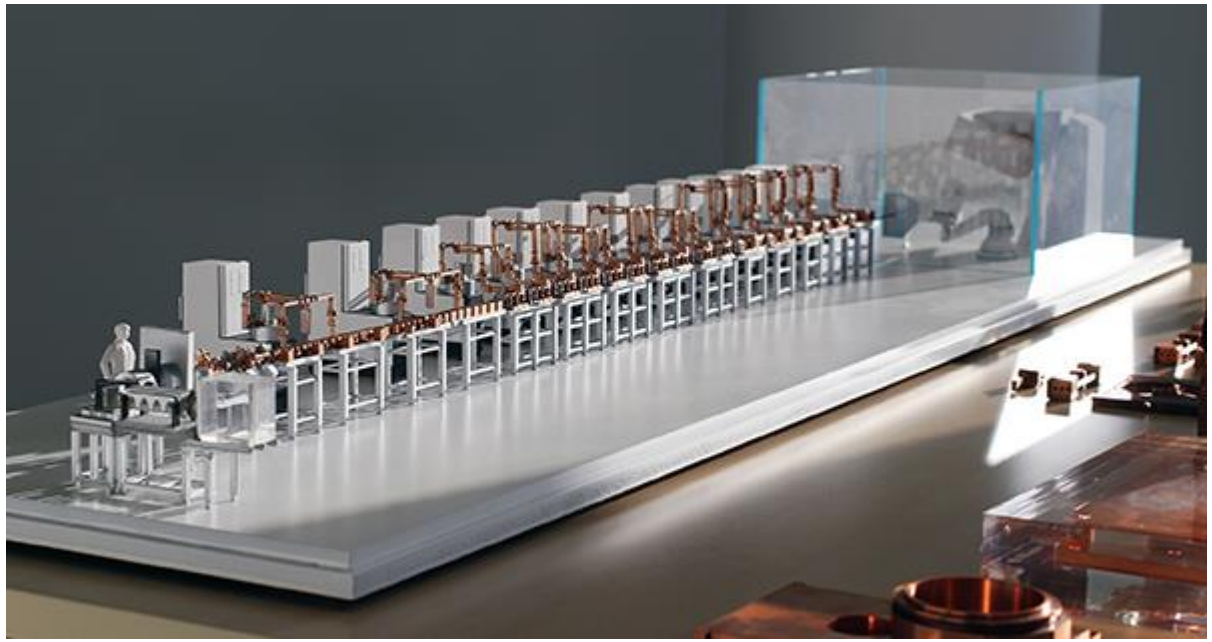


LIGHT – C-band proton linac; CERN Technology

- Advanced Oncotherapy and ADAM (CERN spinoff) have developed the LIGHT system for proton therapy
- 230 MeV in ~24 m of linac, 3 GHz RF power provided by common 7.5 MW klystrons
  - 230 MeV beam has been demonstrated
- Also capable of FLASH delivery with spot scanning



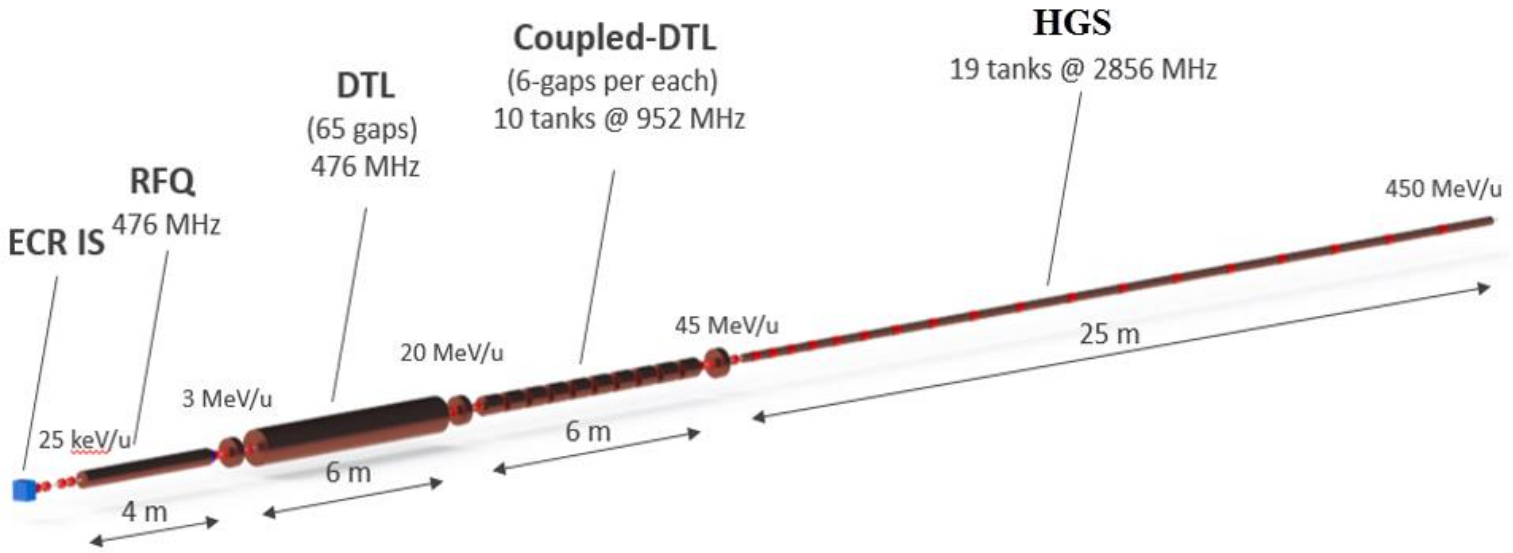
A.M Kolano et al. Particle therapy co-operative group 58 (2019).
http://www.avoplc.com/Portals/0/adam/Newsroom/JT-G-yB62U6zzacNPeYGdg/Link/PTC58-0627.pdf



A. Degiovanni et al. NAPAC2016, https://cds.cern.ch/record/2314160/files/frb1io02.pdf

ACCIL: Argonne National Laboratory and Radiabeam

- The Advanced Compact Carbon high gradient Ion Linac (ACCIL) is being developed by a collaboration of Argonne National Laboratory and RadiaBeam Systems
- ACCIL must provide 1 GV accelerating voltage in a 45m footprint
- ~35 MV/m real-estate and 50 MV/m accelerating gradients are required.
- The project goal is to develop 50 MV/m structures for β=0.3-0.7

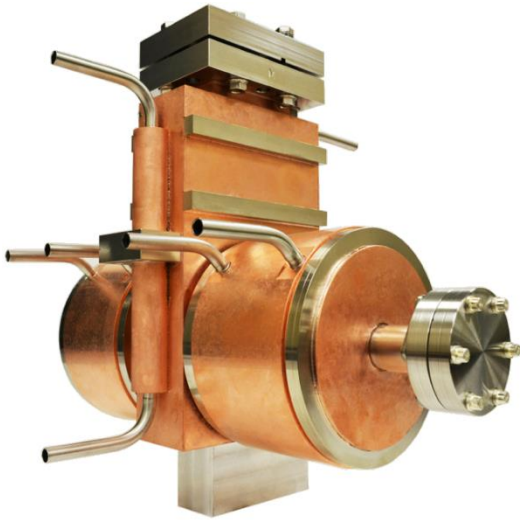


P. Ostroumov *et al.*, Compact Carbon Ion Linac, Proc. NAPAC-2016

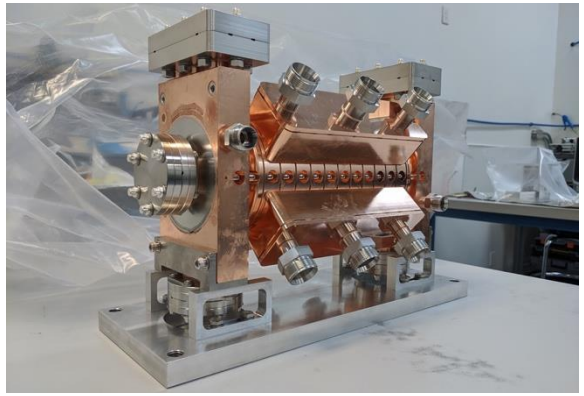
- Capable of accelerating a variety of ion species, proton to neon, up to an energy of 450 MeV per nucleon
- Pulse-to-pulse energy modulation
- Intensity modulation at the source or by changing the pulse rep. rate
- Fast ion beam switching possible from different ion sources in the front-end
- Fast and effective variable energy intensity-modulated multi-ion beam therapy is possible with ACCIL
- In addition to particle therapy, radiobiology research, imaging R&D and other applications are possible

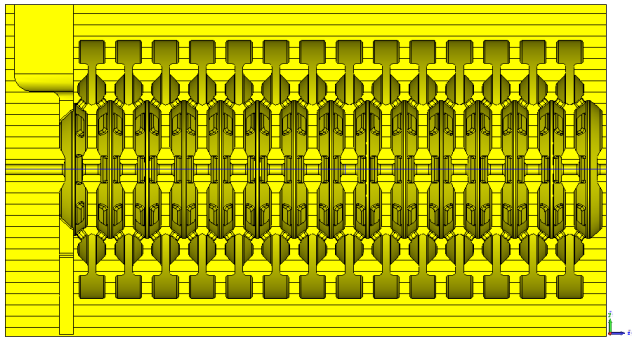
ACCIL Accelerator R&D

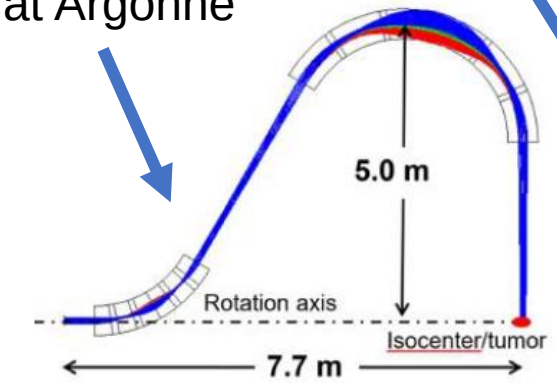
- Development of high-β 50 MV/m CCL structure
  - Developed and built by RadiaBeam, tested at Argonne in 2016
- Negative Harmonic Structure for β=0.3
  - Developed and built by RadiaBeam, tested at Argonne in 2021
- Negative Harmonic Structure for β=0.3 at 1000 Hz rep. rate
  - Under development at RadiaBeam (due 2023)
- Annular Coupled Structure for β=0.4
  - Under development at Argonne
- Compact Ion Beam Scanner & SC Gantry
  - Under development at Argonne



S.V. Kutsaev et al, IEEE Trans. Microw. Wirel. Comp. Lett., 2021



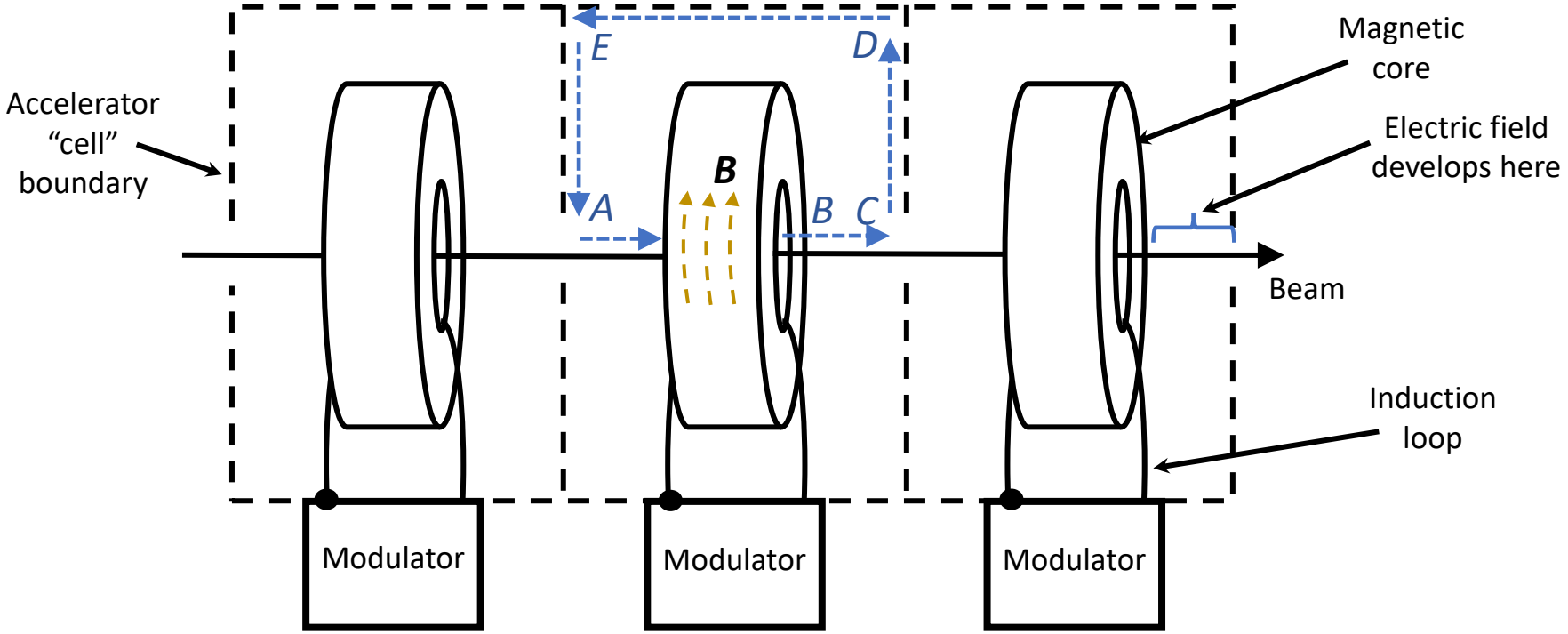




S. Ishmael et al, ASC-2016 Conference, Denver, Co

High current linear induction accelerators (LIAs) use magnetic induction to accelerate particles

From Faraday's Law: $Energy\ gain = q\iint -\frac{\partial B}{\partial t}\,dS = q\oint \boldsymbol{E}\cdot d\boldsymbol{l}$

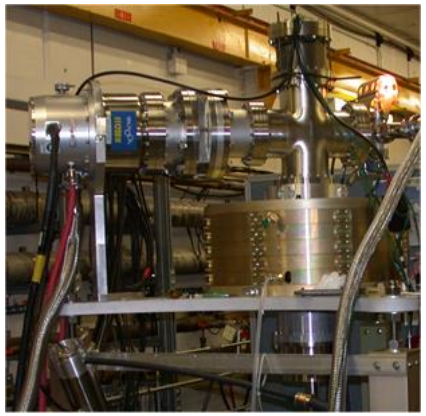


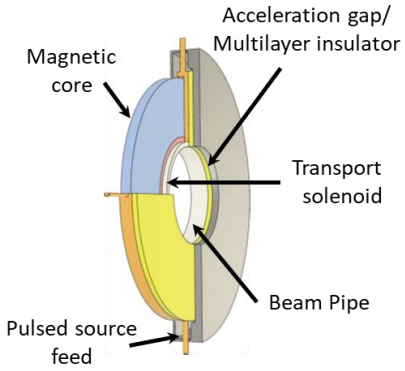
- 2-3 kA electron beam currents typical
- Can accelerate multiple beams in the same structure for conformal therapy
- Technique can be used to accelerate ions or electrons – LBNL demonstrated heavy ions for fusion
- More free parameters are available to suppress wake field effects

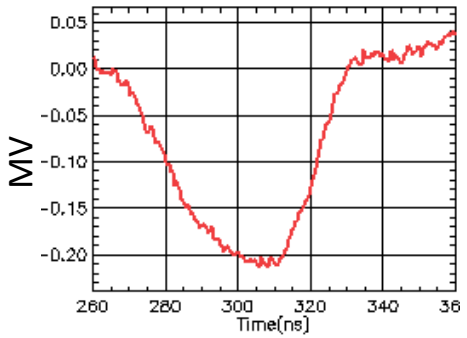
Opcondys

We are developing a compact induction linac for high current electron beams at 1 MHz pulse rate

- Cell Development (LLNL) - Goal 5 MV/m for multi-kA electron beams

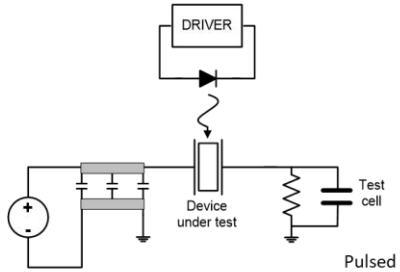


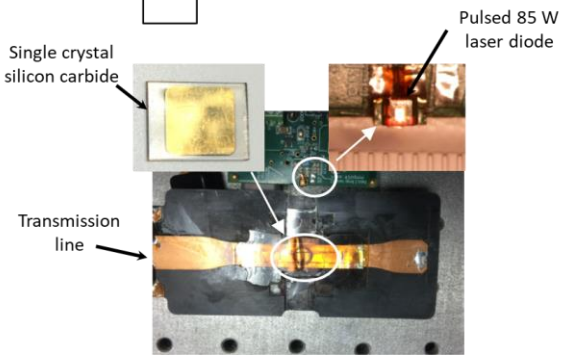


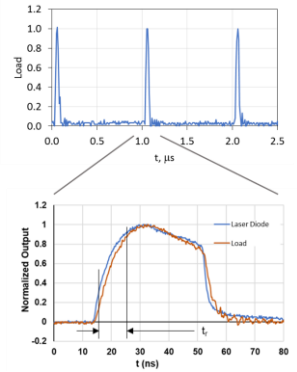


- Accelerator voltage pulse

- Modulator Development - Silicon carbide photoconductive high voltage switching demonstrated >1 MHz repetition rates+







- MHz, short pulse operation has been demonstrated using compact laser diodes

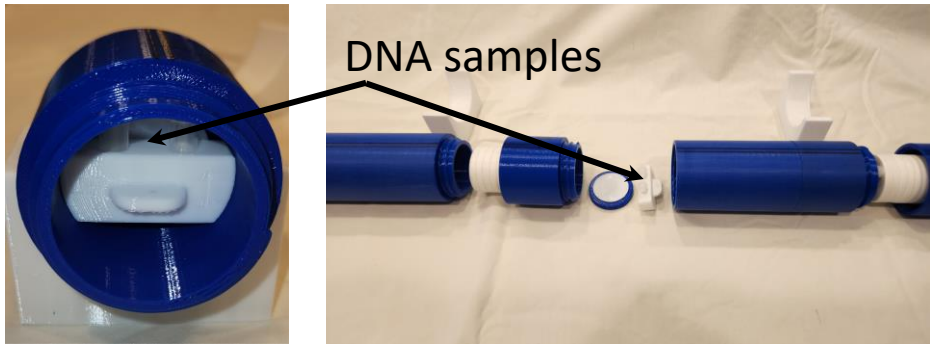
+Patent No. 9,748,859

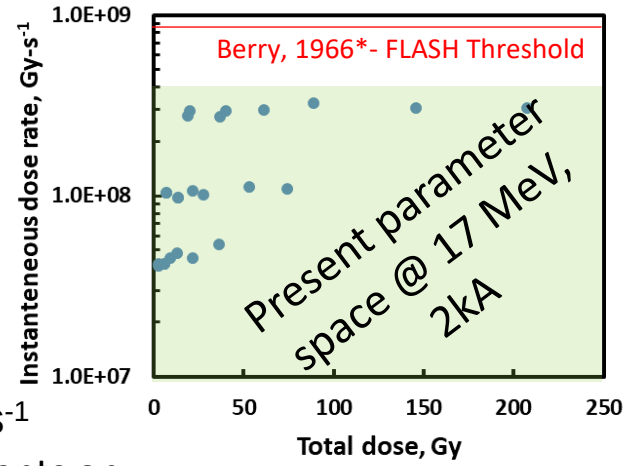
2021 R&D 100 WINNER

arpa·e awardee

Opcondys

In vitro DNA FLASH tests define the accelerator design; a notional multi-beam LIA system design has been completed





*doi/10.1259/0007-1285-42-494-102

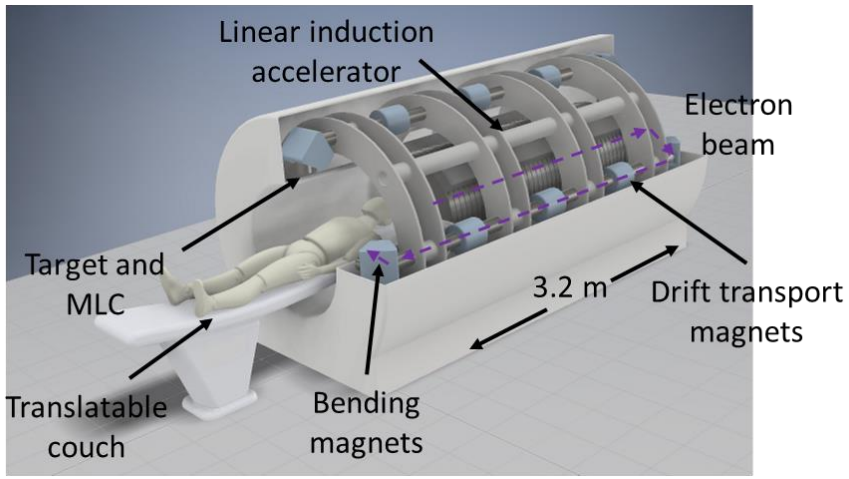
LOMA LINDA UNIVERSITY

- FLASH instantaneous threshold $\dot{D}\approx10^9$ Gy-s^{-1}
- We are performing DNA $\dot{D}$ damage experiments on a 2 kA, 17 MeV LIA to study single pulse thresholds

- Notional multi-pulse system[+]

Parameter	Induction Linear Accelerator
Electron Energy (MeV)	16
Total Beam Current (A)	25
Pulse Width (s)	1.50E-08
Pulse Repetition Frequency (Hz)	10000
Net Gradient (MeV/m)	5.0
Accelerator Length (m)	3.20
Inner Radius (cm)	10.0
Instantaneous Dose Rate (Gy/s)	6.60E+05
Average Dose Rate (Gy/s)	98.9
Total Dose (Gy)	19.8
Time On (s)	0.20

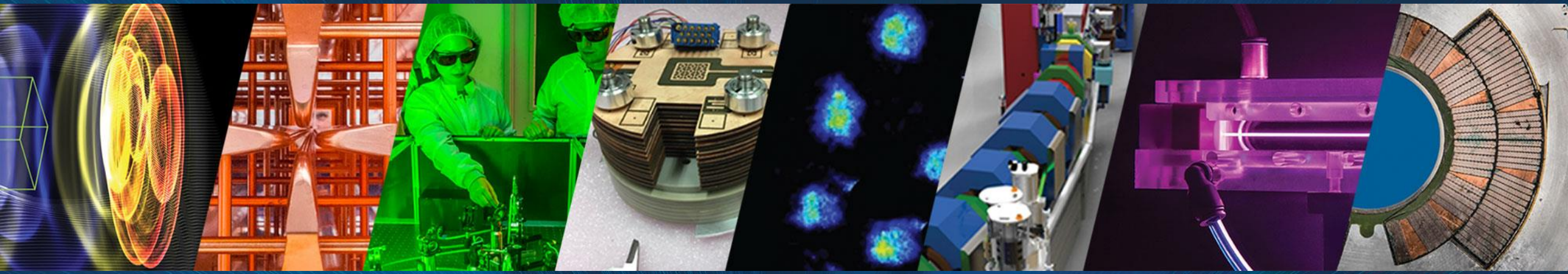
[+]Patent No. 11,697,032



Opcondys

Laser-Driven Proton Sources for Preclinical Radiobiological Studies in the ultra-high dose rate regime

L. Obst-Huebl, Antoine Snijders, K. Nakamura, J. van Tilborg, C. B. Schroeder, C. G. R. Geddes, E. Esarey



09/11/2023

LDRD LABORATORY DIRECTED RESEARCH & DEVELOPMENT

BSE Biological Systems and Engineering

BERKELEY LAB

ACCELERATOR TECHNOLOGY & APPLIED PHYSICS DIVISION ATAP

U.S. DEPARTMENT OF ENERGY | Office of Science

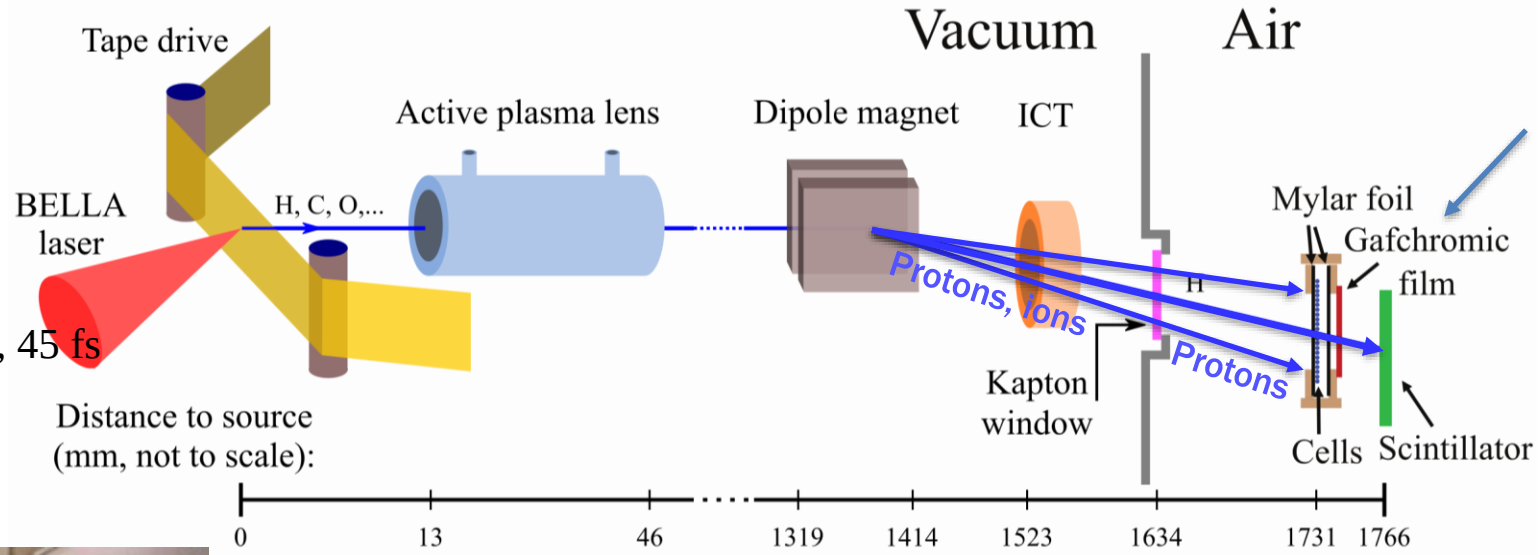
This work was supported by the Laboratory Directed Research and Development (LDRD) funding from LBNL provided by the Director, the U.S. Department of Energy Office of Science Offices of High Energy Physics and Fusion Energy Sciences, under Contract No. DE-AC02-05CH11231, and the LaserNetUS

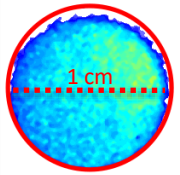
LaserNetUS

Cell samples were irradiated with laser-driven protons bunches of large energy spread and ultra-high instantaneous dose rate generated at the BELLA PW

BELLA PW laser

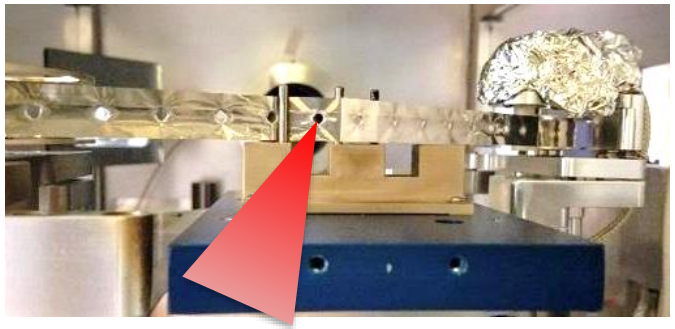
35 J, 45 fs



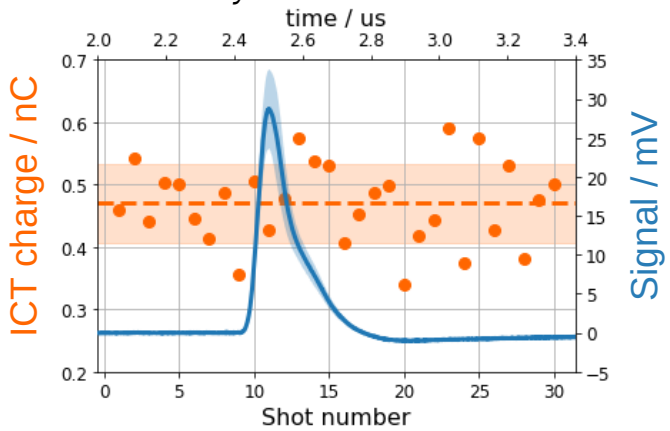


Dose on cells:
1 Gy per shot

Tape drive target



Online dosimetry



Beam Parameter	Value
Dose per pulse	1 Gy
Pulse length	30 ns
Pulse repetition rate	0.2 Hz
Instantaneous dose rate	3×10^7 Gy/s
Mean dose rate	0.2 Gy/s

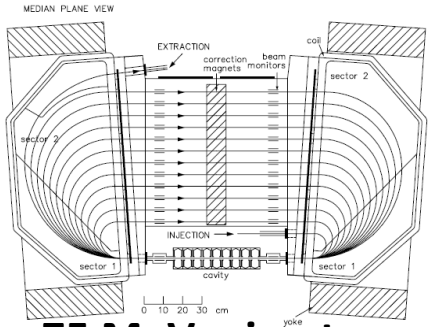
*S. Steinke et al., PRAB **23**, 021302 (2020).*

*J. H. Bin et al., Sci. Rep. **12**, 1484 (2022)*

L. Geulig et al., Rev. Sci. Instruments 93 (2022) 103301.

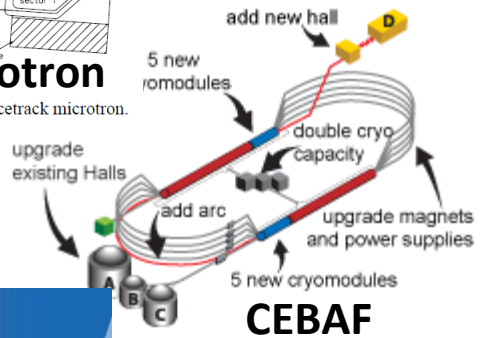
Evolution of Recirculating Electron Accelerators *Hybrid From microtron to a single-arc, fixed-field, CW recirculating Linear Accelerator*

- ***Electron Microtron: 10-75 MeV***
  - Single linac structure; multiple/integer # of RF wavelengths in return paths
  - Single return arc: spectrometer magnet for precision pathlength control per energy
  - Weak-focusing magnets; ultra-small beam emittances – no envelope control
- ***CEBAF – Continuous Recirculating Linear Accelerator (RLA): multi-GeV***
  - Multiple return arcs – each energy has a separate return arc
    - Strong-focusing, chromatically matched optics and independent integer RF pathlengths
- ***CBETA – Energy Recovery Linear Accelerator (ERL): 6-150 MeV***
  - Single linac, single strong-focusing FFA arc, 4 acceleration turns
    - SRF and Permanent magnet – long arcs, but small apetures
- ***Miniaturize CBETA: 10 MeV – 200 MeV***
  - Increase # linacs, for 15-20 acceleration turns (no SRF)
    - Fixed-field Gradient electromagnets, 1T peak B fields
    - Nonlinear field gradient
    - Chromatic correction, matched optics, pathlength control
    - Large beam emittances and high instantaneous currents

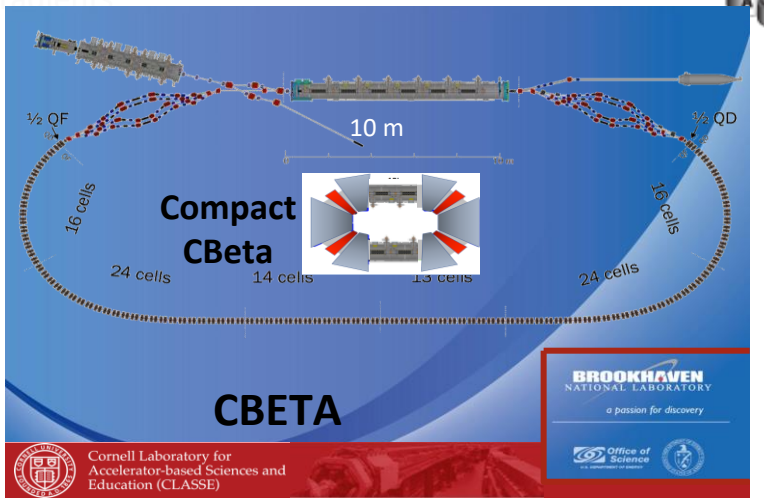


75 MeV microtron

Figure 1: The 10–75 MeV Eindhoven racetrack microtron.



CEBAF



FLASH – a groundbreaking modality in cancer treatment

FLASH targets radiobiology of tumors not healthy tissue

- **Enhanced protection of normal tissue, reduced side effects**
  - Many beam delivery questions
- ***FLASH requires state-of the art Accelerator Technologies***
  - *Proton and Ion Synchrotrons*
    - Synchrotrons are critical to understanding radiobiology and preclinical studies
    - Specifically, the role of the Bragg peak in FLASH
  - *Clinical electron linacs, cyclotrons, Fixed Field Gradient Accelerators (FFAs)*
    - Clinical linac electron beams can only penetrate a few cm
    - FLASH requires ultra-high, instantaneous intensity continuous beams
    - Only (230-250 MeV shoot-through) CW proton beams from iso-cyclotrons achieve FLASH intensities (no energy degrader)
    - Next generation FFAs with nonlinear gradients are being developed with variable-energy CW “synchrotron-like” extraction

FLASH IS IN THE PRE & CLINCAL TRIAL STAGE for specific cancers

Thank you!

A special thanks to my co-authors, especially Reinhard Schulte for his patience in listening to this talk repeatedly and all the impressive researchers and pioneers in understanding and bringing the FLASH effect to the clinical stage and to Radiabeam for keeping me technically honest