The future of medical linacs

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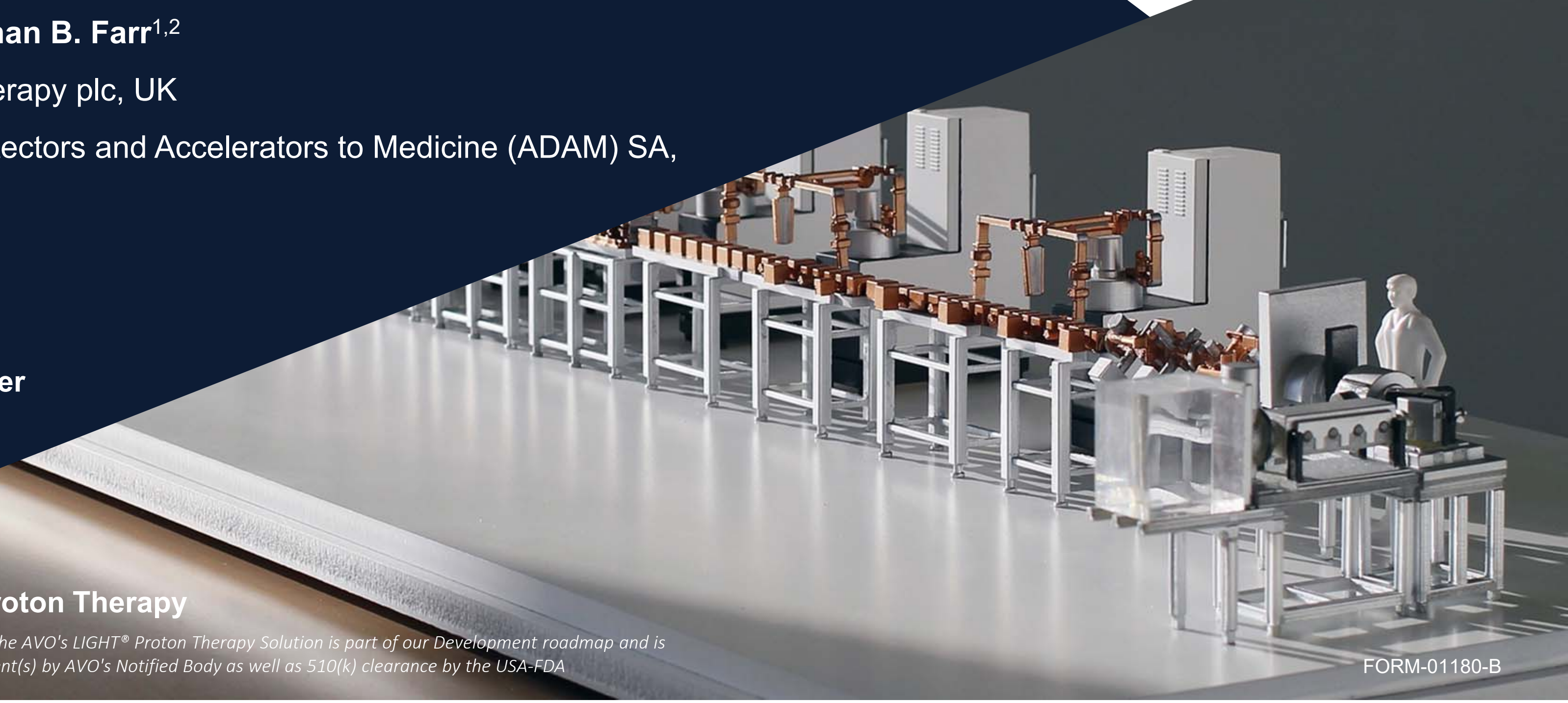
Friday 2nd September



Democratising Proton Therapy

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FORM-01180-B

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Conflict of Interest

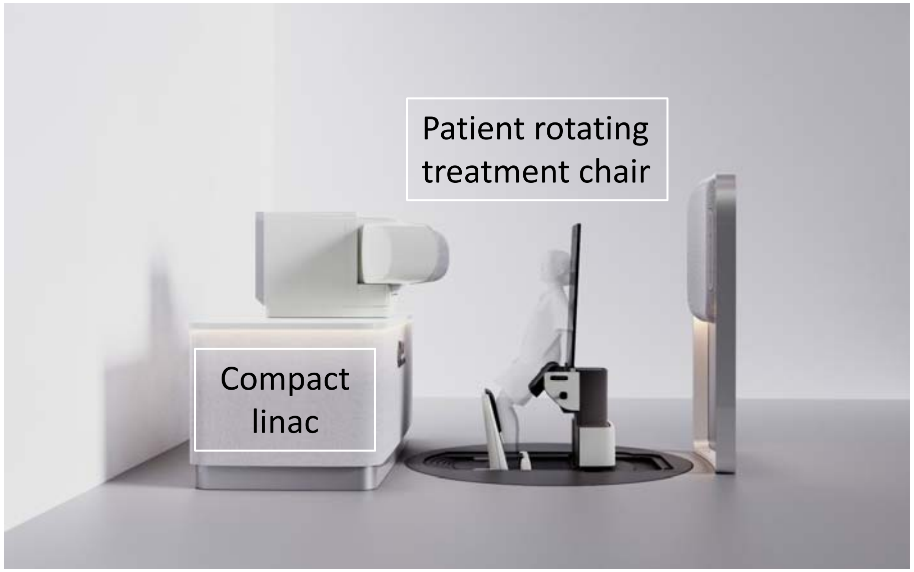
Jonathan Farr holds a senior management position at ADAM SA, Meyrin, Switzerland and is a shareholder in Advanced Oncotherapy, plc, London, UK.

Current Medical Electron (X-ray) Linacs – Radiotherapy

- Linac-based radiation therapy for cancer treatment began with the first patient treated in 1953 in London, UK, at the Hammersmith Hospital, with an 8 MV machine built by Metropolitan-Vickers and installed in 1952, as the first dedicated medical linac (David I Thwaites and John B Tuohy 2006 Phys. Med. Biol. 51 R343).
- A medical linear accelerator is the device most commonly used for external beam radiation treatments for patients with cancer.
- It delivers high-energy (4-20 MV) x-rays or electrons to the region of the patient's tumor.
- The cancer cells are destroyed by inducing double-strand breaks in the DNA molecules.

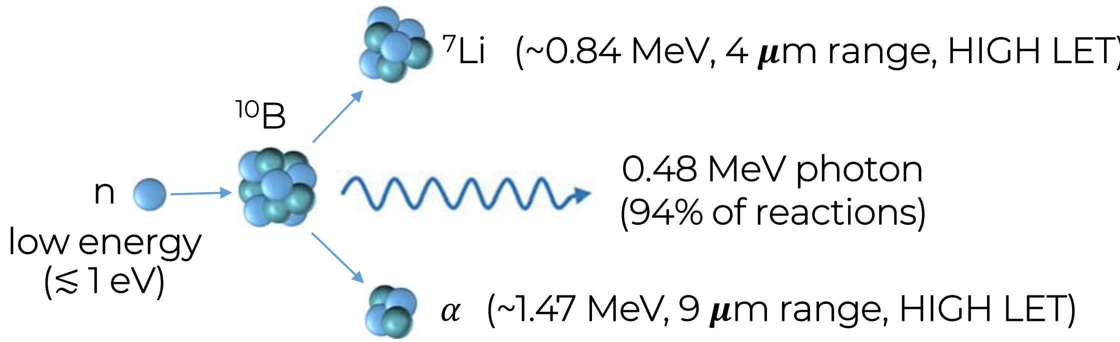
Future Medical Electron (X-ray) Linacs – Upright Treatments

- Although electron medical linacs are the most common type of radiotherapy machine (99 percent), there is significant unmet need in developing countries.
- Concept – rotate the patient instead of the beam.
- Treating patients in the upright position may provide cost, patient comfort and medical benefits.



Source: with permission, Leo Cancer Care

Boron Neutron Capture Therapy (BNCT): Concept



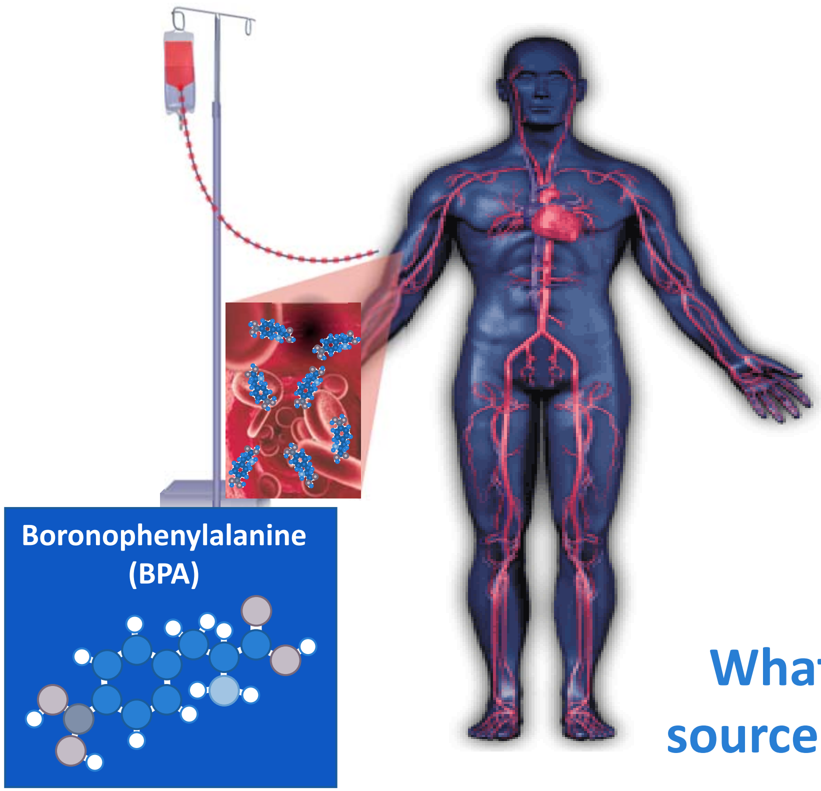
- Low energy neutron + ^{10}B produces ~2.3 MeV of HIGH Linear Energy Transfer (LET) radiation
- Short ^{7}Li and α ranges limit HIGH LET dose to cells with high ^{10}B concentrations
- **BNCT:** Combine a ^{10}B-labeled, tumor-targeting drug and an intense neutron source with epithermal energies (~1-30 keV) that slow down in the patient to less than 1 eV at the tumor location

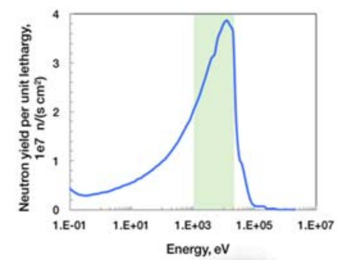
With permission from: Chad Lee, PhD, taeLifeSciences

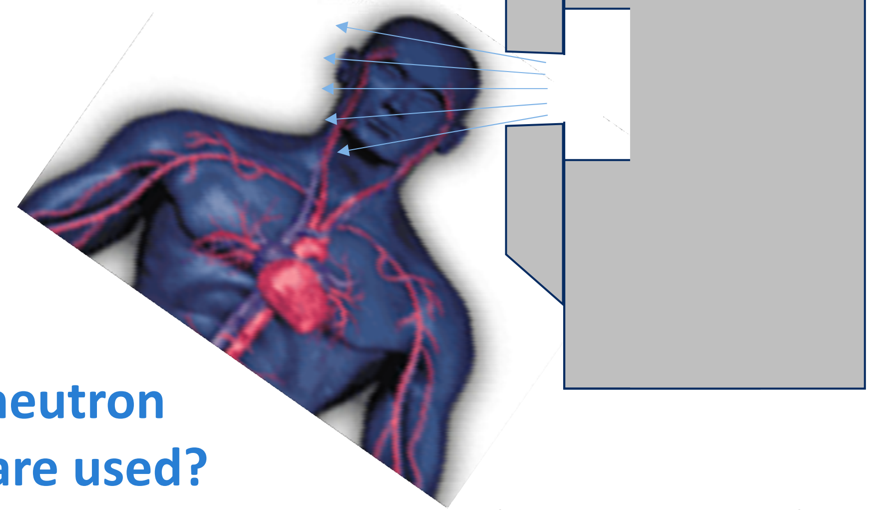
Boron Neutron Capture Therapy (BNCT)

STEP 1: ~2hr Infusion with boronated drug

STEP 2: Irradiate with epithermal neutrons







What neutron sources are used?

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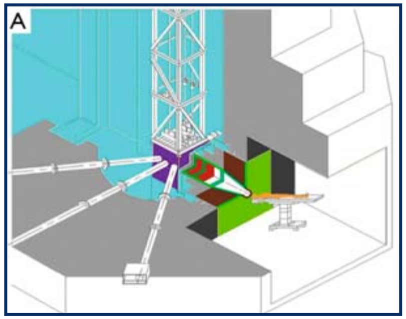
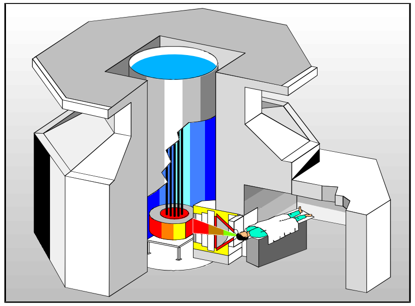
BNCT: Neutron sources

- Historically only nuclear reactors could produce sufficient neutron fluxes for BNCT (~10^9 $n_{epithermal}$/cm^2-s)
- Limited availability of reactors has contributed to slow BNCT expansion for decades
- Particle accelerators (primarily proton) have reached sufficient intensity to replace reactors

Tsing-Hua Open Pool Reactor (THOR)
2 MW Open Pool (Gen. Atomics)



Finland Research Reactor (FiR 1)
250 kW TRIGA Mark II



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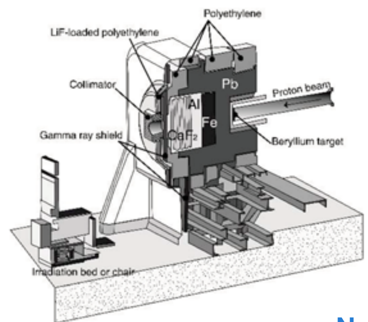
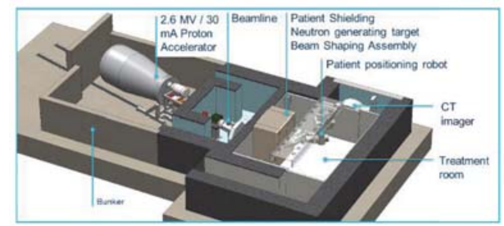
BNCT: Accelerators

- Neutrons are primarily produced with (*p,n*) reactions in ^{7}Li or ^{9}Be
- ^{7}Li: higher yields at lower proton energies (<3 MeV), but with target management challenges to overcome
- ^{9}Be: lower yields require higher proton energies (~30 MeV) & higher neutron source energies, but easier target management
- Electrostatic accelerators are a subset of linear accelerators (linacs) using a fixed accelerating field.
- Multiple electrostatic and alternating gradient linacs are currently being developed and commissioned for BNCT.

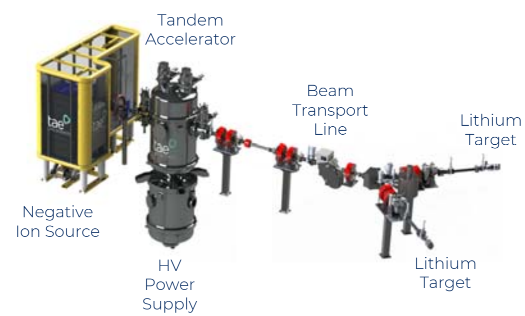
Cyclotron-Based Epithermal Neutron Source (C-BENS)
30 MeV p, ^{9}Be, cyclotron
Kyoto University



nuBeam Treatment Suite
2.6 MeV p, ^{7}Li, electrostatic accel.
Helsinki University Hospital



Neutron Beam System
2.5 MeV p, ^{7}Li, tandem accelerator
Xiamen Humanity Hospital



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BNCT Treatment Centers (accelerator-based)

Country	Center / Location	Vendors	Accelerator	Status
Japan	Kyoto University	Sumitomo HI	Cyclotron	Prototype no longer in operation
Japan	Southern Tohoku BNCT Research Center	Sumitomo HI	Cyclotron	Clinical trials / reimbursed treatments
Japan	Kansai BNCT Medical Center	Sumitomo HI	Cyclotron	Clinical trials / reimbursed treatments
Japan	University of Tsukuba	Home-made accelerator system	Linear	Commissioning
Japan	National Cancer Center Hospital	CICS	Linear	Clinical trials
Japan	Edogawa Hospital BNCT Center	CICS	Linear	Construction
Japan	Nagoya University	Home-made BNCT system based on IBA Dynamitron	Electrostatic	Commissioning
Japan	Shonan Kamakura General Hospital	Neutron Therapeutics, nuBeam	Electrostatic	Commissioning
Finland	Helsinki University Hospital	Neutron Therapeutics, nuBeam	Electrostatic	Commissioning
Argentina	Bariloche Atomic Centre	25 MeV electron linear accelerator	Electrostatic	Construction
Russian Federation	Budker Institute of Nuclear Physics + RONC	Budker institute + RONC	Electrostatic	Developing
Israel	Soreq Applied Research Accelerator Facility	Unknown	Linear	Developing
China	Humanity Hospital Xiamen	Neuboron NeuPex (TAE LS accelerator)	Electrostatic	Developing
China	Dong Guan Peoples Hospital	Home-made accelerator system	Linear	Developing
China	Lanzhou	Home-made accelerator system	Linear	Developing
United Kingdom	University of Birmingham (research system)	Neutron Therapeutics, nuBeam	Electrostatic	Commissioning
United Kingdom	Queen Elisabeth Hospital	TAE Lifesciences	Linear	Developing
Italy	CNAO	TAE Lifesciences	Linear	Developing
Republic of Korea	A-BNCT	Dawsons's	Linear	Commissioning
USA	Mayo Clinic Rochester	TAE Lifesciences	Linear	Developing
France	Grenoble	BNCT Global	Not yet decided	Developing
Belgium	University Hospital of Brussels, Institut Jules Bordet	Neutron Therapeutics, nuBeam	Electrostatic	Developing

Courtesy of Prof Dr Wolfgang Sauerwein and BNCT Global GmbH

BNCT Global

Linac based BNCT predictions

1. Linac based BNCT installations will continue to expand at an increasing rate.
2. Linac based BNCT installations will outnumber reactor based BNCT installations within 5 years.
3. The miniaturization trend for BNCT systems will continue.
4. Eventually, linac based BNCT systems will fit into a "standard radiotherapy vault" based on existing commercial X-ray linacs.

Medical Isotope Production

Medical Isotopes:

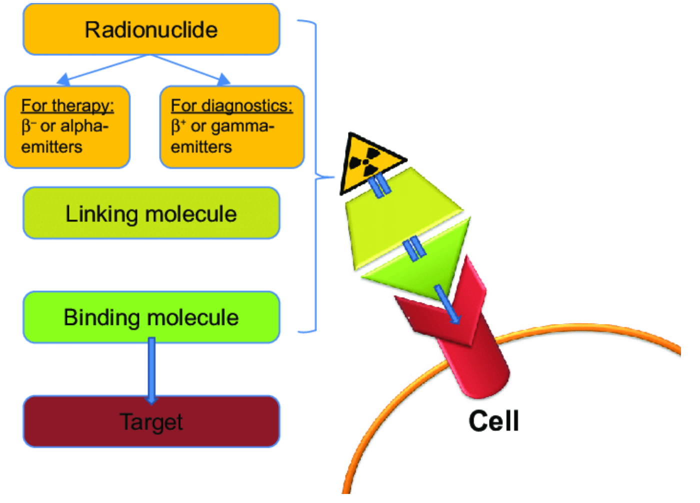
- Diagnostic (mostly PET)
- Therapeutic
- Theragnostic = Diagnostic + Therapeutic

Cyclotrons and reactors are the most common producers of diagnostic isotopes.

Cyclotron = fixed energy, high current, a good choice for a limited range of isotope energy interaction cross-sections.

Why use a linac for isotope production?

1. Electrons or protons
2. Compact
3. Full current at variable energy allows wider isotope species production depending on cross-section, especially theragnostic agents

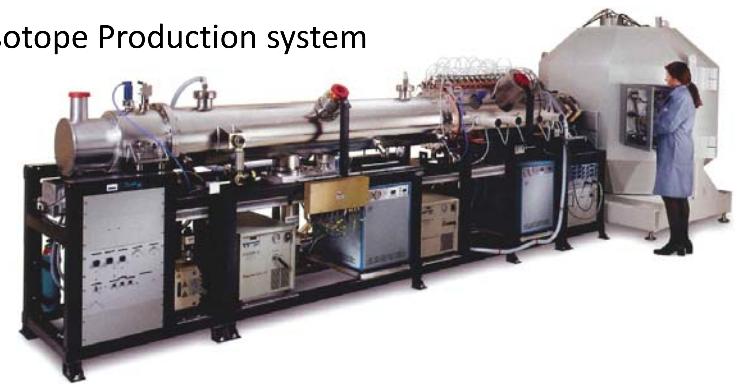


Yordanova et al., "Theranostics in nuclear medicine practice," *Onco Targets Ther*. 2017

Medical Linac Isotope Production

Low E p+ commercial solution

PULSAR® PET Isotope Production system



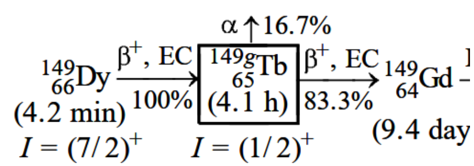
LINAC

Particle	H^+
Energy	7.0 MeV
Current	> 150 μA
Size (L x W x H)	14.5' x 2.5' x 5.5'
Weight	6,100 lbs
Input Power	25 kW
Cooling Water	20 gpm

Example High E p+ isotope production programs

- ISOLDE (CERN)
- Brookhaven (BNL)
- Los Alamos (LANL)
- Many others

2.0 GeV, 6 μA, 5×10^{18} protons in a few days*



"Terbium-149 produces alpha radiation, which is used in radiotherapy to kill resistant cancerous cells."

^{152}Gd$(p, 4n)^{149}$Tb;

Ta$(p$, spall);

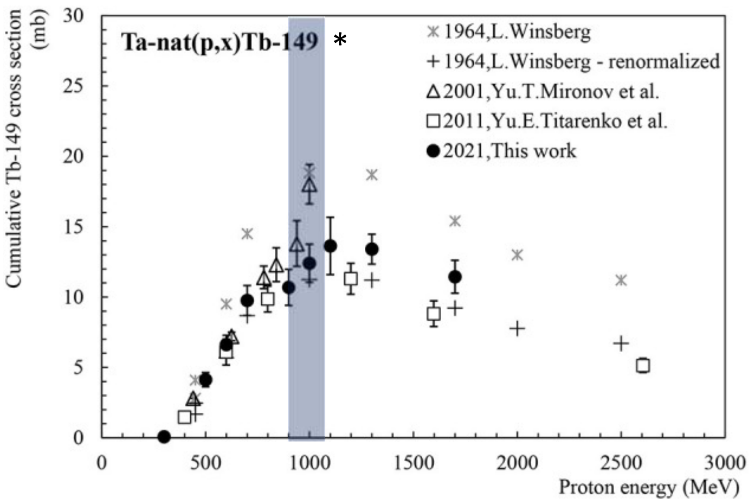
*Dos Santos Augusto RM, et al. CERN-MEDICIS (Medical Isotopes Collected from ISOLDE): A New Facility. Applied Sciences. 2014;4(2):265-281.

Medical Linac Exotic Isotope Production – Needed Energy

$^{152}Gd(p, 4n)^{149}Tb$;

$Ta(p, spall)$;

**Moscow Meson Factory
- Linear accelerator of protons and H- ions
- Beam current 0.5-1.0 mA
- Extraction E=160 MeV.



Radio-nuclide	$T_{1/2}$	Target	Energy range, MeV	Period of bomb, hours	Activity, Ci
Sr-82	25.3d	Rb	100-41	250	15
Na-22	2.6 y	Al	150-35	250	1
		Mg	150-35	250	2
Cd-109	453 d	In	150-60	250	2
Pd-103	17 d	Ag	150-50	100	100
Cu-67	62 hr	Zn	150-70	100	30
Co-57	271 d	Ni	28-15	250	1
Ti-44	47.3y	Sc	60-20	250	0.01
Ge-68	288 d	Ga	50-15	250	0.5
Tl-201	73 hr	Pb	60-52	25	6
		Pb	70-55	25	4

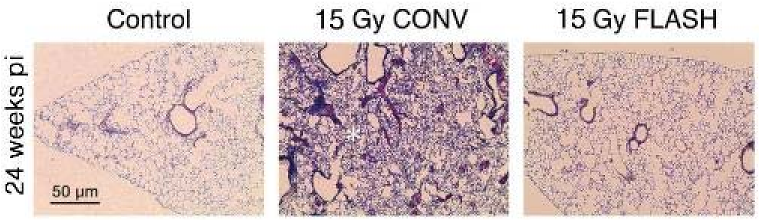
**Duchemin C, et al., "Production Cross-Section Measurements for Terbium Radionuclides of Medical Interest Produced in Tantalum Targets Irradiated by 0.3 to 1.7 GeV Protons and Corresponding Thick Target Yield Calculations," Frontiers in Medicine. 2021

**Esin, S K, et al., "Isotope Production for Medical and Technical Use at Moscow Meson Factory Linac," Proceedings of the XVIII International Linear Accelerator Conference

Medical Linac Isotope Production predictions

1. Lower E commercial medical linacs will continue to compete with cyclotrons in hospital-based (small-scale) isotope production systems.
2. Very large-scale production of low E cross-section isotopes will continue at reactor-based facilities for the foreseeable future (e.g. HFR Netherlands, BR2 Belgium).
3. National and international accelerator facilities will continue to “sideline” exotic medical isotope production largely for research use.
4. Compact, higher energy (50-400) MeV medical proton linacs may be developed for hospital-based use, expanding the variety of medical isotopes available for regular clinical use.

FLASH effect



Visualisation of collagen invasion (Masson trichrome staining)

- Flash appeared in literature/research in early 1970s.
- Electrons delivered at high dose rates within 0.5 s (FLASH) to cancerous tissues inhibit tumour growth as well as with conventional therapy, but significantly sparing surrounding healthy tissues [1,2]
- Tumour cell inhibition is comparable to conventional techniques, however
- Healthy tissue sparing allows dose increase without complications
- Currently electron linacs and proton passive scattering are used to deliver FLASH-like doses
- Dose rate that is relevant for flash is 40-120 Gy/s, above that effect saturates

FLASH PARAMETERS

Mean Dose rate: 40-200 Gy/s

Pulse width: 0.1-2 µs

Repetition rate: 0.1-200 Hz

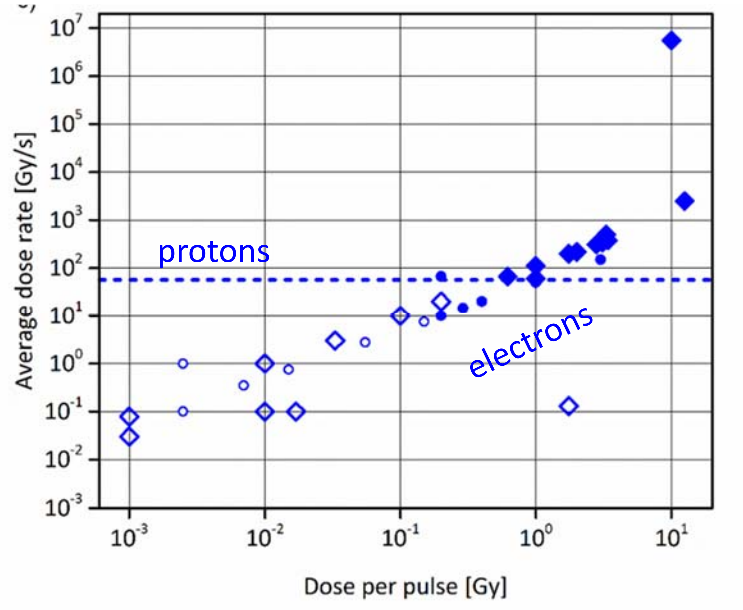
Delivered in < 0.5 s (Optimal ~150 ms)

REF: V. Favaudon, C. Fouillade, M.C. Vozenin, "Ultrahigh dose-rate, "flash" irradiation minimizes the side-effects of radiotherapy," Cancer Radiother **19**, 526-531 (2015).

REF: Sci Transl Med 6: 245ra93, 2014

Critical beam parameters for observing the FLASH Effect

- The filled markers represent combinations of DR_{ave} and D_{pulse} that lead to reduced radiation toxicity of pulsed electron beams.
- The hollow markers indicate at which combinations of the same parameters no reduction in toxicity was observed.
- The dashed blue line indicates the lowest DR_{ave} at which the FLASH effect was reported with proton beams.



Farr J, et al., "Ultra-high dose rate radiation production and delivery systems intended for FLASH," *Med Phys.* 2022. doi: 10.1002/mp.15659.

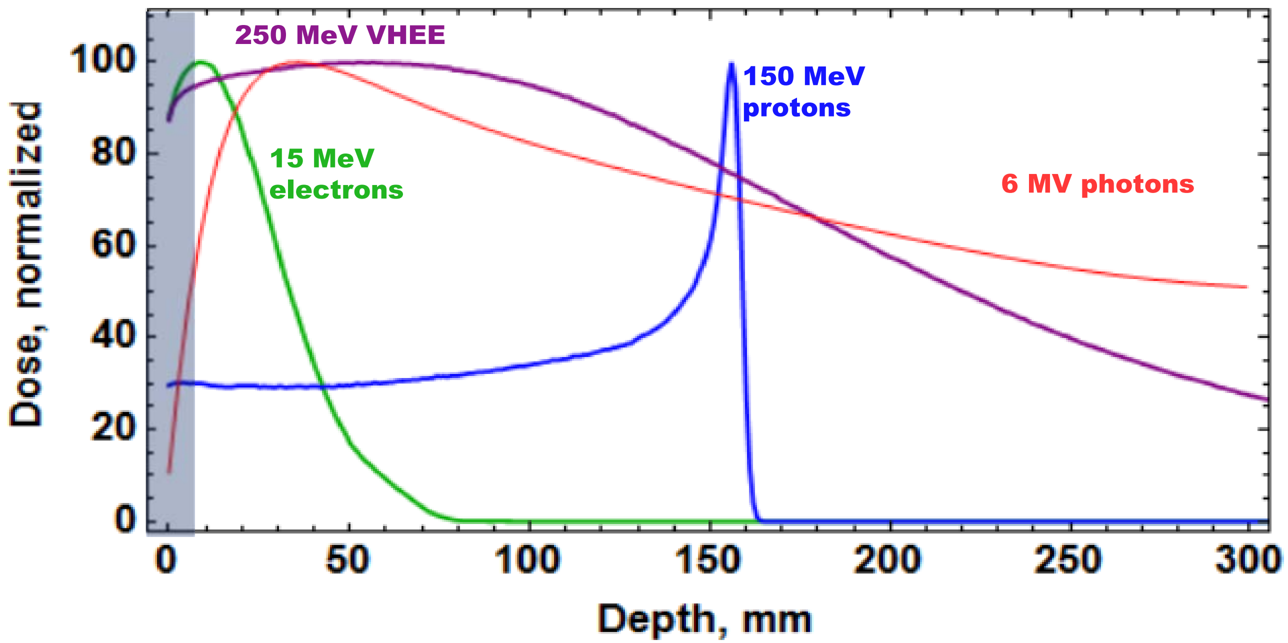
Commercially Available Low E Clinical FLASH Systems

Trade Name	Producer	Accelerator Type	Rf	Energy (MeV)	Depth in Tissue (cm)	D_{ave} (Gy/s)	Pulse width (µsec)	Pulse Repetition Frequency (Hz)	Maximum D_{pulse} (Gy)
Kinetron	(CGR-MeV, Courbeville, France)	Electron linac	S-band	4.5	4	>1000 s	0.1-2.2	10-200	60
Oriatron eRT6	PMB, Peynier, France	Electron linac	S-band	5 and 6	4	>1000	0.5-4	5-250	20
FLASH Knife	PMB, Peynier, France	Electron linac	S-band	10	5	350	0.5-4	10 - 300	1.5
Mobetron	Intra Op, Sunnyvale, CA, USA	Electron linac	S-band	6 and 9	4-5	>1000	0.5 - 4	10 - 90	9.2

PMB-Alcen Flash-Knife

Mobetron

Medical Radiation Beam Properties at Depth

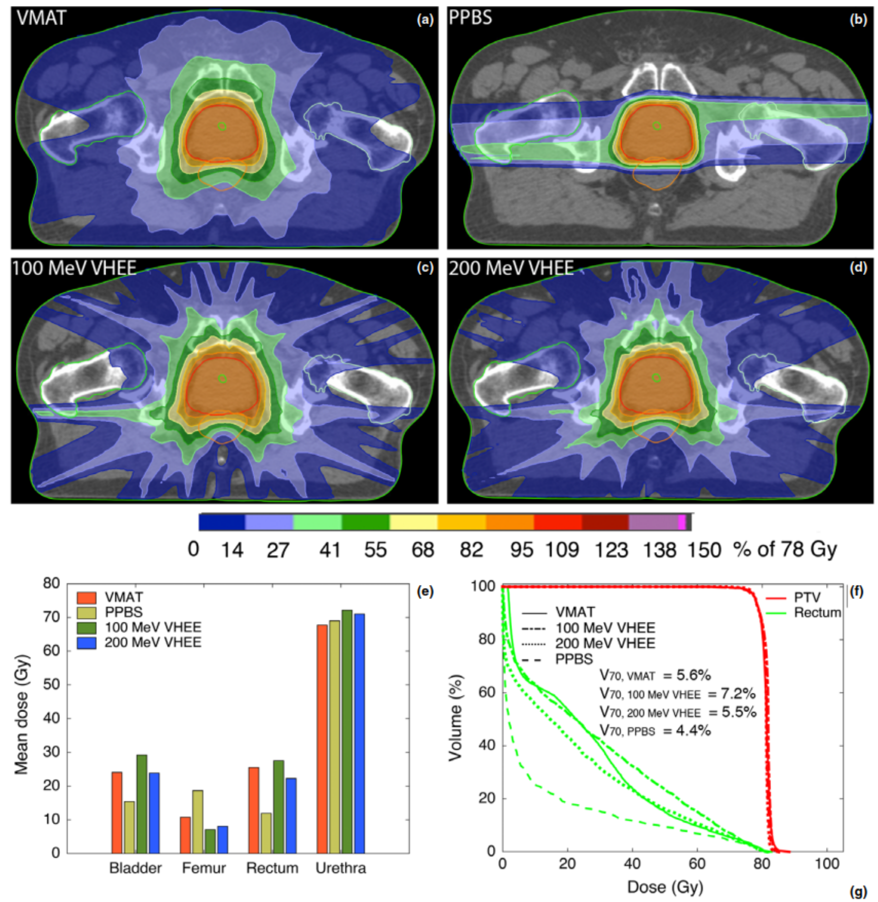


Dose profiles for various particle beams in water (beam widths $r = 0.5$ cm)

Figure: Agnese Lagzda, et al., Eucard-2 Annual meeting, 2017

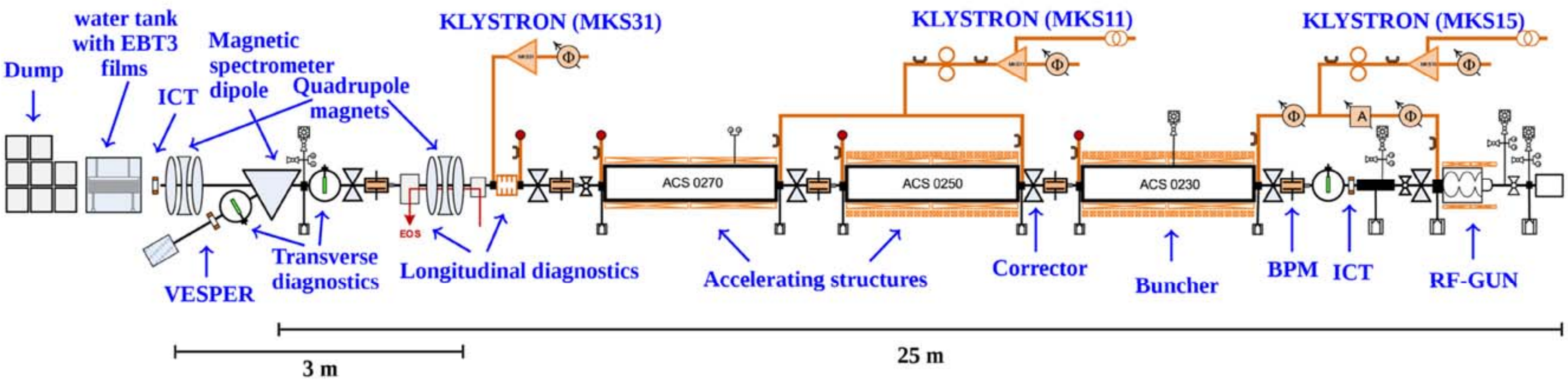
Future Medical Electron Linacs – VHEE

- Concept – treat with the plateau portion of the electron depth dose.
- Requires Very High Energy Electrons (VHEE)
- Provides conformal treatment
- 100-250 MeV electrons
- Low scattering at tissue interfaces



Schüler E, Eriksson K, Hynning E, et al. Very high-energy electron (VHEE) beams in radiation therapy; Treatment plan comparison between VHEE, VMAT, and PPBS Med Phys. 2017;44(6):2544-2555.

Future Medical Electron Linacs – VHEE

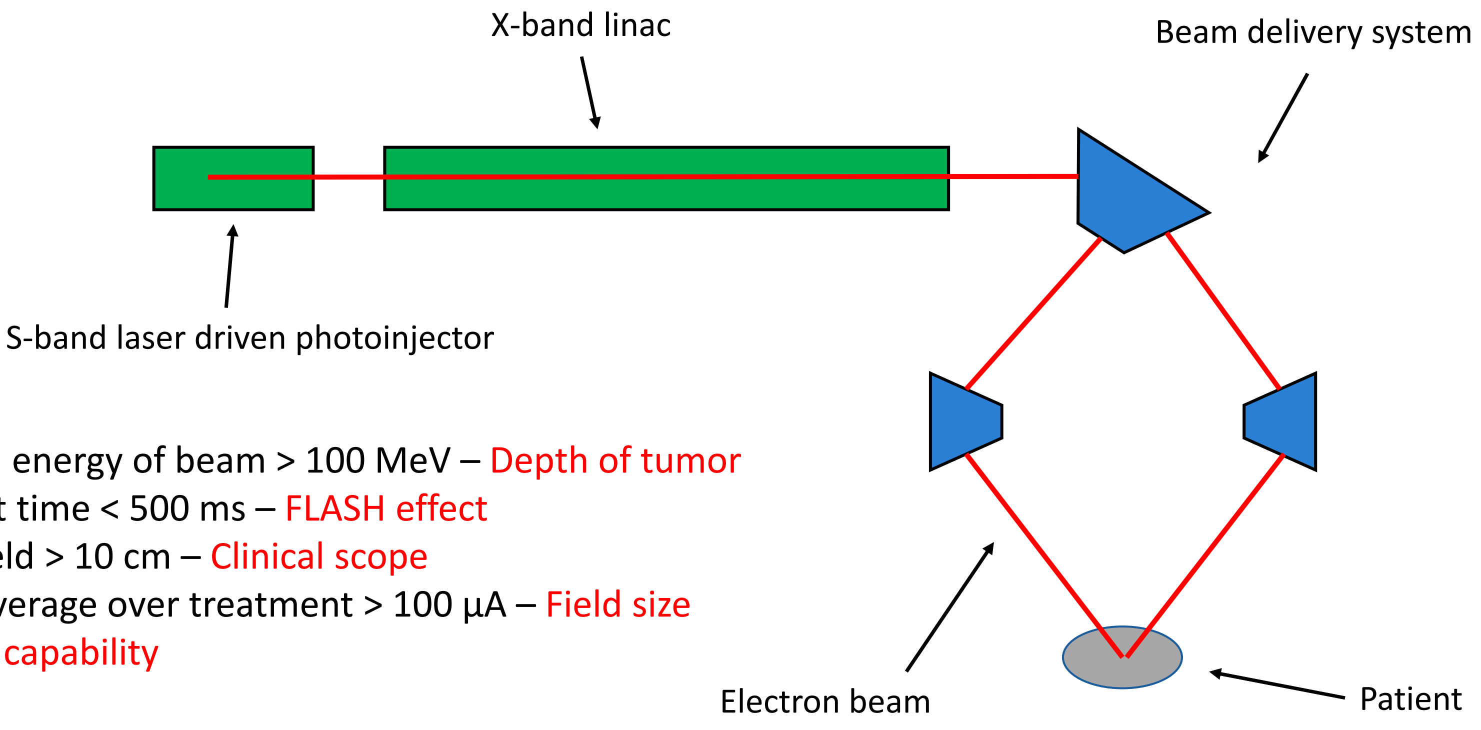


Gamba, D. et al. The CLEAR user facility at CERN. Nucl. Instrum. Methods Phys. Res. A 909, 480–483 (2018)

- CLEAR electron linac at CERN provides up to 220 MeV in more than 20 meters
- Uses S-band (3 GHz) RF accelerator.
- Commercialization is prohibitive in comparison to existing medical linacs.
- Although laser wakefield accelerators continue to be developed, they are long horizon for clini applications.
- X-band (12 GHz) RF accelerators are being considered for higher accelerating gradients.

Electron Linac FLASH Development

Basic parameters

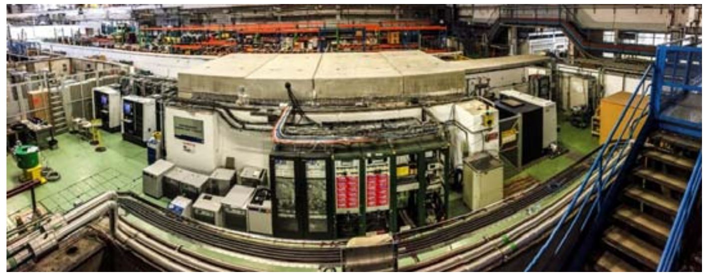


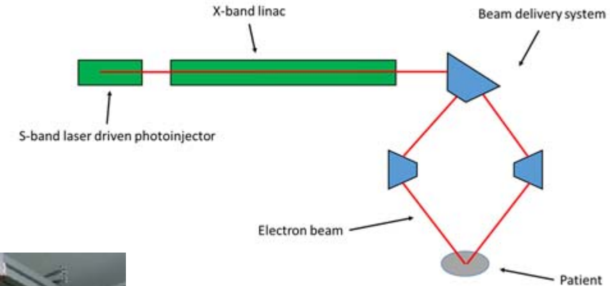
- Maximum energy of beam > 100 MeV – Depth of tumor
- Treatment time < 500 ms – FLASH effect
- Largest field > 10 cm – Clinical scope
- Current average over treatment > 100 µA – Field size over time capability

Slides used with permission: W. Wuensch, CERN

Electron Linac FLASH Development

Based on CLIC accelerating structures and XBox test stands.





CPI 50 MW klystron

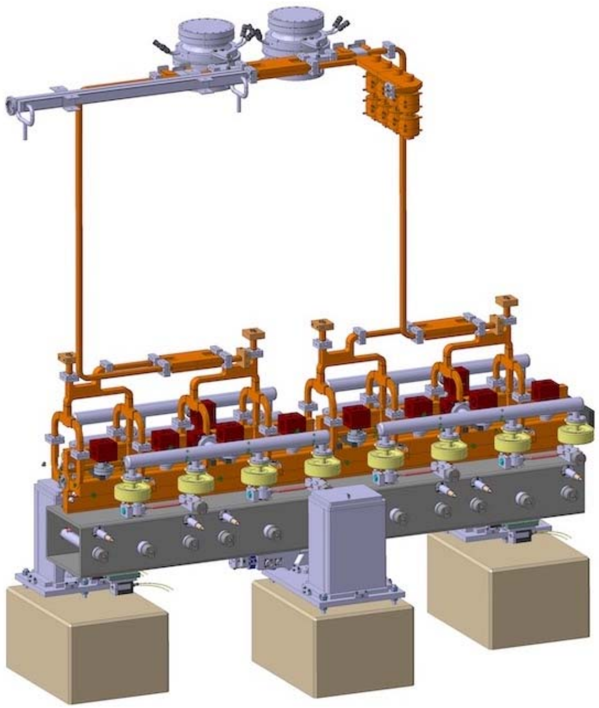
Scandinova solid state modulator

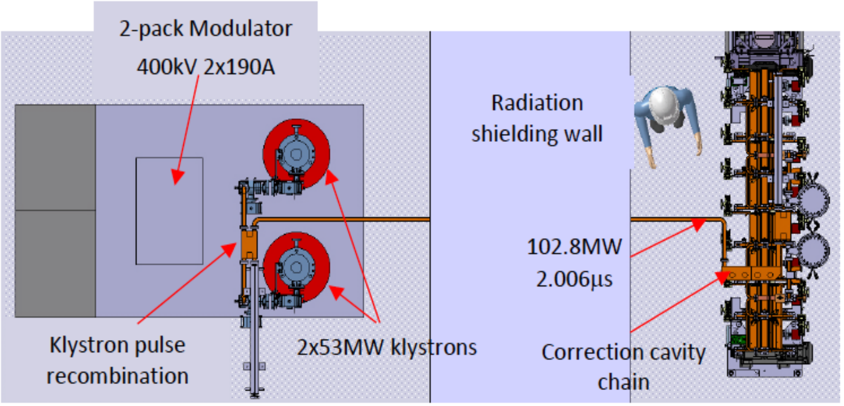
Prototype CLIC accelerating structure

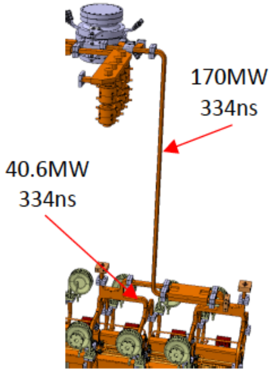
X-band linac hardware

Slides used with permission: W. Wuensch, CERN

Electron Linac FLASH Development







CLIC has as a baseline two-beam RF power generation, but we have also studied a klystron-based version.

- 160 MeV energy gain
- 2 m long
- 1 A beam current
- (round numbers)

CLIC klystron-based rf module

Slides used with permission: W. Wuensch, CERN

Future proton therapy system requirements

#	Characteristic	Advantages
1	reduced maintenance	lower service contract costs, greater availability and higher utilization
2	cheaper	lower facility investment costs;
3	lighter	lower capital and installation costs
4	smaller	lower building construction costs
5	reduced shielding	lower facility investment costs
6	reduced activation	lower decommissioning cost
7	higher energy	ion beam radiography and ion beam CT, penetration through implants and large patients
9	small beam size	greater conformity to target, enables higher doses
9	fast energy changes	shorter treatment times, 3D rescanning
10	energy invariant output	shorter treatment times for lower energies
11	Pulsed	supports FLASH

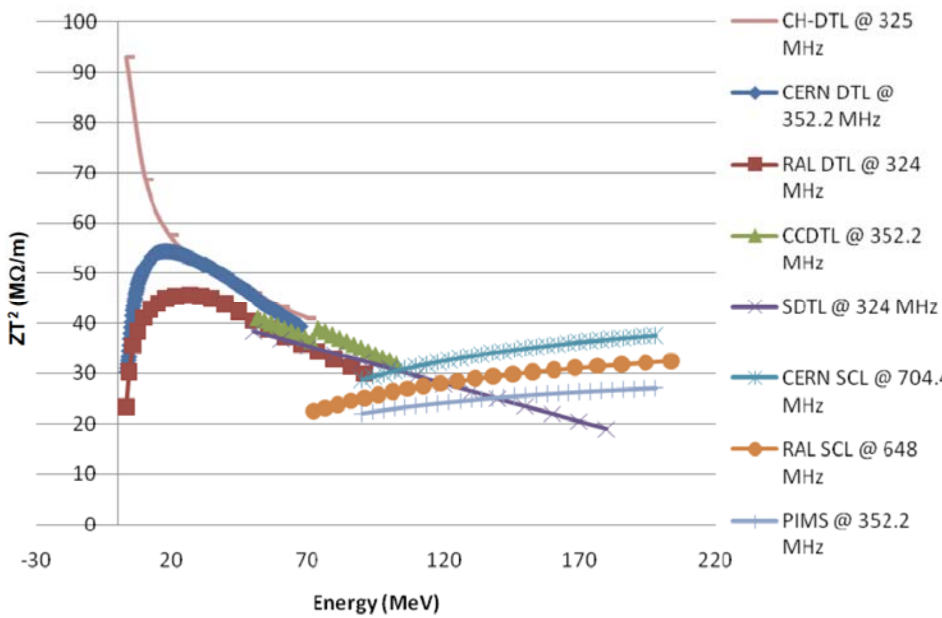
J.B. Farr, J. Flanz, A. Gerbershagen, M.F. Moyers, "New Horizons in Light Ion Beam Treatment Systems," Med. Phys., 2018

Particle therapy accelerator types comparison

Accelerator type → Parameters ↓	Cyclotron	Synchro-cyclotron	Synchrotron	Linac
Beam Emittances (size) (norm.) [pi-mm-mrad]	3.0-9.0 (before ESS)	3.0-6.0 Radial 3.0-4.0 Vertical	1.0-2.5	**0.25**
Energy modulation (variation)	Only with degrader-absorbers	Only with degrader-absorbers	Possible, but slow (now multi flat-top extraction)	**By electronic control**
Proton losses, activation and time structure	High in ESS (1/E dependent)	High in degrader	Small losses in extraction	Low
Change of Energy (speed)	80 ms to 2.1 second	50 ms to 2 seconds	1-3 s	**5 ms**
"Spot Dose" regulation (speed)	By timing spent in each voxel	Pulse by pulse 6e8-1e12 pps	By timing the end of extraction	**Pulse by pulse,** 2e8-1e11 pps
Construction costs (comments)	Shielding and vault opening from the roof	Shielding and vault opening from roof	Big surface hall	**Corridor-like (small amount of shielding close to linac)**
Dismantling or re-location costs	ESS degrader activation	Activated degrader	Activated extraction septum	**Almost no losses**

Future Prospects for Particle Therapy Accelerators in Reviews of Accelerator Science and Technology, A. Degiovanni, **J. B. Farr**, S. Myers, 2018.

Proton Linac Cavity Type Shunt Impedance with Energy



Relation of shunt impedance per unit length with proton energy. Higher shunt impedance provided more efficient energy transfer to the accelerating protons. Adapted with permission from Plostinar.*

*Plostinar C. Comparative Assessment of HIPPI Normal Conducting Structures, CARE-report-08-071-HIPPI. 2014.

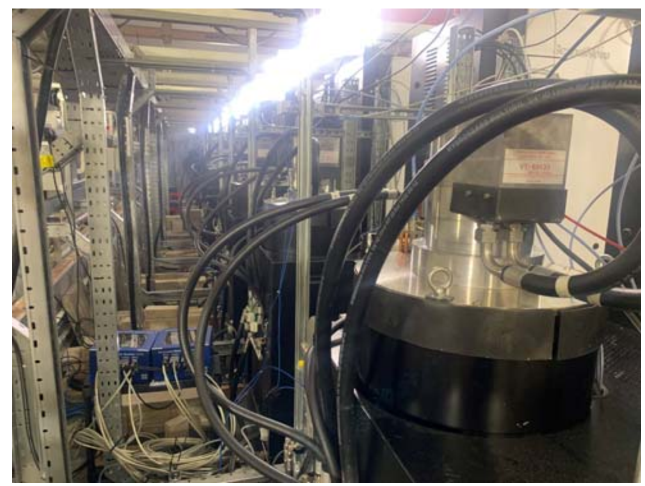
Modulator Klystron System (MKS)

SCANDINOVA Modulator

Parameter	Value
Pulse Voltage	155 KV
Pulse Current	110 A
Pulse Rep. Rate	5 to 200 Hz
Pulse Length (top)	0.5 to 5 µsec
Pulse Flatness (top)	<1%

Toshiba Klystron

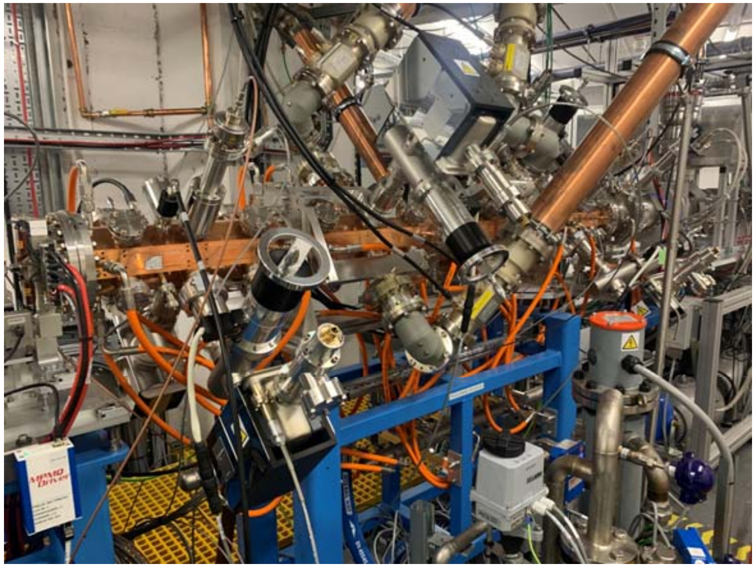
Parameter	Value
Frequency	2998.5 MHz
Peak RF Drive Power	120 W
Peak RF Output Power	7.5 MW
Gain	48 dB
Pulse Width (RF Out P.)	5 µsec

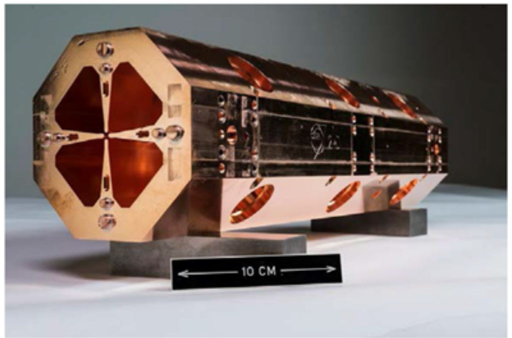


Radio Frequency Quadrupole

- High frequency RFQ designed by CERN
  - 4 vanes type
  - 750 MHz (highest known)
  - 4 modules - 2 m
  - 5 MeV energy gain

Section	RFQ
RF frequency [GHz]	0.749
Energy [MeV]	0.04-5
Length [m]	2

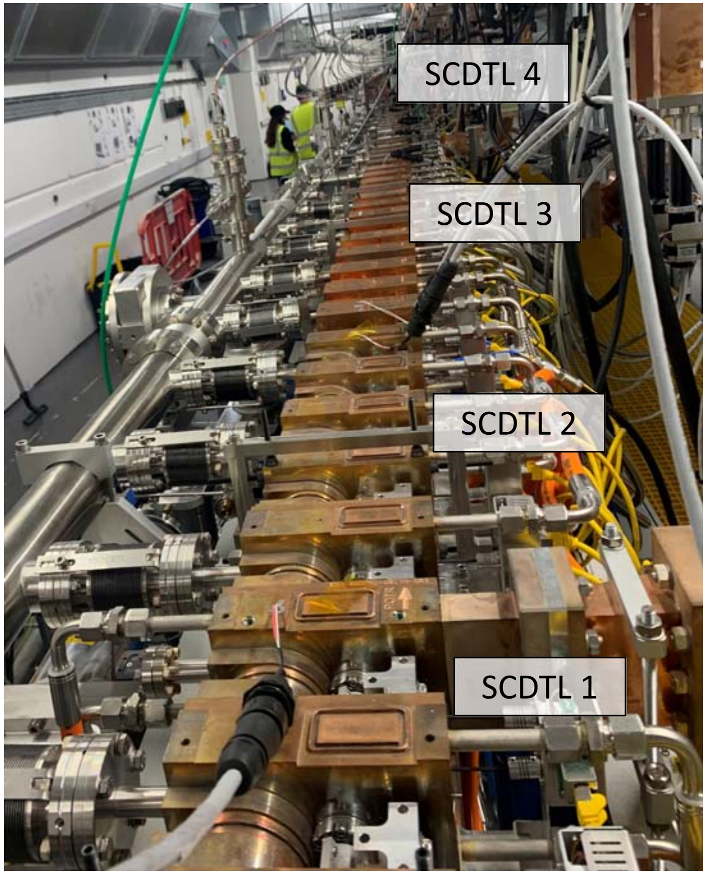




Side Coupled Drift Tube Linac (SCDTL)

- Designed by ENEA (Frascati, I)
- Manufactured at TSC/VDL
- SCDTL 1-4 operational at Daresbury
- Constant E to 37.5 MeV

Section	SCDTL
RF frequency [GHz]	2.998
Energy [MeV]	5-37.5
Length [m]	6.2



LIGHT Coupled Cavity Linac (CCL)

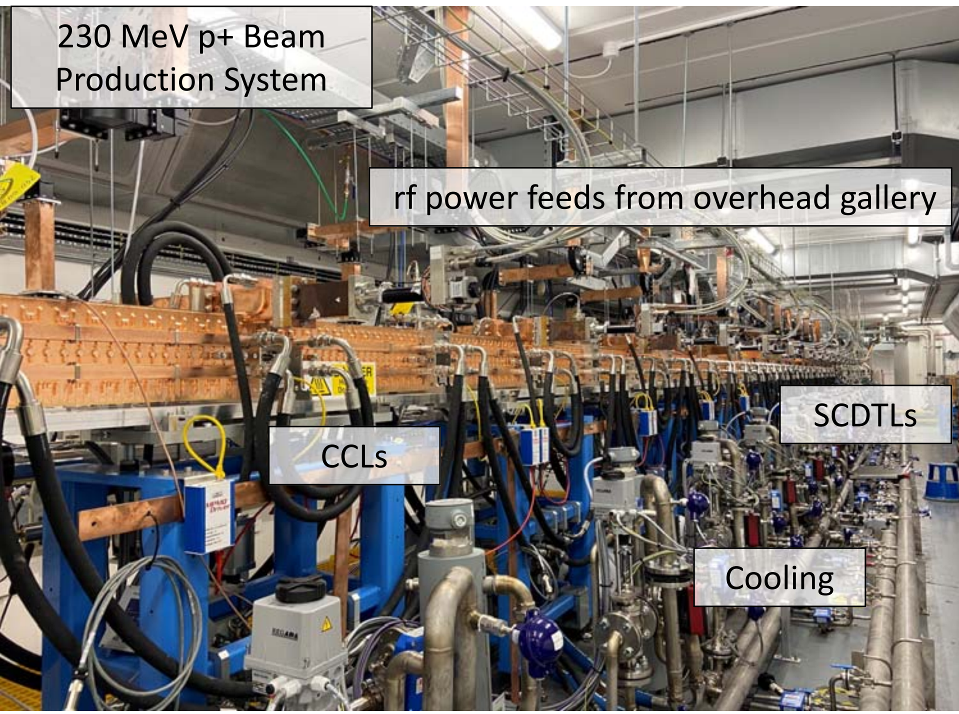
- Designed by ADAM
- Manufactured by VDL
- 15 modules vacuum tested, conditioned, installed at Daresbury

Section	CCL
RF frequency [GHz]	2.998
Energy [MeV]	37.5-230
Length [m]	15.5

LIGHT overview

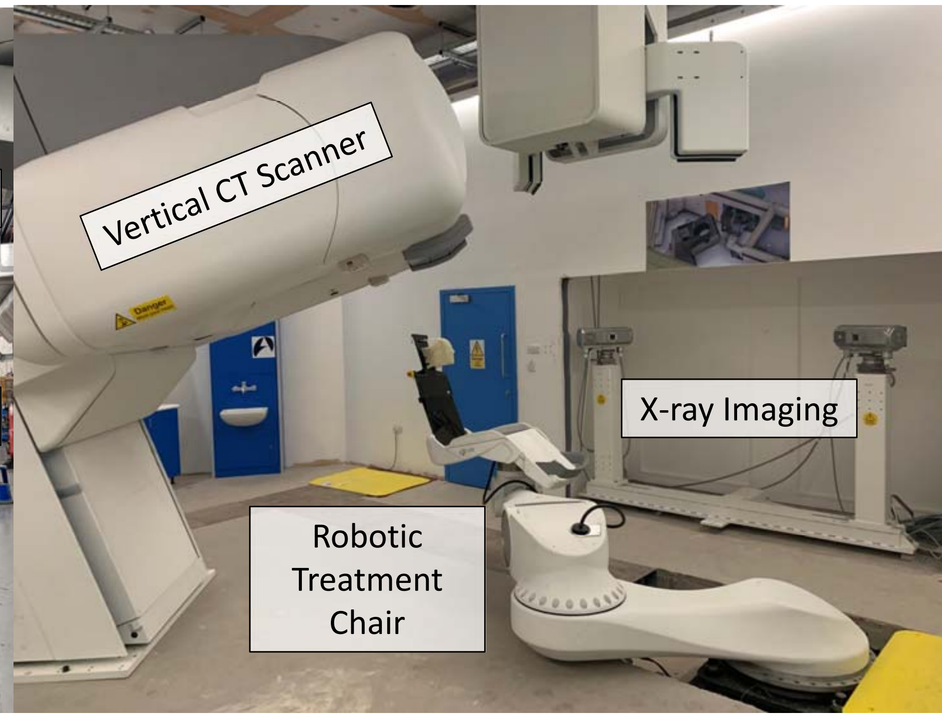
LIGHT Installation at the Daresbury Laboratory, UK

Linac Accelerator Hall



230 MeV Imminent

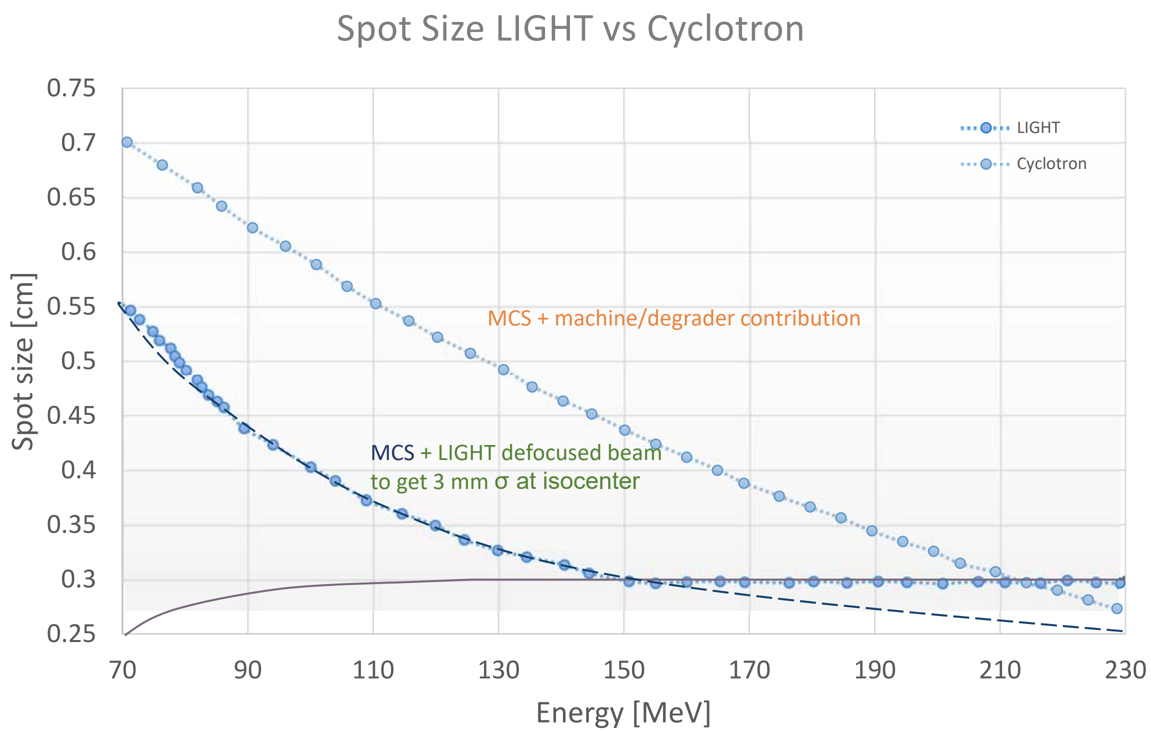
Medical Treatment Room



1st Patient Planned Next Year
(subject to clinical investigation plan approval)

LIGHT®: More Conformal Dose Distribution – Spot Quality

Deliver Better Medical Outcomes



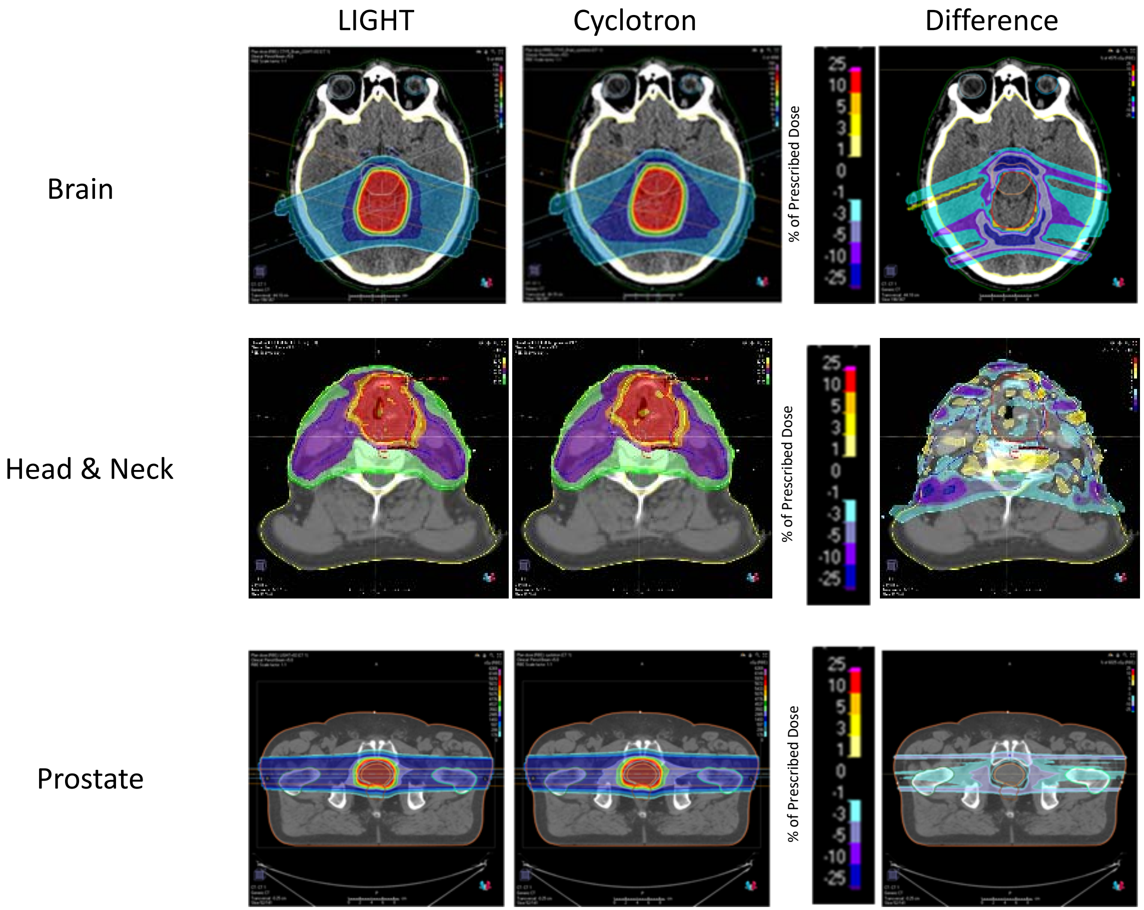
American Society for Radiation Oncology (ASTRO) 2020

"Proton LINAC Transverse Beam Scanning Performance Implications for Therapeutic Quality Improvement"

Jonathan Farr, Anna Kolano, et al.

LIGHT can generate very small spot sizes. In order to match standard 3 mm σ at isocenter, the beam is defocused. In contrast, standard machine spot size is dictated by the beam deterioration after passing through the energy degrader.

Proton Beam Quality – Standard Proton Beam

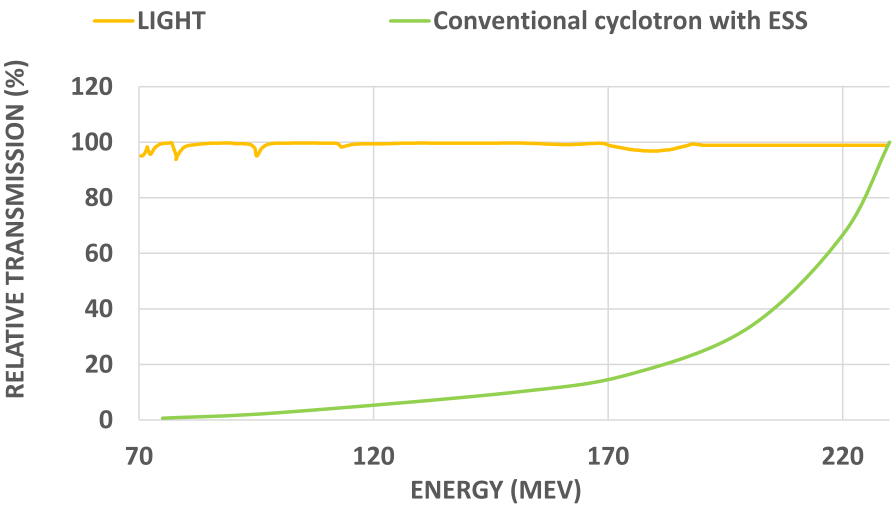


Head and Neck Average Dose to ROI [cGy(RBE)]				
ROI	External	Spinal Cord	Parotid Gland (Left)	Parotid Gland (Right)
LIGHT	763	1958	**1452**	1922
Cyclotron	789	1993	**1670**	1965
Intracranial Case Average Dose to ROIs [cGy (RBE)]				
ROI	External	Brain	Brainstem	Chiasm
LIGHT	165	610	**3073**	25
Cyclotron	189	691	**3367**	77
Prostate Case Average Dose to ROIs [cGy (RBE)]				
ROI	Bladder	Rectum	Femoral head (Left)	Femoral head (Right)
LIGHT	322	**1565**	**1669**	**1489**
Cyclotron	354	**1716**	**1828**	**1639**

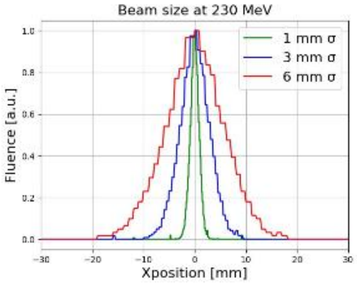
Table 1: Dose Comparison to Site Specific Critical Structures

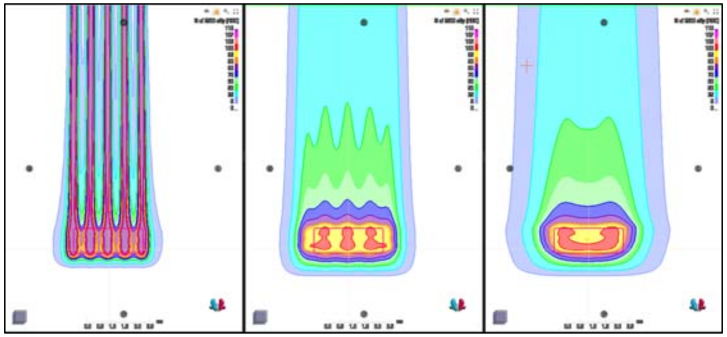
Farr, J.B., et al., *Proton LINAC Transverse Beam Scanning Performance Implications for Therapeutic Quality Improvement.* International Journal of Radiation Oncology*Biology*Physics, 2020. **108**(3, Supplement): p. e351.

Proton FLASH with LIGHT



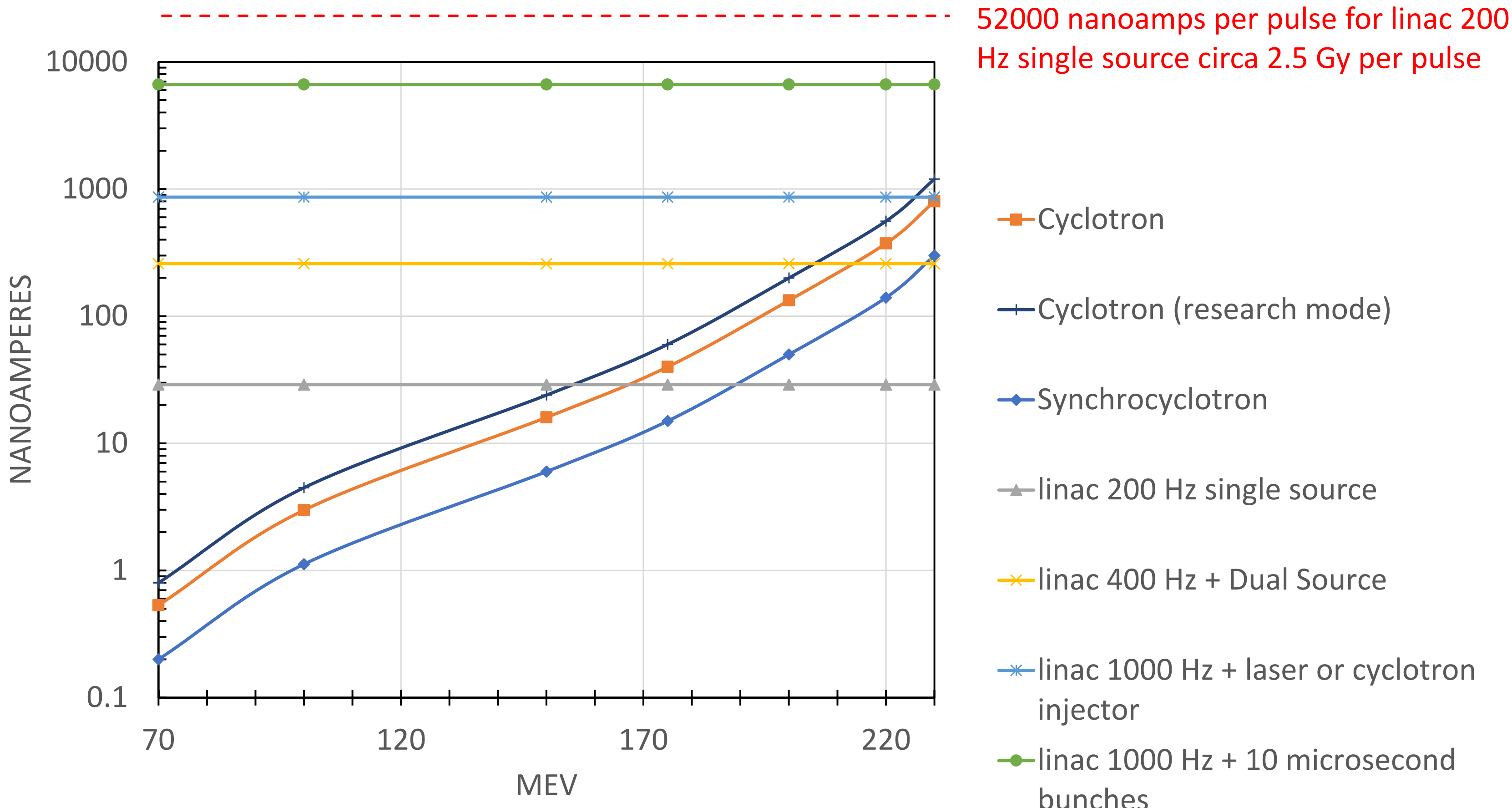
Target	Beam model [mm*σ]	Max spot charge [Mp]	Average Dose [cGy]	Target Distal Depth [cm]	Time [s]	Average Dose Rate [Gy/s]
6 cm3 (I)	1	1600	2470	10	0,615	40
	3	1600	2493	10	0,69	36
	6	1600	2479	10	0,615	40
Intracranial (II)	1	800	3980	5	0.755	53
0.6 cm3 (III)	3	800	2771	3	0,59	47
	3	800	3061	10	0,45	68
	3	800	2626	20	0,6	44
	1	800	4002	3	0,585	68
	1	800	3338	10	0,36	93
	1	800	3045	20	0,54	56
	6	800	945	3	0,58	16
	6	800	2156	10	0,535	40
	6	800	1884	20	0,6	31





Kolano, A.M., A. Degiovanni, and J.B. Farr, *Investigation on the PBS FLASH Beam Delivery Technique Using a Proton Linac.* International Journal of Radiation Oncology*Biology*Physics, 2020. **108**(3, Supplement): p. e331.

Comparative Proton Accelerator Average Beam Currents



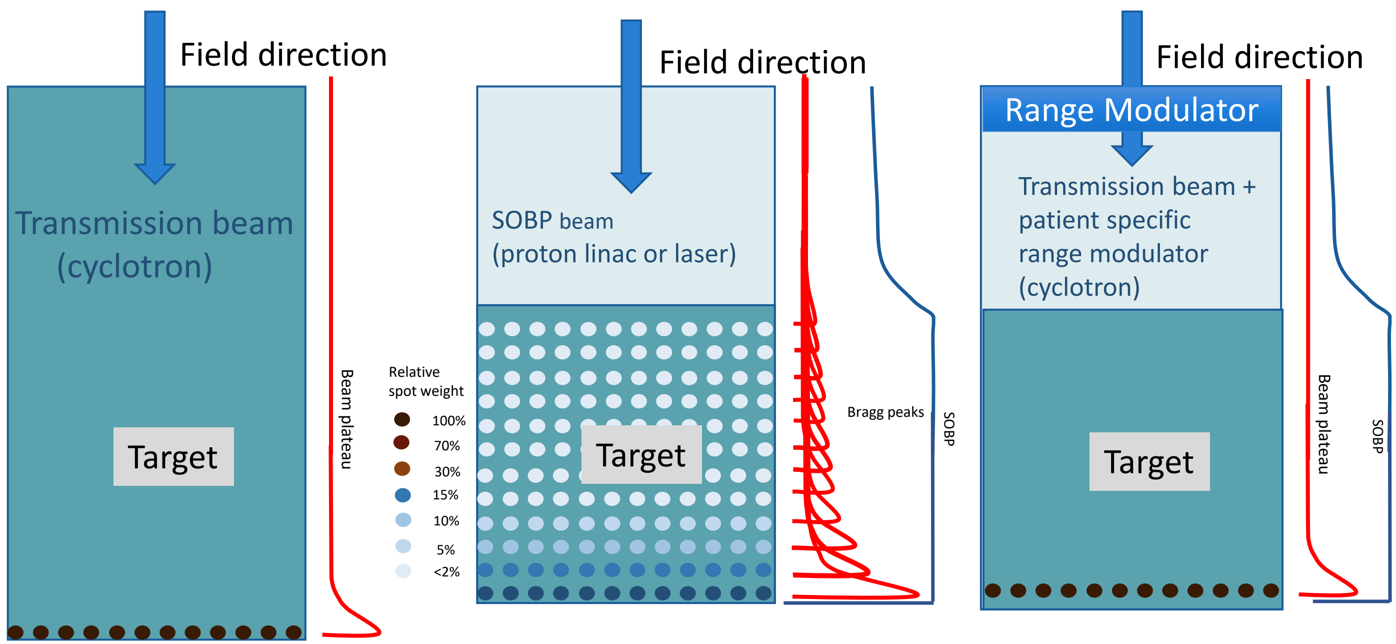
Farr J, et al., "Ultra-high dose rate radiation production and delivery systems intended for FLASH," Med Phys. 2022

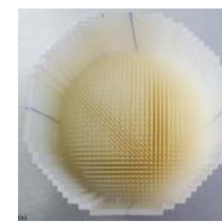
Possible proton FLASH delivery types

Transmission FLASH

Scanned Conformral FLASH

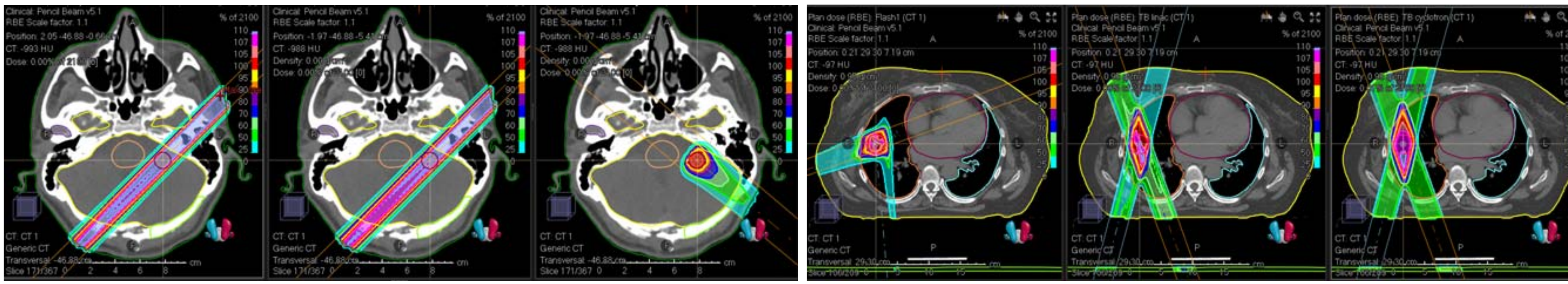
Passive Conformal FLASH





Farr J, et al., “Ultra-high dose rate radiation production and delivery systems intended for FLASH,” Med Phys. 2022

Comparative FLASH delvieries: Transmission vs. Conformal



	Cyclotron Reference Plan (non-flash)	Cyclotron Transmission Beam (TB) flash plan	Linac Transmission Beam (TB) flash plan	Linac Stopping Beam (SB) flash plan
Brain				
Target Volume Prescription Coverage [%]	98	98	93.35	98
Total Brain Dose D_{99}/D_{2} [cGy]	0/830	0/632	0/691	0/440
Lung				
Target Volume Prescription Coverage [%]	98	98	86.37	98
Total Lung Dose D_{Ave} [cGy]	226	314	275	185

Farr J, et al., "Ultra-high dose rate radiation production and delivery systems intended for FLASH," Med Phys. 2022

Conclusion: FLASH System Development needs and Forecast

	Electron	Proton	Heavy Ions
Existing UHDR Accelerators	Linac	Cyclotron, Synchrotron, Synchro-cyclotron	Synchrotron
Existing UHDR Beam Delivery	Low energy, small field size	Only maximum energy, field size up to 10 cm	Variable, small field size
Existing Clinical Use	Superficial, IORT (soon)	Transmission, body extremities, small fields	None
Unmet Clinical Need	Conformal, deep-seated targets, larger field sizes	Conformal beam stopping in target, deep-seated targets, larger field sizes	Conformal beam stopping in target, deep-seated targets, larger field sizes
Enabling Accelerator Technology	**High energy linac, laser**	**High energy linac, laser**	**High-flux synchrotron, linac**
Enabling Beam Delivery Technology	**VHEE, UHDR dose monitoring**	**Ultra-fast energy changes, rapid lateral scanning, UHDR monitoring**	**Ultra-fast energy changes, fast lateral scanning, UHDR monitoring**

Farr J, et al., "Ultra-high dose rate radiation production and delivery systems intended for FLASH," Med Phys. 2022

Future Therapy Linac Predictions

- Initial human Flash results will be obtained for shallow tumours and in the extremities.
- High energy/high dose rate/pulse systems will be needed to fully realize clinical Flash.
- Medical proton linacs will be the next system type used clinically (here in the UK).
- VHEE linacs will continue to develop.
- Trend toward compact, multi-function systems, imaging, treatment, isotopes, flash, BGRT

LINACS FOR MEDICINE