FLASH irradiations at TRIUMF

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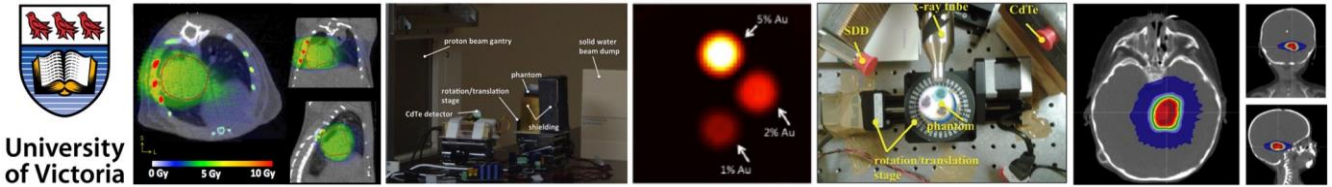

Acknowledgements

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Conny Hoehr

Thomas Planche

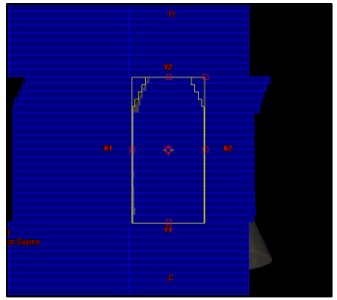
Bill Paley

Groups: Vacuum (Derek Orth), Controls, Elinac operations, Machine shop and Safety

FLASH at TRIUMF

Radiation therapy

Varian Truebeam



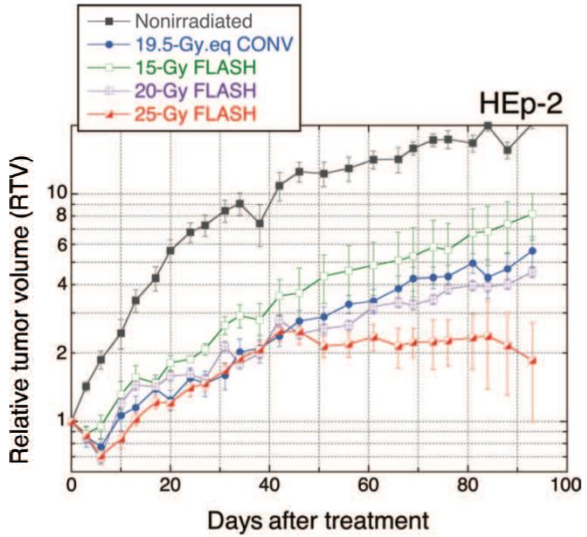
- Delivered in fractions (2 Gy/fraction) to avoid normal tissue toxicity.
- Delivered usually with 6-10 MV photon beams.
- The beams are modulated by means of an MLC.
- Using a full rotation of the linac gantry (**1-2 minutes/fraction**).

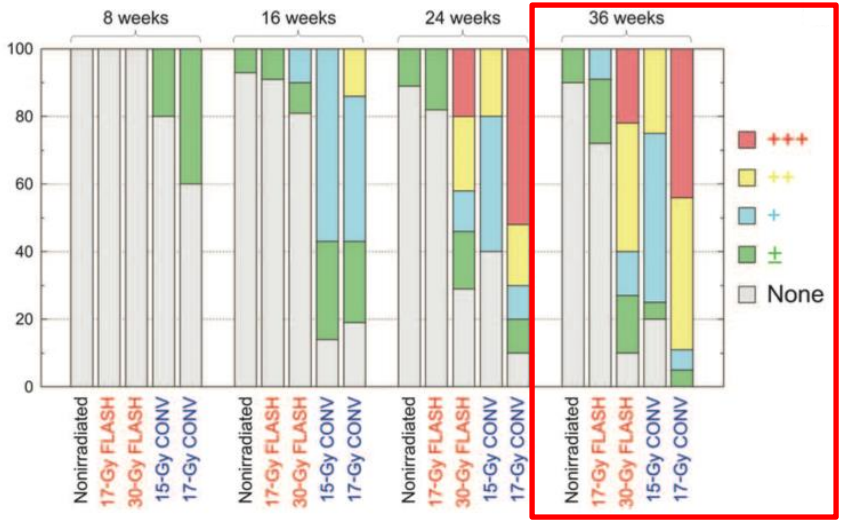
FLASH radiotherapy

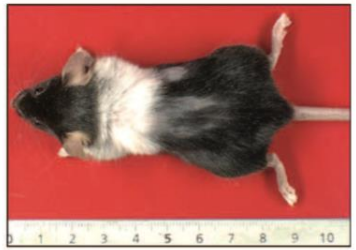
To irradiate target with total treatment dose at ultrahigh dose-rate.

FLASH radiotherapy

- Conventional dose rate ~0.03 Gy/s
- FLASH dose rate ~40 Gy/s
- Usually delivered with a 4.5 – 6 MeV e- beam using high-output linacs





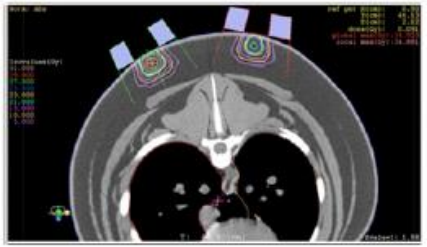


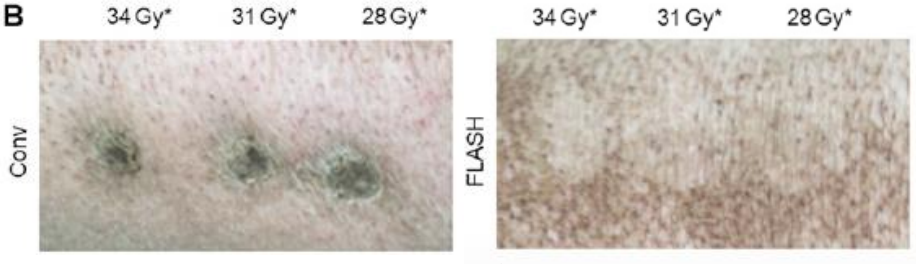
20 Gy FLASH dose
Hair depigmentation, but
no epilation or skin ulceration

Favaudon et *al.*, 2014

FLASH radiotherapy

- Pig skin irradiated with FLASH and CONV
- Lower toxicity observed for FLASH





36 weeks PI

Table 1B. Pig skin toxicity follow-up

RT	Dose (Gy)	7w	10w	14w	20w	24w	32w
Conv	22	L0	L0	L0	L0	R	R
Conv	25	L0	L0	L0	L0	L0	L0
Conv	28	L0	L0	L0	L0	L0	L0 + L4
Conv	31	L0	L0	L0	L0	L0	L0 + L4
Conv	34	L0	L0	L0	L0	L0	L0 + L1 + L4
FLASH	22	–	L0	R	R	R	R
FLASH	25	–	L0	R	R	R	R
FLASH	28	–	L0	R	R	R	R
FLASH	31	–	L0	R	R	R	R
FLASH	34	–	L0	L0	L0	L0	L0

- Six cat patients with SCC treated with FLASH to 25-41 Gy
- Five cats showed complete response at 16 months.

Vozenin *et al.*, 2018

FLASH radiotherapy

- A 75-year-old patient had a CD30+ T-cell cutaneous lymphoma diagnosed in 1999 classified T3 N0 M0 B0.
- Localized skin RT has been previously used over 110 times for various ulcerative and/or painful cutaneous lesions progressing despite systemic treatments.
- A tumor of 3.5 cm (Fig. 1a) was treated with a FLASH dose of 15 Gy in 90 ms using Oriatron eRT6 5.6-MeV electron linac

Fig. 1. Temporal evolution of the treated lesion: (a) before treatment; the limits of th PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

Bourhis *et al., 2019*

Most FLASH data so far: e^- beams

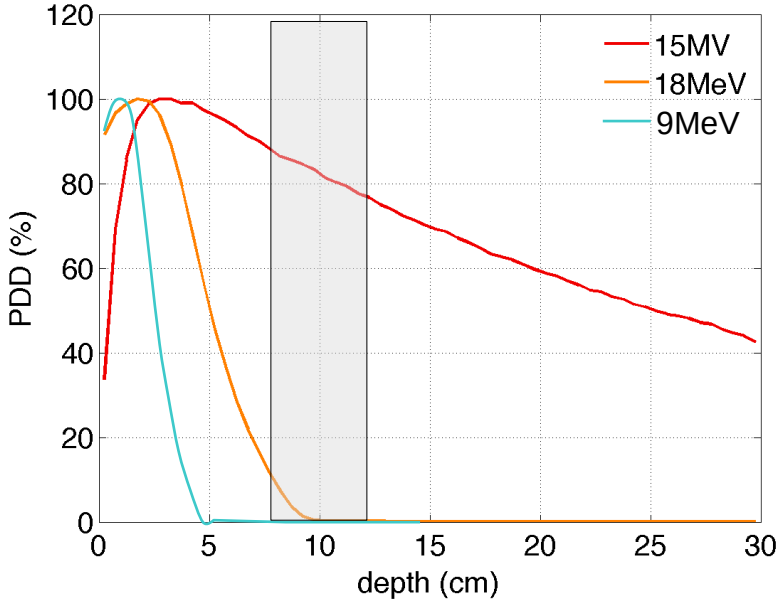
- The French/Swiss group
  - mouse lung irradiations (Favaudon *et al*.)
  - mouse whole brain irradiations (Montay-Gruel *et al*.)
  - mini-pig and cat irradiations (Vozenin *et al*.)

Oriatron: 6 MeV e-

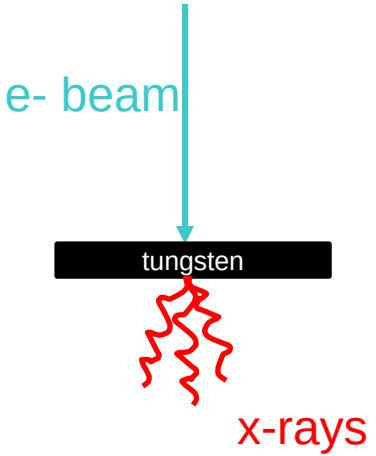
- The Stanford group
  - modification of a clinical linac (Schüler *et al*.)
  - mouse gut irradiations (Loo *et al*.)
  - mouse brain irradiations (Simmons *et al.*)

Clinac: 9 MeV e-

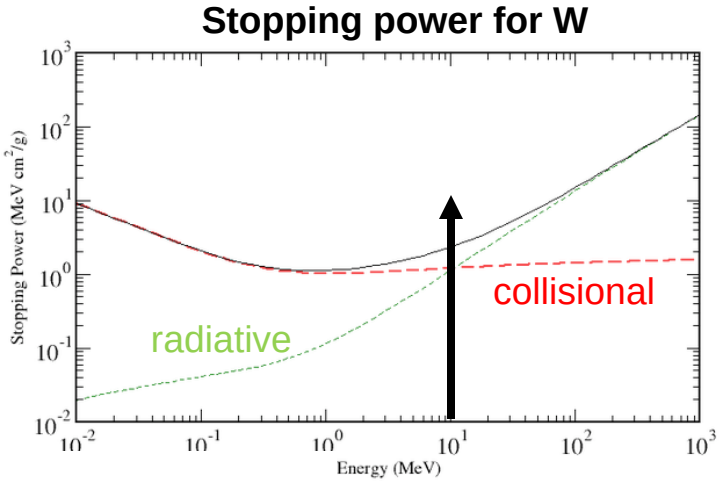
Electron beam depth dose

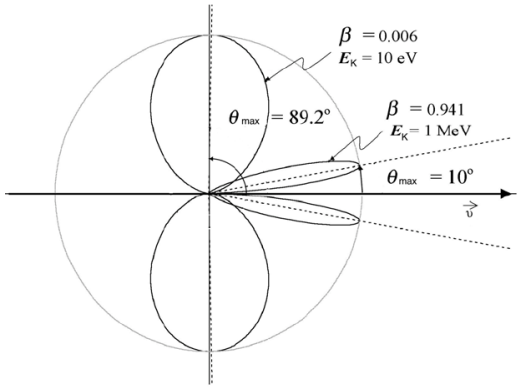


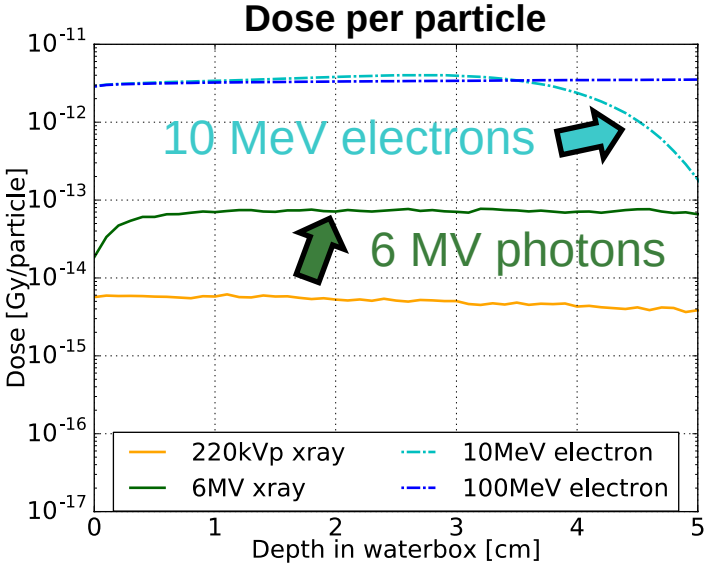
Why electron beams and not photons?



1-5% efficiency







Dunning *et al.* (2019)

Photon beam sources

15 MV: 6 Gy/min
SRS: 10 Gy/min

10 MV: 24 Gy/min

Bremsstrahlung x-rays

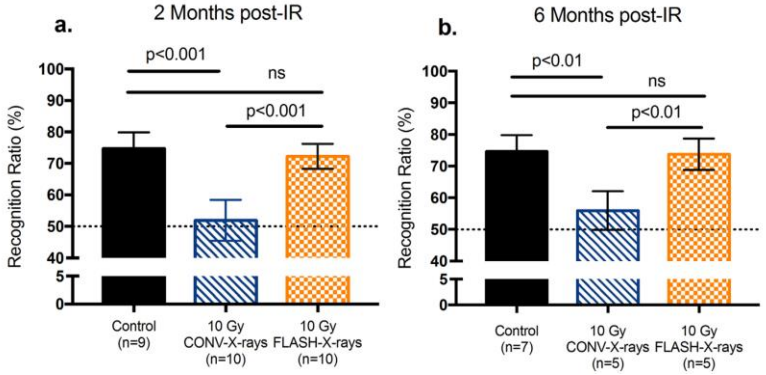
Synchrotron x-rays

Synchrotron: ~10 kGy/s

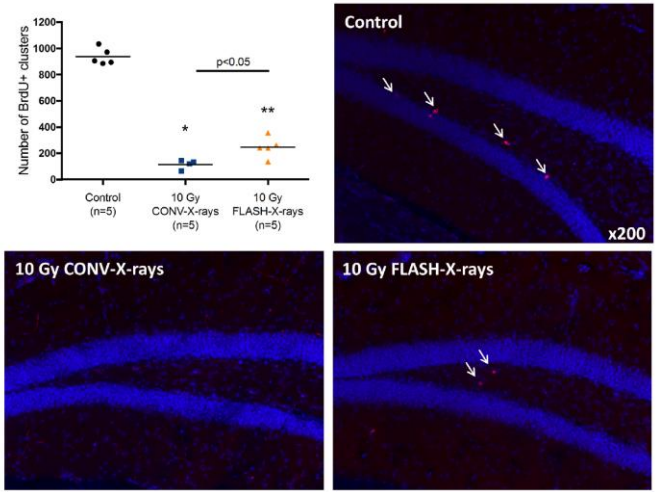
FLASH irradiation with synchrotron x-rays

- Brains of mice irradiated to 10 Gy with FLASH and CONV
- FLASH delivered at ESRF in Grenoble, in slice 16 kGy/s, mean 37 Gy/s
- CONV on SARRP

- Cognitive studies performed at 2 and 6 month
- Recognition ratio reported
- BrdU staining to identify proliferating cells



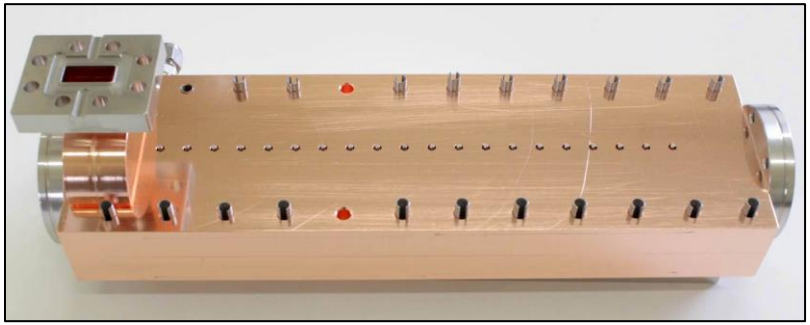
BrdU staining



Montay-Gruel *et al., 2018*

Other high dose-rate sources

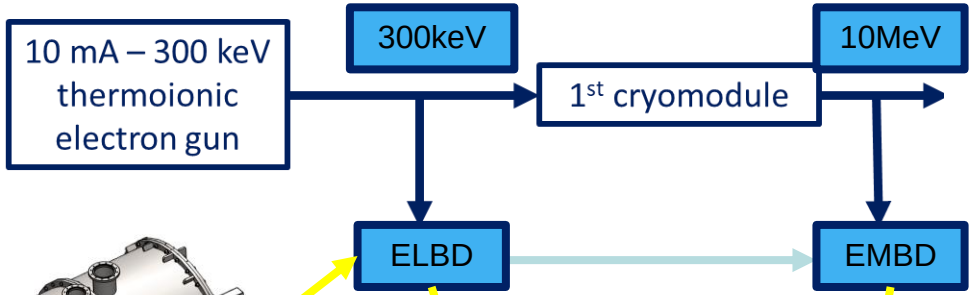
Proton therapy

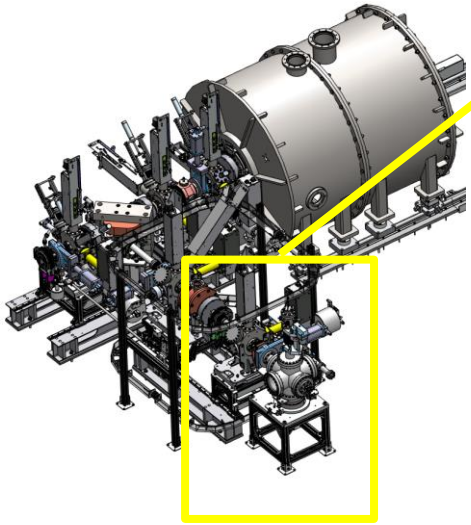


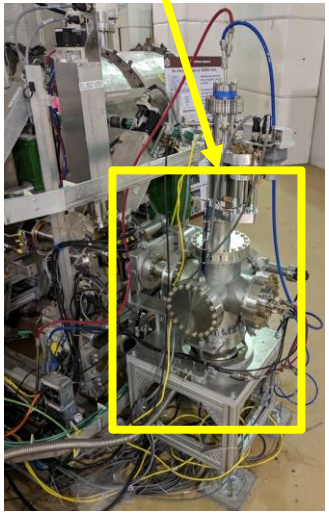
Compact linacs

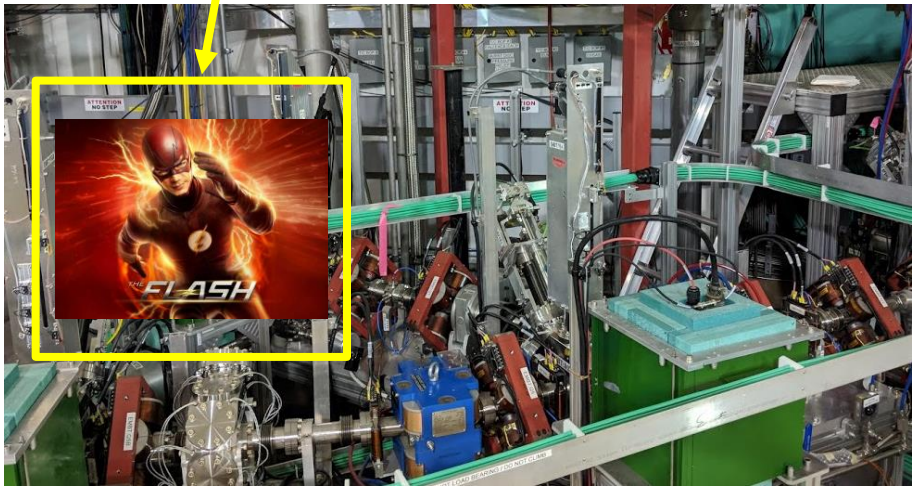
High-energy physics beamlines

ARIEL


10 mA – 300 keV thermoionic electron gun
300keV
1st cryomodule
10MeV
ELBD
EMBD

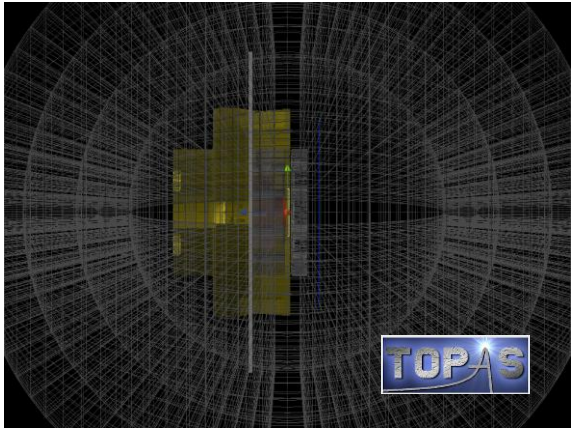


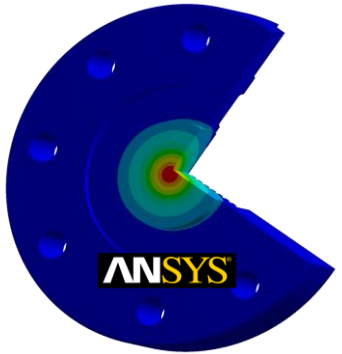



FLASH

Methods

- Analytical estimates inform ‘initial and boundary conditions’
- Monte Carlo simulations using various codes depending on task
  - BEAMnrc – Ta target, beam size and output optimization
  - TOPAS - detailed geometry (CAD) simulation and 3D dose distributions
  - FLUKA – environmental shielding and input for thermo-mechanical simulations
- Finite Element Analysis (ANSYS) for fluid and thermo-mechanical simulation
  - Steady-state and transient



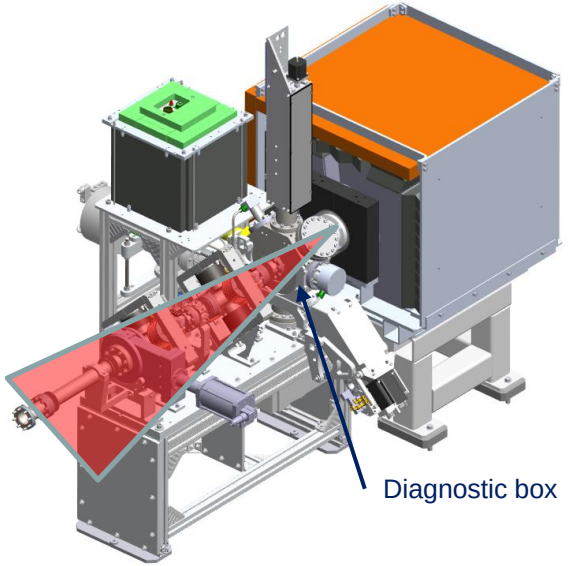


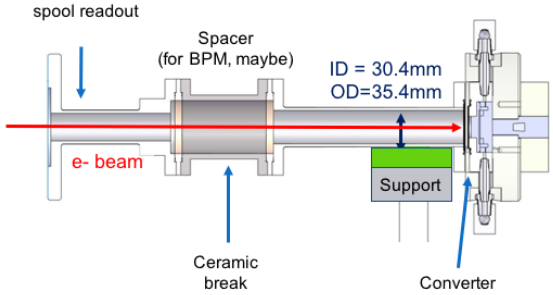
The devil's in the details

Converter design objectives:

- Achieve 'FLASH-compatible' dose-rates
  - Nominally >40 Gy/s** (@ SSD >7 cm)
- No primary electron transmission
  - 0.0002% e- transmission towards biological target
- Al temperatures <300 ℃
- H_2O temperatures <100 ℃
- Ta temperatures < 2000 ℃

- Current readout for output constancy and possible reference dosimetry
  - Requires insulated beamline sections
- Active water cooling required



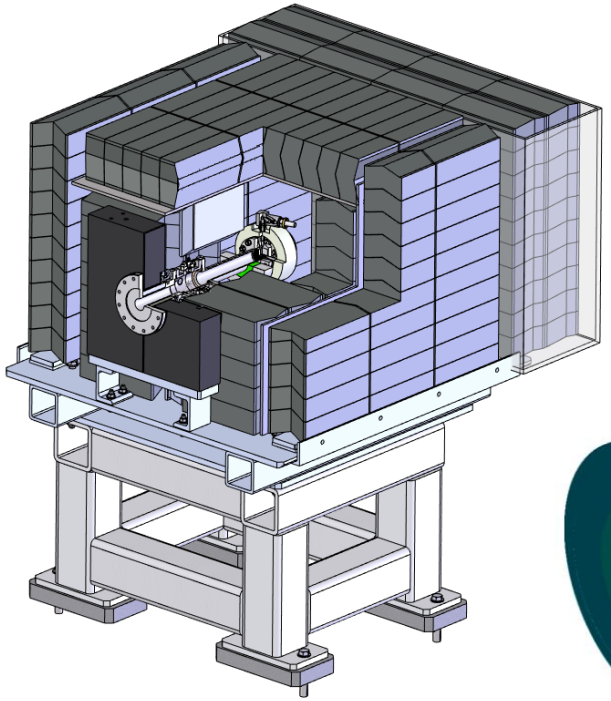


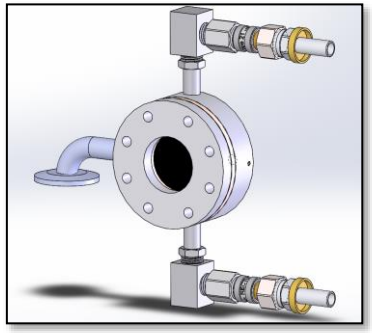
**not necessarily the physical parameter driving FLASH effect

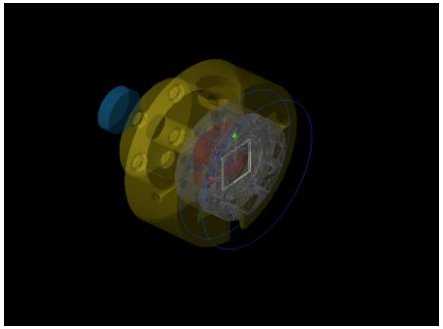
From dump to dream: first results

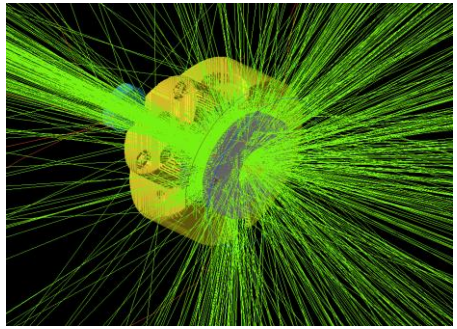
X-ray Cancer Imaging and Therapy Experimental LAB

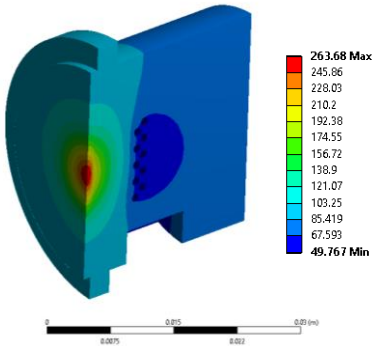
Target design

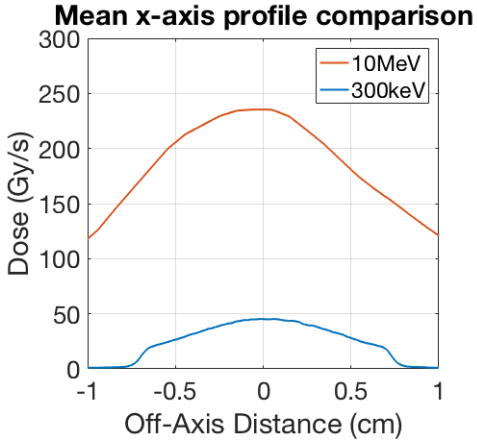


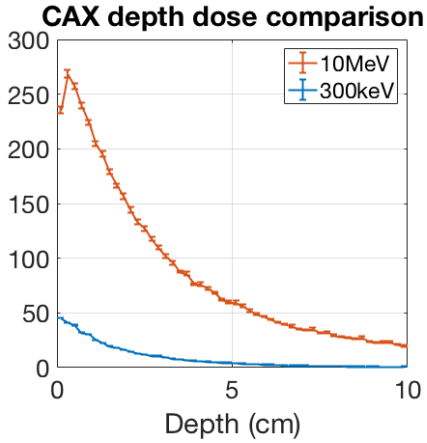








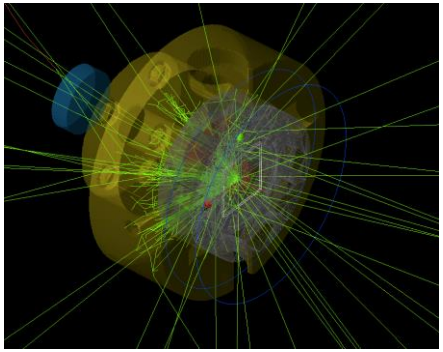


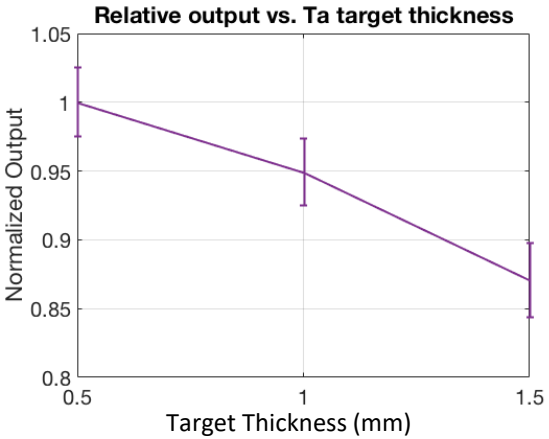


More converter optimization

Energy (MeV)	Quantity	Beam Size (2σ)		
		10mm	5mm	2mm
10	**Dose Rate (Gy/s)**	**290**	**310**	**326**
	T_{Ta} (℃)	1326	1851	2482
8	**Dose Rate (Gy/s)**	**96**	**102**	**101**
	T_{Ta} (℃)	1639	2288	3068

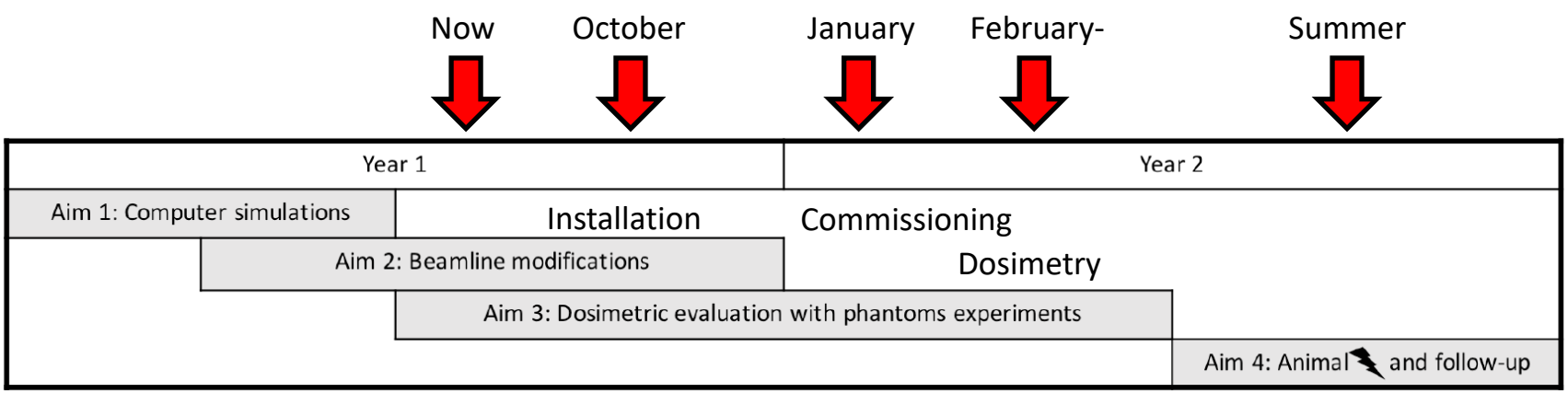
1kW beam power; T_{ta} is steady-state tantalum temp.

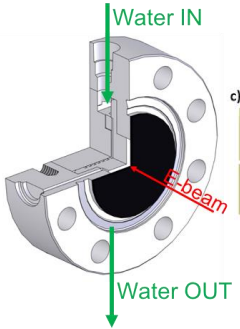


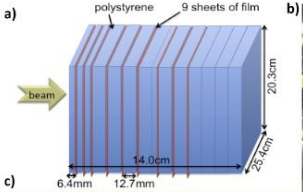


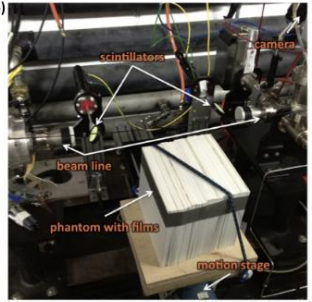
- Output only weakly dependent on spot size
  - open-fields: maximize size to lessen thermal load and target deformation
- 1-mm thick Ta target
  - best gain in thermal mass and e- stopping vs. dose-rate performance

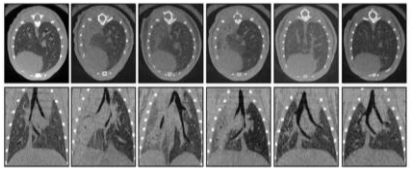
Next steps

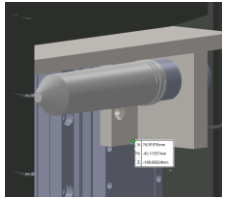






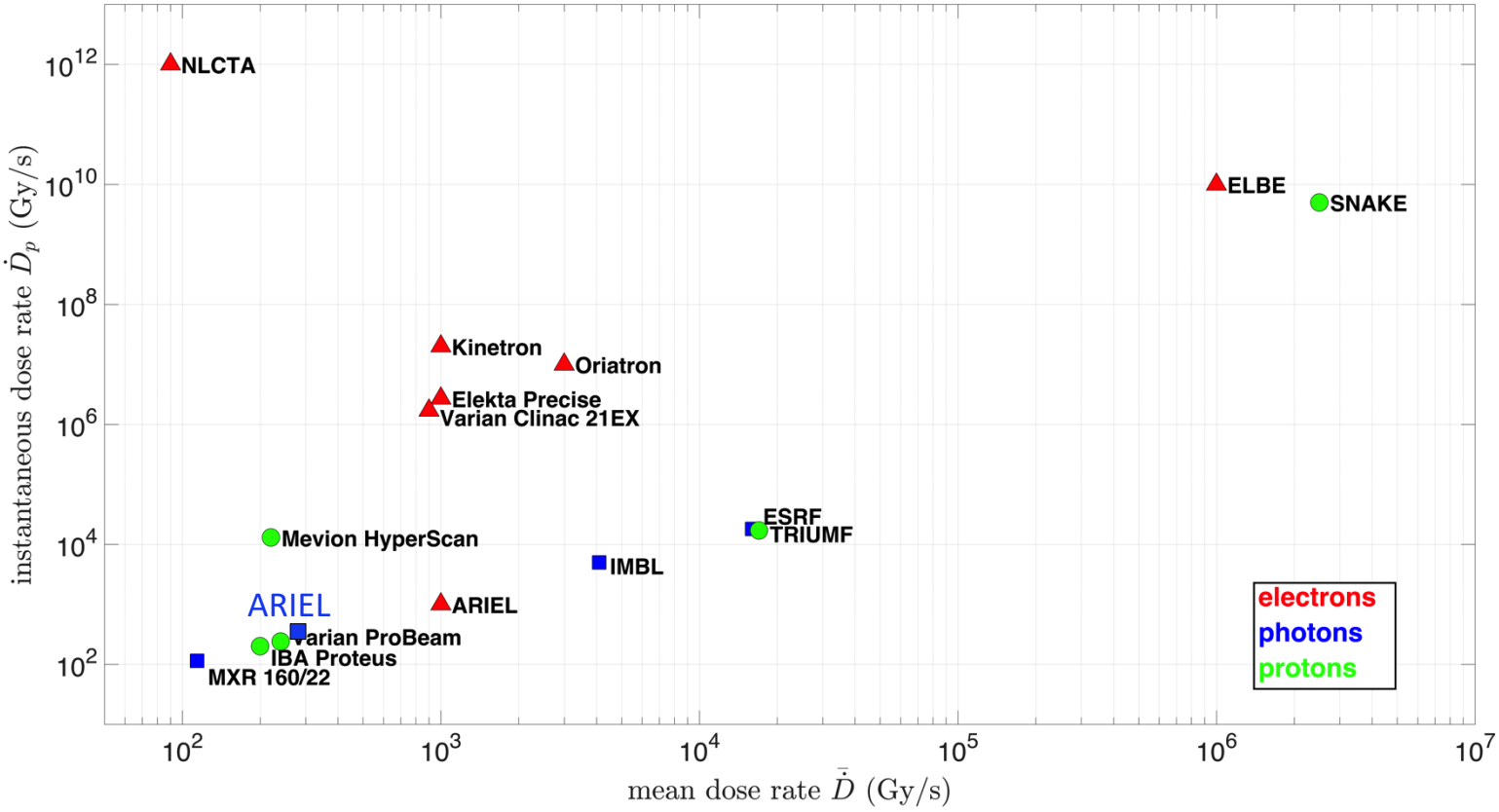






Nancy Ford

Dose rate of available sources



Esplen *et al.*, 2020

Future of FLASH at TRIUMF


Alex Gottberg


Conny Hoehr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FLASH is a mystery!

MENU SCIENTIFIC REPORTS

Article | Open Access | Published: 20 November 2019

Ultra high dose rate (35 Gy/sec) radiation does not spare the normal tissue in cardiac and splenic models of lymphopenia and gastrointestinal syndrome

Bhanu Prasad Venkatesulu, Amrish Sharma, Julianne M. Pollard-Larkin, Ramaswamy Sadagopan, Jessica Symons, Shinya Neri, Pankaj K. Singh, Ramesh Tailor, Steven H. Lin & Sunil Krishnan

Scientific Reports **9**, Article number: 17180 (2019) | Cite this article

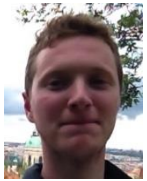
1860 Accesses | **4** Citations | **5** Altmetric | Metrics

An Author Correction to this article was published on 30 June 2020

Summary

- TRIUMF is well positioned to perform consistent FLAS-RT studies with various radiation sources.
- FLASH-RT needs more preclinical studies as it is poorly understood.
- Can be already likely applied clinically to small targets with proton beams.
- Mode of widespread clinical translation is uncertain.
- Might be scary, as like in proton therapy (!) imaging will be crucial (the tumor can be quickly missed).

Acknowledgements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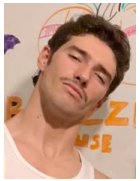
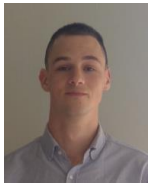

Daniel Cecchi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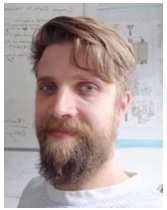
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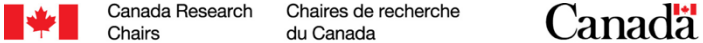

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