TRIUMF | Canada's particle accelerator centre

How nuclear physics can treat cancer

Radiotherapy at TRIUMF

Cornelia Hoehr

Scientist

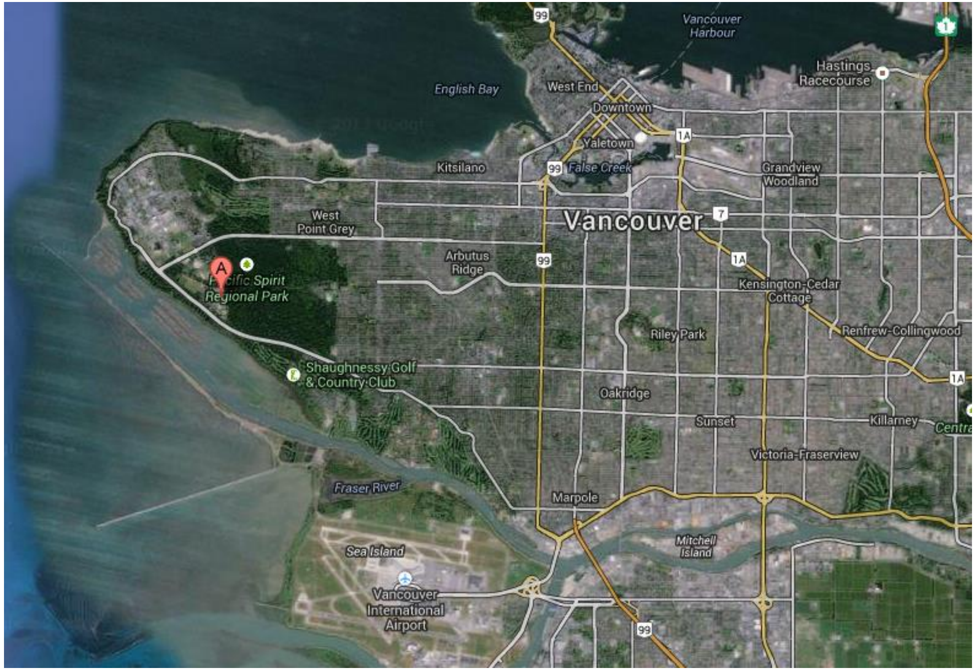
Deputy Associate Laboratory Director | Life Sciences

Introduction

Tourism Vancouver

Introduction

- TRIUMF – Tri University Meson Facility,
- since 1968, now 20 member universities
- Canada's particle accelerator centre



Member Universities:
- University of Alberta
- University of British Columbia
- University of Calgary
- Carlton University
- University of Guelph
- University of Manitoba
- Université de Montréal
- Queen's University
- University of Regina
- Simon Fraser University
- **University of Toronto**
- University of Victoria
- York University

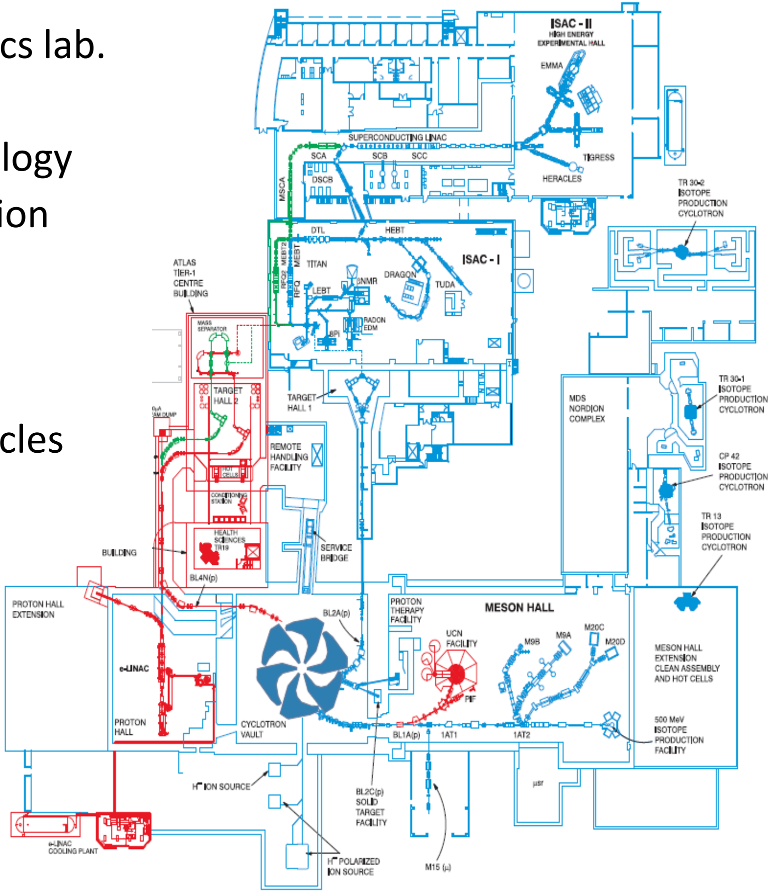
Associate Members:
- McGill University
- McMaster University
- University of Northern BC
- Saint Mary's University
- Université de Sherbrooke
- Western University
- University of Winnipeg

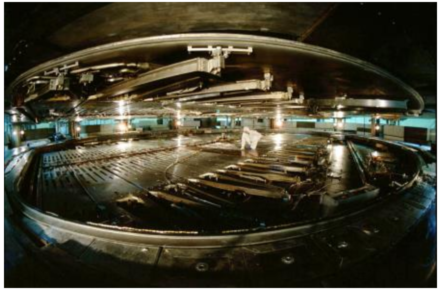
Introduction

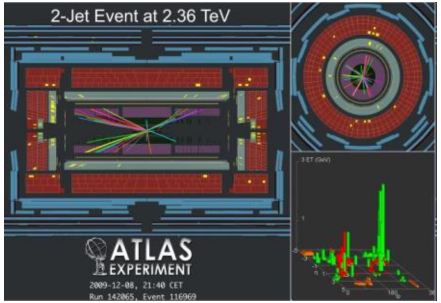
TRIUMF - nuclear physics lab.

Expertise in:

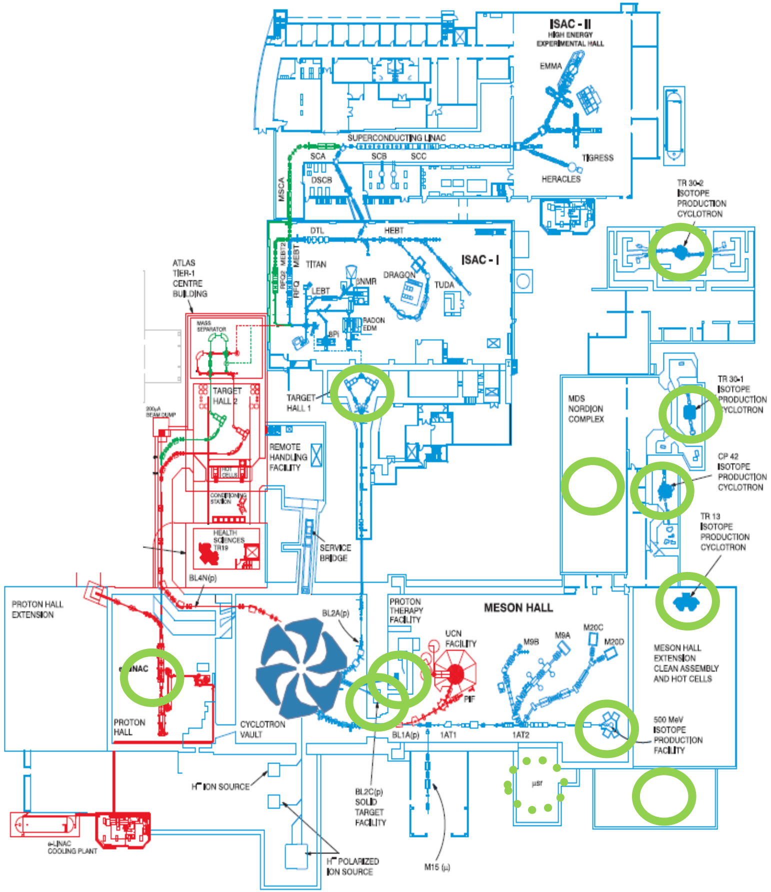
- Accelerator technology
- Accelerator operation
- Detectors
- Targets for isotope production
- Interaction of particles



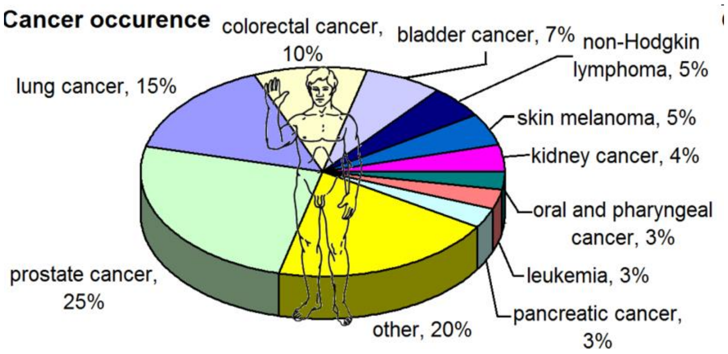


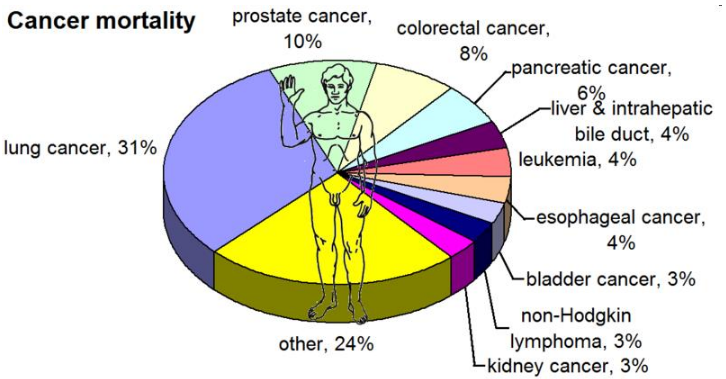


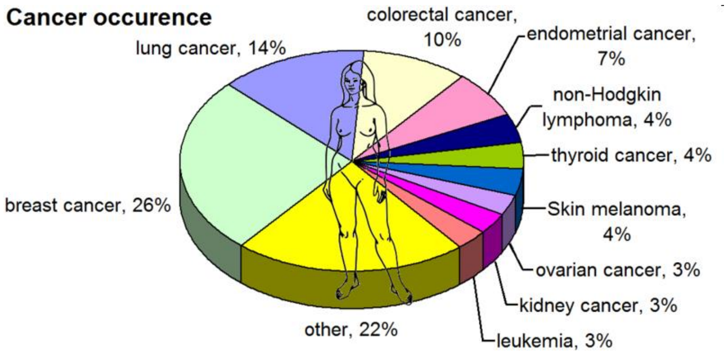
Applicable to medicine

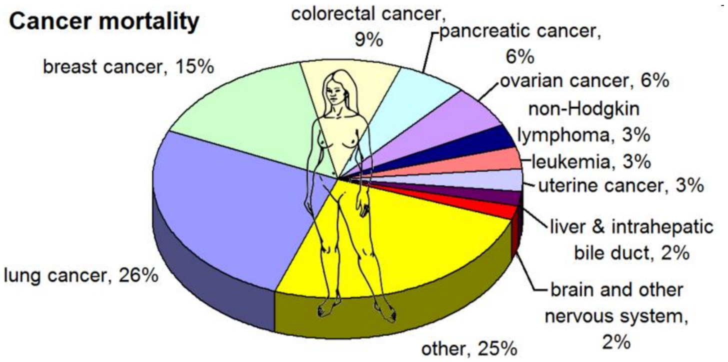


Cancer

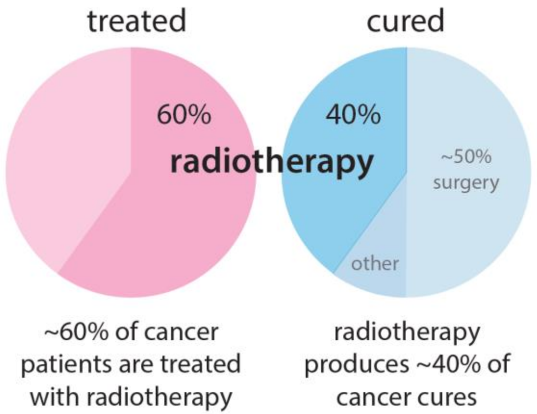

Cancer occurence
colorectal cancer, 10%
bladder cancer, 7%
non-Hodgkin lymphoma, 5%
lung cancer, 15%
skin melanoma, 5%
kidney cancer, 4%
oral and pharyngeal cancer, 3%
prostate cancer, 25%
leukemia, 3%
pancreatic cancer, 3%
other, 20%

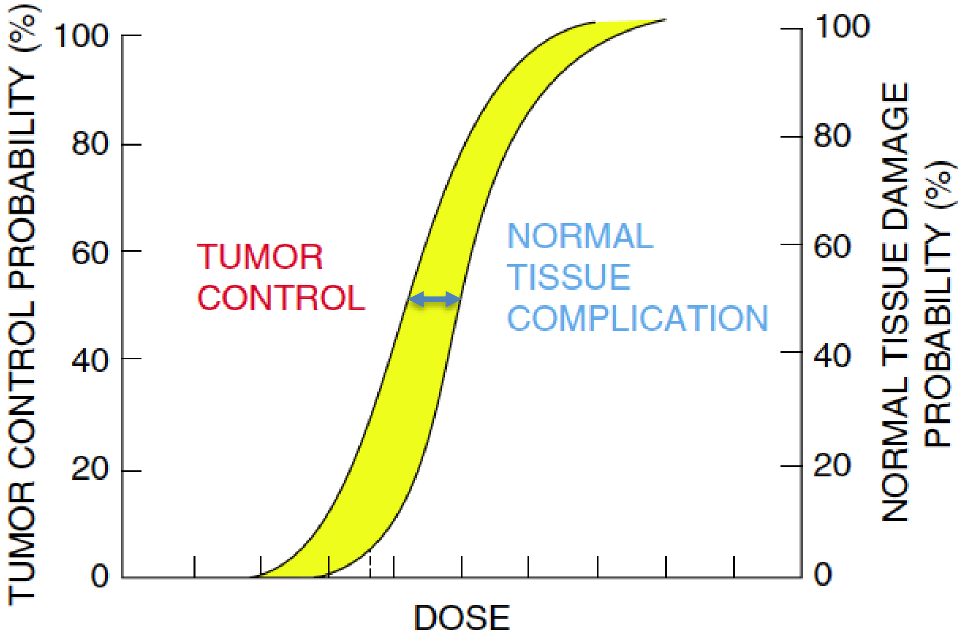

Cancer mortality
prostate cancer, 10%
colorectal cancer, 8%
pancreatic cancer, 6%
liver & intrahepatic bile duct, 4%
lung cancer, 31%
leukemia, 4%
esophageal cancer, 4%
bladder cancer, 3%
non-Hodgkin lymphoma, 3%
other, 24%
kidney cancer, 3%


Cancer occurence
colorectal cancer, 10%
endometrial cancer, 7%
lung cancer, 14%
non-Hodgkin lymphoma, 4%
thyroid cancer, 4%
breast cancer, 26%
Skin melanoma, 4%
ovarian cancer, 3%
kidney cancer, 3%
other, 22%
leukemia, 3%

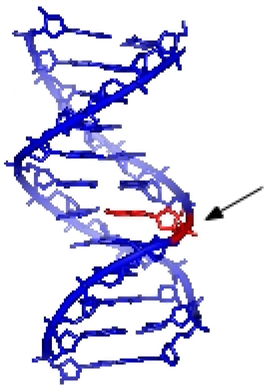

Cancer mortality
colorectal cancer, 9%
pancreatic cancer, 6%
breast cancer, 15%
ovarian cancer, 6%
non-Hodgkin lymphoma, 3%
leukemia, 3%
uterine cancer, 3%
liver & intrahepatic bile duct, 2%
lung cancer, 26%
brain and other nervous system, 2%
other, 25%

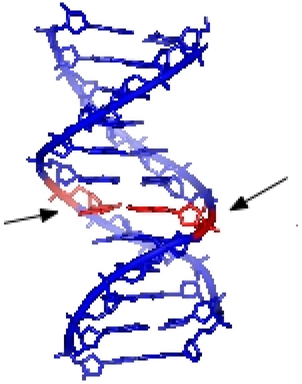
- Surgery
- Chemotherapy
- Ionizing radiation





DNA break

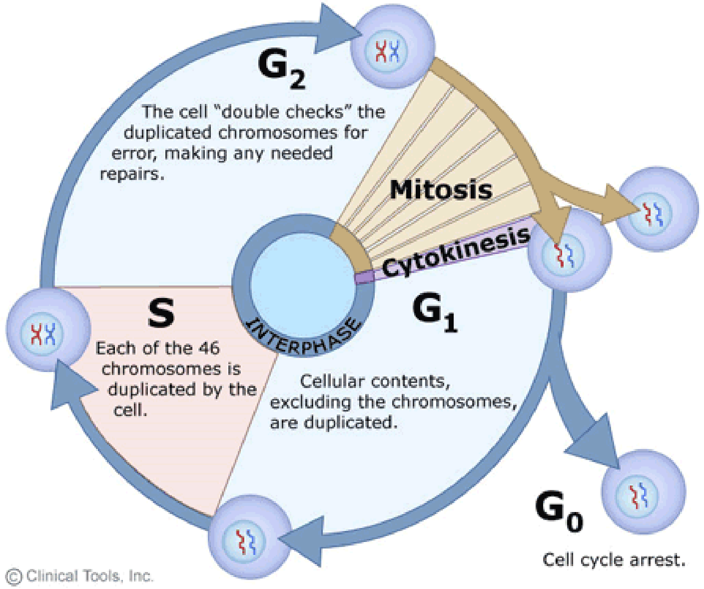




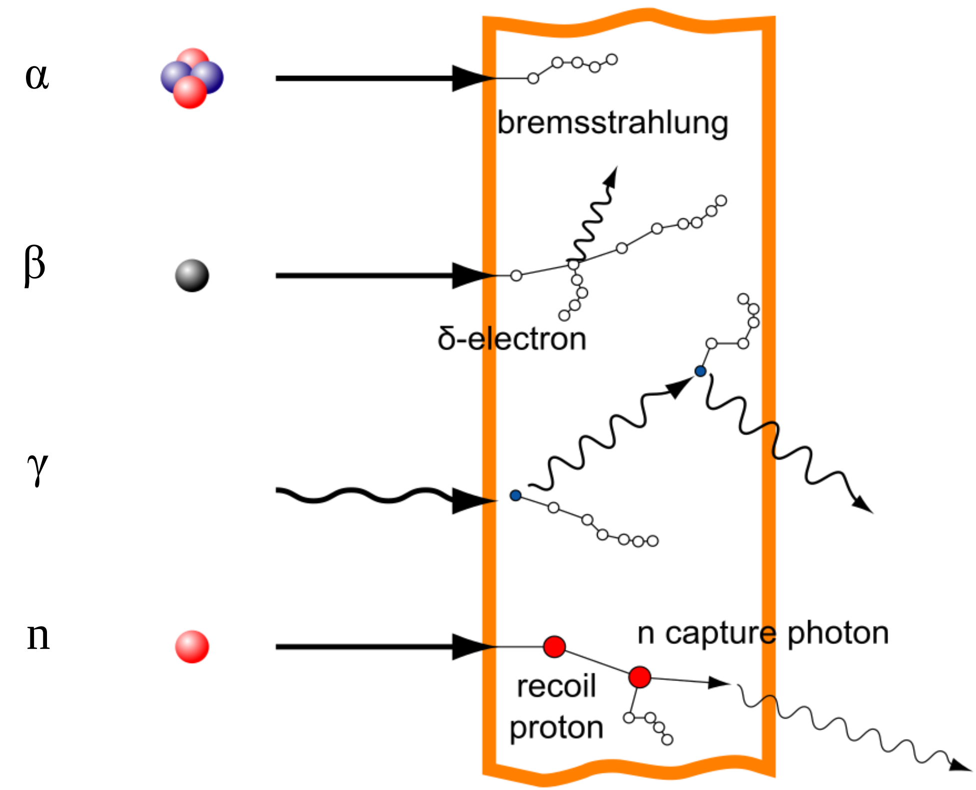
• DNA (Deoxyribonucleic acid): genetic instructions for development and functioning
• Cell needs information from DNA for survival

• Single helix break easy to repair
• Double helix break more difficult to repair
• Cell can not survive

• **Radiotherapy: as many double helix breaks in cancer cells as possible with as few double breaks as possible in healthy cells**



Ionizing Radiation



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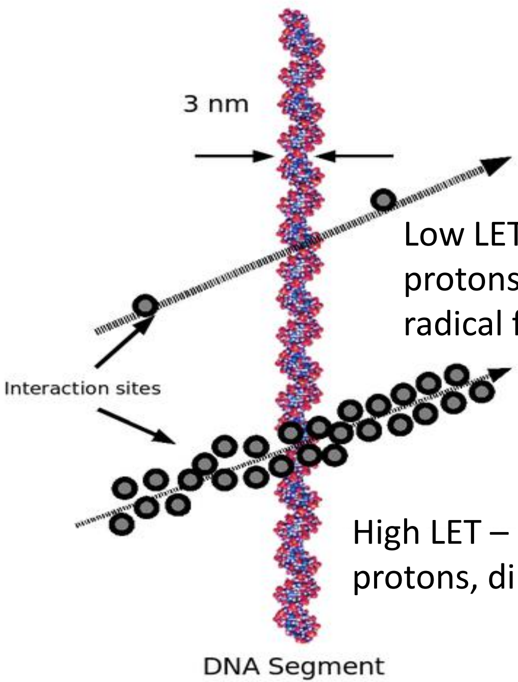
LET – Linear Energy Transfer



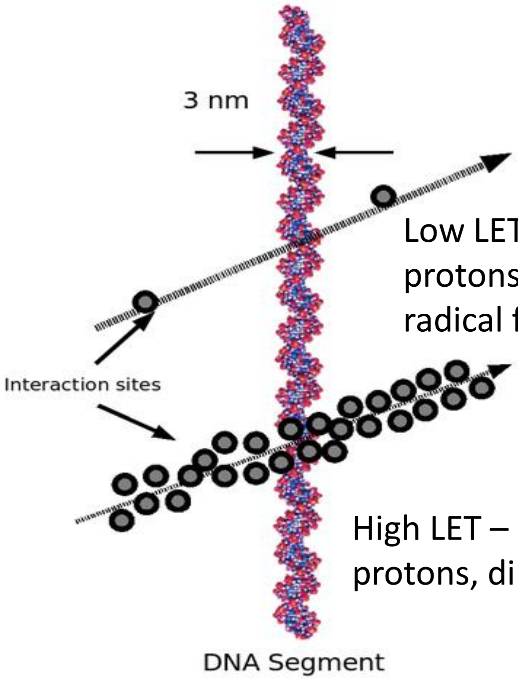
Low LET – photons, electrons, protons, indirect damage via free radical formation

High LET – ions, neutrons, protons, direct damage

Linear Energy Transfer (LET): Energy transferred (ionization, secondary electrons) per unit distance

TRIUMF

LET – Linear Energy Transfer



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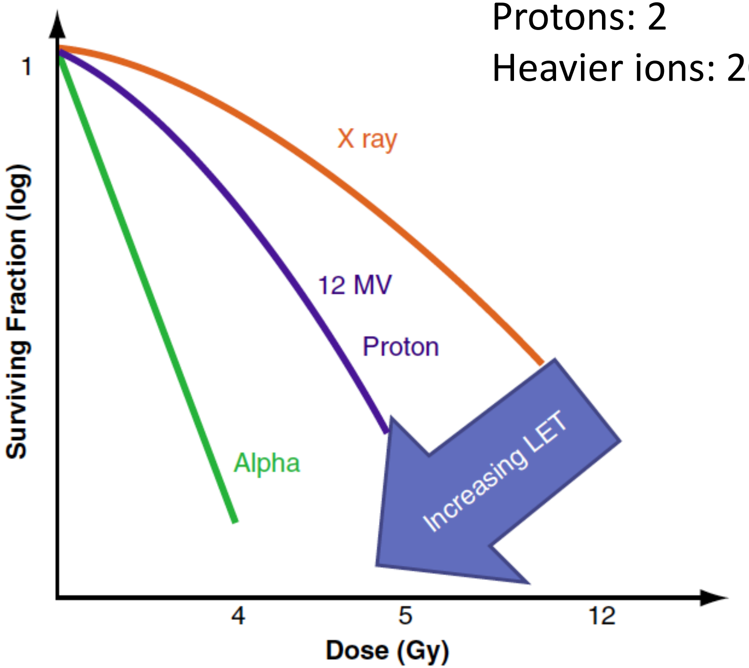
RBE - Relative Biological Effectiveness

X rays: 1
Protons: 2
Heavier ions: 20



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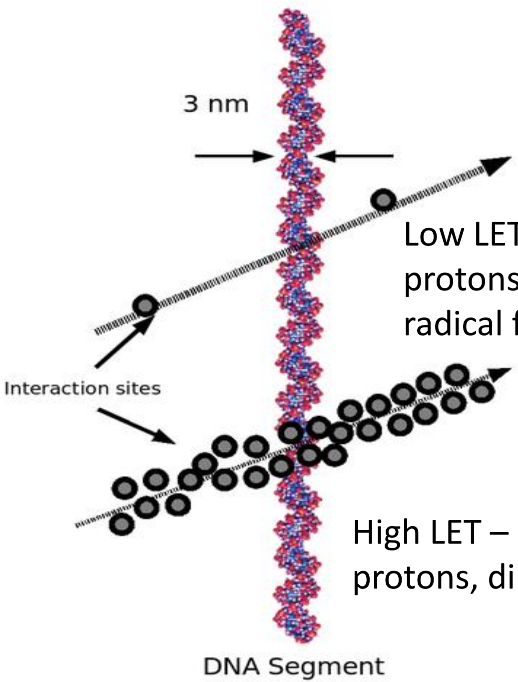

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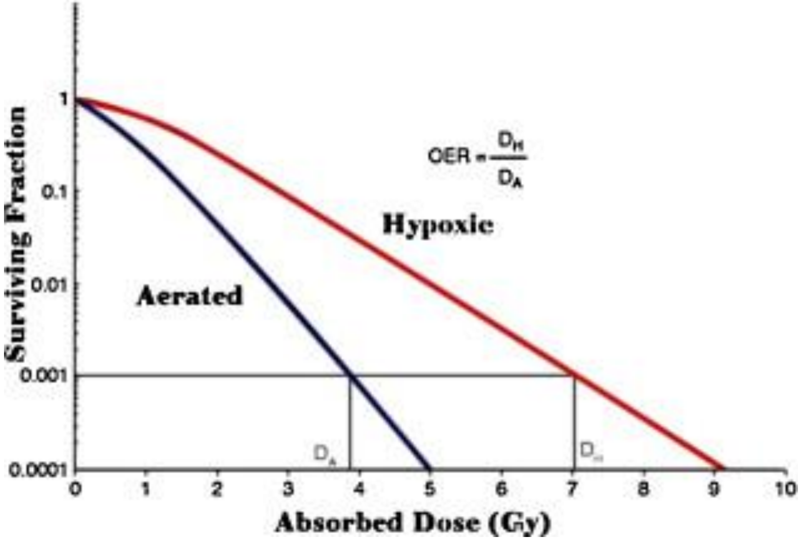
OER – Oxygen Enhancement Ratio

- High LET radiation – low OER
- OER for x rays = up to 4
- OER for ions = 1



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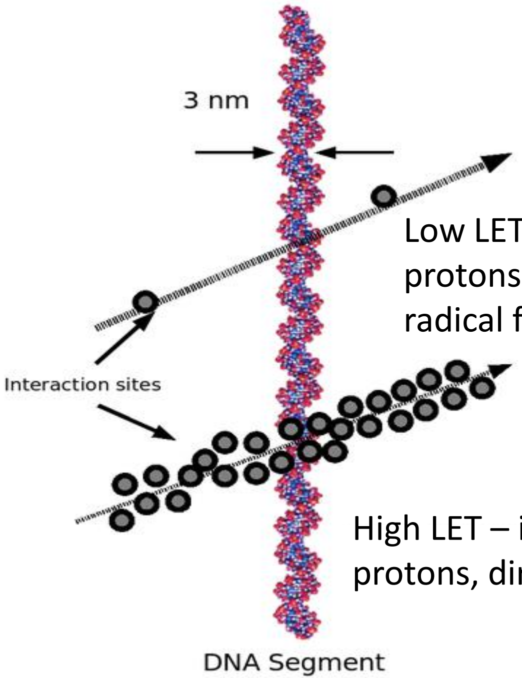

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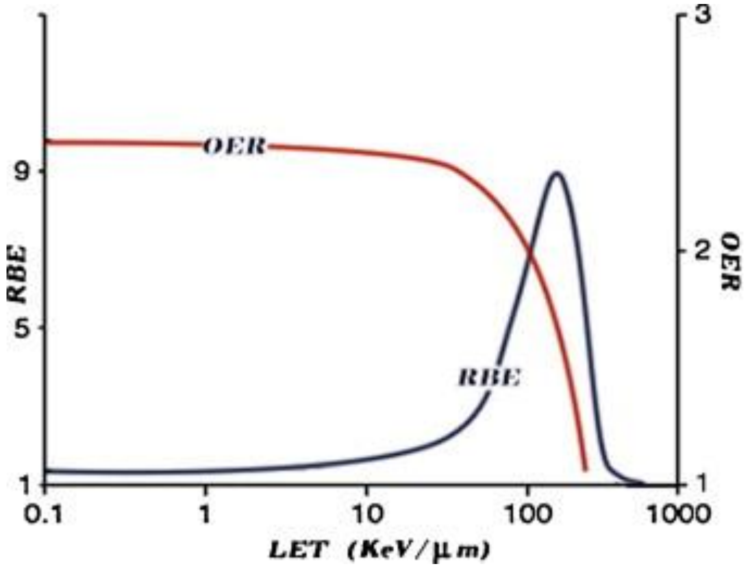
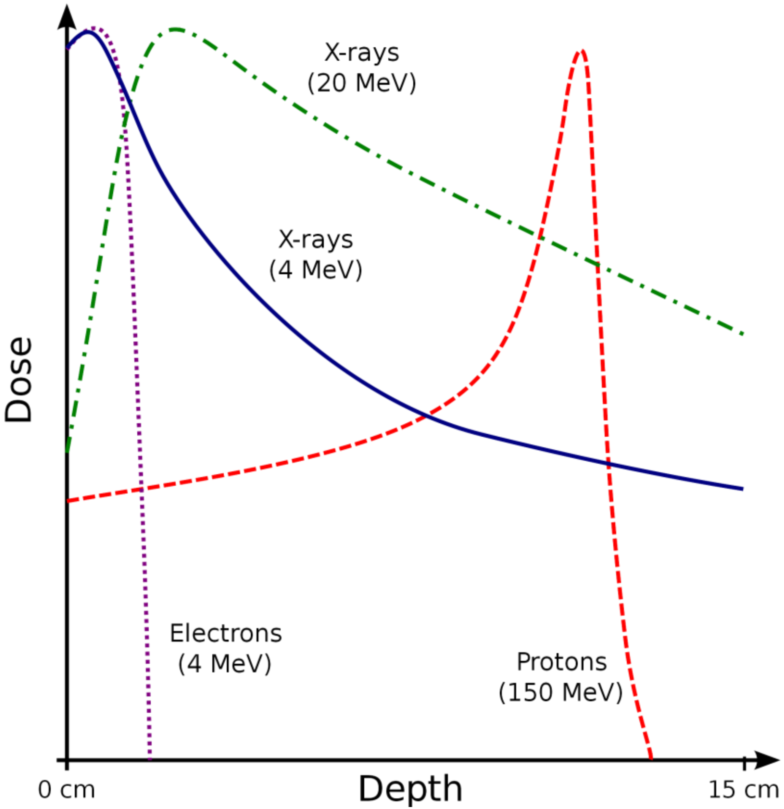


TRIUMF

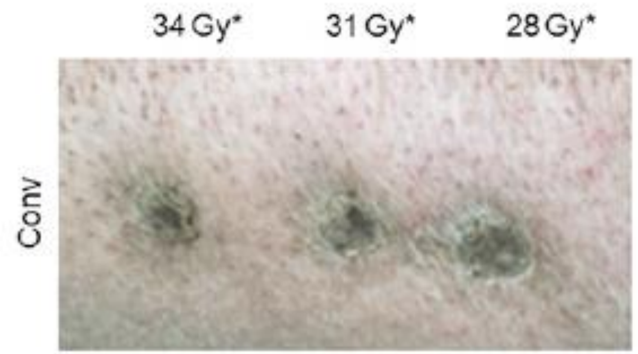
External beam therapy

- **Electrons** only used for surface tumours
- **X-rays** (6-18 MV) most commonly used radiotherapy, many techniques to spare healthy tissue (3D conformal beams, image guided delivery, real-time motion tracking etc.), compact and cost efficient
- **Protons** need 230 MeV accelerator for clinical use, large facility, expensive



Conventional dose rate ~ 0.03 Gy/s

- In 20 – 30 fractions to affect all cell cycle phases, and to reach the hypoxic centre of a tumour



Vozenin *et al.*, 2018

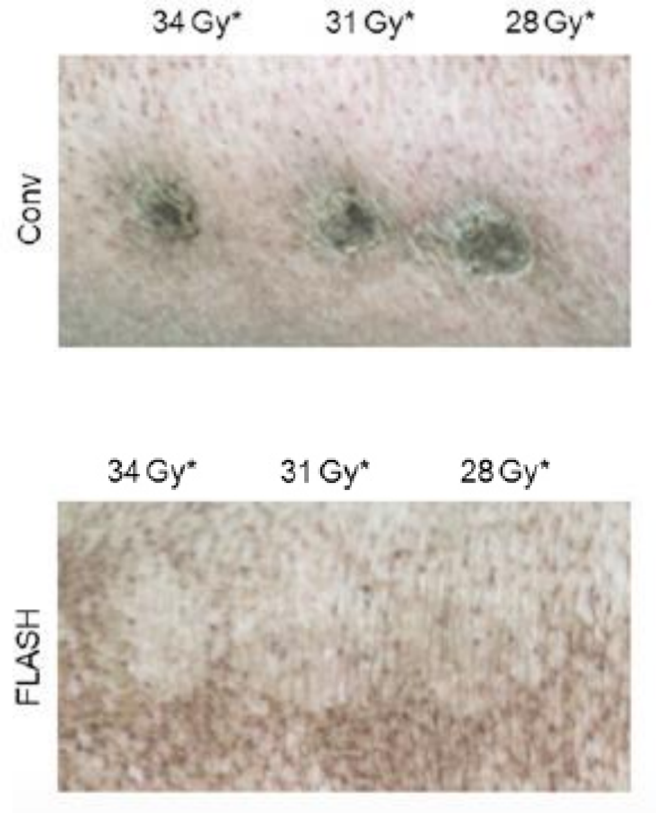
FLASH effect

Conventional dose rate ~ 0.03 Gy/s

- In 20 – 30 fractions to affect all cell cycle phases, and to reach the hypoxic centre of a tumour

FLASH dose rate < 40 Gy/s

- Lower toxicity in healthy tissue but same tumour control
- Effect only consistently observed *in-vivo*, not *in-vitro*
- Oxygen – depletion hypothesis, healthy tissue becomes basically hypoxic
- To reach high dose rates – remove target….. **electron beam**



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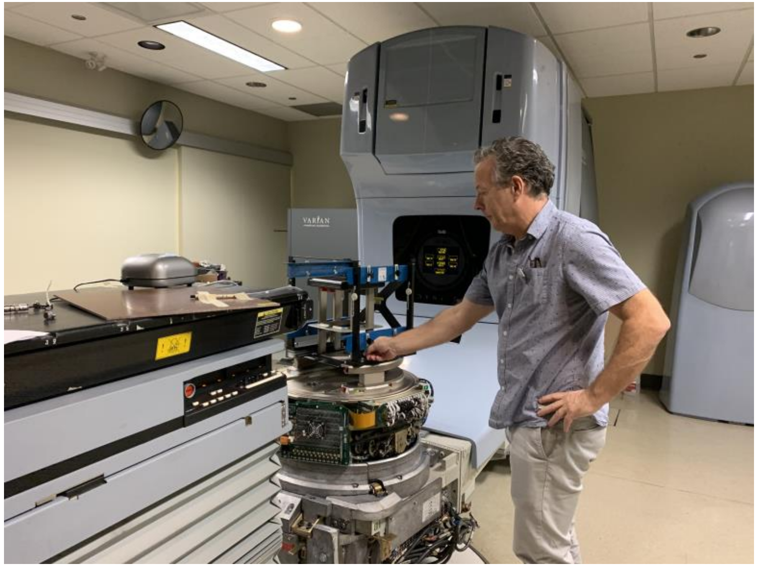
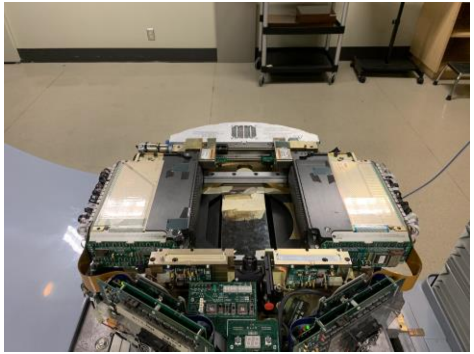
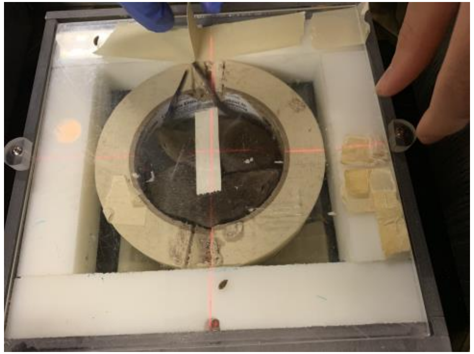
Bourhis *et al.*, 2019

Electron FLASH



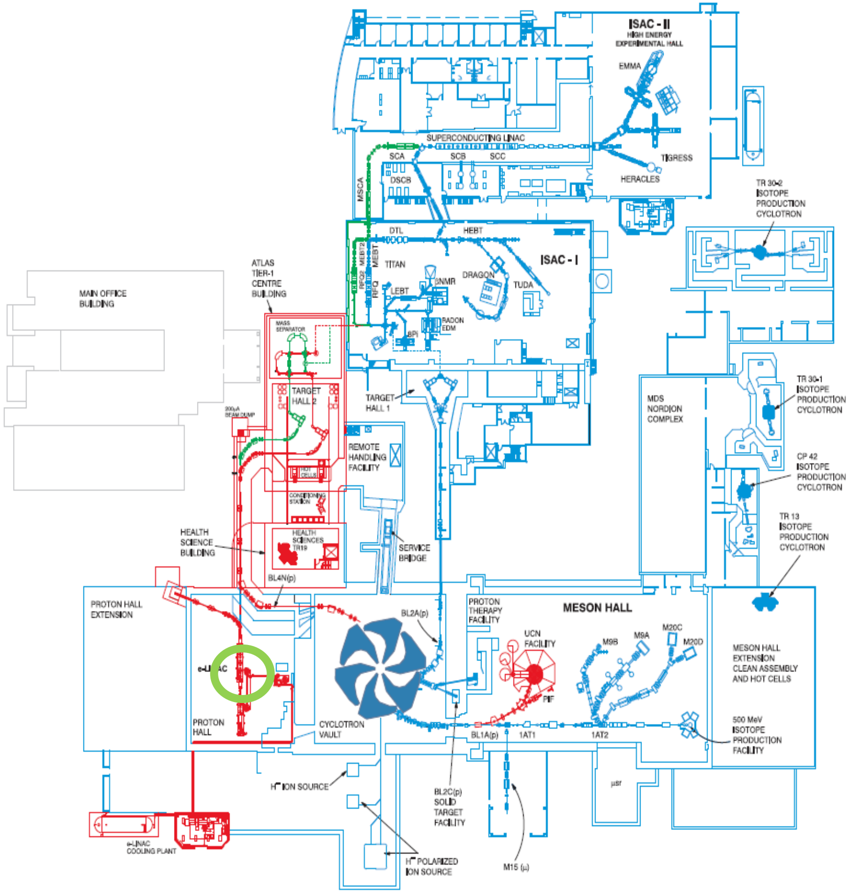




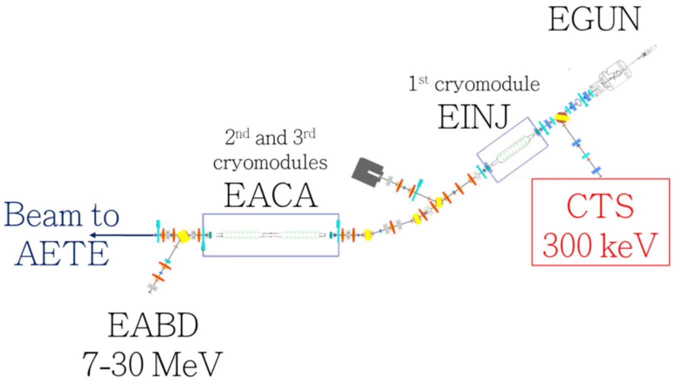
- FLASH in Vancouver
- Around 260 Gy/s
- Data still being analyzed

Andrew Minchinton, BC Cancer

Photon FLASH



- Electron gun 300 keV 10 mA (CW)
- Three accelerating superconductive cryomodules
- Irradiation stations:
  - Low energy (CTS – 300 keV)
  - High energy (EABD – up to 30 MeV)
  - Medium energy (EMBD - up to 10 MeV)

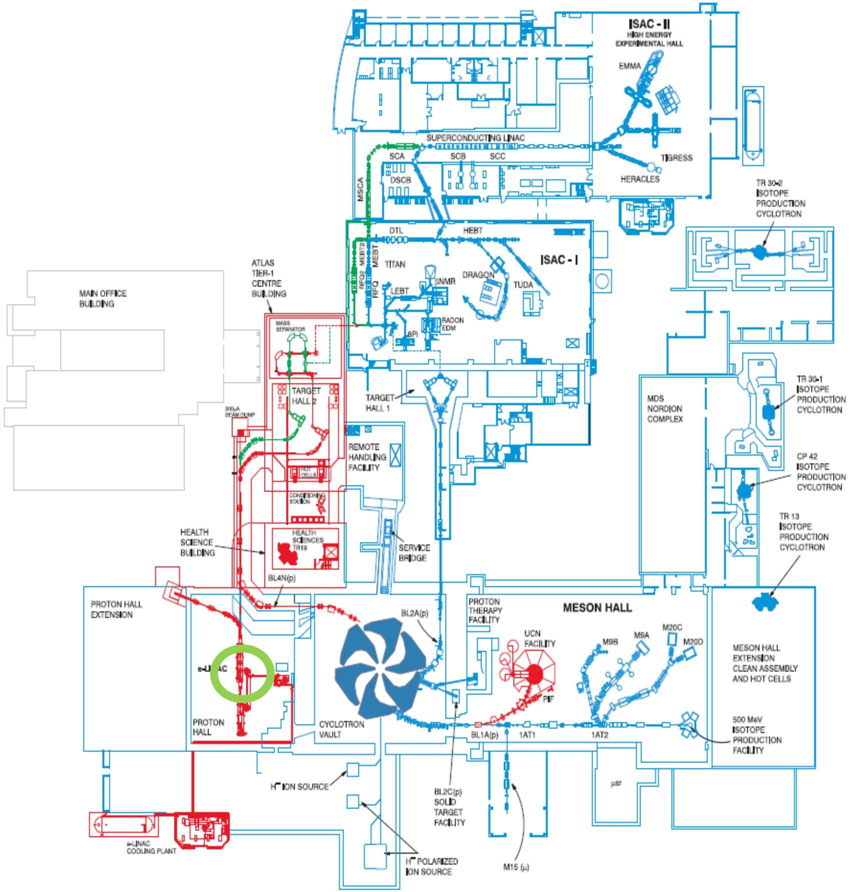


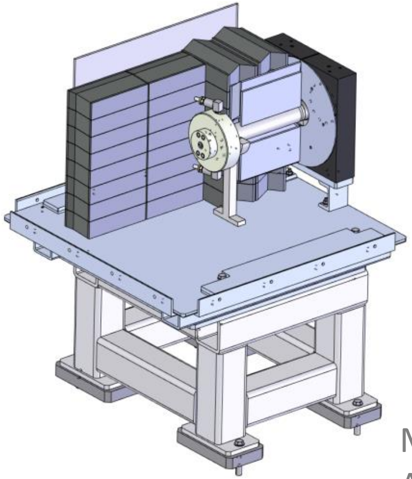
Magdalena Bazalova-Carter, UVic
Alexander Gottberg, TRIUMF

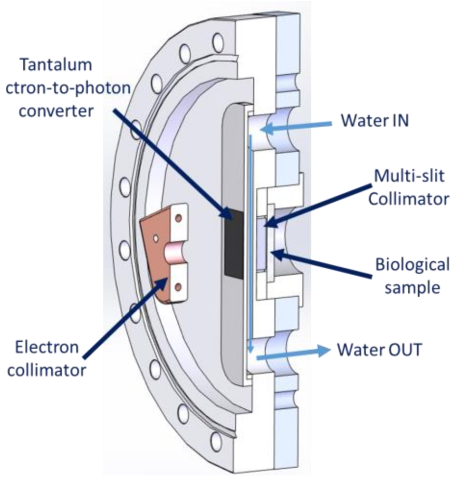
TRIUMF

Photon FLASH

- Electron gun 300 keV 10 mA (CW)
- Three accelerating superconductive cryomodules
- Two side irradiation stations:
  - Low energy (CTS – 300 keV)
  - High energy (EABD – up to 30 MeV)
  - Medium energy (EMBD - up to 10 MeV)



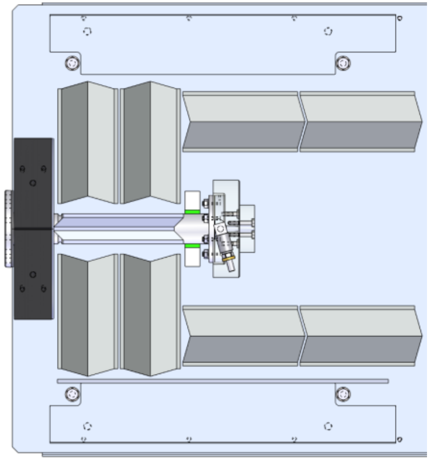


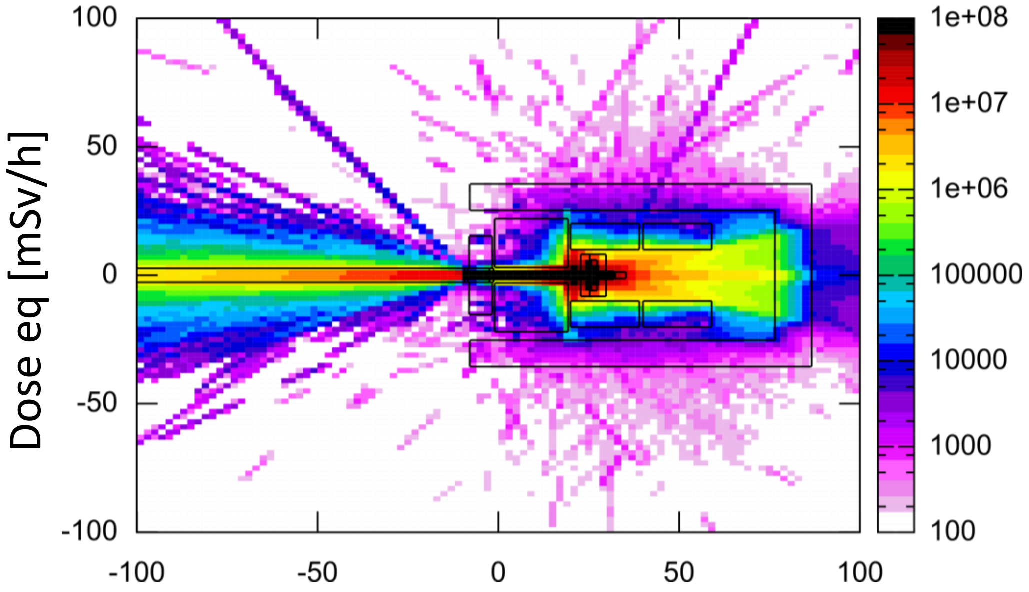


Magdalena Bazalova-Carter, UVic
Alexander Gottberg, TRIUMF

FLASH – DoseEq @ 10 MeV

Average dose rate up to ~ 300 Gy/s

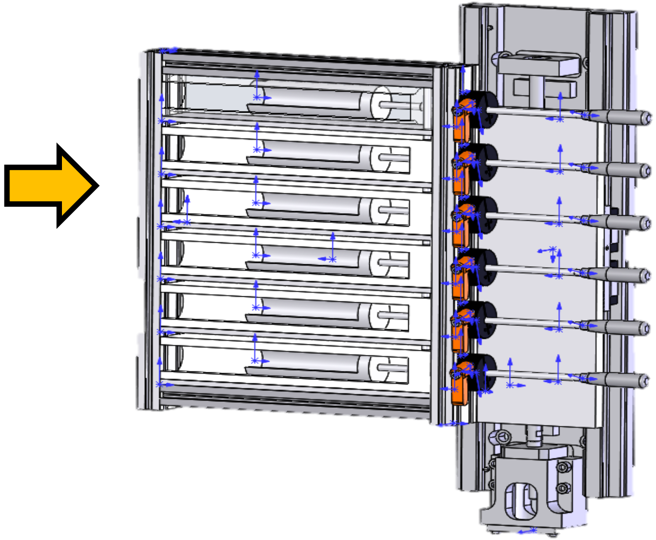




Magdalena Bazalova-Carter, UVic
Alexander Gottberg, TRIUMF

What's next?

- Manufacture, installation and testing until summer 2020
- Experiments with biological samples fall 2020

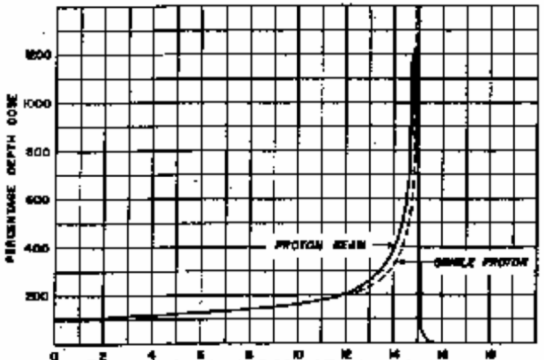


Magdalena Bazalova-Carter, UVic
Alexander Gottberg, TRIUMF

Hans
Bethe

$$-\frac{dT}{dx} = \frac{4\pi e^4 z^2}{m v^2} Z \ln \frac{2 m v^2}{E},$$

Zur Theorie des Durchgangs schneller Korpuskularstrahlen durch Materie, Annalen der Physik. vol. 397, pp. 325-400, 1930

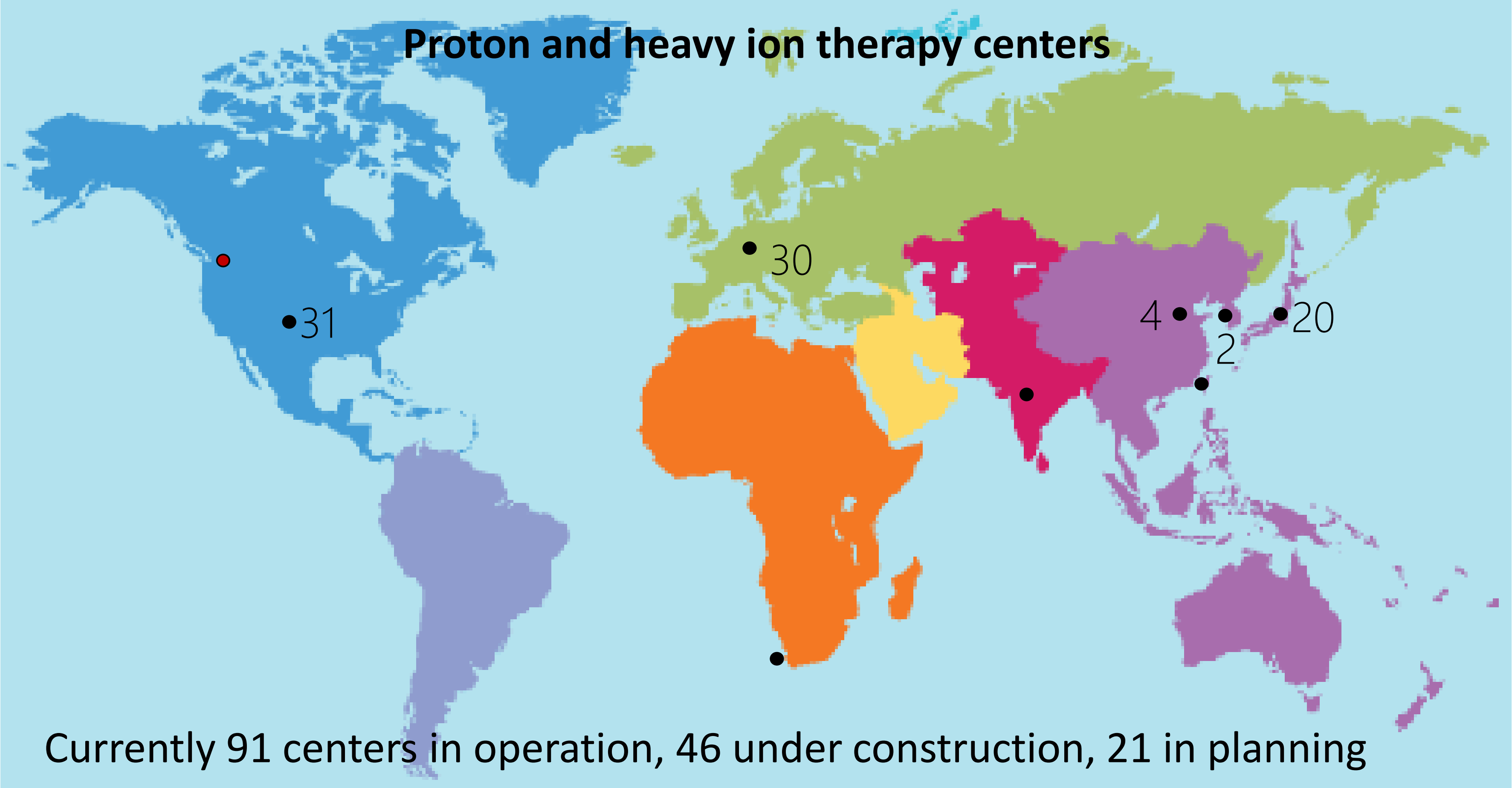


Dosage due to 140 MEV Protons in tissue

Robert
Wilson

Radiological Use of Fast Protons, Radiology vol. 47, pp. 487-91, 1946

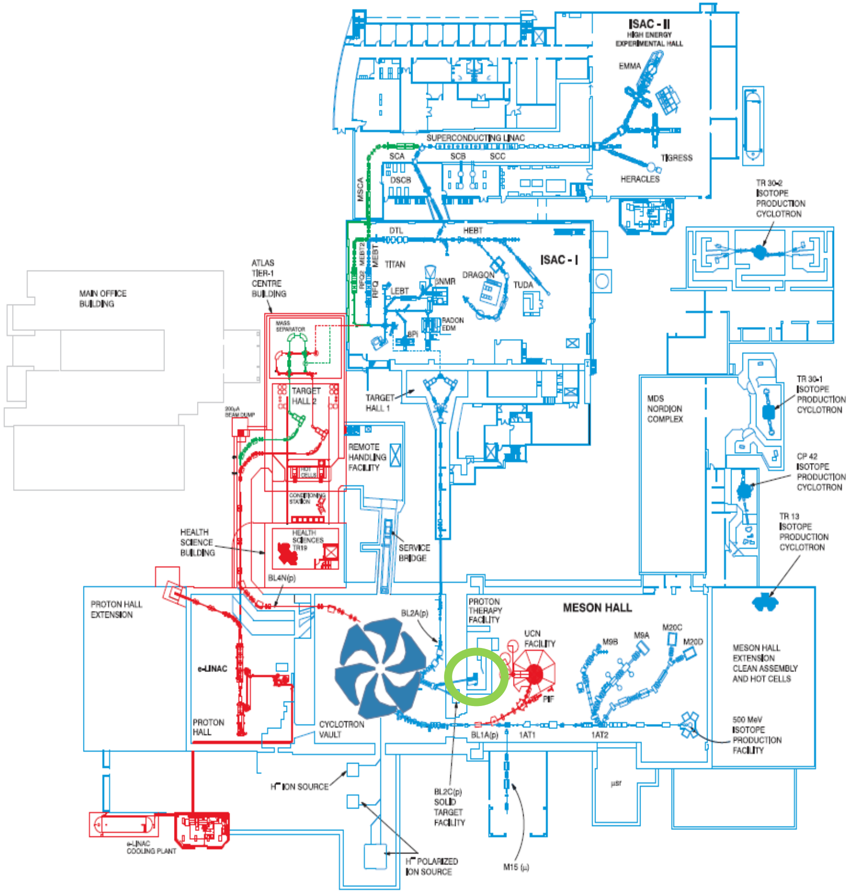
PT around the world



Currently 91 centers in operation, 46 under construction, 21 in planning

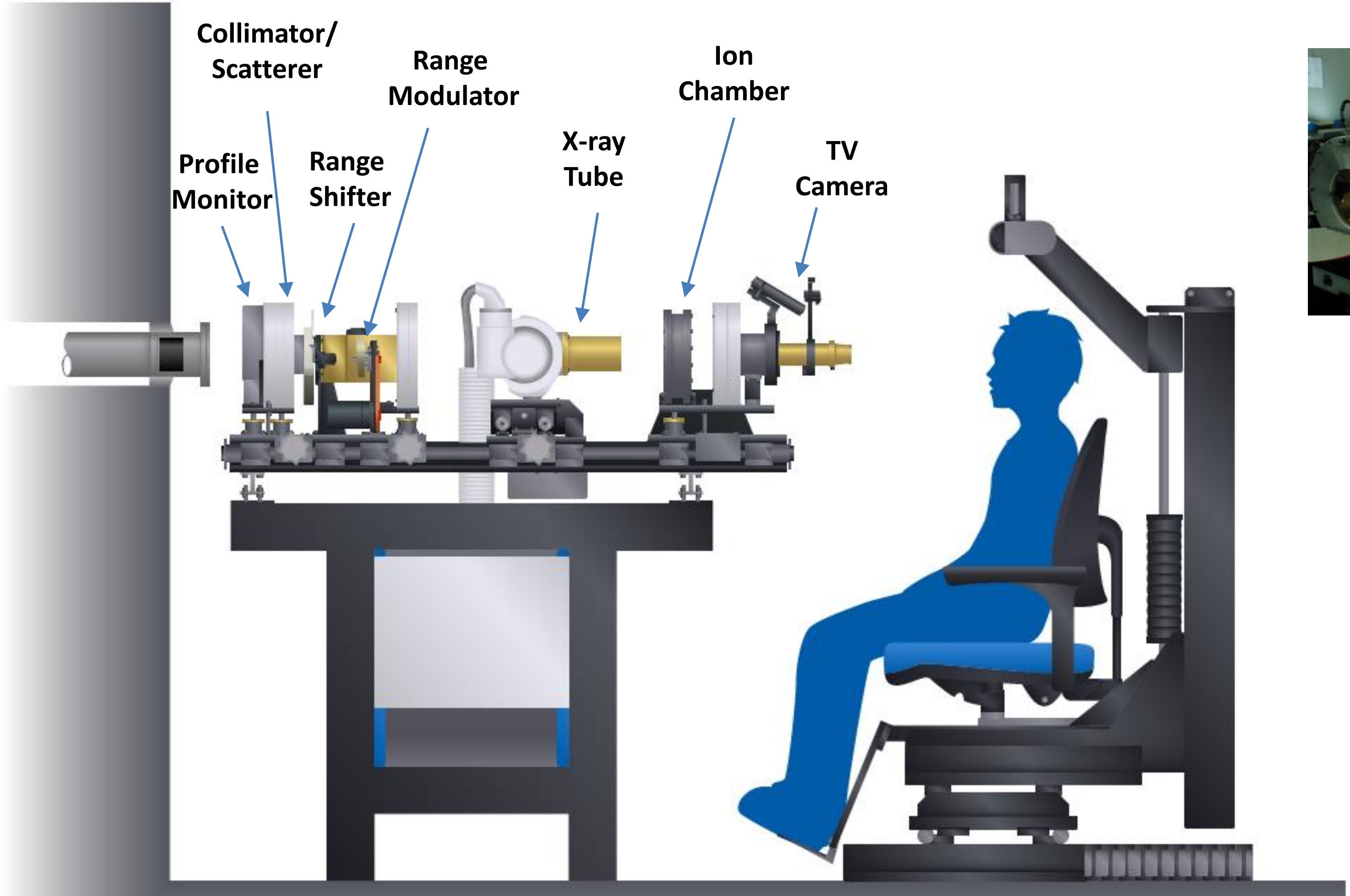
Proton Therapy @ TRIUMF

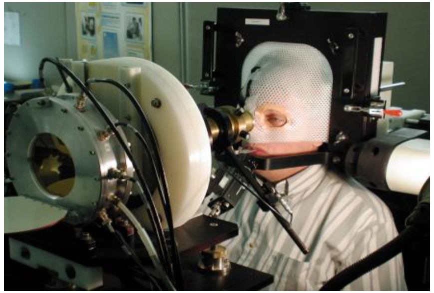
- Clinical operation since 1995
- Canada's only proton therapy facility
- Ocular melanomas
- Clinical treatments ended Feb 2019



TRIUMF

Beamline 2C1

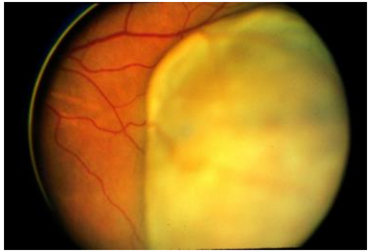




PT Treatment Results

Summary paper with 59 patients
(E. Tran et al., Int. J. Radiat. Oncol. Biol. Phys. 83 (2012) 1425)

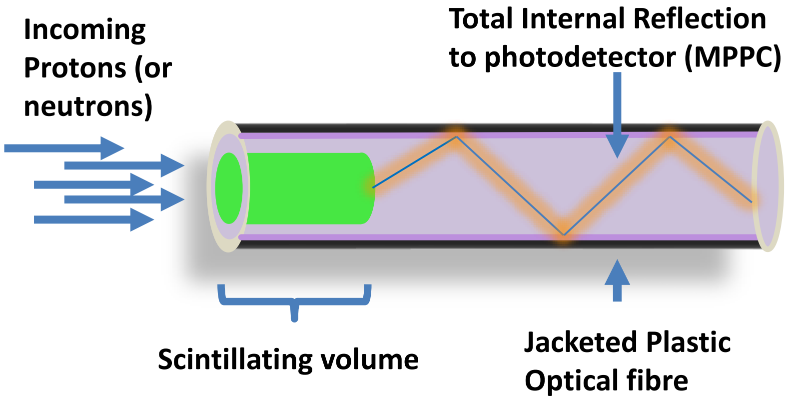
- 20 patients T1, 28 patients T2, 11 patients T3
- Median tumor size: diameter 11.4 mm, 3.5 mm thick
- Median follow-up time 63 month
- 19 patients treated with 54 CGE and 40 patients treated with 60 CGE
- **5-year local control rate 91%**
(T1 100%, T2 93%, T3 59%) **and 97%** with 60 CGE, 83% 54 CGE
- **Metastasis-free survival rate 82%** (T1 94%, T2 84%, T3 47%)
- 5-year neovascular glaucoma 31% (T1-2 23%, T3 68%)
- Enucleation T1 0%, T2 14%, T3 72%

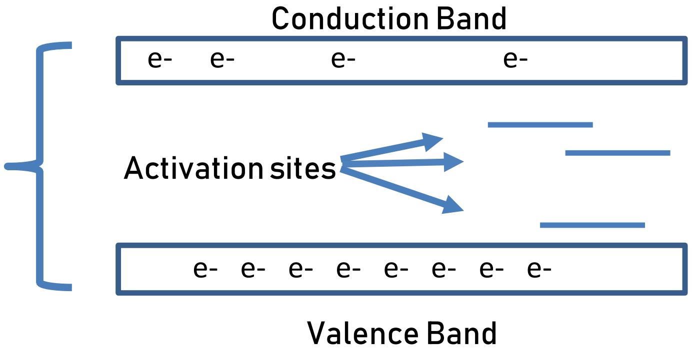


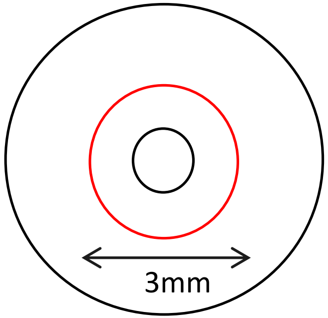
before PT

after PT

PT Small Field Treatment



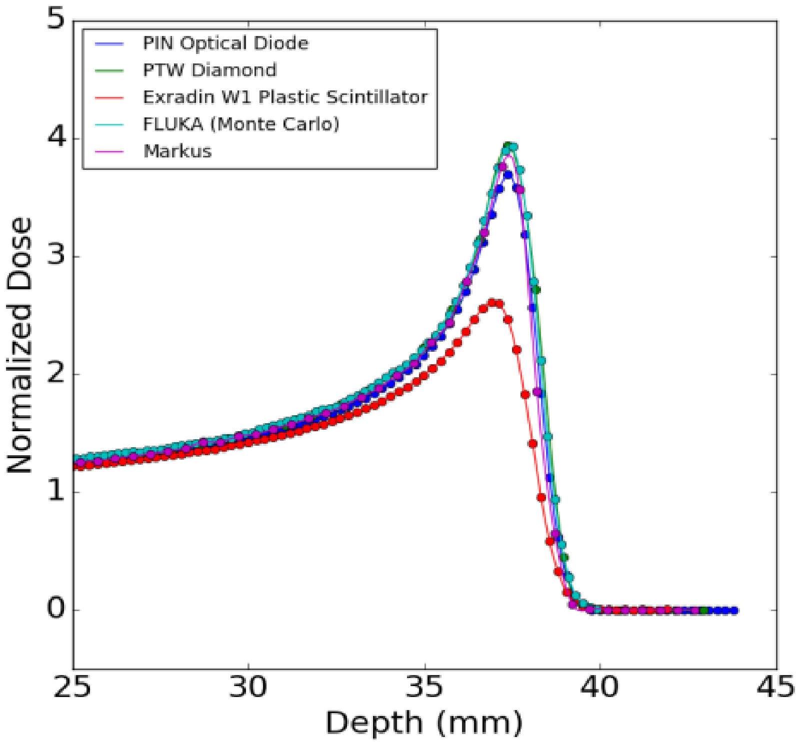


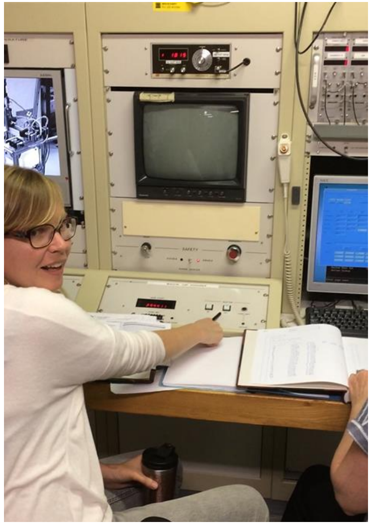


- Typical sensors for dosimetry larger than treatment volume
- Optical fibers can have excellent spatial resolution
- Dose and dose rate independent

Cheryl Duzenli, BC Cancer
Sylvain Girard, St. Etienne

Novel Scintillators for PT Dosimetry





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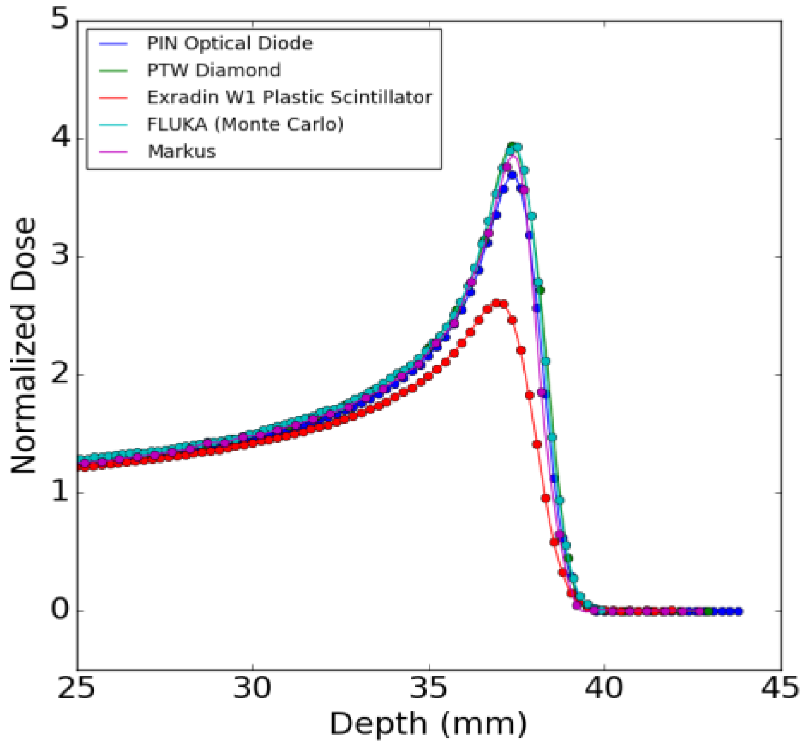
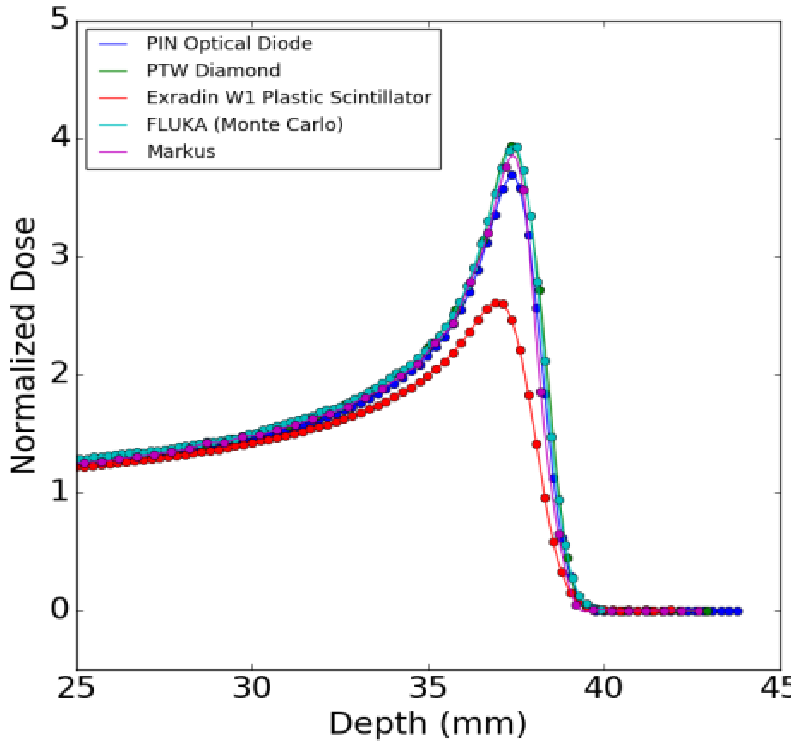


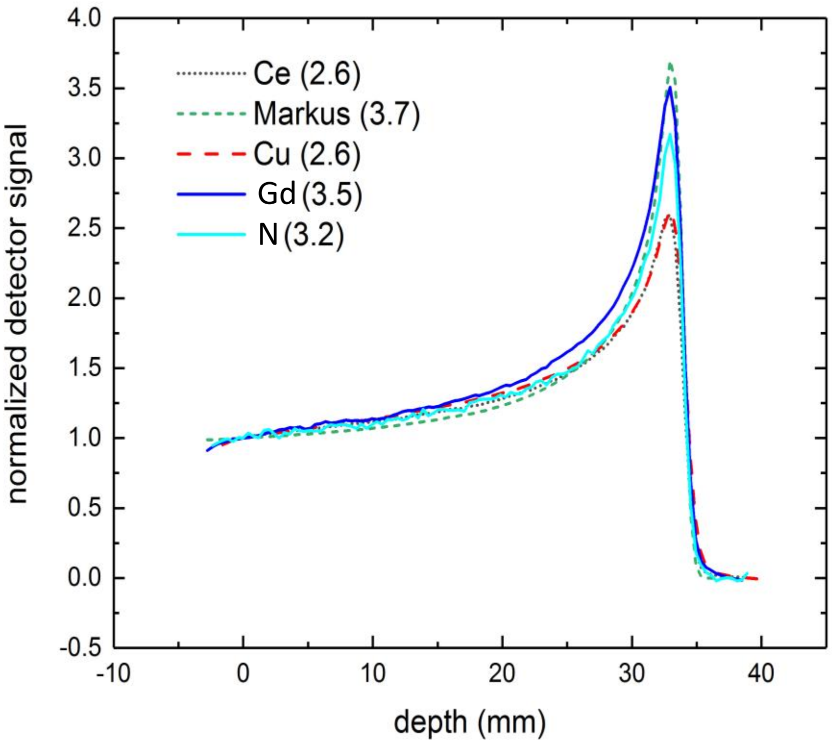
$$\frac{dL}{dx} = \frac{S\frac{dE}{dx}}{1 + k_B\frac{dE}{dx} + C\left(\frac{dE}{dx}\right)^2}$$

- Empirical Craun-Birks equation
- Correction of quenching
- Not practical for Proton Therapy!

Cheryl Duzenli, BC Cancer
Sylvain Girard, St. Etienne

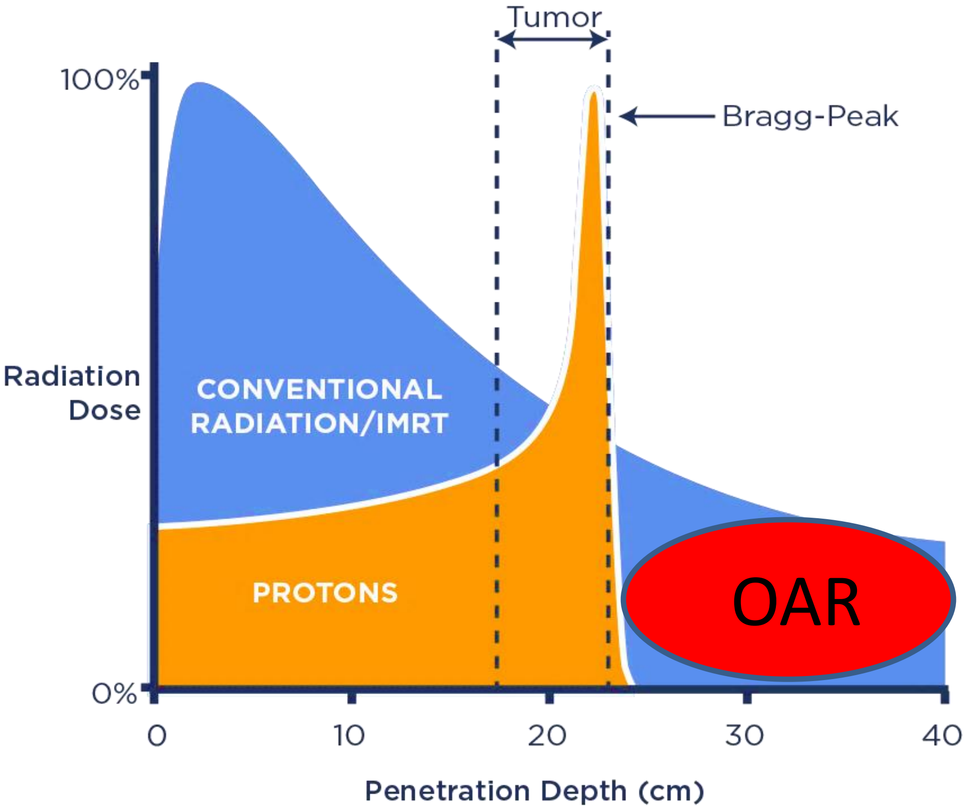
Novel Scintillators for PT Dosimetry





Cheryl Duzenli, BC Cancer
Sylvain Girard, St. Etienne

PT Range verification



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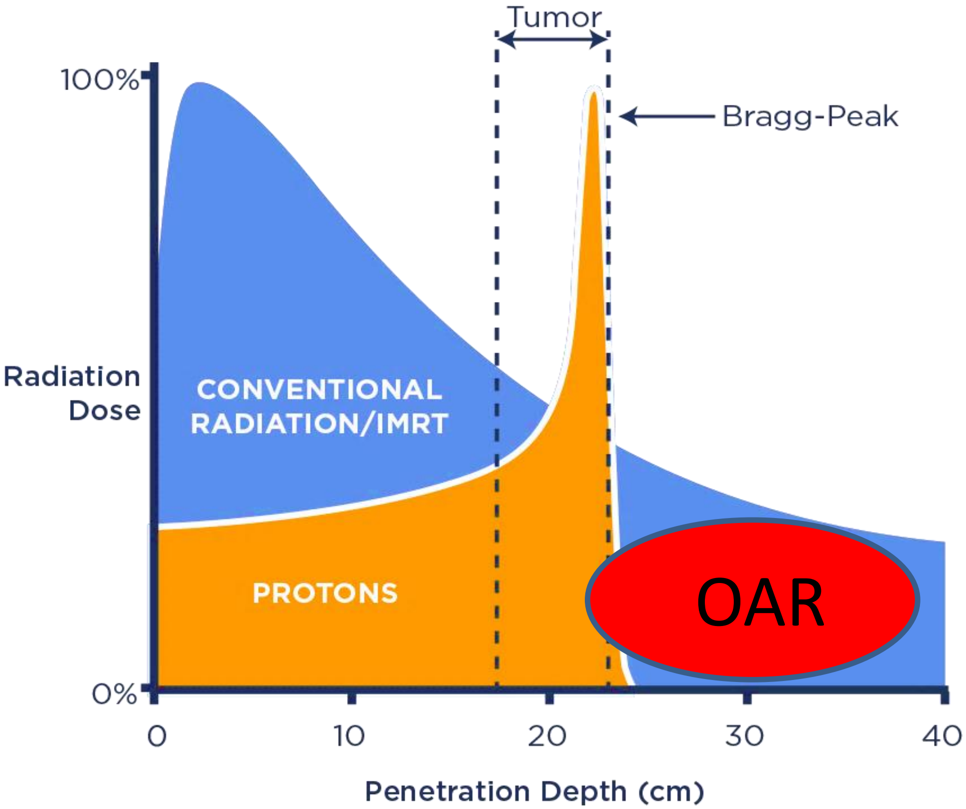

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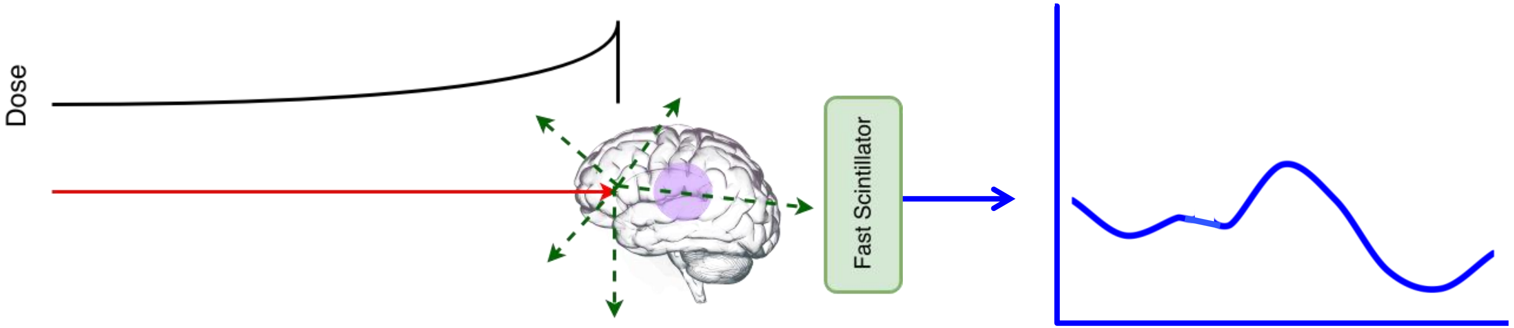

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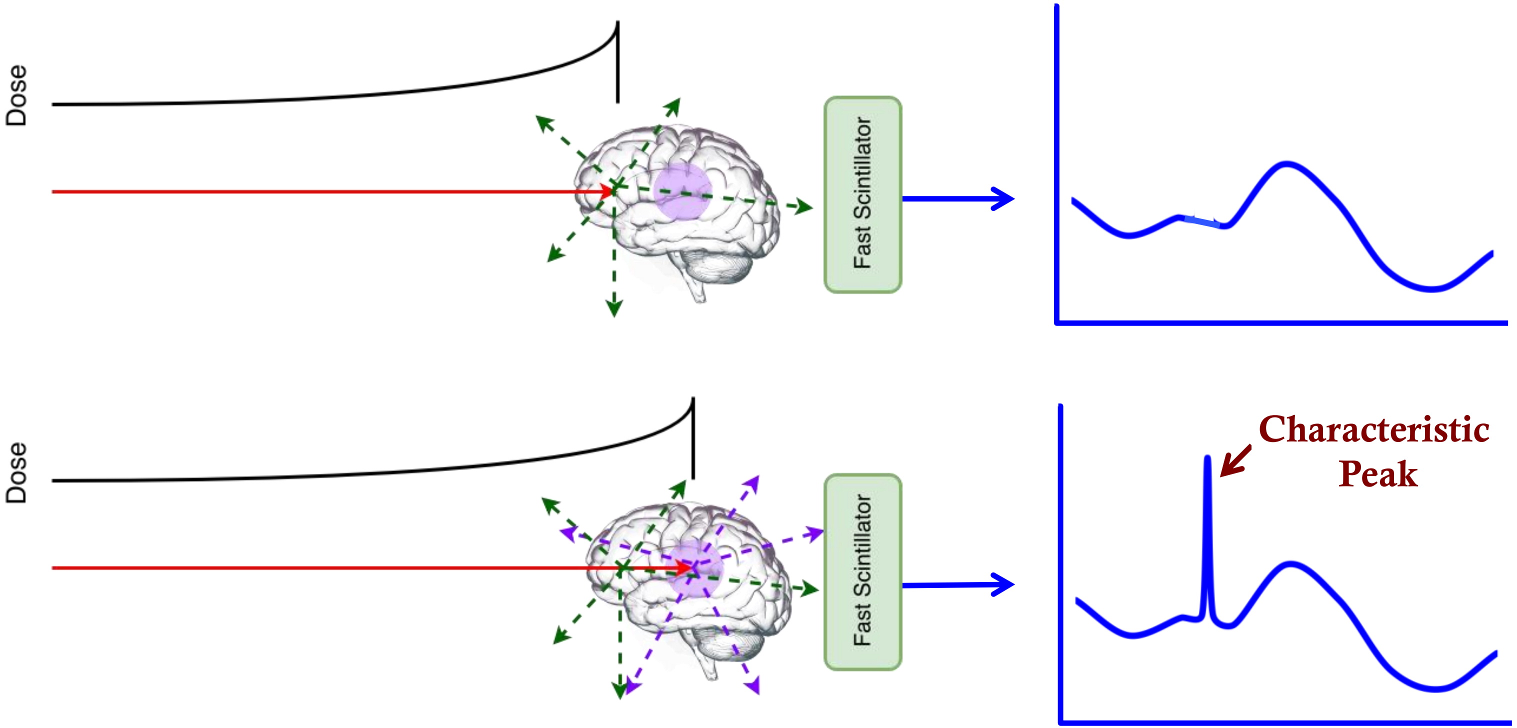
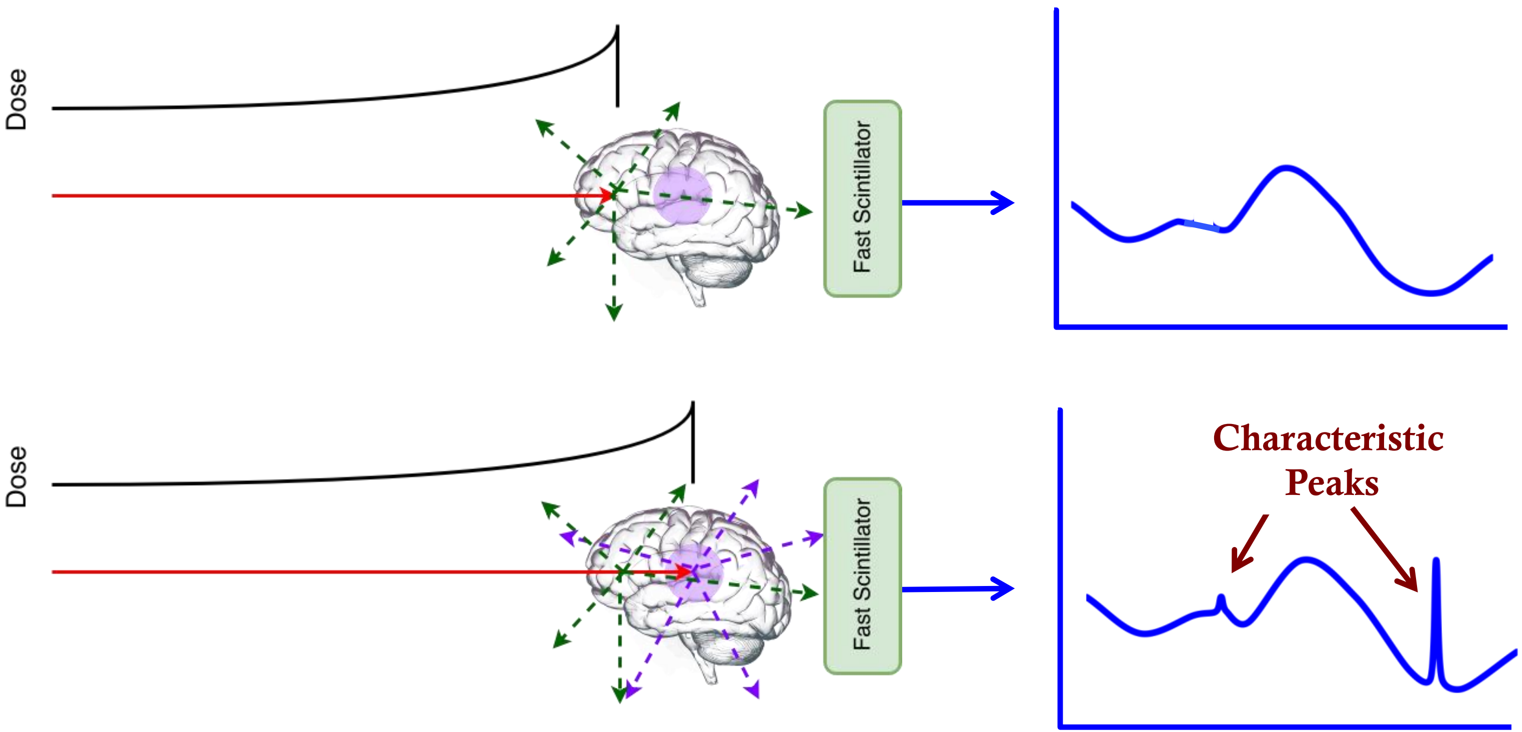


Dennis Muecher, Guelph

PT Range verification



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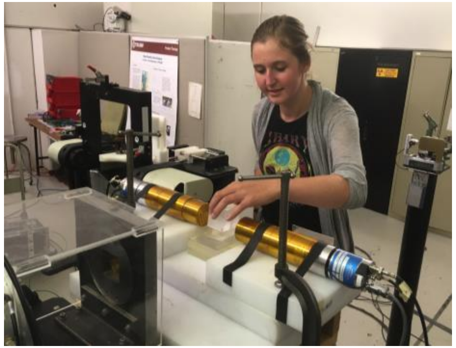
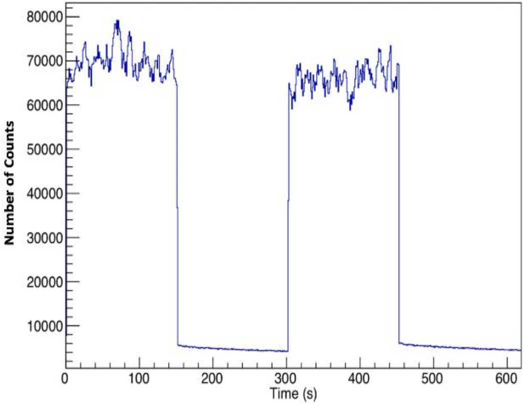
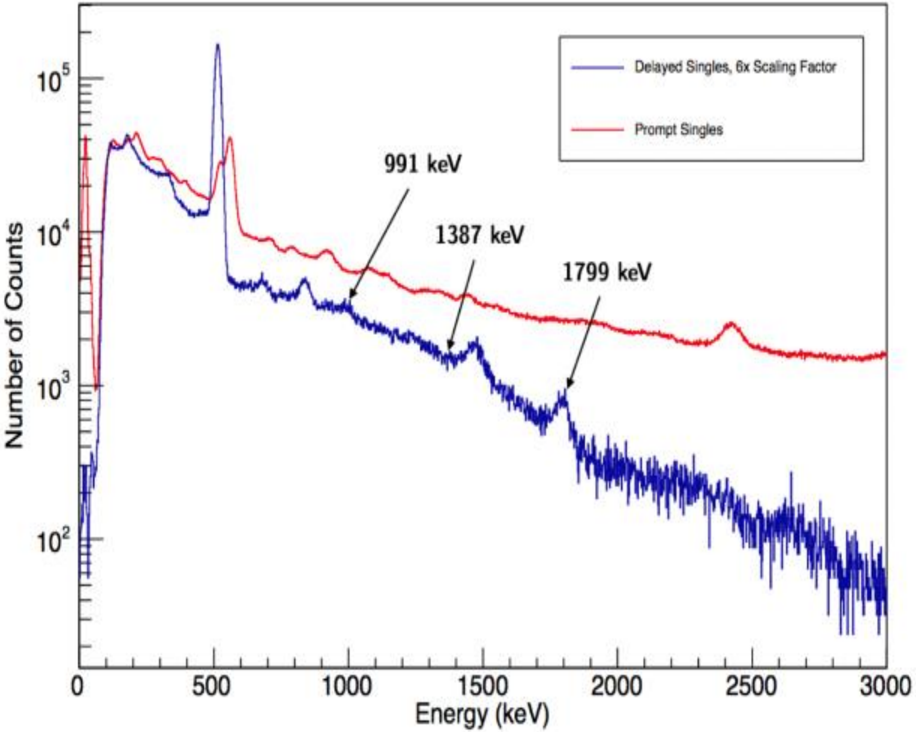
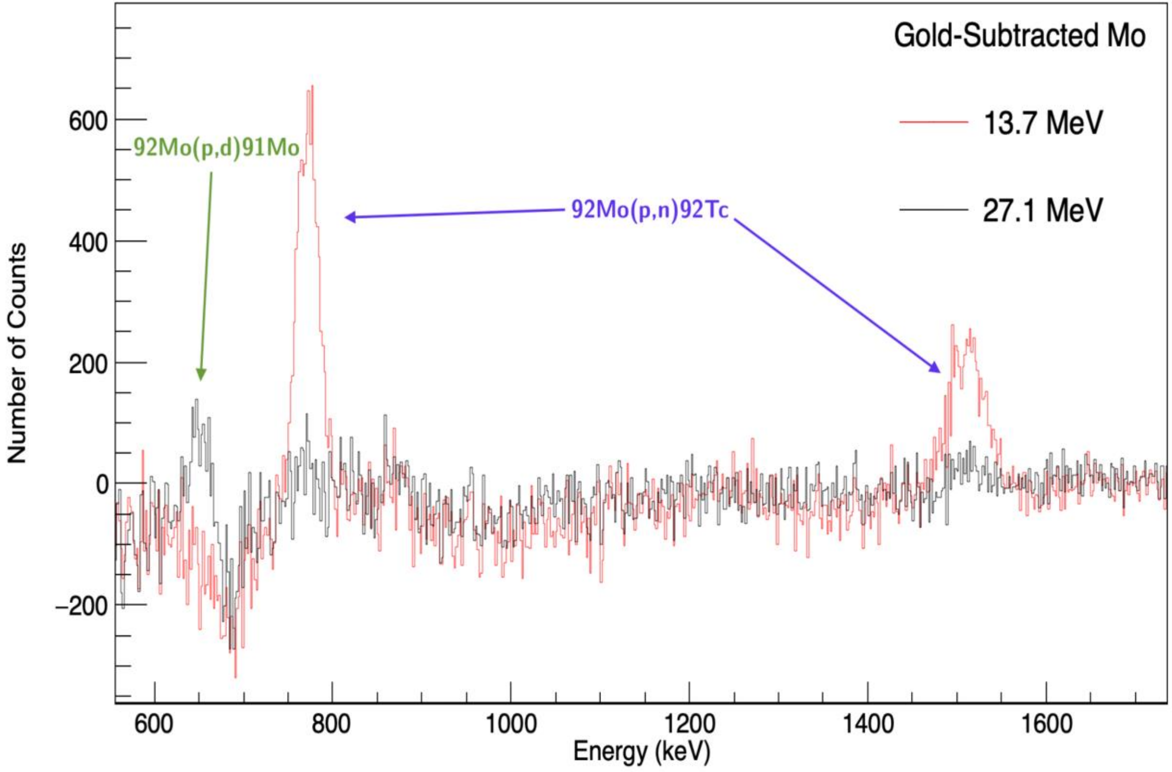






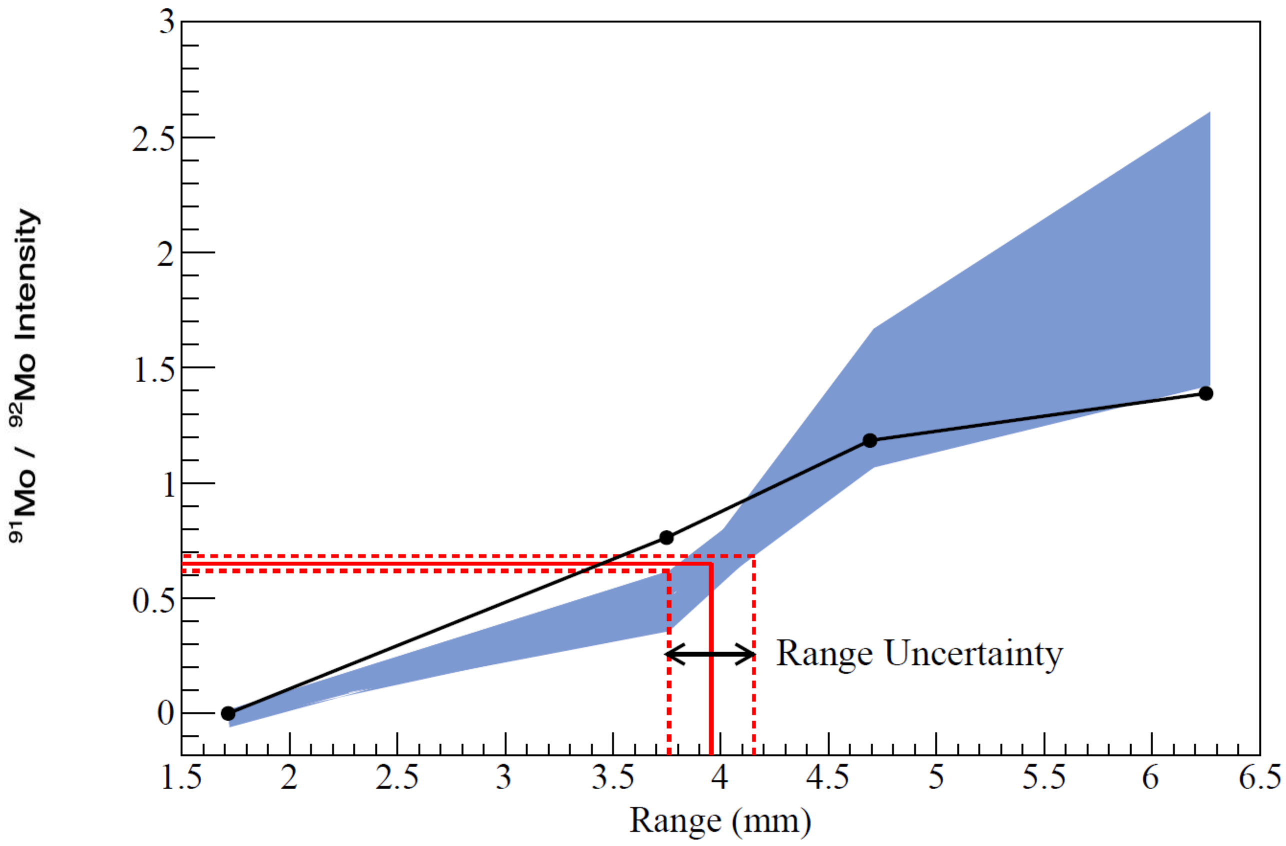
Dennis Muecher, Guelph

PT Range verification



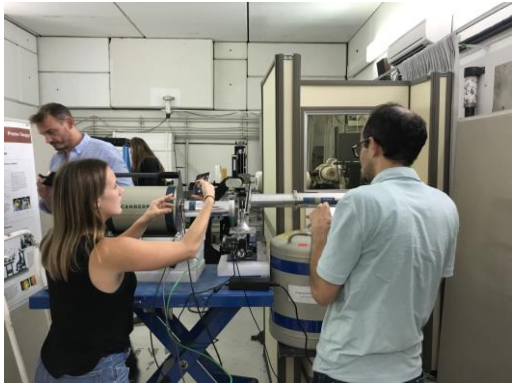
Dennis Muecher, Guelph

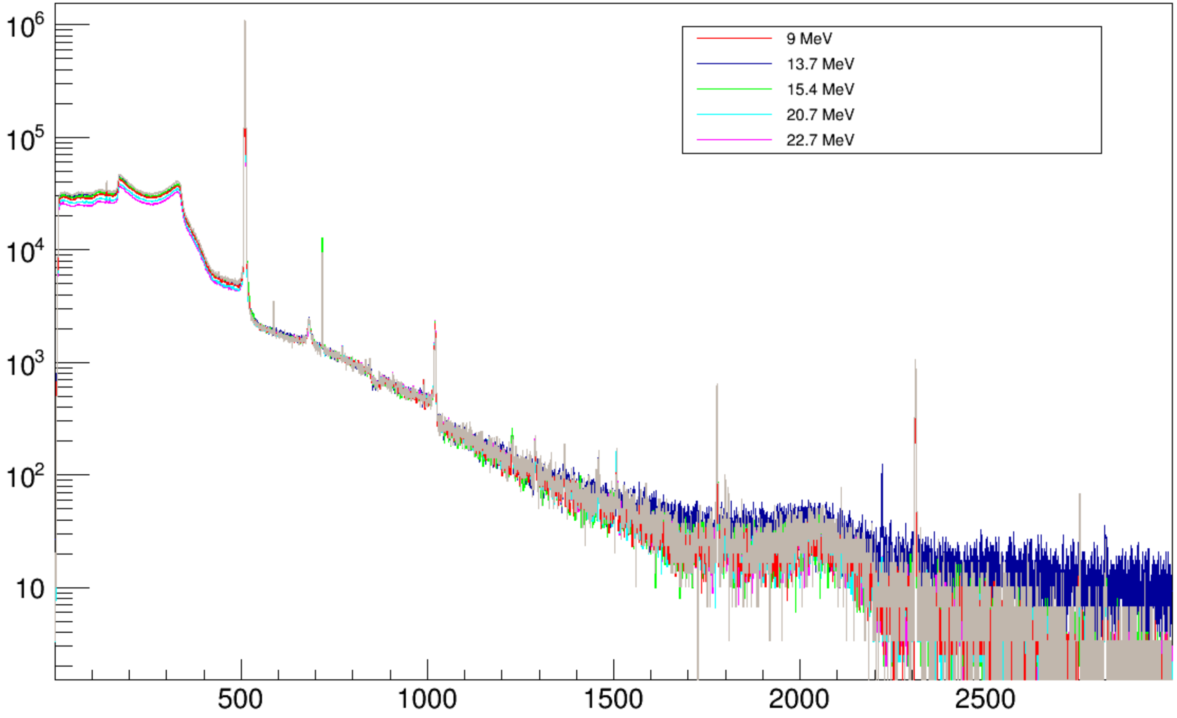
PT Range verification



Dennis Muecher, Guelph

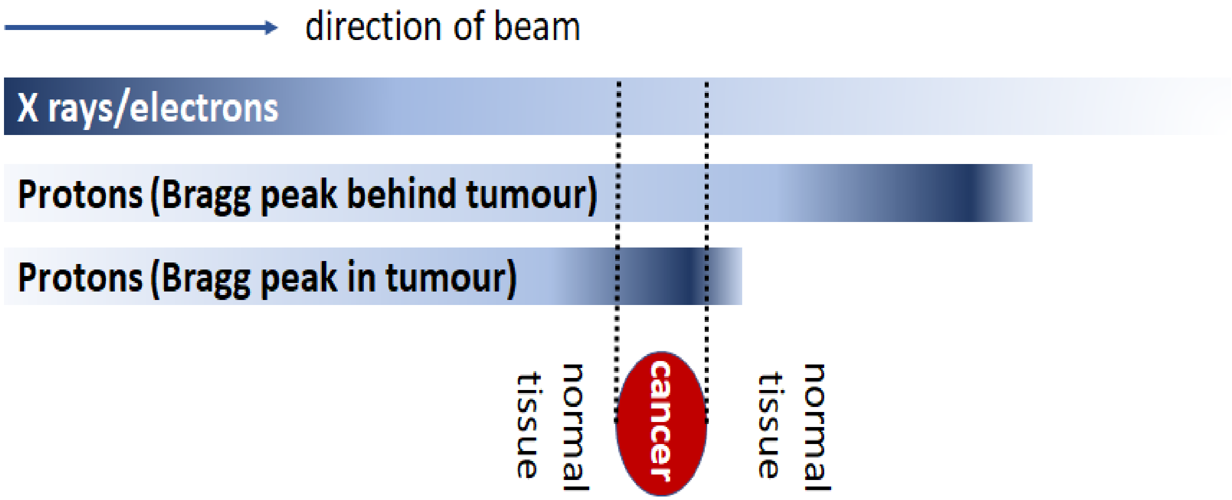
PT Range verification





- Summer 2019: experiment with HPGe detector
- Data currently being analyzed by Eva and Christina

Proton FLASH?

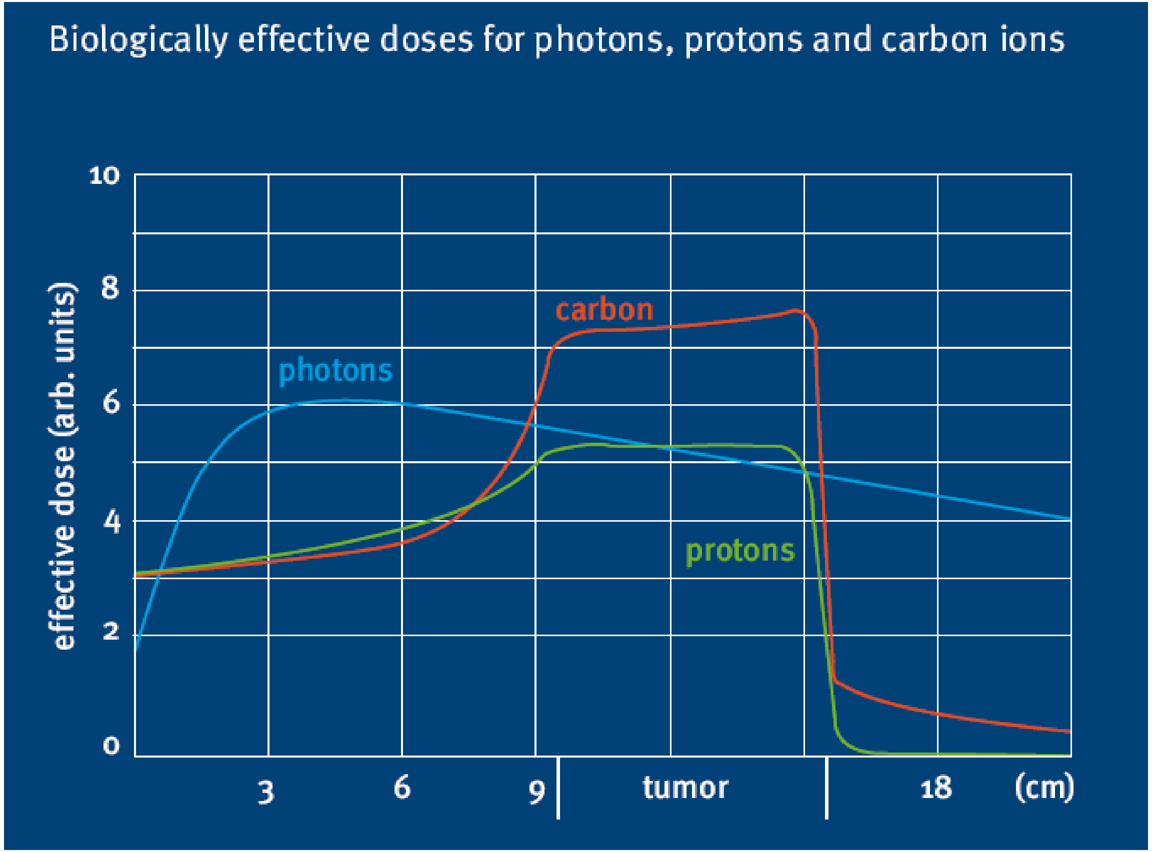


- PT facility (2C1) at TRIUMF limited to 6 nA, or ~ 0.2 Gy/s
- Main cyclotron able to extract 100 uA into 2C4, or up to 3,333 Gy/s

- Will there be a FLASH effect with protons?
- How do you ensure range verification?

Andrew Minchinton, BC Cancer
Oliver Kester, TRIUMF

External beam therapy with ions

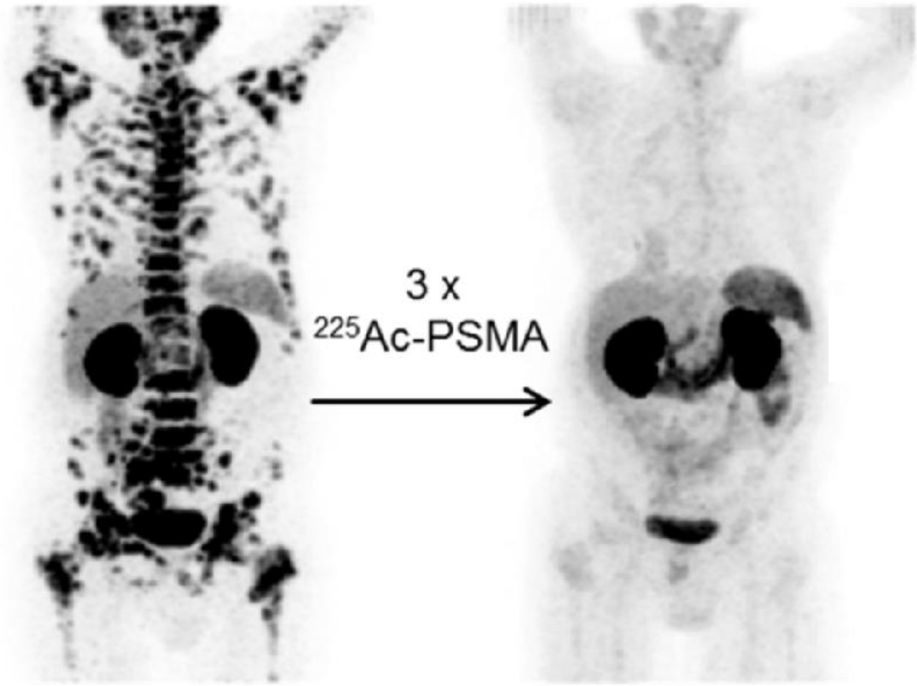


HIT
website

Targeted α Therapy (TAT)

Kratochwil *et al., J. Nuc. Med.* 2016;57(12):1941–1944.

Targeted α Therapy (TAT)



Kratochwil *et al., J. Nuc. Med.* 2016;57(12):1941–1944.

- 11 clinical trials (^{225}Ac and ^{213}Bi)
- > 640 patients (60-80% showed response)
- Want up to 50,000 patient doses a year (120 Ci)

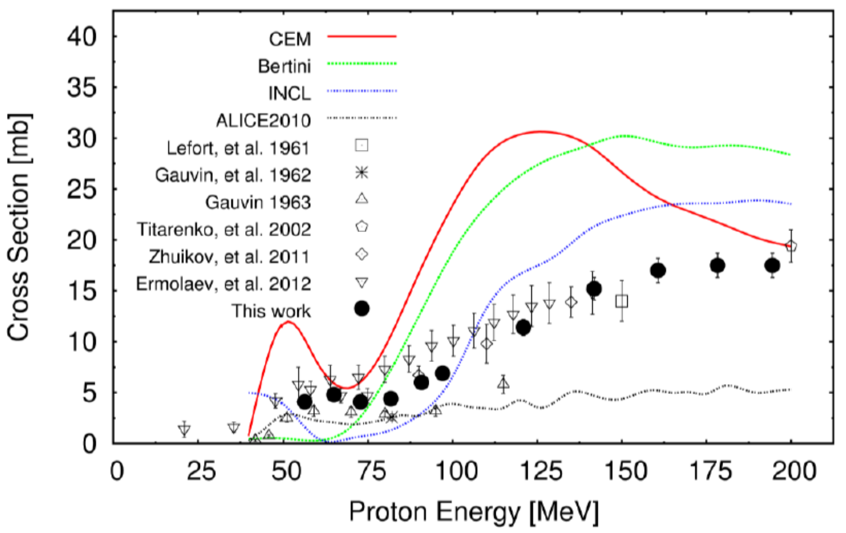
Current ^{225}Ac Production

Primary ^{225}Ac sources:

- ^{229}Th/^{225}Ac generator ($t_{1/2}$ ~ 7880 y) sourced via legacy stockpile, ORNL, ITU
- Alternatives sought
- ^{226}Ra irradiation
- Tri-Lab efforts ^{232}Th(p,x) spallation

Global production is ~10 Ci per year

- Promising early clinical trial results
- Supply vs demand is out of balance, but market needs to be nurtured, and supply needs to increase and be reliable

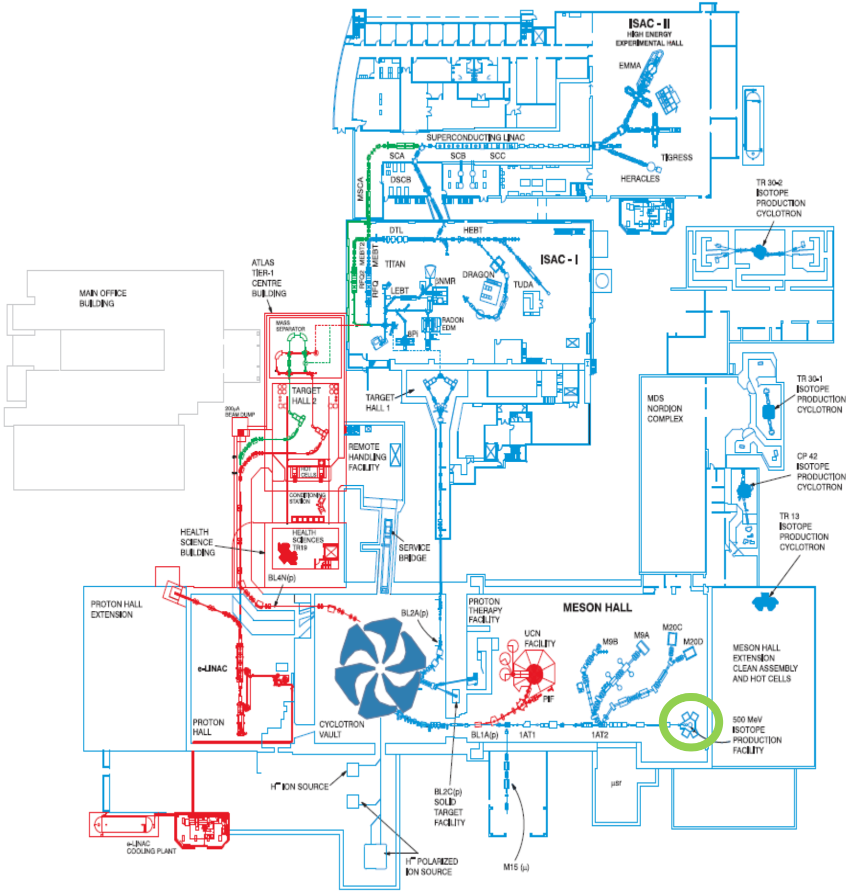


J.W. Weidner et al. Appl. Radiat. Isotop. 2012, 70, 2602

- ^{225}Ac production via Th spallation demonstrated at small scales:

LANL	50 - 200, 800 MeV
INR RAS	40 - 90 MeV

α emitters


ISAC - II
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MSCA
TR 30-2 ISOTOPE PRODUCTION CYCLOTRON
DTL
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MEBT
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TITAN
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RFQ
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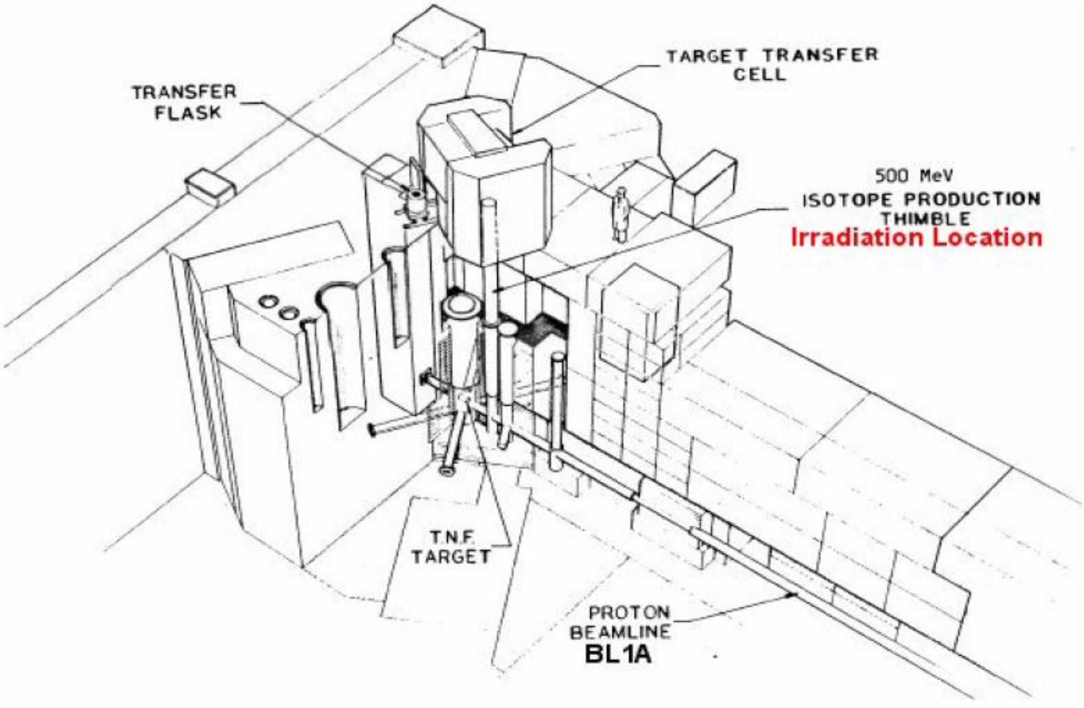
MESON HALL
UCN FACILITY
M9B
M9A
M20C
M20D
MESON HALL EXTENSION CLEAN ASSEMBLY AND HOT CELLS
e-LINAC
PIF
500 MeV ISOTOPE PRODUCTION FACILITY
PROTON HALL
CYCLOTRON VAULT
BL1A(p)
1AT1
1AT2
H⁻ ION SOURCE
BL2C(p) SOLID TARGET FACILITY
μsr
e-LINAC COOLING PLANT
H⁻ POLARIZED ION SOURCE
M15 (μ)

Isotope Accelerator Program: Isotope Production Facility

Isotope production using TRIUMF's
500 MeV infrastructure

IPF (BL1A)
Intermediate activity (MBq), spallation

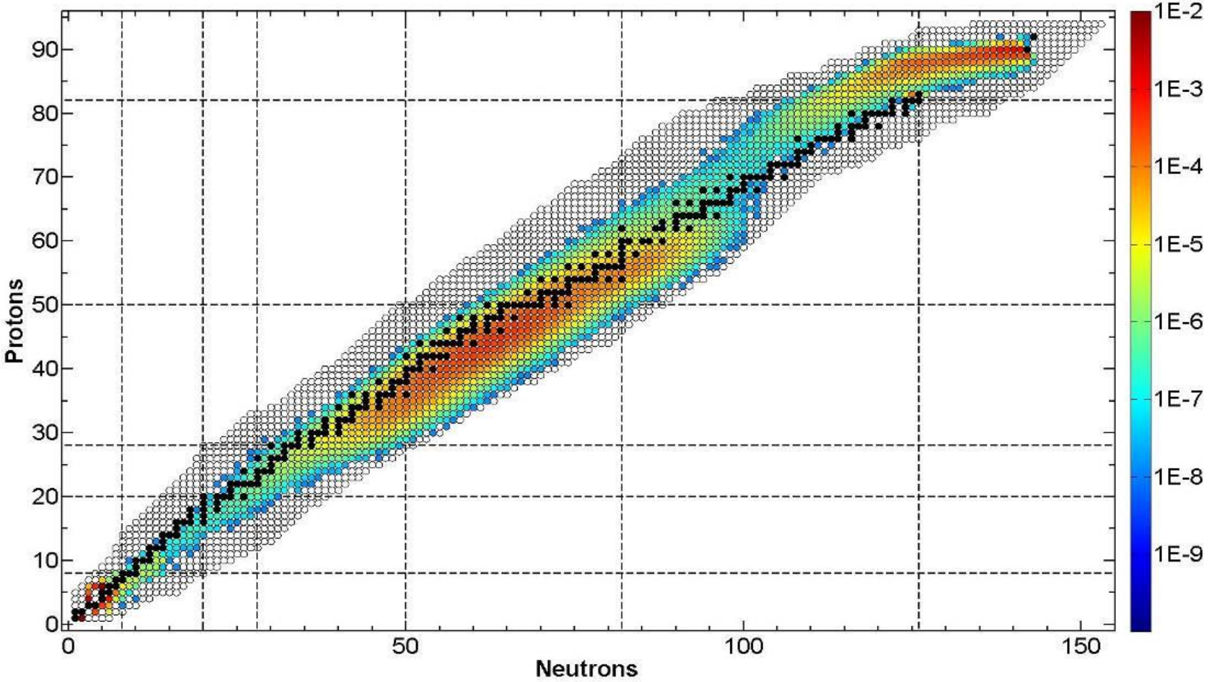
- Routine, independent production

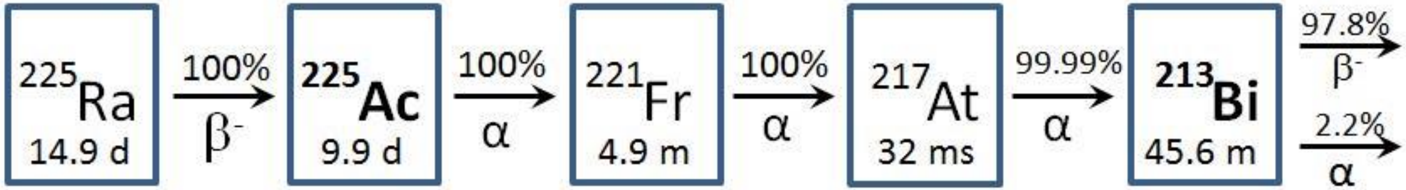


500 MeV Isotope Production Facility

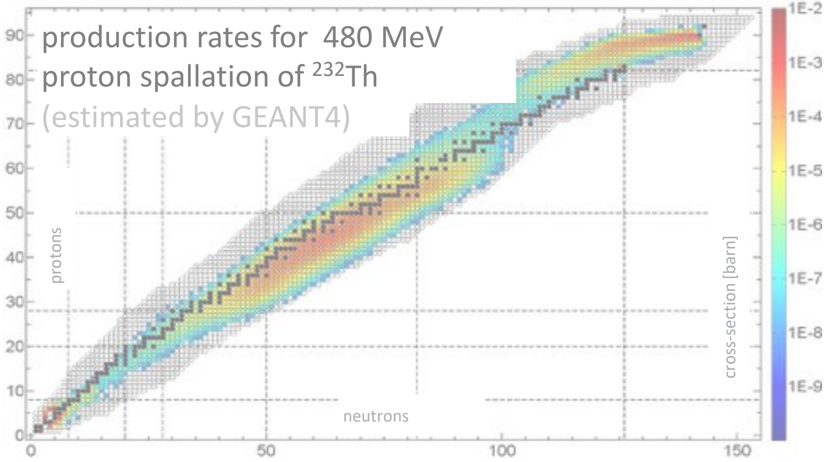
Spallation Reaction on ^{232}Th with 500 MeV Protons

- Hundreds of co-produced isotopes including
- **^{225}Ra, ^{225}Ac**, ^{224}Ra, ^{223}Ra, ^{213}Bi, ^{212}Pb, ^{212}Bi, **$^{209/211}$At**





^{232}Th spallation produces both Ac and Ra isotopes



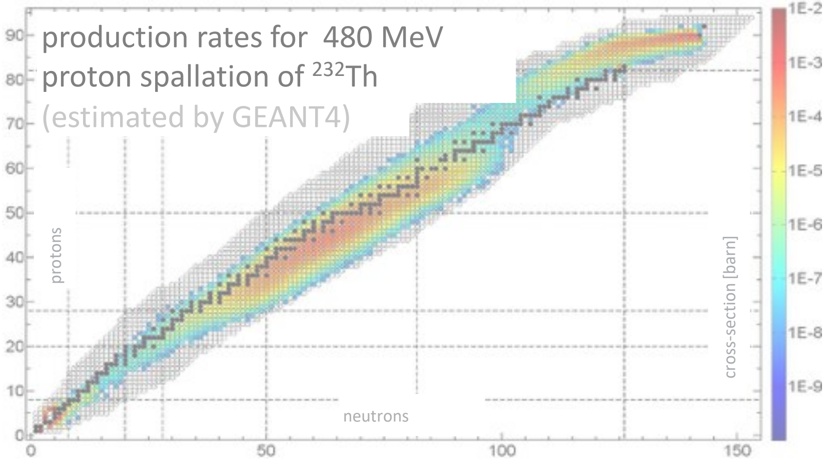
^{225}Ac + ^{224}Ac + ^{226}Ac + ^{227}Ac

$t_{1/2}$ = 9.9 d | $t_{1/2}$ = 3 h | $t_{1/2}$ = 29 h | $t_{1/2}$ = 22 y

concerns (from some) about ^{227}Ac content and impact on waste management — no consensus

directly-produced ^{225}Ac

^{232}Th spallation produces both Ac and Ra isotopes



^{227}Ra + ^{225}Ra + ^{228}Ra + ^{224}Ra + ^{226}Ra

^{227}Ra	^{225}Ra	^{228}Ra	^{224}Ra	^{226}Ra
$t_{1/2}$ = 42 min	$t_{1/2}$ = 14.9 d	$t_{1/2}$ = 5.8 y	$t_{1/2}$ = 3.6 d	$t_{1/2}$ = 1600 y

^{225}Ac + ^{224}Ac + ^{226}Ac + ^{227}Ac

^{225}Ac	^{224}Ac	^{226}Ac	^{227}Ac
$t_{1/2}$ = 9.9 d	$t_{1/2}$ = 3 h	$t_{1/2}$ = 29 h	$t_{1/2}$ = 22 y

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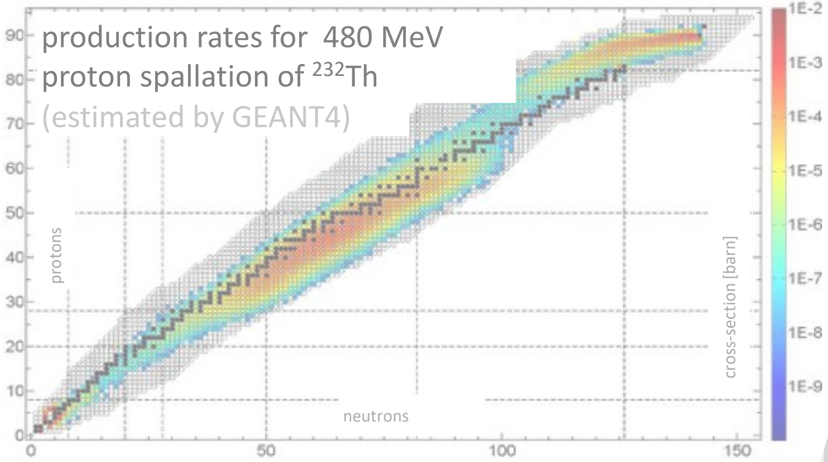


^{227}Ra + ^{225}Ra + ^{228}Ra + ^{224}Ra + ^{226}Ra

$t_{1/2}$ = 42 min; $t_{1/2}$ = 14.9 d; $t_{1/2}$ = 5.8 y; $t_{1/2}$ = 3.6 d; $t_{1/2}$ = 1600 y

^{224}Ra → ^{224}Rn

^{226}Ra → ^{222}Rn

rapid decay

^{225}Ac + ^{224}Ac + ^{226}Ac + ^{227}Ac

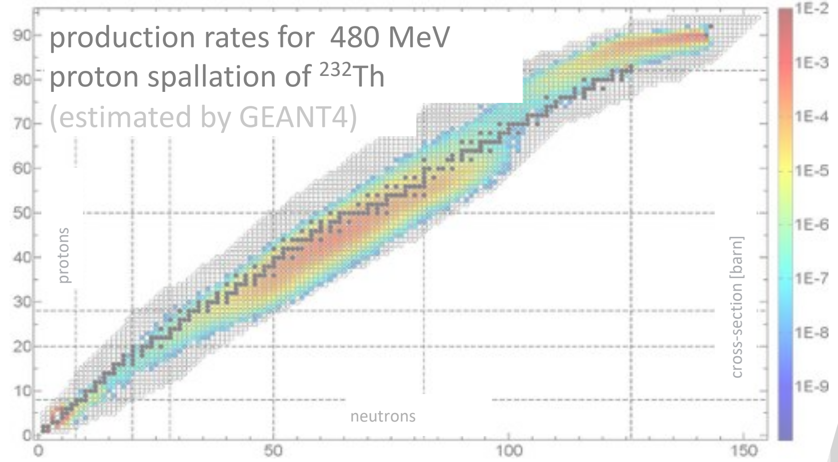
$t_{1/2}$ = 9.9 d; $t_{1/2}$ = 3 h; $t_{1/2}$ = 29 h; $t_{1/2}$ = 22 y

concerns (from some) about ^{227}Ac content and impact on waste management

directly-produced ^{225}Ac

^{232}Th spallation produces both Ac and Ra isotopes

TRIUMF



^{227}Ra + $t_{1/2}$ = 42 min

^{225}Ra + $t_{1/2}$ = 14.9 d

^{228}Ra + $t_{1/2}$ = 5.8 y

^{224}Ra + $t_{1/2}$ = 3.6 d → ^{224}Rn

^{226}Ra $t_{1/2}$ = 1600 y → ^{222}Rn

rapid decay

^{225}Ac + $t_{1/2}$ = 9.9 d

^{224}Ac + $t_{1/2}$ = 3 h

^{226}Ac + $t_{1/2}$ = 29 h

^{227}Ac $t_{1/2}$ = 22 y

concerns (from some) about ^{227}Ac content and impact on waste management

directly-produced ^{225}Ac

^{225}Ac + $t_{1/2}$ = 9.9 d

^{228}Ac $t_{1/2}$ = 6 h

generator-produced ^{225}Ac

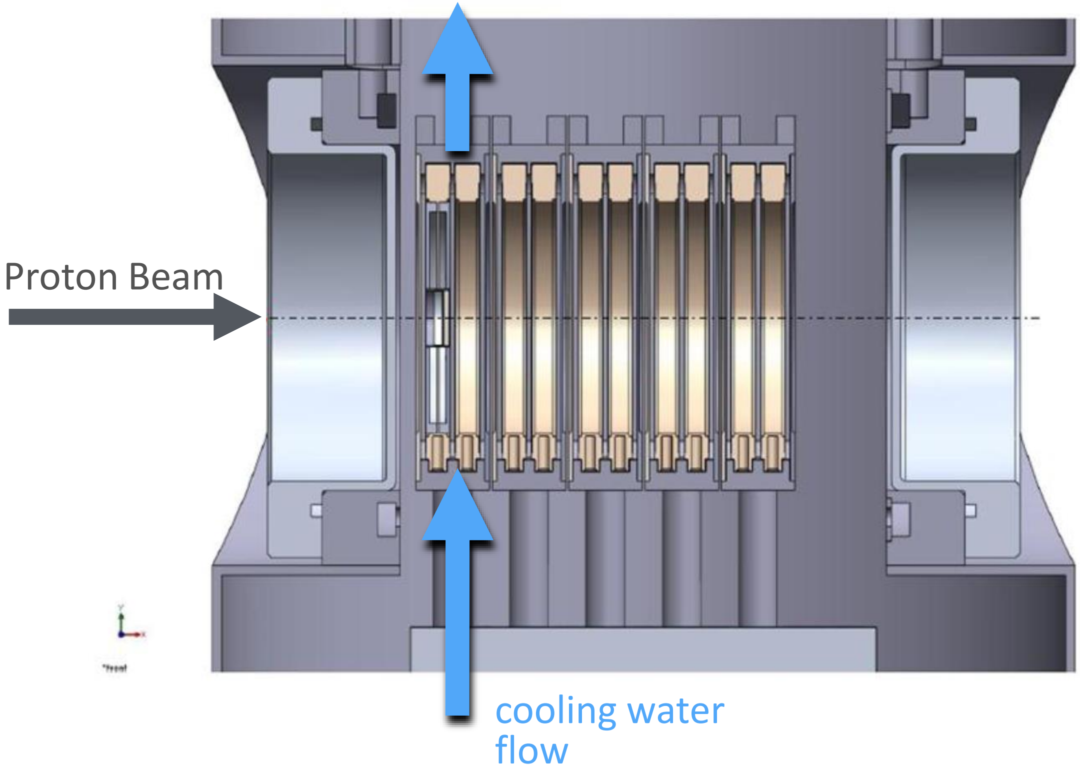
FLUKA: Primary vs Secondary ^{225}Ac

Process steps:
1) Th Irradiation
2) Ra/Ac separation 1 week EOB – gives primary Ac fraction
3) Recovered Ra allowed to sit for 17.5 days
4) Ra/Ac separation – gives secondary Ac fraction

Primary Ac Fraction			
days from Ra/Ac isolation	0	1	5
Ac-225 [MBq]	**42.2**	**39.4**	**29.9**
Ac-228/Ac-225 [%]	0.039	0.003	0.000
Ac-227/Ac-225 [%]	0.185	0.198	0.261
Ac-226/Ac-225 [%]	16.020	9.740	1.330

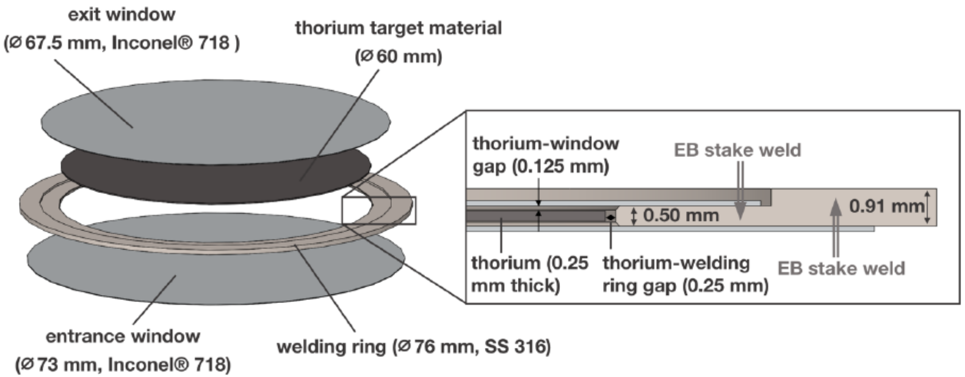
Secondary Ac Fraction		
days from Ra/Ac isolation	0	2
Ac-225 [MBq]	**2.2**	**1.9**
Ac-228/Ac-225 [%]	0.882	0.003
Ac-227/Ac-225 [%]	9.951E-09	9.949E-09
Ac-226/Ac-225 [%]	0.000	0.000

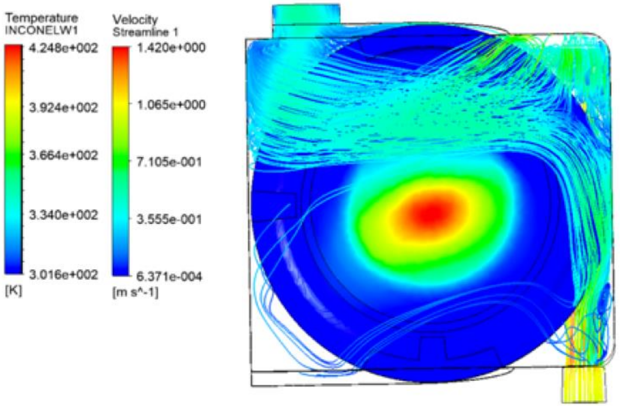
Target Station

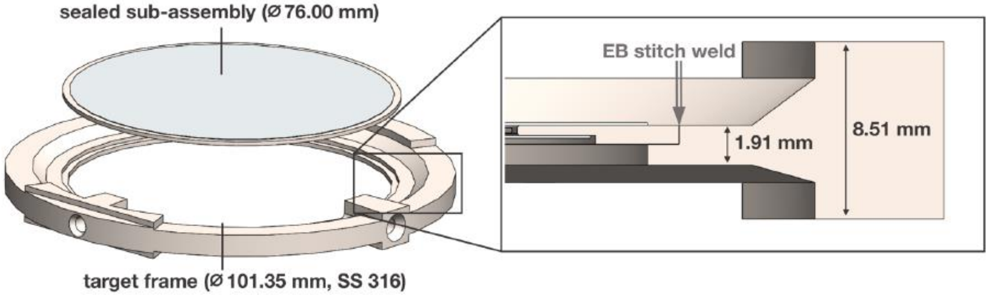


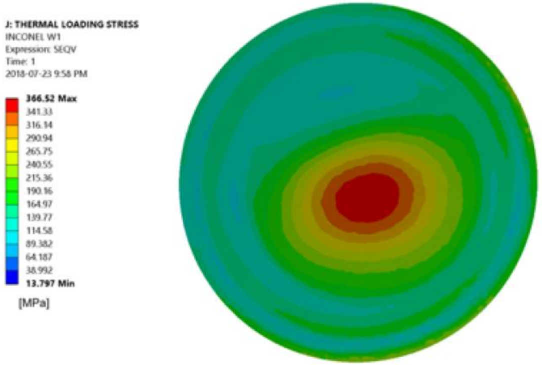
- Up to 6 cassettes, 12 targets
- Targets immersed in circulating water bath
- Thermocouples monitor target, water temperatures
- Cassettes can be moved without beam on/off

Design and ANSYS simulations









Thorium irradiations

Irradiation parameters

- integrated current 2640 µA*h, over **36-40 h**
- 66-73 µA, 454 MeV

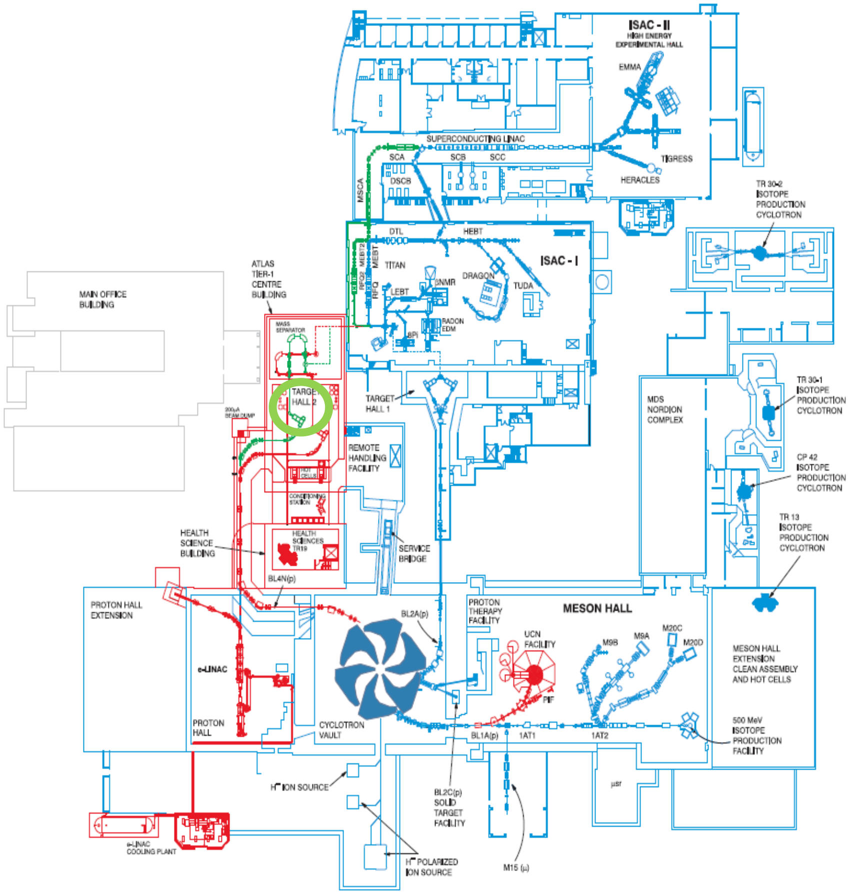
Results (n = 3)

- (521 ± 18) MBq ^{225}Ac and (95 ± 24) MBq ^{225}Ra at EOB
- saturation yields 72 MBq/µA (^{225}Ac), 19 MBq/µA (^{225}Ra)
- (319 ± 11) MBq ^{225}Ac and (69 ± 17) MBq ^{225}Ra at transfer to radiochemistry

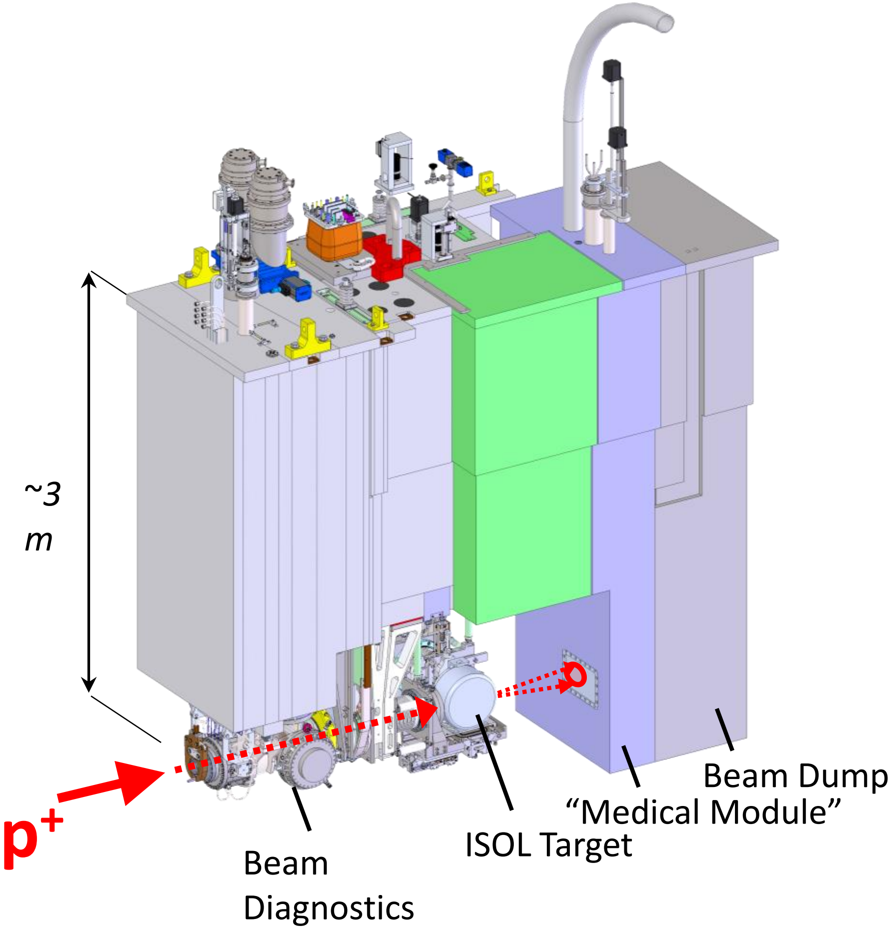
What's next?

- **x12 increase** in yield by irradiating 12 targets
- **x10 increase** in yield by irradiating for full ^{225}Ra half life (15 days)
- Further increase from thicker target and higher current require re-evaluation of target and safety

Targeted α Therapy (TAT)



ARIEL Medical Target Station



Isotope production using TRIUMF's 500 MeV infrastructure

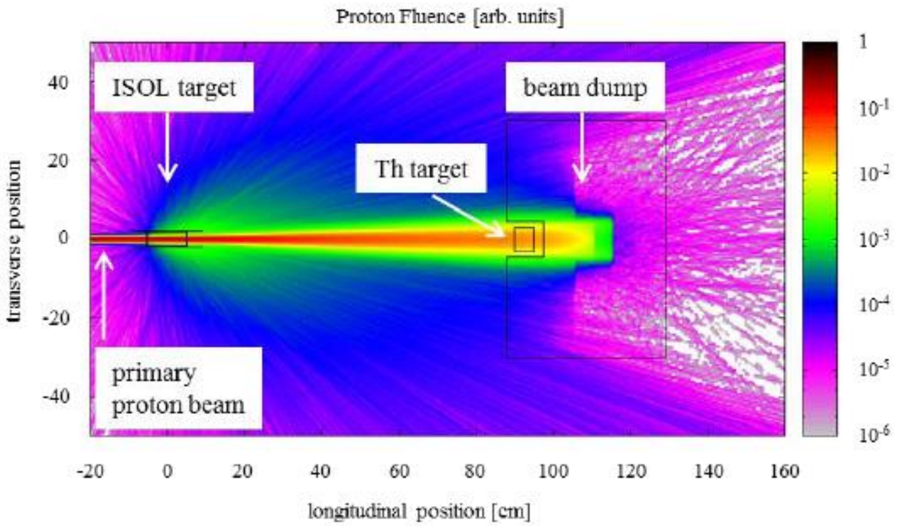
ARIEL/H^+
High activity (GBq), spallation

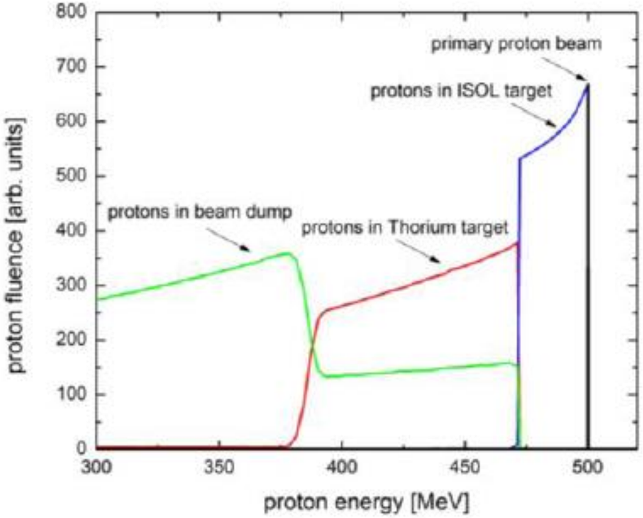
- Enable radiopharmaceutical development and clinical trials

Francois Benard, BC Cancer
Alexander Gottberg, TRIUMF

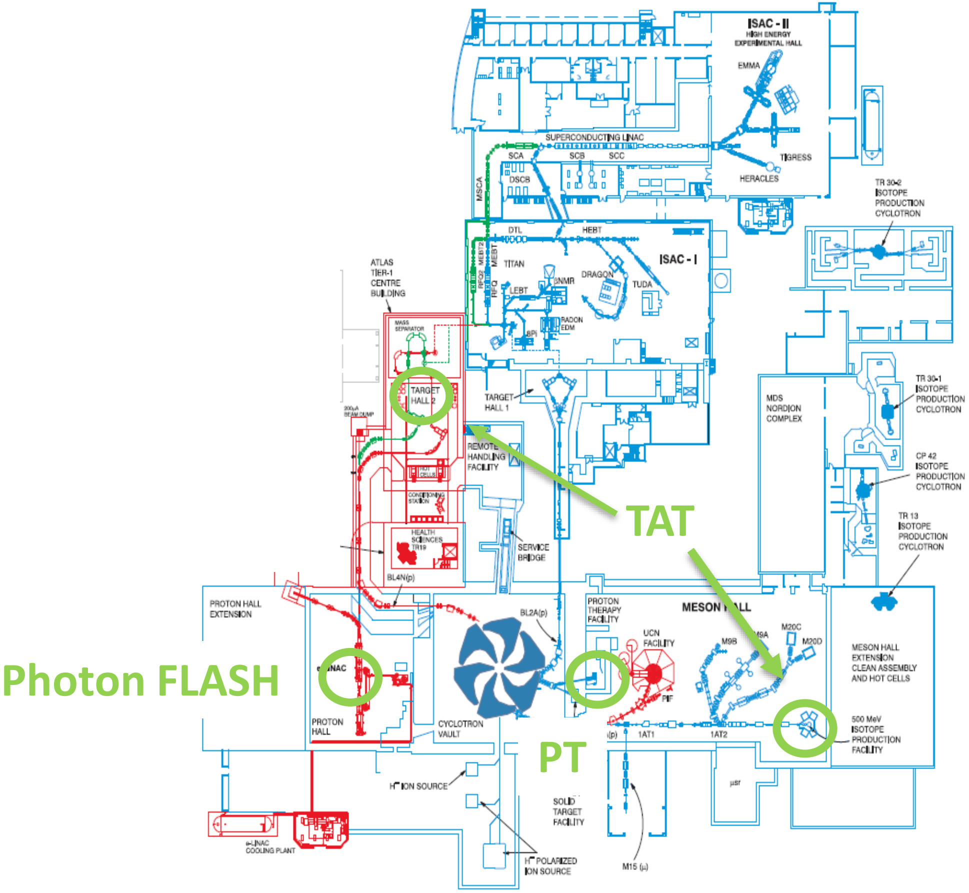
ARIEL Medical Target Station

- 400 mCi (15 GBq) ^{225}Ac per target (FLUKA)
- Irradiation schedule decoupled from science target
- ARIEL Proton Station commissioning scheduled for 2024/5 – 10 M CFI grant





Francois Benard, BC Cancer
Alexander Gottberg, TRIUMF



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500 MeV ISOTOPE PRODUCTION FACILITY
PT
H⁻ ION SOURCE
SOLID TARGET FACILITY
μsr
e-LINAC COOLING PLANT
H⁻ POLARIZED ION SOURCE
M15 (μ)

Acknowledgment

TRIUMF Life Sciences Division

TRIUMF accelerator division, operations and machine shops

Collaborators

- Cheryl Duzenli (BC Cancer)
- Francois Bénard (BC Cancer)
- Andrew Minchinton (BC Cancer)
- Andrew Jirasek (UBC)
- Boris Stoeber (UBC)
- Dennis Muecher (Guelph)
- Magdalena Bazalova-Carter (UVic)
- Raymond Reilly (UoT)
- Sylvain Girard (St Etienne, France)
- Sinead O'Keeffe (Limerick, Ireland)

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Canadian Cancer Society

TRIUMF

Canada's particle accelerator centre

Centre canadien d'accélération des particules

Thank you!
Merci!

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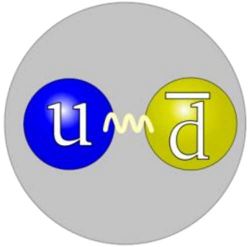
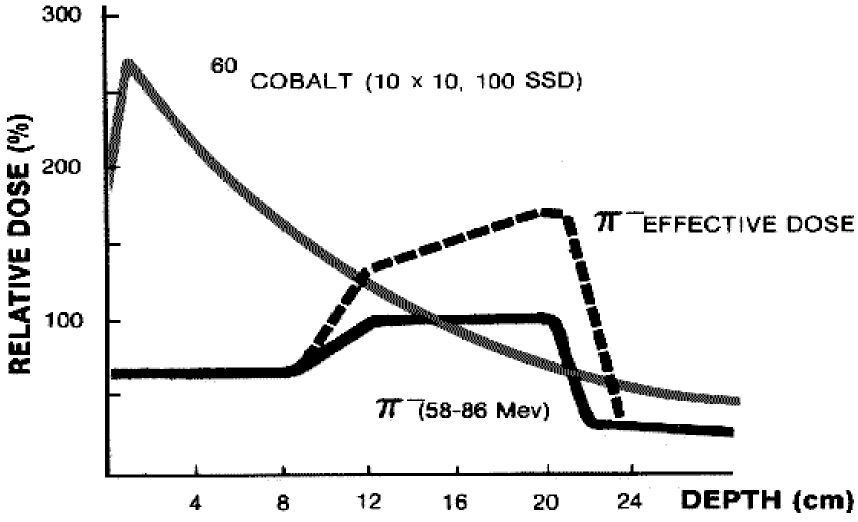
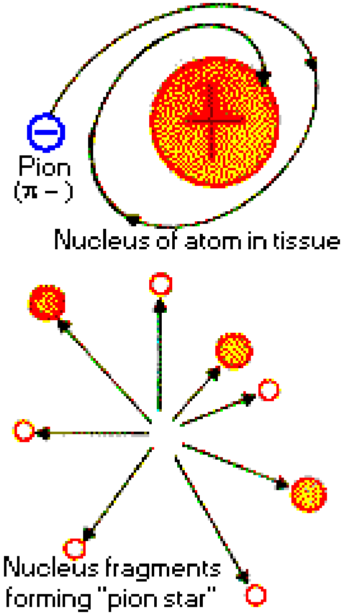
External: Pion- beam Treatment

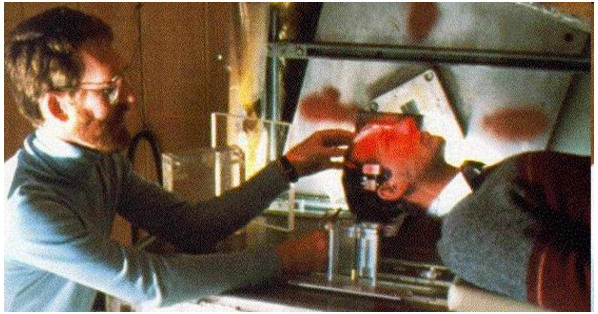


- Pion - subatomic particle, meson
- In nuclei, glue to hold protons and neutrons
- Some are charged
- Have Bragg peak, little damage to surrounding tissue, high LET in Bragg peak
- Lots of damage at Bragg peak ('pion star')





Pion-beam Treatment at TRIUMF



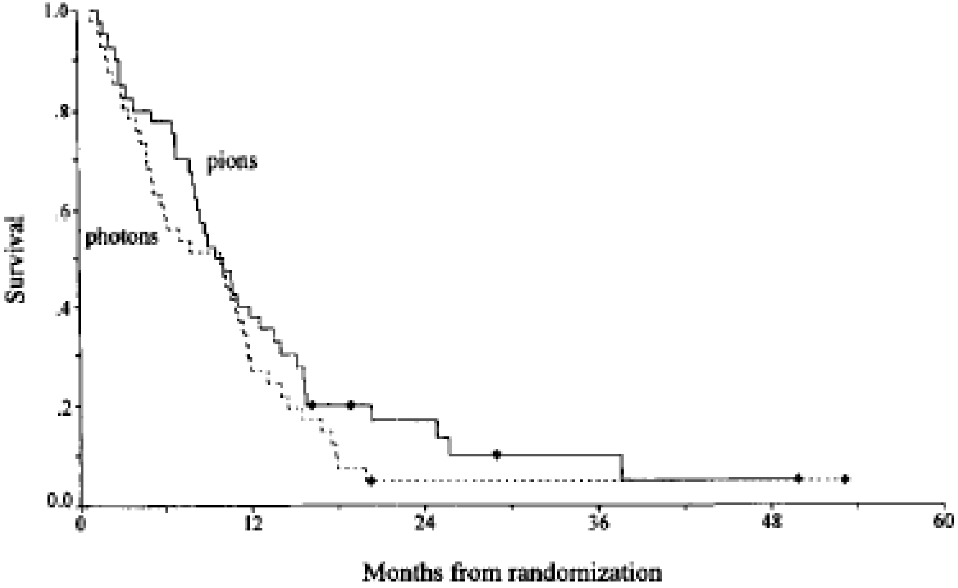


Fig. 2. Overall survival for both treatment groups. Median survivals are: photons, 10 months; pions, 10 months. Log rank: $p = 0.22$.

- Study from 1980 – 1994 (over 300 patients), one of only three in the world
- Brain tumors (glioblastoma) and prostate cancer

- Result of study: no advantage over conventional photon therapy

Int. J. Radiation Oncology Biol. Phys. **37** 491 (1997)