TRIUMF

Canada's particle accelerator centre

How nuclear physics can treat cancer

Radiotherapy at TRIUMF

Cornelia Hoehr

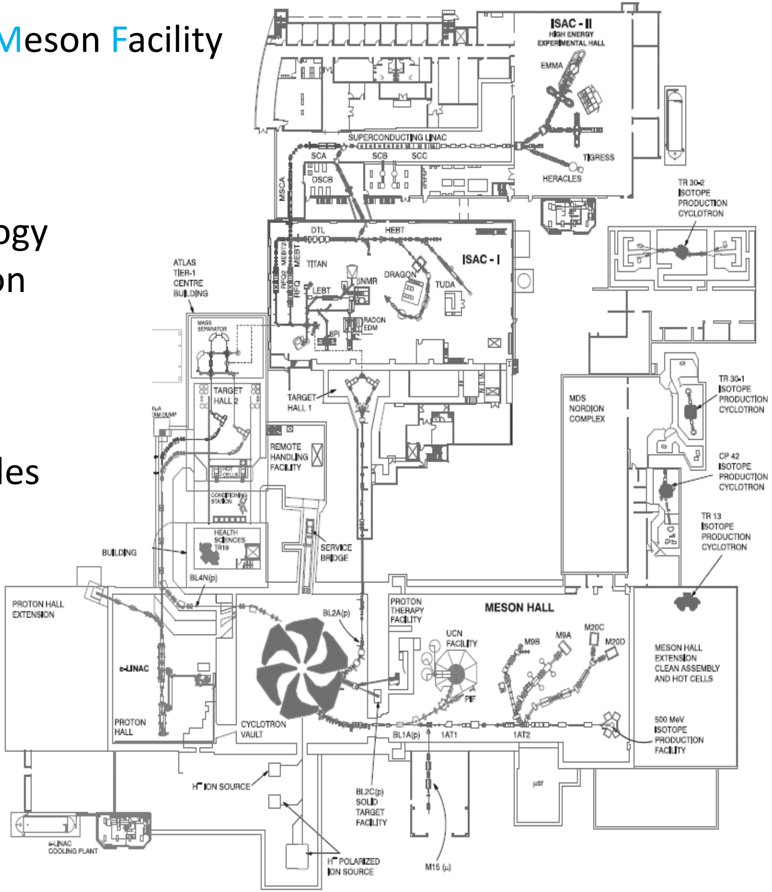
Scientist

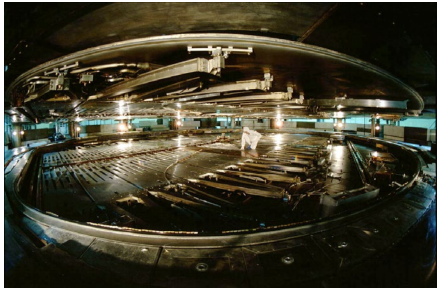
Deputy Associate Laboratory Director | Life Sciences

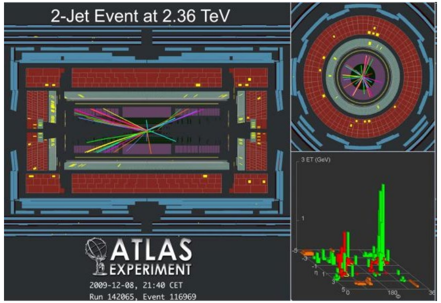
Introduction

TRIUMF – Tri University Meson Facility
- nuclear physics lab.

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

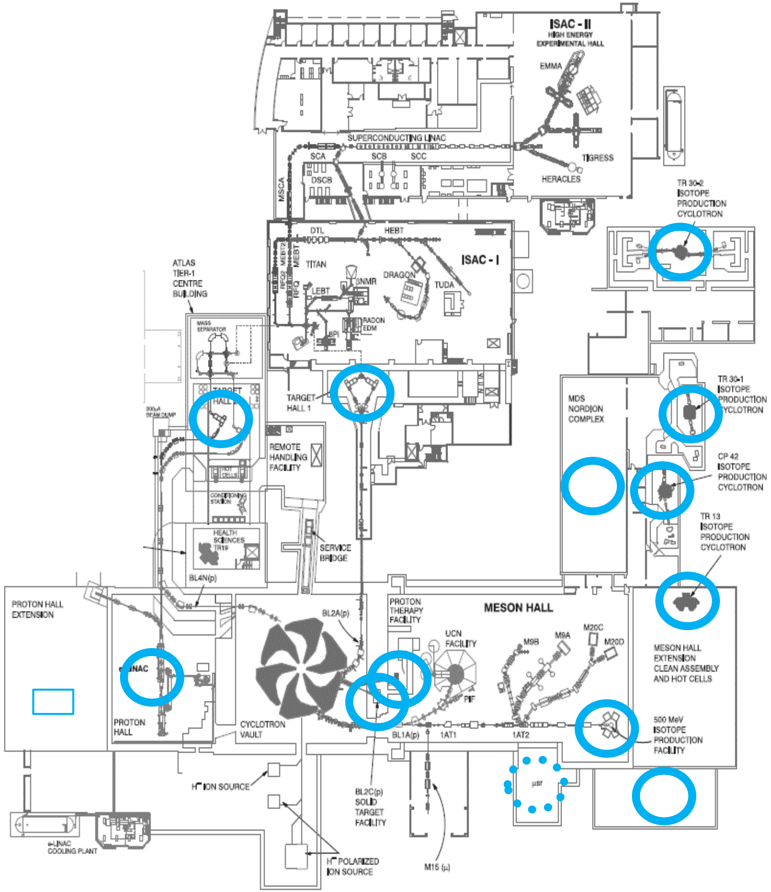




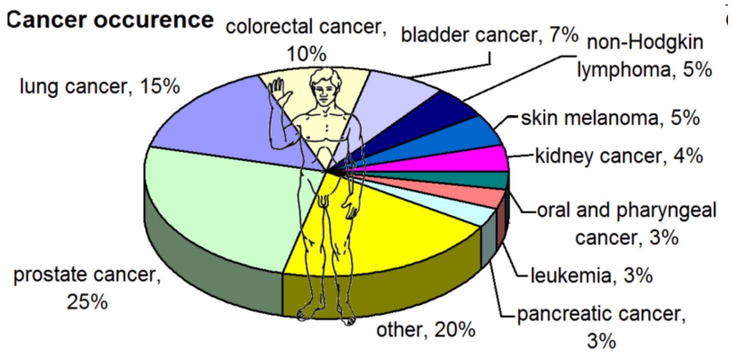


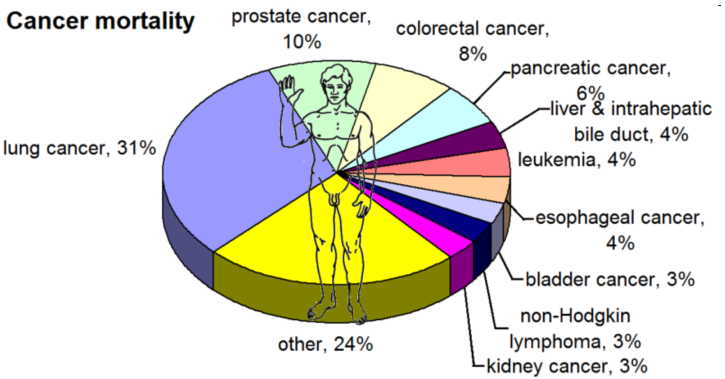
Medical Application @ TRIUMF

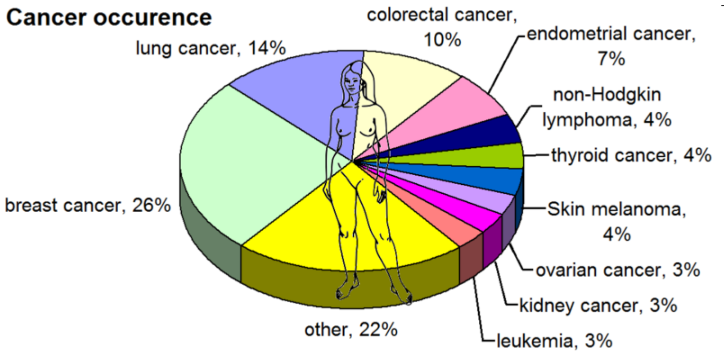
Applicable to medicine

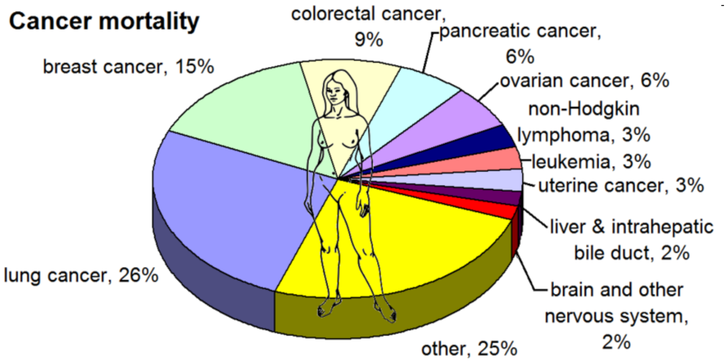


Cancer


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%

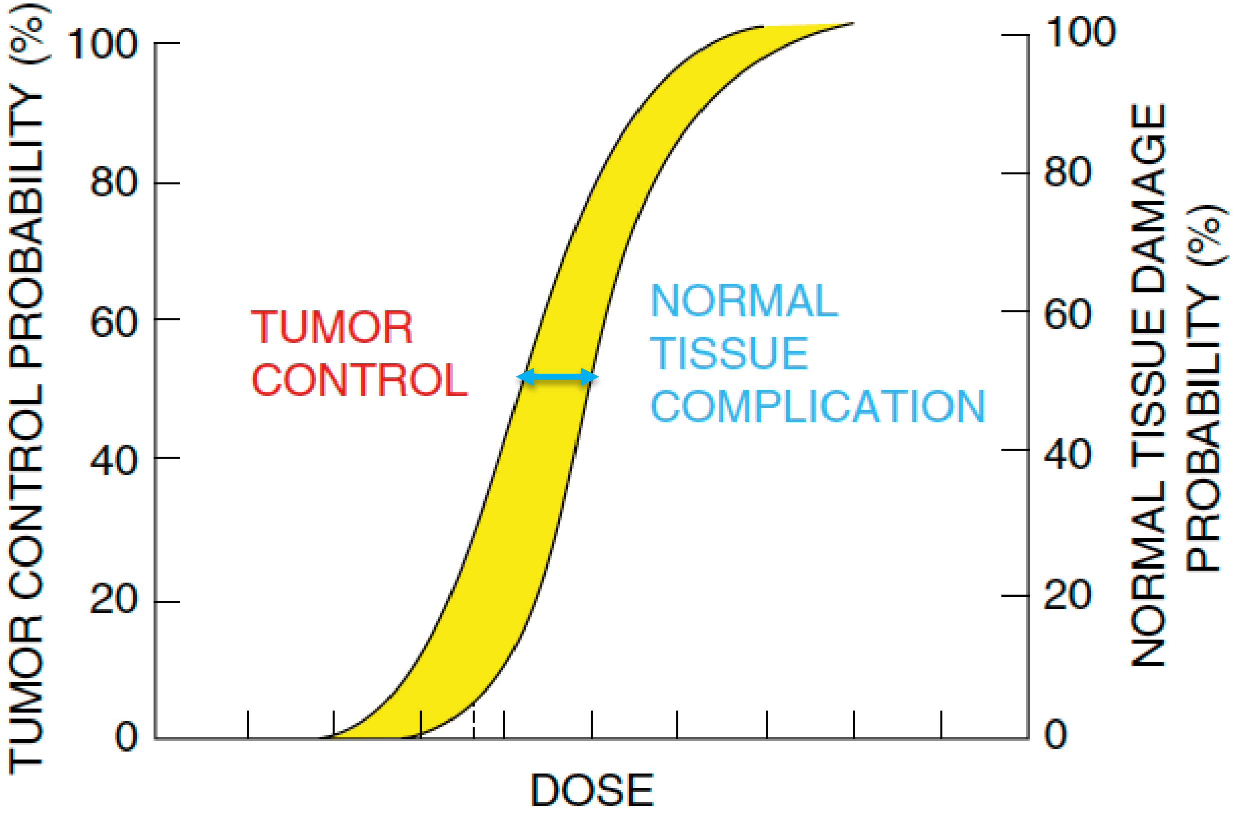

Cancer mortality
prostate cancer, 10%
colorectal cancer, 8%
pancreatic cancer, 6%
liver & intrahepatic bile duct, 4%
lung cancer, 31%
leukemia, 4%
esophageal cancer, 4%
bladder cancer, 3%
non-Hodgkin lymphoma, 3%
kidney cancer, 3%
other, 24%


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

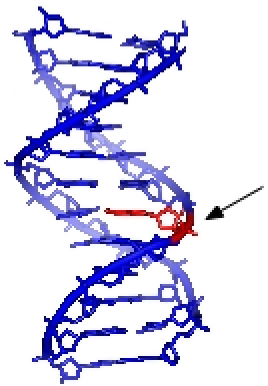

Cancer mortality
colorectal cancer, 9%
pancreatic cancer, 6%
breast cancer, 15%
ovarian cancer, 6%
non-Hodgkin lymphoma, 3%
leukemia, 3%
uterine cancer, 3%
liver & intrahepatic bile duct, 2%
lung cancer, 26%
brain and other nervous system, 2%
other, 25%

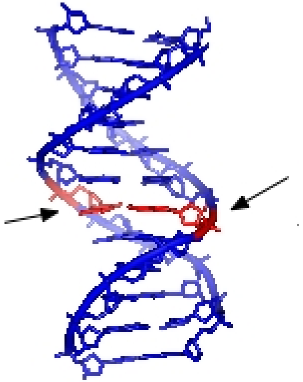
- Surgery
- Chemotherapy
- Ionizing radiation

- Holy grail of cancer research: **Increase gap (therapeutic index/ window) as much as possible**



DNA break



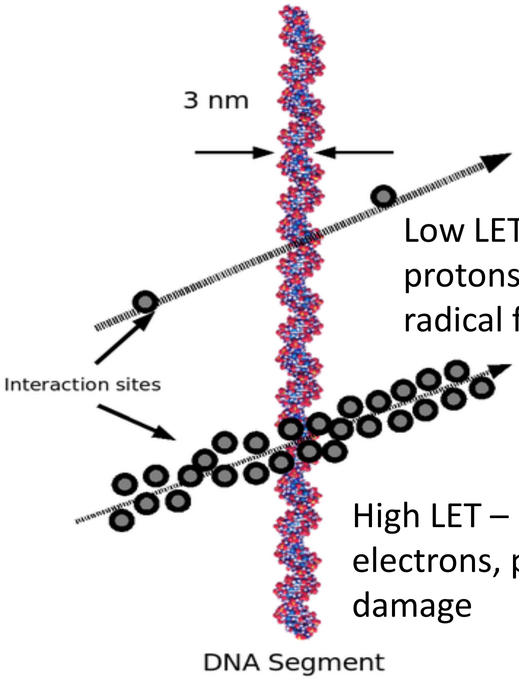


- DNA (Deoxyribonucleic acid): genetic instructions for development and functioning
- Cell needs information from DNA for survival

- 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**

LET – Linear Energy Transfer



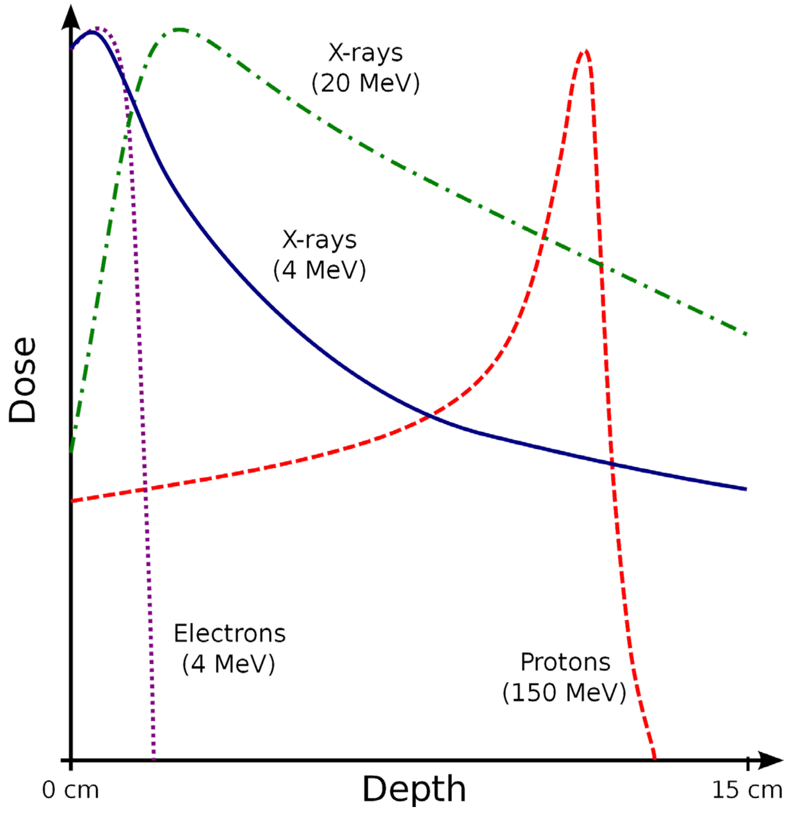
Low LET – photons, electrons, protons, indirect damage via free radical formation

High LET – ions, neutrons, electrons, protons, direct damage

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

External beam therapy

- **Electrons** only used for surface or shallow 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 (**C-12 ions** 430 MeV/u)



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

Vozenin *et al.*, 2018

FLASH effect

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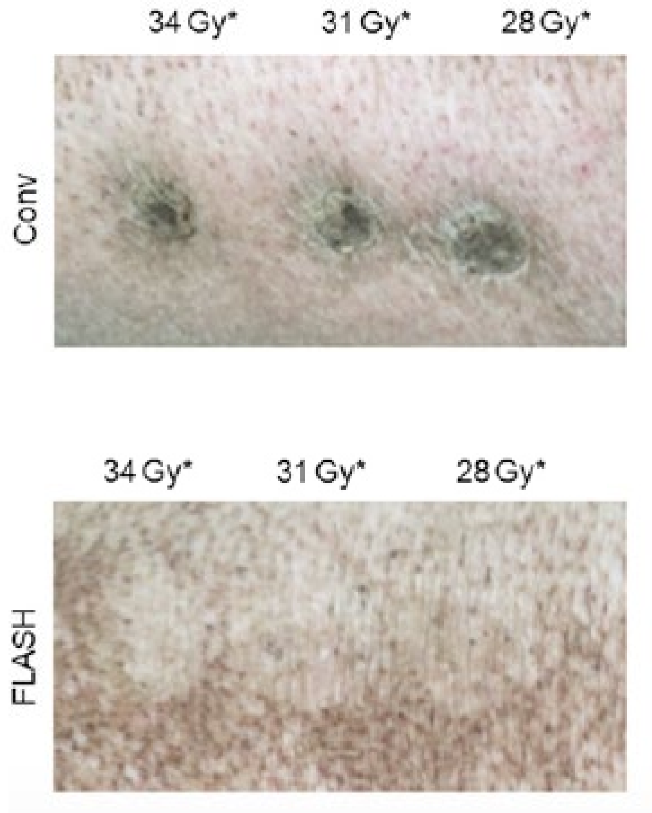
FLASH dose rate **< 40 Gy/s**

- 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**



Vozenin *et al.*, 2018

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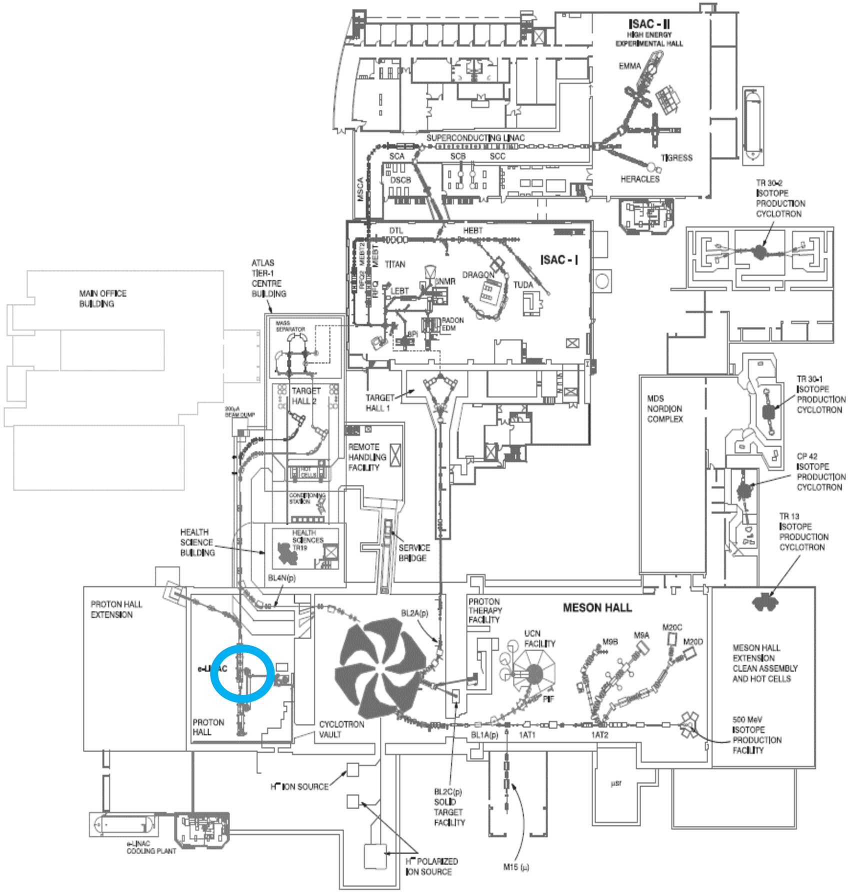
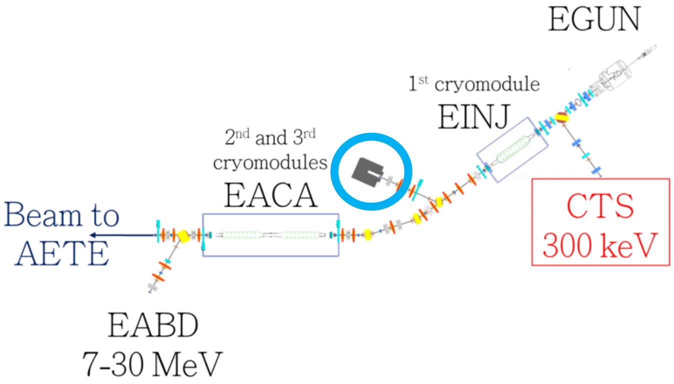
Increase therapeutic index by protecting healthy tissue

Bourhis *et al.*, 2019

Photon FLASH

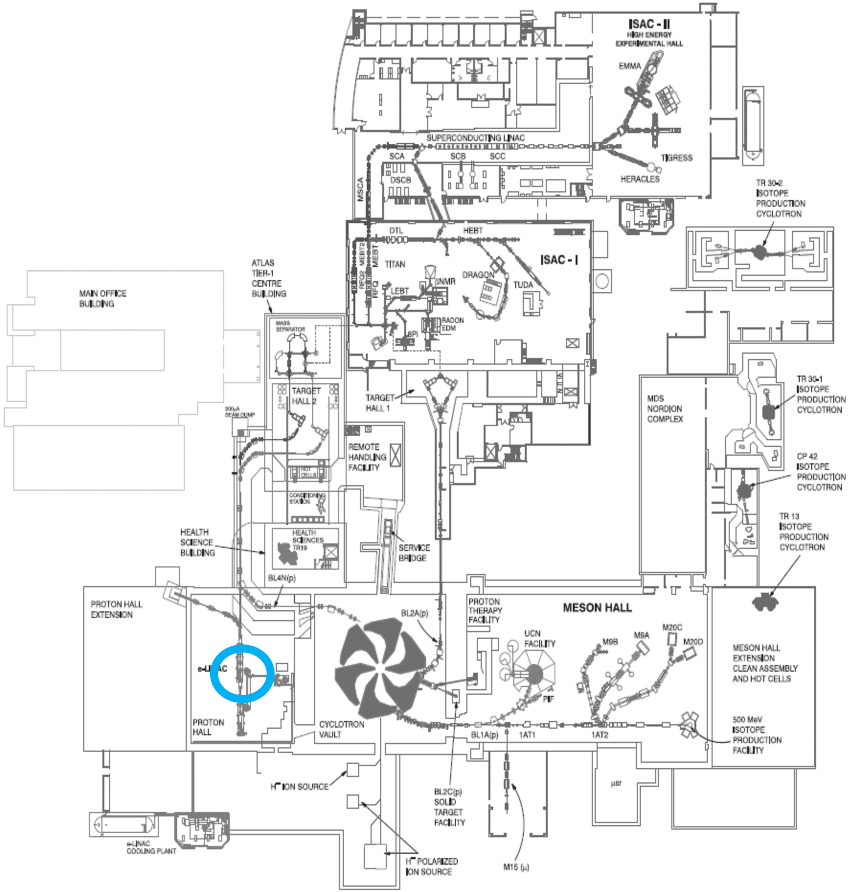


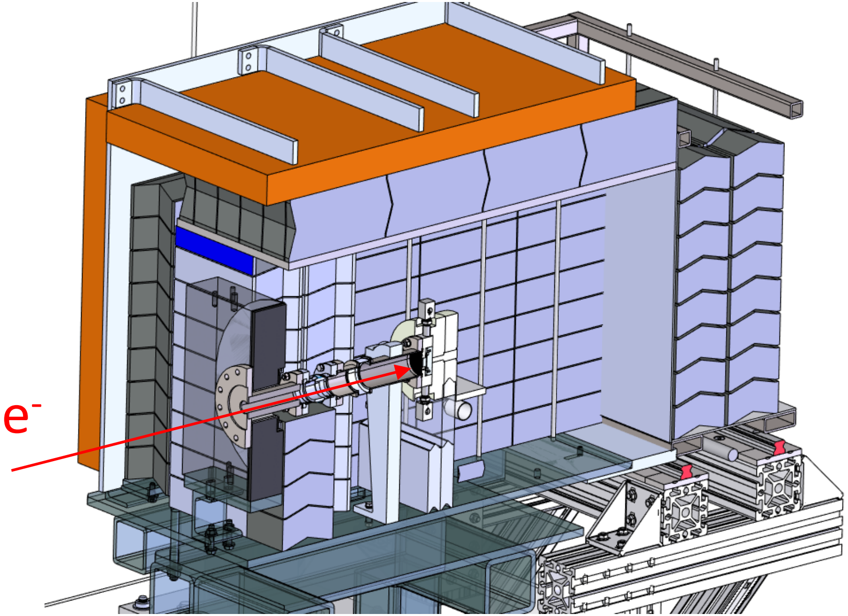
- Electron gun 300 keV 10 mA (CW)
- Three accelerating superconductive cryomodules
- Irradiation stations:
  - Low energy (CTS – 300 keV)
  - High energy (EABD – up to 30 MeV)
  - Medium energy (EMBD - up to 10 MeV)



Magdalena Bazalova-Carter, UVic
Alexander Gottberg, TRIUMF

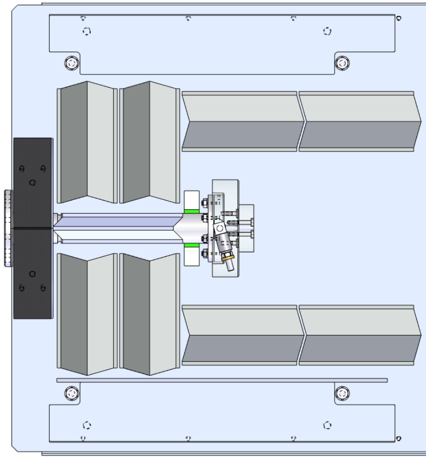
Photon FLASH

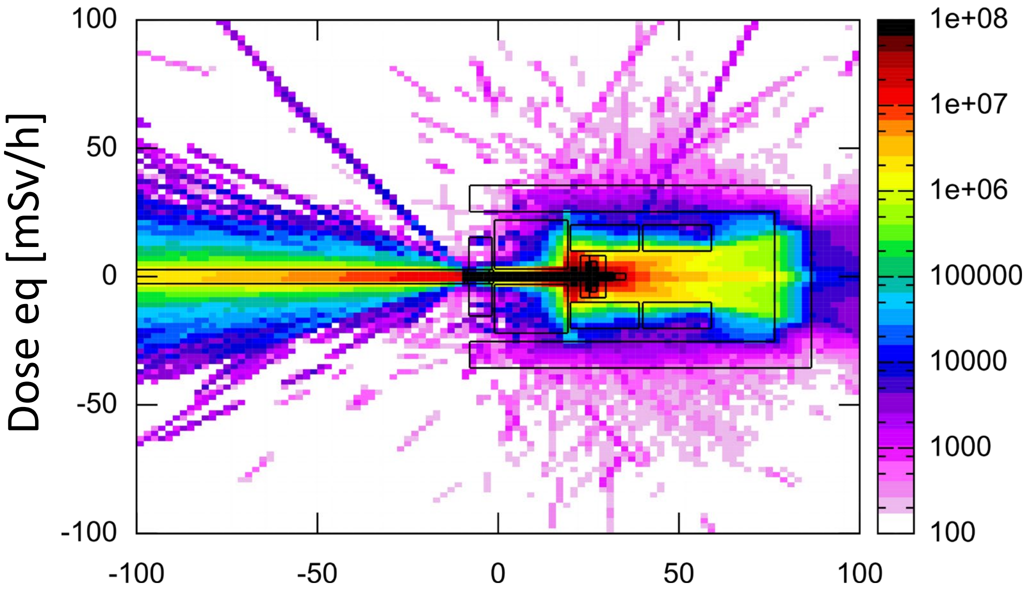




FLASH – DoseEq @ 10 MeV

Average dose rate up to ~ 200 Gy/s





What's next?

- Manufacture, installation and testing winter 2021/2022
- Experiments with biological samples spring 2022

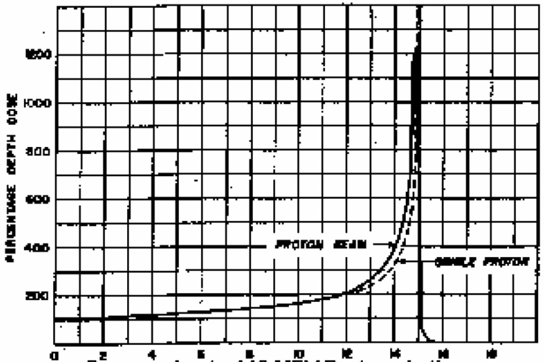
TRIUMF

Proton Therapy

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

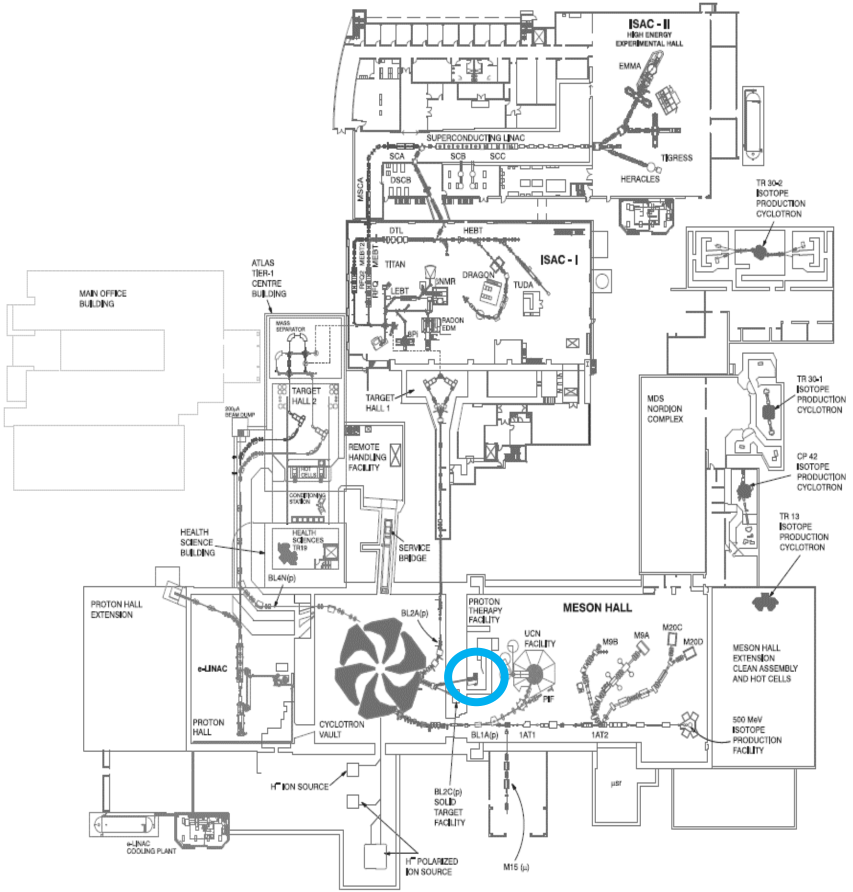
Robert Wilson

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

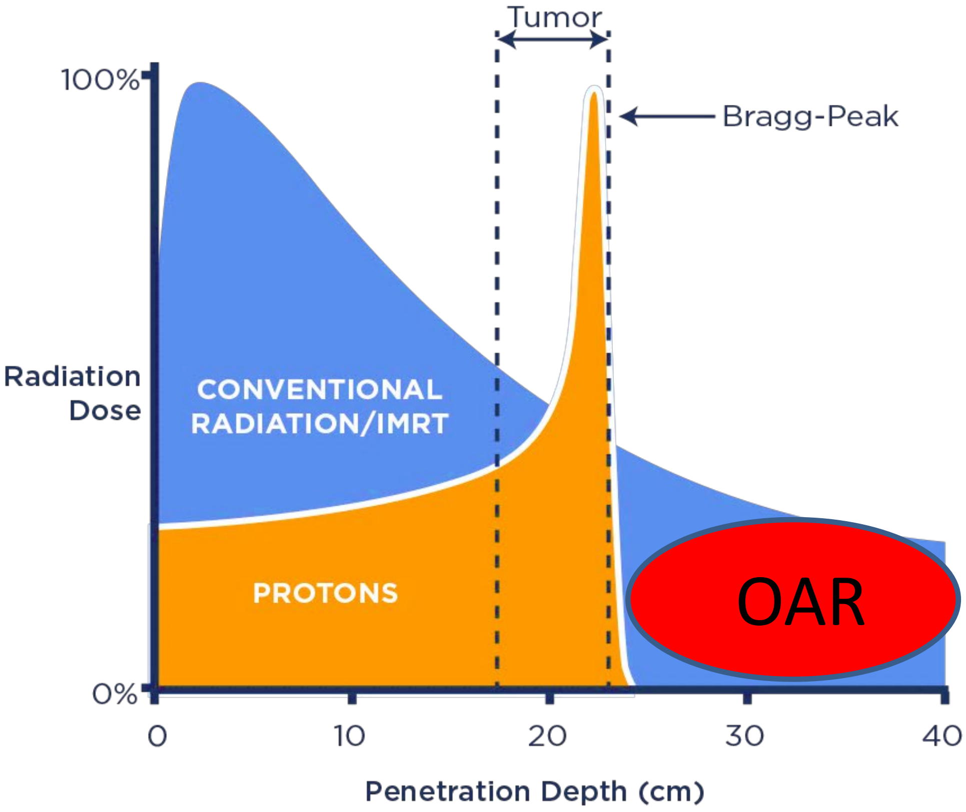
Proton Therapy @ TRIUMF

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

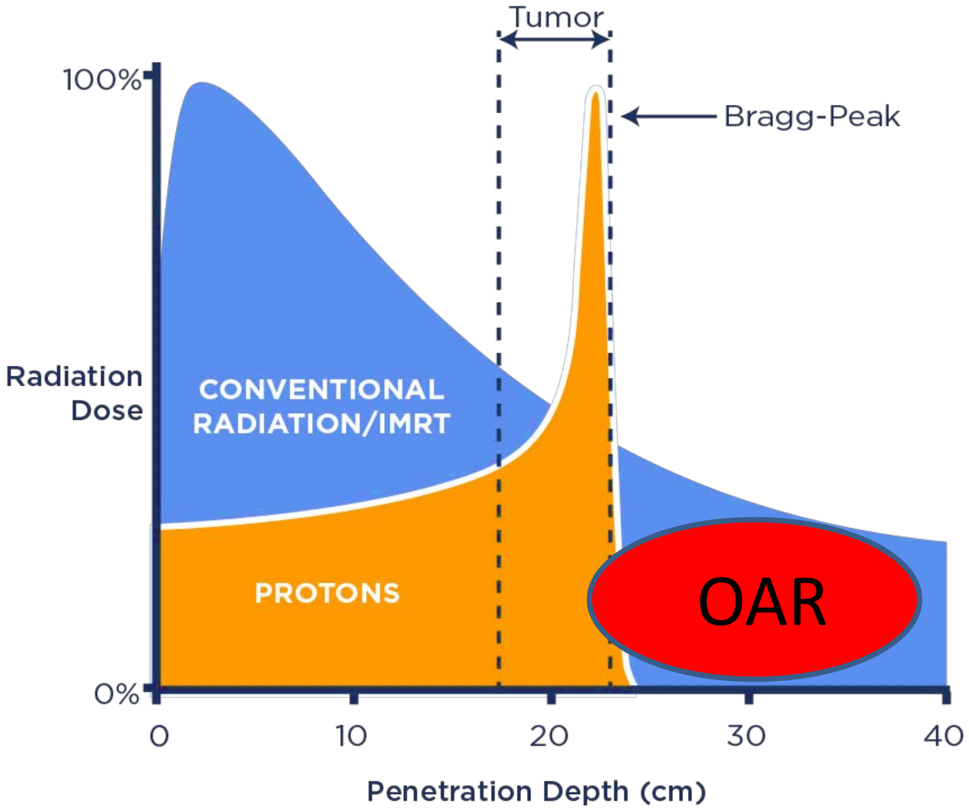
Research into increased therapeutic index ongoing



Safety margins

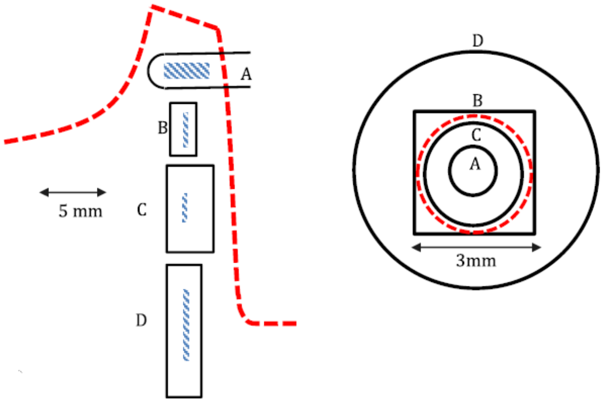


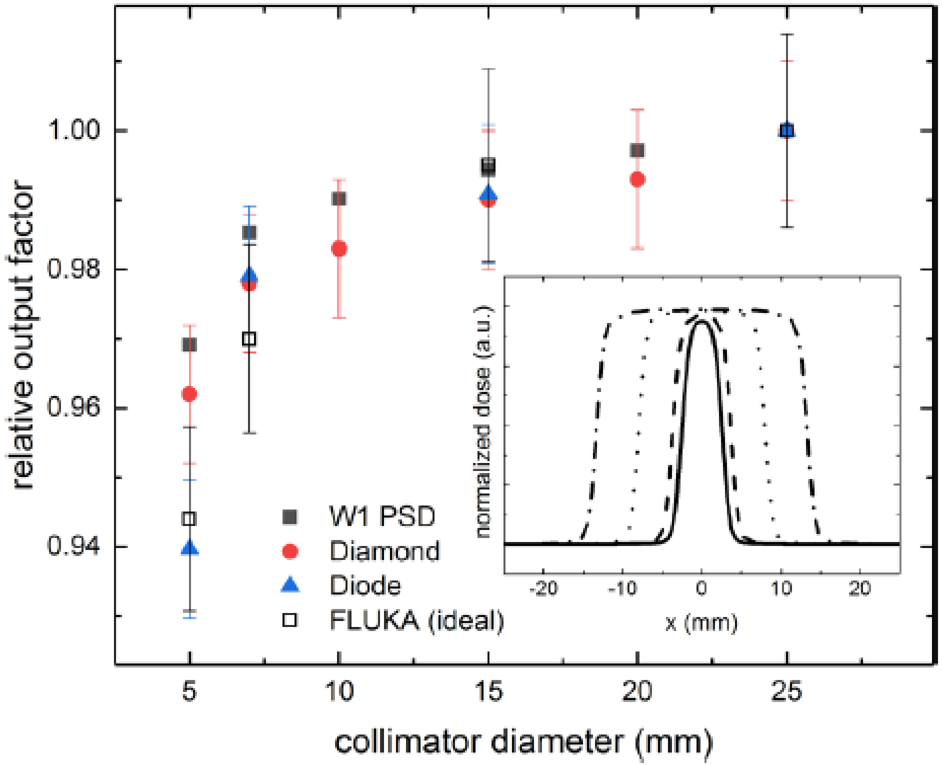
Safety margins



- Currently large safety margins to avoid Organ At Risk (OAR)
- **Increase therapeutic index by minimizing safety margins and dose to healthy tissue**

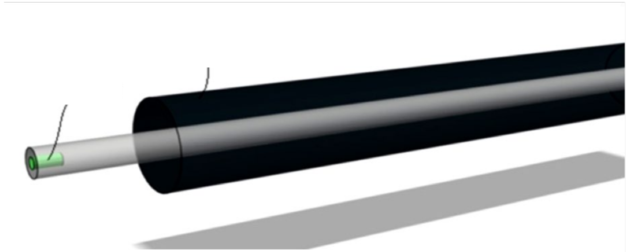
Dosimetry for PT



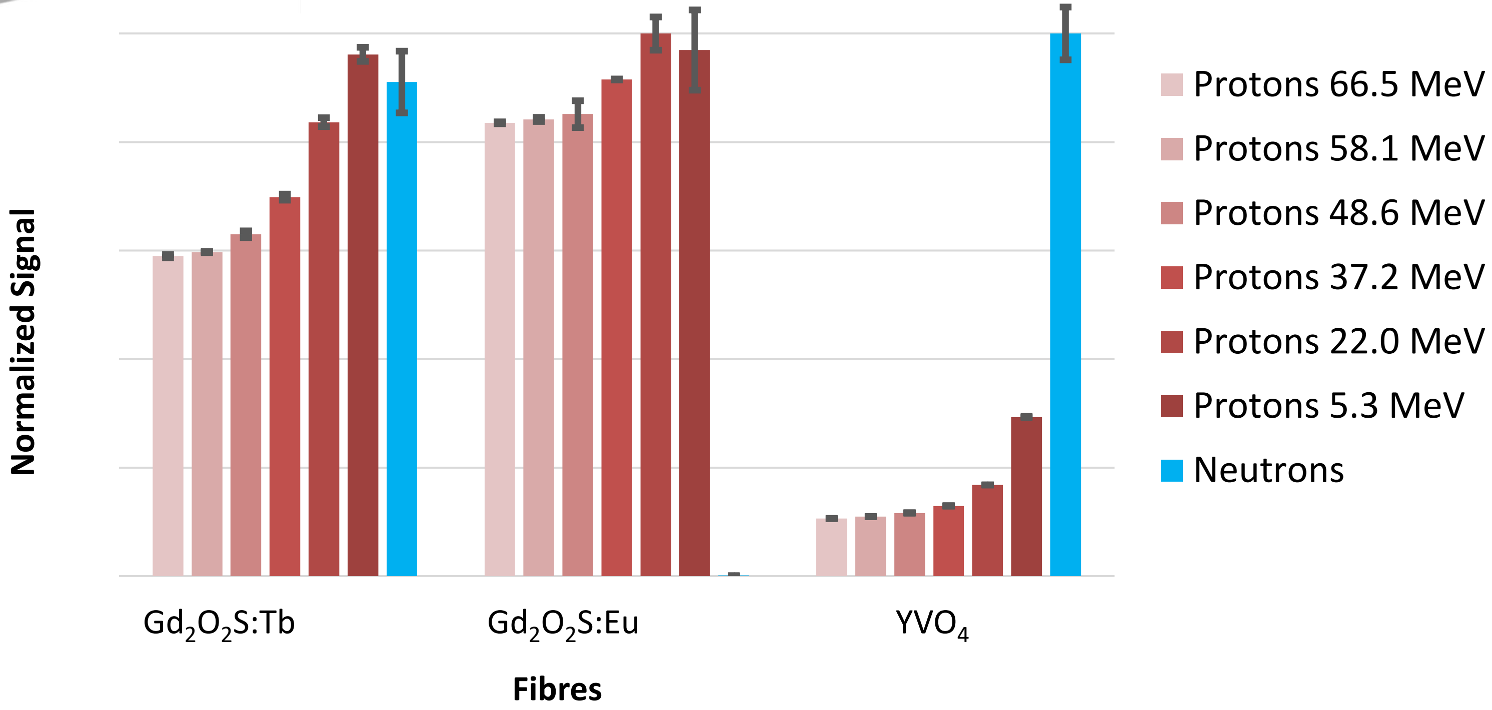


- Typical detectors can be larger than treatment fields, do not measure ‘real’ dose field
- Optical fibers can be small, at least in two dimensions

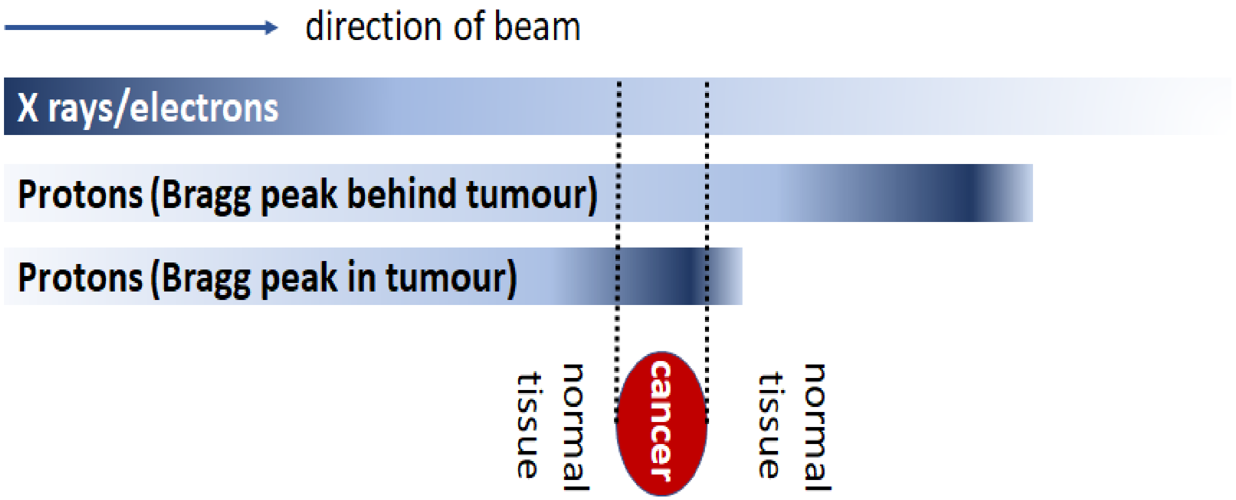
CH, Phys Med Biol



'Biological' dosimeter



Proton FLASH?

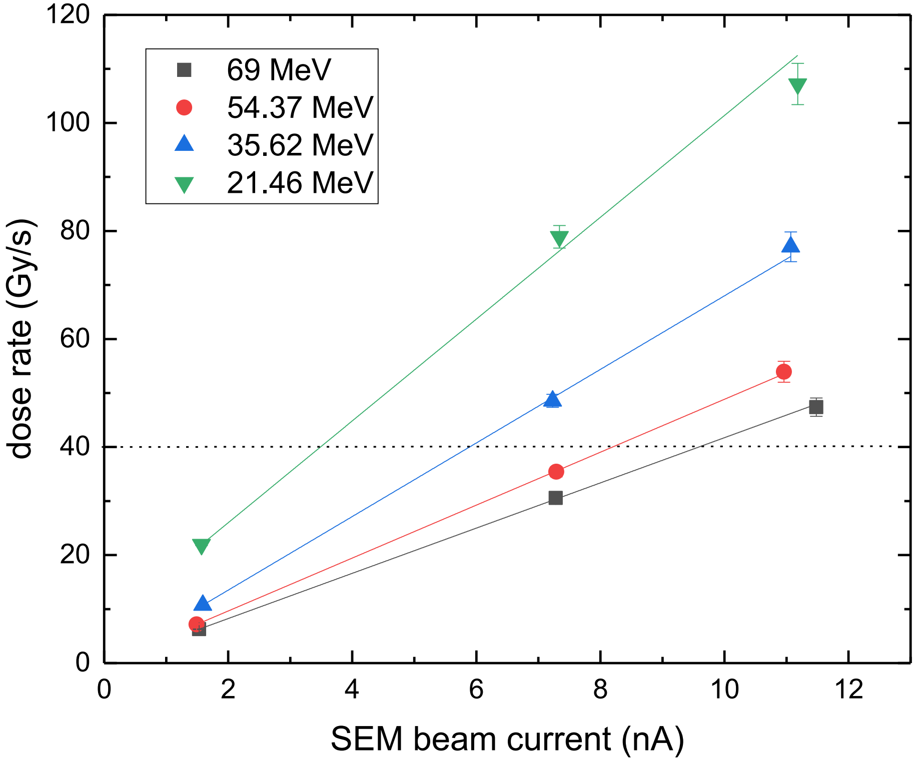


- PT facility (2C1) at TRIUMF limited to 6 nA, or ~ 0.2 Gy/s
- Main cyclotron able to extract 100 uA into 2C4, or over 1,000 Gy/s

Will there be a FLASH effect with protons?

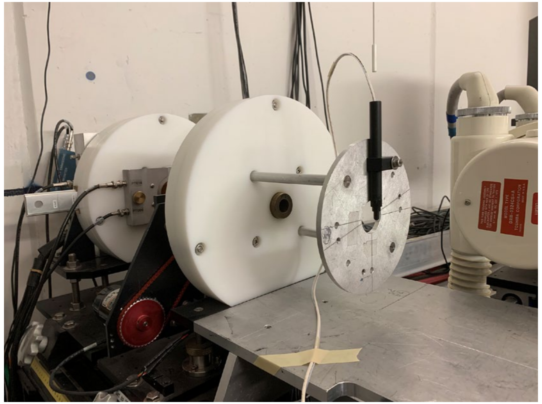
Yes, some other groups seem to observe it.....

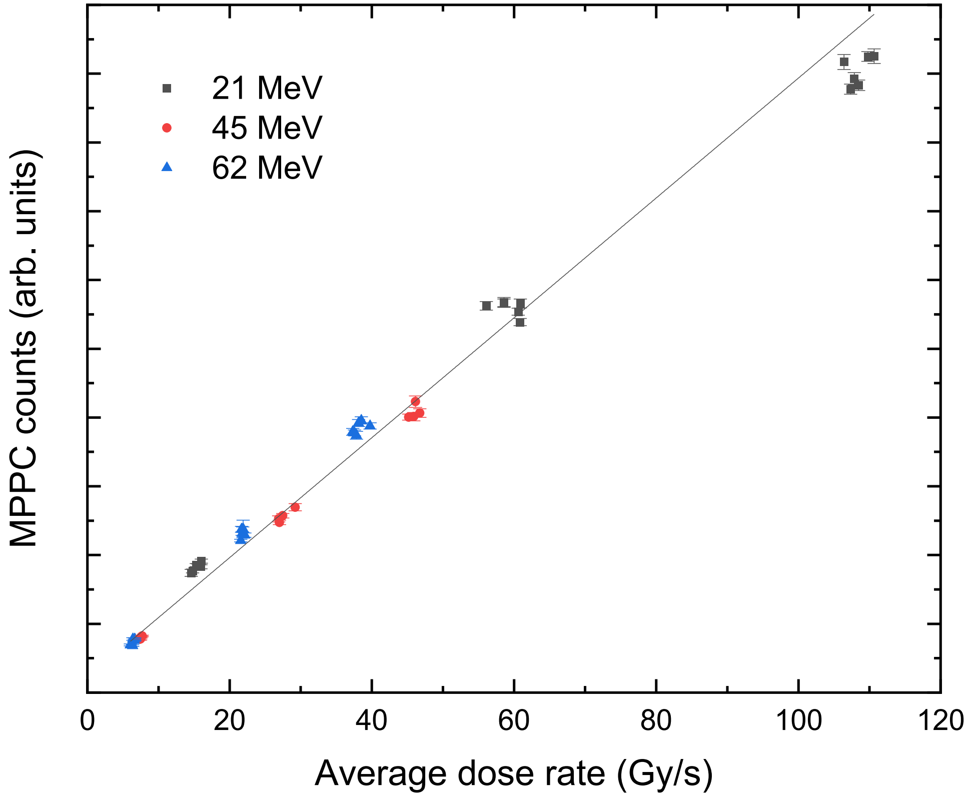
Proton FLASH at TRIUMF



- Started to explore FLASH beam delivery at TRIUMF (Aug 2020: up to 100 Gy/s)

Fibers for Proton FLASH



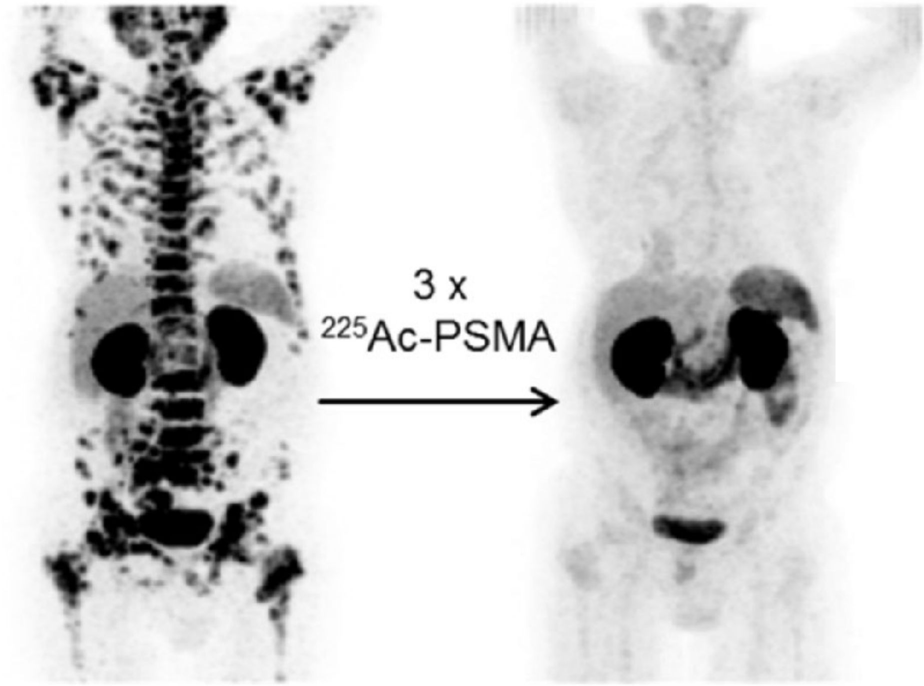


- Tried several fibers – saturated
- Bare PMMA fiber with Hamamatsu MPPC

Targeted α Therapy (TAT)

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

Targeted α Therapy (TAT)



- > 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)

Primary ^{225}Ac sources:

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

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

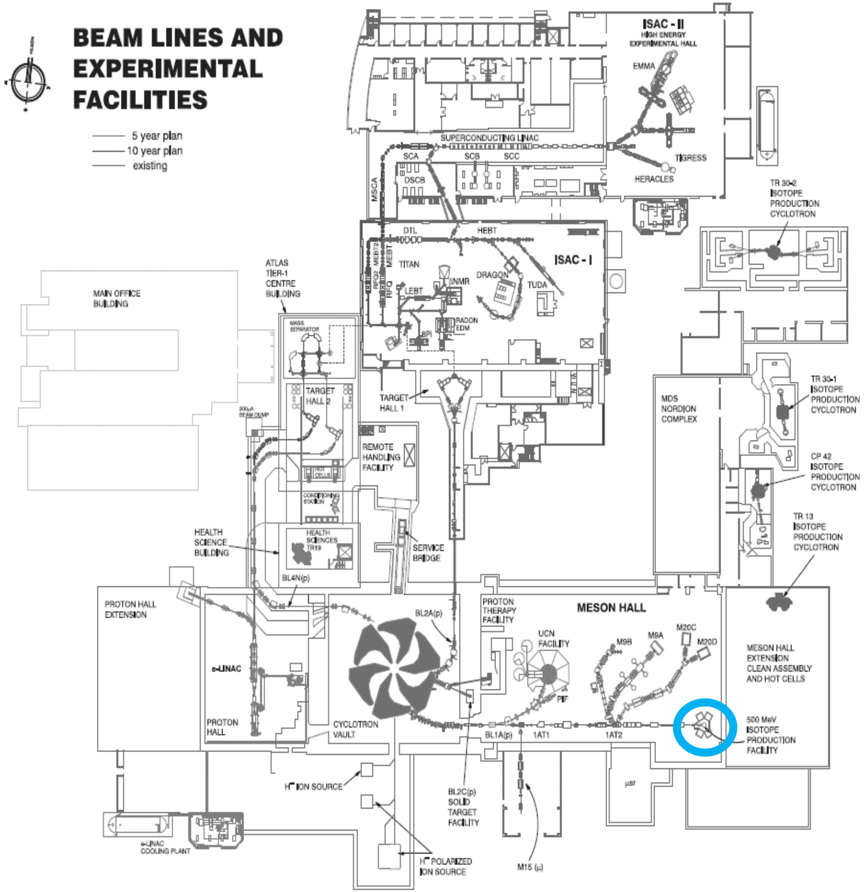
Increase therapeutic index by delivering cell-killing dose targeted to the cancer cells

α emitters

Isotope production using TRIUMF's
500 MeV infrastructure

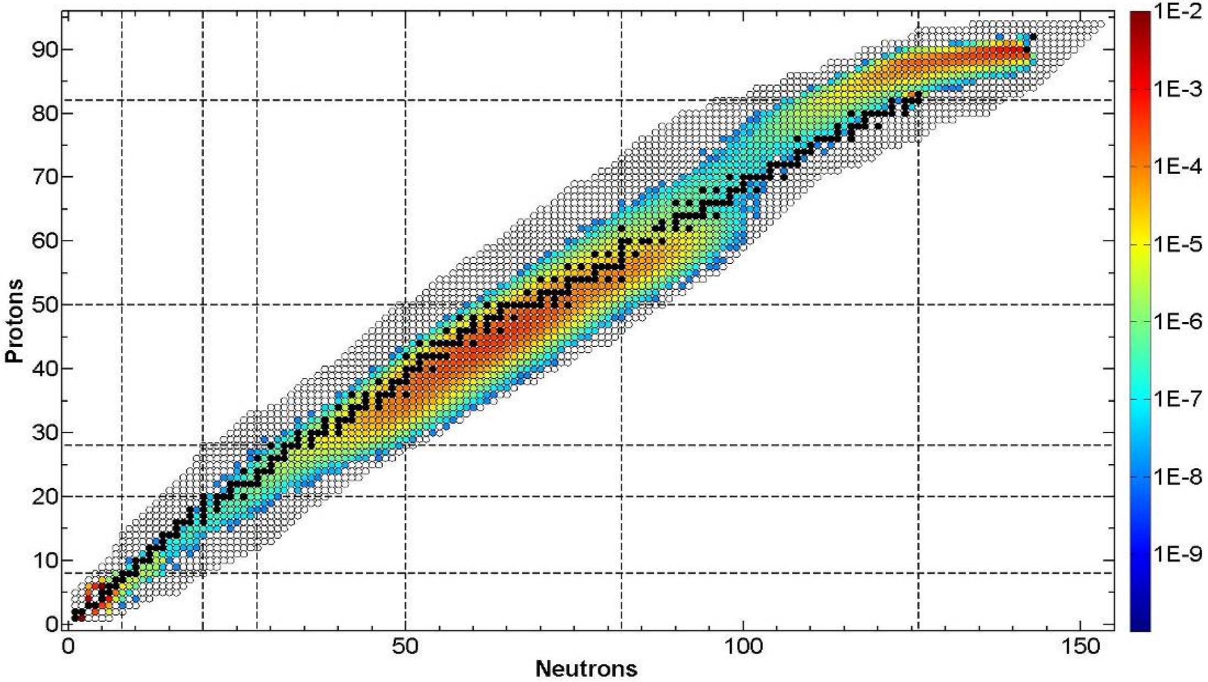
IPF (BL1A)
Intermediate activity (MBq), spallation

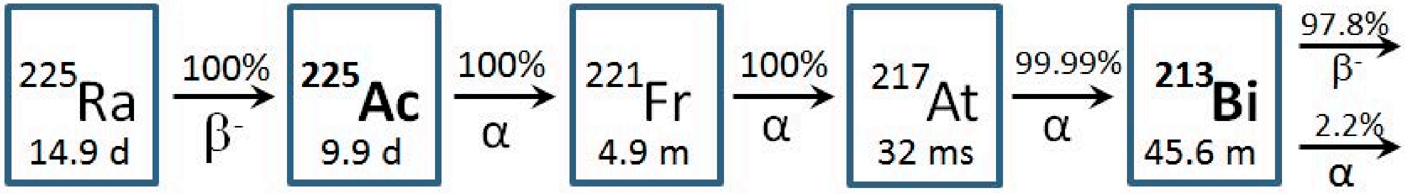
- Routine, independent production



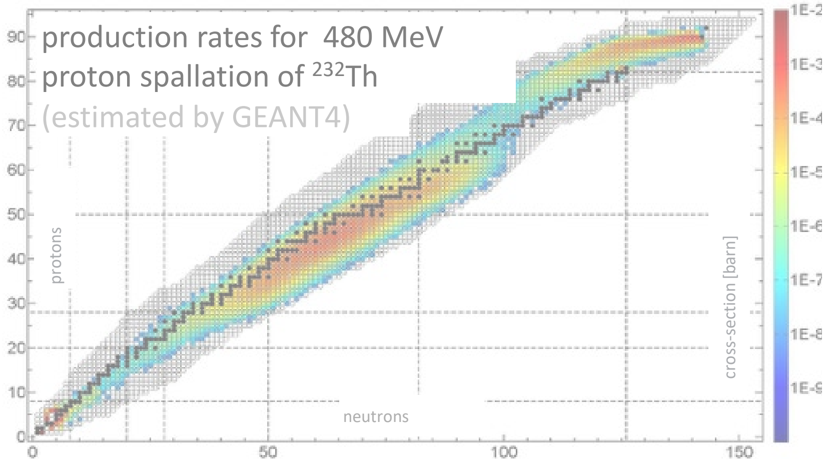
Spallation Reaction on ^{232}Th with 500 MeV Protons

- 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



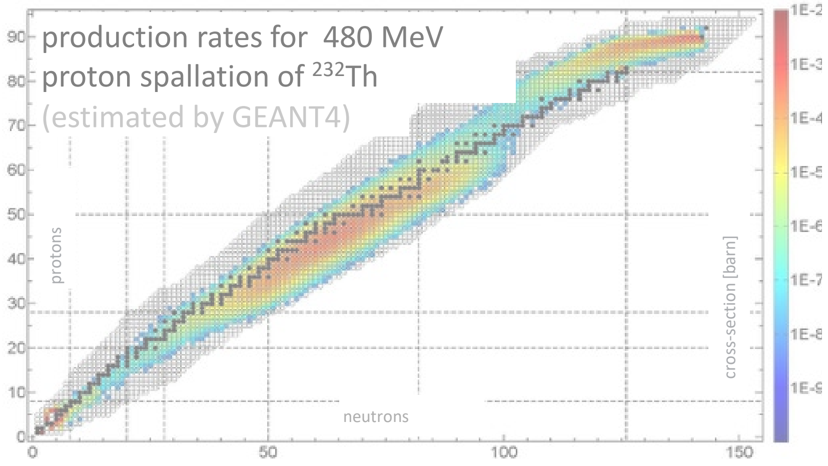
^{225}Ac + ^{224}Ac + ^{226}Ac + ^{227}Ac

$t_{1/2}$ = 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

$t_{1/2}$ = 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

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

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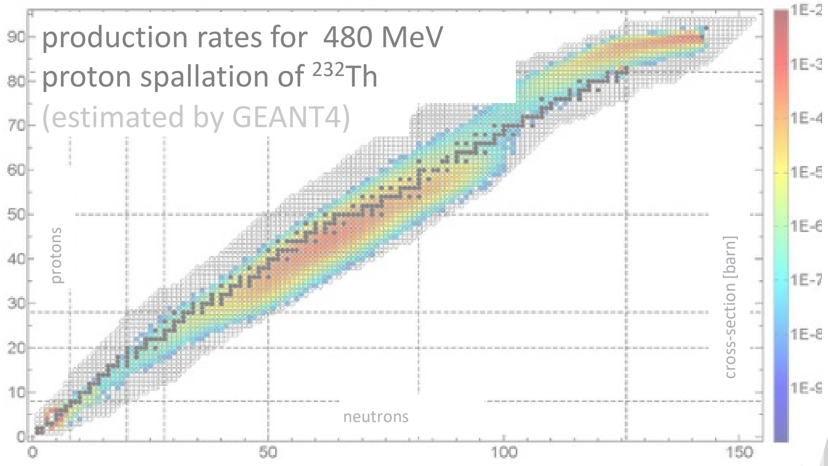

^{227}Ra + ^{225}Ra + ^{228}Ra + ^{224}Ra + ^{226}Ra

$t_{1/2}$ = 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

rapid decay

^{224}Rn ^{222}Rn

^{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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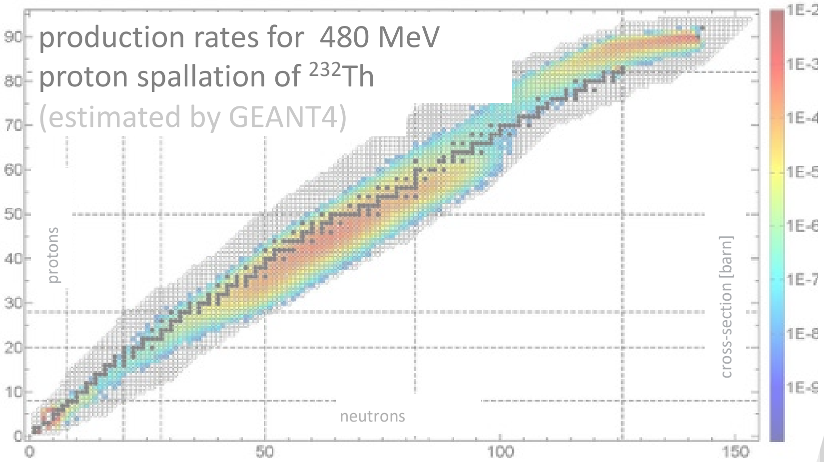

^{227}Ra + ^{225}Ra + ^{228}Ra + ^{224}Ra + ^{226}Ra

$t_{1/2}$ = 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

rapid decay

^{224}Rn ^{222}Rn

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

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

directly-produced ^{225}Ac

^{225}Ac + ^{228}Ac

$t_{1/2}$ = 9.9 d | $t_{1/2}$ = 6 h

generator-produced ^{225}Ac

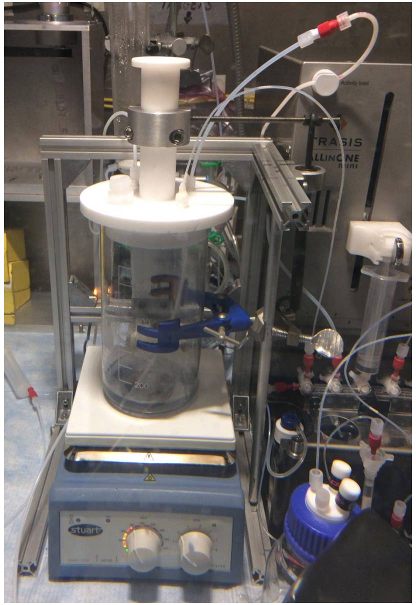
Thorium irradiations

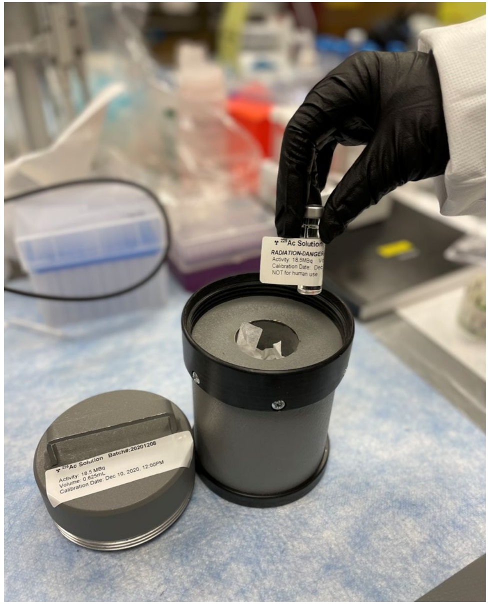
Irradiation parameters

- integrated current 2640 µA*h, over **36-40 h**
- 66-73 µA, 454 MeV
- Achieved at end of synthesis 33.5 MBq

What's next?

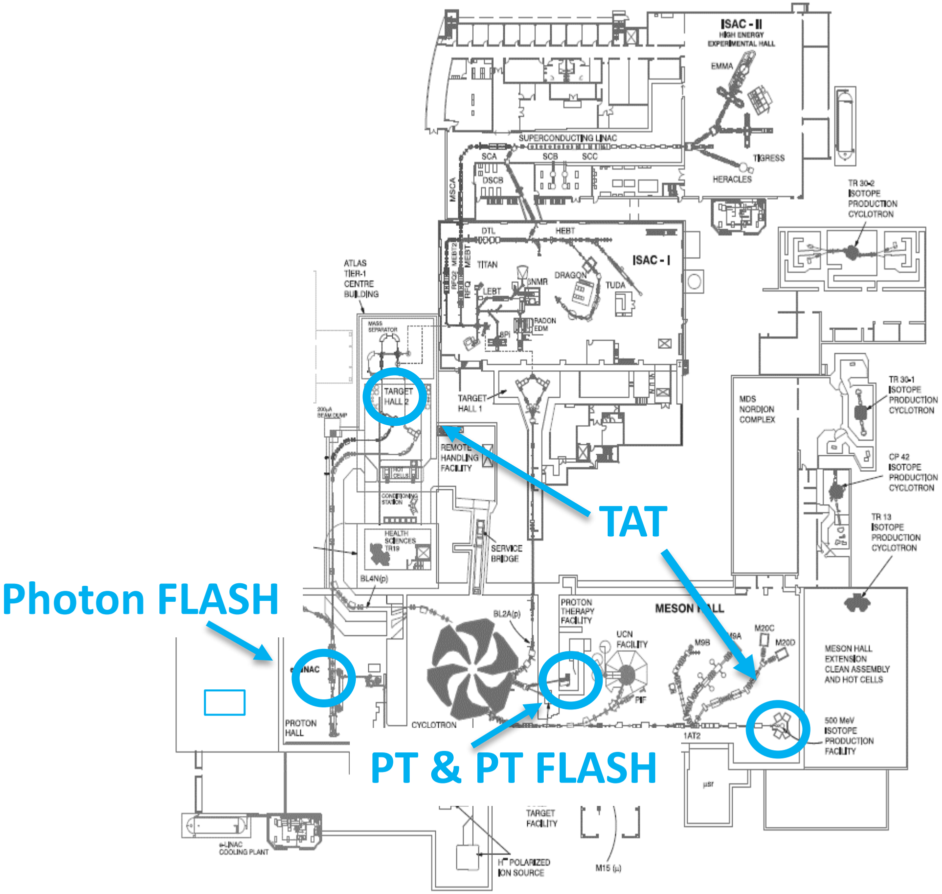
- **x12 increase** in yield by irradiating 12 targets simultaneously
- **x10 increase** in yield by irradiating for full ^{225}Ra half life (15 days)
- Further increase from thicker target and higher current require re-evaluation of target and safety
- **2021 ramping up production**





Andrew Roberson, CH, Phys Rev C

Summary



ISAC - II
HIGH ENERGY EXPERIMENTAL HALL
EMMA
TIGRESS
HERACLES
SUPERCONDUCTING LINAC
SCA
SCB
SCC
DSCB
MSCA
TR 30-2 ISOTOPE PRODUCTION CYCLOTRON
DTL
HEBT
ISAC - I
TITAN
DRAGON
TUDA
LEBT
RADON EDM
ATLAS TIER-1 CENTRE BUILDING
MASS SEPARATOR
TARGET HALL 2
TARGET HALL 1
REMOTE HANDLING FACILITY
MDS NORDION COMPLEX
TR 30-1 ISOTOPE PRODUCTION CYCLOTRON
CP 42 ISOTOPE PRODUCTION CYCLOTRON
TR 13 ISOTOPE PRODUCTION CYCLOTRON
CONDITIONING STATION
HEALTH SCIENCES TR19
SERVICE BRIDGE
BL4N(p)
TAT
Photon FLASH
BL2A(p)
PROTON THERAPY FACILITY
MESON HALL
UCN FACILITY
M9B
M20C
M20D
MESON HALL EXTENSION CLEAN ASSEMBLY AND HOT CELLS
PIF
1AT2
500 MeV ISOTOPE PRODUCTION FACILITY
CYCLOTRON
PROTON HALL
PT & PT FLASH
TARGET FACILITY
e-LINAC COOLING PLANT
H⁻ POLARIZED ION SOURCE
M15 (µ)

TRIUMF

Acknowledgment

- TRIUMF Life Sciences Division - TAT
- Drs. Belanger-Champagne, Trinczek, Blackmore, Yen, TRIUMF – proton FLASH

- Cheryl Duzenli and collaborators (BC Cancer, Vancouver) - dosimetry
- Christian Diget and collaborators (York, UK) – alpha detectors
- Magdalena Bazalova-Carter and collaborators (UVic, Canada) – photon FLASH
- Sinead O’Keeffe and collaborators (Limerick, Ireland) – organic fibers
- Sylvain Girard and collaborators (StEtienne, France) – inorganic fibers

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Canada's particle accelerator centre

Centre canadien d'accélération des particules

Thank you!
Merci!

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