Clinical Trials using Lutetium177 and PSMA Targeting Radiopharmaceuticals To Treat Prostate Cancer Patients with Advanced Disease

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Prostate cancer in British Columbia

- An estimated 2,560 men were diagnosed with prostate cancer in 2018
- 610 men died of this disease
- One in 8 men will develop prostate cancer in their lifetime
- 88% of men are above 60 when the cancer is diagnosed

Primary Treatments for Prostate Cancer

- Initial therapy
  - Surgery (radical prostatectomy)
  - Radiation (brachytherapy or external beam)
  - Active surveillance (low risk patients)
  - Androgen (male hormones) deprivation therapy (ADT)
- Local therapy at relapse
  - Salvage radiation
  - Surgery
- ADT at relapse
  - Continuous or intermittent

Castration Resistant Prostate Cancer

- Eventually, prostate cancer becomes resistant to androgen deprivation
  - Some men are not affected during their lifetime
  - Others develop resistance rapidly
- Once prostate cancer becomes resistant to hormone manipulations the disease can progress rapidly
  - Rising PSA with suppressed testosterone
  - Cancer spreading to bones or other organs

Treatment of advanced prostate cancer

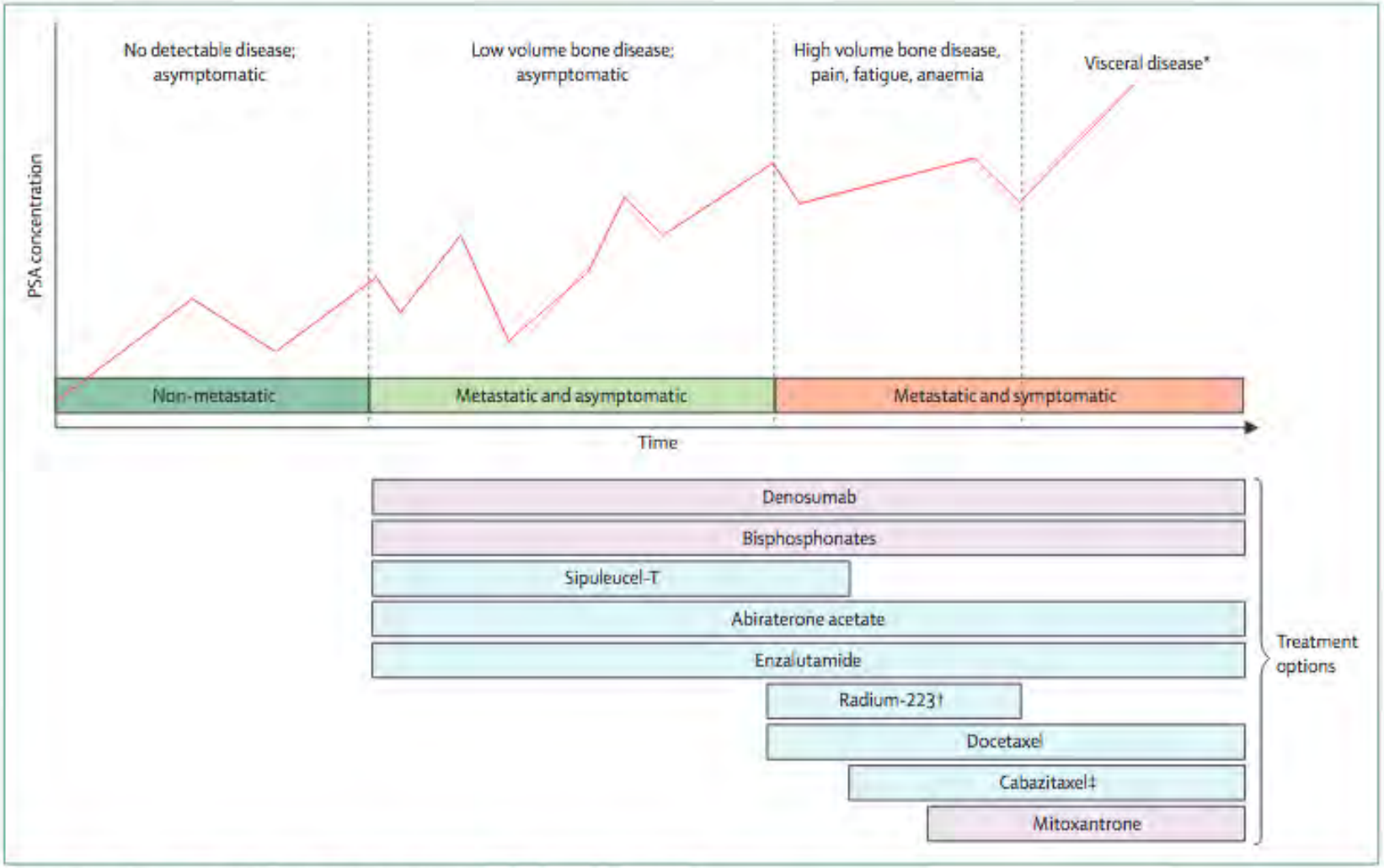


Figure 1: **Typical progression of metastatic castration-resistant prostate cancer**
Treatments licensed for use in the indicated stages as of 2014. PSA=Prostate-specific androgen. The agents in the purple bars have shown no proven survival benefit in randomised clinical trials, whereas those in the blue bars have shown a proven survival benefit in randomised phase 3 trials. *Visceral metastases can also present in the absence of bone metastases. †Ra-223 only in patients with no visceral metastases. ‡Cabazitaxel second-line chemotherapy after progression on docetaxel.

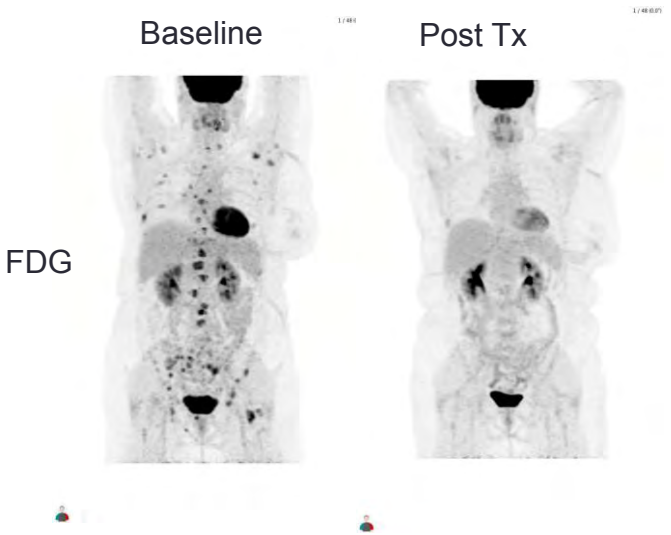
Lorente D. et al., Lancet Oncology 2015; 16: e279–92

Nuclear Medicine 101

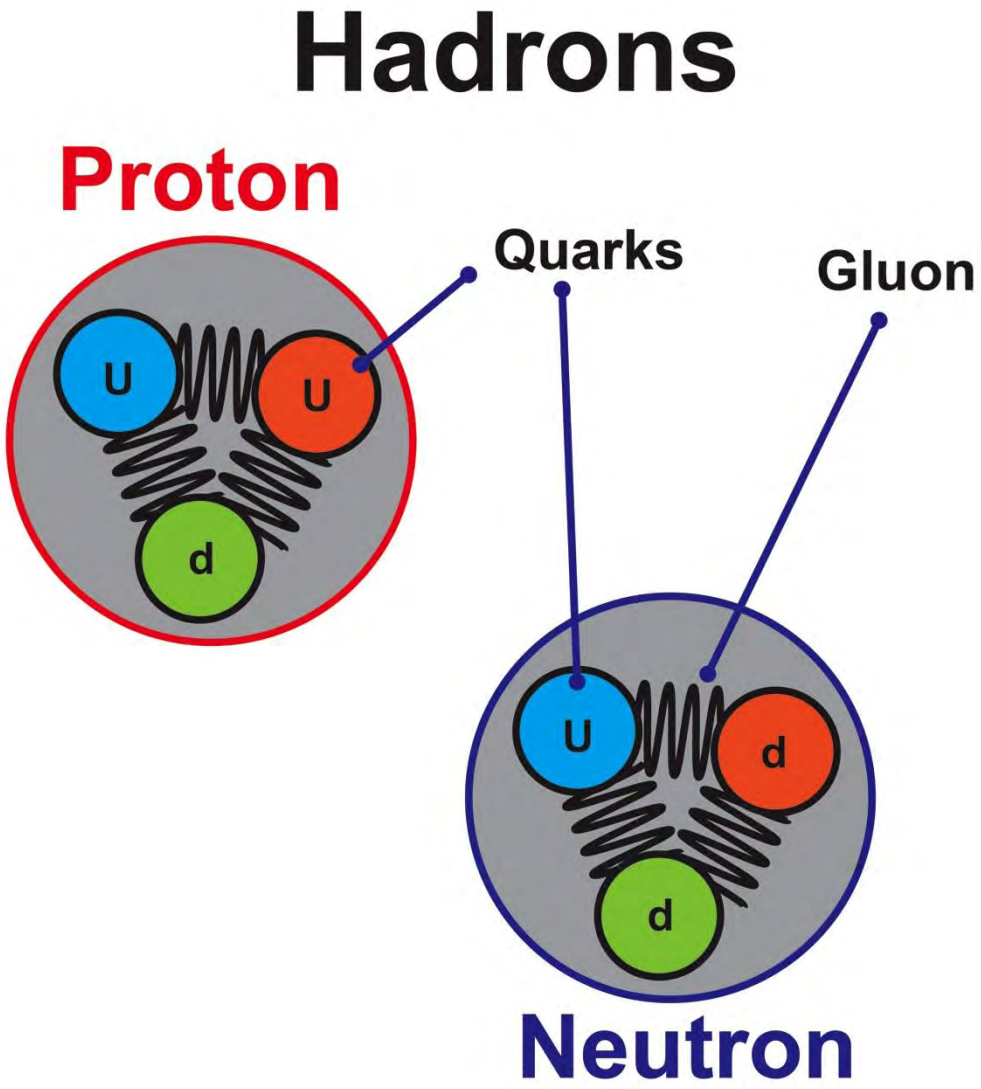
- A radioactive atom is produced in a **nuclear reactor** or **particle accelerator** (cyclotron)
- This radioactive atom is attached to a carrier drug which directs it to the organ or tissue of interest
- The radioactive compound is administered to patients (intravenous, orally, intradermal, inhaled)

^{99m}Tc Bone Scan

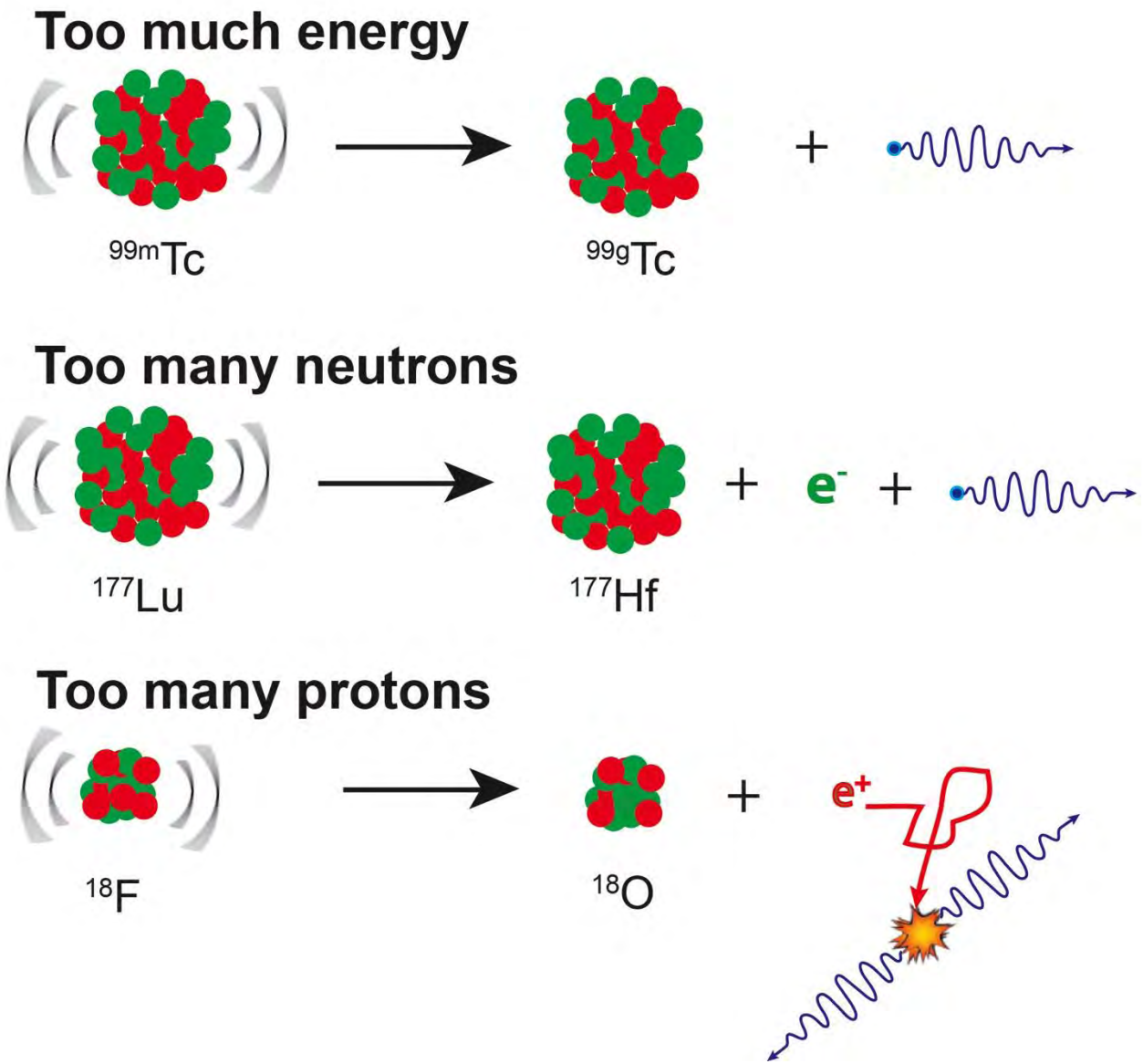
Na^{18}F PET Scan



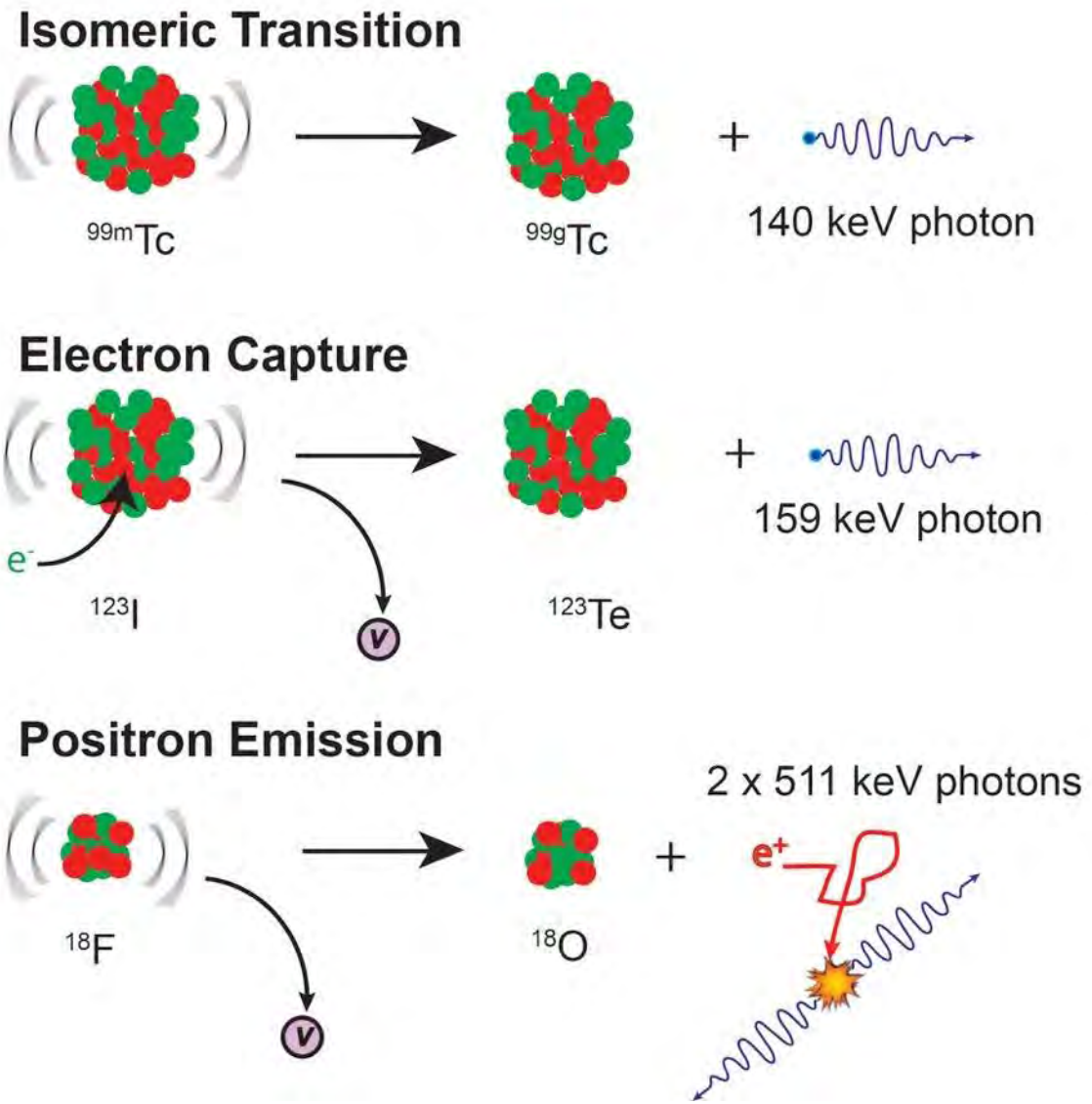
Atoms are made of protons and neutrons



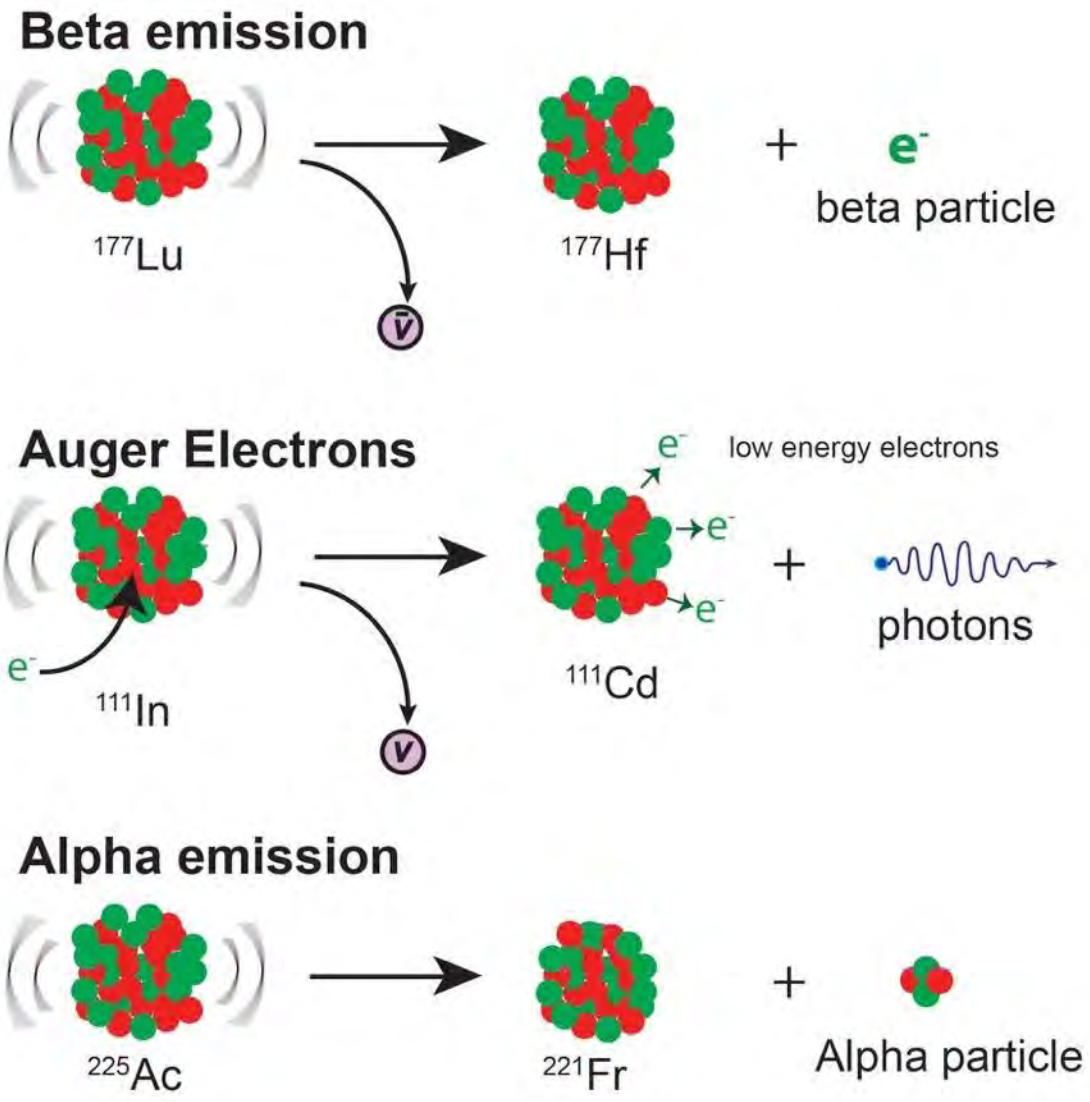
Radioactive atoms are unstable and release energy



Radioisotopes for Diagnosis



Radioisotopes for Therapy



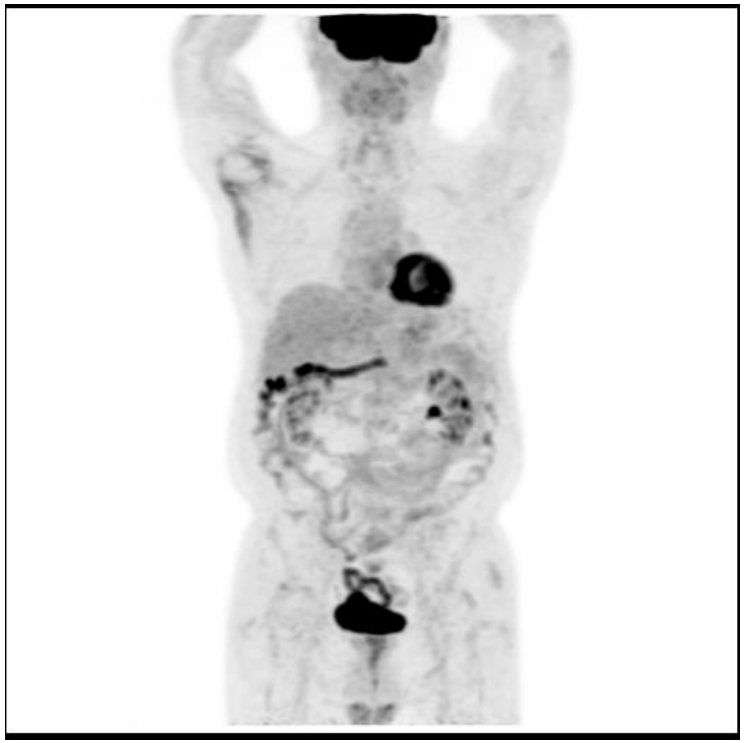
History of Radioisotopes for Cancer Treatment

- First treatment of leukemia in **1936**
- Treatment of thyroid cancer in **1946**
- First report on treatment of bone pain in cancer in **1976**
- Treatment of bone pain in prostate cancer becomes popular in **early 1990's**
- Treatments for neuroendocrine tumours in **1999**
- Lymphoma treatments with radioactive antibodies approved in the US in **2002**
- First report on treatment of bone metastases in prostate cancer with Radium-223 in **2005**

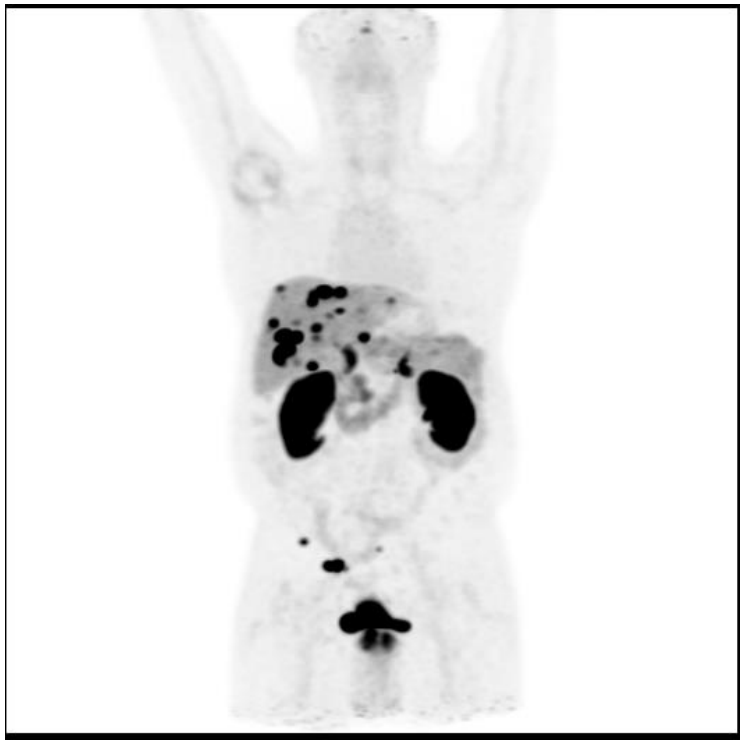
The concept of ‘Theranostics’

Neuroendocrine tumour imaging

- Difficult to localize by CT, MRI or PET/CT scans

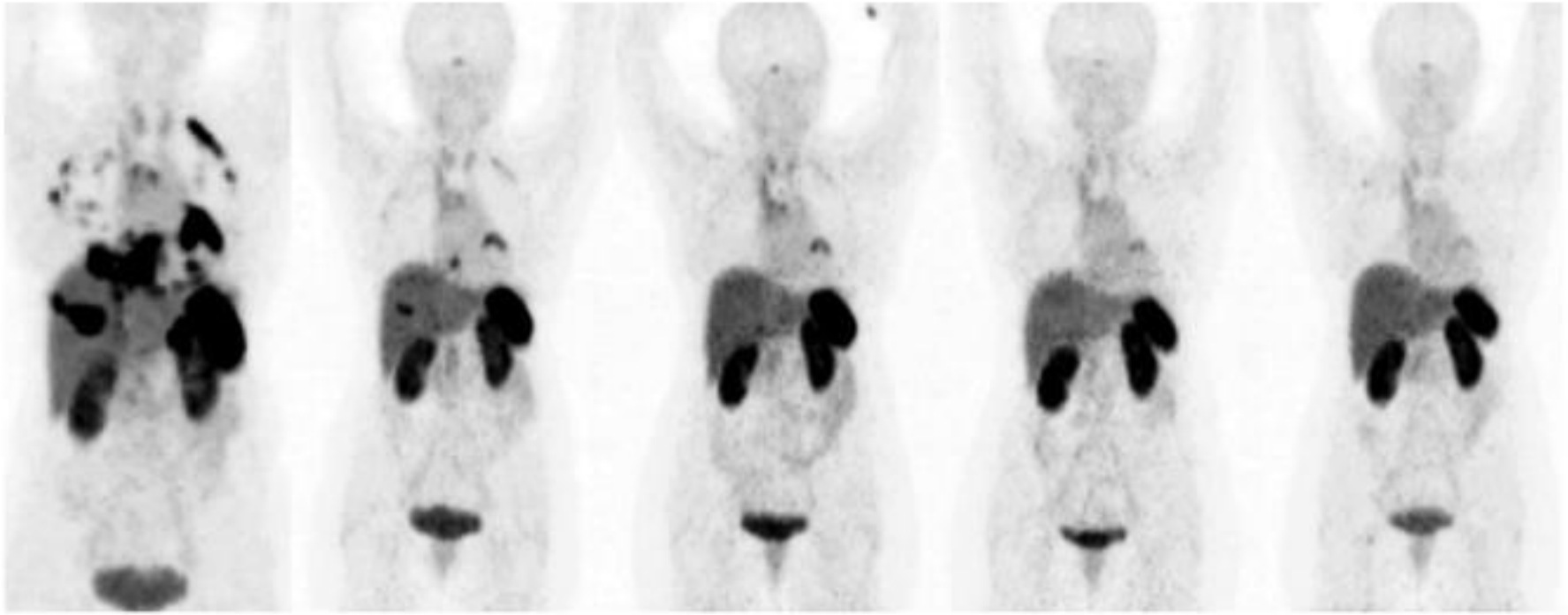


Regular ^{18}F-FDG PET scan



^{68}Ga-DOTATOC PET scan

Radioligand therapy of neuroendocrine tumours



before PRRT-1
4 GBq Y-90
SUV 15.8

3-mo after
PRRT-1
SUV 8.4

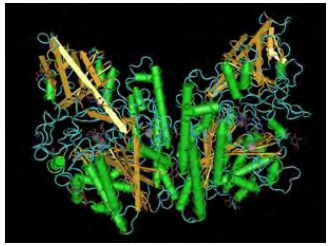
before PRRT-2
4.5 GBq Lu-177
SUV 9.3

before PRRT-3
5.5 GBq Lu-177
SUV 6.9

18-mo after
PRRT-3
SUV 3.4

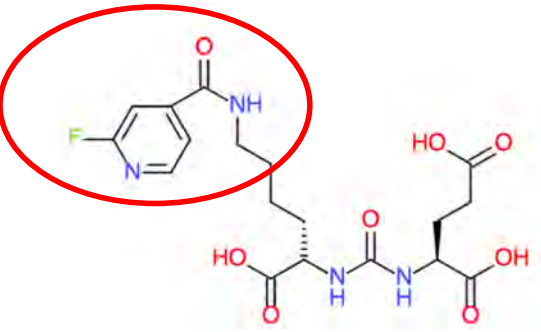
Rosch F, Baum RP. Dalton Trans., 2011, 40, 6104-6111

Prostate Specific Membrane Antigen (PSMA)

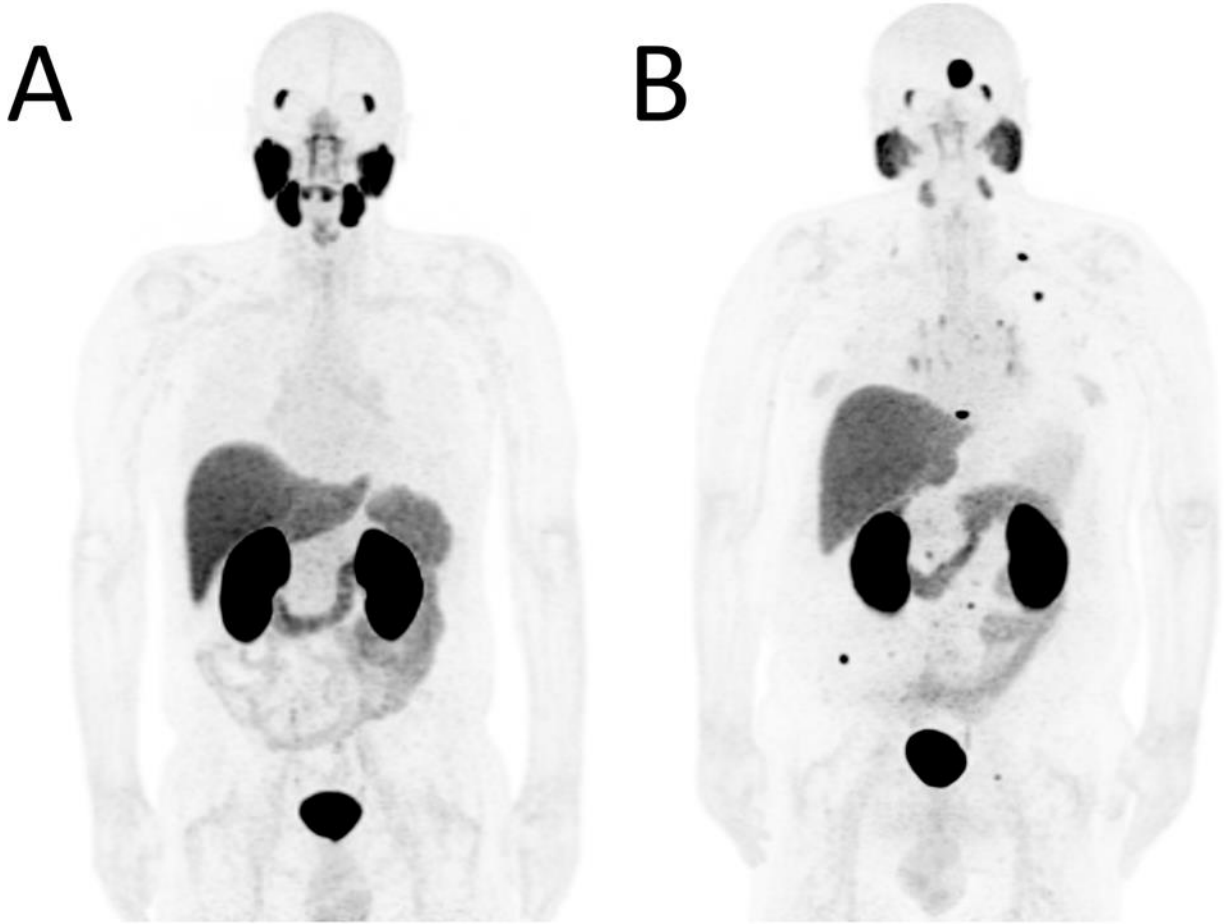


- Protein expressed on prostate cancer cells
- Increased amounts of this protein associated with more aggressive disease
- Higher levels when cancer become unresponsive to androgen deprivation
- The protein is also known by other names
- Was studied for its role in brain damage
- Chemical inhibitors developed to reduce brain damage after stroke

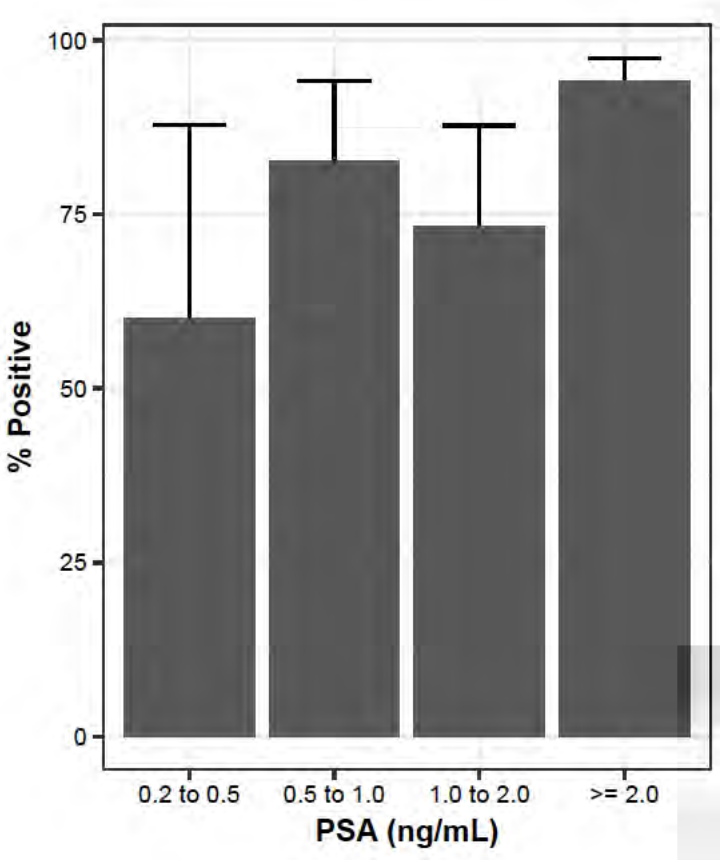
PSMA imaging at BC Cancer



^{18}F-DCFPyL

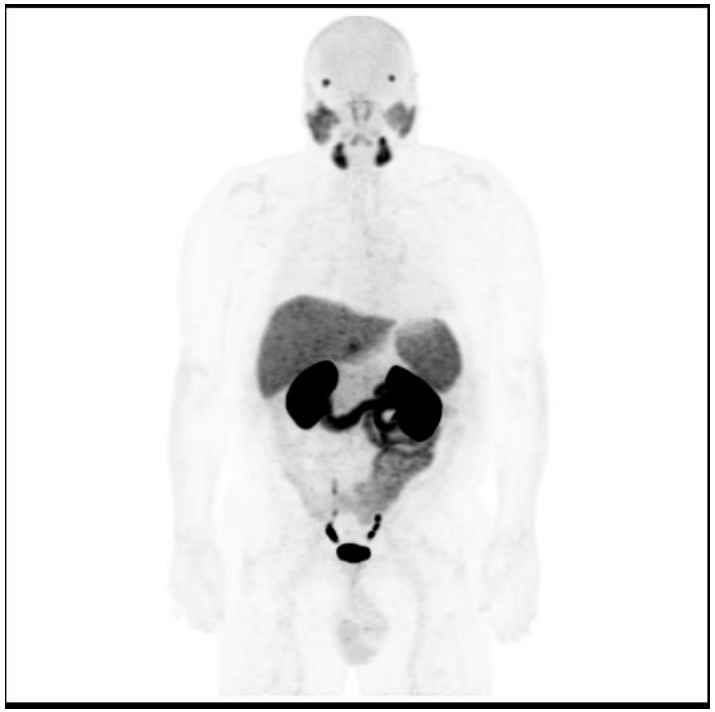


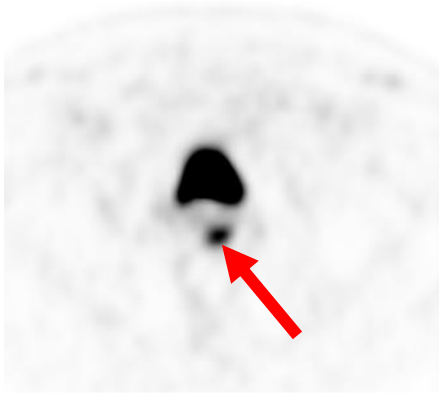
Detection of recurrent prostate cancer BC Cancer experience



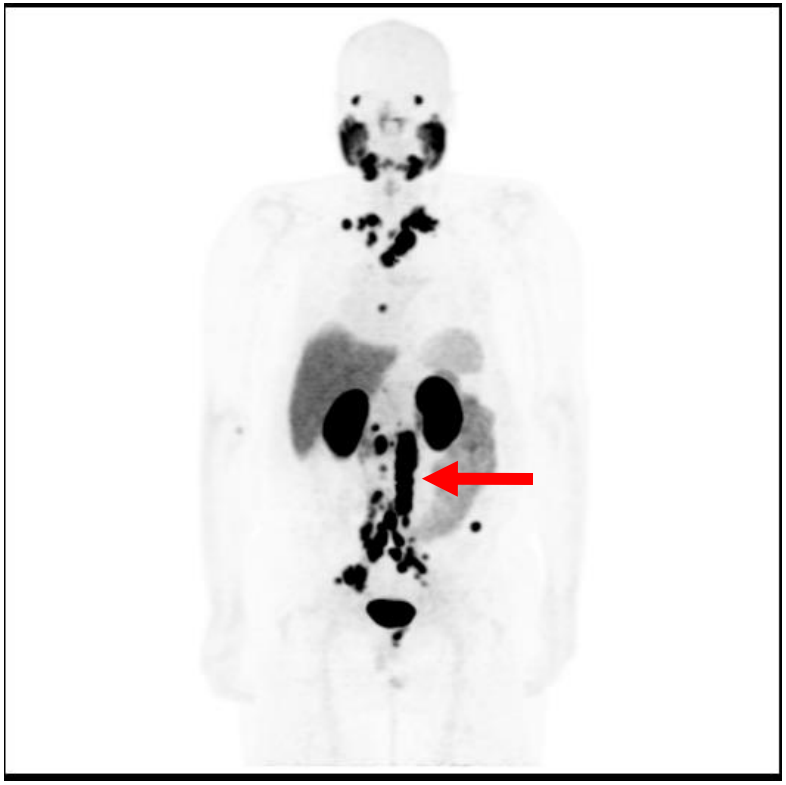
Data from interim analysis of first 200 subjects

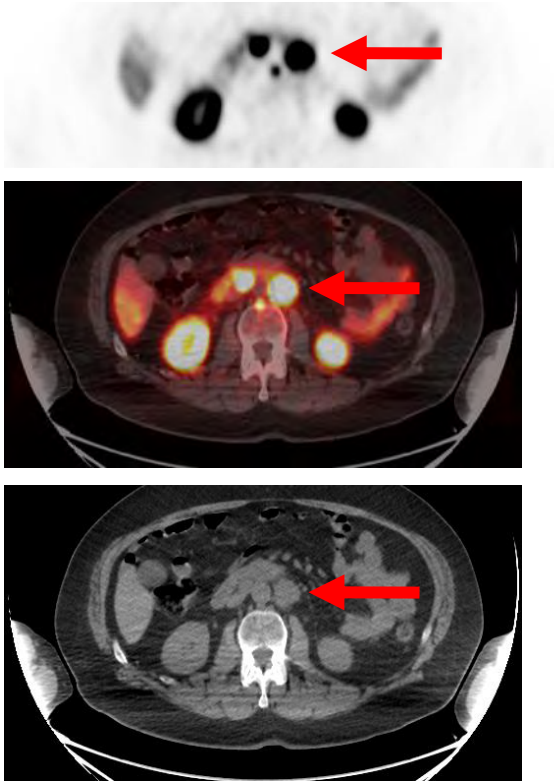
Local recurrence post brachytherapy





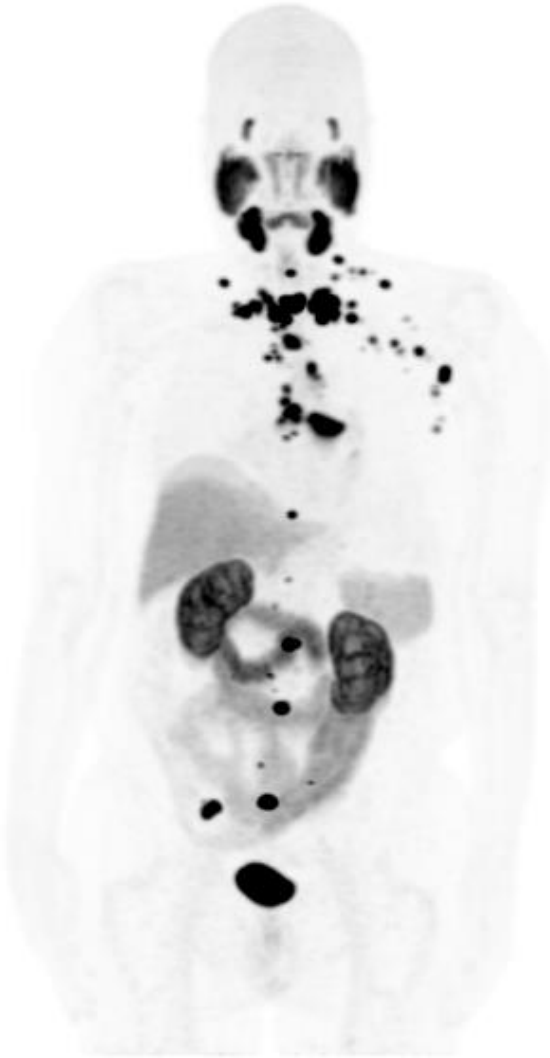
Metastatic recurrence





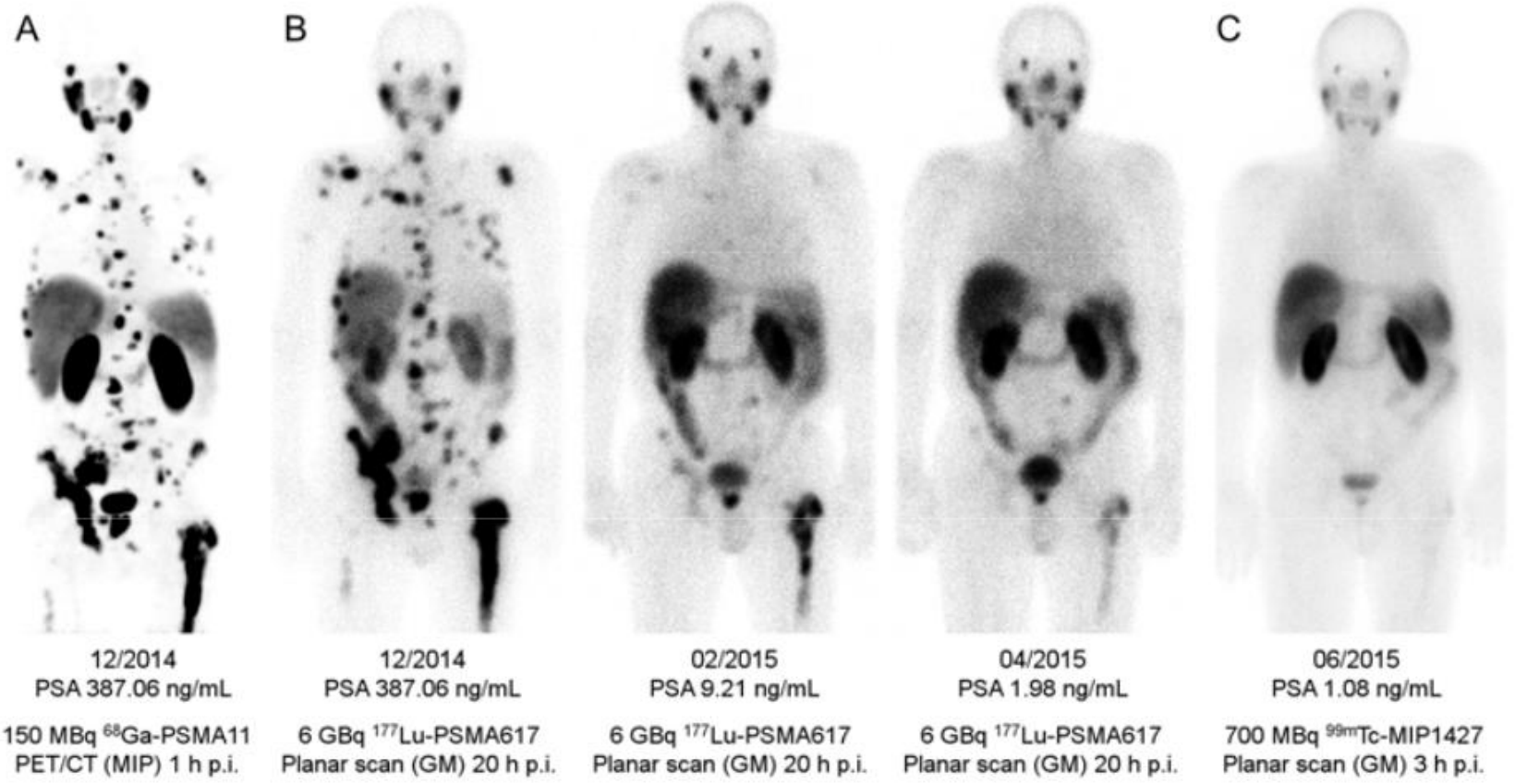
Progression of prostate cancer

Baseline



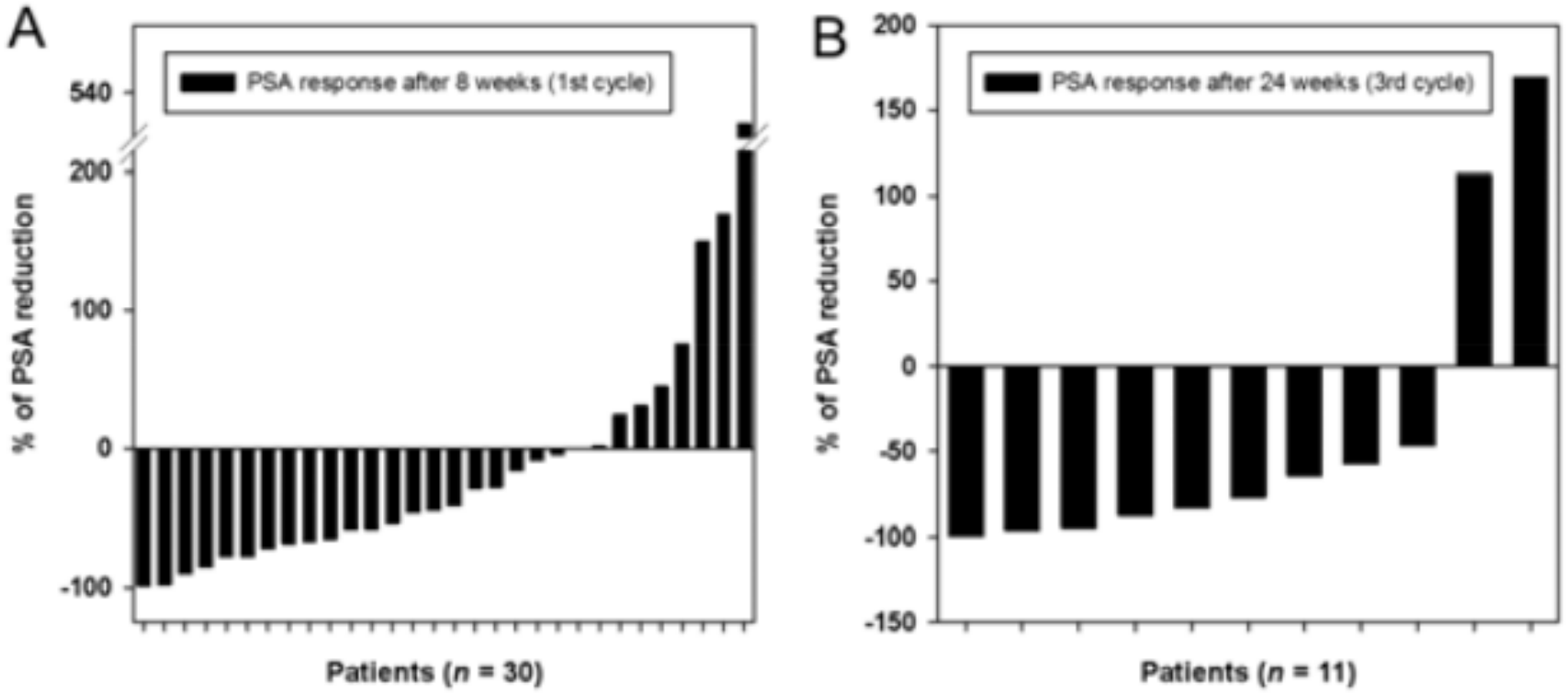
8 months later

Treatment of prostate cancer with ^{177}Lu-PSMA617



Krachtowil et al., J Nucl Med. 2016 Mar 16. pii: jnumed.115.171397. [Epub ahead of print]

Response with ^{177}Lu-PSMA



Krachtowil et al., J Nucl Med. 2016 Mar 16. pii: jnumed.115.171397. [Epub ahead of print]

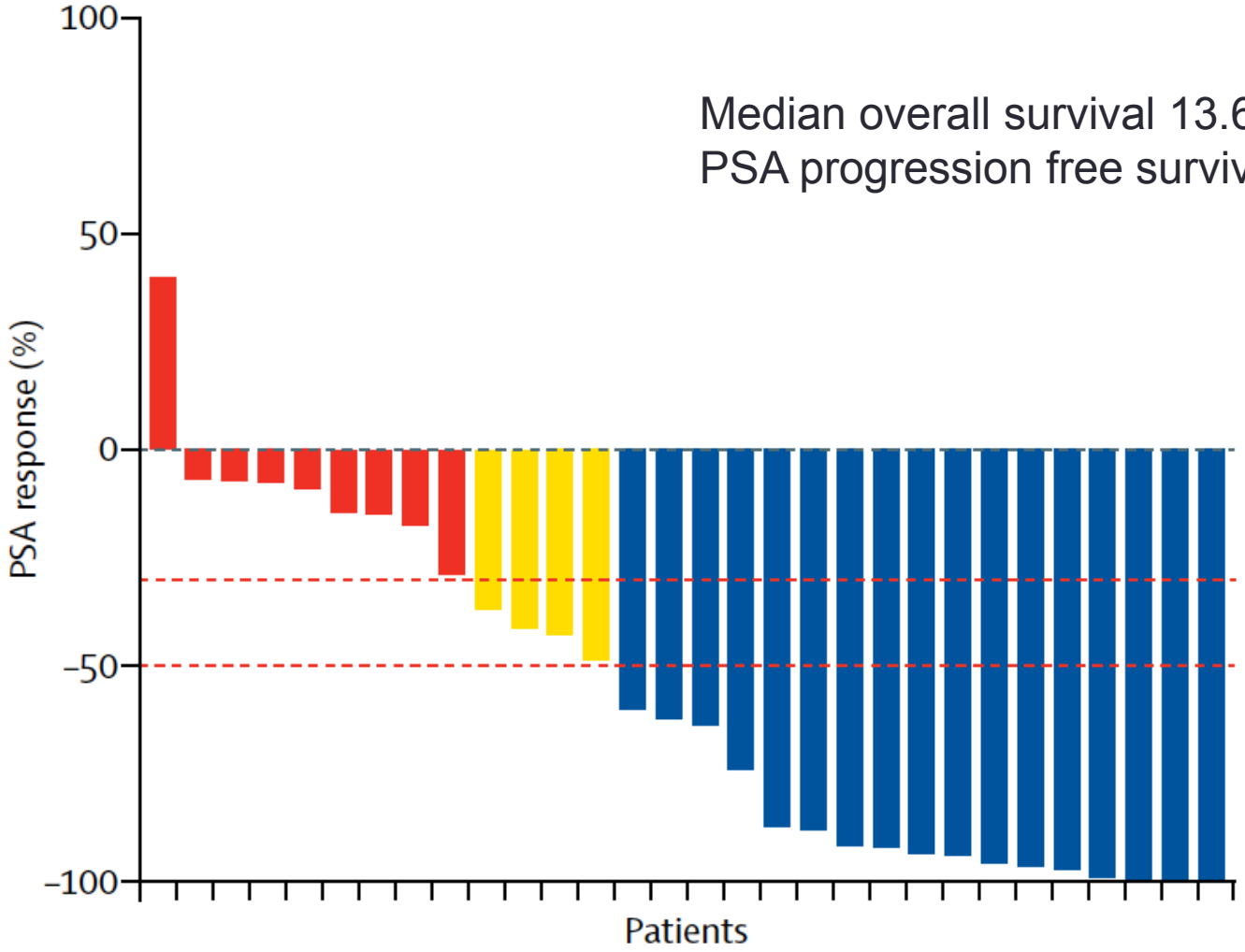
Turning point

[^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study

Michael S Hofman, John Violet*, Rodney J Hicks, Justin Ferdinandus, Sue Ping Thang, Tim Akhurst, Amir Iravani, Grace Kong, Aravind Ravi Kumar, Declan G Murphy, Peter Eu, Price Jackson, Mark Scalzo, Scott G Williams, Shahneen Sandhu*

Lancet Oncol. 2018 Jun;19(6):825-833

Best PSA response



Median overall survival 13.6 months
PSA progression free survival 7.6 monts

Lancet Oncol. 2018 Jun;19(6):825-833

Studies with PSMA radioligand therapy in Canada

- Phase III study sponsored by Endocyte (recently acquired by Novartis) – Vision trial
- Randomized phase II study funded by Prostate Cancer Canada and the BC Cancer Foundation
- Phase II study with personalized dosimetry for ^{177}Lu-PSMA
- Phase I/II study with ^{225}Ac-PSMA

Endocyte study – Vision Trial

- Randomized study of 750 men worldwide
- Patients with metastatic castration-resistant prostate cancer
- Positive PET scan with ^{68}Ga-PSMA-11
- Must have received prior novel androgen axis drug (abiraterone or enzalutamide)
- Adequate bone marrow and kidney function
- Must have received one or two taxane based chemotherapy regimen
- 2:1 randomization
  - 2 subjects 177Lu-PSMA-617
  - 1 subject best standard of care/supportive care
- Product manufactured in USA
- Opened in Vancouver in January 2019

Prostate Cancer Canada Trial

- Randomized study of 200 Canadian Men
- Patients with metastatic castration resistant prostate cancer
- Positive PET scan with any PSMA imaging agent (^{18}F or ^{68}Ga)
- Must have received abiraterone or enzalutamide
- Prior docetaxel only allowed in castration sensitive stage
- Adequate bone marrow and kidney function
- 1:1 Randomization
  - Chemotherapy with docetaxel
  - 177Lu-PSMA-617
- Crossover allowed
  - Docetaxel followed by ^{177}Lu-PSMA-617 upon progression
  - ^{177}Lu-PSMA-617 followed by docetaxel upon progression

Prostate Cancer Canada Trial (cont.)

- Data collection:
  - Imaging to measure radiation dose to tumours and normal organs
    - 2 nuclear medicine scans after first treatment
      - 18-24 hours
      - 72-96 hours
  - Quality of life data
  - Serial measurements by imaging (CT, bone scan) and blood sampling
  - Circulating cell free DNA
  - Baseline and post-treatment PSMA PET/CT scan
- Health economics analysis
  - Cost per quality adjusted life year
  - Cost of treatment

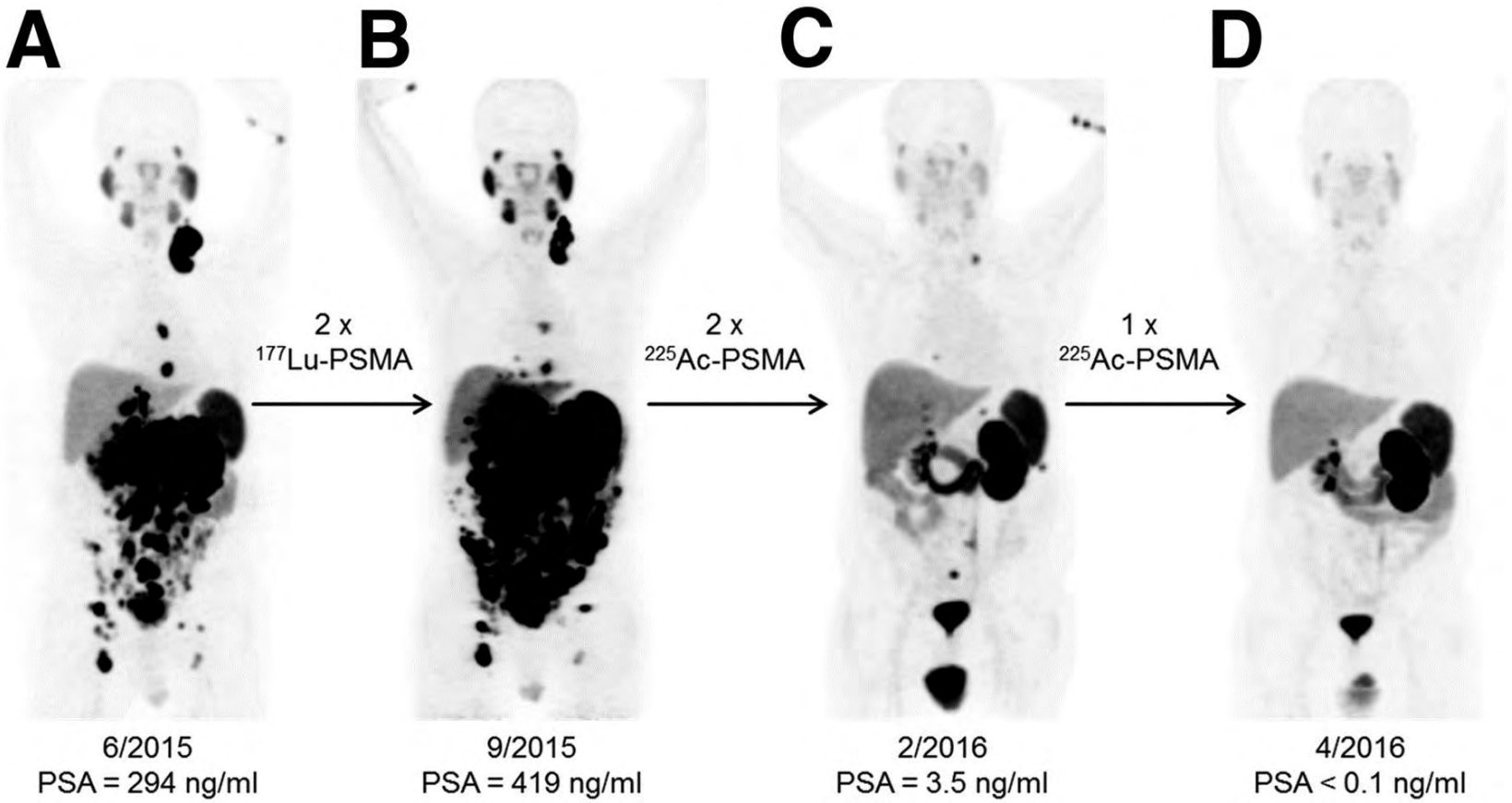
Personalized dosimetry of 177Lu-PSMA

- First treatment dose adjusted to lean body mass
- Personalized dosimetry assessment using nuclear medicine scans
- Subsequent doses adjusted to maximize tumour dose within tolerance of kidneys and salivary glands
- 40 subjects planned for this study

- To be determined:
  - Choice of carrier molecule (PSMA-617, PSMA I&T, other)
  - Preliminary phase I study may be necessary for new molecule

Phase I/II study of ^{225}Ac-PSMA

- Study to determine tolerated dose and establish safety
- Initial dose escalated stepwise until tolerance is established
- Once optimal dose established, confirm with larger number of patients
- Will provide access to potent ^{225}Ac in Canada
- To be determined:
  - Choice of carrier molecule
  - Implementation GMP production
  - Determination of purity of ^{225}Ac supply



68Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting 177Lu-PSMA-617 presented progression (B).

Clemens Kratochwil et al. J Nucl Med 2016;57:1941-1944

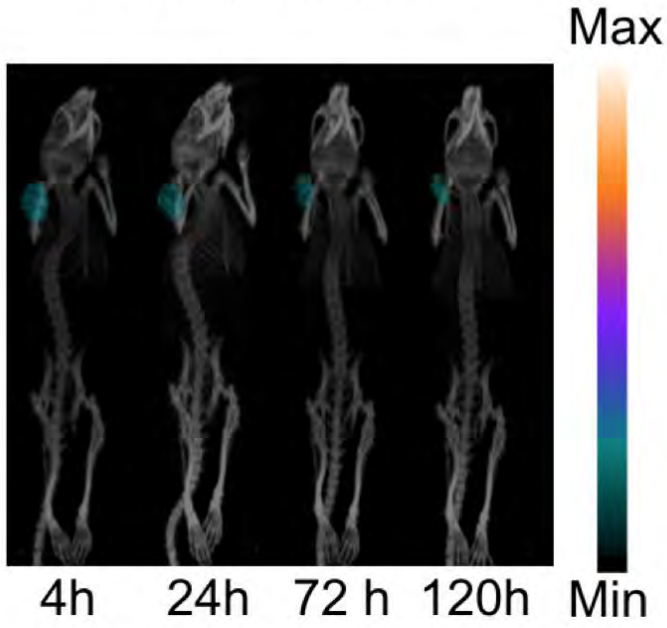
JNM The Journal of NUCLEAR MEDICINE

Timelines

- Vision trial – accrual open in Vancouver
- PCC trial – currently working with Canadian Clinical Trial Group to implement across Canada – target June 2019
- Personalized dosimetry trial – target September 2019 if PSMA-617 available from Endocyte – may be delayed if another compound is selected
- Phase I/II ^{225}Ac trial
  - Depends on compound selection
  - GMP manufacturing progress
  - Target early 2020

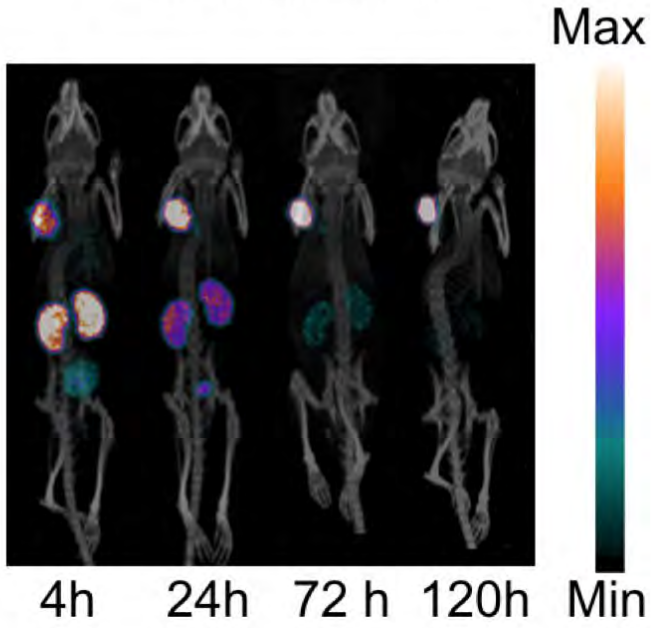
Progress in the lab

^{177}Lu-PSMA-617



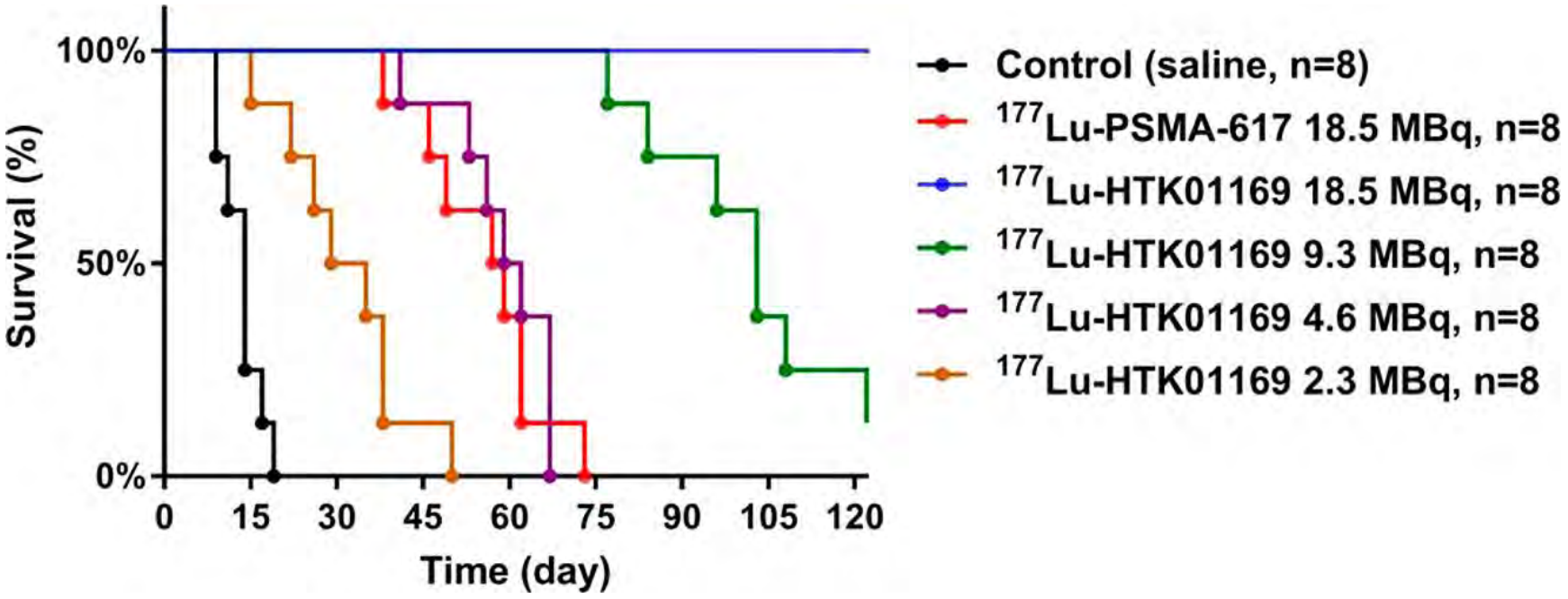
LNCaP Tumor uptake:
4 h: 14.5 ± 1.83 %ID/g
24 h: 10.9 ± 3.30 %ID/g
72 h: 7.80 ± 3.69 %ID/g
120 h: 7.91 ± 2.82 %ID/g

^{177}Lu-HTK01169



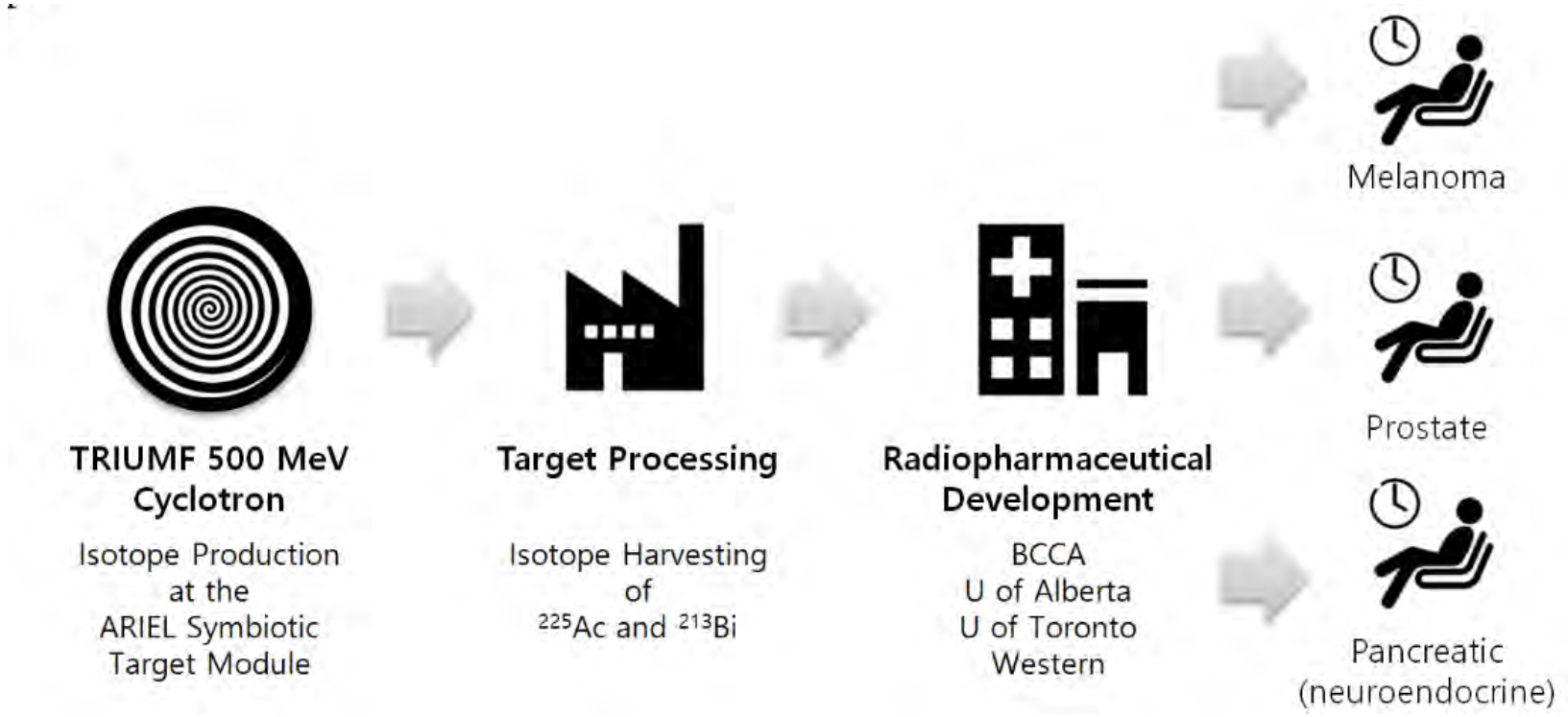
LNCaP Tumor uptake:
4 h: 27.2 ± 5.56 %ID/g
24 h: 55.9 ± 12.5 %ID/g
72 h: 53.6 ± 8.06 %ID/g
120 h: 56.4 ± 13.2 %ID/g

Improved Therapeutic Compounds

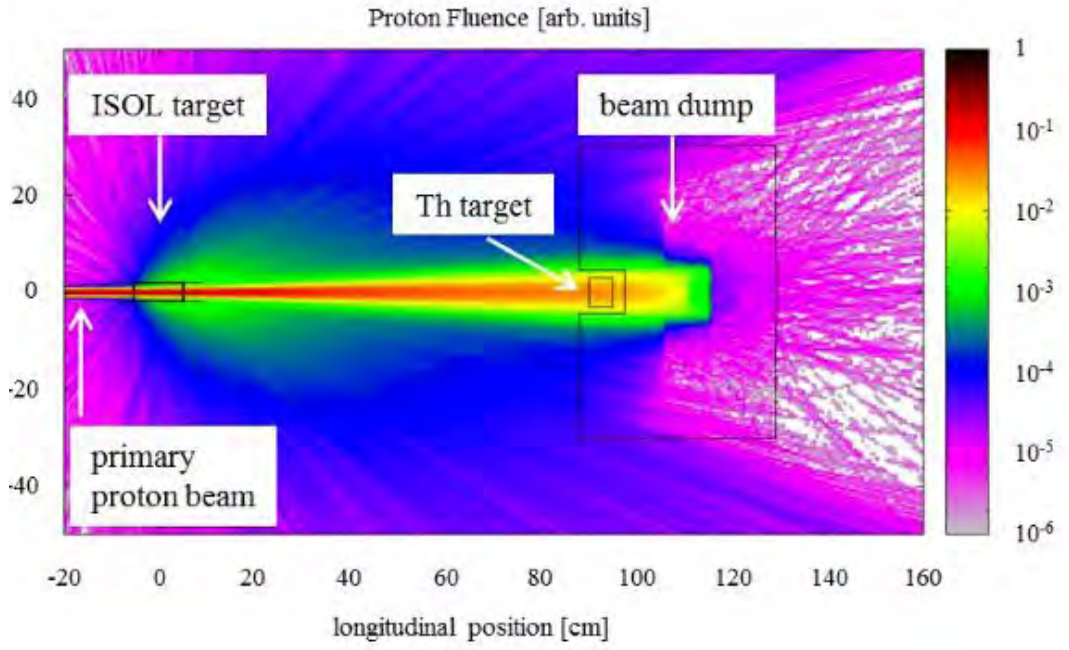


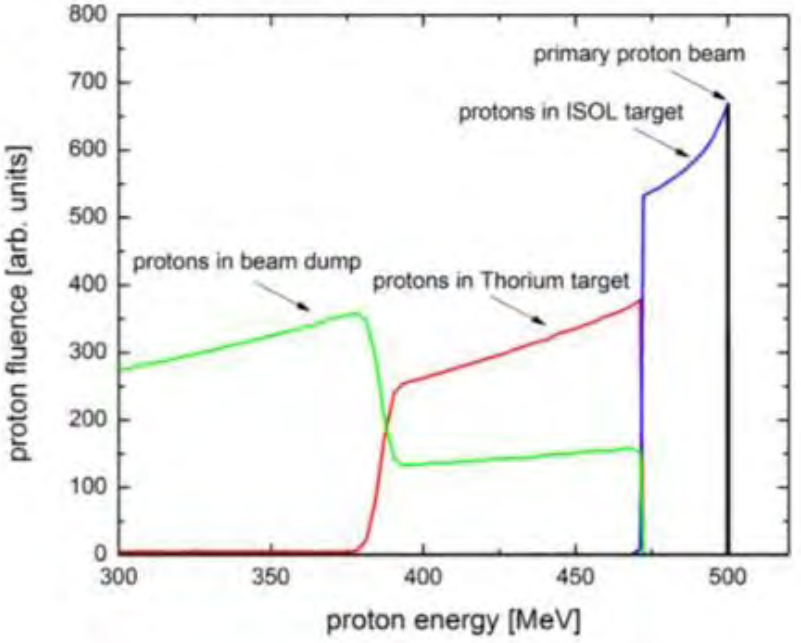
The next frontier: Rare Isotopes for Cancer Therapy

- Newly funded $9.8M addition to TRIUMF's Advanced Rare Isotope Laboratory (ARIEL)



A symbiotic target for alpha emitter production





Potential production yield of 1940 mCi of ^{225}Ac per year
Typical patient dose for PSMA therapy is $\simeq$ 0.2 mCi

Institute for Advanced Medical Isotopes (IAMI)

- New Institute to be built and operated by TRIUMF
- Joint project with BC Cancer and UBC
- Installation of a new cyclotron (backup for BC Cancer)
- Isotope processing and radiochemistry laboratories
- New BC Cancer laboratory for Radionuclide Therapy manufacturing and development

Functional Imaging Investigators

- Radiochemistry: Kuo-Shyan Lin, PhD
- Medical Physics: Arman Rahmim, PhD
- Clinical: Don Wilson, MD
  Kim Chi, MD
  Jonathan Loree, MD
- Translational/Clinical: François Bénard, MD
- Key collaborators: David Perrin, PhD (UBC)
  Chris Orvig, PhD (UBC
  Paul Schaffer, PhD (TRIUMF)
  Rob Britton, PhD (SFU)
- Research Associates and post-docs
  - Chengcheng Zhang, PhD (biochemistry and molecular pharmacology)
  - Zhengxing Zhang, PhD (radiochemistry)
  - Julie Rousseau, PhD (radiolabeled antibodies and biology)
  - Hsiou-Ting Kuo, PhD (radiochemistry)
  - Joseph Lau, PhD (molecular biology and pharmacology, now at NIH)
  - Carlos Uribe, PhD (medical physics)
  - Jason Crawford, PhD (medical physics)
  - Aron Roxin, PhD (radiochemistry)

Students and Technical Staff

- Marin Simunic (MSc candidate)
- Milena Colovic (PhD candidate)
- Daniel Kwon (MD/PhD candidate)
- Etienne Rousseau, MD (fellow)
- Helen Merkens (lab manager)
- Jutta Zeisler (molecular biology)
- Nadine Colpo (preclinical imaging)
- Navjit Hundal (preclinical imaging)
- Katrin Gitschtaler (animal technician)
- Guillaume Langlois (radiochemistry technician)
- Jinhe Pan (radiochemistry technician)
- Ivica Bratanovic (MSc candidate)
- Teresa Law (MSc candidate)
- Shreya Bendre (MSc candidate)
- Hayley Corbett and Iulia Dude, clinical research manager and coordinator
- And the cyclotron (3 FTE), radiochemistry production (5 FTE) and quality assurance (3 FTE) teams