TRIUMF

Canada's national laboratory
for particle and nuclear physics
and accelerator-based science

Medical Isotope Production at TRIUMF and future collaboration with MEDICIS-PROMED

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Life Sciences Division

ICTR-PHE 2016, Geneva, 19.02.2016

TRIUMF

Overview

Part I: TRIUMF

- General presentation
- Life Sciences Division

Part II: Research aims in the Life Sciences Division

- Target development & Isotope production
- Radiopharmaceuticals development

Part III: Medicis-Promed

- New bifunctional (fluorescent/radioactive) bioligands for ovarian cancer

TRIUMF

Canada's national laboratory for particle and nuclear physics

A Fleet of Cyclotrons:

1. 540 MeV: commissioned in 1976
2. CP42: up to 42 MeV and 200 μA, installed 1980
3. TR30-1: up to 30 MeV and 900 μA, installed 1990
   – First TR30 designed, assembled by TRIUMF. Components manufactured by EBCO, commissioned by TRIUMF
4. TR30-2: up to 30 MeV and 1000 μA, installed 2003
   – Manufactured and installed by EBCO, commissioned by TRIUMF
5. TR13: up to 13 MeV and 25 μA, installed 1986
   – Capable of ^{11}C, ^{13}N, ^{18}F, ^{44}Sc, ^{52}Mn, ^{55}Co, ^{64}Cu, ^{68}Ga, ^{86}Y, ^{89}Zr (solid, liquid and gas targets)
6. TR24: up to 24 MeV and 500+ μA, to be installed
   – Future commercial production of ^{99m}Tc

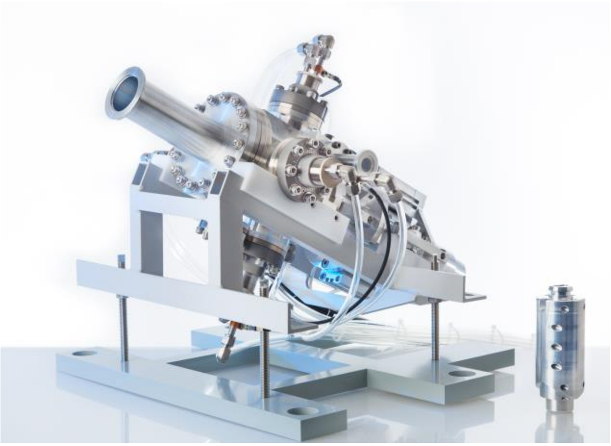
Three pillars of Life Sciences at TRIUMF

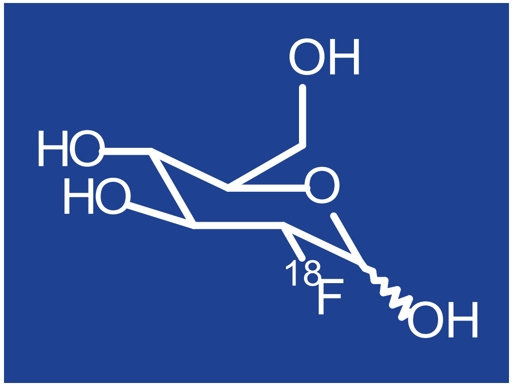
Nuclear Medicine

Accelerator Targets

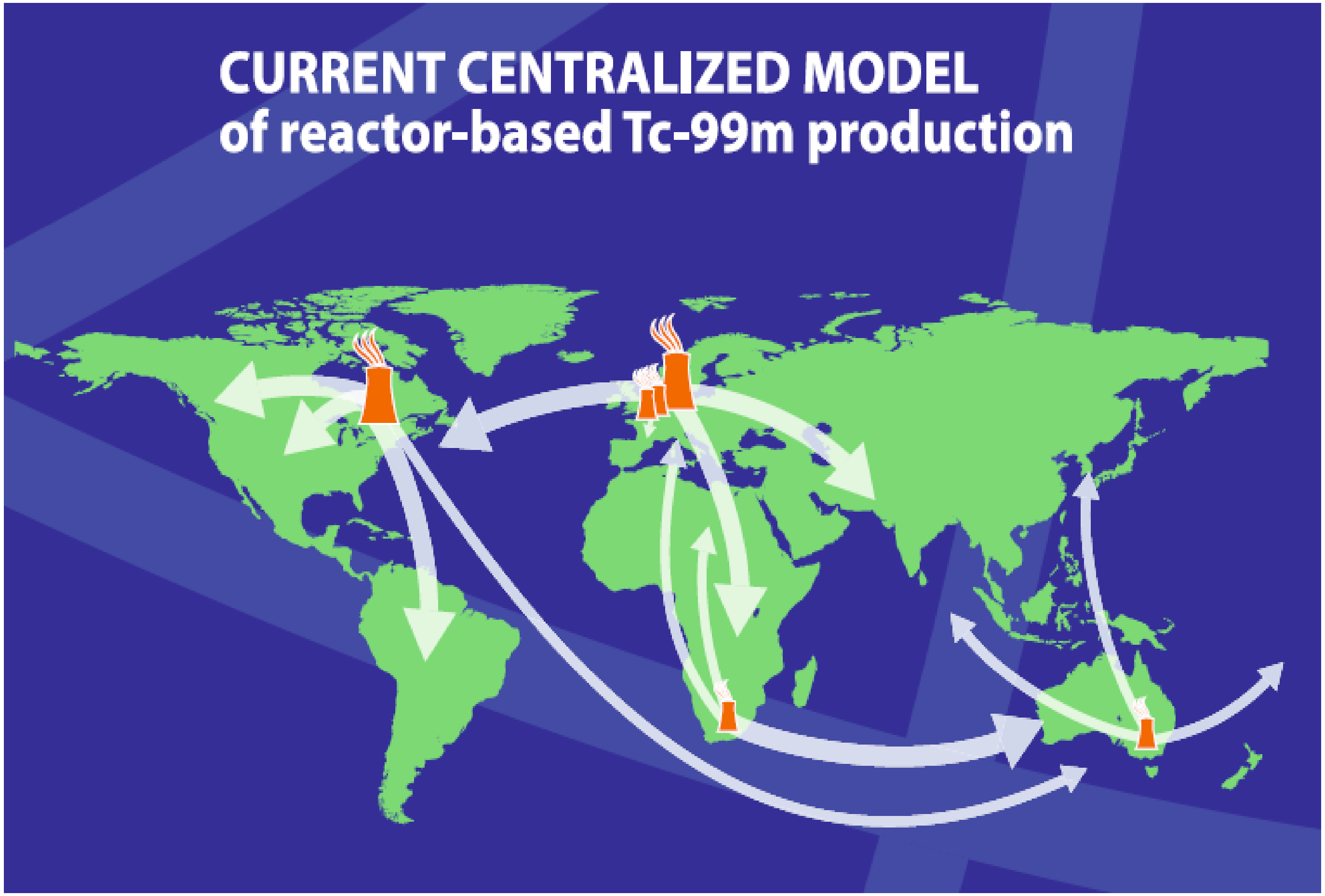
Isotope Production

Radiochemistry



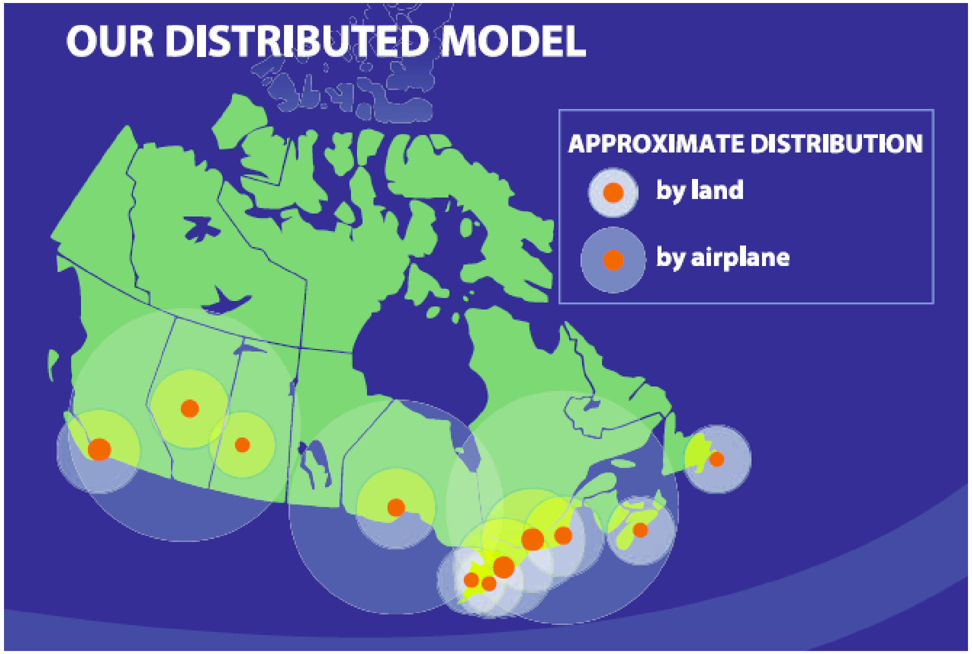


TARGETS &
ISOTOPE PRODUCTION



- ✓ 30-40% of global ^{99}Mo is obtained from NRU in Canada.
- ✓ ^{99}Mo at NRU goes off-line Oct. 2016

ITAP Project – A Decentralized Model

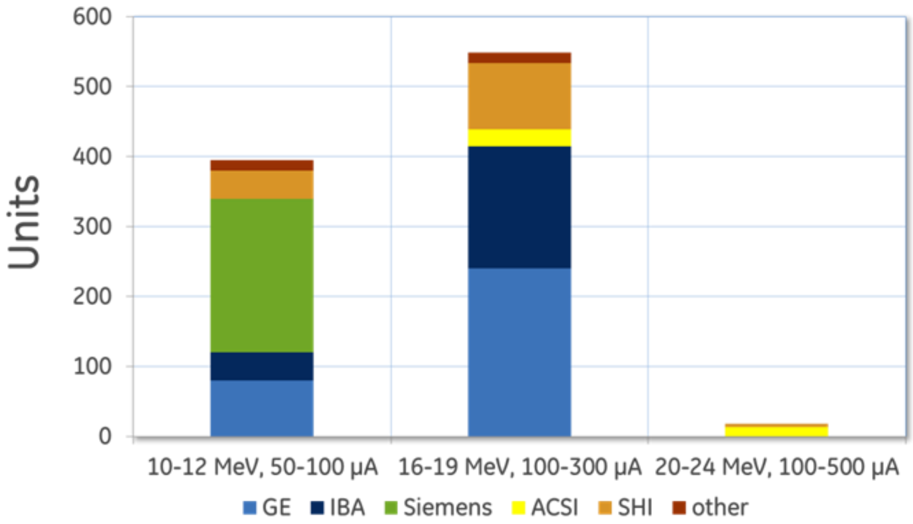


HYPOTHESIS:

Future production will be from variety of sources and market driven

$^{100}Mo(p,2n)^{99m}Tc$

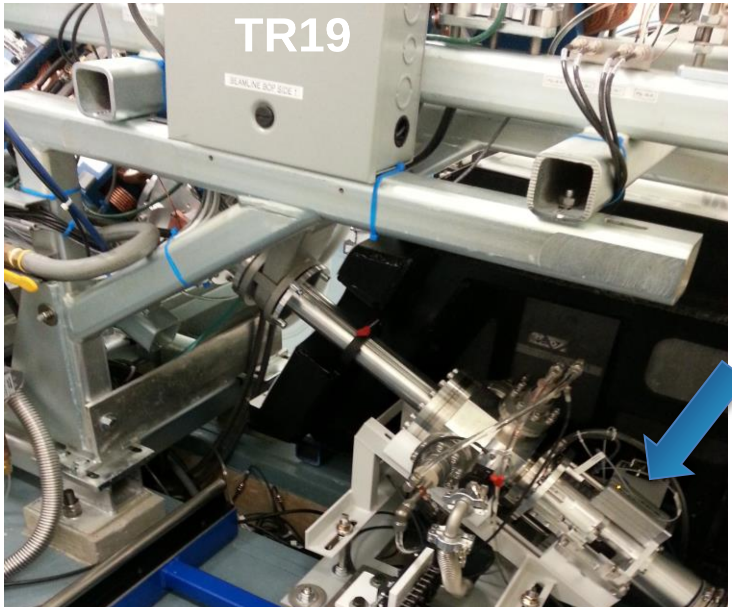
- ✓ Locally produced and locally used
- ✓ Easier to ship than ^{18}F
- ✓ Paradigm well suited to central radiopharmacies
- ✓ Multiple cyclotrons can provide redundancy
- ✓ Synergy between PET & SPECT
  - – Utilize existing PET cyclotrons to diversify ^{99m}Tc supply
  - – More cyclotrons will facilitate the production
- ✓ Complementary to Linac/other sources of ^{99}Mo
  - – Generators freed up for remote areas

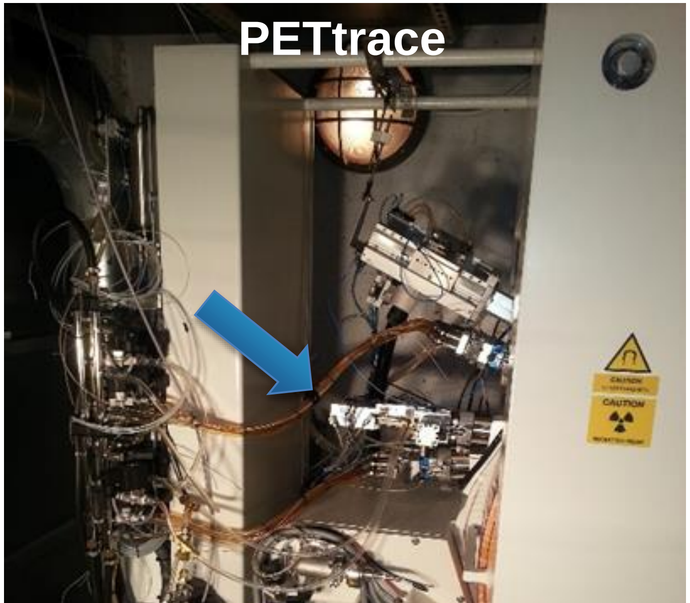


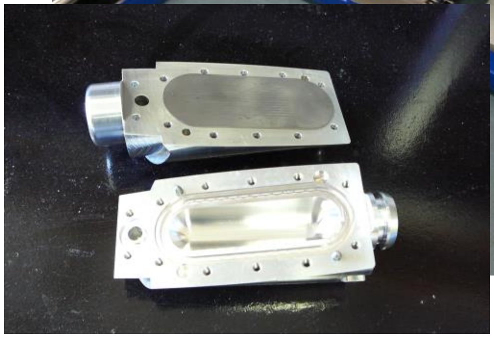
Schaffer et al. Phys. Proc. 2015, 66, 383

TRIUMF

5 Years, 4 Cyclotrons, 3 Cities, 2 Provinces, 1 Effort





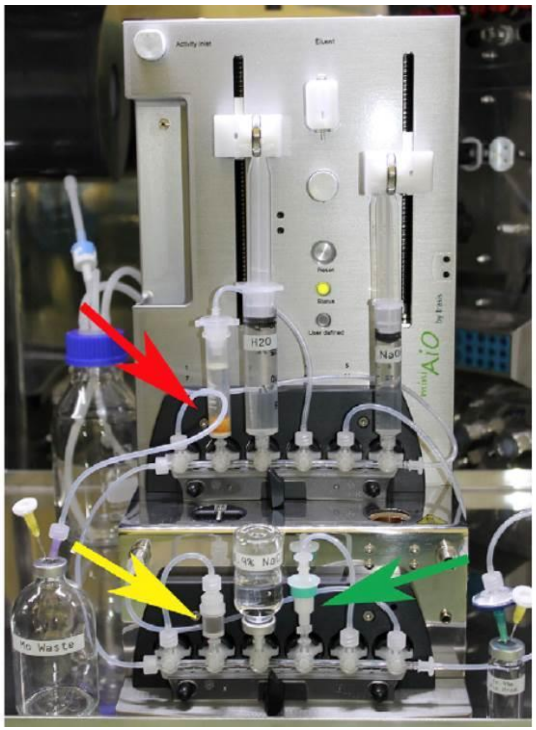


TR19
18 MeV, 300 μA
Theoretical 15.4 Ci (6h)
Achieved 13.9 Ci (@ 240 μA)

TR30 (@24 MeV)
24 MeV, 500 μA
Theoretical 39 Ci (6h)
Achieved ~32 Ci (@ 450 μA)

GE PETtrace
16.5 MeV, 130 μA
Theoretical 4.9 Ci (6h)
Achieved 4.7 Ci

PURIFICATION PARAMETERS OF ^{99m}TC PRODUCED BY CYCLOTRON IRRADIATION OF ^{100}MO



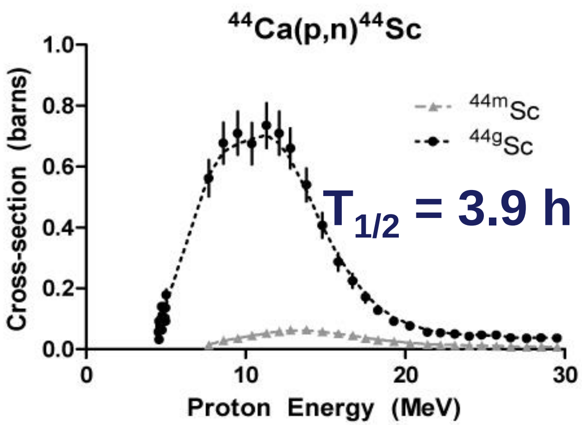
- ✓ SPE-based method
  - Original: DowexTM vs. ABEC
  - New alternative resin: ChemMatrixTM
- ✓ Process time: complete in < 90 min
- ✓ Efficiency range: 92.7 ± 1.1%
- ✓ Radiochemical purity: > 99.99% TcO_4^-
- ✓ Trace analysis: < 10 Bq Mo-99, < 5 ppm Al^{3+}, non-Tc impurities removed
- ✓ Disposable fluid path for GMP
- ✓ Shelf life: 18 h
- ✓ Maximum increase in patient dose < 10%
- ✓ Routine recovery of ^{100}Mo > 99% (acidic precipitation & thermal decomposition)

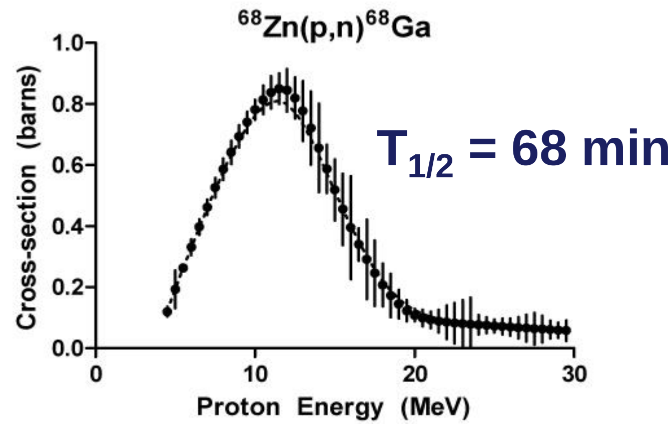
1) Morley et al. Nuc. Med. Biol. 2012, 39, 551
2) Bénard et al. J. Nuc. Med. 2014, 55, 1017
3) Bénard et al. J. Nuc. Med. 2014, 55, 1911
4) Hou et al. Phys. Med. Biol. 2016, 61, 542

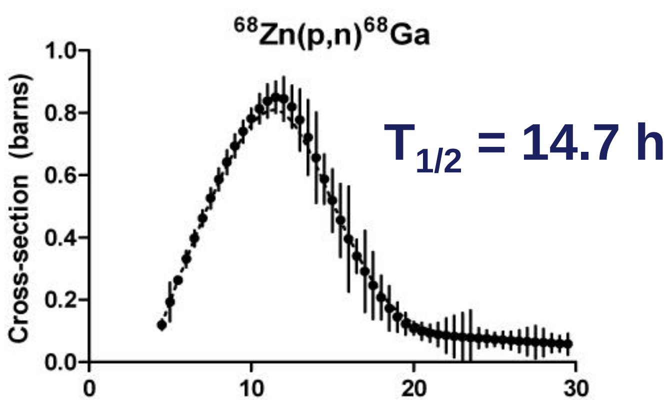
Specific Interests:

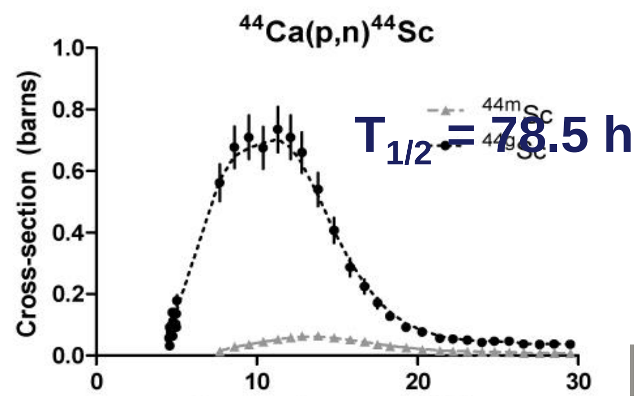
1. $^{94}Mo(p,n)^{94m}Tc$ ($T_{1/2}$ = 52.5 min)
2. $^{44}Ca(p,n)^{44}Sc$ ($T_{1/2}$ = 3.9 h)
3. $^{68}Zn(p,n)^{68}Ga$ ($T_{1/2}$ = 68 min)
4. $^{86}Sr(p,n)^{86}Y$ ($T_{1/2}$ = 14.7 h)
5. $^{89}Y(p,n)^{89}Zr$ ($T_{1/2}$ = 78.5 h)

- TRIUMF: TR13 (13 MeV, 20 μA), standard water target
- BCCA: TR19 (19 MeV, 300 μA), large volume water target









HYPOTHESIS:

Established cyclotron centers will be able to obtain research and possibly clinical quantities of various radiometals by irradiating salt solutions

GOALS:

1. Allow broader access to a variety of radiometallic isotopes
2. Production without generators or solid target station
3. Enable faster optimization of vector-isotope pairing

ACCEPTED TRADE-OFF:

Lower production yields in exchange for isotope versatility

Radiometals Liquid Targets – Production summary

Isotope	Production route	Metal salt	Density (g/mL)	Beam current (μA)	Time (min)	Yield (MBq)	Sat. yield (MBq/μA)
^{44}Sc	$^{44}Ca(p,n)^{44}Sc$	$Ca(NO_3)_2$	1.55	7.6	60	5.55 ± 0.22	4.6 ± 0.3
^{68}Ga	$^{68}Zn(p,n)^{68}Ga$	$Zn(NO_3)_2$	1.65 1.56	6.8 7.0	60 60	275 ± 1 480 ± 30	68 ± 5 141 ± 6
^{86}Y	$^{86}Sr(p,n)^{86}Y$	$Sr(NO_3)_2$	1.43	4.6	60	7.4 ± 0.5	31 ± 1
^{89}Zr	$^{89}Y(p,n)^{89}Zr$	$Y(NO_3)_3$	1.49	7.3	60	32 ± 2	360 ± 9
^{94m}Tc	$^{94}Mo(p,n)^{94m}Tc$	$(NH_4)_6Mo_7O_{24}$	1.66	5.0	60	110 ± 20	40 ± 6

1) Hoehr et al. Applied Radiat. Isot. 2012, 70, 2308
2) Hoehr et al. Nuc. Med. Biol. 2014, 41, 401
3) Oehlke et al. Nuc. Med. Biol. 2015, 42, 842

Radiometals Liquid Targets – Isolation & purification

Isotope	Production route	Column 1	Column 2	Final Eluate		
				Recovery (%)	Volume (mL)	Eluent
^{44}Sc	$^{44}Ca(p,n)^{44}Sc$	DGA	-	88 ± 6	2.5	HCl (0.05 M)
^{68}Ga	$^{68}Zn(p,n)^{68}Ga$	AG 50W-X8	DGA	92 ± 8	1.0	H_2O
^{86}Y	$^{86}Sr(p,n)^{86}Y$	DGA	-	99 ± 4	1.0	H_2O
^{89}Zr	$^{89}Y(p,n)^{89}Zr$	Hydroxamate resin	-	82 ± 5	0.75	Oxalic acid (1M)
^{94m}Tc	$^{94}Mo(p,n)^{94m}Tc$	ABEC-2000	SCX/Alumina	70.9 ± 0.7	6.0	Saline

1) Hoehr et al. Applied Radiat. Isot. 2012, 70, 2308
2) Hoehr et al. Nuc. Med. Biol. 2014, 41, 401
3) Oehlke et al. Nuc. Med. Biol. 2015, 42, 842

Radiometals Liquid Targets – Conclusion

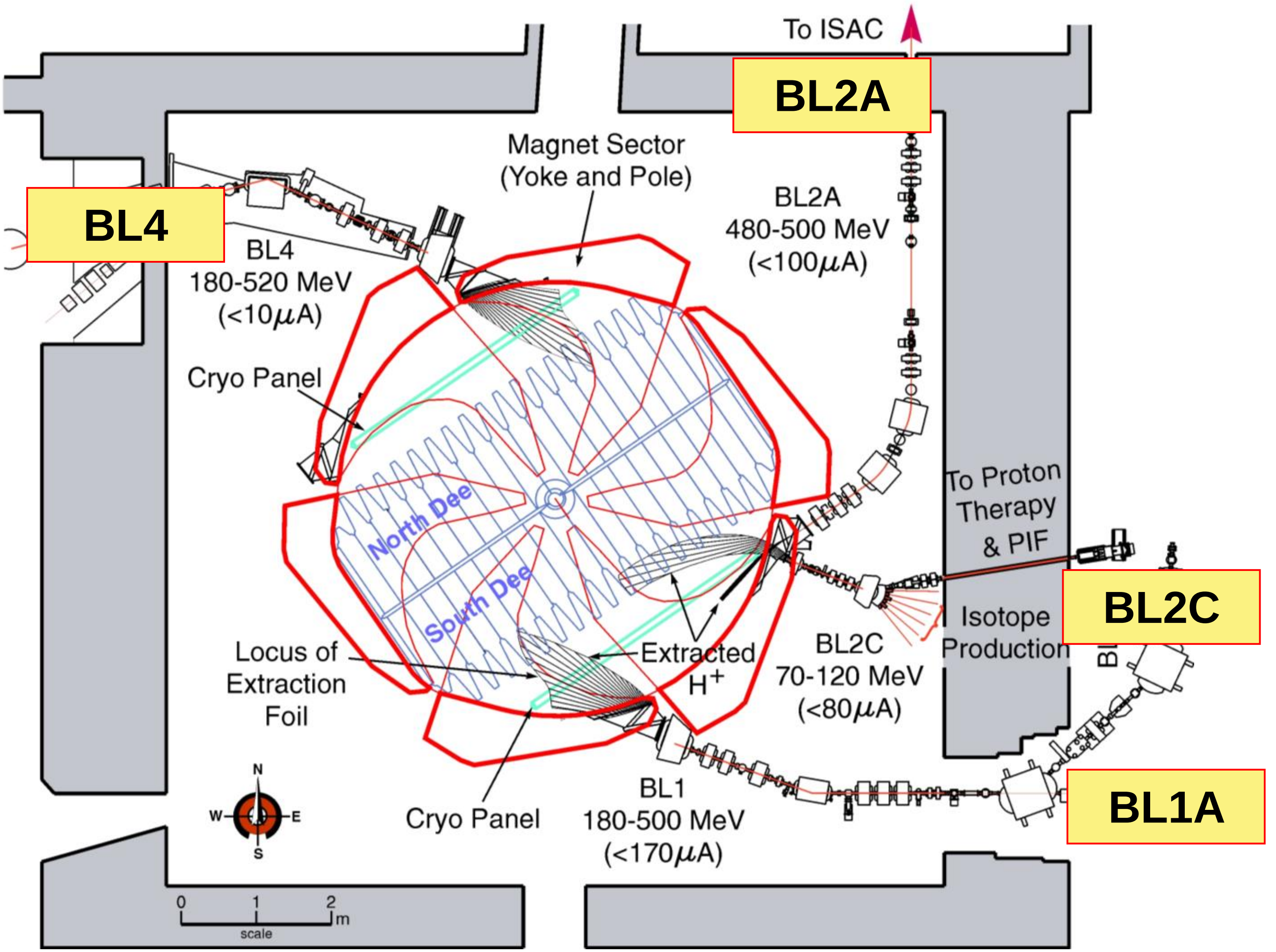
- A simple method for the production of research quantities of various radiometals has been established using a modified liquid-target system
- Salt solutions of natural isotopic abundance were irradiated on our 13 MeV cyclotron
- After irradiation, all solutions were withdrawn from the target and purified using cation exchange or chelating resins
- Several isotopes were produced by using the same target system

Candidate α-emitters for therapy

Isotope	Half-life	Standard Production	1st Ion. E.	ISAC yield	Target	Considerations
^{149}Tb	4.2 h	Spallation, heavy-particle accelerator	5.86 eV	High	Tantalum	Good chemistry, alt. isotopes
^{211}At	7.2 h	α-cyclotron	9.54 eV	Low	Uranium	No stable isotope, thyroid uptake
^{212}Bi	1.0 h	Generator (^{224}Ra/^{212}Bi)	7.29 eV	High for parent	Uranium	Renal uptake
^{213}Bi	0.76 h	Generator ^{225}Ac	7.29 eV	High for parent	Uranium	Renal uptake
^{223}Ra	11.4 d	Generator (^{227}Ac/^{223}Ra)	5.38 eV	High	Uranium	4 α-decays, bone uptake
^{224}Ra	3.7 d	Generator ^{232,228}Th	5.38 eV	High	Uranium	4 α-decays, bone uptake
^{225}Ac	10 d	Generator (^{229}Th/^{225}Ac)	5.38 eV	High	Uranium	4 α-decays

- ISAC yields are high for Tb, Bi, Ra and Ac
- Can exploit low ionization energy of parent isotopes to improve yields (i.e. At)

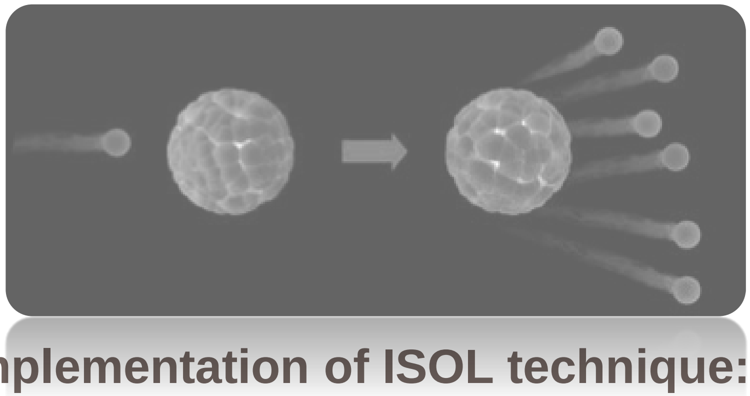
Previous decade: routine operation at 220-250 μA



Recently achieved:

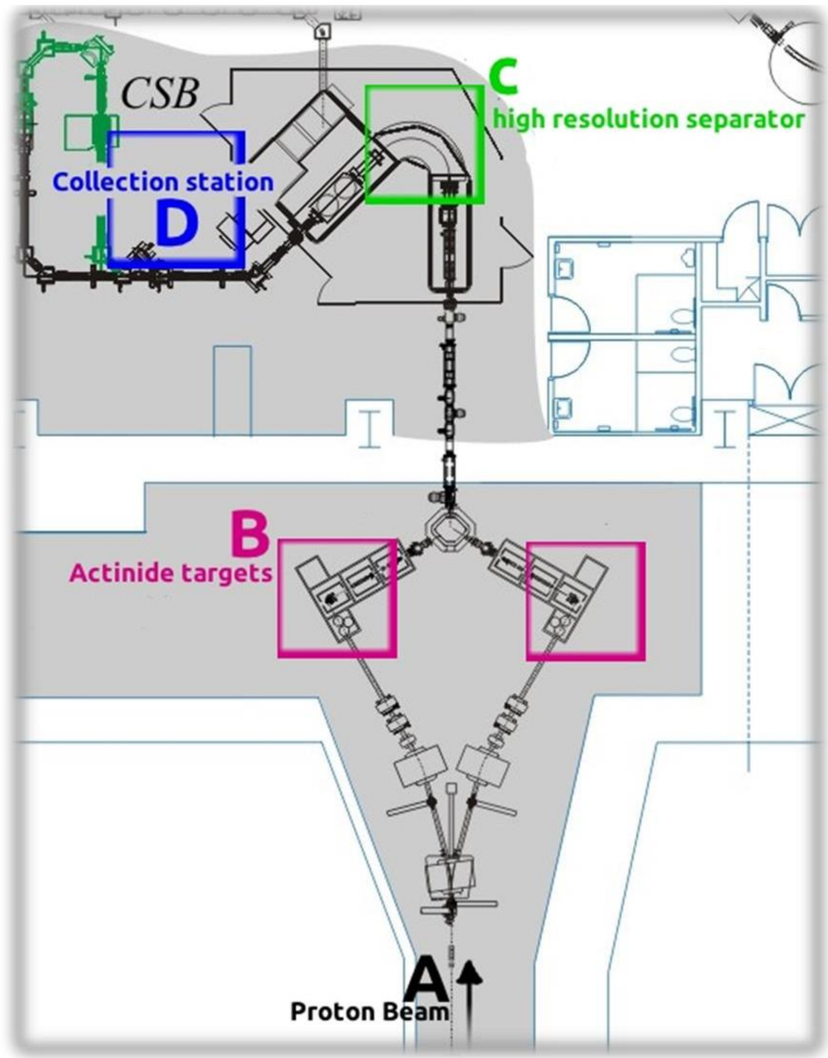
Materials science, 500 MeV isotopes: • BL1A (100μA)
ISAC program: • BL2A (100μA)
Sr production: • BL2C (100μA)
• Total (300μA)

Isotope production via spallation of uranium:



Implementation of ISOL technique:

- Uranium carbide, thorium oxide
- 480 MeV protons, 10 μA
- Various available ion sources
- ~2500:1 mass separation resolution (~10^6–10^9 ions/s)
- Ion energy = ~20-60 keV



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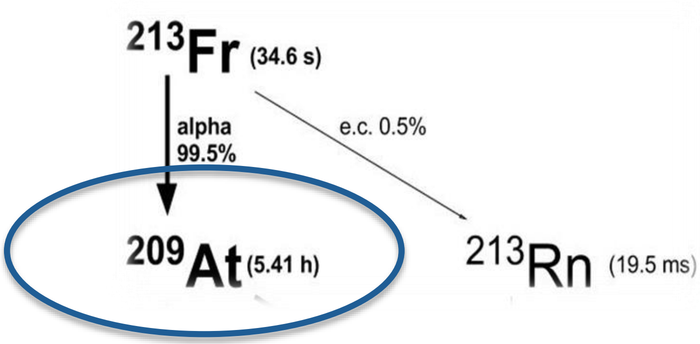
^{209}At-based imaging to establish ^{211}At α-therapy

Imaging

^{209}At

$t_{1/2}$= 5.4 h

(γ-emitter)



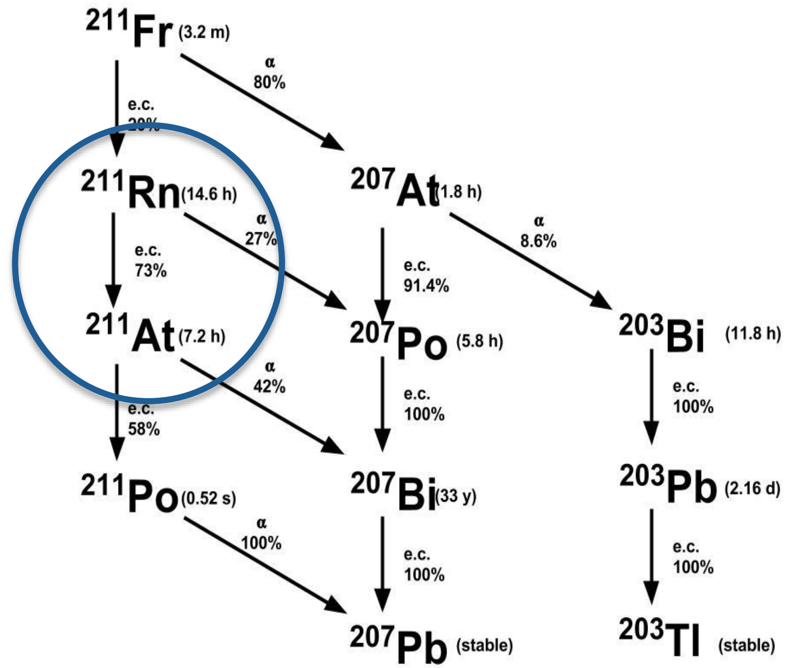
^{209}AT COLLECTED FROM ^{213}FR ION BEAMS

Therapy

^{211}At

$t_{1/2}$= 7.2 h

(α-emitter)



From bench to (preclinical) bedside

Implant ^{211}Fr in NaCl

↓

Submerge target in dodecane

↓

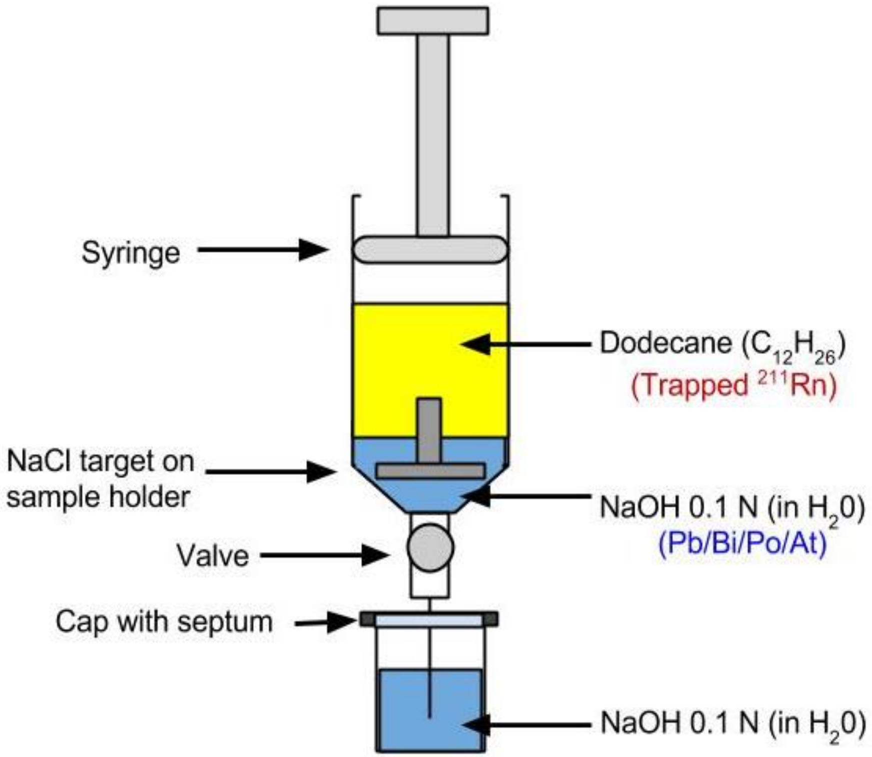
Dissolve NaCl target in dilute NaOH

↓

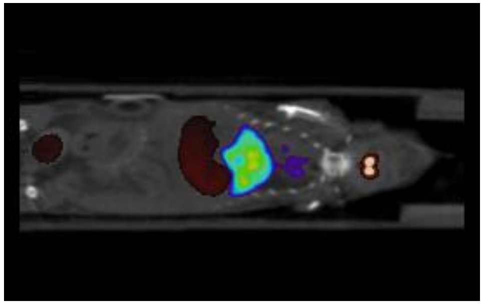
Mix and remove aqueous solution (Pb/Bi/At/Po)

↓

^{211}Rn isolated in dodecane $\rightarrow$ ^{211}At



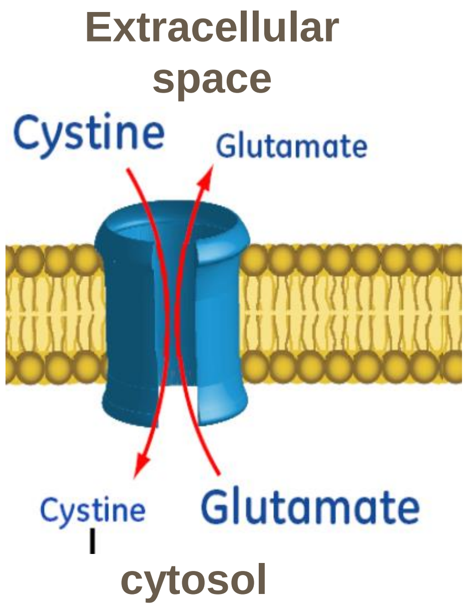
^{209}AT IMAGING FEASIBILITY COMPLETED



Adapted from Maeda et al, 2015 Radioanal Nucl Chem, 303:1465-1468.

RADIOPHARMACEUTICALS DEVELOPMENT

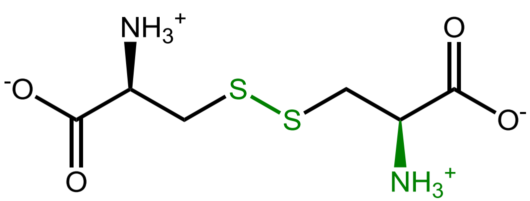
Tracer for System x_c^-



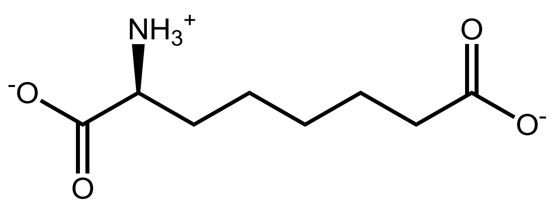
OXIDATIVE STRESS:

- ✓ Imbalance between Reactive Oxygen Species (ROS) and antioxidants.
- ✓ Important in many diseases including: cancer, neurodegeneration, diabetes, strokes, etc.
- ✓ Goal:

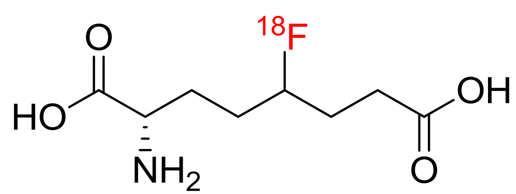
1. Develop ^{18}FASu as a tool to study system x_c- in breast cancer
2. Understand specificity, biodistribution, kinetics of uptake, *in vivo* metabolism



Cystine



Aminosuberic acid (ASu)

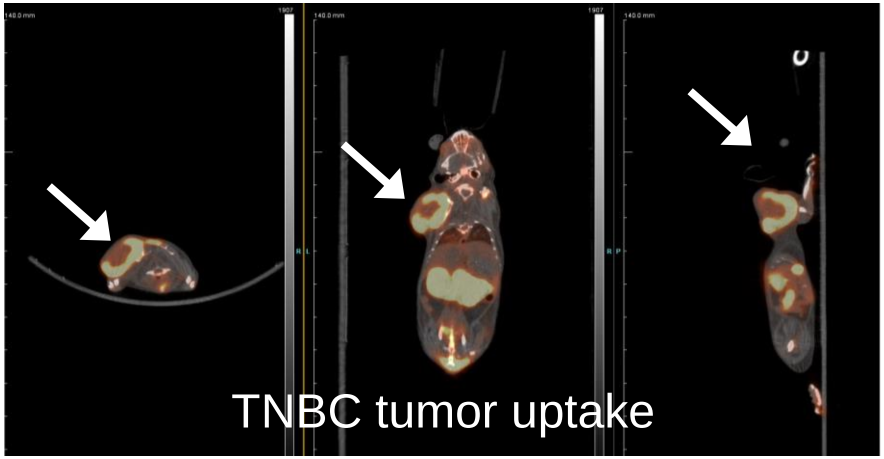


5-[^{18}F]Fluoroaminosuberic acid (^{18}FASu)

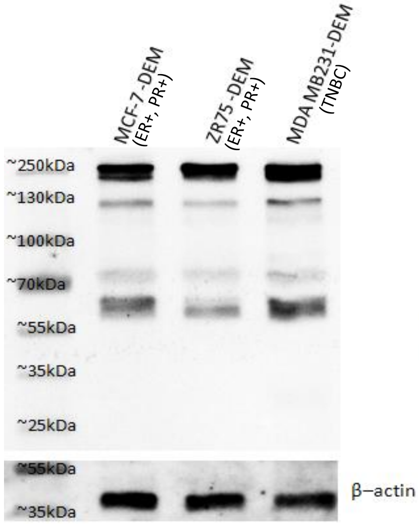
^{18}FASu uptake in breast cancer cells

- ✓ TNBC (triple negative breast cancer) ➔ aggressive, poorest patient prognosis, no targeted therapeutic exists.
- ✓ ^{18}FASu established as a tracer to image TNBC via system x_c-

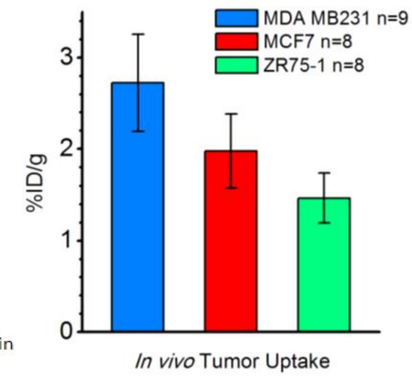
MICROPET/CT



XC⁻ EXPRESSION LEVELS



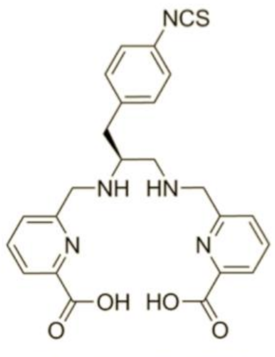
TRACER UPTAKE

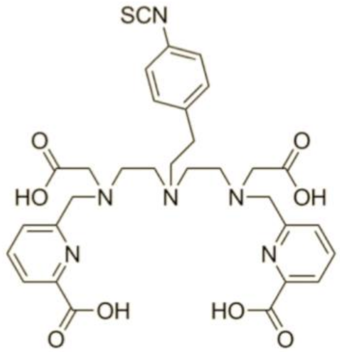


NEXT STEPS:

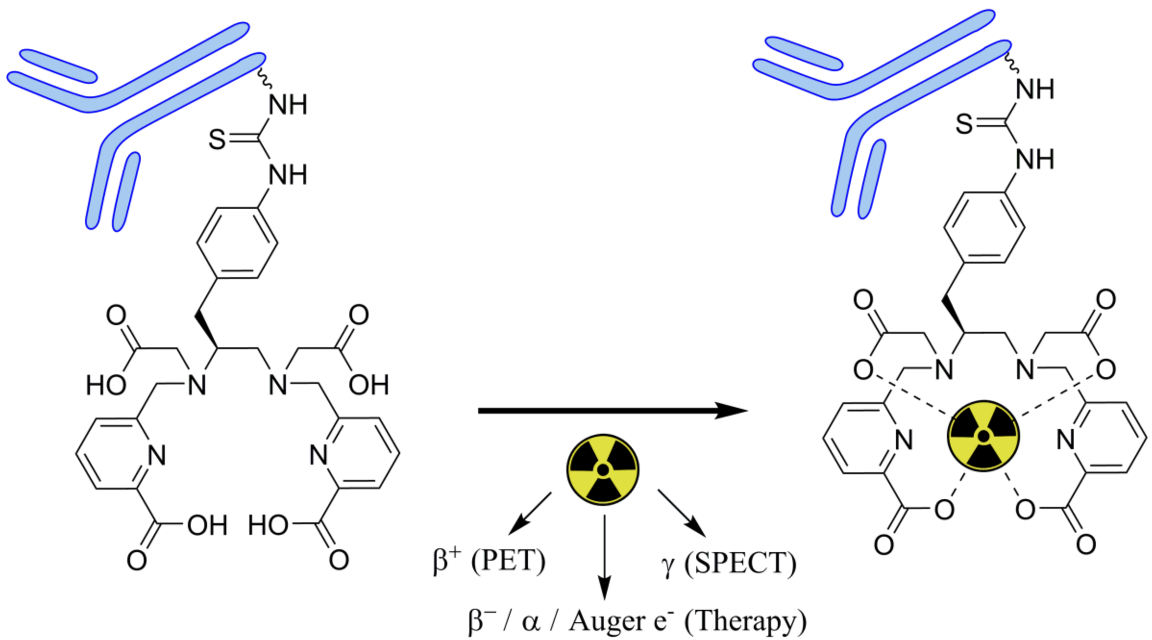
- ✓ *In vivo* and protein expression studies on breast cancer models.
- ✓ Separate/synthesize the stereoisomers and study the *in vitro* and *in vivo* uptake using HEK wt and HEK:xCT tumor models.
- ✓ Uptake kinetics *in vivo*

Chelating agents Development



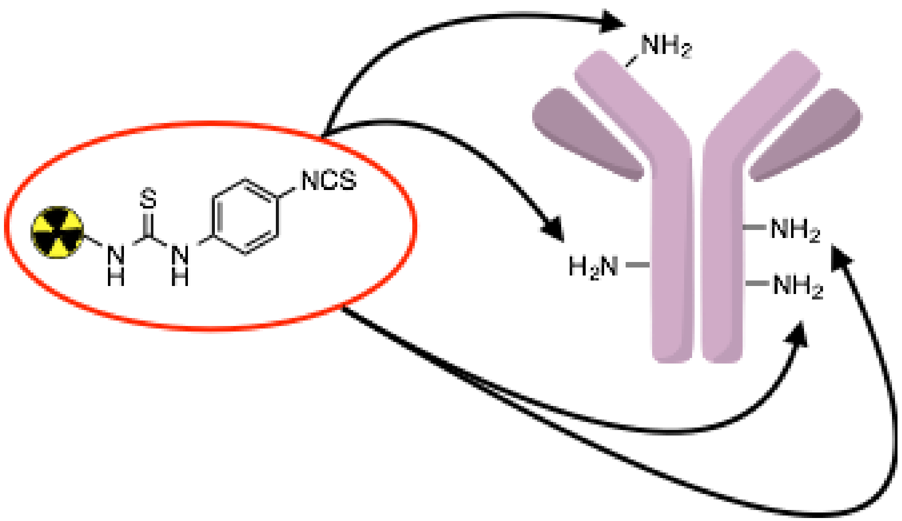


- ✓ Chiral CHX-“pa“ chelates: Ga, In, Zr isotopes
- ✓ Nitroimidazole-dedpa derivatives: hypoxia
- ✓ New high denticity chelators for lanthanides and actinides



Ramogida et al. Inorg. Chem. 2015, 54, 2017

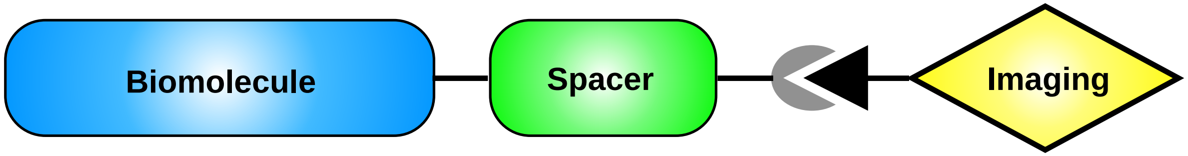
Random bioconjugation approaches



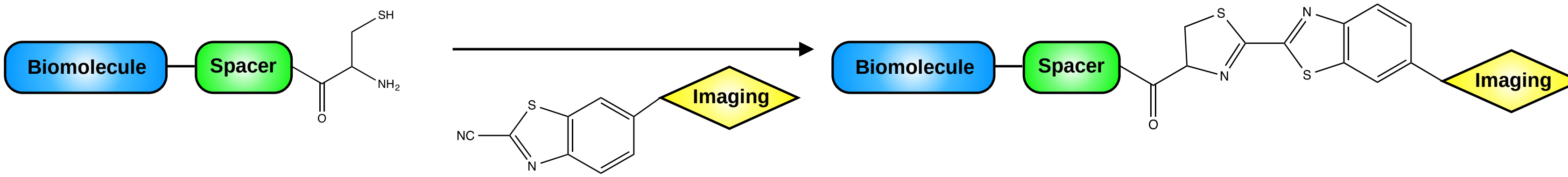
RANDOM BIOCONJUGATION APPROACHES:

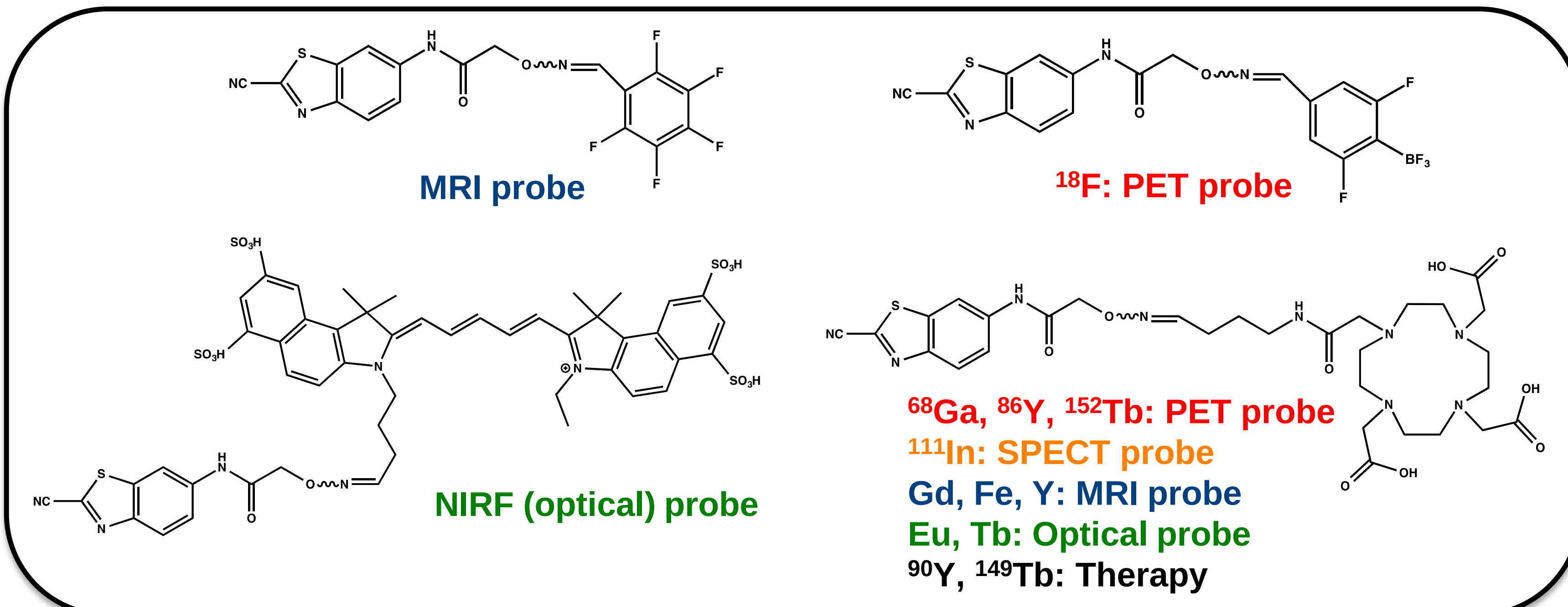
- ✓ Degree of labeling ➔ an average loading of 3 chelators/mAb includes subpopulations with degrees of labeling ranging from 0 to well above 3..
- ✓ Regioisomers ➔ if an antibody has 40 available lysine (with a degree of labeling of 2 chelators/mAb) it results in a mixture of up to 780 different regioisomers. For a degree of labeling of 3 chelators/mAb, the mixture is over 10’000 regioisomers.
- ✓ Batch-to-batch reproducibility issues.

A chemoselective approach for multimodality probes



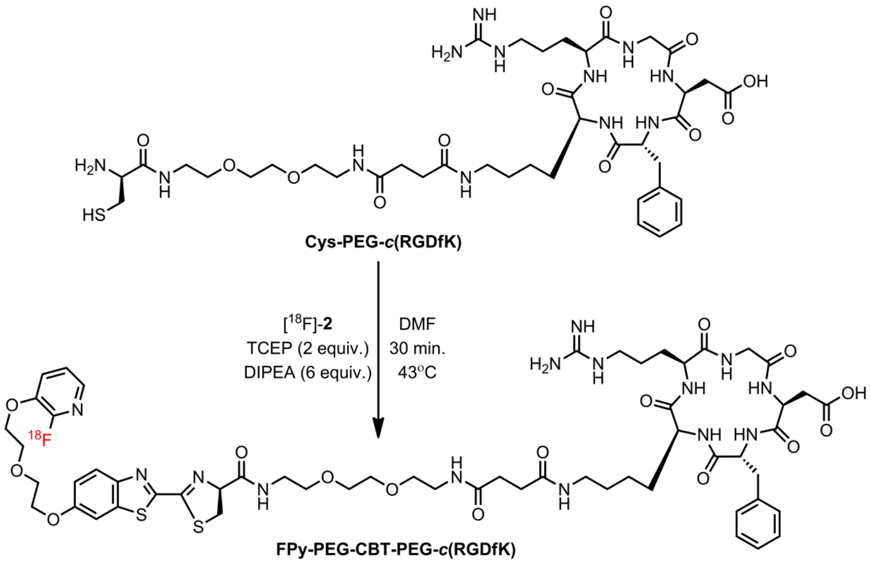
CHEMOSELECTIVE LIGATION BY 2-CYANOBENZOTHIAZOLE / 1,2-AMINOTHIOL CONDENSATION

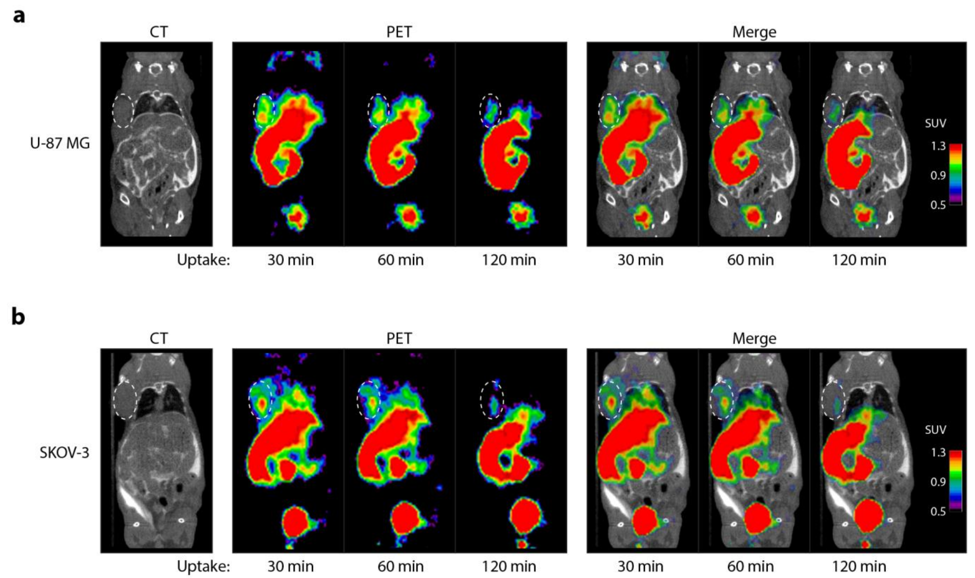




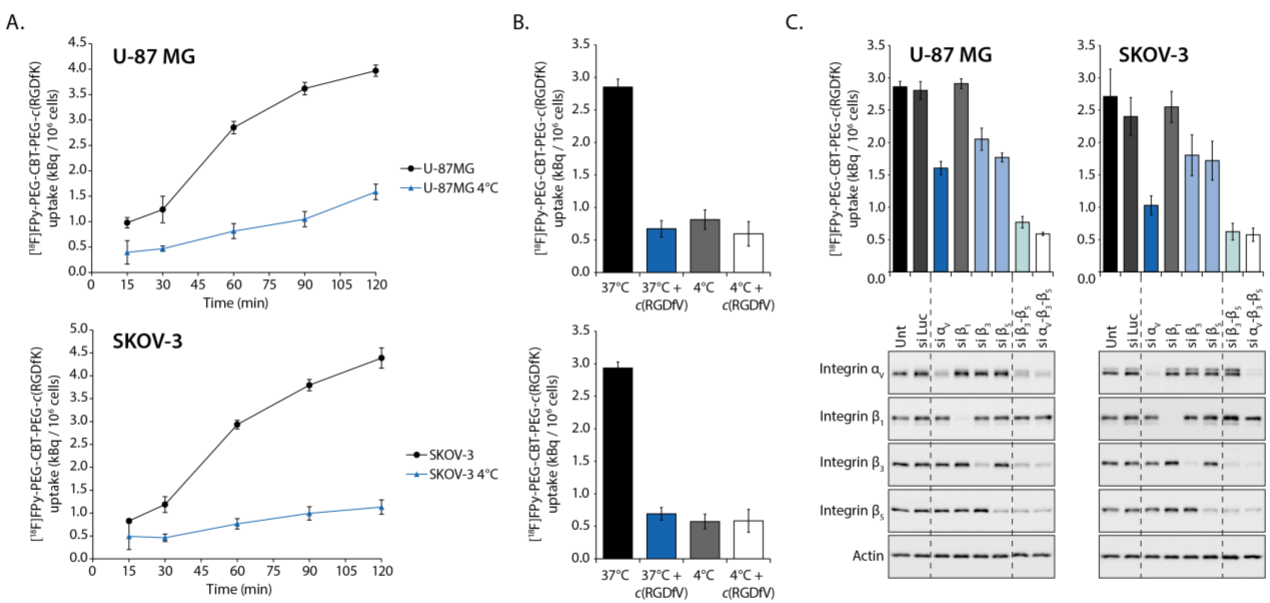
Seimbille et al. Unpublished material

Labeling of c(RGDfK) by Cys/CBT ligation





Inkster et al. Org. Biomol. Chem. 2015, 13, 3667

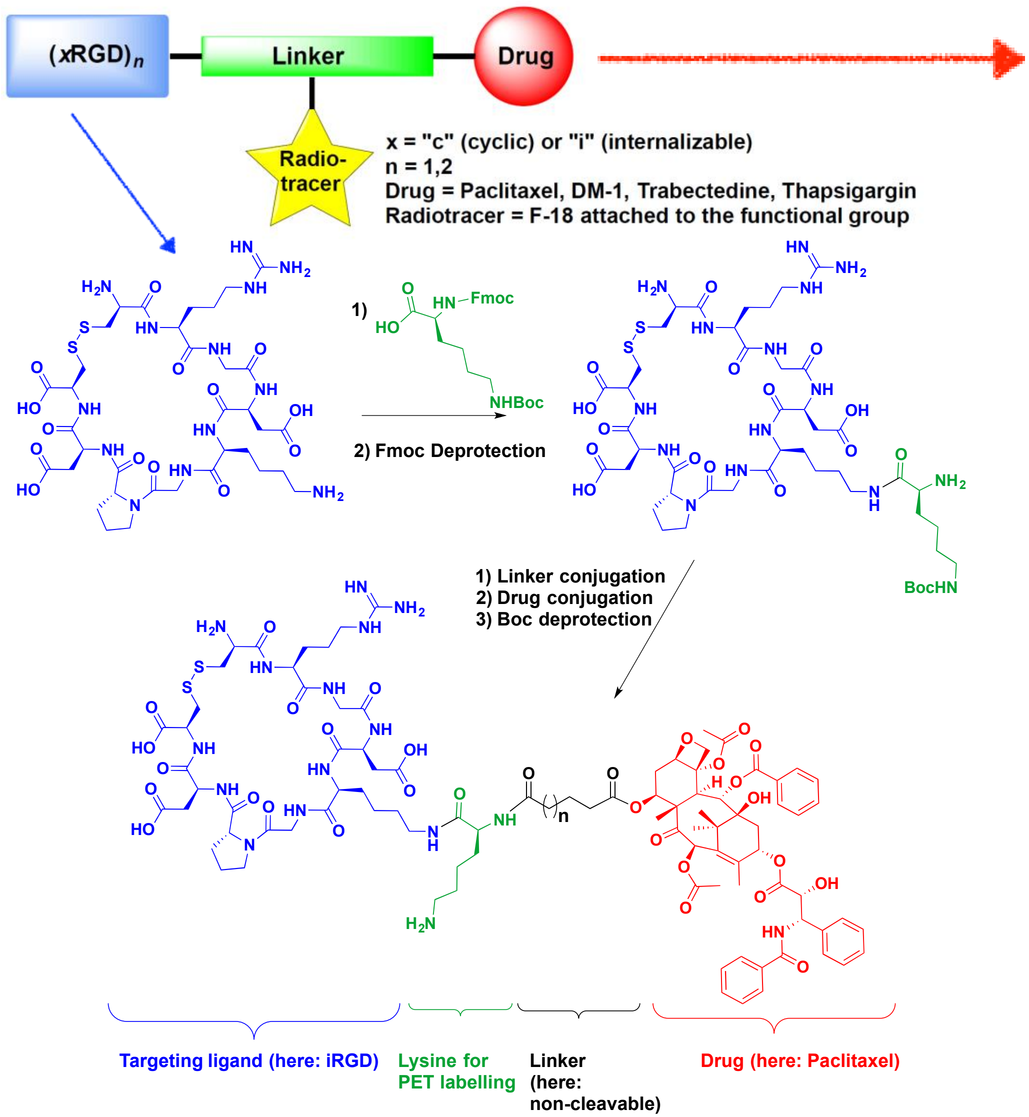


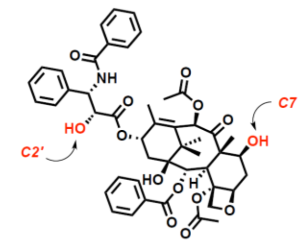
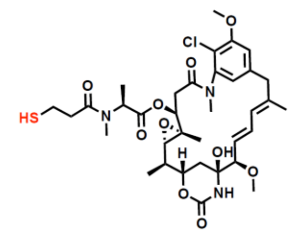
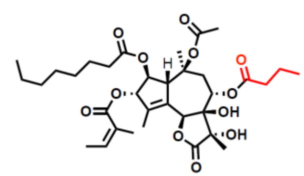
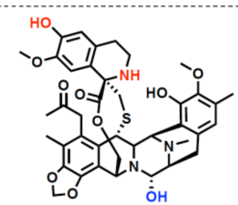
IC$_{50}$ of Fpy-PEG-CBT-PEG-*c*(RGDfK) is 30.8 × 10^{-7} M. [^{18}F]FPyPEGCBT-*c*(RGDfK) cell uptake was mediated by an active transport through binding to $\alpha_V\beta_3$ and $\alpha_V\beta_5$. *In vivo*, this new tracer demonstrated specific tumour uptake with %ID/g of 2.9 and 2.4 in U-87 MG and SKOV-3 tumours 1 h after injection.

Colin et al. Unpublished material

TRIUMF

A Theranostic Approach Towards Targeted Chemotherapy



Name	Structure	Modification points (*in red*)
Paclitaxel		-OH at C2', -OH at C7
DM1		-SH
Thapsigargin		Ester replacement modification
Trabectedin		Phenolic -OH Secondary -NH-

TRIUMF

MEDICIS-PROMED

New bifunctional fluorescent and radioactive bioligands for ovarian cancer

A collaborative effort:

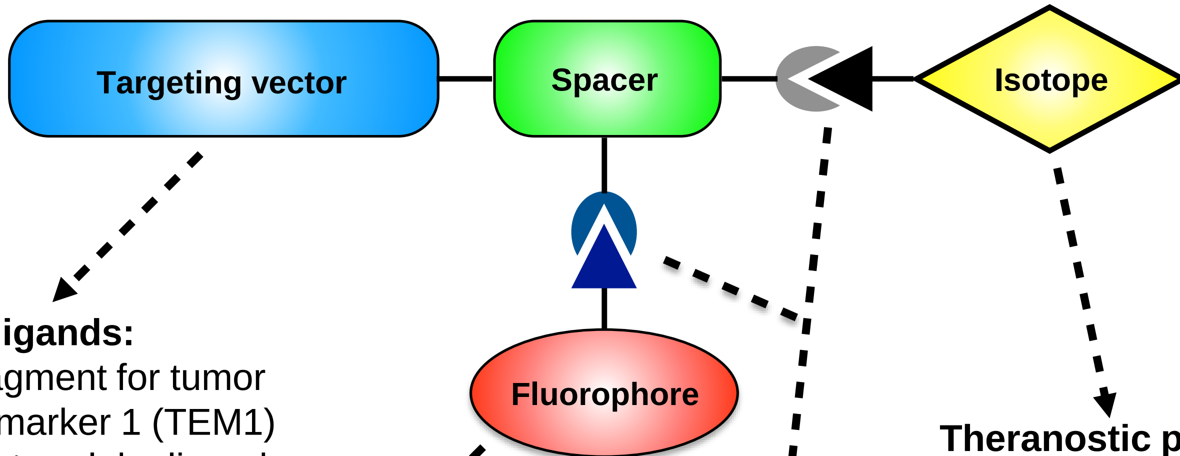
- ✓ CERN-MEDICIS (Dr T. Stora).
- ✓ UNIL / CHUV (Prof J. Prior, Prof G. Coukos).
- ✓ EPFL (Prof E. Dubikovskaya, Prof D. Hanahan)
- ✓ HUG / UNIGE (Prof O. Ratib, Prof. Morel)
- ✓ Advanced Accelerator Applications (Dr S. Buono)
- ✓ TRIUMF (Dr Y. Seimbille)

A consortium with combined expertise in: nuclear physics, oncology, molecular imaging, bioorganic chemistry and radiochemistry.

It should warrant success of this ambitious project:

→ Development of bioligands for treatment and multimodality imaging of ovarian cancer

STRUCTURE OF NOVEL THERANOSTICS FOR PERSONALIZED TREATMENT OF OVARIAN CANCER



Targeting bioligands:
- Antibody fragment for tumor endothelial marker 1 (TEM1)
- Folate receptor-alpha ligands (folic acid, antibody)

Theranostic pairs coordinated in a chelator:

1. Imaging isotope

- PET or SPECT

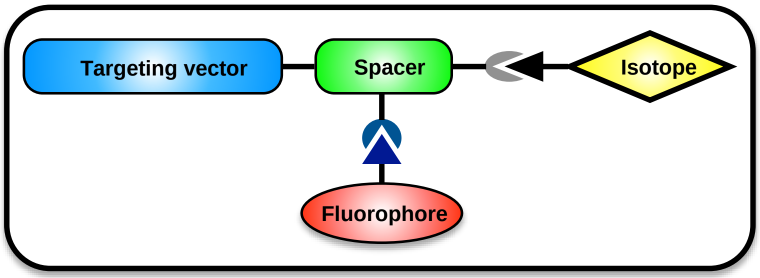
2. Treatment isotope:

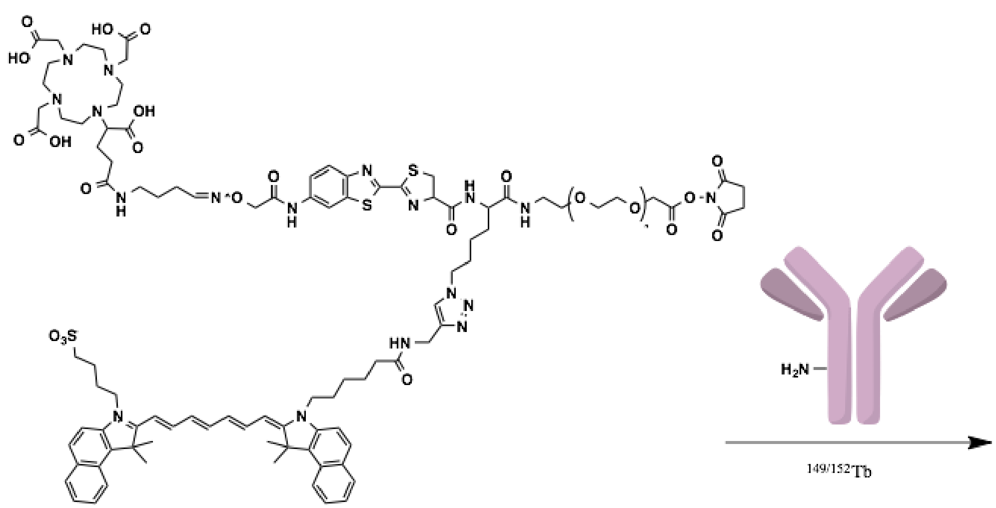
- Beta emitters (treatment of mm-scale tumors)
- Alpha or Auger (micrometastasis)

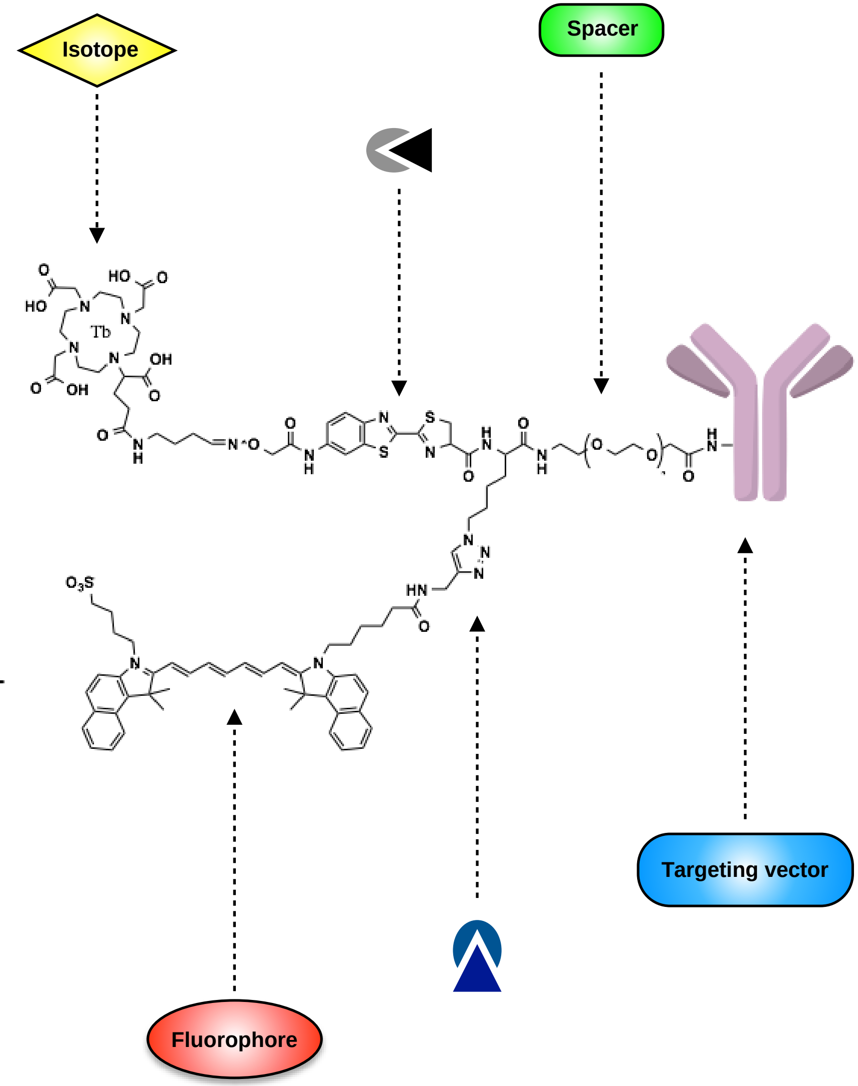
Fluorescent probe:
- Indocyanine green (ICG)

Click handles:
- Chemoselective ligation
- Fast kinetics
- High chemical yields
- Bioorthogonal
- Simple reaction conditions
- Simple product isolation
- Physiologically stable

Structure of the Theranostic







Terbium isotopes:

- ^{149}Tb (α-emitter, $t_{1/2}$ = 4.2 h)
- ^{152}Tb (β^{+}-emitter, $t_{1/2}$ = 17.5 h)

Canada’s national laboratory
for particle and nuclear physics
and accelerator-based science

Thank you!
Merci!

TRIUMF: Alberta | British Columbia | Calgary | Carleton | Guelph | McGill | Manitoba | McMaster | Montréal | Northern British Columbia | Queen’s | Regina | Saint Mary’s | Simon Fraser | Toronto | Victoria | Western | Winnipeg | York

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