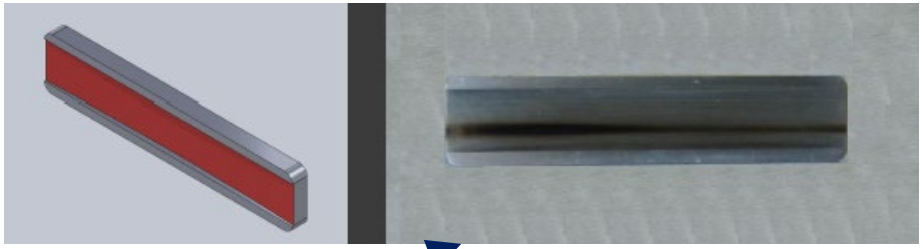
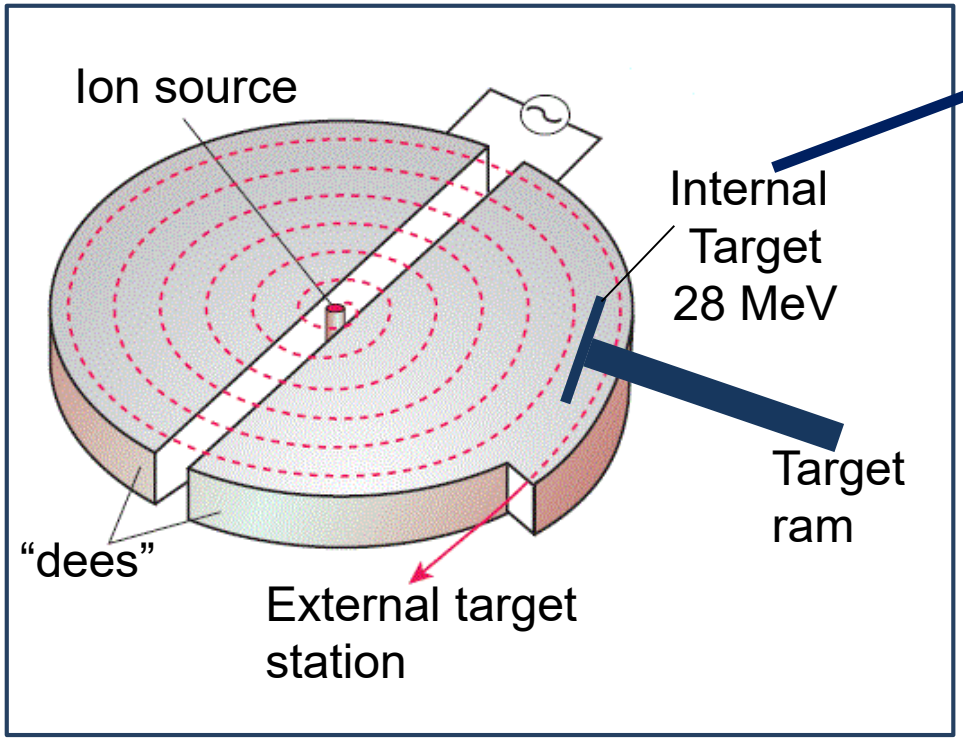
Astatine-211 Studies at Duke: A Ground Level View

Yutian Feng, PhD
Duke University Medical Center

^{211}At Production at Duke





- Internal Bi target positioned at 28 MeV
- Ongoing cyclotron subsystems upgrade in collaboration with Ionetix

Larsen, *et al*. 1996. *Applied radiation and isotopes*, *47*(2), pp.135-143.

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^{211}At Production at Duke

- Maximum Produced: 250 mCi (9.3 GBq)
- Isolation by dry distillation
- Can be shipped to locations within 6-h reach with sufficient activity for a clinical study

Run Number	Irradiation Time (h)	Beam current (μAp)	Target Activity (mCi)	Shipped Activity (mCi)	Shipped Activity per 3 h
1	3.00	50	142	54	54
2	2.75	50	188	58	63
3	2.25	50	156	54	72
4	3.08	40	184	67	65
Average:	*2.77*	*48*	*168*	*58*	*64*

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Targeted α therapy using ^{211}At

Past efforts

- ^{211}At-labeled Chimeric 81C6 for GBM
- ^{211}At MABG

Current projects

- Small molecules can be labeled with retention of biological properties
  - Low-molecular-weight (LMW) PSMA-targeted agents
  - PARP inhibitors
- Single domain antibody fragments (nanobodies, V_HH) have PK compatible with ^{211}At labeling
- Gold nanoparticle platforms for rapid labeling with high stability

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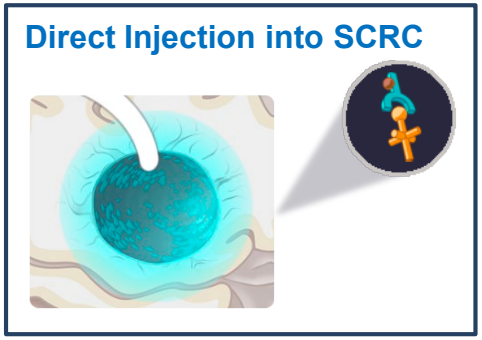
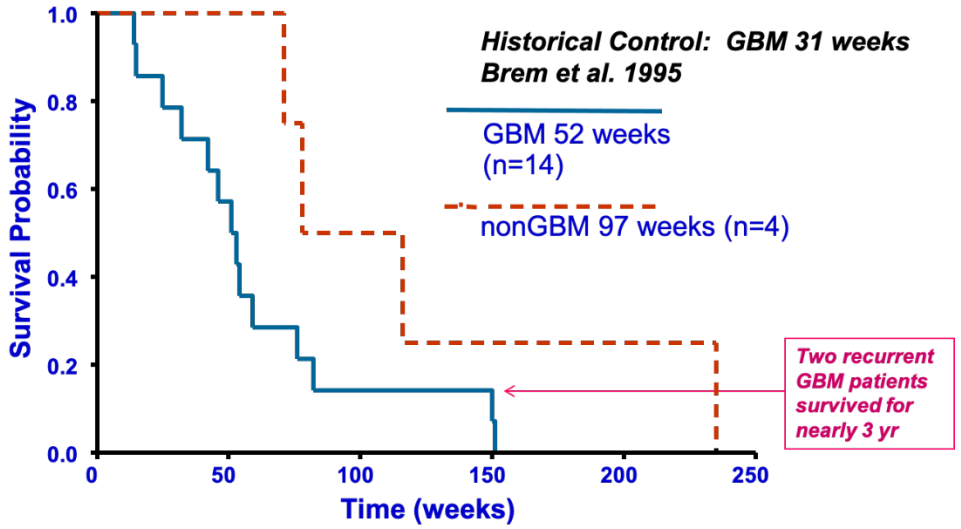
^{211}At-labeled Chimeric 81C6 for GBM

Rationale:

- Surgically created resection cavity (SCRC) administration
- Wealth of experience in patients with ^{131}I-labeled mAb in this setting





Zalutsky, M.R. *et al.* 2008 *Journal of Nuclear Medicine*, *49*(1), pp.30-38.

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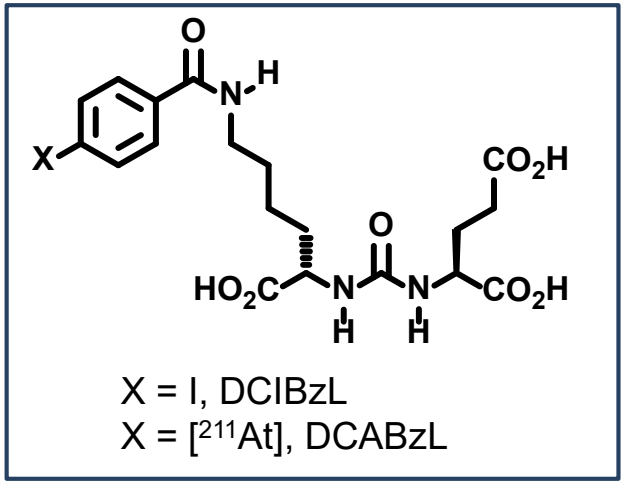
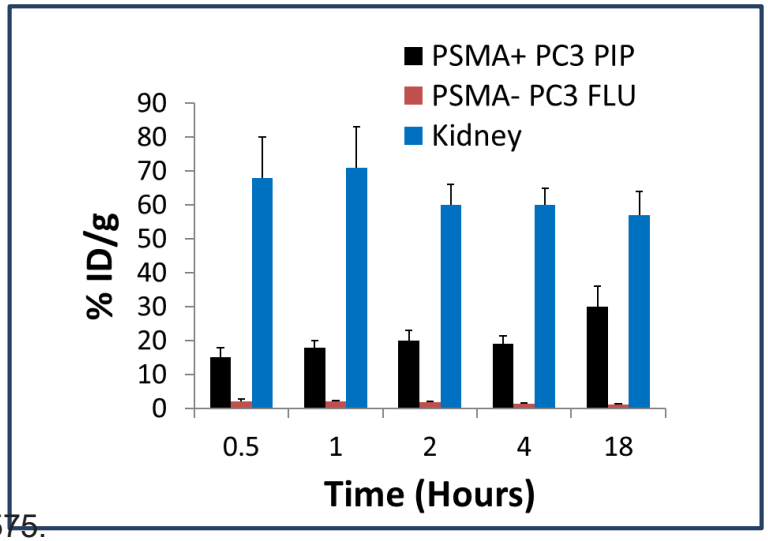
^{211}At labeled LMW PSMA-targeted agents

Rationale:

- Rapid tumor uptake and normal tissue clearance
- 1st generation: [^{211}At]DCABzL
- High binding affinity 0.01 nM (DCIBzL)





Kiess, A.P. *et al.* 2016. *Journal of Nuclear Medicine*, *57*(10), pp.1569-1575.

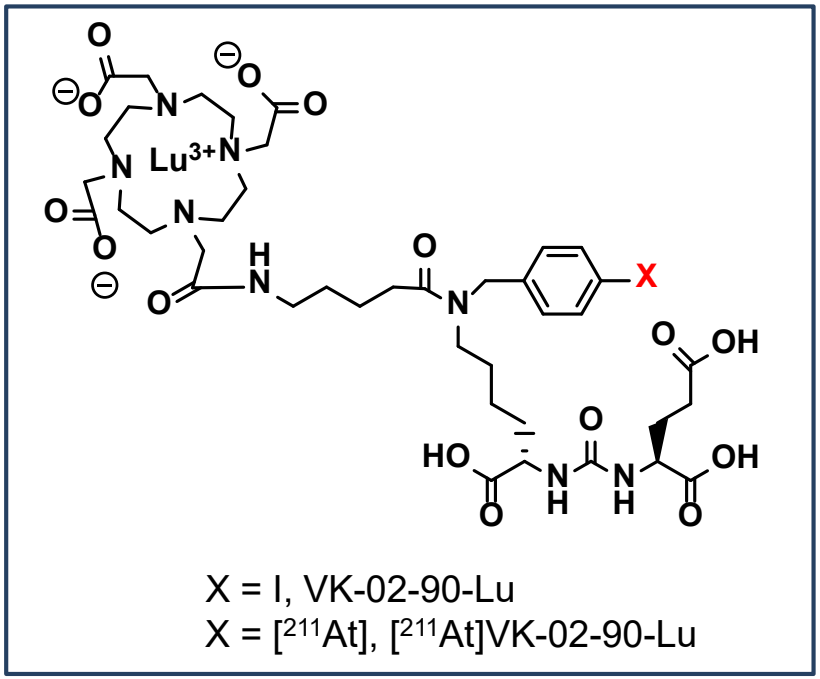
2nd generation: [^{211}At]VK-02-90-Lu

Strategies:

- Improve normal tissue clearance: Kidney, salivary gland and lacrimal gland, while retain tumor uptake
- Develop blocker to selectively lower uptake in normal organs

Chemistry:

- 11.4 % labeling yield at remote location, 26% yield with fresh ^{211}At
- 4 h labeling & purification time



X = I, VK-02-90-Lu
X = [^{211}At], [^{211}At]VK-02-90-Lu

Minn, I. 2019. *Journal of Nuclear Medicine*, *60*(supplement 1), pp.16-16.

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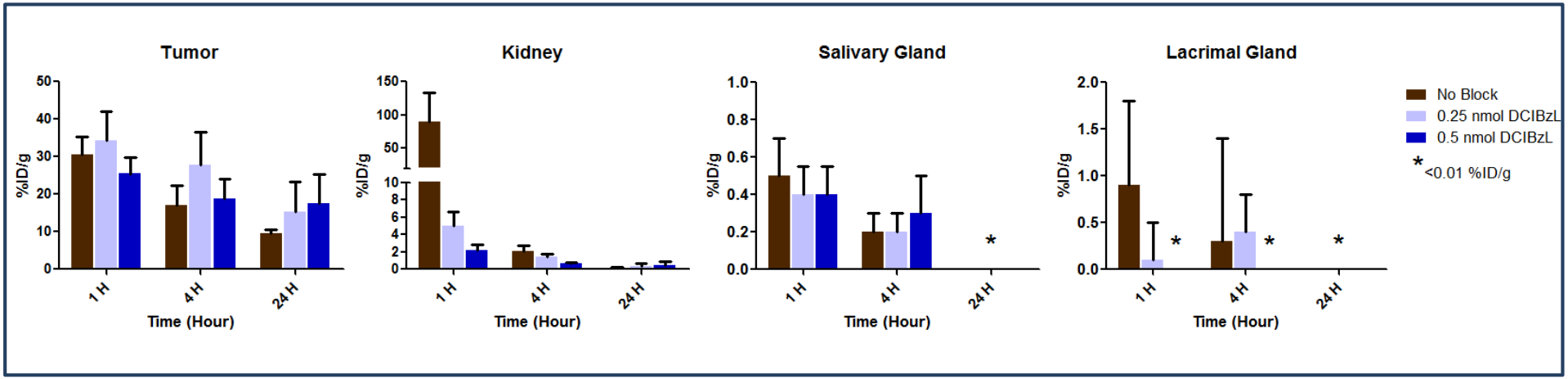
[^{211}At]VK-02-90-Lu Biodistribution in PIP Model



- High tumor uptake and retention
- Reduced kidney uptake and fast clearance (compared with [^{211}At]DCABzL)
- Kidney uptake can be blocked by co-injection of DCIBzL
- Low salivary gland and lacrimal gland uptake

Minn, I. 2019. *Journal of Nuclear Medicine*, *60*(supplement 1), pp.16-16.

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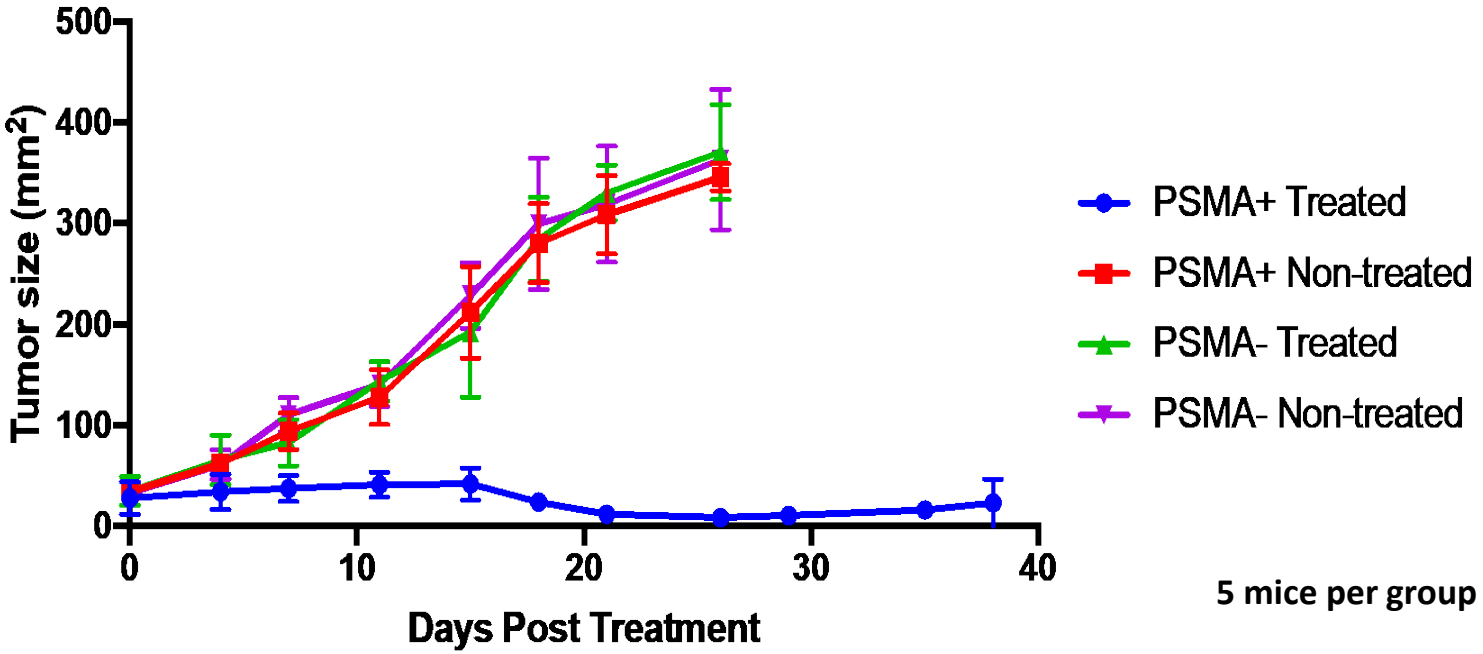
[^{211}At]VK-02-90-Lu: Therapy



- 3.7 MBq (100 µCi) in athymic mice bearing both PSMA+ (PIP) and PSMA- (flu) tumor xenografts
- Ongoing optimization in radiochemistry to facilitate clinical translation

Minn, I. 2019. *Journal of Nuclear Medicine*, *60*(supplement 1), pp.16-16.

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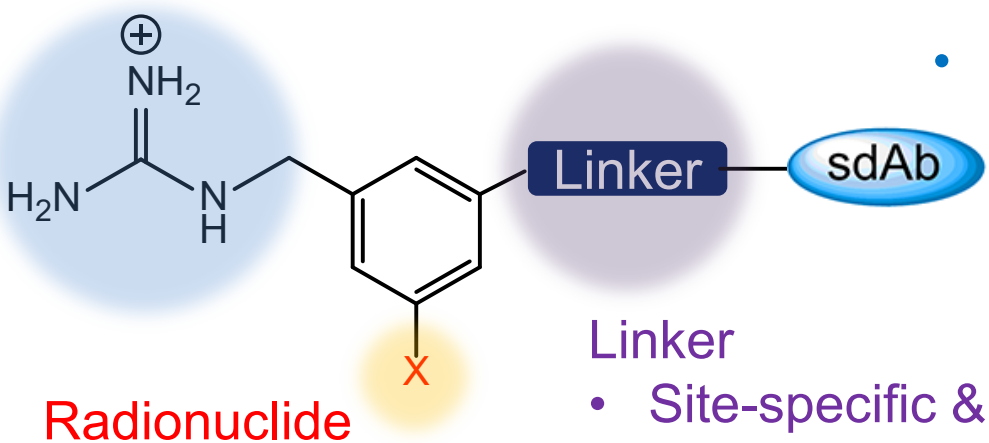
Radiohalogenated Nanobodies

Residualizing group
- Increase intracellular trapping
- Decrease *in vivo* dehalogenation



Nanobody
- 13 kD MW, nM binding affinity
- Stable and resilient

Radionuclide
- ^{18}F
- Radioiodines
- ^{211}At

Linker
- Site-specific & random labeling
- Design to improve PK

Choi, J. *et al.* 2018 *Nuclear medicine and biology*, *56*, pp.10-20.
Feng, Y., *et al.* 2020 *Nuclear Medicine and Biology*.
Zhou, Z. *et al.*, 2020 *Bioorganic & Medicinal Chemistry*: 115634.

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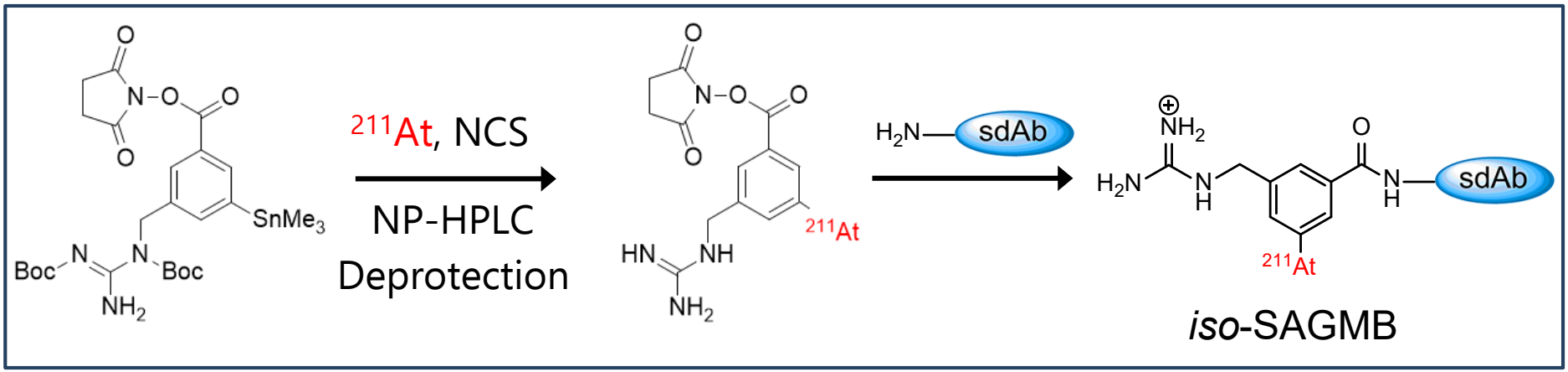
^{211}At Labeled Nanobodies



- 30% overall radiochemical yield, >95% radiochemical purity
- 3.0 ± 0.1 nM binding affinity to HER2

Choi, J. 2018 *Nuclear medicine and biology*, *56*, pp.10-20.

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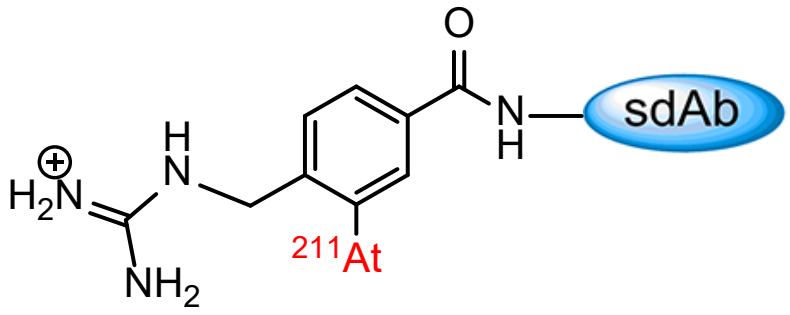
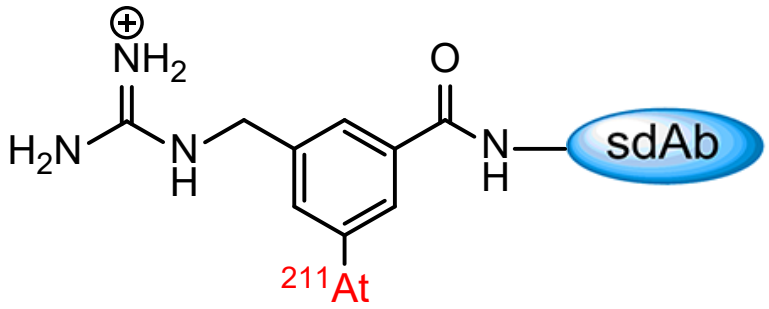
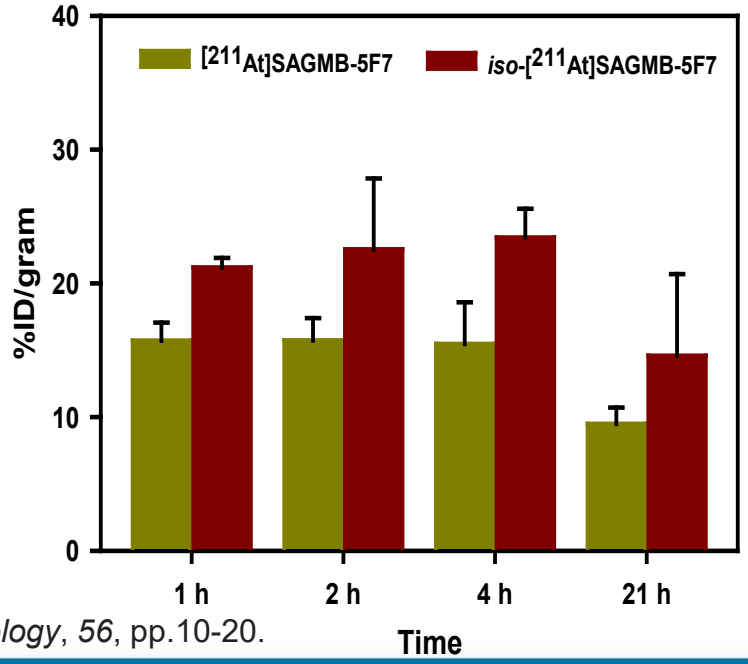
SAGMB vs *iso*-SAGMB: tumor uptake

SAGMB



iso-SAGMB





Choi, J. 2018 *Nuclear medicine and biology*, *56*, pp.10-20.

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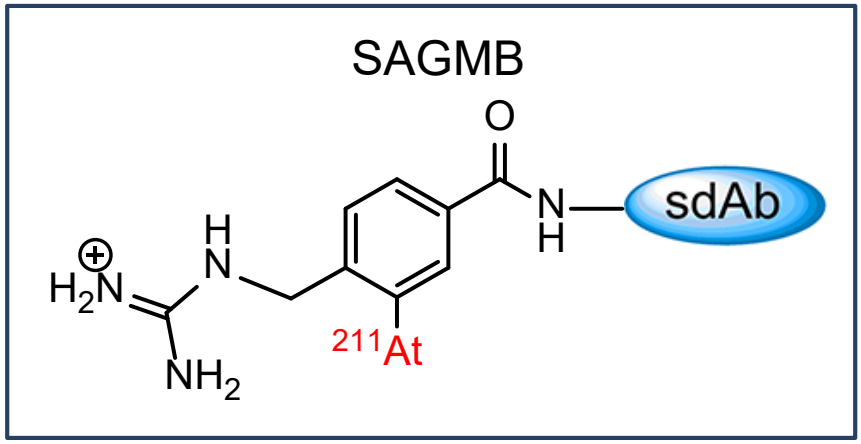
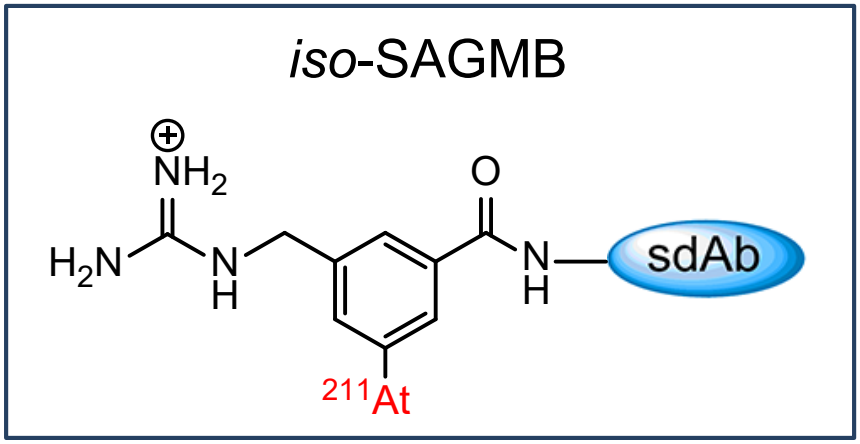
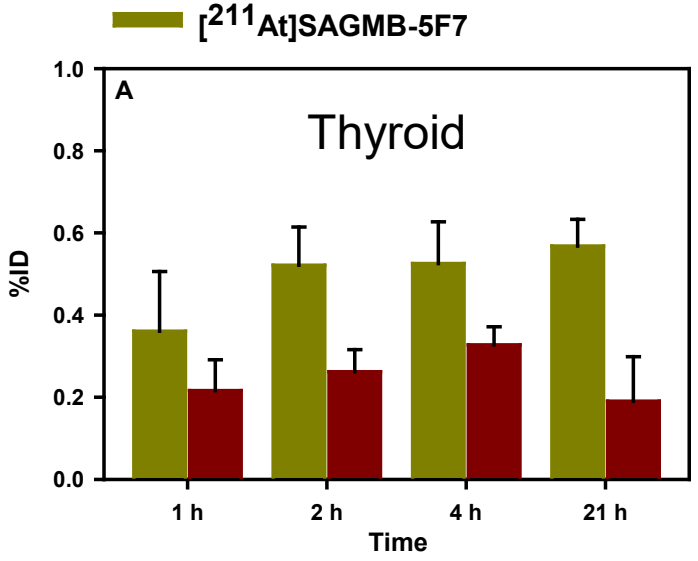
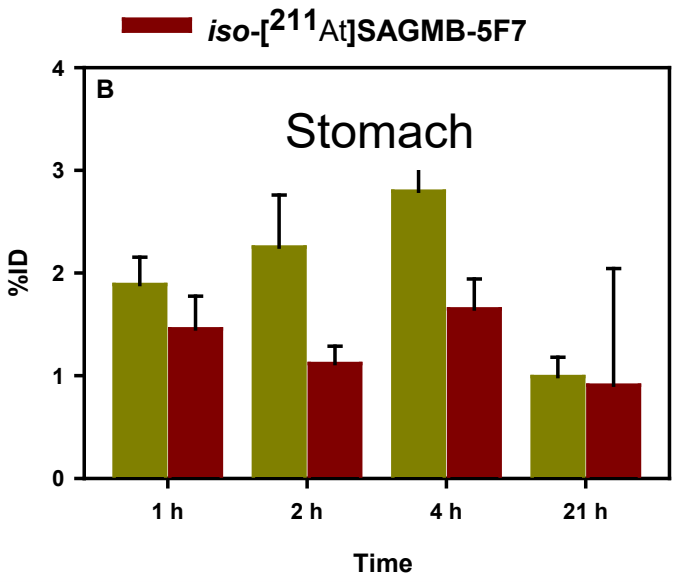
SAGMB vs *iso*-SAGMB: Stomach and Thyroid Uptake (dehalogenation *in vivo*)









Choi, J. 2018 *Nuclear medicine and biology*, *56*, pp.10-20.

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Summary

- Production and purification
  - ~100 mCi ^{211}At available from a single run
- Distribution
  - After ~6-h transportation, sufficient activity for preparing clinically relevant doses
- Radiochemistry
  - Clinical level labeling (>25 mCi labeled mAb)
- Clinical translation – next agents at Duke
  - LMW PSMA-targeted agents
  - Anti-HER2 nanobody conjugate

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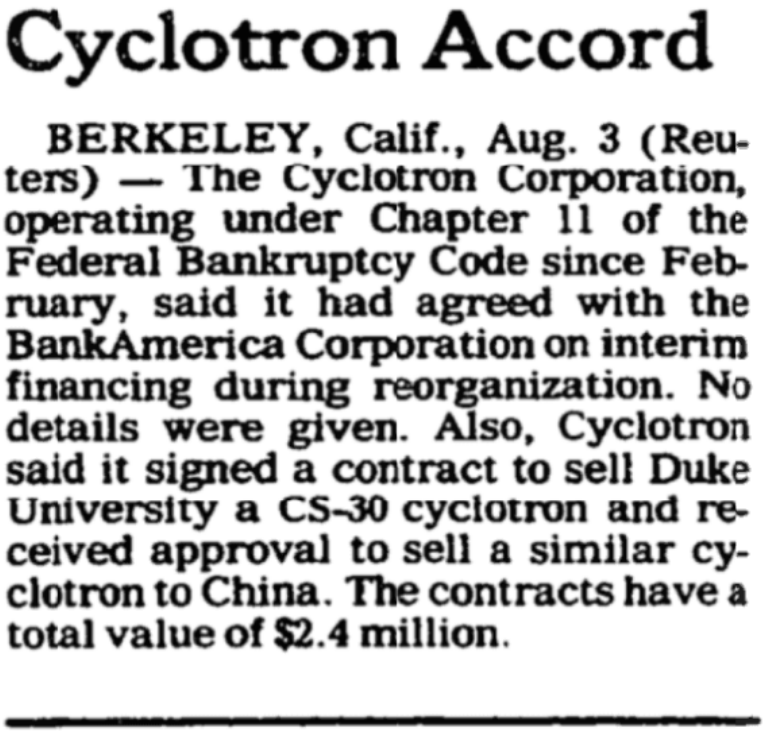
- Shawn Murphy
- Michael Dailey
- DOE
- NIH



Cyclotron Accord

BERKELEY, Calif., Aug. 3 (Reuters) — The Cyclotron Corporation, operating under Chapter 11 of the Federal Bankruptcy Code since February, said it had agreed with the BankAmerica Corporation on interim financing during reorganization. No details were given. Also, Cyclotron said it signed a contract to sell Duke University a CS-30 cyclotron and received approval to sell a similar cyclotron to China. The contracts have a total value of $2.4 million.

Credit: Arne Freyberger, Program Manager Isotope Accelerator Facilities

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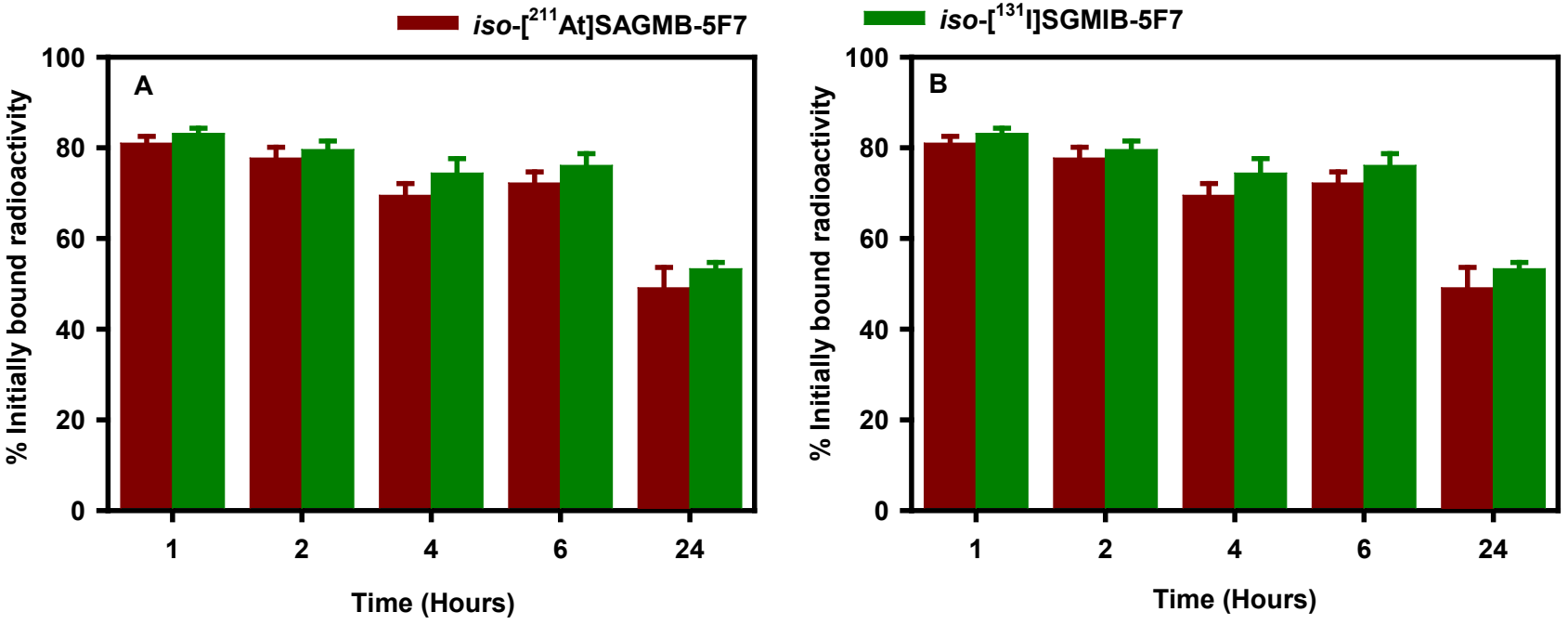
Thank you

Back up slides

Internalization of *iso*-[^{211}At]SAGMB-5F7 and *iso*-[^{131}I]SGMIB-5F7 on BT474 Cells



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