Isotope Program
U.S. Department of Energy

Astatine-211 DOE Isotope User Group Meeting 2022

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UNIVERSITY of WASHINGTON

U.S. DEPARTMENT OF ENERGY

Presentations & Agenda

1:00 – 1:15 PM (ET)	**Yawen Li,** University of Washington - Introduction
1:15 – 1:30 PM (ET)	**Rob Emery**, University of Washington
1:30 – 1:45 PM (ET)	**Lauren McIntosh**, Texas A&M University
1:45 – 2:00 PM (ET)	**Robert Mach**, University of Pennsylvania
2:00 – 2:15 PM (ET)	**Brenda Sandmaier,** Fred Hutchinson Cancer Center/University of Washington
2:15 – 2:30 PM (ET)	**David Eve,** Ionetix Corporation
2:30 – 3:00 PM (ET)	Moderated Q&A

At-211 Production and Research in the U.S.

- Interest in At-211 is increasing in U.S. but significant hurdles (including cost) must be overcome to work with it
- No country-wide effort for At-211 basic chemistry or radiopharmaceutical development
- U.S. Department of Energy Isotope Program is providing funding to increase availability of At-211 – generally no biological studies allowed under that funding
- U.S. NIH provides funding focused on disease treatment – use current methods of labeling – difficult to look at basic chemistry
- There is increasing interest by companies, but some want to see clinical responses before they will invest – no concern about adequate production

At-211 On-going Clinical Trials in the U.S.

- **University of Washington and Fred Hutch (Seattle, USA) – three ongoing Phase I/II clinical trials - Recruiting**
  - High-risk patients with leukemia, myelodysplastic syndrome (**NCT03128034** – **HLA matched**; **NCT03670966** - **Haplo**)
  - Non-malignant diseases with transplant (**NCT04083183**)
  - Low toxicity HCT conditioning regimen
  - ^{211}At-labeled anti-CD45 MAb conjugate [^{211}At]BC8-B10
  - Intravenously injected
  - Treated 59 patients as of August 2022

- **University of Washington and Fred Hutch (Seattle, USA) – two new Phase I clinical trials**
  - Plasma Cell Myeloma; (**NCT04466475** - **recruiting**)
    - RIT + melphalan + transplant
  - High Risk Multiple Myeloma; (**NCT04083183** – **not yet recruiting**)
    - Plasma Cell Myeloma/Recurrent Plasma Cell Myeloma
    - RIT + cyclophosphamide w/wo fludarabine + TBI + transplant
  - ^{211}At-labeled anti-CD38 MAb conjugate [^{211}At]OKT10-B10
  - Intravenously injected
  - Estimated total enrollment of 54 patients (for both trials)

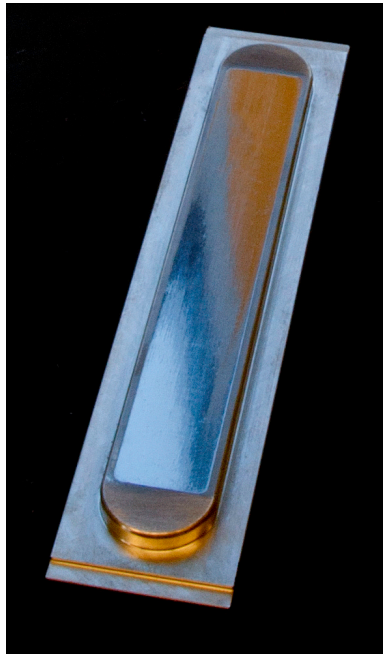
On-going and Planned At-211 Clinical Trials in Japan and Europe

- **Osaka University (Suita, Japan) – NCT05275946, Phase I, Recruiting**
  - Thyroid Cancer
  - [^{211}At]NaAt
  - Intravenously injected
  - Estimated Enrollment: 11 patients
- **Fukushima Medical University, Fukushima, Japan) -Phase I trial** (not posted on Clinicaltrials.gov)
  - Neuroblastomas
  - [^{211}At]*meta*-astatobenzylguanidine, [^{211}At]MABG

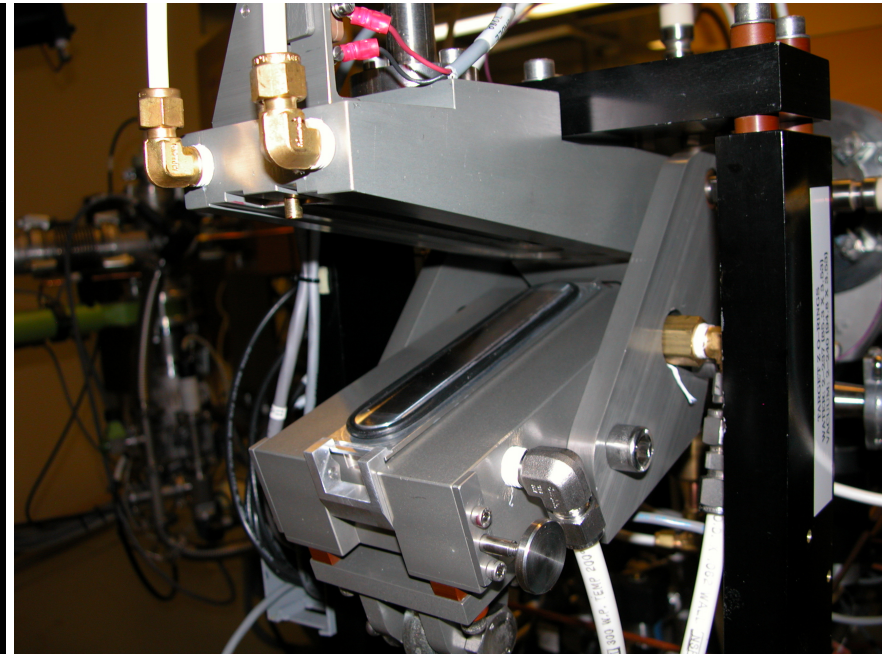
- **Gothenburg, Sweden – NCT04461457 Phase I, Completed in 2012**
  - Ovarian Cancer
  - ^{211}At-labeled MX35 $(Fab)_2$ antibody fragment, targeting NaPi2b
  - Up to 215 MBq/L, or 5.8 mCi/L was administered into the intraperitoneal cavity
  - Treated 12 patients
  - No signs of radiation-related toxicity
  - No decreased tolerance to relapse therapy
  - **Planning for Phase II**

At-211 Production at UW

- $^{209}Bi(\alpha,2n)^{211}At$ nuclear reaction
- External target:
  - Developed in collaboration with TRIUMF, Vancouver, Canada
  - Irradiated at a 10° slant
  - High purity Bi melted onto Al target body, machined to desired thickness
  - Large Bi surface: 120 mm x 18 mm
  - Fully stopping: ~4.25 g of Bi
- 50 µA produces ~26 mCi (0.96 GBq) in 45 min
- 4-5 hour runs for clinical studies to produce 130-150 mCi (4.81 – 5.55 GBq)
- No ^{210}At is observed in the product using 29 MeV alpha beam



Bi target



^{211}At production target station

K. Gagnon, et al., *J. Label Compd. Radiopharm*, 2012, 55 436-440

New At-211 Target and Target Station

- Led by UW Medical Cyclotron Team (Rob Emery and Bob Smith)
- The design is available for DOE University Isotope Network to use

New target and target holder designed to

- Withstand 100 μA of 29 MeV α
- Be compatible with commercial remote retrieval system
- Contain target housing materials that do not to interfere with chemical processing
- Minimize target housing activity for safe handling and minimize long lived rad waste

Target station designed to have

- Ability to remotely load, irradiate, and retrieve targets
- Ability to transfer irradiated targets into shielded pigs or pneumatic target transfer systems connected to hot cells
- Ability to accommodate target material in various forms (e.g. foils, powders, crystals, melted, sputtered or plated material, etc)

“Wet Chemistry” Isolation Method

1. Bi/^{211}At is dissolved in conc. HNO_3

2. HNO_3 is distilled away, leaving Bi salts containing ^{211}At

3. Bi/^{211}At salts are dissolved in 8 M HCl

4. ^{211}At is extracted into DIPE (top layer)

5. Aqueous layer (bottom - HCl) is removed and discarded

6. Wash the DIPE/^{211}At layer 4 times with 8 M HCl

7. ^{211}At is back-extracted into NaOH and transferred to a conical vial

8. The NaOH is neutralized (pH 6.5-7.0) and ^{211}At is ready to be used for antibody labeling

Run time: 2.5 hours

Non-decay corrected yield: ~60%

E.R. Balkin et al., *Applied Sciences, 3, 636-655.*

Production for the NIDC

- **Quotes & Orders: isotopes.gov**
- Batch size:
  - Activity at shipment - 0.518 GBq or 1.85 GBq (14 mCi or 50 mCi)
  - After overnight shipment, ~10% of shipped quantity at receipt due to half-life
- Shipped in near neutral solution (~pH 6.5-7.0)
- Container: plastic V-bottom vial
- Volume: <1 mL
- FedEx Overnight Shipping is used
- Local courier can be arranged if within driving distance from Seattle, WA

Semi-automated Te-packed Column method

1. Pump 15 mL 10 M HNO_3 through the in-line dissolution chamber to dissolve the irradiated Bi target

2. Push air through the fluid path

3. Rinse syringe with D.I. H_2O

4. Add 35% $NH_2OH{\cdot}HCl$ to the ^{211}At/Bi mixture to reduce nitrate concentration

5. Adjust the solution to 1.5 M HCl by adding 8 M HCl

6. Pre-equilibrate the Te column with 1.5 M HCl

7. Transfer 21.5 mL of the prepared ^{211}At/Bi mixture into a 25 mL loop

8. Load the ^{211}At/Bi mixture onto the column at a high flow rate of 6 mL/min

Repeat multiple times to load all the activity

9. Wash the column with 20 mL 1.5 M HCl, followed by 20 mL of D.I. H_2O

10. Elute ^{211}At in 1 mL 1 N NaOH

Te-packed Column Method

- Eliminated the nitric acid distillation step and shortened the overall run time
- Final product contains Te impurity (i.e. Na_2TeO_3) ~20-50 ppm
- Might have breakthrough $NH_2OH{\cdot}HCl$ in the final product
- Semi-automated isolation process takes ~1.5 hours
- Non-decay corrected yield: ~90%
- Radiochemical purity > 99%
- Volume of the final product: 1 mL of 1 M NaOH

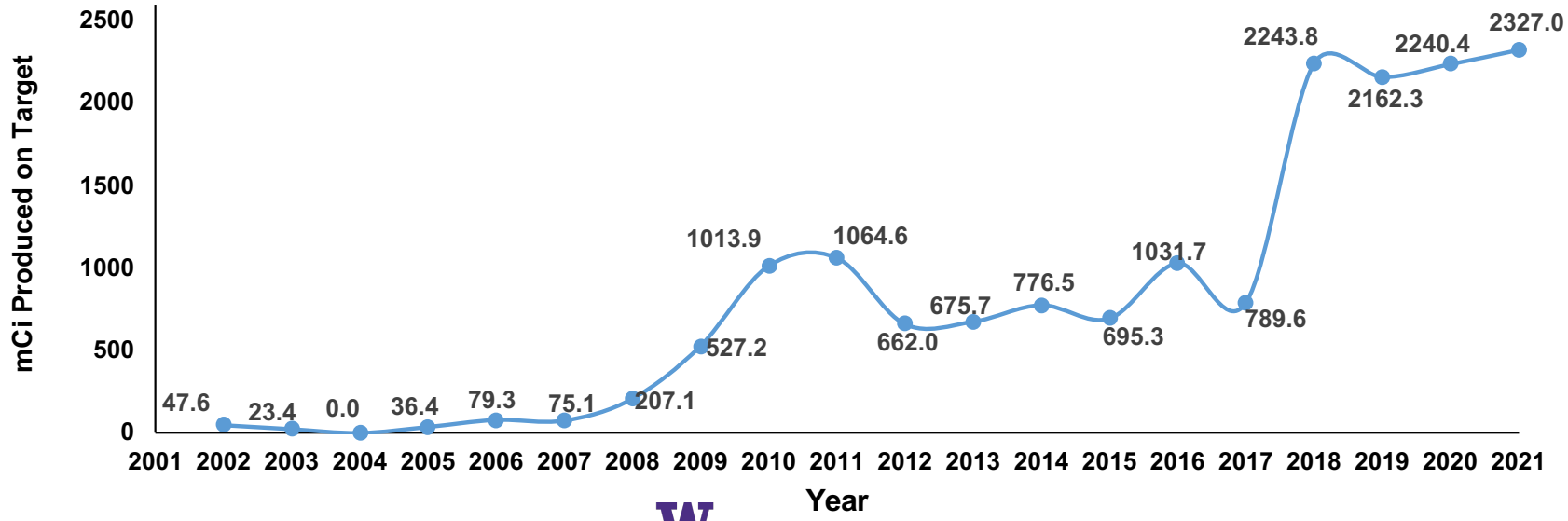
At-211 Obtained Using Te Column Isolation Method

- ^{211}At obtained using the semi-automated Te column method is suitable for labeling of isothiocyanato-phenethyl-closo-decaborate, or B10-NCS conjugated antibodies without added oxidant, providing labeling yields of 70-80%
- The quantities of reagents have been optimized to prevent $NH_2OH{\cdot}HCl$ breakthrough
- A HPLC method using ninhydrin for NH_2OH detection is being evaluated
- Preliminary results suggest the detection limit is lower than 0.05 μg, well below the level known to have any toxicity effect[1,2]

1. Hans Riemann, Acta pharmacol. 1950, 6, 285-292
2. Paul Gross and Roger Smith, CRC Critical Reviews in Toxicology, 14:1, 87-99

Yearly At-211 Production at UW

- Produced and used on average 2.2 Ci (81.4 GBq) ^{211}At per year in the last four years
- ~90 mCi (4%) to other U.S. investigators through the National Isotope Development Center (NIDC)
- ~440 mCi (20%) for chemistry and preclinical studies at the UW and the Fred Hutchinson Cancer Center (FHCC)
- ~1.7 Ci (76%) for three on-going clinical trials evaluating ^{211}At-labeled anti-CD45 antibody BC8



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Research Collaborators

- P.I. Collaborators at the Fred Hutch Cancer Center

Rainer Storb, M.D.

Brenda Sandmaier, M.D.

Ollie Press, M.D., Ph.D. (deceased)

Damian Green, M.D.

Johnnie Orozco, M.D., Ph.D.

Roland Walter, MD., Ph.D.

Hans-Peter Kiem, M.D., Ph.D.

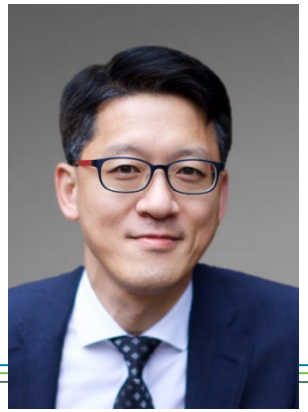
Geoffrey Hill, M.D.

Phuong Vo, M.D.

Seth Pincus, M.D. (now MSU)

PI Collab. at UW

Bob Harrington, M.D.



James Park, M.D.

Fred Hutch / UW At-211 Collaborations

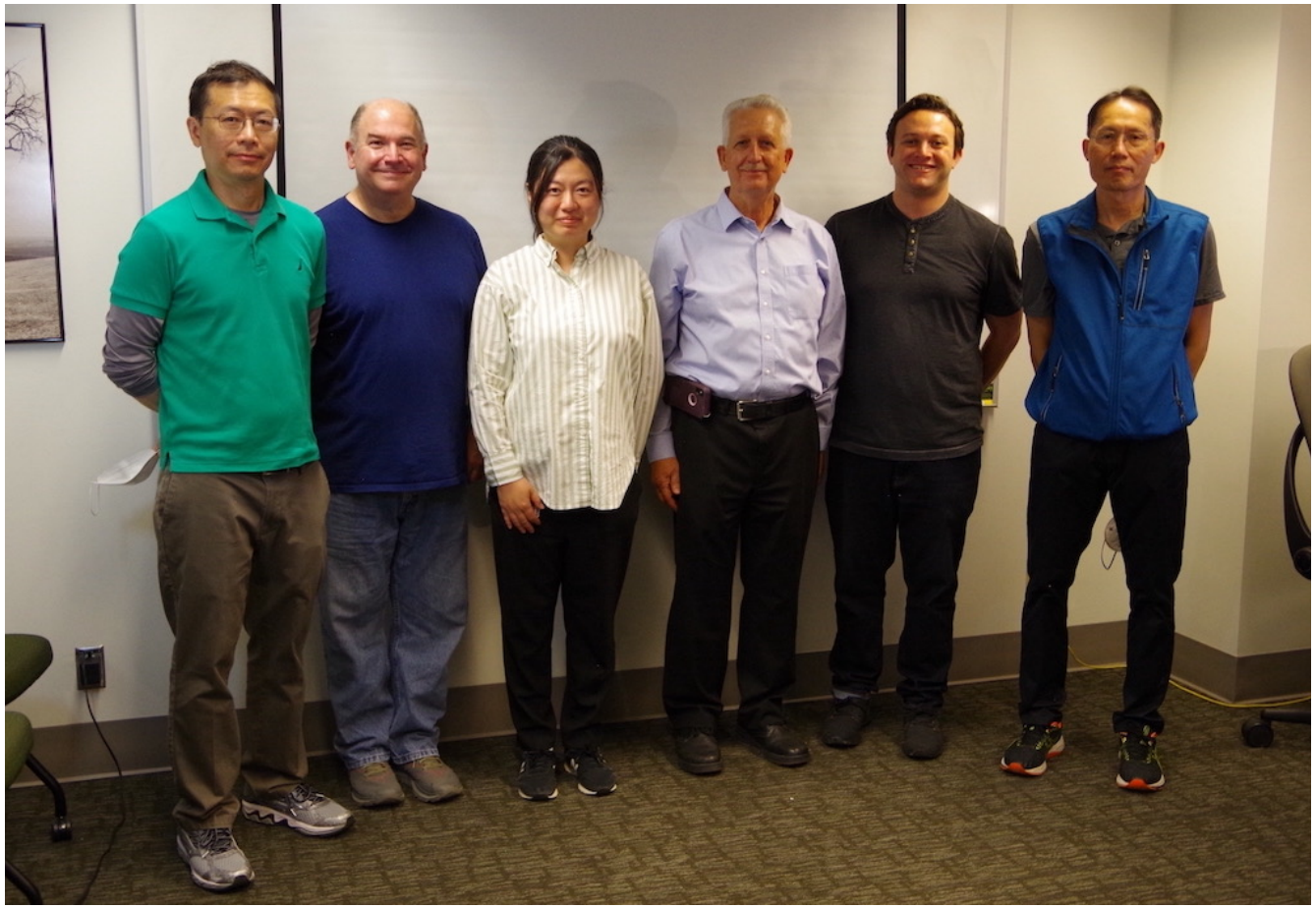
- Non-myeloablative stem cell transplantation
- Cell and gene therapy for nonmalignant blood disorders
- Latent HIV infected cells
- Radioimmunotherapy for lymphoma and leukemias (targeting CD20, CD45, CD33, CD123, CD117)
- Radioimmunotherapy for multiple myeloma (targeting CD38)
- RIT to study graft-vs-host disease
- Radioimmunotherapy with other novel agents for multiple myeloma
- Radioimmunotherapy to treat hepatocellular carcinoma

Our Team

UW Medicine
Radiochemistry Division

From left to right:

- Roger Wong, Research Scientist
- Donald Hamlin, Research Scientist
- Yawen Li, Assistant Professor
- D. Scott Wilbur, Professor Emeritus
- Sean Tanzey, Postdoctoral Fellow
- Ming-Kuan Chyan, Research Scientist



Thank you for your attention!