Astatine-211 DOE Isotope User Group Meeting 2022

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School of Medicine | University of Washington
<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:00 – 1:15 PM (ET)</td>
<td>Yawen Li, University of Washington</td>
<td>- Introduction</td>
</tr>
<tr>
<td>1:15 – 1:30 PM (ET)</td>
<td>Rob Emery, University of Washington</td>
<td></td>
</tr>
<tr>
<td>1:30 – 1:45 PM (ET)</td>
<td>Lauren McIntosh, Texas A&amp;M University</td>
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<tr>
<td>1:45 – 2:00 PM (ET)</td>
<td>Robert Mach, University of Pennsylvania</td>
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<tr>
<td>2:00 – 2:15 PM (ET)</td>
<td>Brenda Sandmaier, Fred Hutchinson Cancer</td>
<td>Center/University of Washington</td>
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<tr>
<td></td>
<td>Corporation</td>
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</tr>
<tr>
<td>2:15 – 2:30 PM (ET)</td>
<td>David Eve, Ionetix Corporation</td>
<td></td>
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<tr>
<td>2:30 – 3:00 PM (ET)</td>
<td>Moderated Q&amp;A</td>
<td></td>
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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 $[^{211} \text{At}] \text{BC8-B10}$
  - 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 $[^{211} \text{At}] \text{OKT10-B10}$
    - 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

- $^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$ 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 $^{210}\text{At}$ is observed in the product using 29 MeV alpha beam

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 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%

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 HNO₃ 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. H₂O

4. Add 35% NH₂OH·HCl to the ²¹¹At/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 ²¹¹At/Bi mixture into a 25 mL loop

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

9. Wash the column with 20 mL 1.5 M HCl, followed by 20 mL of D.I. H₂O

10. Elute ²¹¹At in 1 mL 1 N NaOH

Repeat multiple times to load all the activity
Te-packed Column Method

• Eliminated the nitric acid distillation step and shortened the overall run time

• Final product contains Te impurity (i.e. Na₂TeO₃) ~20-50 ppm

• Might have breakthrough NH₂OH·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

- $^{211}\text{At}$ 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$_2$OH·HCl breakthrough.

- A HPLC method using ninhydrin for NH$_2$OH 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$^{1,2}$

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
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, M.D., Ph.D.

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

Geoffrey Hill, M.D.

Phuong Vo, M.D.

Seth Pincus, M.D.
(now MSU)

Bob Harrington, M.D.

James Park, M.D.

PI Collab.
at UW
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!