Remotely-prepared $^{224}\text{Ra}/^{212}\text{Pb}$ generator columns:

Process overview & recent performance evaluations

Matthew J. O’Hara,
Lucas P. Boron-Brenner
Purpose of Work

- Limited generator availability in the U.S.
  - NIDC presently supplies generators
  - Historically a manual assembly process
    ✓ Time & dose intensive

- Generator demand is increasing
  - Requires improved assembly efficiencies w/ decreased production team dose

- PNNL set out to develop a fully automated fluidic system to isolate $^{224}$Ra from $^{228}$Th feedstock and prepare $^{224}$Ra-loaded generator columns
  - In FY21, we set up & demonstrated the process up to ~3 mCi level
  - In FY22, we scaled up to clinically relevant levels (11-19 mCi)
Part I.
Automated preparation of $^{212}\text{Pb}$ generator
Research Objectives

- Developed the process chemistry for in-line isolation of $^{224}$Ra from $^{228}$Th, and the remote assembly of $^{224}$Ra-loaded generator columns
• Developed the process chemistry for in-line isolation of $^{224}\text{Ra}$ from $^{228}\text{Th}$, and the remote assembly of $^{224}\text{Ra}$-loaded generator columns

• Developed three fluidic modules
  ▪ Module 1: $^{224}\text{Ra}$ purification from $^{228}\text{Th}$
    ✓ In-line removal of dose contributors
    ✓ Radionuclidically pure $^{224}\text{Ra}$
    ✓ Recovery and reuse of $^{228}\text{Th}$
Research Objectives

- Developed the process chemistry for in-line isolation of $^{224}\text{Ra}$ from $^{228}\text{Th}$, and the remote assembly of $^{224}\text{Ra}$-loaded generator columns

- Developed three fluidic modules
  - Module 1: $^{224}\text{Ra}$ purification from $^{228}\text{Th}$
    - In-line removal of dose contributors
    - Radionuclidically pure $^{224}\text{Ra}$
    - Recovery and reuse of $^{228}\text{Th}$
  - Module 2: $^{224}\text{Ra}$ preparation step
    - Convert $^{224}\text{Ra}$ form for optimal CatIX sorption
    - Progeny-free, low-dose
Research Objectives

- Developed the process chemistry for in-line isolation of $^{224}\text{Ra}$ from $^{228}\text{Th}$, and the remote assembly of $^{224}\text{Ra}$-loaded generator columns

- Developed three fluidic modules
  - Module 1: $^{224}\text{Ra}$ purification from $^{228}\text{Th}$
    - In-line removal of dose contributors
    - Radionuclidically pure $^{224}\text{Ra}$
    - Recovery and reuse of $^{228}\text{Th}$
  - Module 2: $^{224}\text{Ra}$ preparation step
    - Convert $^{224}\text{Ra}$ form for optimal CatIX sorption
    - Progeny-free, low-dose
  - Module 3: $^{224}\text{Ra}$/resin binding and column packing
    - Homogenously loaded column beds
    - $^{224}\text{Ra}$ adsorbed across all resin beads
    - High $^{224}\text{Ra}$ binding yield
Research Objectives

- Integrated the modules into an end-to-end system
Research Objectives

- Integrated the modules into an end-to-end system
- Current: Process optimization & generator testing
  - ~1 h end-to-end, from $^{228}$Th feedstock injection to packed $^{212}$Pb generator column ready for load-out
  - Human intervention limited to:
    - $^{228}$Th stock insertion (front end, accomplished inside hot cell)
    - Generator column disconnect (back end)
Research Objectives

• Integrated the modules into an end-to-end system
  • Current: Process optimization & generator testing
    ▪ ~1 h end-to-end, from $^{228}$Th feedstock injection to packed $^{212}$Pb generator column ready for load-out
    ▪ Human intervention limited to:
      ✓ $^{228}$Th stock insertion (front end, accomplished inside hot cell)
      ✓ Generator column disconnect (back end)
  • Near future: Transition from “R&D” to routine production
    ▪ Build system into a hard-walled radiological containment structure
Final generator packing step

- $^{224}$Ra-loaded resin is slurried & delivered in-line to generator column housing assembly

- New acrylic shell assures reduction of:
  - Bremsstrahlung radiation (primarily from $^{208}$Tl beta ($\beta_{max}=1.8$MeV); and
  - Containment of virtually all $^{220}$Rn
Part II.

$^{212}$Pb generator performance evaluations

- Recent testing performed up to ~19 mCi
212Pb / 212Bi generator column performance testing

- Conduct daily milking tests for 10-12 days
  - Evaluate 212Pb + 212Bi co-elution in 2 M HCl
    ✓ (w/ & w/o a disposable “catch column”)
  - Evaluate in-line 212Pb conversion to acetate buffer
- All milkings performed using digital pumps for absolute volume & flow rate control

**Daily 212Pb ingrowth**
\[^{212}\text{Pb}\] milking yield: Traditional milking

- Simple generator column milking process:
  - Flow rate = 1.0 mL/min
  - 1.0 mL 2 M HCl, followed by 1.0 mL H\textsubscript{2}O flush & air for storage
    - Elutes \[^{212}\text{Pb}\] & \[^{212}\text{Bi}\] together

<table>
<thead>
<tr>
<th>Activity level</th>
<th>Generator</th>
<th>Mean yield, (%)</th>
<th>Uncertainty, ±1σ (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-clinical</td>
<td>3</td>
<td>93.64</td>
<td>1.52</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>93.77</td>
<td>1.33</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>92.02</td>
<td>3.57</td>
<td>3</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>93.14</td>
<td>2.22</td>
<td>9</td>
</tr>
<tr>
<td>Clinical</td>
<td>7</td>
<td>92.48</td>
<td>2.88</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>94.81</td>
<td>0.84</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>94.98</td>
<td>0.75</td>
<td>4</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>93.69</td>
<td>2.38</td>
<td>14</td>
</tr>
<tr>
<td>Grand mean</td>
<td></td>
<td>93.48</td>
<td>2.28</td>
<td>23</td>
</tr>
</tbody>
</table>

Traditional milking
212Pb milking yield: w/ “catch column”

- Simple generator column milking process:
  - Flow rate = 1.0 mL/min
  - 1.0 mL 2 M HCl, followed by 1.0 mL H2O flush & air for storage
    - Elutes 212Pb & 212Bi together
  - Generator milked with “catch column”
    - “catch column” placed between generator outlet & 212Pb collection vessel

<table>
<thead>
<tr>
<th>Activity level</th>
<th>Generator</th>
<th>Mean yield, (%)</th>
<th>Uncertainty, ±1σ (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-clinical</td>
<td>3</td>
<td>93.64</td>
<td>1.52</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>93.77</td>
<td>1.33</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>92.02</td>
<td>3.57</td>
<td>3</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>93.14</td>
<td>2.22</td>
<td>9</td>
</tr>
<tr>
<td>Clinical</td>
<td>7</td>
<td>92.48</td>
<td>2.88</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>94.81</td>
<td>0.84</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>94.98</td>
<td>0.75</td>
<td>4</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>93.69</td>
<td>2.38</td>
<td>14</td>
</tr>
<tr>
<td>Grand mean</td>
<td></td>
<td>93.48</td>
<td>2.28</td>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity level</th>
<th>Generator</th>
<th>Mean yield, (%)</th>
<th>Uncertainty, ±1σ (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-clinical</td>
<td>3</td>
<td>92.20</td>
<td>3.87</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>88.00</td>
<td>8.49</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>86.84</td>
<td>1.42</td>
<td>3</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>88.22</td>
<td>6.88</td>
<td>12</td>
</tr>
<tr>
<td>Clinical</td>
<td>7</td>
<td>84.00</td>
<td>5.13</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>92.48</td>
<td>0.63</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>90.06</td>
<td>6.24</td>
<td>4</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>88.44</td>
<td>5.73</td>
<td>15</td>
</tr>
<tr>
<td>Grand mean</td>
<td></td>
<td>88.34</td>
<td>6.14</td>
<td>27</td>
</tr>
</tbody>
</table>

Traditional milking

w/ “catch column”

Disposable ~100µL MP-50 resin bed
\( \text{212}\text{Pb milking yield: Tandem column} \)

- Tandem column milking process (method adapted from [1]):
  - Flow rate = 1.0 mL/min
  - 1.0 mL 2 M HCl generator milking volume, followed by 2 M HCl wash of tandem col.
  - DI water rinse of tandem col.
  - \( \text{212}\text{Pb} \) elution w/ 1.0 mL NaOAc (pH ~6)
  - Elutes \( \text{212}\text{Pb} \) sans \( \text{212}\text{Bi} \)

<table>
<thead>
<tr>
<th>Activity level</th>
<th>Generator</th>
<th>Mean yield, (%)</th>
<th>Uncertainty, ±1s (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-clinical</td>
<td>3</td>
<td>93.64</td>
<td>1.52</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>93.77</td>
<td>1.33</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>92.02</td>
<td>1.57</td>
<td>3</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>93.14</td>
<td>2.22</td>
<td>9</td>
</tr>
<tr>
<td>Clinical</td>
<td>7</td>
<td>92.48</td>
<td>2.88</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>94.81</td>
<td>0.84</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>94.98</td>
<td>0.75</td>
<td>4</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>93.69</td>
<td>2.38</td>
<td>14</td>
</tr>
<tr>
<td>Grand mean</td>
<td></td>
<td>93.48</td>
<td>2.28</td>
<td>23</td>
</tr>
</tbody>
</table>

Traditional milking w/ “catch column”

<table>
<thead>
<tr>
<th>Activity level</th>
<th>Generator</th>
<th>Mean yield, (%)</th>
<th>Uncertainty, ±1s (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-clinical</td>
<td>3</td>
<td>92.20</td>
<td>3.87</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>88.00</td>
<td>8.49</td>
<td>3</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>88.22</td>
<td>6.88</td>
<td>12</td>
</tr>
<tr>
<td>Clinical</td>
<td>7</td>
<td>84.00</td>
<td>5.13</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>92.48</td>
<td>0.63</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>90.06</td>
<td>6.24</td>
<td>4</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>88.44</td>
<td>5.73</td>
<td>15</td>
</tr>
<tr>
<td>Grand mean</td>
<td></td>
<td>88.34</td>
<td>6.14</td>
<td>27</td>
</tr>
</tbody>
</table>

Tandem column

<table>
<thead>
<tr>
<th>Activity level</th>
<th>Generator</th>
<th>Mean yield, (%)</th>
<th>Uncertainty, ±1s (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-clinical</td>
<td>6</td>
<td>92.93</td>
<td>0.29</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>94.55</td>
<td>1.35</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>92.45</td>
<td>0.93</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>92.85</td>
<td>1.87</td>
<td>11</td>
</tr>
</tbody>
</table>

Evaluation of $^{224}$Ra breakthrough

- Each milked $^{212}$Pb product fraction evaluated for presence of $^{224}$Ra
- We age the milked products to determine $^{224}$Ra content @ $t = 0$
  - Count data modeled by two-component exponential decay best fit (*SigmaPlot 14.0*)
  - Generator 9 (~19 mCi) milkings are illustrated here

Example $^{224}$Ra determination @ $t=0$ approach
Evaluation of $^{224}$Ra breakthrough

- Each milked $^{212}$Pb product fraction evaluated for presence of $^{224}$Ra
- We age the milked products to determine $^{224}$Ra content @ $t = 0$
  - Count data modeled by two-component exponential decay best fit (*SigmaPlot 14.0*)
  - Generator 9 (~19 mCi) milkings are illustrated here

Traditional milking (Ra-1)*

* y-axis is $^{212}$Pb+$^{212}$Bi activity, as ‘030’ setting on Capintec CRC-25R
Evaluation of $^{224}$Ra breakthrough

• Each milked $^{212}$Pb product fraction evaluated for presence of $^{224}$Ra
• We age the milked products to determine $^{224}$Ra content @ $t = 0$
  ▪ Count data modeled by two-component exponential decay best fit (*SigmaPlot 14.0*)
  ▪ Generator 9 (~19 mCi) milkings are illustrated here

\[ \text{Activity, MBq} \]
\[ \text{Generator age, d} \]

* y-axis is $^{212}$Pb+$^{212}$Bi activity, as ‘030’ setting on Capintec CRC-25R
Evaluation of $^{224}\text{Ra}$ breakthrough

- Each milked $^{212}\text{Pb}$ product fraction evaluated for presence of $^{224}\text{Ra}$
- We age the milked products to determine $^{224}\text{Ra}$ content @ $t = 0$
  - Count data modeled by two-component exponential decay best fit (*SigmaPlot 14.0*)
  - Generator 9 (~19 mCi) milkings are illustrated here

*Tandem column (Ra-3)*

* y-axis is $^{212}\text{Pb} + ^{212}\text{Bi}$ activity, as ‘030’ setting on Capintec CRC-25R
Evaluation of $^{224}\text{Ra}$ breakthrough, cont’d

- $^{224}\text{Ra}$ breakthrough fractions for Generator 9 are illustrated below
Evaluation of $^{224}$Ra breakthrough, cont’d

- $^{224}$Ra breakthrough fractions for Generator 9 are illustrated below
- Overall mean values across all generators prepared to date ($\pm 1\sigma$):
  - Traditional: $(3.0 \pm 2.1) \times 10^{-3}$ (n=20)
  - w/ catch col.: $(1.9 \pm 1.7) \times 10^{-4}$ (n=25)
  - Tandem col.: $(1.8 \pm 1.8) \times 10^{-4}$ (n=17)
Radiolabeling studies on $^{212}$Pb product fractions

- Conducting $^{212}$Pb product titrations with TCMC chelate [2] to assess $^{208+212}$Pb binding affinities in NaOAc sol’ns
  - $1/10^{th}$ of product added to increasing quantities of TCMC, in pH 6 NaOAc buffer
  - [Preliminary] evaluation of differences in $^{208+212}$Pb binding to TCMC between the various milking methods described herein
    - ✓ To date, we see a ~10x Pb:TCMC binding improvement when employing the tandem column method

[2] 1,4,7,10-Tetrakis(aminocarbonylmethyl)-1,4,7,10-tetraazacyclododecane
Next steps for FY23:

- PNNL working towards becoming a NIDC supplier (≤ 15 mCi)
  - Would begin with monthly production schedule, with capacity to increase production frequency as demand dictates

- Concurrently, we will evaluate our ability to produce higher-activity generators (≤ 50 mCi)
  - And will assess whether higher activities result in diminishing generator performance / radiolytic effects

- [Contact NIDC if interested in conducting an independent performance evaluation on these generators]
Summary

• Developed a remote fluidic system for auto-preparation of generators
  ▪ Dramatic reduction in production staff dose
  ▪ End-to-end processing time of ~1 h
  ▪ Reproducible $^{224}$Ra loading (±2%)
  ▪ Near-quantitative $^{228}$Th feedstock recycling (99.6±1.2%)
  ▪ Acrylic shell inhibits Bremsstrahlung & $^{220}$Rn leakage

• FY22 was first generator testing at clinical (11-19 mCi) levels
  ▪ Pb milking yields (~90% in 1mL of 2M HCl)
  ▪ Radionuclidic purity ($^{224}$Ra breakthrough) is dependent on three milking options evaluated
  ▪ $^{208+212}$Pb product binding evaluations w/ TCMC chelate are ongoing
    ✓ Pb:TCMC binding is dependent on milking option; with tandem column method demonstrating highest TCMC binding efficacy

• In FY23:
  ▪ Anticipate transition to production on behalf of NIDC
  ▪ And, anticipate evaluating generators w/ scaled-up $^{224}$Ra levels
Acknowledgements

• This research was supported by the U.S. Department of Energy Isotope Program, managed by the Office of Science.

• PNNL’s Shielded Facilities Organization (SFO):
  ✓ Johnny Trevino
  ✓ April Wickersham
  ✓ Robert Cox
  ✓ Nicole Strom
  ✓ Jordan Condray
  ✓ Michael Hansen

• Radiological safety:
  ✓ Woody Buckner
  ✓ Marilyn Wirth

• System & software support:
  ✓ Jared Johnson

Thank you!