Medical Countermeasures for Treating Internal Deposits of Radionuclides

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Goal of Decorporation

- Decorporation
  - Dose Reduction
    - Risk Reduction
Decorporation Strategy

- Nuclide
  - Local Deposit
    - Blood
      - Tissue
        - Systemic
          - Deposit
        - Excretion
      - Excretion
Decorporation Strategy

- Nuclide
- Local Deposit
- Prevent Absorption
  - Prevent Translocation
  - Systemic Deposit
- Blood
- Tissue
- Enhance Excretion
  - Excretion
- Reduce Local Dose
Treatment Strategies for Highly Contaminated People

- **Chemical Methods for Soluble Materials**
  - Blocking agents (KI)
  - Isotopic dilution (Ca, Zn, K)
  - Ion exchange (Prussian Blue, alginates)
  - Chelating agents
    - EDTA (Pb, Zn, Cu, Cd, Cr, Mn, Ni)
    - DTPA (Pu, Am, Cm, Lanthanides)
    - DMSA, DMPS, BAL (Hg, Pb, Cd, As, Au, Po)

- **BARDA stockpile (USA)**
Features of DTPA (diethylenetriaminepentaacetic acid)

- Ca and Zn chelates (Ca better on day 1)
- Administered dose: 30 μmole kg\(^{-1}\) (1 g per 70 kg)
- Accepted routes of administration
  - Intravenous injection or infusion
  - Nebulized DTPA solution
- GI absorption: about 3%
- Effective for Th, Pu, Am, Cm, Cf
  - Not U, Np
- **Matching drug and actinide biokinetics is key to successful decorporation**
Example of DTPA Efficacy in Humans

- 1976 Hanford $^{241}$Am accident in which one worker received an intake of about 200 MBq

- DTPA treatment begun within 2 h of exposure; multiple treatments daily over first weeks, daily for about 1 y, then more separated.
  - 583 g administered 1976-1980

- Surgery plus daily surface decon during first week
  - 185 MBq → 14 MBq in 10 d

- Total excretion:
  - 41 MBq (half in first 3 d)
  - 80% in urine
  - 98% in 1 y

- About 99% dose sparing to systemic organs
Issues and Research with Actinide Decorporation

- **Oral forms:**
  - Need for stockpiling

- **Targeting intracellular deposits:**
  - Liposomes

- **Targeting inhaled deposited radionuclides:**
  - Aerosols

- Need for better chelating agents?
Efficacy of an Oral Formulation of DTPA

- Rats given single inhaled dose of $^{241}\text{Am(NO}_3)_3$
- CaDTPA at 1 d
- Either IV or oral (high and low dose) ZnDTPA daily through 7 d
- Sacrifice at 14 d
- Material balance design (>90% recovery)
Efficacy of Oral Formulation of DTPA for Decorporating Am-241 In Rats

Excretion of $^{241}\text{Am}$ Excreted in Urine in Rats That Inhaled Am-Nitrate

- Control
- IV DTPA
- Low Dose oral
- High Dose oral

Fractional $^{241}\text{Am}$ Excretion Rate (% d$^{-1}$)

Time after $^{241}\text{Am}$ Inhalation (d)

(proprietary data)
Efficacy of Oral Formulation of DTPA for Decorporating Am-241 In Rats

Liver Retention of $^{241}$Am in Rats 14 Days after Inhalation of Am-Nitrate

Liver Content of $^{241}$Am (% ID)

- Control
- IV DTPA
- Low Dose Oral
- High Dose Oral

Treatments daily on d 1-7; sacrifice on d 14

(proprietary data)
Enhancing Intracellular Uptake of DTPA for Decorporation

- $^{238}$Pu-citrate injected IV in rats
- DTPA (free, or conventional or “stealth” liposome) @ 2 h
- At 16 d:

<table>
<thead>
<tr>
<th>Sample</th>
<th>Ctrl</th>
<th>Free</th>
<th>Lip(conv)</th>
<th>Lip(stlth)</th>
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<tbody>
<tr>
<td>Liver</td>
<td>4.8</td>
<td>3.6</td>
<td>1.5</td>
<td>2.6</td>
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<tr>
<td>Bone</td>
<td>63</td>
<td>50</td>
<td>45</td>
<td>42</td>
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<tr>
<td>Urine</td>
<td>7</td>
<td>16</td>
<td>25</td>
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</table>

- Prolonged retention of stealth liposomes; increased intracellular uptake

Phan et al. 2004
Targeting Inhaled Actinide in Lung

- Dry powder DTPA powder
- Insufflated into rats exposed to $^{238}$Pu-nitrate 2 h or 7 d previous

<table>
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<tr>
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<th>% Initial Lung Dose</th>
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<tr>
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<td>Lung</td>
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<td>Control</td>
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<td>DTPA-iv (1h)</td>
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<td>DTPA-aer (1h)</td>
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<td>DTPA-iv (7d)</td>
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<td>DTPA-aer (7d)</td>
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</table>
Efficacy of LBNL HOPO Compounds for Decorporating Pu-239 in Dogs

- Groups of 3 female dogs
- Single IV injection of $^{239}$Pu-citrate
- $3,4,3$ Li[$1,2$ HOPO] (octadentate) or $5$-LiO[Me $3,2$ HOPO] (tetradentate) ligands
  - Single oral administration given at 0.5, 3, 7 days after Pu
  - $3,4,3$ Li[$1,2$ HOPO] @100 µmole/kg; $5$-LiO[Me $3,2$ HOPO] @300 µmole/kg
- Sacrifice 7 days after therapy
- Material balance design (about 87% average recovery)
Efficacy of LBNL HOPO Compounds for Decorporating Pu-239 in Dogs

Average % Recovered Dose in Cumulative Combined Urine and Feces Following Pu-239 Administration

Graph showing the average % recovered dose in cumulative urine and feces for different groups over various time periods.
Efficacy of LBNL HOPO Compounds for Decorporating Pu-239 in Dogs

Average % Recovered Dose in **Liver** Following Pu-239 Administration

Average % Recovered Dose in **Total Bone** Following Pu-239 Administration
Summary

- For trivalent and tetravalent actinides, good treatments exist using DTPA
- Recent research seeks to improve efficacy and ease of administration by:
  - Oral formulation
  - Dry powder aerosols for inhaled radionuclide
  - Enhancing intracellular uptake
  - Demonstrating new compounds
- Chelators for other radionuclides needed:
  - For example, Co, Sr, Ir, Po, Ra
  - Pediatric formulations needed
Fig. 3. Comparison of predicted urinary excretion rates after acute intake of transportable plutonium with DTPA administered immediately and 2 days after contamination.

Hall et al. Health Phys. 1978
TREATMENT STRATEGIES FOR HIGHLY CONTAMINATED PEOPLE

Reduce the dose to be received by accelerating radionuclide removal

- Physical Methods for Insoluble Materials
  - Skin decontamination
  - Nasal irrigation
  - Emetics, gastric lavage, purgatives
  - Surgical excision
  - Bronchopulmonary lavage