Lead-212/Bismuth-212 in Preclinical Research

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Candidate Alpha Emitters

	Half-life	Production	Emissions
• Astatine-211	7.2 h	cyclotron	1 α
• Bismuth-212	60 m	generator	1 α
• Bismuth-213	46 m	generator	1 α
• Actinium-225	10 d	generator	4 α
• Radium-223	11 d	generator	4 α
• Terbium-149	4 h	cyclotron	α, $\beta+$
• Fermium-255	20 h	generator	1 α

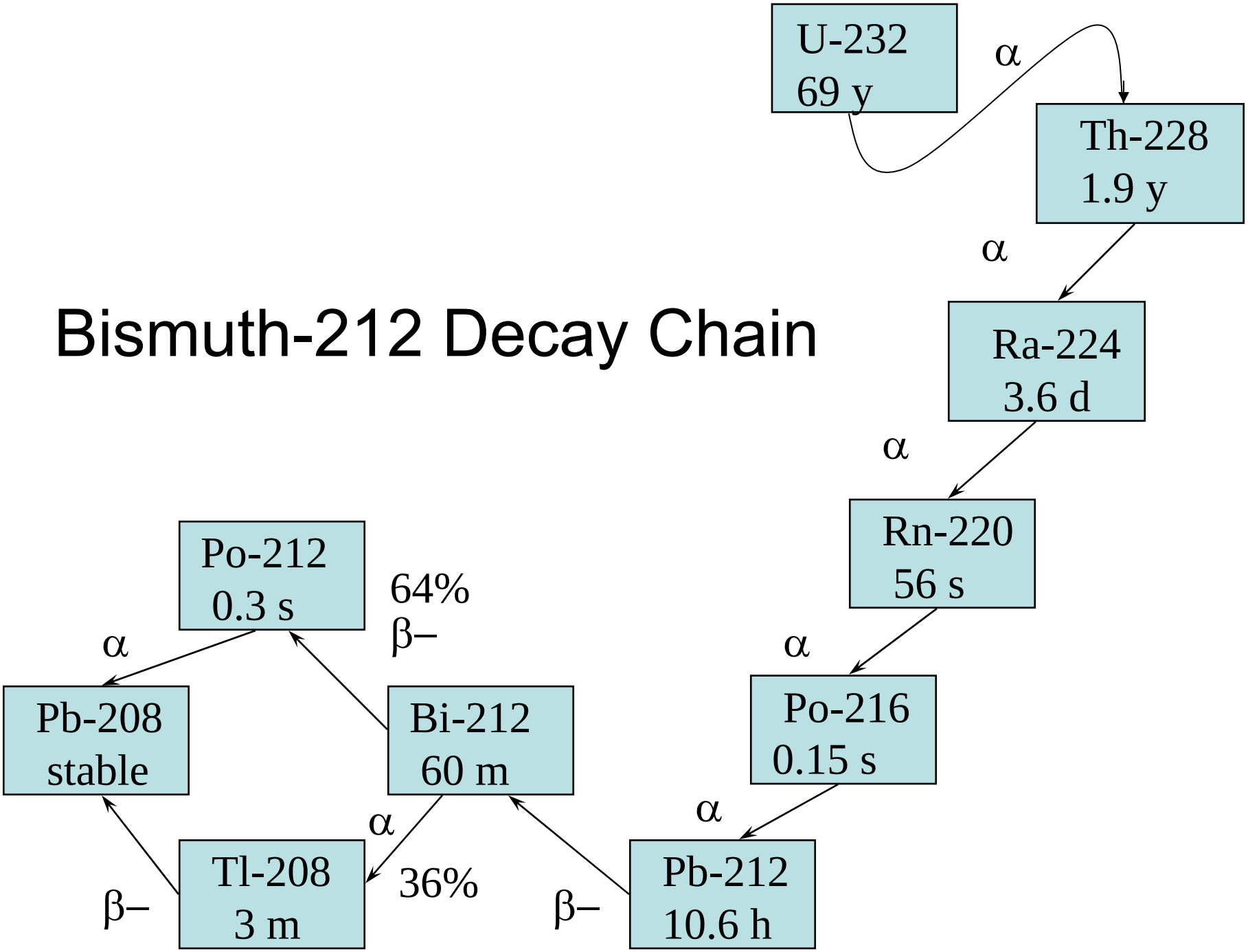
Why Alpha Emitters?

- Effective cell killing owing to high ionization density radiation (100 keV/μm), producing double-strand DNA breaks--with little chance of cell repair and survival
- Ideal path length for (40 to 80 μm) for treating micrometastases and sparing adjacent normal tissues
- Effective under hypoxic conditions
- Not dose-rate limited

Disadvantages

- Challenging chemistry
- Limited availability
- High production-campaign costs
- Decay chains whereby the daughter products are not linked to the carrier molecules
- Physical half-lives that may be too long or too short
- Short particle ranges in large tumors compared to beta emitters

Bismuth-212 Decay Chain



Bismuth-212 (60 m)

- ☺ Potentially abundant starting material
- ☺ Generator chemistry from parent Ra-224
- ☺ Lead and bismuth chelates available (DTPA and DOTA families)
- ☺ Antibody and peptide labeling experience
- 😐 Moderately expensive
- ☹ Short physical half-life
- ☹ High-energy gamma (2.6 MeV) from daughter Tl-208 requires heavy generator shielding

Historical perspectives

- Alpha particle radiobiology experiments (Barendsen), 1960s
- Bismuth chelates developed (Kozak, Brechbiel, Gansow, *et al.*), 1986
- Successful Bi-212-antibody treatment of EL-4 ascites in mice (Macklis *et al.)*, 1988
- Bi-212 generator (Atcher), 1989
- Clinical trials at Memorial Sloan-Kettering Cancer Ctr. with Bi-213-Hum195 in leukemia (Scheinberg),1997
- At-211-81C6 (anti-tenascin) therapy of cystic gliomas (Bigner and Zalutsky), 1997
- Successful Pb-212/Bi-212-peptide therapy of metastatic melanoma in mice (Miao, 2005)

Alpha-emitter Applications

- Radioimmunotherapy of cancer
  - diffuse tumors (leukemia, lymphoma)
  - solid tumors (brain, lungs, liver, colon, etc.)
- Metastases (melanoma)
- Agents targeting neuroendocrine tumors
- Pleural ascites and ovarian cancer
- Bone pain relief (breast and prostate metastases)
- Bone cancer

AlphaMed Ra-224/Pb-212 Generator System

- 300 mCi U-232 transferred by DOE to AlphaMed, Inc., from stocks at the U of Chicago and Oak Ridge National Laboratory
- Hot cell and dedicated glove box space to minimize exposures and Rn-220 (thoron) release
- AlphaMed proprietary chemistry: separating Ra-224 from an equilibrium mixture of U-232 and Th-228
- Loading Ra-224 onto a shielded generator column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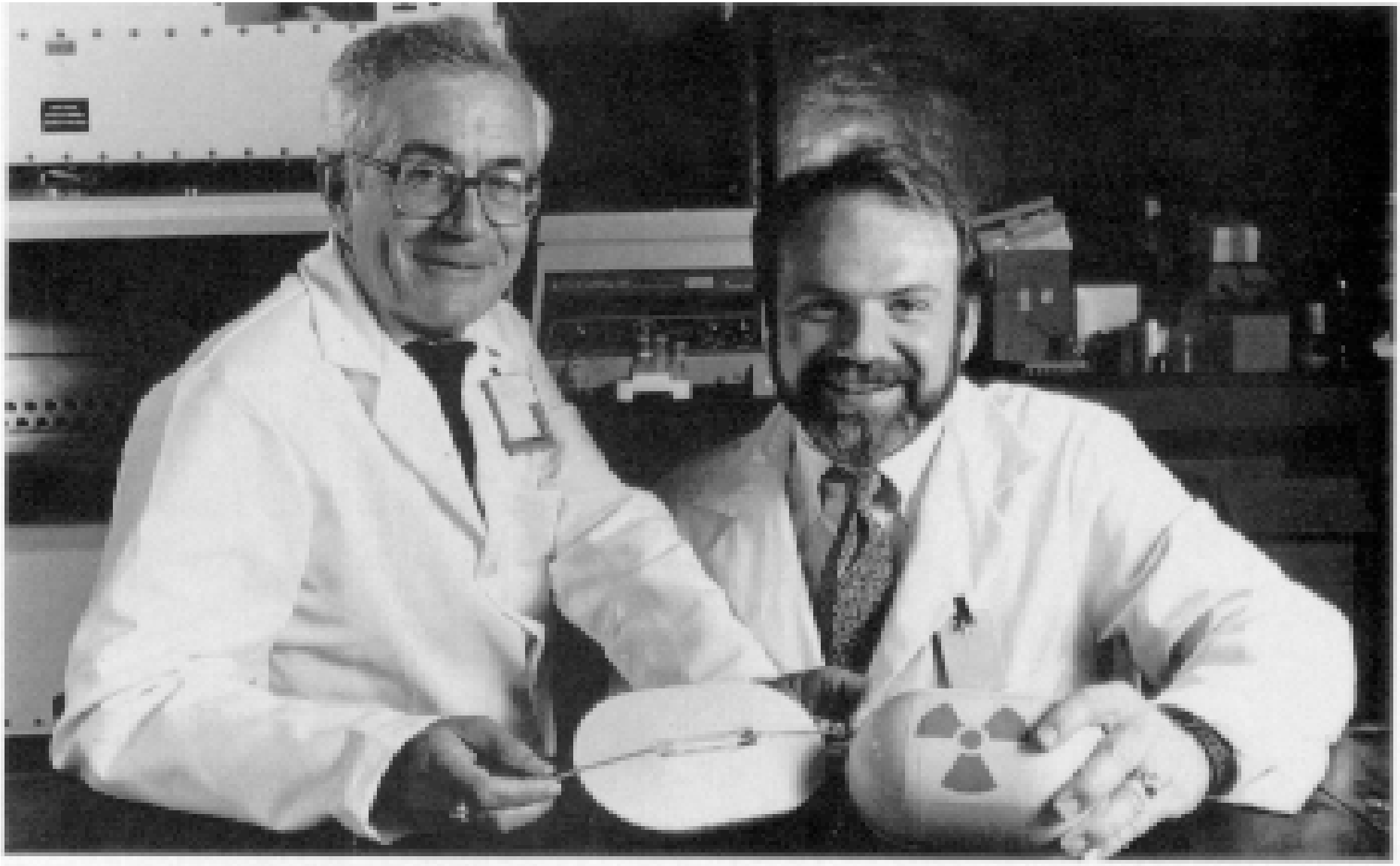
Generator material loading into standard shipping container



Argonne National Laboratory scientists John Hines (left) and Bob Atcher with their device for the production of bismuth-212

Pb-212/Bi-212 Generator

Prior technology: US. Patent 4663129 (1987) by Atcher, Friedman and Hines; *Appl Radiat Isot 3*9:283-286 (1988)

- Thorium-228 and a carrier solution added to a generator system
- Th-228 retained by a strongly basic anion exchange column
- Ra-224 passed through, and transferred to an acidic cationic exchange column
- Cationic column retained the radium-224
- Natural decay generated lead-212 bismuth-212
- Pb-212 and Bi-212 eluted for use

Early Antibody Labeling Studies

- Kozak *et al*., 1986, “Bismuth-212-labeled anti-Tac monoclonal antibody: alpha-particle-emitting radionuclides as modalities for radioimmuno-therapy.” *Proc Natl Acad Sci U S A.* 83(2):474–478; (1986)
- Antibody directed to the human interleukin-2 (IL-2) receptor using a bifunctional ligand of DTPA--*provided the scientific basis for use of alpha-particle-emitting radionuclides in immunotherapy*

Contemporary Studies

- Lead-212 (10.6 hrs) complexed to the delivery protein to allow longer time for cancer cell uptake; serves as *in vivo* generator for decay product Bi-212
- Applications in
  - ovarian and breast cancer (Brechbiel and others, NCI-Bethesda)
  - melanoma metastases (Quinn, Miao and others, University of Missouri-Columbia)
- Co-labeling with Pb-203 for gamma imaging and dosimetry (half-life = 52 hr) (Miao *et al*., 2008)

Preclinical Studies

- Complete elimination of beast cancer xenografts using Pb-212 linked to an anti-HER2/neu mAb: Brechbiel and Waldmann, 2000. "Anti-HER2 Radioimmunotherapy," *Breast Dis*. 11:125-32.
- ERB2/neu is a receptor protein whose overexpression strongly correlates with poor prognosis in breast carcinomas; *this work showed the application of Pb-212 antibody against breast cancer metastases and suggested a pretargeting strategy*.

Preclinical Studies (continued)

- Therapy of disseminated peritoneal disease using Pb-212-labeled Herceptin as an in vivo generator of Bi-212: Milenic et al., 2005, “Alpha-particle radioimmunotherapy of disseminated peritoneal disease using a Pb-212-labeled radioimmunoconjugate targeting HER2,” *Cancer Biother Radiopharm*. 20(5):557-68.
- This pilot radioimmunotherapy experiment treated mice bearing LS-174T intraperitoneal xenografts and determined a maximum tolerated dosage of 20-40 uCi with i.p. administration.

Preclinical Studies (continued)

- Treatment of melanoma metastases in mice using Pb-212-peptide: Miao *et al.*, 2005, "Melanoma Therapy via Peptide-Targeted Alpha Radiation." *Clin Cancer Res* 11:5616-5621. This work showed that treatment of B16/F1 murine melanoma-bearing mice with ^{212}Pb[DOTA]-Re(Arg11)CCMSH significantly decreased tumor growth rates resulting in extended mean survival times, and in many cases, complete remission of disease.
- Pb-212-DOTA-Re(Arg11)CCMSH was *shown to be a promising radiopharmaceutical for targeted radionuclide therapy of melanoma*.

Conclusions

- Lead-212/Bi-212 can be delivered via radionuclide generator for preclinical studies leading to clinical applications.
- Can be co-labeled with Pb-203 for imaging and dosimetry.
- Enables effective therapy of cancer, particularly metastases, with substantial future promise.
- Clinical studies likely to begin in the next year or two.
- DOE could help secure additional quantities of U-232 for expanded use.