Isotope Production at MU Research Reactor Center

ISMTR

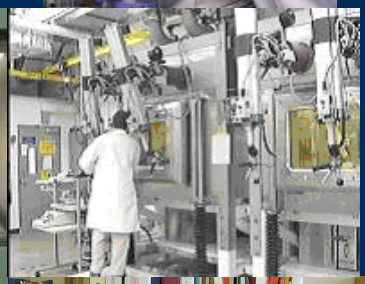
September 2009

University of Missouri Research Reactor Center

The MURR Center

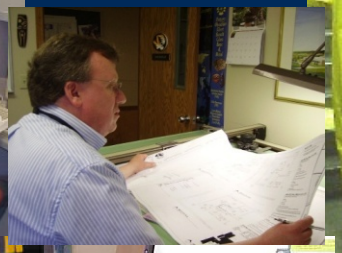
- A 10 MW reactor that operates 24 hours a day, 6.5 days a week, 52 weeks a year
- 150 full time employees
- In 2008, produced 49 different isotopes with >1000 shipments to 14 different countries
- Each and every week MURR supplies the active ingredients for FDA approved Quadramet® and TheraSpheres®









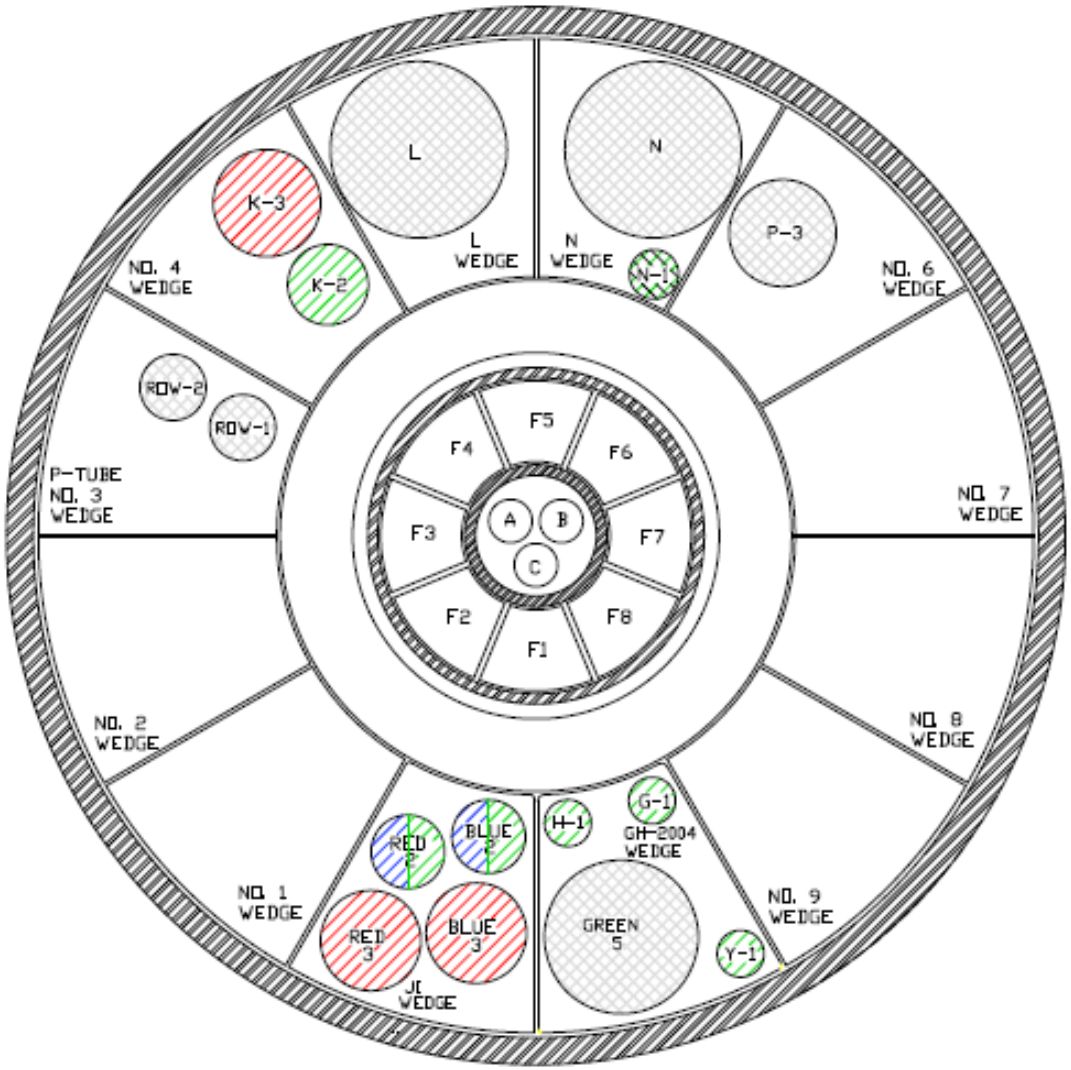






University Research Reactors (Power ≥ 1 MW)

Facility	Power (MW)
University of Missouri-Columbia	10
Massachusetts Institute of Technology	5
University of California – Davis	2
Rhode Island Nuclear Science Center	2
Oregon State University	2
University of Texas – Austin	1
North Carolina State University	1
Pennsylvania State University	1
Texas A&M University	1
University of Massachusetts – Lowell	1
University of Wisconsin	1
Washington State University	1

Irradiation Positions



Flux trap

1E14 to 5E14 n cm^{-2} s^{-1}

Reflector

2E13 to 8E13 n cm^{-2} s^{-1}

Pneumatic tubes

5E13 & 8E13 n cm^{-2} s^{-1}

Recent Infrastructure Upgrades

R&R Grant, DOE, $6.6M, 9/29/00 – 12/31/08

Description	Expenditure
New Fire Detection/Suppression System	713,919
New Primary and Pool Coolant Heat Exchangers (3)	578,780
2006 Beryllium Reflector	533,624
Engineering Assessments for relicensing	519,721
Type B Shipping Casks	480,000
Radioactive Liquid Waste Disposal System Upgrades	430,810
Facility Electrical Distribution System Upgrades	424,566
Security & Surveillance Enhancements	326,941
Revised/Updated Safety Analysis Report for relicensing	288,000
Hot cell Processing	160,665
New Reactor Plant Make-Up Water Storage Tanks (2)	149,423
New Stack Monitor	119,429
New Control Blades	115,647
Containment Building 15-Ton Overhead Crane Catwalk	95,436
New Graphite Reflector Elements	84,831
Reactor Instrumentation Upgrades	65,097

Infrastructure Upgrades for Continued Operation

Description	Estimated Cost
New Type B shipping containers (2009)	1,300,000
Beryllium Reflector (2013)	800,000
Control Room Instrumentation	25,000
New Control Rod Drives	15,000
Replace HVAC Fume Hoods	100,000
Replace Cooling Tower	1,500,000

"Some isotopes are produced at the 10-MW Missouri University Research Reactor" U.S. DOE Workshop on The Nations

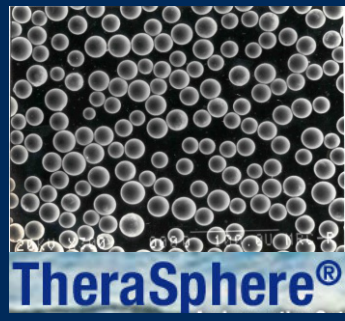
Need for Isotopes: Present and Future, August 2008

Isotopes Shipped in 2008 (49)		
As-76	Ho-166	S-35
Au-198; Au-199	Ir-192	Sb-122; Sb-124
Ba-135m	K-42	Sc-46
Ca-45; Ca-47	La-140	Se-75
Ce-141	Lu-177	Sm-153
Co-60	Na-24	Sn-125
Cr-51	Nd-147	Sr-89
Cs-134	P-32; P-33	Tb-161
Eu-154	Pd-109	Tl-204
Fe-55	Pm-149	Y-90
Fe-59	Pt-195	Yb-169; Yb-175
Gd-159	Rb-86	Zn-65
Ge-71	Re-186; Re-188	Zr-95; Zr-97
Hg-197; Hg-203	Rh-105	

Isotope R&D for Radiopharmaceuticals

A 25-year history of successful and innovative radiopharmaceutical R&D and collaborations with industry….

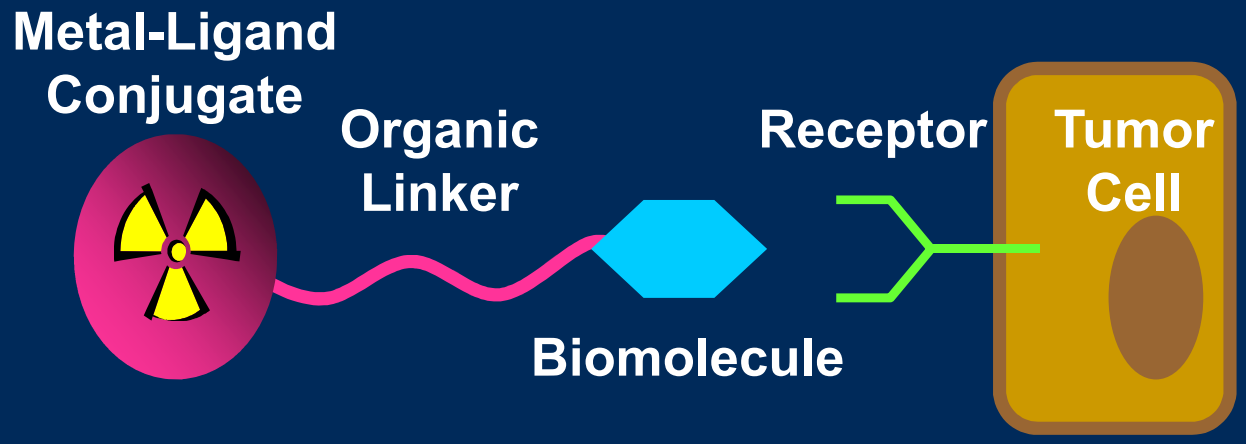
- **Ceretec™** (with Tc-99m), a diagnostic used to evaluate cerebral blood flow in patients & label white blood cells
- **Quadramet®** (with Sm-153), a therapeutic for treatment of pain associated with metastatic bone cancer
- **TheraSphere®** (with Y-90), a glass microsphere used to treat patients with inoperable liver cancer



Isotope R&D for Targeted Radiotherapy

Currently developing a suite of ***carrier free lanthanides*** to work in conjunction with ***selective targeting agents*** to locate and treat cancer.

Ln	$t_{1/2}$	β_{max}	E_γ (I_γ)	Avg Range (cell diameter)
^{177}Lu	6.7 d	0.5 MeV	208 keV (11%)	20
^{166}Ho	1.1 d	1.8 MeV	81 keV (7%)	120
^{149}Pm	2.2 d	1.1 MeV	286 keV (3.1%)	60



Isotope R&D for Targeted Radiotherapy

$^{176}Lu\ (n,\gamma)\ ^{177}Lu$

$^{176}Yb\ (n,\gamma)\ ^{177}Yb \xrightarrow[1.9\ h]{\beta^-} {}^{177}Lu$

Currently supplying 10-20 Ci per week. Typical dose ~ 200 mCi

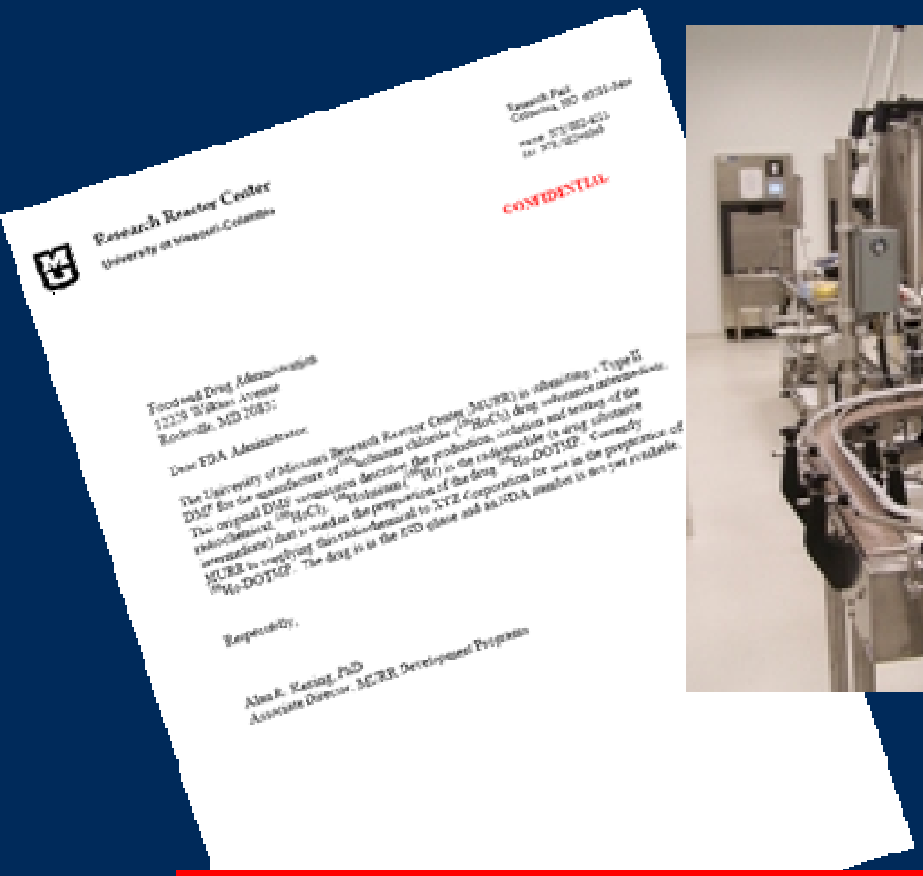
- Direct ~20 Ci/mg
- Indirect ~ 100 Ci/mg

Lu-177 from MURR is currently being evaluated in over 30 clinical applications for radiotherapy of cancer including:

- Prostate cancer
- Non-hodgkins lymphoma
- Ovarian cancer
- Metastatic bone cancer
- Renal cell carcinoma

Radiolabelled Regulatory Peptides for Imaging and Therapy, W.A.P. Breeman, et al., *Anti-Cancer Agents in Medicinal Chemistry*, 7, 345-357 (2007).

cGMP Lu-177
Fall 2009


Research Reactor Center
University of Missouri-Columbia

CONFIDENTIAL

Dear FDA Administrator,

Respectfully,

Alan A. Kaissi, PhD
Associate Director, MURR Developmental Programs

1906 - 2006 FDA Centennial

U.S. Food and Drug Administration

U.S. Department of Health and Human Services

Isotope R&D for Targeted Radiotherapy

Rh-105

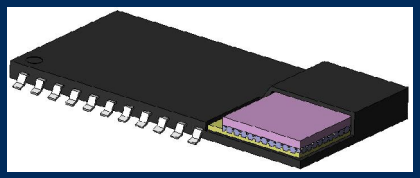
- Carrier free from fission production of Mo-99
- 1.5 d half-life
- Medium energy beta emitter (0.566 MeV)
- Forms kinetically inert complexes

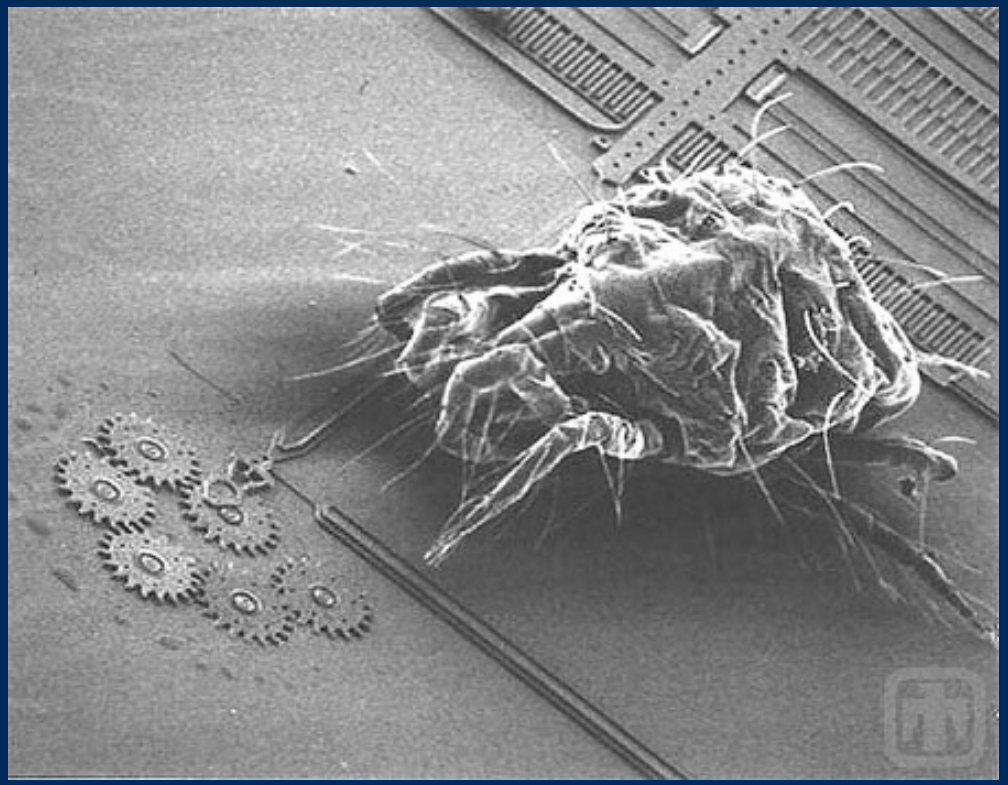
Au-199

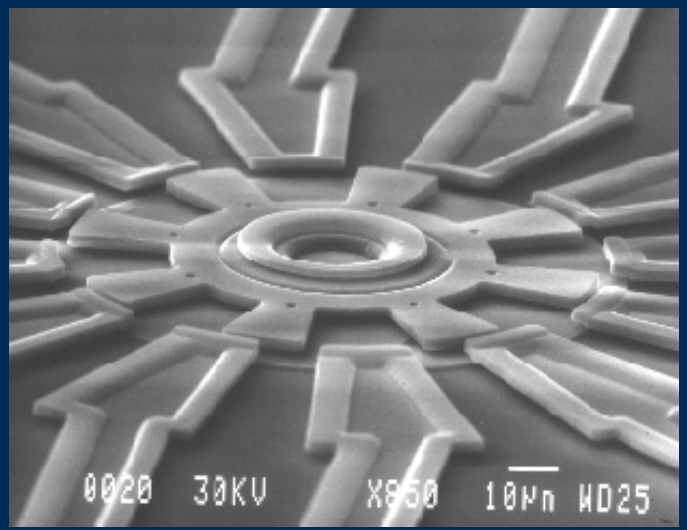
- Carrier free from $^{198}Pt(n,\gamma)^{199}Pt \rightarrow {}^{199}Au$
- 3.1 d half-life
- Medium energy beta emitter (0.453 MeV)
- 158 keV γ-ray (37%) for imaging
- Potential for delivery as nanoparticle

Radioisotope R&D for Micropower Sources

- Unattended sensors for intelligence and surveillance – 1-10 mW
  - Ground based
  - Space based
  - Unmanned air and sea vehicle based
- Microvalve - < 1 mW
- Accelerometer – 2-12 mW
- Motion/intruder detection – 2-12 mW
- Biomedical MEMS devices – 6-10 mW







Courtesy SNL, SUMMiTTM Technologies, www.mems.sandia.gov

Radioisotopes For Micropower Sources

Energy Content Comparison

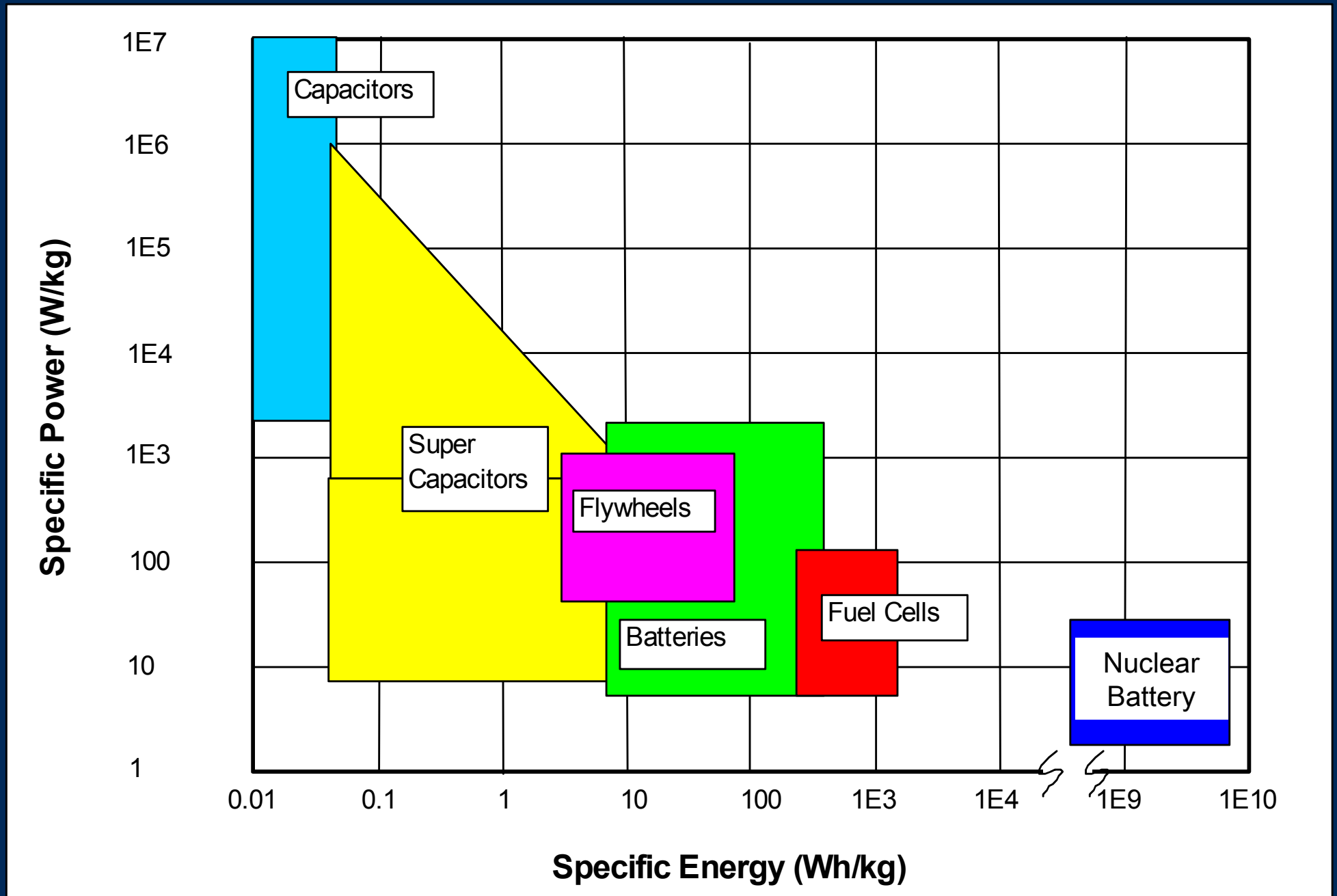
1 mg Energy Source	Energy Content (mW-hr)
Li-ion chemical battery	0.3
CH_3OH fuel cell (50% eff)	3
^{210}Po (5% eff, 4 years)	3000
^{3}H, (5% eff, 4 years)	500

Energy change per event:

- Chemical reaction, 1 to 5 eV
- Beta decay, 100 to 500,000 eV
- Alpha decay, 5,000,000 eV

Radioisotopes For Micropower Sources

Ragone Plot



Potential Isotopes for Radioisotope Micropower Source Applications

Radioisotope	E_{avg} (keV)	Half-life (years)	Maximum BOL activity (TBq/cm^3)	Maximum BOL source power (mW/cm^3)	Particle range in source (μm)	"Realistic" BOL P_{out} ($\mu W/cm^2$)
^{147}Pm	61.8	2.6	247	2448	9.6	141.1
^{210}Po	5304	0.38	1566	1.3E6	1	1.4E4

β source

- 100% isotope enrichment
- η_{conv}=10%, η_{source}=30%
- source thickness=2 x beta range

α source

- 100% isotope enrichment
- η_{conv}=10%, η_{source}=90%
- source thickness=1 μm

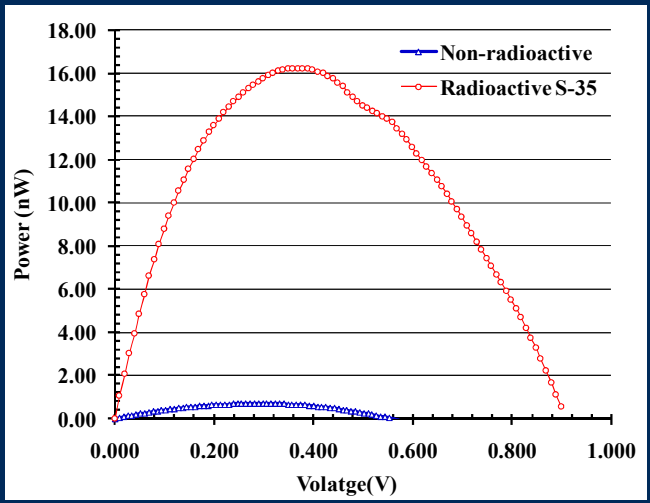
Liquid Semiconductor RIMS

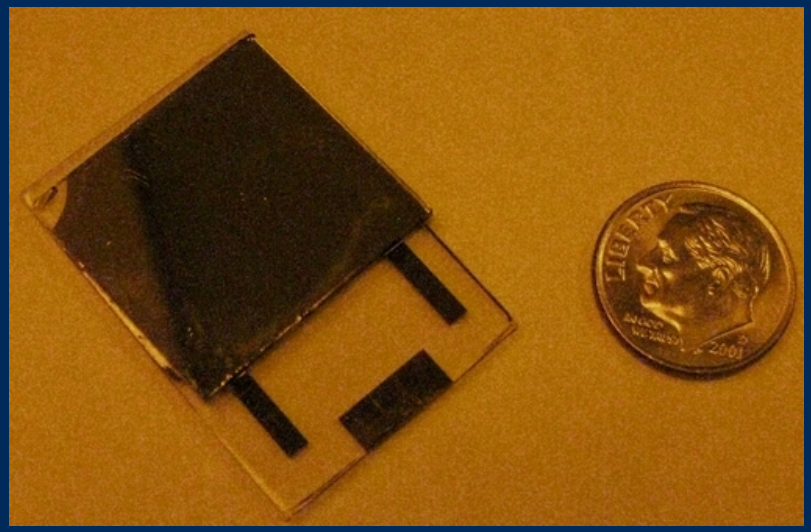
$$KCl + {}^{35}SO_4^{2-} + Ba^{2+} \xrightarrow{HCl/K_2SO_4/BaCl_2} Ba^{35}SO_4$$

$${}^{35}SO_4^{2-} + 2PO_4^{3-} + 4Sn^{2+} + 16H^+ \xrightarrow{N_2/-H_2O} H_2S + 4Sn^{4+} + P_2O_5 + 7H_2O$$

$$H_2S + OH^- \rightarrow HS^- + H_2O$$

$$2HS^- + I_2 \rightarrow 2S(s) + 2I^-$$





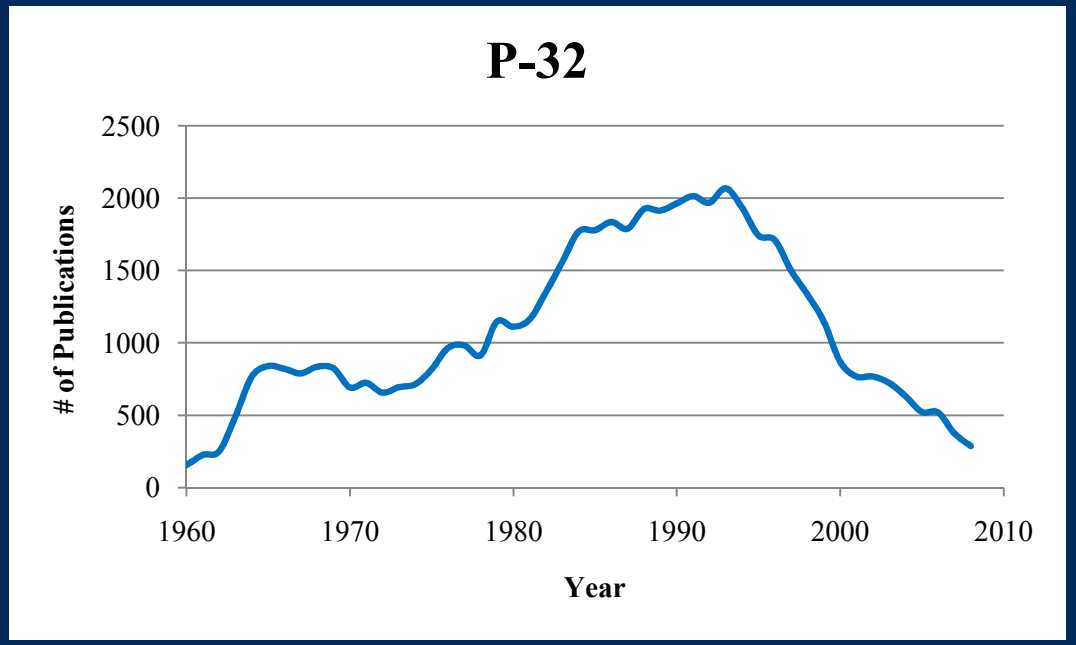
Radioisotope Microbattery Based Upon Liquid Semiconductor
Applied Physics Letters 95, 014103-1-3 (2009)

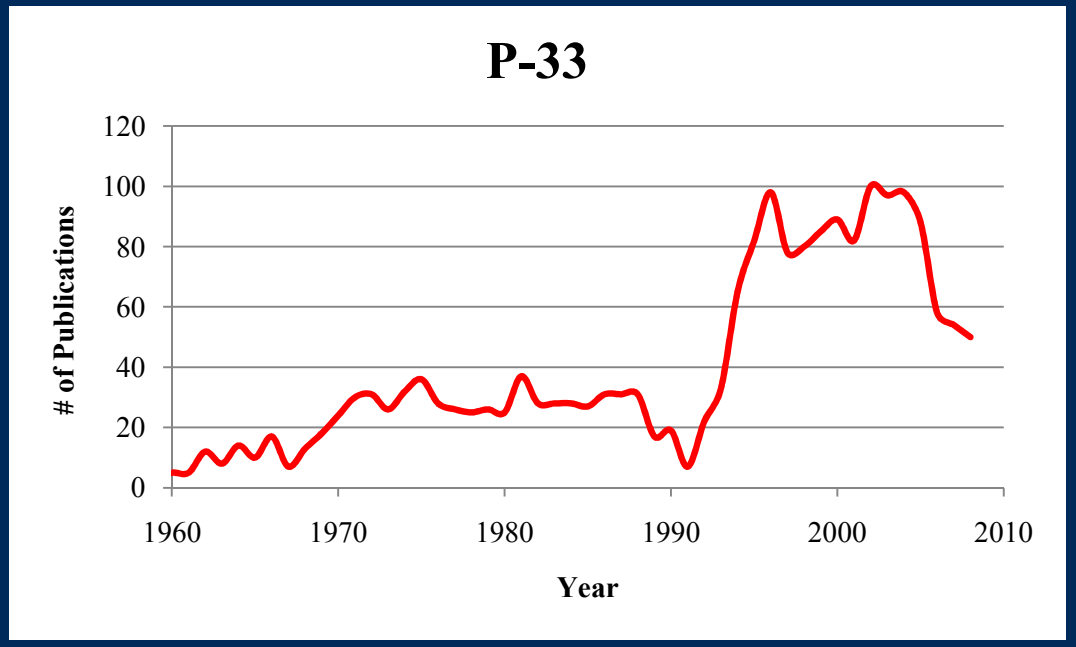
P-32 & P-33 Life Science Radiotracers

P-33 Production Line

4500 - 5000 Ci/mmol P

Theoretical 5161 Ci/mmol P





Se-75 Life Science Radiotracer

~ 5-10 shipments/year
Produced at a loss

Our Mission: Providing quality nuclear research, education and services to a global community.

- Methanococcus vannielii selenium-binding protein (SeBP): Chemical reactivity of recombinant SeBP produced in Escherichia coli. **PNAS** (2005)
- Characterization of potential selenium-binding proteins in the selenophosphate synthetase system. **PNAS** (2005)
- Selenophosphate synthetase genes from lung adenocarcinoma cells: Sps1 for recycling L-selenocysteine and Sps2 for selenite assimilation. **PNAS** (2004)
- Direct detection of potential selenium delivery proteins by using an Escherichia coli strain unable to incorporate selenium from selenite into proteins. **PNAS** (2002)
- The iscS gene is essential for the biosynthesis of 2-selenouridine in tRNA and the selenocysteine-containing formate dehydrogenase. **PNAS** (2002)
- Formation of a selenium-substituted rhodanese by reaction with selenite and glutathione: possible role of a protein perselenide in a selenium delivery system. **PNAS** (2001)
- Mammalian thioredoxin reductase: oxidation of the C-terminal cysteine/selenocysteine active site forms a thioselenide, and replacement of selenium with sulfur markedly reduces catalytic activity. **PNAS** (2000)

Medical Isotope Production Without HEU
National Research Council, NAS 2009

- Current (2006) demand for Mo-99 in the U.S. is between 5000 and 7000 6-day curies per week.
- Tc-99m is used in about two thirds of all nuclear medicine procedures performed in the U.S.
- Demand growth for Mo-99/Tc-99m in the U.S. over the next 5 years could range from 0% to 5% per year. Demand growth for diagnostic imaging will likely continue over the long term as the U.S. population ages.
- Reliability of supply is impacting the availability of Mo-99 for medical use and the continuity of patient care in the U.S. and elsewhere. Reliability of Mo-99 supply is likely to continue to be a serious problem for the U.S. in the early part of the next decade without new sources of Mo-99 supply.

Proposed LEU Fission Target Processing Facility

DOE Workshop on The Nations Need for Isotopes: Present and Future, 8/08
Table 11. Isotopes considered in short supply or unavailable from DOE for research and applications

Radioisotope	Half-life	Status	Applications
Cs-137	30 y	Not available	Gamma source for cargo imaging, blood irradiators and sterilizers
Mo-99	2.7 d	Not available	Parent for Tc-99m which is used in about 85% of all nuclear medicine procedures
Pm-147	2.6 y	Not available	Beta emitter for radioisotope micro power sources

Rh-105 – targeted radiotherapy

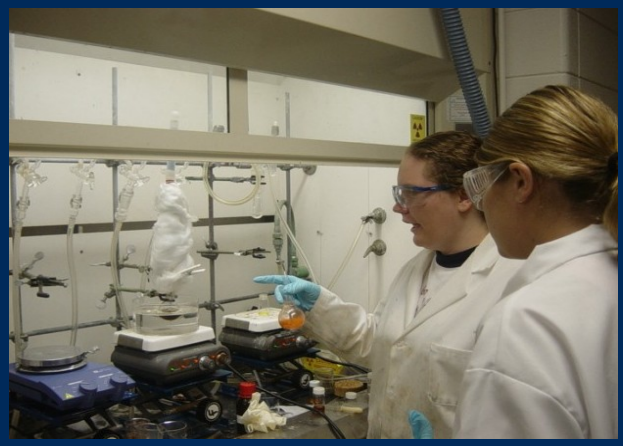
- 1.5 d half-life
- Medium energy beta emitter (0.566 MeV)
- Forms kinetically inert complexes

Proposed LEU Fission Target Processing Facility

- Overall objective is to develop the capability to produce Mo-99 from LEU.
- Production objective is ~50% of current U.S. weekly demand.
- Have submitted a letter of intent to NRC for licensing 99Mo production facility.
- Missouri Life Science Research Trust Fund, $1.1M, to begin work on the design and licensing, 1/1/09-12/31/10.
- ANL/MURR Cooperation in Pursuing Mo-99 Production, $439,000, 5/1/06 - 5/31/08
- ANL, LEU Based Mo-99 Production at MURR – Conceptual Study $304,600, 5/6/08 to 3/31/09
- Have submitted (9/09) a proposal to DOE/GTR for Phase 1 Development and Design.

Preparing the Next Generation

- Introduction to Radiochemistry course (with lab) – annual enrollment of 45-55 students.
- NIH NIBIB Radiopharmaceutical Sciences training grant
- DOE OBER Research Projects for Interrogations of Biological Systems: Training for the Development of Novel Radiotracers
- Host for the 2007 & 2009 SSAC Course



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Acknowledgments