INITIAL CONCEPT, PROMOTION, AND PRACTICAL APPLICATIONS OF THE GAME-CHANGER PARADIGM "THERAGNOSTICS"

Suresh Srivastava

Brookhaven National Laboratory
Upton, New York, USA

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NUCLEAR
MEDICINE

Paving the Way to Personalized Medicine: Production of Some Promising Theragnostic Radionuclides at Brookhaven National Laboratory

Suresh C. Srivastava, PhD

This article reintroduces and reinforces our proposed paradigm that involves specific individual "dual-purpose" radionuclides or radionuclide pairs with emissions suitable for both imaging and therapy and which, when molecularly (selectively) targeted using appropriate carriers, would allow pretherapy low-dose imaging as well as higher-dose therapy in the same patient. We have made an attempt to sort out and organize a number of such theragnostic radionuclides and radionuclide pairs that may thus potentially bring us closer to the age-long dream of personalized medicine for performing tailored low-dose molecular imaging (single-photon emission computed tomography/computed tomography or positron emission tomography/CT) to provide the necessary pretherapy information on biodistribution, dosimetry, the limiting or critical organ or tissue, the maximum tolerated dose, and so forth, followed by performing higher-dose targeted molecular therapy in the same patient with the same radiopharmaceutical. Beginning in the 1980s, our work at Brookhaven National Laboratory with such a "dual-purpose" radionuclide, tin-117m, convinced us that it is arguably one of the most promising theragnostic radionuclides, and we have continued to concentrate on this effort. Our results with this radionuclide are therefore covered in somewhat greater detail in this publication. A major problem that continues to be addressed, but remains yet to be fully resolved, is the lack of availability, in sufficient quantities, of a majority of the best candidate theragnostic radionuclides in a no-carrier-added form. A brief description of the recently developed new or modified methods at Brookhaven National Laboratory for the production of 5 theragnostic radionuclide/radionuclide pair items, whose nuclear, physical, and chemical characteristics seem to show great promise for personalized cancer and other therapies, is provided.
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During the past 3 decades, the development, production, and application of therapeutic radionuclides and radiopharmaceuticals have experienced a number of issues, problems, and challenges. This process has undergone rapid and constant evolutionary cycles of nuclear medicine, starting with empirically prepared radiopharmaceuticals in the past to the present intelligent designing of specific agents for molecular imaging and targeted therapy. Unfortunately, only a very few from among all the radionuclides, which have ever been produced, or those that continue to be investigated for production, have or will end up with the required combination of favorable nuclear, physical, and biological characteristics to become clinically useful imaging or therapeutic medical radionuclides.

Significant and rapid advances in molecular biology continue to lead to a better understanding of cancer and other disease states, and parallel research has shown promise for biological vehicles, such as monoclonal antibodies (MAbs), specific proteins and peptides, and a variety of other systematically designed molecules, to serve as carriers to selectively deliver imaging photons to diagnose disease or therapeutic electrons to deliver cell-killing radiation, in a highly localized manner.[1-5] These developments have led to a renewed interest in the exciting possibility of treating, in particular, the disseminated human malignancies and various other disorders, with the systemic administration of radionuclides. A number of relatively new radiotherapeutic modalities and procedures, such as the treatment of metastatic bone pain, radiation synovectomy, bone marrow ablation, and treatment of inflammatory diseases (including cancer, cardiovas-

Medical Isotope Research and Production Program, Brookhaven National Laboratory, Upton, NY.
Address reprint requests to Suresh C. Srivastava, PhD, Medical Isotope Research and Production Program, Building 801, Brookhaven National Laboratory, Upton, NY 11973-5000. E-mail: suresh@bnl.gov

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Srivastava S.C. Semin Nucl Med 42; 151-163, 2012

Brookhaven National Laboratory

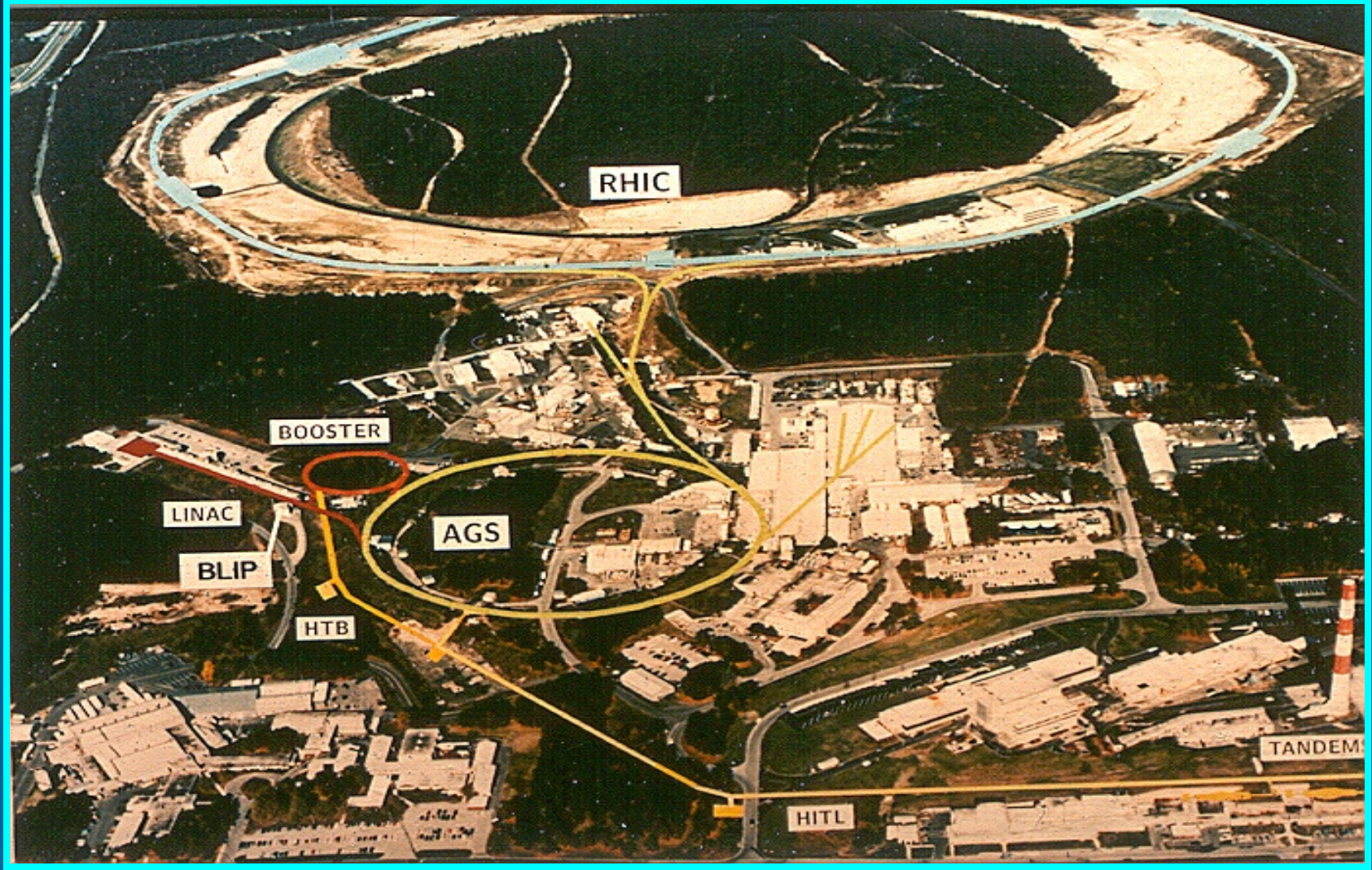
- Brookhaven National Laboratory is a multipurpose research institution funded by the U.S. Department of Energy.

- Located on Long Island, New York, Brookhaven operates large-scale facilities for studies in physics, chemistry, biology, medicine, applied science, and advanced technology.

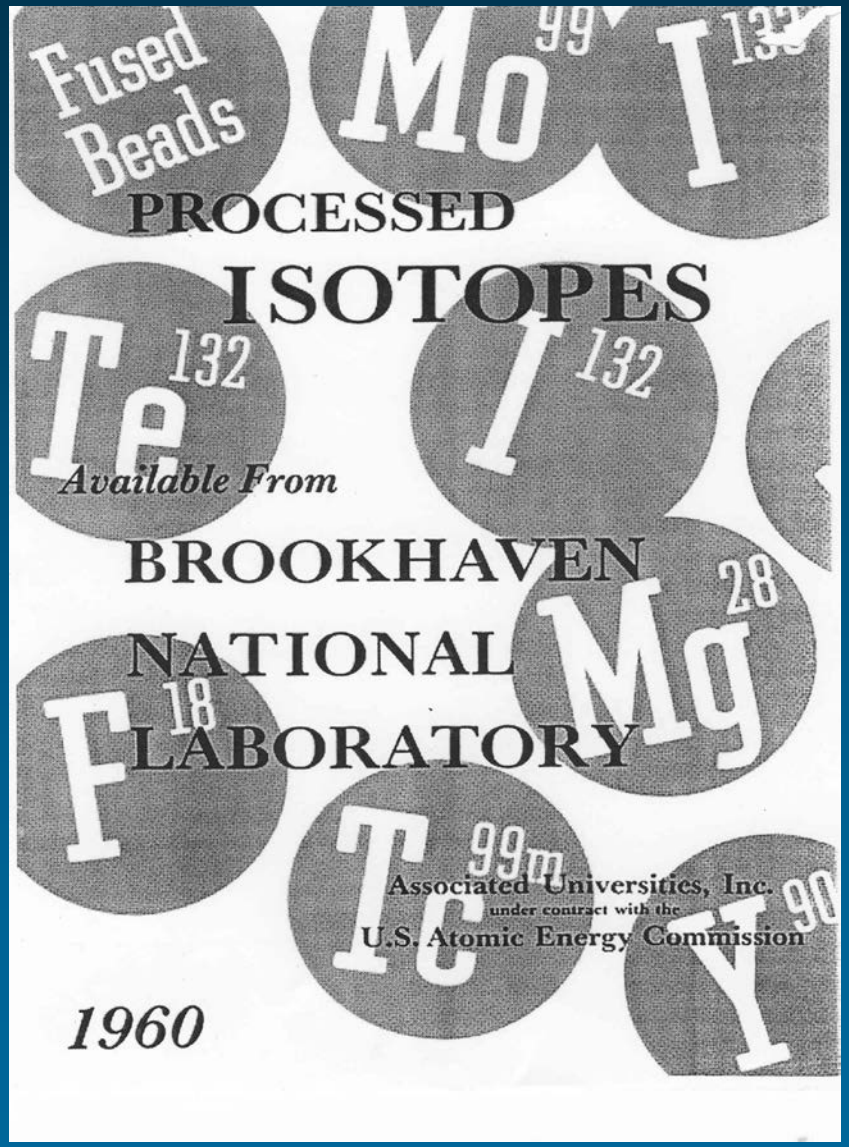
- The Laboratory's almost 3,000 scientists, engineers, and support staff are joined each year by more than 5,000 visiting researchers from around the world.

Brookhaven National Laboratory

A Bird's Eye View of the Accelerator Complex



BNL 1960 Isotope Catalog



Clinically Useful Generator Systems Developed at BNL

- $^{132}Te/^{132}I$
- $^{99}Mo/^{99m}Tc$*
- $^{90}Sr/^{90}Y$
- $^{68}Ge/^{68}Ga$
- $^{52}Fe/^{52m}Mn$
- $^{81}Rb/^{81m}Kr$
- $^{82}Sr/^{82}Rb$
- $^{122}Xe/^{122}I$

*Most commonly used for diagnostic imaging; >20 million procedures/yr in USA; >60 million worldwide

Srivastava S.C. Appl. Radiat Isot 1982

Nuclear Medicine Research at Brookhaven

60 years of Innovation in Health Care

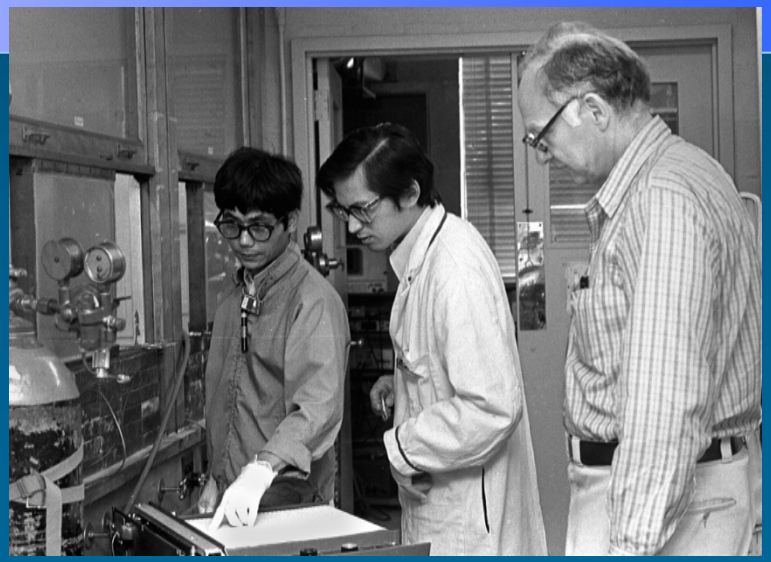
Technetium-99m (Tc-99m)

In the late 1950's, Brookhaven scientists developed a generator system for producing Tc-99m and suggested its use for medical imaging. This revolutionized the practice of nuclear medicine; Tc-99m is the work horse and still now used in over 80% of all nuclear medicine imaging procedures worldwide (>60 million/year).

Walter Tucker and Powell Richards, developed the original prototype Tc-99m generator (right)

[^{18}F]Fluorodeoxyglucose (^{18}FDG)

In 1976, scientists at Brookhaven, led by Alfred Wolf (at right in the picture), developed the method for producing F-18 FDG (fluoro-deoxy glucose). Collaboration with the University of Pennsylvania and the NIH led to a combined expertise in chemistry, neuroscience and instrumentation to develop F-18 FDG for brain imaging, that revolutionized the study of the human brain. Also, in 1980, BNL scientists first reported high FDG uptake in tumors, leading to the use of FDG/PET for managing the cancer patient. The rest is history.



BROOKHAVEN NATIONAL LABORATORY

MEMORANDOM

DATE: December 4, 1958

TO: Addressees Below

FROM: Daniel M. Schaeffer, Head
BNL Patent Office

SUBJECT: P-701 and P-702 - PREPARATION OF CARRIER-FREE MOLYBDENUM AND OF TECHNETIUM FROM FISSION PRODUCTS

The New York Patent Group has carefully studied the information available relative to the above-identified item. The AEC does not at present desire to prepare a patent application on this item for the following reason:

"The method of producing carrier-free molybdenum-99 from fission products is disclosed in U. S. Patent Application S.N. 732, 108, Green, Powell, Samos& Tucker (BNL Pat No. 58-17). It is noted that molybdenum-99 may be separated from its radioactive daughter, technetium-99, by absorption of a solution of molybdenum-99 on alumina and subsequent elution of its daughter with .1 nitric acid. ***While this method is probably novel, it appears that the product will probably be used mostly for experimental purposes in the laboratory. On this basis, no further patent action is believed warranted."***

A determination has also been made by the Research Corporation (a private patent management organization acting for AUI). They have recommended the following:

"The process for producing carrier-free molybdenum has apparently been made the subject of an AEC patent application. This leaves the separation of technetium to be considered. The patentability of the technique of "milking" technetium from a molybdenum generator over that of "milking" I^{132} from tellurium is debatable. Apparently the ***AEC is not interested in filing on the technetium-99m separation and We believe that this attitude is significant. We are not aware of a potential market for technetium 99m great enough to encourage one to undertake the risk of patenting in hopes of successful and rewarding licensing.***
We would recommend against filing on the Tucker, Greene and Murrenhoff separation process."

Srivastava S.C. Appl. Radiat Isot 1982

In 1996, at the celebration of the 100th anniversary of the discovery of radioactivity during the Society of Nuclear Medicine Annual Meeting in Denver, Colorado, the late Glenn Seaborg, Nobel Laureate and co-discoverer of the element Tc-99, is seen here holding the first Tc-99m generator. Next to him is Suresh Srivastava of the Medical Department at BNL where the generator was developed.

1970 - 1975

Sn+2 was found to be the best reducing agent for Tc-99m Pertechnetate for preparing Tc radiopharmaceuticals

1975 - 1985

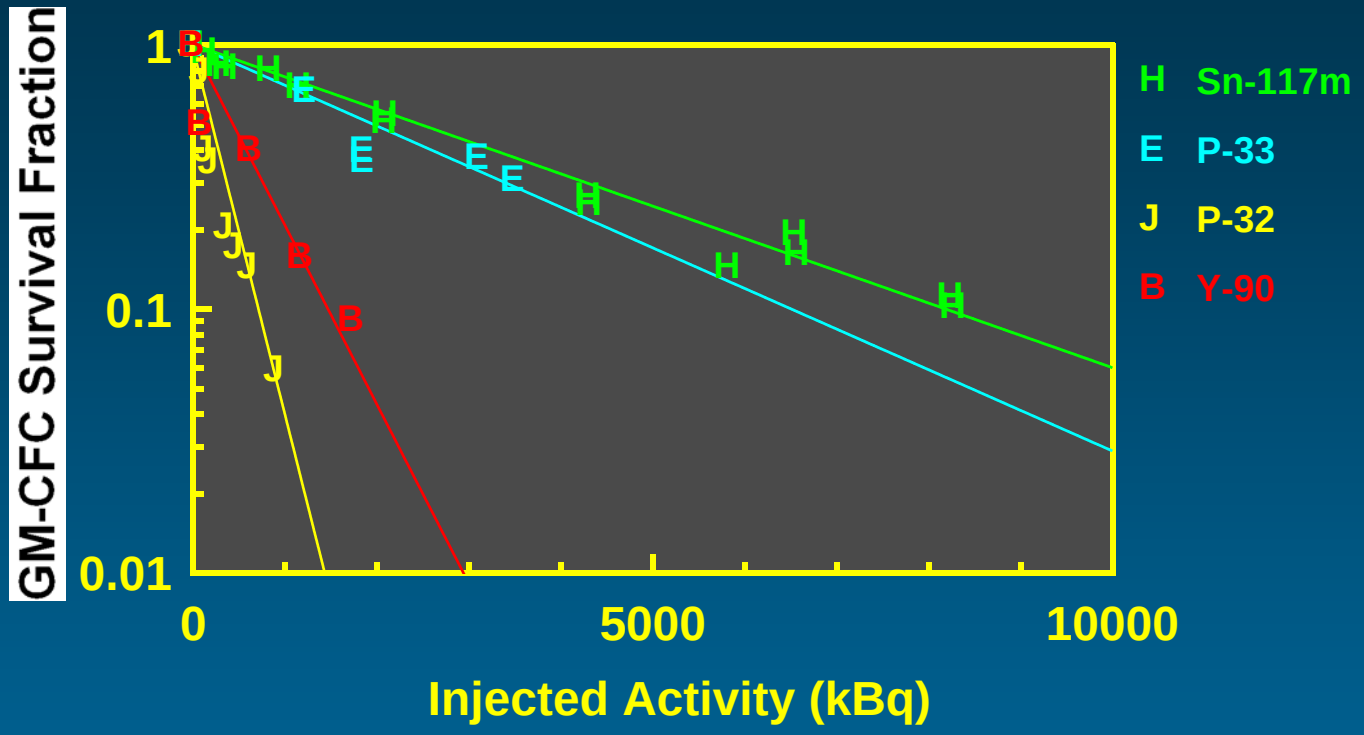
Development of 'Instant Kits'
(Shake and Bake)
for various Tc-99m radiopharmaceuticals

Earlier Work with Tin-117m as a tracer to determine the biochemistry and safety of Tin in the Tc-99m kits (1980's)

1. S.C. Srivastava, G.E. Meinken, P. Richards, et al., The Development and In vivo Behavior of Tin Containing Radiopharmaceuticals-I: Chemistry, Preparation, and Biodistribution in Small Animals. *Int. J. Nucl. Med. Biol.,* 12, 167-174 (1985).

2. Z.H. Oster, P. Som, S.C. Srivastava, et al., The Development and In vivo Behavior of Tin Containing Radiopharmaceuticals-II: Autoradiographic and Scintigraphic Studies in Normal Animals and in Animal Models of Bone Disease. *Int. J. Nucl. Med. Biol.,* 12, 175-184 (1985).

GM-CFC SURVIVAL VS. INJECTED ACTIVITY



<u>Conclusion</u>: Tin-117m causes the <u>least</u> myelotoxicity

Howell, et al; UMDNJ-NJ Medical School

Autoradiography in rats (top) and in mice (middle and bottom) demonstrates selective targeting and high uptake of tin-117m DTPA in bone and not in bone marrow or other organs

Oster, Som, Srivastava,et al, Int J Nucl Med Biol 12, 175-184, 1985

Nuclear Properties of the Dual-Purpose ("Theragnostic") *

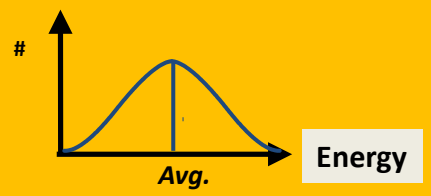
Radionuclide ^{117m}Sn (T ½=14.0 d)

Major Emissions	Energy, KeV	Intensity, %
Auger-L	3	91.0
Auger-K	21	10.8
CE*-K1	126.8	66.3
CE-K2	129.4	11.9
CE-L1	151.6	27.3
CE-L2	154.1	1.5
CE-M1	155.1	5.6
Gamma	158.6	86.4

* Word coined in 1992 at BNL
* C.E. = Conversion Electron

A schematic comparison of energy types for therapeutic radionuclides

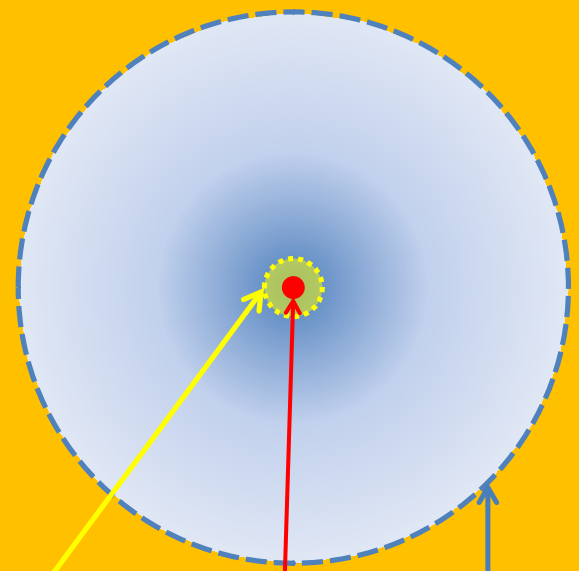
Beta



Produces a range of tissue penetration, some deep

Conversion Electron

Penetrates a set distance



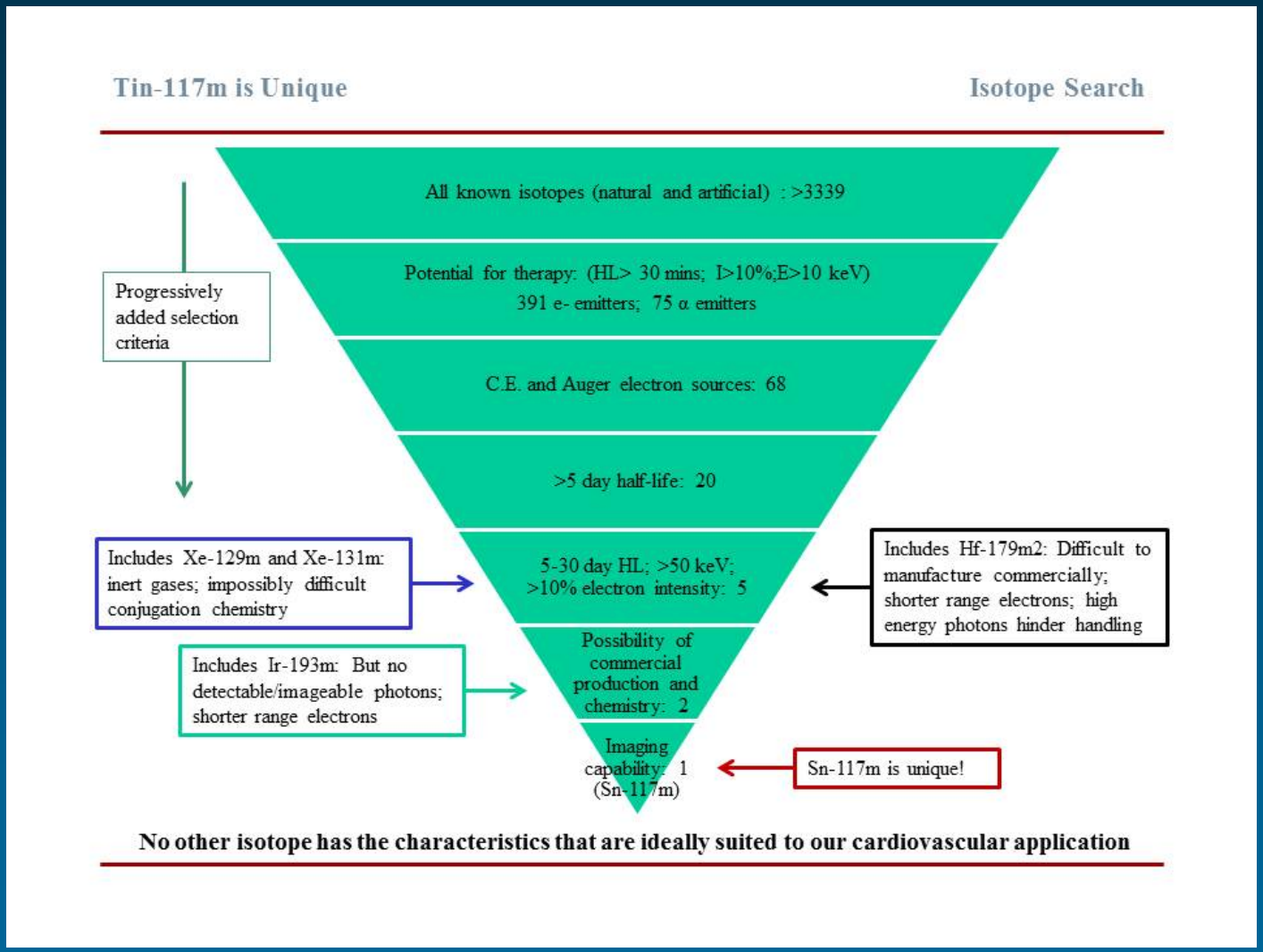
	Tin-117m	Alpha Particles	Beta Particles
Range in tissue (µm)	290	40-90	50-5000
Patient shielding for therapeutic doses/Hospital stay requirement	No/No	No/Yes?	Yes/Yes

Tin-117m Has Unique Capabilities

- Mono-energetic conversion electrons of ~140 KeV (avg) discrete energy for therapy have an average range of 290 µm
  - Lower external radiation
  - Easier handling and reduced hospitalization containment
  - C.E. have been proven to induce apoptosis
- Half-life of 14 days is consistent with treatment requirements
  - Logistic flexibility
  - Cell division cycles and therapy dosing
- Gamma ray (159 KeV) similar toTc-99m (140 KeV) allowing for existing standard gamma camera imaging & techniques

Tin-117m

Arguably the Best Theragnostic Radionuclide?



Courtesy: Nigel Stevenson

Basic Requirements for a "Theragnostic" Radiopharmaceutical

- ***Ideally,*** **the molecularly targeted radiopharmaceutical should constitute the same dual-purpose radionuclide with both imaging and therapeutic emissions.**
- **In the second best situation, a radionuclide pair (imaging photon emitter, either gamma or positron, and a congener therapeutic particle emitter, with the same electronic structure) can be used as well.**
- **A low-dose initially would allow molecular imaging (SPECT/CT or PET/CT) to provide the required pre-therapy information on biodistribution, dosimetry, limiting or critical organ or tissue, and the maximum tolerated dose (MTD).**
- **If the imaging results then warrant it, it would be safe and appropriate to follow up with dose ranging experiments to allow higher-dose targeted therapy with the greatest effectiveness.**
- **All these factors are required to successfully enable *tailored* imaging *plus* therapy in the same patient with the same radiopharmaceutical (personalized medicine) -- no ifs and buts!**

Srivastava S.C. Semin Nucl Med 42; 151-163, 2012

Selected Theragnostic* Radionuclides

Radionuclide	T1/2 (d)	Principal γ energy for imaging, KeV (%)	Therapeutic particle(s) (Avg. Energy, KeV, % abundance)
Scandium-47	3.35	159 (68)	β- (162)
Copper-67	2.58	185 (49)	β- (141)
Gallium-67	3.26	93, 184, 296 (40, 24, 22)	15 Auger, 0.04-9.5 KeV, 572% 10 C.E., 82-291 KeV, 30%
Indium-111	2.80	171, 245 (91, 94)	6 Auger, 0.13-25.6 KeV, 407% 12 C.E., 144-245 KeV, 21%)
Tin-117m	14.0	159 (86)	8 C.E. (141 KeV avg., 114%)
Samarium-153	1.94	103 (30)	β- (280)
Bismuth-213	46 min	441 (26)	β- (425); α (98%, from Tl-209 daughter, 2% from Bi-213)
Actinium-225	10.0	99, 150, 187 (93, 73, 49)	α (7030, 93%)
Iodine-123	13.3h	159 (83)	12 Auger, 23-30.4 KeV,1371% 7 C.E, 0.014-32 keV, 17%
Astatine-211	7.2 h	79 (21)	α (5867, 42%)

** Word coined at BNL in 1992*

Selected Theragnostic* PET/Therapy Radiometal Pairs

Radionuclide Pair Imaging/Therapeutic	T1/2 (days)	Imaging positron, KeV (%)	Therapeutic particle(s) (Avg. Energy, KeV)
Copper-64/Copper-67	0.53 / 2.6	γ ± 511 (38 %)	β- (141)
Scandium-44m/ Sc-47	2.4 / 3.35	γ ± 511 (94%)	β- (162)
Gallium-68/Gallium-67	68 min / 3.26	γ ± 511 (176 %)	15 Auger, 0.04-9.5 KeV, 572% 10 C.E., 82-291 KeV, 30%
Yttrium-86/Yttrium-90	0.61 / 2.7	γ ± 511 (35 %)	β- (935)

* Word coined at BNL in 1992

Potential Imaging and Therapies (Theragnostics) with Tin-117m

I. Treatment of Cancer in Bone

Metastatic Bone Pain

Metastatic Prostate/Breast Cancer Disease

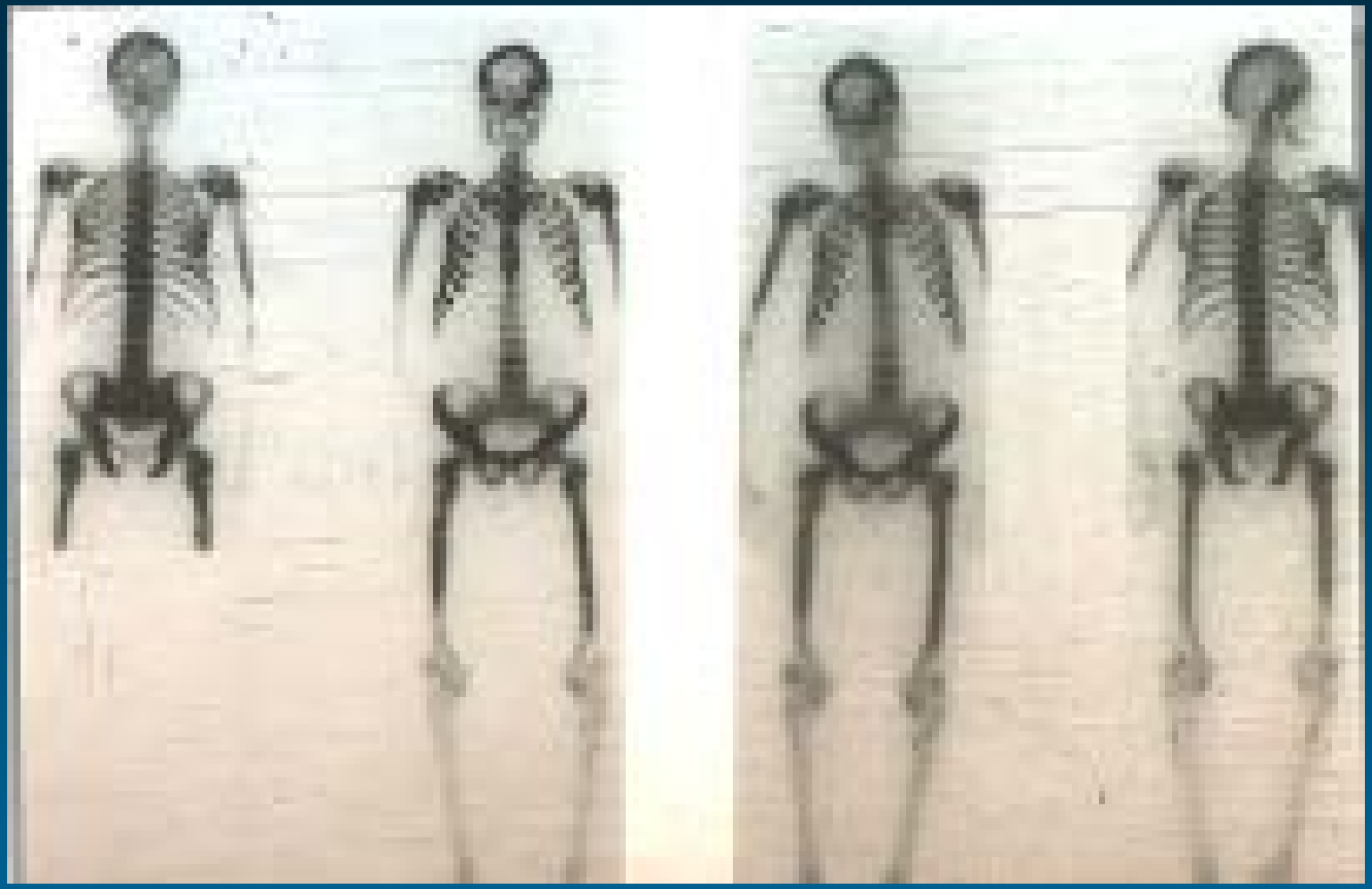
II. Cardiovascular Therapies:

Treatment of Active Atheromatous Disease (Vulnerable Plaques)

III. Treatment of Arthritic Disease and Bone and Joint Pain (Radiosynovectomy)

IV. Radioimmunotherapy

Tin-117m Stannic DTPA (STANAMET®) for Bone Pain Palliation Phase I/II Clinical Studies

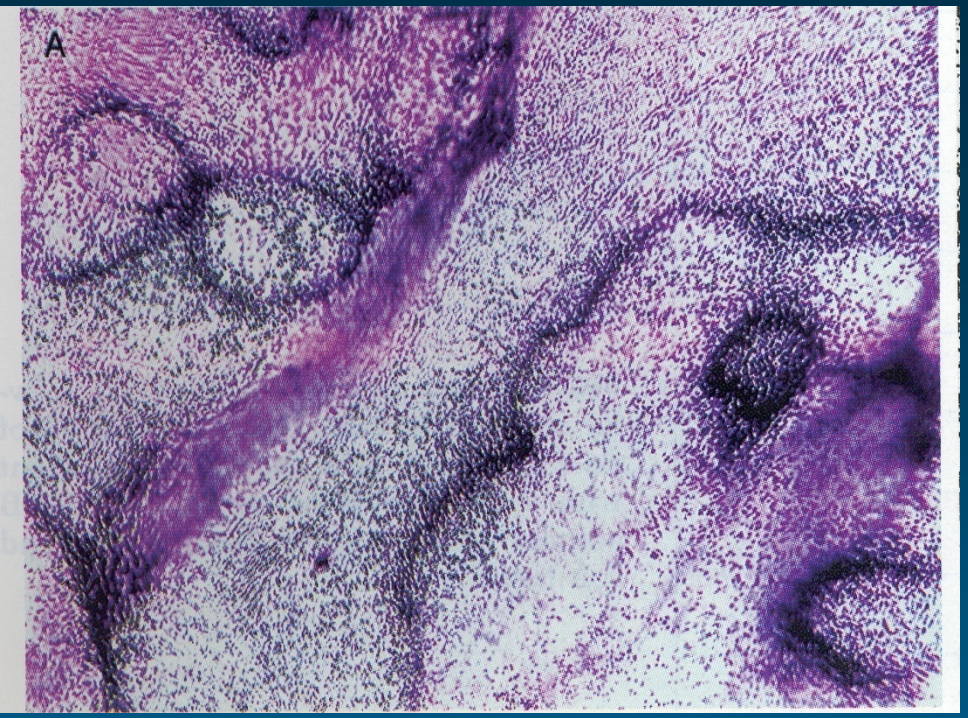


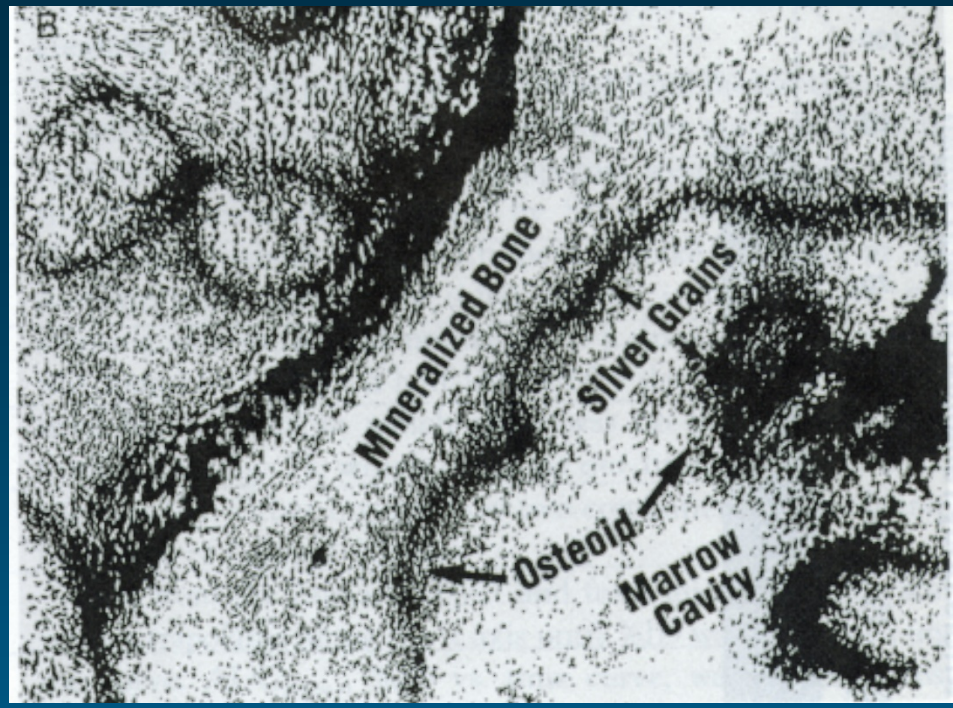
Whole body images in a prostate cancer patient, who had developed extensive bone metastases. Scan on the left (posterior, anterior views) was obtained using the standard Tc-99m MDP bone imaging agent. On the right are scans (anterior, posterior) obtained using tin-117m DTPA, which is promising for treatment of metastatic bone pain and of osseous metastases.

Srivastava et al., Clin. Cancer Res., 1998

Histology

Microautoradiograph



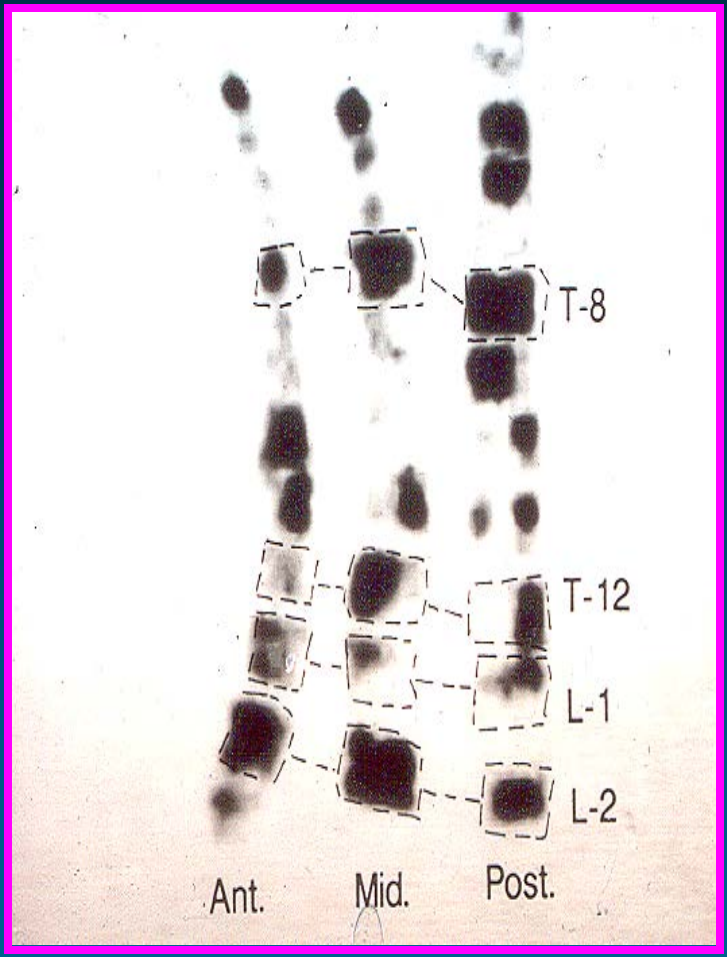


This figure of a bone section from a prostate cancer patient shows highly localized concentration of tin-117m (exposed silver grains, in the microautoradiograph on right) in "osteoids" and not in "bone marrow cavities"

(Krishnamurthy and Srivastava et al, J. Nucl. Med.,1997)

A

B



Photographic picture (A) and bone scintigraph (B) of three coronal slices (each 5mm thick) of thoraco-lumbar vertebrae from the same patient as in the previous Figure . Partial involvement within a single vertebra indicates nonuniform distribution of radioactivity within the lesion, suggesting heterogeneous distribution of metastatic foci. Note the uptake in diseased areas in various sections according to the range of the Sn-117m conversion electrons.

Swailem, Krishnamurthy and Srivastava, et al, 1998

Myelotoxicity Levels*

Agent	Dose group (MBq/kg)	n	No. of Patients, Grades ≥2[1] WBC	Platelets
Sr-89 Cl_2[2]	5.7	67	25 (37%)	41 (61%)
Sm-153 EDTMP[3]	37	20	3 (15%)	5 (25%)
	111	4	(100%)	2 (50%)
Sn-117m DTPA[4]	6.6	5	0 (0%)	0 (0%)
	10.6	12	1 (8%)	0 (0%)

*NCI criteria used: 0, none; 1, mild; 2, moderate; 3, severe; 4, unacceptable. [2]Porter et al, Int. J. Radiat. Oncol. Biol. Phys. 25:805, 1993; [3]Collins et al, J. Nucl. Med. 34:1839, 1993; [4]Srivastava et al, Clin. Cancer Res. 4:61, 1998.

Clinical Status of Tin-117m 4+ DTPA for Treatment of Bone Pain and Metastatic Bone Disease in Prostate and Breast Cancer Patients

-Bone Pain

Phase I – II -Completed by BNL/SUNY-SB N=57

Phase II/III (Sponsor- Diatide/Berlex)

- **Dose Ranging (Multicenter) 4Q 98-4Q02**
- **Osteoblastic (Prostate) N=100 (72)***
- **Osteolytic (Breast; Others) N=25 (5)***

Future Studies for *Treatment of Prostate and Breast Cancer Metastases*

- **Phase I-III 2Q 17→**
- **Expected FDA Approval 2Q 20→**

* Number of patients actually studied

Imaging and Treatment of Vulnerable Plaques

- **Tin-117m shows promise for the non-invasive molecular imaging and treatment of atherosclerotic disease, in particular of vulnerable plaques, through the use of:**
  - **Coronary stent implants electroplated with tin-117m; and**
  - **Specific tin-117m labeled molecules systemically targeted to vulnerable plaque components.**

U.S. DEPARTMENT OF ENERGY
Office of Science
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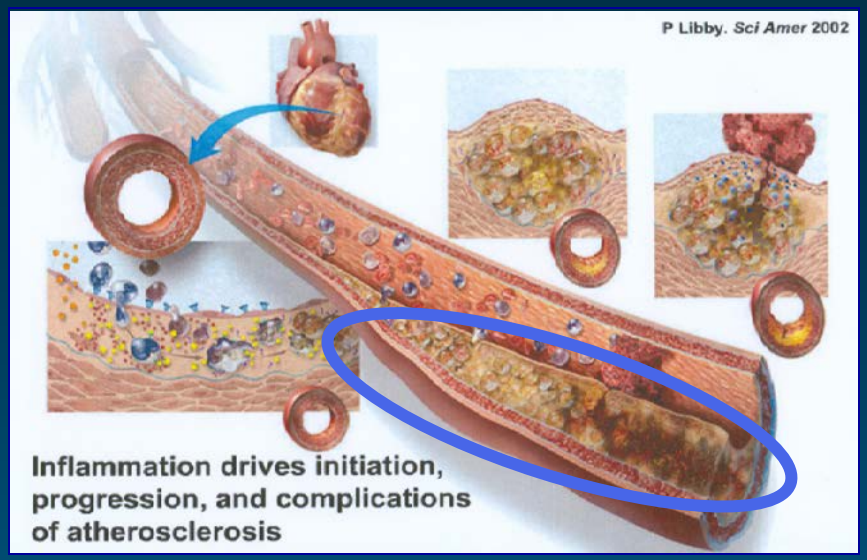
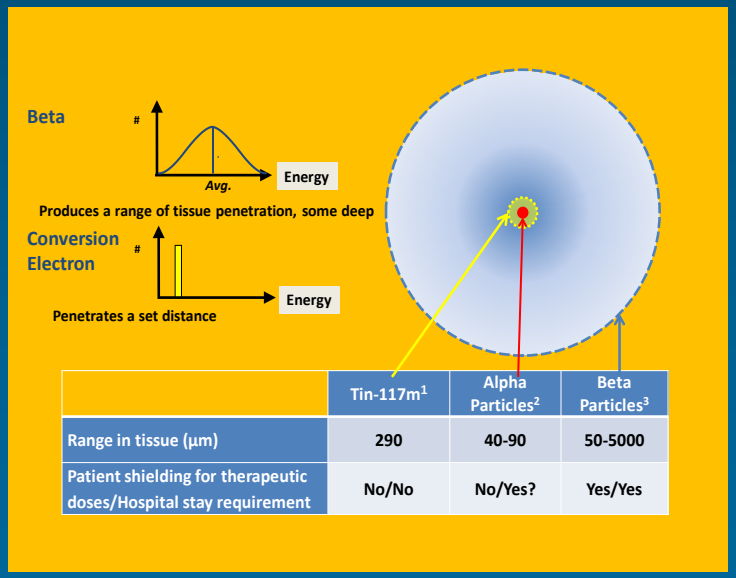


- *VP is non-luminal, multifocal, and is responsible for* a majority of all significant cardiac events (60-70%) leading to MI and sudden cardiac death.
- VP forms outside of the lumen in coronary artery walls - inflammation is the main driver. It is usually covered by a thin cap on the lumen side [thus also called thin cap fibroatheroma (TCFA)].
- Ruptured thin cap "releases" highly thrombo-genic material activating clotting cascade and inducing thrombosis.

WHY TIN-117m?



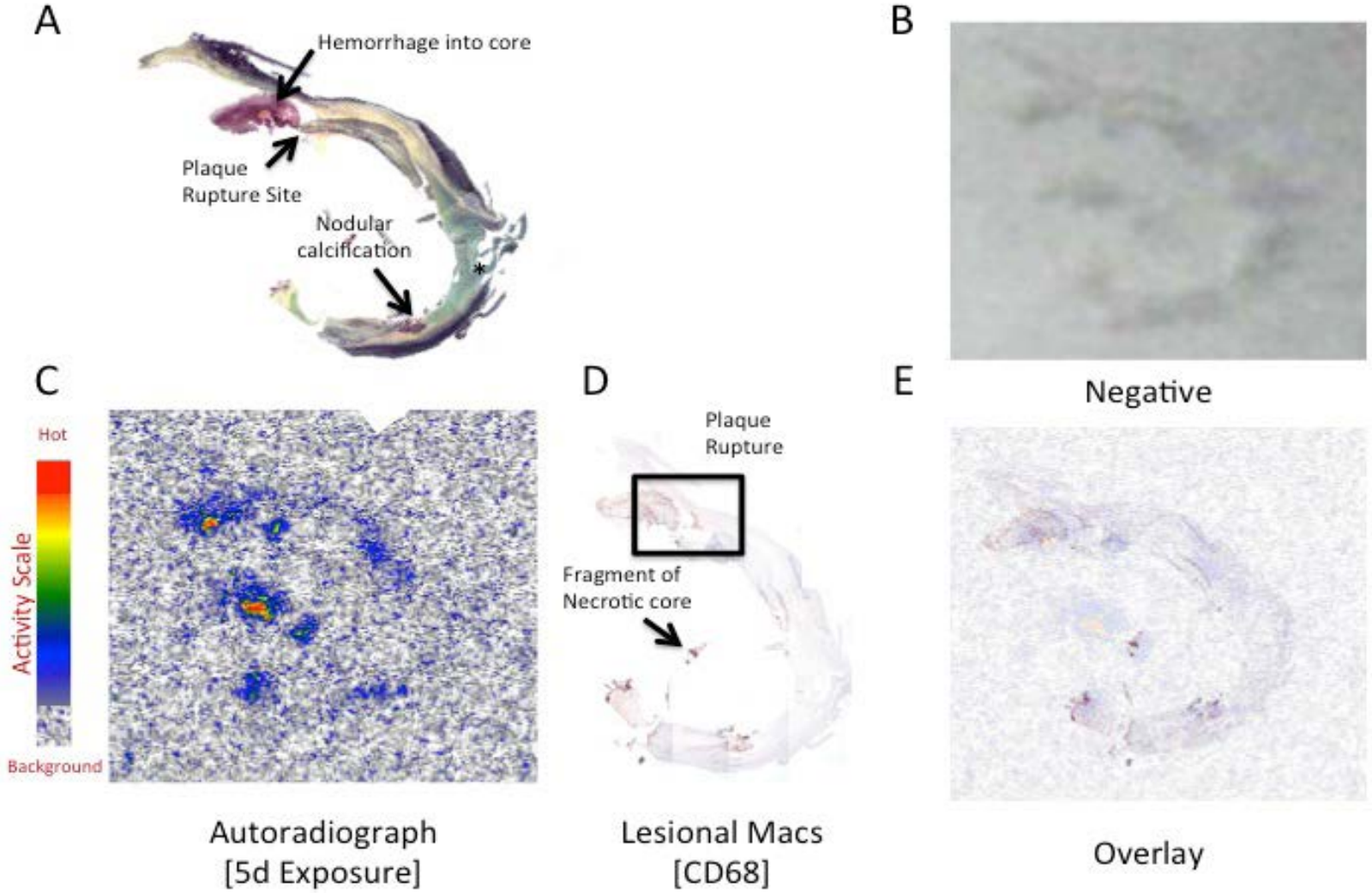
	Tin-117m[1]	Alpha Particles[2]	Beta Particles[3]
Range in tissue (µm)	290	40-90	50-5000
Patient shielding for therapeutic doses/Hospital stay requirement	No/No	No/Yes?	Yes/Yes

Theragnostic Tin-117m has the Capability for Simultaneous Imaging and Treatment of VP

- Mono-energetic conversion electrons of ~140 KeV (avg) discrete energy for therapy have an average range of 290 µm, almost same as the VP thickness
  - Lower external radiation
  - Easier handling and reduced hospitalization
  - C.E. have been proven to induce apoptosis
- Half-life of 14 days is consistent with treatment requirements
  - Logistic flexibility , and corresponds with cell division cycles and therapy dosing
- Gamma ray (159 KeV, 86%) perfect for SPECT/CT imaging

Patient 10 – Level B1

CAROTID HUMAN CLINICAL STUDY SUBJECT # 10



Production of No-Carrier-Added Tin-117m from Proton Irradiated Antimony

S.V. Ermolaev, B.L. Zhuikov, V.M. Kokhanyuk,
N.R. Togaeva, S.V. Khamianov,
S.C. Srivastava*

Journal of Radioanalytical and Nuclear Chemistry, Vol. 280, No.2 (2009) 319–324

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Accelerator-Produced NCA Tin-117m for Clinical Use

- Using the methodology developed in collaboration with INR/IPPE in Russia, several curies of NCA tin-117m (sp. act. >1000Ci/g) can be produced per week in presently available accelerators
- Efficiency of radiochemical isolation of Sn-117m:
  - Chemical Yield 85-90 %
  - Specific Activity 1000 - 5000 Ci/g
  - Radionuclidic Purity >99 %
  - Purification factor from Antimony $>10^6$

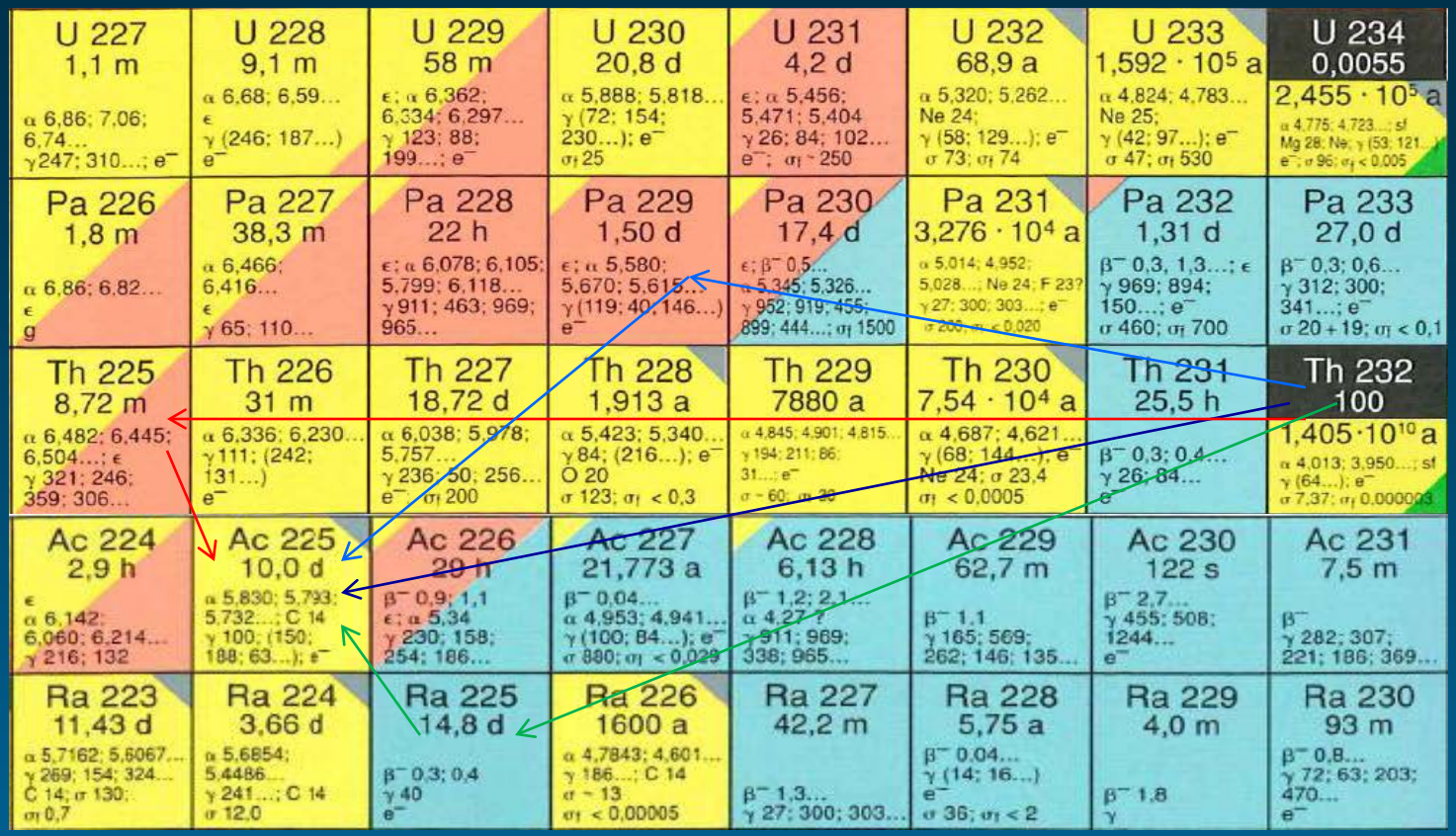
Development of Ac-225 production

- Ac-225 as an in-vivo generator and as a source of Bi-213 has shown promise in early radioimmunotherapy clinical trials against leukemia.
- Properties: $T_{1/2}$=10.0 d, 3 alpha particles emitted, mean Eα= 5.9 MeV, Eγ (keV): 99.7 (2.9%)
- Monthly multi-Ci quantities of Ac-225 are required to support clinical trials
- Present global supply <1 Ci annually from decay of Th-229 (most from ORNL generator)

Three Institution Consortium

- In response to the shortage of Ac-225, DOE has formed a collaboration between Brookhaven, Los Alamos, and Oak Ridge National Laboratories to investigate an alternative production approach.
  - BNL role is to develop target designs, irradiate and ship to ORNL, then scale up production levels for clinical use.
  - ORNL role is to develop the separation chemistry.
  - LANL role is to measure reaction cross sections and develop thick targets for eventual large scale production

High energy routes to Ac-225



Production routes

$^{232}Th(p,x)^{225}Ac$

$^{232}Th(p,x)^{225}Th \rightarrow ^{225}Ac$

$^{232}Th(p,4n)^{229}Pa \rightarrow ^{225}Ac$

$^{232}Th(p,x)^{225}Ra \rightarrow ^{225}Ac$

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Early Results

- To date, in the BLIP accelerator at BNL, more than a couple of dozen targets for ^{225}Ac have been successfully irradiated at various high energies from 128 MeV to 192 MeV for periods of several hours.
- Up to 8 – 10 d irradiations at effective beam currents have been carried out, without any failures.
- It would be possible to produce *Curie amounts* with each run in the near future.
- This would be a very exciting development *for theragnostic alpha therapy*.

Conclusions from Theragnostic Studies to Date and Future Prospects

- The **game changer paradigm of "Theragnostics"** when properly enforced, would constitute a major step forward to meet the challenges of enabling the age-long dream of ***personalized medicine.***
- ***Theragnostic radiopharmaceuticals*** have the power to drive advances in personalized medicine that will offer better-targeted diagnosis and treatments.
- We can envision a future where ***treatments are tailored*** to patient's specific disease parameters, imaging data are analyzed in real-time and in advance to predict likely effectiveness of therapy, and learn what would or would not work.
- We will enable ***tailored radionuclide therapy*** in cancer patients, as well as in the treatment of many other disorders that respond to radionuclide therapy.
- ***It is worth emphasizig that our nuclear medicine modality is the only modality that can fulfill the dream of carrying out personalized medicine by way of enabling diagnosis followed by therapy in the same patient with the same radiopharmaceutical. This would be an exciting development with a very promising future, and may very well mark the future of the field of nuclear medicine.***

Srivastava S.C. Semin Nucl Med 42; 151-163, 2012

A Unique Opportunity and Another Important Future for Nuclear Medicine?

Theragnostic Radiopharmaceuticals for Molecular Imaging

Plus

***Targeted Radionuclide* Therapy**

On our way to Personalized Medicine !

Theragnostics Research Team

Brookhaven National Laboratory
S. C. Srivastava, Ph.D. (P.I.)
L.F. Mausner, Ph.D.
R. Adzic, Ph.D.
G. E. Meinken, M.S.
S. Kurczak, B.S.
E. Korach, M.S.
U.C. Davis Medical Center
C. F. Meares, Ph.D. (P.I.)
U.C. Irvine Medical Center
J. Narula, M.D., Ph.D. (P.I.)
A. Petrov, M.D., Ph.D.
S. Ohshima, M.D, Ph.D
Univ. of Washington
D. S. Wilbur, Ph.D. (P.I.)
Isotherapeutics Group
J. Simone, Ph.D. (P.I.)
St. Joseph Research Institute
N. Chronos, M.D. (P.I.)
K. Robinson, Ph.D.
J. Li, M.D.

N. Chronos, M.D. (P.I.)
K. Robinson, Ph.D.
J. Li, M.D.
Institute of Nuclear Research, Russia
B. Zhuikov, Ph.D. (P.I.)
S.V. Ermolaev, Ph.D.
N.A. Konyakhin
Clear Vascular, Inc.
G. Gonzales, M.D. (P.I.)
N. Stevenson, Ph.D.
D. Mueller, Ph.D.
CV PATH
R. Virmani, M.D. (P.I.)
R-NAV, LLC
G.Gonzales. M.D (P.I)
N.Stevenson, Ph.D.
Cynthia Doerr, M.D.

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