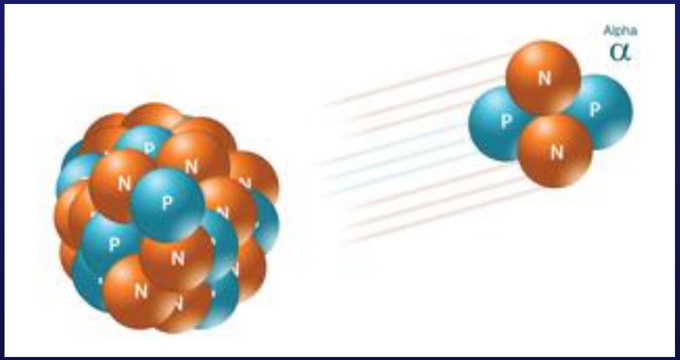
# Radionuclide Therapy

## Targeted Radionuclide therapy with Alpha Particles

Shankar Vallabhajosula, Ph.D.



| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 Pnictogens | 16 Chalcogens | 17 Halogens | 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 H Hydrogen 1.008 | Atomic Sym Name Weight | | | | | | | | | | | | | | | | 2 He Helium 4.0026 |
| 2 | 3 Li Lithium 6.94 | 4 Be Beryllium 9.0122 | | | | | | | | | | | 5 B Boron 10.81 | 6 C Carbon 12.011 | 7 N Nitrogen 14.007 | 8 O Oxygen 15.999 | 9 F Fluorine 18.998 | 10 Ne Neon 20.180 |
| 3 | 11 Na Sodium 22.990 | 12 Mg Magnesium 24.305 | | | | | | | | | | | 13 Al Aluminium 26.982 | 14 Si Silicon 28.085 | 15 P Phosphorus 30.974 | 16 S Sulfur 32.06 | 17 Cl Chlorine 35.45 | 18 Ar Argon 39.948 |
| 4 | 19 K Potassium 39.098 | 20 Ca Calcium 40.078 | 21 Sc Scandium 44.956 | 22 Ti Titanium 47.867 | 23 V Vanadium 50.942 | 24 Cr Chromium 51.996 | 25 Mn Manganese 54.938 | 26 Fe Iron 55.845 | 27 Co Cobalt 58.933 | 28 Ni Nickel 58.693 | 29 Cu Copper 63.546 | 30 Zn Zinc 65.38 | 31 Ga Gallium 69.723 | 32 Ge Germanium 72.630 | 33 As Arsenic 74.922 | 34 Se Selenium 78.971 | 35 Br Bromine 79.904 | 36 Kr Krypton 83.798 |
| 5 | 37 Rb Rubidium 85.468 | 38 Sr Strontium 87.62 | 39 Y Yttrium 88.906 | 40 Zr Zirconium 91.224 | 41 Nb Niobium 92.906 | 42 Mo Molybdenur 95.95 | 43 Tc Technetium (98) | 44 Ru Ruthenium 101.07 | 45 Rh Rhodium 102.91 | 46 Pd Palladium 106.42 | 47 Ag Silver 107.87 | 48 Cd Cadmium 112.41 | 49 In Indium 114.82 | 50 Sn Tin 118.71 | 51 Sb Antimony 121.76 | 52 Te Tellurium 127.60 | 53 I Iodine 126.90 | 54 Xe Xenon 131.29 |
| 6 | 55 Cs Caesium 132.91 | 56 Ba Barium 137.33 | 57–71 | 72 Hf Hafnium 178.49 | 73 Ta Tantalum 180.95 | 74 W Tungsten 183.84 | 75 Re Rhenium 186.21 | 76 Os Osmium 190.23 | 77 Ir Iridium 192.22 | 78 Pt Platinum 195.08 | 79 Au Gold 196.97 | 80 Hg Mercury 200.59 | 81 Tl Thallium 204.38 | 82 Pb Lead 207.2 | 83 Bi Bismuth 208.98 | 84 Po Polonium (209) | 85 At Astatine (210) | 86 Rn Radon (222) |
| 7 | 87 Fr Francium (223) | 88 Ra Radium (226) | 89–103 | 104 Rf Rutherfordiu (267) | 105 Db Dubnium (268) | 106 Sg Seaborgium (269) | 107 Bh Bohrium (270) | 108 Hs Hassium (277) | 109 Mt Meitnerium (278) | 110 Ds Darmstadtiu (281) | 111 Rg Roentgeniu (282) | 112 Cn Copernicium (285) | 113 Nh Nihonium (286) | 114 Fl Flerovium (289) | 115 Mc Moscovium (290) | 116 Lv Livermoriur (293) | 117 Ts Tennessine (294) | 118 Og Oganesson (294) |

C Solid
Hg Liquid
H Gas
Rf Unknown

**Metals**: Alkali metals; Alkaline earth metals; Lanthanoids; Actinoids; Transition metals; Post-transition metals
Metalloids
**Nonmetals**: Other nonmetals; Noble gases

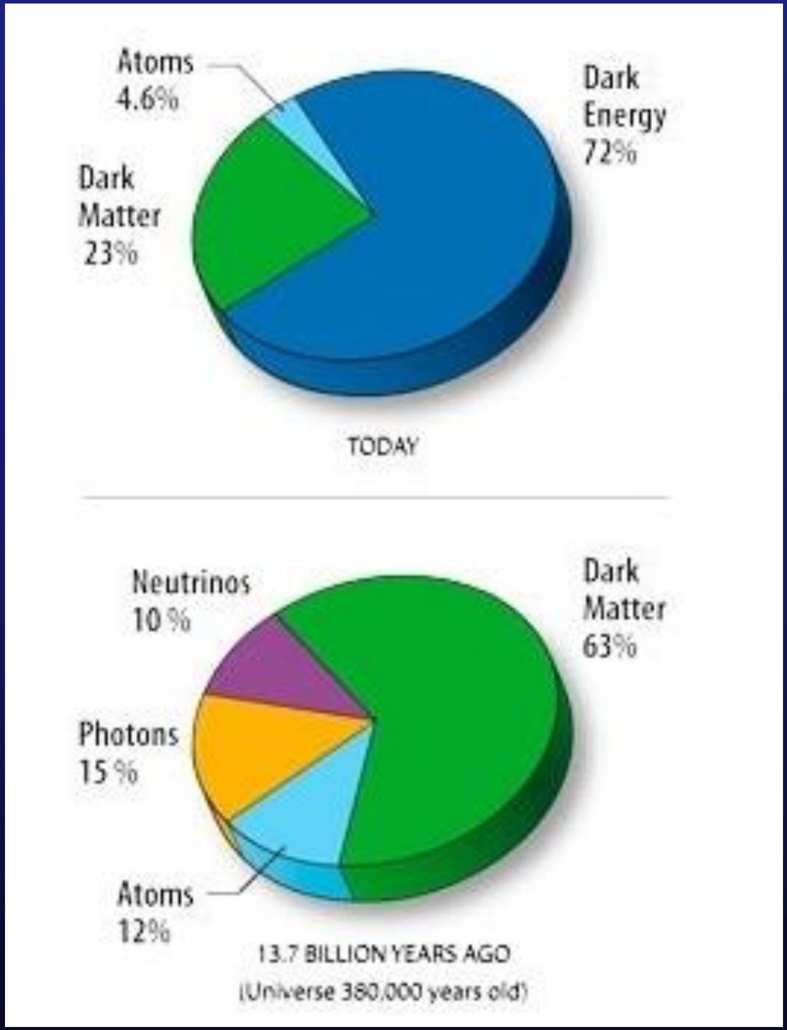
273

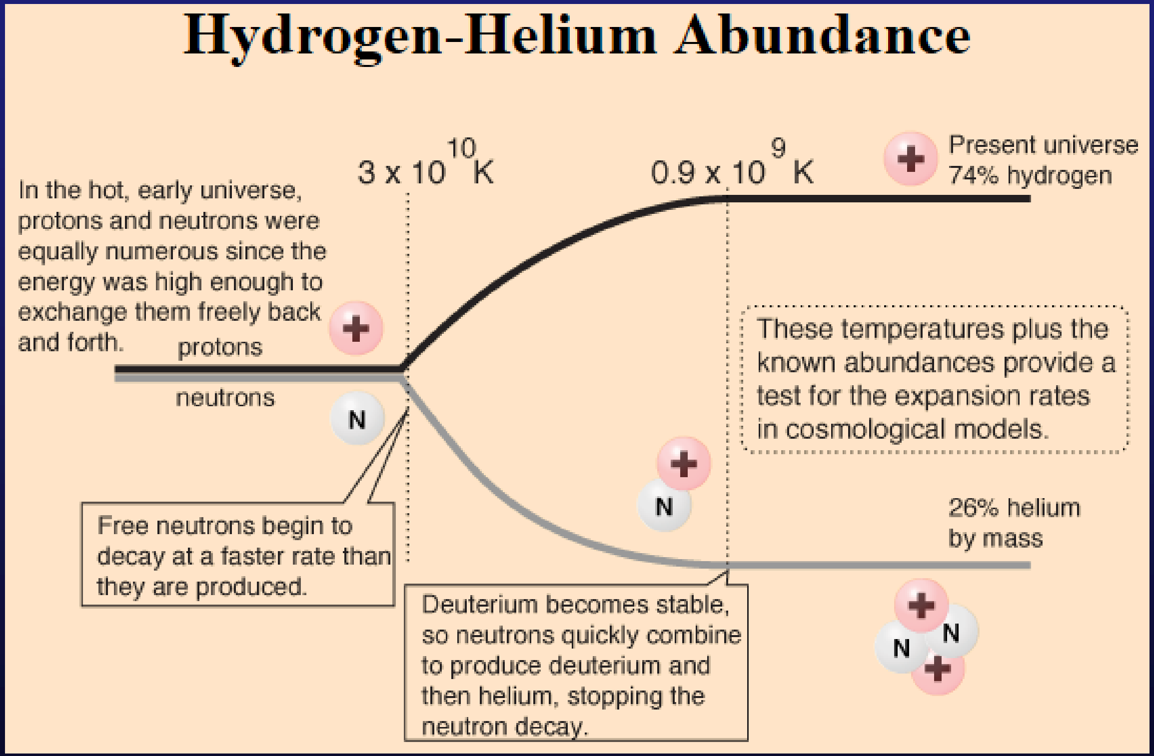
For elements with no stable isotopes, the mass number of the isotope with the longest half-life is in parentheses.

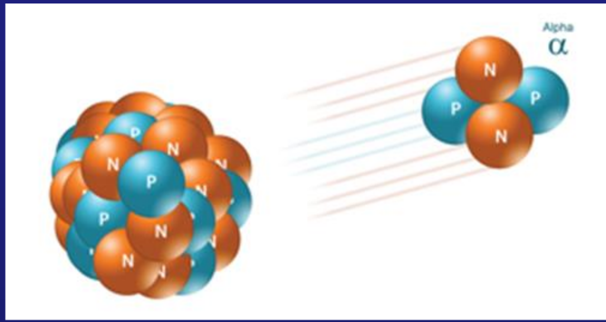


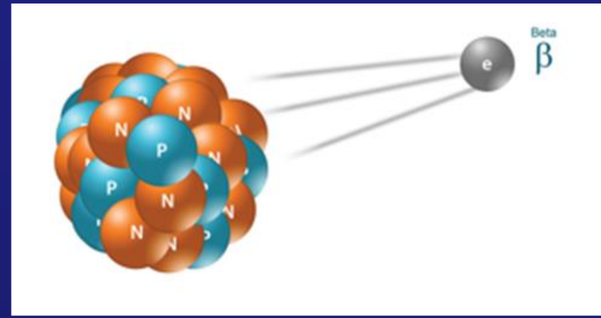
| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 57 La Lanthanum 138.91 | 58 Ce Cerium 140.12 | 59 Pr Praseodymi 140.91 | 60 Nd Neodymiur 144.24 | 61 Pm Promethium (145) | 62 Sm Samarium 150.36 | 63 Eu Europium 151.96 | 64 Gd Gadolinium 157.25 | 65 Tb Terbium 158.93 | 66 Dy Dysprosium 162.50 | 67 Ho Holmium 164.93 | 68 Er Erbium 167.26 | 69 Tm Thulium 168.93 | 70 Yb Ytterbium 173.05 | 71 Lu Lutetium 174.97 |
| 89 Ac Actinium (227) | 90 Th Thorium 232.04 | 91 Pa Protactinium 231.04 | 92 U Uranium 238.03 | 93 Np Neptunium (237) | 94 Pu Plutonium (244) | 95 Am Americium (243) | 96 Cm Curium (247) | 97 Bk Berkelium (247) | 98 Cf Californium (251) | 99 Es Einsteinium (252) | 100 Fm Fermium (257) | 101 Md Mendeleviu (258) | 102 No Nobelium (259) | 103 Lr Lawrencium (266) |

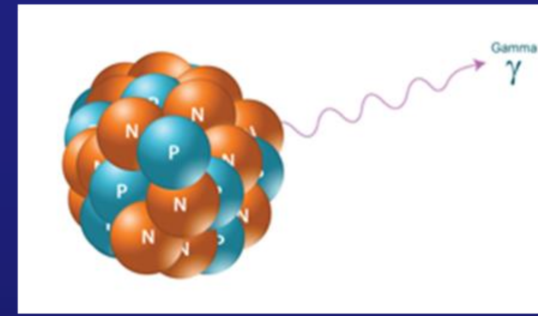
# 74% H and 26% He

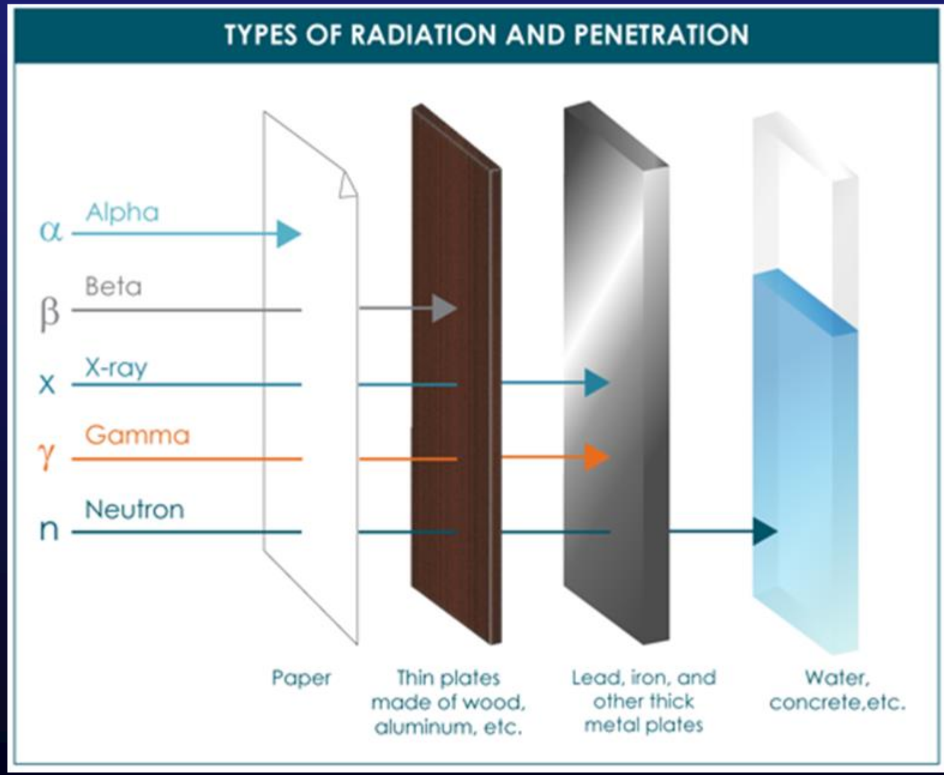

Atoms
4.6%
Dark
Energy
72%
Dark
Matter
23%
TODAY
Neutrinos
10 %
Dark
Matter
63%
Photons
15 %
Atoms
12%
13.7 BILLION YEARS AGO
(Universe 380,000 years old)


Hydrogen-Helium Abundance
In the hot, early universe, protons and neutrons were equally numerous since the energy was high enough to exchange them freely back and forth.
protons
neutrons
N
$3 \times 10^{10}$ K
$0.9 \times 10^{9}$ K
Present universe
74% hydrogen
These temperatures plus the known abundances provide a test for the expansion rates in cosmological models.
N
26% helium
by mass
Free neutrons begin to decay at a faster rate than they are produced.
Deuterium becomes stable, so neutrons quickly combine to produce deuterium and then helium, stopping the neutron decay.
N
N


Alpha
α


Beta
β
e


Gamma
γ


TYPES OF RADIATION AND PENETRATION
α Alpha
β Beta
x X-ray
γ Gamma
n Neutron
Paper
Thin plates made of wood, aluminum, etc.
Lead, iron, and other thick metal plates
Water, concrete,etc.

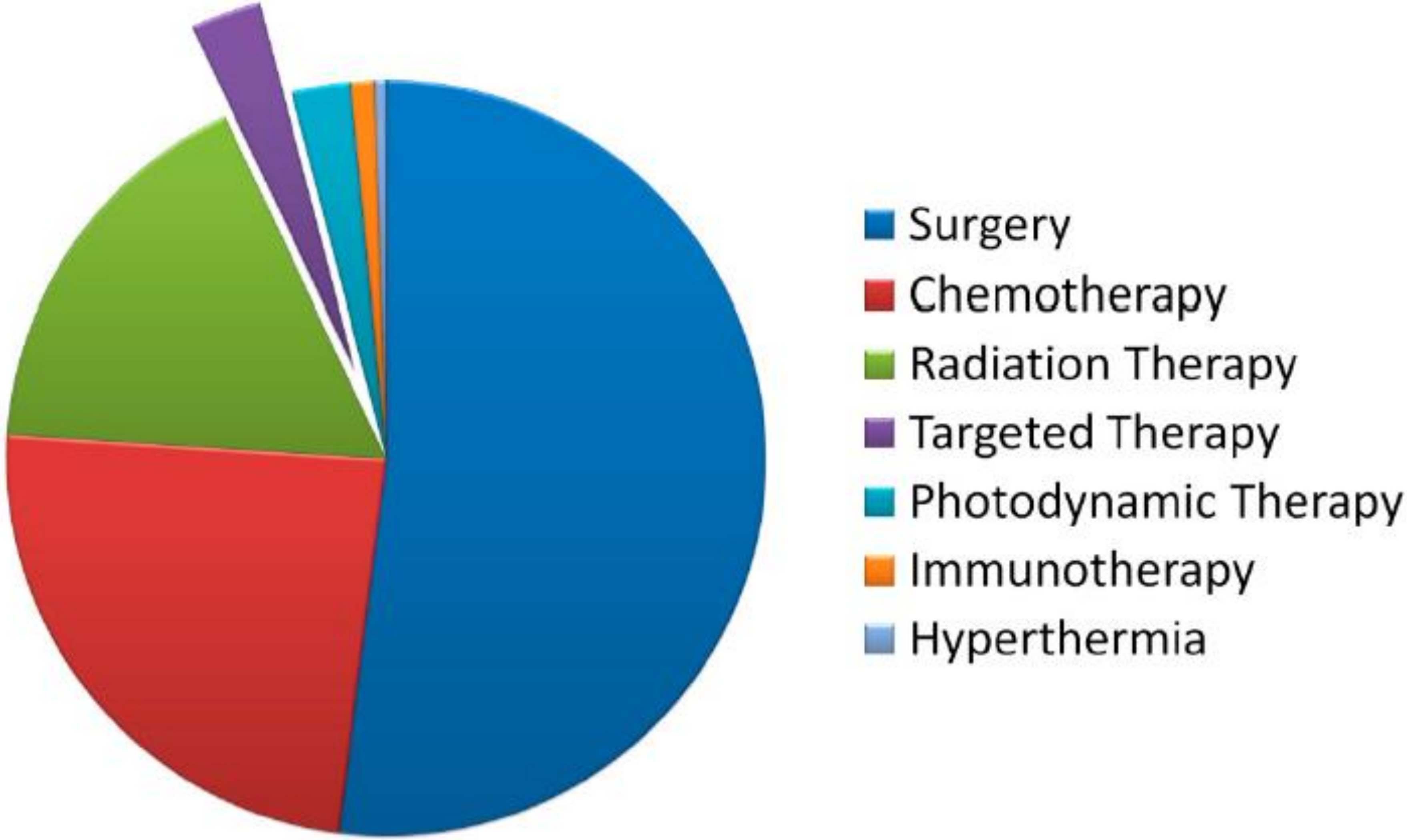



**Figure 1.** A pie chart of the prevalence of cancer treatments.

**$^{131}$I sodium iodide**

**$^{89}$Sr chloride**

**$^{153}$Sm-EDTMP**

**$^{90}$Y Microspheres**

**$^{223}$Ra chloride**

**$^{90}$Y-Zevalin**

**$^{131}$I-Bexaar**

**$^{177}$Lu-DOTATATE**

**$^{131}$I-MIBG**

**$^{177}$Lu-DOTA-huJ591 mAb**

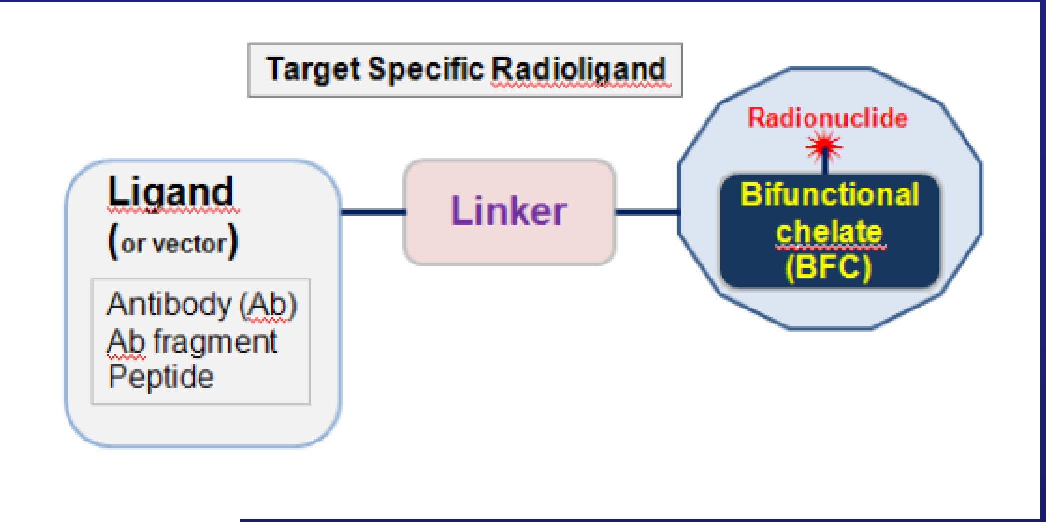
**$^{225}$Ac-DOTA-huJ591 mAb**

**$^{131}$I-Actimab**

**$^{225}$Ac-Lintuzumab**

**$^{177}$Lu-PSMA-617**

# Targeted Radionuclide therapy



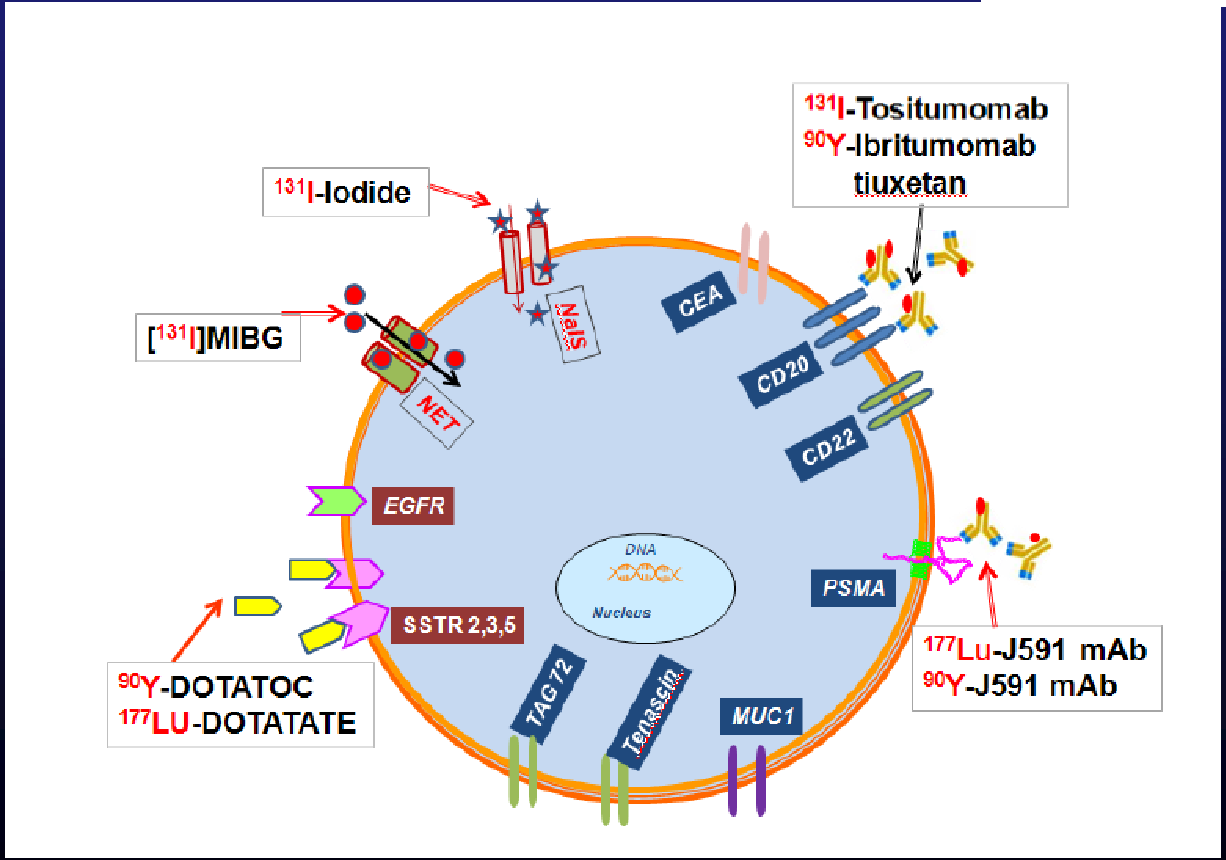
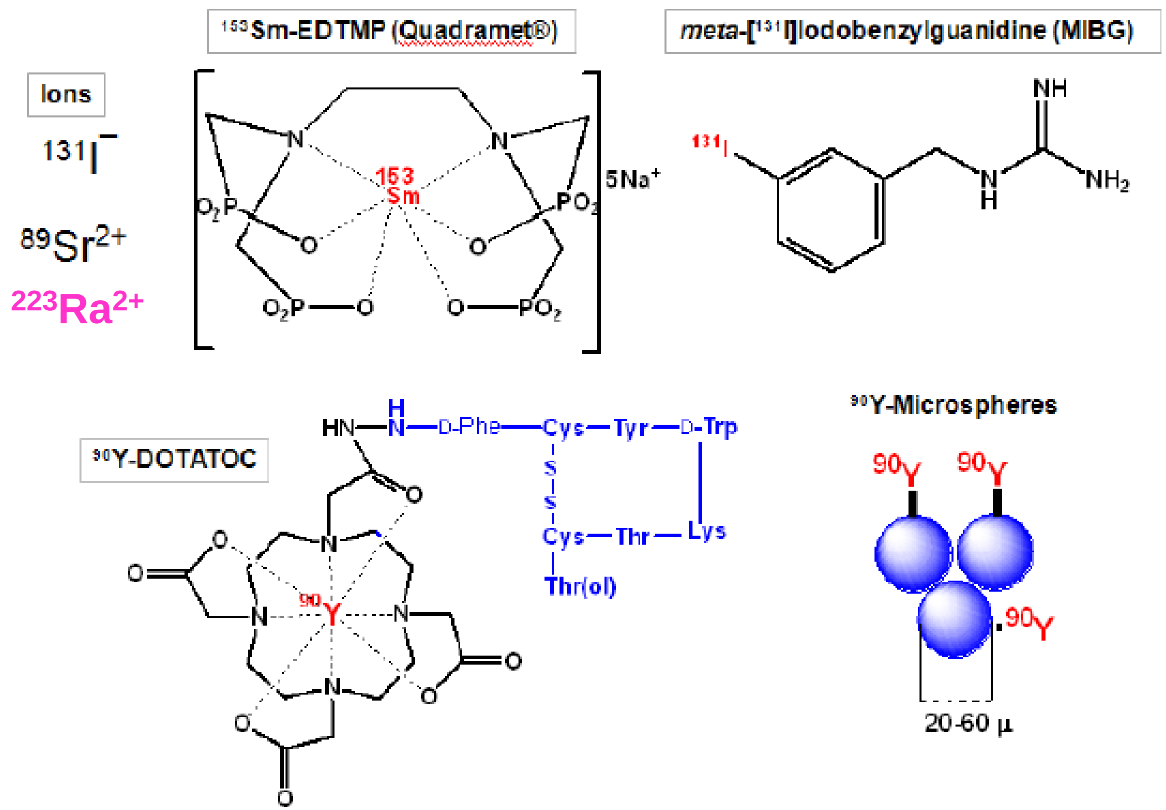



**Figure 1: Diverse chemistry of radiopharmaceuticals used in TRT. These drugs may be structurally simple ions ($^{131}$I sodium iodide), small molecules ($^{131}$I-MIBG and $^{153}$Sm-EDTMP), biomolecules ($^{131}$I, $^{90}$Y or $^{177}$Lu labeled mAbs or peptides) or even particles ($^{90}$Y labeled microspheres).**



# Radionuclides For Therapy

| | $T_{½}$ (Days) | Decay Mode | E (MeV) Max. | Average | Range (mm) Max | Mean | γ photon (KeV) |
|---|---|---|---|---|---|---|---|
| $^{90}Y$ | 2.67 | β- | 2.28 | 0.935 | 12.0 | 2.76 | None |
| $^{89}Sr$ | 50.5 | β- | 1.49 | 0.58 | 8.0 | - | None |
| $^{153}Sm$ | 1.95 | β- | 0.81 | 0.225 | 3.0 | 0.53 | 103 |
| $^{131}I$ | 8.04 | β- | 0.61 | 0.20 | 2.4 | 0.4 | 364 |
| $^{177}Lu$ | 6.7 | β- | 0.497 | 0.133 | - | - | 208 |
| $^{213}Bi$ | 45.6 m | α | 8.0 (98%) | | <0.1 | | |
| $^{211}At$ | 0.30 | α | 6.0 – 7.5 (42, and 58%) | | 65.0µm | | |
| $^{223}Ra$ | 11.4 | α | 5.0 – 7.5 (95%) | | <0.1 | | |
| $^{225}Ac$ | 10.0 | α | 6.0 (4 alphas) | | 65.0µm | | 218, 440 |
| $^{227}Th$ | 18.0 | | | | | | |
| $^{125}I$ | 60.3 D | EC | 0.0004(Auger $e^-$) | | 10.0 nm | | 25-35 KeV |

# Radionuclide therapy

- Radionuclide selection
- LET for α-particles: ~80 keV/μ
  β- particles: 0.2–2.0 keV/μ
  Auger electrons: 4-16 KeV/μ

- Choice of Carrier Molecule
- Selection of a Target Antigen
  (or receptor) of Tumor Cells
- Determination of the Dose Load in TRNT

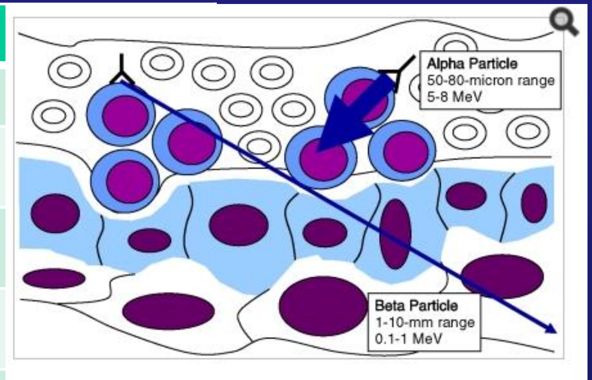
- Leukemias Vs. solid tumors
- Radionuclide half-life, Effective half-life

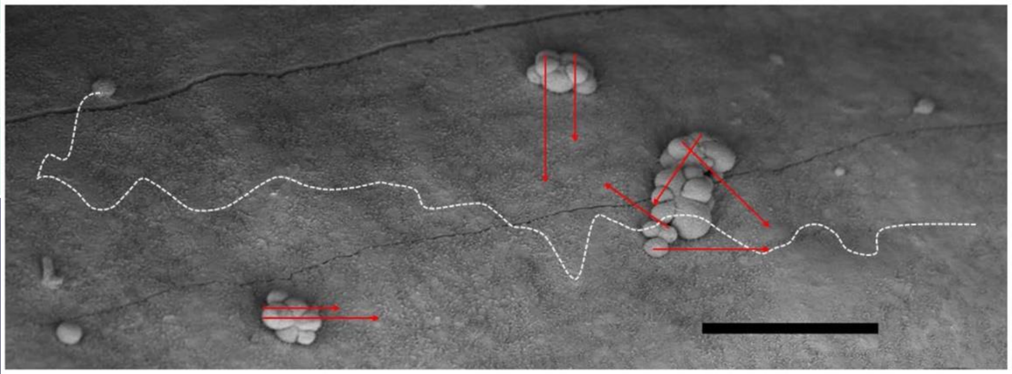
# Alpha emitting radionuclides for therapy

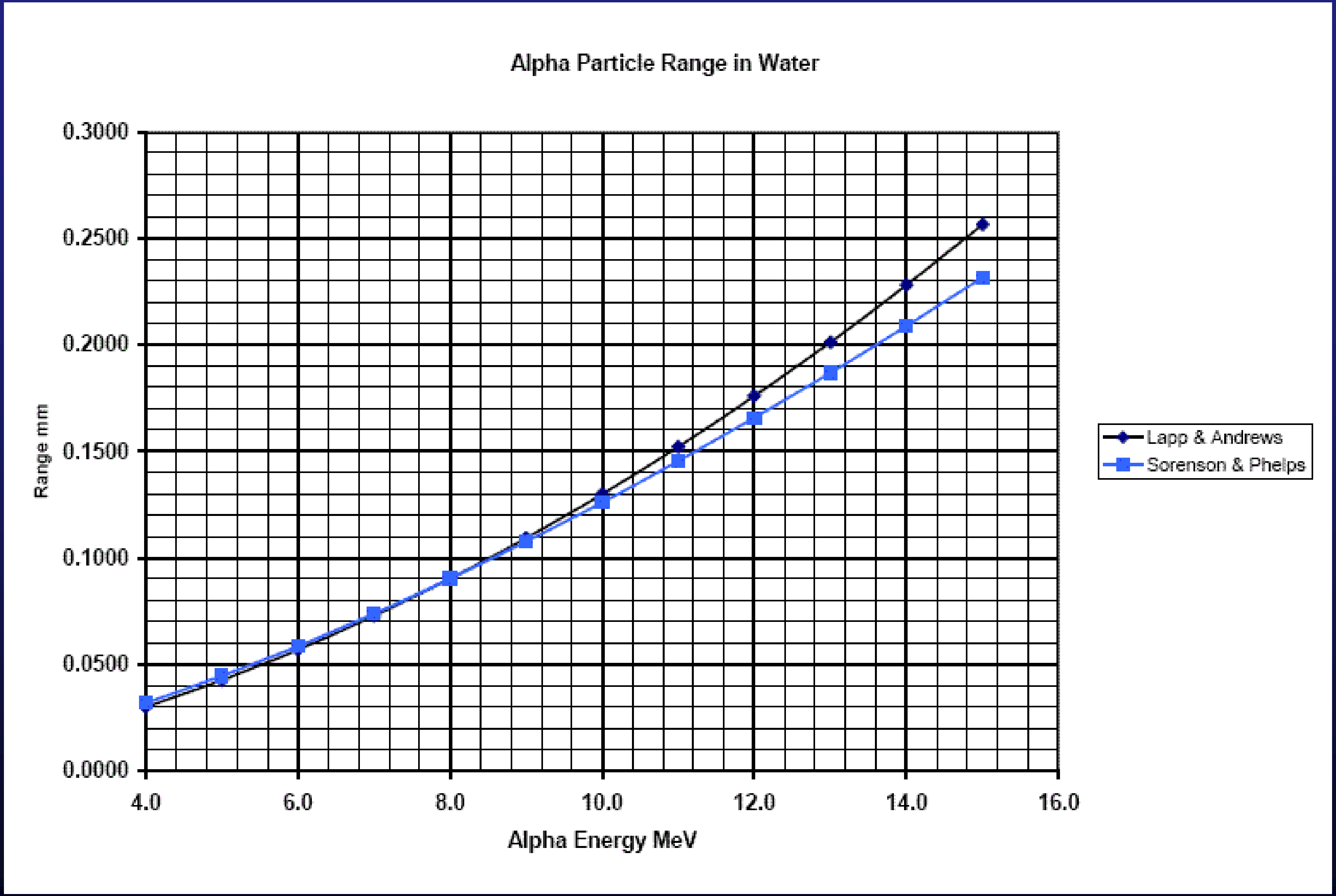
- Short penetration depth; about 6 cell diameters (50-100 μm)
- High LET gives an α particle increased RBE compared to other radiation (electrons)
- Cell death due to alpha particles is largely independent of oxygenation or active cell proliferation
- Very effective in destroying metastasis, especially micrometastasis
- Bi-213 (45.6 m) and At-211 (7.2 h) – short half-life is good for easily accessible tumors
- Ra-224, Ra-223, and Ac-225 long lived nuclides

# Range of Beta and alpha particles in tissue

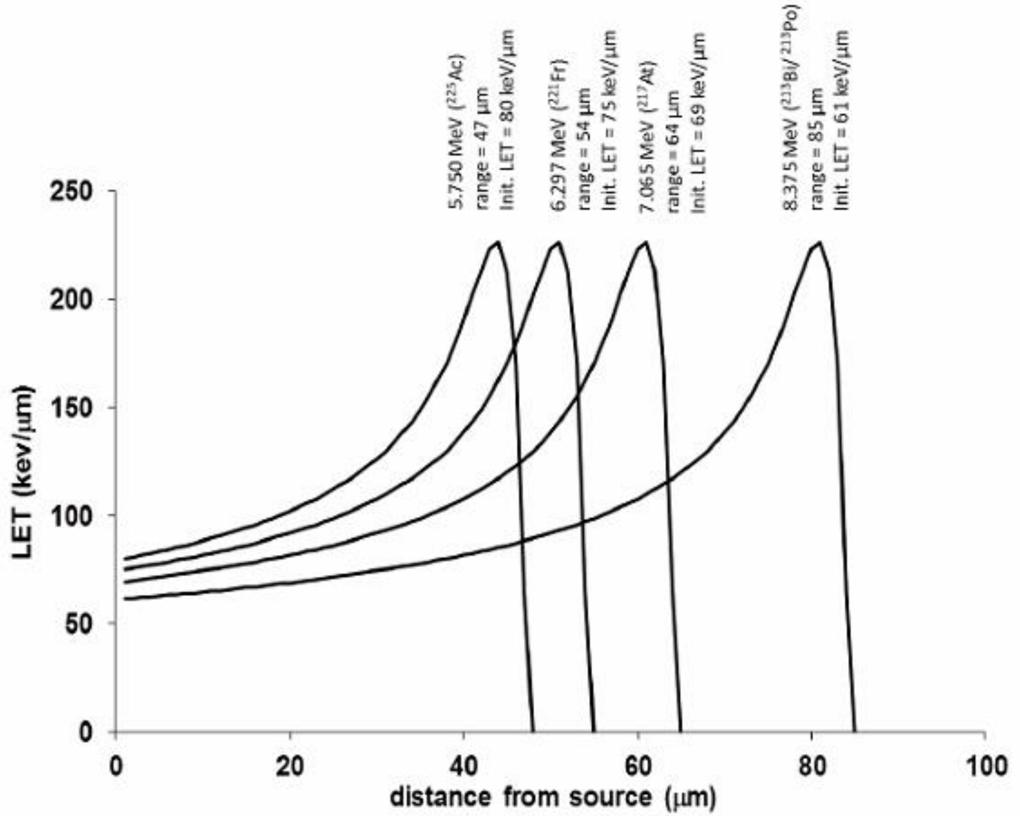
| | | E (MeV) | | Range (mm) | |
|---|---|---|---|---|---|
| | | Max | Mean | Max | Mean |
| **I-131** | β– | **0.61** | **0.20** | **2.4** | **0.4** |
| **Lu-177** | β– | **0.497** | **0.133** | **1.5** | **-** |
| **Y-90** | β– | **2.28** | **0.935** | **12.0** | **2.76** |
| | | | | | |
| **$^{213}$Bi** | α | **8.0** | | **< 0.1** | **-** |
| **$^{211}$At** | α | **5.87** | | **0.065** | **-** |
| **$^{225}$Ac** | α | **5.83** | | **0.065** | |
| | | | | | |




Alpha Particle Range in Water
Range mm
0.3000
0.2500
0.2000
0.1500
0.1000
0.0500
0.0000
4.0
6.0
8.0
10.0
12.0
14.0
16.0
Alpha Energy MeV
Lapp & Andrews
Sorenson & Phelps

# LET and Tissue Range of $^{225}$Ac and Daughter Nuclides




Supplemental Fig. 2: Linear Energy Transfer and respective tissue range of the 4 alpha particles emitted from $^{225}$Ac and its daughter nuclides (*courtesy of George Sgouros, Director of Radiopharmaceutical Dosimetry at Johns Hopkins School of Medicine*).

JNM April 2017

# Radium-223 dichloride,  XOFIGO®

**Each mL contains 1100 kBq (29.7 μCi); 0.58 ng;**
**SA = 1.9 MBq (51.4 μCi) / ng**

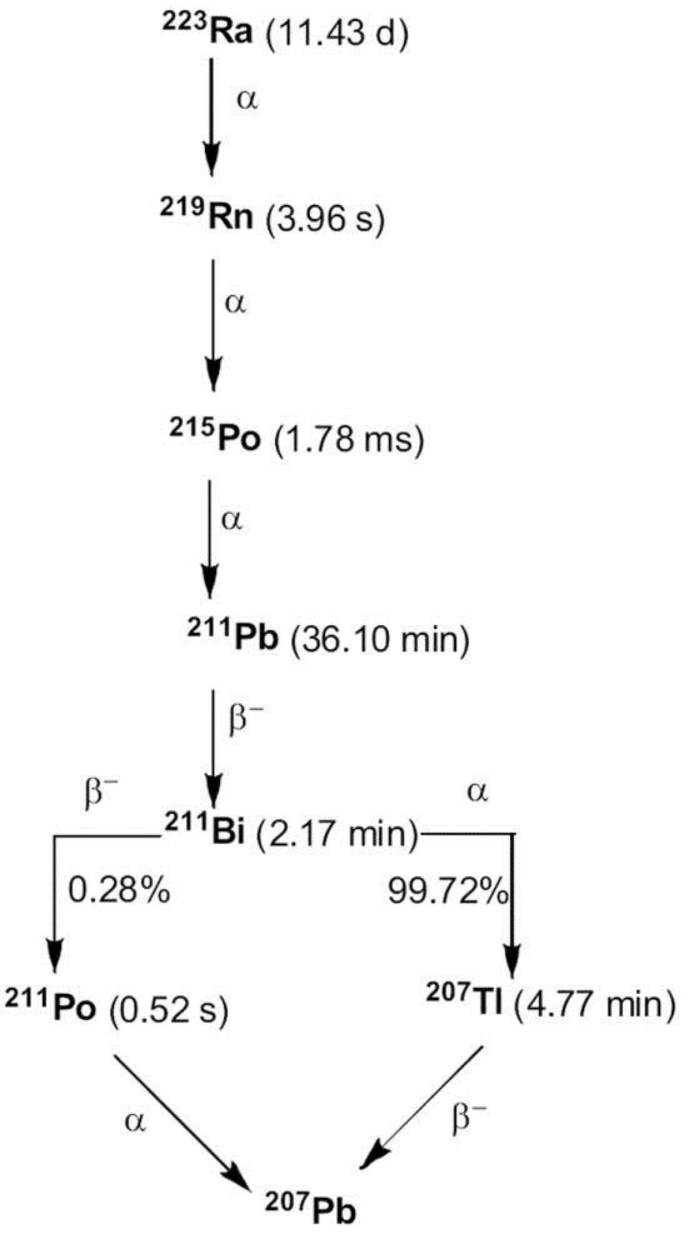
**The vial contains 6.0 mL**

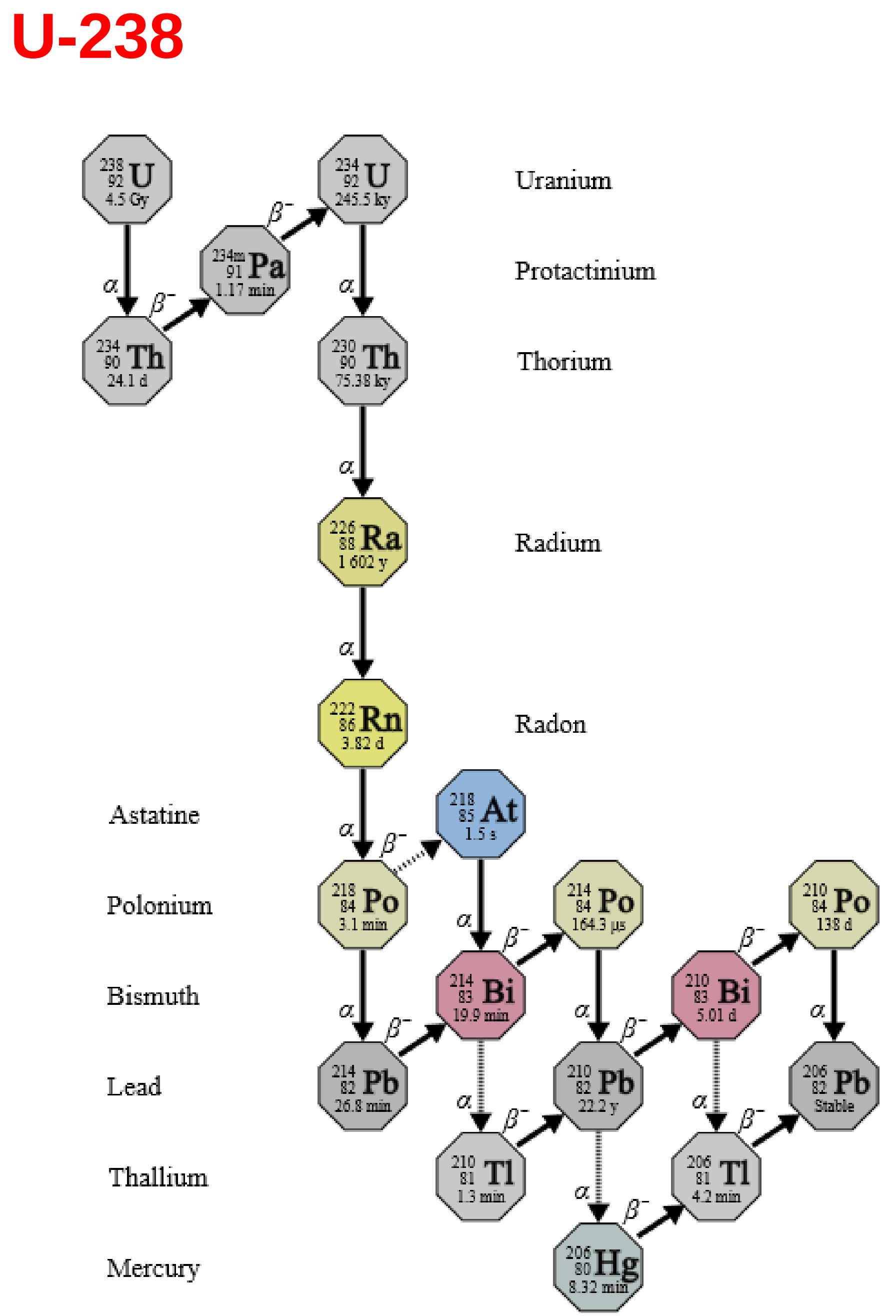
**Ra-223 is present as a divalent cation; $Ra^{++}$**

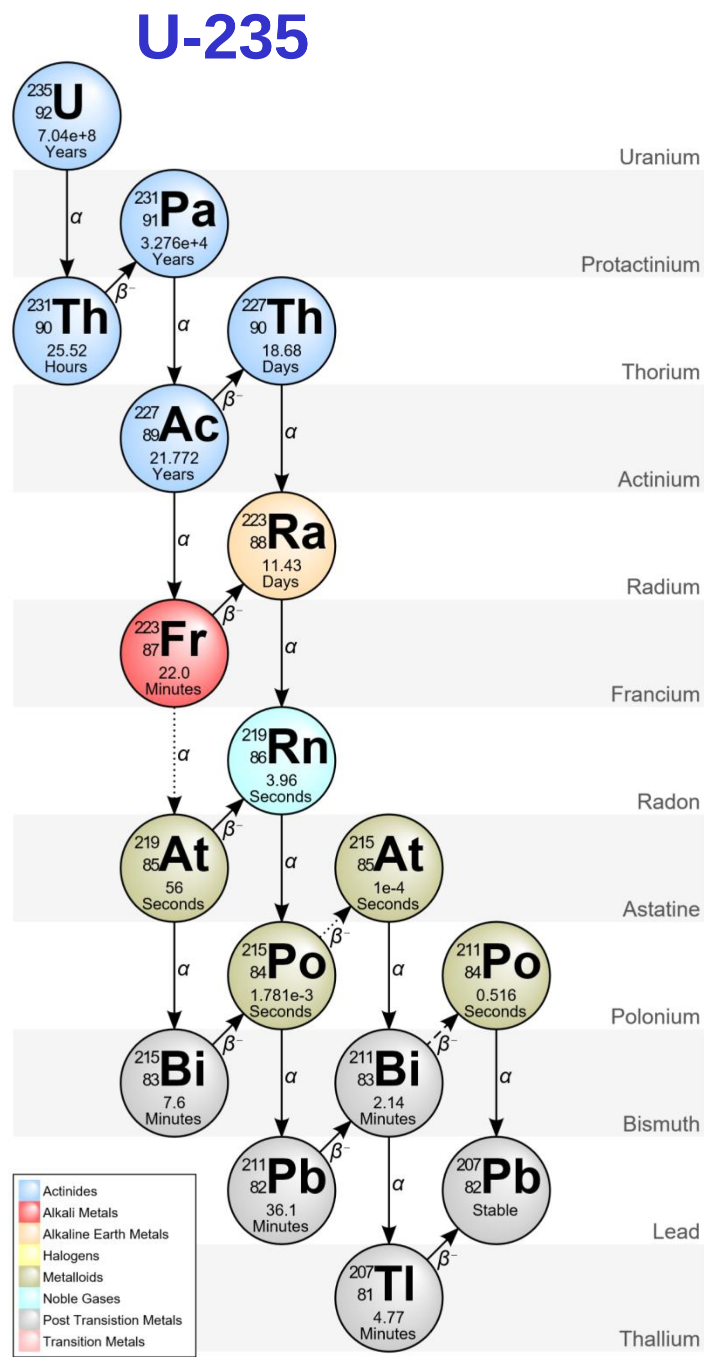
**α partiles (95.3%), 5.0 – 7.5 MeV**
**β– particles(3.6%), 0445 and 0.492 MeV average**
**γ  Photons (1.1%), 0.01 – 1.27 MeV**

**Indications: Therapy of bone mets in mCRPC.**

**Dose: 55 kBq (1.49 μCi)/kg; 6 doses; every 4 wks.**




U-238
238 92 U 4.5 Gy
234 92 U 245.5 ky
234m 91 Pa 1.17 min
234 90 Th 24.1 d
230 90 Th 75.38 ky
226 88 Ra 1 602 y
222 86 Rn 3.82 d
218 85 At 1.5 s
218 84 Po 3.1 min
214 84 Po 164.3 µs
210 84 Po 138 d
214 83 Bi 19.9 min
210 83 Bi 5.01 d
214 82 Pb 26.8 min
210 82 Pb 22.2 y
206 82 Pb Stable
210 81 Tl 1.3 min
206 81 Tl 4.2 min
206 80 Hg 8.32 min
Uranium
Protactinium
Thorium
Radium
Radon
Astatine
Polonium
Bismuth
Lead
Thallium
Mercury


U-235
235 92 U 7.04e+8 Years
231 91 Pa 3.276e+4 Years
231 90 Th 25.52 Hours
227 90 Th 18.68 Days
227 89 Ac 21.772 Years
223 88 Ra 11.43 Days
223 87 Fr 22.0 Minutes
219 86 Rn 3.96 Seconds
219 85 At 56 Seconds
215 85 At 1e-4 Seconds
215 84 Po 1.781e-3 Seconds
211 84 Po 0.516 Seconds
215 83 Bi 7.6 Minutes
211 83 Bi 2.14 Minutes
211 82 Pb 36.1 Minutes
207 82 Pb Stable
207 81 Tl 4.77 Minutes
Uranium
Protactinium
Thorium
Actinium
Radium
Francium
Radon
Astatine
Polonium
Bismuth
Lead
Thallium
Actinides
Alkali Metals
Alkaline Earth Metals
Halogens
Metalloids
Noble Gases
Post Transition Metals
Transition Metals

# Production of Alpha emitting Radionuclides

Ra-223 is formed by the decay of U-235.

It is made artificially in large quantities by $^{227}Ac$ generator

$^{226}Ra$ (n, $\gamma$) $^{227}Ra$ ($\beta$ $T_{½}$=43 m) → **$^{227}Ac$ → $^{227}Th$**

$$^{227}Th \xrightarrow{\alpha,\ 18.7\ \text{days}} {}^{223}Ra$$

α, 18.7 days

**$^{223}Ra$**

**Ac-225 and Bi-213 are extracted from Th-229, which is obtained from U-233**

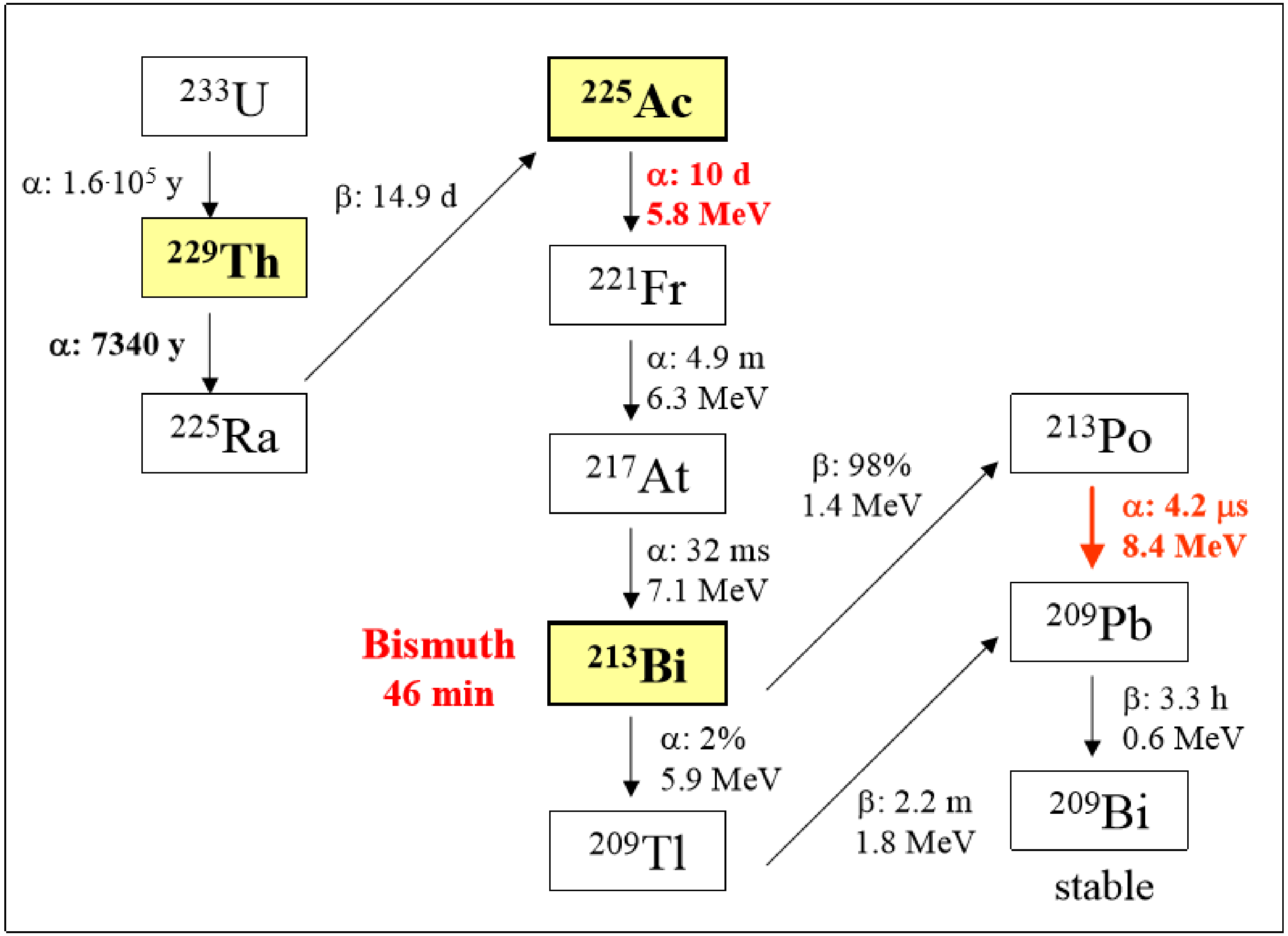
$^{232}Th\ (n,\gamma)^{233}Th \xrightarrow{\beta}\ ^{233}Pa \xrightarrow{\beta}\ ^{233}U \xrightarrow{\alpha}\ ^{229}Th$

## Cyclotron production of $^{225}Ac$

$^{226}Ra\ (p,\ 2n)\ ^{225}Ac$ using 16 MeV protons

Typically, 1 mg Ra-226; should generate 35 mCi

# The Ac-225/Bi-213 system



# Theranostics:
# Targeted Radiopharmaceuticals For Diagnosis and Therapy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New York Presbyterian Hospital
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President
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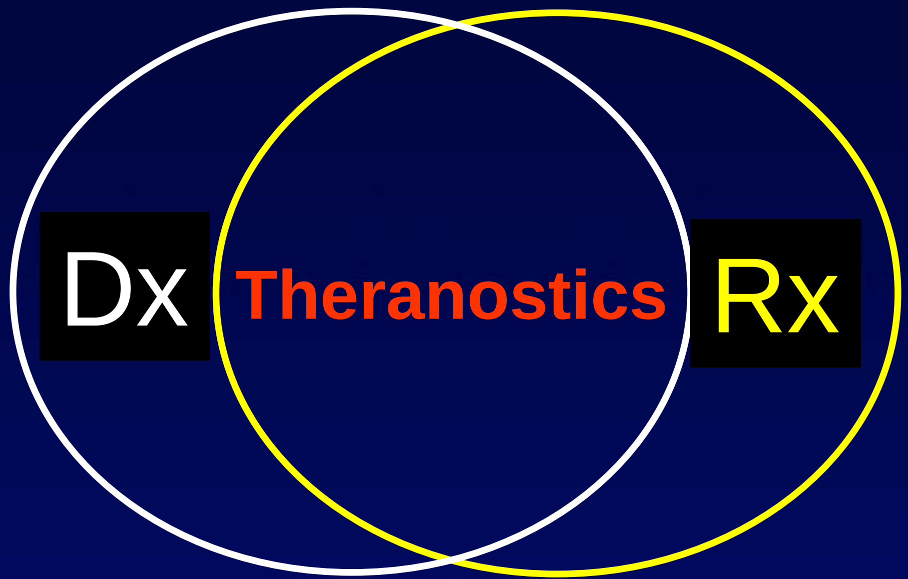
# Theranostics: The right drug and dose to the right patient at the right time




- Merge Diagnostics & Therapeutics
- Molecular-targeted drug with a companion diagnostic test for Personalized medicine
- Drug and diagnostic go to market simultaneously

# Theranostics: The Principle

- A theranostic system integrates some form of **diagnostic testing** to determine the presence of a molecular target for which a **specific drug** is intended.

- **Molecular imaging** serves this diagnostic function and provides powerful means for noninvasively detecting disease.

## Paradigms in Nuclear Medicine:

- Thyroid imaging: Thyroid therapy
- SSTR Imaging: Rdiolabeled Octreotide therapy
- PSMA Imaging: J591 anti-PSMA mAb therapy

# Biomarker: definition

- **Biomarker: a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention**

- **Biomarkers are biologic indicators of disease or therapeutic effects, which can be measured through dynamic imaging tests (such as PET, SPECT, MRI) as well as tests on blood, tissue and other biologic samples.**

  - **(Oncology Biomarker Qualification Initiative (OBQI ), a joint enterprise of US FDA, NCI and CMS)**

# Theranostics: Diagnostics and Therapy

**Target** | **Target Specific agent** | **Dx or Rx**

**Target**

- Antigen
- Receptor
- Enzyme

**Ligand**
(or vector)

- Antibody (mAb)
- Peptide
- Enzyme inhibitor
- Small molecule

Linker

[1]

Drug

RN

[2]

Bifunctional chelate (BFC)

# Theranostics

**Thyroid cancer**

$^{123}$I, $^{124}$I, $^{131}$I sodium iodide

**Neuroendocrine tumors (NETs)**

$^{111}$In-Octreotide; $^{68}$Ga-DOTATOC
$^{90}$Y-DOTATOC, $^{177}$Lu-DOATATE

$^{123}$I-MIBG or $^{131}$I-MIBG

**Prostate Cancer**

$^{111}$In or $^{89}$Zr-J591 mAb
$^{90}$Y, $^{177}$Lu, $^{225}$Ac-J591 mAb

$^{123}$I, $^{99m}$Tc, $^{124}$I, $^{18}$F, $^{68}$Ga – PSMA ligands
$^{131}$I, $^{177}$Lu, $^{225}$Ac –PSMA ligands

# Neuroendocrine Tumors (NETs)
# Diagnosis and Therapy

- NETs are a heterogeneous group of slow-growing rare neoplasms characterized by their endocrine metabolism and histology pattern.

- NET cells belong to the amine precursor uptake and decarboxilation (APUD) system and can take up, accumulate, and decarboxylate amine precursors, such as 3,4-dihydroxylpheny-lalanine (DOPA) and 5-hydroxytryptophan (HTP). Tumors deriving from these cells consequently were called APUDomas.

- Express several different peptide receptors (for somatostatin, VIP, Gastrin, CCK) in high quantities.

# Somatostatin and Octreotide Analogs

**Somatostatin**

**Ala – Gly – Cys – Lys – Asn – Phe – *Phe – Trp – Lys – Thr* – Phe – Thr – Ser – Cys**

**DTPA-Octreotide (OctreoScan®)**

**DTPA - D-Phe – Cys – *Phe – D-Trp – Lys – Thr* – Cys – Thr(ol)**

**DOTA-Tyr$^3$-Octreotide (DOTATOC)**

**DOTA- D-Phe – Cys – *Tyr – D-Trp – Lys – Thr* – Cys – Thr(ol)**

**DOTA-Tyr$^3$-Octreotate (DOTATATE)**

**DOTA- D-Phe – Cys – *Tyr – D-Trp – Lys – Thr* – Cys – Thr(OH)**

**DOTA-Tyr$^3$-Octreotide (DOTANOC)**

**DOTA- D-Phe – Cys – *Nal – D-Trp – Lys – Thr* – Cys – Thr(ol)**

*Nal* = 3- (1-naphtalenyl )-*L*-alanyl

# Affinity profiles ($IC_{50}$) of Octreotide analogs for human Somatostatin receptors (SSTR)

| Peptide | $SSTR_2$ | $SSTR_3$ | $SSTR_5$ |
|---|---|---|---|
| Somatostatin | 2.7 | 7.7 | 4.0 |
| [In-DTPA]Octreotide | 22 | 182 | 237 |
| [DOTA-$Tyr^3$]Octreotide (DOTATOC) | 14 | 883 | 393 |
| [DOTA-$Tyr^3$]Octreotate (DOTATATE) | 1.5 | >1000 | 187 |
| [Ga-DOTA-1-$Nal^3$]Octreotide (DOTANOC) | 1.9 | 40 | 7.2 |
| [Y-DOTA-1-$Nal^3$]Octreotide (DOTANOC) | 3.3 | 26 | 10 |
| [Y-DOTA-$Tyr^3$]Lanreotide (DOTALAN) | 23 | 290 | 16 |

Jong M. Eur J Nucl Med (2003) 30:463–469

# Which tumors to be treated?

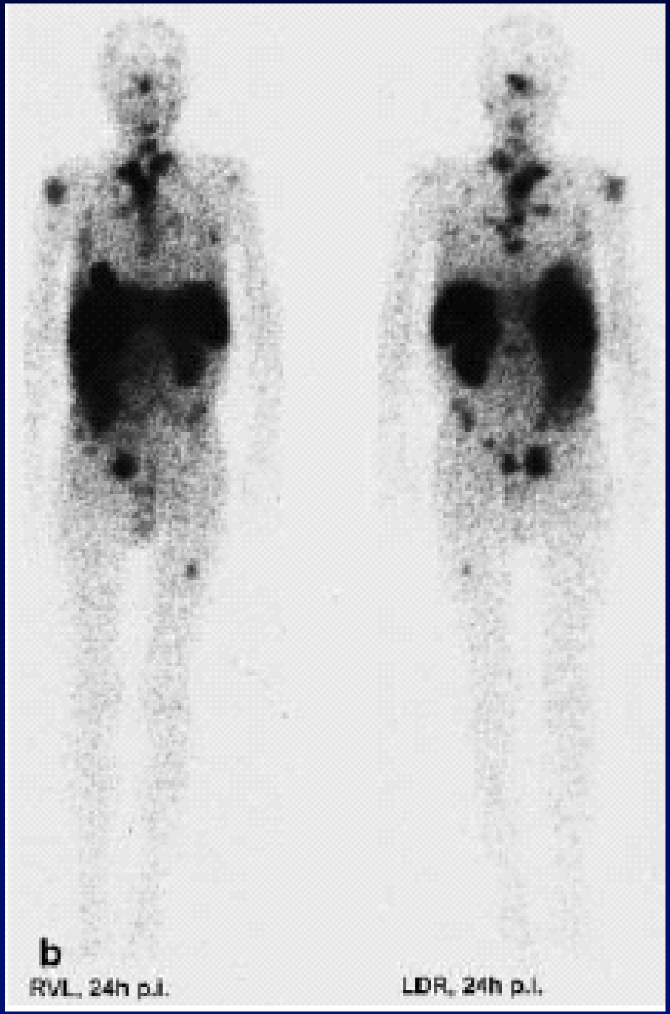
**tumors with high $SSTR_2$ receptor expression:**

- **GEP NET**
- paragangliomas
- pheochromocytomas
- medullary thyroid carcinomas
- breast carcinomas
- lymphomas...

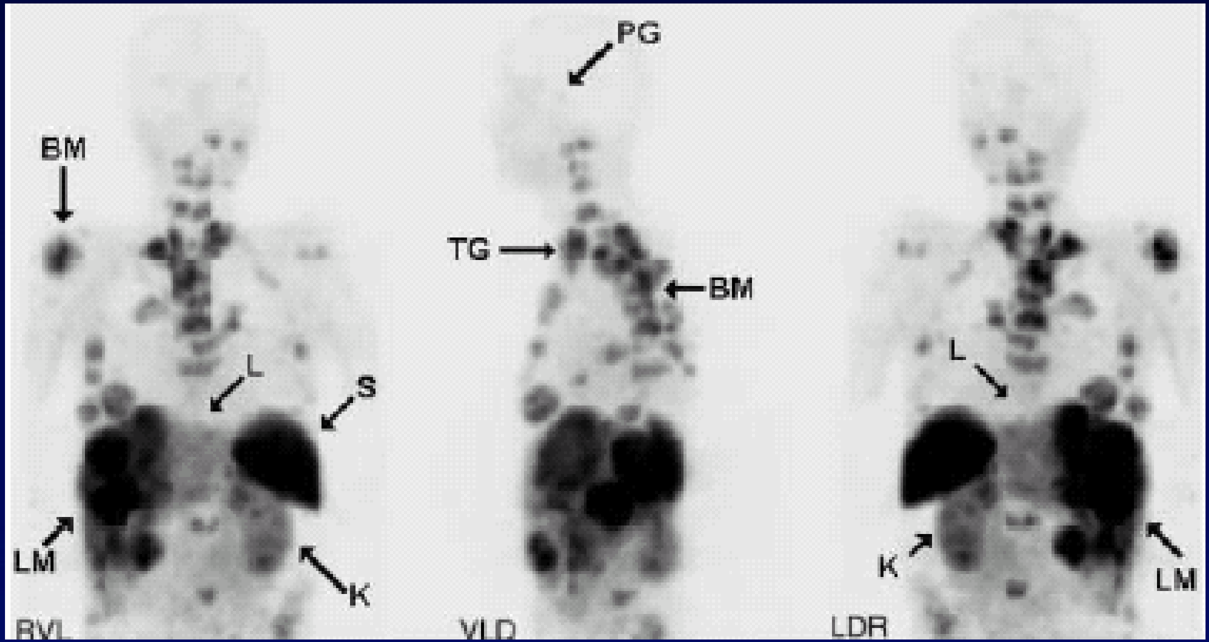
*** Patients with liver mets are candidates**

# $^{68}$Ga-DOTATOC vs OctreoScan

$^{111}$In-OctreoScan, 24 p.i.




$^{68}$Ga-DOTATOC, 90 min p.i.




Hofmann M et al. Eur J Nucl Med 2002

- **Lisa Bodei, European Institute of Oncology, Milano**

**NETSPOT (kit for the preparation of gallium Ga 68 dotatate injection)**

**SomaKit TOC edotreotide for Ga-68 labeling**

- **Received orphan drug designation from both the EMA and the FDA (06/01/2016)**

**LUTATHERA, a Lutetium Lu 177 dotatate**

approved by the FDA in January 2018 for GEP-NET

**Advanced Accelerator Applications USA, Inc.**

# Tumor Imaging and Therapy Using Radiolabeled Somatostatin Analogues

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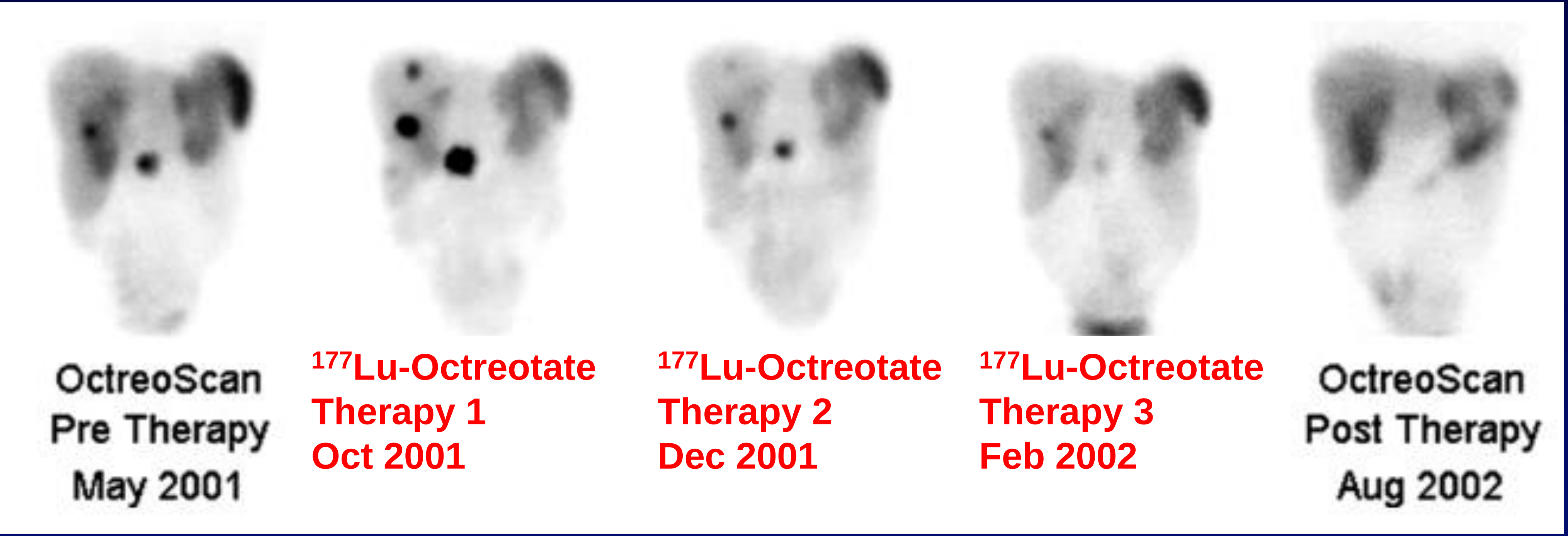
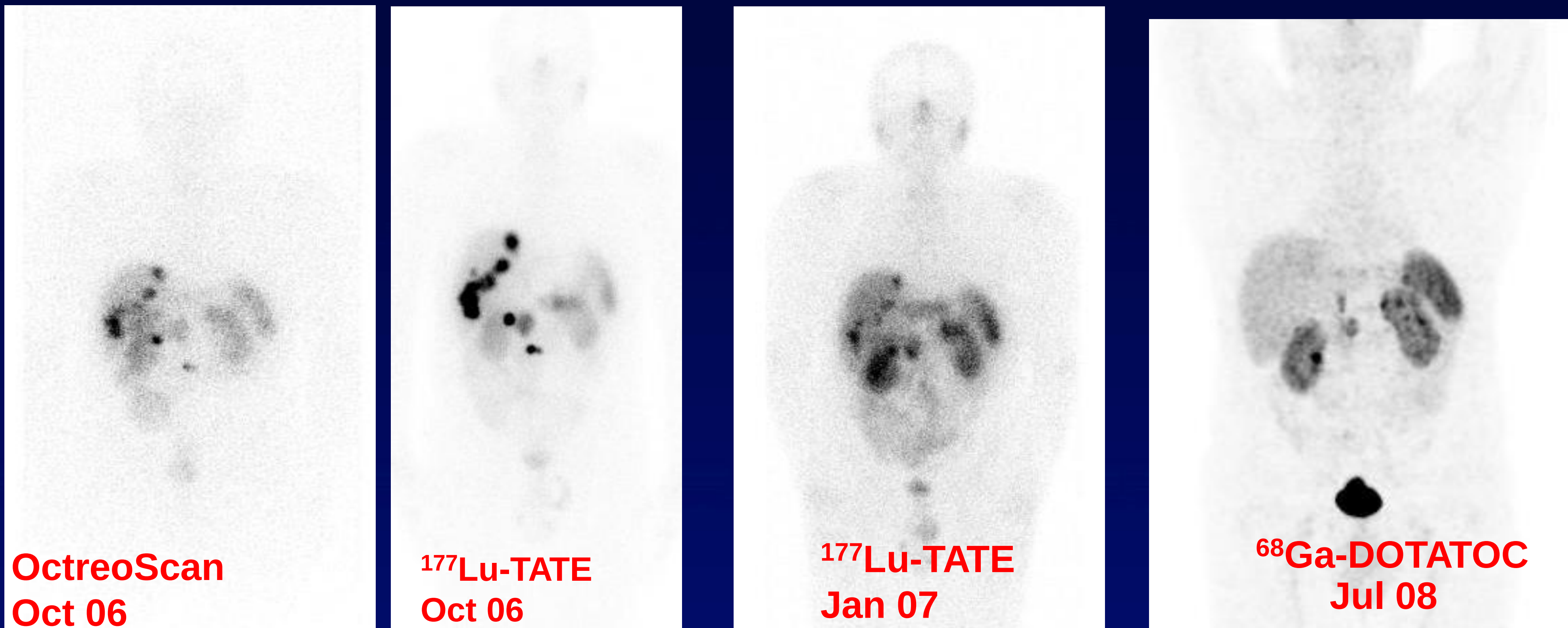



ACCOUNTS OF CHEMICAL RESEARCH 42, July 2009 873-880

# $^{177}$Lu-DOTATATE
# IEO S189/104: phase I-II study

Pt with liver mets from unknown primary neuroendocrine carcinoma




**→ Complete response on liver**
**→ Primary located at the head of the pancreas**

- **Lisa Bodei, European Institute of Oncology, Milano**

# Prostate Cancer

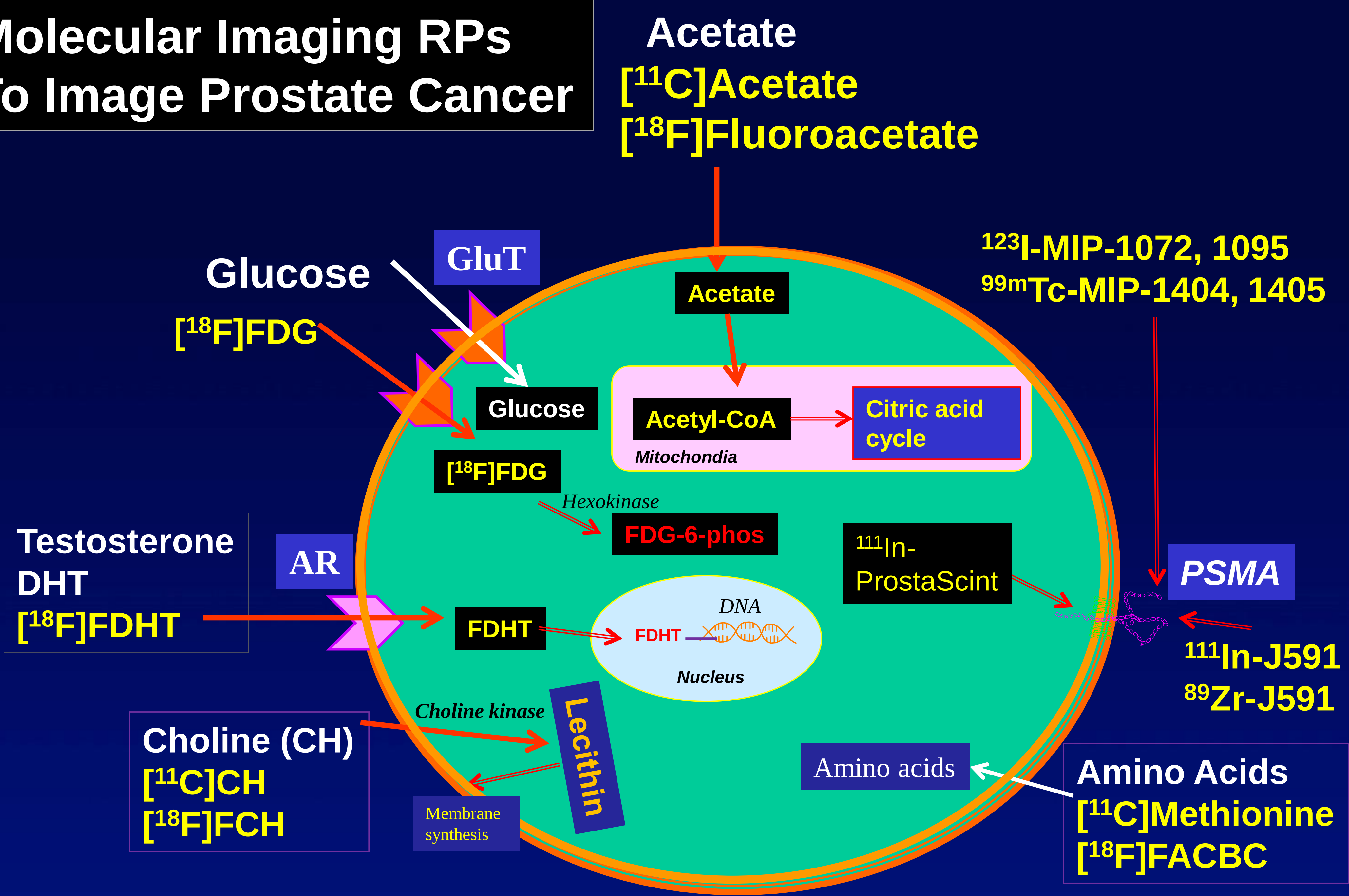
# FDA Approved Radiopharmaceuticals

**Planar and SPECT Bone Scan:** $^{99m}$Tc-MDP

**ProstaScint® Scan:** $^{111}$In-Capromab pendetide (anti-PSMA mAb)

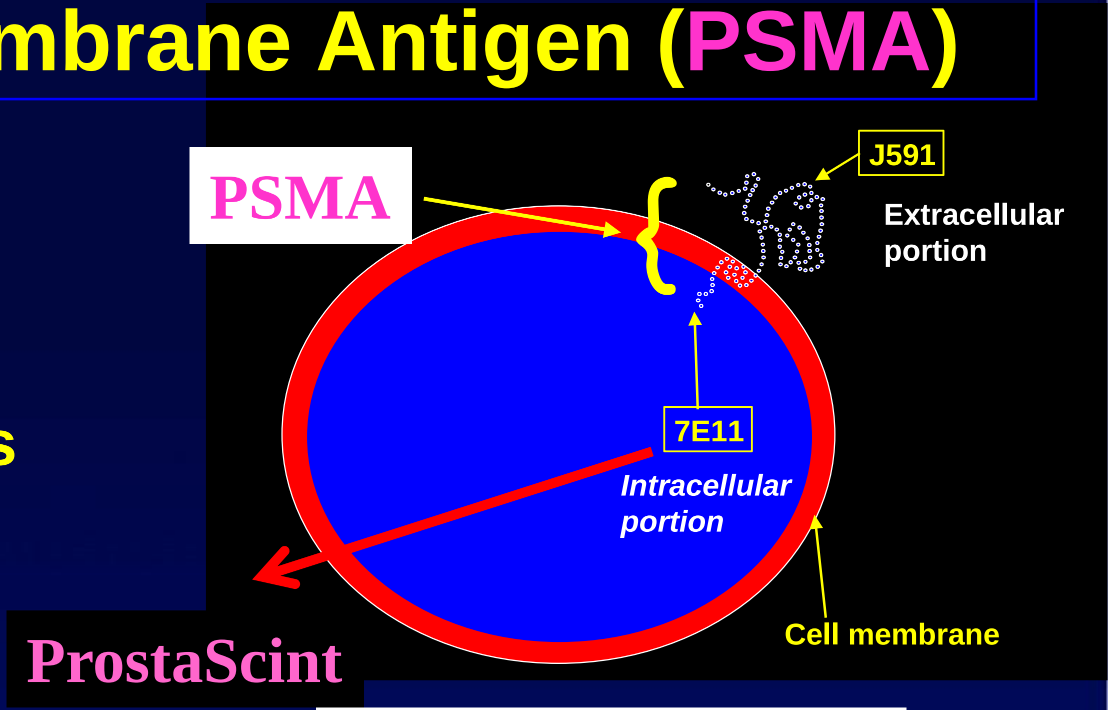
**PET/CT Bone Scan:** [$^{18}$F]NaF
**Choline-PET:** [$^{11}$C]Choline
**Glucose Metabolism:** [$^{18}$F]FDG

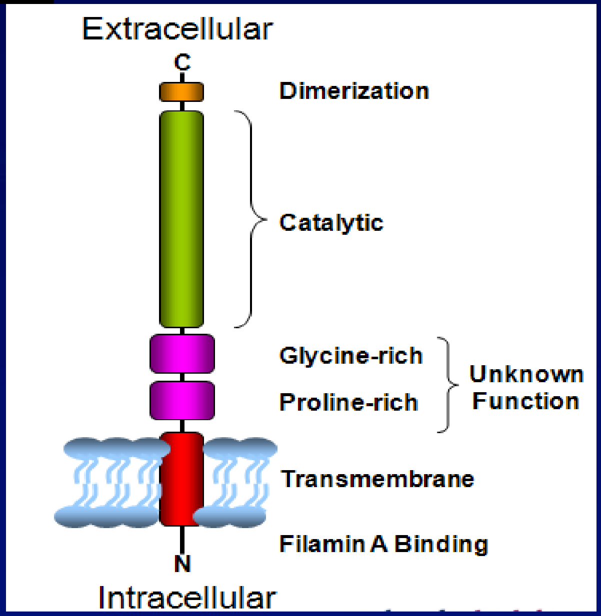
# Molecular Imaging RPs To Image Prostate Cancer



# Prostate Specific Membrane Antigen (PSMA)

- PSMA is a surface antigen expressed virtually on all prostate cancer cells
- PSMA expression increases progressively in:
  - Higher grade tumors
  - Metastastic disease
  - Hormone-refractory Prostate cancer
- PSMA is internalized
- PSMA is expressed also on the neo-vasculature of solid tumors but not on normal tissue



# Radiolabeled J591 mAb

## Diagnostic RPs

- $^{111}In$-DOTA-huJ591
- $^{89}Zr$-DFO-huJ591
- $^{89}Zr$-DOTA-IAB2M
  (J591 minibody)

## Therapeutic RPs

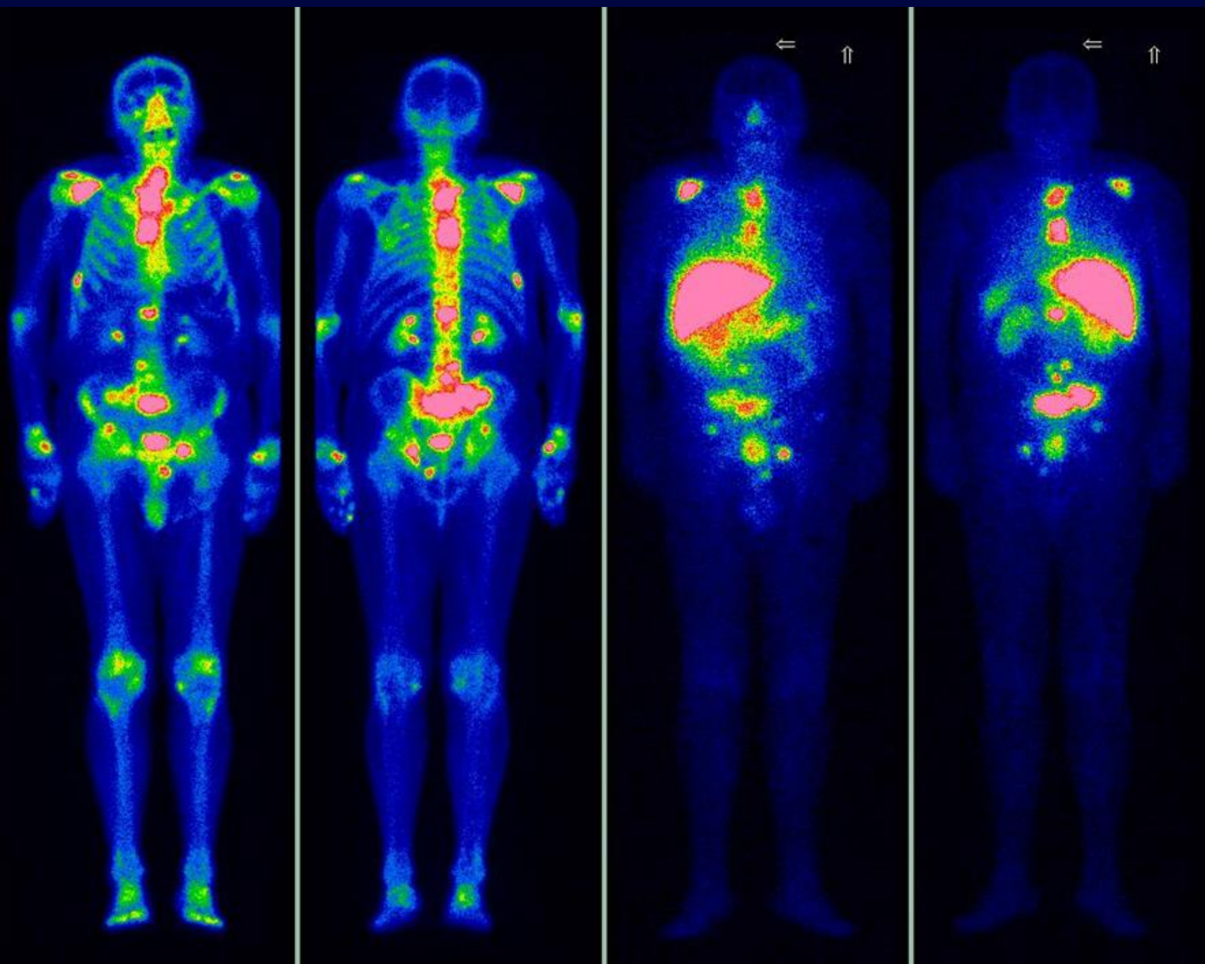
- $^{131}I$-huJ591
- $^{90}Y$-DOTA-huJ591
- $^{177}Lu$-DOTA-huJ591
- $^{225}Ac$-DOTA-huJ591

# $^{177}$Lu-J591 Rx: Excellent Targeting & PSA Response

**30/32 (94%) with accurate targeting of known sites of disease**

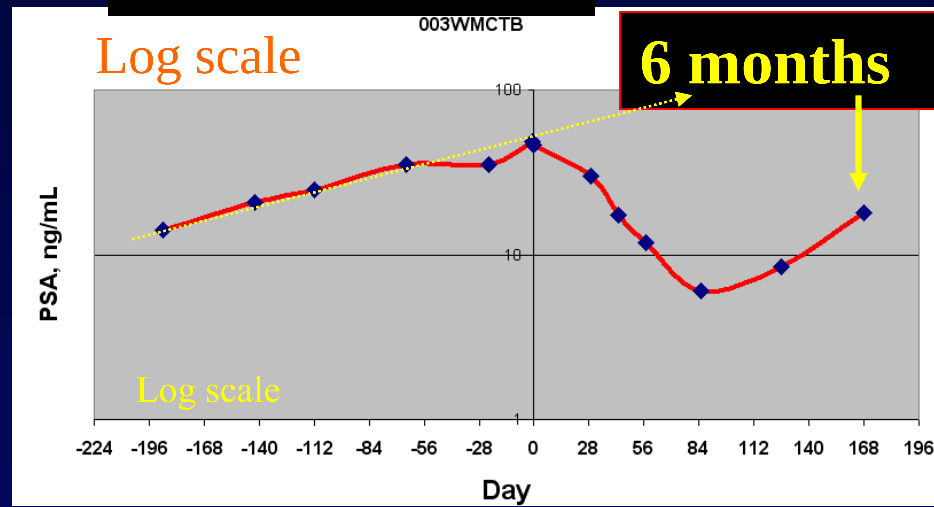
$^{99m}$Tc-MDP bone scan

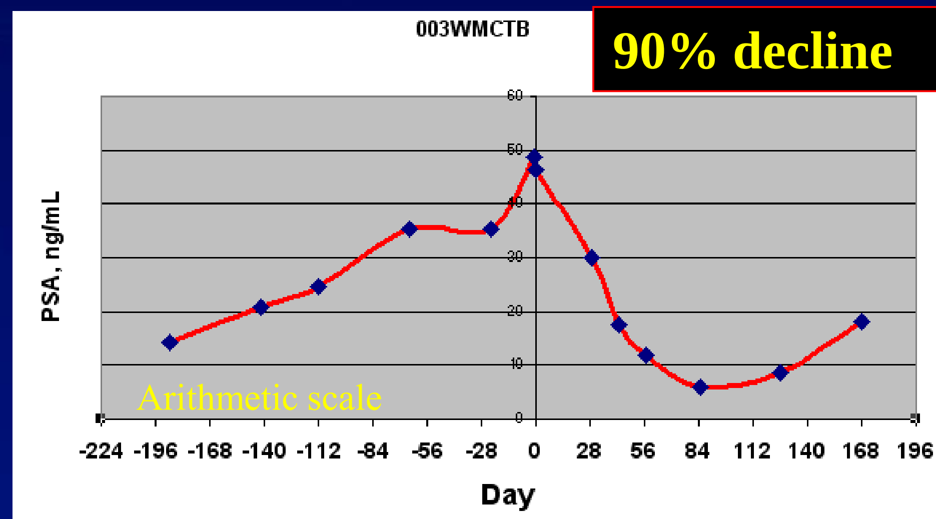
$^{177}$Lu-J591 mAb



Ant Post Ant Post

PSADT=3.9 mo



# Phase I dose−escalation trial of $^{225}$Ac−J591 in patients with mCRPC

## Weill Cornell Medicine Protocol

**Division of Hematology & Medical Oncology and Urology**

***Scott T. Tagawa, MD, MS***
David M. Nanus, M.D.,
Ana M. Molina, M.D.,
Himisha Beltran, M.D.,
Bishoy Faltas, M.D.,
Keriann Scavone, PA,
Tessa Chamberlain, NP,
Jaspreet S. Batra, M.D.,

**Division of Nuclear Medicine, Radiology**

Yuliya S. Jhanwar, M.D.
Stanley J. Goldsmith, M.D.
Honglei Zhang, M.D.
Trisha Youn, M.D.
Shankar Vallabhajosula, Ph.D.
John Babich, Ph.D.

## Radiation Dosimetry: 225Ac-DOTA-J591

| Organ | Dose limit | Dose | Activity limit* | |
|---|---|---|---|---|
| | Gy | mGy/MBq | MBq | mCi |
| Red Marrow | 2 | 66 | 6.06 | 0.16 |
| Kidney | 23 | 382 | 12.04 | 0.33 |
| Liver | 40 | 591 | 13.54 | 0.37 |
| Lung | 20 | 79 | 50.93 | 1.38 |

* Activity limits estimated with weighting factor (RBE = 5)

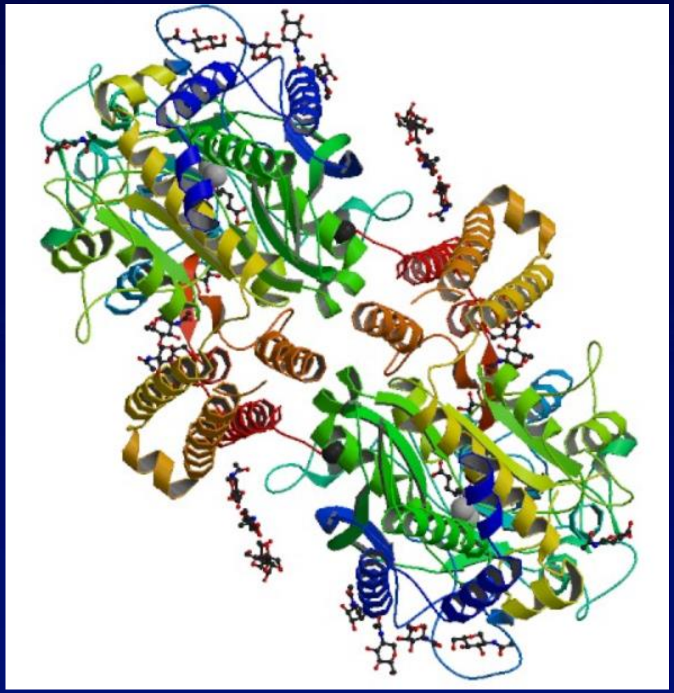
## Dose-Escalation Treatment Plan with $^{225}$Ac−J591

| Cohort | Treatment Dose | | N |
|---|---|---|---|
| | KBq/Kg | µCi/Kg | |
| 1 | 13.3 | 0.36 | 1−6 |
| 2 | 26.7 | 0.72 | 1−6 |
| 3 | 40.0 | 1.08 | 3−6 |
| 4 | 53.3 | 1.44 | 3−6 |
| 5 | 66.7 | 1.80 | 3−6 |
| 6 | 80.0 | 2.16 | 3−6 |
| 7 | 93.3 | 2.52 | 3−6 |

# PSMA is Glutamate carboxypetidase II (GCPII)

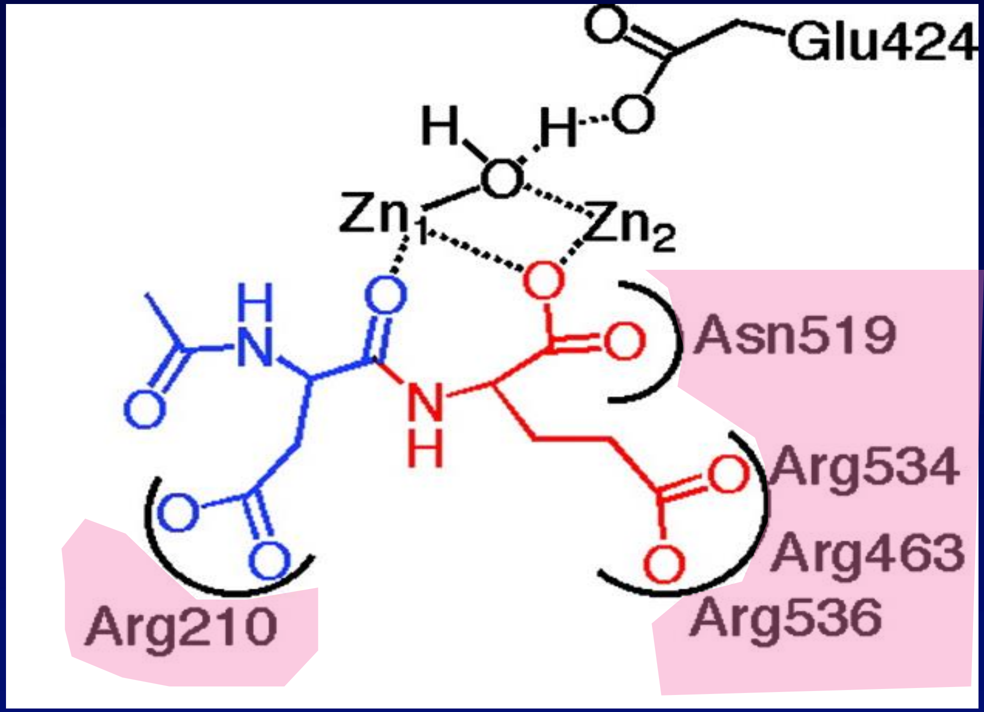
- N-acetylated-alpha-linked acidic dipeptidase (NAALADase),
- folate hydrolase (FOLH1), a zinc-dependent peptidase
- PSMA

**Human GCPII conforms to the pattern typical for type II transmembrane proteins having a short N-terminal cytoplasmic tail (amino acids 1 – 18), a single membrane-spanning helix (amino acids 19 – 43) and a large extracellular part (amino acids 44 – 750).**



# *Enzymatic Site of PSMA is known*
# *(NAALADASE and PSMA are Homologous)*

**NAAG Binding to PSMA**



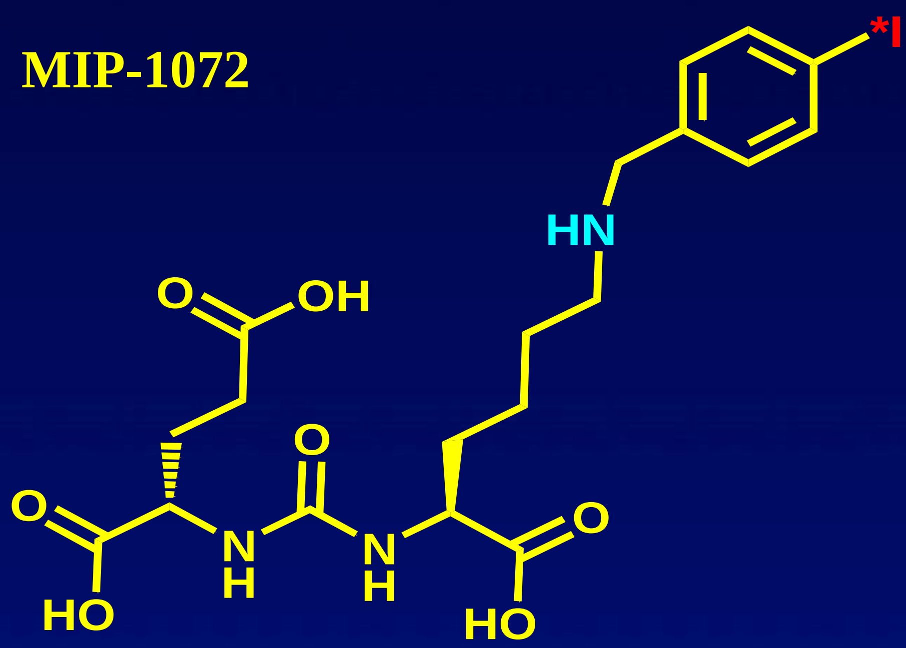

- **Substrate binding domain contains two basic sub-pockets.**
- **Catalytic domain contains a bi-nuclear zinc binding site coordinating a water molecule where hydrolysis of peptide bond occurs**
- **The major basic patch binds glutamate via electrostatic interactions**

*Davis et al. (2005) Proc. Natl. Acad. Sci. USA 102, 5981-5986*

# MIP-1072 and MIP-1095

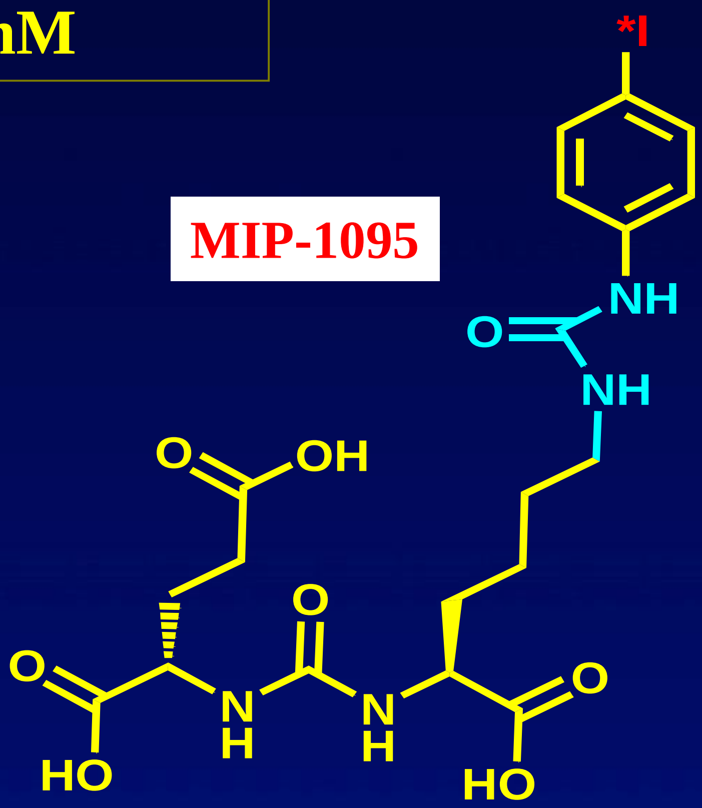
| *NAALADase* Inhibition (*Ki*) | |
|---|---|
| MIP-1072 | 6 nM |
| MIP-1095 | 0.3 nM |

MIP-1072




2-(3-(1-carboxy-5-(4-iodo-benzylamino)-pentyl)-ureido)-pentanedioic acid

MIP-1095

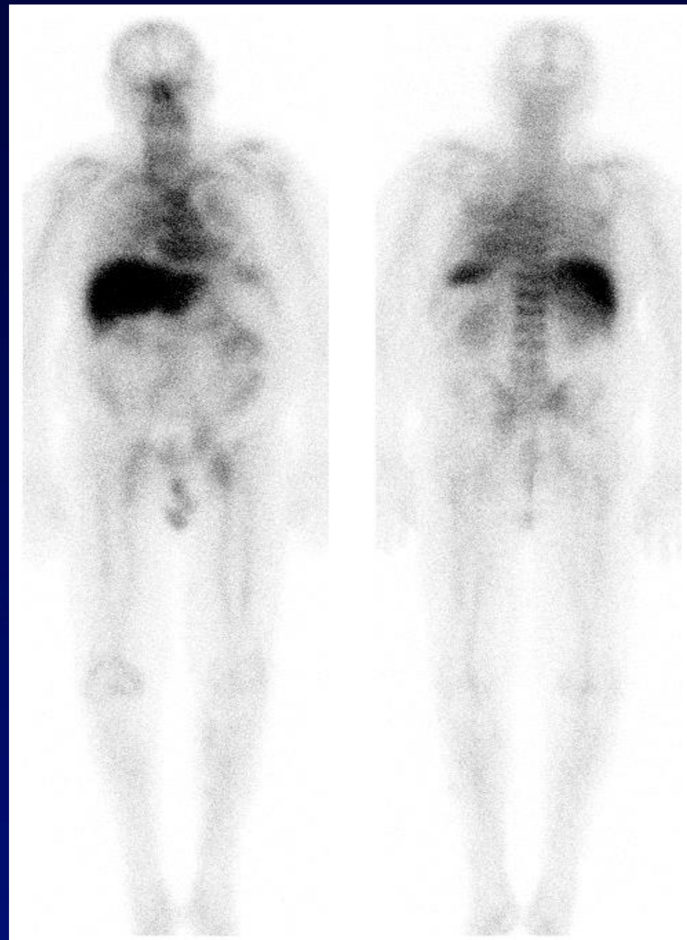



(S)-2-(3-(R)-1-carboxy-5-(3-(4-iodophenyl) ureido)pentyl)ureido)pentanedioic acid

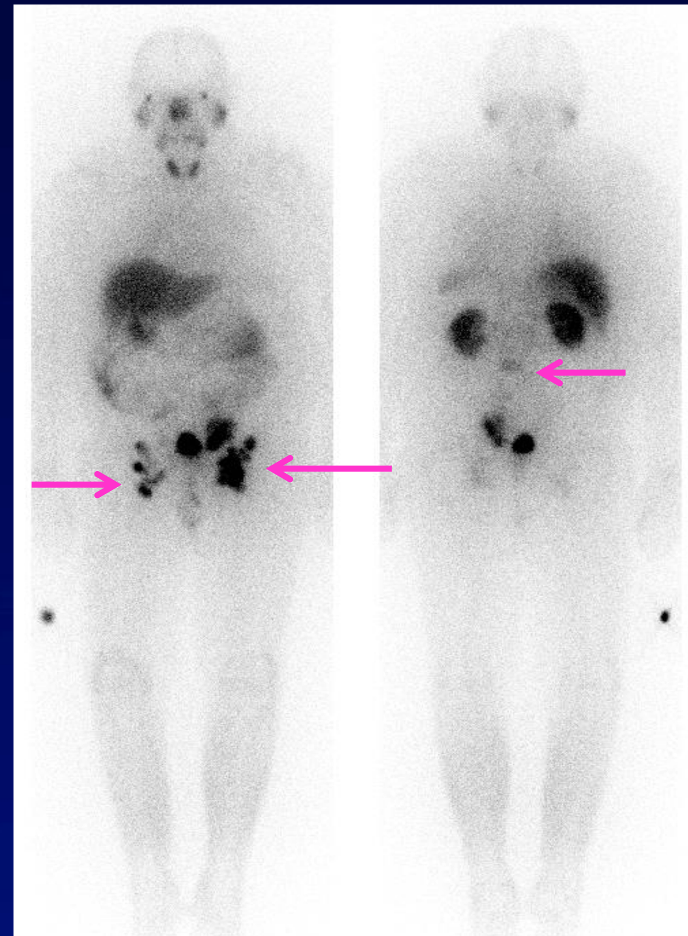
Maresca KP, et al. J Med Chem. 2009 Jan 22;52(2):347-57.

$^{99m}$Tc-MDP Bone Scan

$^{111}$In-ProstaScint 5 days



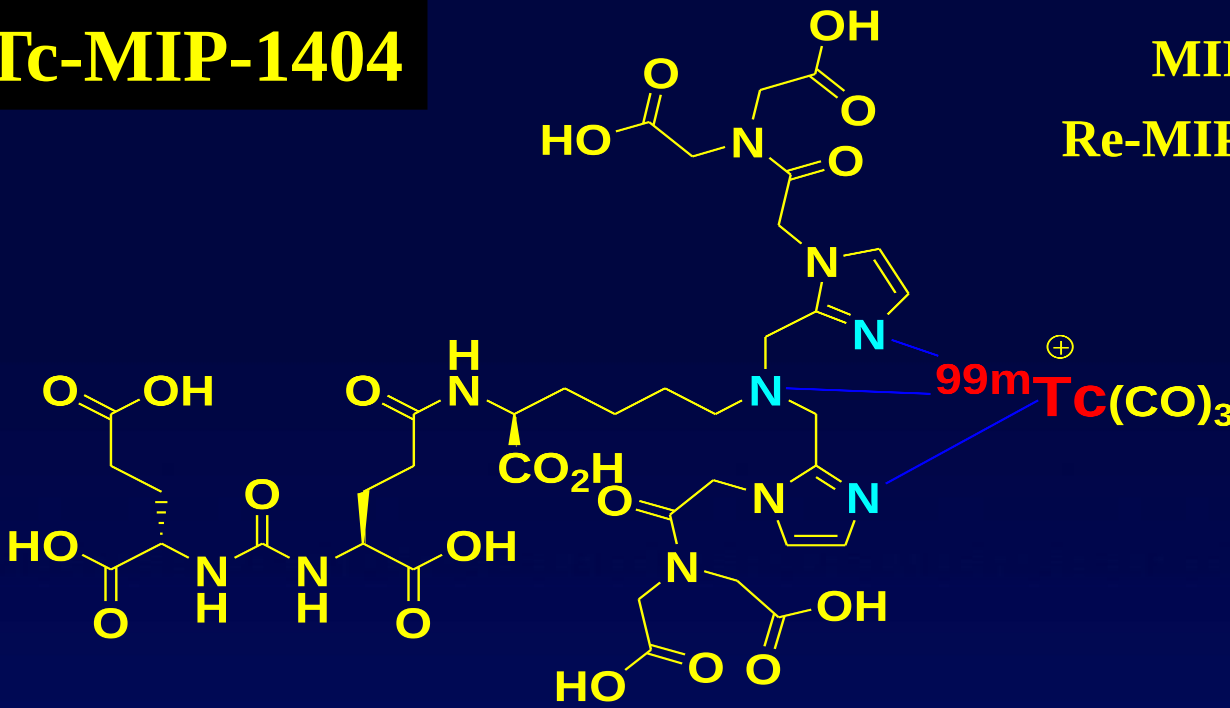
$^{123}$I-MIP-1072 4 Hours



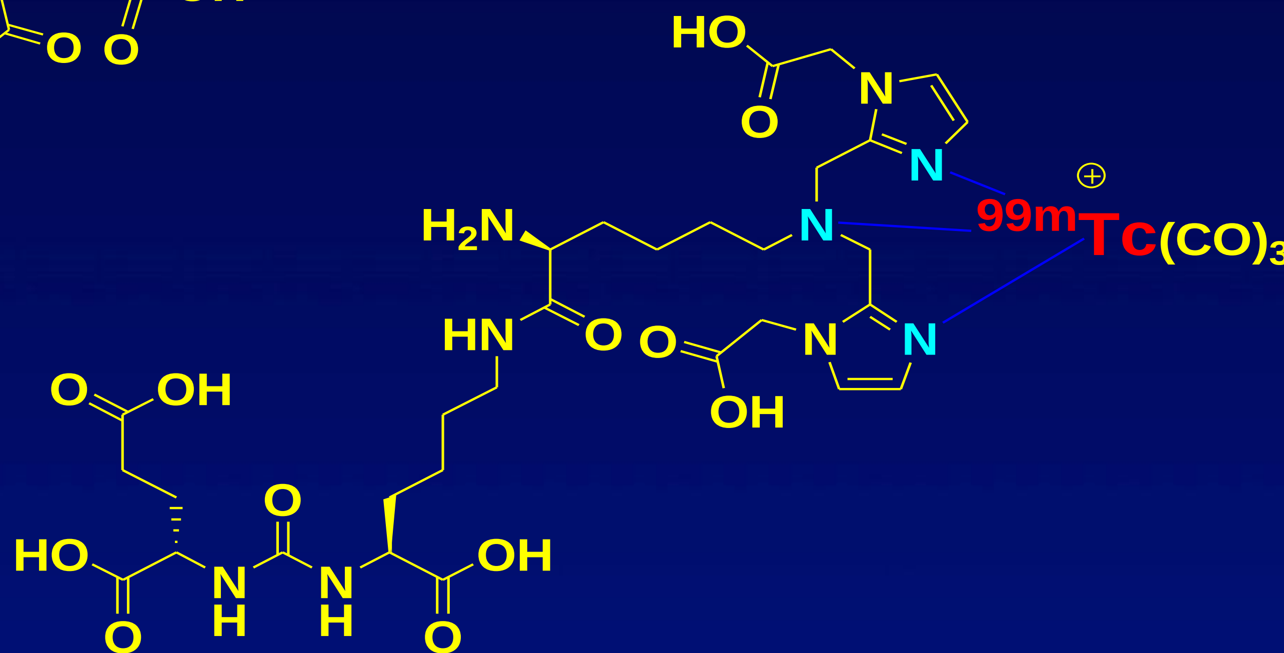
# $^{99m}$Tc-MIP-1404

MIP-1404 (104 nM)

Re-MIP-1382 (2.0 nM)



# $^{99m}$Tc-MIP-1405



MIP-1405 (31 nM)

Re-MIP-1340 (20 nM)

# Disease progression identified by anti-PSMA $^{99m}$Tc agents earlier than bone scan

*71 yr old male with rapidly rising PSA*

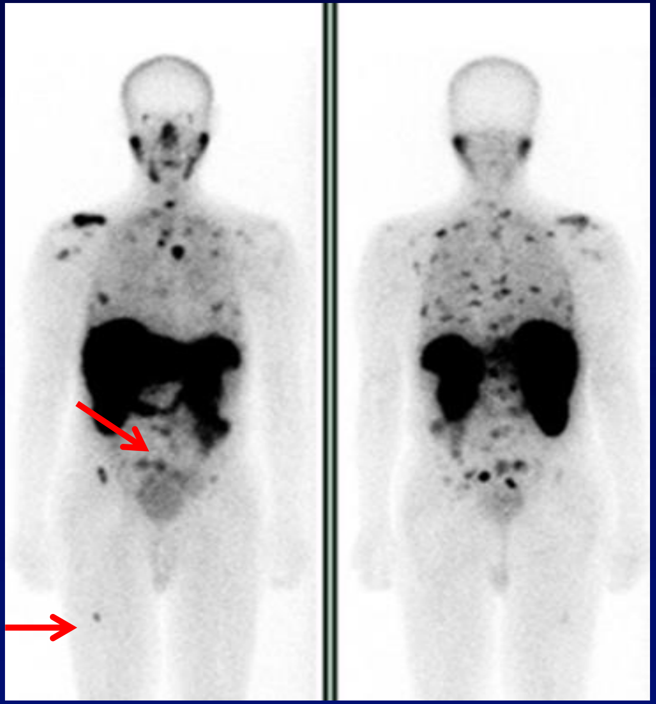
| | | |
|---|---|---|
| 11/2010 | = | 1.37 ng/mL |
| 01/2011 | = | 2.48 ng/mL |
| 03/2011 | = | 8.90 ng/mL |

**January 2011**

$^{99m}$Tc-MDP

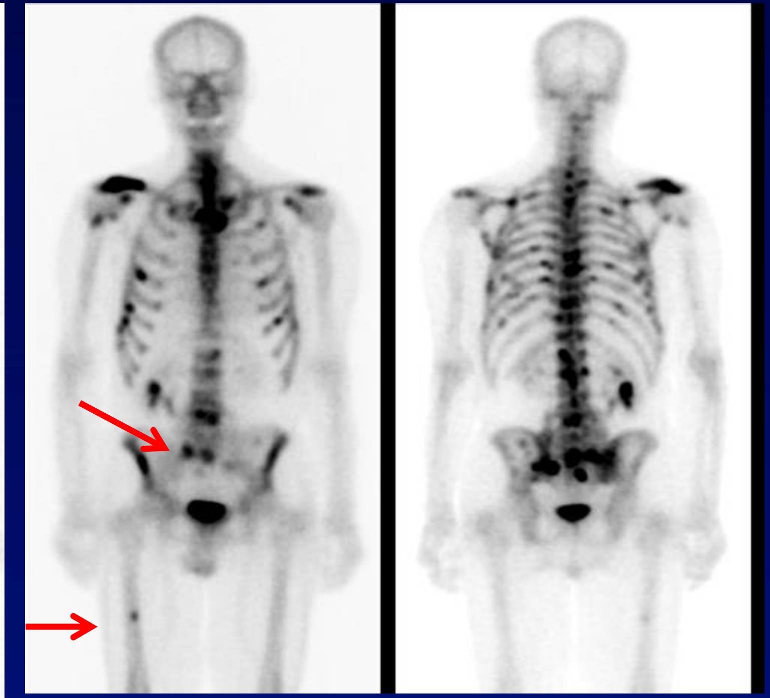
**March 2011**

$^{99m}$Tc-MIP-1404

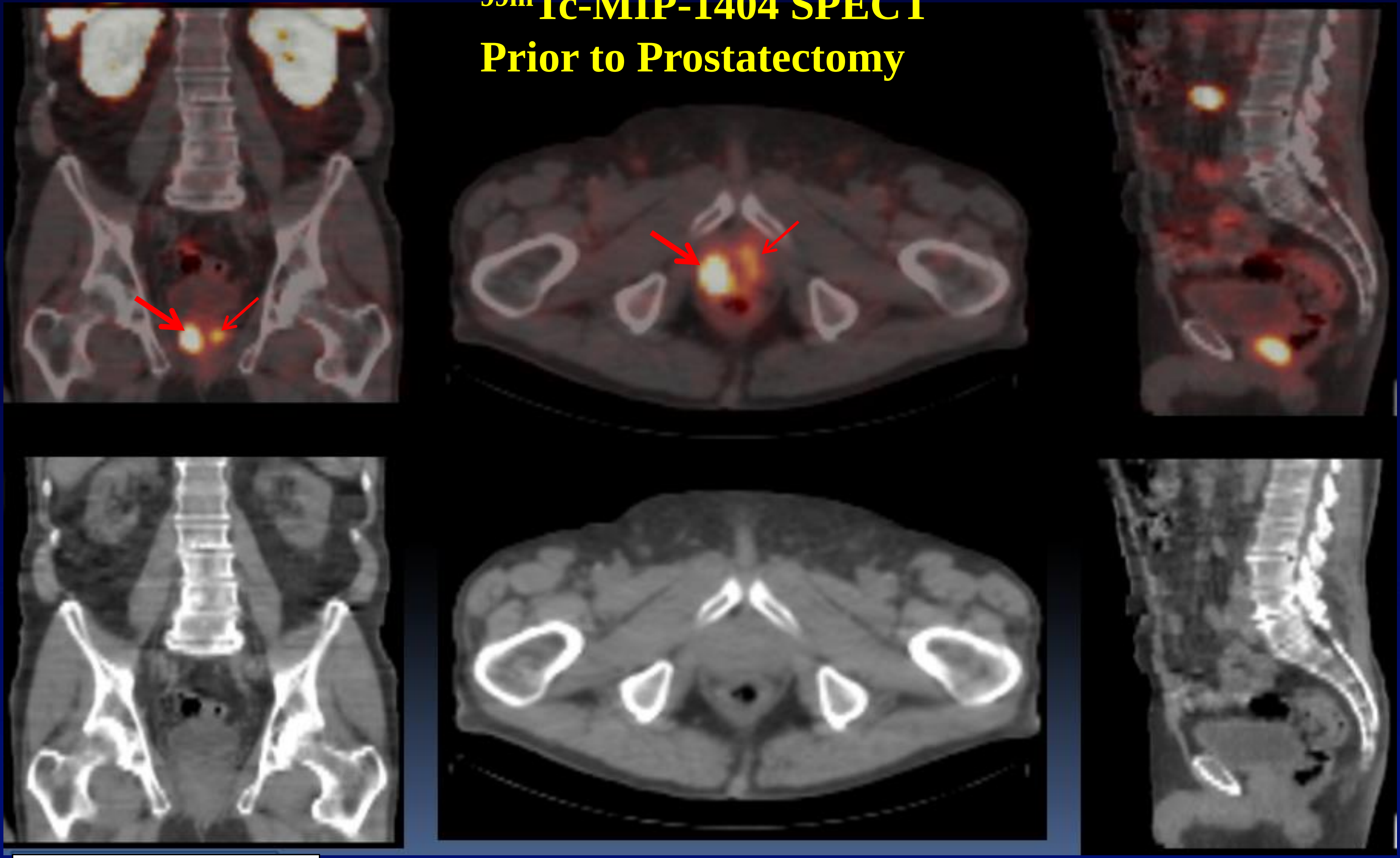


**June 2011**

$^{99m}$Tc-MDP



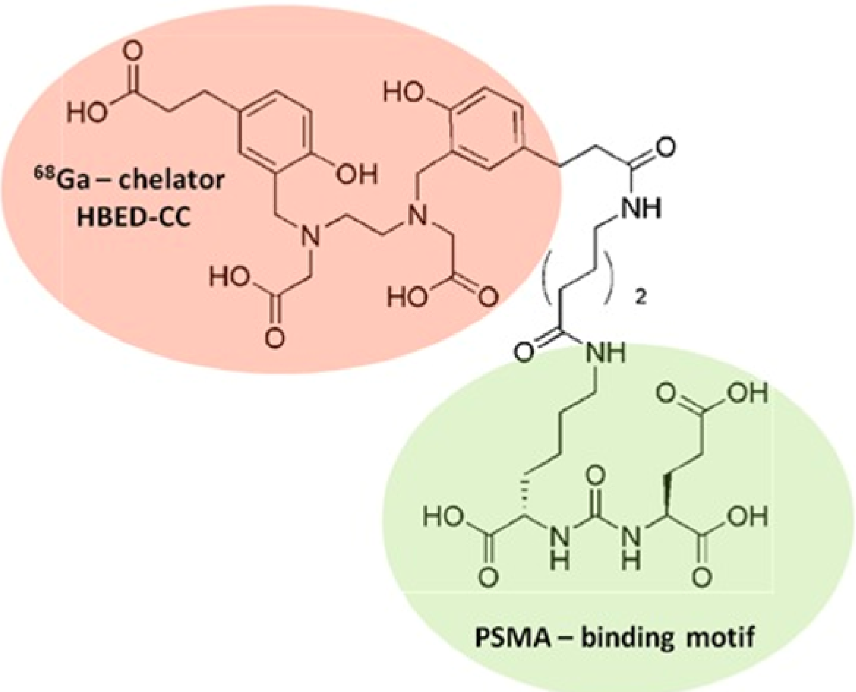
# $^{99m}$Tc-MIP-1404 SPECT
# Prior to Prostatectomy



TcTX-P104-01-02

# $^{68}$Ga-PSMA
# $^{68}$Ga-PSMA-HBED-CC

Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED CC)]
trivial name: $^{68}$Ga-PSMA




**Quick transfer from „bench to bedside“**

***6/2012*** first publication of patient data from the Haberkorn group in Heidelberg:
*Afshar-Oromieh A, Haberkorn U, Eder M, Eisenhut M, Zechmann CM. Eur J Nucl Med Mol Imaging. 2012 Jun;39(6):1085-6*

since ***12/2013*** clinical routine patients at the LMU München

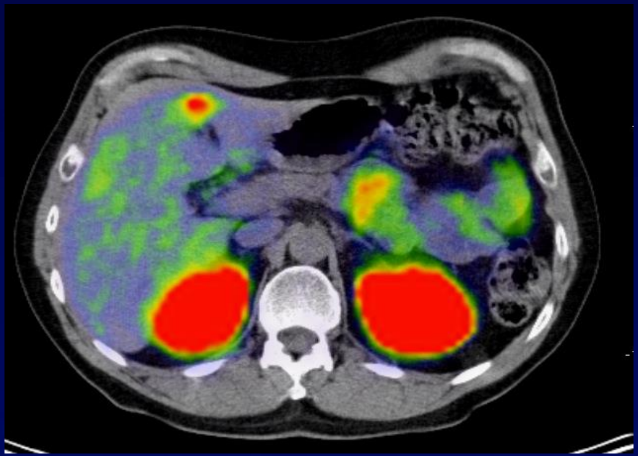
# PSMA – initial clinical experience

Biochemical recurrence

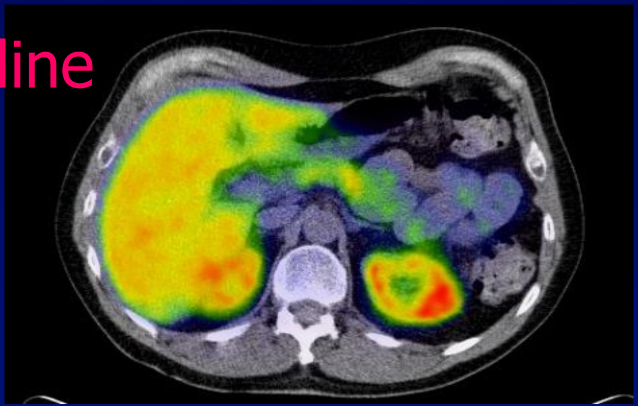
$^{68}$Ga-PSMA

$^{18}$F-choline

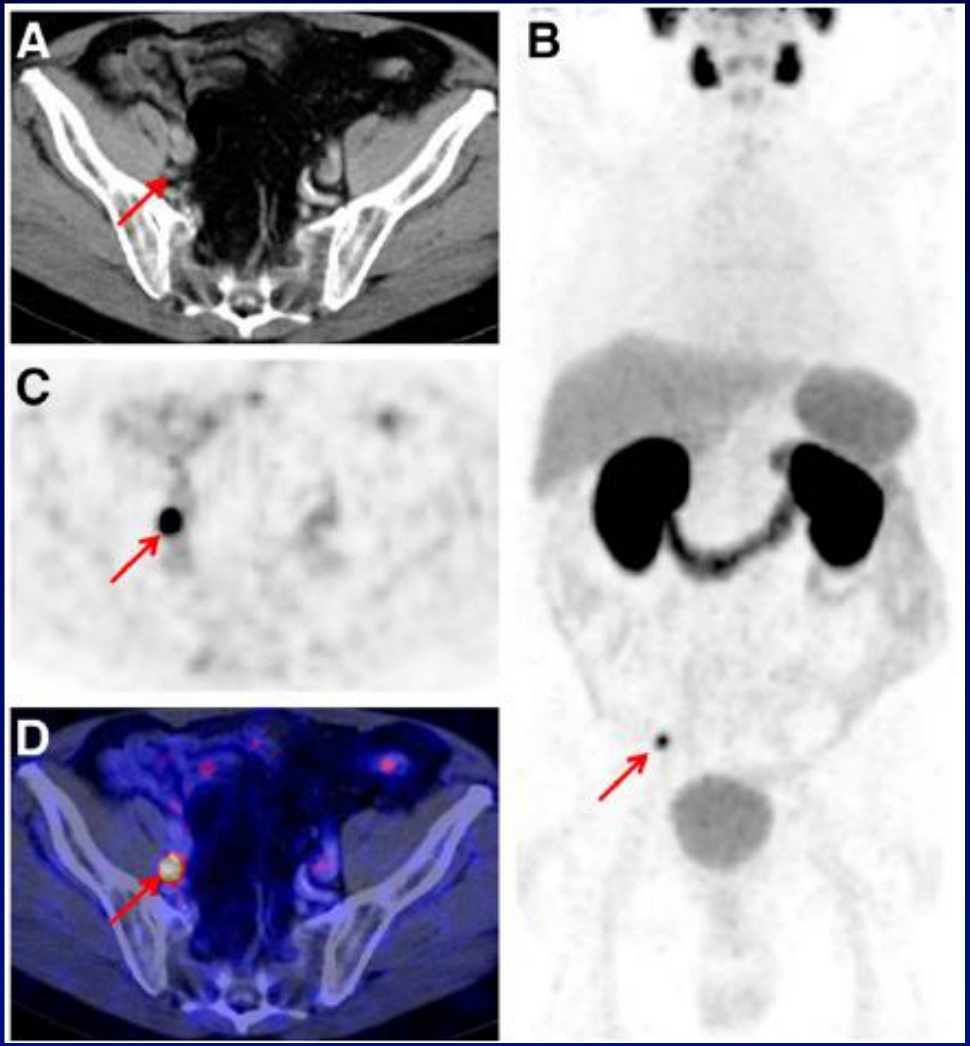
$^{68}$Ga-PSMA



$^{18}$F-choline



# $^{68}$Ga-PSMA PET/CT in patients with biochemical recurrence after radical prostatectomy (RP):




In a 75-y-old patient with after RP , radiation therapy, and rising PSA value of 1.09 ng/mL

Eur J Nucl Med Mol Imaging (2016) 43:34–41
DOI 10.1007/s00259-015-3188-1

ORIGINAL ARTICLE

# $^{68}$Ga-PSMA-11 PET/CT: a new technique with high potential for the radiotherapeutic management of prostate cancer patients

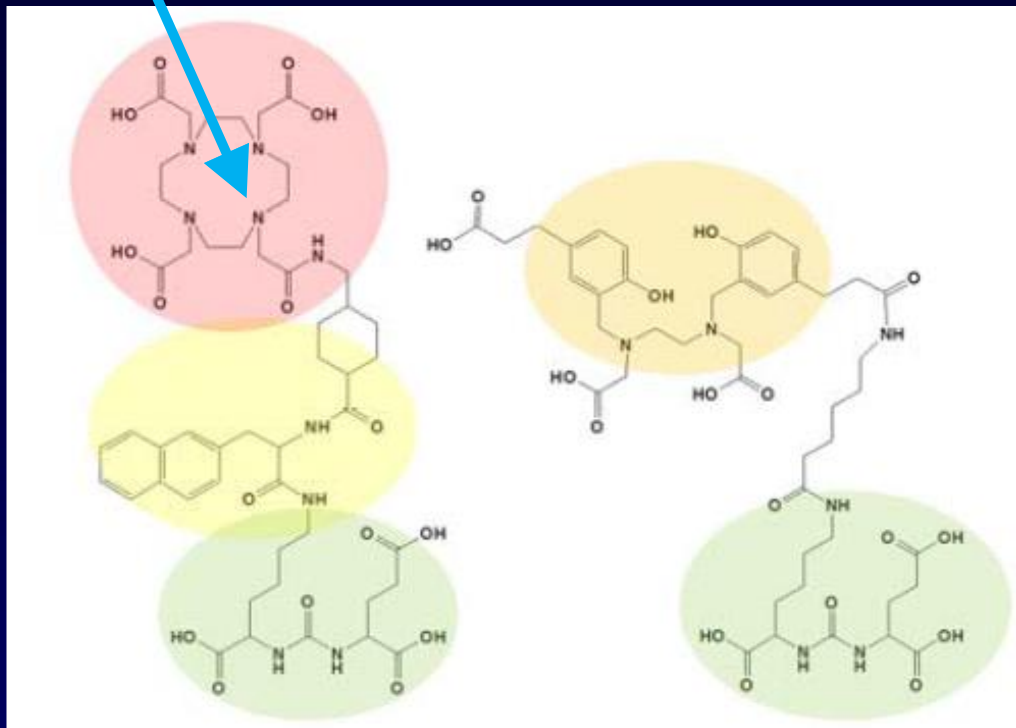
**Florian Sterzing[1,2,4] · Clemens Kratochwil[3] · Hannah Fiedler[3] · Sonja Katayama[1,4] · Gregor Habl[5] · Klaus Kopka[6] · Ali Afshar-Oromieh[3] · Jürgen Debus[1,2,4] · Uwe Haberkorn[3,7] · Frederik L. Giesel[3,7]**

# Early side effects and first results of radioligand therapy with $^{177}$Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study

Hojjat Ahmadzadehfar[1*†], Kambiz Rahbar[2†], Stefan Kürpig[1], Martin Bögemann[3], Michael Claesener[2], Elisabeth Eppard[1], Florian Gärtner[1], Sebastian Rogenhofer[4], Michael Schäfers[2,5] and Markus Essler[1]

EJNMMI Research (2015) 5:36

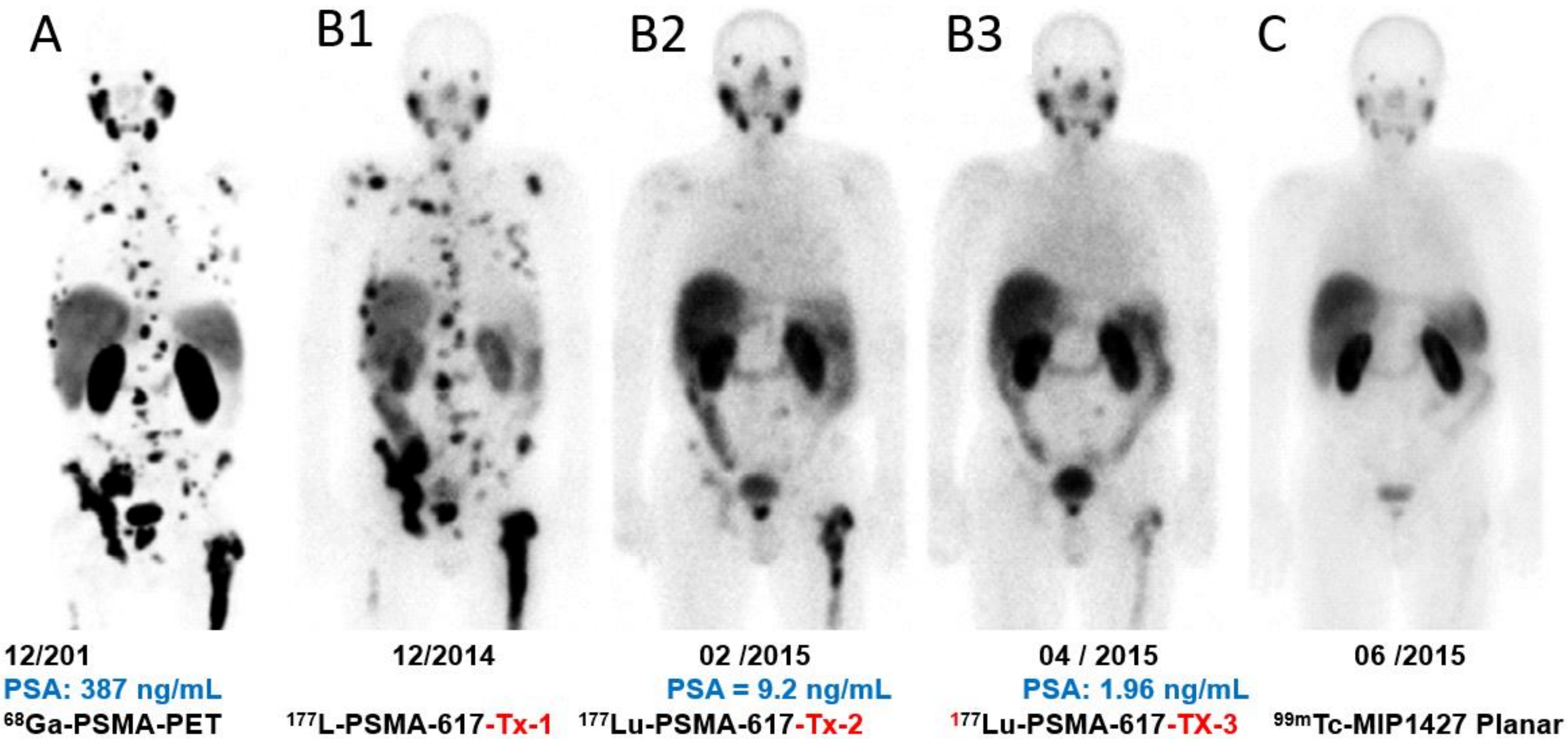
**$^{177}$Lu or $^{225}$Ac**



PSMA-617

PSMA-11

# $^{177}$Lu-DKFG-617 ($^{177}$Lu-PSMA-617)




Kratochwil, et al JNM 2016

Journal of Nuclear Medicine, published on July 28, 2016 as doi:10.2967/jnumed.116.178673

# $^{225}$Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer

Clemens Kratochwil*[1], Frank Bruchertseifer*[2], Frederik L. Giesel[1], Mirjam Weis[2], Frederik A. Verburg[3], Felix Mottaghy[3], Klaus Kopka[4], Christos Apostolidis[2], Uwe Haberkorn[1], and Alfred Morgenstern[2]

*[1]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany; [2]European Commission, Joint Research Centre, Institute for Transuranium Elements, Karlsruhe, Germany; [3]Department of Nuclear Medicine, RWTH University Hospital Aachen, Aachen, Germany; and [4]Division of Radiopharmaceutical Chemistry, German Cancer Research Center, Heidelberg, Germany*

# $^{225}$Ac-PSMA-617

J Nucl Med 2016; 57:1–4

9 – 10 MBq (0.27 mCi);
100 kBq/kg x 3 cycles

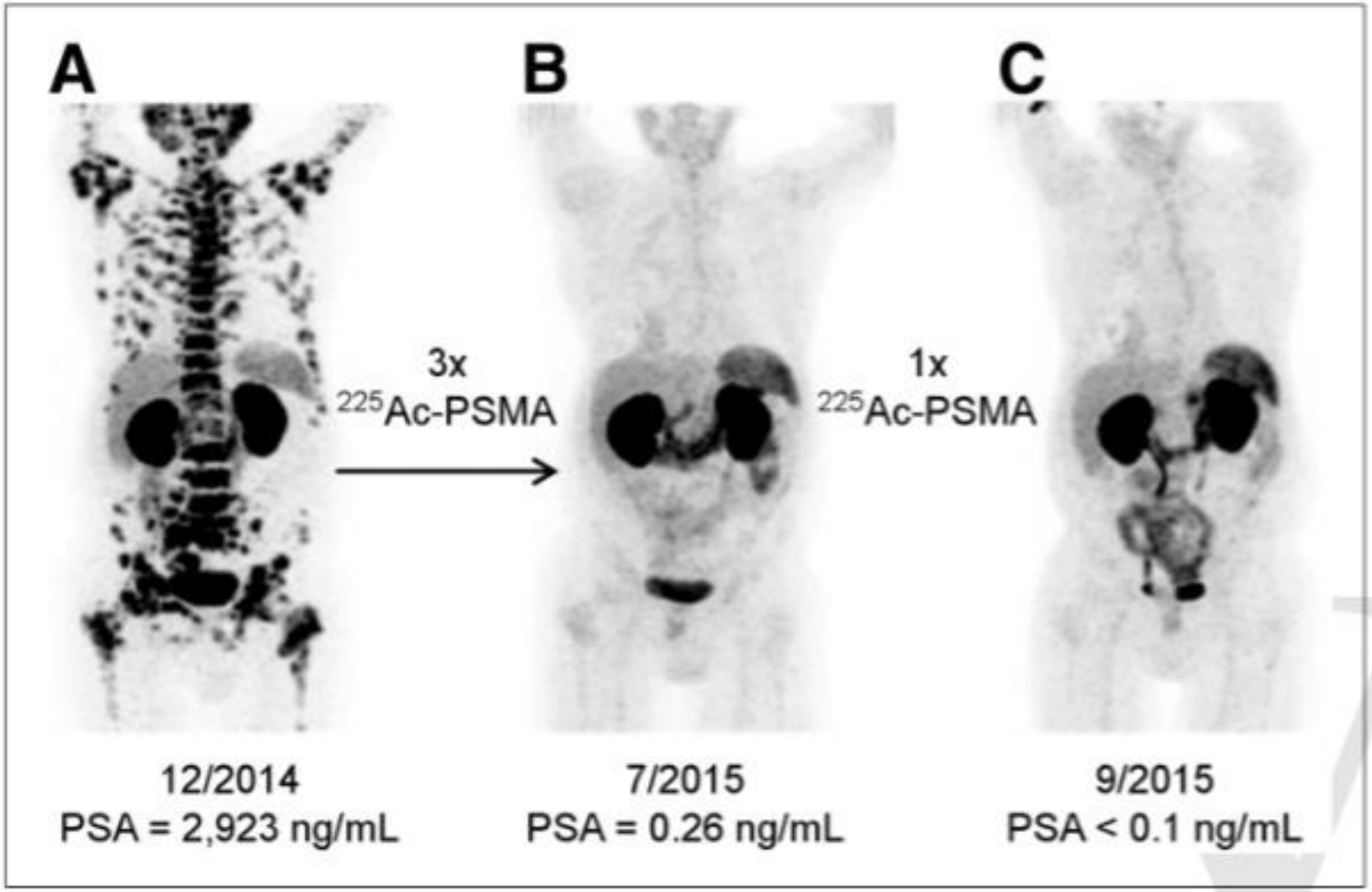



**FIGURE 1.** $^{68}$Ga-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 mo after third cycle of $^{225}$Ac-PSMA-617 (B), and restaging 2 mo after one additional consolidation therapy (C).

# $^{177}$Lu-PSMA-617 and $^{225}$Ac-PSMA-617

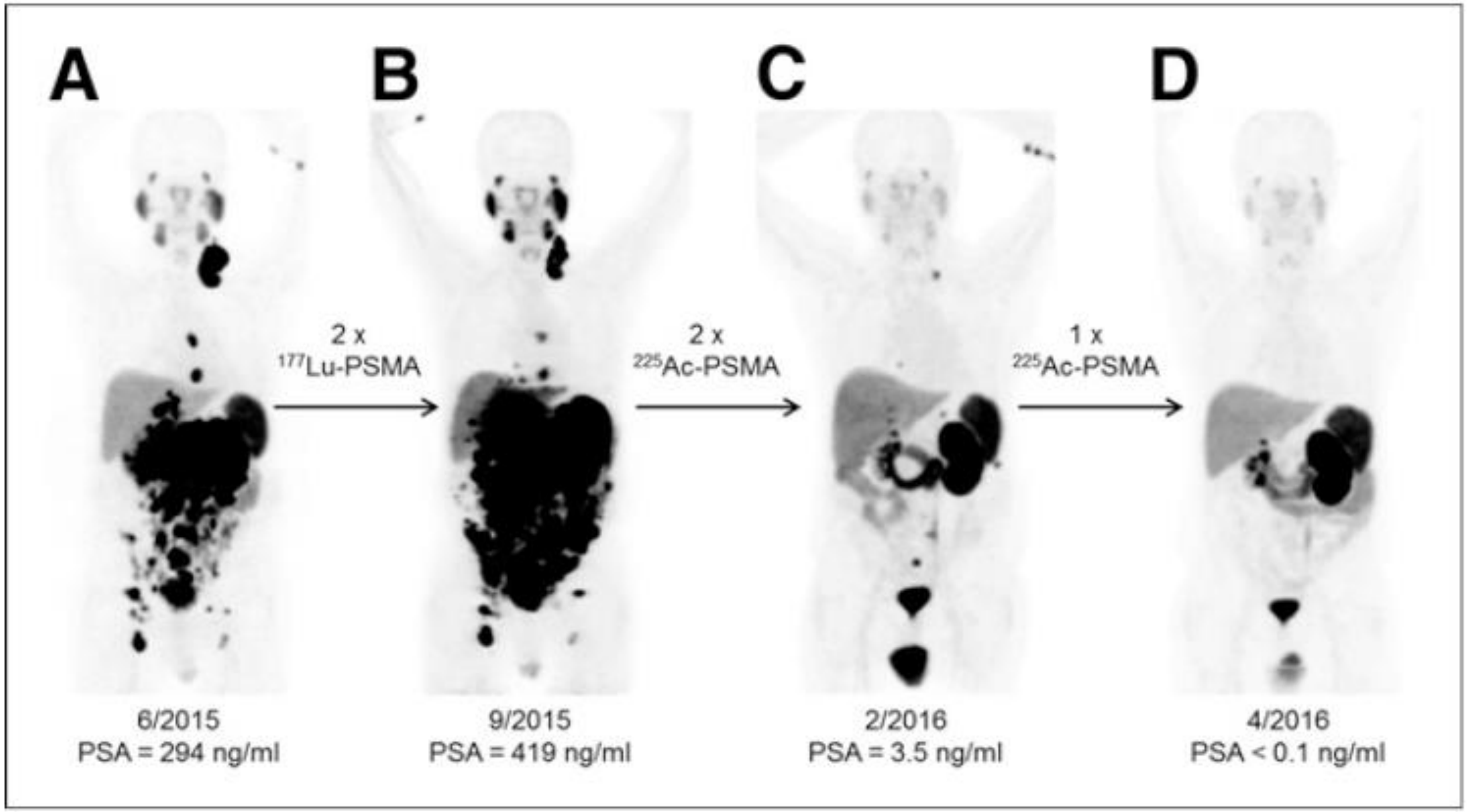
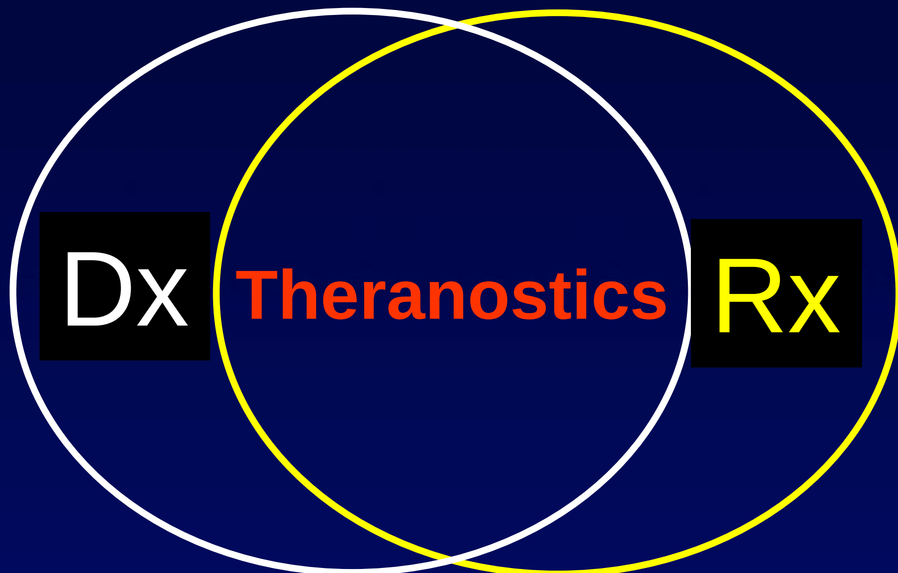



**FIGURE 3.** $^{68}$Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting $^{177}$Lu-PSMA-617 presented progression (B). In contrast, restaging after second (C) and third (D) cycles of α-emitting $^{225}$Ac-PSMA-617 presented impressive response.

# Theranostics: The right drug and dose to the right patient at the right time




- Merge Diagnostics & Therapeutics
- Molecular-targeted drug with a companion diagnostic test for Personalized medicine
- Drug and diagnostic go to market simultaneously

# Thank You