Lutetium-177 : the new prodigy in therapeutic nuclear medicine

Sharmila Banerjee
Radiation Medicine Centre
BARC

Outline of the Talk

- Scope of radionuclide therapy
- Targeted therapy – Selection of therapeutic radioisotope
- Advantages of Lutetium-177 as a therapeutic radionuclide
- Lutetium chemistry, radiolabeling, use of bifunctional chelates
- Production of ^{177}Lu - possible routes
- Optimization of production route
- Clinical translation of Lu-177 radiopharmaceuticals
- Peptide Receptor Radionuclide Therapy
- Theranostic potential of ^{177}Lu
- Lu-177-based Therapy in Radiation Medicine Centre
- Summary

Selection of a Therapeutic Radionuclide

- Mode of decay : Particulate emitter (α, β^-, Auger electron), β^- is the choice
- Energy of the β^- particle : Depends on the application
- Presence of low energy low yield γ photons : Suitable for scintigraphy and dosimetry calculations
- Half-life: Advantageous to have a long half-life (few days)
- Easy production, simple radiochemical processing
- Availability with high specific activity and excellent radionuclidic purity
- Strong and irreversible binding with carrier molecules

Radionuclide therapy beyond ^{131}I and ^{32}P
Emergence of Lu-177 as a therapeutic radioisotope

Why Lu-177

- Presence of high energy gamma components with large abundance (364 keV, 81%) in ^{131}I
- High energy β^- particles of ^{32}P not ideal for targeted radiotherapy

Thus the need for other isotopes for radiotherapy

⇩

^{177}Lu and ^{90}Y the most viable options

Advantages of ^{177}Lu as a Therapeutic Radionuclide

- Suitable nuclear decay characteristics

- Maximum β^- energy not very high
  - ➢ Low tissue penetration
  - ➢ Advantages for targeting microstatic disease
  - ➢ Lower dose to the non-target organs, mainly kidneys

- Presence of low energy γ photon in low abundance
  - ➢ Simultaneous scintigraphy and dosimetric studies

- Comparatively longer half-life
  - ➢ Permits broad distribution

- Possibility of production with high specific activity using medium flux reactors (σ = 2100 b)

- Simple post-irradiation radiochemical processing

BARC an early entrant in use of ^{177}Lu

- Our group - one of the first few researchers to recognize the favourable nuclear decay characteristics and feasibility of production

- First irradiation of ^{176}Lu - 1999

- Optimization of irradiation parameters and processing methods

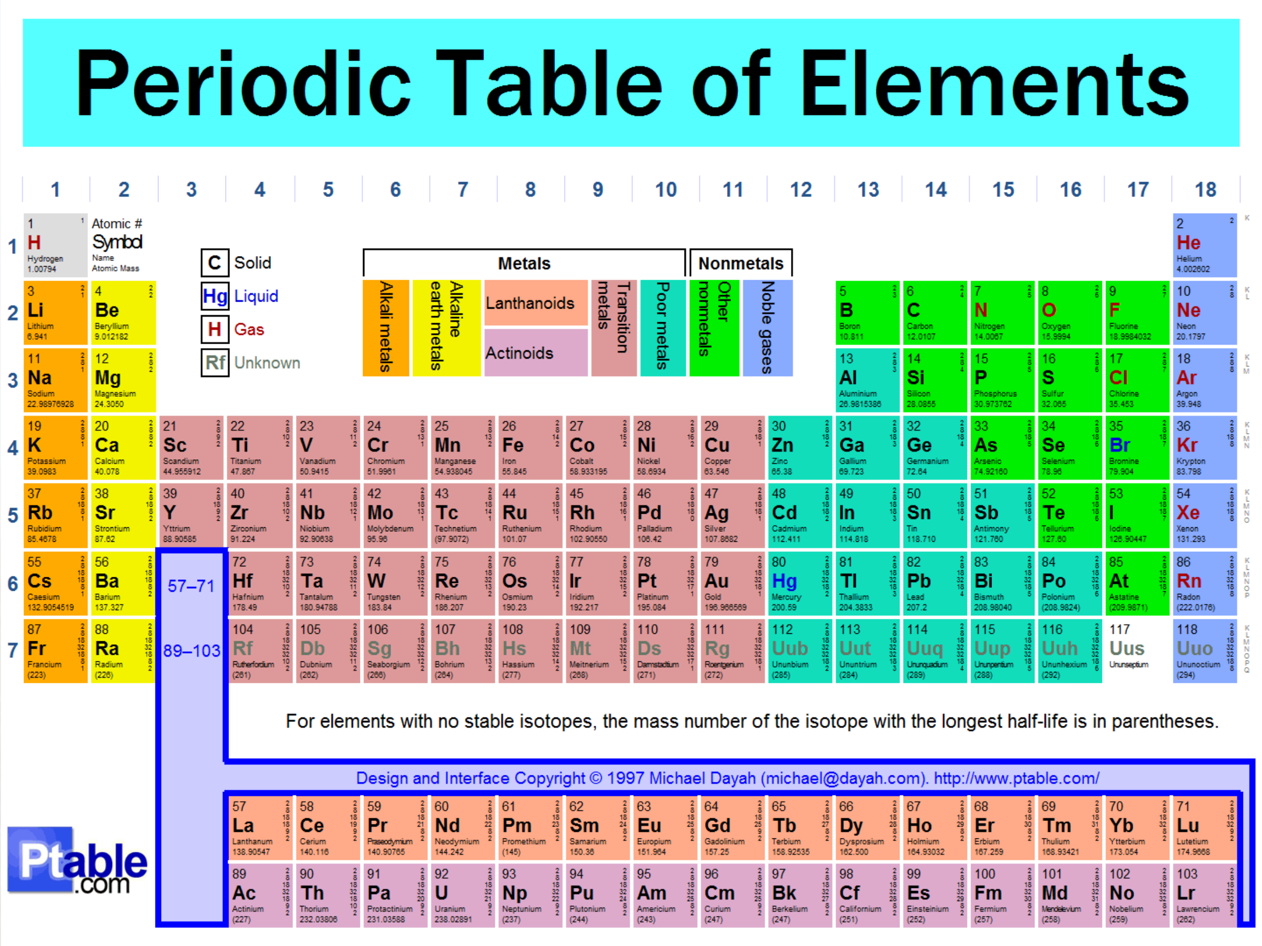
- Preparation of potential radiotherapeutic agents using ^{177}Lu documented

- Regular supply of ^{177}Lu to AIIMS for formulation of the therapeutic agents started from September 2006

Potential Applications of ^{177}Lu

- Palliative care in painful skeletal metastasis
  - Lower dose to bone marrow
  - Less decay loss post-preparation
- Radiation synovectomy of small / medium joints
- Targeted tumor therapy using
  Monoclonal Antibody (RIT)
  Receptor specific Peptides (PRRT)
  - Useful for small tumor / metastases
  - Lower kidney toxicity

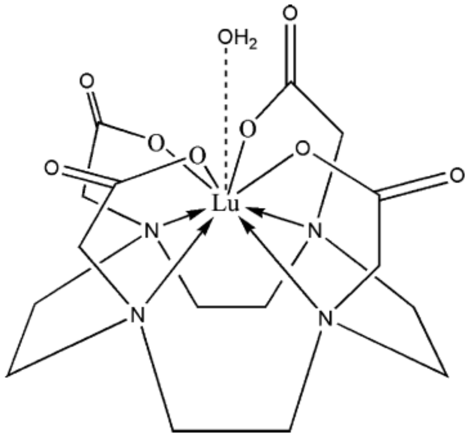
Lutetium-177



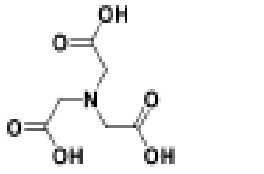
- Lutetium -The heaviest lanthanide
- Atomic Number - 71
- Electronic configuration $[Xe]4f^{14}5d^{1}6s^{2}$
- Highly stable +3 oxidation state
- Lu^{+3} has 89.1 pm ionic radius
- High stability of 8/9 coordinated chelates with N,O, P, S donor ligands

Complexation of Lu^{+3} with polydentate chelators

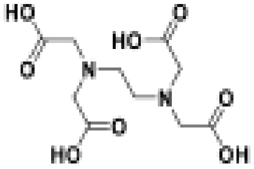
chelating agent	log stability constant
diethylenetriaminepentaacetic acid (DTPA)	12.5
ethylenediaminetetraacetic acid (EDTA)	19.8
nitrilotriacetic acid (NTA)	22.4
1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)	25.4
1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (DO3A)	23.0
1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA)	15.3



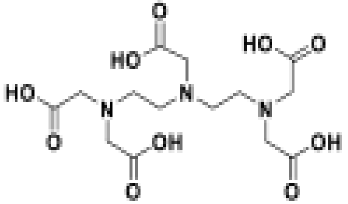
Representative structure of Lu-DOTA complex



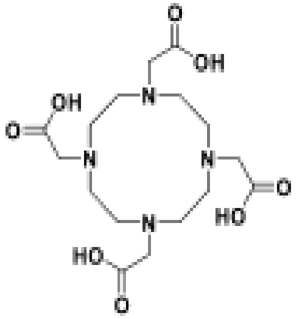
Nitrilotriacetic acid (NTA)



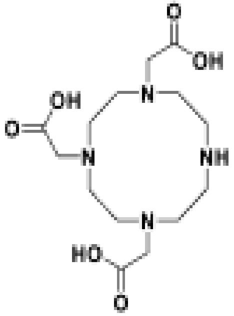
Ethylenediaminetetraacetic acid (EDTA)



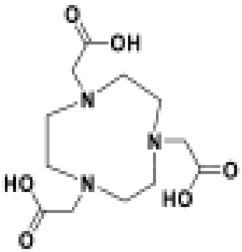
Diethylenetriaminepentaacetic acid (DTPA)



1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)



1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid (DO3A)



1,4,7-Triazacyclononane-1,4,7-triacetic acid (NOTA)

Production of Lutetium-177

Lutetium-177 production – points to consider

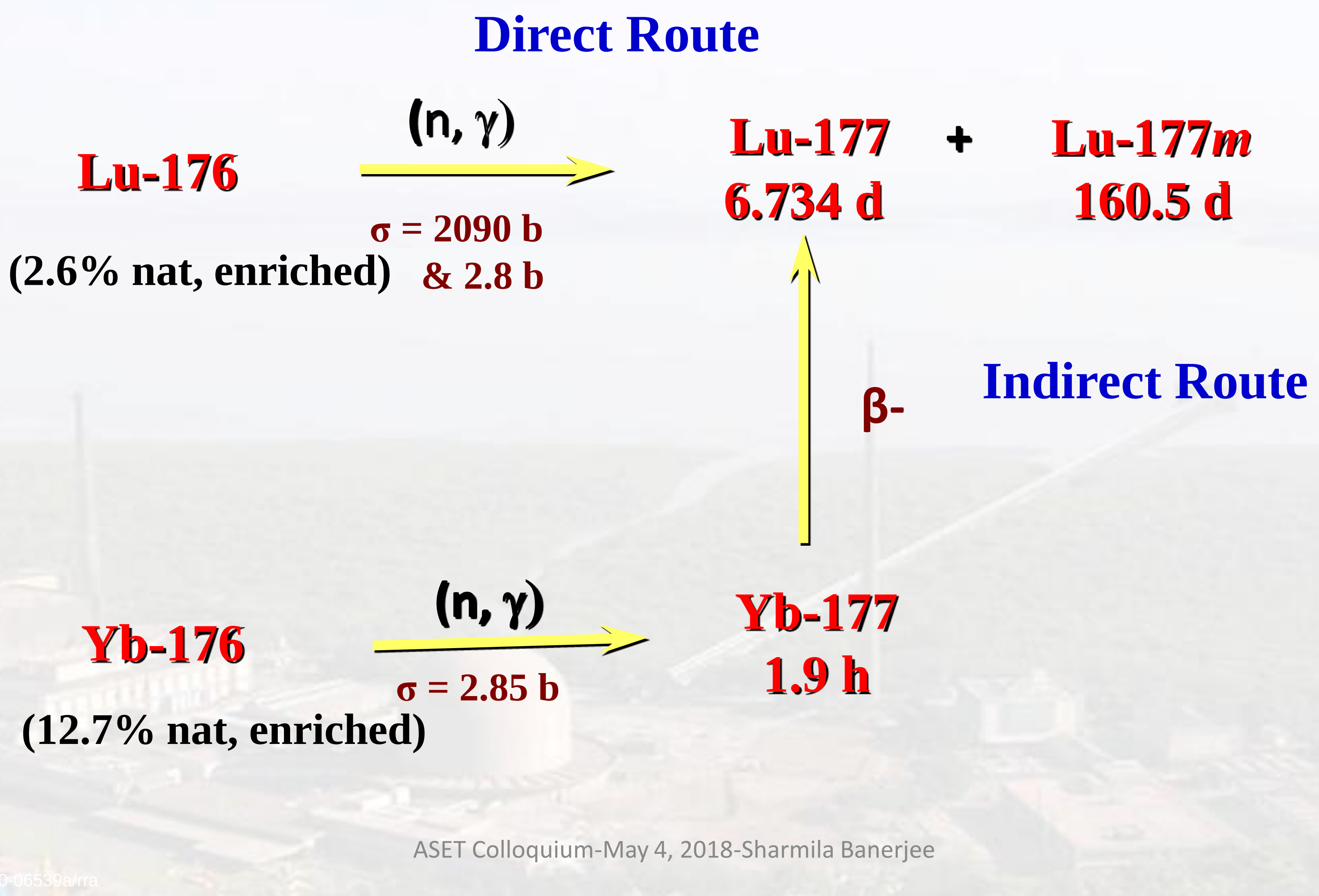
Activity =$N\sigma\phi(1-e^{-\lambda t})$ Bq

- N is the target atoms
- **σ is the cross section**
- ϕ is the flux of the reactor
- λ is the decay constant
- t is the time of irradiation

Lutetium

- σ **2100** barns
- $^{176}Lu(n,\gamma)^{177}Lu$
- Minimum radiochemical processing
- >20 Ci/mg at $1x10^{14}$ $n.cm^2.sec.$
- Half life 6.73 days
- β- energies 608 keV (89.9%), 330 keV (7.27%)
- γ energy 113 keV (6.4%), 208 keV (11%)

Production of ^{177}Lu in a Research Reactor



The Dhruva Reactor –The largest research reactor in India

- 100 MW reactor
- ~1x10^{14} n.cm^2.sec – maximum flux
- Medical Isotopes produced in sufficient quantity
- Processing done in BARC

Clinical Translation of ^{177}Lu-radiopharmaceuticals

Neuroendocrine Tumors/Cancers

- Neuroendocrine Tumors/cancers (NET) are the tumors/cancers of the ‘Neuroendocrine system’ which is the combination of ‘Endocrine system’ and ‘Nervous system’, or more specifically, the various interfaces between the two systems

- Incidence of NETs is estimated to be around 3 new case per 1,00,000 people per year

- Every year, new cancer patients registered: Over 7 lakh

- **Treatment of NET**
  - Chemotherapy: Most common therapy
  - Surgery: Only therapy that can cure GEP-NETs
  - **Targeted radionuclide therapy - Peptide Receptor Radionuclide Therapy (PRRT)**

PRRT: Only effective treatment known for the in-operable & metastasized NET

^{177}Lu in context of Peptide Receptor Radionuclide Therapy (PRRT)

Somatostatin receptors - over-expressed in a variety of cancers of neuroendocrine origin (NET)

- Neuroblastomas
- Some medullary carcinomas
- Some prostate cancer
- Small cell lung cancer

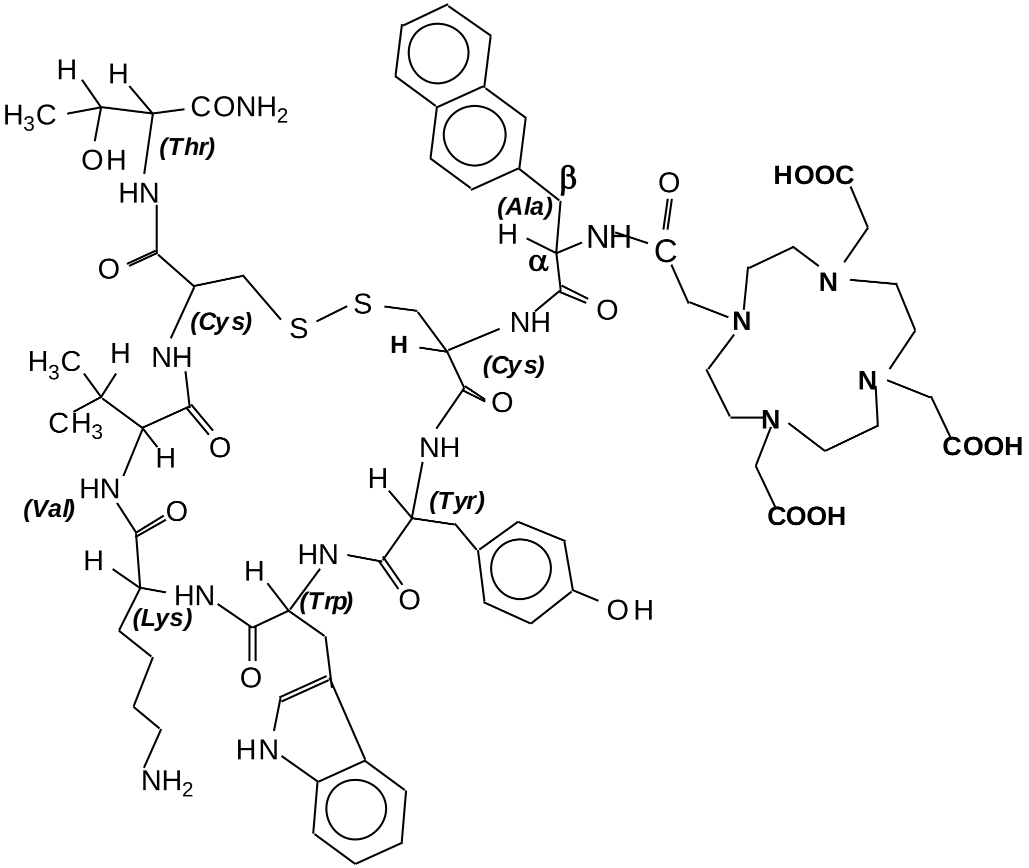
Example of a peptide which mimic somatostatin hormone is tyrosine octreotate or TATE (a synthetic octapeptide)

TATE is conjugated with DOTA to give DOTA-TATE

DOTA-TATE is labeled with ^{177}Lu to target the somatostatin receptors overexpressed in NET

^{177}Lu is ideally suited for PRRT & ^{177}Lu-DOTA-TATE the first approved Lu-radiopharmaceutical in India

Our PRRT Journey began with ^{177}Lu-labeled Lanreotide-DOTA



LANREOTIDE-DOTA

Lanreotide

↓ Ditertiarybutyl dicarbonate (BOC)
Dioxane, pH =10, RT, 30 min

Lanreotide-BOC

↓ DOTA
N - hydroxy succinimide, DCC
DMF, pH =9, RT, 16 h

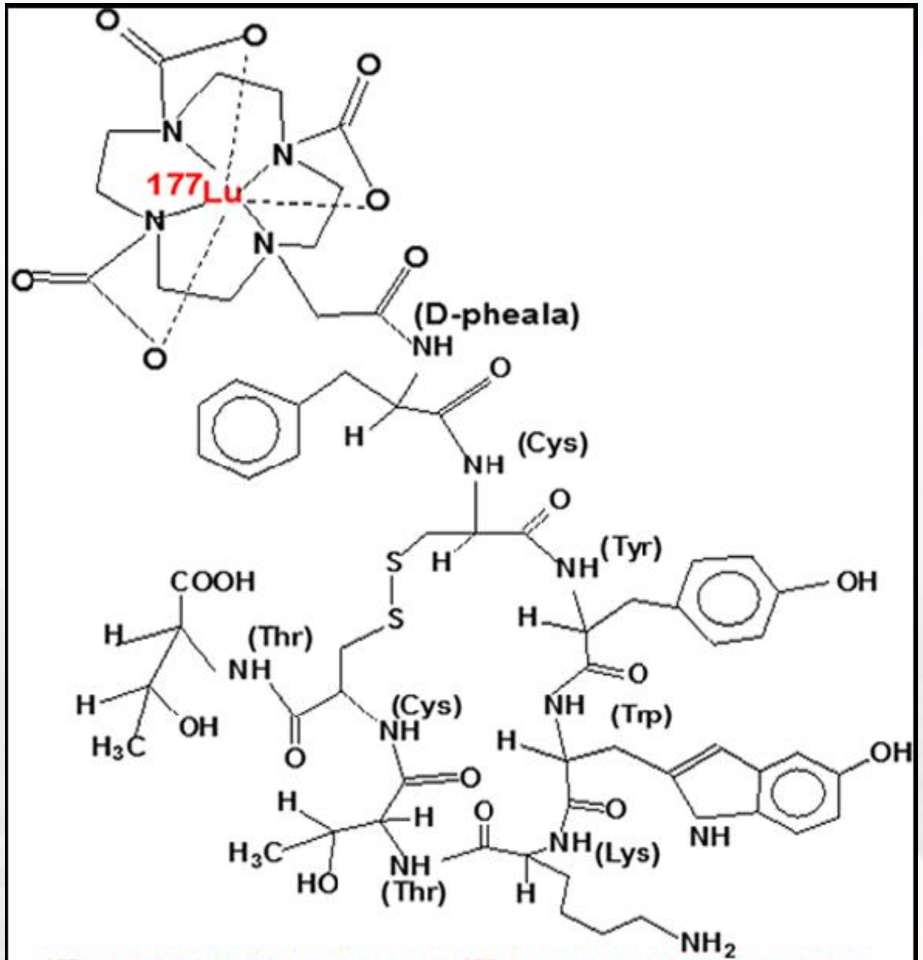
DOTA-Lanreotide-BOC

↓ Trifluoroacetic acid
Dichloromethane, 30 min, RT

DOTA-Lanreotide

^{177}Lu-DOTA-Lanreotide: A novel tracer as a targeted agent for tumor therapy. Sharmila Banerjee, et al , ***Nucl. Med. Biol****. 31, 2004, 753-759.*

Switching over to DOTA-TATE :
A better vector in terms of receptor targeting



^{177}Lu-DOTATATE : The first ^{177}Lu radiopharmaceutical approved for clinical use,

A radiopharmaceutical indigenously developed by BARC using Lutetium-177 produced in Dhruva reactor

- India is one of the countries to use this radiopharmaceutical
- Being used in several hospitals in India, using the method developed in BARC
- \> 2500 patients have been treated in RMC alone till October 2017

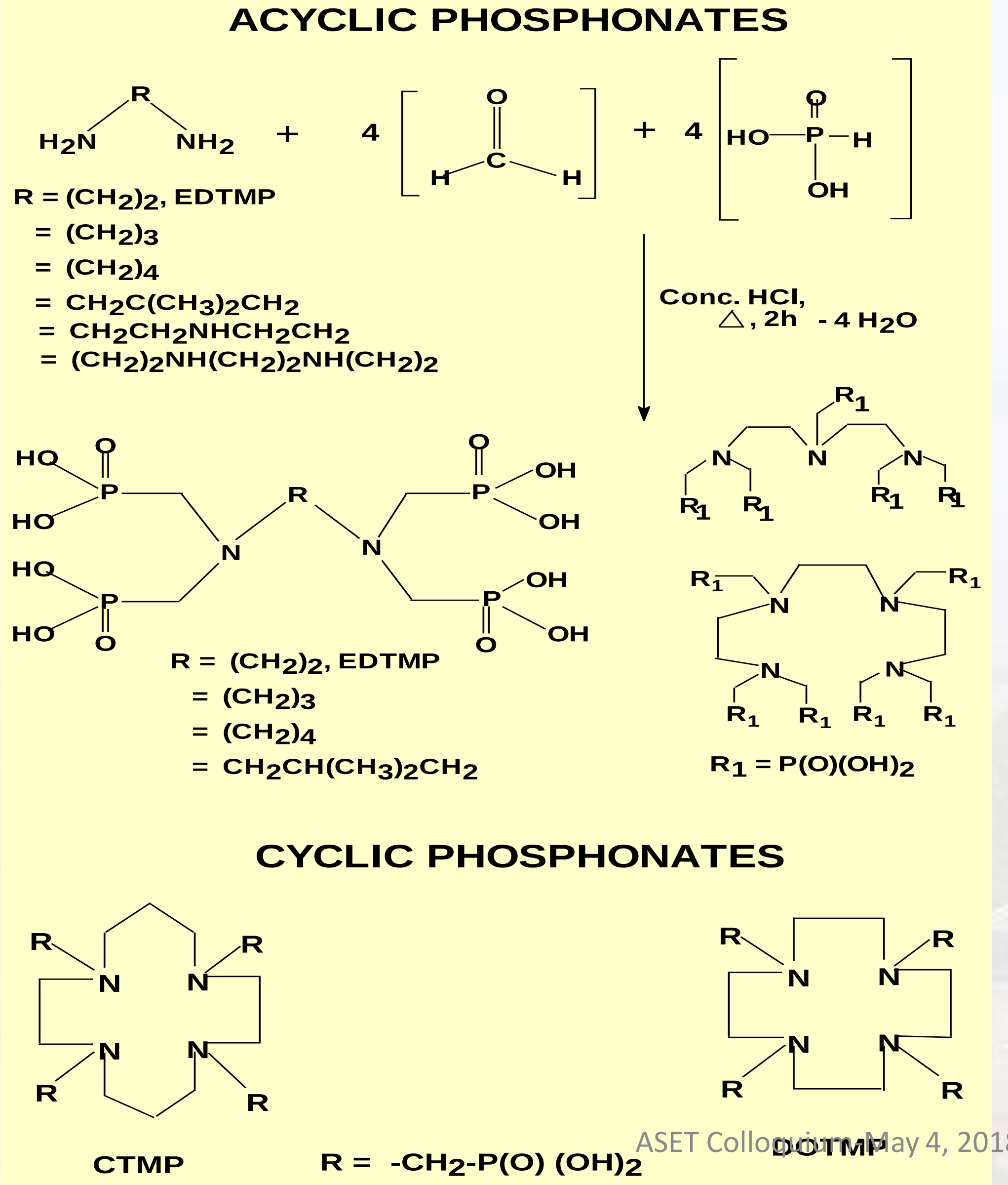
On the preparation of a therapeutic dose of ^{177}Lu labeled DOTA-TATE using indigenously produced ^{177}Lu in medium flux reactor.
Sharmila Banerjee, et al, ***Appl. Radiat. Isot.,*** *65, 2007, 301-308*

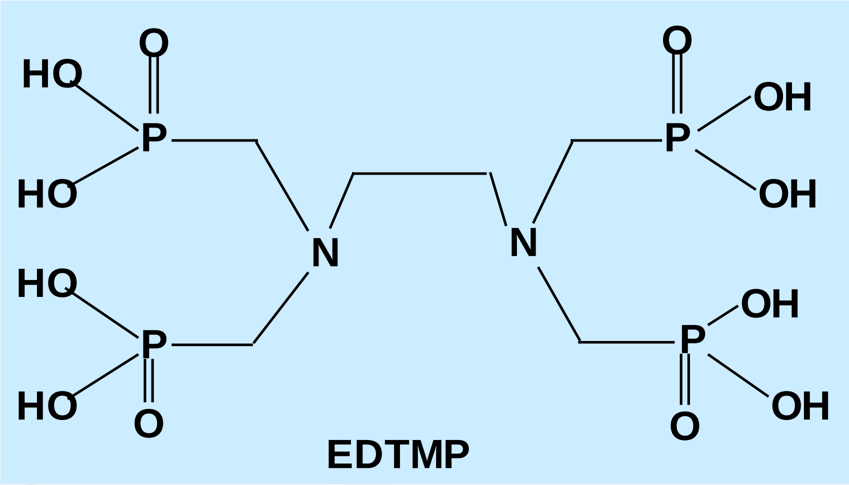
PRRT in India

- All India Institute of Medical Sciences, New Delhi
- Bangalore Institute of Oncology, Bangalore
- Inlaks and Budhrani Hospital, Pune
- Jaslok Hospital and Research Centre, Mumbai
- Radiation Medicine Centre, Mumbai
- SPECT Lab., Pune
- Post Graduate Institute of Medical Education and Research, Chandigarh
- Kovai Medical Centre and Hospital, Coimbatore

Today there are about 25 Centres

Phosphonates in MBPP





Radiopharmaceuticals for metastatic bone pain palliation: Available options in the clinical domain and their comparisons", Tapas Das, Sharmila Banerjee, Clinical and Experimental Metastasis 34, 2017, 1-10.*

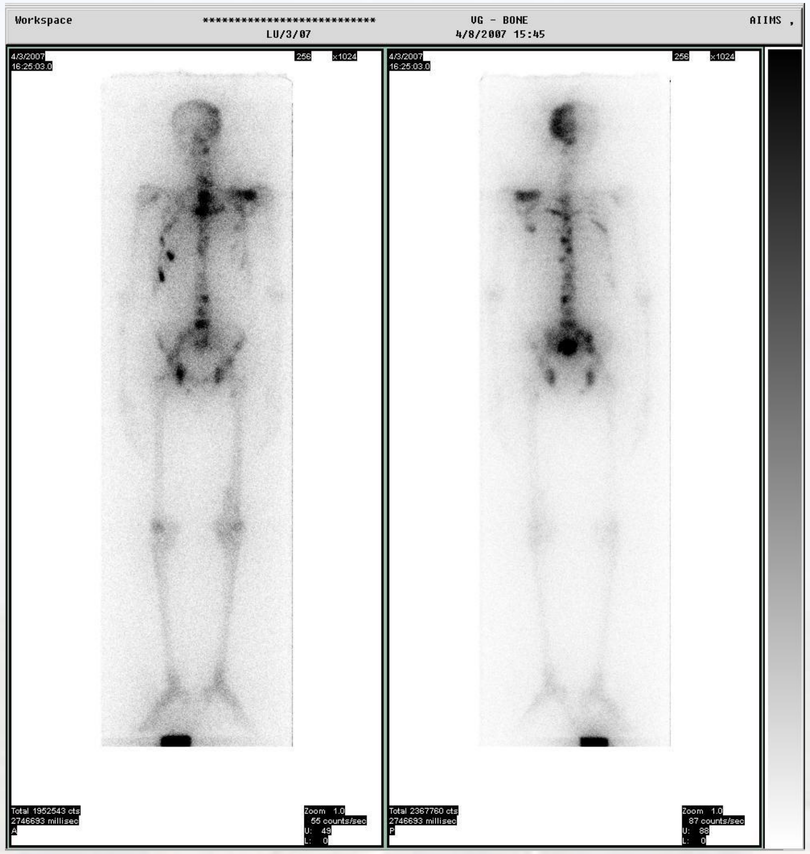
^{177}Lu labeled polyaminophosphonates as potential agents for bone pain palliation.
***S. Banerjee, Nucl. Med. Commun. 23**, 2002, 67-74.*

Development of ^{177}Lu-EDTMP – Uniting the Favourable Features of EDTMP and Lu-177

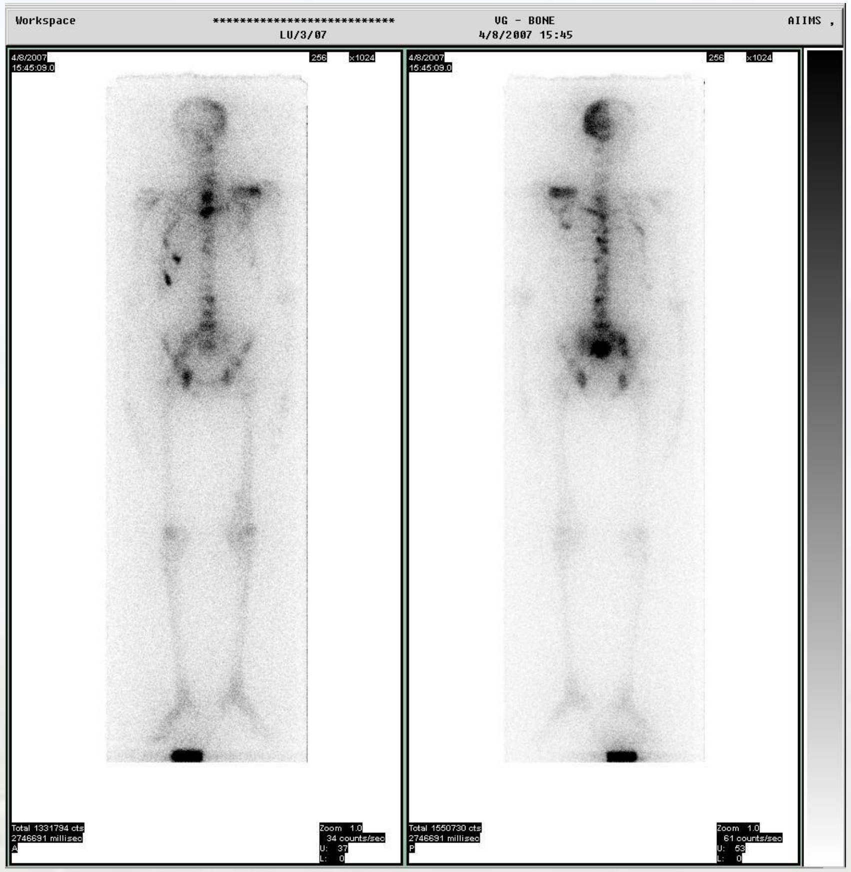
- Prepared and studied a number of cyclic and acyclic phosphonates forming stable complexes with ^{177}Lu in high yields
- ^{177}Lu identified as an ideal isotope for bone pain palliation
  - Medium energy β^{-}_{max}, imageable γ, long half life
- Production and availability of ^{177}Lu in adequate quantity and therefore cost-effective and logistically viable for distribution
- Higher animal study with ^{177}Lu-EDTMP was possible with help of Hungarian counterparts in a Collaborative project
- Regulatory approval obtained

Formulation, pre-clinical evaluation and preliminary clinical investigation of an in-house freeze-dried EDTMP kit suitable for the preparation of ^{177}Lu-EDTMP
***Sharmila Banerjee**. Et al, **Cancer Biotherapy and Radiopharm** 29, 2014, 412-421.*

^{177}Lu-EDTMP in human patients



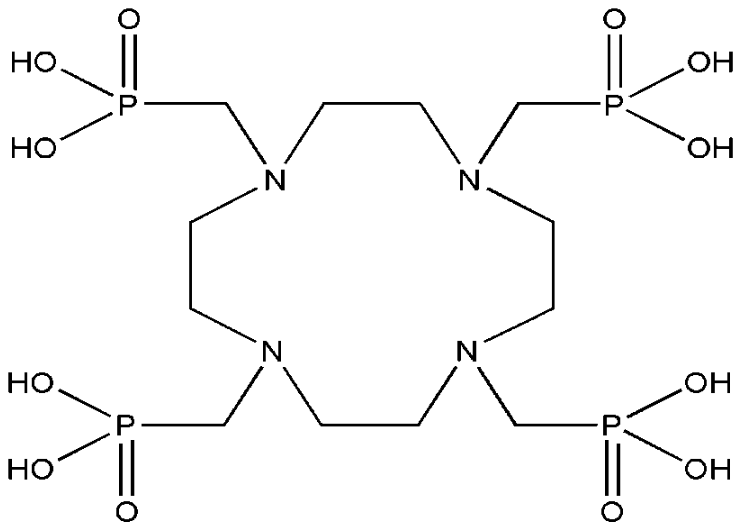
1 d post-administration



6 d post-administration

^{177}Lu-EDTMP : A viable bone pain palliative in skeletal metastasis.
***S. Banerjee**, et al.: Cancer **Biotherapy and Radiopharm.** 23, 2008, 202-213.*

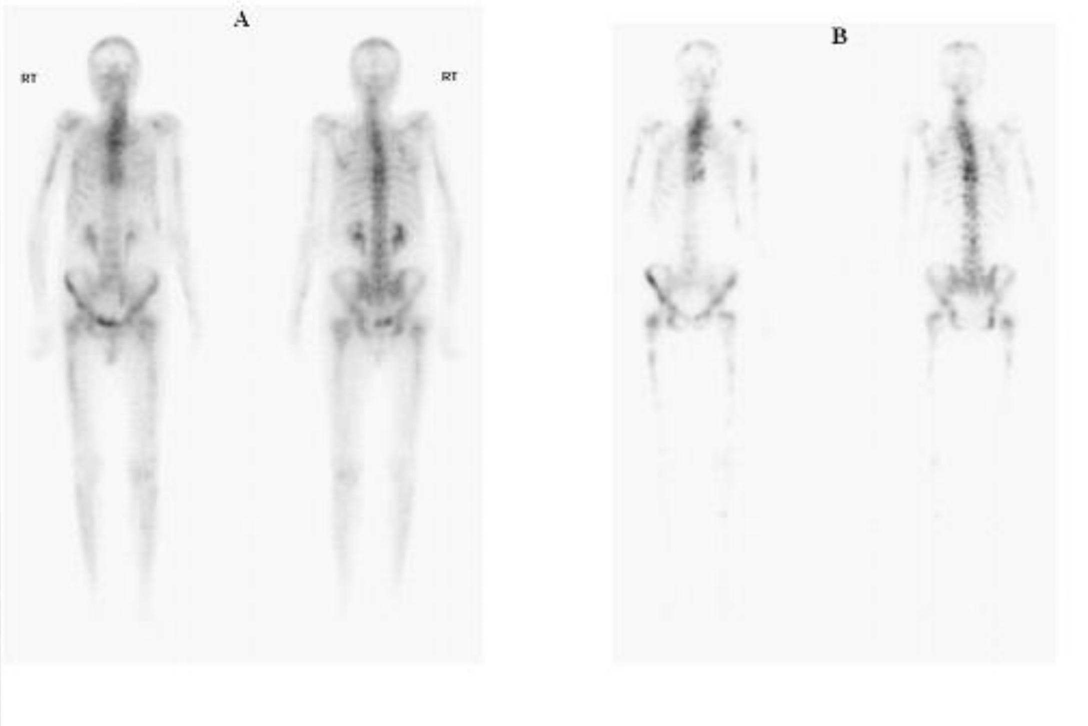
^{177}Lu-DOTMP yet another promising candidate



DOTMP

*Theranostic Treatment of metastatic bone pain with ^{177}Lu-DOTMP: S **Banerjee et al Clinical Nuclear Med.** 41, 2016, 966-967.*

*Formulation and evaluation of freeze-dried DOTMP kit for the preparation of clinical-scale ^{177}Lu-DOTMP and ^{153}Sm-DOTMP at the hospital radiopharmacy, **Sharmila Banerjee e tal. Radiochim. Acta,** 193, 2015, 594-604.*



Whole-body scans of a man (67 years, suffering from skeletal metastases originated from ca prostate) recorded by administering 3.7 GBq (100 mCi) of ^{177}Lu-DOTMP at 6 hours and 7 days post-administration (anterior and posterior views)

Radioimmunotherapy with ^{177}Lu

- ^{177}Lu-labeled Rituximab

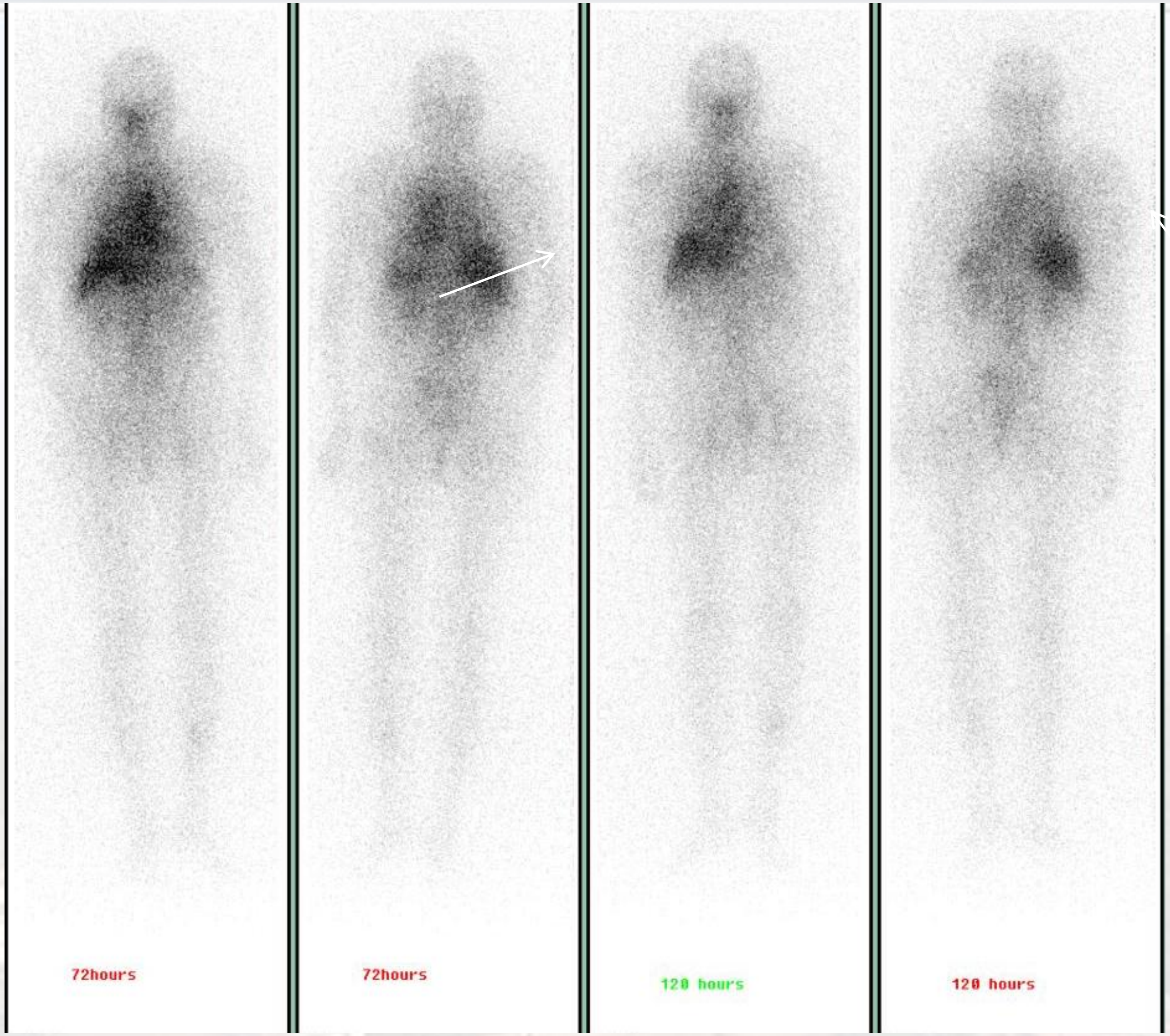
  for Non Hodgkins Lymphoma

- ^{177}Lu-labeled Trastuzumab

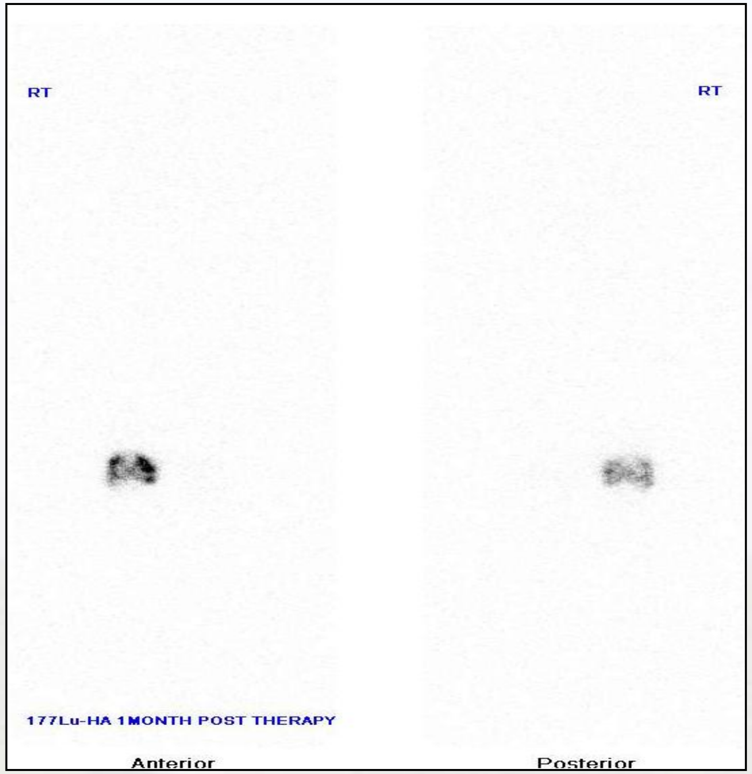
  for Her2-positive-Breast cancer

Preparation of clinical-scale ^{177}Lu-Rituximab: Optimization of protocols for conjugation, radiolabeling and freeze-dried kit formulation ***Sharmila Banerjee* et al,***
J. Labld. Cpds. Radiopharm., *60, 2017, 234-241.*

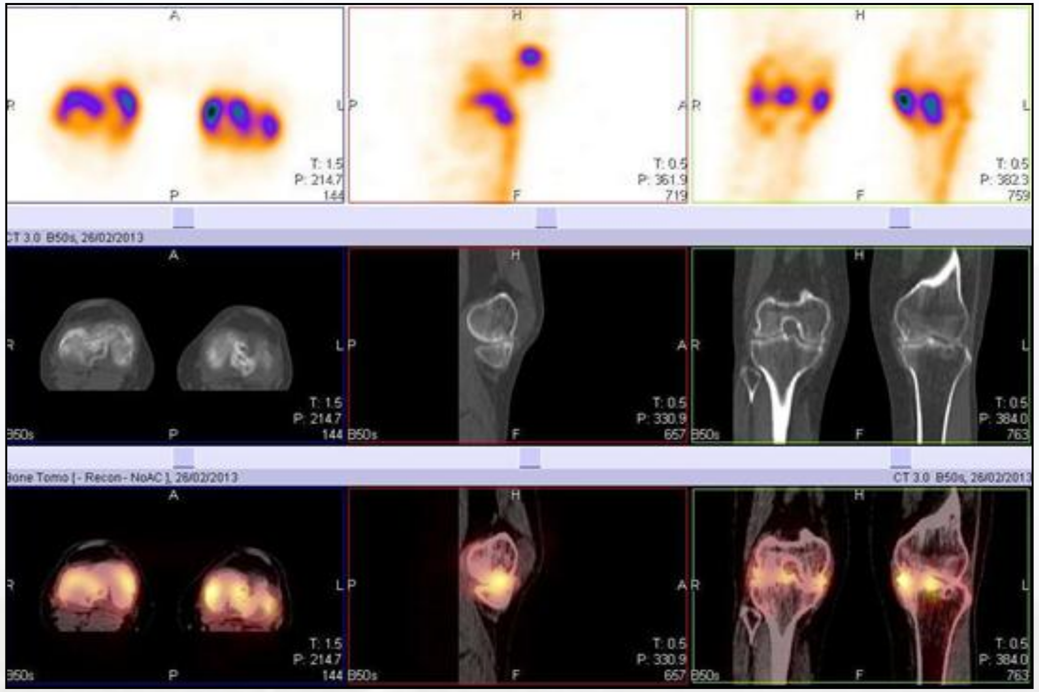
Images 72 h and 120 h post-administration of ^{177}Lu-trastuzumab



Clinical studies with ^{177}Lu-Hydroxyapatite for Radiationsynovectomy



Whole-body images of a patient recorded after 1 month of administration of ^{177}Lu-HA

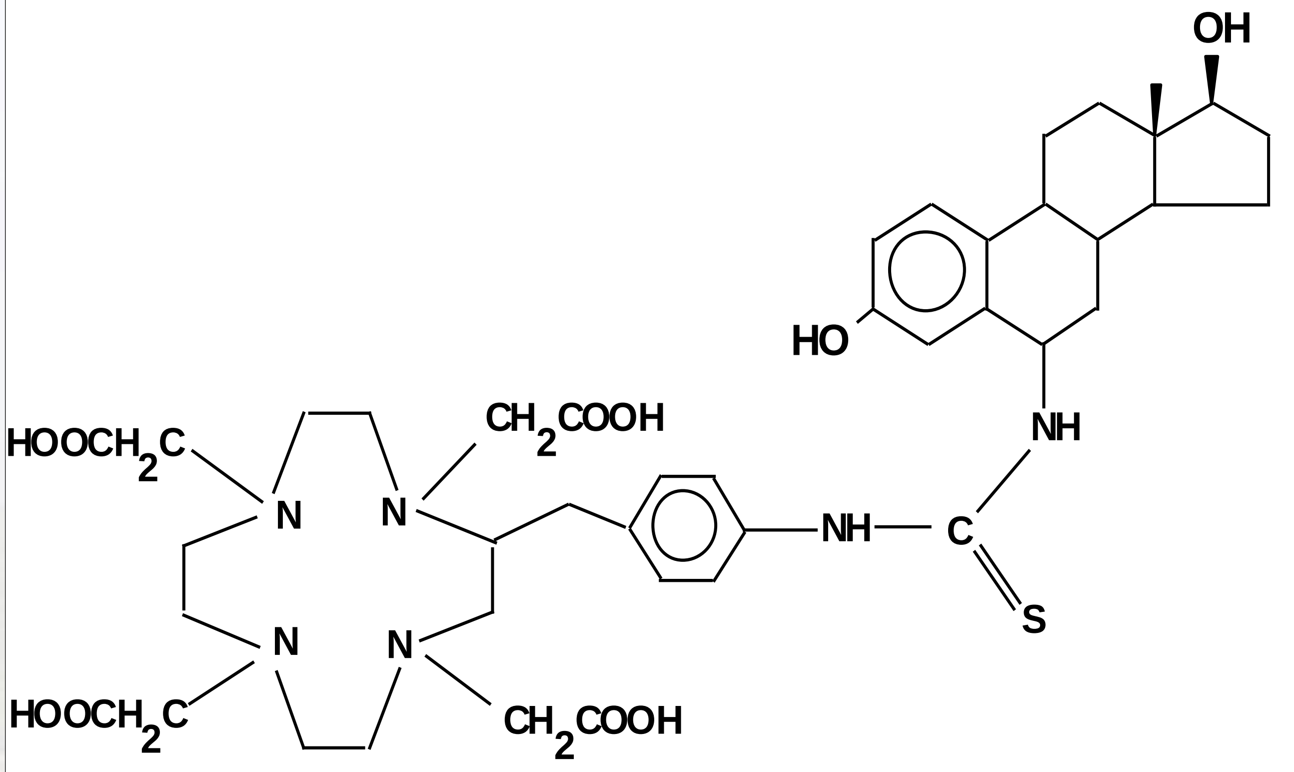


SPECT-CT images of the knee joints recorded after 1 month of administration of ^{177}Lu-HA

Preparation and preliminary studies on ^{177}Lu-labeled hydroxyapatite particles for possible use in therapy of liver cancer., Sharmila Banerjee, et al. **Nucl. Med. Biol.** 35, 2008, 589–597.

Preparation and preliminary biological evaluation of ^{177}Lu labeled hydroxyapatite as a promising agent for radiation synovectomy of small joints, Sharmila Banerjee, et al ***Nucl. Med. Commun.*** *27, 2006, 661-668.*

^{177}Lu-DOTA-17β-estradiol for targeting receptor overexpression

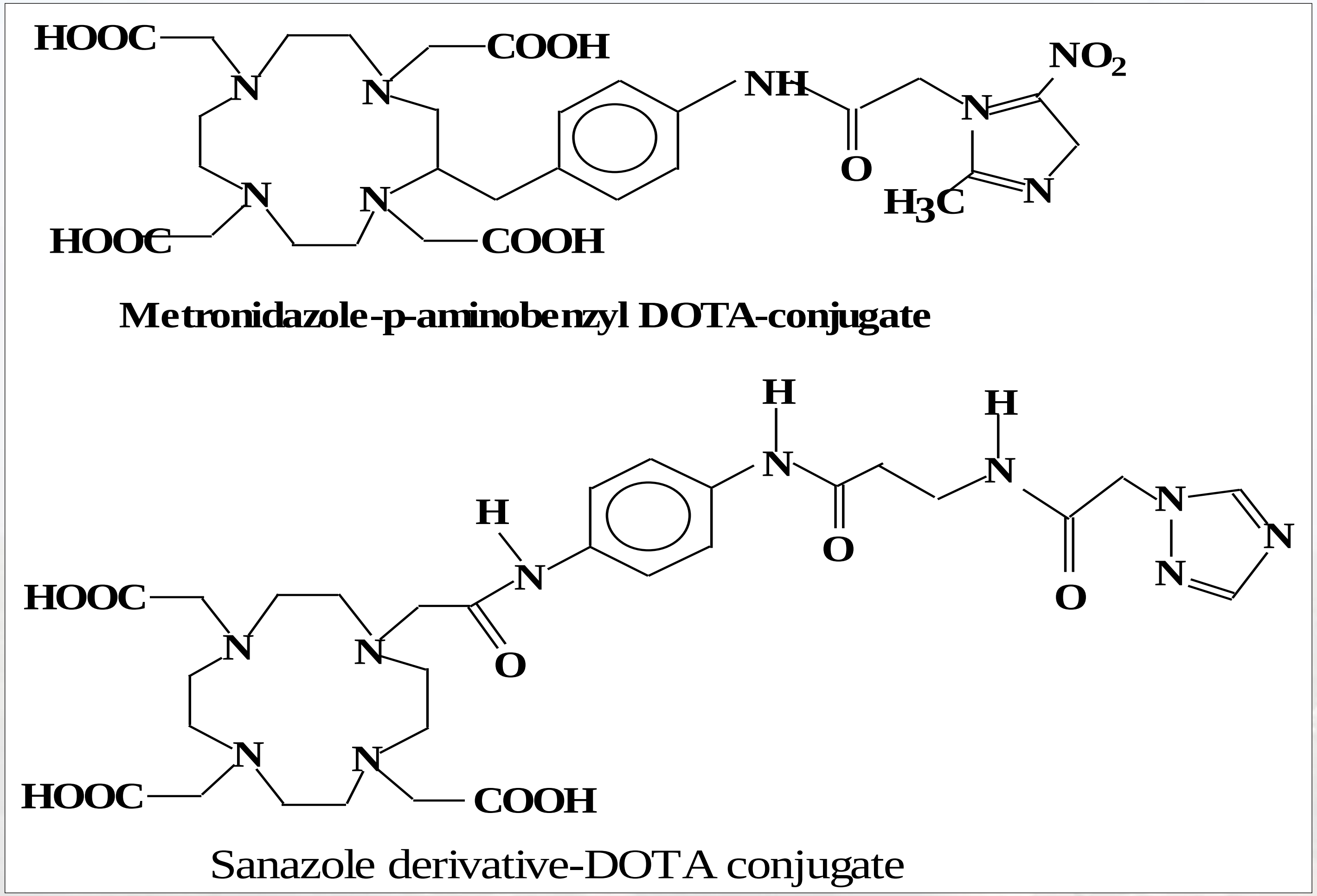


p-NCS benzylDOTA-estradiol-conjugate

Agent for therapy of ovarian cancer

An estradiol-conjugate for radiolabeling with ^{177}Lu : An attempt to prepare a radiotherapeutic agent., Sharmila Banerjee, et al, ***Biorg. Med. Chem.*** *13, 2005, 4315-4322.*

^{177}Lu labeled DOTA-Metronidazole/Sanazole

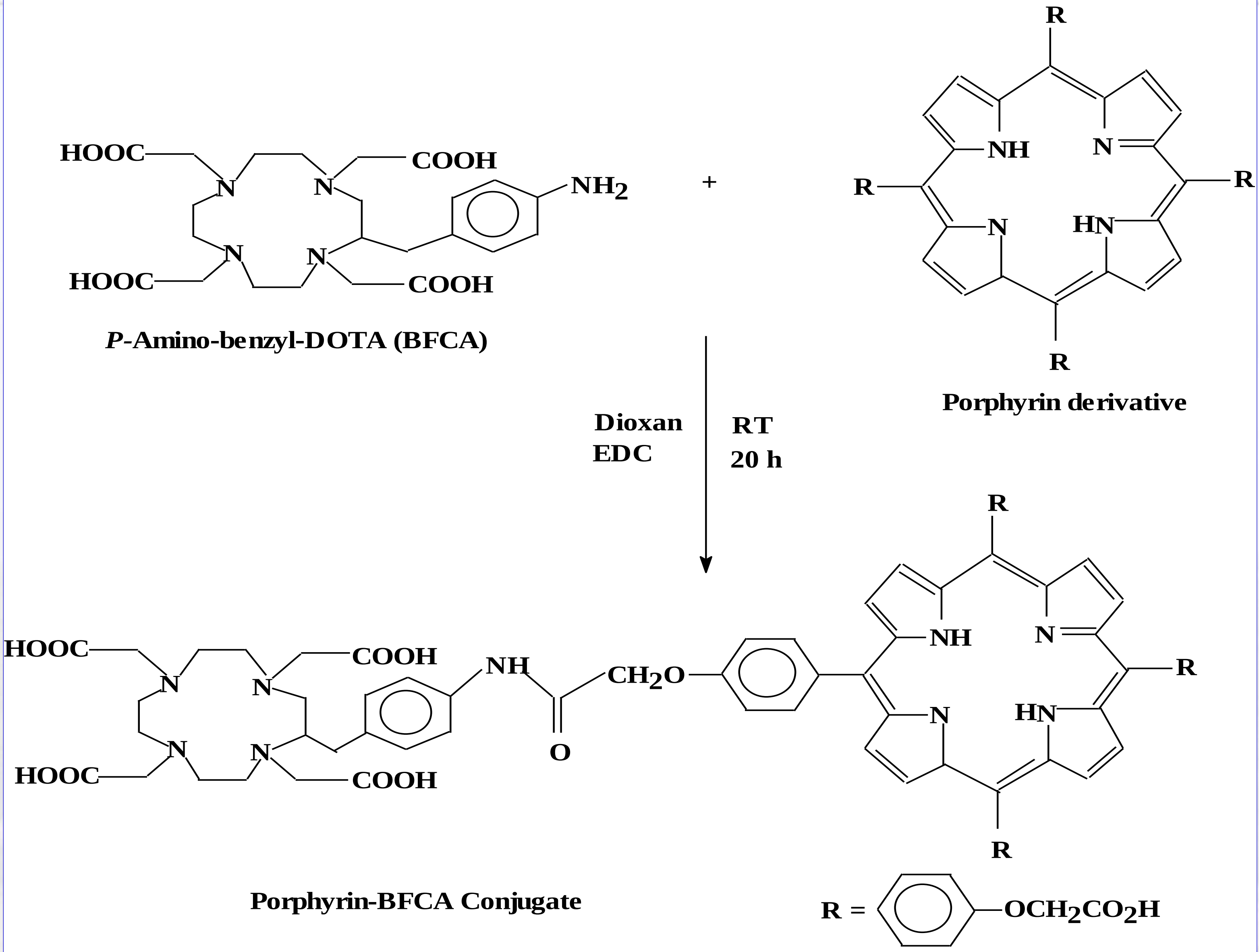


Agent for therapy of hypoxic tumors

Preparation and preliminary biological evaluation of a ^{177}Lu labeled sanazole derivative for possible use in targeting tumour hypoxia, Sharmila Banerjee, et al. ***Bioorg. Med. Chem.*** *12, 2004, 6077-6084.*

^{177}Lu-Labeled Metronidazole for possible use in Targeting Tumor Hypoxi, Sharmila Banerjee ***et al.****,.****Radiochim. Acta*** *94, 2006, 375-380.*

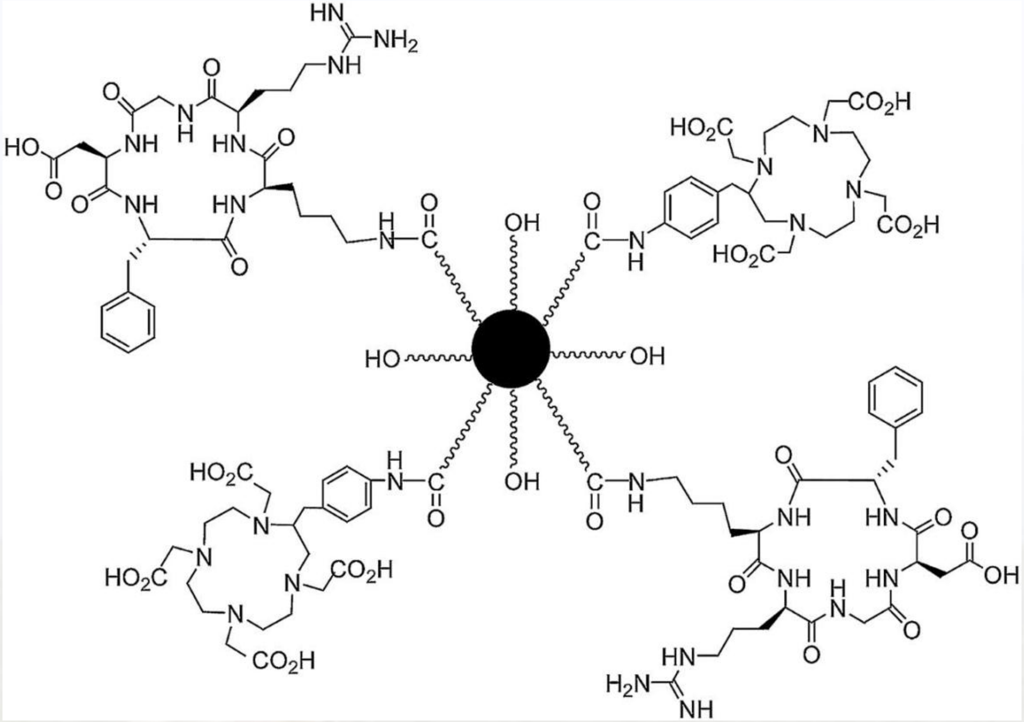
^{177}Lu-Porphyrin for Targeted Tumor Therapy



Agent for tumor therapy

Synthesis and biological evaluation of ^{177}Lu-DOTA-porphyrin conjugate as a potential agent for targeted tumor radiotherapy Sharmila Banerjee et al.,* ***Q. Journal of Nucl. Med****. 58, 224-233, 2014.*

^{177}Lu-labeled carbon nanospheres an example of radionanomedicine



^{177}Lu-DOTA-CNS–cRGDfK) for efficient nano-targeting of melanoma tumors expressing integrin $\alpha_v\beta_3$ receptors

Carbon nanospheres conjugated with p-NH_2-Bz-DOTA and cRGDfK

^{177}Lu-labeled Carbon Nanospheres: A New Entry in the Field of Targeted Radionanomedicine Sharmila Banerjee et al, RSC Advances 6, 2016, 50761-50769.*

Theranosis - A new concept in Personalized Medicine

- Theranosis : A combination of two interdependent applications - therapy and diagnosis, using the same agent
- Individualized treatment regime **for planning a specific dose for a specific patient -** 'personalized medicine'
- Theranosis - particularly relevant in nuclear medicine practices.
- A diagnostic radioisotope in a radiopharmaceutical replaced with a therapeutic radioisotope eg : ^{188}Re for ^{99m}Tc, using the same molecular vector & not compromising the biological avidity
- A diagnostic dose augmented to a therapeutic one in order to tailor the therapy in a specific patient
- Pre-therapy information of biopharmacokinetics and dosimetry utilized to personalize the therapeutic regime

^{177}Lu –Ideal from theranostic perspective

Theranosis - **Diagnosis and Therapy using same isotope**

Moderate β^- energy [497 keV maximum]

- Low tissue penetration
- Lower dose to the non-target organs

Presence of low energy γ photon in low abundance [113 keV (6.4%), 208 keV (11%)]

- Simultaneous scintigraphy and dosimetric studies

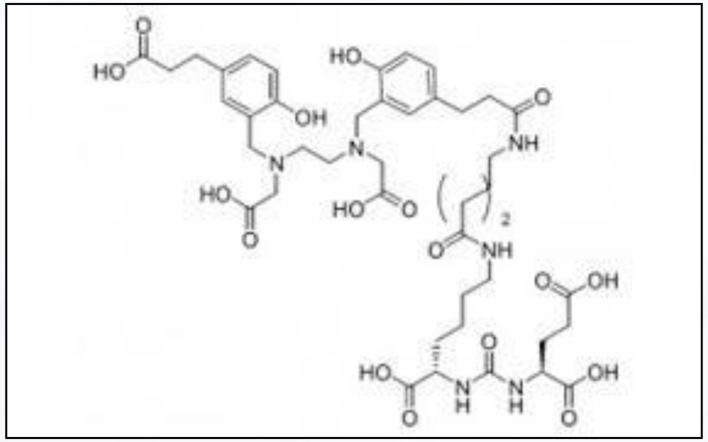
Theranostic applications of Lutetieum-177 in radionuclide therapy
Tapas Das, Sharmila Banerjee, Thematic Issue on Lu-177 Radiopharmaceuticals: Current Radiopharmaceuticals, 9, 2016, 94-101.*

New Developments : Prostate Cancer Detection and Treatment

^{68}Ga-PSMA-11 for detection

PSMA = Prostate specific membrane antigen

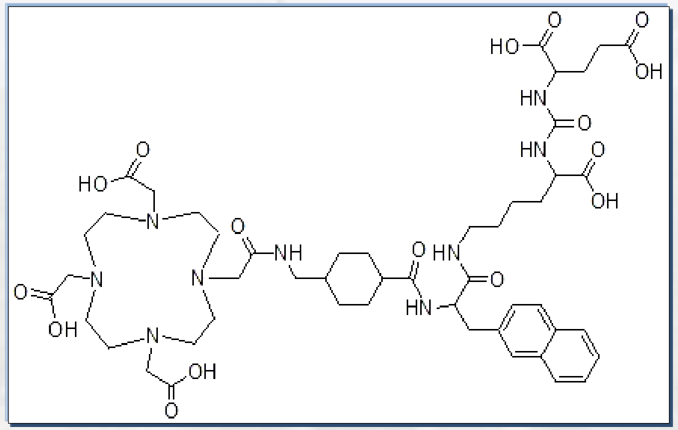
- High potential for the detection of small recurrent PCa lesions
- Early detection in patients
- High accumulation in small metastases
- Rapid clearance from background tissue



^{68}Ga-PSMA-11

^{177}Lu-PSMA-617 for treatment

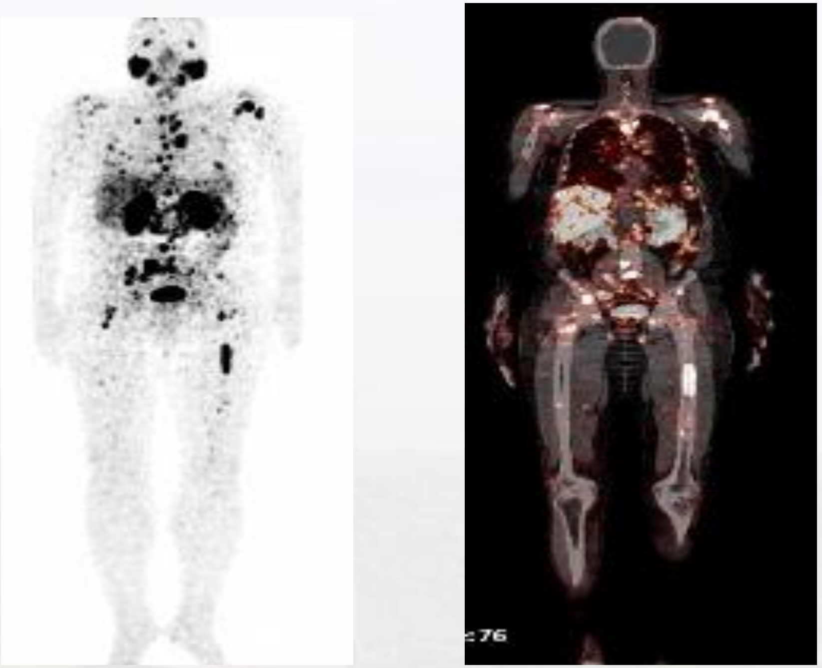
- PSMA-617 has the highest binding affinity to PSMA receptors reported till date
- Radiotherapy with ^{177}Lu-PSMA-617 in prostate cancer patients have shown high promise in initial studies *(First time reported only in 2015)*



^{177}Lu-PSMA-617

^{68}Ga/^{177}Lu Theranostic pair for prostate cancer management developed and used in RMC

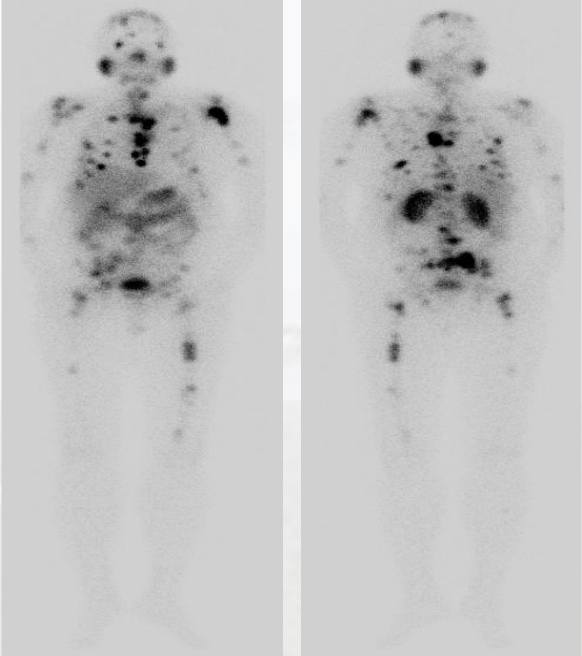
^{68}Ga-PSMA PET/CT Scan started on a regular basis in RMC after RPC approval in April 2017



^{68}Ga-PSMA PET-CT in a patient of metastatic Prostate Carcinoma with raised serum PSA level

280 patients so far

^{177}Lu-PSMA Therapy in Metastatic Castrate Resistant Prostate Carcinoma (mCRPC)



^{177}Lu-PSMA in a patient of metastatic prostate carcinoma

80 therapies till date after RPC approval in April 2017

^{177}Lu-based radionuclide therapy provided in RMC

Radiopharmaceutical	Used Since	Number of Patients	Cost
^{177}Lu-DOTATATE for neuroendocrine cancer	February 2013	2300	Rs. 10,000/- per patient dose Vs. Rs. 1.5 L per patient dose
^{177}Lu-PSMA	Since April 2017	85 patients	Rs. 25,000-30,000 Vs. 1.25-2.00 L in private centres

Approved ^{177}Lu-based agents from BARC

- **LU-2** :
  - sterile, pyrogen-free, clinical grade $^{177}LuCl_3$
  - specific activity >20 Ci/mg - adequate for formulation of receptor based radiopharmaceuticals.

- **LUK-1** :
  - EDTMP cold kits (to be used as ^{177}Lu-EDTMP in bone pain palliation

- **LUM-1** :
  - ^{177}Lu-EDTMP as a ready-to-use injectible

- ^{177}Lu-DOTATATE for NET

- ^{177}Lu for radiation synovectomy

- ^{177}Lu-PSMA for castrate resistant prostrate cancer

^{177}Lu radiopharmaceuticals in clinical use

Product	Target	Biological carrier	Application
^{177}Lu-CC-49	Tumor associated antigen (TAG-72)	Murine monoclonal antibody specific to tumor associated glycoprotein 72 (TAG 72) MoAb	Colon, ovarian, adenocarcinoma
^{177}Lu-J591	Prostate specific membrane antigen	PSMA antigen	Prostate cancer
^{177}Lu-Rituximab	CD 20-MoAb	Chimeric mouse-human monoclonal antibody	Non-Hodgkin's lymphoma
^{177}Lu-DOTATATE Lutathera®	Somatostatin receptors (sub-type 1-5)	Peptide-DOTATATE	Neuroendocrine cancer
^{177}Lu-EDTMP	Skeletal metastases	Ethylenediaminetetramethylene phosphonic acid	Metastatic bone pain palliative

Summary

^{177}Lu- is a gold mine- relatively less explored till recently

- Various possibilities making use of widely different targeting molecules
- Therefore wide range of applicability- Theranostic potential to be explored for application in personalized medicine
- Suitability as the most potential radioisotope in therapy of cancer other than that of the thyroid
- Immense potential of ^{177}Lu is available within India

*Emergence and present status of Lu-177 in targeted radiotherapy: The Indian scenario., **Sharmila Banerjee**, Tapas Das, Sudipta Chakraborty and Meera Venkatesh , Review Article : **Radiochim. Acta, 100**, 2012, 115-126.*

*Lutetium-177 Therapeutic Radiopharmaceuticals–Linking Chemistry, Radiochemistry and Practical Applications **Sharmila Banerjee,** M. R. A. Pillai* and F. F. (Russ) Knapp, Jr. **Chem. Rev.** 115, 2015, 2934-2974.*

Thank You