Role of the
INTERNATIONAL ATOMIC ENERGY AGENCY
in Development & Deployment of Radiopharmaceuticals

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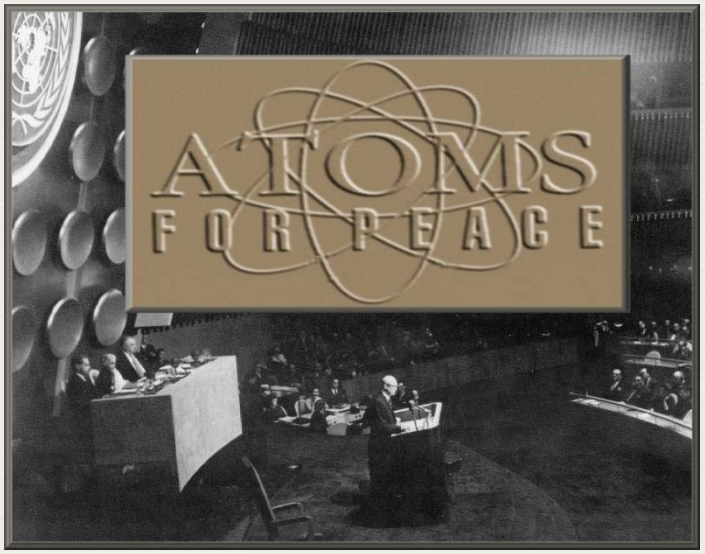
International Atomic Energy Agency

IAEA : Atoms for Peace

IAEA Statute:

"The Agency shall seek to accelerate and enlarge the contribution of atomic energy for peace, health and prosperity throughout the world



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IAEA Program implementation Mechanisms

- Fostering relevant developments and dissemination of information
  - Co-ordinated research projects (CRP)s
  - Thematic meetings
  - Technical documents
- Technology transfer, capacity building
  - TC Projects- National, Regional, Inter-regional
- Building synergies-partnership, net-working
- Co-operation support to International initiatives

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Coordinated Research Projects

- Project theme/title relevant to the needs of the time, esp. for developing Member States (MS)
- Theme – promising/demonstrated techniques/technologies
- Participation of researchers from several MSs
- Aim : collective research/studies and collation of results to achieve reliable results; dissemination of techniques/technologies in the MSs

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Thematic Technical Meetings

- A focused meeting on contemporary themes
- Participation by a large number of MSs
- Presentations reflecting the existing status, exchange of information on work done, brain storming
- Often fore runners of CRPs

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Publications

- Detailed publications on various subject matters of relevance to the area
  - Manuals – reference ; with detailed procedures that can be followed
  - Comprehensive books on subject matter
  - Technical documents (TECDOCs) – compilation of the results achieved in the CRPs
  - Technical Reports – more general (compared to TECDOCs) and a ‘stand alone’ document

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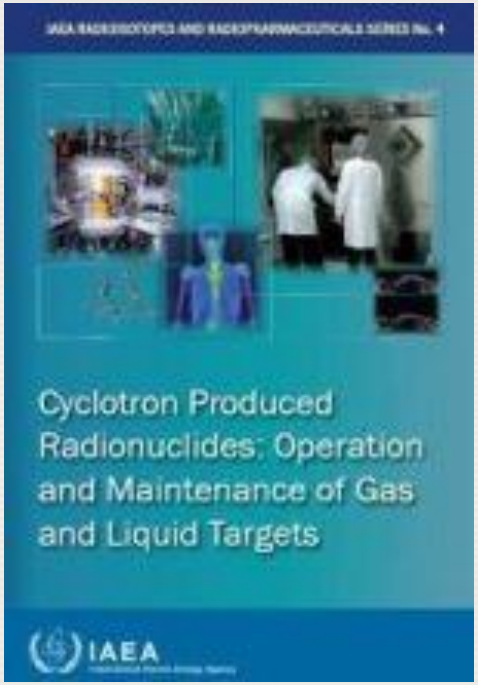
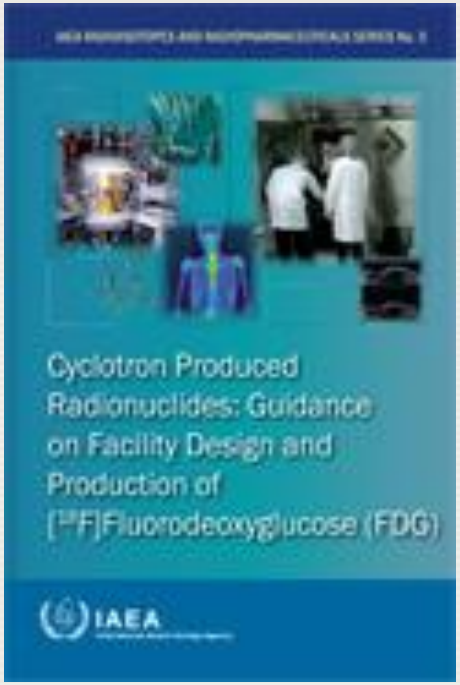
Some publications in 2012

1. **Cyclotron Produced Radionuclides: Guidance on Facility Design and Production of [F-18]Fluorodeoxyglucose (FDG)**
2. **Cyclotron produced radionuclides: Operation and Maintenance of Gas and Liquid Targets.**





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Technical Co-operation (TC)

- Aimed at capacity building in the developing MSs
  - Country specific – e.g. setting up a medical cyclotron in a country
  - Region specific – e.g. a Training course on ‘GMP in Radiopharmaceutical production
  - Inter regional – topics of universal interest – e.g. ‘production of Mo-99 without using highly enriched U-235’

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Cooperations

- Organizing International periodic Conf./Symp.s
  - 2013-Nucl. Cardiology (with NA HU)
- Facilitating and managing Net working among MSs with similar goals
  - E.g. : Research Reactor Users
- Management of databases
  - E.g.: Cyclotrons; nuclear data;
- Cooperating/co-organizing International events
  - Training courses – with Intl. bodies; e.g ISORBE
  - Conferences etc.

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Radiopharmaceuticals – Areas of activities

- *Motto : holistic approach- 'Bench to Bed'*
- Radioisotopes – production, purification, availability (generator systems etc.)
  - E.g. $^{99}Mo/^{99m}Tc$ production-non conventional; $^{90Sr}/^{90}Y$ & $^{68}Ge/^{68}Ga$ generator systems;
- Preparation of the well established radiopharmaceuticals (labeling methods, purification, QA/QC, enhancement of quality/stability etc.)
  - E.g. ^{18}F-FDG; ^{18}F-FLT etc.

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Radiopharmaceuticals – Areas of activities

- Development of methodologies for proven radiopharmaceuticals –through CRP mechanism; rarely through individual contracts
  - ^{177}Lu-EDTMP; ^{188}Re-S colloid
- Exploring promising radiolabelled products in areas lacking ideal/near ideal products (mode as above)
  - ^{99m}Tc based molecule/s for SLN detection

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Radiopharmaceuticals – Areas of activities

- Clinical trials – in cooperation with the colleagues from Health Unit (full involvement from the start)
  - ^{177}Lu-EDTMP; SLND products
- Training/HRD-GMP compliance; regulatory aspects; setting up facilities etc.
  - On-line modules for setting up a medical cyclotron facility

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Current Activities

- Coordinated Research Products – 10
- Technical Cooperation Projects – >30
- Web based training module for medical cyclotron facility set up-completed
- Designing courses on GMP requirements for Radiopharmaceutical production – initiated
- Addressing issues related to regulatory approvals for clinical deployment of radiopharmaceuticals – planned/initiated at concept level
- Co-operation with International Bodies

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Co-ordinated Research Projects

- Diagnostic Radiopharmaceuticals
  - ^{99m}Tc-well established; but secured availability challenged a few years ago; few areas with no ideal agent still need to be looked into
  - ^{18}F-FDG & a few other molecules well established; other molecules labeled with 18F will be beneficial to hospitals with cyclotron
  - ^{68}Ga – a PET tracer that can be availed from a radionuclide generator; has high potential for use in hospitals akin to ^{99m}Tc

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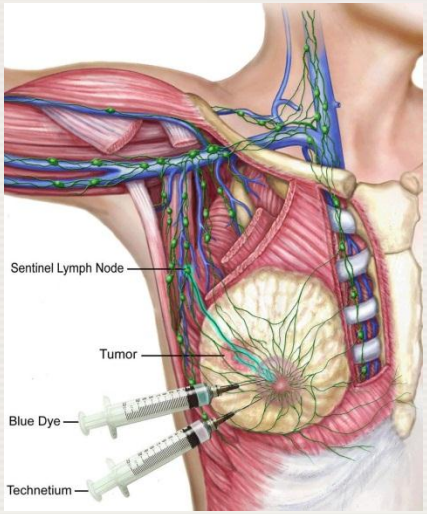
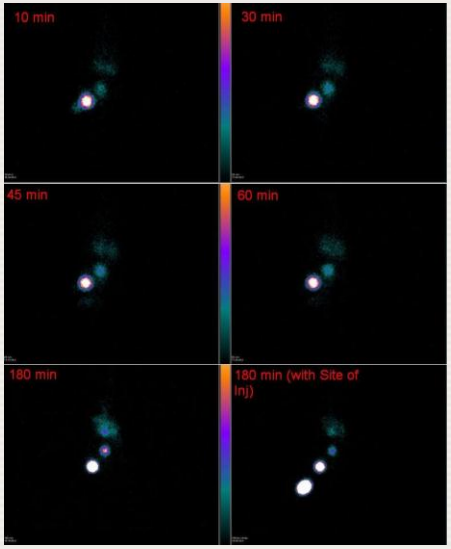
Co-ordinated Research Projects

- Sentinel Lymph node detection with 99mTC based radiopharmaceuticals – recently concluded
  - Potential application in wide range of cancers
  - Need for an ideal specific agent- lacking now





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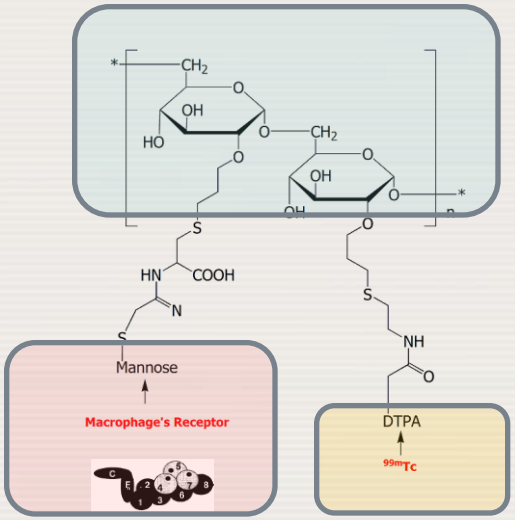
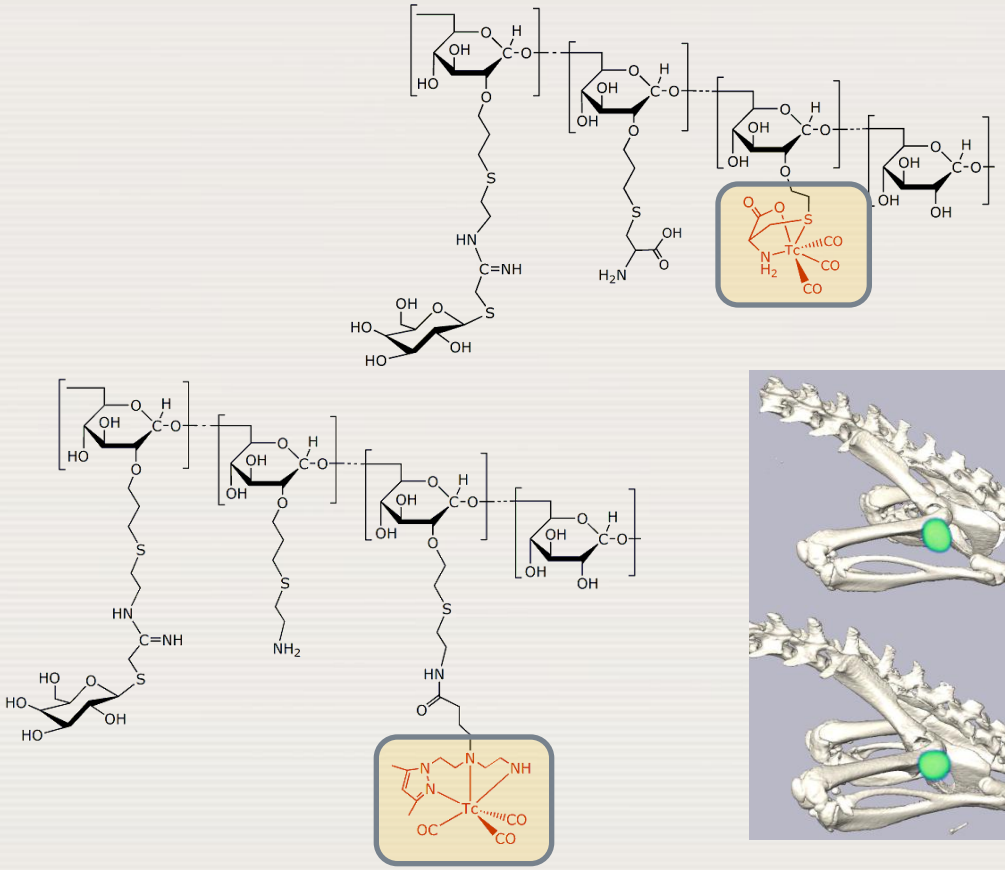
CRP on Sentinel Lymph Node Detection - Achievements

- Few specific molecules for SLND identified





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Co-ordinated Research Projects

- 'Development of Fluorine-18(F-18) labelled radiopharmaceuticals (beyond [F-18]FDG) for use in Oncology and Neurosciences' - successfully concluded in 2012.- 14 MS Institutions participated
  - Synthesis of the selected F-18 radiopharmaceuticals at lab scale and augmented scale
  - QA/QC procedures for the selected F-18 radiopharmaceuticals.
- Results:
  - MSs capacity for producing new ^{18}F-molecules; e.g. potential of ^{18}F-nicotinamides and benzamides for melanoma detection-Saudi Arabia
  - Publication entitled "Guidelines on preparation of F18 labelled radiotracers such as FET, FLT, FAZA, Choline, DOPA

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Co-ordinated Research Projects

- 'Development of ^{68}Ga based Radiopharmaceuticals for Management of Cancer and other Chronic Diseases' - 17 Institutions from 16 MS participate; observers from Industry
- Very good results achieved
  - Standardisation of the procedures (availing pure 68Ga – post processing; radiolabeling molecules etc.)
  - Animal, Pre-clinical and Clinical studies for several molecules

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^{68}Ga based Radiopharmaceuticals-Achievements so far

- Development of radiolabeling methods
  - Peptides (RGD, bombesin, minigastrin, VIP, NT, UBI)
  - Small molecules (BPPMD, BPAMN, citrate, folate)
- Preclinical studies
  - Minigastrin, Bisphosphonates, UBI, Siderophores, RGD, Citrate etc.
  - semicarbozone, HSA nanocolloid , bombesin for myocardial perfusion imaging.

^{68}Ga based Radiopharmaceuticals-Achievements so far

- Clinical studies
  - ^{68}Ga DOTATATE vs ^{11}C Choline in patients with prostate cancer, post surgery and after increase in PSA.
  - Comparison of Galgas vs Technegas in COPD,
  - ^{68}Ga-DOTATOC in 'head and neck' squamous cell carcinoma.
  - ^{68}Ga -Rituximab for NHL,
  - ^{68}Ga- bisphosphonates for bone metastasis.
  - ^{68}Ga -Minigastrin for Medullary Thyroid cancer (MTC),
  - ^{68}Ga-bombesin for prostate cancer,
  - ^{68}Ga NOTA- RGD for lung cancer.
  - ^{68}Ga- Citrate for infection imaging.

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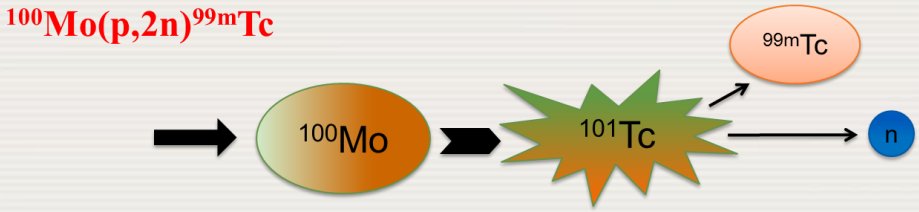
Co-ordinated Research Projects

- 'Development of Accelerator-based alternatives to fission production of Mo-99 /Tc-99m' - first RCM held in TRIUMF, Canada**. - 15 MS Institutions participate ; keen observers from Industry**
  - Result of recent global ^{99}Mo crisis; ageing major producing reactors; promising results from the Canadian scientists
  - As a possible back-stop in MSs with cyclotrons during outages



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Co-ordinated Research Projects

- Therapeutic Radiopharmaceuticals
  - Few well established radionuclides focused for product development and use in MSs
  - Few highly promising radionuclides explored for future use

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Established Therapeutic Radionuclides Pursued

Radionuclide	Half-life	Mode of decay	Energy (keV)
THERAPY			
^{90}Y	64.1 h	β^-	2282.0
^{131}I	8.0 d	β^-, γ	970.8
^{153}Sm	46.3 h	β^-, γ	808.4
^{89}Sr	50.5 d	β^-	1496.6
^{177}Lu	6.7 d	β^-, γ	498.2
$^{188/186}Re$	16.9 h	β^-, γ	2120.4

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CRP's completed in Therapy Area

Radionuclide	TOPICS
^{177}Lu	DOTATATE, EDTMP, BIOTIN, COLLOIDAL PARTICLES, METHODS FOR SEPARATION AND QUALITY CONTROL
^{90}Y	
^{188}Re	BIOTIN, NEW DIPHOSPHONATE LIGANDS

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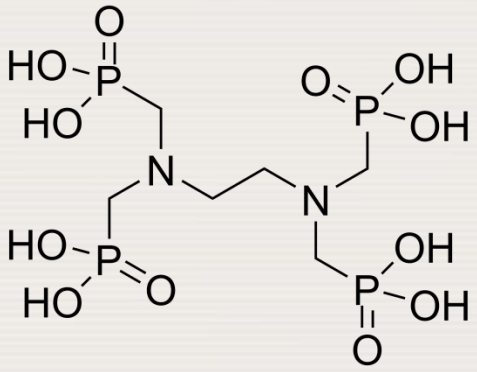
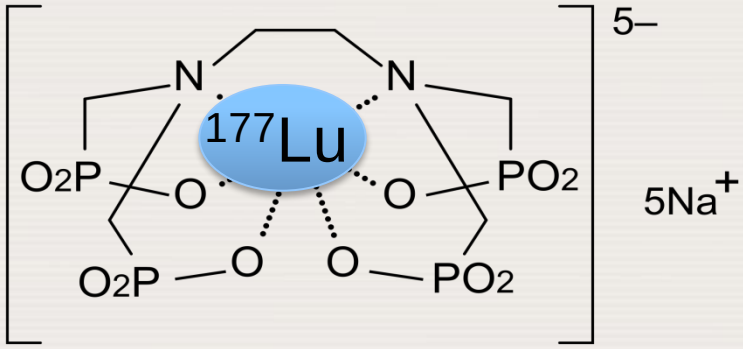
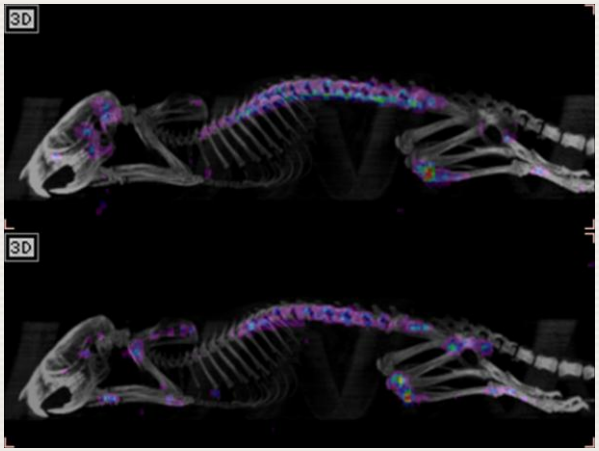
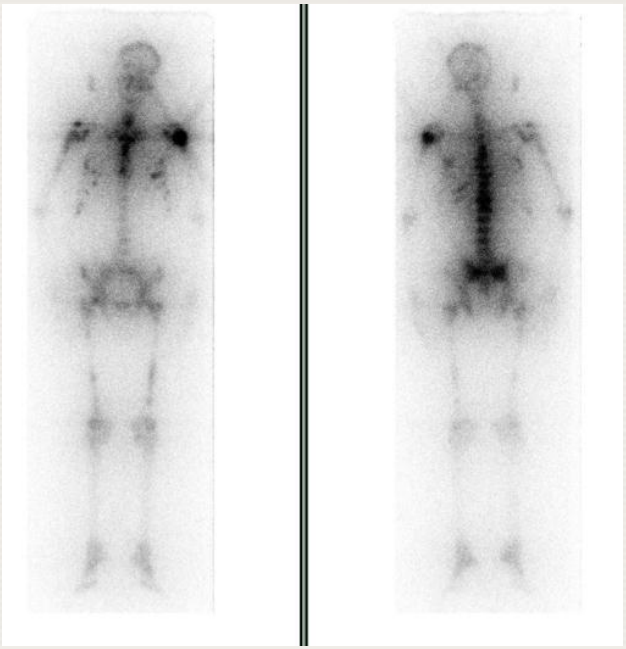
CRP-^{177}Lu-EDTMP for Bone Pain Palliation









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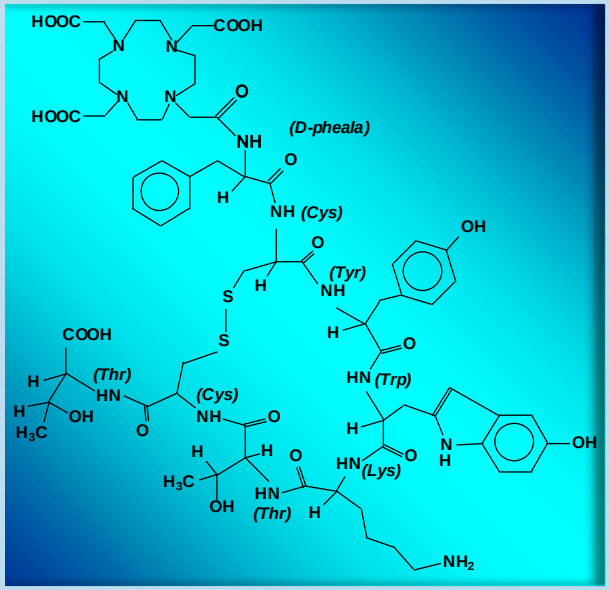
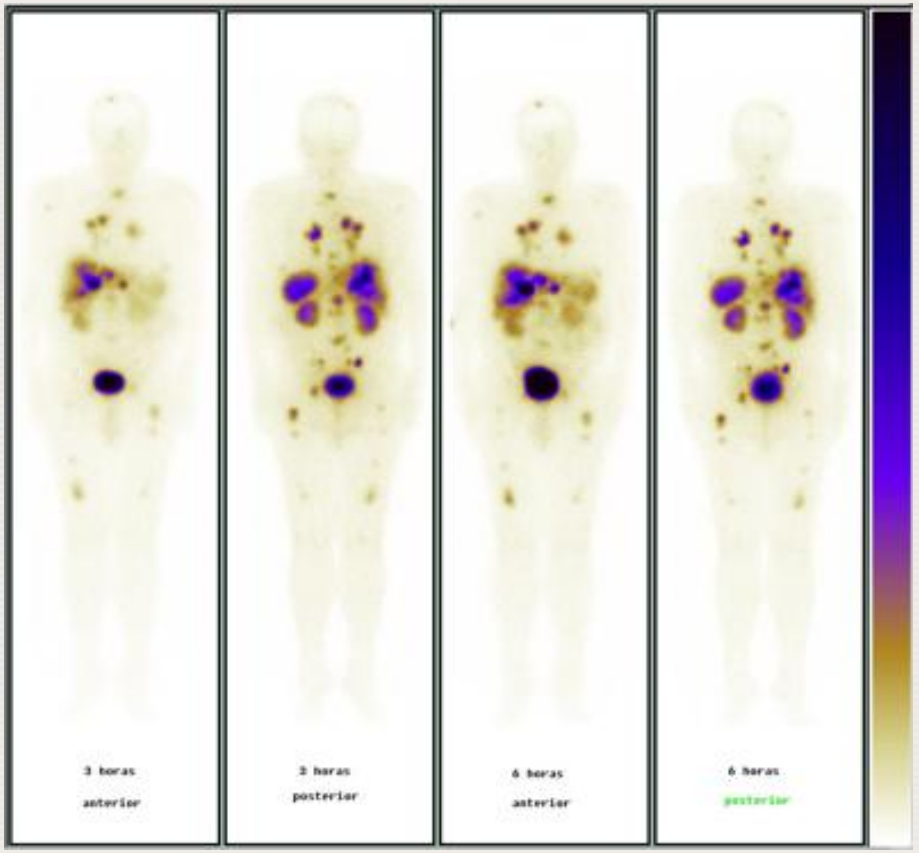
CRP-^{177}Lu-DOTATATE

- for Treatment of Somatostatin Receptor Expressing Cancers





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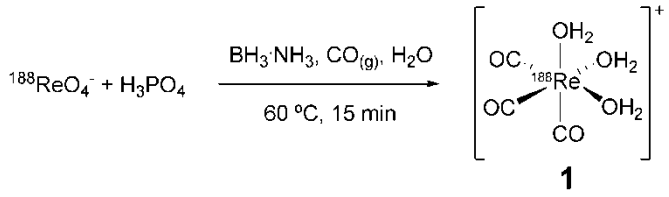
CRP-^{188}Re-bis Phosphonate for Bone Pain Palliation



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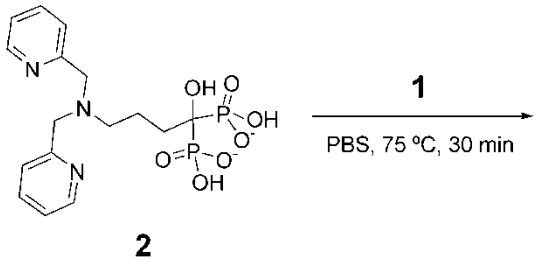
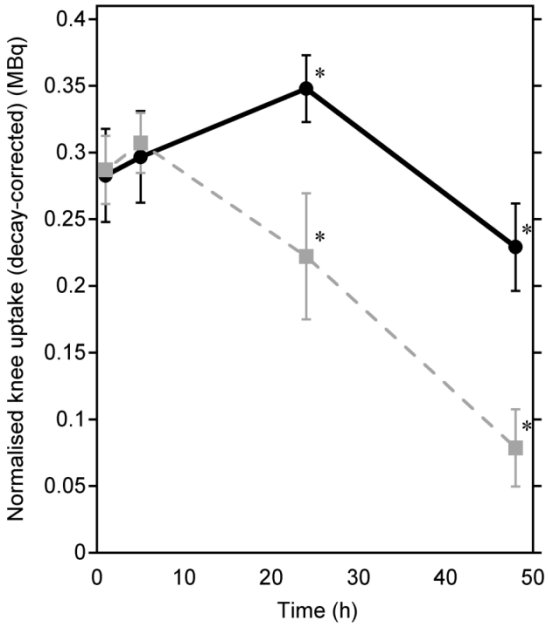


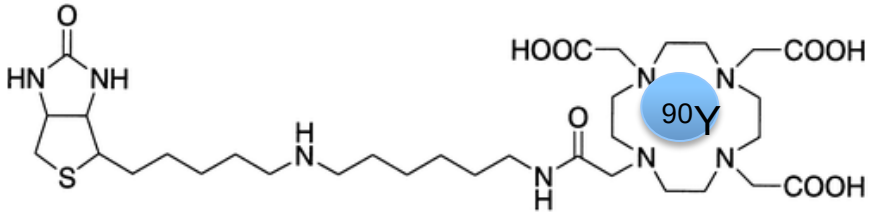
2

1

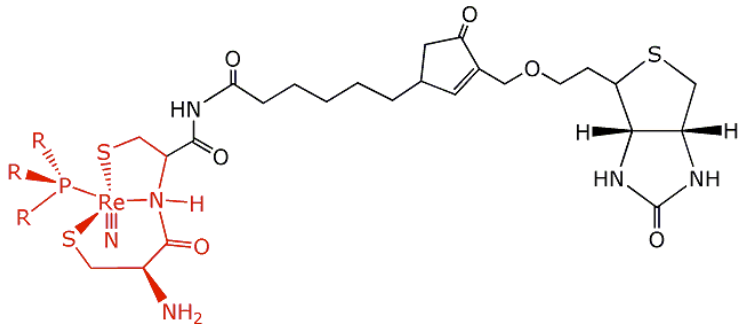
PBS, 75 °C, 30 min

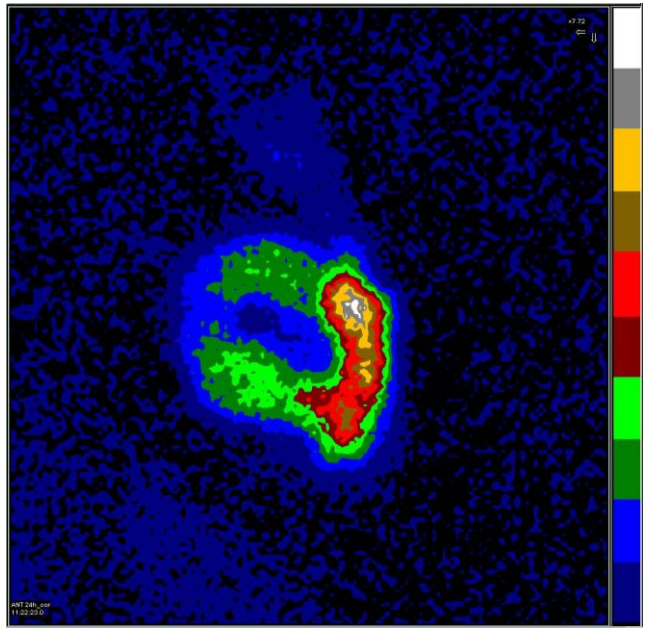


^{90}Y-biotin and use with Avidin



Intra operative Avidination with Radiolabelled Biotin for Therapy





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Current CRPs - Therapeutic Radiopharmaceuticals

Radionuclide	TOPICS
^{177}Lu	DEVELOPMENT OF KITS FORMULATIONS FOR LABELLING ANTIBODIES AND PEPTIDES
^{90}Y	
^{64}Cu	PRODUCTION METHODS

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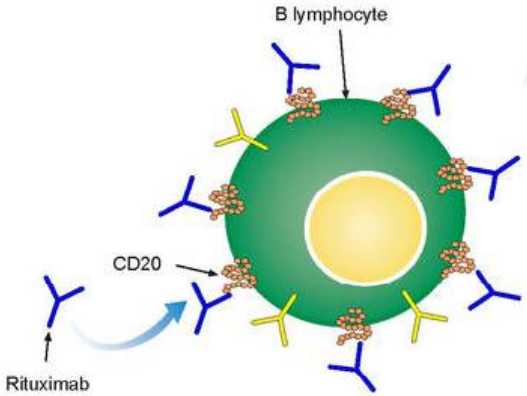
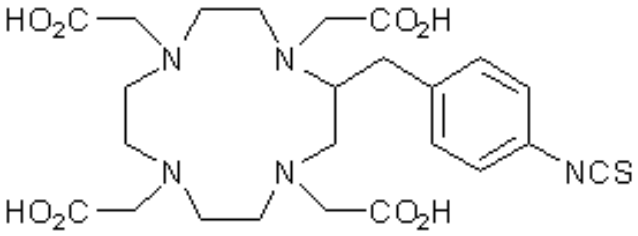
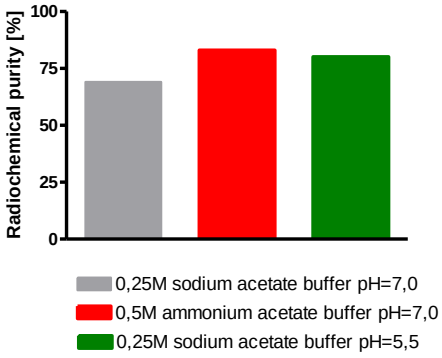
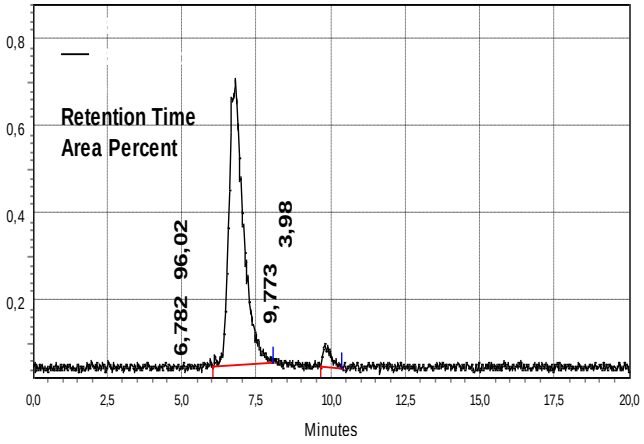
^{177}Lu-MoAb (Rituximab)





Incubation at 38^{0}C, 24h,
specific activity ~380 MBq/mg





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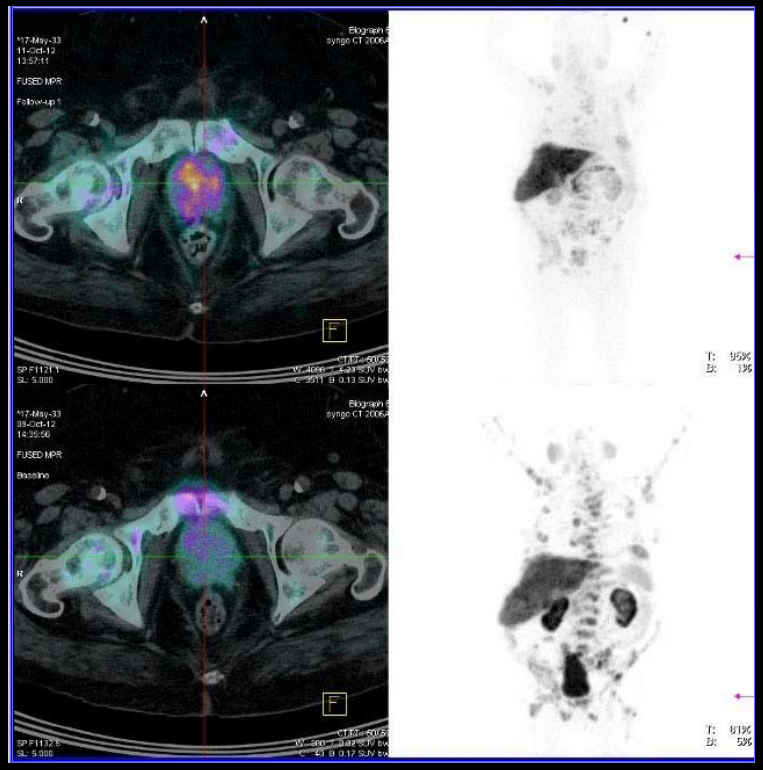
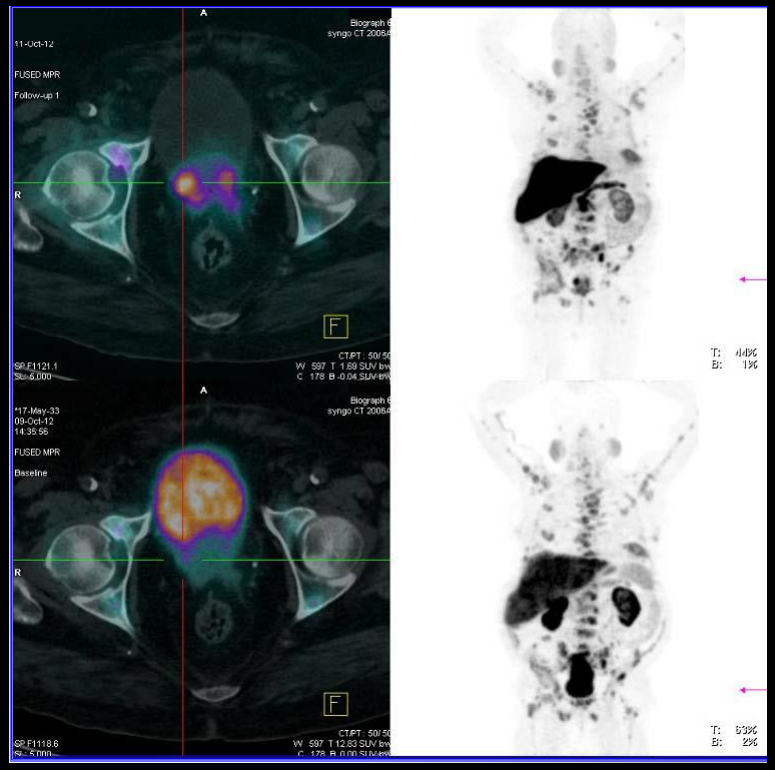
^{64}Cu-Outstanding Example of Excellent Potential



^{64}Cu

^{18}FCH



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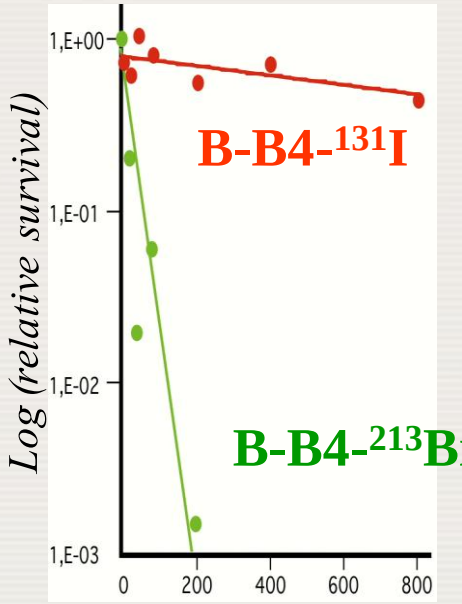
Future Plans

- Infection Imaging - SPECT/PET radiopharmaceuticals.
- Cu-64 and I-124 – for PET imaging
- Exploring other radionuclides incl. α emitters for therapy

RN	Half-life	Mode of decay	Energy (keV)
THERAPY			
^{211}At	7.2 h	α	6790
^{67}Cu	61.9 h	β^-, g	577
$^{212/213}$Bi	60/46 min	α	8320
^{225}Ac	10.0 d	α	5750
^{223}Ra	11.43 d	α	5780



Biological efficiencies of radiolabeled B-B4 antibody on a multiple myeloma cell-line

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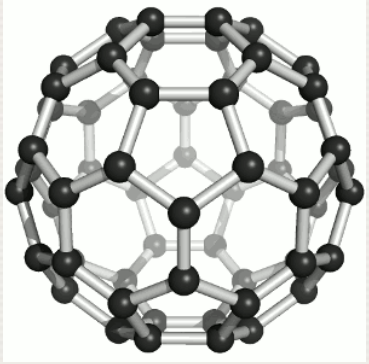
- Nano particles for encapsulation of therapeutic radionuclides



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Capacity Building through TC Projects

At any time ~30 Projects handled . Few examples of the recently concluded TC Projects

Technetium-99m Generator Production facility in Philippines was completed and put into operation

Cyclotron facility for PET radiopharmaceutical production in the University of Warsaw, Poland (Radiopharmaceuticals Production and Research Centre)

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Capacity Building through TC Projects

- Setting up new Cyclotron and radiopharmay centres
  - Macedonia, Cuba, Iraq, Slovakia, Poland, Dominican Republic, Libya etc.

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Capacity Building

Web-based Training Module on 'Radiopharmaceutical Production':

Cyclotron F

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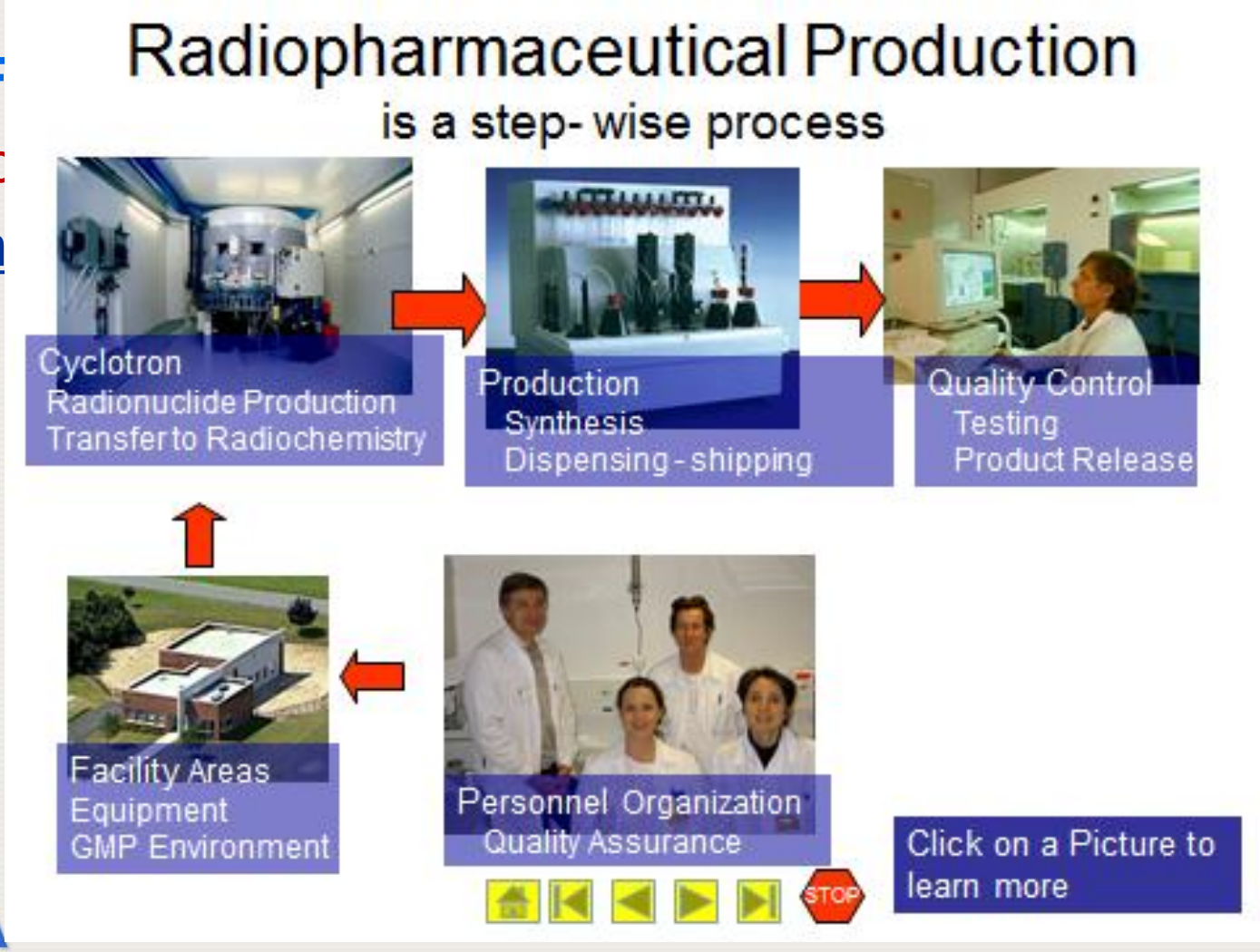
http://www-n



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Capacity Building

- **Role in International Pharmacopoeia –WHO:** Provides guidance on the quality and safety aspects of pharmaceutical products. Radiopharmaceutical Section is updated in collaboration with the IAEA. Monographs of new and emerging SPECT and PET radiopharmaceuticals being updated currently.
- **Quality Management Systems (QMS) and Good Manufacturing Practice (GMP) guidelines** with emphasis on training module development being developed.
- **PG level 'Certificate' and 'Masters' Radiopharmacy** programs through 'e-learning' and 'm-learning' with collaborating centres – Syllabi being worked upon.

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Joint Training Initiatives in Blood Cell Labelling With ISORBE

- Cell labelling for infection, inflammation imaging as well as for cell tracking studies – important!.
- IAEA supports and collaborates with ISORBE in regional training programs where participants could be certified through competency assessment.
- Training programs were successfully conducted in 2012 in Turkey and South Africa.
- Training in new applications of cell labelling such as Stem Cell Tracking is to be encouraged.

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Example of Radiolabelled Stem Cells tracking in Heart Failure Treatment implemented in member state Slovakia.

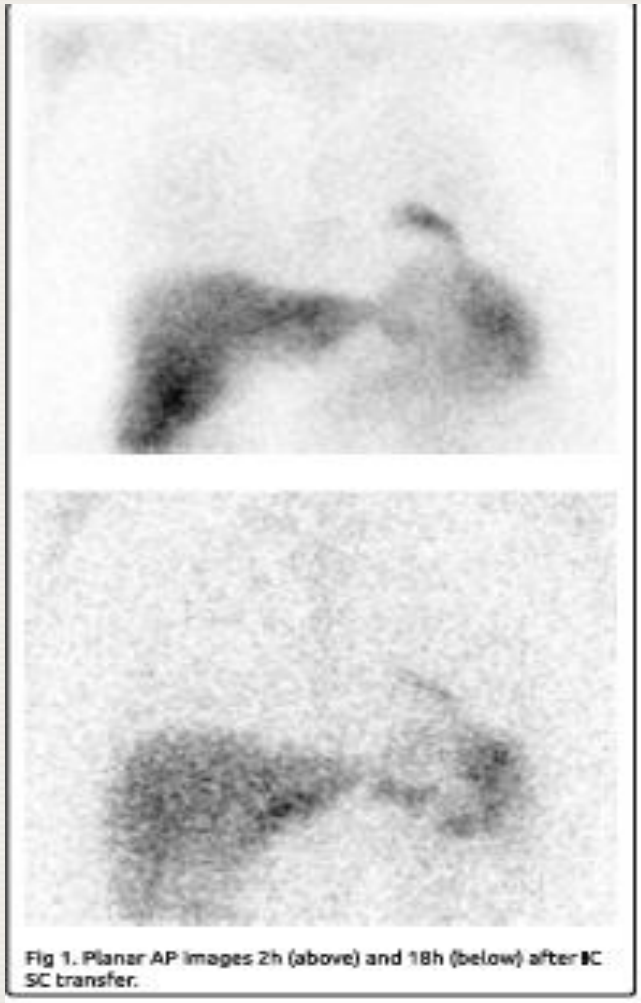

Fig 1. Planar AP images 2h (above) and 18h (below) after IC SC transfer.

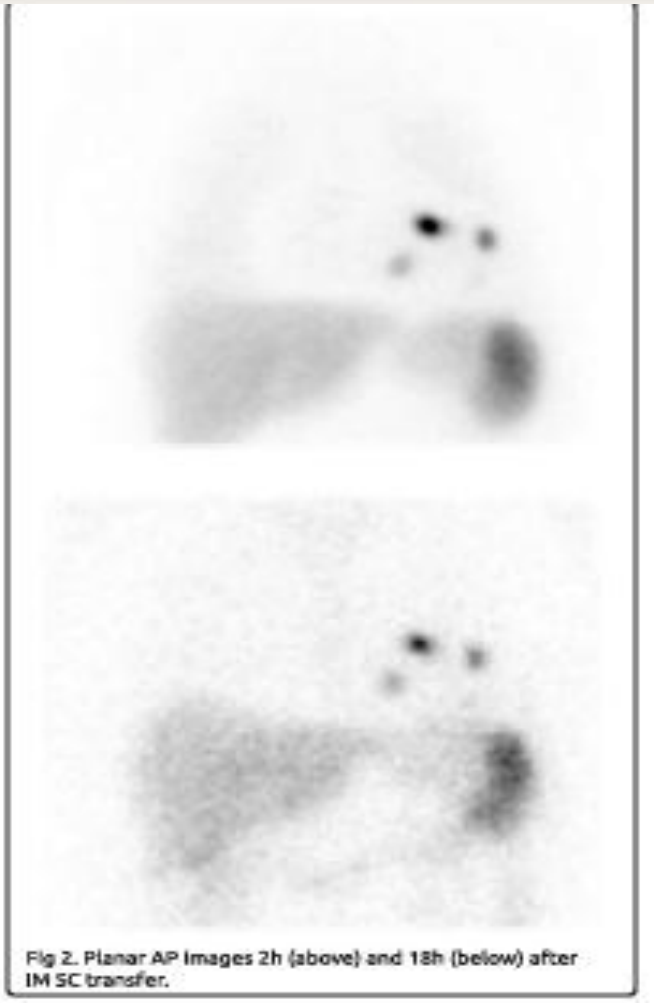

Fig 2. Planar AP images 2h (above) and 18h (below) after IM SC transfer.

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International Conference on Integrated Medical Imaging in Cardiovascular Diseases,

Vienna, Austria,

30 Sept. – 4 Oct. 2013

(Joint event with NAHU)

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Thank You

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