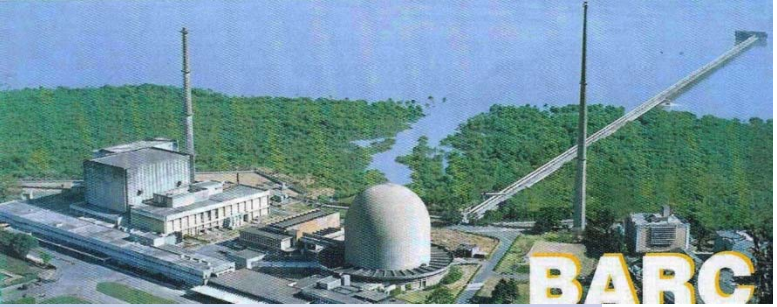

An overview of the Production, Quality Control and Feasibility of using ^{90}Yttrium as a Therapeutic Radionuclide

Meera Venkatesh

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Bhabha Atomic Research Centre,

Mumbai, India- 400085

Why ^{90}Y for therapy?

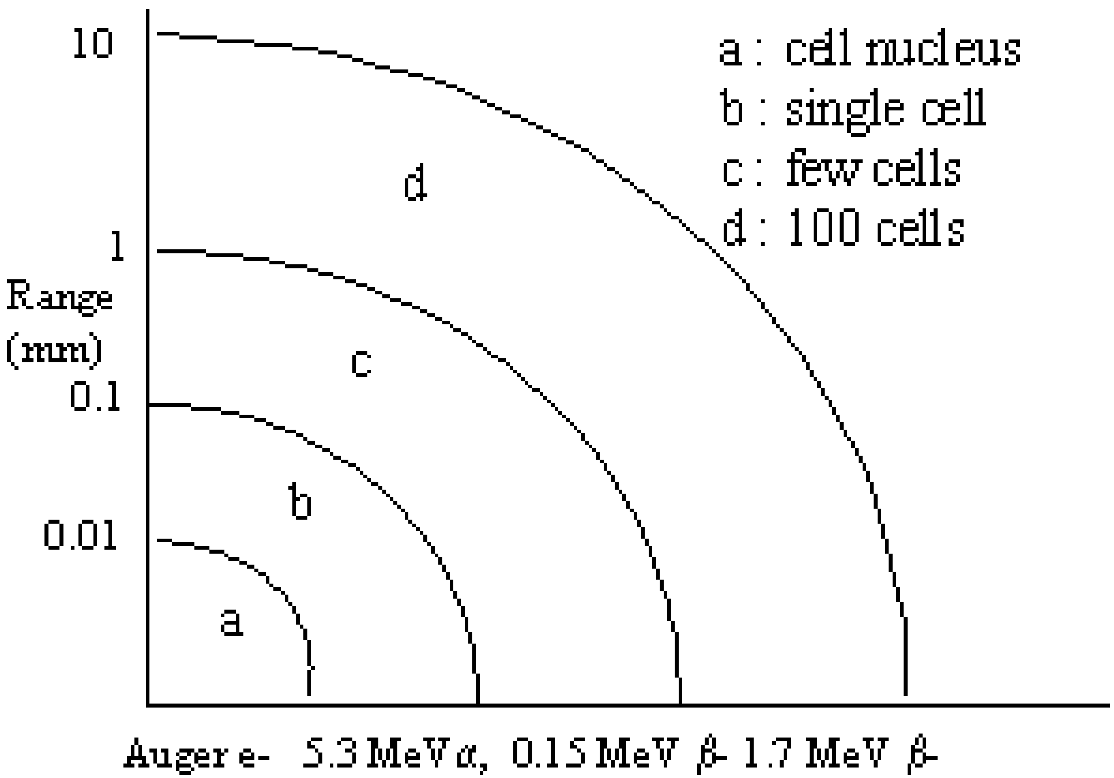
Considerations for therapy

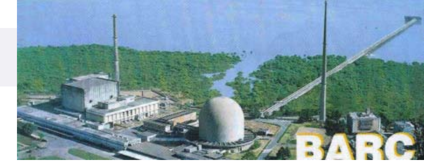
- High LET

Attributes of ^{90}Y

- Hard beta rays; 2.28 MeV; 12 mm max. tissue penetration; by-stander effect very effective!

Range of particulate radiations





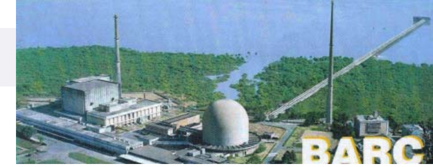
Why ^{90}Y for therapy?

Considerations for therapy

- High LET
- Good chemistry
- Reasonable $T_{1/2}$
- Availability in high specific activities
- Production feasibility
- Easy availability

Attributes of ^{90}Y

- Hard beta rays; 2.28 MeV; 12 mm max. tissue penetration
- Y^{+3} similar to lanthanides; forms very stable complexes
- 64.1 h
- √
- √
- √



^{90}Y: Attractive Attributes for Therapy

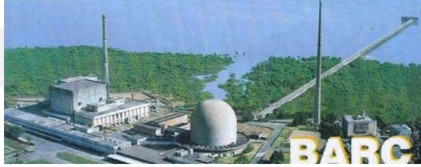
- $T_{1/2}$: 2.67 d ; neither too short nor too long
- $E_{\beta\ max}$: 2.28 MeV; good for large volume irradiation
- +3 charge; similar to lanthanides; well established chemistry; extremely stable conjugates with 14 membered cyclic O,N based ligands like DOTA

^{90}Y Radiopharmaceuticals – Currently used/under trials

- **^{90}Y-Silicate/citrate colloid** : Radiation synoviorthesis
- **^{90}Y-microspheres (glass or resin) :** Liver cancers:
- **^{90}Y-Ibritumomab (zevalin)** Non-Hodgkin's lymphoma
- **^{90}Y-DOTATATE**- Neuroendocrine tumours
- **^{90}Y-labeled Mabs /peptides various cancers**

^{90}Y-Epratuzomab
^{90}Y-Anti-CEA mAb
^{90}Y-pretargeted bispecific Ab
^{90}Y-PAM4 Ab
^{90}Y-Anti-CEA mAb
^{90}Y-Bombesin/GRP analog

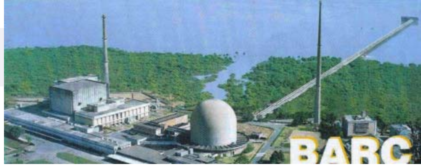
- Lymphoma, Colon, Pancreatic, Liver, Lung, prostate, breast cancers



Sourcing ^{90}Y

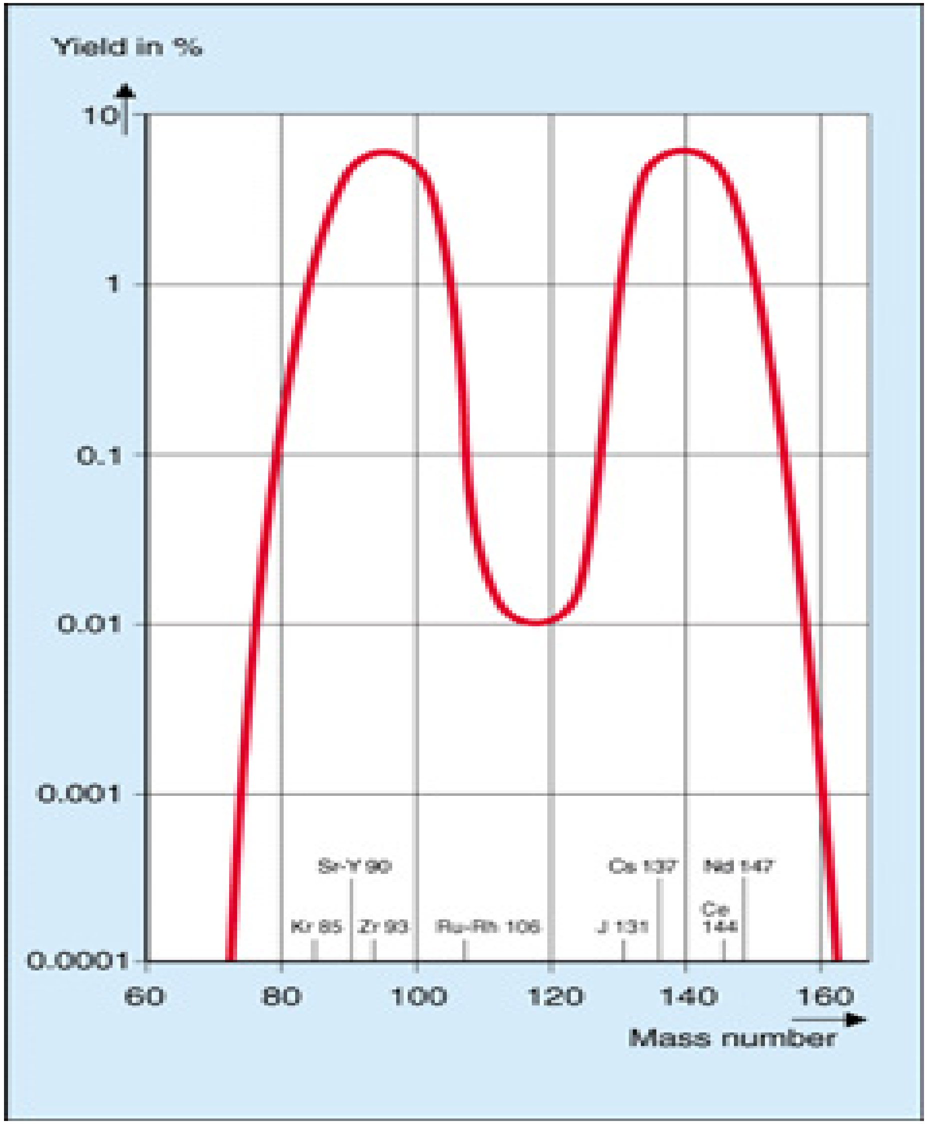
- (n,γ) on ^{89}Y
  - Poor specific activities; σ_{th} few mb, though θ_{nat} is 100%; unsuitable for most therapies
- From ^{90}Sr

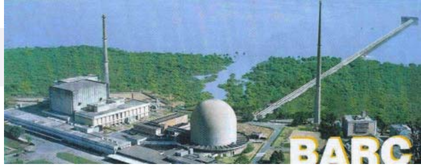
^{90}Sr → (β- 540 keV; 28.8 y) → **^{90}Y** → (β- 2,28 MeV; 64.1 h) → **^{90}Zr** (stable)



Source of ^{90}Sr

F.P. of nuclear fuels; High fission yield; 5.8% for ^{235}U; availability of large quantities (Mci/PBq) from processed spent nuclear fuel





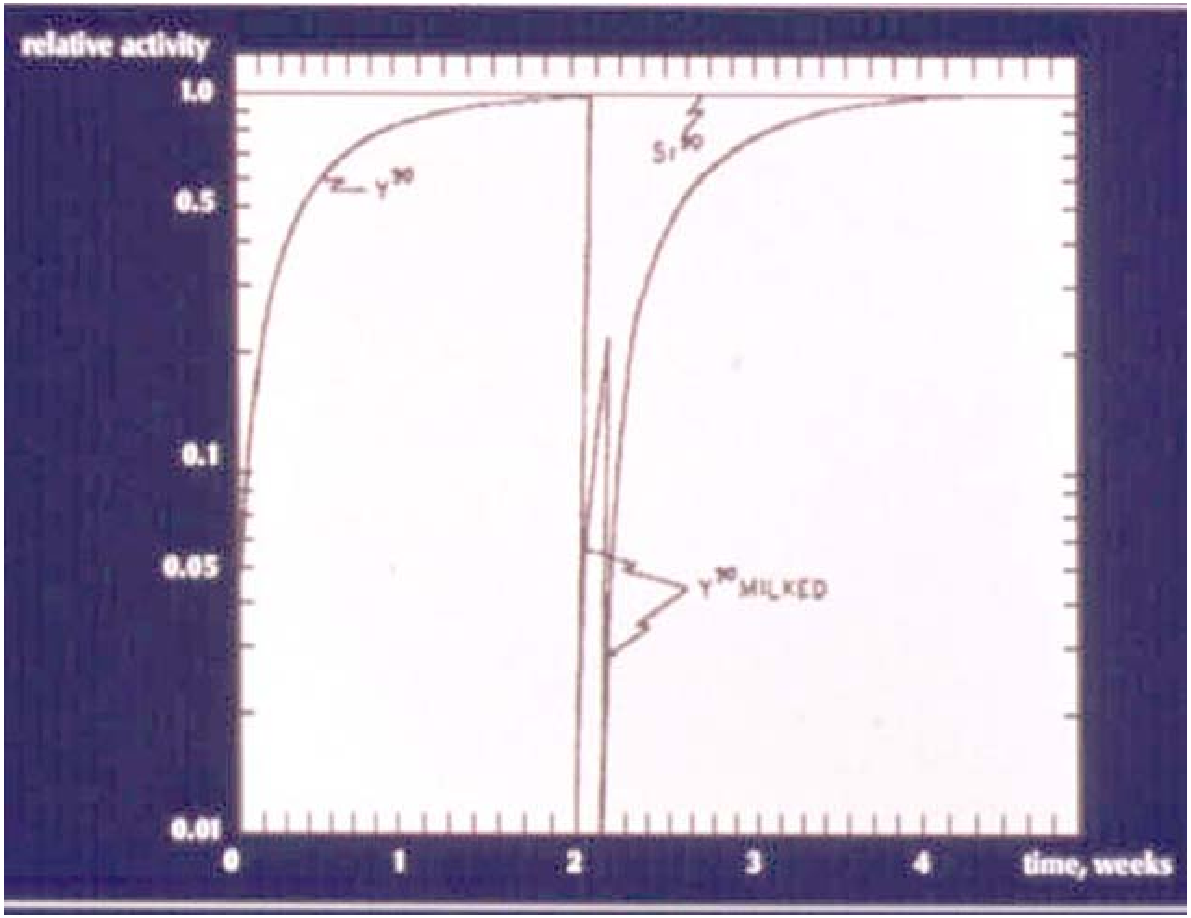
Advantages of ^{90}Sr as source of ^{90}Y

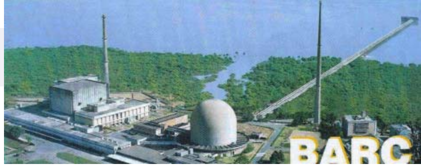
$$^{90}\mathrm{Sr} \xrightarrow[\text{28.8 y}]{\beta^-\ \text{540 keV}} {}^{90}\mathrm{Y} \xrightarrow[\text{64.1 h}]{\beta^-\ \text{2,28 MeV}} {}^{90}\mathrm{Zr}\ (\text{stable})$$

- Very long $T_{1/2}$ (28.8 years) of ^{90}Sr parent
- Short $T_{1/2}$ (64.1 hours) of daughter ^{90}Y
- Possibility of equilibrium & availing **^{90}Sr/^{90}Y generator**
- Separation chemistry very well established & proven
- ^{90}Sr stocks in huge amounts from spent fuel processing (HLW); adequate for decades!!

$^{90}Sr/^{90}Y$ Generator systems

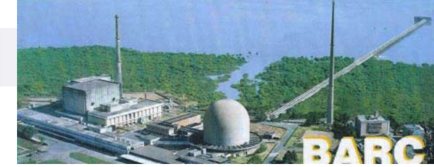
- t_{max} ~ 11d;
- ~ 80% in 3-4 d
- Based on differences in chemistry of Sr^{+2} and Y^{+3}
- Sol. extraction, column chy, extraction chy., eletrochemical, etc.





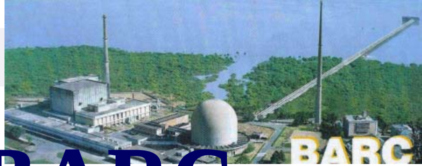
Generator systems developed in the past

- Solvent extraction of ^{90}Y in 0.3M HDEHP/n-dodecane from 0.3M HNO_3
  - *(Bray and Webster, U.S. Pat. No. 5,512,256)*
- Centrifugal Semi-counter flow extraction
  - *(Kodina et al)*
- Ion exchange based generators using a variety of solvents



Ion exchange based generators

- AG50×16 resin and 0.6 M NaAc pH 5.5
  - *(Chinol M. et al , U.S. Pat. No. 5,902,566)*
- Aminex-A5 resin and α-hydroxyisobutyrate
  - *(Malja S. et al)*
- Multiple coulmns : Dowex & AG 50 W, elution with EDTA; & HCl
  - *CENTIS , CUBA.*
- Novel Inorganic Exchange materials
  - *(Sylvester P. et al, U.S. Pat. Appl. 20030231994; 20040005272,)*



$^{90}Sr/^{90}Y$ generators – From BARC

1. **Supported Liquid Membrane(SLM) based Generators**

   Based on preferential transport of Y^{+3} ions through PTFE membranes loaded with Y specific chelates.

2. **Electrochemical generator**

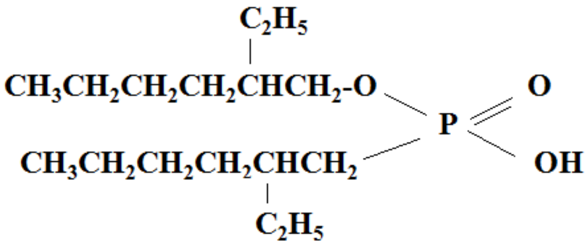
   Based on preferential deposition of Y^{+3} ions on cathode owing to the differences in deposition potentials for Sr^{+2} and Y^{+3}

Separation Science and Technology 42, 1107-1121 2007

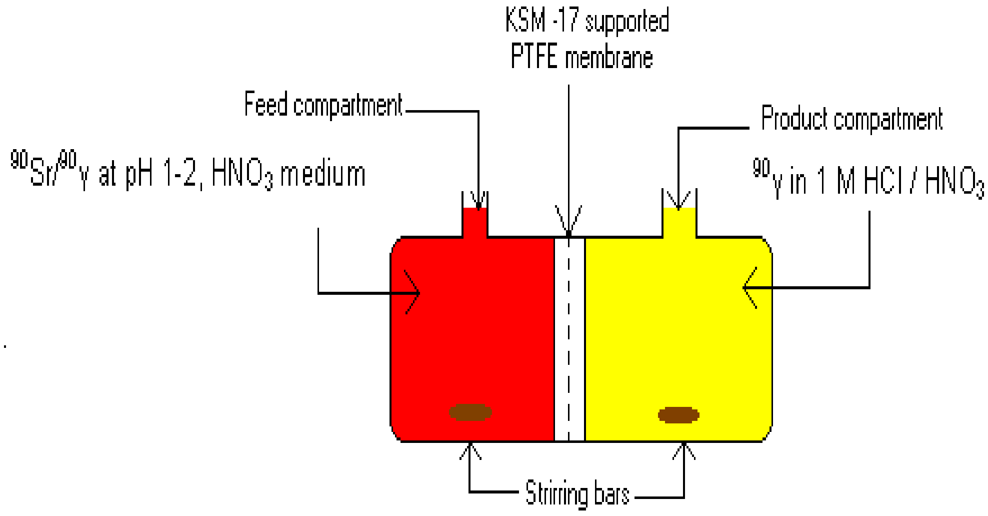
Nuclear Medicine and Biology 35, 245-253, 2008

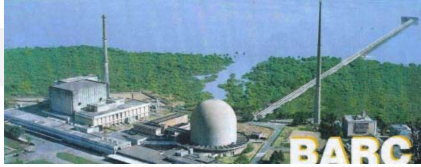
SLM based Generators

- Single stage – with one PTFE membrane & one ligand KSM-17/PC88A



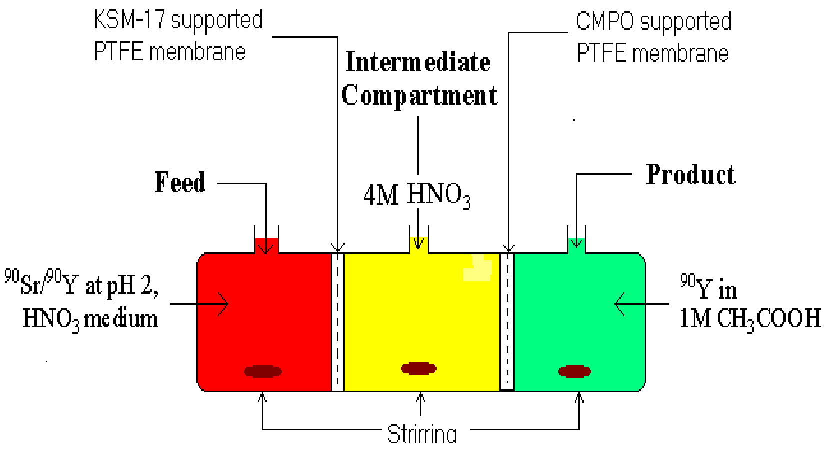
2-ethylhexyl 2-ethylhexyl phosphonic acid (KSM –17)

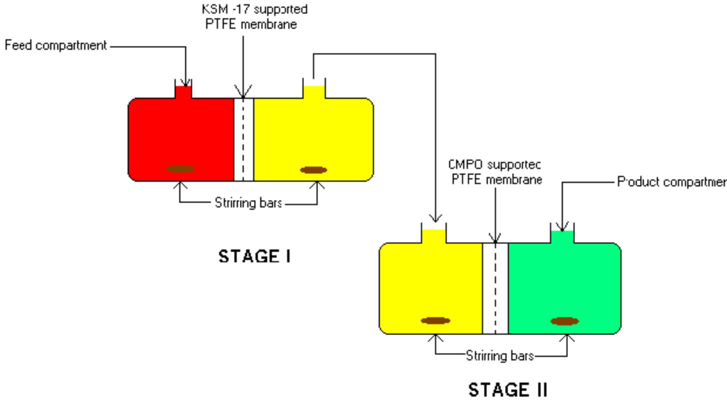


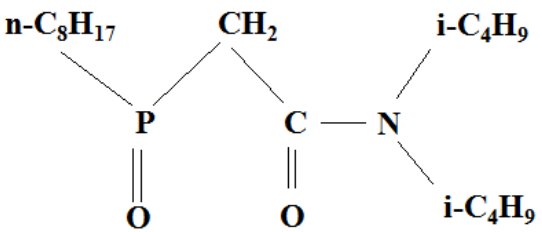


Two Stage SLM Based Generators

- 2 PTFE Membranes & 2 different solvents; KSM17 & CMPO
- Simultaneous mode
- Sequential mode



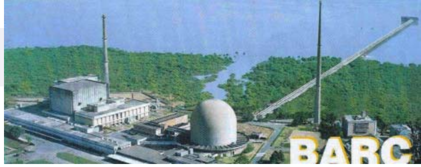




Octyl(phenyl)-N,N diisobutylcarbamoylmethylphosphine oxide (CMPO)

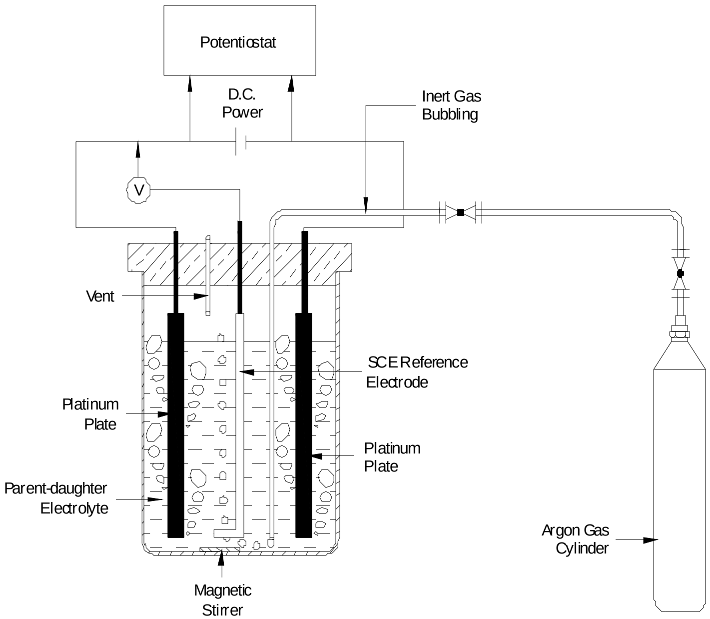
Tests performed to ensure the quality of ^{90}Y obtained

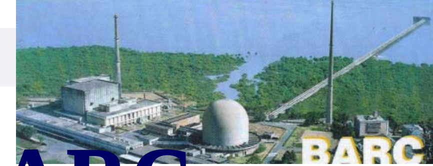
- Chromatographic Techniques; Paper chromatography , Paper electrophoresis
- Radiometric Techniques; γ-& α- Spectrometry, spiking with $^{85+89}Sr$ tracer; following Radioactive decay
- ICP-AES for trace metal analyses
- HPLC/GC for solvent /ligandresidues



Electrochemical generator

- **Simple set up & Easy procedure**
- Electrolysis of $^{90}Sr/^{90}Y\ NO_3$ at pH 2.5-3.0 for 90 minutes
- ^{90}Y gets deposited in the Pt cathode; taken out & rinsed with acetone
- Purification by electrolysis in HNO_3 at pH 2.5-3.0 using the above electrode as anode in a fresh cell with another Pt cathode. ^{90}Y leaches out and gets deposited in the new cathode , which is taken out and pure ^{90}Y recovered by washing with dilute acid





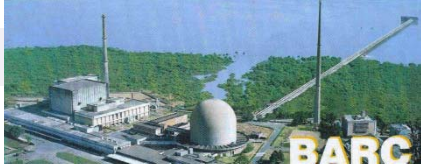
$^{90}Sr/^{90}Y$ generators from BARC

1. **Supported Liquid Membrane(SLM) based Generators**

   Single stage generator demonstrated the potential of SLM for separation of ^{90}Y from ^{90}Sr. Two Stage generators yielded ^{90}Y of adequate purity. In sequential mode, 80% yields of ^{90}Y in ~9 h, at very high purity, (>99.999%) suitable for medical use could be obtained repeatedly

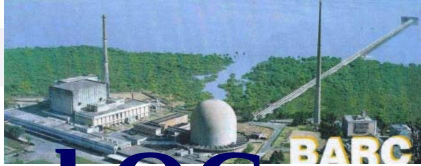
2. **Electrochemical generator**

   The EC technique could be shown to be effective as well as quick route to avail ^{90}Y in high yields and purity; In 2 stages, > 95% yields of ^{90}Y in ~90 min, at very high purity, (>99.999%) suitable for medical use could be obtained.



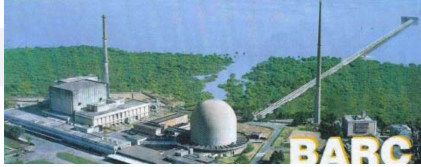
^{90}Yttrium Kamadhenu

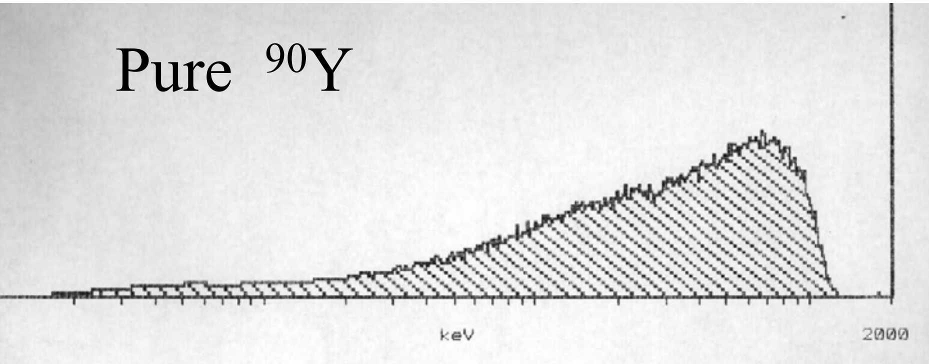
- A $^{90}Sr/^{90}Y$ generator based on Electrochemical technique demonstrated by us, has been automated and scaled up by a commercial manufacturer (ITD) under IAEA's initiative. Prototype ready to be deployed.
- Named after the eternally milk yielding mythological "Cow" "Kamadhenu"
- Holds lots of promise for long term supply of ^{90}Y at reasonable rates.



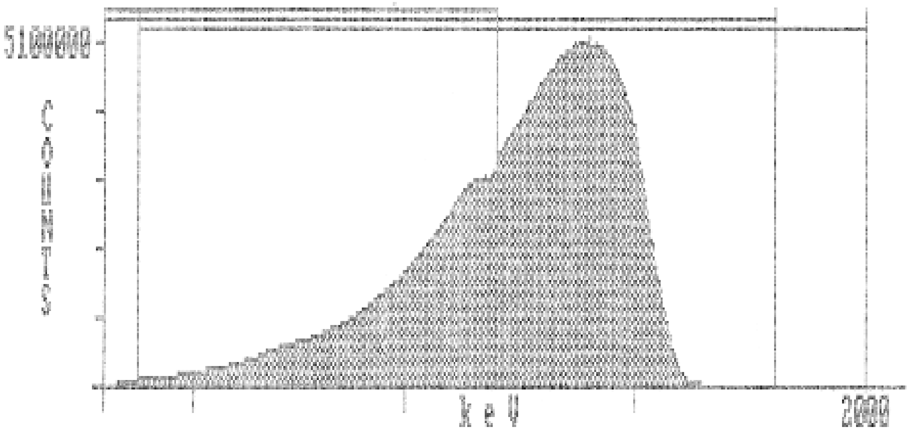
Concerns about ^{90}Y Quality and QC

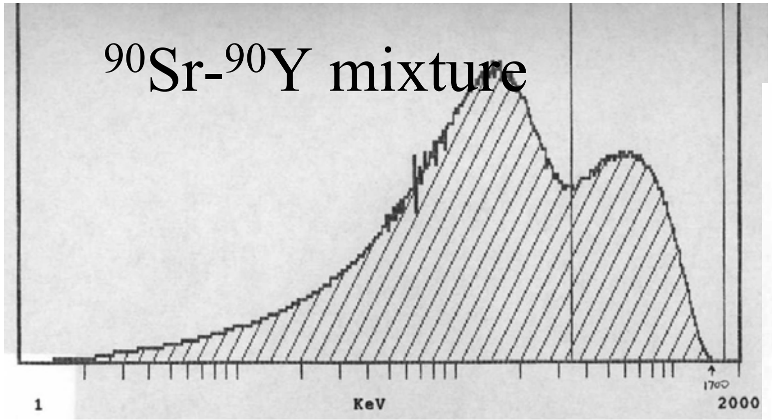
- ^{90}Sr, toxic bone seeking radionuclide – stringent limits for body burden (74 MBq life time dose!); needs strict QC.
- Considering multiple treatments with ~ 37 MBq ^{90}Y each time, a limit of $10^{-4}\%$ has been set for ^{90}Sr content in ^{90}Y; i.e. just 2 ppm of ^{90}Sr content in ^{90}Y.
- This is a challenge, as both ^{90}Y as well as ^{90}Sr are pure β emitters with over lapping beta spectra, compounded with the need for sub-ppm levels of ^{90}Sr to be measured
- Most often, post-facto analysis done for records. Estimation of $T_{1/2}$ of the ^{90}Y for a reasonably long period and/or measurement of ^{90}Sr in the decayed ^{90}Y, are resorted to.
- Uncertainties in these measurements are likely to exceed the desired limits of detection!!



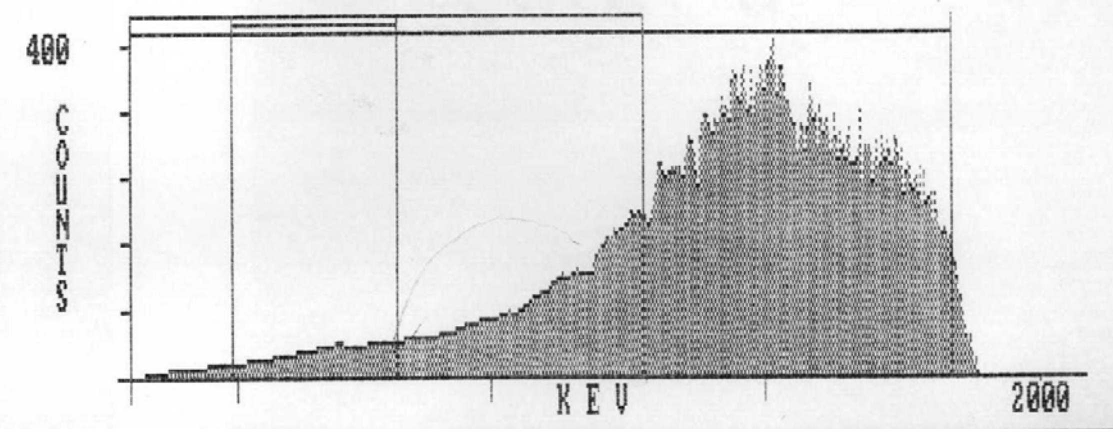


Pure ^{90}Y

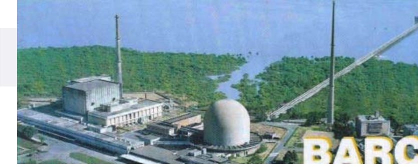


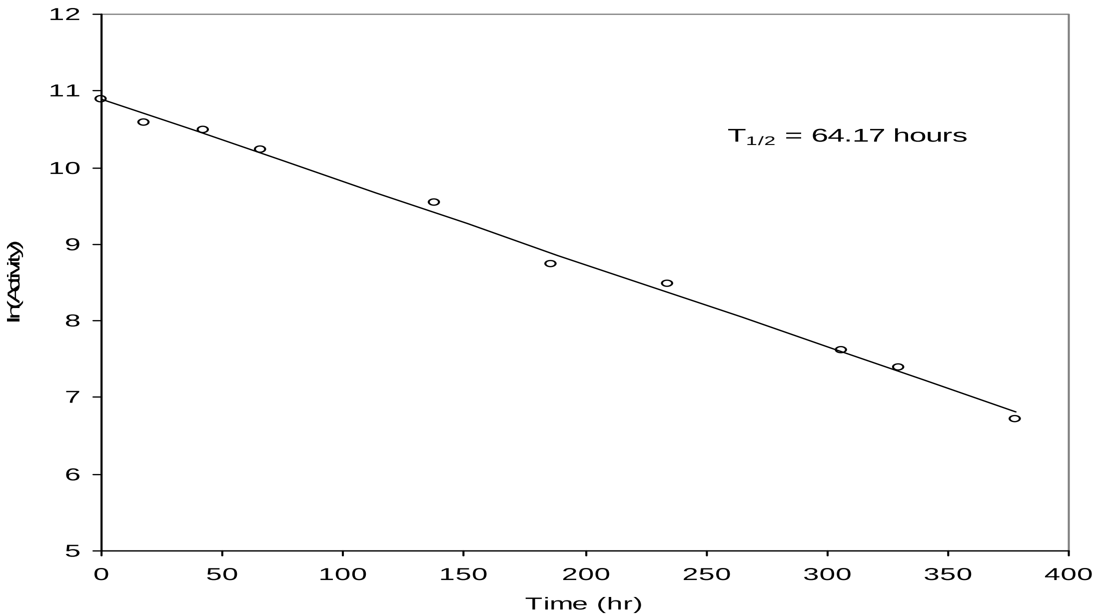


^{90}Sr-^{90}Y mixture



^{90}Y contaminated with ^{90}Sr

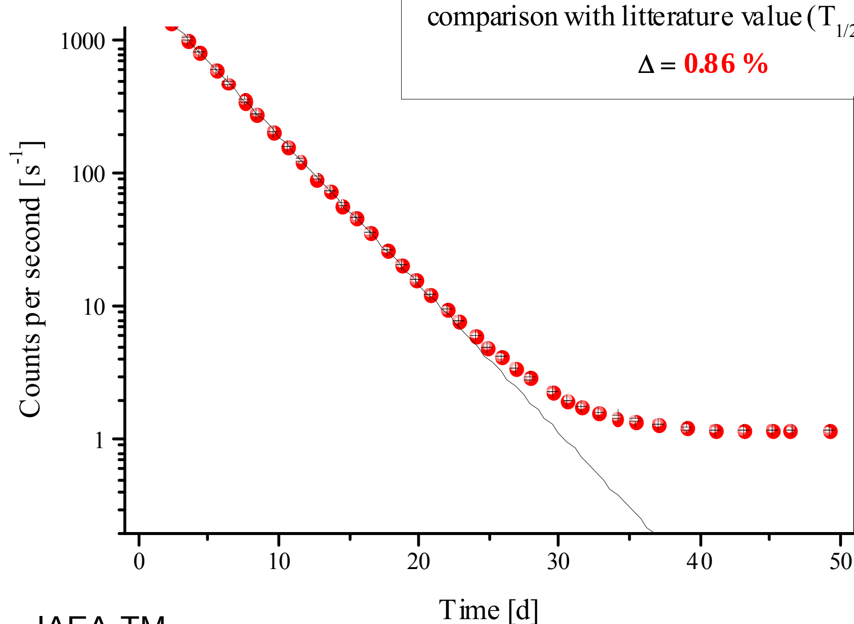


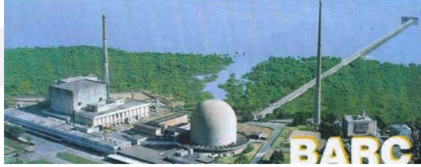


$T_{1/2}$ = 64.654 ± 0.003 h

comparison with litterature value ($T_{1/2}$ = 64.14 h)

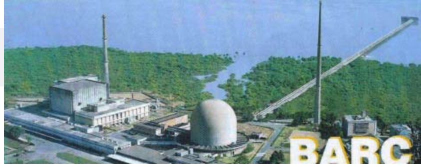
Δ = **0.86 %**





Our Efforts towards 'Real-time QC of ^{90}Y'

- A novel sensitive real time quick reliable estimation of **Bq levels (nCi) ^{90}Sr in MBq levels (mCi) of ^{90}Y** (**sub-ppm**) developed and validated for the first time in the world by us!
- **Principle:** ^{90}Y retained at Rf 0 by a specific ligand in the PC paper while ^{90}Sr moves with Rf ~1, resulting in a clean, reproducible, quantitative separation. Combination of extraction using a solvent with paper chromatography, named as **"Extraction paper chromatography" : EPC**

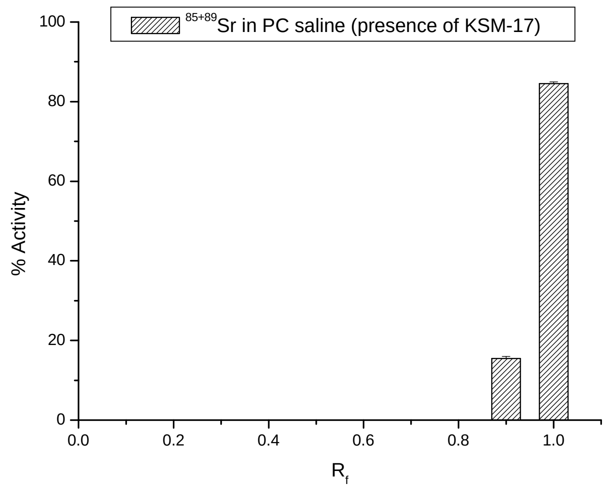


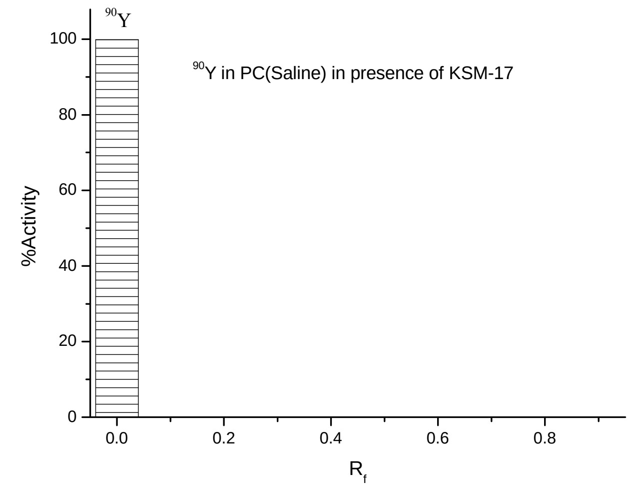
Extraction Paper Chromatography (EPC)

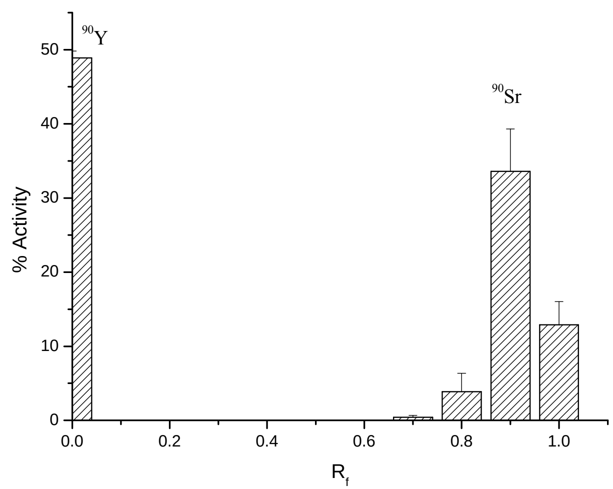
U. Pandey, P.S. Dhami, P. Jagasia, M.Venkatesh, M.R.A. Pillai
EPC technique for the radionuclidic purity estimation of ^{90}Y.
Anal. Chem. 80 (2008) 801-807.

- A simple technique, adaptable in a hospital radiopharmacy set up.
- KSM-17, a established chelate for ^{90}Y, is placed at the point of application (Rf 0) on a PC strip and allowed to absorb & dry
- The test sample is applied to the chelate impregnated portion at Rf 0 of the chromatography paper
- The paper is developed in saline, dried and cut into 3 pieces (bottom, mid and top regions)
- ^{90}Sr which moves to the solvent front is estimated by placing the top region (Rf 1) in cocktail and counting by LSC for 60 minutes.

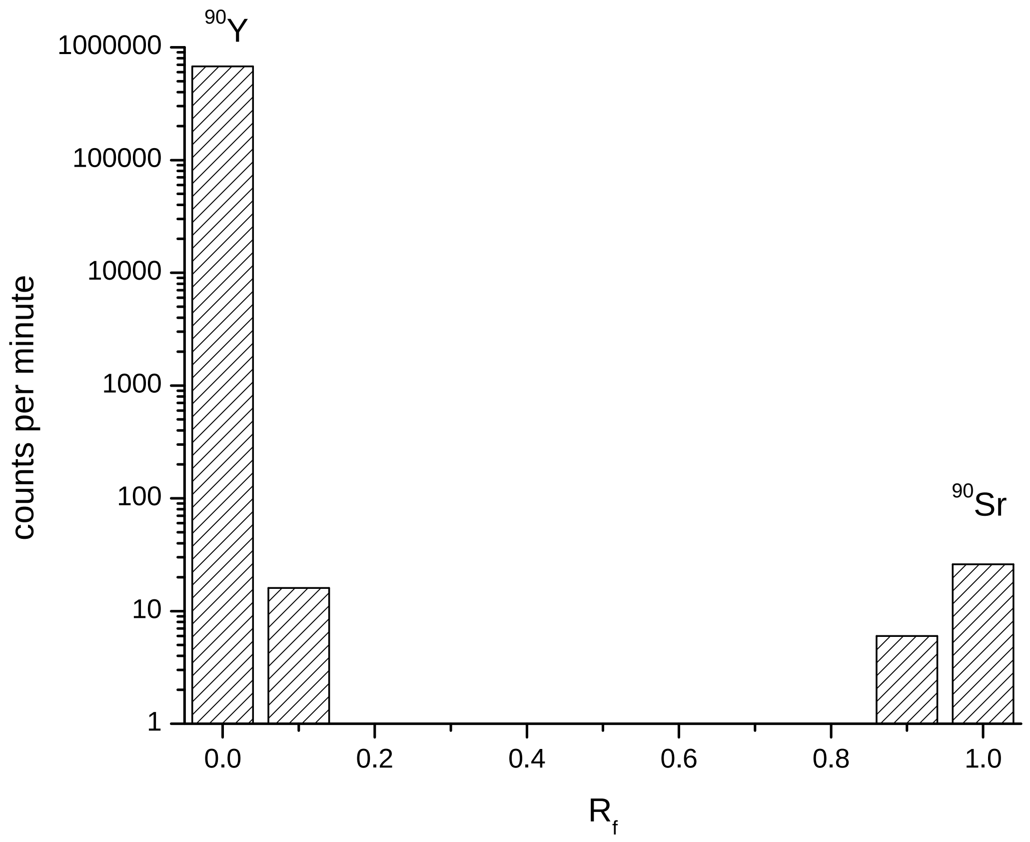
A Glimpse at the Efficiency of EPC in Separating ^{90}Sr from ^{90}Y

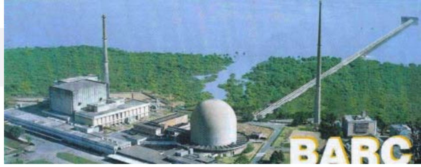






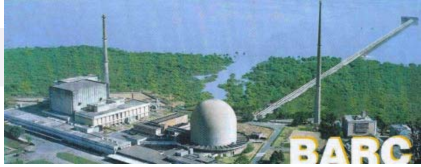
Typical EPC pattern of ^{90}Y sample eluted from a generator





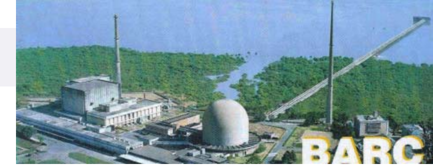
In Conclusion

- ^{90}Y holds great promise as an important therapeutic radionuclide, owing to it’s excellent attributes. This is evident from the large number of useful ^{90}Y based therapeutic radiopharmaceuticals that are already under use or under various stages of clinical trials/ demonstration/development.
- The possibility of real time QC analyses with adequate sensitivity, that can be performed at a hospital radiopharmacy set up, is expected to be a major factor in wider acceptability of ^{90}Y based radiopharmaceuticals from the regulatory angle.



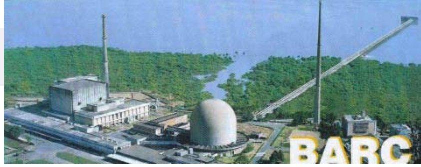
Conclusion Continued ..

- ^{90}Sr/^{90}Y generator is a viable feasible option to avail ^{90}Y in quantities and quality, desirable for regular wide spread use in therapy
- Several generator concepts have been shown to be useful, among which the most suited are emerging as automated modules that could be set up at a hospital radiopharmacy.



Conclusion Continued ..

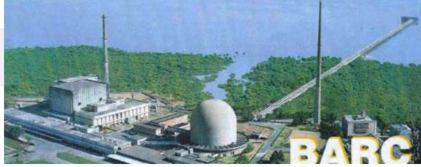
- However, there is an important concern which should be given proper attention. Using ^{90}Sr in large quantities is indeed a big challenge, as the tolerance for maximum body burden of ^{90}Sr is indeed very low. The possibilities of misuse/mischievous use of ^{90}Sr makes it necessary to have controlled access to and proper end disposal of ^{90}Sr and perhaps this makes it suitable for a central protected radiopharmacy rather than hospital radiopharmacy.



Work related to $^{90}Sr/^{90}Y$ generators carried out at BARC

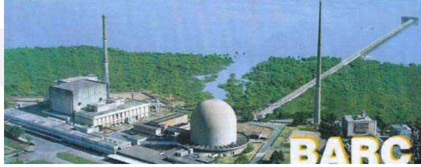
- Work on $^{90}Sr/^{90}Y$ generators started nearly 8 years ago at BARC, as a collaborative effort between us in the Radiopharmaceutical arena with Spent Fuel Reprocessing Scientists, to avail ^{90}Y via ^{90}Sr from ILW.

- The IAEA CRP on "Therapeutic Radionuclide Generators" from 2004-2007 happened at an opportune time. We had the good fortune of participating in this CRP and it's sequel on "Development of radiopharmaceuticals based on ^{188}Re and ^{90}Y for radionuclide therapy " that is on-going now.



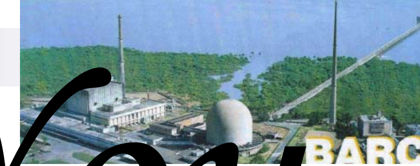
IAEA's Vital Role

- These co-ordinated projects have been highly impactive and have enabled us to pursue this program with great zeal, resulting in very satisfying outcome for us as the participating lab - both in terms of demonstration of ^{90}Y as a viable therapeutic nuclide as well as in contributing to the success of the project as a reciprocation of the invaluable support from the IAEA .



IAEA’s Vital Role

- Similar situation of synergistic working between the participating lab and the IAEA yielding heartening results, is perhaps true to many other nations, for which **we are all very grateful to the IAEA**.
- In particular, the co-ordination among countries and enthusing the commercial manufacturer to develop automated system is a commendable achievement.
- It would be most gratifying if these co-ordinated work would lead to quicker regulatory approvals and deployment of ^{90}Y based radiopharmaceuticals for regular use!



Thank You