A MYRIAD OF NEW OPPORTUNITIES IN RADIONUCLIDE THERAPY

FROM RADIOACTIVE ELEMENTS TO NANOPARTICLES

John L. Humm Ph.D.
Attending Physicist
Depts. of Medical Physics and Radiology
Memorial Sloan Kettering Cancer Center

Session TH-AB-206-0
Thursday August 4th
7:30 AM - 9:30 AM Room: 206

Contents

- 1. Radioactive Elements
  - Radioiodine management of thyroid cancer (127 Daltons)
  - Radium-223 in the treatment of castrate resistant prostate cancer metastatic to bone (223 Da)
- 2. Small peptides
  - Peptides in neuroendocrine cancers (1 to 2 kDa)
- 3. Antibodies
  - Intact IgG (160 kDa) and multi-step targeting
- 4. Nanoparticles
  - ^{124}I-cRGDY–PEG–C dot particles (50kDa - MDa)

Part 1 – Radioactive Elements

The oldest targeted radionuclide therapy

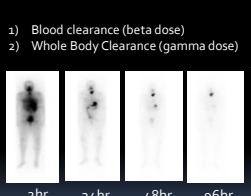
In 1943, Dr Samuel Seidlin (Montefiore) administered the 1st radioiodine therapy to a patient with metastatic thyroid cancer.

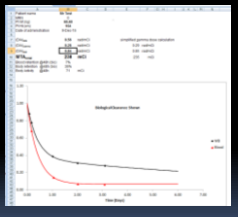
Seidlin recognized early that some thyroid metastases would take up radioiodine , but only after the normal thyroid gland was ablated, an essential preliminary procedure before radioiodine therapy should be administered.

The maximum tolerated activity (MTA)

Bone marrow is the dose limiting for many radionuclide therapies

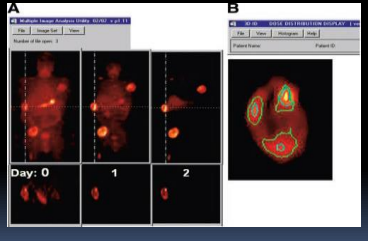
1) Blood clearance (beta dose)
2) Whole Body Clearance (gamma dose)





Benua RS et al, The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. **American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine,** 87:171–182. 1962
Furhang EE, Larson SM, Buranapong P, and Humm JL, Thyroid dosimetry using clearance fitting. J.Nucl.Med.40: 131-136, 1999.

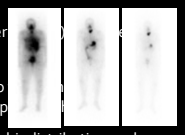
The use of ^{124}I PET for thyroid lesion dosimetry

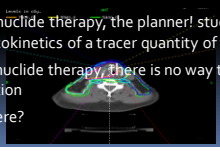


Sgouros et al, Patient-Specific Dosimetry for 131I Thyroid Cancer Therapy Using 124I PET and 3D –Internal Dosimetry (3D–ID) Software, J Nucl Med 2004; 45:1366–1372

Difference between external beam radiotherapy and radionuclide therapy

- In XRT the treatment planner use a CT (and other) volume defined by the radiation oncologist.
- In XRT there are normal tissue constraints and so jostle with the beam directions and weights to op
- In radionuclide therapy, the planner! studies the biodistribution and pharmacokinetics of a tracer quantity of the intended therapeutic.
- In radionuclide therapy, there is no way to modulate the radionuclide distribution
- Or is there?



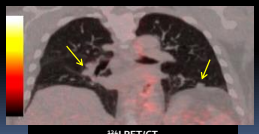


Restoring Radioiodine Uptake in Thyroid Cancer: A Paradigm Shift

New drugs are under development, such as selumetinib.

Selumetinib is a MAP kinase inhibitor that downregulates MEK enzymes.

Drugs that block this signaling pathway may restore the NaI symporter expression, and thus reverse the refractoriness to radioiodine in patients with metastatic thyroid cancer.



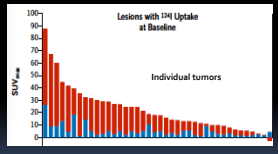
^{124}I PET/CT
Baseline

^{124}I PET/CT
After Selumetinib

MEK inhibition restores radioactive iodine uptake

- MEK inhibition restores iodine uptake
- Selumetinib increased ^{124}I uptake in 12/20 pts (4/9 *RAF*, 5/5 *NRAS* mutant)

NRAS-mutant, poorly differentiated thyroid ca

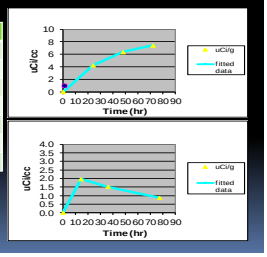


Ho AL, et al , Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med. 2013 Feb 14;368(7):623-32

The use of ^{124}I PET to characterize the changes in individual lesions

	Thyroid lesions
n	83 lesions (16 patients)
# organification	44
Lesions clearance	39
Average Clearance Tau	85.3 hr of the 39 lesions
Min	4.95 hr
Max	infinite

Test the hypothesis - is the biological half-life in re-differentiated lesions the same as baseline iodine avid lesions?



1 R01 CA201250-01 "^{124}I-NaI PET: Building block for precision medicine in metastatic thyroid cancer"


John Humm


Steve Larson (Contact PI)


Mike Tuttle


James Fagin

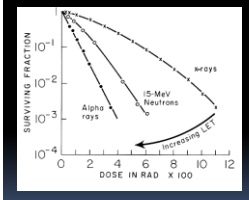

Alan Ho


Ravi Grewal

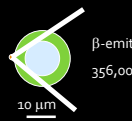

Keith Pentlow

Iodine-131 is a β-emitter. Should we consider α-emitters?

Why the interest in α-emitters?



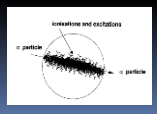
α-emitters
300 decays

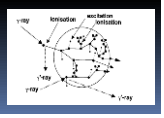


β-emitters
356,000 decays

10 μm

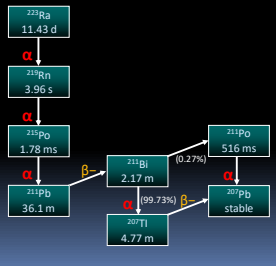
20 μm





Radium-223 (Xofigo) was a recently approved for the treatment of refractory prostate cancer, metastatic to bone

- Radium-223 is an alpha-emitter
- $t_{1/2}$ = 11.43 days
- Of the total decay energy
  - 93.5% emitted as 4 α particles
  - < 4% emitted as β particles
  - < 2% emitted as γ or X-rays



Henriksen G, et al. *Cancer Res.* 2002;62:3120–3125.

Suspected Organ Toxicities from Radium-223 therapy

- Bone Marrow
- Kidney (a consequence of the Ra-223 daughters, in particular bismuth)
- G.I. tract

The Ra-223 Spectrum

α	α	α	β	α	
Ra-223 →	Rn-219 →	Po-215 →	Pb	Bi-211 →	Pb-207
11.4 days	4 s	1.8 ms	36m *	2.2 m	

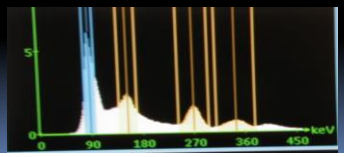
84 keV X-rays ~41%
154 keV (9%),
269 keV (14%)

271 keV
10%

Nothing imageable

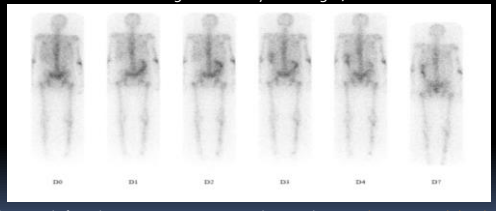
351 keV + higher
13%

5 energy windows used:
84 keV, 154, 269, 351 and 403 keV



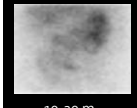
Serial WB Images from Royal Marsden

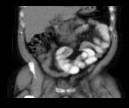
Posterior Images from Day 0 through 7

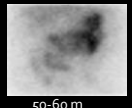


Chittenden SJ, Hindorf C, Parker CC, Lewington VJ, Pratt BE, Johnson B, Flux GD., A Phase 1, Open-Label Study of the Biodistribution, Pharmacokinetics, and Dosimetry of 223Ra-Dichloride in Patients with Hormone-Refractory Prostate Cancer and Skeletal Metastases. J Nucl Med. 2015 Sep;56(9):1304-9.

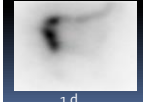
Detailed spot views to show G.I, kidney, lumbar vertebra and pelvis


10-20 m

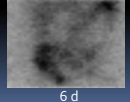


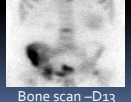

50-60 m


232 min post


1 d

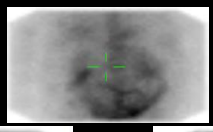

2 d


6 d


Bone scan –D13

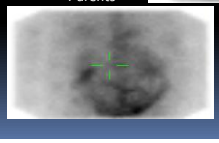
Where do the final daughters go?

Day o Pre-void

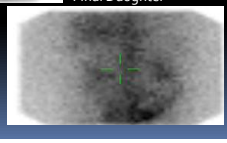


All Counts

Parents

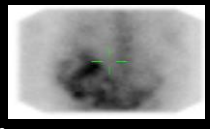


Final Daughter



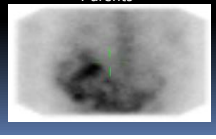
Parent and Daughter Sequence

Day o Post-void

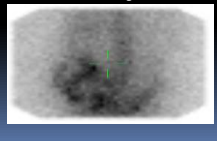


All Counts

Parents



Final Daughter



Radium Activity dominated by gut activity

Day 1

Ant Post

Parent

Daughter

Radium seems to be in the gut contents.
The intestinal crypt cells are beyond the range of the α – particles.

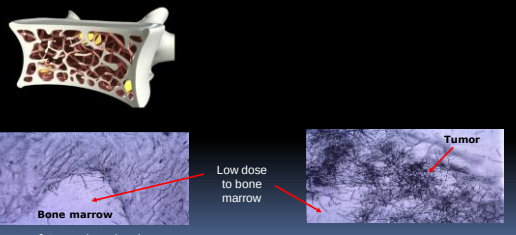
We do not see Pb or Bi daughters leaving gut contents and re-locating in kidney.

What about the ^{223}Ra dose to Bone Marrow?

- Less than 1% of 292 patients treated in phase I & II trials receiving between 50 and 250 kBq/kg of ^{223}Ra had grade 4 hematological toxicity; 2%-4% had grade 3 toxicity. *
- Yet individual red marrow absorbed doses based on standard MIRD estimates were often above 3 Gy.

* Cheetham & Petrylak, Alpha Particles as Radiopharmaceuticals in the Treatment of Bone Metastases: Mechanism of Action of Radium-223 Chloride (Alpharadin) and Radiation, ONCOLOGY. Vol. 26 No. 4, 2012.

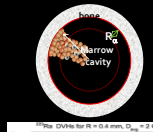
Autoradiograph of ^{223}Ra in dog

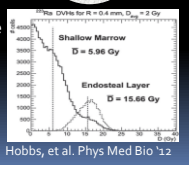


Courtesy of Oyvind Bruland

What can we say about tumor dose?

- Unable to determine tumor doses by gamma camera imaging.
- Estimates need to rely on accurate bone modeling and microdosimetric calculation.
- Tumor cells close to the bone surface receive significant doses of α-radiation.
- But marrow stem cells located deeper in the marrow are out of range of the α-particles





Hobbs, et al. Phys Med Bio '12

Dose Rates to the Public from Xofigo

The administered activities in Xofigo therapies are extremely low (50 kBq or 1.35 µCi per kilogram body weight).

Therefore the exposure rates to staff and the public resulting from patients undergoing this therapy are very small.

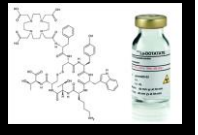
Contrast this to the 90 µSv/hr (contact) after a ^{99m}Tc bone scan

Time after administration		~0 h		~24 h		T~48 h		T~1 week	
	Activity	Contact	1 m	Contact	1 m	Contact	1 m	Contact	1 m
Mean	50kBq	1.03	0.17	1.8	0.4	2.1	0.1	0.16	0.02

Dauer et al, Health Phys., 106, 494, 2014

Part 2 - Peptide Theranostics

Peptide Receptor Radionuclide Therapy (PRRT)



- There is been a recent explosion of interest is small molecule targeted therapies.
- Radiolabeled somatostatin receptor (sst) agonists, e.g. ^{177}Lu-DOTATATE, have become an integral part of therapeutic management in patients with neuro-endocrine tumors .
- These are ideal theranostic agents, where the molecule can be labeled with ^{68}Ga for diagnosis and ^{177}Lu for dosimetry and therapy.
- Radiolabeled sst antagonists are not established for tumor targeting, because they do not internalize into tumor cells.

^{68}Ga-JR11 Peptide for PET imaging Evaluating a new theranostic

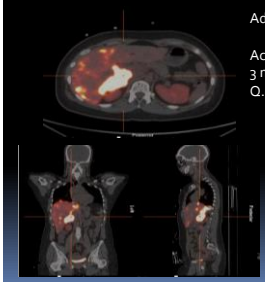
Wolfgang Weber

What does it take to establish a new theranostic peptide?

Joe O'Donoghue

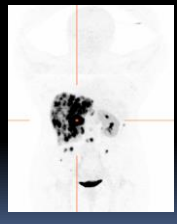
Wild D, Fani M, Fischer R, Del Pozzo L, Kaul F, Krebs S, Fischer R, Rivier JE, Reubi JC, Maecke HR, Weber WA.
Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: a pilot study. J Nucl Med. 2014 Aug;55(8):1248-52.

^{68}Ga-DOTA-JR11: Example #1



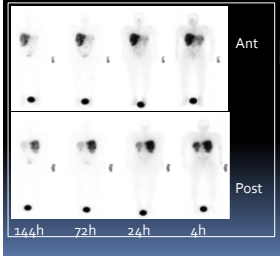
Administered Activity: 4.4 mCi (163MBq)

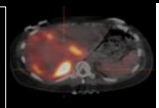
Acquired 60 min pi
3 min per bed
Q.clear recon (350)

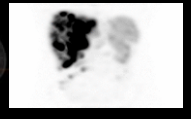


^{177}Lu-DOTA-JR11: Example #1

Dosimetry Administration: 49 mCi





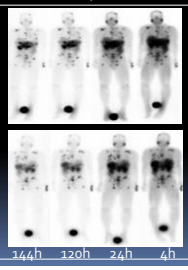


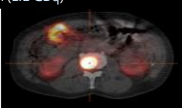
Projections for Therapy:

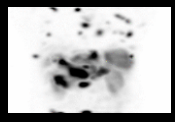
Activity limits: 789 mCi (RM); 861 mCi (Kidney)
29 GBq 32GBq
Index Lesion: 22 cGy/mCi
Lesion dose @ 200 mCi: 44 Gy
Lesion dose @ 789 mCi: 174 Gy

^{177}Lu-DOTA-JR11: Example #2

Dosimetry Administration: 33 mCi (1.2 GBq)







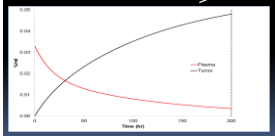
Projections for Therapy:

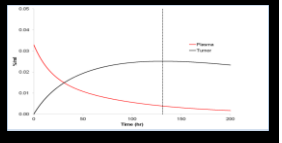
Activity limits: 618 mCi (RM); 522 mCi (Kidney)
22.9 GBq 19.3GBq
Index Lesion: 15 cGy/mCi
Lesion dose @ 200 mCi: 30 Gy
Lesion dose @ 522 mCi: 78 Gy

Part 3 - Antibody Theranostics

Antibody Imaging Pharmacokinetics

Radionuclide $T_{1/2}$ = 8 days
Tmax = 0.083 at T = 96 hr; T/P = 6.5



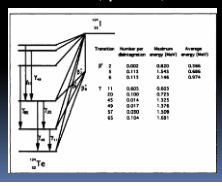


Effect of radionuclide half-life on:
Maximum tumor activity (Tmax)
Time for Tmax
T/P ratio at Tmax

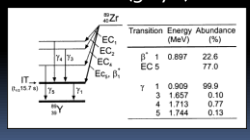
Long-lived positron-emitting radionuclides for ImmunoPET

- Required for imaging to suit the antibody kinetics

^{124}I (4.12 d)



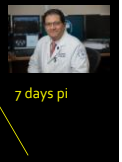
^{89}Zr (3.27d)



ImmunoPET: Timecourse

CRPC: ^{89}Zr-anti-STEAP antibody: 185 MBq (5mCi)

- Soon after injection all antibody is in the circulation - uninformative
- Slow clearance from circulation - metabolism/excretion and slow take up in target tissues – mostly uninformative
- Circulation continues to clear, ongoing take up in target tissues – informative but suboptimal
- Circulation almost clear - antibody distribution reaches "final" state – maximally informative



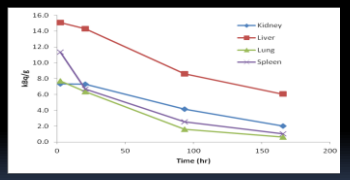
7 days pi

Dosimetry of ^{89}Zr-labeled antibodies

- Whole body counting
- Blood/serum pharmacokinetics
- ROI analysis of serial PET/CT scans

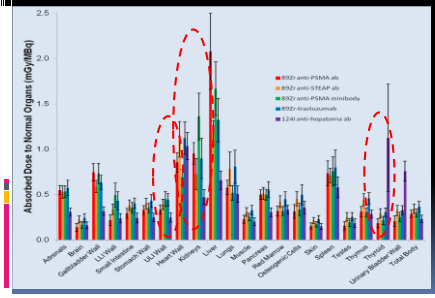
PET ROI Analysis

- Regions drawn on organs of interest
- Integrate to get AUC
- Multiply by organ mass
- Residence time for organ = AUC_{ORG}/A_0



Pandit-Taskar N, O'Donoghue JA et al, ^{89}Zr-huJ591 immuno-PET imaging in patients with advanced metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2014 Nov;41(11):2093-105.

Differential ImmunoPET Dosimetry



Greatest variation in liver & kidney dose

Minibody dose comparable to ab except reduced heart wall dose

^{124}I-ab dose generally lower than ^{89}Zr-ab except thyroid & UB

Consequences for radiolabeled antibodies

- For solid tumors, even in the highest antigen density expressing tumors (CA-IX in renal cell carcinoma), radioimmunotherapy failed.
- So does it work or where might it work?
- We have seen such successive in radiosensitive tumors e.g. B-cell lymphoma (Bexxar and Zevalin)

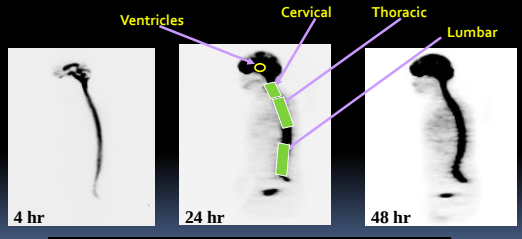
How can we break out of this impasse?

- Intra-compartmental
- Multi-step targeting

Intrathecal antibody therapy for leptomeningeal Disease: Dosimetry using ^{124}I-labeled Ab

Kim Kramer

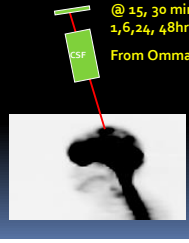
Serial whole body ^{124}I labeled Ab PET scans



Perform ROI analysis on each of the 3 time point images

Dosimetry for CSF (& blood) from direct samples

- Serial samples are aliquoted into scintillation vials
- Counted in a well counter alongside a standard
- The data is fitted to a dual exponential function.



@ 15, 30 min & 1,6,24, 48hr

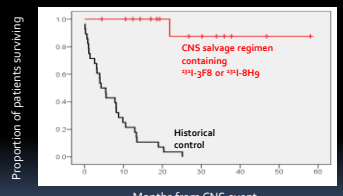
From Ommaya

Projected dosimetry to the CSF from ^{131}I-8H9 (n = 44)

Dose	Samples	4th Ventricle	Cervical CSF	Thoracic CSF	Lumbar CSF
cGy/MBq	2.27	0.54	0.45	0.54	0.57

Approx 1,000 cGy per 50 mCi treatment based on PET VOI analysis
Dose to blood is 2 cGy/mCi or 100cGy per therapy (therapeutic index 10:1)
Each patient may receive up to 4 therapy treatments

Recurrent neuroblastoma metastatic to the CNS



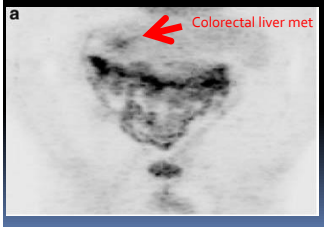
Kramer et al, J. Neurooncology, 2010;97(3):409-18. **Compartmental intrathecal radioimmunotherapy: results for treatment for metastatic CNS neuroblastoma.**

Multi-Step Targeting

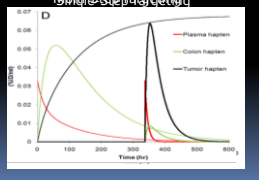
Bi-specific antibody approach

Graphic – Sarah Cheal, MSKCC

Modeling multi-step targeting with A33 antibody in humans



Red – Blood
Green – Normal Colon
Black - Tumor



Part 4 – Nanoparticle Theranostics

Nanoparticles

Wiki definition
Nanoparticles are particles between 1 and 100 nanometers in size. In nanotechnology, a particle is defined as a small object that behaves as a whole unit with respect to its transport and properties.

- Intra-hepatic arterial administration of microspheres (glass or resin) for radioembolization of liver lesions (classified as medical devices)
- Targeted delivery by surface functionalization (cRGDY-peptides binding to integrins)
- Add all sorts of imaging capabilities to the nanoparticle (^{124}I, Cy5, Fe)
- Incorporate all sorts of weapons in the nanoparticle e.g. water-insoluble drugs like paclitaxel, radionuclides etc.

Biologic Principle of Cancer Nanomedicine: Enhanced Permeability and Retention (EPR)

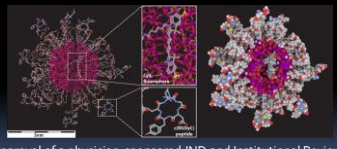
Chow et al. Science translational medicine . 2013

^{124}I-cRGDY-PEG-C dots

C-Dots (Cornell dots) are functional core-shell silica particles , that may be grown from nano to micron sized particles and covalently linked to dyes to create high fluorescent particles.

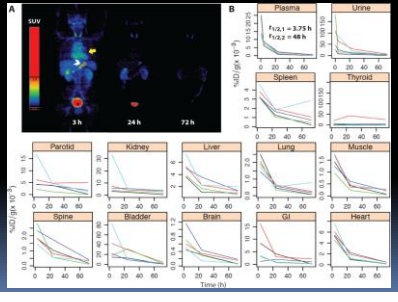
Uli Weisner

Michelle Bradbury



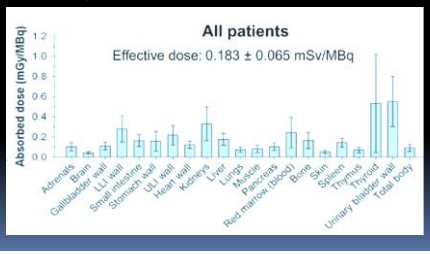
After FDA approval of a physician-sponsored IND and Institutional Review Board (IRB) approval, a microdosing study was initiated using the 6 nm sized particles (to favor renal excretion) targeting $\alpha_v\beta_3$ integrins in *5 human subjects with metastatic melanoma.*

Biodistibution of hybrid ^{124}I-cRGDY-PEG-C dots



Phillips E, et al , **Clinical translation of an ultrasmall inorganic optical-PET imaging nanoparticle probe.** Sci Transl Med. 2014 Oct 29;6(260):260

Dosimetry for ^{124}I-cRGDY-PEG-C from 5 patients



Summary

- The management of patients with poorly differentiated metastatic thyroid cancer is undergoing a revolution due to the emergence of new targeted drugs that cause thyroid re-differentiation.
- The use of peptide therapies as theranostic agents and truly a remarkable success story in radionuclide therapies that will continue to grow and improve.
- Early hiccups in the field of radioimmunotherapy could have heralded the end of an era. However, new radiolabeled antibody theranostic agents are emerging that combine immunoPET (^{89}Zr, ^{124}I) with therapy isotopes
- The poor AUCs tumor/blood ratios (only 5 to 1 for macromolecular targeting agents) may be improved by intra-compartmental administration and multi-step targeting.
- Nanoparticle strategies are evolving that offer full multiplexing of imaging with therapeutic approaches.
- This is a new era of personalized medicine where the quantitative capability of nuclear medicine may provide immense insights.