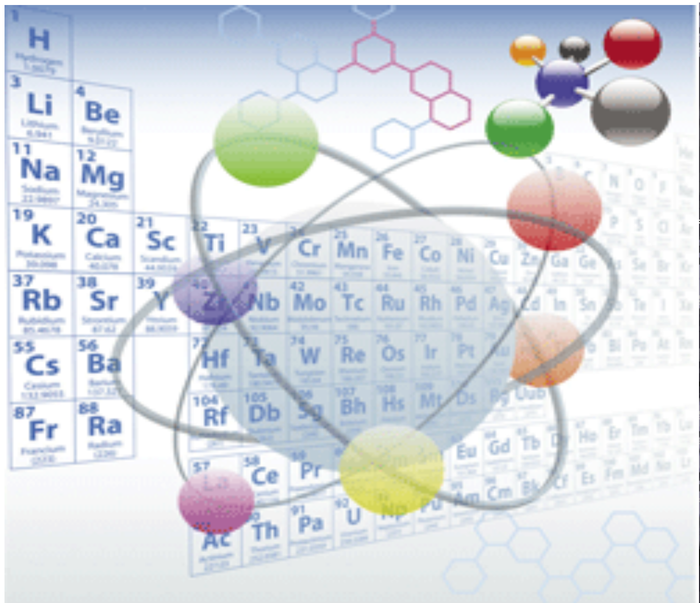
MOLECULAR TARGETING WITH RADIOISOTOPES: APPLICATION OF LASER-DRIVEN ISOTOPIC PRODUCTION

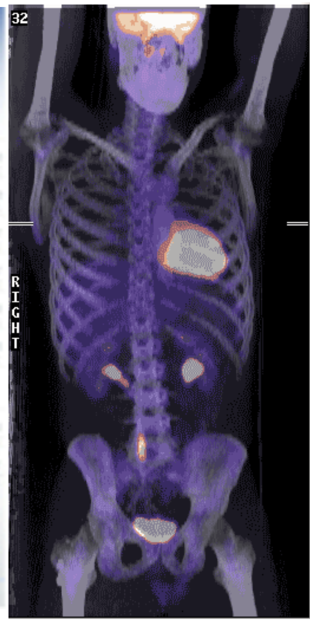
Dana Niculae, PhD

Horia Hulubei National Institute for Physics and Nuclear Engineering, IFIN-HH, Romania

overview

- (Some) statistics about use of radioisotopes in nuclear medicine
- What are the needs of modern medicine?
- Examples of the use of medical radioisotopes
- Emerging radioisotopes and production routes
- Estimates of the production of radioisotopes at ELI-NP

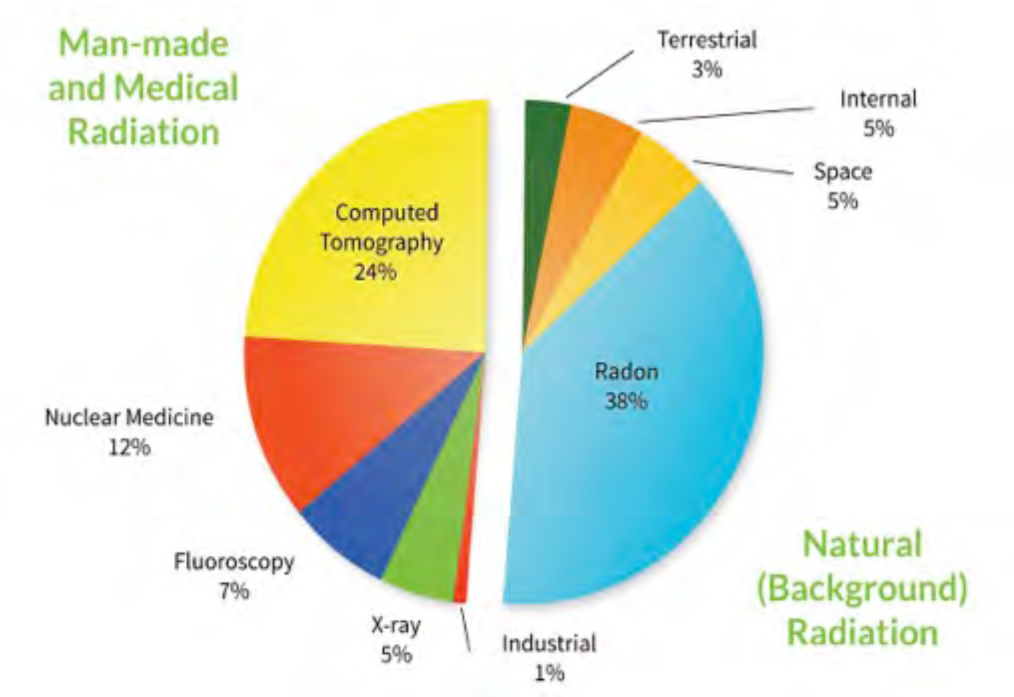




Statistics - radioisotopes in nuclear medicine

- The number of requests by both patients and doctors for state-of-the-art nuclear medical imaging procedures has increased seven fold in the last 25 years
- Computed X-ray tomography (CT) scans and nuclear medicine contribute 36% of the total radiation exposure and 75% of the medical exposure to the US population, average total yearly radiation exposure had increased from 3.6 mSv to 6.2 mSv per year since the early 1980s due to medical-related procedures.

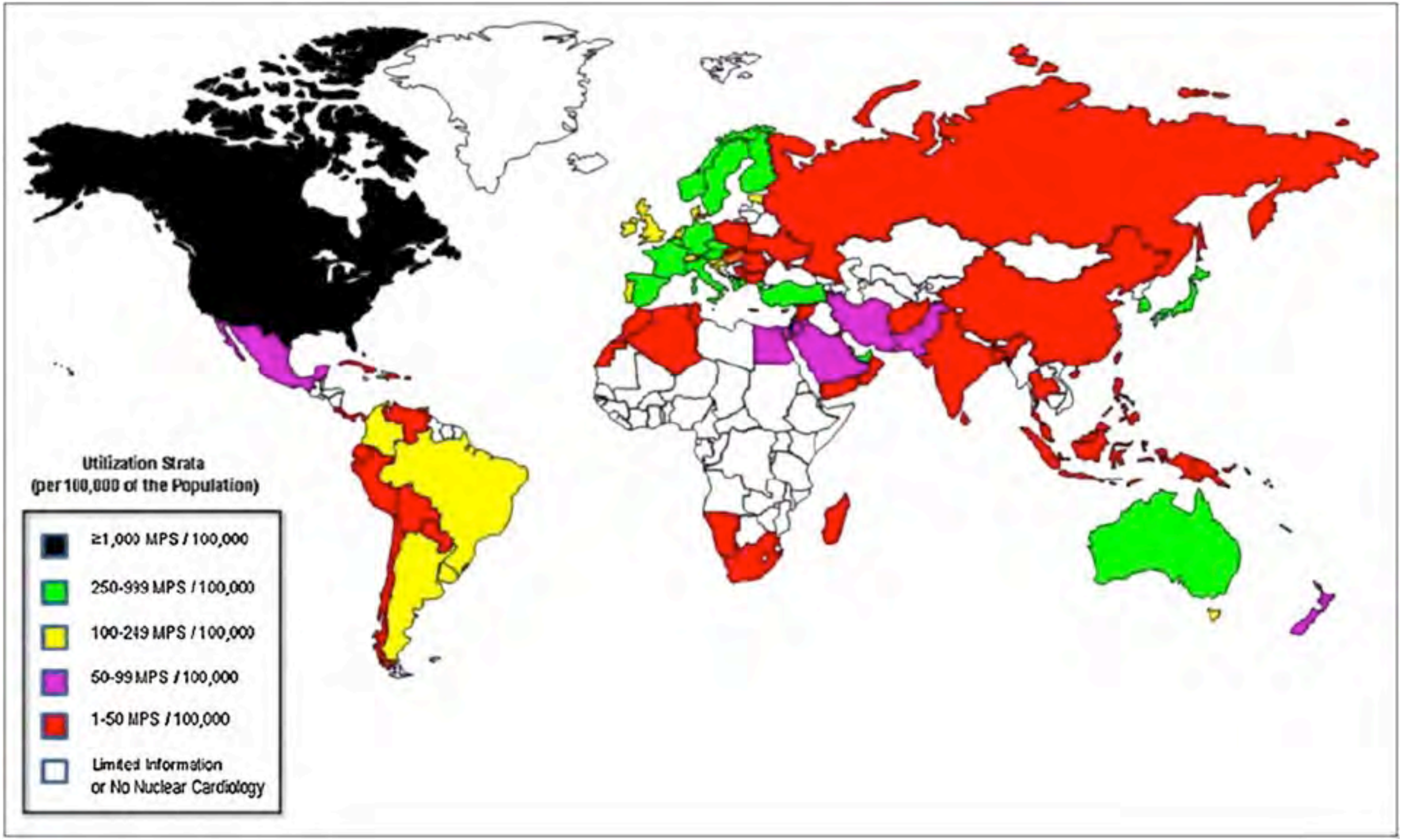
(*Report of the National Council on Radiation Protection and Measurements, 2009*)



Statistics - radioisotopes in nuclear medicine

- Over 10,000 hospitals worldwide use radioisotopes in medicine, and about 90% of the procedures are for diagnosis.
- The most common radioisotope used in diagnosis is Tc-99m, accounting for about 80% of all nuclear medicine procedures
- Over 40 million nuclear medicine procedures are performed each year, and demand for radioisotopes is increasing at up to 5% annually.
- In developed countries (26% of world population) the frequency of diagnostic nuclear medicine is 1.9% per year. In the USA there are over 20 million nuclear medicine procedures per year among 311 million people, and in Europe about 10 million among 500 million people.
- The global radioisotope market was valued at $4.8 billion in 2012, with medical radioisotopes accounting for about 80% of this, and is poised to reach about $8 billion by 2017. North America is the dominant market for diagnostic radioisotopes with close to half of the market share, while Europe accounts for about 20%.

(*World Nuclear Association*, http://www.world-nuclear.org *updated September 2016*)



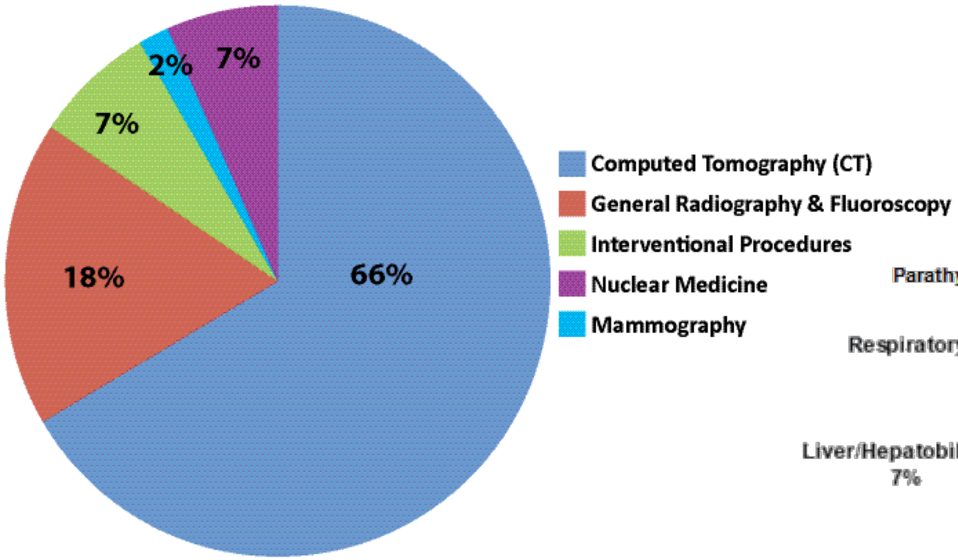
Estimates of worldwide use (per 100,000 people) of nuclear cardiology procedures.

Dominique Delbeke, and George M. Segall J Nucl Med 2011;52:24S-28S

JNM The Journal of NUCLEAR MEDICINE

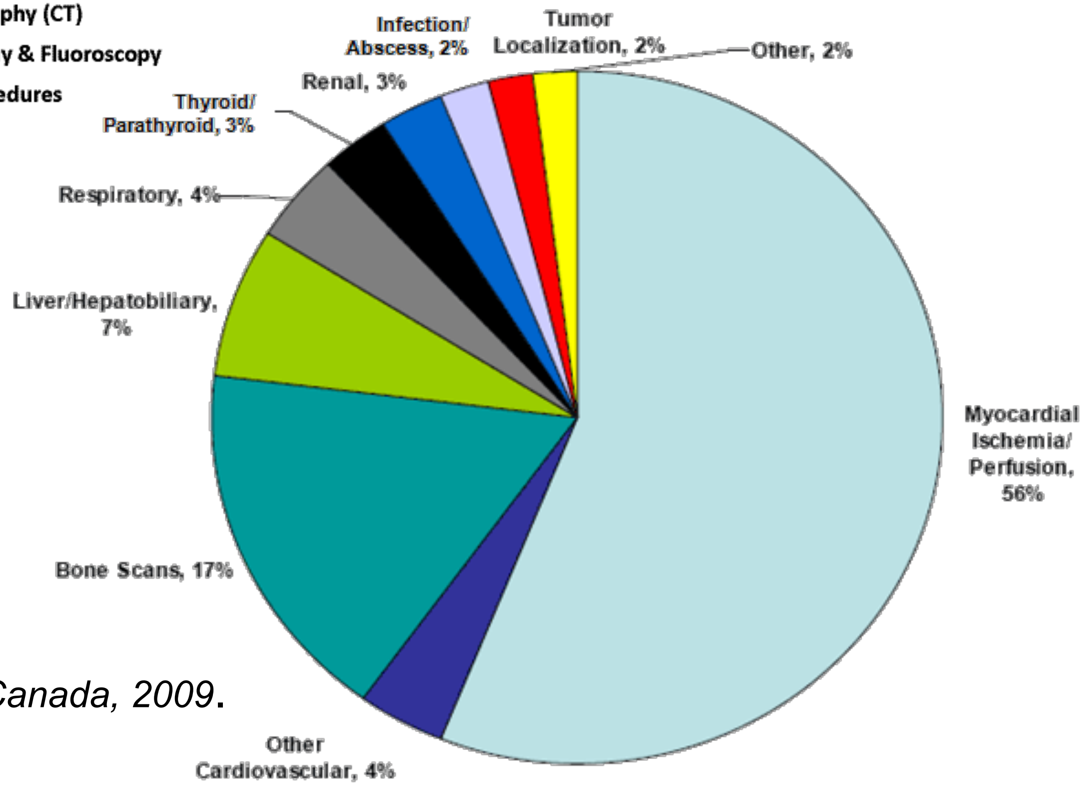
Statistics - radioisotopes in nuclear medicine

Breakdown of diagnostic imaging procedures



Source: http://www.arpansa.gov.au

Composition of Nuclear Medical procedures where Tc-99m is predominant



Source: Natural Resources Canada, 2009.

What are the needs of modern medicine ?

What is the major challenge in medical research?

Cancer

One person in three will have cancer

Heart Disease

50% die after 1st heart attack

Brain Disorders

20% aged 75-84 suffer from Alzheimer's disease

Personalized Medicine

Predictability → Diagnosis → Information → Treatment

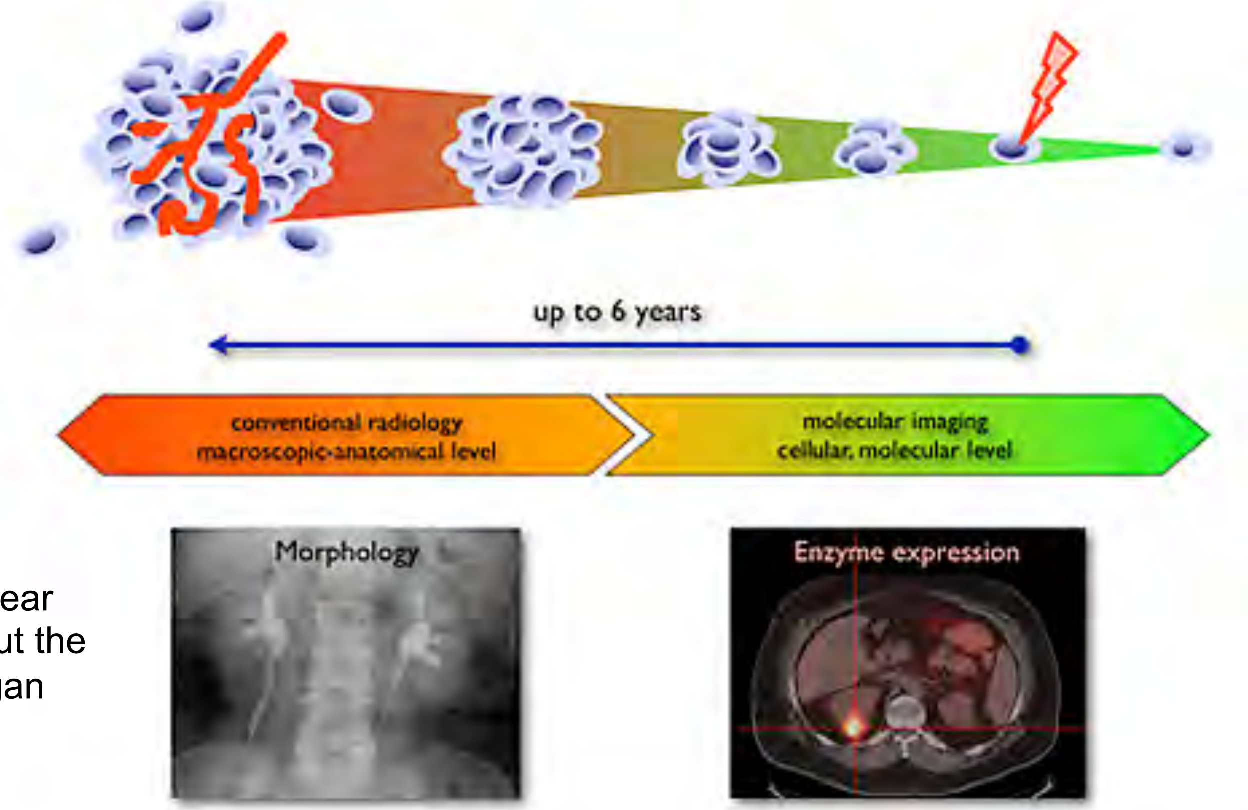
What are the needs of modern nuclear medicine ?

- **Imaging**
  - **Early diagnosis**
  - **Therapy follow-up**

  High quality images

  Low radiation dose

Advances in technology, including hybrid imaging,
Introduction of new radiopharmaceuticals for diagnosis/therapy
Development of molecular imaging based on the tracer principle

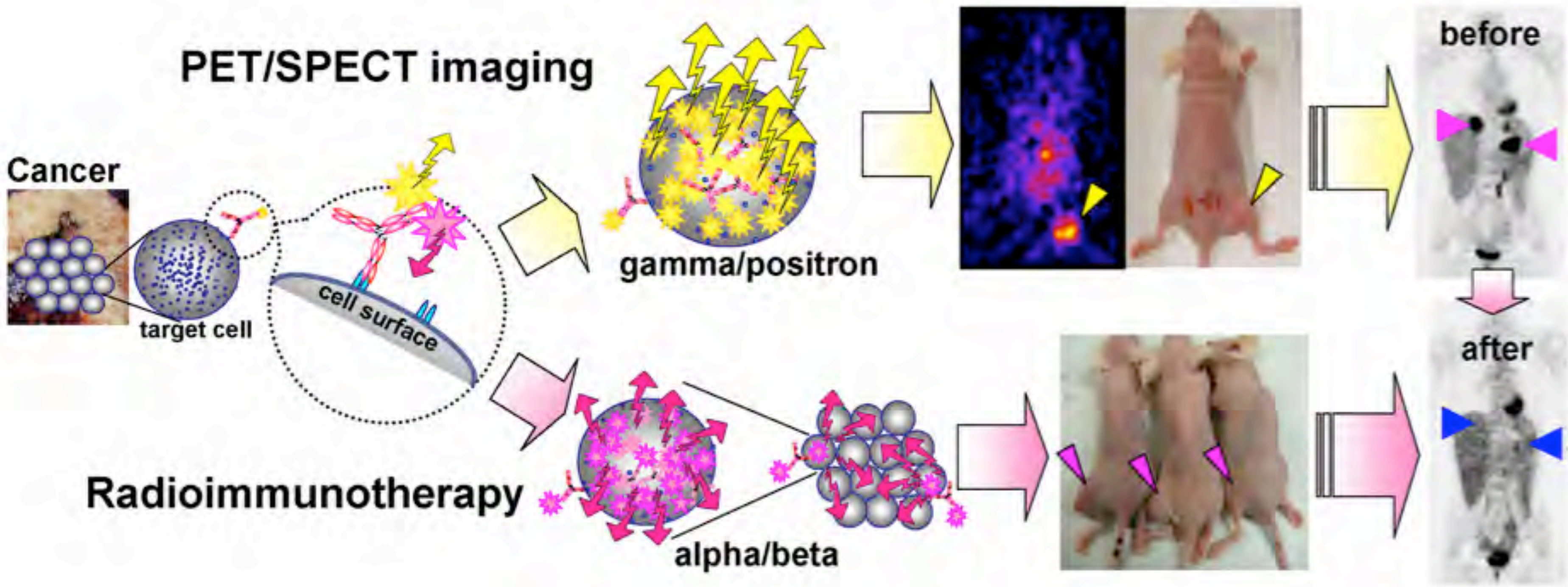


Unlike other tests/procedures, nuclear medicine provides information about the function of virtually every major organ system within the body.

What are the needs of modern nuclear medicine ?

- **Targeted therapy**
  - **Targeting** high specificity
  - **Efficacy** high selectivity
  - **Therapy follow-up**

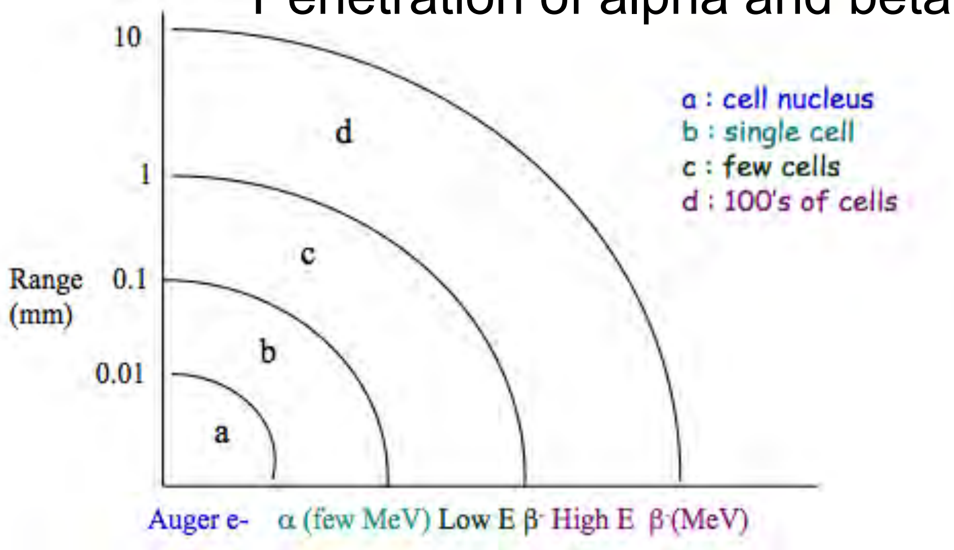
High amount of energy imparted to the target tissue (to destroy cancer cells) relative to critical normal organs and tissues (to prevent radiation damage and side-effects)

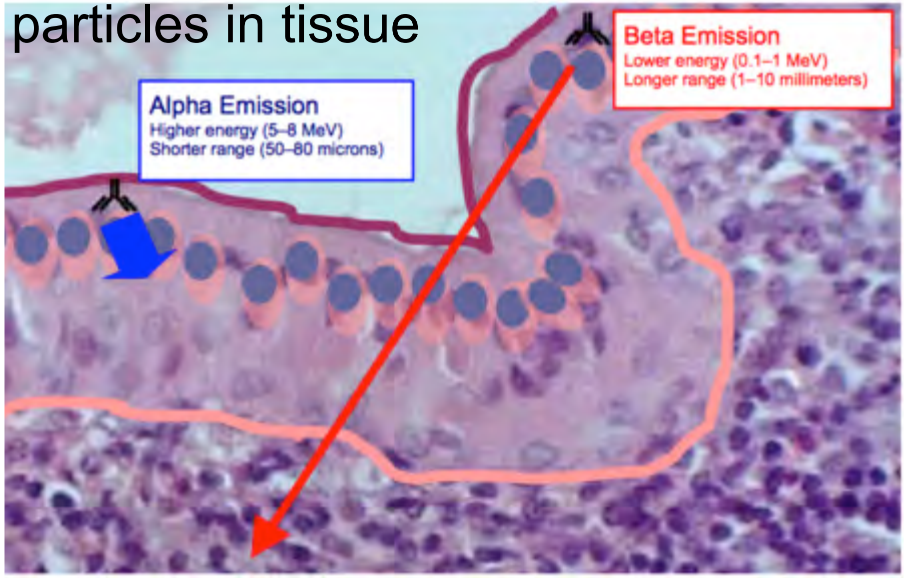


Emerging radioisotopes and (alternative) production routes

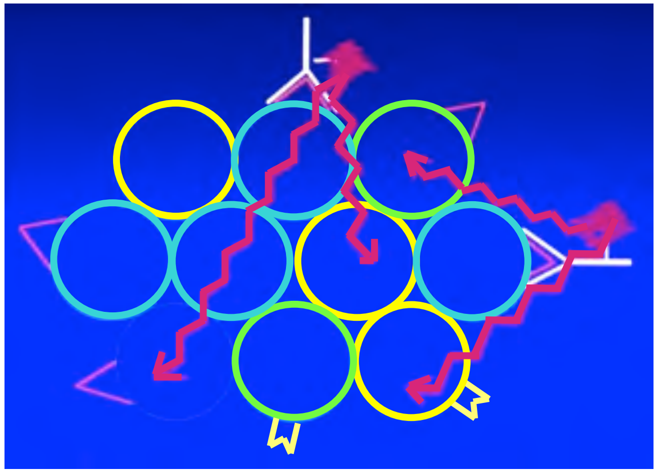
Therapeutical radioisotopes

Penetration of alpha and beta particles in tissue





Advancing Nuclear Medicine Through Innovation
Natl. Academies Press

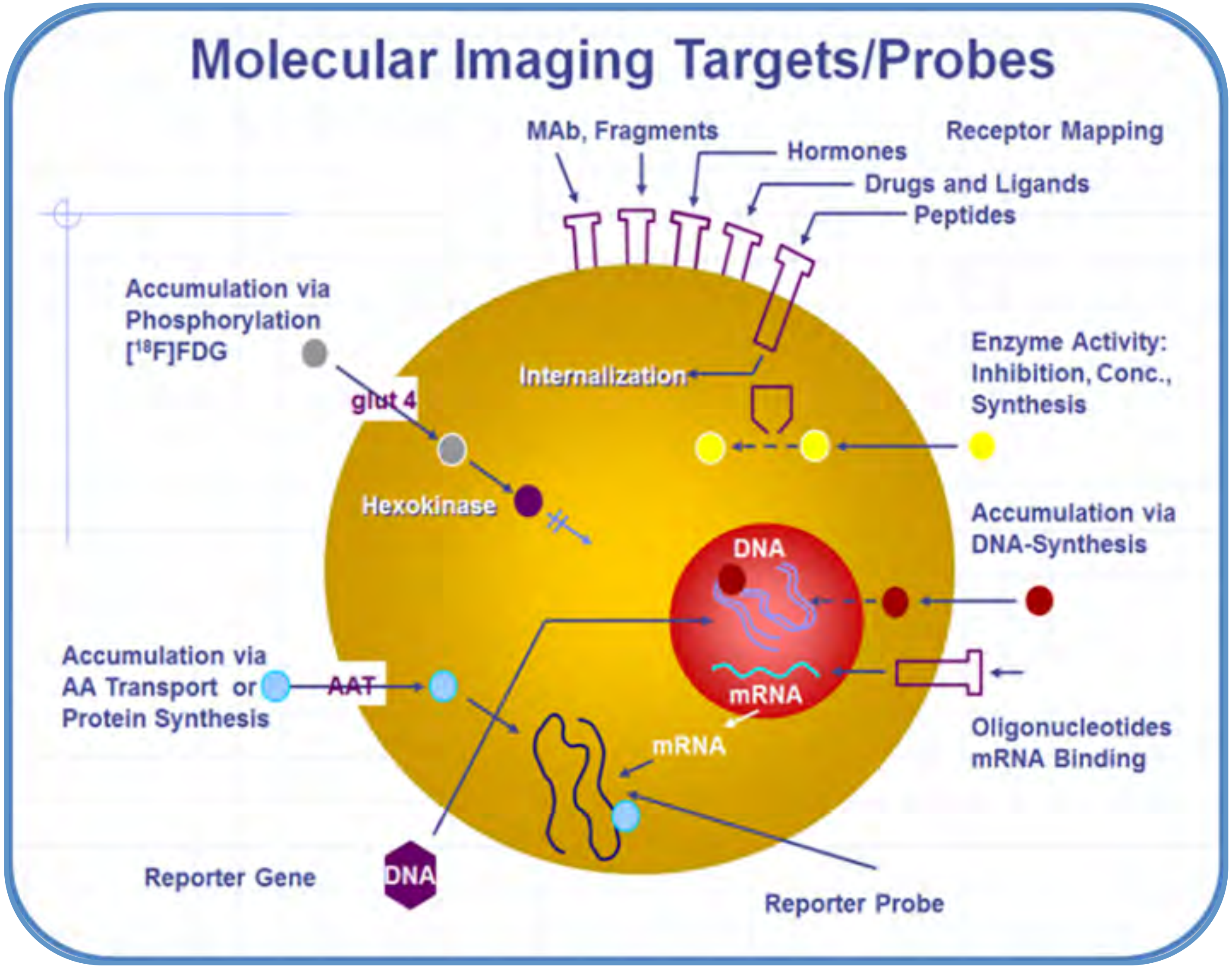


Due to the **crossfire effect** more complex (heterogeneous) tumors may benefit from targeted radionuclide therapy

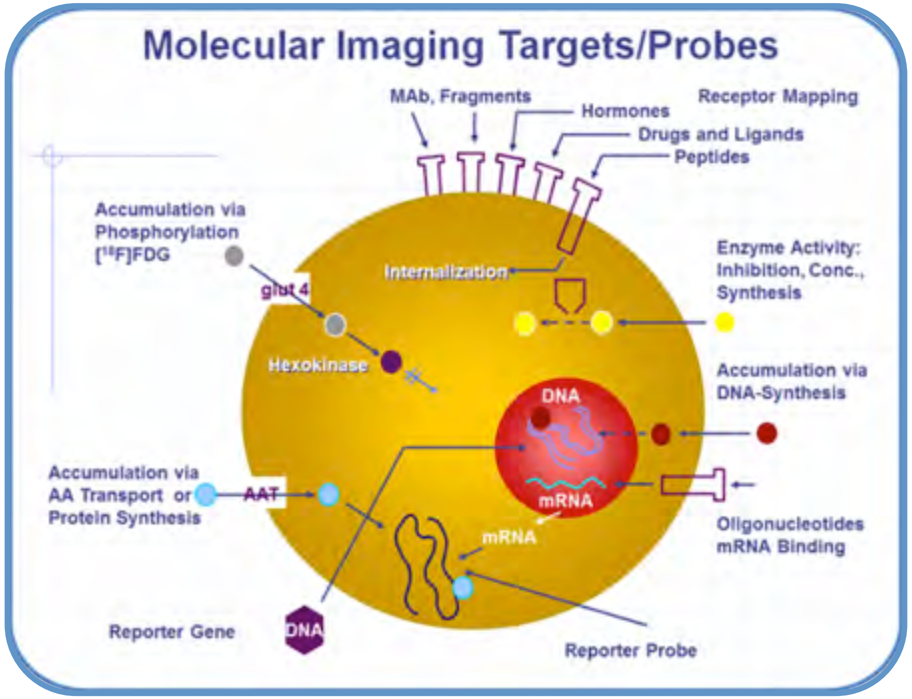
The **bystander effect** in should be investigated as it contribute to the total therapeutic effect

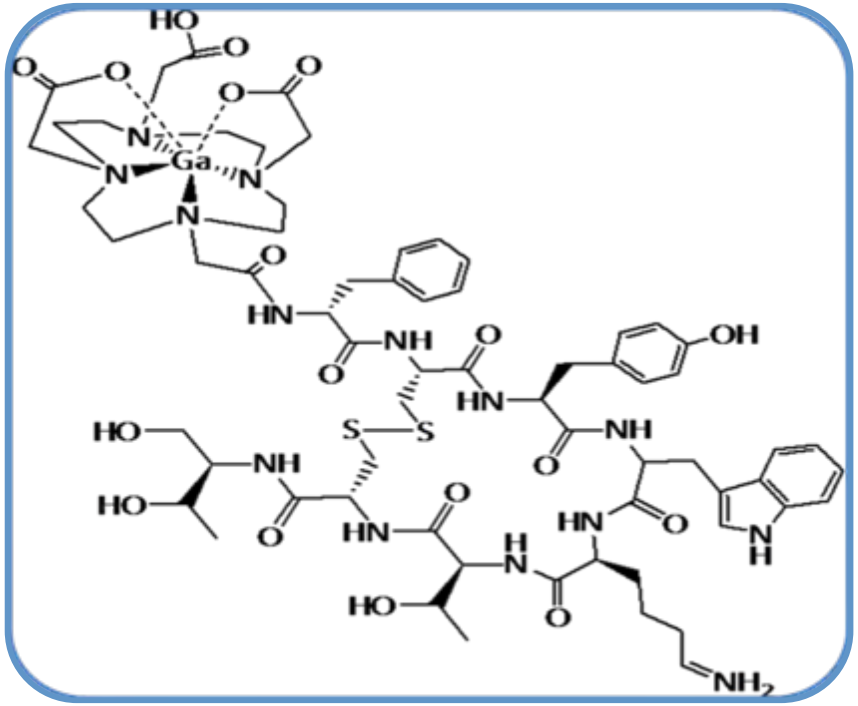
Induced radioresistance and **radiosensitivity**

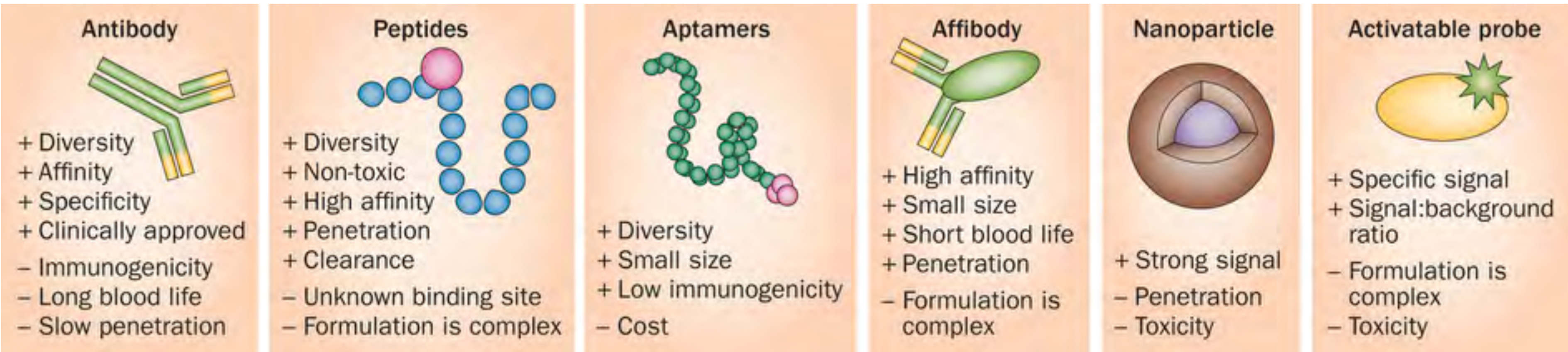
Targeting moieties on cell surface/inside cell



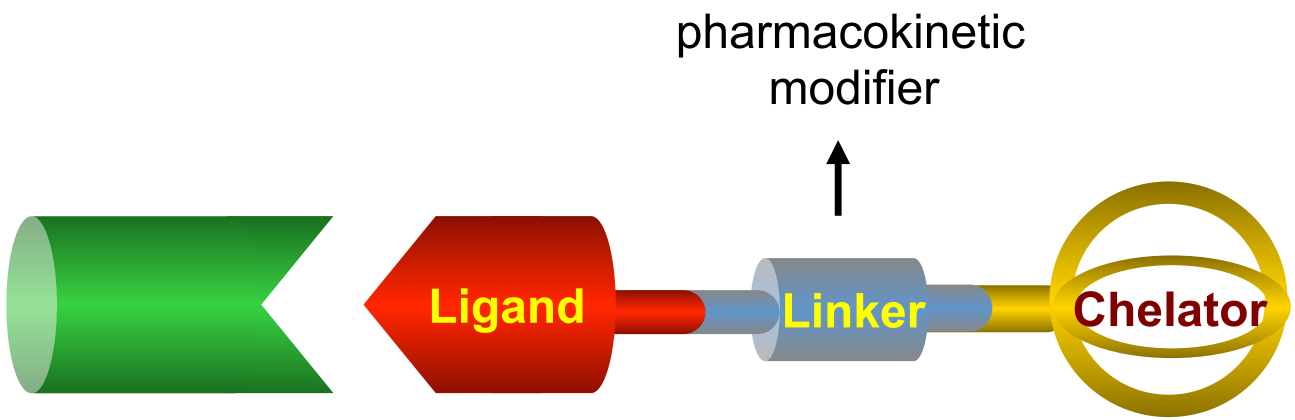
MOLECULAR IMAGING / SYSTEMIC RADIOTHERAPY
RADIOPHARMACEUTICALS







SCHEMATIC REPRESENTATION OF A DRUG FOR IMAGING AND TARGETED THERAPY



Target

- Antigens (CD20, HER2)
- GPCRs
- Transporters

Molecular Address

- Antibodies, their fragments and modifications
- Regulatory peptides and analogs thereof
- Amino Acids

Reporting Unit

- ^{99m}Tc, ^{111}In, ^{67}Ga
- ^{64}Cu, ^{68}Ga
- Gd^{3+}

Cytotoxic Unit

- ^{90}Y, ^{177}Lu, ^{213}Bi
- ^{105}Rh, ^{67}Cu, $^{186,188}Re$

Courtesy prof H. Maecke, Basel

Examples - use of medical radioisotopes

Neurologic Applications:

Stroke
Alzheimer's Disease
Demonstrate Changes in AIDS Dementia
Evaluate Patients for Carotid Surgery Localize
Seizure Foci
Evaluate Post Concussion Syndrome Diagnose
Multi-Infarct Dementia

Ortophedic Applications:

Identify Occult Bone Trauma (Sports Injuries)
Diagnose Osteomyelitis
Evaluate Arthritic Changes and Extent
Localize Sites for Tumor Biopsy
Measure Extent of Certain Tumors
Identify Bone Infarcts in Sickle Cell Disease

Cardiac Applications:

Coronary Artery Disease
Measure Effectiveness of Bypass Surgery Measure Effectiveness of Therapy for Heart Failure
Detect Heart Transplant Rejection
Select Patients for Bypass or Angioplasty
Identify Surgical Patients at High Risk for Heart Attacks
Identify Right Heart Failure
Measure Chemotherapy Cardiac Toxicity
Evaluate Valvular Heart Disease
Identify Shunts and Quantify Them
Diagnose and Localize Acute Heart Attacks before Enzyme Changes

Pulmonary Applications:

Diagnose Pulmonary Emboli
Detect Pulmonary Complications of AIDS Quantify
Lung Ventilation and Perfusion
Detect Lung Transplant Rejection
Detect Inhalation Injury in Burn Patients

Renal Applications:

Detect Urinary Tract Obstruction
Diagnose Renovascular Hypertension
Measure Differential Renal Function
Detect Renal Transplant Rejection
Detect Pyelonephritis
Detect Renal Scars

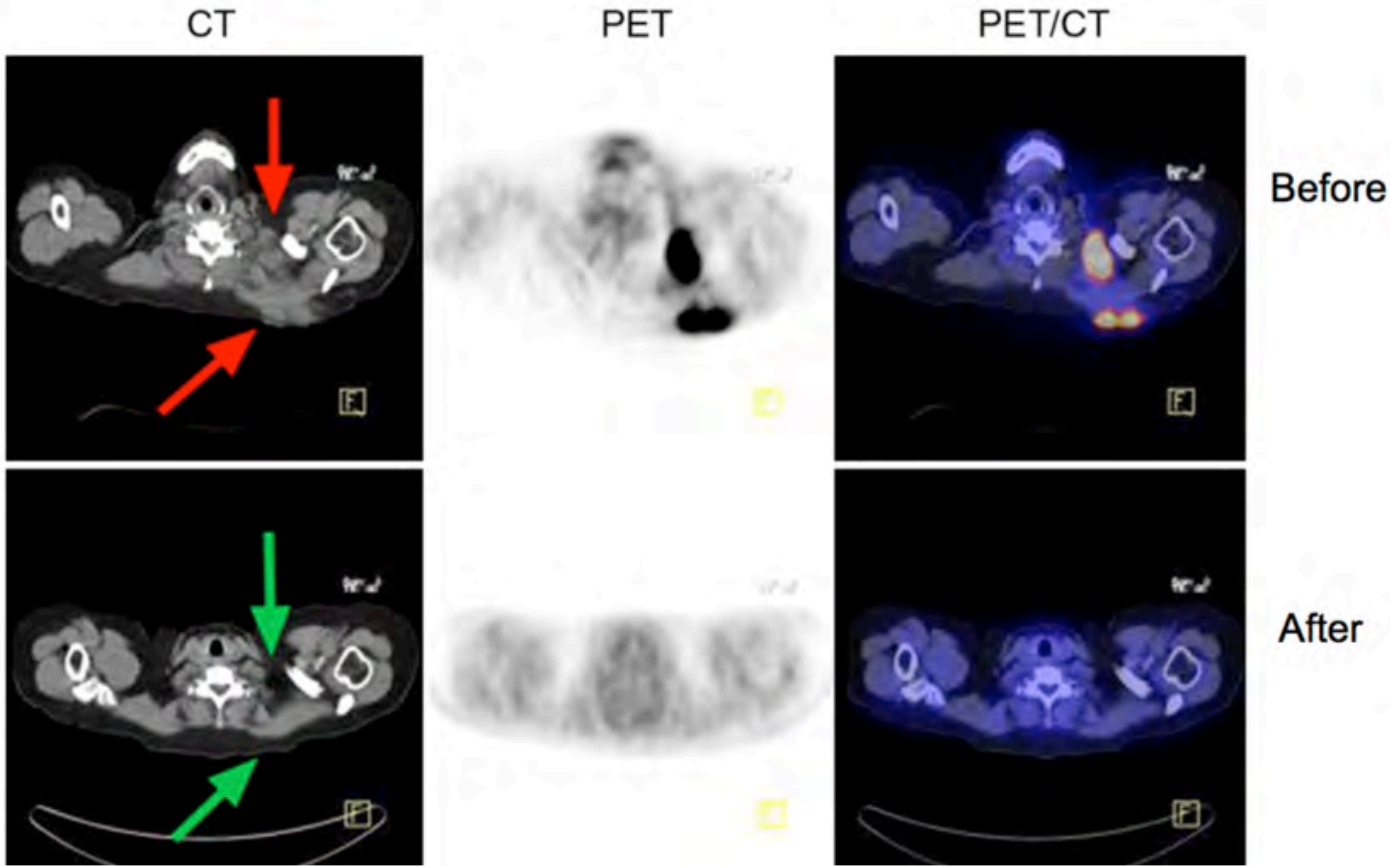
Oncology Applications:

Tumor Localization
Tumor Staging
Identify Metastatic Sites
Judge Response to Therapy
Relieve Bone Pain Caused by Cancer

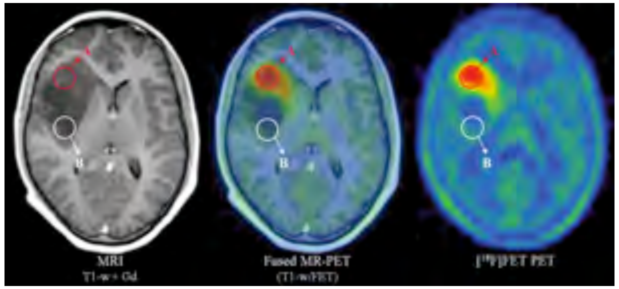
Other Applications:

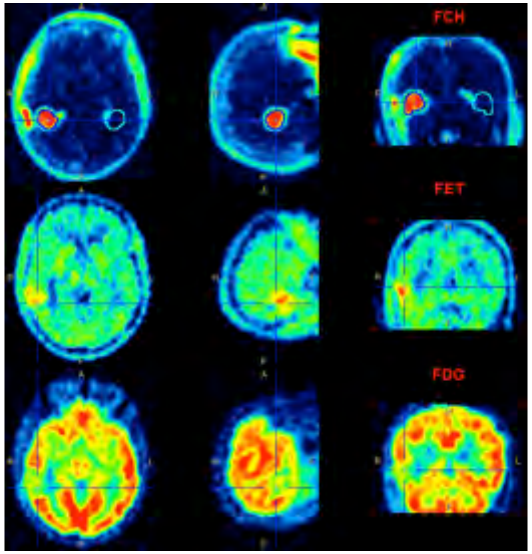
Detect Occult Infections
Diagnose and Treat Blood Cell Disorders
Diagnose and Treat Hyperthyroidism (Graves' Disease)
Detect Acute Cholecystitis
Chronic Biliary Tract Disfunction
Detect Acute Gastrointestinal Bleeding
Detect Testicular Torsion

Cancer therapy demonstrated with ^{90}Y–ibritumomab tiuxetan *(Zevalin)*
Peter Conti, University of Southern California – NCI Report 2008

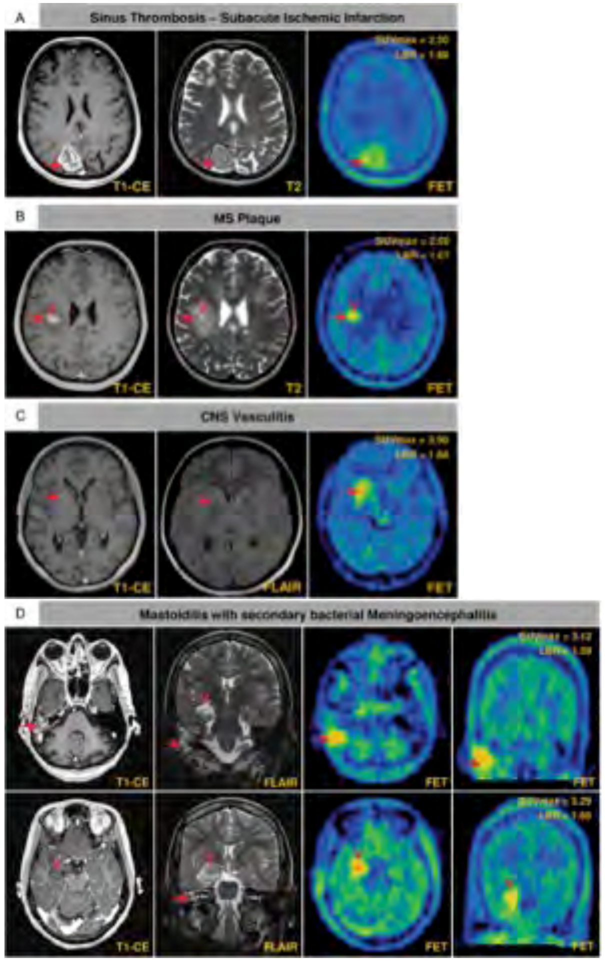


F-18-FET



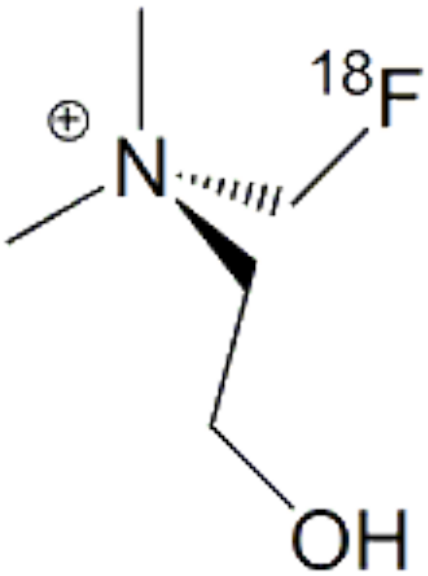


Brain tumor

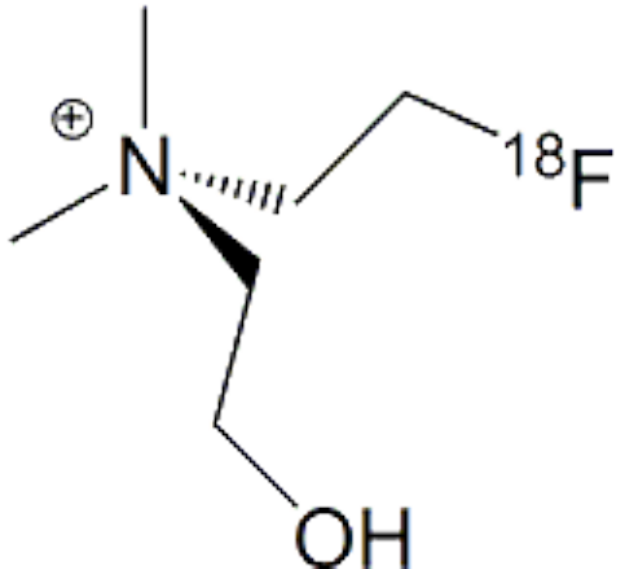


Neuroinflammation

[^{18}F]CHOLINE

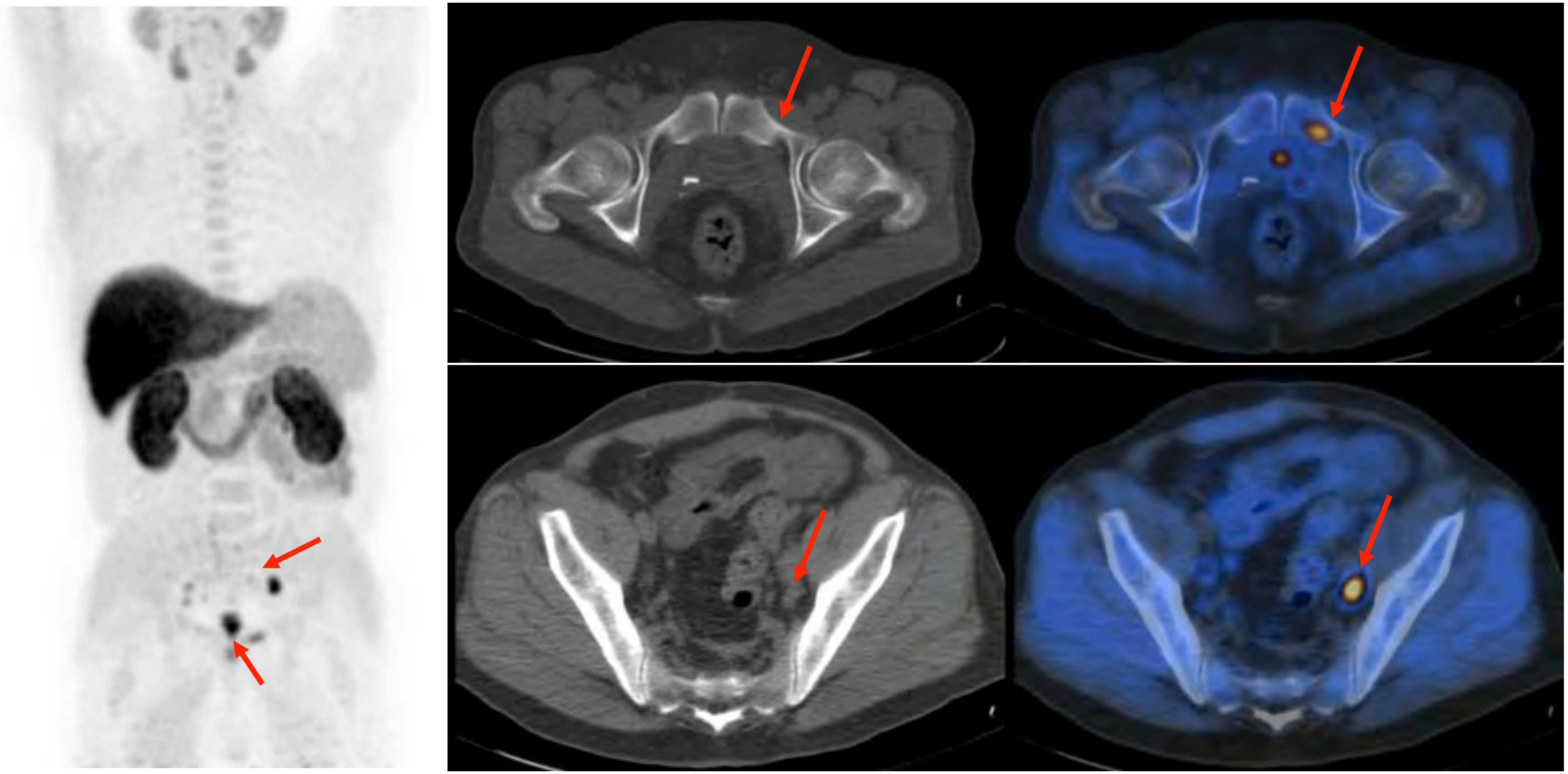


[^{18}F]Fluoromethylcholine



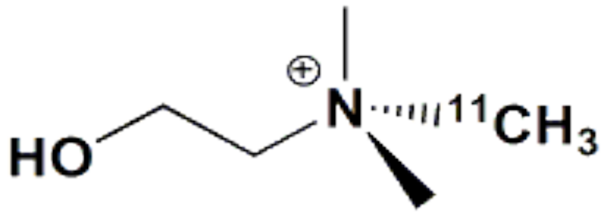
[^{18}F]Fluoroethylcholine

[^{18}F]CHOLINE



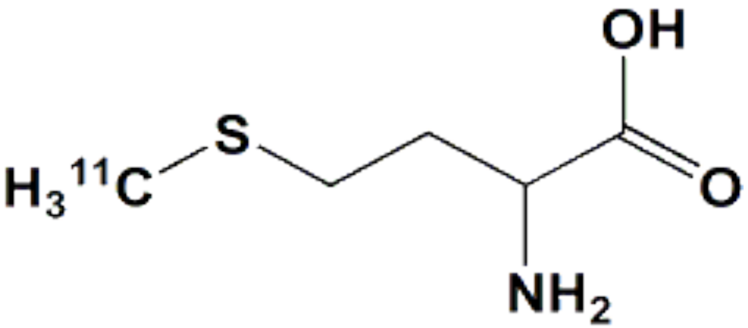
Prostate cancer

$[^{11}C]$Tracers



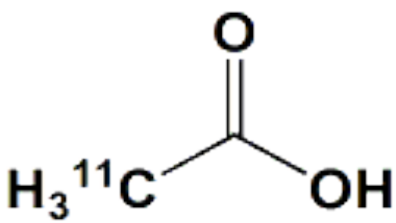
$[^{11}C]$Choline

Synthesis of cell membrane phospholipids



$[^{11}C]$Methionine

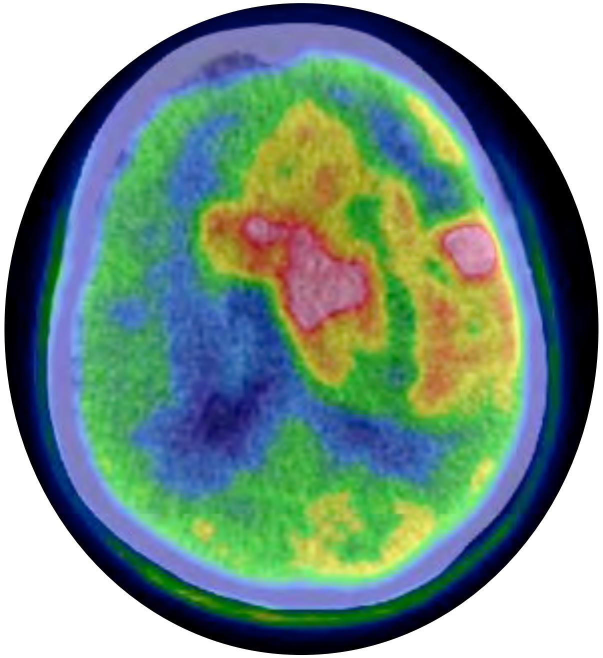
Protein synthesis

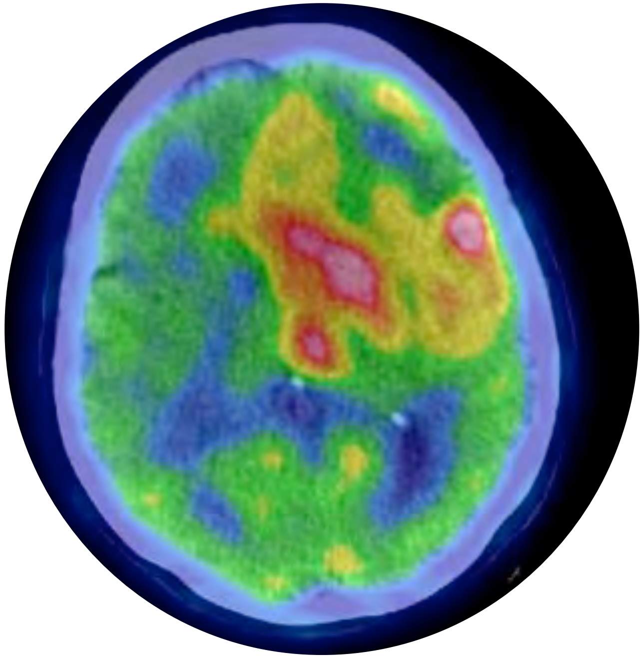


$[^{11}C]$Acetate

Fatty-acid metabolism

[^{11}C]Methionine





Before therapy After therapy

Astrocytoma (no response)
(courtesy by PET Centre St. Orsola Hospital, Bologna)

Emerging radioisotopes and (alternative) production routes

All medical radioisotopes now produced in reactors **can be produced alternatively** or **can be replaced** by isotopes which can be produced other than in a nuclear reactor

Particle Accelerators

Linear

- Ge-68/Ga-68, and Sr-82/Rb-82, Zn-65, Mg-28, Fe-52, Rb-83 (200 MeV proton beam, 150 uA)

Cyclotrons (10-100 MeV, up to 2 mA)

- F-18, Sr-82, Cu-64,O-15, C-11, Br-77, I-124, Y-86, Ga-66/68, Cu-60/61, Zr-89, Tc-99m

New routes

Compact systems (Bench-scale electronic devices for achieving various high-energy nuclear reactions):

proton accelerator: production of F-18, In-111, I-123, C-11, N-13, O-15

alpha linac: Sn-117m, Ac-225, As-73, Fe-55, At-211, Cd-109, Y-88, Se-75, Po-210

neutron sources

Electron-beam accelerator

- Bremsstrahlung 10-25 MeV electrons proposed for isotope production through:

- ❑ Photo-fission of heavy elements
- ❑ (γ ,n) reactions
- ❑ Photo-neutron activation and (n,2n) reactions

Emerging radioisotopes and (alternative) production routes

Emerging medical radioisotopes: β-emitters and theragnostic agents – *in preclinical and clinical research*: Lu-177, Ho-166, Re-186/188, Cu-67, Pm-149, Au-199, Y-90

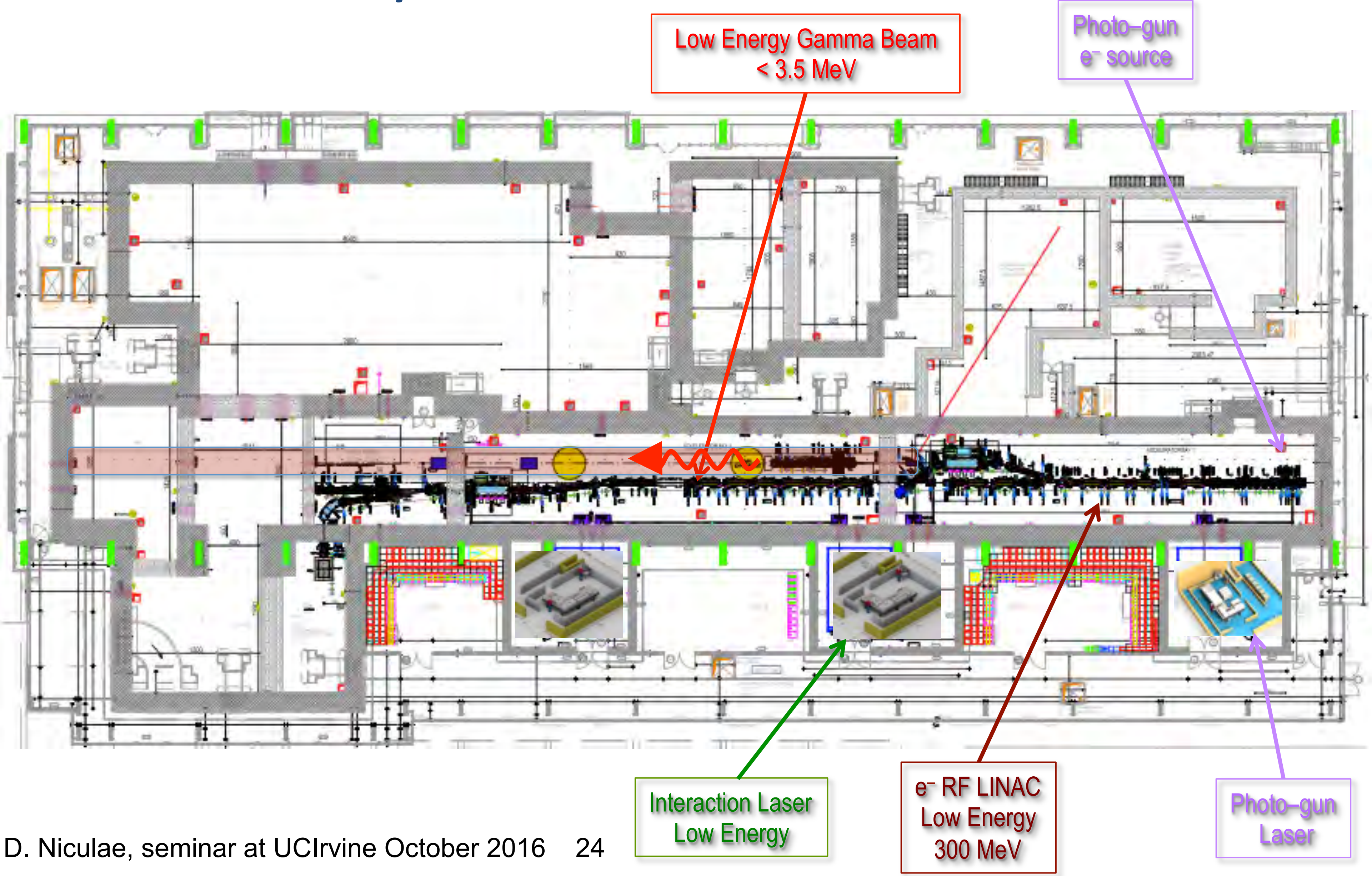
Radio nuclide	Emission	Half-life (hrs)	Production Mechanism	Particle/gamma Energy (MeV)
^{67}Cu	β (0.14 MeV) γ (0.18 MeV)	62	^{68}Zn(p, 2p) ^{70}Zn(p,α) ^{67}Zn(n,p) ^{68}Zn(γ,p)	Ep (>> 30) Ep (>> 30) Reactor Eγ (>19) σ = 0.03 barn
^{47}Sc	β (0.16 MeV) γ (0.16 MeV)	3.35 d	^{48}Ti(γ,p)	Eγ (>27) σ = 0.01 barn
^{186}Re	β (0.35 MeV) γ (0.14 MeV)	3.7 d	^{187}Re(γ,n)	Eγ (>15) σ = 0.6 barn
^{149}Pm	β (1.072 MeV)	53.08	$^{150}Nd(γ,n)^{149}Nd$	Eγ (>12.5) σ =0.22 barn
$^{152/155/161}Tb$	$β^+$ (1.08 MeV) EC (0.86, 0.10 MeV) $β^-$ (0.154 MeV), Auger	17.5/ 127,2 165.3	$^{152}Tb/^{155}Tb$ proton-induced spallation $^{160}Gd(n,γ)^{161}Gd$	Neutron source Reactor

Emerging radioisotopes and (alternative) production routes

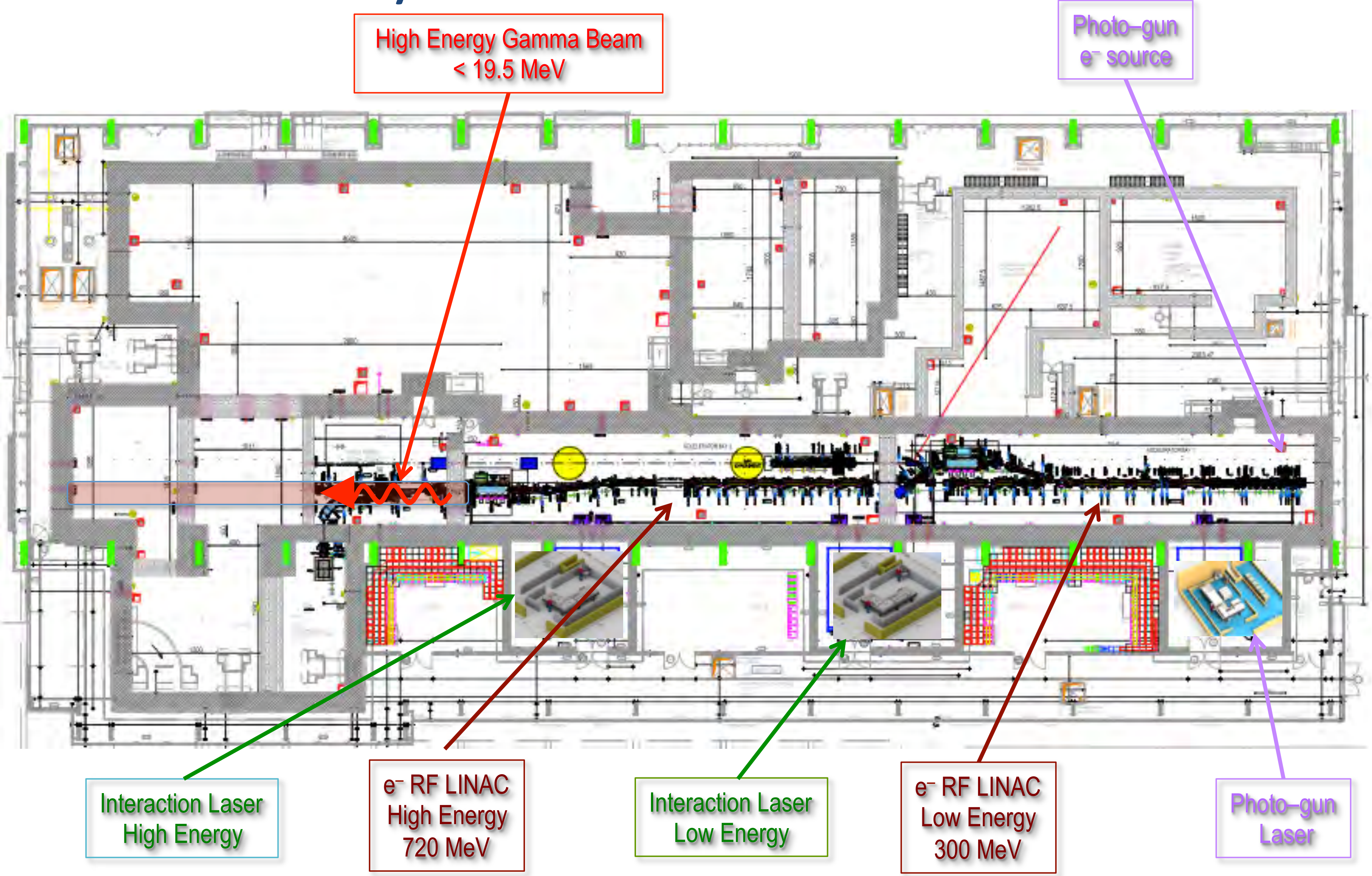
Emerging medical radioisotopes: α-emitters and Auger-electrons emitters

Radio nuclide	Emission	Half-life (hrs)	Production Mechanism	Particle Energy (MeV)
^{211}At	α	7.2	^{210}Bi(α,2n)	Eα (30)
^{225}Ac	α (5.8 MeV) β (0.1 MeV)	240	^{229}Thorium generator Ion exchange from ^{225}Ra ^{226}Ra(p,2n) ^{226}Ra(γ,p)	 Reactor Ep (25–8) Eγ (>19) σ = 0.02 barn
^{224}Ra/ ^{212}Pb/ ^{212}Bi	α (5.7 MeV)/ $β^-$ (0.1 MeV)/ α (6.0 MeV), *β* (0.77 MeV)	3.7/ 10.64 h /60 .6 m	^{226}Ra(*γ*,2n)	Eγ (>16) σ = 0.1 barn
^{165}Er	A (0.038 MeV) γ (0.05 MeV)	10.3	^{166}Er(γ,n)	Eγ (>13) σ = 0.3 barn
^{149}Tb	α (3.967 MeV) β (0.7MeV)	4.12	^{152}Gd(p,4n)^{149}Tb, Ta(p, X)^{149}Tb	

ELI–NP GBS Layout

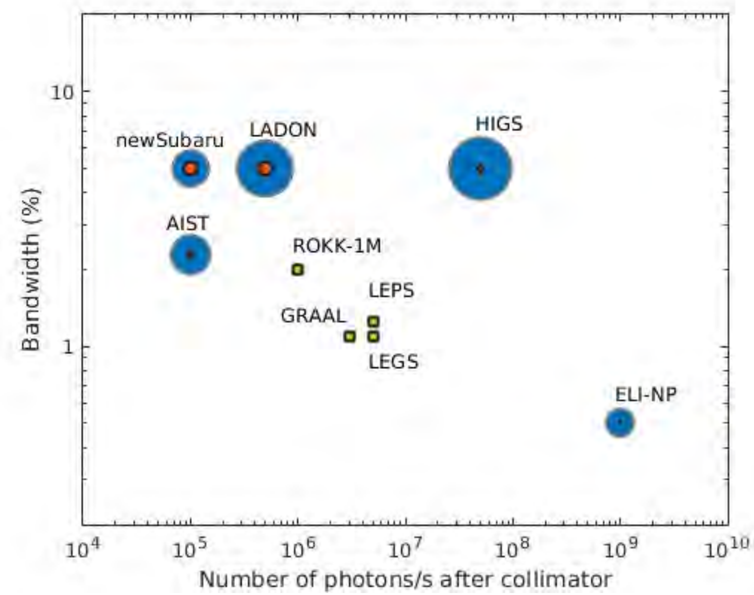


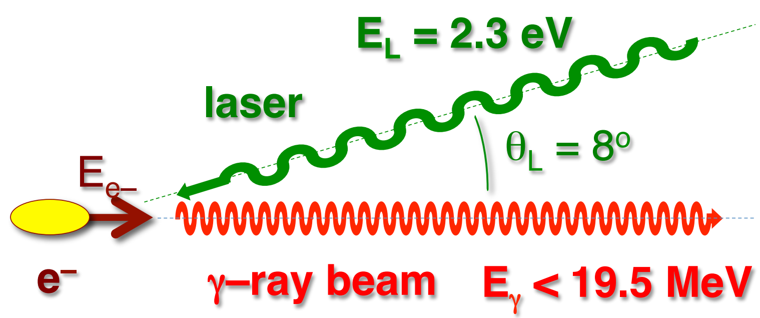
ELI–NP GBS Layout



ELI–NP GBS Parameters

Energy (MeV)	0.2 – 19.5
Spectral Density (ph/s·eV)	> $0.5 \cdot 10^4$
Bandwidth rms (%)	≤ 0.5
# photons per pulse within FWHM bdw.	~10^5
# photons/s within FWHM bdw.	$10^8 – 10^9$
Source rms size (μm)	10 – 30
Source rms divergence (μrad)	25 – 200
Peak brilliance (N_{ph}/sec·mm^2·mrad^2·0.1%)	$10^{20} – 10^{23}$
Radiation pulse length rms (ps)	0.7 – 1.5
Linear polarization (%)	> 95
Macro repetition rate (Hz)	100
# pulses per macropulse	32
Pulse–to–pulse separation (nsec)	16





Potential radioisotopes produced in (γ,n), (γ,p) or (γ,2n) reactions

D. Habs · U. Köster, Appl Phys B (2011) 103: 501–519

Product isotope	$T_{1/2}$	Emission energy (MeV)	Target isotope	Reaction type	E_γ MeV	σ (barn)	Purpose
^{47}Ca	4.5 d	0.4 (β) 1.3 (γ)	^{48}Ca	(γ,n)	19	0.09	Targeted radiotherapy, SPECT
^{64}Cu	12.7 h	0.28 (β^+) 0.191 (β) 0.511 (γ)	^{65}Cu	(γ,n)	17	0.09	PET, Various other applications
^{99}Mo/ ^{99m}Tc	2.8 d /0.25	0.39 (β^+)/ 0.14 (γ)	^{100}Mo	(γ,n)	14	0.16	SPECT
^{103}Pd	17 d	0.036 (CE) 0.02 (γ)	^{104}Pd	(γ,n)	17	*0.05**	Targeted radiotherapy, Brachytherapy
^{165}Er	10.36 h	0.005, 0.038 (Auger) 0.05 (γ)	^{166}Er	(γ,n)	13	0.3	Tumor therapy
^{169}Er	9.4 d	0.1 (β)	^{170}Er	(γ,n)	12	*0.3**	Targeted radiotherapy

Potential radioisotopes produced in (γ,n), (γ,p) or (γ,2n) reactions -cont

D. Habs · U. Köster, Appl Phys B (2011) 103: 501–519

Product isotope	$T_{1/2}$	Emission energy (MeV)	Target isotope	Reaction type	E_γ MeV	σ (barn)	Purpose
^{186}Re	3.7	0.35 (β) 0.14 (γ)	^{187}Re	(γ,n)	15	0.6	Bone pain palliation, radiosynovectomy, and targeted radionuclide therapy
^{225}Ra/ ^{225}Ac	14.8/	0.10 (β)/ 5.8 (α)	^{226}Ra	(γ,n)	12	*0.2**	Targeted alpha therapy
^{47}Sc	3.35	0.16 (β) 0.16 (γ)	^{48}Ti	(γ,p)	19	*0.02**	Targeted radiotherapy, SPECT or γ-camera
^{67}Cu	2.6	0.14 (β) 0.18 (γ)	^{68}Zn	(γ,p)	19	*0.03**	Targeted radiotherapy, SPECT or γ-camera
^{44}Ti/ ^{44}Sc	59.1 y 3.97 h	0.07 (γ)/ 632 keV (β^+), 511, 1157 keV (γ)	^{46}Ti	(γ,2n)	**27**	*0.01**	PET, Compton telescope

Potential radioisotopes produced in (γ,n), (γ,p) or (γ,2n) reactions -cont

D. Habs · U. Köster, Appl Phys B (2011) 103: 501–519

Product isotope	$T_{1/2}$	Emission energy (MeV)	Target isotope	Reaction type	E_γ MeV	σ (barn)	Purpose
^{224}Ra/ ^{212}Pb/ ^{212}Bi	3.7/ 10.64 h /60 .6 m	5.7 (α)/ 0.1 (β^-)/ 6.0 (α), 0.77 (β)	^{226}Ra	(γ,2n)	16	*0.1**	Targeted alpha therapy

For β and ε decay mode, the emission energy is the mean energy. *Estimated cross sections are marked in italics.

$$^{170}\mathrm{Er} \xrightarrow{(\gamma,n)} {}^{169}\mathrm{Er} \xrightarrow{\beta^-,\ 100\ \mathrm{keV}} {}^{169}\mathrm{Tm}$$

Stable — T_1= 9.4 d — Stable

Abundance:14.9%

- Due to the low ^{168}Er(n$_{th}$, γ) cross section, it cannot be produced with higher specific activity[1] by neutron capture.

$$^{166}\mathrm{Er} \xrightarrow{(\gamma,n)} {}^{165}\mathrm{Er} \xrightarrow[\gamma,\ 0.05\ \mathrm{MeV}]{\varepsilon,\ 5\ \mathrm{and}\ 38.4\ \mathrm{keV}} {}^{165}\mathrm{Ho}$$

Stable — T_1=10.4 h — Stable

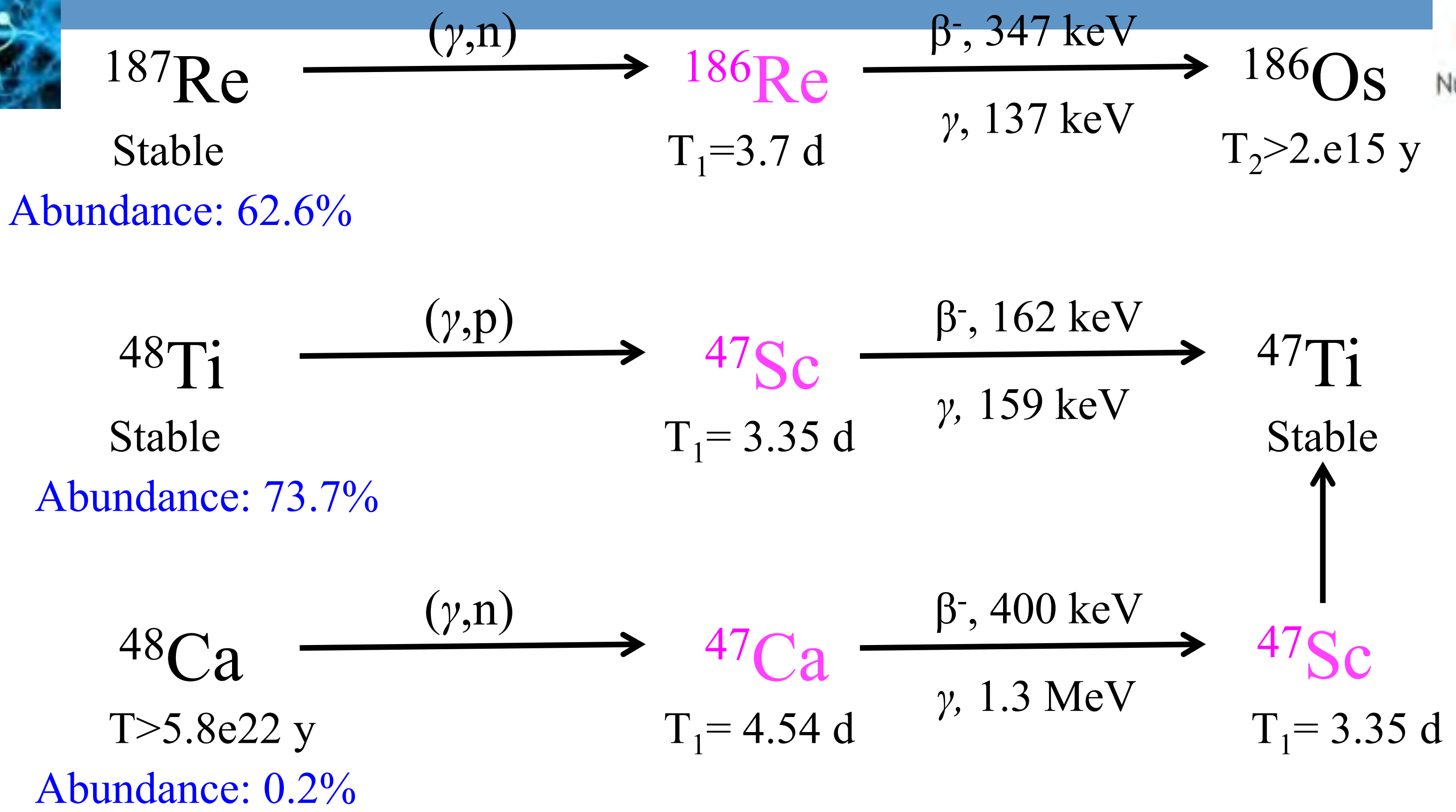
Abundance: 33.5%

$$^{65}\mathrm{Cu} \xrightarrow{(\gamma,n)} {}^{64}\mathrm{Cu} \xrightarrow[\varepsilon\ ,\ 278\ \mathrm{keV};\ \gamma\ ,\ 0.511]{\beta^-,\ 191\ \mathrm{keV}} {}^{64}\mathrm{Ni}\ \ \mathrm{Stable};\ {}^{64}\mathrm{Zn}\ \ T_2>7.e20\ \mathrm{y}$$

Stable — T_1= 12.7 h

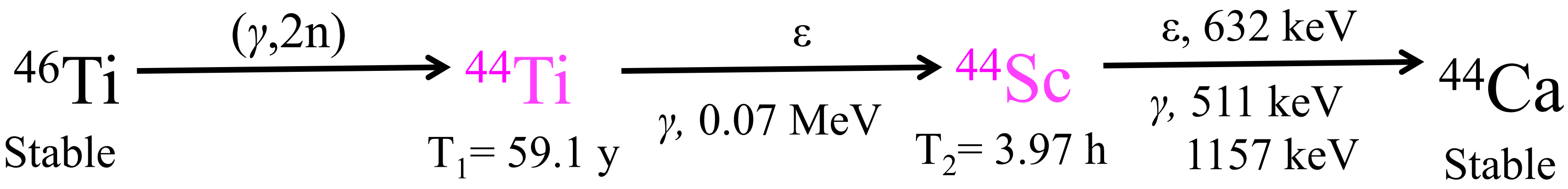
Abundance:30.85%

- Today, ^{64}Cu is mainly produced with small cyclotrons by the ^{64}Ni(p,n) reactions, which require the rare and expense ^{64}Ni targets and saves the chemical separation step.



- The ^{47}Sc could be chemically separated from the irradiated Ca or Ti element. The Sc/Ti separation schemes were established. The alternative production via ^{46}Ca(n,γ)^{47}Ca→^{47}Sc is uneconomic due to the extremely low natural abundance of ^{46}Ca, 0.004%.

[1] J.C. Reubi, H.R. Mäcke, E.P. Krenning, J. Nucl. Med. 46, 67S (2005)
[2] M.J. Rivard, L.M. Bobek, R.A. Butler, M.A. Garland, D.J. Hill, J.K. Krieger, J.B. Muckerheide, B.D. Patton, E.B. Silberstein, Appl. Radiat. Isotopes 63, 157 (2005)



Abundance: 8.25%

- ^{44}Sc has very favorable properties, but not yet used in clinical routine, since the generator isotopes ^{44}Ti is difficult to produce and therefore prohibitively expensive. Exposing enriched ^{46}Ti to an intense γ-beam allows producing ^{44}Ti by (γ,2n) reactions.

^{104}Pd —(γ,n)→ ^{103}Pd —(CE, 36 keV; γ, 20 keV)→ ^{103}Rh

^{104}Pd: Stable, Abundance: 11.14%

^{103}Pd: T_1=17 d

^{103}Rh: Stable

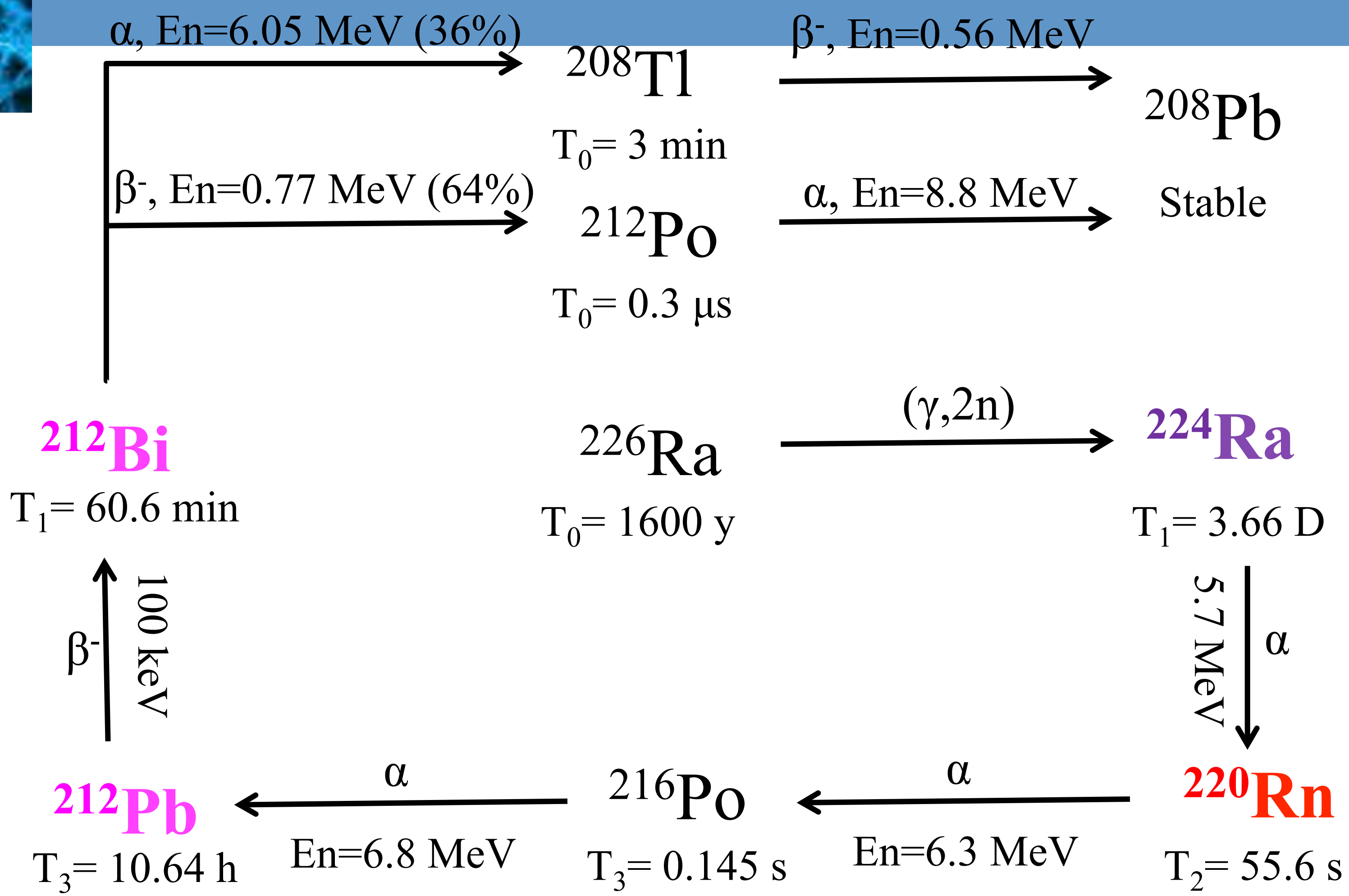
^{68}Zn —(γ,p)→ ^{67}Cu —(β^-, 141 keV; γ, 185 keV)→ ^{67}Zn

^{68}Zn: Stable, Abundance: 18.5%

^{67}Cu: T_1= 2.6 D

^{67}Zn: Stable

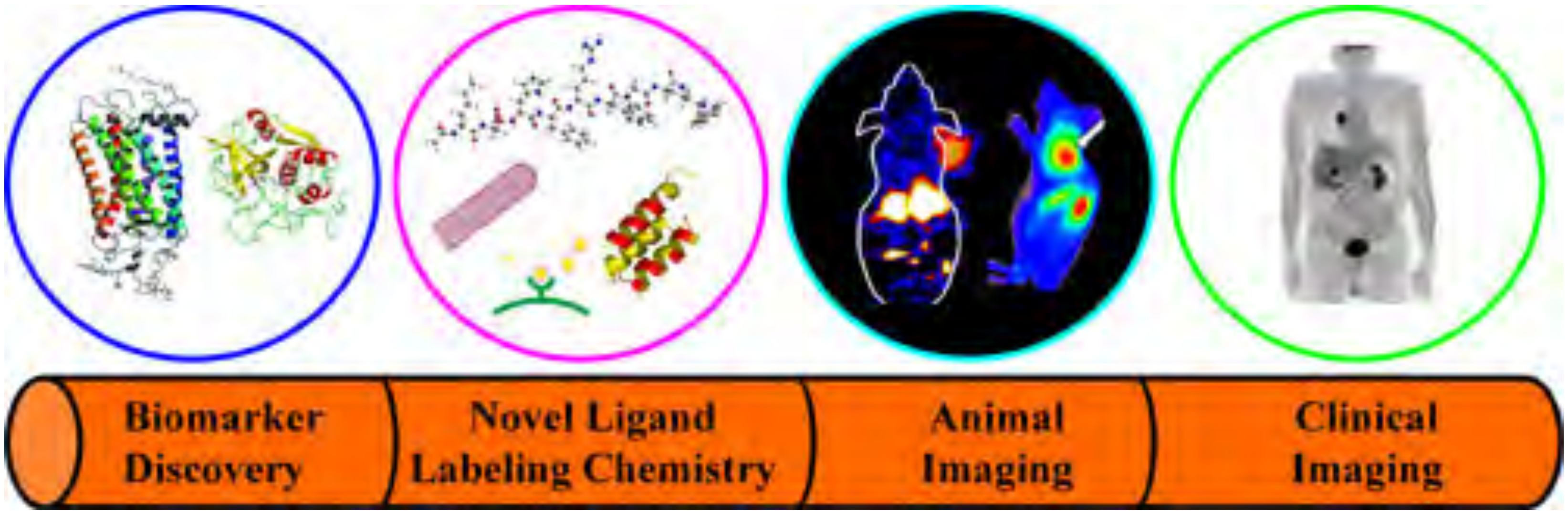
- Alike ^{47}Sc, ^{67}Cu has a sufficiently long half-life for accumulation in the tumor cells when bound to antibodies and its 185 keV gamma-ray allows imaging with SPECT or gamma cameras.
- The usual production routes ^{68}Zn(p,2p), ^{70}Zn(p,α), or ^{64}Ni(α,p), are all characterized by low yields. The former requires energetic protons (>30 MeV from larger cyclotrons) and the latter two methods use expensive enriched targets with low natural abundances, of the order of 0.5%.
- Production via ^{68}Zn(γ,p) reactions, more abundant and hence cheaper ^{68}Zn targets could be used. An established Cu/Zn separation schemes.



- The noble gas ^{220}Rn isotope can be extracted easily. The α emitter ^{212}Bi and its mother isotopes ^{212}Pb are also considered for targeted alpha therapy, e.g., for malignant melanoma metastases. A competing reaction $^{226}Ra(\gamma,n)^{225}Ra$ could be used for $^{225}Ac/^{213}Bi$ generator also for targeted alpha therapy.

Conclusions

- Are there “ideal” radioisotopes for imaging/therapy (physical, chemical and biological properties)?
- What emerging radioisotopes can improve in any of these views?
- What are the limitations for both “traditional” and “emerging” radioisotopes in term of production routes, availability, processing, to access into clinical practice?
- Can radioisotopes address functionality / early diagnosis / personalized medicine ?



Conclusions

Photonuclear reactions with γ beams allow to produce certain radioisotopes, ^{47}Sc, ^{44}Ti, $^{67}Cu/(^{64}Cu)$, ^{103}Pd, ^{117m}Sn, ^{169}Er, ^{195m}Pt , ^{225}Ac, ^{99}Mo (^{99m}Tc), ^{111}In

with higher specific activity and/or more economically than with classical methods.

New clinical applications of radioisotopes:

Monitoring of the response to therapy (in real-time)

Theragnostic agents $^{64/67}Cu$ used as reporting and therapeutical

Increased availability of very promising radioisotopes *innovative isotopes like ^{47}Sc, ^{67}Cu and ^{225}Ac could be produced for the first time in sufficient quantities for large-scale application in targeted radionuclide therapy.*

Development of alternative methods for producing well established radioisotopes in clinical practice

Thank you for attention!