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New Perspecives in Radionuclide Research

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New Perspectives in Radionuclide Research for Medical Applications

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- INM-5: Nuklearchemie
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- Lecture delivered during the Workshop on Nuclear Data for Science and Technology:
- Medical Applications, Abdus Salam ICTP, Trieste, Italy, 30 September to 4 October 2013

Topics

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A. Production

- Supply of standard radionuclides
- Development of novel radionuclides
- Development of exotic radionuclides
- Possible use of new technologies

B. Applications

- Quantification of SPECT radiopharmaceuticals

  (Combination of SPECT and PET)

  - isotopic pairs, e.g. ^{94m}Tc/^{99m}Tc, ^{120}I/^{123}I, etc.
- PET and endoradiotherapy

  - theragnostic pairs, e.g. ^{64}Cu/^{67}Cu, ^{86}Y/^{90}Y, ^{124}I/^{131}I, etc.
- Multiple mode imaging

  (CT/SPECT, CT/PET, MRI/PET)
- Radioactivity and nanotechnology

Summary of Present Status of Use of Radionuclides in Medicine

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Diagnosis

- 35 million diagnostic investigations/year using ^{99m}Tc and SPECT

- 4 million patients/year investigated using [^{18}F]FDG and PET

- use of ^{68}Ga is increasing

There is some jeopardy in supply of ^{99m}Tc

Therapy

- Several million treatments/year via external radiation therapy

- Application of internal radionuclide therapy is rapidly enhancing

Production of Tc-99m ($T_{1/2}$ = 6.1 h)
(via alternative routes)

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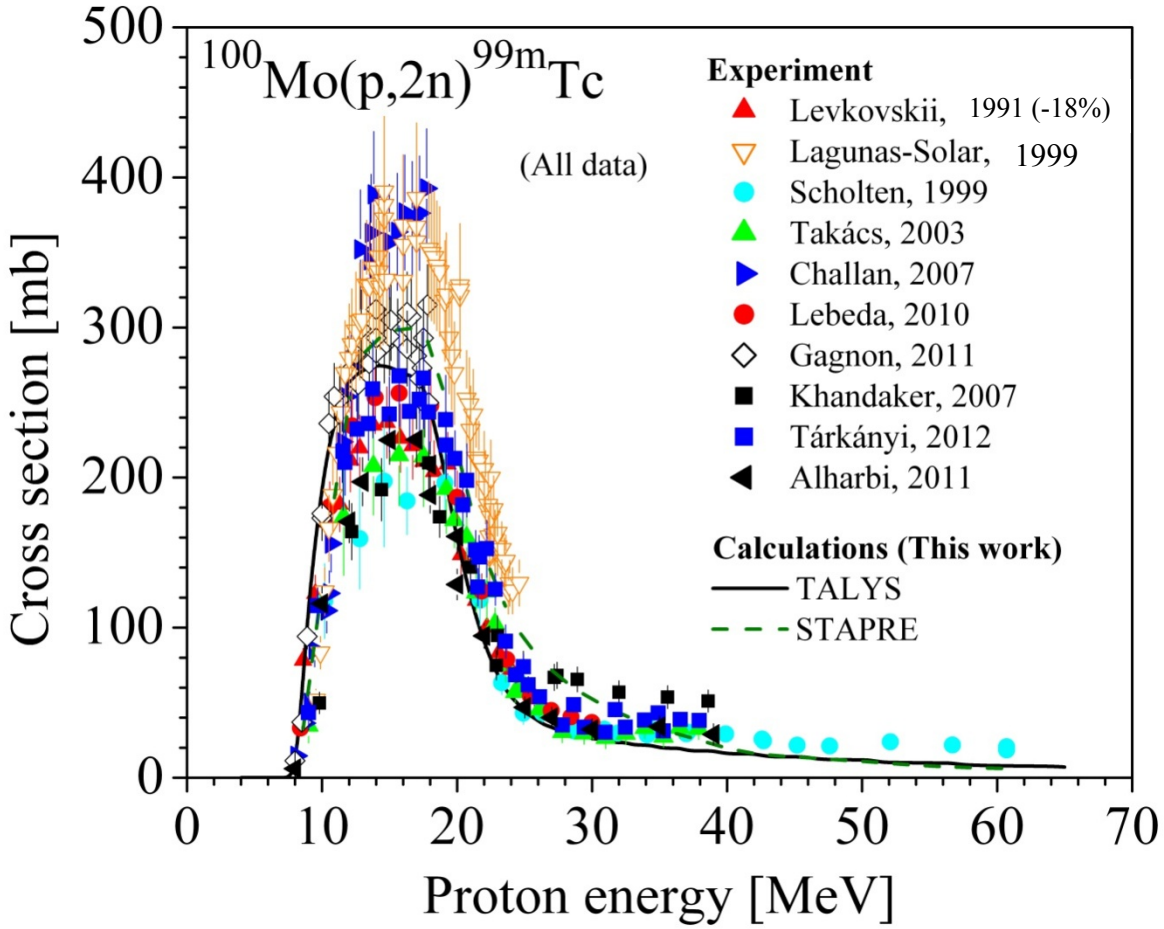
Due to ageing reactors, production via $^{235}U(n,f)$-route is in jeopardy. Alternative suggested routes include:

$^{nat}U(\gamma,f)^{99}Mo$	(σ = 160 mb at 15 MeV)	Evaluated data
$^{232}Th(p,f)^{99}Mo$	(σ = 34 mb at 22 MeV)	Abbas et al, NIM B**278**, 20 (2012)
$^{100}Mo(\gamma,n)^{99}Mo$	(σ = 150 mb at 14 MeV)	Crasta et al, JRNC **290**, 367 (2011)
$^{100}Mo(n,2n)^{99}Mo$	(σ = 1000 mb at 14 MeV)	Nagai et al, J Phys.Soc. **78**, 033201 (2009)
$^{100}Mo(p,pn)^{99}Mo$	(σ = 140 mb at 40 MeV)	Extensively investigated
$^{100}Mo(p,2n)^{99m}Tc$	(σ = 300 mb at 15 MeV)	Extensively investigated

All reactions leading to the formation of ^{99}Mo are presently not feasible. The only promising route is direct formation of ^{99m}Tc via the $^{100}Mo(p,2n)$ reaction.

Excitation Function of the $^{100}Mo(p,2n)^{99m}Tc$ Reaction



Evaluation of data completed

Qaim et al.,
ARI in press (2013).

Suitable energy range for production of ^{99m}Tc

E_p = 22 → 10 MeV
Yield = 720 MBq/μA·h

Production of ^{99m}Tc via the ^{100}Mo(p,2n)-Reaction

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- Discrepancies in data removed
- Production and radiopharmaceutical quality of ^{99m}Tc demonstrated in low-energy range (< 18 MeV), i.e. with ^{99}Tc/^{99m}Tc ratio of < 5.

Guerin et al, JNM **51**, 13N (2010); Morley et al, NMB **39**, 551 (2012)

Further investigations needed

- effect of higher $^{99g+98}$Tc/^{99m}Tc ratio

- increase of impurities with decreasing in enrichment of ^{100}Mo target

The method will offer only a regional solution, because

- daily production schedule necessary; extensive personnel needed

- low-yield; high cost

For global supply, presently the fission of ^{235}U is inevitable.

Efforts to use LEU are most essential.

Gallium-68 ($T_{½}$ = 1.1 h)

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- Generator produced radionuclide
- Good generator systems available, efficient processing of ^{68}Ga-eluate, e.g.

  Zhernosekov et al, JNM **48**, 1741 (2007)

Jeopardy about supply of parent ^{68}Ge ($T_{½}$ = 270 d)

Alternative Routes of Production

^{68}Zn(p,n)^{68}Ga

^{65}Cu(α,n)^{68}Ga Szelecsenyi et al, RCA **100**, 5 (2012).

Prospects for direct production of ^{68}Ga are good; but adopted procedure will remain limited for in-house application.

Novel Positron Emitters for Medical Applications Produced via Low-Energy Reactions (E ≤ 20 MeV)

Nuclide	Major production route	Energy range [MeV]	Application
^{55}Co (17.6 h)	^{58}Ni(p,α) ^{54}Fe(d,n)	15 → 7 10 → 5	Tumour imaging; neuronal Ca marker
^{64}Cu (12.7 h)	^{64}Ni(p,n)	14 → 9	Radioimmunotherapy
^{66}Ga (9.4 h)	^{66}Zn(p,n)	13 → 8	Quantification of SPECT
^{72}As (26.0 h)	^{nat}Ge(p,xn)	18 → 8	Tumour localisation; immuno-PET
^{76}Br (16.0 h)	^{76}Se(p,n)	15 → 8	Radioimmunotherapy
^{82m}Rb (6.2 h)	^{82}Kr(p,n)	14 → 10	Cardiology
^{86}Y (14.7 h)	^{86}Sr(p,n)	14 → 10	Therapy planning
^{89}Zr (78.4 h)	^{89}Y(p,n)	14 → 10	Immuno-PET
^{94m}Tc (52 min)	^{94}Mo(p,n)	13 → 8	Quantification of SPECT
^{120}I (1.3 h)	^{120}Te(p,n)	13.5 → 12	Iodopharmaceuticals
^{124}I (4.2 d)	^{124}Te(p,n)	12 → 8	Tumour targeting; dosimetry

Exotic Radionuclides

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Examples : Positron and α-particle emitting radionuclides of lanthanides

β^+ Emitter

Tb-152 ($T_{½}$ = 17.5 h)
(EC = 87 %; β^+ = 13 %;
E_{β^+} = 2.8 MeV)

Production routes

$^{151}Eu(\alpha,3n)^{152}Tb$
$^{155}Gd(p,4n)^{152}Tb$

α-particle Emitter

Tb-149 ($T_{½}$ = 4.1 h)
(EC = 79 %; β^+ = 4 %; α = 16.7 %;
E_{α} = 3.97 MeV)

Production routes

$^{141}Pr(^{12}C,4n)^{149}Tb$
$^{151}Eu(\alpha,6n)^{149}Tb$
$^{155}Gd(p,7n)^{149}Tb$

$^{181}Ta(p,spall)^{149,152,155}Tb$ at 1.4 GeV
(isotope separation on-line device: ISOLDE/CERN

Besides nuclear data work, versatile irradiation and separation technology is needed

Possible Use of New Technologies

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Spahn et al.,
RCA **92**, 183 (2004).

A. Spallation Neutrons

Example: Measurement of σ(n,p) with 14 MeV "d(Be)-breakup"-neutrons
(Simulation study for production at a spallation neutron source)

Therapeutic radionuclide	Nuclear reaction	Spectrum averaged cross section (mb)	
		Fission neutrons	14 MeV d(Be)-neutrons
^{32}P	^{nat}S(n,p)^{32}P	69	152
^{67}Cu	^{67}Zn(n,p)^{67}Cu	1.07	5.13
^{89}Sr	^{89}Y(n,p)^{89}Sr	0.31	0.91
^{153}Sm	^{nat}Eu(n,p)^{153}Sm	0.015	0.26

- Spallation neutron source should be more suitable than a fission reactor for production of radionuclides via the (n,p) process

B. Photonuclear Reactions

High-energy and high-intensity electron LINAC could yield powerful beam of high-energy bremsstrahlung. Such a beam has some potential for production of radionuclides via

- (γ,n)-reaction; ***Examples***: $^{100}Mo(\gamma,n)^{99}Mo$, $^{102}Pd(\gamma,n)^{101}Pd$;

  $^{124}Xe(\gamma,n)^{123}Xe \xrightarrow{EC} {}^{123}I$; $^{226}Ra(\gamma,n)^{225}Ra \xrightarrow{\beta^-} {}^{225}Ac$

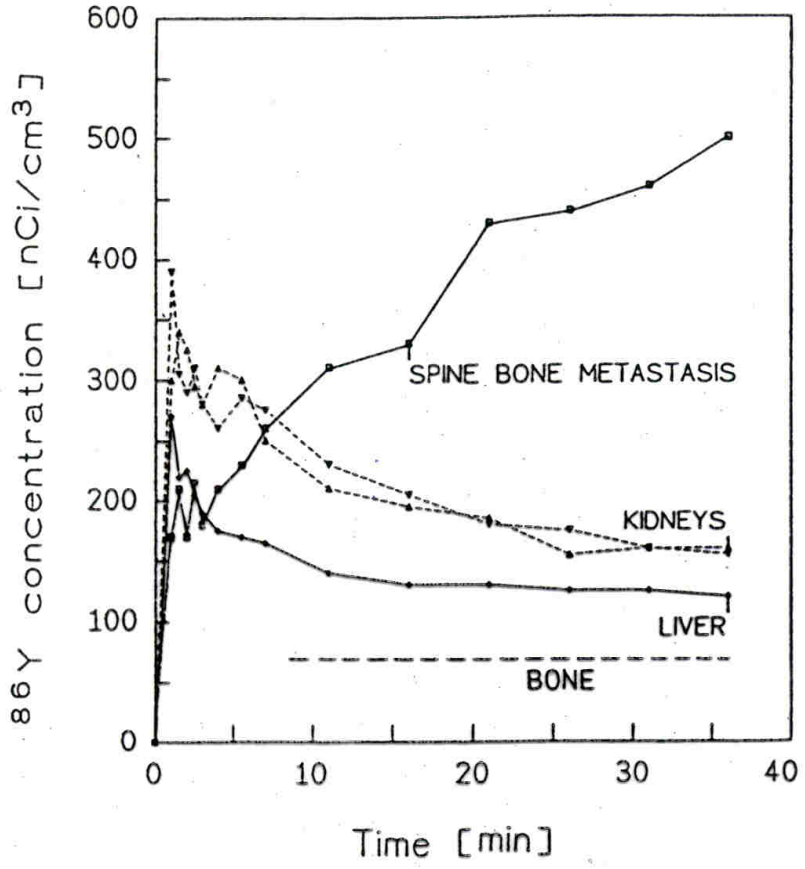
- (γ,p)-reaction; **Examples:** $^{68}Zn(\gamma,p)^{67}Cu$; $^{178}Hf(\gamma,p)^{177}Lu$

- $(\gamma,fission)$-process; **Examples**: $^{232}Th(\gamma,f)^{99}Mo$; $^{nat}U((\gamma,f)^{99}Mo$

Extensive efforts are required to make meaningful use of photonuclear reactions

Combination of PET and Endoradiotherapy
(Determination of Uptake Kinetics and Enrichment Factor)

- Addition of β^+ emitting ^{86}Y analogue to the therapy nuclide ^{90}Y
- Pharmacokinetic data obtained using PET



- Exponential uptake of [^{86}Y]-citrate in bone metastasis
- Enrichment factor (bone metastasis/normal bone): **8 (at 5h)**

Herzog et al.,
JNM **34**, 2222 (1993).

Accurate dosimetry and therapy planning possible

Multimode Imaging: MRI/PET

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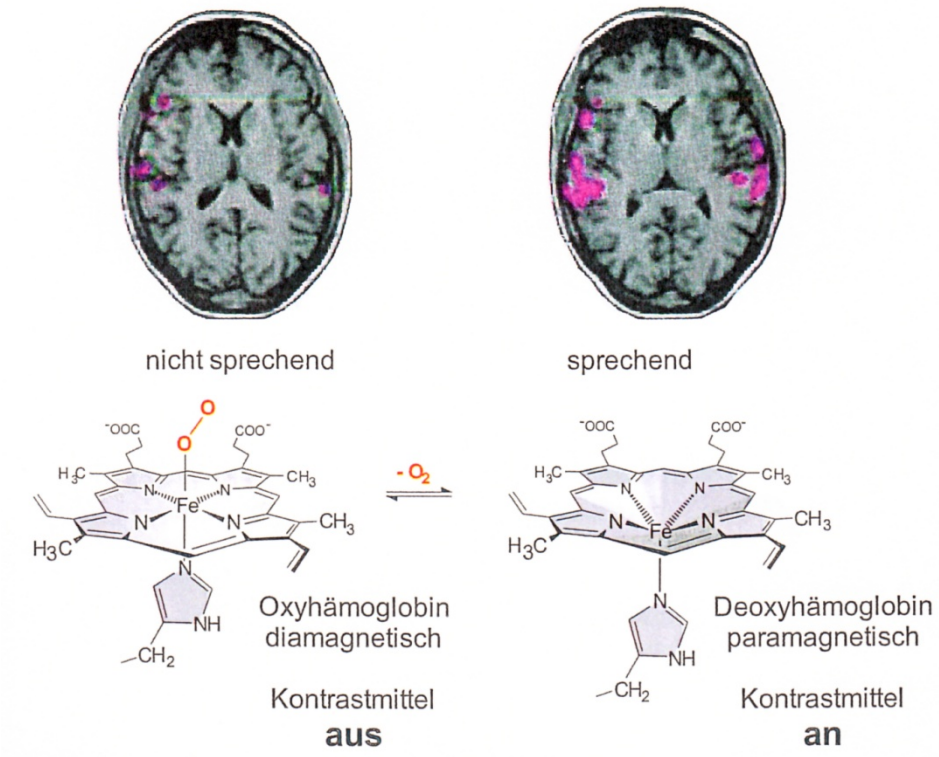
- Combining good resolution of MRI with dynamic and quantitative nature of PET

Possibilities

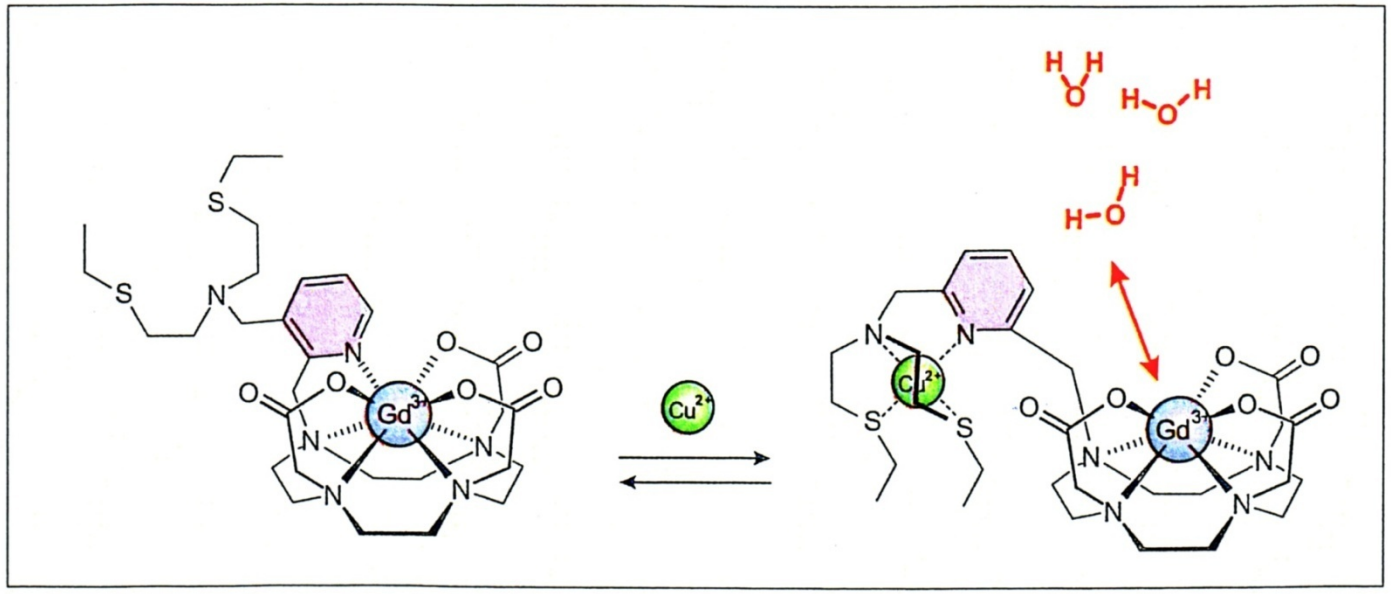
- use of β^+ emitting contrast agents (e.g. ^{51,52}Mn)
- blood oxygenation-level dependent (BOLD) process
- development of ***intelligent contrast agent***, e.g. by chemically binding the MRI contrast agent Gd with another metal, for example Cu, through pyridine
- spin cross over for contrast agent

BOLD Process



- Haemoglobin is a natural contrast agent for MRI
- In deoxygenated form haemoglobin is paramagnetic (active contrast agent)
- Uptake of oxygen converts haemoglobin to diamagnetic form (inactive as contrast agent)
- If Fe is β^+ emitting ^{52}Fe, multimode imaging could be applied

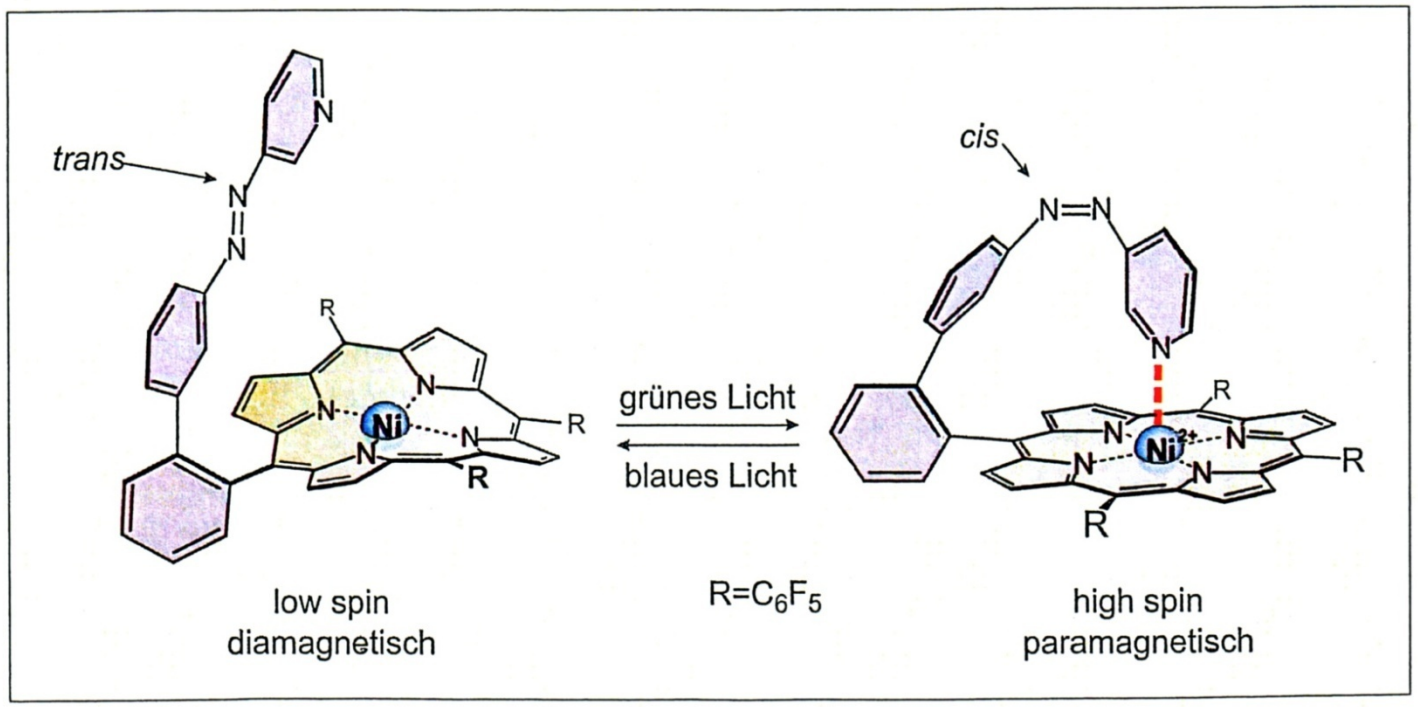
Intelligent Contrast Agent



R. Herges,
Nachr. Chemie **59**,
817 (2011).

- Gd^{3+} is an important contrast agent in MRI
- In presence of Cu^{2+} and pyridine, Gd^{3+} forms a complex with a free co-ordination space where water is a quickly bound.
- The complex increases the contrast appreciably (decreasing the toxicity of Gd)
- If Cu^{2+} is β^+ emitting ^{64}Cu, multimode imaging is possible.

Spin Cross Over



R. Herges, Nachr. Chemie **59**, 817 (2011).

- The shift of a metal complex from diamagnetic (**low spin, no contrast**) to paramagnetic (**high spin, high contrast**) is termed as spin cross over phenomenon
- Transition metals (Fe, Ni, etc.) are very suitable
- If the metal, for example Ni, contains β^+ emitting ^{57}Ni, then PET and MRI could be advantageously combined

Combination of Radioactivity and Nanotechnology

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Concept

- Transport of the radionuclide via a “drug delivery system” to the malignant tissue, where the emitted radiation allows imaging or causes therapeutic effect.

Current targeting strategies for metallic radionuclides

- monoclonal antibodies (mAb)
- peptides

Often insufficient delivery of radionuclide to tumour site

Drug delivery systems based on nanotechnology

- liposomes
- iron oxide
- polymers
- dendrimers
- quantum dots
- carbon nanotubes

Nanocarrier systems could provide platforms to improve delivery of radionuclides to tumour sites.

Some Examples of Nanotargeted Metallic Radionuclide Systems*

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Nanoparticles	Radionuclide ($T_{½}$), radiation	Application
Iron oxide	^{64}Cu (12.7 h), β^+	PET/MRI dual modality tumour angiogenesis imaging
Liposomes	^{186}Re (3.7 d), β^-	Therapeutic efficacy studies on tumour bearing animals
Liposomes	^{225}Ac (10.0 d), α	Therapeutic studies on micrometastases cancer

* Taken from Ting et al., J. Biomed. Biotech. 2010, Article ID953537

Nanotargeted radionuclide therapy has great potential, provided toxicity effects are clarified.

Conclusions

- Extensive efforts are needed to assure continued supply of ^{99m}Tc for patient care
- Continued research is called for (including nuclear data activities) to achieve further progress in molecular imaging and internal radionuclide therapy
- Development of new technologies may be useful for production of radionuclides