In vivo Tracking of Magnetic Nanoparticles

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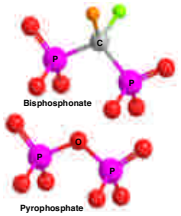
Overview

- Nuclear imaging techniques (PET/SPECT) for tracking magnetic particles
- Bisphosphonate groups for magnetic particle functionalisation

Bisphosphonates (BPs)



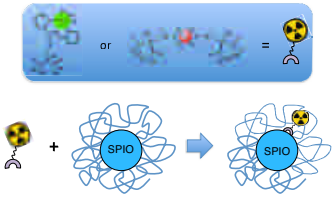
- **BPs** are similar in structure to pyrophosphate
  - 1865 → used as anticorrosive & anti-scaling agents
- 1960s → Pyrophosphate inhibits calcification of tissues
- Pyrophosphate + ^{99m}Tc (SPECT isotope) → bone imaging → hydrolysis
- **BPs** → resistant to hydrolysis + high hydroxyapatite binding

Imaging Bone Metastases with BPs

- **^{99m}Tc-MDP** is the standard agent for the detection of bone metastases
- **^{99m}Tc-MDP** accumulates in regions of high bone-turnover.
- However, to date, the **structure is still unknown.**

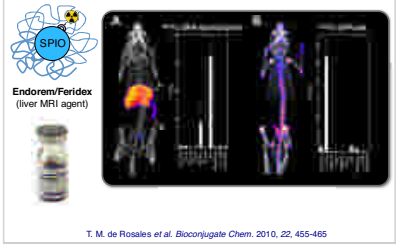
^{99m}Tc-MDP SPECT image showing uptake in bone metastases

Radiolabeling superparamagnetic iron oxide nanoparticles with BPs



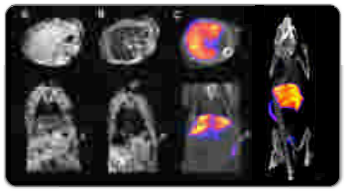
Easy labeling; stable bond *in vitro* (up to 48 h at 37 C in human serum or saline)

BP-iron oxide bond is stable *in vivo*



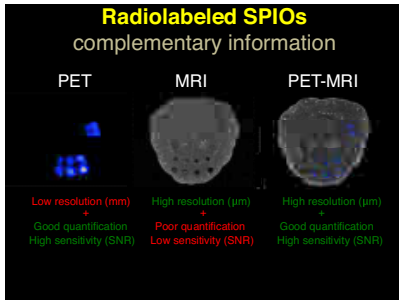
T. M. de Rosales *et al. Bioconjugate Chem.* 2010, *22*, 455-465

Radiolabeled SPIOs can be detected using two imaging modalities (nuclear-MRI)

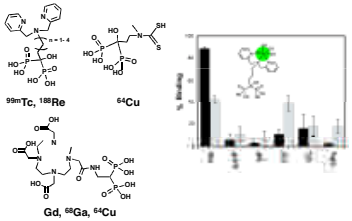


T. M. de Rosales *et al. Bioconjugate Chem.* 2010, *22*, 455-465

Radiolabeled SPIOs complementary information



Metal-binding bifunctional BPs: imaging bone metastases and calcified tissues



T. M. de Rosales *et al. Chem. Commun.* **2009**, 4847; *Bioconjugate Chem.* **2010**, *21*, 811; *Angew. Chem. Int. Ed.*, **2011**, *50*, 5509

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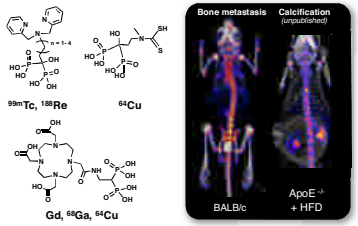
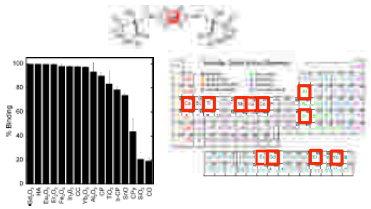


T. M. de Rosales *et al. Chem. Commun.* **2009**, 4847; *Bioconjugate Chem.* **2010**, *21*, 811; *Angew. Chem. Int. Ed.*, **2011**, *50*, 5509

BPs also bind strongly to many metal oxide materials

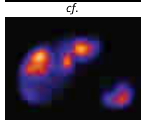


T. M. de Rosales *et al. Angew. Chem. Int. Ed.*, **2011**, *50*, 5509

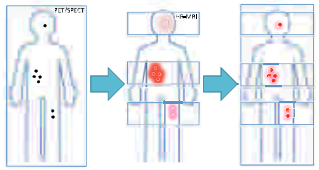
Superparamagnetic iron oxide nanoparticles

SPIOs
- MRI contrast agents
- Mainly T2 contrast
- Biocompatible
- Poor quantification
- Difficult to locate

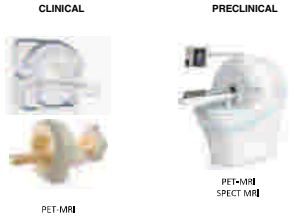
cf.



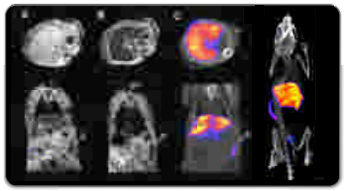
Efficient detection/quantification of SPIO biodistribution using PET-MRI



PET-MR (SPECT-MRI) now available



To achieve targeting need to avoid RES uptake

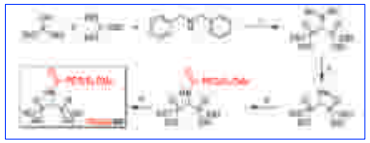


T. M. de Rosales *et al. Bioconjugate Chem.* 2010, *22*, 455-465

PEGylation prevents RES uptake

Scheme taken from: Jokerst *et al.* Nanomedicine (Lond). 2011 June ; 6(4): 715

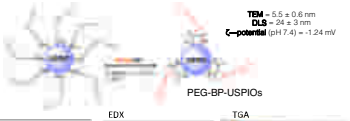
PEG-BP synthesis

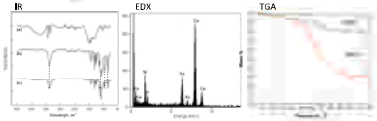


2 kDa
5 kDa
10 kDa

Sandiford *et al. ACS Nano*, **2013**, *7*, 500

PEG-BP efficiently coats SPIOs





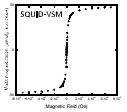
→ **High PEG surface density**: 0.9 PEGs/nm² (76 %) or 86 PEGs/USPIO

Magnetic properties at 3T MRI

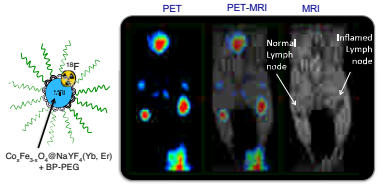
USPIO	D_{core} (nm)	D_H (nm)	coating	r_1 (mM^{-1}s^{-1})	r_2 (mM^{-1}s^{-1})	r_2/r_1	medium	T (°C)
PEG(5)-BP-USPIOs	5.5	23	PEG-BP	9.5	28.2	2.97	H_2O	RT
ESION	2.2		PEG-PO	4.8	17.5	3.65	H_2O	
VSOP-C184	8.6	19	citrate	8.0	34.0	4.25	H_2O	37
ESION	3	15	PEG-PO	4.8	29.2	6.08	H_2O	
Feruspio XS		18	carboxydextran	5.4	36.3	6.72	H_2O	RT
Ferucarbotran (Sapreist)	3 – 5	21	carboxydextran	7.3	57.0	7.81	H_2O	37
Ferumoxytol (CT228)	6.7	35	carboxymethyldextran	7.5	92.0	12.27	H_2O	37
Ferumoxtran-10 (Sinerem)	4.5	34	dextran + citrate	5.0	66.0	13.20	H_2O	37
ESION	12	-	PEG-PO	2.4	58.8	24.50	H_2O	-

Properties of PEG-BP-USPIOs

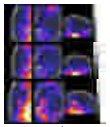
- Small iron oxide core → low mass magnetisation
- Strong and stable BP-FeO binding (> 9 months in H_2O and saline)
- High surface density (76%)
- PEG-BP → hydrophilic (water molecules reach the NP surface)
- No aggregation in H_2O/saline/serum (prevents increase in r_2)
- → no protein binding



Bimodal SPIOs: Non-invasive lymph node imaging Using PET-MRI

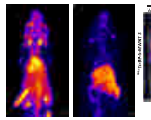


Other applications



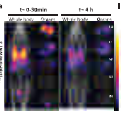
Brain uptake
Intranasal delivery PET-SPIOs

Collaboration with
Prof Ijeoma Uchegbu UCL
Dr M C Jones (Birmingham)
Unpublished results



Macrophage blocker PET-SPIOs

Collaboration with
Prof Kerry Chester UCL
Manuscript in preparation



Radiolabeling of SPIO-CNTs

Collaboration with
Dr K. Al Jamal, KCL
Adv. Funct. Mater. **2014**, *24*, 1880–1894
Small **2016**, *IN PRESS*

Conclusions

- **BPs are excellent anchors** to functionalise iron oxide, nanomaterials
  - Radiolabeling → Imaging
  - PEG → Stealth (High density and stability) + T1 MR contrast
  - Targeting → Imaging/therapy
- **Radiolabelling** enhances magnetic nanoparticle contrast agents (in the context of PET-MRI) by:
  - Increase **sensitivity** and **quantification** properties
  - **PET signal to guide HR-MR** → surgery/therapy planning

Acknowledgements

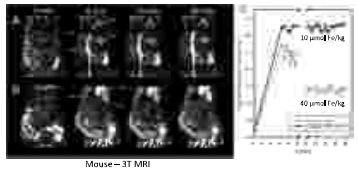
- Dr Richard Tavare (Now at UCLA, USA)
- Dr Lydia Sandiford (Now at UNSW, Australia)

Collaborators

- Prof Blower (KCL, Radiochemistry)
- Rene Botnar / Alkystis Phinikaridou (KCL, MRI)
- Yves Gossuin (Mons, Relaxometry)
- C. Halldin & B. Gulyas (Karolinska Institutet)
- Michael Douek (KCL/NHS, breast cancer/melanoma surgeon)

Medical Engineering Centre at King's
EPSRC Engineering and Physical Sciences Research Council
King's College London
wellcome trust
NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and KCL

PEG-BP-USPIOs have long circulation times

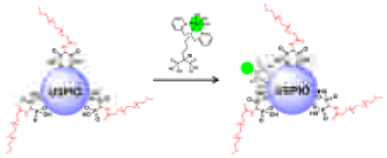


Mouse – 3T MRI

Low injected dose
Standard- 40-70 µmol Fe/kg
Adverse effects – 60 µmol Fe/ kg

Long-blood half-life → useful for **high-resolution MRA**
- tumour angiogenesis
- aneurysms
- internal bleeding

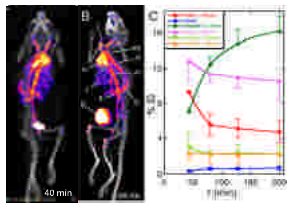
Radiolabeling PEG-BP-USPIOs



Radiolabeling yield – 47%
In vitro stability – 94% after 48h in serum at 37°C
Doesn't affect properties – size, magnetic

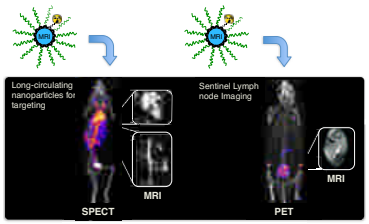
Sandiford *et al. ACS Nano*, **2013**, *7*, 500

PEG-BP-USPIOs have long circulation times



Approx. 85% remain in the bloodstream after 3.3 h.

Bimodal SPIOs – other applications



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Bioconjugate Chem., **2010**, *22*, 455
Angew. Chem. Int. Ed., **2011**, *50*, 5509

PET-MR (SPECT-MR)

- The use of MRI benefits from:
  - higher anatomical soft-tissue contrast
  - More than anatomy – (contrast agents, ^{1}H, ^{19}F, ^{31}P, Hyp, CEST…)
  - no ionising radiation
  - simultaneous acquisition of the two modalities (PET-MR)
    - Motion/attenuation correction of PET using MRI