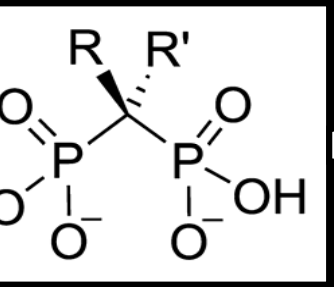
Bisphosphonate-SPIO Nanoparticle Conjugates for Dual-modality PET/SPECT-MR Medical Imaging

Rafael Torres

Division of Imaging Sciences & Biomedical Engineering

KING'S College LONDON

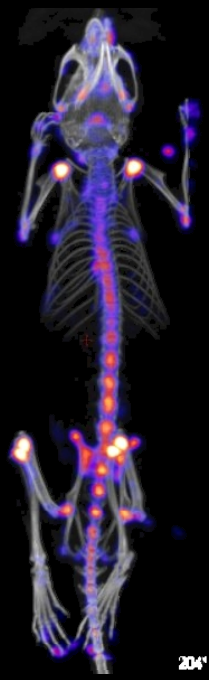
Bisphosphonates as Imaging Agents



+ Fe_3O_4 NPs

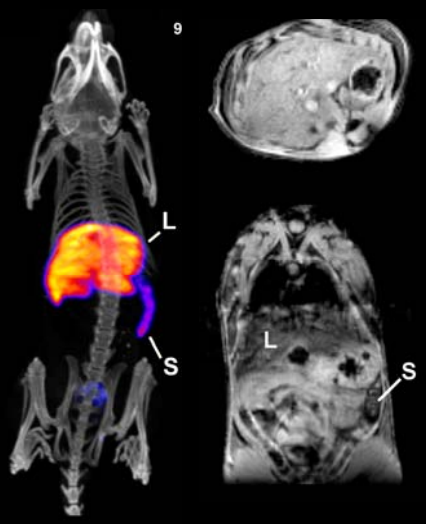
+ Fe_3O_4 NPs

1



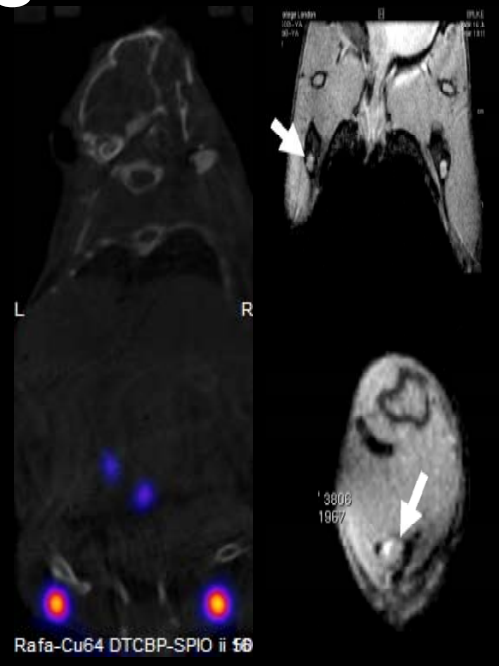
PET/SPECT
Bone metastases imaging and therapy

2



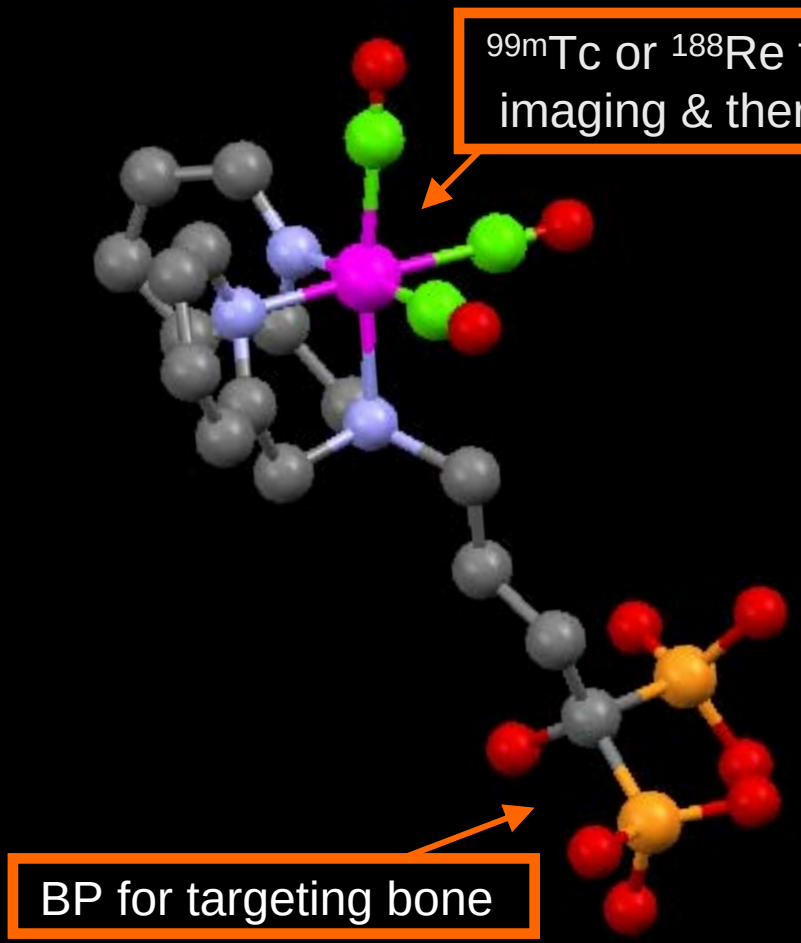
SPECT-MRI
Vascular target imaging

3



PET-MRI
Lymph node imaging

^{99m}Tc/^{188}Re-DPA-Ale

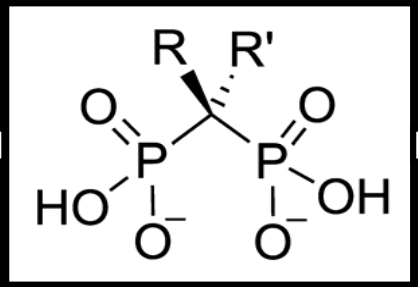


SPECT-CT

R. Torres *et al. Chem. Commun.* **2009**, 4847
R. Torres *et al. Bioconjugate Chem*. **2010**, *21*, 811

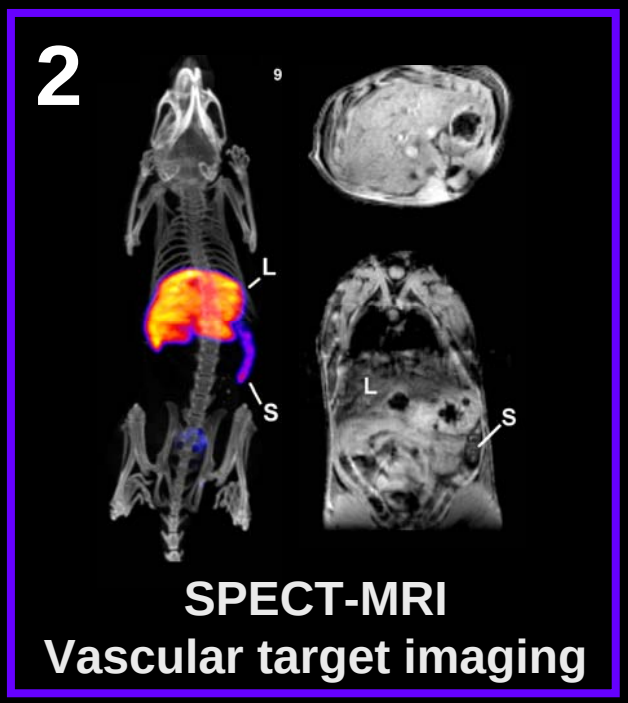
Bisphosphonates as Imaging Agents

PET/SPECT
Bone metastases imaging and therapy

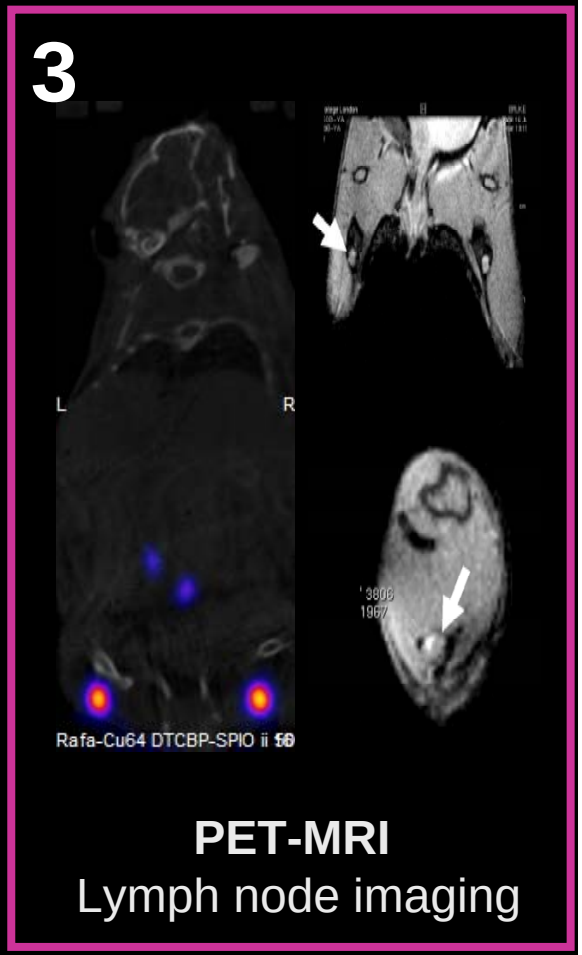


+ Fe_3O_4 NPs

+ Fe_3O_4 NPs



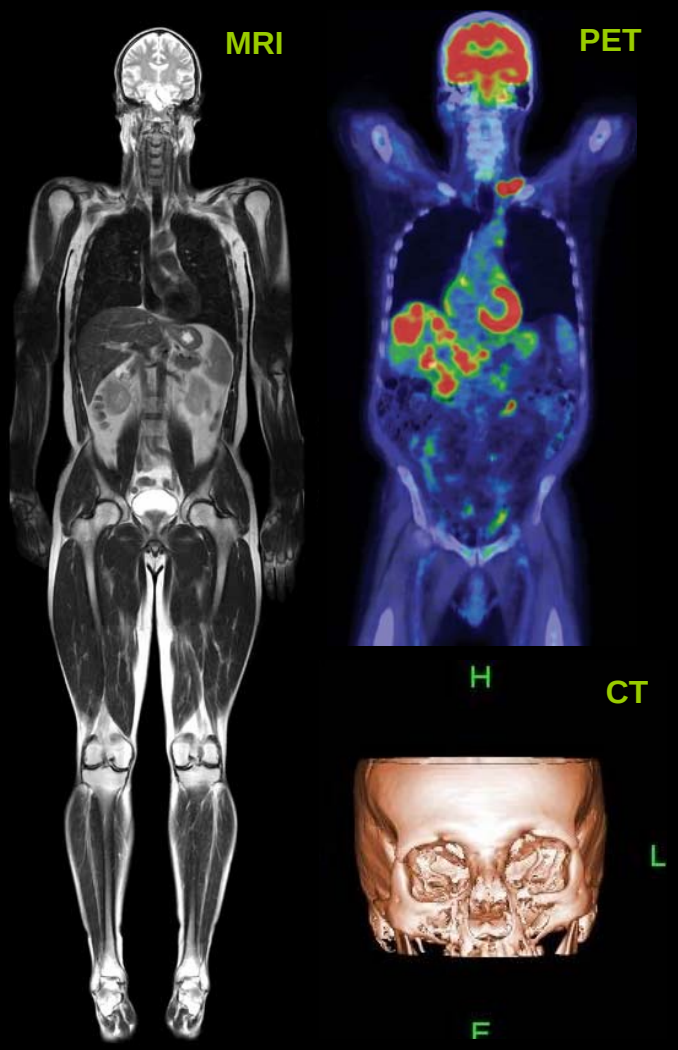
SPECT-MRI
Vascular target imaging



PET-MRI
Lymph node imaging

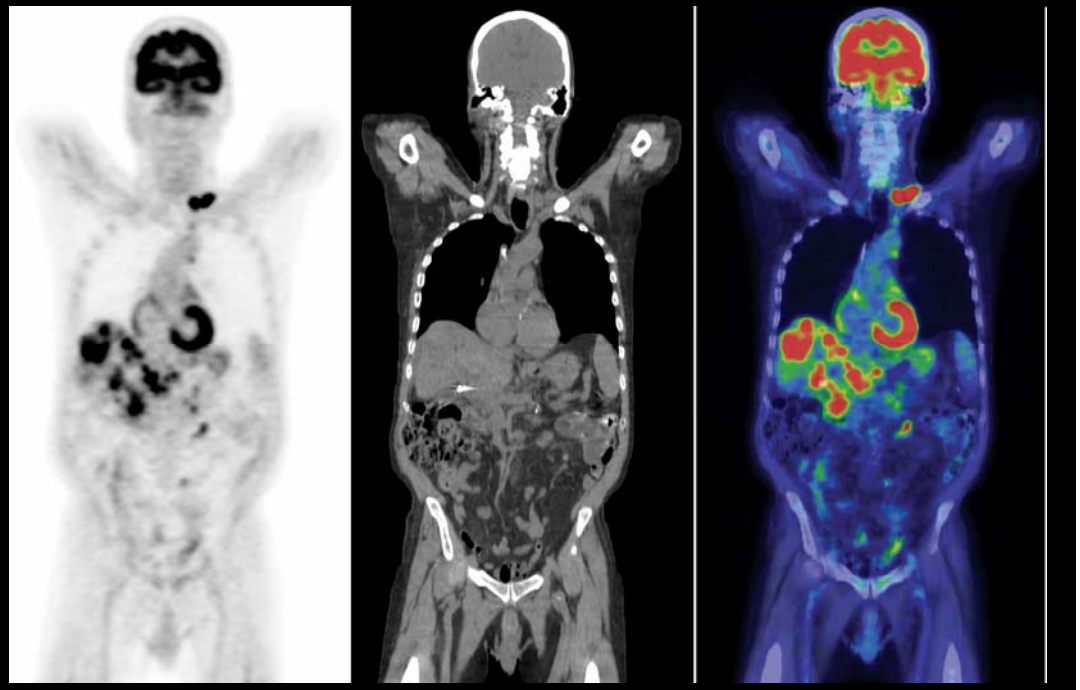
Medical Imaging Techniques: strengths and weaknesses

- Radionuclide-based techniques (PET & SPECT)
  - very sensitive
  - spatial resolution is low (≥ 1 cm)
- Non-radionuclide based techniques (CT and MRI)
  - high spatial resolution (≤ 0.01 cm)
  - low sensitivity
- Lack of a “perfect imaging technique” drives the efforts to develop **dual-modality imaging instruments and agents** → strengths of techniques can be synergistically combined



Dual-modality imaging instruments

- Dual-modality instruments are already being used in most clinics (SPECT-CT and PET-CT)
- The SPECT or PET component provides molecular information of the physiology and the CT anatomical information.



PET + CT = PET-CT

PET-MR (SPECT-MR?)

- The most promising alternative for CT in dual-modality instruments is MRI.
- The use of MRI benefits from:
  - no ionising radiation
  - High soft-tissue contrast
  - possibility of simultaneous acquisition of the two modalities (PET-MR)
    - reducing time spent by patients in the scanner
    - two modalities taken under the same physiological conditions and spatial positioning

Siemens Healthcare

Dual Modality PET-MR imaging agents

- **Recent interest in dual-modality imaging agents** → complementary information from both imaging techniques can be gained.

- *E. g.,* **quantification** of the biodistribution **of SPIO-based** contrast agents **using MRI** is often difficult to perform.
  - Artifacts from air, tissue/air interfaces and motion.
  - Can be time-consuming.

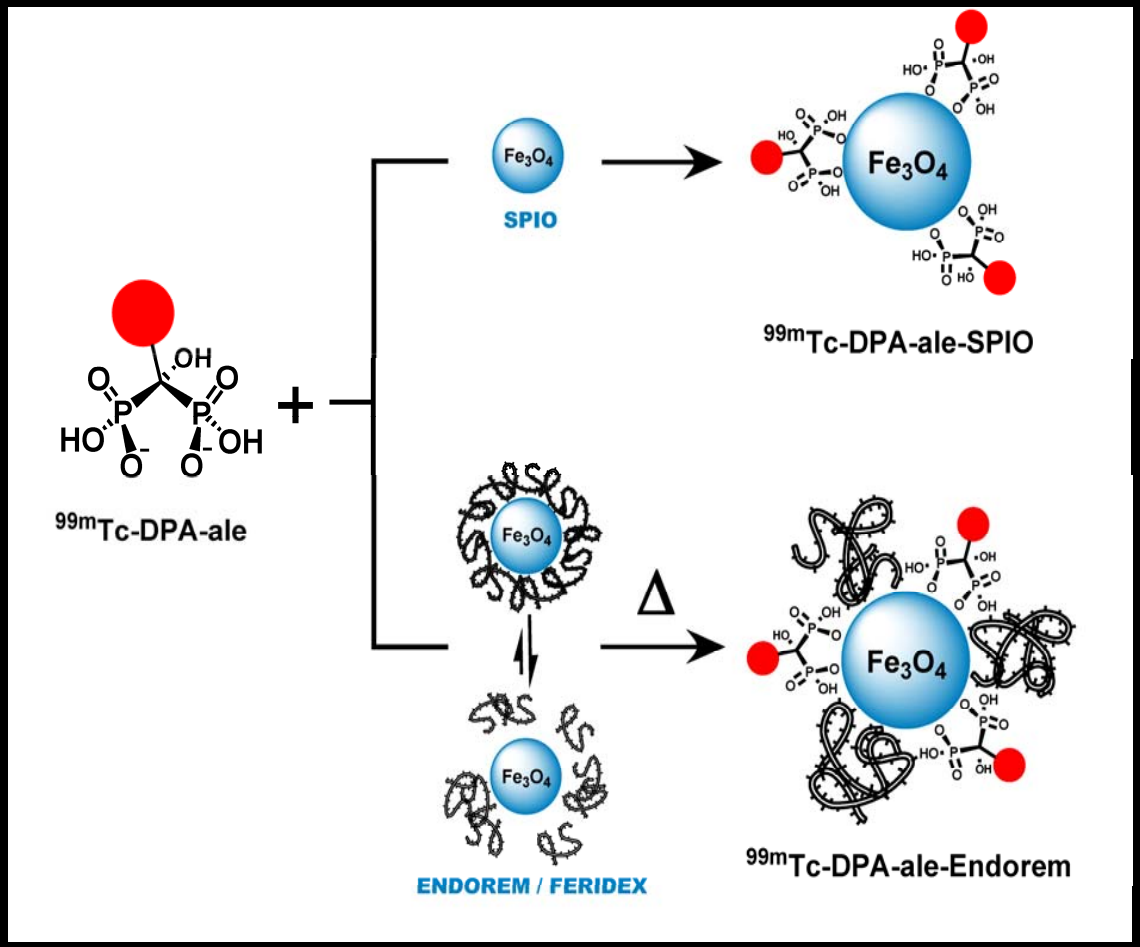
- On the other hand, **quantification** of photons emitted by radionuclides **using PET or SPECT** is an accurate and fast process
  - Unlike for MRI, quantification of the tracer is independent of its micro-environment *in vivo*.

Dual Modality PET-MR imaging agents?

- Adding a radionuclide component to SPIO-based MRI agents should allow **easy and accurate quantification** of their biodistribution, even with low amounts of tracer

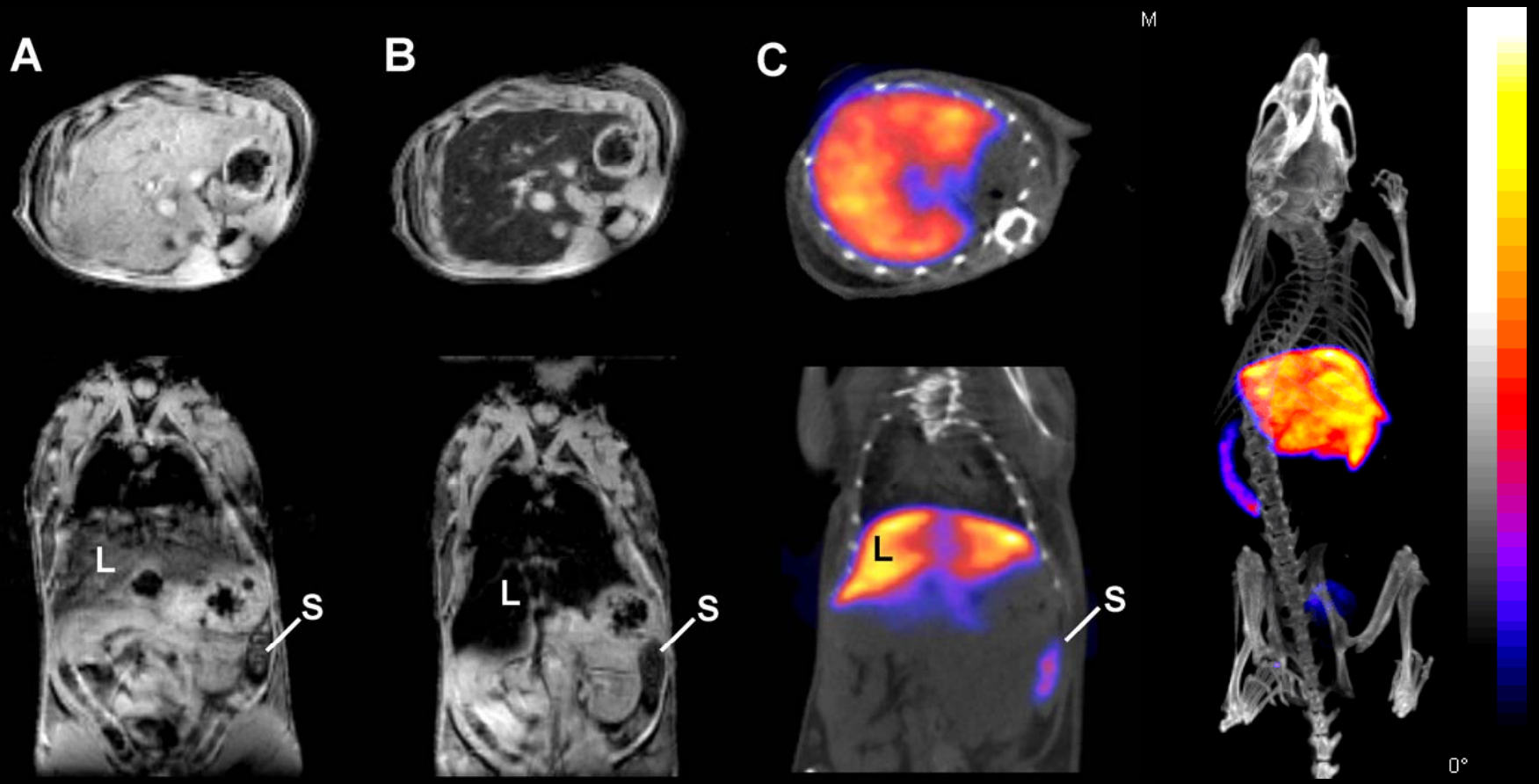
→ Increase sensitivity of SPIO tracers

Bisphosphonates as SPECT/PET-MR Imaging Agents



1. BP-SPIO interaction is highly stable (at least 48 h in PBS & serum)
2. Can label coated and non-coated SPIOs
3. Radiolabeled Endorem, a liver and spleen MR contrast agent.
4. Labeling does not affect size or relaxometric properties

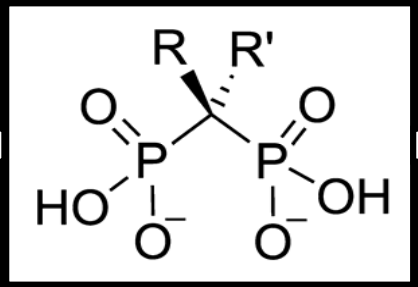
^{99m}Tc-DPA-ale-Endorem: *In vivo* MRI & SPECT-CT studies



R. Torres et al. Bioconjugate Chem. **2010**, *22*, 455-465

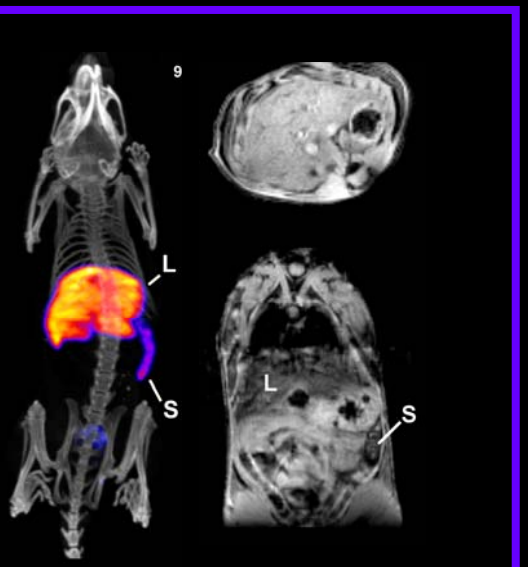
Bisphosphonates-nanoparticle Conjugates as Imaging Agents

PET/SPECT
Bone metastases imaging and therapy

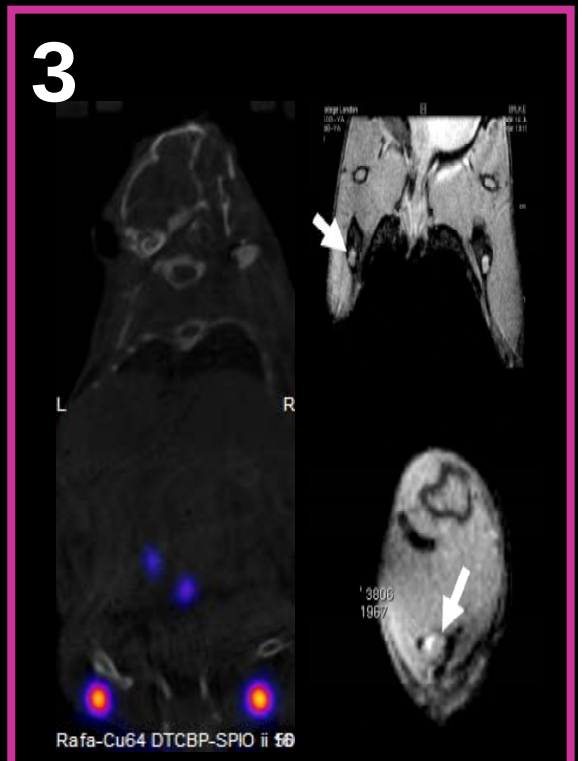


+ Fe_3O_4 NPs

+ Fe_3O_4 NPs

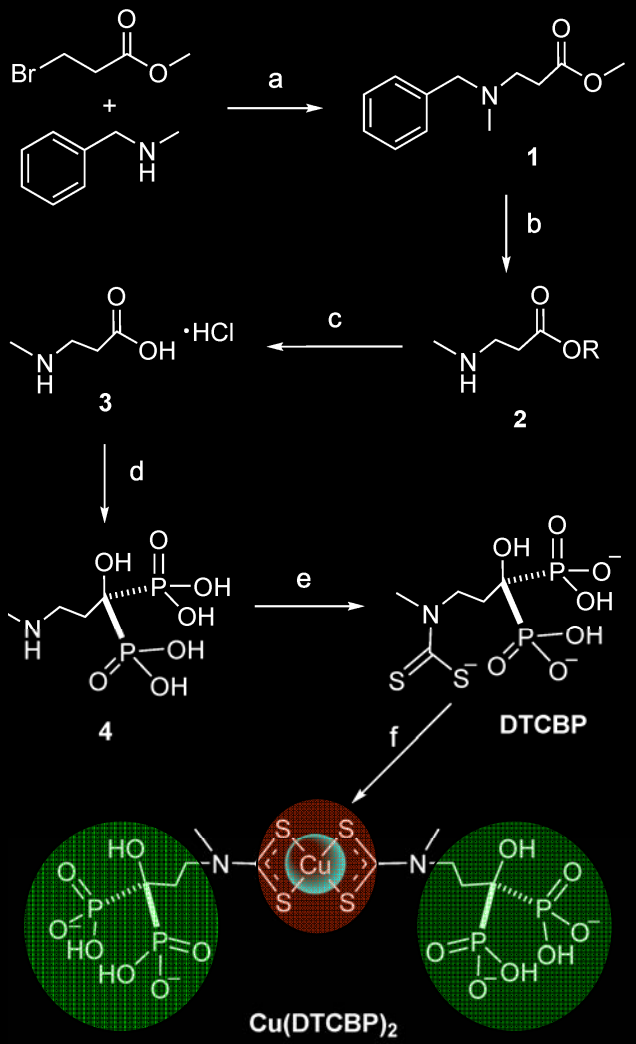


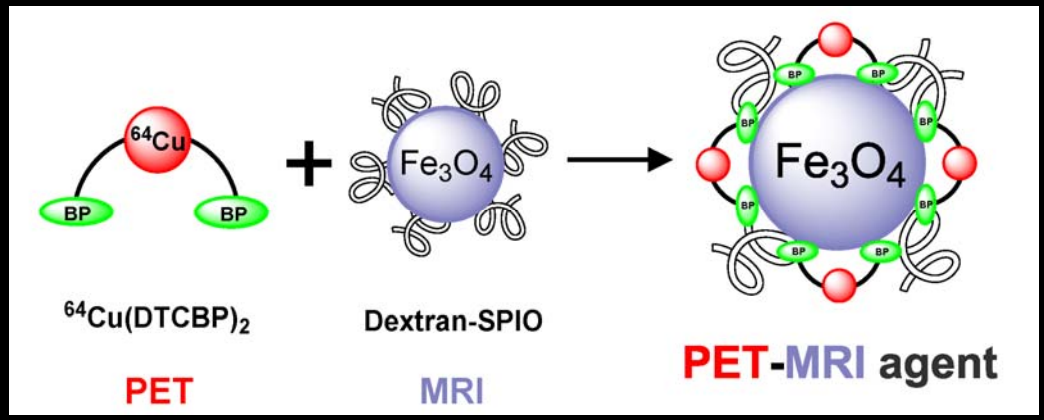
SPECT-MRI
Vascular target imaging



PET-MRI
Lymph node imaging

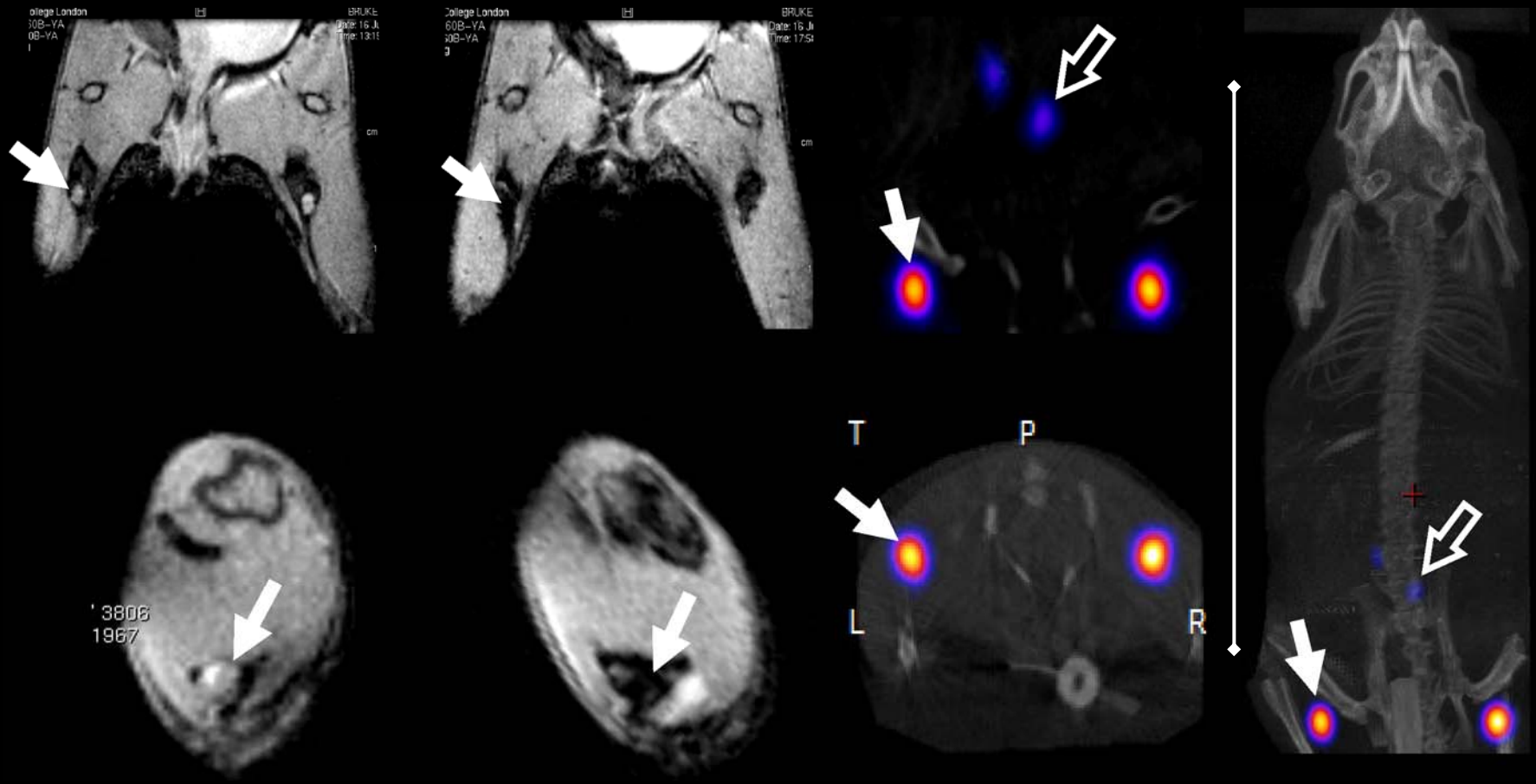
Bisphosphonates as PET-MR Imaging Agents





R. Torres *et al. Angew. Chem. Int. Ed.*, **2011**, (in press)
DOI: 10.1002/anie.201007894

$^{64}Cu(DTCBP)_2$-ENDOREM: *In vivo* PET-MR studies



R. Torres *et al. Angew. Chem. Int. Ed.*, **2011**, In Press, DOI: 10.1002/anie.201007894

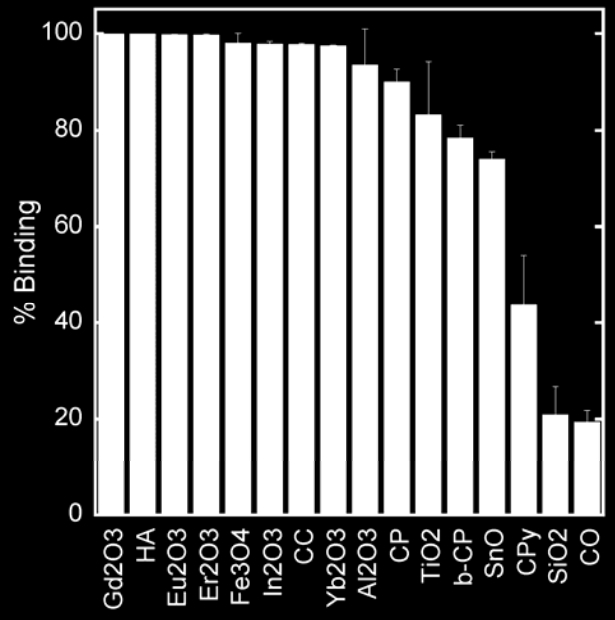
Conclusions

1. The BP is a versatile group for the development of metal-based imaging agents
2. We have developed a series of BP-based bifunctional chelators for several metallic radionuclides of interest in PET and SPECT imaging and therapy (^{99m}Tc, ^{64}Cu, ^{188}Re)
3. Developed a new class of multimodal imaging agents based on the BP-iron oxide interaction

Conclusions

5. Addition of a PET or SPECT component to SPIO NPs may be useful for the *in vivo* tracking and quantification of SPIOs and SPIO-labelled cells.

5. BPs bind strongly to many materials with proven and/or potential applications in imaging & biomedical engineering



- Gd_2O_3, Fe_3O_4, Mn_2O_3 → MRI contrast
- Eu_2O_3 → Fluorescence
- HAp, CC, CP, TiO_2, SiO_2 → Highly biocompatible, drug delivery

Acknowledgements

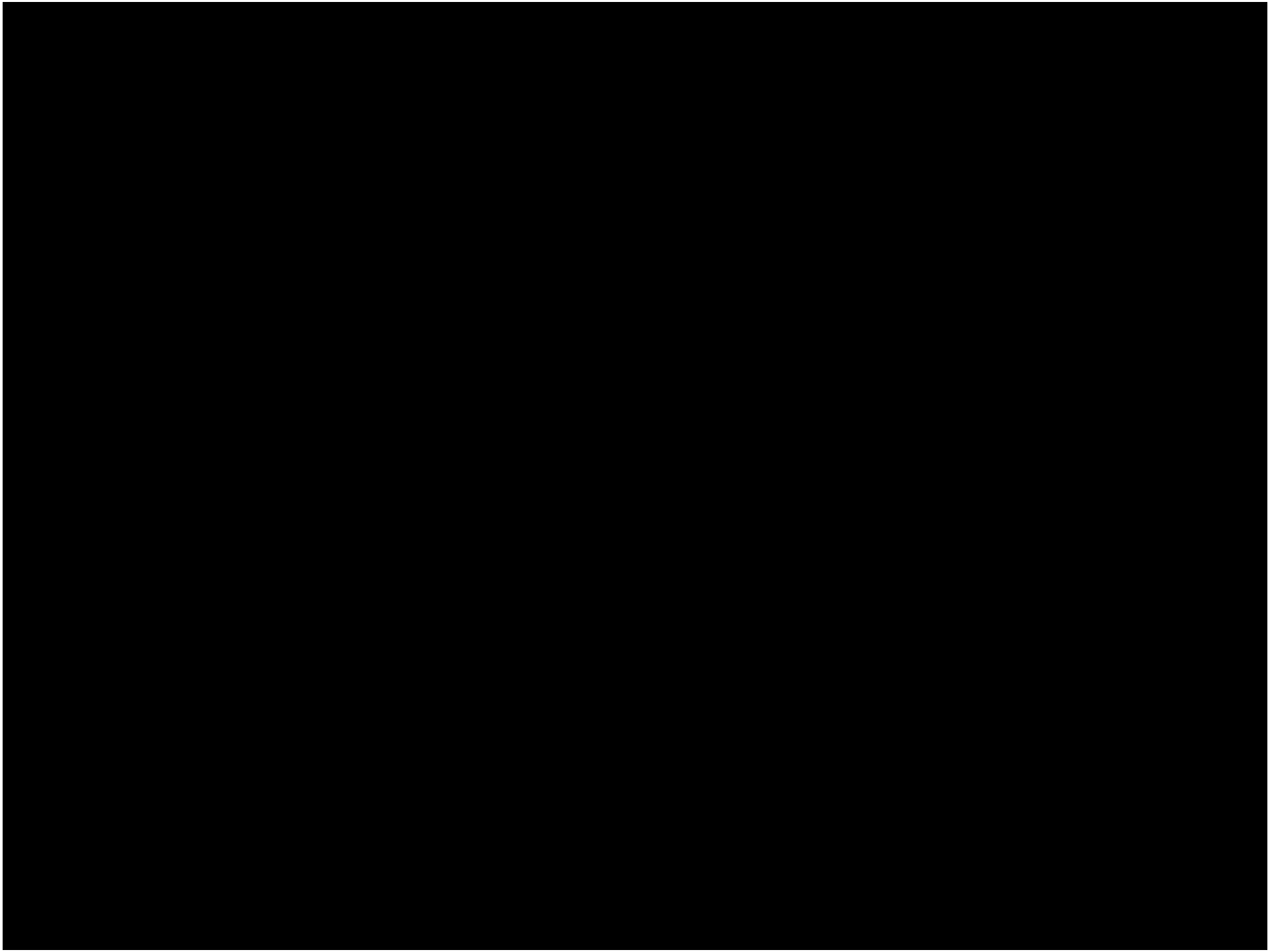
- Department of Imaging Chemistry & Biology at King's (Phil Blower)
- A. Protti, G. Varma & K. Shaw (MRI, NMR)
- R. Tavare, I. Szanda & K Sunassee (PET & SPECT imaging)
- A. Glaria, M. Green (TEM & DLS)
- R. Paul. M. Jauregui & K. Shaw (Cu-64)

- **Funding:**

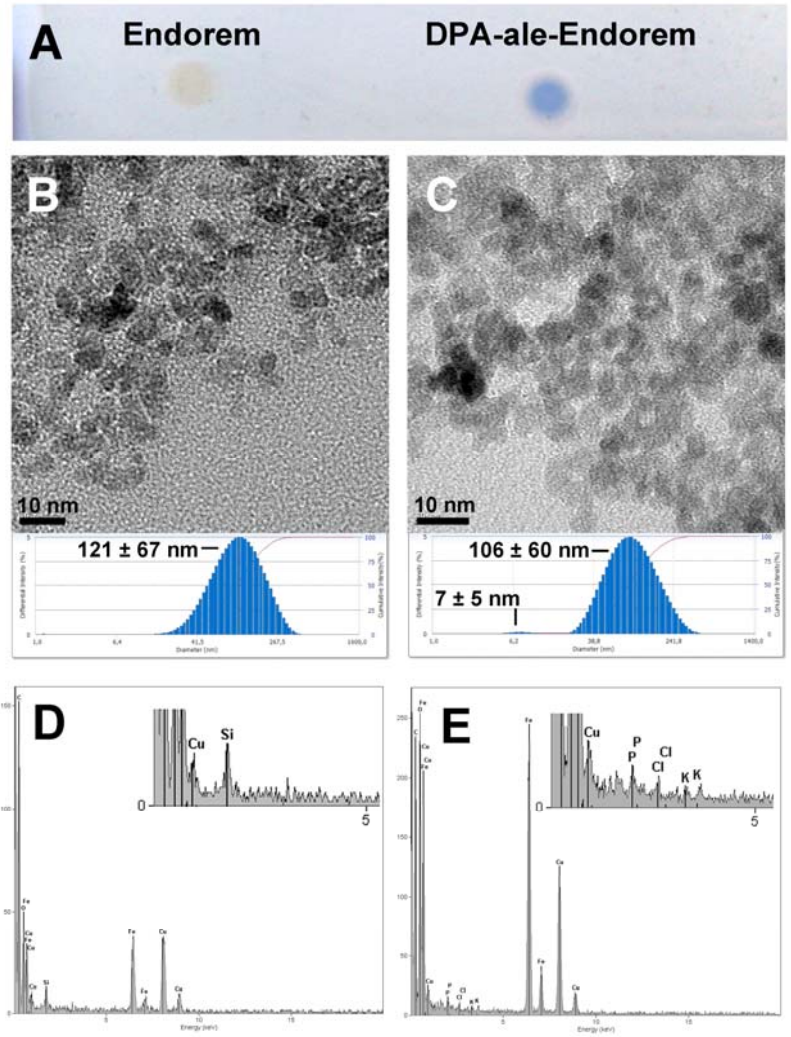
CANCER RESEARCH UK

EPSRC
Engineering and Physical Science Research Council

wellcome trust



BP-SPIO: Characterisation



TEM

DLS

EDX