Research Objectives

Fernando Herranz and Juan Pellico Sáez, together with their collaborators, research nanoparticles that produce signal in positron emission tomography (PET) and magnetic resonance imaging (MRI) at the same time.

Detail

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Bio

Fernando Herranz is an organic chemist working in nanomedicine for the last 15 years. His expertise is focused on the development of imaging probes for the multimodal diagnosis of cardiovascular diseases. Currently, he leads the NanoMedMol group of the Spanish Research Council.

Juan Pellico Sáez obtained his PhD degree in Chemistry from the Complutense University of Madrid (UCM) in 2016. Then, he got a Spanish grant to conduct postdoctoral research in the Spanish Centre for Cardiovascular Research (CNIC). In 2018, he moved to the University of Oxford as a PDRA. Finally, he joined to the group of Dr Rafael T.M. de Rosales at King's College London in 2019 as a Post-Doctoral Research Associate. His main area of interest combines novel particulate PET tracers with the application of nanotechnology in biomedicine to develop a new generation of imaging agents for multimodal molecular imaging applications.

References


Personal Response

What are the next steps in your research? Do you plan to test your probes in human patients?

The next steps with these probes are centred in two aspects: first, we are using the 68Ga core-doped iron oxide nanoparticles to study neurovascular diseases, focusing on the early diagnosis and characterisation of stroke. We have always been interested in the diagnosis of vascular diseases and find particularly appealing the vascular feature of neurological diseases. Secondly, we are testing our probe in atherosclerotic pigs as a translational model, with the final aim of testing them in humans. Pigs are the best atherosclerotic model at the moment, the closest to humans, and this is allowing us to tune several aspects of the nanoparticles to solve the differences you find when moving from mice to rabbits and pigs.
**68Ga core-doped iron oxide nanoparticles for the development of PET and positive contrast MR imaging probes**

Recent developments in molecular imaging have enabled the direct and non-invasive visualisation of pathological processes. Dr Juan Pellico Sáez at King’s College London and Dr Fernando Herranz with his team from the Nanomedicine and Molecular Imaging group, at Medicinal Chemistry Institute, a centre of the Spanish Research Council, have developed and optimised a new kind of imaging probes, which contain a radioactive isotope (68Ga) embedded in the core of iron nanoparticles. Their nano-tracers produce signals in positron emission tomography (PET) and positive contrast in magnetic resonance imaging (MRI) at the same time, allowing diagnostic methods to be developed that exploit the best features of both techniques.

Molecular imaging is one of the most promising tools for the advancement of medicine, as it allows to diagnose diseases in a non-invasive fashion. Key to this approach is the use of imaging probes that are capable of detecting biological events by producing signals in, at least, one imaging technique.

Dr Fernando Herranz and his team from the Nanomedicine and Molecular Imaging group, at Medicinal Chemistry Institute, a centre of the Spanish Research Council, research and optimise iron oxide nanoparticles that produce signals in both positron emission tomography (PET) and positive contrast in magnetic resonance imaging (MRI) at the same time. The combination of these two imaging techniques is one of the most advantageous in the medical imaging field. The Herranz team’s approach combines the sensitivity of PET with the anatomical resolution of MRI.

Dr Herranz and Dr Juan Pellico Sáez at King’s College London, together with their collaborators, demonstrate that this new kind of imaging probes, which contain a radioactive isotope (68Ga), ensure a strong PET signal that can be used successfully for the diagnosis of different cardiovascular diseases, including atherosclerosis and thrombosis.

**SYNTHESIS AND OPTIMISATION OF THE NANOPARTICLE TRACERS**

The design of dual-modality PET/MRI nanoscale systems for use in medical imaging requires the combination of a radioisotope and a bio-compatible nanomaterial. Gallium-68 is a positron-emitting radionuclide with a relatively short half-life, which makes it ideal for limiting the dose exposure to patients. Iron nanoparticles are a well-known system that has been used in medical imaging for some time.

The nanoparticles are ‘core-doped’ with 68Ga through a process where the radionuclide is incorporated in the nanoparticle core by a microwave-driven, fast temperature ramping. Dr Herranz and his team carried out the core-doping of iron oxide nanoparticles without the use of chelators, molecules acting as a bridge between the iron and the radioisotope. By adopting this approach, the team was able to produce extremely small (2.5 nm) nanoparticles.

Unlike traditional imaging approaches where the signal consists in a darkening of the image through negative contrast, the method developed by Dr Herranz and his colleagues produces positive signals. The findings demonstrate how nanotechnology and nuclear imaging can be combined for the non-invasive detection of inflammation.

The PET/CT imaging and MRI scan of a rabbit with circulating 68Ga iron oxide nanoparticles.
During acute inflammation, neutrophils are the first cell type to migrate from the bloodstream to the site of injury. Neutrophils have the very important function of eliminating pathogens by engulfing them and attacking them chemically with enzymes and reactive oxygen species. However, neutrophil invasion can cause major tissue damage in diseases like COPD and asthma.

IN VIVO IMAGING OF ATHEROSCLEROTIC LESIONS
Atherosclerosis is a complex disease of the blood vessel wall in which the accumulation of plaques inside the arteries is associated with a chronic inflammation state of the blood vessel’s inner lining, which is in part exacerbated by the oxidation of low-density lipoprotein (LDL).

Although many imaging probes of atherosclerosis have been studied, the search for a tool that provides clear in vivo detection is still ongoing. In a study published in 2019, Dr Herranz and Dr Pellico optimised their hybrid MR/PET nano-tracers for use in the diagnostic imaging of atherosclerosis lesions. Among the many targets present in the disease, they focused their attention on oxidised LDL, given its role in the initiation and progression of atherosclerosis.

Using a mouse model of atherosclerosis, they first treated the lungs of atherosclerosis-prone mice with an injection of chemically modified antibodies against oxidised LDL, followed by an injection with the MR/PET nano-tracers after 24 hours. The nanoparticles selectively accumulated in atherosclerotic plaques, by in vivo biorthogonal reaction, allowing the unambiguous detection of the lesions and enabling the structural characterisation of the damaged tissue.

These results show that the method developed by Dr Herranz and his team can be adapted and expanded to cardiovascular diseases and other in vivo imaging applications.

IN VIVO DETECTION OF THROMBOTIC EVENTS
Thrombo-inflammatory disease, which includes ischemic heart disease and stroke, is the single most common underlying cause of death worldwide. Thrombotic events can take place in a range of minutes and can lead to potentially devastating consequences, such as long-term disability.

Current detection methods in patients are performed indirectly, by visualising the lack of blood flow rather than the thrombus itself. This implies that the size of thrombus has to be estimated rather than measured, and that non-occlusive thrombi are likely to be left undetected. The development of methods that directly assess and measure the size of thrombi in tissues is an urgent biomedical need that would be of benefit in many clinical settings, including stroke or deep vein thrombosis.

In a recent paper published in 2020, Dr Herranz and his colleagues reported on the use of the 68Ga core-doped iron oxide nanoparticles as PET/MRI nano-tracers for the in vivo detection of thrombi in mice. To achieve their aim, they developed an in vivo generated probe, named thrombo-tag, capable of detecting thrombus formation by PET in only minutes. Thrombo-tag consists of an antibody that targets the membrane of platelets accumulating in thrombi and the imaging probe generating the PET/MRI signal. Thrombo-tag only exists in vivo, coming into existence when its two main components react after co-injection.

The findings presented in the study demonstrate how nanotechnology and nuclear imaging can be combined for the non-invasive detection of inflammation with high in vivo selectivity towards neutrophils. The high level of labelling and the high specificity for neutrophils confirmed unambiguously the state of acute inflammation in the lungs, with unprecedented clarity of the images produced.

The nanoparticles selectively accumulated in atherosclerotic plaques, allowing the unambiguous detection of the lesions and enabling the structural characterisation of the damaged tissue.

CONCLUDING REMARKS

Dr Herranz and Dr Pellico with their team have optimised an extremely versatile in vivo imaging method, which involves the use of nano-tracers that combine the properties of iron oxide nanoparticles with the unparalleled sensitivity of PET imaging. The incorporation of 68Ga isotope in the iron oxide core allows multiple applications without the drawbacks associated with the use of chelators and the small size of the nanoparticles allows the production of a positive-contrast, bright MRI signal.

Their multifunctional nano-tracers have been used for the successful in vivo diagnosis of lung inflammation, atherosclerosis and thrombi formation in animal models.

The nanoparticles under the microscope.
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