STARSTEM

2018
Newsletter

Shedding new light on regenerative medicine

STARSTEM | NanoSTARS imaging for STEM cell therapy for arthritic joints

STARSTEM is poised to revolutionise cell therapy by providing unprecedented understanding about how these therapies actually work. Understanding the hallmarks of the healing process will help researchers and doctors to treat a wide range of human diseases.

We use nanotechnologies for imaging in regenerative medicine – a branch of medicine that is dedicated to developing therapies which can regrow, repair, or replace damaged or diseased cells, organs, or tissues. Regenerative cell therapy, which involves the use of stem cells to restore healthy function, represents one of the most promising therapeutic modalities for chronic diseases. Over the years, regenerative medicine research has demonstrated some promising findings for everything from heart disease to cancer, diabetes to Alzheimer's disease, and arthritis.

In STARSTEM, gold nanostars will be used to tag cells and sub-particles of cells called extracellular vesicles and exosomes. Sophisticated photo-acoustic imaging technologies will be employed to monitor the cells' pathways and interactions in the healing processes. STARSTEM specifically examines osteoarthritis, but our approach will have a wider impact on a spectrum of biologic therapies.

STARSTEM is a European project, with partners hailing from five countries; Ireland, Germany, England, Spain, and Italy. The project brings together leaders in the nano-materials, regenerative medicine, osteoarthritis, and bio-imaging fields from across Europe. We are using fundamental advances in the physics of imaging to validate stem cell treatments for arthritis. The project results will allow researchers and eventually, hospital doctors, to detect and measure the healing effects of novel cell therapies, even where they occur under the skin. We hope that this will ultimately result in better treatments for patients.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 761214.

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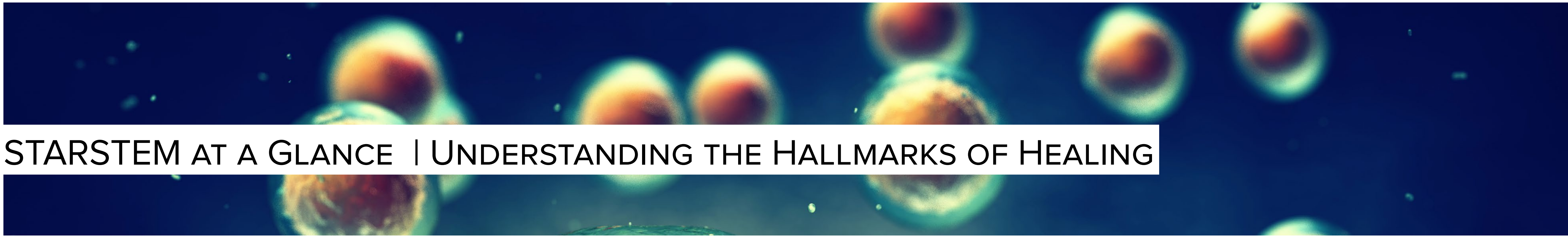


STARSTEM AT A GLANCE | UNDERSTANDING THE HALLMARKS OF HEALING

STARSTEM is devoted to understanding how mesenchymal stem cells (MSCs) and extracellular vesicles lead to healing. Understanding the hallmarks of the healing process will help researchers and doctors to treat osteoarthritis and a wide range of diseases. Arthritis is the most prevalent disease worldwide, with osteoarthritis affecting around 10% of the global population, and around 70 million patients in Europe. There is no effective cure for osteoarthritis at present and the majority of the treatments are symptomatic and not restorative.

Stem cell therapy provides a unique opportunity for osteoarthritis. Nevertheless, one of the major hurdles in stem cell therapy is the inability to detect the biodistribution and successful engraftment of cells and sub-cell particles in real time. Conventional imaging techniques are simply not sufficient.

STARSTEM is developing methods to image stem cell engraftment in arthritic joints at clinically relevant depths. We do this by using nanoparticles with novel optical properties. Plasmonic gold nanostars will be attached to stem cells and exosomes prior to therapeutic infusion. We then harness the best properties of light and sound with a photo-acoustic (PA) imaging system to exploit the unique advantages of our nanostars for differential and deep-tissue imaging. These nanostars greatly enhance molecular sensing and diagnostics by increasing the signal contrast during the visualization process.

PA imaging enables the real-time monitoring of engraftment and the therapeutic processes at the site of interest, while highly sensitive anatomical imaging using MRI (via magnetic nanoparticles as the contrast agent) enables tracking

"STARSTEM is an exciting opportunity to use fundamental advances in the physics of imaging to validate stem cell treatments for arthritis. Once demonstrated in this application the STARSTEM technology can be used to enable a wide range of stem cell therapies." - Prof. Martin Leahy.

of the movement and retention of transplanted cells and exosomes. In parallel, STARSTEM is developing new algorithms for co-registered PA-MRI imaging which will enable the monitoring of the therapeutic processes with high sensitivity and in series over time. Crucially, PA imaging is non-invasive and non-traumatic. For regenerative medicine, this means we can track cell therapies across multiple treatments, over time via multiple images or indeed in real time.

STARSTEM brings together leaders in the nano-materials, regenerative medicine, and bio-imaging fields from across Europe. We are using fundamental advances in the physics of imaging to validate stem cell treatments for arthritis. The project results will allow researchers and eventually, hospital doctors, to detect and measure the healing effects of novel stem cell therapies, even where they occur under the skin. Understanding the dynamics and distribution of stem cells means that it will be possible to optimise treatments for patients.

The key problems to be solved:

STARSTEM is devoted to understanding how stem cells and exosomes lead to healing.

Key questions to be asked:

- Where do they go and how quickly do they get there?
- How many stem cells actually engraft themselves in the area of interest?
- How does healing occur over time?

STARSTEM at a Glance | The Story so far

STARSTEM kicked-off in January 2018 and will run for four years. In the first 6 months of the project, we held our kick-off consortium meeting, launched our website (starstem.eu), have worked on the necessary regulatory issues and ethical approvals, and have begun work on our novel nanotechnologies and cell therapy for osteoarthritis.

Events and conferences

The initial six months of the project have been busy, and the team has presented STARSTEM at a number of key conferences and events.

Dr. VJ Raghavan of the Tissue Optics and Microcirculation Imaging (TOMI) Lab at the National University of Ireland Galway presented STARSTEM at the SPIE Bios Photonics West conference. This conference ran from 27th January to 1st February 2018 at the Moscone Center in San Francisco, California, USA. VJ's presentation entitled "Plasmonic gold nanostars for biomedical imaging and theranostic applications" illustrates some of the research on which STARSTEM is founded.

Dr. Joshua Kaggie, a post-doctoral researcher, of the University of Cambridge presented at The International Society for Magnetic Resonance in Medicine (ISMRM), European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) conference in Paris which ran from 16th to 21st of June 2018. Josh's abstract, entitled "Magnetic Resonance Tracking ofIron-Labeled Stem Cells After Osteochondral Defect in Ovine Model" presents results from several studies, which will help inform the work carried out in STARSTEM.

STARSTEM brings together leaders in the nano-materials, regenerative medicine, osteoarthritis, and bio-imaging fields from across Europe.

As an invited speaker, PI Dr. Mary Murphy of the Regenerative Medicine Institute (REMEDI) presented STARSTEM at the Cúram Centre for Research in Medical Devices third annual retreat held in Nass, Co. Kildare in Ireland on 20th June 2018.

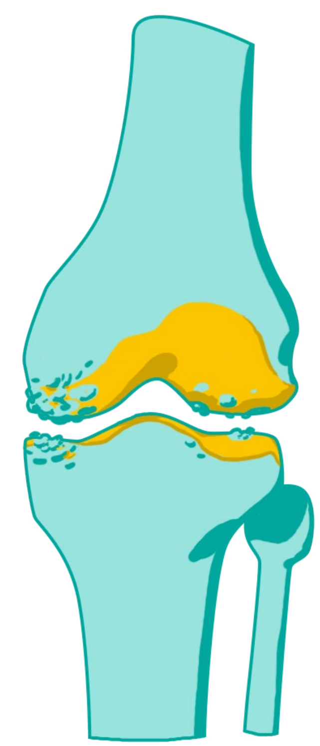
THE STARSTEM SCIENCE | MANAGING OSTEOARTHRITIS

Osteoarthritis is the most common form of arthritis and is a leading cause of disability worldwide. It affects around 10% of the global population and around 70 million patients in Europe. Osteoarthritis is caused by the wear and tear of cartilage in the joints over time. The breakdown of this protective cartilage means that the surface of joints become damaged and the surrounding bone grows thicker.

Knees are most commonly affected. The hands, hips, and the spine are often affected, but osteoarthritis can also affect any joint in your body. The primary symptom of osteoarthritis is pain, which leads to impaired mobility in older adults. Pain in the knees typically starts intermittently with weight-bearing before progressing to chronic pain. This means that over time, osteoarthritis makes it difficult to use affected joints and perform daily activities. Ultimately, this can have wide-reaching effects beyond the patient as support networks and family members step in to support the person afflicted. Signs and symptoms of osteoarthritis include pain, stiffness, weakness, swelling, limited range of motion, and clicking noises on movement.

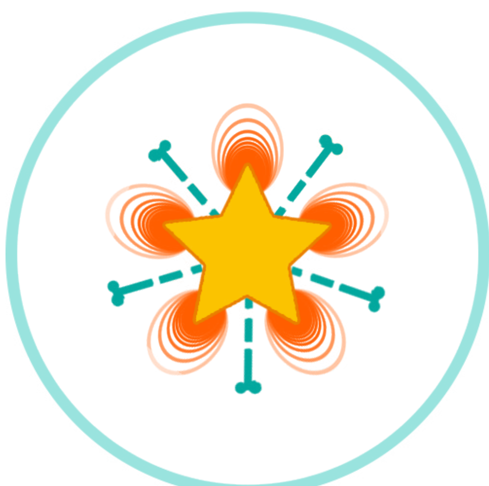
Osteoarthritis affects around 10% of the global population. There is no effective cure for osteoarthritis at present.

There is no effective cure for osteoarthritis at present, and the majority of treatments tackle the symptoms rather than treating the disease itself. Regenerative medicine, in particular, stem cell and exosome therapies, provides a unique opportunity for the regeneration of injured cartilage.



The STARSTEM Science | Regenerative Therapies

Regenerative medicine is a branch of medicine dedicated to developing methods which can help repair or replace cell, organ, and tissue function that has been lost. This could be due to age, disease, damage, or congenital defects. In STARSTEM, we use mesenchymal stem cells (MSCs) and extracellular vesicles (exosomes) to create cell therapies. MSCs are a type of cell which can be isolated from the mix of cells which comprise the bone marrow. Exosomes are extracellular vesicles, or small structures within the cells, which support regeneration. MSC therapies have shown promising pre-clinical results in the treatment of a wide range of conditions, including specific complications of diabetes, osteoarthritis and cornea transplant rejection.



The STARSTEM nanostar

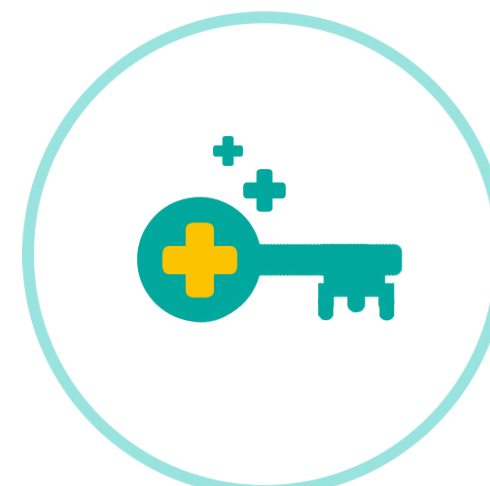
We will manufacture novel nanostars, and use them to tag therapeutic stem cells and exosomes.

Nanostars and osteoarthritis

Nanostars will be administered for *in-vitro* and *in-vivo* models of arthritis.

Photo-acoustic imaging

PA imaging and MRI will be used to monitor the distribution, engraftment, and activity of the stem cells and exosomes.



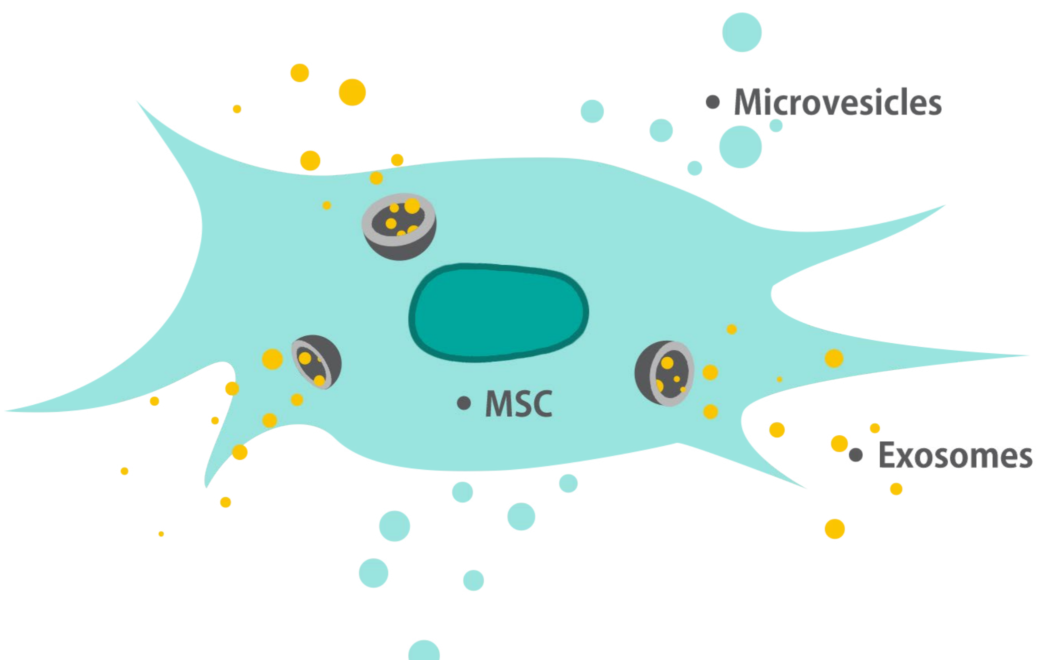
Hallmarks of healing

Better understanding of therapeutic efficacy can lead to new therapies and a subsequent clinical trial.

How do MSCs and exosomes actually work?

It is not yet clear how MSCs and exosomes actually work inside the body. This uncertainty makes it difficult for regulators to approve new stem cell therapies. Thus, a key question for regenerative medicine is the nature of the therapeutic agent – do MSCs lead to healing directly, or do they 'communicate' with the body via sub-cellular particles, and trigger healing 'at a distance'?

STARSTEM will carry out two parallel sets of studies, one with nanostar-labelled stem cells and the other with labelled exosomes, to see if exosomes are as effective as stem cells in treating arthritis and if they act in the same way. The functional markers of healing to be examined include the level of oxygen in the blood, evidence of inflammation, and the development of new blood vessels. These are important indicators or hallmarks of the healing process.



STARSTEM will help scientists and clinicians to understand how stems cells actually work by providing better imaging technologies to 'see' what is happening inside the body during therapy. We do this to explore the nature of the therapeutic agent. This means looking at where they go, how quickly they get there, how do they behave once on site, and how healing occurs over time. Cells and exosomes that are tagged with nanostars will be administered for in vitro and in vivo models of arthritis.

The next step for nanostars will be to pass through the clinical trial process. After the project is completed, we will aim to run a clinical trial to examine the nanostar contrast medium.

STARSTEM is devoted to understanding how stem cells and exosomes lead to healing. Understanding the hallmarks of the healing process will help researchers and doctors to treat a wide range of human diseases.

The STARSTEM Science | Nanotechnology and Imaging

STARSTEM proposes imaging of MSC biodistribution and engraftment in arthritic joints at clinically relevant depths, using nanoparticles with novel optical properties which enable unprecedented penetration depth and sensitivity.

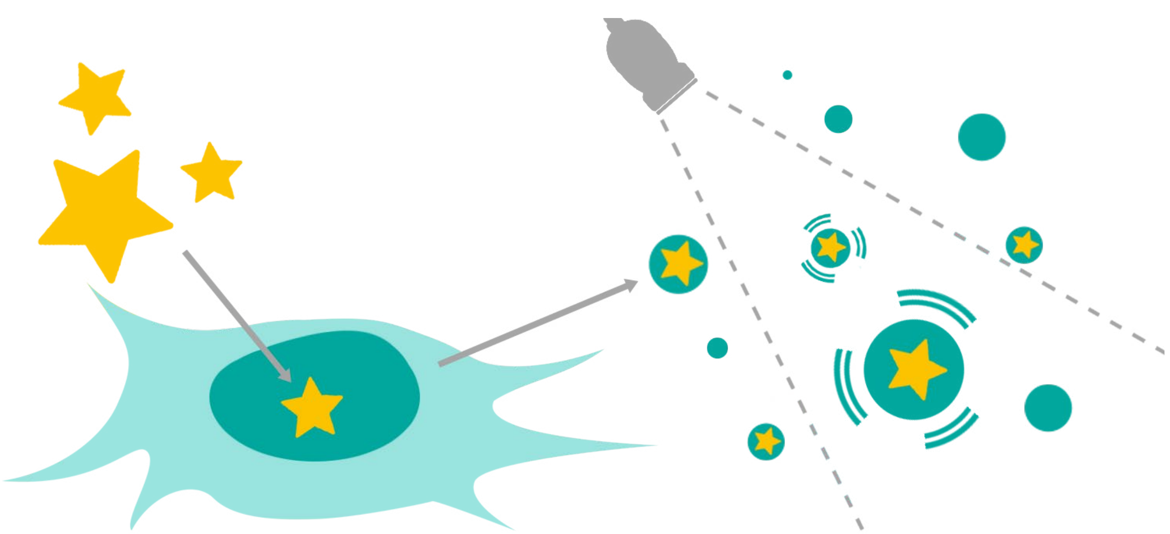
Photo-acoustic (PA) imaging is an exciting imaging modality, with unique capabilities that have yet to be applied in a clinical setting. PA imaging takes advantage of the photothermal effect and is used to produce ultrasound in soft tissue caused by vibrations. When a tissue is illuminated with a bright light, such as a pulsed laser, some of that light is absorbed and converted to heat. The heat leads to an expansion of the illuminated material. This expansion creates vibrations, which can be detected using ultrasound detectors. Because different substances expand in different ways, and in response to different light wavelengths, a sophisticated image can be assembled from the ultrasound readings caused by illumination with multiple laser wavelengths.

PA imaging is, however, held back by its limited operating depth beneath the skin. Nanoparticle contrast agents have

Where the physics of imaging meets validation of stem cell treatments.

the capacity to improve this limitation and have widespread diagnostic applications and can help with the visualization and assessment of various disease processes. In particular, nanostars have the potential to greatly enhance the technology, by increasing its useful depth. Recently published studies using PA imaging indicate that nanoparticle-tagged cells might be detectable to a depth of up to 4 cm in the human body, based on detection limits of other contrast agents.

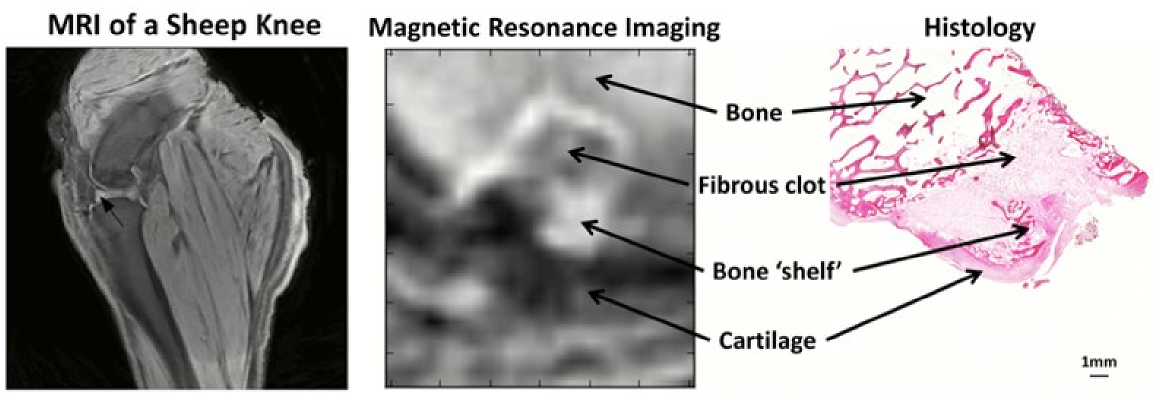
The STARSTEM nanostar is a novel gold nanoparticle, shaped like a star. Its unique makeup and shape mean that it greatly enhances the photo-acoustic effect. It does this by concentrating the thermal response at the tips of the star's arms. This helps to generate a strong PA imaging signal. This effect is further enhanced by nanostars' responsiveness to long-wavelength PA imaging lasers, which generates maximum thermal



conversion and has deep penetration. In effect, these nanostars greatly improve the image while having no impact on the therapy that is being monitored.

In STARSTEM, we will attach these nanostars to stem cells and exosomes. These tagged targets can then be detected in very small amounts and at a greater depth in order to track their distribution, engraftment, and subsequent activity. Crucially, PA imaging is non-invasive and non-traumatic. For regenerative medicine, this means that we can track multiple treatments and can model the effects over time via multiple images or indeed in real time. This will enable researchers to capture an unprecedented level of detail about how stem cells behave and how they contribute to healing over time.

STARSTEM will also use Magnetic Resonance Imaging (MRI) to track labelled MSCs and regeneration. Nanoparticle labelled MSCs cause a change in the speed that MRI signals decay, due to their effect on the local magnetic environment. This signal decay can be measured, which allows the tracking of nanoparticles. With MRI, we will also follow the repair of the joint after administration of MSCs to monitor overall health and regeneration of cartilage and bone. We use specialised methods that capture fast decaying signals that can occur in MRI, such as in bone and when there are significant amounts of nanoparticles.



An important novelty in STARSTEM is the use of an NUIG-patented approach to the quantitative measurement of different substances detected using PA imaging. This technique enables us not only to detect the presence of a substance but the amount of that substance. This is particularly useful when measuring oxygenated blood versus non-oxygenated blood because blood oxygen is a key hallmark of healing.

In addition to PA imaging, STARSTEM will also further develop NUI Galway's novel nano-sensitive optical coherence tomography (nsOCT) imaging modality. This is capable of detecting changes in cell shape at the nanometre scale, with a relatively large (1mm x 1mm) field of view.

We see STARSTEM-enhanced PA imaging as being just one of a suite of imaging modalities in a well-equipped hospital, alongside MRI, x-ray, ultrasound, PET scans, etc. Advanced MRI is a particularly good fit – it offers greater depth than PA images and excellent resolution, particularly when the nanostars are conjugated with tiny magnetic particles (SPIONs), to enhance the MRI signal. STARSTEM will develop and demonstrate co-registration software that combines PA imaging and MRI data to provide more sophisticated images.

While we focus on stem cells and exosomes, the STARSTEM technology has great promise for use in other cell therapies, enabling us to track, for example, CAR T cells (used in novel cancer therapies) or Natural Killer Cells (another important new cancer therapeutic). Nanostars could also be used to tag nanocapsules (tiny spheres of alginate, chitosan or other materials) containing genetic payloads or other forms of biologic therapy.

STARSTEM is an exciting project which harnesses fundamental advances in the physics of imaging to validate stem cell treatments. We believe that understanding the dynamics and distribution of MSCs is critical for optimising therapies and hope that the result will ultimately be better outcomes for patients.

Meet the Team

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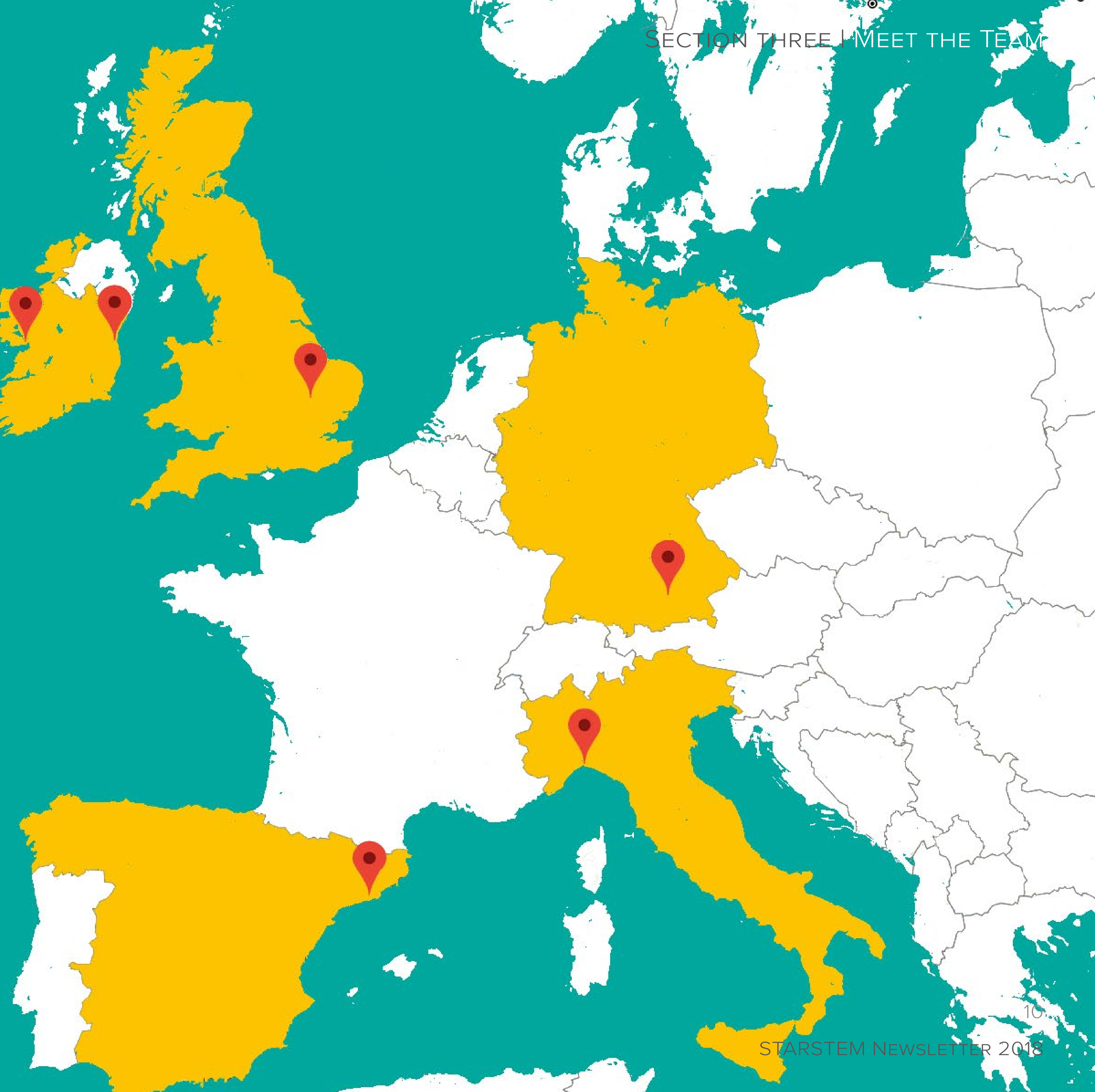

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