Impact Objectives

- Functionalisation of nanoparticles for selective targeting and for carrying different anti-cancer agents
- Investigation of the biodistribution of nanoparticles and their toxicity in animal models
- Development of new technologies for heat treatment and the detection and quantification of nanoparticles in tissues, blood and urine

New nanomedicines

By drawing on extracts from the MULTIFUN newsletters and the final project workshop in 2015, we provide some insights into the project team's perspective on how this collaborative research programme has advanced a novel approach to using nanomedicines in the fight against breast and pancreatic cancer

How important were the first stages of activity to setting a clear pathway for the project?

During the first six months of the project, the consortium was able to start multiple tasks and achieve several short-term objectives. The synthesis of the magnetic nanoparticles using different methods was started. The magnetic and thermal characterisations of nanoparticles got underway with the aim of defining the optimal particle size and magnetic field for the hyperthermia effect. The functionalisation of the nanoparticles (provided by industrial partners) has led to the first generation of nanostructures, where NUCANT (nucleolin antagonist) provides a unique functionality. The cancer cell lines have been distributed to those partners involved in this area and preliminary cytotoxicity tests of different MNP (magnetic iron oxide nanoparticles) have provided a first insight into the selection of the most biocompatible coatings. The nanoparticles will be handled following standardised protocols for comparison of results from different partners.

In what ways will the nanoparticles created by MULTIFUN target cancer, and why is this important?

The MULTIFUN consortium has developed a comprehensive strategy in order to generate highly selective and efficient multifunctional nanoparticles for detecting and treating cancer. The combination of magnetic heating and other therapeutic modalities for cancer allows new therapeutic approaches. MULTIFUN nanoparticles will target cancer cells including the highly tumorigenic stem cells as the putative root of cancer. These types of cell are associated with drug resistance and tumour relapse and hence their targeting may lead to a significant improvement in therapeutic outcomes. Several members of the consortium have already demonstrated that it is feasible to target cancer stem cells efficiently using multimodal strategies which lead to tumour regression and dramatically enhanced long-term survival in relevant tissue xenograft models.

How does the technological originality that is being nurtured by the MULTIFUN consortium differ from other similar research projects?

MULTIFUN provides an opportunity for the development of scientific instrumentation directed to the use of magnetic nanoparticles in biomedical applications. Besides the instrumentation to perform in vitro and in vivo magnetic hyperthermia experiments, MULTIFUN will develop particles with optimal properties for the development of a device to detect magnetic nanoparticles in tissue, blood and urine. Magnetic resonance detection allows for the detection and quantification of magnetic nanoparticles in the sample. The resonant method is selective and sensitive, with reduced heat dissipation in biological tissues. As the magnetic particles are stable this will allow monitoring of slow kinetic processes in cost-effective ways. The device will be compared to other systems with a similar sensitivity. This technique involves the use of low magnetic fields and hence the heat generation within the tissue is reduced. This will allow the feasibility of ex vivo measurements to be explored during the project. The presence of two nanoparticle manufacturers in the MULTIFUN consortium will ensure that the materials developed will be suitable for the scale-up of production of biocompatible magnetic nanoparticles with optimised contrast and heat induction features for oncological applications.

Can you explain more about the therapeutic approach that your team has been investigating, and how this can change the way we manage some cancers?

The therapeutic approach developed within the project includes a synergistic effect between the therapeutic effect produced by magnetic hyperthermia and that due to the intracellular drug delivery selectively targeted to tumour cells. Some of the designed formulations have proven their efficiency, safety and non-toxicity in in vivo models, making them promising candidates to produce new nanomedicines against breast and pancreatic cancer.

What do you see as one of the most successful outcomes of the MULTIFUN project?

During the last four years the MULTIFUN consortium has focused its activity on the development and validation of new systems based upon minimal invasive nanotechnology for the early and selective detection and elimination of breast and pancreatic cancer. The project has successfully produced multifunctionalised MNP that combine diagnostic and therapeutic features against these two types of cancer.

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Turning up the heat

With cancer now one of the four leading causes of death from non-communicable diseases, there is a huge focus on cancer research around the world. By devising a novel nanoparticle-based 'theragnostic' tool incorporating magnetic hyperthermia concepts, the MULTIFUN project is furthering knowledge on how to detect and kill cancer cells

On 4 February 2016, World Cancer Day highlighted the importance of research on how cancer starts in the human body and the ways in which it spreads. The EU's Eurostat office states that cancer is responsible for one in four deaths in the Union. There are two cancers that have particularly troubling statistics: breast cancer, which is the most frequent cause of death due of cancer among women at 16 per cent; and cancer of the pancreas, which according to the Pancreatic Cancer Action UK has the lowest survival rate of all cancers, with between 3 and 6 per cent of those diagnosed surviving for five years. In order to reduce deaths and improve recovery rates, one of the main target areas for cancer research is how to improve early detection and treatment. As such, looking at novel ways to address the impacts of breast and pancreatic cancer is crucial.

With nanotechnology quickly becoming an important player in biomedical applications due to the unique properties it offers for imaging, drug delivery, and as building blocks of three-dimensional components, the European Commission has set up a research theme to develop nanotechnology-based systems for detection, diagnosis and therapy for cancer. Under this theme a consortium of hospitals, universities, research centres, and large and small companies from across the EU with experience in biomedicine, chemistry, oncology and information technology, have come together to study cancer in a unique way that differs from the other EU nanotechnology research programmes.

FOCUS ON MULTIFUNCTIONALISED MAGNETIC NANOPARTICLES

Launched in 2011, the Multifunctional Nanotechnology for Selective Detection and Treatment of Cancer (MULTIFUN) project aims to create a minimally invasive nanotechnology system to advance the diagnosis of cancer and its treatment. At the very core of the MULTIFUN effort is the concept of multifunctionalised magnetic nanoparticles (MMN), which can be used to target, and ultimately eliminate, breast and pancreatic cancer (stem) cells. The theory is that they can use alternating magnetic fields to heat up functionalised magnetic iron oxide nanoparticles (MNP), meaning therapeutic agents can be targeted towards the cancer site. Following this, magnetic resonance imaging (MRI) can be used to find the cancer cells that have taken up nanoparticles. Through this approach MULTIFUN is able to deliver a 'theragnositc' tool, essentially combining therapeutic and diagnostic processes.

To achieve this, the researchers are looking for superparamagnetic nanoparticles which have optimal magnetic and magneto-thermal properties. A lot of their effort has gone into assessing how the coatings and surface charges of nanoparticles influence cell viability and uptake. The first 18 months of the project saw the start of the synthesis of the magnetic nanoparticles by utilising a number of different methods. This was by no means an easy task, but by examining two chemical routes the team saw they could get nanoparticles with narrow size distribution, high saturation magnetisation and specific absorption rate values. The reaction parameters that led to improved properties of the nanoparticles, including magnetic and magneto-thermal, have been assessed by the scientists. A great deal of effort is going into determining the optimal particle size and magnetic field conditions, with the

ultimate goal being the confirmation of an experimental setup which diminishes heat losses with the surroundings. Academic and industrial partners of MULTIFUN have provided functionalisation of the nanoparticles, enabling the first generation of functionalised nanostructures.

TESTING EFFICIENCY, SAFETY AND NON-TOXICITY

As a part of this work the safety and toxicity of the nanoparticles developed were studied using a range of animal-model in vitro and in vivo toxicity and biodistribution tests. One area where the team had promising results was the preliminary in vivo studies where they looked at the hyperthermia effects on tumour evolution. Through testing on animal models, they have shown that the tumour volume can be reduced after a few magnetic field sessions. The success of these experiments gave them the confidence to further refine and optimise the hyperthermia therapeutic approach. The final report from the project notes that some of the designed formulations have proven their efficiency, safety and non-toxicity in in vivo models, 'making them promising candidates to produce new nanomedicines against breast and pancreatic cancer'. After four years of intensive investigations the MULTIFUN group has been successful in producing multifunctionalised MNP that combine diagnostic and therapeutic features against both breast and pancreatic cancer.

Maintaining excellence in results is important for the MULTIFUN team. In order to scrutinise the project's work and outcomes, an external and independent Scientific Advisory Board was set up in the earlier stages. Professor Rogerio Gaspar, Professor Massimo Masserini and Dr Simo Schwartz undertook an independent evaluation of the work and helped guide the project's direction, as well assisting with directing how the results were translated. MULTIFUN findings have been presented at several meetings and workshops such as the European Technological Platform of Nanomedicine, the 'Targeted Nano-Pharmaceuticals and Early Diagnostics' Cluster and 'The Future of Medicine: 2020 Vision' Symposium. Heading into 2016 and 2017, the consortium is hoping to continue with similar activities supporting dissemination of their results, including the publication of manuscripts, project reviews and attending conferences proceedings.

REAL-WORLD APPLICATION

As a part of this project protocols have been developed that are helping to advance future collaborative research projects and funding opportunities, including training and know-how transfer within biomedical and pharmaceutical industry in order to provide educational and training on the responsible use of nanotechnology applied to medicine. The knowledge developed by MULTIFUN on exploiting mammalian handling of MNP certainly has the potential to be replicated to treat less common cancers, such as bone cancer and liver cancer.

The proof of a successful research project is in its application in the real world. Following the experiments conducted within MULTIFUN, 11 exploitable results were identified as having high potential in the marketplace; six of these have had a business plan developed. For example, a series of chemical modifications for siRNAs have been progressed which will be useful for identifying more potent small interfering RNAs and micro RNA mimetics for cancer treatment in research projects. Understanding the role of magnetic parameters in the production of biocompatible MNP means that there is greater knowledge about how magnetic properties of nanoparticles can be customised for specific applications. Two of these six exploitable results have now been protected by a patent to enable their potential development as a therapeutic treatment.

The future looks bright for cancer research as a direct result of the MULTIFUN project. This new understanding about the impact on cancer cell survival from combining multifunctionalised MNP and magnetic heating offers a number of exciting potential applications, including transfer of the therapeutic modality to the clinical situation, new collaborations with pharma industry and research institutions, and a testing platform for functionalised MNP.

Project Insights

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CONTACT

Rodolfo Miranda
Scientific Coordinator

IMDEA Nanociencia
Spain

T: +34 91 2998700
E: rodolfo.miranda@imdea.org
W: www.multifun-project.eu

PROJECT LEADER BIO

Rodolfo Miranda is the MULTIFUN Scientific Coordinator and Madrid Institute for Advanced Studies (IMDEA) Nanoscience Director. He has authored/co-authored more than 220 scientific publications, and supervised more than 40 PhDs and postdoctoral researchers. Together with collaborators he has developed a number of nanoscience instruments to perform valuable nanoscience research. He has served on Advisory Committees for different institutions, including the European Synchrotron Radiation Facility at Grenoble.

SEVENTH FRAMEWORK PROGRAMME

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