MAGNETIC NANOCONTAINERS FOR COMBINED HYPERThERMIA AND CONTROLLED DRUG RELEASE

Reporting

Project Information

MAGNIFYCO
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Periodic Report Summary - MAGNIFYCO (Magnetic nanocontainers for combined hyperthermia and controlled drug release)

Project context and objectives:

Introduction

The European Union (EU) funded ‘Magnetic nanocontainers for combined hyperthermia and controlled drug release’ (MAGNIFYCO) project has the aim to design, assemble and fabricate a new generation of multifunctional nanostructures for performing combined hyperthermia and controlled drug release, specifically targeted to cancer cells. These multiple tasks are made possible by combining three components within the nanostructures:

1. magnetic nanoparticles that allow detection by magnetic resonance imaging (MRI), provide magnetic targeting towards tumours, treat cancer by hyperthermia and thermally induce drug release
2. nanocontainers, such as tobacco mosaic virus, zeolites, biological vesicles, polymeric nanogels, solid lipid nanoparticles or self-assembled peptides, that protect the drug from enzymatic degradation and are sensitive to external stimuli, e.g. heat and pH change, which control the release of chemotherapeutic drugs
3. antibody fragments (Fabs) attached to the surface of the containers or of the magnetic particles, that allow selective delivery of the structure to ovarian cancer cells, which overexpress the folate receptor alpha (FRα).

The individual building blocks and their assemblies are characterised with respect to physical, chemical and biological features, followed by dissemination of the newly acquired knowledge. Additional in vitro experiments are ongoing and will allow understanding the performance of the novel nanotools. Given the long-term objective directed towards application in patients, in the second part of the project in vivo animal studies will be carried out with the most successful magnetic nanocontainers.

The consortium

The consortium of partners was built for achieving the multiple aims of the MAGNIFYCO project, hence an interdisciplinary collaboration among chemists, physicists and biologists with expertise in basic aspects and in translational medicine was required. A European network collaboration was proposed between academic partners, who developed new solutions for nanofabrication and characterisation, and industrial partners, whose key expertise was in fields close to the MAGNIFYCO research activities. The responsible of MAGNIFYCO was the Italian National Research Council (CNR), Italy, contact person Teresa Pellegrino, represented by the National Nanotechnology Laboratory Institute (NNL). CNR was in charge of functionalising inorganic magnetic nanoparticles and of developing stimuli-responsive polymeric nanovectors, in strong synergy with the Italian Institute of Technology (IIT), Italy, contact person Albert Figuerola. IIT additionally developed and studied novel types of colloidal iron-based nanoparticles. Four of the other academic partners developed various types of nanocontainers, such as tobacco mosaic virus nanotubes produced by CIC nanoGUNE (nanoGUNE, Spain, Alexander Bittner), zeolites as hard
nanocontainers produced by the University of Twente (uni-Twente, Netherlands, Luisa de Cola), self-assembled peptides produced by the Universidade de Santiago de Compostela (USC, Spain, Juan R. Granja) and the mammalian vesicles produced by the Laboratoire Matières et Systèmes Complexes (CNRS, France, Claire Whilelm). The Universidad Complutense de Madrid (UCM, Spain, Miguel A. Garcia) and the Instituto Nazionale dei Tumori (INT, Italy, Silvana Canevari) were both involved in the characterisation of the materials. While UCM contributed to the structural and magnetic characterisation of the nanostructures, INT offered support for the in vitro characterisation and would be involved in the in vivo characterisation of the best performing nanocontainers with ovarian tumour models. Three companies were members of the consortium, namely MagForce Nanotechnologies (Magforce, Monika Fischler, Germany), with a strong expertise in in vivo hyperthermia characterisation based on iron oxide nanoparticles, Nanovector (Nanov, Paolo Gasco, Italy), experts in solid lipid nanoparticles for drug delivery and Dompè Pharma (Dompe, Italy, Candida Cesta), who developed and produced antibody fragments on a large scale.

The overall project plan

The aims of the MAGNIFYCO project were:

1. synthesis and evaluation of new inorganic nanomaterials for hyperthermia treatment
2. preparation and investigation of various types of soft and hard materials for drug encapsulation
3. assembly of the magnetic nanoparticles with the nanocontainers
4. in vivo applications of the best performing magnetic containers

The project was divided into eight specifically defined and interconnected work packages (WPs). WP1 and WP2 provided the building blocks, magnetic inorganic nanoparticles and soft and hard nanocontainers, which were then assembled in WP3. WP4 dealt with the functionalisation of the magnetic nanoparticles or the nanocontainers with the antibody fragments. The nanomaterials obtained by these WPs were characterised magnetically and structurally in WP5 and they were tested on tumour cells in in vitro studies in WP6. The prototype device that exhibited the best performing features for drug delivery and hyperthermia treatment would then start the WP7 for in vivo applications. In WP8, started at month 18, MagForce would function as ‘end user company’ and would help the consortium to identify possible products for further industrial development.

Project results:

Results obtained at mid-term

The EU project MAGNIFYCO dealt with an innovative and multivalent approach of cancer treatment by exploiting new nanometric magnetic containers. In the first 18 months of the MAGNIFYCO project efforts were dedicated to fabricate various types of nanocontainers and to merge them with magnetic nanoparticles. This required including research objectives such as control of the nanostructures’ size and shape, understanding of the hydrophilicity and hydrophobicity properties of the nanocontainers and their colloidal stability. It was possible to associate magnetic nanoparticles to zeolites, to polymeric nanogels, both pH-responsive (Langmuir, 26, 10315, 2010) and thermo-responsive (Nanoscale, 3, 619 2011), and
to decorate tobacco mosaic virus with magnetic nanoparticles (ACS Nano, 8, 4531, 2010). In addition, magnetic nanoparticles were linked to biogenic vesicles from endothelial cells or macrophages in two different geometries, firstly decorating the vesicles' membrane (Nanomedicine 5, 727, 2010) and secondly encapsulating them within the vesicles (Biomaterials 27, 7061, 2010). Self-assembled peptides, envisaged to be used as nanocontainers, showed severe problems of solubility in physiological media. However, dimer-forming models were studied (Chem. Asian J. 6, 110, 2011; Amino Acids DOI10.1007/s00726-011-0886-2) and a new strategy for the application of this type of nanocontainers was designed, namely attaching magnetic nanoparticles to peptide dimers, which included a cytostatic drug in a sandwich like configuration between the peptide moieties.

Depending on the type of nanocontainers, the most suitable drugs, already in use in ovarian cancer treatment, were identified. Drug encapsulation and release capacities were tested after applying the proper stimuli, such as acidic pH, temperature and alternating magnetic field, directly to the magnetic nanocontainers. Within the different nanocontainers so far developed and tested, it was found that for zeolites coated by the polymeric PNIPAM it was impossible to achieve a temperature controlled release since the polymer network blocked the zeolite pores. However, preliminary in vitro studies on tumour cells were performed with magnetic nanocontainers that had already passed those tests (Advanced Materials, 23, 787, 2011, Nanoscale 3, 619 2011).

In parallel, a broad variety of inorganic nanoparticles, synthesised by thermal decomposition methods, were produced and magnetically characterised. The continuous feedback between the groups involved in the synthesis and those involved in the magnetic characterisation allowed excluding those particles that had poor magnetic performance for hyperthermia. On the basis of this screening, iron-platinum alloy particles of 9 nm in diameter, particles of the ferrite Fe2MnO4 of 9 nm in diameter and iron oxide nanocrystals prepared by seeded growth with diameters between 4 and 18 nm were excluded (as detailed in a submitted manuscript), as well as extremely small Fe3O4 crystals on virus particles (as would be presented by a manuscript in preparation by the end of the reporting period). Of the other magnetic nanoparticles, those that had shown the most promising magnetic features would be further exploited by the whole consortium in the second part of the project. The functionalisation with Fabs had already been achieved on some of the magnetic nanoparticles and preliminary binding studies had shown their binding specificity and improved targeting to the antigen of interest, the FRα receptor. This finding, which went beyond the planned activities, could become a key result. In fact, in the case that it would be impossible to directly functionalise the containers with the Fabs, functionalisation of the containers with magnetic nanoparticles that bore the antibody fragment could become a valid alternative.

In conclusion, important results were already obtained after 18 months of this three year project, and therefore the experimental data collected so far allowed us to forecast a successful outcome.

Potential impact:

The expected final results and their potential impact and use

The MAGNIFYCO target was motivated by the need to find more efficient and less invasive cancer therapies. The ovarian carcinoma, chosen as a tumour model for the study, represents the principal cause
of death among gynecological cancers. Since initial symptoms are indistinguishable and non-specific, this form of cancer is often diagnosed in an advanced stage of the disease. So far, surgery is the preferred treatment of the disease, associated with chemotherapy, which is used after surgery to treat residual disease. In this project an alternative approach was proposed, based on hyperthermia combined with drug delivery, upon injection of drug-loaded magnetic nanocontainers into the specific tumour site. This system should have the potential to combine hyperthermia with a drug therapeutic approach, thus being more effective than either method used on its own. To establish the response of the magnetic nanocontainers in tumour therapy, a locoregional treatment was opted for, targeted to intraperitoneally growing solid tumour masses and to tumoral ascites, both of which were reasonable models for achieving a high tumour drug uptake, due to their confined localisation.

Heat therapy, also called hyperthermia, has made huge advances, thanks to the current developments of nanometric heat-generating 'foci', which could be activated by externally applied magnetic fields. Iron oxide nanoparticles as heat sources have decisive advantages over macroscopic implants and more invasive surgery treatment. Being available in the form of colloidal suspensions they could, like contrast agents, be injected through a variety of non-invasive routes. Their subsequent distribution within the body could be controlled by various targeting strategies, thereby optimising their concentration in therapeutic target zones, or even specifically within tumour cells. The nanoparticles are sufficiently small to cross biological barriers and therefore heat could be generated very close to and even inside the targeted cells. Finally, the heat generated in this way is more homogeneous than that obtained with macroscopic implants. It is also proportional to the local concentration of nanofoci and it is limited solely to the site of nanoparticle accumulation. To date, magnetic nanoparticles based on iron trioxide (Fe2O3) and black iron oxide (Fe3O4) have been proven to be useful materials for hyperthermia.

In MAGNIFYCO, the heat generation from new types of nanoparticles, prepared by colloidal methods, was under investigation. The aim was to find new iron-based inorganic nanoparticles that would provide at the same time higher colloidal stability and more efficient heat generation, thereby reducing in vivo dosing and toxic side effects.

Additionally, the materials being implemented as nanocontainers represented a new generation of drug carriers. Most of the nanocontainers (all of them when functionalised with magnetic particles) had never been explored so far, therefore new know-how was generated by MAGNIFYCO. Finally, a decisive point was the active targeting by means of surface functionalisation of the magnetic nanocontainers with specific Fabs, in order to obtain high selectivity in tumour targeting.

Given the multifunctionality of the nanodevices, the investigated tools held huge promises in cancer treatment, which should extended also to other forms of cancer.

Final scenario forecast

The results obtained in the first 18 months offered to the MAGNIFYCO consortium the possibility to identify promising products for performing hyperthermia and drug release at the same time, within the planned 36 months period. An already satisfying scenario would be the identification of magnetic nanocontainer prototypes, which would work not only in vitro but also in vivo. However, a successful scenario would be
the identification of magnetic nanocontainers that could allow systemic administration, besides having better hyperthermia performance at lower doses of iron oxide nanoparticles than available so far. The ideal magnetic nanocontainers would have also additional key features. They would be easily sterilised, they would offer versatile procedures for scaling up their fabrication and they would not show immunogenicity.

On the medium to long time scale one could envision that the MAGNIFYCO results would contribute at the social level to:

1. a direct significant increase in life expectancy of ovarian cancer patients, due to the efficacy of the treatment and due to the reduced toxicity of the treatment as a consequence of its targeting
2. an indirect improvement of the quality of life of the relatives of the patients
3. a future wider social impact if the approaches proposed by MAGNIFYCO were successful, because of new perspectives in the therapeutic intervention against other solid and also haematologic tumours.

The benefits of the application of a nanotechnological approach, as compared to conventional pharmacological treatments, were expected to be accompanied by a direct health service cost reduction because of:

1. less drug needed for an equivalent efficacy, as a consequence of its encapsulation and targeting
2. reduced hospitalisation time as a consequence of reduced toxicity
3. indirect reduced social cost in term of reduced 'disease absence from work' (it should be taken into account that ovary cancer incidence is at a median age of 55 to 60 years, i.e. at an active working age).

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Related documents

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