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PROJECT FINAL REPORT

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Name, title and organisation of the scientific representative of the project's coordinator[1]:

Antoine FERREIRA

Université d'Orléans

Tel: +33 2 4848 4079

Fax:+33 2 4848 4050

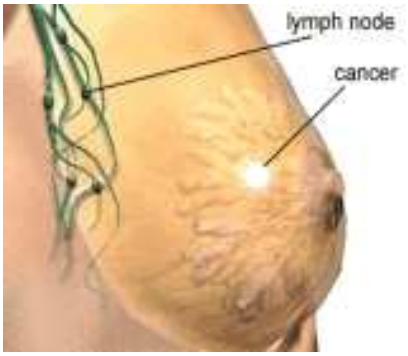
E-mail: antoine.ferreira@ensi-bourges.fr

Project website[2] address: http://www.nanoma.eu

[1] Usually the contact person of the coordinator as specified in Art. 8.1. of the grant agreement

FINAL PUBLISHABLE SUMMARY REPORT

1) MRI-based Microrobotic Platform for Drug delivery



The NANOMA project aimed at the development of a drug delivery microrobotic system (consisting of nanoActuators and nanoSensors) for the propulsion and navigation of ferromagnetic microcapsules in the cardiovascular system through the induction of force from magnetic gradients generated by a clinical Magnetic Resonance Imaging (MRI). The main motivation for the NANOMA project is the early diagnosis and treatment of women's breast cancer. Current treatments of chemotherapy may help shrink or control the cancer for a while, but it usually won't completely cure the cancer. The NANOMA goal presents one of the most challenging tasks of modern noninvasive medicine. A noninvasive therapy could avoid infections and scar formation; it would require less anesthesia, reduce recovery time, and possibly also reduce costs. This study investigated whether human breast cancer can be effectively treated with a novel combination of image guidance and magnetic microcapsule delivery, noninvasive magnetic resonance imaging -guided untethered magnetic microcapsule. Nearly 216,000 U.S. women are expected to receive a diagnosis of breast cancer in 2009, with about 40,000 deaths according to the American Cancer Society (ACS). Detected at early stage, the five-year survival rate for women treated for stage I breast cancer is 98 percent.

The new approach to diagnosing and treating breast cancer is based on three pillars:

- **Enhanced diagnostics:** The clinical Magnetic Resonance Imaging (MRI) provides a new imaging system to test and refine the diagnostics of breast cancer. The 3D images provided to the radiologists will provide a detailed three-dimensional view of the breast and tumors compared to the two dimensional view produced by mammograms where some tumors inside the breast can be hidden behind other tumors or structures. The MRI's diagnostic effectiveness is improved through the use of contrast agents.
- **In-vivo propulsion and navigation**: The MRI tool is used for propulsion and navigation of the drug delivery capsule. The propulsion of the ferromagnetic micro-capsule in the cardiovascular system is realized through the induction of force from magnetic gradients provided by the MRI. The MRI tool will guide the micro-capsule in vivo through tumor-induced capillary networks with sustainability in the tumor mass.
- **Drug delivery**: The magnetic microcapsule surface is coated with polymers and sugars, making it nearly invisible to the body's immune system. Antibodies (joined with a

[2] The home page of the website should contain the generic European flag and the FP7 logo which are available in electronic format at the Europa website (logo of the European flag: http://europa.eu/abc/symbols/emblem/index_en.htm ; logo of the 7th FP: http://ec.europa.eu/research/fp7/index_en.cfm?pg=logos). The area of activity of the project should also be mentioned.

radioactive substance) on these probes latch onto receptors that are on the surface of tumor cells. The heating of the probes can be activated and controlled by the use of a magnetic field generated outside of the body. By applying an alternating magnetic field to the tumor region, the magnetic spheres change polarity thousands of times per second and create heat. This heat weakens—and destroys—breast cancer cells.

2) Methodologies

The present NANOMA project aims at breaking with this tradition and proposes new therapeutic devices. The identification of the key and selective molecular alterations, which sustain breast cancer growth and progression allows the possibility to *develop specific molecular target treatments* at a very early stage. The relevant efforts of basic multidisciplinary research carried out in NANOMA studies the development of an unthetered microrobotic capsule navigating in the bloodstream and directly targeting the operative site of the tumor vessels for controlled drug delivery in infected cells. Microrobotics is a field which calls for collaborative efforts between physicists, chemists, biologists, roboticians, nanomanufactures and computer scientists to work towards this common objective. Figure 1 details the various fields of research involved in the project.

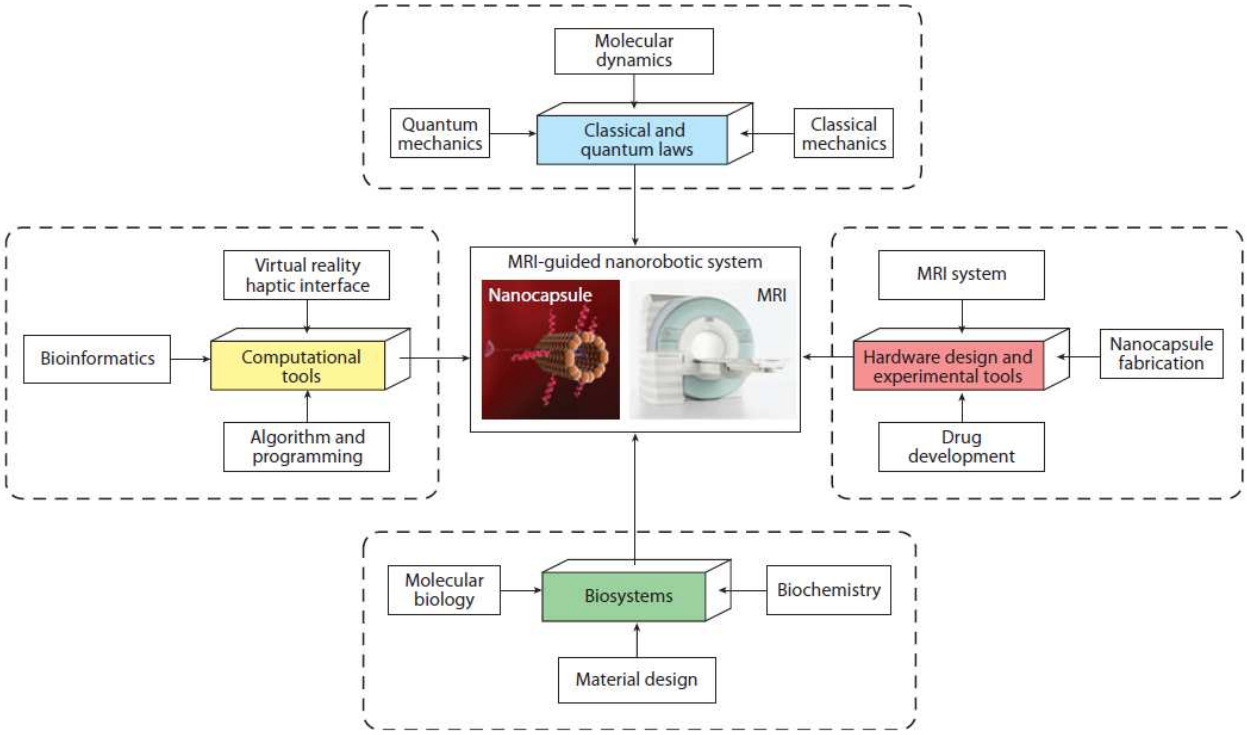


Figure 1: Magnetic resonance imaging (MRI)-based nanorobotic systems: a multidisciplinary field. Scientific domains associated with the field of MRI-based nanorobotics are shown.

A systematic approach toward MRI-based guidance of nanoscale, functionalized robotic capsules began for the first time in the summer of 2008 in the context of the European Commission's NANOMA project. The innovative concept of MRI-guided microrobotic systems is to use an MRI scanner to apply to the nanoparticles an external driving force to guide them and retain them at a localized target. The direction and magnitude of the forces applied on the microparticles are generated according to a control law, whose feedback—the endovascular position of the microparticles—is provided by processing the MRI data. Navigation techniques in combination with appropriate chemical modification of the nanoparticles' surfaces yield a more localized and

controlled treatment as well as controlled drug-release mechanisms. The research consortium comprises approximately 80% of the European groups who are at the forefront of the research on nanorobotics; in the context of a European worldwide dominance.

The structure of this proposal is multidisciplinary in terms of *technologies*, i.e. synthesis of new inorganic materials, nanomanufacturing, magnetic and biological functionalization, encapsulation, actuation, and *techniques*, i.e. MRI magnetic steering control/tracking/guiding, and biological targeting. The combination of these individual components into more complex assemblies will lead to the generation of MRI based magnetic steering/guiding/targeting nanocapsule. Such magnetic nanocapsules will be dedicated to elicit hyperthermia and controlled drug release for the treatment of cancer upon application of precise stimuli.

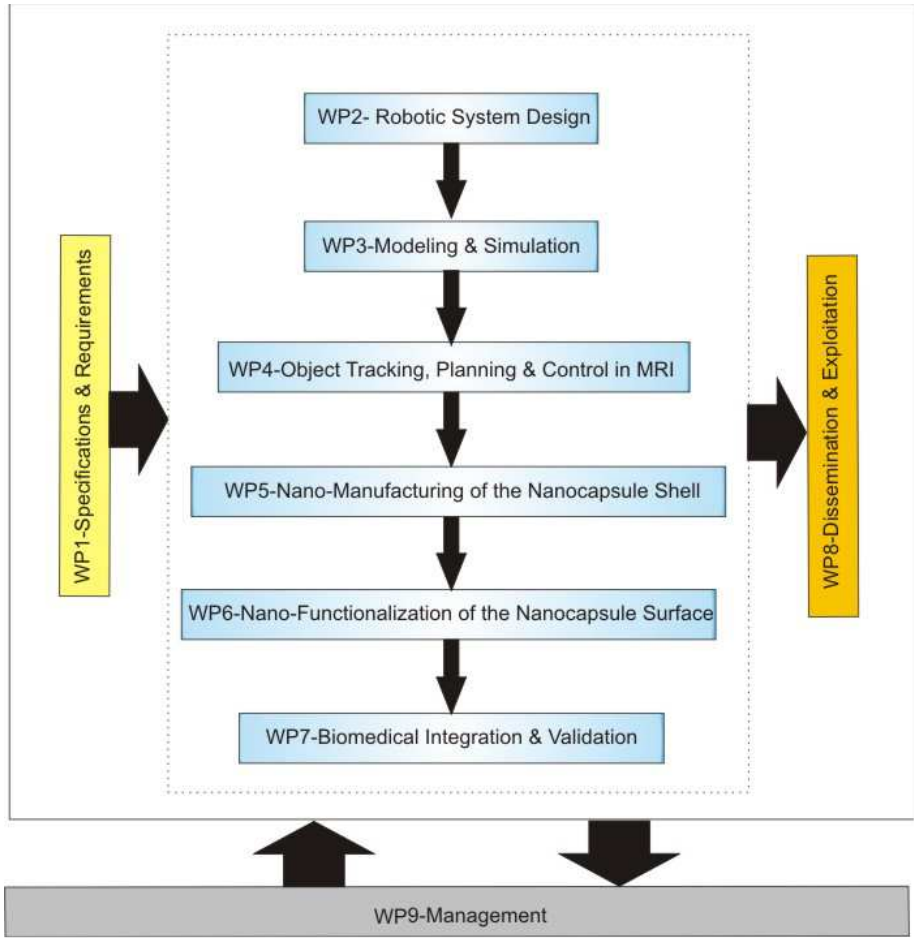


Figure 2: NANOMA project flow.

3) The consortium and the Work Plan

NANOMA Consortium had 8 partners: University of Orléans (UORL)– France (coordinator), Zenon company and Biomedical Research Foundation (BRFAA) from Greece, ETH Zurich and FemtoTools from Switzerland, University of Oldenburg and Pius Hospital from Germany, and University of Cyprus.. Project started in May 2008 and after duration of 40 months finished in September 2011. The total costs were 3,3 M€. Work was organised into four main layers:

- **The design and modeling of nanorobotic capsules:** Engineered aggregates of magnetic micro-/nanocapsules as successful vehicles for transporting, delivering and targeting drugs have been designed, prototyped, simulated and optimized.

- **The fabrication and functionalization-based targeting of nanocapsules:** This trend is viewed as an integration of different biological and magnetic functionalization processes at the nanocapsule, i.e., functionalized nanoparticles (*f*-NPs) and functionalized carbon nanotubes (*f*-CNTs) for in-vitro and in-vivo protein delivery in breast cancer models.
- **The implementation of MRI-based microrobotic platform for navigable magnetic microcapsules in blood vessels :** The MRI imaging, tracking, steering, navigation and control of the NANOMA micro-nano-capsules through magnetic gradients were investigated and implemented in a clinical 3T MRI system.
- **The in-vitro and in-vivo drug delivery in mouse cancer models**: Efficiency of drug release at specific site (breast cancer cell and/or tumor) has been a challenging issue of the project. As proof-of-concept is of primary importance, we generated a tumor cell line by putting in culture one of Kras* mammary tumors. For in vivo testing, we will generate Ef1/Kras*; WAPcre mice.

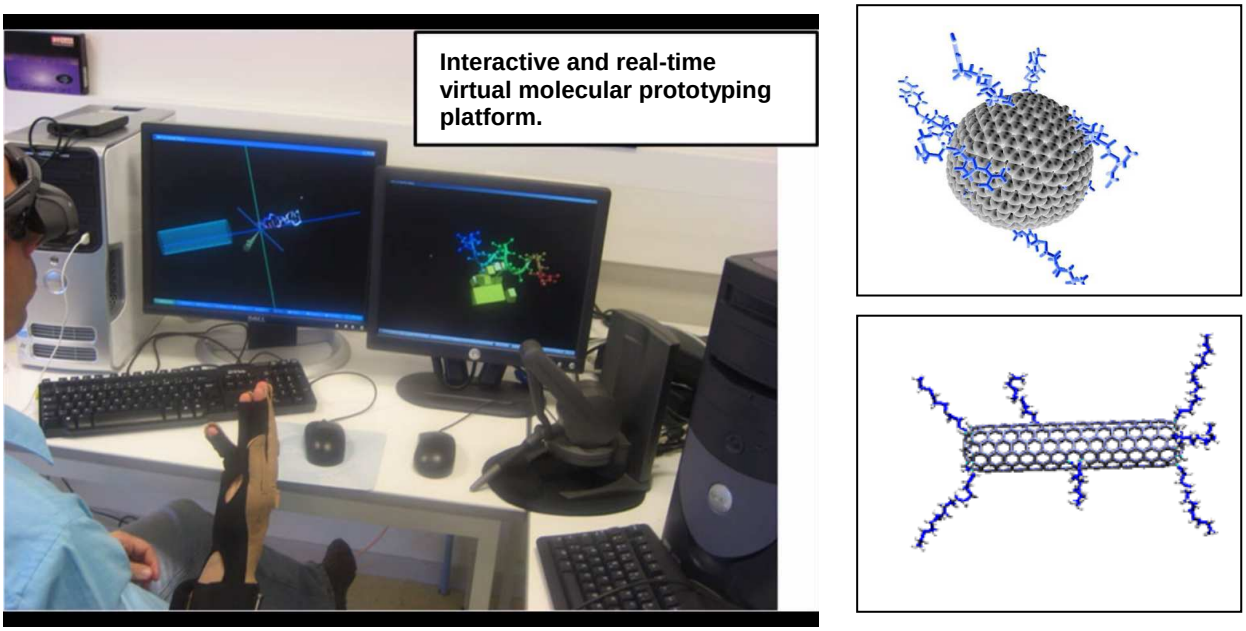
Fig. 2 presents the flow through the main building blocks of a general technical platform for generating information services, and the corresponding Work Packages in NANOMA.

4) NANOMA Key Results

4.1. Design an Modeling of Nanocapsules (WP2 &WP3)

A) Molecular Dynamics for drug delivery nanocapsule design

The innovative designs proposed in the NANOMA capsules have been based on a modular nanoassembly approach where molecular elements that can function as sensors, actuators, drug delivery mechanisms are assembled with magnetic components for achieving navigation inside the human body. University of Orléans developed an experimental interactive simulation platform using virtual reality interfaces and haptics (Figure 3-a).



(a) **(b)**

Figure 3: (a) NANOMA prototyping platform based on virtual environment and haptics technology coupled to multiphysics computational methods for drug delivery magnetic nanocapsule simulation. (b) nanocapsule designs based on ferromagnetic and superparamagnetic nano particles and carbon nanotubes (*University of Orléans*).

In the virtual molecular dynamics (VMD) environment, the user applies forces to bionanorobotic structures in the simulation via a force-feedback haptic interface while manipulation is performed through a virtual hand. The headtracker is mounted on a pair of shutter glasses for operator immersion. The functions of several of these molecules have been studied at the biochemical level in order to be categorized, as locomotion module, sensor module, actuation module, etc. The simulation of the proposed nanocapsule designs are based on a bottom-up approach for the modelling, understanding and simulation of biological (living cells, proteins), chemical (drugs releasing) and inorganic materials (*f*-NPs and *f*-SWNTs) interactions (see Fig.3-b). The proposed methodology focused on the finest atomistic scales of detail governed by quantum mechanics (QM) as the starting point, molecular dynamics (MD) and reaching up to large, macroscopic continuum mechanics (CM). The simulation platform demonstrated that the the magnetic gradient of a generic clinical MRI cannot provide sufficient magnetic forces to drive physically isolated nano/microparticles to a tumor lesion. To overcome this problem it was proposed by beneficiary ZENON to appropriately design magnetic particles and exploit the magnetic MRI homogenous field so that the nano/microparticles become aggregated when inside the blood vessels.

B) Particle modelling for self-assembly and breakup process

The aggregated particles posses greater magnetic volume and therefore can be pulled more efficiently by the weak magnetic forces of the clinical MRI. A simulation tool was deemed essential for examining the physical parameters that affect the aggregation process, and for determining how the nanoparticle properties could be optimized to lead in greater aggregations.

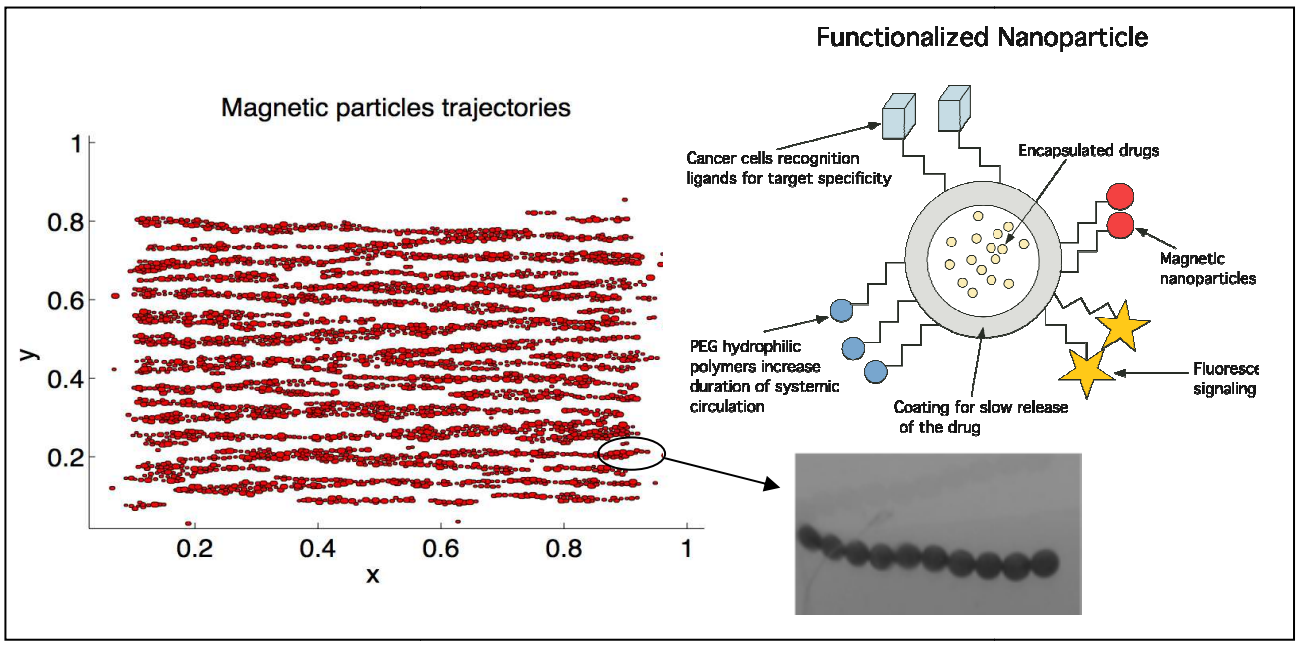


Figure 4: Simulation and experimentation of 3000 aggregated microparticles (10 μm) caused by an external 1 T field (*Zenon*).

Existing SW packages were based either on Finite Element Methods or on Molecular dynamics, and none of these provided functionalities allowing to study efficiently the dynamic behavior of interacting magnetic rigid bodies subject to forces arising from different physical domains at the nano/microscale. Therefore, there was an unmet need for a computational tool. The ZENON team developed this new SW to provide the tools that are necessary to study the multiphysics dynamics among interacting magnetic micro/nano particles within fluid.

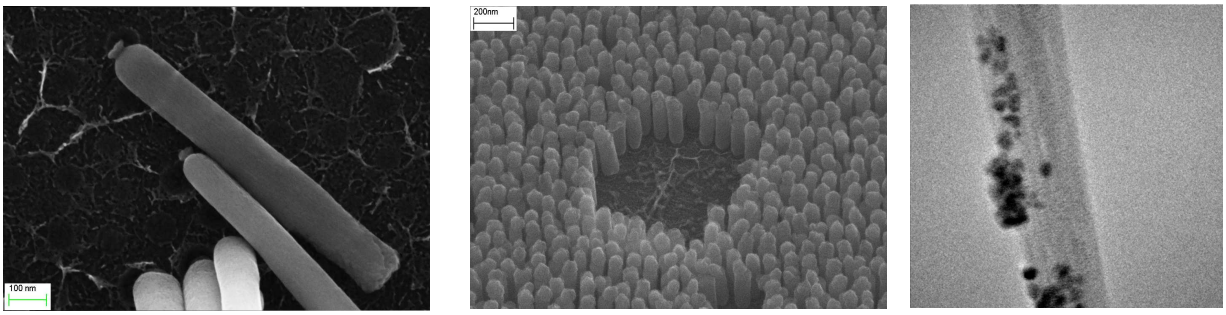
The work done in workpackages WP2 and WP3 was a fundamental work in the design, characterization, computational validation of an MRI-based navigational platform for endovascular microdevices including microparticles as drug delivery vectors developed in WP5 and WP6.

4.2. **Functionalization-based targeting of Nanocapsules (WP5 and WP6)**

Engineered micro-/nanodevices will enable drug delivery to move beyond bio distribution-driven mechanisms to true molecular targeting. This trend is viewed as an integration of different surface functionalization processes at the nanocapsule surface. Functionalized magnetic carbon nanotubes (f-CNTs) for in vitro and in-vivo protein delivery in breast cancer models have been manufactured. These magnetic nanocapsules will be used for magnetic field actuation/guiding/tracking of the f-CNT capsules in WP4.

A) Design, fabrication, bio-functionalization and delivery of magnetic carbon nanotubes

Researchers at ETH Zürich have tried various approaches to synthesize magnetic nanomaterials. They were primarily focused on bottom-up approaches, but top-up approaches may also be used to fabricate magnetic nanotubes efficiently and effectively. Nanostructures fabricated in the bottom-up approach usually have lower defects, a more homogenous chemical composition, and better short and long range ordering. During the NANOMA project, ETH Zürich researchers have successfully developed a process for producing Ferromagnetic Filled Multi-walled Carbon Nanotubes (FMWCNT). Their process is capable of producing vertically aligned multi-walled carbon nanotubes filled with high aspect ratio *Nickel* (Ni), *Iron* (Fe) and *Cobalt* (Co). Moreover, their process is repeatable and gives a very high yield. These magnetic nanocapsules features very high magnetic saturation properties (Ms_{Iron}≈1700 kA/m; Ms_{Cobalt}≈1400 kA/m, Ms_{Nickel}≈500 kA/m) which makes it very attractive for steering/imaging using magnetic gradients.

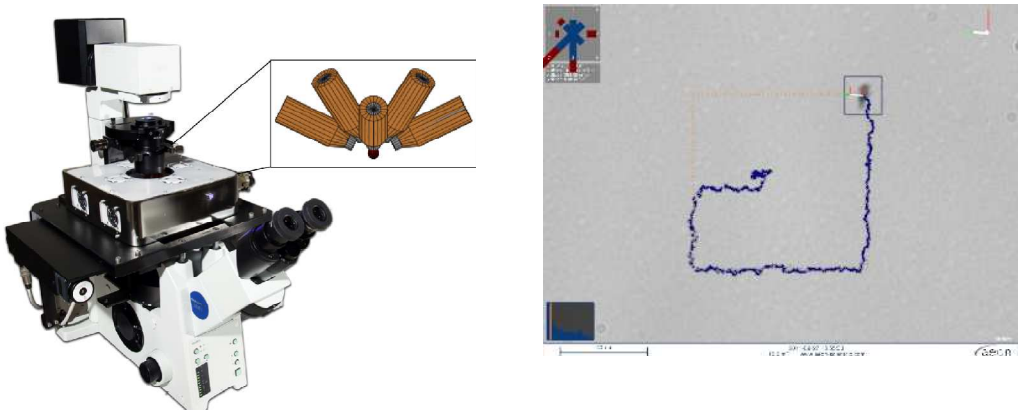


a) b) c)

Figure 5: NANOMA magnetic nanocapsule fabrication: a) Fe nanowires inside AAO templates, b) Ni- filled carbon nanotube and c) TEM image confirms the attachment of QDs with an average diameter of 5.2 nm. (ETHZ).

ETH Zürich demonstrated the capability to grow Fe NWs as the initial step towards magnetic functionlization. To coat, these NWs with high quality (sp^2) carbon, immense efforts were carried out to develop a repeatable and a reliable chemical vapour deposition (CVD) process. CVD synthesis of graphene on Fe NWs offers a viable approach to the magnetic drug targeting by graphene coated Fe NWs. There have been many efforts on demonstrating the feasibility and potential for the use of carbon nanotubes in a variety of biomedical systems and devices. Significant efforts have been made to overcome some of the fundamental and technical barriers toward bio-applications of the above-mentioned nanomaterials. For the exohedral functionalization, it was proposed to activate the surface for localized drug-delivery as well as a quantum dots in order to enable a preliminary in-vitro tracking of the nanocapsules. Unique fluorescent properties of QDs

allow the visibility of the nanometer-sized quantum dots under an optical microscope (Fig.5-c). It also allows tracking as well as the morphology change of individual decorated nanotubes in a liquid environment.



(a) (b)

Figure 6: a) Magnetic **NanoMag** setup for magnetic steering of agglomerate of graphene coated Fe NWs, and b) Closed-loop control is shown where the agglomerate is servoed along a square shaped path of 4x80 µm in perimeter. The scale bar is 40 µm (ETHZ).

For drug delivery, a new system was designed that is incorporated with an inverted fluorescent microscope and is called the Inverted **NanoMag**. "AEON Scientific" (www.aeon-scientific.com/), spin-off company of beneficiary ETHZ, was launch early February 2011 in order to develop magnetic platforms for steering and navigation of magnetic microparticles in a 6 d.o.f workspace. The eight individual electromagnets are arranged similar as presented before, however are now pointing downwards, as shown in Fig. 6-a. The system was further upgraded with respect to the power. Fields in excess of 80 mT and gradients up to 6 T/m can now be achieved in order to orientate and translate magnetic aggregates of graphene coated Fe NWs in real microfluidic channels under flow (Fig. 6-b). The magnetic material properties of the carriers and nano-capsules developed by partner ETHZ was measured on real microfluidics conditions. The maximum driving forces than can be created inside the magnetic field, to perform navigation in the cardiovascular system, have been measured using a MEMS force sensor developed specifically by beneficiary FemtoTools with a nanoNewton resolution. Based on these force measurements, the best technology as nanocapsules was graphite (sp^2) coated Fe NWs with a diameter of 85-120 nm and a length of 500 nm-1.5 µm.

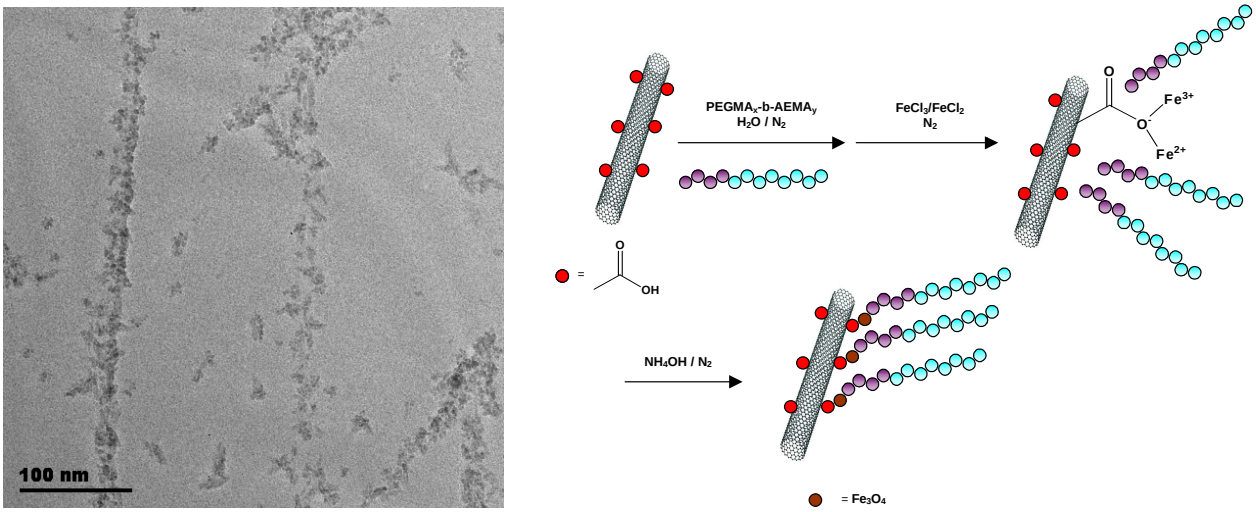
B) Mechanisms of Drug release

The beneficiary University of Cyprus (UCY) was investigating two thermal actuation nano-heater technologies for drug release: i) stimuli-responsive amphiphilic diblock copolymers containing pH and temperature-responsive functionalities and ii) reactive exothermic nanoheaters elements (WP7).

Nano-container using stimuli-responsive amphiphilic diblock copolymers

It is mainly based on the synthesis of novel polymer micelle hybrids, based on water-soluble amphiphilic block copolymers bearing chelating functionalities.Structural, molecular characterization and thermal properties measurements of the SWCNT/Fe_xO_y/$PEGMA_x$-*b*-$AEMA_y$ nanohybrids validated the magneto-responsive polymer micelles approach (Fig.7-a). Furthermore, the anti-cancer drug doxorubicin (DOX) was loaded successfully into the $HEGMA_x$-*b*-$DEAEMA_y$ diblock copolymer micelles using the oil/water emulsion method. DOX.HCl was dissolved in chloroform in the presence of triethylamine. The presence of pH-responsive DEAEMA moieties in

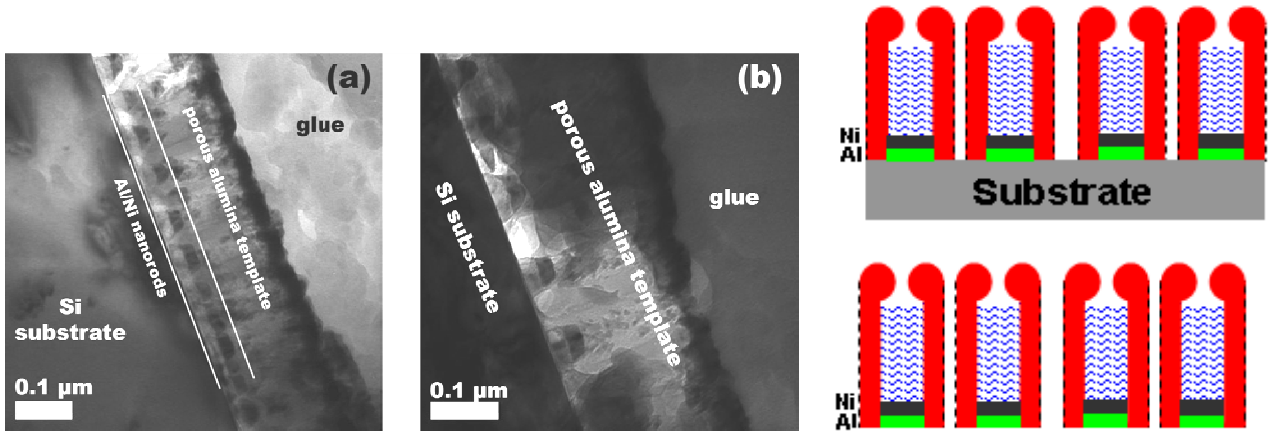
the $HEGMA_x$-b-$DEAEMA_y$ micelles renders these systems capable of responding to pH changes occurring in the surrounding environment. In particular, the DEAEMA units are hydrophobic (non-ionizable) above a certain pH value (the pKa value of the DEAEMA) whereas below this value they become ionizable and hydrophilic. In DPBS solution where the pH is about 7.2, the $HEGMA_x$-*b*-$DEAEMA_y$ block copolymers self-assemble into micelles consisting of a HEGMA hydrophilic corona and a DEAEMA hydrophobic core (Fig.7-b).



(a) (b)

Fig. 7. a) TEM image of SWCNTs decorated with iron oxide nanoparticles and stabilized in aqueous solution in the presence of the $PEGMA_x$-*b*-$AEMA_y$ diblock copolymers. b) Synthetic methodology followed for the fabrication of SWCNT/Fe_xO_y/$PEGMA_{75}$-b-$AEMA_{23}$, magnetic nanohybrids stabilized in aqueous media. (UCY)

The latter serves as a nano-container for the encapsulation of hydrophobic pharmaceutical compounds such as DOX *via* the presence of attractive hydrophobic interactions developed between the drug and the hydrophobic (neutral) DEAEMA units. Upon decreasing the pH below the pKa, the DEAEMA units become hydrophilic resulting in the collapsing of the micelles into unimers and the release of the drug. The drug releasing technology was successfully tested on mouse cancer cells method and demonstrated that the DOX release rate from the micelles is accelerated upon decreasing the pH of the outer environment from 6.0 to 4.6.



(a) (b) (c)

Fig. 8. Formation of Anodized Aluminum Oxide nanopores, a) and b): Deposition of Ni-Al nanoheater nanodots in AAO templates. C) Method of AAO nanotubes capped with Ni-Al nanoheaters (UCY).

Nano-container using nanoheater nanorods

This task targets coating of the nanocapsule surface and elements with reactive exothermic nanoheater elements, which are ignited upon remote microwave/IR irradiation, to produce thermal actuation for cauterization of malignant cells or infrared imaging. Two forms of nanoheater elements have been investigated. The first consists of multiple thin film layers of a reactive bimetallic system (Al-Ni), sputtered in alternating nanolayers of thickness 10-50 nm each (Fig.8 a-b). The second form consists of Al-Ni nanorods, fabricated by electrodeposition of Ni and evaporation of Al in the opened nanopores of very thin anodized aluminium oxide (AAO) membranes, with diameter 20-30nm and height 40-60 nm, which can be functionalized and attached to the capsule surface, as self-heating coating material (Fig.8-c). The team has experience with the nickel-aluminum system, which is pre-eminent for heat generation, since its intermetallic compounds ($NiAl_3$, Ni_2Al_3, NiAl, Ni_3Al) are accompanied by exothermic formation enthalpies (-37.85 to -71.65 kJ/mol, room temperature). Finally, the obtained results demonstrated that regional hyperthermia of localized superficial breast tumors is possible using microwave radiation at a frequency of 2.45 GHz. The SAR limit mandated by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) – published guidelines for prolonged exposure at this frequency is 4 W/kg.

4.3. MRI based microrobotic platform for endovascular navigation (WP4)

The generic architecture of the MRI-based nanorobotic system that has been developed in the framework of the NANOMA project is depicted in Fig.9. It offers a level of flexibility, provide concentration and tracking information, real-time interventional capabilities and are already widespread in hospitals. Steering forces can be applied to magnetic nanocapsules along any direction, using the orthogonal gradient coils normally used for image encoding. Moreover, the high sensitivity of MRI systems to magnetic susceptibility combined with fast matching sequences allows real-time in vivo imaging of the biodistribution of the nanocapsules. Finally, the real-time software architecture of modern MRI systems makes it possible to link tracking information and steering force to establish closed-loop control over the position of the particle agglomerate. The most critical components of the architecture of MRI-guided nanorobotic system developed by beneficiaries University of Oldenburg (UNOL), Pius Hospital (Hold) and University of Orléans (UORL) are described below.

3T MRI Propulsion System

The 3T Siemens MRI installation contains the following main hardware building blocks. Its functionality is shared by the propulsion system and the tracking system. The static magnetic field is the most important and most expensive component of an MRI system. A field strength of 0.5 T can be achieved through the use of permanent magnets. Three gradient-coil-system arrangements are needed in an MRI system. The gradient coils are used for both propulsion and tracking. In the case of propulsion, the gradient coils generate gradient fields, which, in combination with the magnetic properties of the nanoparticles attached onto or encapsulated in the nanocarrier, induce the actuation forces and torques that drive the nanocapsule. A distributed computer system has been developed by UNOL to control all components of the MRI system. It carry out image reconstruction and control of the gradient fields and RF coils.

MRI Tracking unit

The team from University of Oldenburg developed innovative concepts of MRI imaging, magnetic artifact detection and tracking of magnetic micro/nanocapsules. For magnetic articfact detection and tracking, the gradient coils described above are used for spatial encoding of the magnetic resonance signals and echo formation. These signals are then processed by a tracking software module that consists of (*a*) the MRI image 3D reconstruction software and (*b*) the image processing

software. The module's role is to estimate the 3D position and accumulation of the nanocapsules within the vasculature, the tissues, and the organs of the human. The image processing software run as closely as possible (in a temporal sense) to the image generation, to avoid communication

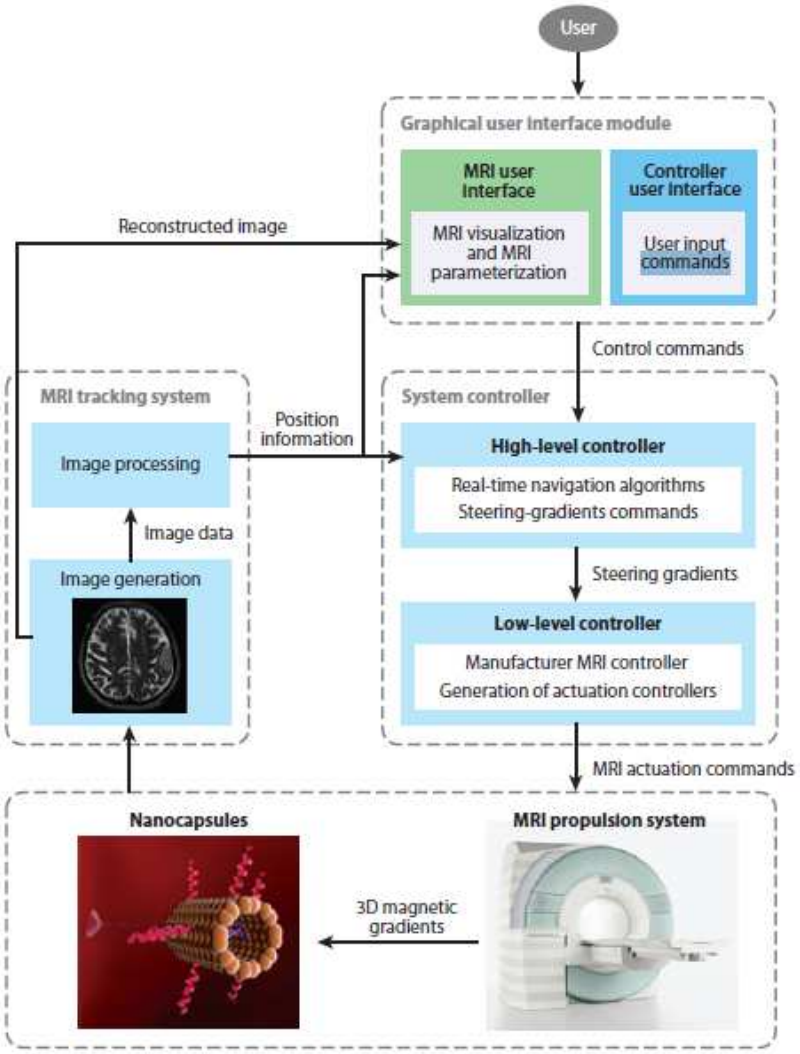


Figure 9: MRI-guided microrobotic system architecture developed in the NANOMA project (UNOL and UORL).

latencies and delays (more than several hundred thousandths of a second) by the image transfer and processing, which can hinder fast controller reaction.

System controller

The team from University of Orléans developed a high-level predictive controller subsystem—i.e., the subsystem that performs robust endovascular navigation— that can be implemented by integrating real-time navigation algorithms with the MRI propulsion system and tracking events. The navigation algorithm is coordinated through the development of proprietary control modules embedded in the clinical MRI system (Siemens IDEA software). Optimal navigation performance required different trade-offs in terms of refresh rate, duty cycle of the propulsion gradients, and repetition time of the tracking sequence (GRE and spin-echo sequences). Automatic, stable trajectory tracking requires robust controller implementation by plug-in control architectures without modification of the hardware of clinical MRI systems. Different perturbations have been taken into account during the controller design process, i.e., nonnegligible pulsatile blood flow, whose variations in waveform, amplitude, and frequency from one vessel to another, add

complexity in the conveyance of the micro/nanocapsule to the targeted area through a preassigned path. A specific graphical user interface $^{M}N_{PET}$ (MRI-baed Navigation Path Extraction Tool) developed by UORL for optimized path extraction and planning is actually implemented within the Siemens software environment (ICE and IDEA) for future integration on the 3T MRI system. A spin-off company of beneficiary UORL, will launch early 2012.

Different experiments on two types of "phantom" demonstrators have been carried out (Figure 10) with different types of capusles, i.e.**,** swimming capsule (agglomerate ferrofluids) travelling around simple obstacle (left) and in fluidic in-pipe demonstrator **(**capsule filled with iron oxide nanoparticles in oil and air**)**. Successful tests have been conducted including tracking, planning and navigation of magnetic microcapsules in a 3T MRI available at the Hospital of Oldenburg.

Figure 11: NANOMA fluidic demonstrators with MRI compatibility: (left) swimming capsule embedding ferrofluids and (righ) in-pipe navigation of a capsule filled with iron oxide nanoparticles in oil and air (Pius Hospital).

4.4. **In-vivo ad in-vitro experiments in mouse cancer models (WP7)**

Efficiency of drug release at specific site (breast cancer cell and/or tumor) is the challenging issue of the project. A very important component of the project is the in vitro and in vivo validation of the nanoparticles using cells in culture and mice. We have chosen to use the chemotherapeutic agent Doxorubicin (Dox) in our in vitro and in vivo experiments after loading it onto functionalized nanoparticles. As proof-of-concept is of primary importance, we generate a tumor cell line by putting in culture one of Kras* mammary tumors developed by the partner BRF. For in vivo testing, we generated Ef1/Kras*; WAPcre mice. Upon pregnancy/lactation (essential for Cre recombinase expression) mice will be monitored for the development of mammary tumors. The advantage of breast as a target tissue is that the tumor size can be assessed early by palpation and can be followed and measured with the use caliper throughout the process.

The team from BRF has generated (i) mouse cell lines from the Ef1/Kras* tumors which can be used for in vitro testing of the nanoparticles. Furthermore, (ii) a robust colony of mice that can support our experiments throughout the duration of the project and (iii) finalization of the choices regarding the drug and the tumor cell recognition agent. Intensive xperiments in tumour cell culture systems has demonstrated the stability (hence minimal cytoxicity) of the DOX-loaded micelles in neutral pH. The effect of Dox-loaded micelles on cell growth of Kras* cells grown in acidic pH showed interesting results attributed to the action of released Doxorubicin. Toxicity of the nanocapsules in interaction with cells demonstrated the low toxicity of agglomerates of grapheme coated Fe nanowires capsules.

1.2. Potential Impact and Use

The project aims at providing a broad framework for a comprehensive and multidisciplinary approach for the development of innovative intelligent and multifunctional unthetered nanocapsules in oncology. The strategy we will exploit is based on the optimal selective delivery of known chemoterapeutics by magnetic nanocapsules, which will be specifically designed, produced and tested. The magnetic nanocapsules will perform in concomitance drug delivery and hyperthermia treatment and won't be limited to the conventional strategy of selective delivery. Our research will have a significant impact on basic Nanotechnology, Medecine and Intelligent Systems science.

The NANOMA project has the potential to develop novel and revolutionary nanomedicine technologies that can contribute significantly in the cure of very important diseases such as cancer. The proposed NANOMA technologies and devices have the ability to re-shape important sectors of biomedical industry, therefore strengthening European position in the global market with high added-value products. The development of dynamic nanodevices based on protein molecular motors/sensors constitutes a paradigm shift in the area of biomedical microdevices. These bio nanodevices have a competitive edge as drug discovery and diagnostic devices and therefore have the potential for a greater impact on industry, especially novel high value added products. The NANOMA project will focus on the design, fabrication and implementation of dynamic nano-Actuators and nano-Sensors based on non-bio interactions between nanostructures (i.e., carbon nanotubes, engineered surfaces…) with protein molecular motors/sensors. NANOMA will leverage on the already commanding position of European research in molecular-based nanodevices and contribute to the consolidation of the high added value of European biomedical industry.

List of beneficiaries:

Université d'Orléans (coordinator) Laboratoire PRISME Château de la Source 45000 Orléans FRANCE	
Prof. Dr. Antoine Ferreira	antoine.ferreira@ensi-bourges.fr

Zenon Automation Technologies S.A. 1: Georg. Papathanasiou Peania GREECE	
Prof. Dr. Constantinos Mavroidis	mavro@coe.neu.edu

Eidgenoessische Technische Hochschule Zuerich (ETHZ) Institute of Robotics and Intelligent Systems Tannenstrasse 3 CH-8092 Zürich SWITZERLAND	
Prof. Dr. Bradley Nelson	bnelson@ethz.ch

Carl Von Ossietzky Universitaet Oldenburg Department für Informatik - AMiR 26111 Oldenburg GERMANY	
Prof. Dr. Sergej Fatikow	fatikow@uni-oldenburg.de

Biomedical Research Foundation Academy of Athens 4 Soranou Ephessiou 115 27 Athens GREECE	
Dr. Dimitris Thanos	thanos@bioacademy.gr

University of Cyprus Department of Mechanical and Manufacturing Engineering 1687, Nicosia, CYPRUS	
Prof. Dr. Haris Doumanidis	cdoumani@ucy.ac.cy

FemtoTools GMBH Tannenstrasse 3 CH 8092 Zurich SWITZERLAND	
Dr. Felix Beyeler	felix.beyeler@femtotools.com

Pius Hospital Georgstraße 12 26121 Oldenburg GERMANY	
PD Dr. Alexander Kluge	alexander.kluge@pius-hospital.de

1.3 Relevant Contacts

Antoine Ferreira
Professor
University of Orléans
Laboratoire PRISME
ENSI Bourges, 88 Boulevard Lahitolle
18000 Bourges, France
Tel: +33 2 4848 4079
Fax: +33 2 4848 4000
Email: antoine.ferreira@ensi-bourges.fr

http://www.nanoma.eu

USE AND DISSEMINATION OF FOREGROUND

Section A: Public

This section details dissemination activities developed within the project framework from June 2008 to September 2011 (both included).
These activities consist in:

- Scientific publications (journals and congresses) related to NANOMA project.
- Special issues in international journals.
- Scientific events where NANOMA technologies has been presented
- Organization/Participation on project meetings and conferences
- Other dissemination activities and material, such as project website, brochures, logo, dissemination on scientific media and press releases, etc

The following scientific disciplines have been targeted: Drug delivery, Nanoscale science, Bio/abiotic interfacing, Nanorobotics, Nanotechnology, although several other disciplines would also qualify such as: Imaging and optics, Self-assembly, Biology, Nanofluidics, Nanomanufacturing and so on.

4.2.1. Organization Project Meetings/Conferences

Particular care is devoted to involve all scientific and technological communities who can bring a differing perspective to the field: from the areas of drug delivery and cancer therapy to those of material science and nanotechnology. The organization of events workshops involving mainly the academic community on the domain of nanorobotics and nanotechnology has been carried out:

- Co-organization of European Symposium on Carbon Nanotubes for Nanomedecine (A. Ferreira), Brussels*, Belgium, Nov. 2011.*
- Co-organization of Nanofabrication and Nanomanufacturing Session (C. Doumanidis), 2nd Intl. Conf. from Nanoparticles & Nanomaterials to Nanodevices & Nanosystems (IC4N), Rhodes*, Greece*, June 2009. http://www.new.ucy.ac.cy/goto/nano/en-US/NewsEventsandAnnouncements.aspx*.*
- Organization and Chair (T. Krasia) of the International Scientific Conference on "Nanotheranostics: Fabrication & Safety Concerns"*,* April, 27-30, 2010, Ayia Napa, Cyprus. URL: http://www.nanotheranostics-cyprus.org/
- Organization and chair (C. Rebholz), ICTCMF Conference, Session on Exothermic Reactive Materials, San Diego, CA, April 2011.
- Organization and Chair (C. Doumanidis), NSF CMMI Grantees Conference, Atlanta, GA, Session on New Directions of Nanomanufacturing Program at NSF, January 2011.
- Organization and Chair (C. Doumanidis), NSF Nanoscale Science and Engineering Grantees, Scalable Nanomanufacturing Initiative Conference, Arlington VA, December 2010.
- Organization and Chair of a common one-day meeting workshop with the consortium ANTICARB: Monoclonal antibody-targeted carbon nanotubes against cancer (HEALTH-

2007-2.4.1-7). Session on Novel carbon nanotube technologies in clinically established targeted cancer therapeutics, July 2010, Paris.

- Organization and Chair (C. Mavroidis and A. Ferreira) of the Workshop on "Current State of the Art and Future Challenges in Nanorobotics" of the *IEEE/RSJ 2008 International Conference on Intelligent RObots and Systems,* September, 22-26, 2008, Nice, France. URL: http://iros2008.inria.fr/workshops.php

1.1.1. Journal Special Issues

Different special issues in well known international journals in the scientific domains releted to NANOMA technologies, e.g., nanorobotics, nanotheranostics, nanomedecine and nanotechnology has been published by project partners as guest editors.

- Guest Editors (N. Jalili, P. Liu, G. Alici, Ferreira A.), Special Issue "Mechatronics for MEMS and NEMS", *IEEE/ASME Transactions on Mechatronics*, Vol. 14, Issue 4, Aug. 2009.
- Guest Editors (C. Mavroidis, A. Ferreira), Special Issue on" Current State of the Art and Future Challenges in Nanorobotics," *International Journal of Robotic Research*, SAGE, April 2009.
- Guest Editor (T. Krasia), Special Issue on "Nanotheranostics: Fabrication & Safety Concerns ", *International Biomedical Engineering Research Journal*, Inderscience 2011.
- Guest Editor, (A. Ferreira), Special Issue on "Multi-Scale Simulation Tools for Nanotechnology Applications", *IEEE Magazine on Nanotechnology*, vol.3, Issue 1, September 2009.

1.1.2. Best Paper Awards and Distinctions

- Graduate Student Gold Medal Award Winner , K. Fadenberger, I.E. Gunduz, F. Nahif, K.P. Giannakopoulos, B. Schmitt, J.M. Schneider, P.H. Mayrhofer, C.C. Doumanidis and C. Rebholz, "*The effect of interface quality on Self Propagating Exothermic Reactions (SPER) in Ni-Al multilayer foils"*, Proc. 38th International Conference on Metallurgical Coatings and Thin Films – ICMCTF2011, May 3, 2011, San Diego, USA.
- Materials Today Cover Competition Winner (Annex III), M. Arif Zeeshan, Kaiyu Shou, Kartik M. Sivaraman, Thomas Wuhrmann, Salvador Pané, Eva Pellicer and Bradley J. Nelson Nanorobotic drug delivery: If I only had a heart…, *materialstoday*,Vol.14 Feb.2011.
- Nominated for the Best Paper Award, T. Wortmann, C. Dahmen, C. Geldmann, S. Fatikow: "Recognition and Tracking of Magnetic Nanobots using MRI", Proc. of Int. Symposium on Optomechatronic Technologies (ISOT), Toronto, Canada, October 25-27, 2010.
- Selection for Interactive Session, D. Folio, C. Dahmen, T. Wortmann, A. Muhammad Zeeshan, K. Shou, S. Pane, B. J. Nelson, A. Ferreira, S. Fatikow, "MRI Magnetic Signature Imaging, Tracking and Navigation for Targeted Micro/Nano Capsule Therapeutics, IEEE International Conference on Intelligent Robots and Systems (IROS11), San Francisco, USA, 23-29 Sept 2011.
- Best Manipulation Paper Award, M. Kummer, J. J. Abbott, B. E. Kratochvil, R. Borer, A. Sengul, B. J. Nelson, "OctoMag: An Electromagnetic System for 5-DOF Wireless

Micromanipulation", *Proc. of IEEE International Conference on Robotics and Automation (ICRA)*, May 2010.

1.1.3. Project dissemination in scientific and other events

Throughout the project lifetime, the consortium have net to exchange information and knowledge, both pedagogical and technical online seminars and workshops have been conducted. As was pointed out above, the consortium was very active in taking part in external workshops and conferences. More than 68 keynote lectures, oral presentations and invited talks have been given by the consortium beneficiaries.

1.2. ORGANISATION OF NANOMA RELATED ACTIVITIES

Different workshops have been organized by the NANOMA consortium beneficiaries during the project at different stages of NANOMA technologies development:

2.4.1: NANOROBOTICS Activities

Three dissemination activities have been conducted during the NANOMA project: workshop, special issue in international journal and edition of a Nanorobotics book. The Nanorobotics Group of UORL and ZENON company coordinated these dissemination activities and most part of consortium members, as well as members of project Advisory Board, were involved in the design, contribution and management.

1) NANOROBOTICS Workshop at IEEE IROS 2008 :

The organisation of a workshop on “Current State of the Art and Future Challenges in Nanorobotics” at the beginning of the project. This event was included in the IEEE International Conference on Intelligent Robots and Systems (IROS 2008) in September, 22-26, 2008, Nice, France.

The workshop addressed the issues related with a novel discipline known as Nanorobotics. In the workshop, international experts presented new advances on Medical Nanorobotics and the challenges bound with this emerging discipline. In this context the workshop also addressed the relation between Translational Nanorobotics and the application of the same principles to the new discipline defining the concept of Translational Nanomedecine.

Nanorobotics implies a huge potential for providing robotic tools needed to fully exploit the possibilities of nanomedicine, including diagnostic, therapeutic, prognostic and preventive procedures. This workshop aims to summarize the current open research lines in this area and provide a general scenario in order to understand the deep impact that this discipline can achieve

in biomedical research and practice. Specific workshop presentations are available in the NNAOMA website [3].

2) NANOROBOTICS Special Issue in the Int. Jour. of Robotics Research -- 2009:

In addition, a special issue prepared by some Consortium members, e.g. Prof. Antoine Ferreira (UORL) and Prof. Constantinos Mavroidis (ZENON) titled — *Current State of the Art and Future Challenges in Nanorobotics* — was published in April 2009 in the first ranked robotics journal entitled *International Journal of Robotic Research* — see Annex II.

The specific papers provided an overview about the change in Nanorobotics due to advances in nanomedicine and nanotechnologies. In view of advances in the two areas, three articles papers written beneficiaries positioned efforts and provided insight about the forthcoming NANOMA technologies. The Table Of Contents is presented in Annex II.

2.4.2: NANOTHERANOSTICS Conference at ESF 2010

(http://www.nanotheranostics-cyprus.org/)

This international Conference that is mainly funded by the European Science Foundation took place as a 4-day event in Cyprus from the 27th- 30th April 2010 at the Callisto Holiday Village, in Ayia Napa. The topics discussed were devoted to Fabrication of nanoparticulate systems for theranostic applications

- NPs in drug delivery and gene-transfection
- Nanotechnology in tissue engineering
- Nanodiagnostics

and Safety concerns of NPs destined for theranostic applications.

- Interactions of NPs with biological systems

[3] Slides presented during the workshop are available through the NANOMA Wiki: www.nanoma.eu/

- Kinetics and biodistribution of NPs in biological systems
- Safety by design for nanoscience
- Standards for nanotechnology-ensuring safe nano for the future

This workshop aims to discuss the fabrication of nanoparticulate systems (NPs) destined for use in therapeutic and diagnostic applications, as well as the need to urgently address nanosafety issues related to biomedical applications of nanomaterials These issues have attracted considerable scientific and societal attention. This conference aims to bring together scientists working on the design and fabrication of such theranostic NPs, with scientific teams involved in the understanding of NP-biological system interactions and the interconnection of the latter to question of nanosafety. The emphasis on understanding bionanointeractions, and the role of proteins and other biomolecules as mediators of the interactions between NPs and living systems, is also a key goal of the ESF Networking Program, EpitopeMap, which deals with promotion of the understanding of the nature of the surface-adsorbed protein layer on biomaterials and nanoparticles and the effect of this on biocompatibility and nanoparticle safety.

A specific concern addressed in the workshop was the applicability of NANOMA technology in the medical field involves the development of novel nanomaterials and nanodevices with potential use as therapeutic and diagnostic (theranostic) applications. Such nanomaterials include among others nanoparticulate systems (NPs) used as drug delivery and gene transfection agents, polymeric nanomaterials employed in tissue engineering applications and nanosystems introduced as diagnostic tools. Three oral presentations and two posters were presented by Consortium members.

2.4.3 : NANOMEDECINE Workshop 2011

Extraordinary physical and chemical properties render carbon nanotubes promising candidates as biomedical agents for diagnostic and therapeutic applications led to the funding of different EU projects related to DDS (Drug Delivery System). All these projects carbon nanotubes as drug containers with tailored materials forms packages in which the active content is encapsulated by a protecting carbon shell. In order to highlight the potential as well as critically reviewing risks and challenges of applying carbon nanotubes in biomedicine, a workshop on Nanomedecine has been organized at the end of the project (30 November 2011) by three funded EU projects coordinators: NANOMMUNE- FP7 NMP (www.**nanommune**.eu/), ANTICARB – FP7 HEALTH (www.**anticarb**.eu/) and NANOMA – FP7 ICT (www.**nanoma**.eu/). The goal of the workshop will be to disseminate in the scientific community the overall NANOMA results on the impact of NANOMA carbon nanotubes as magnetic carriers for drug delivery. The workshop will combine 3 contributions from each consortium in chemistry, physics, biology, engineering, and medicine.

Topics:

- synthesis and biofunctionalisation routes
- physical properties of carbon nanotubes relevant to biomedical applications
- Interaction of CNT with biological environments (toxicity, cellular uptake, immune response, environmental impact,...)
- Drug delivery and Targeting
- Sensoring and Imaging
- Hyperthermia

These topics fits very well the main objectives of the three EU projects summarized herein :

www.**nanommune**.eu/

The main concept in the **NANOMMUNE** project is that the recognition versus non-recognition of ENs by immune-competent cells will determine the distribution as well as their toxic potential. Moreover, we aim to assess whether ENs interfere with key functions of the immune system in vitro and in vivo, such as macrophage engulfment of cellular (apoptotic) debris and antigen-presentation by dendritic cells to lymphocytes.

www.**anticarb**.eu/

ANTICARB (*Monoclonal ANTIbody-targeted CARBon Nanotubes against Cancer*) is a European Commission FP7 funded research programme. The main objective of ANTICARB is the design and development of carbon nanotube-antibody (CNT-Ab) constructs. They are investigated as novel platforms for cancer treatment with the purpose to act as combinatory therapeutic/diagnostic agents.

www.**nanoma**.eu/

The **NANOMA** scientific and technological objectives focus on the development of untethered nanodelivery robotic carrier for breast cancer treatment combining diagnostic, targeting and therapeutic actions.

Three invited talks have been scheduled from the NANOMA consortium :

- A. Ferreira, “Current Challenges of NANOMA Technologies for Drug Delivery Systems” (Keynote Talk), *Nov.*30, Brussels, Belgium, 2011.
- B. J. Nelson, “Magnetic Nanodevices for Targeted Drug Delivery” (Keynote Talk), *Nov.*30, Brussels, Belgium, 2011.
- A. Klinakis, “In Vitro and In Vivo Validation of Nanodevices for Targeted Therapy” (Keynote Talk), *Nov.*30, Brussels, Belgium, 2011.

1.3. NANOMA BOOKS EDITED BY SPRINGER – 2011

Two books have been written by NANOMA partners (as shown in Annex V):

- Title: Design, Modeling And Characterization of Bio-Nanorobotic Systems (Springer 2010)

  Authors: Mustapha HAMDI and Antoine FERREIRA

- Title : Nanorobotics : Current Approaches and Techniques (Springer 2011)

  Authors: Constantinos MAVROIDIS and Antoine FERREIRA

Profs Mavroidis and Ferreira signed an agreement with Springer for publishing a book with the title: *NanoRobotics: Current Approaches and Techniques* where 7 chapters have been written by our NANOMA partners. The book is expected to be published towards the end of 2011.

1.4. NANOMA PUBLICATIONS IN INTERNATIONAL JOURNALS AND CONFERENCES

Whenever during the life-time of the project, the possibility of publication arises; the beneficiary's involved will promptly inform the coordinator who will consult all the other beneficiaries either by means of extraordinary meetings of the SC or through a rapid e-mail consultation, according to urgency. This procedure is foreseen in order to make sure that if IPR issues are involved, beneficiaries are informed in good time and can act to protect their knowledge. Practically all intermediate results of the programme can qualify for scientific publications, most of them even as fundamental science. However since the consortium will push for outcomes in terms of patenting, before publishing the results of the project, the Consortium will verify the opportunity of patenting. After clarification of possible patent issues, we aim at timely publication of the results. To this end, the choice of journals is important to assure a large and competent readership (see examples in Annex I).

- Publications in journals related to nanomedicine applications:
  - IEEE Transactions on Biomedical Engineering
  - Annual Reviews of Biomedical Engineering
  - Journal of Nanomedecine

- Publications in journals related to nanotechnology:
  - Nanotechnology Journal
  - IEEE Transactions on Nanotechnology
  - Journal of Nanoengineering and Nanosystems
  - Microelectronics Engineering (Elsevier)
  - Journal of Applied Physics

- Publications in journals related to robotics:
  - Advanced Robotics
  - International Journal of Robotics Research
  - IEEE Transactions on Control Systems Technology
  - IEEE Transactions on Mechatronics

- Publications in journals related to nanomanufacturing and nanomaterials
  - International Journal of Nanomanufacturing
  - Nature Materials
  - Nanomaterials Today

TEMPLATE A: LIST OF SCIENTIFIC (PEER REVIEWED) PUBLICATIONS, STARTING WITH THE MOST IMPORTANT ONES										
NO.	Title	Main author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Year of publication	Relevant pages	Permanent identifiers[4] (if available)	Is/Will open access[5] provided to this publication?
PUBLICATIONS IN REFEREED JOURNALS (MAY 2008- SEPTEMBER 2011)										
1	Synthesis and Characterization of Water-Dispersible, Superparamagnetic Single-Wall Carbon Nanotubes Decorated with Iron Oxide Nanoparticles and Well-Defined Chelating Diblock Copolymers	Papaphilippou P., Turcu R., Krasia-Christoforou T	Journal of Polymer Science Part B: Polymer Physics	*In print*	Wiley		2011		*(not available)*	no
2	MRI-Guided Nanorobotic Systems for Therapeutic and Diagnostic Applications	P.Vartholomeos M. Fruchard , A. Ferreira , C. Mavroidis	Annual Review of Biomedical Engineering	Vol. 13	Annual Reviews		2011	pp.157-184	doi : 10.1146/annurev-bioeng-071910-124724	no
3	Three Dimensional Controlled Motion of a Microrobot using Magnetic Gradients	K. Belharet, D. Folio, A. Ferreira	Advanced Robotics	Vol.25	VSP		2011	pp. 1069-1083	doi:10.1163/016918611X568657	No
4	MRI-based Imaging and Tracking for the Pre-Operative Navigation of Microrobotic Capsule	C. Dahmen D. Folio T. Wortmann A. Ferreira S. Fatikow	IEEE Transactions on Mechatronics	*Submitted*	IEEE Transactions		2011		*(not available)*	no

[4] A permanent identifier should be a persistent link to the published version full text if open access or abstract if article is pay per view) or to the final manuscript accepted for publication (link to article in repository).
[5] Open Access is defined as free of charge access for anyone via the internet. Please answer "yes" if the open access to the publication is already established and also if the embargo period for open access is not yet over but you intend to establish open access afterwards.

5	Endovascular Magnetically-Guided Robots: Navigation Modeling and Optimization	L. Arcese M. Fruchard A. Ferreira	IEEE Transactions on Biomedical Engineering	*Submitted*	IEEE Transactions		2011		*(not available)*	no
6	Adaptive Backstepping Controller and High Gain Observer for an MRI-Guided Microrobotic System	L. Arcese M. Fruchard A. Ferreira	IEEE Transactions on Control Systems Technology	*Revision*	IEEE Transactions		2011		*(not available)*	no
7	Simulation Platform for Magnetic Responsive Micro and Nano-Particles for Robotic Applications	P. Vartholomeos C. Mavroidis	International Journal of Robotics Research	*Submitted*	SAGE		2011		*(not available)*	no
8	Structural and magnetic characterization of batch-fabricated nickel encapsulated multi-walled carbon nanotubes	M. Zeeshan, K. Shou, S. Pané, E. Pellicer, J. Sort, K. Sivaraman, M. D. Baró, B. J. Nelson	Nanotechnology	Vol.22	*IOP Science*		2011	275713 (10pp)	doi: 10.1088/0957-4484/22/27/275713	no
9	Ultrasonic Consolidation and Ignition Characteristics of Thermite Composites	Pillai K.S, Hadjiafxenti A, Ando T, Doumanidis C.C, Rebholz C,	International Journal. of Applied Ceramic Technology		Wiley		2011	pp.1-8	doi:10.1111/j.1744-7402.2011.02655.x	no
10	Exothermic reaction characteristics of continuously ball-milled Al/Ni powder compacts	A. Hadjiafxenti, E. Gunduz, T. Kyratsi, C.C. Doumanidis, C. Rebholz	Powder Technology	*Submitted*	Elsevier		2011		*(not available)*	no
11	Optical Microscopy Imaging of Substrate Nano-Roughness using Nematic Liquid Crystals	Kossivas F, Kyprianou A, Doumanidis C,	Measurement Science and Technology	*Submitted*	IOP		2011		*(not available)*	no
12	A novel tumour-suppressor function for the Notch pathway in myeloid leukaemia	Klinakis A, Lobry C, Abdel-Wahab O, Oh P, Haeno H, Buonamici S,	Nature	473 (7346)	Nature		2011	pp. 230-233	doi:10.1038/nature09999	no

		van De Walle I, Cathelin S, Trimarchi T, Araldi E, Liu C, Ibrahim S, Beran M, Zavadil J, Efstratiadis A, Taghon T, Michor F, Levine RL, Aifantis I.								
13	Propulsion and Navigation Control of MRI-Guided Drug Delivery Nanorobots	L. Arcèse, M. Fruchard, A. Ferreira	Nanorobotics: Current Approaches and Techniques	Chapter	Springer		2011		*(not available)*	no
14	Generating Magnetic Fields for Controlling Nanorobots in Medical Applications	S. Schürle, B. K. Kratochvil, S. Pané, A. M. Zeeshan, B. J. Nelson	Nanorobotics: Current Approaches and Techniques	Chapter	Springer		2011		*(not available)*	
15	MRI-based Nanorobotics	C. Dahmen, T. Wortmann S. Fatikow	Nanorobotics: Current Approaches and Techniques	Chapter	Springer		2011		*(not available)*	
16	Nanorobotic drug delivery: If I only had a heart…	M. Arif Zeeshan, Kaiyu Shou, Kartik M. Sivaraman, Thomas Wuhrmann, Salvador Pané, Eva Pellicer and Bradley J. Nelson	materialstoday	Vol.14 (12)			2011	pp.54		
17	Exothermic reaction characteristics of continuously ball-milled Al/Ni powder compact	Hadjiafxenti A, Gunduz I,E, Agelaridou A, Kyratsi T, Doumanidis C.C, Rebholz C	Intermetallics	*Submitted*	Elsevier		2011		*(not available)*	no
18	Study of MRI	T. Wortmann,	Journal of	Vol.1 (4)	ASME		2010	041002 (5	doi:10.1115/1.4002501	no

	Susceptibility Artifacts for Nanomedical Applications	C. Dahmen, S. Fatikow	Nanotechnology in Engineering & Medicine					pages)		
19	In-situ observation of rapid reactions in nanoscale Ni-Al multilayer foils using synchrotron radiation	K. Fadenberger, I.E. Gunduz, C. Tsotsos, M. Kokonou, S. Gravani, S. Brandstetter, A. Bergamaschi, B. Schmitt, P.H. Mayrhofer, C.C. Doumanidis C. Rebholz,	Applied Physics Letters	Vol.97	AIP		2010	144101 (3 pages).	doi:10.1063/1.3485673	no
20	The influence of structure on thermal behavior of reactive Al–Ni powder mixtures formed by ball milling	A. Hadjiafxenti, I.E. Gunduz, C. Tsotsos, T. Kyratsi, S.M. Aouadi, C.C. Doumanidis C. Rebholz	Journal of Alloys and Compounds	Vol.505 (2)	Elsevier		2010	pp 467-471	doi:10.1016/j.jallcom.2010.03.250	no
21	Growth and Characterization of Ge100-xDyx (x<2) Nanowires	Paul K.B, Athanasopoulos G.I, Doumanidis C.C, Rebholz C	Advances in Condensed Matter Physics	Vol. 2010	Hindawi		2010	ID 107192 (6 pages),	doi:10.1155/2010/107192	no
22	Biodegradable Cellulose Acetate Nanofiber Fabrication via Electrospinning	Christoforou T, Doumanidis C.	J. of Nanoscience & Nanotechnology	Vol.10(9)	American Scientific Publishers		2010	pp. 6226-33	PMID:21133179	no
23	MRI-based Microrobotic System for the Propulsion and Navigation of Ferromagnetic Microcapsules	K. Belharet, D. Folio, A. Ferreira	Minimally Invasive Therapy and Allied Technologies	Vol.19(3)	Informa Heathcare		2010	pp. 157-169	PMID:20497068	no
24	Nanocrystalline Electroplated Cu–Ni: Metallic Thin Films with Enhanced Mechanical	E. Pellicer, A. Varea, S. Pané, B. J. Nelson,	Advanced Functional Materials	Vol.20 (6)	Wiley InterScience		2010	pp. 883-891	doi:10.1002/adfm.200901732	no

	Properties and Tunable Magnetic Behavior	E. Menéndez, M. Estrader, S. Suriñach, M. Dolors Baró, J. Nogués, J. Sor								
25	Modeling of the self propagating reactions of nickel and aluminum multilayered foils	I.E Gunduz K. Fadenberger M. Kokonou C. Rebholz C.C. Doumanidis T. Ando	Journal of Applied Physics	Vol. 115 Issue 7	American Institute of Physics		2009	pp. 74903	doi: 10.1063/1.3091284	no
26	Reactive bimetallic Al/Ni nanostructures for nanoscale heating applications fabricated using a porous alumina template	K.P. Kokonou	Microelectronic Engineering	Vol. 86 Issue 4-6	Elsevier		2009	pp. 836 - 839	doi:10.1016/j.mee.2008.12.089	no
27	Superparamagnetic Hybrid Micelles, Based on Iron Oxide Nanoparticles and Well-Defined Diblock Copolymers possessing beta-ketoester functionalities	T. Krasia-Christoforou	Biomacromolecules	Vol.10 (9)	ACS Publications		2009	pp. 2662-2671	doi:10.1021/bm9005936	no
28	MRI-Guided Nanorobotic Systems for Drug Delivery	P.Vartholomeos M. Fruchard , A. Ferreira , C. Mavroidis	Handbook of Nanophysics: Nanorobotics and Nanomedecine	Vol.7	CRC Press, Taylor &Francis Group		2010	Chap.45-1	*Print ISBN: 978-1-4200-7546-5*	
29	A Six-Axis MEMS Force–Torque Sensor With Micro-Newton and Nano-Newtonmeter Resolution	F. Beyeler S. Muntwyler B. J. Nelson	IEEE Journal of Microelectromechanical Systems (JMEMS)	Vol 18, Issue 2	IEEE Transactions		2009	pp. 433-441	doi:10.1109/JMEMS.2009.2013387	no
30	Igf1r as a therapeutic target in a mouse model of basal-like breast cancer	A. Klinakis	Proceedings of the National Academy of Sciences of the United States of America	Doi: 10.1073/pnas.0810221106	The National Academy of Sciences of the USA		2009	*pp.* 134101	http://link.aip.org/link/?APPLAB/93/134101/1	no
31	Tittin forms the most extensible biological	E. Klotzsch M.L. Smith	Proceedings of the National Academy	Vol. 106 No. 43	PNAS		2009	pp. 18267-18272	doi: 10.1073/pnas.09075181	no

	fibers displaying switchable force-exposed cryptic binding sites	K.E. Kubow S. Muntwyler F. Beyeler	of Sciences of the United States of America (PNAS)						06	
31	DNA Nanorobotics	A. Ferreira	Microelectronics Journal	*No 39,* Issue 8	Elsevier Science Publishers		2008	*pp.* 1051-1059	*http://portal.acm.org/citation.cfm?id=1387558*	no
32	Low aspect-ratio porous alumina templates	M. Kokonou	Journal of Microelectronic Engineering	Vol.85, Issue 5-6	Elsevier Science Publishers		2008	pp. 1186-1188	http://portal.acm.org/citation.cfm?id=1375101	no
33	Reversible pH-controlled DNA-binding peptide nanotweezers: An in-silico study	G. Sharma	International Journal of Nanomedecine	Issue 4	DovePress		2008	pp. 505-521	http://www.dovepress.com/	yes

PUBLICATIONS IN REFEREED INERNATIONAL CONFERENCES (MAY 2008- SEPTEMBER 2011)

1	MRI Magnetic Signature Imaging, Tracking and Navigation for Targeted Micro/Nano Capsule Therapeutics	D. Folio, C. Dahmen, T. Wortmann, A. Muhammad Zeeshan, K. Shou, S. Pane, B. J. Nelson, A. Ferreira, S. Fatikow	IEEE International Conference on Intelligent Robots and Systems		IEEE	San Francisco, USA, 23-29 Sept 2011	2011		*ieeexplore.ieee.org/*	
2	Adaptive Backstepping and MEMS Force Sensor for an MRI-guided Microrobot in the Vasculature	L. Arcese, M. Fruchard, F. Beyeler, A. Ferreira, B.J. Nelson	IEEE International Conference on Robotics and Automation		IEEE	Shanghai, China, May 2011	2011	pp.??	*ieeexplore.ieee.org/*	
3	Fabrication of CNT-based Magnetic Nanocapsules for Minimally Invasive Medicine	A.Z. Muhammad, K. Shou, E. Pellicer, K.M. Sivaraman, S. Schuerle, M.D. Baró, J. Sort, B.J. Nelson	Euromat 2011			Montpellier, France	2011		euromat2011.fems.eu/	
4	Fabrication and ignition characteristics of thermite composites prepared by ultrasonic powder consolidation	Pillai, S.K, Hadjiafxenti A, Ando T, Doumanidis C.C. Rebholz C	Mediterranean Conference on Innovative Materials and Applications			Beirut, Lebanon	2011		www.cima1.org/	
5	The effect of interface quality on Self Propagating Exothermic Reactions (SPER) in Ni-Al multilayer foils	K. Fadenberger, I.E. Gunduz, F. Nahif, K.P. Giannakopoulos, B. Schmitt, J.M. Schneider, P.H. Mayrhofer, C.C. Doumanidis C. Rebholz,	38th International Conference on Metallurgical Coatings and Thin Films			San Diego, USA	2011		www.nanokalender.de/NANOicmctf11.html	

6	Coaxial nanofibers with tunable release properties as drug delivery and tissue engineering platforms: the case of Γ-Tocopherol in intestinal tissue regeneration	Kokonou M, Trifonos A, Doumanidis C.C, Odysseos A	3rd International Conference from Nanoparticles and Nanomaterials to Nanodevices and Nanosystems			Hersonisso s, Crete	2011		www.uta.edu/**ic4n**/	
7	Coaxial nanofibers by electrospinning for drug delivery with tunable release properties	Trifonos A, Kokonou M, Rebholz C, Doumanidis C, Odysseos A	3rd International Conference from Nanoparticles and Nanomaterials to Nanodevices and Nanosystems			Hersonisso s, Crete	2011		www.uta.edu/**ic4n**/	
8	Ultrasonic Consolidation of Al and Ni Powder Compacts	A. Hadjiafxenti, D. Erdeniz, I.E. Gunduz, T. Ando, C.C. Doumanidis C. Rebholz	Euromat 2011			Montpellier, France	2011		euromat2011.fems.eu/	
9	Drug-loaded nanocapsules embedded in a porous template for controlled drug release rate	Ioannou G, Kokonou M, Odysseos A, Doumanidis C	3rd International Conference from Nanoparticles and Nanomaterials to Nanodevices and Nanosystems			Hersonisso s, Crete	2011		www.uta.edu/**ic4n**/	
10	Ignitable Al/Ni compacts produced by mechanical alloying: structural, chemical and thermal characterization	A. Hadjiafxenti, I.E. Gunduz, S.M. Aouadi, T. Kyratsi, C.C. Doumanidis and C. Rebholz	38th International Conference on Metallurgical Coatings and Thin Films			San Diego, USA	2011		www.nanokalender.de/NANOicmctf11.html	
1	Optimal trajectory for a microrobot navigating in blood vessels	L. Arcese A. Cherry M. Fruchard A. Ferreira	32nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society		IEEE/EMBS	**August 31 - September 4,** Buenos Aires, Argentina	2010		*ieeexplore.ieee.org/*	no

2	High Gain Observer for Backstepping Control of a MRI-guided Therapeutic Microrobot in Blood Vessels	L. Arcese A. Cherry M. Fruchard A. Ferreira	3rd International Conference on Biomedical Robotics and Biomechatronics,		IEEE/EMBS	September 26-29, Tokyo, Japan	2010		*ieeexplore.ieee.org/*	no
3	3D MRI-based Predictive Control of a Ferromagnetic Microrobot Navigating in Blood Vessels	K. Belharet D. Folio A. Ferreira	3rd International Conference on Biomedical Robotics and Biomechatronics		IEEE/EMBS	September 26-29, Tokyo, Japan	2010		*ieeexplore.ieee.org/*	no
4	Ferromagnetic Nanowires as Potential Drug-Delivery Wireless Nanorobots	M. Zeeshan, K. Shou, S. Schuerle, E. Pellicer, S. Pané, J. Sort, K. Sivaraman, S. Fusco, S. Muntwyler, M. D. Baró, B. J. Nelson	IEEE International Conference on Nano/Molecular Medicine and Engineering,		IEEE	HongKong/ Macau	2010	pp.??	*ieeexplore.ieee.org/*	no
5	MiniMag: A Hemispherical Electromagnetic System for 5-DOF Wireless Micromanipulation	B. E. Kratochvil, M. Kummer, S. Erni, R. Borer, D. R. Frutiger, S. Schuerle, B. J. Nelson	12th International Symposium on Experimental Robotics		IFRR	New Delhi, India	2010	pp.??	iser2010.grasp.upenn.edu/	no
6	Endovascular Navigation of a Ferromagnetic Microrobot Using MRI-based Predictive Control	K. Belharet D. Folio A. Ferreira	IEEE International Conference on Intelligent Robots and Systems		IEEE	October 18-22, Taipei, Taiwan	2010		*ieeexplore.ieee.org/*	No
7	Dynamic behavior investigation for trajectory control of a microrobot in blood vessels	L. Arcese A. Cherry M. Fruchard A. Ferreira	IEEE International Conference on Intelligent Robots and Systems		IEEE	October 18-22, Taipei, Taiwan	2010		*ieeexplore.ieee.org/*	No
8	Computational Studies of Controlled Nanoparticle	P.Vartholomeos S. Aylak C. Mavroidis	2010 ASME Dynamic Systems and Control		ASME Proceedings	Sept 13-15, Cambridge, MA, USA	2010		www.dsc-**conference**.org/	no

	Agglomerations for MRI–Guided Nanorobotic Drug Delivery Systems		Conference							
9	Simulation Platform for Self-assembly Structures in MRI-guided Nanorobotic Drug Delivery Systems	P. Vartholomeos C. Mavroidis	IEEE International Conference on Robotics and Automation		IEEE Proceedings	Anchorage, May 2010	2010	pp. 5594-5600	*ieeexplore.ieee.org/*	no
10	Diblock copolymers based on PEGMA and DEAEMA functionalities: Synthesis, characterization and investigation of their ability to act as drug delivery systems	P. C. Papaphilippou, Z. Kanaki, A. Klinakis T. Krasia-Christoforou	42rd IUPAC World Polymer Congress			Glascow, UK	2010		www.**iupac**2011.org/	no
11	Magnetic Resonance Imaging of Magnetic Particles for Targeted Drug Delivery	C. Dahmen T. Wortmann S. Fatikow	ASME 2010 First Global Congress on NanoEngineering for Medicine and Biology (NEMB2010)		ASME Proceedings	Feb. 7-10, Huston, TX, 2010	2010		www.**asmeconference**s.org/nemb**2010**/	no
12	Recognition and Tracking of Magnetic Nanobots using MRI	**T. Wortmann C**. Dahmen, C. Geldmann, S. Fatikow	International Symposium on Optomechatronic Technologies							
13	Magnetic Targeting of Aggregated Nanoparticles for Advanced Lung Therapies: A Robotics Approach	P. Vartholomeos C. Mavroidis N. Hata	2010 IEEE BIOROB,		IEEE Proceedings	September 26-29, 2010, Tokyo, Japan	2010	pp. 861-868	*ieeexplore.ieee.org/*	no
1	Aluminum/Nickel (Al/Ni) Heterogeneous Nanostructures: Synthesis, Characterization and Nano-Heater Applications	Q. Cui K. Pelealuw PN. Gibson SJ. Hinder T. Ando	AIChE Annual Meeting,			November, Nashville TN	2009		www.**aiche**.org/**annual**/	no

2	Nonlinear modeling and robust controller-observer for a magnetic microrobot in a fluidic environment using MRI gradient	L. Arcese M. Fruchard A. Ferreira	Proc. IEEE International Conference on Intelligent Robots and Systems (IROS)		IEEE Proceedings	Oct ., St. Louis, MO, USA	2009	pp. 534-539	*ieeexplore.ieee.org/*	no
3	Tailoring the mechanical and magnetic behavior of electrodeposited nanocrystalline CuNi thin films	E. Pellicer	Proc. in the International Conference on Advanced Materials (ICAM2009)		Int. Union of Material Research Societies	Sept. 20-25 Rio de Janeiro, Brazil	2009		www.icam2009.com/submission/autor/arquivos/R513.pdf	no
4	Preliminary studies on the electrodeposition of cobalt-yttrium from baths containing glycine	S. Pané	Proc. in 216th ECS Meeting		American Institute of Physics	Oct. 3, Vienna, Austria	2009		http://link.aip.org/link/?MAECES/902/3132/1	no
5	Magnetic properties of electrodeposited cobalt-nickel thin films from acidic baths containing glycine	O. Ergeneman	Proc. in 216th ECS Meeting		American Institute of Physics	Oct.3, Vienna, Austria	2009		http://link.aip.org/link/?MAECES/902/3124/1 - top	no
6	Towards Nanorobots	B.J. Nelson	Proc. Solid-State Sensors, Actuators and Microsystems Conference, 2009. TRANSDUCERS 2009. International		IEEE Proceedings	June 21-25, Denver, CO, USA	2009	pp. 2155 - 2159	10.1109/SENSOR.2009.5285633	no
7	Noncontact manipulation of Ni nanowires using a rotating magnetic field	L. Zhang, Y. Lu, L. X. Dong, R. Pei, J. Lou, B. E. Kratochvil, B. J. Nelson	*Proc. in the 9th IEEE Conf. on Nanotechnology (NANO2009)*		IEEE Proceedings	*July 27-30, Genoa, Italy*	2009	pp. 487-490	*ieeexplore.ieee.org/*	no
8	Magnetoresponsive polymer micelles based on iron oxide nanoparticles and diblock copolymers with	P. Papaphilippou T. Krasia-Christoforou N.C. Popa A. Han	Proc. In European Polymer Congress		EPC Proceedings	July 12-17 , Graz Austria	2009	pp. 217	In print	no

	β-ketoester groups	L. Vekas								
9	Superparamagnetic Hybrid Micelles, Based on Iron Oxide Nanoparticles and Well-Defined Diblock Copolymers Possessing β-Ketoester Groups	P. Papaphilippou T. Krasia-Christoforou N.C. Popa A. Han L. Vekas	Proc. 1st International Conference on Multifunctional, Hybrid and Nanomaterials		Elsevier	March 15-19, Tours, France	2009	pp. B2.1.61	In print	no
10	Magneto-responsive polymer micelles based on Fe3O4 and diblock copolymers with β-Ketoester functionalities: Fabrication, characterization and in vitro biocompatibility	P. Papaphilippou L. Loisou N.C. Popa A. Han L. Vekas	Proc. 1st International Conference on BioNano: Inspiring Responsible Development for Society and the Environment,		European Science Foundation	15th & 16th October, Dublin, Ireland	2009	pp. 22	In print	no
11	In-situ observation of rapid reactions in nanoscale Ni-Al multilayer foils using synchrotron radiation	K. Fadenberger I.E. Gunduz C. Tsotsos M. Kokonou S. Gravani	Proc. SLS Conference			11th September Villingen PSI Switzerland	2009			no
12	Synthesis and Structural Characteristics of CeO2 Thin Films and Nanowires	S. Gravani K.Polychronopoulou PN. Gibson SJ. Hinder Z. Gu	14th Israel Materials Engineering Conference		IMEC	13th & 14th December, Tel Aviv, Israel	2009			no
13	Design and Calibration of a Microfabricated 6-Axis Force-Torque Sensor for Microrobotic Applications	F. Beyeler S. Muntwyler B.J. Nelson	Proc. IEEE International Conference on Robotics and Automation (ICRA),		IEEE Proceedings	Kobe, May 2009	2009	pp. 520-525	*http://dx.doi.org/10.1109/ROBOT.2009.5152253*	no
14	Characterization of Structure and Reactions in Magnetron-Sputtered Ni/Al Multilayers Showing Self-Propagating Exothermal Reactions	F. Nahif K. Fadenberger KP. Giannakopoulos IE. Gunduz CC. Doumanidis	14th Israel Materials Engineering Conference		IMEC	13th & 14th December, Tel Aviv, Israel	2009			no
15	Novel Nanostructures by Anodization of Al Wires	M. Kokonou IE. Gunduz K. Fadenberger	14th Israel Materials Engineering		IMEC	13th & 14th December, Tel Aviv,	2009			no

		CC. Doumanidis	Conference			Israel				
6	NEMS-on-a-tip: Force Sensors Based on Electromechanical Coupling of Individual Multi-Walled Carbon Nanotubes	K. Shou	IEEE I International Conference on Intelligent RObots and Systems -	22 Sept. 2008, in Nice, France	IEEE	Acropole Nice - France	2008		http://iros2008.inria.fr/	no
7	Metal-filled Carbon Nanotubes for Nanomechatronics	L. Dong	2008 IEEE/ASME Int. Conf. on Advanced Intelligent Mechatronics (AIM2008)	July 2-5 August 2008 Xi'an, China	IEEE				*http://www.ee.cuhk.edu.hk/~qhmeng/aim2008/*	no

3 SECTION B (CONFIDENTIAL)

TEMPLATE B1: LIST OF APPLICATIONS FOR PATENTS, TRADEMARKS, REGISTERED DESIGNS, ETC.			
Type of IP Rights: Patents, Trademarks, Registered designs, Utility models, etc.	Application reference(s) (e.g. EP123456)	Subject or title of application	Applicant (s) (as on the application)
Patent	EP09156798.2	Package and Interface of a Micro Force Sensor for Sub-Millinewton Electromechanical Measurements	F. BELEYER
Patent	ARC 10/003	Logiciel de supervision pour la propulsion guidée de microtransporteurs magnétiques pour un système d'Imagerie à Résonnance Magnétique	D. FOLIO, K. BELHARET, A.FERREIRA

Please complete the table hereafter:

TEMPLATE B2: OVERVIEW TABLE WITH EXPLOITABLE FOREGROUND					
Exploitable Foreground (description)	**Exploitable product(s) or measure(s)**	**Sector(s) of application**	**Timetable, commercial use**	**Patents or other IPR exploitation (licences)**	**Owner & Other Beneficiary(s) involved**
C***ontrol algorithms for endovascular steering and navigation of magnetic nanoparticles.***	Dedicated to IDEA and ICE software packages for GUI interfaces for MRI scanners.	MRI manufacturers	Creation of a SPIN-OFF company : **COMMERCIALLY AVAILABLE IN 2012**	FRENCH PATENT IPR EXPLOITATION BY **NANO-IRM SPIN-OFF**	UORL
Design of the "minimag", and 6DOF magnetic manipulation system for light microscopes	Dedicated to steering and navigation of magnetic microcarriers for targeted drug delivery	Surgery, Otology, Eye, Pharmacology ...	Creation of a SPIN-OFF company AEON SCIENTIFIC: **COMMERCIALLY AVAILABLE NOW**	EUROPEAN PATENT IPR EXPLOITATION BY **AEON SCIENTIFIC SPIN-OFF**	ETHZ
Design and fabrication of the magnetic NANOMA nanocapsule	Functionalized magnetic microcarriers for targeted drug delivery	Pharmacology	----	IPR EXPLOITATION	ETHZ
Imaging softwares: ***a)MRI based propulsion/imaging sequences***; b) ***Detection of ferromagnetic particles in the MRI***; c) ***Tracking of ferromagnetic particles in the MRI***.	Upgraded software packages for Siemens MRI scanners	MRI manufacturers	----	IPR EXPLOITATION WITH **SIEMENS**	AMIR

TEMPLATE B2: OVERVIEW TABLE WITH EXPLOITABLE FOREGROUND					
Exploitable Foreground (description)	**Exploitable product(s) or measure(s)**	**Sector(s) of application**	**Timetable, commercial use**	**Patents or other IPR exploitation (licences)**	**Owner & Other Beneficiary(s) involved**
Package and Interface of a Micro Force Sensor for Sub-Millinewton Electromechanical Measurements	Packaging possibilities for highly miniaturized, highly sensitive force sensors	BIOLOGICAL APPLICATIONS	**COMMERCIALLY AVAILABLE NOW**	EUROPEAN PATENT	**FEMTOTOOLS**
NANOMA Simulation Platform for Inner Ear Drug Admnistration	Computational tool for nanoparticles based drug administration	PHARMACOLOGY	----	IPR EXPLOITATION WITH **SANOFIS-AVENTIS** COMPANY	**UORL**
Micellar nanocapsules as an intravenous drug delivery vector	Anticancer biopharmaceuticals	BIO-PHARMACOLOGY	----	IPR EXPLOITATION WITH **REGULON** COMPANY	**UCY**
Nanofiber meshes containing the medicine as a transcutaneous or implantable reservoir for controlled drug release	Liposomic and dendrimeric technologies	BIO-PHARMACOLOGY	----	IPR EXPLOITATION WITH **REGULON** COMPANY	**UCY**

3.2 EXPLOITATION OF THE FOREGROUND

The project aimed at providing a broad framework for a comprehensive and multidisciplinary approach for the development of innovative intelligent and multifunctional unthetered nanocapsules in oncology. The strategy exploited is based on the optimal selective delivery of known chemotherapeutics by magnetic nanocapsules, which has been specifically designed, produced and tested. The magnetic nanocapsules will perform in concomitance drug delivery and hyperthermia treatment and are not limited to the conventional strategy of selective delivery. Our research has a significant impact on basic Nanotechnology, Medecine and Intelligent Systems Science.

The NANOMA project has the potential to develop novel and revolutionary nanomedicine technologies that can contribute significantly in the cure of very important diseases such as cancer. The proposed NANOMA technologies and devices have the ability to re-shape important sectors of biomedical industry, therefore strengthening European position in the global market with high added-value products. The development of dynamic nanodevices based on protein molecular motors/sensors constitutes a paradigm shift in the area of biomedical microdevices. These bio nanodevices have a competitive edge as, steering magnetic tools for unthetered drug delivery, drug discovery and diagnostic devices and therefore have the potential for a greater impact on industry, especially novel high value added products. **The NANOMA project has focused on the design, fabrication and implementation of dynamic nano-Actuators and nano-Sensors based on non-bio interactions between nanostructures** (i.e., carbon nanotubes, engineered surfaces…) with protein molecular motors/sensors. NANOMA will leverage on the already commanding position of European research in molecular-based nanodevices and contribute to the consolidation of the high added value of European biomedical industry.

3.3 IPR EXPLOITABLE MEASURES TAKEN

A successful development of a new drug delivery method could have a major economical impact. The involvement of bodies as diverse as a company, various independent research institutes, and universities necessitates carefully balanced rules for intellectual property. Setting up a contract that clarifies all relevant points has been initiated at the consortium agreement. It required the involvement of legal representatives and experts from each institution. The basic structure and input for the contract will be decided at the kick-off meeting. The first point will consider the level of confidentiality, including safe storage of collected data. However, the general policy of the NANOMA consortium will be to widely share knowledge produced, with as few limitations as possible in term of access to results. The support of a highly organized staff of people with international experience in the field of patent policy will guarantee direct access to international patent libraries, patent filing procedures, technology transfer issues etc.

A valid contribution to Intellectual Property issues and to Technology Transfer has been initially provided by the ZENON, and continued by Hospital of Oldenburg. Specialized ZENON staff has assisted the consortium through all financial, legal, and more generally, administrative issues that may arise in the development of the project. Since January 2011, beneficiary Pius Hospital is in charge of the Technology Implementation Plan. Template B1 shows the list of applications for patents, trademarks and registered designs, etc. since the beginning of the NANOMA project.

We are particularly excited about a spin-off company in the Medtech sector, which indicates that our strategic research objectives are starting to pay off. “AEON Scientific” (www.aeon-scientific.com/), spin-off company of beneficiary ETHZ, was launch early February 2011 in order to develop magnetic platforms for steering and navigation of magnetic microparticles in a 6 d.o.f workspace. Applications for targeted drug delivery (inner cochlear ear, internal eye, *in vitro* and *in vivo* cell medication ...) are under way in order to act as reservoirs for long-term medication (see Annex VI). Furthermore, a new spin-off company “Nano-MRI”, from beneficiary UORL, will be

launched in 2012. This spin-off will be dedicated to bring software solutions for MRI scanners necessitating 3-D navigation capabilities using MRI imaging.

3.4. POTENTIAL/EXPECTED IMPACT

This project will provide major advantages for biomedical applications, well beyond the state of the art, and will affect the following research areas (see Template B2):

(a) Cancer biology and possible industrial markets:

Breast cancer is the most lethal breast malignancy, and is the second leading cancer – related to death in women (at least in the United States). In 2005, the American Cancer Society estimated that there were 22,200 cases of breast cancer. Similar estimates (adjusted for population) can be expected in all developed countries. The high mortality rate is due mainly to the inability to detect disease early with approximately 80% of patients being diagnosed of such form of cancer when this is already in an average stage (stage 3: the cancer has spread to the lymph nodes near the breast). However, even if those patients that have been diagnosed with early-stage disease, the five-year survival rate ranges from 60% to 90%, depending the degree of tumor differentiation. Even thought the response rate to conventional therapies in patients with advanced disease is generally high, with 80%-90% of tumors responding in the first instance, the disease re-occurs again within 5 years. Moreover, the inherent resistance of 10%-20% of cases to first line chemotherapy and the development of resistance in most cases of relapse to subsequent therapy, represent the major hurdle to effective management of late-stage breast cancer therapy.

On the basis of these considerations, a high unmet medical need is evident in the case of advanced breast cancer, and therefore the nanotechnological approach could be helpful in the management of the late phases of treatment. On the medium-to-long time scale, we can envision that the studies and further advances stemming from NANOMA, which will extend the investigation to new therapeutic approaches for the treatment of several cancerous diseases, will contribute to the increase in a significant manner of the life expectancy of women. It will therefore improve the quality of life and health of the human population. If the techniques proposed by NANOMA are successful, the results obtained with nanotechnological approaches will open new perspectives in the therapeutic intervention against other solid and/or haematologic tumors. It presents a clear social impact measured as an increase of life expectancy. The developed therapeutic approaches has a great interest for MRI manufacturers. All hardware and software systems developed by partners UNOL, UORL and PIUS Hospital are dedicated to MRI systems manufactured by Siemens. After a pre-validation and certification of the MRI setup located at PIUS Hospital, an agreement with SIEMENS will be discussed for the transfer of IPR issues.

We need to keep in mind however, and also as stated by European Commission in this call, that in order to reach the final goal of the present proposal it is of primary importance to understand: 1) the interactions of the nano-Actuators and nano-Sensors integrated in the magnetic multifunctional nanocapsule within its “in-vitro” and “in-vivo” biological environment. Basic technological research has to be tackled at first instance, before application to tumor therapy with potential commercialization applications.

(b) Pharmaceutical area: By developing magnetic nanocapsules, we are also addressing an important pharmaceutical problem, which is the identification of a suitable way of administrating potential hyperthermic-chemotherapeutic agents. In order to be locally administered within the subcutaneous and intraperitoneal area of tumor, the multifunctional nanocapsule that we want to develop has to preserve a final dimension that cannot be larger than a few hundred nanometers. Such miniaturization will open up new opportunities in application where magnetic nanotools might finally only require intravenous injection to reach the taget. To date, no system is available for this purpose. Furthermore, in order to overcome typical drug delivery problem, such as drug aggregation and drug solubility, we are proposing magnetic nanocapsules that will protect the drugs from degradation by encapsulating them. Also, since such nanocapsules will have an active

surface, their functionalization with antibody fragments (Fab) will make them more selective towards cancer cells and will therefore help to reduce the drug doses that are needed for treatment. Both issues are considered as major steps towards the exploitation of novel drug delivery systems in pharmaceutics. In the NANOMA consortium, beneficiaries UCY, UORL and ETHZ are discussing IPR exploitation with different biopharma companies (REGULON from Greece, SANOFIS-AVENTIS from France).

REPORT ON SOCIETAL IMPLICATIONS

Replies to the following questions will assist the Commission to obtain statistics and indicators on societal and socio-economic issues addressed by projects. The questions are arranged in a number of key themes. As well as producing certain statistics, the replies will also help identify those projects that have shown a real engagement with wider societal issues, and thereby identify interesting approaches to these issues and best practices.

A General Information

JU Grant Agreement Number:	224594
Title of Project:	Nano-Actuators and Nano-Sensors for Medical Applications
Name and Title of Coordinator:	Antoine FERREIRA, Professor

B Ethics

1. Did you have ethicists or others with specific experience of ethical issues involved in the project?	○	**Yes**
	●	**No**

2. Please indicate whether your project involved any of the following issues (tick box) :	***YES***
INFORMED CONSENT	
• Did the project involve children?	
• Did the project involve patients or persons not able to give consent?	
• Did the project involve adult healthy volunteers?	
• Did the project involve Human Genetic Material?	
• Did the project involve Human biological samples?	
• Did the project involve Human data collection?	
• Did the project involve Human Embryos?	
• Did the project involve Human Foetal Tissue / Cells?	
• Did the project involve Human Embryonic Stem Cells?	
• Did the project involve processing of genetic information or personal data (e.g. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)	
• Did the project involve tracking the location or observation of people?	
• Did the project involve research on animals?	
• Were those animals transgenic small laboratory animals?	
• Were those animals transgenic farm animals?	
• Were those animals cloning farm animals?	
• Were those animals non-human primates?	
RESEARCH INVOLVING DEVELOPING COUNTRIES	
• Use of local resources (genetic, animal, plant etc)	×
• Benefit to local community (capacity building i.e. access to healthcare, education etc)	
DUAL USE	
• Research having potential military / terrorist application	

C Workforce Statistics

3 Workforce statistics for the project: Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Type of Position	Number of Women	Number of Men
Scientific Coordinator	2	1
Work package leader	1	9
Experienced researcher (i.e. PhD holders)	1	10
PhD Students	4	9
Other		

4 How many additional researchers (in companies and universities) were recruited specifically for this project?	
Of which, indicate the number of men:	8
Of which, indicate the number of women:	3

D Gender Aspects

5 Did you carry out specific Gender Equality Actions under the project? ● Yes ○ No

6 Which of the following actions did you carry out and how effective were they?

	Not at all effective				Very effective
❑ Design and implement an equal opportunity policy	○	○	●	○	○
❑ Set targets to achieve a gender balance in the workforce	○	○	○	●	○
❑ Organise conferences and workshops on gender	○	●	○	○	○
❑ Actions to improve work-life balance	○	○	●	○	○

○ Other:

7 Was there a gender dimension associated with the research content – i.e. wherever people were the focus of the research as, for example, consumers, users, patients or in trials, was the issue of gender considered and addressed?

○ Yes- please specify

● No

E Synergies with Science Education

8 Did your project involve working with students and/or school pupils (e.g. open days, participation in science festivals and events, prizes/competitions or joint projects)?

● Yes- please specify: Joint projects

○ No

9 Did the project generate any science education material (e.g. kits, websites, explanatory booklets, DVDs)?

○ Yes- please specify

● No

F Interdisciplinarity

10 Which disciplines (see list below) are involved in your project?

○ Main discipline[6]:

● Associated discipline[6]: 2.2 ○ Associated discipline[6]:

G Engaging with Civil society and policy makers

11a Did your project engage with societal actors beyond the research community? *(if 'No', go to Question 14)* ○ Yes ● No

11b If yes, did you engage with citizens (citizens' panels / juries) or organised civil society (NGOs, patients' groups etc.)?

● No

○ Yes- in determining what research should be performed

○ Yes - in implementing the research

○ Yes, in communicating /disseminating / using the results of the project

[6] Insert number from list below (Frascati Manual)

11c In doing so, did your project involve actors whose role is mainly to organise the dialogue with citizens and organised civil society (e.g. professional mediator; communication company, science museums)?	○ ●	Yes No

12 Did you engage with government / public bodies or policy makers (including international organisations)

- ● No
- ○ Yes- in framing the research agenda
- ○ Yes - in implementing the research agenda
- ○ Yes, in communicating /disseminating / using the results of the project

13a Will the project generate outputs (expertise or scientific advice) which could be used by policy makers?

- ○ Yes – as a **primary** objective (please indicate areas below- multiple answers possible)
- ○ Yes – as a **secondary** objective (please indicate areas below - multiple answer possible)
- ● No

13b If Yes, in which fields?

Agriculture		Energy		Human rights	
Audiovisual and Media		Enlargement		Information Society	
Budget		Enterprise		Institutional affairs	
Competition		Environment		Internal Market	
Consumers		External Relations		Justice, freedom and security	
Culture		External Trade		Public Health	
Customs		Fisheries and Maritime Affairs		Regional Policy	
Development Economic and Monetary Affairs		Food Safety		Research and Innovation	
		Foreign and Security Policy		Space	
Education, Training, Youth		Fraud		Taxation	
Employment and Social Affairs		Humanitarian aid		Transport	

13c If Yes, at which level?

- ○ Local / regional levels
- ○ National level
- ○ European level
- ○ International level

H Use and dissemination

14 How many Articles were published/accepted for publication in peer-reviewed journals?	**33**
To how many of these is open access[7] provided?	**2**
How many of these are published in open access journals?	**2**
How many of these are published in open repositories?	**none**
To how many of these is open access not provided?	
Please check all applicable reasons for not providing open access:	
❑ publisher's licensing agreement would not permit publishing in a repository ❑ no suitable repository available ❑ no suitable open access journal available ❑ no funds available to publish in an open access journal ■ lack of time and resources ❑ lack of information on open access ❑ other: ……	

15 How many new patent applications ('priority filings') have been made? *("Technologically unique": multiple applications for the same invention in different jurisdictions should be counted as just one application of grant).*		
16 Indicate how many of the following Intellectual Property Rights were applied for (give number in each box).	Trademark	**2**
	Registered design	
	Other	
17 How many spin-off companies were created / are planned as a direct result of the project?		**2**
Indicate the approximate number of additional jobs in these companies:		**3**

18 Please indicate whether your project has a potential impact on employment, in comparison with the situation before your project:

■	Increase in employment, or	■	In small & medium-sized enterprises
❑	Safeguard employment, or	❑	In large companies
❑	Decrease in employment,	❑	None of the above / not relevant to the project
❑	Difficult to estimate / not possible to quantify	❑	

19 For each project partner, please estimate the employment effect resulting directly from your participation in Full Time Equivalent (*FTE = one person working fulltime for a year*) jobs:	*Indicate figure:*
Difficult to estimate	■

[7] Open Access is defined as free of charge access for anyone via the internet.

I Media and Communication to the general public

20 As part of the project, were any of the beneficiaries professionals in communication or media relations?

○ Yes ● No

21 As part of the project, have any beneficiaries received professional media / communication training / advice to improve communication with the general public?

○ Yes ● No

22 Which of the following have been used to communicate information about your project to the general public, or have resulted from your project?

●	Press Release	●	Coverage in specialist press
●	Media briefing	❑	Coverage in general (non-specialist) press
●	TV coverage / report	●	Coverage in national press
❑	Radio coverage / report	●	Coverage in international press
●	Brochures /posters / flyers	●	Website for the general public / internet
❑	DVD /Film /Multimedia	●	Event targeting general public (festival, conference, exhibition, science café)

23 In which languages are the information products for the general public produced?

❑	Language of the coordinator	●	English
❑	Other language(s)		

***Question F-10*:** Classification of Scientific Disciplines according to the Frascati Manual 2002 (Proposed Standard Practice for Surveys on Research and Experimental Development, OECD 2002):

FIELDS OF SCIENCE AND TECHNOLOGY

1. NATURAL SCIENCES

1.1 Mathematics and computer sciences [mathematics and other allied fields: computer sciences and other allied subjects (software development only; hardware development should be classified in the engineering fields)]

1.2 Physical sciences (astronomy and space sciences, physics and other allied subjects)

1.3 Chemical sciences (chemistry, other allied subjects)

1.4 Earth and related environmental sciences (geology, geophysics, mineralogy, physical geography and other geosciences, meteorology and other atmospheric sciences including climatic research, oceanography, vulcanology, palaeoecology, other allied sciences)

1.5 Biological sciences (biology, botany, bacteriology, microbiology, zoology, entomology, genetics, biochemistry, biophysics, other allied sciences, excluding clinical and veterinary sciences)

2 ENGINEERING AND TECHNOLOGY

2.1 Civil engineering (architecture engineering, building science and engineering, construction engineering, municipal and structural engineering and other allied subjects)

2.2 Electrical engineering, electronics [electrical engineering, electronics, communication engineering and systems, computer engineering (hardware only) and other allied subjects]

2.3. Other engineering sciences (such as chemical, aeronautical and space, mechanical, metallurgical and materials engineering, and their specialised subdivisions; forest products; applied sciences such as geodesy, industrial chemistry, etc.; the science and technology of food production; specialised technologies of interdisciplinary fields, e.g. systems analysis, metallurgy, mining, textile technology and other applied subjects)

3. MEDICAL SCIENCES

3.1 Basic medicine (anatomy, cytology, physiology, genetics, pharmacy, pharmacology, toxicology, immunology and immunohaematology, clinical chemistry, clinical microbiology, pathology)
3.2 Clinical medicine (anaesthesiology, paediatrics, obstetrics and gynaecology, internal medicine, surgery, dentistry, neurology, psychiatry, radiology, therapeutics, otorhinolaryngology, ophthalmology)
3.3 Health sciences (public health services, social medicine, hygiene, nursing, epidemiology)

4. AGRICULTURAL SCIENCES
4.1 Agriculture, forestry, fisheries and allied sciences (agronomy, animal husbandry, fisheries, forestry, horticulture, other allied subjects)
4.2 Veterinary medicine

5. SOCIAL SCIENCES
5.1 Psychology
5.2 Economics
5.3 Educational sciences (education and training and other allied subjects)
5.4 Other social sciences [anthropology (social and cultural) and ethnology, demography, geography (human, economic and social), town and country planning, management, law, linguistics, political sciences, sociology, organisation and methods, miscellaneous social sciences and interdisciplinary , methodological and historical S1T activities relating to subjects in this group. Physical anthropology, physical geography and psychophysiology should normally be classified with the natural sciences].

6. HUMANITIES
6.1 History (history, prehistory and history, together with auxiliary historical disciplines such as archaeology, numismatics, palaeography, genealogy, etc.)
6.2 Languages and literature (ancient and modern)
6.3 Other humanities [philosophy (including the history of science and technology) arts, history of art, art criticism, painting, sculpture, musicology, dramatic art excluding artistic "research" of any kind, religion, theology, other fields and subjects pertaining to the humanities, methodological, historical and other S1T activities relating to the subjects in this group]