European Cooperation in Science and Technology
- COST -

Secretariat

Brussels, 16 December 2010

COST 4193/10

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action TD1004: Theranostics Imaging and Therapy: An Action To Develop Novel Nanosized Systems For Imaging-Guided Drug Delivery

Delegations will find attached the Memorandum of Understanding for COST Action TD1004 as approved by the COST Committee of Senior Officials (CSO) at its 180th meeting on 1 December 2010.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as

COST Action TD1004
THERANOSTICS IMAGING AND THERAPY: AN ACTION TO DEVELOP NOVEL NANOSIZED SYSTEMS FOR IMAGING-GUIDED DRUG DELIVERY

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4159/10 "Rules and Procedures for Implementing COST Actions", or in any new document amending or replacing it, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to exploit nanotechnology advances in pharmaceutical and biomedical imaging fields to develop innovative image-guided therapies for the cure of highly social impact diseases.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 56 million in 2010 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter V of the document referred to in Point 1 above.

A. ABSTRACT AND KEYWORDS

This Action brings together the major European research groups working on the development of novel combined diagnostic/therapeutic agents (theranostic agents). Properly designed agents will allow the *in vivo* quantitative assessment of the amount of drug reaching a pathological region and the visualisation of molecular changes due to the therapeutic effects of the delivered drug.
The main objective of the Action is to demonstrate the potential of image-guided therapies in the treatment of diseases with high social impact.
Researchers will join efforts to develop novel therapeutic treatments based on the visualisation of drug delivery/release processes and the monitoring of associated therapeutic effects.
The Action goals will be reached thanks to a strong interdisciplinary coordination work mostly focused to get a better understanding of crucial aspects of the whole drug delivery process *in vivo*, in particular regarding the efficiency of drug targeting and release and the relationship with the therapeutic effect.
The implementation of therapies and surgical interventions with imaging technologies will provide physicians with an extraordinary tool for accelerating the desirable translation towards molecular and personalized medicine, thus considerably extending the armoury of solutions for successfully combating the diseases.
Keywords: In vivo imaging, Drug delivery, Image-guided therapies, Interventional imaging, Nanocarrier

B. BACKGROUND

B.1 General background

The search for novel drug delivery technologies is essentially driven by the need to increase efficacy or improve safety and patient compliance. Drug delivery systems are most needed for improving treatment of cancer, diseases of the respiratory and central nervous system and cardiovascular disorders. Many therapeutic agents have failed due to their limited ability to reach the target tissue and/or because they damage both diseased and healthy cells.
In general, the use of drug delivery systems can solve problems associated with drug instability in the biological environment and problems of rapid clearance and metabolism. Privileged routes to theranostic delivery are the use of lipid-based self-assembled systems, polymeric/inorganic particles, “host-guest” supramolecular adducts and naturally occurring systems like lipoproteins and protein aggregates, viral capsids and even cells. Drug and imaging reporter release from the carrier can be spontaneous or activated by endogenous or exogenous stimuli such as heat, ultrasound or magnetic effects.

Depending on the method of preparation, these nanosystems can be obtained with quite different properties and release characteristics. Much attention has been devoted to the use of biodegradable materials that allow sustained drug release within the target site over a period of days. Besides drugs, the development of efficient nanocarriers also involves the delivery of nucleic acids for gene and RNAi (RiboNucleic Acid interface) therapeutics.

Targeted delivery can be achieved by either active or passive targeting. Active targeting is pursued by conjugating the nanocarrier with suitable vectors that recognize characteristic epitopes at the surface of the diseased cells or in the extracellular matrix of the pathological region. Passive targeting occurs through the enhanced permeability and retention (EPR) effect that characterizes neo-formed vessels. In case of lipid-based nanocarriers, the binding to epitopes on the diseased cells is important also for the activation of a mechanism called “contact facilitated drug delivery” that, through lipid-lipid exchange with the surface of the nanoparticle, accelerates the connective flux of lipophilic drugs dissolved in the outer lipid membrane. Depending on the target epitope, cell-bound nanocarriers can also be internalized by the target cells to allow intracellular drug delivery.

Induced by the great achievements in the field of molecular imaging (MI), the design of suitable probes composed of highly sensitive imaging reporters and efficient recognizing moieties has shown that molecules or molecular events occurring at the cellular level may be visualized *in vivo* with one, or more, imaging modalities. The impact of MI on medical diagnosis is impressive as it allows an early diagnosis and real-time monitoring of the therapeutic outcome. Combining disease diagnosis and therapy is of huge interest. In recent years significant steps were made in the interventional field with the use of surgical ultrasound. This approach is under intense scrutiny for curing different types of tumours and has been extensively applied in the treatment of uterine fibrosis.

Drug delivery will most certainly benefit from MI in various ways: image guided drug delivery, triggered drug release, drug delivery monitoring or therapy monitoring by imaging. The so-called "theranostic" field can thus have different forms.

New Magnetic Resonance Imaging (MRI) scanners equipped with ultrasound (US) transducers were recently introduced. Such scanners couple the superb spatial resolution of MRI with the possibility of using US as a physical means to induce local heating in pathological regions (e.g. in tumours) or to promote heat- or cavitation-mediated biological events (e.g. change in cell permeability or controlling gene expression using heat-inducible promoters). Another achievement that might be pursued in the near future is the use of ultrasound to trigger drug release from nanocarriers whose accumulation at the site of interest can be clearly assessed by MRI detection. Another area where imaging can guide therapy could involve heating-based treatments like hyperthermia or thermal-ablation, which are carried out by applying external alternating magnetic fields on iron oxide particles, widely used as MRI agents. One may easily envisage a number of fields where the combined use of imaging and therapeutic agents has the potential to improve the cure of a given disease. Worth highlighting in this regard is the field of Neutron Capture Therapy (NCT). The successful use of this anticancer treatment requires that the number of neutron-activatable atoms per cell has to be higher than a given threshold (e.g. 10^9 in the case of B-10 nuclei). The *in vivo* assessment of the achievement of this threshold could be pursued by endowing the NCT-probe with imaging detectable characteristics.

The development of theranostic agents, and related imaging protocols, is expected to grow markedly in the forthcoming years as new and powerful tools to demonstrate the potential of the personalized medicine armoury will be provided. This clearly is an interdisciplinary field, where contributions from chemists, physicists, biologists, physicians, and imaging technologists merge to design new approaches for curing major diseases.

Therefore, it is time to activate this COST Action in order (1) to give structure to the field, and (2) to strengthen the collaboration among scientists but also with industry by gathering emerging topics that are expected to open new scientific and technological horizons in the battle against major diseases.

Reasons why COST offers the appropriate framework for the Action:

- The field of Imaging Theranostics is still maturing and many possible directions can be undertaken. The project term “Theranostics” refers to any molecular or supramolecular entity that enables an efficient image-guided therapy. In terms of materials for the delivery of drugs/imaging agents, an in-depth comparison among polymers/micelles/liposomes/solid-lipid nanosystems (SLN), microemulsion droplets/inorganic nanoparticles, etc. has to be carried out. Analogous evaluation is necessary to assess the most suitable imaging modality for a given condition. This scenario requires a tight collaboration among groups that are developing their own approaches. Within the COST framework an evaluation and comparison of the achievements can become reality, thus enabling a fruitful exchange of technologies and practices.
- The COST Action will enable the access to a wide range of materials, animal models, targeting and drug release modalities and imaging technologies. This will allow chemists and pharmaceutical scientists to evaluate their novel “smart” carriers on the most suitable animal models and will provide access to tailored theranostics using their newly developed animal models for biologists and physicians. The network will offer the possibility to any participant to access the state-of-the-art of imaging technologies.

- The scope of the Action is much wider than that attainable with other collaborative schemes. In addition, the Action will provide the proper environment in which new, more specialised and applied research projects will be elaborated. Moreover, the presence of major European industry players in the field of Contrast Agents (CAs) that consider theranostics as one of the very important avenues for the development of their product pipeline will offer the possibility for new collaborations. The Action will also cover specific initiatives to support the creation of "spin-off" companies from the achievements of the co-ordination work.

B.2 Current state of knowledge

By targeted drug delivery one can selectively direct a drug to the pathological site in the body, thus enhancing its therapeutic efficacy and/or direct a drug away from body regions that are particularly sensitive to its toxic action. For instance, several formulations of the potent anti-tumour drug Doxorubicin into liposomes are currently used in clinical practice. In the last decades the field of drug delivery is under intense scrutiny. The nanocarriers are typically in the size range of a few to 200 nm and can be roughly divided into macromolecular systems and nanoparticles. The first category includes proteins and antibodies, as well as polymeric macromolecules and dendrimers. Nanoparticles include micelles, liposomes, solid-lipid nanosystems, as well as inorganic particles. Most attention has been so far devoted to liposomes that consist of a bilayer of phospholipids (analogous to a cellular membrane) entrapping an aqueous compartment. They proved to be flexible carriers as hydrophilic molecules can be easily loaded in the inner compartment, whereas lipophilic molecules can be associated with the bilayer. Being formed by natural lipids, they are well tolerated by living organisms. Their size, as well as their ability to release their payload, can be modulated to efficiently deliver and release the drug at the site of interest. Current limitations of liposomes are their poor stability and delicate industrial scale up. Biodegradable polymers and micelles are also of great interest as they allow sustained drug release over a period of days. Inorganic nanoparticles are under intense scrutiny as they offer a range of possible architectures that may be exploited to control loading and release of drugs, once these nanocarriers are properly delivered at the target site. However, their use for *in vivo* application still requires proper toxicology evaluation.

Imaging technology enormously progressed in the last decades and is a major driving force in changing our views regarding diagnoses and the way to monitor therapeutic treatments for major diseases. The outstanding achievements of molecular and cellular biology, in combination with the knowledge gained from sequencing of mammalian genomes, led to a growing understanding of cellular mechanisms that mediate biological processes and diseases. This led to the recognition of (patho)-physiological processes occurring at the onset of major diseases and paved the way for developing new tools for monitoring therapeutic treatments. These cellular mechanisms have been so far largely investigated by *in vitro* techniques. Now, the emerging science of Molecular Imaging aims at using analogous approaches for the *in vivo* visualization and quantification of molecules and molecular events. The potential for clinical translation is huge, as the same modalities used in medical imaging are also used in molecular imaging investigations.

The European Union has already recognized the importance of these fields for the future medicine by activating Networks of Excellence in the field of Molecular Imaging (EMIL- European Molecular Imaging Laboratories and DiMI-Diagnostics for Molecular Imaging). In the COST scheme, two Actions are related to the background of this Action. They are BM0607, Targeted Radionuclide Therapy (TRNT),and D38, Metal Based Systems for Molecular Imaging Applications . The European Technology Platform on Nanomedicine backs up the development of these fields as described in its last “Technology Roadmap” report (November 2009).

This Action aims at going a further step ahead by merging the most advanced achievements in the field of drug delivery, imaging technologies and molecular imaging to develop the new field of theranostic agents. The possibility of carrying out image-guided therapies within a molecular imaging approach represents an outstanding contribution to personalized molecular medicine-based treatments. These cutting edge developments will benefit first to clinical healthcare but also to drug development in the preclinical phase (on animal models).

B.3 Reasons for the Action

Basically, the Action will involve two scientific communities, namely the chemistry/pharmacology/pharmaceutical teams, devoted to the development of drug delivery systems and strategies, and the imaging groups, which focus on the development of new avenues for innovative diagnostic approaches, respectively. The two communities aim at merging their efforts to pursue novel highly efficient therapeutic treatments based on the use of theranostic compounds that will provide the possibility of carrying out therapy associated with diagnosis. This new field will become an important anchor in molecular imaging as it relies on the same scientific approach based on the visualization of molecules or molecular events that occur at the cellular level. The applied methods will be the same ones as developed for molecular imaging investigations. Thus, chemists and pharmaceutical scientists will work at the design and testing of the theranostic molecules, biologists will tackle the basic understanding of the physio-pathological processes associated with a given disease and identify targets (and vectors to reach the targets), physicists and imaging technologists will improve image acquisition and processing, and physicians will coordinate the translational procedures towards the clinic applications.

The Action will have strong interdisciplinary character. Hence, to be successful, a strong tendency to collaborate, which relies on the integration of quite different scientific backgrounds, will be necessary. It is anticipated that COST can provide the most suitable environment for fostering such collaborative efforts.

The potential impact of the Action is huge: in terms of the scientific/technological advances it will provide the identification of efficient image-guided therapies that could overcome the major issues associated with currently used treatments. Furthermore, there will be important economic advantages for European industries thanks to the know-how (and related intellectual property rights (IPR)) developed in the Action. Among the participants, there are already scientists working at research centres of big European industries active in the field of medical diagnosis products.
The objective is to create a robust network of research activities, already properly designated for future clinical translation in the field of molecular imaging and theranostics based on the tight integration of competences spread in different disciplines and European countries.

The expected results are cooperative research networks, highly innovative to compete with the teams in the US, Japan and Far-East countries. Key tools to achieve these results rely on the organization of workshops and Working Group meetings, Short-Term Scientific Missions for young researchers, and access to advanced facilities.

B.4 Complementarity with other research programmes

The Action will bring together scientific expertise that currently is not organized in a specific EU supported initiative. Rather, it is expected that the new Action will attract the most advanced experiences matured in other COST initiatives, such as BM0607 and D38 Actions. The work carried out in the FP6-Integrated Project "Targeted Delivery of Nanomedicines" (Meditrans) and within the framework of the EU-NOEs EMIL (European Molecular Imaging Laboratories)-(2004-2009) and DiMI (Diagnostic Molecular Imaging)-(2005-2010) was very important to the elaboration of this proposal.

C. OBJECTIVES AND BENEFITS

C.1 Main/primary objectives

The main objective of the Action is to demonstrate the extent to which image-guided therapies can impact the cure of important diseases. The procedures will allow overcoming major drawbacks that are encountered in the currently applied therapeutic treatments and strongly limiting efficacy, such as systemic toxicity, *in vivo* degradation, and/or poor localization of the drug at the pathological sites. Researchers will join efforts to develop novel therapeutic treatments based on the visualisation of drug delivery/release processes and the monitoring of associated therapeutic effects. The members of this network have well established expertise in a number of complementary fields, ranging from chemistry to biology, from medicine to ICT. This interdisciplinary character will allow tackling all steps of the complex process associated with the development of innovative theranostic procedures. The use of imaging reporters suitably co-added to the payload of nanometric delivery structures, will allow in vivo visualization of drug targeting and drug releasing steps. The imaging tool will provide information on the microenvironment of the diseased region (pH, temperature, enzymatic activity, concentration of metabolites).

Thanks to its superb spatial resolution, MRI appears to be the most appropriate technique although important insights for a detailed understanding of the drug delivery process and for monitoring the therapeutic output may be gained with other imaging modalities. The synergy between the characteristics of the nanocarrier and the potential of the MI assessment will be exploited in order to develop innovative interventional procedures for operating drug release also through the use of external devices that expose the region to ultrasound or magnetic fields. The external control of drug release, together with the monitoring of biomarkers, will offer clinicians the possibility to provide patients with a more efficacious and much safer therapy. The involved groups will develop nanocarriers including liposomes, polymersomes, nanoemulsions and different types of nanoparticles based on inorganic materials or polymers. They will be designed in order to be responsive to specific physical or chemical stimuli either endogenous (e.g. changes in pH, enzymatic activity) or exogenous (e.g. changes in temperature upon the application of ultrasound pulse or proper light irradiation). Work on the functionalization of the nanocarriers will be fundamental to control their blood lifetime (design of stealth systems, control of macrophage uptake, and development of new types of surface coating materials) as well as to target them to the sites of interest. The *in vivo* efficacy of the targeting procedures relies on the differences in the expression of a given epitope in the diseased and healthy regions. Thus, MI methods for assessing the effective expression of the target of interest will be set-up. The pathologies of interest are malignant, neurological and cardiovascular diseases. Therefore, suitable animal models will be used for validating concepts of systems developed in the Action. When possible, investigations on cellular systems will precede animal work, which is fundamental to assess the mode of action of the tools and the procedures developed. In addition, cells loaded with nanocarriers and detectable by imaging modalities will be investigated in the context of cell-based therapy procedures. The systems displaying the best performances will be subjected to preclinical investigations in order to monitor pharmacokinetic and toxicology aspects.

C.2 Secondary objectives

The secondary objectives of the Action are to:

- prompt the activation of new research activities in the field of polymer and supramolecular chemistry by the peculiar requisites of the drug carriers (responsiveness, biocompatibility, biodegradability, etc.);
- stimulate an innovative development of the available instrumentation based on technological work on the release of the drug/imaging agents from the carrier upon an external stimulus;
- involve specialized bioinformatic teams with regard to the set-up of procedures to image theranostics and the improvement of the currently used image processing tools.

C.3 How will the objectives be achieved?

The achievement of the ambitious objective of defining new therapeutic strategies through the use of theranostic agents requires converging efforts of different scientific fields and the availability of specialized imaging facilities. The members of the network have the complementary skills and expertise required to achieve the tasks of the various research lines. Furthermore, they may share an impressive number of “state of the art” imaging scanners. All together, the Action will involve human resources in the order of a few hundred researchers, including scientific as well as technical staff and PhD students. During the lifetime of the Action, new groups will be invited to join the Action in order to reach the critical mass necessary for tackling all the tasks of the project at the highest level possible.

C.4 Benefits of the Action

The topics addressed are largely unmet medical needs. The advances that will be attained will certainly give important feedback to the innovation potential of the research cluster that has already been settled.

The primary benefit is related to the development of innovative work in the field of personalised medicine based on the quantitative visualisation of drug delivery to diseased cells, the assessment of its release from the nanocarriers as well as the evaluation of the therapeutic effects on the basis of properly designed MI protocols, also including cell therapy-based approaches.

The strong collaboration between academic and industrial research in the field of innovative therapeutic procedures involving skills from different scientific backgrounds including chemistry, material scientists, biologists, and physicians will have a relevant impact on the future development of the field in Europe.

An early involvement of approval authorities like European Medicines Agency as observers (or advisors) will shape the future approval process of these theranostic agents.

C.5 Target groups/end users

All the research work carried out within the Action will be potentially translational into clinical use. The availability of theranostic agents is expected to open up new avenues to treat important diseases, and to be an important tool in the era of personalised molecular medicine. Thus, the end users are patients that expect improved therapeutic outcomes by virtue of the progress of the research, in particular from converging technologies such as bio- and nano-technologies, imaging and molecular medicine. Pharmacologists and physicians will also represent the end users, who will investigate the pharmacokinetic and pharmacodynamic properties of the theranostics.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The objective of the Action is the development of innovative image-guided drug delivery procedures. This task will be approached by focusing on different topics among which the study of novel methods for drug delivery and imaging reporters to target sites by using synthetic or naturally occurring nanocarriers will play a central role. Vesicles containing genetic materials will also be considered for gene therapy as well as whole cells (e.g. mesenchymal stem cells (MSC), endothelial progenitor cells (EPC)) for cell-based therapies. The accumulation of the nanocarriers at the diseased cells/organ may occur either by passive targeting (for instance by exploiting the so called EPR effect) or by active targeting (endowing the carrier with suitable recognition synthons). *In vivo* quantitative assessment of the amount of drug in the pathological region will be carried out by MRI. The paramagnetic payload in the vesicles, particles or cells will cause a characteristic relaxation enhancement of water protons that is concentration dependent.

Moreover, activities to design MRI contrast agents that act as efficient reporters (1) of the microenvironment in which the carrier distributes and (2) of changes that reflect the therapeutic effect of the delivered drugs will be encouraged. When cells are used as delivery systems, their specific homing properties will allow the development of cell therapy procedures. By using cells as vectors to the diseased region, the Action aims to exploit a recently reported finding in which a high payload of MRI agent and drug can be anchored to the outer surface of cells by exploiting multivalent electrostatic forces. In the field of particles, privileged approaches are those based on biodegradable systems. Much work will be devoted to acquire detailed understanding of the microscopic picture underlying the overall process of drug delivery/release and therapeutic effect, also by using tailored fluorescent dyes detectable by confocal microscopy and/or optical imaging experiments. Such procedures aim at getting full validation of the MRI-guided drug delivery process, thus obtaining all relevant information at the cellular level.

All aspects that can make image-guided targeted nanomedicine-based therapies a realistic opportunity in therapeutic treatment of major diseases will be covered.

The work plan covers the exploration of the different approaches through which image-guided therapies can be carried out.
First of all, work to assess how the use of drug carriers (such as liposomes and other types of nanoparticles) can be improved by theranostic approaches will be conducted. Particles endowed with targeting capabilities (through the introduction of proper ligands on their external surface) will be compared with analogous systems deprived of the targeting moieties in order to assess their *in vivo* fate and distribution. It is anticipated that trafficking and biodistribution of these particles can be assessed through a kinetic analysis of the different types of contrast (T_1, T_2 and CEST – Chemical Exchange Saturation Transfer) these particles may be endowed with. Of course, other *in vivo* imaging approaches (e.g. intravital optical microscopy) or *ex-vivo* microscopy investigations (confocal and electron microscopy) will also be carried out to validate the overall work.

A central task in the work plan is the design and testing of responsive theranostic agents that release their payload upon the action of endogenous stimuli. These responsive agents require a careful chemical design and the imaging response has to be designed in order to inform about "what, when and where" the drug is released. Analogously, the imaging response generated by a proper contrast agent will be exploited to pursue successful Neutron Capture Therapies likely through the use of theranostics made of Gd- and B-containing moieties.

Next, the Action will identify the route that makes the imaging to a reporter for the action of the drug at the target site. Although very challenging, this task appears feasible on the basis of the skills and chemical expertise available among the members of the network.

Analogous work will be carried out on theranostic agents responsive to external stimuli such as ultrasound, heat and light illumination. Besides liposomes, the latter application will make use also of specifically tailored block-copolymers, as well as of ultrasound-sensitive microbubbles.

Another line of activities will deal with the use of naturally occurring nanocarriers. Systems like apoferritin, lipoprotein particles, viral capsides and lipid microvesicles will be of potential interest in the development of theranostic approaches. Suitable imaging reporters will be designed with much attention to maintain the biocompatibility of the naturally occurring carriers.

Much work in the Action will be devoted to the preparation of suitable cellular and animal models for the evaluation of the image-guided therapies. The models will be made available to all the Action members in order to offer homogeneous testing systems to the theranostics development groups. Synergic relationships with clinic-oriented teams will be developed in order to exploit their inputs for the design of pre-clinical theranostic procedures that have, already at this stage, potential for future clinical translation. The Action offers the most suitable environment for this communication exchange, as it gathers top-medical teams together with outstanding basic science groups in the field of biomedical imaging research.

D.2 Scientific work plan - methods and means

The members of the network cover the major skills required for a successful achievement of the objectives of the Action:

• Chemistry/Pharmaceutical Technologies

a) synthesis and testing of imaging agents, including T_1, T_2 and CEST agents for MRI investigations, F-18 and Ga-68 containing tracers for PET (Positron Emission Tomography) studies, Tc-99m and In-111 for SPECT (Single Photon Emission Computed Tomography) tracers, fluorescent dyes for optical imaging and microbubbles for Ultrasound applications;

b) preparation and full characterization (shape, surface, charge, size, dispersion, payload, stability) of nanocarriers for drug delivery, including self-assembled block-copolymers based on polylactic, polyvinyl pyrrolidone and other constituents;

c) isolation and loading of naturally occurring nanocarriers such as apoferritin, low- and high-density lipoproteins, viral capsides, lipid microvesicles.

• Biology

The members of the network have a well-established expertise in the development of:

a) cellular cultures including cell transfection, starving, etc.;

b) animal models including xenografted or transgenic models for the most important diseases.

Several groups have demonstrated high level skills in the biopsy characterization by confocal and electron microscopies, FACS (Fluorescence Activated Cell Sorting) and molecular biology investigations.

• Imaging Technologies

Most of the members of the network have already developed one or more imaging modalities for their research work. Some of the groups have access to facilities equipped with all kinds of imaging scanners available for preclinical work. It is assumed that MRI will be the technique of choice for theranostic procedures because of its very high spatio-temporal resolution attainable. However, the Action will not be limited to this modality and actually it will be a task of the Action to assess whether other imaging approaches will become competitive for the theranostic applications like the combined diagnostic and therapeutic use of radioisotopes or the peculiar theranostic properties of US. Thus, the access to imaging modalities different from MRI will be pursued not only in the context of providing a validation to MRI results but also with the aim of evaluating their effective potential in tackling image-guided therapeutic procedures. Lightweight imaging modalities like optical or US imaging or optoacoustic should be also investigated due to their benefits for use during surgical operation. It will be equally important to explore multimodal approaches, where the high complementarity of some imaging technologies (e.g. PET-CT, PET-MRI, Optical Imaging-MRI) may be exploited to improve the clinic potential of the theranostic.

The work plan will be organised in Working Groups committed to fulfil the above defined tasks. As already outlined, the objective of the Action is to demonstrate to what extent image-guided therapies can beneficially impact the therapy of important diseases.

Each Working Group (WG) will be formed on the basis of a proper mixing of interdisciplinary and complementary skills necessary to meet the objectives of the project through a fruitful scientific exchange**:**

WG1 – Imaging reporters for theranostic agents

WG1 will gather groups with proper expertise in the design and preparation of imaging reporters for technologies of interest for image-guided therapies (MRI, ultrasound, optical, nuclear). Reporters should be optimized in order to display high sensitivity (especially for MRI detection), good efficiency to be loaded in nanocarriers, and ability to modulate the contrast as a function of endogenous/external stimuli that could trigger drug release or act as imaging reporter of the therapeutic efficacy of the drug. Attention will be also paid to the design of dual (e.g. PET/MRI or Optical/MRI) imaging reporters that will together with the drug from the theranostic construct.

WG2 – Nanocarriers for theranostic agents

This WG aims at gathering research teams with strong expertise in designing and preparing consolidated or innovative nanocarriers, which can efficiently load drugs and imaging reporters. Several classes of nanocarriers will be considered including those based on lipids (micelles, liposomes, emulsions or solid lipid nanoparticles), on polymers (polymer-drug conjugates, polymersomes, nanocapsules, nanospheres), or based on inorganic materials (metal oxides, zeolites, silica nanoparticles). Particular attention will be devoted to the study of naturally occurring carriers (apoferritin, clathrin-based vesicles, lipoproteins, virus capsides, yeast wall particles, etc.) that may have important advantages (lack of immunogenicity, defined metabolic pathways, high tolerability, etc.) with respect to the "synthetic" carriers.

An important task will deal with the study of proper bio-conjugation procedures in order to endow the theranostic agent (especially those based on natural carriers) with the necessary targeting capabilities and/or the ability to bypass the opsonisation process that decrease the blood circulation time of the agent. Attention will also be paid to investigate the release properties of both the drug and the imaging reporter from the nanocarrier.

WG3 – Preparation and selection of targeting vectors

This WG is focused on the preparation, selection and testing of the targeting moieties necessary to optimize the performance of the theranostics. The active targeting strategy could benefit to most of the drug delivery systems examined. Once a biomarker for a given pathology is identified/selected, specific vectors could be obtained using consolidated high throughput screening tools (e.g. phage display technique) and their targeting ability will be tested first on cultured cell lines. The vectors showing the best properties will be conjugated to a given theranostic nanocarrier and the targeting property of the whole construct will be again evaluated. The same vector could be conjugated to different nanosystems in order to optimize the pharmacokinetic and the image response of the theranostic.

WG4 – Theranostic agents responsive to endogenous and external stimuli

This WG will gather research work dealing with the design of theranostic agents whose drug release, and consequently the image contrast variation, can be triggered by endogenous chemical variables that characterize the disease to be cured (e.g. pH or enzymatic activity) or physical means (US, temperature, light) externally applied on the diseased tissue/organ. In the latter approach, in addition to the proper design of the theranostic agent, it will be fundamental to involve teams with the proper technological skills to develop tools to be integrated in the imaging instrumentation. Furthermore, this WG will have the task of assessing the potential of novel image-guided procedures in NCT. By exploiting targeting systems consisting of the imaging reporter and the NCT moiety, it will be possible to assess the effective amount of the NCT agent at the targeting site and proceed with a successful irradiation only when the NCT agent is above the well-established threshold value.

WG5 – Set-up of preclinical theranostic protocols

This WG will represent the terminal in order to pre-clinically validate the theranostic agents developed in the other WGs. Particularly important in this regard will be the presence of research groups involved in the development of specific animal models for the diseases of interest as well as imaging technologists, who will optimize the detection and the post –acquisition image processing of theranostic image-guided therapy. Dual theranostic agents especially that one based on PET/MRI combination, where the great complementarity and potential of this hybrid technology could be successfully exploited for significantly improving the impact of image-guided therapies will be tested. Another important task will be the set-up of theranostic protocols where the imaging reporter may provide relevant and early information on the therapeutic efficacy of the drug.

This WG also has the role to explore the possibility that the most promising agents could be industrialized and translated to the clinic.

E. ORGANISATION

E.1 Coordination and organisation

Management Committee

The Action has a Management Committee (MC) responsible for the overall activities. The MC consists of the national representatives from the countries who will sign the Memorandum of Understanding. During the first meeting, the MC will appoint the Chair, the Vice-Chair and the Working Group Leaders. The MC will have at least 1 annual meeting where it will discuss and vote on the annual activity. The MC may delegate specific activities such as the management of the Short-Term Scientific Missions to one of the MC members. The activities of participating laboratories will be coordinated and organized in dedicated Working Groups led by a scientist selected by the MC.

Steering Committee

To pursue an efficient organisational structure of the Action, a Steering Committee formed by the Chair, the Vice-Chair, the WG Leaders and the Short-Term Scientific Missions Coordinator will be established. The Steering Committee will assess the correct implementation of the work plan and will identify possible corrections needed to reach the expected milestones. The Steering Committee will be responsible for the organization of the scientific programme of the Annual Workshop, which will (1) report on the major research achievements and (2), integrate the most innovative contributions from top scientists in the field of theranostic agents into the Action (through the invitation of external experts). The Steering Committee will also support the Chair in the preparation of the Annual Reports. The Steering Committee will hold bi-monthly conference calls to fulfil its duties; the agendas of the conference calls will be communicated by the Chair one week before the date of the conference calls and they can be integrated by suggestions arising from the Steering Committee members.

At the Kick-Off Meeting of the Action, an efficient co-ordination strategy will be established in order to successfully implement concerted actions. This offers an efficient communication exchange of knowledge between the participating groups and provides the coordination necessary to reach the milestones.

By the correct identification of milestones and their due dates it will be properly assessed whether the work plan tasks have been accomplished or not. Definitions of milestones and due dates are in the responsibility of the Management Committee based upon specific proposals from the Chair.

The following milestones are foreseen:

- Imaging methodologies for assessing the in vivo distribution of nanosized carriers and their payload established.
- Imaging methodologies for assessing the responsiveness of nanocarriers to release their payloads at the target sites on the basis of the bio-chemical characteristics of the microenvironment established.
- Imaging methodologies for assessing the responsiveness of nanocarriers to release their payloads upon the application of external stimuli.
- Imaging methodologies to assess the therapeutic effect of the applied theranostic procedures in animal models for the major diseases (cancer, cardiovascular and neurological diseases) established.
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The organisational structure has to be such that the overall dimension of the Action adds synergic contributions to the results obtained from each member of the network and, importantly, through the merging of the results, the Action will drive the members of the network to a fulfilment of the tasks of the work plan.

The Action will strengthen the coordination of national research through the activation of initiatives that will involve other teams to collaborate in the field of Imaging and Theranostics. As this field is expected to be an important component in practical medicine of the forthcoming years, it seems sound to interact with research teams that, although not directly involved in the development of theranostic procedures, can contribute on specific topics with competence.

To attract the interest of these groups, national participants will be asked to organize Training Schools and seminars to present the aims and achievements of the Action to a larger audience. Furthermore, a variety of communication means will be used to reach the broader stakeholder community in the field. Thus, an Action website will be developed as a powerful tool to disseminate information on the topics and foster further exploitation of the achieved results. As the clinical exploitation of the novel theranostic procedures developed in the Action involves relevant economic impact, much attention will be devoted to advising the Action's members on Intellectual Property issues. Furthermore the Action will provide its support to facilitate academic-industrial collaborations, first of all through the involvement of the European companies as partners.

E.2 Working Groups

As stated under D.2, the Action will carry out its work plan through the activities of five Working Groups. Depending on the available budget and after MC approval, WGs will organize WG meetings (no more than one/year, also possible joint meeting between two WGs) focused on discussing specifying issues of relevance for achieving the WG tasks. The meetings will also offer a good possibility to update the research tasks of the Action, and should be organized at least 4 months prior or after to the annual meeting and should be properly advertised within the Action.

E.3 Liaison and interaction with other research programmes

Topics that will be developed in this Action root in at least two currently ongoing Actions, respectively D38 “Metal based systems for Molecular Imaging Applications” and BM0607 “Targeted Radionuclide Therapy (TRNT)”. Moreover, the subject matter of Imaging and Theranostics has received seminal contributions in the FP-6 Integrated Project “Targeted Delivery of Nanomedicines” (MediTrans) and in the FP-7 “European Network for Cell Imaging and Tracking Expertise” (ENCITE).
This Action aims at fostering the development of concepts and methods of the previous initiatives. The field is huge and the available results just show the tip of the iceberg. Starting from these achievements, enrolling new skills, pointing towards the in vivo studies on animal models of defined diseases is what the new Action has to do.

Of course the Action will organize the communications links with the above mentioned European initiatives, as well as with international and European scientific societies focused on the topic of the Action, through the organization of dedicated meetings, workshops, lectures, seminars, and training activities. Clearly, the Action will embrace all the initiatives as it represents the future projection of the underlying concepts for imaging-guided drug delivery.

E.4 Gender balance and involvement of early-stage researchers

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. The Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas.

F. TIMETABLE

The duration of the Action is four years. Activities of the WGs shall proceed with continuous interaction in order to facilitate the transfer of any important achievement for its exploitation by the whole Action. The following timetable will be pursued:

Year 1	Exploration of novel nanocarrier architectures and imaging reporters Identification of suitable cellular and animal models
Year 2	In vivo testing of promising architectures in cellular and animal models
Year 3	In vivo optimization of the responsive properties of the carriers for the release of the drug at the diseased sites/cells Improvement of the use of theranostics for NCT-based therapies
Year 4	Selection of the most promising theranostic procedures for a potential industrial/clinical translation

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: AT, BE, CH, CZ, DE, DK, ES, FR, IL, IT, NL, PT, SI, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 56 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

The Chair will be responsible for the overall dissemination strategy of the "Imaging and Theranostics" Action. In the dissemination plan, different target groups will be identified (internal dissemination, dissemination through the participating institutions to the large bio-medical community, dissemination to specific scientific disciplines, to specific clinical disciplines, to healthcare providers and law makers, to the general public) and it will be specified how these different groups will be addressed (through conferences, the Action website, mailing lists, seminars, workshops).

A specific "dissemination plan" will be set up by a dedicated body (dissemination platform) to facilitate the transfer of information to industries and to favour the presentation of the results by young scientists. The dissemination platform will draft and regularly update the Action`s dissemination plan. This includes an update of target groups already identified prior to the Action start and the widest possible further dissemination consistent with the intellectual property rights of its members. The members of this network with its well-maintained contacts with industry and international associations (more than 200 institutes) will provide the link between all these institutes and associations and will ensure a well-structured dissemination approach.

H.2 What?

Specifically, dissemination material to be generated will include:

- an “Imaging & Theranostics” graphical image (logo, templates, etc.);
- an “Imaging & Theranostics” public website to allow appropriate worldwide access to all validated dissemination documents;
- dissemination material articles, a press portfolio and press releases for the wider public audience and decision makers;
- presentations at conferences and events;
- support participation to public events, scientific conferences, etc. of Action’s partners.

The dissemination plan will be revised by the Steering Committee on an annual basis. A key-appointment for the dissemination of the Action’s achievements is represented by an Annual Workshop at which all the Action’s Member Teams have to attend and contribute.

H.3 How?

The widespread dissemination of results and knowledge is in the prime interest of all the Action’s participants, as it is instrumental to achieve the overall acceptance and implementation of the research work carried out in the Action.

An important part of the transfer of scientific results to the wider scientific audience will be achieved through the publication of results in peer-reviewed international journals and conferences. Based on the dissemination plan, the Steering Committee will define a list of the main conferences for presenting the achievements of the Action. Next to these conventional dissemination channels, the Action will organize internal meetings (in addition to the annual workshop), eventually dedicated to the specific activities of a given Working Group. Ample participation will be promoted to ensure that most of the researchers (staff, students, and technicians) contribute to the communication exchange. Together with industry partners significant measures will be taken in order to get dedicated support for the wider participation in the events promoted by the Action.