European Cooperation in Science and Technology
- COST -

Secretariat

Brussels, 8 December 2011

COST 4162/11

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action CM1105: Functional metal complexes that bind to biomolecules

Delegations will find attached the Memorandum of Understanding for COST Action as approved by the COST Committee of Senior Officials (CSO) at its 183rd meeting on 30 November 2011.

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

COST Action CM1105
FUNCTIONAL METAL COMPLEXES THAT BIND TO BIOMOLECULES

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 4154/11 "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 develop and evaluate in a structure-targeted approach new metal-based compounds that exert their function as metallo-drugs, as research tools, or as diagnostic tools by binding to biomolecules, and to understand their modes of action.

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 60 million in 2011 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 will focus on the development of novel metallo-drugs in a structure-targeted approach. By targeting specific protein clefts, RNA, and less common but functional DNA structures, biomolecular recognition processes involving metal complexes will be exploited in the design of innovative metallo-drugs. A particular focus will be given to structural details of the molecular interaction between the metal complexes and their biomolecular targets. In addition, the process of targeting and delivery, the interactions of the metallo-drugs on the cellular level, and prodrugs with novel activation strategies that get activated only at their target site will be investigated. The metal complexes include bioorganometallic compounds, rigid polynuclear complexes of defined shape, and other coordination compounds. Drugs based on metal complexes offer an extremely diverse structural chemistry and are excellent candidates to explore new three-dimensional space when targeting biomacromolecules. The ultimate aim will be the development of new therapies for cancer, infectious, and virus-related diseases. An additional benefit will be the design of metal complexes as tools for diagnostics and in fundamental research.
Keywords: medicinal inorganic chemistry, structure-targeted biomolecular recognition, metal-based drugs

B. BACKGROUND

B.1 General background

The development of new anticancer, antiviral and antibiotic drugs is of exceptional importance for society. Cancer and virus-related diseases continue to be of serious concern, because successful approaches for their treatment are still scarce. In contrast, bacterial infections had been considered a problem of the past that has disappeared with the advent of modern antibiotics about 60 years ago. However, recently antimicrobial resistance has become a challenging issue of increasing significance. Reports estimate that multi-resistant *Staphylococcus aureus (*MRSA) bacteria cause more U.S. deaths annually than HIV/AIDS (*J. Am. Med. Assoc.* 2007, *298*, 1803). In combination with the fact that hardly any new antibiotics have been developed over the last 20 years, the danger associated with resistant and virulent bacteria is considerable.

In general, drugs based on metal complexes offer an extremely diverse structural chemistry and are therefore excellent candidates for the exploration of new three-dimensional space when targeting biomacromolecules. While carbon is restricted to linear, trigonal planar, and tetrahedral geometries, metal complexes with coordination numbers greater than four can offer greater structural diversity. In fact, a metal complex with octahedral geometry comprising six different ligands can exist in 30 stereoisomeric forms as compared to just two for an asymmetric tetrahedral carbon. The properties of metal complexes can also be fine-tuned in terms of their ligand exchange kinetics, catalytic properties, redox behaviour, and more. As a result, the metallo-drugs are expected to have a clinical advantage over traditional organic molecules. The development of new metal-based drugs always requires a joint effort of scientists from numerous disciplines. It involves synthetic chemists, spectroscopists, pharmacologists, medical scientists, biologists, and many more. Hence, COST offers an ideal framework for this Action because it enables an intense networking and collaboration of the above-mentioned scientists. Moreover, the strong emphasis of this Action on Short-Term Scientific Missions (STSMs) of PhD students and postdocs will lay the foundations for well-educated future generations of researchers, leading to significant capacity building and ensuring that the prominence of European Medicinal Inorganic Chemistry will be retained and strengthened.

B.2 Current state of knowledge

The fortuitous discovery of the anticancer activity of cisplatin, a simple metal coordination compound, in the 1960s in the U.S. led to the development of a new class of metallo-drugs with an unprecedented spectrum of activity. As a result, the cure rate (e.g. for testicular cancer) increased from approximately 5% to more than 95%. Also from a monetary viewpoint, the development of this simple, entirely inorganic drug has been highly successful: even nowadays, the three most prominent platinum-based drugs cisplatin, carboplatin, and oxaliplatin have a total sales volume of more than 3 billion € per year. Hence, the quest for other first-in-class drugs is unwaning. In this context, European researchers have been very successful and competitive in the design of new potential metallo-drugs arising from cisplatin. Examples for such metal complexes are the ruthenium-based compounds NAMI-A (currently in phase I/II trials) and NKP-1339 (currently in phase I/IIa trials) or the gallium complex KP-46 (currently in phase I/IIa trials).

The current competitiveness of European scientists can be attributed to a large extent to previous, excellent European networking possibilities. Having created this opportunity, it is paramount that European researchers will be able to build on it in the future.

At present, important new trends are rapidly emerging in the field of Medicinal Inorganic Chemistry: influenced by cisplatin, earlier research had focused on the interaction of potential metallo-drugs with DNA (deoxyribonucleic acid) duplexes. However, proteins, RNA (ribonucleic acid), and less common but functional DNA structures are now emerging as important potential targets for metallo-drugs. For example, NAMI-A is opening up new perspectives in cancer chemotherapy by inhibiting metastasis formation, probably by binding to protein targets such as integrins. Other examples for relevant targets include proteins known to act as biomarkers for tumour activity such as GRP78 (*Curr. Mol. Med.* 2006, *6*, 45), proteins currently under investigation in the context of personalized cancer medicine such as kinases (*Nat. Rev. Drug Discovery* 2009, *8*, 709), enzymes (*J. Med. Chem.* 2011, *54*, 3), non-duplex DNA structures such as the replication fork (*Chem. Biol.* 2008, *15*, 1258), and RNA structures involved in gene regulation such as riboswitches (*Nature* 2008, *455*, 1263). Targeting riboswitches offers a tremendous potential in the context of developing new classes of antibiotics, as antibiotic resistance has been found to be at least in part the result of mutations in bacterial riboswitches.

B.3 Reasons for the Action

In a most general definition, this COST Action is primarily concerned with developing functional metal complexes that exert their function by interacting with biomolecules. The most prominent application of such complexes is certainly their use as metal-based anticancer, antibiotic, or antiviral drugs. However, other applications as tools for diagnostics or for fundamental research will also be dealt with, e.g. metal complexes capable of signalling the success or failure of a therapy in a non-invasive way. The development of compounds with these properties will only be possible in an intense collaboration of scientists from various fields, also based on the concomitant exchange of knowledge. Synthetic chemists have the expertise to create such compounds, spectroscopists and biochemists investigate various aspects of their interaction with biomolecules,

structural biologists probe the topology of the adduct between metal complex and its targeted biomolecule, and biologists, pharmacologists as well as medical scientists are involved in preclinical and clinical trials. In essence, the aim of this Action intrinsically requires the establishment of a network of experts, ensuring that Europe keeps a leading position in this field in a concerted action. Additional important benefits of this Action will be the multidisciplinary training of Early-Stage Researchers (ESRs) and a further defragmentation of European research activities in Medicinal Inorganic Chemistry, both eventually increasing Europe's competitiveness.

In the short and medium term, this Action is aimed at scientific advance. However, once a metal complex designed during the course of this Action has successfully passed clinical trials, the resulting metallo-drug will certainly serve the European societal needs in the context of improving the health of all citizens. In addition, the pharmaceutical industry is expected to be interested in the results of the Action in the long term, due to its high demand for first-in-class drugs.

B.4 Complementarity with other research programmes

At the moment, no COST Action exists within the CMST (Chemistry and Molecular Sciences and Technology) Domain that focuses on applying metal complexes in biological systems. One Trans-Domain Action (TD1004, "Theragnostics Imaging and Therapy: An Action to Develop Novel Nanosized Systems for Imaging-Guided Drug Delivery", running until October 2015) is currently open. However, while having related objectives, this Action and TD1004 apply totally different approaches towards reaching these objectives. TD1004 will apply nanotechnology advances to develop image-guided therapies for the cure of diseases, whereas this Action focuses on the design and application of metal complexes as anticancer, antibiotic, or antiviral drugs.

This COST Action will contribute to achieving central objectives of the general FP7 health theme, i.e. improving the health of European citizens and increasing the innovative capacity of European health-related businesses, by providing the necessary fundamental knowledge. Moreover, it is directly aligned with areas identified by the EuCheMS (European Association for Chemical and Molecular Sciences) in their "Initial input on the future of the EU's Research Framework Programme" to be of priority in Horizon 2020, the Framework Programme for Research and Innovation (2014-2020), namely the development of new therapies for cancer and infectious diseases.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The aim of the Action is to develop and evaluate in a structure-targeted approach new metal-based compounds that exert their function as metallo-drugs, as research tools, or as diagnostic tools by binding to biomolecules, and to understand their modes of action.

C.2 Objectives

Secondary objectives of this Action are

- to promote the field of Medicinal Inorganic Chemistry by developing novel metal-based antibiotic, anticancer, or antiviral drugs for diagnostic and therapeutic applications;
- to consolidate the prominence of European research on metal-based drugs;
- to investigate the possibility of drugging specific targets, thereby opening up a way to more efficient probes and diagnostics that help clinicians to diagnose and decide on follow-up therapies;
- to develop new tools for fundamental research, e.g. in molecular biology;
- to generate intellectual property or the potential to license new technology;
- to generate networking opportunities for ESRs;
- to disseminate the results of this Action (see also section H.2). For example, the intense networking of the Action will become obvious from collaborative publications, where approximately 120 publications in internationally renowned, peer-reviewed journals are expected during the course of the Action.

C.3 How networking within the Action will yield the objectives?

The objectives of this Action will be achieved by

- organizing annual Whole Action Meetings (WHAMs) and regular Working Group (WG) meetings, ensuring a rapid flow of information amongst the participating scientists and strong collaborations also across different WGs;

- establishing new and consolidating existing research collaborations, as a result of regular WG meetings and WHAMs;
- conducting Short-Term Scientific Missions (STSMs) with a particular focus on PhD students and postdocs, thereby leading to capacity building and at the same time promoting interdisciplinary research collaborations;
- organizing summer schools in Medicinal Inorganic Chemistry to teach the results of the latest cutting-edge research to PhD students and postdocs;
- disseminating the research outcomes (for more details, see section H.2).

C.4 Potential impact of the Action

As outlined also in section B.3, the development of new anticancer, antiviral and antibiotic drugs will have a significant impact on the EU healthcare system and on society. Additionally, metal complexes developed during this Action are expected to be useful tools for diagnostics and for fundamental research in molecular biology.

Moreover, the Action will foster the careers of ESRs by increasing their mobility, by enhancing their training as well as their exposure to other research groups, and in essence by providing a framework for highly interdisciplinary research. Ultimately, the Action will lead to significant capacity building and ensure that European research will stay competitive with that in the USA and Asia.

C.5 Target groups/end users

The short-term target group to exploit the results of this Action will be scientists at universities and other research institutions. In the medium term, health-related businesses such as pharmaceutical companies involved in developing new first-in-class drugs will be interested in the results of this Action. The long-term target group comprises all European citizens, as they will benefit from the anticancer, antiviral, and antibiotic drugs to be developed during the course of this Action.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The COST Action will focus on the development of novel metallo-drugs in a structure-targeted approach. Towards this end, new metal complexes such as bioorganometallic compounds, rigid polynuclear complexes of defined shape, or other coordination compounds will be designed and synthesized. Their respective modes of action will be established by investigating the structural details of the molecular interaction with their targets or their selective activation at the respective target site. The design of the complexes will be facilitated by exploiting new three-dimensional space. Hence, molecules will be created with a well-defined structure capable of binding to the respective biomolecular target in a unique fashion. Information gained with respect to the mode of action will be used to fine-tune the structure of the metal complex to improve its efficacy as a metallo-drug. Targets to be investigated in this Action include proteins such as kinases and receptors, enzymes, less common but functional DNA structures, and RNA. In this structure-targeted approach, it is the aim of the Action to develop further the entire field rather than zooming in on one target area only.

The objectives will be achieved with a highly interdisciplinary network of scientists from different areas of research. The structural characterization of biomacromolecules and their adducts with metallo-drugs will be performed using various complementing methods. These include single-crystal X-ray diffraction analysis, multidimensional NMR spectroscopy, biochemical and biomolecular methodologies, and modelling approaches that yield insights into the interaction of target and metal complex. To ensure an open and flexible framework of the Action, no limitations will be imposed on the individual project proposals, as long as they contribute to achieving the objectives mentioned in section C.

To be able to achieve the objectives, the following technical equipment (funded from other sources such as national funding agencies) is available to potential participants of this Action:

- fully equipped synthesis laboratories
- functional genomics centre

- NMR (Nuclear Magnetic Resonance) centres
- mass spectrometric core facility
- macromolecular X-ray facilities, including access to X-ray diffraction beamlines at synchrotron facilities and robotic systems for protein crystallography
- fluorescence microscopy and single-molecule fluorescence spectroscopy
- high resolution continuum source atomic absorption spectrometer
- radioanalytical laboratories with imaging equipment
- fully equipped cell culture laboratories, including equipment for cell testing and quantitative evaluation of light irradiation
- equipment for preclinical testing of potential metallo-drugs

D.2 Scientific work plan - methods and means

The following five important research themes have been identified. They will be the basis for establishing five WGs, which will also reflect established collaborations and complementary skills of the scientists who already expressed their interest in joining this Action. Apart from the mere development of functional metal complexes and understanding their modes of action, research in all WGs will also focus on the application of these metal complexes as metallo-drugs, as tools for diagnostics (where applicable), and in fundamental research. Moreover, the establishment of structure-activity relationships of promising new metallo-drugs will be of priority in all WGs. All five research themes relate to the targeted approach of this Action: two WGs will focus on the interaction between metal complex and its biological target molecule, one WG will investigate the process of targeting and delivery, one WG will study the consequences of targeting on the cellular level, and one WG will develop metal-based prodrugs that are activated only at their respective biological target site.

Working Group 1: Protein targets. Enzymes, or proteins in general, have evolved as important targets for metal-based drugs. Targeted proteins include - amongst others - protein kinases, receptors (surface and intracellular), histone deacetylases, and proteases. The anticipated modes of action of the metallo-drugs are extremely diverse and vary from target to target.

Inhibiting an enzyme is often achieved by applying a metal complex that perfectly fits into a binding pocket of the protein, outcompeting the natural binding partner and thereby down-regulating the enzyme's activity. In addition to this non-covalent interaction, coordinative bonds may be formed between a metal complex and amino acid residues in the active site of the target. Accordingly, such metal complexes have in common that their design is based on the knowledge of the three-dimensional structure of the binding site within the protein. In particular in the context of targeting proteins, metal complexes often excel traditional purely organic inhibitor compounds as a result of their extreme structural diversity. One approach applied by this WG for the development of metal-based inhibitors is closely related to well-established strategies in medicinal chemistry for organic compounds. For example, combinatorial chemistry followed by a screening will provide initial lead structures that will be used for obtaining a co-crystal structure of such a complex bound to the active site of the target and later will serve as a starting point for structure-based design. In addition, research towards the identification of the physiological (pathological) role of the identified proteins will be performed. Targeting proteins relevant for controlling or sustaining cell growth, cell survival and malignancy/virulence with metal-based drugs can be of extreme importance for controlling tumours or infectious diseases. Hence, within this WG, new protein targets for metal-based drugs will be identified, and metal complexes targeting these as well as established protein targets will be developed and evaluated.

Working Group 2: Emerging nucleic acid targets (beyond the double helix). Based on the currently accepted mode of action for the well-established anticancer drug cisplatin, most research with respect to novel metal-based drugs has been (and still is being) devoted to investigating their interaction with the DNA double helix. This approach neglects the fact that functional DNA, i.e. DNA while it is being processed, often adopts different structural motifs (e.g. three-way junctions, four-way junctions, or tetrastranded helices). It is therefore likely that by specifically targeting these DNA conformations, metal complexes can be developed that serve as metallo-drugs with entirely new modes of action and potentially leading to new therapies for cancer and other diseases. To give an example: the 3' ends of eukaryotic chromosomes known as telomeres typically contain single-stranded guanine-rich overhangs that are in principle able to adopt a tetrastranded structure. In somatic cells, telomeric DNA progressively shortens during each round of replication as a result of the inability of DNA polymerase to fully replicate single strands. In more than 80% of all tumour cells, the length of the telomeric DNA is maintained by the enzyme telomerase, leading to "immortal" cells, whereas in healthy cells the enzyme is inactive.

Telomerase requires the telomeric DNA to be single-stranded. Hence, the development of metal complexes capable of selectively stabilizing a quadruplex structure is expected to lead to a novel and selective anti-cancer therapy. In addition, RNA is emerging as an important new target for metal-based drugs. For a long time, RNA was considered an intermediate carrier of genetic information only. However, during the past few decades knowledge has been gained showing that RNA is of utmost importance also in a variety of other biological aspects, e.g. as a catalyst (ribozymes, Nobel Prizes in 1989 and 2009) or in regulating gene expression (RNA interference, Nobel Prize in 2006; riboswitches). Hence, the development of metallo-drugs that specifically target functional RNA is a highly promising and topical area of research. In particular, riboswitches (i.e. small, highly conserved elements within the untranslated regions of mRNA that are capable of binding to small-molecule metabolites and concomitantly regulating gene expression) are an interesting target in the context of developing new classes of antibiotics. As riboswitches are found exclusively in prokaryotes (with a single exception), interfering with these riboswitches by means of metallo-drugs automatically means that only bacteria will be targeted. Within this WG, metal complexes that specifically interact with nucleic acids of unusual conformation will be developed, and their interaction with nucleic acids will be characterized.

Working Group 3: Metal bioconjugates for targeting and delivery. Instead of targeting specific biomolecular binding sites, metal-based drugs can also be delivered to their designated site of action by attaching receptor-specific targeting vectors. In general, by choosing appropriate targeting vectors such as peptides, nucleic acids, anti-metabolites, drugs or other bioactive vehicles, specific cell compartments (e.g. mitochondria, nuclei) can be addressed. The biological distribution processes are strongly influenced by the nature of the metal ion or metal complex due to the involvement of metal-specific transporter systems. Relevant examples include ruthenium species that are transported via transferrin receptors. Many organometallic species display favourable properties based on their biological stability and thereby provide optimized structural elements for combining metals with appropriate targeting vectors. The metal bioconjugates will be based on the multi-modality concept. Ideally, they contain a bioactive moiety which targets specific cell membrane receptors for selective cell uptake as the first modality. This will initiate preferential uptake at sites with enhanced expression of this particular receptor.

After receptor-mediated endocytosis, they comprise as a second modality a structural feature which targets e.g. the enzyme, tightly binds to it and exerts the action of the metal complex. It is of utmost interest for later application to not only have a therapeutic but also a diagnostic option. On the *in vitro* level, fluorescence markers can support the detection of cellular distribution of the conjugates within the micro-compartments of the cell. Elucidation of quantitative distribution of multi-modality compounds within the cell by e.g. fluorescence markers will facilitate a better understanding of the mode of action of the metallo-drug. Accordingly, radiolabelling will allow for *in vivo* imaging, thus, the success or failure of a therapy can be imaged non-invasively. Ideally, the therapeutic and the diagnostic compounds are structurally identical. These multi-modality type metal bioconjugates for targeting and delivery can conceptually be applied to all targets within the scope of this Action. Within this WG, the design, syntheses, biological behaviour and physico-chemical properties of such bioconjugates will be evaluated.

Working Group 4: Interactions of metallo-drugs on the cellular level. It is also of utmost importance to understand how metal-based compounds interact with and affect cellular systems, and how they are processed by cells with the goal of developing drugs with novel mechanisms of action. The effects of the potential metallo-drugs on cellular signal-transduction pathways, metal-ion homeostasis, redox responses, cell transformations and cell death will be elucidated. Interactions between the designed compounds and selected biomolecules such as metallochaperones, metallotransporters and genetic material will be analyzed by both theoretical and experimental methods. The fate of the compounds in cells will be studied by measuring metal uptake, speciation and biotransformations, and the elimination of metals and ligands. By better understanding interactions between metal-based compounds and cells, targeted therapeutic strategies with improved specificity can be developed. Hence, within this WG, the processing of metallo-drugs on the cellular level will be investigated.

Working Group 5: Prodrugs with novel activation strategies. In particular in the context of targeting cancer, it is highly desirable to develop metal-based prodrugs that get activated only at their respective target sites. Compared with standard organic drugs, metal complexes benefit from their ability to undergo reduction and oxidation reactions, often depending on changes of the biological environment. In view of the hypoxic milieu present in tumour tissue, metal-based prodrugs will be developed and investigated in which the change of oxidation state of the central metal ion generates the biologically active metallo-drug. In addition, tumours are known to have an acidic environment.

Accordingly, this WG will also deal with the design of prodrugs that are activated by an acidification, e.g. by applying pH-sensitive ligands. Another prominent example for prodrugs to be investigated within this WG are metal complexes that become active drugs after irradiation with light. For example, inert (and hence inactive and scarcely toxic) complexes will be prepared that, upon irradiation with visible light, rapidly release one or more ligands, thus becoming activated. Another example concerns metallo-porphyrin compounds that exploit the tumour-localizing and light-harvesting ability of the porphyrin ligands. Light absorption from the chromophore is followed by energy transfer to the metal, inducing ligand dissociation and thus selective activation. Complexes activated by light are expected to display reduced side effects in healthy (non-irradiated) tissue. Hence, within this WG, prodrugs based on these (and also on other newly developed) activation strategies will be devised, characterized, and developed.

E. ORGANISATION

E.1 Coordination and organisation

In this Action, apart from the Management Committee (MC), a total of five WGs will be established. To ensure a continuous management of the Action and to be able to discuss unforeseen questions and challenges promptly, a Steering Group (SG) will be elected during the first MC meeting. The SG will comprise the MC Chair, the MC Vice-Chair, the Grant Holder, the STSM Manager (see below), and four additional MC members. The SG will prepare MC meetings and will communicate electronically. Similarly, a WG Coordinator mailing list will be set up to facilitate internal discussions regarding the coordination of the WGs. An STSM Manager will be elected during the first MC meeting who is responsible for approving and reviewing STSMs. Whole Action Meetings (WHAM) will be organized annually, ensuring a lively Action with a constant flow of information and a broad exchange of ideas amongst all participants. In-between the WHAMs, individual WG meetings will take place. In addition, two whole Action summer schools on Medicinal Inorganic Chemistry will take place specifically for ESRs. Because of the highly interdisciplinary research carried out by the participating groups, hands-on training schools for a limited small number of PhD students will take place in the groups with the respective competence.

To increase the visibility of the Action, the WHAMs will be scheduled close to international conferences in Europe like EUROBIC (European Conference on Biological Inorganic Chemistry), ICBIC (International Conference on Biological Inorganic Chemistry), or ECCLS (European Conference on Chemistry for Life Sciences). The annual MC meetings will be held in conjunction with the WHAMs whenever possible. As an innovative tool to establish a successful scientific network and to better get to know each other, the first WHAM will include flash presentations of each principal investigator's (PI's) research interests. For an efficient communication within the Action, but also for outreach activities, a website will be set up highlighting the scientific programme of the Action, giving an up-to-date summary of its most current achievements, and informing about areas currently underrepresented in the Action, thereby attracting new members to join the network. For internal discussions (e.g. manuscripts prior to their submission/publication) and for the distribution of proprietary information, the website will have a restricted-access section, based on a well-established e-learning platform. A Website Manager responsible for setting up the website and for keeping it up-to-date will be elected during the first MC meeting.

E.2 Working Groups

This Action will be organized with a total of five Working Groups. The WGs are defined in a manner to cover the topics described in detail in section D.2:

- WG1: Protein targets
- WG2: Emerging nucleic acid targets (beyond the double helix)
- WG3: Metal bioconjugates for targeting and delivery
- WG4: Interactions of metallo-drugs on the cellular level
- WG5: Prodrugs with novel activation strategies

Participants of this COST Action will be invited to join one (or several) of these Working Groups. The MC will ensure that each WG composition is optimal for complementary skills, existing collaborations, ESRs, gender balance, and industrial membership. Each WG will be led by a WG Coordinator, responsible for communication with the MC. WG meetings will be organized in-between the WHAMs. To facilitate internal discussions with respect to the coordination of the WGs, a WG Coordinator mailing list will be set up.

E.3 Liaison and interaction with other research programmes

There does not seem to be another COST Action with a focus closely related to the one of this Action. Nevertheless, some potential participants of this Action are also involved in other Actions (MP0802: "Self-assembled guanosine structures for molecular electronic devices"; CM0902: "Molecular machineries for ion translocation across biomembranes"). While the aims of those Actions differ completely from the aims of this Action, some overlap exists in terms of biomolecules involved or methodologies applied. Hence, all necessary efforts will be made to exchange information and, where appropriate, organize shared meetings.

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.

A particular focus of this Action will be given to ESRs. In this context, about 50 STSMs are expected to take place during the course of the Action. The possibility to participate in STSMs will be given specifically to PhD students and postdocs, rather than PIs. In addition, as a result of the highly interdisciplinary research carried out by the participating groups, hands-on training schools for a limited number of PhD students will take place in the groups with the respective competence. Moreover, two whole Action summer schools on Medicinal Inorganic Chemistry that target (and to a large extent will be organized by) ESRs will take place. These activities will contribute significantly to capacity building. Involvement of ESRs will be further promoted by encouraging them to act as session chairs during Action meetings, and by dedicating entire sessions of Whole Action Meetings to oral presentations given by ESRs.

Measures to promote gender equality will include a special mentoring for female ESRs who intend to pursue an academic career, e.g. by including a session in the summer schools devoted to (and held by) leading female scientists who may serve as role models.

F. TIMETABLE

This Action will last for four years. The following table gives an overview of the timing of the milestones and deliverables. Additional information is given below.

	Year 1	Year 2	Year 3	Year 4
MC Meetings	1	1	1	1
WHAMs	1	1	1	1
WG Meetings	1 per WG	1 per WG	1 per WG	1 per WG
Summer Schools	-	1	-	1
Training Schools	1	1	1	1
STSMs	5	15	15	15

Annual WHAMs will ensure strong and successful collaborations also across different WGs. WHAM 1 will include flash presentations of each PI's research interests as an innovative tool to establish a successful scientific network and to better get to know each other. WHAM 2 will specifically target industrial attendees in addition to the Action participants, to establish closer ties with industry. The summer schools on Medicinal Inorganic Chemistry will include lectures by leading experts to train in particular PhD students and postdocs and will be organized to a large extent by ESRs. They will also include measures to promote gender equality. The training schools for PhD students will give hands-on training on specialized methodologies and will take place in the groups with the respective competence.

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: AT, CH, CZ, DE, ES, FR, HU, IE, IL, IT, NL, PT, SE, 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 60 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?

There are several target groups for the dissemination of the results of this Action:

- Scientific community (including, but not limited to, scientists from chemistry, pharmacy, medicine, and structural biology)
- Pharmaceutical industry as potential end users (indicating that drug development is not only the domain of organic chemistry by showing that inorganic compounds can also act as highly efficacious drugs)
- National and European funding agencies (e.g. by making a bid to the European Science Foundation (ESF) for organizing an ESF High-Level Conference on Medicinal Inorganic Chemistry, potentially in collaboration with the Gordon Conference Series)
- General public (including both those who are scientifically trained and those without scientific training)

H.2 What?

This Action will make use of the following dissemination methods:

- Posting information on the Action website
- Publishing research articles and reviews in peer-reviewed scientific journals
- Publishing articles in popular science media
- Using mailing lists for dissemination amongst the Action participants
- Releasing press statements via the respective home institutions of the Action participants
- Organizing conferences, workshops, and symposia (in fact, some of the established international conferences on Bioinorganic and Medicinal Inorganic Chemistry within the timeframe of this Action will be organized by potential members of the Action)
- Outreach activities at international conferences to promote the Action and to encourage scientists to join the network also at a later stage

- Patents (where applicable)
- Organizing outreach activities such as public lectures or open days, keeping the excitement and the dynamic introduced by the International Year of Chemistry 2011

H.3 How?

The dissemination of the results of the Action will be a standard item on the agenda of all MC meetings. Accordingly, it will be continuously evaluated and updated as part of the annual assessment of the progress of the Action.

Electronic mailing lists will be set up for an efficient distribution of Action-related news amongst the participating scientists. To increase visibility of the Action within the scientific community, it will be acknowledged in all Action-related publications. Furthermore, the annual Whole Action Meetings will be scheduled close to well-established international conferences in Europe to facilitate the dissemination of the Action's progress. All meetings, workshops, and summer schools will be open to the wider scientific audience. To establish ties with industry, the second WHAM will specifically target industrial attendees in addition to the Action participants. Scientists participating in the Action who are involved in outreach activities will use this Action to educate the public. To increase the awareness of chemistry in society, trainings in "communication to the public" will take place for participating ESRs. Such training could include the development of press releases related to the Action's science. Very promising initiatives in this respect have already started in collaboration with a local Science Museum.

The Action website will comprise of two parts: the freely accessible part will inform about the Action's activities and highlight the most current achievements. Moreover, it is intended to inform about areas of research currently underrepresented in the Action, thereby attracting new potential members to join the network. The restricted-access section of the website will enable the distribution of proprietary information amongst the participating groups and will give an opportunity for internal discussions e.g. of manuscripts prior to their publication.