Brussels, 13 April 2018

COST 015/18

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "New diagnostic and therapeutic tools against multidrug resistant tumors" (STRATAGEM) CA17104**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action New diagnostic and therapeutic tools against multidrug resistant tumors approved by the Committee of Senior Officials through written procedure on 13 April 2018.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA17104
NEW DIAGNOSTIC AND THERAPEUTIC TOOLS AGAINST MULTIDRUG RESISTANT TUMORS (STRATAGEM)

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

a. "Rules for Participation in and Implementation of COST Activities" (COST 132/14 REV2);
b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14 REV);
c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14 REV2);
d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14 REV).

The main aim and objective of the Action is to find new biomarkers predictive/diagnostic of MDR (multidrug resistance) that can be suitable therapeutic targets; and to design and validate new therapeutic tools active on MDR tumors, formulate them as nanosystems and verify the efficacy and safety of the new MDR-reversing compounds. This will be achieved through the specific objectives detailed in the Technical Annex.

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 44 million in 2017.

The MoU will enter into force once at least seven (7) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14 REV2.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14 REV2.

TECHNICAL ANNEX

OVERVIEW

Summary

This Action will build the first multidisciplinary network, including academic laboratories, research institutes, small and medium enterprises (SMEs), with a wide range of excellent and non overlapping expertise, aiming at improving at the same timethe diagnosis and therapy of multidrug resistant (MDR) solid tumors.

Until now, there are fragmented knowledge on biomarkers and therapeutic tools used against MDR tumors; there are not algorithms predictive/diagnostic of MDR tumors ex ante; all the past therapies against MDR tumors failed. The key challenge of this Action is to fill these gaps, by producing a comprehensive, open and user-friendly platform of knowledge on MDR tumors, identifying new diagnostic/predictive biomarkers, producing new and safe compounds applicable to personalized treatments of MDR tumors.

Up to 70% of solid tumors are resistant at the diagnosis: this means poor life quality and poor prognosis for patients, high management costs for the European healthcare systems. This Action is working to improve diagnosis and treatment of patients with MDR tumors and reduce the costs for their management.

Second, by creating fruitful collaborations between basic and industrial research, we will give impulse to the creation of new Start-up and SMEs in Europe.

Finally, the Action aims at raising the level of European research on MDR, reducing the disparity in the research quality between EU countries and ITC, providing the necessary training for European early stage researchers (ESRs) to grow as future independent research leaders, regardless of location, age or gender.

Areas of Expertise Relevant for the Action	**Keywords**
● Biological sciences: Biochemistry ● Chemical sciences: Molecular chemistry ● Medical biotechnology: Databases, data mining, data curation, computational modelling ● Basic medicine: Pharmacology, pharmacogenomics, drug discovery and design, drug therapy	● Multidrug resistant tumor biomarkers ● Therapeutic tools against multidrug resistant tumors ● Computer-assisted drug design, computational biology ● Nanosystems for drug delivery ● Safety pharmacology

Specific Objectives

To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination

● Build a network of multi- and interdisciplinary research teams [from small and medium enterprise (SME) centre to research institutes] with an unusually wide range of expertise, sharing research tools (e.g. cell lines, in vitro and in vivo models, compounds) and know-how (experimental models and procedures) to tackle a common challenge.

● Develop innovative and integrated approaches to tightly link outcomes/results to achieve results that are difficult to obtain by individual partners: the network will ensure a comprehensive approach in defeating MDR tumors and accelerating the translation of the results of basic research activities into healthcare applications.

● Build a platform that integrates diagnostic needs (identification of new MDR biomarkers) and therapeutic needs (identification of new therapeutic tools), by integrating the skills of the different groups.

● Involve the stakeholders to ensure that the research activity of the network really meets the needs of the final users.

● Join the results of the basic research and industrial research: our main goal is to acquire and publish

freely available knowledge, although intellectual property may derive from Action activities.
● Improve the European/international visibility of the network by establishing a dedicated website and organizing meetings and workshops to attract researchers, investors, industry policy makers and health care system providers/managers: so doing, the fruits of innovation will be quickly and appropriately translated into healthcare applications.

Capacity Building
● Promote the integration of skill-sets and know-how of the individual partners, to provide a coherent approach through web-based resources, annual meetings, workshops and mobility programs The use of contextual knowledge will have a significant impact on biomarkers and drug discovery, reducing cycle times, costs and attrition rates.
● Overcome the fragmentation of the European research field and reducing the duplications in the MDR research field.
● Stimulate mobility and making better use of the potential of women researchers.
● Improve links with less research-intensive countries across Europe (i.e. ITC countries).
● Forge close partnerships that can apply for research funding from the appropriate EU programs, including training programs (i.e. Marie-Curie fellowships by ECIs).
● Stimulate the scientific growth of ECIs by their intensive introduction into the interdisciplinary work of this Action through either the organization or the participation to the training schools and STSMs to research groups working in other disciplines and countries.
● Provide to ECIs working in academic and industrial context the possibility of STSMs, following all the steps of the research process, from the discoveries to the pre-clinical validation and development. These mutual exchanges will aid the transfer of knowledge, with consequent benefits for the scientific and professional growth of ECIs.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. CHALLENGE

1.1.1. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

The challenge of this Action is to improve the diagnosis and therapy of multidrug resistant (MDR) tumors, that are incurable at the present. The main aims are:
1) finding new biomarkers predictive/diagnostic of MDR that can be suitable therapeutic targets;
2) designing and validating new therapeutic tools active on MDR tumors, including synthetic drugs and natural products; formulate them as liposomes and nanoparticles; verify the efficacy and safety of the new MDR-reversing compounds.

1.1.2. RELEVANCE AND TIMELINESS

Biomarkers predictive and/or diagnostic of MDR phenotype ex ante have been identified only for few tumors (Guestini, 2015; Crawley, 2015; Nymoen, 2015; De Mattia, 2015; Mirzaei, 2016; Bourguignon, 2016; He, 2017). Moreover, all the past therapies against MDR tumors have failed, for their poor specificity and high toxicity (Dlugosz, 2016; Lorendeau, 2017).
The relevance of the proposal is represented by the fact that:
1) the Action aims at identify diagnostic biomarkers of MDR tumors beyond the presence of ATP binding cassette (ABC) transporters: the project will perform an in depth analysis to retrieve new biomarkers shared by MDR tumors of different origin, in order to:
- build the first predictive/diagnostic algorithm for MDR tumors
- identify new therapeutic targets for MDR tumors;
2) the Action aims at produce new therapeutic tools against MDR tumors: the identification of new therapeutic targets will drive the correct selection of new MDR-reversing agents, including both natural products and synthetic chemotherapeutic drugs tailored on specific target of MDR cells;
3) the Action aims at identify compounds that, besides being tailored on MDR tumors, possess also satisfactory pharmacokinetic and toxicological features, identified by the ADMET processes.
About 6,400 papers on chemoresistance have been published in the last 10 years; only 63 clinical trials on the topics have been registered in the same timeframe, reporting mixed results. This indicates that diagnostic and therapeutic approach on MDR tumors still need improvement.
Such goal can be achieved only by joining the skills and competence of a multidisciplinary network that is crucial to achieve the objectives of the project within the timeframe of the project.
Indeed, the identification of biomarkers and the development of natural and synthetic compounds, with freely available information on efficacy and safety, is best done by collaboration between experts in each aspect, cooperating to pool results and expertise, as facilitated by a COST Action. The frequent and close communication required in a COST Action represents an excellent way to tackle the challenge, providing a coordinated access to resources and knowledge that will catalyse the identification of novel targets for therapeutic intervention against MDR tumors. The exposure to this breadth of information and experts discussion on a regular basis will enable in particular European early stage researchers (ESRs) to grow scientifically, to be trained by experts in the field, to start innovative interdisciplinary collaborations.

1.2. OBJECTIVES

1.2.1. RESEARCH COORDINATION OBJECTIVES

The main objectives in the research coordination are:
1) building a network of multi- and interdisciplinary research teams [from small and medium enterprise (SME) centre, academic laboratories, research institutes] with an unusually wide range of expertise, sharing research tools (e.g. cell lines, in vitro and in vivo models, compounds) and know-how (experimental models and procedures) to tackle a common challenge;
2) developing innovative and integrated approaches to tightly link outcomes/results from the Structural and Cellular Biology, Drug Design, Medicinal Chemistry, Bioinformatic, Computational Biology, Pharmacology, Medical Oncology, ADME (absorption, distribution, metabolism, and excretion) /Toxicology and Pharmaceutics areas, to achieve results that are difficult to obtain by individual partners: the network will ensure a comprehensive approach in defeating MDR tumors and accelerating the translation of the results of basic research activities into healthcare applications;
3) building a platform that integrates diagnostic needs (identification of new MDR biomarkers) and therapeutic needs (identification of new therapeutic tools), by integrating the skills of the different groups;
4) involving the stakeholders to ensure that the research activity of the network really meets the needs of the final users;
5) joining the results of the basic research and industrial research: the main goal is to acquire and publish freely available knowledge, although intellectual property may derive from Action activities;
6) improving the European/international visibility of the network by establishing a dedicated website and organizing meetings and workshops to attract researchers, investors, industry policy makers and health care system providers/managers: so doing, the fruits of innovation will be quickly and appropriately translated into healthcare applications.

1.2.2. CAPACITY-BUILDING OBJECTIVES

The main “Capacity –building” objectives of this COST Action include:
1) promoting the integration of skillsets and know-how of the individual partners, to provide a coherent approach to Structural and Cellular Biology, Drug Design, Medicinal Chemistry, Bioinformatic, Computational Biology, Pharmacology, Medical Oncology, ADME/Toxicology and Pharmaceutics through web-based resources, annual meetings, workshops, mobility programs: all these tools will enable researchers and students from the different groups of the Action to undertake short term missions (STMs) for work and/or studies. The use of contextual knowledge will have a significant impact on biomarkers and drug discovery, reducing cycle times, costs and attrition rates;
2) overcoming the fragmentation of the European research field and reducing the duplications in the MDR research field;
3) stimulating mobility and making better use of the potential of women researchers;
4) improving links with less research-intensive countries across Europe (i.e. ITC countries);
5) forging close partnerships that can apply for research funding from the appropriate EU programs, including training programs (i.e. Marie- Curie fellowships by ESRs);
6) stimulating the scientific growth of ESRs by their intensive introduction into the interdisciplinary work of this Action through either the organization or the participation to the training schools and STMs to research groups working in other disciplines and countries;
7) providing to ESRs working in academic and industrial context the possibility of reciprocal STMs, that will allow to follow all the steps of the research process, from the discoveries of basic research to the pre-clinical validation and development. These mutual exchanges will aid the transfer of knowledge, with consequent benefits for the scientific and professional growth of ESRs.

1.3. PROGRESS BEYOND THE STATE-OF-THE-ART AND INNOVATION POTENTIAL

1.3.1. DESCRIPTION OF THE STATE-OF-THE-ART

Achieving a good efficacy of chemotherapy is one of the major challenge still unresolved in oncological patients. The main limitation to the efficacy of chemotherapy is the MDR phenotype, a multiple cross-resistance towards different anticancer drugs. One of the main mechanisms of MDR is the overexpression of ABC transporters - such as P-glycoprotein (Pgp) and MDR-related proteins (MRPs) - that efflux classical chemotherapeutic drugs as well as new “smart drugs” for targeted therapies (Dlugosz, 2016). Such transporters are particularly rich in cancer stem cells (CSCs), the most chemoresistant and prone to induce tumor development, progression and recurrence (McIntosh, 2016). The pharmacological inhibitors of ABC transporters have failed in clinical stages due to their low

specificity and high toxicity. Recent high-throughput screenings of pharmacological libraries identified however specific compounds, which were unexpectedly more effective in the chemoresistant cells than in the chemosensitive ones. The molecular bases of this hypersensitivity - known as “collateral sensitivity” (CS) - are far from being understood (Lorendeau, 2017).

1.3.2. PROGRESS BEYOND THE STATE-OF-THE-ART

MDR solid tumors represent a serious clinical problem. The main limitations in approaching to MDR diagnosis and treatment by pre-clinical and translational research are the lack of:
1) a comprehensive analysis of genomic/transcriptomic signatures predictive of MDR phenotype, a necessary requisite to build a precision medicine for MDR patient;
2) predictive/diagnostic algorithm designed for MDR tumors;
3) effective strategies reversing MDR applicable at clinical level.
Indeed, despite the multiple MDR-reversing strategies proposed in the past (Li, 2016), all approaches have failed because they have been focused on targeting the cell surface ABC transporters, without considering other biomarkers of MDR phenotype as suitable targets: there are no chemotherapeutic drugs specifically tailored on MDR cells CS inducers designed in a biomarkers-driven way.
This COST Action aims to fill these gaps by integrating different skills and know-how and favouring the exchange of scientists, background and expertise between the partners of the COST Action. The main innovations beyond the state-of the-art proposed by this COST Action are:
- to perform the first comprehensive analysis of MDR signatures in solid tumors by integrating high-throughput bioinformatic, genomic/transcriptomic and proteomic tools, analysing data-resources available for large clinical cohorts;
- to identify molecular biomarkers indicative of MDR that will be used to: i) build up a diagnostic/predictive algorithm for the early identification of MDR patients; ii) guide the design and synthesis of new drugs, tailored on MDR tumors (i.e. targeting specific biomarkers);
- to build the first platform for the personalized treatment of MDR solid tumors.

1.3.3. INNOVATION IN TACKLING THE CHALLENGE

This COST Action will use multiple tools – including high throughput bioinformatic analysis, different “OMICS” technologies, ad hoc in vitro and in vivo biochemical and pharmacological assays, rational design and formulation of synthetic chemotherapeutic drugs, rational choice of natural compounds – to realize an integrated platform for the identification of new diagnostic/predictive biomarkers and therapeutic targets in MDR tumors.
This integrated approach is new in the field of MDR-reversing strategies and will allow to:
1) map the existing knowledge on MDR biomarkers and therapeutic tools by high-throughput computational biology analysis, overcoming the fragmentation of information existing in the scientific literature and building a comprehensive and uniform database – progressively updated on the bases on the knowledge acquired - on this issue;
2) identify robust biomarkers to construct a reliable algorithm for the early diagnosis and/or prediction of MDR phenotype, a procedure that is missing at the present;
3) unveil new therapeutic targets in MDR tumors and produce safe drugs able to reprogram drug-resistant tumors into drug-sensitive ones. The therapeutic tools (i.e. natural products and synthetic chemotherapeutic drugs) proposed by this COST Action differ from the drugs currently used: by screening drug-target bipartite networks, exploring pharmacogenomic data-resources and exploiting metabolic and functional differences at the basis of the MDR phenotype, this COST Action aims to select natural products and design drugs able to hit targets selectively present in MDR cancer cells (not in chemosensitive or non-transformed cells).
The analysis of point 1) will drive the discovery of biomarkers (point 2) and therapeutic tools-tailored on these biomarkers (point 3). Such integration – that is basis for a theranostic approach in the diagnosis and treatment of MDR patient - will accelerate the application of precision medicine for MDR patients, making this COST Action highly innovative in tacking a still unsolved challenge.

1.4. ADDED VALUE OF NETWORKING

1.4.1. IN RELATION TO THE CHALLENGE

This is the first COST Action that tackles the challenge of defeating MDR tumors at the diagnostic and therapeutic levels at the same time. This mission, that is at the forefront in science and technology, is

possible thanks to the exchange of researchers, technologies, knowledge, skills and know-how among the teams involved in the Action.
The research activity in the MDR tumors arena has high costs but also a high potential for significant social and economic returns. It is a time-consuming process and requires multidisciplinary expertise as well as availability of the most advanced technological resources.
These limitations can be overcome by this funding opportunity that allows sharing, creation, dissemination of researchers, knowledge, expertise and technologies among the partners, all currently funded by national or international funding bodies for their own research,
Whereas the successes of the past have come often from single research groups, it is now recognized that the important questions in cancer research are too complex to be tackled by a single team or method. Hence, it is important to develop multi-interdisciplinary consortia of highly skilled scientists that will bring complex tools and technologies together.
Since the identification of biomarkers and the rational design of new therapeutic tools against MDR tumors faces considerable challenges, the frequent and close communication required in a COST Action is an excellent way to achieve results that would be difficult to obtain by individual partners and to ensure comprehensive approach in understanding MDR biology and defeating MDR tumors. Moreover, better education, training and mobility of ESRs will guarantee the establishment of a new generation of highly talented researcher working in the field of MDR tumors, giving them the chance to acquire the necessary skills to become leaders in academic or industrial research and technology. The involvement of academic partners and 2 SME leading in the area of bioinformatics and drug discovery, efficacy and ADME/toxicology assays, will ensure that ESRs will be trained on all aspects of biomarkers and drug discovery, from the basic research issues to their integration into a commercial portfolio, and vice-versa.

1.4.2. IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

There are no European consortia studying the diagnostic, therapeutic and toxicological challenges related to the diagnosis and treatment of MDR tumors at the same time.
There are no consortia combining different approaches to improve the diagnosis (i.e. bioinformatic, genomic and proteomic technologies, biochemical methods) and therapy (i.e. use of natural products, rational synthesis and formulation of new chemotherapeutic drugs tailored on MDR cells, safety of the natural products and synthetic drugs) of MDR tumors.
The breadth of the proposal in terms of techniques and know-how can only be tackled on a European scale: it would be difficult to find all the same expertise in one country outside the USA. Although the European research in this area can be considered competitive in principle, it nevertheless suffers of a lack of coordination, especially in terms of integration of inter/multi- disciplinary points of views and dissemination of results between relevant industry and technology sectors. This project is designed to overcome the fragmentation of the European research field, reduce duplications, stimulate mobility, make better use of the potential of women researchers and improve links with less research-intensive countries across Europe (i.e. ITC countries involved in this proposal). There has always been a great strength in cancer research in Europe and it is important to maintain this lead, increasing the visibility and integration of researchers to the leading knowledge hubs of Europe and identifying excellence across Europe to achieve the Horizon 2020 objectives.
This COST Action is aimed at raising the level of European science on a world-leading stage in the MDR field.

2. IMPACT

2.1. EXPECTED IMPACT

2.1.1. SHORT-TERM AND LONG-TERM SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS

At **short term**, the Action will increase:
1) the scientific knowledge on the MDR tumor, by identifying new diagnostic biomarkers and conceiving new therapeutic tools;
2) the visibility of the European research in the field of MDR tumors;
3) the cooperation between academic and industrial entities working on MDR, by STMs of ESRs, training schools, workshops.
At **long term**, this cooperation will create the basis for:
1) a new bioinformatic platform that integrates in a comprehensive manner information on biomarkers and therapeutic tools on MDR solid tumors;

2) a new predictive/diagnostic algorithm for MDR tumors;
3) a new generation of effective and safe therapeutic tools for MDR tumors;
4) integration between diagnosis and therapy applicable to different MDR tumors, through the rational production of biomarker-driven drugs;
5) a leading multidisciplinary consortium that will be actively involved in training ESRs working in MDR field, disseminating the obtained results to the relevant stakeholders, applying to competitive funding calls in the next years.
The **technological impacts** are represented by the production of:
1) high-throughput technologies predictive/diagnostic of MDR tumors;
2) new synthetic chemotherapeutic drugs and new applications of natural products;
3) new nanosystems for the active targeting of chemotherapeutic drugs on MDR tumor cells in order to reduce side effects and to enhance therapeutic index improving the physico-chemical properties of the drugs by altering their pharmacokinetics and increasing their accumulation in the target tissue.
Under a **socio-economic** perspective, the progressive increase of life expectation in European countries is accompanied by a progressive increase of age-related diseases, like cancers. This process will increase the number of oncological patients with MDR tumors, that require the highest healthcare costs. Indeed, the management costs of oncological patients is supposed to increase by 39% in the period 2010-2020 in the Western countries (Serrier, 2014.) Such costs represent a significant burden for the healthcare systems of European countries. This burden in many European countries is sustained by citizens taxes. By proposing earlier diagnosis and more effective therapeutic approaches, the project will create the basis for the reduction – on a long-term perspective – of the care costs of MDR tumor-bearing patients, producing direct benefits on the healthcare systems and indirect benefits on the citizens.

2.2. MEASURES TO MAXIMISE IMPACT

2.2.1. PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

In traditional research, scientists and experts often drive the research activities with a narrow and incomplete understanding of the needs of end users; in this way, the research findings result poorly aligned with the information needs of the real-world decision-makers. The practice of stakeholder engagement is intended to eliminate this division by actively involving stakeholders across the phases of the research process to ensure the utility and relevance of research results for decision-makers. This Action aims at launching a dialog focused on the needs of end users:
1) private diagnostic/pharmaceutical companies;
2) national regulatory agencies, governments, policy makers, healthcare system managers/providers;
3) charities, foundations and patient organisations.
To involve the stakeholders 1) the SMEs have a fundamental role for the involvement of relevant stakeholders, thanks to the contact with many pharmaceutical companies around the world. Ad hoc meetings with diagnostic/pharmaceutical companies will be planned to present the results of the Action and exchange reciprocal feedback on the further development of biomarkers, drug discovery and toxicology research.
To involve the stakeholders 2) and 3) this COST Action will plan to organize ad hoc scientific/dissemination meetings, involving “disease-oriented” groups, healthcare system managers/providers and all the European and national official institutions and authorities interested to maximise the benefits of the research against MDR tumors.
Moreover, all the dissemination tools presented in paragraph 2.2.2. will contribute to involve the stakeholders in the Action activities.

2.2.2. DISSEMINATION AND/OR EXPLOITATION PLAN

Dissemination and management of knowledge coming from the Action will be realized by external communication activities. Due to the particularly high health, social, economic and industrial impact of the research results, target groups for dissemination will be identified, and will include:
-secondary disseminators (e.g. journalists, national and international foundations for the diffusion of information on health, scientific associations),
-the broad scientific community, including both academia and industry,
-ESRs,
-decision-makers and leaders of health policies and legislation,
-health operators (hospitals, associations of preventive medicine, specialized clinicians, general practitioners),

-patients organisations.
The strategy for the dissemination and management of knowledge coming from the Action will take place through: COST Action website and Virtual Forum; COST Action leaflet; open access scientific articles, book chapters, meeting proceedings; conferences, meetings, seminars participation and organization; audiovisual production (project video and interviews); lay press and social media; training schools organization.
An Action-specific website will be built and dedicated to the Action to promote scientific discussion for the specialists and to raise public awareness, with appropriate access for experts and non-experts. The Management Committee (MC) will assign this task to a partner (web-site coordinator). The website will show the structure of the WGs, provide links to the participants' websites and to related institutions and organizations, announce events (workshops, conferences, etc.), list the publications of the participants and the proceedings of meetings, and contain audiovisual production and material from the didactic activities. There will be an accurate security policy, based on encryption techniques and digital keys, to ensure the system integrity and the security of the project critical data. Content will be regular updates, at least every 3 months. Moreover, a centralized "Virtual Forum" will be created for the discussion of the activities of each WGs.
A leaflet will be produced at the beginning of Action describing its objectives and planned activities. This will be distributed to scientists, representatives from the industry, policy and society in major international conferences and meetings.
The scientific results will be communicated in international meetings, symposia and workshops and published in open access peer-reviewed international journals in the form of either original or review articles. These will be published either by a single WG, according to their specific expertise, or by two or more WGs in cooperation. To increase the visibility of the Action, the proceedings of WG meetings and final conference will be published as special issues in international high impact journals.
Dissemination through lay press, social media (Facebook, Twitter, Linkedin), YouTube channel will contribute to raise public participation and awareness.
Moreover, the Action's results will also be communicated to the next generation of scientists, especially originating from developing regions, through training schools.
The interaction with external experts will be pursued through inviting ad hoc clinical and industrial experts to meetings, training schools and conferences, in order to improve the interdisciplinary knowledge, experiences and skills and bring new ideas and cooperation into the Action. The dissemination plan will be updated periodically, to strengthen specific methods, as well as to introduce new measures.
Although the main goal of the Action is to ensure that the scientific and technology related results, outcomes and impacts will be widely shared with the respective research and innovation community, including industry, as well as with EU and national policy makers setting, intellectual property may rise during COST activities. Management, sharing or exploitation of this intellectual property will be regulated by a Consortium Agreement (CA), which will take into account relative contributions and will be formulated by the proponent, discussed and approved by all partners before contract signature. Furthermore, the proprietary issues and protection of innovation will be managed by the technology transfer offices of each partner institution that will work in support to the MC.

2.3. POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

2.3.1. POTENTIAL FOR SCIENTIFIC, TECHNOLOGICAL AND/OR SOCIOECONOMIC INNOVATION BREAKTHROUGHS

The innovative idea at the basis of the Action is that performing an in depth analysis to identify new diagnostic/predictive biomarkers of MDR will aid to rationally design therapeutic tools against MDR tumors that remains still incurable. This approach will:
-produce the first bioinformatic-based platform and the first algorithm for the early diagnosis and/or prediction of MDR phenotype that is missing at the present;
-identify suitable therapeutic targets in MDR cells, in order to select the best drugs (either natural products or synthetic drugs) able to reprogram MDR tumors into drug-sensitive ones.
Biomarkers-driven drug discovery is a necessary tool to finely design a precision medicine for MDR tumors and identify the safest and most selective therapeutic targets.
Natural products have always been important resources either as therapeutic agents or as lead compounds for the synthesis of drugs of pharmaceutical interest.
As for the synthetic chemotherapeutic agents produced in the Action, they represent a strong innovation compared to the conventional cytotoxic agents. Indeed, the new chemotherapeutic drugs proposed by the this COST Action differ from the drugs currently used, because they are tailored on MDR tumors:

by exploiting the metabolic/functional differences at the basis of the MDR phenotype, we will design for the first time drugs able to hit targets selectively present in MDR cancer cells (but not in chemosensitive or non- transformed cells). The creation of new multi-target drugs by engineering existing drugs represents another technological breakthrough innovation of the Action. The design of new compound series is primarily based on the exact knowledge of the potential cell targets: by unveiling new therapeutic targets in MDR cells, this Action will further aid to optimize the synthesis of targeted compounds active on resistant tumors.
Given the short time, this Action created a consortium of experts in all the above-mentioned fields: computational biology and high-throughput analysis of biomarkers in resistant tumors, library of natural and synthetic compounds reversing MDR, safety analysis of the lead compounds have been already realized by the partners involved in this Action. This broad range of expertise constitutes a solid basis that will be deeply developed throughout the Action.
The development of industrial technologies in the field of nanotechnology and biotechnology, and the new application of existing or emerging technologies, has been indicated as a priority for the next years by European Institution. The approach of this Action follows exactly this direction, and - again - relies on the consolidated expertise of the partners involved. The participating groups are currently funded by national or international funding bodies for their own research.

3. IMPLEMENTATION

3.1. DESCRIPTION OF THE WORK PLAN

3.1.1. DESCRIPTION OF WORKING GROUPS

This COST Action will be performed by 4 Working Groups (WGs), each with complementary and not overlapping skills and know how. The tasks of each WG will be strictly integrated, thanks to the sharing of biological samples and experimental model systems, the researchers meetings, the STMs. To ensure the maximal level of data reproducibility and the reliable comparison between the results obtained by each partner, at the first MC meeting standardized operative guidelines for the activities of each WG will be established. All participants of the Action will be invited to join one or more of the WGs, according to their expertise and scientific interests.
Common milestones of this COST Action are:
1) build a comprehensive and friendly platform mapping the existing knowledge of MDR phenotype (including gene signatures, causal gene/protein discovery, drug/target networks), in order to improve and speed up the discovery of new diagnostic/predictive biomarkers and new therapeutic targets specific for MDR solid tumors;
2) develop innovative and safe pharmacological approaches, rationally designed on the basis of the new potential therapeutic targets identified, effective and specific against MDR solid tumors;
3) participate to WGs, MC, SG meetings, annual conferences, workshops, final conference;
4) favour the training and the transfer of knowledge between ESRs.
Common deliverables of the project are:
1) STMs of ESRs among laboratories involved in the Action;
2) reports on WG, MC, SG meetings, workshops, annual conferences, STMs, final conference;
3) joint publications in peer-reviewed journals, dissemination of results in conferences, meetings, social media (Facebook, Twitter, Linkedin), YouTube channel and through Action website.

WG1
Objectives
- Analysis of the available data-resources on large clinical cohort of patients bearing solid tumors by bioinformatic and computational biology, to quickly integrate data of gene expression profile, proteome, RNOme/miRNOME profile in chemosensitive and isogenic MDR cancer cells, in order to identify new biomarkers predictive/diagnostic of MDR phenotype and new therapeutic targets in MDR tumors.
- Identification of specific biomarkers/therapeutic targets involved in the MDR phenotype of cancer stem cells (CSCs).
- Identification of specific biomarkers/therapeutic targets involved in the intercellular transfer of MDR phenotype, focusing on microvesicles released by MDR tumors.
- Assessment of the clinical robustness of the identified biomarkers on primary MDR tumors.
- Creation of a starting hub for WG2 to properly refine drug design/selection of natural compounds, for WG3 for the biological efficacy assay, for WG4 to verify the safety of hitting a specific therapeutic target, thanks to high-throughput pharmacogenomic and pharmacoproteomic analyses.

Tasks
- Analysis of data-resources available to quickly map the existing knowledge of genomic, transcriptomic, proteomic and pharmacogenomics profile of MDR tumors
- Development and implementation of methods for "omics data analysis" focusing on the integration of genomic, transcriptomic, proteomic and pharmacogenomics data in order to identify gene signatures, interactomes and protein networks typical of MDR tumors
- Development and implementation of pathways analysis tools discriminating MDR and not-MDR tumors
- Sharing samples [chemosensitive and isogenic MDR cell lines, primary MDR tumors, circulating cells, biological samples (urine, blood)] obtained from patients bearing MDR tumors, and extracellular vesicles obtained from MDR cell lines.
- Identifying new biomarkers predictive/diagnostic of MDR phenotype and new therapeutic targets common to the majority of MDR tumors.
- Identifying new biomarkers predictive/diagnostic responsible for the MDR phenotype of CSCs and new therapeutic targets in CSCs.
- Identifying new biomarkers and new therapeutic targets involved in the intercellular transfer of MDR phenotype.

Activities
- Analysis of whole transcriptome using RNA microarray in MDR samples.
- Analysis of copy number variation (CNV) and (single nucleotide polymorphism (SNPs) of specific genes that increase the susceptibility to develop tumors resistant to chemotherapy.
- Analysis of the proteome and surfaceome of MDR samples.
- Analysis of microRNAs and other non-coding RNAs expressed in MDR samples.
- Analysis of CSCs pathways related to MDR, in particular in aldehyde dehydrogenase-positive (ALDH+)-clones, which are the most chemoresistant tumor clones.
- Analysis of the protein, microRNA and RNA present in extracellular vesicles (such as exosomes or microvesicles), as potential mediators of the intercellular transfer of MDR phenotype and potential therapeutic targets to block this event.
- Set up a paradigmatic screening platform for the diagnosis/prediction of MDR phenotype, by integrating the different OMICS screening performed by the partners of WG and verify its robustness on samples from patients with MDR tumors.
- Transfer the necessary information for drug design/selection of natural compounds, efficacy and safety assays to WG2, WG3, WG4 and remodulate the search for further therapeutic targets according to the feedback received by other WG.

Deliverables
- Identification of new biomarkers and therapeutic targets of MDR tumors, validated in different tumor types and samples (cell lines, primary tumors, circulating cells, other biological samples, extracellular vesicles).
- Training schools on OMICS techniques, single cell as well as extracellular vesicles analysis assays.

Milestones
- Comprehensive review of the data-resources available and their implementation by computational biology tools, to set up a common – and progressively updated - platform of genomic, transcriptomic, proteomic and pharmacogenomic knowledge on MDR phenotype, intended as starting point for WG2-4 activities and innovative tool available for the scientific community.
- Set up a shared collection of MDR samples, thus creating a standardized tool to identify and validate potential biomarkers and therapeutic targets of MDR tumors.
- Mid-term reviews on the new technological frontiers in the diagnosis of MDR

WG2

Objectives
- Application of computational biology tools to identify drug-target networks to support the rational design of compounds active against MDR tumors
- Application of ligand- and structure-based approaches to support identification and rational design of bioactive compounds as modulators of MDR in tumor cells.
- Identification of new substances that can be used to modulate the transport activity of some ABC-transporters (P-gp, MRP1, MRP2, BCRP).
- Realization of new pharmacological tools, starting from natural products or synthetic drugs useful to clarify the MDR mechanisms, that could be tested by WG3 and WG4.

Tasks
- Analysis of protein-drug interactions and drug-target bipartite networks in MDR cancer cells
- Leads and target identification.
- Synthesis, through a rational design, of small libraries of compounds to deduce structure-activity and structure-property relationships.

- Optimization of pharmacokinetic properties.
- Improving selectivity of drug targeting using folic acid-conjugated liposomes and albumin-conjugated nanocarriers.

Activities

- Analysis of the current needs and trends in design and synthesis of MDR modulating drugs.
- Use of contemporary methods like high-throughput synthesis, solution- and solid-phase multiple-parallel approaches, microwave approach.
- Virtual screening to locate new lead compounds.
- Interpretation of the biological data by standard 2D and 3D QSAR methods to optimize the existing lead structures.
- Use of bioisostere replacement methods to predict chemically novel alternatives for existing active compounds.
- Selection of validated as well promising and innovative pharmacological targets.
- Synthesis of novel prodrug systems -specifically targeting the malignant tumor tissue-, by binding the most promising compounds to albumin-based nanocarriers.
- Encapsulation of new promising compounds in biocompatible nanoparticles like liposomes that could accumulate in cancer tissue via EPR effect, and then undergo degradation leading to the release of the entrapped compounds in the cancer cells as free drug, obtaining a safer profile.
- Encapsulation of the best compound in folic acid-conjugated liposomes in order to increase the tumor selectivity and, consequently, improve the therapeutic outcome.

Deliverables

- Planning and coordination of the research capacities for in silico design.
- Realisation of new chemical tools able either to show cytotoxic activity on MDR cells, test performed by WG3, or to help the identification of MDR mechanisms studied by WG1.
- Delivery of the most promising compounds by liposomes and albumin-based nanocarriers to obtain an improved targeting towards MDR cells, to be confirmed by WG3 and WG4.
- Organization and participation in training schools on in silico methods to support lead generation and optimization in anticancer drug discovery and MDR overcoming.

Milestones

- Realize a library of new antitumor compounds acting on MDR cell lines or able to elucidate MDR mechanisms.
- Identify one or more lead compounds to be developed on the basis of the WGs interconnections
- Create knowledge (e.g. SAR, pharmacological and pharmacokinetic/ADMET profiles) in the field of MDR-reversing compounds which could speed up pre-clinical studies.
- Write mid-term reviews on the new potential drugs challenging MDR.

WG3

Objectives

- Evaluation of the efficacy of synthetic and natural compounds, and their formulations developed by WG2:

a) against the variety of samples (MDR cells lines, CSCs, primary samples derived from patients studied by WG1) in in vitro and in vivo;
b) against the pro-invasive behaviour of MDR cells;
c) on the activation of the host immune system against MDR tumors;
d) on the process of the intercellular transfer of the MDR phenotype by targeting proper biomarkers carried by MDR tumor-released microvesicles.

Tasks

- Building a database of the compounds developed by WG2, correlated with the therapeutic target hit (identified by WG1) and the safety profile of the drug (studied by WG4).
- Analysing the synergisms between the compounds and formulations developed by WG2 or natural products and canonical chemotherapeutic drugs.
- Studying the impact of the compounds and formulations developed by WG2 on peculiar aspects of MDR phenotype, such as stemness, resistance to the host immune system, invasion, MDR intercellular transfer.

Activities

- Creation and update of the compounds database every 6 months, favouring the exchange of compounds by proper Material Transfer Agreements between the Actions partners' Institutions.
- In vitro evaluation of synthetic and natural compounds cytotoxicity against MDR tumors by methods shared by all WG partners, using various MDR samples, screened in depth by WG1.
- Analysis of the synergisms between the compounds and formulations developed by WG2 and conventional chemotherapeutic drugs already used in the clinical practice, using IC50 calculation and

proper software; decision-maker policy with the clinical oncologists to develop the most easy-to-use assays and the most significant parameters to verify on primary samples from patients.
- Analysis of the effects of compounds developed by WG2 on: the expression, activity and localization of ABC transporters (Pgp, MRP1, BCRP); the pathways inducing chemoresistance in CSCs tumors, in particular in ALDH+ CSCs clones; the energy metabolisms, mitochondria functions and endoplasmic reticulum functions of MDR cells; the pathways involved in tumor invasion in MDR cells; the immune system activity against MDR cells; the changes in protein, RNA and miRNA carried by extracellular vesicles and responsible for the intercellular transfer of MDR phenotype in cell lines and xenografts.
Deliverables
- Integration between WG2 and WG3, by providing a unique database of compounds and protocols to validate the compounds efficacy in vitro and in vivo; between WG1 and WG3, by indicating which and how the biomarkers/therapeutic targets change expression and activity after the treatment of MDR samples; between WG4 and WG3, by refining the choice of the compounds on the basis of their anti-tumor efficacy and their safety profile.
- Validation of the most promising compounds and formulations developed by WG2 as agents targeting peculiar aspects of MDR phenotype (e.g. stemness properties, tumor energy metabolism, endoplasmic reticulum functions, tumor-immune system interaction, invasion properties, intercellular transfer of MDR).
- Training schools on in vitro and in vivo experimental approaches to validate the antitumor properties of new compounds active against MDR tumors.
Milestones
- Development and implementation of computational biology tools supporting the rational design of compounds, by quickly analysing data-resources available on drug-target networks or unveiling druggable targets in MDR tumors
- Set up a unique database of compounds and of methodological approaches, carefully evaluated together with clinical oncologists, that may represent the golden standard for the future validation of the cytotoxic efficacy of unknown compounds against MDR tumors.
- Investigate simultaneously the effects of the compounds developed by WG2 on the ABC transporters functions and on several other aspects of the MDR phenotype, thanks to the multiple collaborations that will be established between the researchers involved in the Action.
- Write mid-term reviews on the methodological approaches used to evaluate the efficacy of unknown compounds on MDR tumors.

WG4
Objectives
- Pharmacokinetic and ADME-Toxicology evaluation of synthetic and natural compounds and their formulations (developed by WG2, correlated with the therapeutic targets identified by WG1 and tested for their efficacy by WG3) by a series of in silico, in vitro and in vivo assays.
- Safety assessment of the hitting therapeutic target identified by WG1
Tasks
- In silico toxicity prediction
- Metabolic stability assessment, metabolite profiling and identification, drug-drug interaction appraisal
- Pharmacokinetic profile characterization
- Acute and long-term cardiovascular and hepatic toxicity assessment
Activities
- Design and set-up in silico models and filters for metabolic properties, cardio- and hepato-toxicity
- Assessment of metabolic stability in human microsomes and hepatocytes by LC/MS analysis.
- Metabolite profiling and identification in rat and human microsomes by mass spectrometric techniques.
- Evaluation of drug-drug interaction in human and rat liver microsomes, rat liver precision cut slices, human HEPG2 cells and freshly isolated rat hepatocytes by using specific substrates and markers of CYP450 enzymes activities.
- In vivo analysis of pharmacokinetic parameters: Tmax, C max, AUC0-t, AUCt-∞, F, t½, Vd, Cltot.
- Evaluation of viability, mitochondrial function, apoptosis, autophagy, and redox state in cardiac and vascular myocytes, endothelial cells and hepatocytes.
- Evaluation of the effects on Ca2+, Na+ and K+ channels (in particular Kv11.1, the target of virtually all QT interval-prolonging drugs) in cardiac and vascular myocytes, and hERG-HEK293 cell line.
- Evaluation of vascular responsiveness to various agents in vascular preparations.
- Evaluation of cardiac function and ECG recording in Langendorff-perfused rat/guinea pig heart.
- Assessment of cardiac damage in both/either homogenized hearts and/or concentrated coronary effluent (assessment of creatine kinase and troponin T, NT-proBNP).
- Evaluation of plasma alanine or aspartate aminotransferase, bilirubin, alkaline phosphatase, keratin18

All the above analysis refer to synthetic and natural compounds and formulations developed by WG2 and tested for their efficacy by WG3.
Viability assessment of hepatocytes or cardiomyocytes in which the gene coding for therapeutic targets identified by WG1 will be silenced by RNAinterference.

Deliverables

- Optimization of the lead compound/s (developed by WG2, correlated with the therapeutic targets identified by WG1, and tested for their efficacy by WG3) on the basis of the pharmacokinetic and ADME-Toxicology properties.
- Optimization of therapeutic targets identified by WG1
- Training school on computational and experimental toxicology.

Milestones

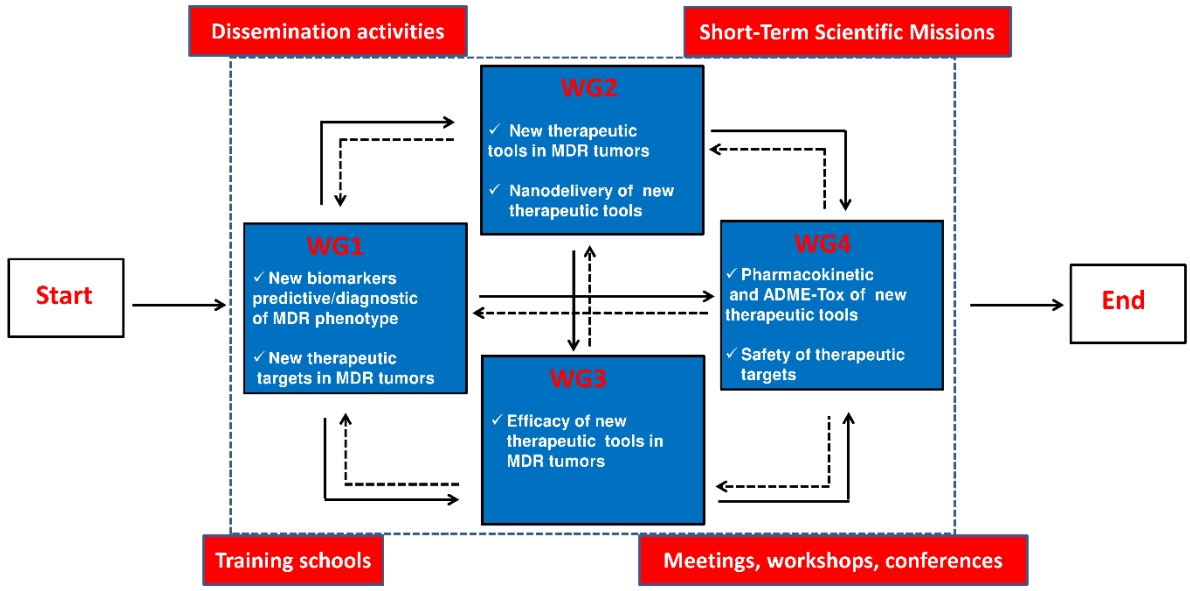
- Generation of reliable in silico models.
- Optimization of analytical methodology for hepatic metabolism as well as cardiovascular and hepatic safety end-points.
- Promotion of Action researchers' collaborations to identify either promising compounds, endowed with MDR reverting activity and devoid of cardiovascular and hepatic toxicity, or novel and safe therapeutic targets
- Write mid-term reviews on the methodological approaches used to evaluate either the pharmacokinetic and ADME-Toxicology profile of novel compounds or the safety of novel therapeutic targets, also in cooperation with one or more WGs.

3.1.2. GANTT DIAGRAM

MCM = Management Committee Meeting
SGM = Steering Group Meeting
WGM = Working Group Meeting

Activity	***Year 1***				***Year 2***				***Year 3***				***Year 4***			
	1/4	1/2	3/4	1	1/4	1/2	3/4	1	1/4	1/2	3/4	1	1/4	1/2	3/4	1
First MCM	X															
MCM				X				X				X				
WGM			X				X				X				X	
Training School						X				X				X		
SGM				X				X				X		X		X
Workshop				X				X				X				X
STSMs	X				X				X				X			
Action annual conference				X				X				X				
Web site set-up		X														
Web site update			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Closing Conference																X

3.1.3. PERT CHART (OPTIONAL)



3.1.4. RISK AND CONTINGENCY PLANS

This Action aims to setting up an algorithm for the diagnosis/prediction of the MDR phenotype, thanks to the identification of several biomarkers associated with MDR tumors (WG1). It may occur that only few biomarkers have a sufficiently high predictive/diagnostic value. Different expertise in the field of biomarker discovery are present in Action in order to successfully achieve some significant results by combining and integrating the different approaches. If other expertise are needed in the field of biomarkers discovery (i.e. groups with a strong background on metabolomics, circulating nuclear acids, etc.), new partners with these specific expertise and technologies will be actively involved thanks to the dynamic structure of the COST Action.

The scientific history of MDR-reversing strategies has been characterized by repeated failures; although this Action proposes different strategies from those followed in the past, a potential pitfall is that the pharmacological tools realized in the Action do not achieve sufficient efficacy and specificity to produce therapeutic benefits in vivo, have an excessively high toxicity or an unfavourable pharmacokinetic profile. As for the biomarkers field, different know-how are present in this Action for the identification of therapeutic targets and production of innovative therapeutic tools: it will be not exceedingly difficult change technical strategies of design, synthesis and formulation of the compounds, if we verify that some compounds are ineffective or toxic. Also in this case, further partners may be recruited to support the Action to meet specific needs. Even if no compounds reach a significant efficacy against MDR tumors or results toxic for their safety pharmacology profile, this action will be useful in a diagnostic perspective. Indeed, the only expression levels of surface drug efflux transporters are not sufficient to determine how and if a tumor responds to chemotherapy. By discovering new biomarkers associated with the MDR phenotype, this Action may represent the starting point to plan future clinical screenings.

Since the resistance of tumors to conventional chemotherapeutic drugs, as well as to new targeted-therapy agents, is very rapidly induced, it is not possible to exclude that resistance to the natural products used and to the new pharmacological tools produced will arise. This issue will be investigated in animal models, where mice are exposed to the compounds for prolonged times: the changes in MDR biomarkers in the propagated tumors, will periodically assess in order to verify whether new markers of chemoresistance, indicative of a secondary resistance, appear.

Translational projects require the integration of many scientific disciplines and breaking down of the cultural barrier that sometimes exist between the disciplines. Interdisciplinary meetings and seminars can help break down these barriers.

The measure of success in translational research is best not defined in terms of drugs produced or first-in-human trials because the associated time-scaled and success rates are prohibitive. Although these may be the ultimate goals, other successful outcomes of translational research can be equally compelling. Developing probes to understand biological mechanisms, enhancing research funding, building collaborations with an industry partner can all be viewed as successful outcomes.

Overall, even in the worst perspective (i.e. failure to identify a consistent number of biomarkers and compounds effective against MDR tumors), this COST Action will generate new insights into the MDR field at diagnostic and therapeutic level. The results obtained will guide other researches to select the best strategy for diagnosis and treatment of MDR tumors, and/or to avoid specific strategies/tools that

have failed in this Action. Moreover, independently on the experimental results obtained, this Action will create the basis for a scientific network able to apply to further COST Actions and European-funding opportunities.

3.2. MANAGEMENT STRUCTURES AND PROCEDURES

The main goal of this COST Action is to establish a network of researchers (from SMEs and Universities) with complementary and interdisciplinary expertise in MDR tumors. Their core funding is assured by different national and international programs, but this Action will support future grant applications. This Action will implement the following organisational structures according to the Cost document (132/14) "Rules for Participation in and Implementation of COST Activities":
1) The Management Committee (MC, representatives from each signatory country), will oversee all planning and coordination during the Action.
MC will elect the Action Chair and Vice-Chair during the first MC meeting and also the Grant Holder, an established legal entity, of which one of the MC members must be affiliated to.
The MC will plan, define and approve the Action's scientific activities and the WGs composition or membership, leadership and structure, and will monitor the milestones achievements and timeline. Moreover MC will establish specific provisions linked to the management, share, creation, dissemination or exploitation of knowledge, including Open Access policy and management of IP that may rise from an Action. The MC will approve the admission of new partners. Future partners will be welcome and integrated in the existing structure. The MC will meet once a year for the duration of the Action and will remain in close contact at other times.
2) For administration and implementation, a Steering Group (SG) will be formed, comprising the Chair, the vice Chair and up to four selected MC members or experts (one of whom will act as STMS manager). One member will be an ESR. The SG will be responsible for routine matters, information for the MC and WG meetings, preparation of required documents, such as annual reports and web site content. The SG will use electronic and virtual communication on a regular basis and will meet once a year.
Four highly integrated WGs will be formed according to expertise (see 3.1). Collaborations between WGs will provide a truly innovative environment for the scientific programme of this Action and contribute to the achievement of Action objectives. Conferences, workshops, Training Schools and STMSMs will channel and implement WGs work.
Each WG will hold an annual meeting to present new results, discuss them in depth and plan the way forward, in addition to the annual meetings of the full Action.

Each WG will have a WG leader and a deputy-WG leader (the latter, wherever feasible, being an ESR) elected by the MC. WG leaders will organise the schedule of the WG meetings in coordination with the MC, and will lead the scientific discussions and report to the MC on progress once a year.
Both the MC and the WGs will meet at least once a year in different member countries. The same sessions will usually also comprise Action's plenary meetings and workshops in order to gather most of interested partners and reduce their travel costs.
This COST Action will respect an appropriate gender balance in all its activities and will encourage participation of young talented researchers to build up the next generation of leaders in science and technology.
One training school will be organized during the second and third, two training schools during the fourth year of the Action. Six-eight STSMs in the first year and at least ten in the subsequent years will enable the best collaboration between the research teams and good training for ESRs.

3.3. NETWORK AS A WHOLE

The network of this Action includes partners with complementary and non overlapping know-how and expertise ranging from, granting to each partner the access to high-level technical facilities. The network is composed by partners experts in:
- bio-informatic and computational biology tools (genome, transcriptome, proteome, interactome, pharmacogenomics, pathways and drug/target networks analyses): these skills will help the network to quickly achieve a baseline knowledge of different features of MDR phenotype and to develop its own computational tools to integrate the already known information with the newly acquired knowledge. This comprehensive platform will represent a unique and innovative tool, available for the scientific community working on MDR tumors, and will speed-up the results sharing and dissemination of the results;
- high-throughput screening techniques (i.e. genome, transcriptome, RNome/miRNome, proteome and surfaceome analysis), that will be strictly integrated: thanks to the multiple approaches used, the network

will be able to successfully identify different types of biomarkers associated with MDR phenotype, useful in a diagnostic and in a therapeutic perspective;
- in silico design of pharmacological compounds, molecular modelling, rational synthesis of new antitumor compounds: the integration of these expertise will enable the network to produce a high number of compounds tailored on the metabolic/molecular features of MDR cells, increasing the possibility of obtaining compounds effective against MDR tumors;
- chemosensitizing properties of natural products: these products represent further and/or alternative tools to the synthetic compounds in killing MDR cells;
- nanotechnology-based drug delivery systems: the use of nanotechnology-based systems is an added value, since it increases the specificity of drug delivery towards tumor cells, by the active targeting of the compounds;
- different aspects of in vitro and in vivo biology of MDR tumors (i.e. correlation between MDR and stemness, MDR and immune system response, MDR and cell invasion, mechanisms of intercellular MDR transfer): the integration of these different expertise will aid the identification of reliable biomarkers predictive/diagnostic of specific aspects of MDR phenotype and will increase the possibility of finding compounds targeting specific pathways activated in MDR tumors and crucial for MDR cell survival;
-computational toxicology, CVD cardiovascular and hepatic safety, metabolic stability and biotransformation of the compounds: these expertise will help to select the compounds endowed by the greatest efficacy against MDR tumors, the greatest safety and the most favourable pharmacokinetic profile, suitable for a further development in pre-clinical applications.
- strict interaction with medical oncologists, to receive feedback on the clinical robustness of the identified biomarkers/therapeutic targets and on the potential translation of the developed compounds/formulations.
SMEs participation in this Action are included in the network: their involvement is crucial to support the research and for the training of high-level young European ESRs. As well, the SMEs have a fundamental role for the project results dissemination for the involvement of relevant stakeholders, thanks to their contact with many pharmaceutical companies around the world. At the same time, SMEs may be strongly interested in building a network of contacts, in order to closely follow up on the new advances in the field of MDR tumors, borrow infrastructures and obtain specific advice and feedbacks beyond formal contracts. The multiple expertise present in the network will represent a unique opportunity for the scientific growth of ESRs, who will be enabled to gain new skills and know how, and to develop new collaborative mini-projects framed in the scope of this Action.