Brussels, 13 April 2018

COST 060/18

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "Cancer nanomedicine - from the bench to the bedside" (NANO2CLINIC) CA17140**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Cancer nanomedicine - from the bench to the bedside 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 CA17140
CANCER NANOMEDICINE - FROM THE BENCH TO THE BEDSIDE (NANO2CLINIC)

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 develop nanosystems carrying anticancer drugs from their initial design, pre-clinical testing of efficacy, pharmacokinetics and toxicity to the preparation of protocols needed for the first phase of their clinical studies. 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 84 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
Finding efficient cancer therapies is an urgent and still unresolved problem and, in the fight against this disease, scientists are devoting tremendous efforts towards the utilization of nanomedicines. Nanotherapeutics exhibit major benefits with respect to unmodified drugs, including improved half-life, more efficient tumour targeting, and reduced side effects. However, only a few nanotherapeutics have reached the commercial level, most still being in the investigational phase. Accordingly, this Action aims at developing and strengthening industry-academia relations with an ultimate goal: fostering the clinical translation of nanomedicine from bench to bedside. This will be achieved by creating the first, pan-European interdisciplinary network of representatives from academic institutions and small and medium enterprises including clinical research organizations (CROs) devoted to the development of nanosystems carrying anticancer drugs from their initial design, pre-clinical testing of efficacy, pharmacokinetics and toxicity to the preparation of detailed protocols needed for the first phase of their clinical studies. By promoting scientific exchanges, technological implementation and innovative solutions, the Action will provide a timely instrument to rationalize and focus research efforts at the EU level in dealing with the grand challenge of nanomedicine translation in cancer, one of the major and societal-burdening human pathologies. By virtue of its quality, the Action network will also generate research core teams of excellence for funding applications, patent filling and discovery of major scientific impact. The network will also be actively devoted to raising awareness on the high potential on nanomedicine through publications in international peer-reviewed journals, and presentations at open events.

Areas of Expertise Relevant for the Action	**Keywords**
● Nano-technology: Nano-technology for pharmaceutical applications	● nanomedicine ● cancer ● drug carrier ● translational research ● targeted therapy

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

Research Coordination
● Promoting and fostering active and multidisciplinary collaborations between industry and academia on each aspect of the design, development, and translation of cancer nanomedical agents
● Fostering synergies between complementary EU groups of excellence, thereby expanding the network beyond existing collaborations between Action partners, with particular attention to the strong, active involvement of SMEs, regulatory agencies, academic clinical research centers, clinical research organizations, and other public/industrial entities.
● Promoting cross-pollination of competencies and transferring results within the EU actors belonging to public and privates sectors by extensive exchange of PhD students, young researchers and senior scientists, meetings and workshops, and collaborative scientific publications and patents.
● Disseminating results to all potential stakeholders, including public organisms, funding agencies, patients associations and the general public to increase EU citizen awareness of the social benefits of the Action results.

Capacity Building
● Creating strong partnership between academia and industry by the equal participation of these two groups.

● Training and mentoring of young generations of researchers working in academia and industry to pave their way towards autonomous research leadership.
● Ensuring equal opportunities by providing equal access to COST activities, respecting balanced gender distribution.
● Involving participants from less research active countries according to the inclusiveness policy of COST.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. CHALLENGE

1.1.1. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Cancer is a major cause of morbidity and mortality in the world, and its incidence has been steadily increasing since 1980. Cancer kills more people on a global scale than AIDS, malaria and tuberculosis combined and is accounted for 14 million new cases and 8 million related deaths in yearly. In the Western World, cancer represents the second leading cause of death after cardio-vascular diseases. Moreover, the impact of cancer in the developing world is growing at an alarming rate and low and middle income countries are projected to account for two thirds of all cases of cancer worldwide by 2050. Cancer cost in the EU is more than €12 billion yearly, with health care accounting for more than €50 billion.

Nanomedicine is the controlled application of nanotechnology to achieve breakthrough innovations in healthcare. Physical properties of materials change at the nanometer scale and nanomedicine exploits these specific properties to change healthcare treatment paradigms. Early detection of cancer cells is a major opportunity for an accurate diagnosis and efficient treatment. It drastically improves the chance of survival and recovery of patients. Nanoparticles can already be used as innovative contrast agents to improve the performances of imaging techniques as Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, and fluorescence imaging. Nanoparticles can also be used to enhance the signal and better detect cancer biomarkers. These are molecules indicative of the presence of cancer in the body, whether produced by the tumour itself or by the body as a specific response to the presence of the tumour. Last, but certainly not least, nanomedicine products can improve the efficiency of chemical and biological based treatments, e.g., nano-carriers can encapsulate drugs to enable them to reach their target, the tumour, with higher accuracy, thus simultaneously improving treatment efficiency and reducing drug-related toxicity. In 2016, the nanomedicine market was estimated to be between $90 and $120 billion and was projected to steadily increase. 230 nanomedicine products were identified on the market or under clinical development for different therapeutic areas including cancer, diabetes, cardiovascular, neurodegenerative, osteo-articular, infectious diseases, etc. Focusing on cancer prevention, diagnosis and treatment, more than 80 products were identified worldwide under clinical development or on the market (including the first generation of nanomedicine products such as Abraxane, Doxil, DaunoXome, Evacet,Lipo-Dox, MyCare Assays, NanoTherm).

Considering the countless and tireless efforts of academic/industrial groups devoted to the development of cancer nanomedicine around the word, this economical picture is rather gloomy. In fact, just 1/3 of nanomedicines undergoing market/clinical trials are devoted to oncology and, given the facts and figures reported above, only a minute number of the nanomedicinal products that have been conceived and developed find their way from bench to bedside. This is indeed not surprising, as the multidisciplinary translational road of nanomedicines is still poorly paved and hampered by several major obstacles, which include (aside from the obvious scientific and technological inherent difficulties), regulatory, industrial scale/up and quality control aspects just to name a few.

In this scenario, this Action will directly address, for the first time, all translational aspects of cancer nanomedicine from a comprehensive and multidisciplinary perspective, thereby yielding i) an unprecedented, comprehensive knowledge in the field and ii) a fundamental contribution by removing those critical hurdles in developing effective cancer-targeting nanomedicines, which, nowadays, impede both the effective application of nanotechnology in medical applications and the subsequent definition of rationally-conceived clinical trial based nanomedicines. To face this ambitious goal, the Action aims at networking EU scientists as well as those in neighbouring countries involved in cancer nanomedicines. Indeed, laboratories of excellence in nanomedicine research (both in academia and R&D departments of companies) from 21 different EU countries have already pioneered major discoveries in the field. These groups cover a wide range of expertise with the involvement of organic and medicinal chemists, cell physiologists, structural and molecular biologists/biochemists, and *in vitro* and *in vivo* pharmacologists and clinicians. By promoting scientific exchanges, technological implementation and innovative solutions among both academic and industrial partners, the Action will rationalize and focus research efforts at the EU level in dealing with the grand and timely challenge of nanomedicine translation in cancer, one of the major and societal-burdening human pathologies. The quality of the Action network also guarantees the critical mass for the aggregation of research core teams of excellence for further funding applications (e.g., H2020 calls, EraNet calls and IMI initiatives), major scientific impacts (e.g., via public dissemination in international peer-reviewed journals, conferences and events open to citizens), and patent filings.

1.1.2. RELEVANCE AND TIMELINESS

Cancer is the uncontrolled growth and spread of cells that arises from a change in one single cell. This change may be initiated by external agents and/or inherited genetic factors and can affect almost any part of the body. The transformation from a normal cell into a tumour cell is a multistage process where growths often invade surrounding tissue and can metastasize to distant sites. Developing nanomedicines able to stop the disease along this complex and winding pathway is an incredibly daunting task. The EU is currently strongly promoting and supporting public and private efforts towards increasing human well-being, overall health, and ageing of EU citizens. For instance, within H2020 much of the financial strategy is focused on cancer-treatment related topics. This Action, by assembling and organizing a complete field of research with potential outcomes in cancer nanomedicine development, is therefore coherent with EU priorities. Cancer poses an enormous societal challenge to Europe. Across the EU, the health-care costs of cancer have been estimated to be equivalent to €102 per citizen, but with substantial variation from €16 per person in Bulgaria to €184 per person in Luxembourg. Productivity losses because of early death cost €42.6 billion and lost working days €9.43 billion. In this scenario, proposing the present Action is therefore appropriate not only scientifically but also in its timeliness. In fact, this Action will set up the first pan-European, multidisciplinary task force to achieve an unprecedented, multifaceted knowledge of cancer-targeting nanomedicines and to foster its translational research in the prevention, diagnosis and cure of some of the most troublesome, currently socially burdensome diseases.

1.2. OBJECTIVES

1.2.1. RESEARCH COORDINATION OBJECTIVES

Moving cancer nanomedicines from bench to market is a long, inherently multidisciplinary pathway that requires the tight, intertwined contribution of highly qualified scientists, regulatory entities, enterprises and medical practitioners. The EU is in the prominent position of having the required, highly qualified expertise residing in its member States. Therefore, this Action will gather them together with the eventual aim of removing at least some of the major obstacles that hamper the translational aspects of cancer nanomedicine. From this perspective, this Action has four major aims:

● **to promote and foster active and multidisciplinary collaborations** on each aspect of the design, development, and translation of cancer nanomedicinal agents in order to advance global, fundamental knowledge, to address actual unsolved questions, and accelerate major discoveries

in cancer nanomedicine research, to ultimate benefit health of EU society. To foster the translational route from nanomedicine design and discovery to its pre-clinical validation, this Action will create a whole new community of people cross-trained in computational biology and drug design, biology, biochemistry, toxicology, pharmacology, physics, and medicine. The jointed efforts of this new multidisciplinary community will not only yield a more holistic picture of this complex trail but the tight feed-forward and feed-back flow of information from the lowest (i.e., design and synthesis) to the highest (i.e., in vivo assays) biological levels involved - combined with the massive use of computational nanomedicine at each step of this inherently multiscale pathway - will ensure the translational steps to be successfully reached within the Action timeframe;

● **to foster synergies between complementary EU groups of excellence**, thereby expanding the network beyond existing collaborations between Action partners, with particular attention to the strong, active involvement of SMEs, regulatory agencies, academic clinical research centers, clinical research organizations (CROs) and other public/industrial entities from the very beginning of the Action activity. The constitution of this blended academic, industrial and regulatory network is the major pre-requisite to abate the major hurdles that encumber the successful use of nanomedicines in oncology;

● **to promote cross-pollination of competencies and transfer of results within the EU actors** belonging to public and private sectors by extensive exchange of PhD students, young researchers and senior scientists, meetings and workshops, and collaborative scientific publications and patents. In this perspective, special care will be paid to provide training opportunities for young scientist, to ensure proper gender balance and to promote participation of scientists from emerging EU countries;

● **to disseminate results to all potential stakeholders, including public organisms and funding agencies** and, by means of dedicated didactical events, to patients associations and the general public, to increase EU citizen awareness of the social benefits of the Action results. In particular, this Action will have an important informative and educatory role in that the network will, during these dedicated events, explain and debates – together with expert stakeholders – more general concepts such as what nanomedicines are and what are some of the related, reported risks, which benefits can be derived from the use of nanomedicines, and how should nanomedicine be conceptualize in health and law ethics.

1.2.2. CAPACITY-BUILDING OBJECTIVES

The Action is based on four main pillars: **(1)** strong partnership between academia and industry by the equal participation of these two groups; **(2)** training and mentoring of young generations of researchers working in academia and research & development industrial departments, to pave their way towards autonomous research leadership; **(3)** ensuring equal opportunities by providing equal access to COST initiatives respecting balanced gender distribution; **(4)** involving participants from less active countries according to the inclusiveness policy of the COST.

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

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

Anticancer chemotherapy often involves the use of small molecules such as alkylating agents, anti-metabolites, anti-microtubule agents, topoisomerase and cytotoxic inhibitors. These active agents kill not only highly proliferative cancer cells but also other normally-proliferating cells in different tissues and organs, leading to common side effects such as a compromised immune system, inflammation, ulceration of the GI tract, and cardiotoxicity. The ability to efficiently deliver a drug to a tumour site is dependent on a wide range of factors including circulation time, interactions with the mononuclear phagocyte system, extravasation from circulation at the tumour site, targeting strategy, release from the delivery vehicle, and uptake in cancer cells. Nanotechnology provides the possibility of creating a variety of delivery systems (Fig. 1), where the design constraints are decoupled, allowing new approaches for reducing the unwanted side effects of systemic delivery, increasing tumour accumulation, and improving efficacy.

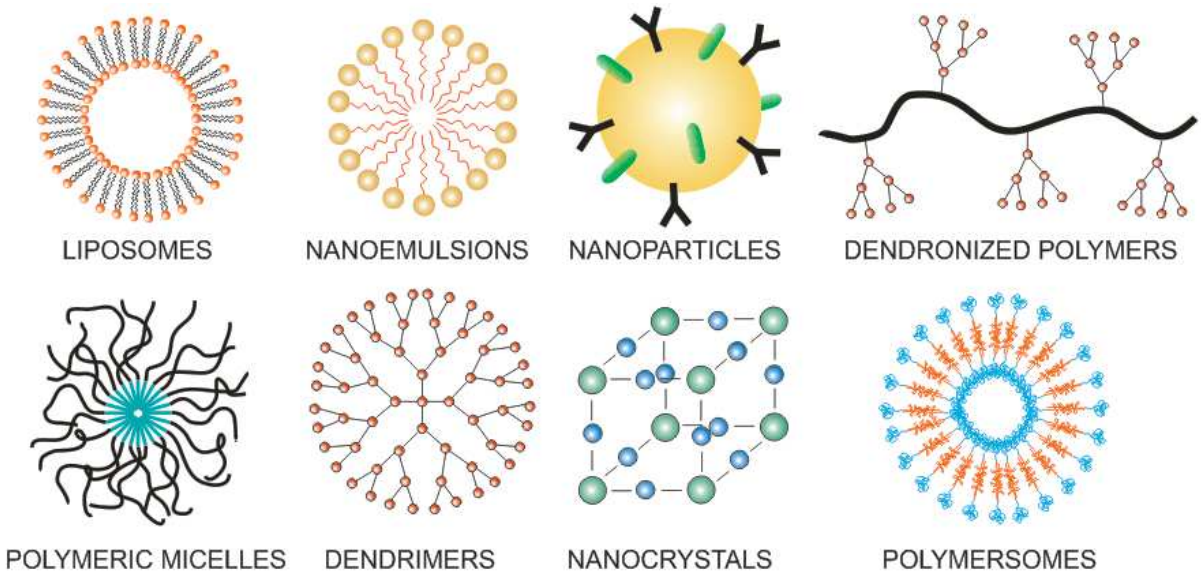
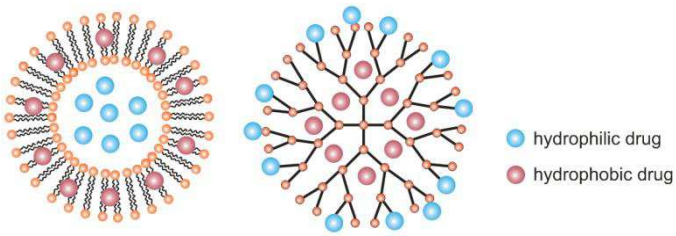


Fig. 1. Examples of nanosystems with pharmaceutical potential (the systems are not drawn to the same scale).



Key properties for drug delivery systems are biocompatibility, stability in circulation, and increasing the fraction of the dose accumulating in the tumour. Drug toxicity can be reduced by encapsulating /binding the free drug in/onto a nanocarrier (Fig. 2) or by locally activating a pro-drug.

Fig. 2. Location of hydrophilic and hydrophobic drugs in a liposome (left) and in a dendrimer (right).

Stability in circulation can be improved by developing strategies to minimize protein binding and evade the immune system. The efficiency of accumulation at a tumour site can be improved by active targeting of the delivery system or by increasing extravasation by the enhanced permeation and retention (EPR) effect.

The FDA-approved nanomedicines in clinical use have demonstrated the potential for increasing bioavailability, enhancing drug solubility, active targeting, and high drug loading. However, there are many challenges in exploiting advances in nanotechnology and bioengineering for the development of systems that will have significant impact on patient survival rates. The development of delivery systems remains largely empirical and the lack of standardization of pre-clinical studies is a barrier to establishing design rules for nanomedicines. While studies of complex systems with combined reporting/sensing functions along with drug delivery may ultimately improve diagnosis and treatment, there are many fundamental issues that need to be addressed to establish the relationship between physico-chemical properties, pharmacokinetics, biodistribution, and survival rates.

There are currently six FDA-approved nanomedicines: Brentuximab vedotin, Trastuzumab emtansine, Doxil, DaunoXome, Marqibo, and Abraxane. The first two are antibody-drug conjugates (ADCs), conceptually one of the simplest nanomedicines with an anticancer drug (vedotin and emtansine, respectively) conjugated to a targeting molecule. Specifically, Brentuximab targets the protein CD30, a glycosylated phosphoprotein expressed by B cells, including B-cell lymphomas, some leukemias, and melanoma cancer stem cells. Trastuzumab targets the human epidermal growth factor receptor 2 (HER2) overexpressed in HER2 positive breast cancer. Since the two drugs vedotin and mertansine are too toxic to be used alone, coupling to a targeting antibody reduces toxic side effects. Doxil, DaunoXom, and Marquibo are liposomal formulations of doxorubicin, daunorubicin, and vincristine, respectively. Doxorubicin encapsulation minimizes side effects, such as cardiotoxicity associated with high doses of the free drug, contributes to stability,

and results in a long circulation half time, thereby increasing tumour accumulation by the EPR effect. DaunoXome and Marqibo are again liposomal formulations encapsulating daunorubicin and vincristine, respectively. In contrast to Doxil, the design strategy for DaunoXome and Marqibo is to promote uptake by the mononuclear phagocyte system, providing a reservoir from which the free drug can enter circulation, similar to a slow infusion. Lastly, Abraxane, is lyophilized human serum albumin non-specifically bound to paclitaxel. Paclitaxel has very low solubility and is administered with the toxic non-ionic solvent Cremophor which can lead to a wide range of allergic reactions. On injection, Abraxane particles dissociate into smaller albumin-paclitaxel complexes or unbound paclitaxel. Since albumin is abundant in circulation, Abraxane provides a reservoir of a very low solubility drug in a non-toxic platform.
This small number of FDA-approved nanosystems briefly described above undeniably highlights the tremendous difficulty in translating even relatively simple nanomedicines from bench to bedside.

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

At present, there are several fundamental problems and technical barriers that still must be understood and overcome in order to progress beyond the current state of the art of cancer nanomedicines. Nanoparticle-based delivery systems provide new opportunities to overcome the limitations associated with traditional drug therapy. However, the physicochemical properties of nanoparticle-based delivery platforms introduce additional complexity associated with nanoparticle surface opsonization (surface 'fouling' by nonspecific protein adsorption), nanoparticle pharmacokinetics, tumour accumulation, biodistribution, biopersistence of nanomaterials and degradation products for long-term safety. Due to the complex nature of nanomedicines it is important to take special considerations of its ADME and pharmacokinetics properties at early stages of the development program. These studies are critical to identify an adequate dose and schedule for the safety/toxicologic studies and the early first-in-human clinical studies.
By gathering together researchers from every branch of science involved, the coordinated activities of the Action Working Groups (WGs) will permit important developments in all these aspects. This Action is well aware that, in order to rapidly harness the potential of nanotechnology to meet the challenge of eliminating suffering and death from cancer in Europe, there are also a number of non-scientific barriers that impede the rapid translation of cancer nanotechnology research into clinically useful, paradigm-changing advances in diagnosing, treating, and preventing cancer. Though too numerous to be described in detail, these potential barriers can be categorized as follows:
***Cross-Disciplinary Collaborations*:** for cancer nanotechnology to have its biggest impact, barriers to multidisciplinary and multiple partner collaborations must fall. This Action is an ideal instrument to overcome such barriers. Specifically, this Action will encourage, promote and increase collaborations among the public, private, and non-profit sectors and reduce overall development risk.
***"Gap" Between Late Discovery and Early Development of Diagnostics and Therapeutics*.** Too many potential products that reach clinical development fail as they move forward because of a lack of solid science to back up regulatory filings. Moreover, to conduct clinical trials, there is insufficient financial and intellectual support for smaller companies to move novel products through the testing and regulatory approval process and, ultimately, failure to match development goals with clinical and patient need. By bringing together research groups from public and private sectors, medical doctors, and other stakeholders, this Action provides an ideal locus to fill this gap at the EU level.
***Regulatory Uncertainty*.** There is no clear regulatory pathway for approval of nanoscale devices, increasing the risk for private-sector development of promising new diagnostics, therapies, and preventive agents. In particular, there is a concern that each new use of a given nanoscale device, such as a particular type of particle, will require full-scale preclinical and clinical testing, a requirement that would dramatically drive up development costs. There is also concern about the difficulty of gaining regulatory approval for nanoscale devices that combine diagnostic and therapeutic modalities or multiple therapeutic agents in the same construct. In this Action, scientists, regulatory entities, clinicians and, above all, industrial partners will work together to elaborate new ideas and schemes for fostering nanomedicine regulatory aspects by addressing specific objectives such, e.g. identifying and discussing the gap in regulatory status of cancer

nanomedicines with the regulatory authorities such as European Medicine Agency (EMA); assessing the available data to define the required proof of concept and toxicology studies, in line with the existing and prospective regulatory guidelines; defining and assessing the level of good laboratory practice (GLP) requirements for in vitro and in vivo studies; setting-up procedures and training for good research practices and quality systems focusing on the research and development of new medicinal products, also taking into account nanosimilars and all types of promising biologicals; and elaborating a tentative roadmap gathering all the relevant information on the nanosystems (a proved methodology and methodological gaps). All of the regulatory affairs activities will be performed by taking into account the EU scientific guidelines: Roadmaps in Nanomedicine Towards 2020: Joint European Commission/ETP Nanomedicine expert report. European Commission/ETP Nanomedicine 2009 [1]; in the framework of the guidelines of medicinal product (GTMP) (Report from the Commission to the European Parliament and the Council in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004).

***Standardization and Characterization*.** Because nanotechnology is such a new field, there are few standards and few reference physical and biological characterization data that researchers can use to choose which nanodevices might be most suitable for a given clinical or research application. A lack of standard assay and characterization methods also makes it difficult to compare results from different laboratories. This Action constitutes a prototypical environment where such issues can be discussed at the EU level.

***Technology Transfer and Knowledge Exchange*.** Cancer nanotechnology is inherently a discipline that will succeed because of its combinatorial nature - any given nanoscale technology or device may be combined with any number of diagnostic, imaging, therapeutic, or preventive agents. As a result, there is a need for new mechanisms for sharing and cross-licensing intellectual property to facilitate technology. This Action is the perfect instrument to achieve this goal by acting as a facilitator among the multiple interest groups and by convening roundtable events for discussion and problem-solving.

In this scenario, this Action, in addition to its canonical missions, aims at holding several workshops and symposia exploring the intersections of nanotechnology and various areas of cancer research, and will solicit input from a broad cross-section of the cancer research and clinical oncology communities. The networked Action Working Groups will discuss how best to apply the lessons of their initial forays into nanotechnology to a concerted translational research effort that will have near-term benefits for patients. The Action will also convene round tables of leaders from the private sector, foundations, patient advocacy groups, academia, and other government agencies to identify new ways of leveraging nanomedicine technology to aid in the battle against cancer.

1.3.3. INNOVATION IN TACKLING THE CHALLENGE

Existing efforts to find new nanotechnology-based therapies for cancer are comprised of fragmented small-scale studies with little communication between scientists and industry. In fact, in the current procedure of drug design, pre-clinical discovery is substantially the work field of academia whereas industry takes the lead in advancing only the few, most promising lead compounds. Moreover, most of the academic work is destined to fail or, at most, constitute material for international journal publications since university and other scientific laboratory researchers are generally unaware of or underestimate the inherent industrial problems underlying successful drug approval, such as scale up, reproducibility, standardization and regulatory issues, just to name a few. **This Action will fill this fundamental gap by virtue of an innovative conception for drug discovery – namely, industry along with experts in pre-clinical and clinical drug discovery and development and in regulatory issues will participate along the entire chain of new nanomedicine conception and production, from bench to bedside.** Upon implementation of this Action, the timeline from preliminary basic results to clinical studies will be substantially shortened. Moreover, by virtue of its interdisciplinary composition, the **Action will also focus on underestimated or underconsidered nanosystems that have not yet reached the clinical practice.** Many of these systems are endowed with great potential, as measured by numerous scientific publications. For instance, when the number of articles about doxorubicin and dendrimers is compared with the number of articles on doxorubicin and liposomes published before the introduction of Doxil (nanoformulation based on liposomes and doxorubicin), it seems that the

critical scientific mass of knowledge has now been achieved to further develop nanoformulations based on dendrimers. Notwithstanding, the final, critical leap to establish e.g. dendrimers as new nanovectors for clinical applications requires the fundamental advancement of technological and regulatory knowledge that only industrial stakeholders can contribute.

1.4. ADDED VALUE OF NETWORKING

1.4.1. IN RELATION TO THE CHALLENGE

As detailed previously, the application of nanotechnology in the field of cancer therapeutics remains an urgent, and yet unsolved, complex issue, mainly due to the poor liaison between academic discoveries and relevant industrial exploitation. To build such a fundamental bridge between these two seemingly separate universes, this Action will constitute a formidable stepping-stone to open an unparalleled and unprecedented opportunity to increase collaboration and networking between basic (i.e. academic) and applied (i.e. industrial) research. As said, all skills necessary to promote major basic scientific discoveries in cancer nanotherapeutics, to develop the best biological tools and candidate molecules for clinical trials, and to address the relevant, fundamental industrial scale up, standardization, and regulatory issues will be gathered in the present Action network.
To reach this ambitious goal, the industrial partners will support each scientific project developed within this Action from the very beginning. Active involvement of the representatives of SMEs will be instrumental in overcoming industry's reluctance to invest in nanotherapeutics and to foster the development of new, efficient, European nano-based medicines.
Representatives from the academic community and industry will meet on a regular basis to discuss the on-going projects during the Action's dedicated conferences and Working Group meetings. Such events will constitute unique opportunities for sharing information and discoveries while, at the same time, they will be venues for indispensable, unbiased and multidisciplinary brainstorming. A new generation of young researchers will especially benefit from Short Term Scientific Missions (STSMs) during which exchanging staff between academia and industry will be prioritized. Therefore, STSMs will help in building partnership and linkages between academia and industry. Results achieved during STSMs will all be presented and discussed, and their efficacy assessed, during the Action's promoted workshops.

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

The Action is in agreement with key recommendations of the document "Contribution of Nanomedicine to Horizon 2020" that encourages projects leading to more efficient translation of nanotechnology [2].

The Action will use the expertise of the European Nanomedicine Characterization Laboratory – a European project founded by the EU framework program Horizon 2020 (e.g. by inviting experts). The European Characterization Laboratory was launched on 1 June 2015 with a clear-cut goal to help bringing more nanomedicine candidates into the clinic and to the market for the benefit of patients and the European pharmaceutical industry [3].

The Action will cooperate with the European Foundation for Clinical Nanomedicine, a non-profit institution aiming at advancing medicine to the benefit of individuals and society through the application of nanoscience. Aiming at prevention, diagnosis and therapy through nanomedicine as well as at exploration of its implications, the European Foundation for Cinical Nanomedicine reaches its goals through support of clinically focussed research and of interaction and information flow between clinicians, researchers, the public, and other stakeholders [4].

Aiming at strengthening the links between academia and industry and to promote the research and application of nanomedicines, this Action will set a link with the European Technology Platform on Nanomedicine (ETPN), an initiative led by industry and supported by the European Commission, addresses the application of nanotechnology to achieve breakthroughs in health care and to intensify innovation in nanobiotechnologies [5].

By virtue of some members of the network, the Action will contact the ongoing EU Actions and Projects in the critically important regulatory field (i.e. PRECIOUS (NMP-11-2015-Nanomedicine therapy for cancer project) “Scaling-up biodegradable nanomedicine for multimodal precision cancer immunotherapy” (www.up2.europe.eu); NABBA (MSCA-ITN-ETN project) “Design and development of advanced nanomedicines to overcome biological barriers and to treat severe diseases” (www.nabbaproject.eu), NANOGLIO (EURONANOMED IIJoint Transnational Call for Proposals (2016) for“EUROPEAN INNOVATIVE RESEARCH & TECHNOLOGICAL DEVELOPMENT PROJECTS IN NANOMEDICINE)“Nanotechnology based immunotherapy for glioblastoma” and NANoREG II (Horizon2020 project) “Development and implementation of Grouping and Safe-by-Design approaches within regulatory frameworks” (www.nanoreg2.eu/structure) and will strongly benefit from active interactions with these parties. Finally, the Action will establish contacts with the plethora of ongoing EU initiatives and projects on similar subjects (e.g., the Innovative MedicineInitiative (IMI), (www.imi.europa.eu/content/ongoing-projects) and the EURONANOMED calls (www.euronanomed.net/joint-calls/all-funded-projects/). Importantly, the actors populating the network of the Action and the projects they will be carrying out in it will constitute an ideal trans-disciplinary competence assembly and critical mass to make applications to the upcoming H2020 dedicated calls in the field.

2. IMPACT

2.1. EXPECTED IMPACT

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

In the modern, industrialized world, cancer has become the most feared of all diseases. It might not be the commonest cause of death yet, occurring much less frequently than death due to heart pathologies, but it has the reputation of usually being a variety of progressive fatal conditions for most of which no ultimate treatment has been discovered. In particular, the psychological cost of the word cancer on the diagnosed patient is tremendous; equally high is the economical impact during the first year after cancer diagnosis, a period of intensive treatment. In this scenario, the discovery of new, efficient and less toxic anti-cancer therapeutics represents a fundamental milestone in relieving both psychological and economical cancer-related burdens. Such an overambitious goal can never be achieved without a genuine, consolidated cooperation between basic (e.g., academic and research groups) and applied (i.e., industrial) researchers and stakeholders. This Action introduces, for the first time, the new concept of matching industry and science representatives in specific projects in cancer therapeutics development. This, in turn, will substantially contribute to strengthening EU research and innovation capacities in the field while, contextually, the new nanomedicines developed during the Action drugs will not only enrich the existing therapeutic resources but, most importantly, will place Europe at the forefront of nanotechnology-in-cancer applications.
In terms of short-term impact, the goals pursued by this Action not only offers potential to address the above challenging issues but it can also provide significant value to pharma portfolios. This Action will contribute in enhancing the drug discovery process by speeding up cancer nanomedicine design, synthesis, production and testing at the pre-clinical level in a reliable way. It will also result in reducing the cost of drug discovery, design and development and will result in the faster introduction of new cost-effective products to the market. The concomitant application of in silico and in vitro biological techniques will exponentially increase the hit rate for promising compounds that can be screened for each target in the pipeline. Nanoformulations with optimal

pharmacokinetics can only be achieved through interdisciplinary research where knowledge from all sources, including organic/inorganic chemistry, polymer synthesis, toxicology, molecular and clinical pharmacology is integrated. In this sense, the implementation of pharmacokinetics/pharmacodynamics strategies at early stages of nanomedicine discovery projects will guide an efficient clinical development strategy.
Therefore, all scientific and practical results emerging from the efforts of this Action represent a great opportunity for the drug industry as a whole, even in a short-term timeframe.
To move beyond short-term cancer management – or single outcomes, like delaying tumour growth using a nanoparticle drug formulation – and to enable long-term or potentially permanent disease management, the field of nanomedicine discovery inevitably needs to be paired with advanced strategies to rapidly determine dosing conditions that can simultaneously optimize for efficacy and safety. This is one of the main objectives of this Action, and the set-up network is perfectly armed to reach this goal in the short term set by its duration. Also in terms of long-term impact, by virtue of its constitutive members and the others who will likely join, the results stemming from this Action may provide new solutions for the millions of people in developing countries who lack access to basic services, including production using little labour, high productivity, low cost, and modest requirements for materials.
In the spirit of the COST framework, this Action will focus on training and mentoring a new generation of researchers working in academia and industry. Besides the laboratory activity, Early Career Investigators will also receive training in (1) the role of publications and (2) patenting, and how these two forms of dissemination results can promote openness of knowledge and technology but on different terms and conditions.
From the business perspective, a further, non-secondary role of nanodrugs is that they offer the ability to reposition and/or extend the economic life of proprietary drugs, and create additional revenue streams, thereby significantly affecting the drug commercialization landscape [6, 7]. Moreover, active agents that failed as conventional formulations due to unacceptable toxicity profiles, poor bioavailability, or solubility issues may be reconfigured as nanoformulations. Business-to-business relationships between SMEs will lead to opening new market opportunities. Creation of new jobs is expected accordingly. It can be easily anticipated that, upon conclusion of the present Action, SMEs and start-ups will continue to pursue research and investment in nanomedical applications.
Finally, efficient international collaborations will be beneficial for groups from less research-intensive countries which also are expected to expand beyond the timeframe of the Action.

2.2. MEASURES TO MAXIMISE IMPACT

2.2.1. PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

The key idea at the core of this Action is the direct involvement of the major stakeholders (i.e., SMEs and other industrial entities) as the Action's partners. Industry will act as host institutions for short-term scientific missions (STSMs), providing not only staff exchange during realization of the projects but, most importantly, enforcing an improved understanding by academics and research organizations of the requirements of the pharmaceutical and medical devices industry and of medical regulators. This last, fundamental activity will be realized by organizing specific training workshops, meetings and schools involving all Action network partners while promoting external participation. In doing so, industrial and regulatory members of the Action network will leverage the results produced during the most successful projects by enforcing the industry-driven quality-by-design concept and implementing the quality guidelines indicated by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which are normally under-considered during pre-clinical nanomedicine development.
Lastly, considering that nanosystems can be divided into two categories: (1) exploited nanotherapeutics with translational success, and (2) underestimated ones that still wait to be fully discovered, good examples from the first group will be studied by using expertise of those who have successfully introduced nanotherapeutics to the market, e.g. by inviting them as experts.

2.2.2. DISSEMINATION AND/OR EXPLOITATION PLAN

The Action will exploit a rich and diversified pathway for results dissemination. Accordingly:
A **website** will be created and regularly updated, both for the partners and general public. It will be managed by the Action's Management Committee (MC) and organised in sections according to the Action's Working Groups (WGs). A restricted area will be accessible only to partners for internal exchange and dissemination of documents such as MC meeting reports, WG activity progress reports, STSM reports and mailing lists. Joint **scientific publications** and **patent filing** among participants from both industrial and academic sectors in peer-reviewed journals and books will be strongly encouraged by the MC. This will constitute a good opportunity to promote the Action and disseminate the main results and progress obtained through common research activities and STSMs. **Open access** publications will be encouraged, to reach the widest readership. Dissemination to the general public will be achieved by **reports to media**, and by organizing **dedicated events** such as Cancer Nanomedicine Awareness weeks in all countries participating in the Action. **Regular reports** will be deposited, which will include a summary of the on-going projects, the planned/achieved objectives, and the main expected/potential impact achieved.
Training schools, workshops and **dissemination meetings** on specific, focused topics will also be organized aiming at detail know-how and expertise transfer and exchange to all partners, especially to Early Career Investigators.
Nanomedicine sometimes receives an unfair negative public reception (often without clear scientific evidence), and to tackle this the Action will popularize knowledge about nanomedicine by maintaining the website and via **social media**.
Finally, as a perspective to the Action, we will establish a Standing Committee of Practitioners (SCP), constituted by the Core Group of the Action (see Management Structure and Procedure), members from industrial partners and a group of appointed lawyers from both parties in order to prepare the most adequate and ethical transfer of the produced knowledge from bench to industry, for the concrete and adequate development of cancer nanomedicines, to bedside, with translational results exploited to drive the design and positively shape the fate of future nanomedicine clinical trials.

2.3. POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

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

The present Action will boost collaboration and coordination of European research in nanomedicine and, particularly, their therapeutic potential and diagnostic impact in cancer. The direct impact of the Action will be to build a strong scientific/industrial network, to enhance well-educated competences in all aspects of nanomedicines, including the too-often neglected issues of, e.g., scale up, standardization and regulatory affairs. This, in turn, will provide unprecedented scientific, technological and/or socioeconomic innovation breakthroughs, in that the European young researchers involved in the Action will forge their minds and their modus operandi in the most comprehensive way, a prerequisite for the successful discovery and *de facto* clinical translation of nanomedicines. More established researchers will equally benefit from this enriched knowledge, and will be thus able to train further generations of junior researchers from this global perspective.
Industry and related stakeholders will also gain enormously from being founder members and an active part of this Action, since, by indicating and imposing the technological but also fundamental criteria essential for clinical application of nanomedicines to the pre-clinical world, they will not only reduce failures and/or poor in vivo performances of the developed nanotech-based therapies, but also, and perhaps most importantly, minimize the time scale to clinic/market. This, in turn, will ultimately benefit society, as people will be able to access more selective, efficient, targeted and less toxic treatments sooner and, likely, at more accessible costs.
Too often nanotechnology scientists concentrate on presenting their results about e.g., nanovectors for cancer therapy to scientific meetings while dedicated presentations to the medical and pharmaceutical communities are neglected. Also, most of those presentations deal with synthetic and characterization details of the newly produced nanotech-based product instead of focusing on e.g., specific medical needs that require improvement and describing how the new nano-entities could address these needs. The philosophy of "If you build it they will come" does not

work in reality, and the ability of nanomedicines to solve specific medical shortcomings needs to be convincingly demonstrated. With this Action, this confidence will be established from the beginning since, for the first time, industry and academia will join their intellectual efforts and share their knowledge from the initial steps of nano-based drug discovery. In actual practice, pharmaceutical companies are (understandably given the underlying economical burden) quite hesitant when it comes to bringing a new potential product into the clinic. Despite depleting pipelines, the pharma mantra of de-risking is very strong, and an overwhelming amount of pre-clinical data is generally expected from (too often) small, investigator-driven trials before pharma is willing to adopt any new product/technology. Therefore, only the fusion of nanotechnology scientists, medical doctors and researchers operating in a clinical setting, with industrial realities from the initial steps of nanomedicine discovery, such as that proposed by the current Action, can boost the clinical translation of nanomedicines.

3. IMPLEMENTATION

3.1. DESCRIPTION OF THE WORK PLAN

3.1.1. DESCRIPTION OF WORKING GROUPS

Working Group 1 – Manufacturing Nanodrugs

Main tasks and activities: efforts of the chemical groups will focus on (a) reducing production costs of nanomaterials and their conjugates with drugs, (b) obtaining high yield of the final product, (c) achieving reproducibility from batch-to-batch. The synthetic protocols will be in accordance with Good Manufacturing Practice (GMP) guidance. Computer scientists will belong to this WG and will assist the experimental groups with the design of new chemical entities, the optimization of existing chemical structures and the formulation of new nanomaterials.

Deliverables **(D)** and Milestones **(MS)**:

D1.1. Protocols and recipes for computer-assisted design/optimization of new/existing chemical entities and/or nanomaterials.
D1.2. Chemical recipes, pathways and mechanisms for the synthesis of new chemical entities and/or nanomaterials.
D1.3. Roadmap and consensus protocols for cost reduction, yield optimization and reproducibility of the chemical entities and/or relevant nanomedicines.
D1.4. Roadmap and consensus protocols for GMP production of chemical entities and nanomedicines.
MS1. Optimized/de novo design, synthesis and GMP production of selected new nanomedicines

Working Group 2 – Physico-Chemical Characterization of Nanodrugs

Main tasks and activities: full physico-chemical characterization nanoproducts. Batch-to-batch consistency of nanoproducts will be verified with effective quality control methods.

Deliverables **(D)** and Milestones **(MS)**:

D2.1. Consensus protocols for full physico-chemical characterization of nanoproduct
D2.2. Roadmap and consensus protocols for controls of nanoproducts production quality
MS2. Full characterization, stability and quality control of selected new nanomedicines.

Working Group 3 – Preclinical Studies of Nanodrugs

Main tasks and activities: groups of biologists and pharmacologist will gather information to demonstrate a thorough understanding of the lead's mechanism of action, its adequate developability properties, its biocompatibility and safety of nanomaterials (esp. long term toxicity).

Studies will be performed *in vitro* and *in vivo*. *In vitro* studies will focus on: (a) cellular uptake and localization of the compounds, (b) controlled release, (c) mechanism of the anticancer activity (POC). *In vivo* studies will check (a) efficacy assessment in relevant oncology models (xenografts/syngeneic models) (b) ADME (absorption, distribution, metabolism and elimination) properties, (c) characterization and modeling o the pharmacokinetics/ pharmacodynamics (PK/PD) relationship, (d) ability to elude the immune system long enough to release a therapeutic cargo, (e) safety and toxicology studies in two clinically relevant animal models.
All animal studies will be done according to high ethical standards.

Deliverables **(D)** and Milestones **(MS)**:

D3.1. Consensus protocols for *in vitro* testing of nanomaterials
D3.2. Consensus protocols for *in vivo* testing of nanomaterials (efficacy, toxicology and pharmacokinetic studies)
MS3.1. Complete determination of key factors/mechanisms imparting *in vitro* proof of concept in oncology and cellular uptake/trafficking of selected nanomedicines
MS 3.2. Complete determination of *in vivo* efficacy, ADME and the toxicity profile characterization of selected nanomedicines in preclinically relevant animal models.

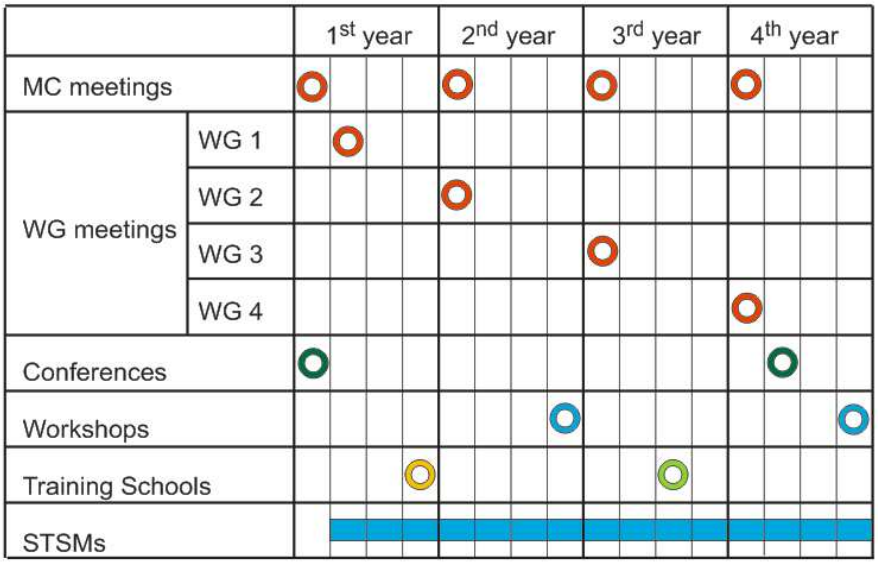
Working Group 4 – Guidelines for Clinical Trials and Regulatory Aspects of Nanomedicines

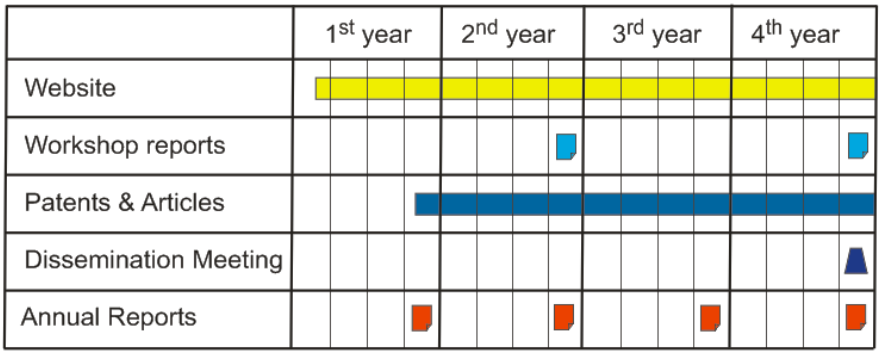
This WG will be devoted to the necessary steps to foster the translation of the developed nanomedicine cancer drug to bed/market . Specifically: 1) guidelines and documents describing in details the objectives, protocol design, methodology, statistical consideration and organization of eventual early clinical trials in oncology of the selected nanotechnology will be prepared, and 2) challenges in nanomedicines regulatory science will be tackled by solving prototypical translational issues: like fostering a suitability dose scaling technique for estimation of clinical first-in-man dosed from preclinical data for nanotechnology cancer drugs, validation of adequate preclinical and toxicologic models and a deeper understanding of the PK/PD relationship will allow an adequate drug positioning in oncology targeting a relevant disease stage and disease evolution conditions, within the current setting to address appropriate personalized medicine questions.

Deliverables **(D)** and Milestones **(MS)**:

D4.1. Formulation of guidelines and documents for translation of nanomedicines from bench to bed/market
D4.2. Formulation of guidelines and documents concerning regulatory aspects of nanomedicines
MS4.1. Documents for translation of selected nanomedicines
MS4.2. Documents for suggested regulatory aspects of selected nanomedicines

3.1.2. GANTT DIAGRAM





1st Training School – Art of Communication – course on writing scientific publications

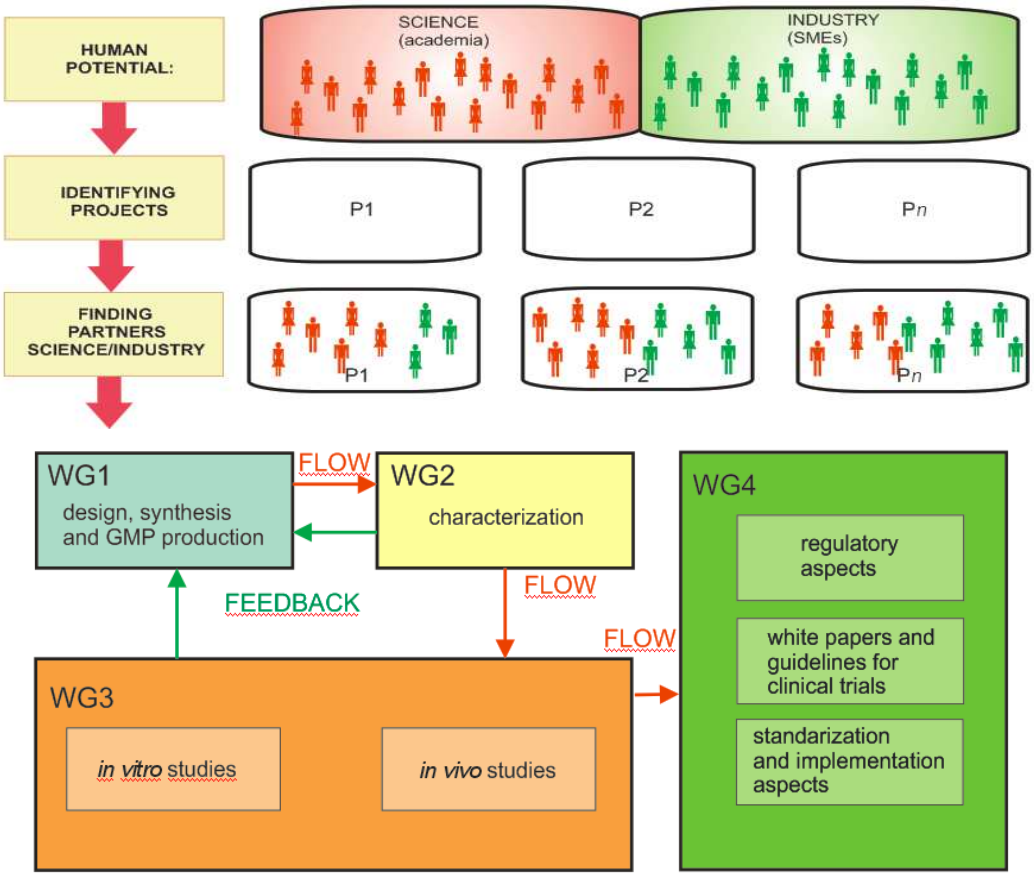
2nd Training School – Intellectual Property Rights Matter – course on preparing patents

Workshops will serve as a showcase for the completed STSMs.

Based on the workshops reports will be prepared.

For broader dissemination of the results the Action will be presented at the Dissemination Meetings. The choice of the projects will be made by the Core Group. Presenting results at **the European Society for Medical Oncology Congress** or at other prestigious cancer conferences will promote the achievements of the Action.

3.1.3. PERT CHART (OPTIONAL)



3.1.4. RISK AND CONTINGENCY PLANS

Risk Category	Risk	Risk Level	Contingency Plan
Science & Technology	toxicity and lack of biodegrability of nanosystems	medium	experienced teams of chemists will modify the chemical structures of nanosystems to eliminate the problems
Project implementation	slow pace of moving novel nanosystems through testing and regulatory approval process	high	companies will receive intellectual support from academia, scientific meetings will increase competences in designing clinical trials
Networking	lack of trust between academia and companies	low	networking tools (such as conferences, workshops, meetings, STSMs) will diminish the problem
Networking	complexity of running a project with high number of participants	low	organizing participants in smaller groups devoted to specific scientific projects will make the large network easily manageable
Commercial	Products are not appreciated by the industry due to competitive advantage-matrix evaluation	low	change product characteristics from time point zero
Research and development	Fail at the lab scale due to technical problems	high	introduce designs with frequent exit scenario at every step of development
	Fail in industrial development and application	medium	

The Action is impact-orientated and is based on an original idea to develop new cancer nanotherapeutics. As shown in the PERT Chart, a few projects will be launched and for the selected

ones deliverables will be provided and milestones achieved within the duration of the Action (four years). Some formulations will need more modification to successfully pass earlier stages (i.e. meet desirable physico-chemical and biological requirements). However, the collaboration between the participants and the involvement of industry will expand beyond the time frame of the Action and finally it is envisaged that most projects that will start within the Action will be completed successfully.

3.2. MANAGEMENT STRUCTURES AND PROCEDURES

The first MC Meeting (kick-off meeting) will elect the **Chair** and the **Vice-Chair** of the Action. The Vice-Chair of the Action will be responsible for the procedure of accepting STSMs. Working Groups will be constituted based on the partners' expertise. **Working Group Leaders** will be elected at the kick-off meeting. The **Core Group** will consist of the Chair, the Vice-Chair, and WG Leaders. The Core Group will have regular video-conferences to monitor the progress of the Action.
The Management Committee will supervise the appropriate allocation and use of funds and implement COST mission and policies. It will control the achievements of the Action's objectives, and approve the Work & Budget Plans.
At every MC meeting and WG meetings the **policy towards inclusiveness, gender balance and engagement of Early Career Investigators** (ECIs) will be revised and updated by providing: (1) leadership roles in the Action structure for partners from the COST Inclusiveness Target Countries (ITCs), women and ECIs, (2) access to the Action's tools for these groups, (3) geographical diversity when choosing location of Action meetings and events to make sure that ITCs are included.
The Standing Committee of Practitioners (SCP) will meet regularly every three months via conference calls, and once a year in person (and Skype video-conference for those unable to attend), in concomitance with the MC meetings. Should urgent IP/ethical issues arise along the Action, the SCP can be convened on demand any time via conference call to discuss the relevant matter.

3.3. NETWORK AS A WHOLE

The Action has gathered the critical mass of 40 network participants to achieve the goals. The participants will work in smaller groups devoted to specific scientific projects. Therefore this big network will be easily manageable. The Action participants come from academia and research institutes, clinics, companies, standard organizations, one European foundation, and one European Technology Platform. This provides a balance between the main stakeholders. Scientists represent all required fields: computer modelling, chemistry, physics, biology, and medicine. All of them have expertise in nanosciences. Industrial partners are actively involved in nanomedicine. Many basic medicine participants are connected with clinical centres and participate actively in translational and early phase clinical investigations of cancer therapeutics. In each Working Group geographical diversity of the partners is achieved to ensure international collaboration. There are presently16 partners from 11 COST Inclusiveness Target Countries.

The Action will also support the involvement of researchers from **Near Neighbour Countries** (NNCs). The participation of NNCs will be based on mutual benefit, e.g. experts from these countries will be trainers in the Training Schools and will attend the conferences. The presence of Near Neighbour Countries will allow a more equal distribution of benefits (including technical and/or economic) associated with the Action to less reach affluent nations and contributing in decreasing the wealth gap between developed and developing nations.