European Cooperation in the field of Scientific and Technical Research
- COST -

Secretariat

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COST 244/07

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding (MoU) for the implementation of a European Concerted Research Action designated as COST Action BM0703: Cancer and Control of Genomic Integrity (CANGENIN)

Delegations will find attached the Memorandum of Understanding for COST Action BM0703 as approved by the COST Committee of Senior Officials (CSO) at its 169th meeting on 15 - 16 November 2007.

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

COST Action BM0703

CANCER AND CONTROL OF GENOMIC INTEGRITY

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

1. The Action will be carried out in accordance with the provisions of document COST 299/06 "Rules and Procedures for Implementing COST Actions" (or in any new document amending or replacing it), the contents of which the Parties are fully aware of.

2. The main objective of the Action is to advance knowledge on dysregulation of cellular protective responses against cancer and of epigenetic events involved.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at 66 million EUR in 2007 prices.

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

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

A. ABSTRACT AND KEYWORDS

The main objective of the CANGENIN Concerted Research Action will be to advance our knowledge on mechanisms that protect healthy cells from transforming into cancer cells. This Action will provide an interaction platform for research focused on genomic integrity and epigenetics and their dysregulation in cancer. The Action will combine expertise in the fields of DNA damage response, transcriptional control, chromatin organization, and cancer epigenetics, and explore the mechanisms underlying normal and deregulated functions. It will combine multidisciplinary expertise in biochemical, biological and functional genomics approaches and in exploiting animal models. The Action will link experts in basic sciences with approaches in translational cancer research. Due to the highest clinical significance of understanding of the molecular basis of cancer progression, it will be of vital importance for the European researchers to develop strong points of interaction to provide them with a competitive edge, new research models and tools in cancer research.

Keywords: DNA damage, repair, checkpoints, chromatin, transcription, translation, epigenetics, animal models

B. BACKGROUND

B.1 General background

The focus of the Action is on two key open issues relating to cancer, namely genome integrity and epigenetics. The rapid development of techniques related to basic cancer research creates great urgency to efficiently peruse basic problems in oncogenesis and to rapidly transfer the hitherto acquired knowledge into new clinical procedures. Such procedures will be based on the better knowledge of dysregulated events and will include better prognosis and prevention as well as improved therapeutic intervention.

Why is COST the right instrument?
With the support of a COST Action, the results that are expected to be gained as part of this consorted research effort are likely to result into concrete outcomes eventually leading to patient benefit. The added value of the concerted effort will be the possibility to use the combined expertise and technology available to the consortium which is not at the disposal of any individual participant. The COST Action will provide all participating experts and countries access to a large variety of advanced technologies required to transfer benchside knowledge into clinical application. The networking and research training opportunities provided by the Action will play a critical part of achieving these goals.

B.2 Current state of knowledge

Genomic integrity and epigenetic changes in cancer:
To maintain genome integrity cells have evolved DNA damage responses. These responses elicit direct DNA repair and transient cell cycle arrest in order to allow for efficient DNA repair, or senescence and apoptosis to permanently arrest or eliminate cells that might become potentially harmful for the survival of the entire organism. Mutations in gene products controlling DNA damage checkpoint and repair pathways cause predisposition to a large number of sporadic cancers and hereditary cancer syndromes underscoring the vital need for the fidelity of checkpoint control and efficiency of DNA repair machineries. Checkpoint functions are ensured by multiple, often parallel pathways and show specificity with respect to the nature of the damage, the cell cycle stage and the subsequent cellular response.

Regulation of the chromatin structure is critically important during transcription, DNA repair and cellular senescence, processes that are affected by both genetic and epigenetic means. For example, unwinding of chromatin is essential during transcription and nucleotide excision repair and is mediated by RNA polymerase II-associated proteins. At the same time, transcription, repair and cellular senescence are extensively affected by epigenetic marking of the nucleosome components, histones, through multiple modifications such as phosphorylation, methylation, acetylation, sumoylation and ubiquitylation. For example, phosphorylation of histone H2AX provides rapid focal signal for the presence of DNA double strand breaks spanning over 50 kilobases of DNA, whereas during senescence histone H3 trimethylation is lost. Conversely, overproduction of histone methyltransferases that catalyse the methylation histone H3 residues are frequent events in neoplasia. Importantly, although the impact of these modifications on the chromatin structure and the ensuing events is enormous, how such events are regulated at the mechanistic level is still not fully understood.

Strikingly, during cancer development, several key cancer predisposition genes become frequently epigenetically deregulated. The underlying mechanism for this deregulation involves remodelling of chromatin structure, in addition to posttranslational modifications of the histones, by direct DNA modifications. These include global alterations, such as hypomethylation of DNA and hypoacetylation of chromatin, as well as gene-specific hypomethylation and hypermethylation. Global DNA hypomethylation leads to chromosomal instability and increased tumour frequency. This is evident both in vitro and in vivo mouse models and may lead to gene-specific oncogene activation. In addition, the silencing of tumour-suppressor genes, like retinoblastoma, p16 and von Hippel–Lindau tumour suppressor is associated with promoter DNA hypermethylation and chromatin hypoacetylation.

Epigenetic marking not only affects transcription of individual genes, but also mediates positioning of subchromosomal scaffolds. Thus, epigenetic aberrations perturb normal chromosomal interactions. Therefore it will be vital to decipher the epigenetic code in the control of transcription and DNA repair in cancer progression.

Detailed information has been accumulated on how dysfunction of the epigenetic marking affects the cellular damage responses and predisposition to cancer. Several of these features and molecules involved in the above processes are currently being exploited for diagnostics and new strategic therapies, which involve attempts to complement the repair deficiencies and strategies to enhance tumour cell killing by provoking unscheduled cell death in the presence of replication, transcription or recombination errors. These new treatment modalities may offer effective therapeutic opportunities even in the cases of severe mutational loads such as in hereditary cancer repair

syndromes. It is anticipated that these approaches will provide more targeted and effective treatments with less drug-related adverse reactions than for existing therapies.

Innovation from multidisciplinarity and advanced technology:
This Action will provide an interaction platform for researchers aiming to understand the dysregulation of genomic integrity and epigenetics in cancer progression. The interaction platform that will be created through this Action will provide participating groups access to a great variety of advanced technologies that will greatly facilitate the progress made towards the full understanding of these phenomena, as well as facilitate the translation of this fundamental knowledge into clinically applicable strategies. The Action will combine expertise in DNA damage response, repair, checkpoint and transcription control, chromatin organization, and epigenetics. It will combine multidisciplinary expertise in biochemical, biological and functional genomics approaches and animal models. The Action will bridge experts in basic sciences with approaches in translational cancer research.

B.3 Reasons for the Action

The Action is highly significant, as it will provide added value to the active European research community on the control of genome integrity and epigenetics in cancer development. It will bridge several research fields with a new united focus point, and combine expertise and technological platforms providing efficient research tools.

The immediate benefits of the Action will come in the form of enhancing the quality of science and research training in the participants' countries in the areas of cancer, epigenetics and control of genomic integrity. It is expected that an early outcome of the research will be improved knowledge of the DNA damage checkpoint pathways and pathways sensing the damage and instigating repair, potentially rapidly paving the way to improved cancer diagnostics and identification of genetic susceptibilities to cancer. In the medium and longer-terms, the translation of these basic research findings through development of relevant disease models will form a basis for the rational therapy of cancer.

The objective of the Action is to extend knowledge in control of genomic integrity and its epigenetic dimensions through a synergistic effort among participants. The expected outcomes are an advance in scientific knowledge and improved technologies in this important field, identification of new leads to develop cancer diagnostics, new models of cancer due to defective control of genomic integrity and epigenetics, and potentially new strategies to treat cancer. The means to accomplish these goals include an integrated close-knit network of European scientists with an outstanding scientific knowledge and state-of-the-art technologies in this field.

There is a great need for experts in the Action area, both within academia and industry. For students and young investigators, the Action will provide sound interactions and platforms for future career development. These can take place in the form of recruitment to the Action countries thus increasing mobility, technology and knowledge transfer within Europe. For the established groups, the Action provides, both during and after the operating period, collaborative interactions and possibilities to continue these e.g. in the form of EU-funded framework programs.

Due to the open and flexible networking possibilities, COST will be an ideal framework that rises to the challenge of allowing expansion of meaningful interactions in this fast progressing research field. Furthermore, COST will provide n opportunity to efficiently co-ordinate research activities

financed by the participating countries.

B.4 Complementarity with other research programmes

Cancer and control of genomic integrity is an area where it is essential that the strong European research base be strengthened through increased interaction and multidisciplinarity taking advantage of emerging technologies to provide innovations to the European market. The strengths in focused areas are demonstrated by the number of EU Framework Program 6 and 7 projects in which a number of COST member countries are involved. During the preparation of this application a strong sentiment of excitement for the possibility of having an integrative umbrella concerted Action was felt amongst the contacted experts and FP6 and FP7 project coordinators. It is also notable that both of the two currently ongoing cancer-related COST Actions are expected to be complementary to this Action as specified below after listing of the FP projects:

FP6 Integrated Project 2004-2009
INTACT: Identification of Novel Targets for Cancer Therapy
In this program genome-wide screenings are used to identify novel targets for cancer therapy. The technologies in this program are relevant for this COST Action, but overlap is limited including the time frame.

FP6 Integrated Project 2004-2009
Active p53: Manipulating tumour suppression: a key to improve cancer treatment
Addresses the regulation of p53 in normal and tumour cells, with the major goal of finding new strategies aiming at the re-activation of p53 in tumour cells. Since p53 is a major downstream responder to DNA damage (but not a direct sensor of it), the current COST Action will complement in a productive way with the FP6 project.

FP6 Integrated Project 2004-2009
Mutp53: Mutant p53 as target for improved cancer treatment
This IP is focused on mutant p53 in tumours, and the approaches for mutant p53 reactivation by small molecules are a promising area, which can be developed within this Action.

FP6 Integrated Project 2005-2009
DNA REPAIR: DNA damage response and repair mechanisms
Compared to this COST application the program is more restricted in its subject and primarily focuses on basic molecular understanding of the DNA damage response and does not have much medical application.

FP7 Specific Targeted Research Project (STREP) 2007-2009
EuroCSC: Targeting Cancer Stem Cells for Therapy
This STREP on cancer stem cells revolves around functional characterization of CSCs and development of therapeutic targets. This effort is complementary, in that the EuroCSC is directed towards exploitation of CSCs as a cellular target.
FP6 Integrated Project 2005-2010
HEROIC: High-throughput epigenetic regulatory organisation in chromatin
This IP will develop global biochemical and high throughput genomic tools and screens that will identify novel gene regulators and determine when and where transcription factors, histone modifying enzymes and chromatin remodelling proteins, interact with the primary genetic code. It is non-overlapping with this COST as it is not involved with cancer, but is complementary in the way that the tools generated will be very useful in the approaches described here.

FP7 Proposals
In addition, there are several (4) pending FP7 proposals in the fields of DNA damage responses which however, do not overlap with general common theme presented in this COST Action, and which have been discussed with the coordinators. The possibility of a COST Action on Genomic Integrity in Cancer has generated excitement among all the consortia, and there is great interest to the possibility of having an umbrella concerted Action for the relatively narrowly focused projects. The subjects include investigations to the role of microRNAs in cancer and while no link to DNA damage induced checkpoints has been proven so far this project is anticipated to complement the current COST Action in finding out such activities. Another project application involves a translational perspective to mechanisms leading to genomic instability in human precancerous lesions and will do so by utilizing large-scale genomic analyses of human clinical specimens. There is no overlap with the specific actions proposed in this COST Action.

Ongoing COST Actions in cancer (2/19 of all BMBS actions)
There are currently only two (total 19) running COST Action in cancer. The number is low considering that the relative incidence and economical relevance of cancer is increasing in Europe rapidly due to the aging population and lowered cardiovascular mortality. Both of the two Actions are relevant to this Action:

1. COST Action BM0606 2007-2011
Collaborative association studies in breast cancer
This Action aims to associate genetic variance (SNPs) to breast cancer to provide reliable assessment of the risks associated with SNPs and the interactions with lifestyle risk factors and BRCA1 and BRCA2 in large patient materials. The data produced in this study would be very interesting to integrate with outcomes of the current Action.

2. COST Action BM0607 2007-2011
Targeted Radionuclide Therapy (TRNT)
This Action aims to enhance radiotherapy of cancer patients, but also includes aims to search for new targets and new vectors (WG1) and animal models, and preclinical studies (WG4); these may provide interaction possibilities and synergism.

C. OBJECTIVES AND BENEFITS

C.1 Main/primary objectives

Advance knowledge of dysregulation of cellular protective responses against cancer and of epigenetic events involved.

C.2 Secondary objectives

- Establish a network with top-level high impact research groups in genomic integrity, transcription control and cancer epigenetics;
- Promote scientific interactions and excellence in Europe;
- Promote rapid dissemination of information;
- Bring together experts in cancer biology, animal models, and translational cancer research;
- Support young investigators by providing interactions, technological advancements and intellectual feed-back;
- Provide scientific and methodological research training for students.

This Action will provide novel information on pathways and molecules acting as barriers against cancer and their dysregulation during tumorigenesis. The detailed biological understanding of cancer will further promote the development of novel diagnostic, prognostic, and therapeutic anticancer strategies. The main end users are the scientific community, pharmaceutical industry and cancer patients.

C.3 How will the objectives be achieved?

The participants in this COST Action will form an outstanding group of scientists in the area of control of genomic integrity and epigenetics. The commitment of these groups to launch on an integrated effort to achieve the objectives will provide strong support in the form of outstanding scientists at all levels (professors, group leaders, post-doctoral scientists, graduate students) from various fields. For successful completion, the Action will need to train early stage scientists with specific skills. The estimated 300 person-years in the countries already expressing a strong interest in this Action will provide excellent means in regard to manpower. The complementing state-of-the-art technologies and sophisticated equipment in use in the participating groups will be exploited to their maximum with this Action, and the activity will result in the further development of these technologies as one outcome.

C.4 Benefits of the Action

This Action will provide novel information on pathways and molecules acting as barriers against cancer and their dysregulation during tumorigenesis. The detailed biological understanding of cancer will further promote the development of novel diagnostic, prognostic, and therapeutic anticancer strategies.
The main immediate and long-range benefits from this Action will be to:

- Provide new opportunities for therapy development through the identification of pathways and processes dysregulated in cancer.
- Facilitate testing of critical modifiers in several experimental and animal models through the overlapping and synergistic structure of the Action.
- Provide sound interactions and platforms for future career development for young investigators.
- Increase researcher mobility and technology transfer within Europe.
- Training of multidisciplinary experts in cancer biology, epigenetics, animal models and translational research.

C.5 Target groups/end users

The main target groups and end users benefiting from the outcomes are:

- Young scientists that can utilize the innovative approaches and novel technologies developed within the Action, and disseminated in Training Schools.
- A wide variety of scientists in basic and applied research in the health care sector (public and private)
- The pharmaceutical industry, who will be provided both with new information to target DDR pathways in cancer, with new lead targets to start development of new drugs, and with results from clinical trials with several interesting molecules investigated in this Action
- A wide range of cancer patients, including breast cancer and acute myelocytic leukemia (AML), and selected gastrointestinal cancer patients.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

This Action will advance our knowledge of the cellular protective responses against cancer and the epigenetic control of chromatin organization, and provide novel links between these processes. This will be realized through extensive structured interactions between European leaders in the fields of DNA repair, DNA damage response, checkpoint control, transcriptional control, chromatin organization, translational cancer research, and cancer epigenetics. These groups are experts in one or several of the following technologies: molecular cancer biology, functional genomics, proteomics, imaging, high throughput analyses and animal models (yeast, C. elegans, and mouse). The wide span of the participants extending from basic sciences to experts in preclinical models provides valuable multidisciplinary approaches and possibilities for extensive genetic and mechanistic testing of the phenotypes.

Specifically, the following scientific questions will be addressed:

- Identification of cellular DNA damage response proteins and mechanistic studies towards defining their function, regulation and dysregulation in human tumorigenesis.
- Identification of alterations in DNA damage response and repair pathways in human cancer, and exploitation of this information in diagnostics and in drug development.
- Testing the impact of chromatin modifying events on the transcriptional and repair programmes.
- Identification of epigenetic events controlling cellular senescence, somatic cell stemness, and their deregulation in neoplasia.

Several of the dedicated Action participants are involved in drug discovery based on the identified dysfunctional pathways, and the first lead compounds have already entered clinical trials. Continued interaction of researchers and experts will be critically important in order to take these findings forward towards functions, cell phenotypes and inhibitor/drug development. The Action will foster multidisciplinary approaches promoting the rapid progress of potential therapy applications towards clinical trials.

D.2 Scientific work plan – methods and means

The main actions through which the scientific objectives will be realized are:

- Combining individual expertise through a network allowing rapid lateral transfer of scientific insight, technological platforms and expertise.
- Providing synergy and critical mass facilitating optimal experimental testing of the observed phenomena and validation of the findings.
- Recruiting centres with special expertise required for the progress of the research and technological advancements.

The work plan is divided into four areas planned to form Working Groups in the Action.

D.2.1. Cellular DNA damage signalling pathways (Working Group 1)

The main objective of Working Group 1 is:

- To advance the knowledge of cellular responses activated by cancer-predisposing genetic insults, elucidate the molecular workings of signalling barriers against cancer development, and identify how these are deregulated during multistep tumorigenesis.

The main research tools and experimental models include:

- High throughput single cell-based screens (based on culturing living cells on siRNA arrays) for new genome 'caretakers' (cellular factors whose deregulation causes genomic instability, elicit a DNA damage responses (DDR), or interfere with proper function of the main genome surveillance pathways).
- Identifying new DDR proteins in yeast and mammalian cells by a range of approaches such as yeast 2-hybrid screens, protein purification/proteomics and bioinformatics-based methods.
- Dynamic biochemical, genetic and imaging approaches to elucidate the function of the newly identified genome surveillance pathways in their physiological environment (nucleus of a living mammalian cell).
- Validation of the obtained knowledge and testing the emerging concepts directly on clinical cancer samples such as biopsy specimen or tissue arrays. This part of the project includes development new probes and tools (e.g. monoclonal antibodies) applicable on clinical material
- Exploiting various model organisms such as C. elegans to identify novel genes that participate in cellular DNA damage signalling pathways.

Expected outcomes are:

- Novel information on pathways and molecules activated by DNA damage and acting as barriers against cancer, and elucidate their deregulation during tumorigenesis, including information on the cancer-relevant p53 tumour suppressor.
- Identify the types of DNA damage that may lead to activation of the DNA damage response in normal cells.
- Understand how dysregulation of DNA damage responses can contribute to human cancer development.
- Identification of novel diagnostic markers and possible targets for drug intervention in cancer.
- Promotion of the much-needed interdisciplinary interaction (especially of young scientists at the beginning of their careers) and disseminate advanced technologies and the state-of-the art approaches in cancer biology.
- The detailed biological understanding of molecular mechanisms behind the anti-cancer barriers will further promote the development of novel diagnostic, prognostic, and therapeutic anticancer strategies.

D.2.2. Chromatin modifications and transcriptional control (Working Group 2)

The objectives of Working Group 2 are:

- To understand how chromatin modifications are connected to the deregulation of transcriptional control by oncogenes, including signalling molecules (e.g. Ras) or transcription factors (e.g. Myc or E2F).

- To understand how these regulatory changes underlie the tumour suppressor responses - and in particular the DNA damage response (DDR) - elicited by the oncogenes themselves, and how they might be exploited for therapeutic purpose.

- Identify new chromatin modifications and chromatin modifying enzymes that impact on cellular responses to DNA damage.

The first objective will be achieved by means of profiling technologies, based on both high-throughout and quantitative techniques (i.e. microarrays and real-time PCR, respectively). Multiple levels of gene regulation will be profiled, including mRNA expression, transcription factor binding and epigenetic modifications (the latter two based on chromatin immunoprecipitation). The biological systems to be utilized will include cultured cells and transgenic mouse models: in all instances, conditions will be studied in which "oncogenic stress" is being elicited, restraining cellular transformation and tumour progression. In particular, pre-tumoral lesions and tumours from transgenic mice expressing given oncogenes (e.g. Myc, Ras) in selected tissues (e.g. mammary gland, lymphocytes) will be studied. Particular attention will be given to the regulation of genes involved in DDR pathways (see Working Group 1).

The second objective will be achieved by genetic means, including RNA interference and/or gene knockout technologies, aiming at functional impairment or ablation of key regulatory genes. The genes to be studied include genes involved in DDR pathway, as well as genes encoding epigenetic regulators. Particular attention will be given to histone-modifying enzymes catalyzing addition and removal of acetyl- and methyl-groups (see Working Group 3), which will be prioritized according to the epigenetic changes identified. The role of the histone modifiers in the epigenetic- and gene expression-changes elicited by oncogenes at their target loci will be addressed.

At the cellular level, we will address the role of all targeted genes in the tumour-suppressive responses associated with oncogenic stress (DDR, apoptosis and senescence), as well as in tumour-promoting mechanisms (cell cycle progression, proliferation, phenotypic transformation).

Mouse tumour models will be used to address the role of targeted genes in tumour promotion or suppression, through the analysis of disease onset, progression and pathology. We will also study the consequences of targeting selected genes on therapeutic responses (see Working Group 4). In parallel with the cell- and mouse-based studies, we will use genetic and immuno-histochemical approaches to address whether candidate genes are (epi-) genetically altered and/or deregulated in human tumours.

Expected outcomes are:

- Increased knowledge of the changes in both epigenetic state and gene expression elicited by oncogenes

- Increased knowledge on the identity of the target genes and pathways associated with oncogenic stress.

- Identification of target genes, DDR- and epigenetic-regulators that have a major impact on disease progression and maintenance. Some of these genes, and in particular those encoding "druggable" enzymes, will constitute new candidate targets for drug screening and development.

- Understand functional consequences of chromatin alterations taking place at sites of radiation-induced DNA damage

D.2.3. Cancer epigenetics (Working Group 3)

A major challenge in cancer of today is to understand how epigenetic states contribute to the various steps of neoplastic transformation and how this information could be used for diagnosis and treatment. This task is monumental; while there is only one diploid genome, there are thousands of epigenomes in a single mammalian organism. Nonetheless, the longer-term objectives to diagnose and treat cancer will require an understanding of the functions of the epigenome, the initial causes for epigenetic instability and its roles in cancer progression. While epigenetic lesions are known to trigger cancer there is little, or no evidence that the metastatic potential is fueled by genetic events - rather, malignant progression of cancer might be associated primarily with changes in the expression repertoire and hence chromatin states.

The main objective of Working Group 3, therefore, is to understand the epigenetic underpinnings of cancer from early to late stages. This will be achieved by integrating the expertise of participating member countries with respect to global chromatin modifications and changes in nuclear organization and replication timing. Outstanding research groups and experts in chromatin profiling technology have been identified and will bring unique chromatin profiling technologies and hands-on knowledge of gene products regulating histone modifications and are probably involved in cancer. Furthermore the recent identification of epigenetically regulated chromosomal networks regulating transcription and replication timing in trans will be further developed in regard to involvement in cancer. Interactions are expected with Working Groups 2 and 4 for histone modifications and chromosomal networks. In addition, the link between DNA repair machinery and replication timing/higher order chromatin conformations promotes interaction with Working Group 1.

Apart from generating novel angles of cancer mechanisms, the expected outcomes will include the dissipation of information of advanced technologies to the participating labs. This is likely an essential feature of this endeavour and can include high throughput tools to identify higher order chromatin conformations (e.g. circular chromosomal conformation capture (4C), which allows the dissection of chromosomal folding patterns in high throughput manners), ChILL (a new ChIP method allowing the analysis of multiple chromatin marks on a single DNA-nucleosome unit with superior resolution and sensitivity) and ISPLA (allowing the visualization of protein-protein interactions in intact mammalian nuclei).

D.2.4. Cancer model systems and translational research (Working Group 4)

Cancer is a disease where the responses of normal cells and tissues are critically involved in addition to the malignant cells with disrupted DNA damage checkpoints and epigenetic deregulation. These responses can both inhibit or paradoxically stimulate the growth of the population of malignant cells, and therefore it is essential to study cancer in models resembling as closely as possible relevant clinical settings for cancer with rapidly increasing economical relevance in Europe.

The objectives for Working Group 4 are:

- Utilize existing breast cancer mouse models with potential to advance knowledge of DNA damage responses and the epigenetic events involved in cancer
- Develop a platform to efficiently integrate discoveries and innovations made in the Action to human cancer specimens translating basic discoveries to patient benefits
- Generating and utilizing new cancer mouse models based on discoveries made in WG1-3
- Translating the new knowledge to clinical trials and diagnostics at least partly in collaboration with relevant SMEs or other enterprises.

In regard of the first objective the BRCA1 and BRCA2 hereditary breast cancer genes are involved in DNA integrity and cancer, and provide an interesting and relevant model to investigate. For this purpose the Action will undertake i) Genetic dissection of human breast cancer through the use of advanced mouse models; ii) Identify genotype-phenotype relations and novel cancer-relevant genes in breast oncogenesis from these tumours by array-CGH analysis, gene expression profiling and insertional mutagenesis screens; iii) Breast cancer drug target validation studies and preclinical studies using mouse models. Other tumorigenesis mouse models with expertise among member state participants will also be utilized and are likely to include gastrointestinal tumorigenesis models (Apc, Lkb1), acute myelocytic leukemia (AML) xenograft models,

For the second objective regarding breast cancer model systems developed in member countries with epithelium restricted deletion of conditional alleles of Brca1, Brca2, E-cadherin and p53 generating models for i) p53-induced breast cancer; ii) BRCA1- and BRCA2-associated hereditary breast cancer; iii) E-cadherin-mutated metastatic breast cancer will be used. Furthermore luminescence-tagged cell lines generated from these models will be used in a combination of high-throughput gene identification experiments in vitro and drug target validation and preclinical studies in orthotopic mouse models enabling non-invasive imaging of tumour growth and response via bioluminescence imaging (BLI). Ultimately, (combinations of) drugs will be tested in the spontaneous mammary tumour models. This combination of an in vitro platform, in vivo grafting models and spontaneous tumour models offers unparalleled flexibility in throughput and predictive power.

Drug target validation studies in the mouse mammary tumour cell lines and the corresponding orthotopic grafting models are performed by siRNA-mediated silencing using synthetic siRNAs or transduction with shRNA-expressing lentiviruses. For in vivo target validation in orthotopic grafting models, lentiviral systems will be utilized for stable, tetracycline-regulatable production of shRNAs in tumour cells. For validated targets, (conditional) knockout mice in order to study the effects of loss-of-function of the targets in an intact organism.

For preclinical tumour intervention studies with novel compounds, a mouse cancer clinic that can house up to 1000 mice in individually ventilated cages (IVCs) and that is equipped with advanced imaging modalities including an optical imaging system for bioluminescence, fluorescence, and near-infrared probe imaging, a small-animal SPECT-CT system and an X-ray system will be required and would be available for this Action based on contacts with local experts.

In regard of the third objective, genes identified to be important for various aspects of DDR and epigenetic regulation within work in WG1-3 will be subjected to translational studies through generation of assays in cancer cell lines, cancer mouse models and patient specimens. The

approaches will be similar to those described above for breast cancer. Examples of areas of interest include
- Novel p53 target genes and p53 biosignature modulation following chemotherapy
- Post-translational modifications on DDR proteins as diagnostic or prognostic markers for cancer
- Developing small chemical inhibitors for different parts of the DNA damage response
- Novel strategies for treatment of prostate cancer (including animal models)

The fourth objective will be accomplished through collaboration with relevant SMEs with which experts are expected to be associated with. Relevant areas here include
- Contributing to trials on reactivation of mutant p53 with small molecule compounds in human cancer
- Contributing to trials using PARP inhibitors in the treatment of BRCA1 and BRCA2 breast cancer
- Testing DDR inhibitors (targeting PARP1, ATM and DNA-PK) on cancers bearing mutations in various DDR proteins (such as MDC1)

Expected outcomes are:

- Validated mouse models for human breast cancer, AML, and to-be-identified cancer types where DDR and epigenetic deregulation have a significant role
- Multi-level platforms for in vitro and in vivo drug target validations and compound testing
- Knowledge on the extent of involvement of DDR and epigenetic deregulation in hereditary polyposis syndromes and gastrointestinal cancer.
- Identification of novel breast cancer genes and drug targets with possible expansion to other cancer types.
- Enhanced early-stage testing and validation of drug targets decreasing time from identification to clinical trials.
- Initiation of clinical trials in collaborative efforts.
- Results on the efficacy of DDR inhibitors in human cancer in trials being initiated.

E. ORGANISATION

E.1 Coordination and organisation

The Action will be implemented through the Management Committee (MC; with elected Chair and Vice-Chair) and Working Groups 1-4 (WG1-4; with Leaders selected by MC) organized and operated according to the COST Actions procedures, and where aim is to maintain gender equality and promote inclusion of young investigators.

The Action will start following the joining of member countries (>10 expected based on contacts during application preparation) with an **Inaugural Meeting** (organized by the COST Office), where the MC (national experts appointed by the Signatory countries) selects the **MC Chair/Vice Chair**, the **Grant Holder**, and **WG Leaders**, and a workplan and budget for the first year is drafted to enable an efficient start to Action through use of the financial instruments. Also a **Short-Term Scientific Missions (STSM) Assessment Panel** (subset of MC, 2 + Chair, rotating annually) a **STSM Manager** (coordination of STSMs with applicants, MC, COST Office, Grant Holder), and a **Training School (TS) Manager** are selected.

Following the start the Action is organized as depicted in Table 1 (Section F.) demonstrating significant events and their responsibilities in Year 1-4 (and the Final Annual Conference at beginning of Year 5). The Action is organized in annual units, where a Annual Conference (AC1-4) is arranged in conjunction with a significant other (non-Action) event in the field, and where also WG meetings and a MC meeting are held to minimize travelling expenses (MC has an additional annual meeting). Other significant annual events are formed by Training Schools arranged by WGs.

The Management Committee is in charge of implementing, supervising and co-ordinating the activities of the Action. The MC also sets Action Milestones during Year 1. As the COST Office provides significant scientific and administrative support, and the Grant Holder has an important part in the financial arrangements and reporting, coordination and efficient transfer of information will be ensured by the MC clear determination (flowcharts) of reporting on WG actions (from WG to MC to BMBS), of STSMs (from applicant to STSM Manager to Assessment Committee to MC Chair to BMBS and Grant Holder) , TSs (from WG to TS Manager to MC Chair to BMBS and Grant Holder), and Annual Conferences. Reporting will be integrated in a way to aid the MC and Grant Holder in preparing scientific and financial reports in a timely fashion.

Coordination of national activities relevant to this Action is at the responsibility of the national Management Committee members.

The Action will integrate the following elements:

• Annual Conferences (1-4)
The Annual Conferences are organized by WGs in conjunction with a significant other (non-Action) activity in that area. They are expected to attract a wide audience and an important goal for the Action is dissemination of information at the ACs through Conference Proceedings and other means. This size of the ACs is expected to be 100-200 participants.

• Short-Term Scientific Missions
STSMs are a critical part of this Action, which relies on efficient lateral transfer of technologies and infrastructures such as state-of-the art imaging facilities, high-throughput robotics setups, and mouse clinics. For successful completion of the objectives at least 20 annual STSMs are required..

• Training Schools (TS)
Training Schools (3-5 days) will be arranged in relevant technologies (e.g. live-cell/high-throughput imaging, proteomics, animal models) aimed for researchers participating in the Action and arranged by WGs in Year 2 (WG3-TS1; WG4-TS1), Year 3 (WG1-TS1; WG2-TS1; WG3-TS2; WG4-TS2), and Year 4 (WG1-TS2; WG2-TS2). Optimally TSs are arranged as summer schools, and are targeted for a size of 10-30 researchers.

• CANGENIN website
The Action website will complement the COST website information on the Action: distribute information on scientific discoveries within and to non-Action scientists, integrate information on available reagents, technologies and facilities among Action participants, and serve as an STSM and TS portal, where advertisements and applications are available. The Action website will also be used to coordinate efforts among workgroups and group efforts in participating countries. An important role for this site will be to disseminate outcomes of the Action and aid in exploitation of these outcomes. Responsibility for the website will be determined following decision of how the General Action Support Grant (GASG) Instrument will be utilized.

E.2 Working Groups

Four Working Groups will be included, and the MC at the Inaugural Meeting selects a Leader for each. Subsequently WGs Leaders are responsible for organizing the WG into tasks together with WG members. All participating institutions are expected to be represented in at least one WG. WG help the MC in setting the milestones of the Action in the first year, and report annually (Year 2,3,4) to the MC on accomplishments including dissemination of information. Each Working Group will be the primary organizer of an Annual Conference (Table 1). The Working Groups are:

1. Cellular DNA damage signalling pathways
2. Chromatin modifications and transcriptional control
3. Cancer epigenetics
4. Cancer model systems and translational research

The aims and approaches described within the Working Groups will be closely integrated and coordinated with other workgroups in the consortium by means of:

- Establishing a network within the Working Groups of top-level high impact research groups in genomic integrity, cell cycle regulation, transcription control and cancer epigenetics;
- Promoting scientific interactions, privileged dissemination of information and exchange of materials;
- Encouraging multidisciplinary collaborations;
- Promoting exchange of young investigators with an emphasis on methodological training. Here, the complementary state-of-the-art technologies and sophisticated equipment in participating groups will be exploited to their maximum. In addition to the educative purposes, this initiative will be essential to further develop these technologies and/or improve their application to the key tasks of cancer biology.

E.3 Liaison and interaction with other research programmes

The significant expected complementation of FP6, FP7, and COST Actions (See Section B4) requires a proactive role of this Action in ensuring efficient coordination of joint activities with national and European (FP, COST, ESF) activities and overlapping interest. This task is primarily the responsibility of the Management Committee, but as the Annual Conferences will be arranged as concerted actions, the respective WG Leaders will also play a significant role here. The usefulness of integrating activities from some of these activities on the Action website will be considered.

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

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

Special attention will be directed to involve women at all management and scientific levels of the Action. It is also a strong encouragement for female scientists to join the Action and to take advantage of the scientific opportunities it offers.

The strong element of Training Schools in this Action is aimed to ensure capacity building among the young scientists, and has been identified as one of the secondary objectives.

F. TIMETABLE

The Action will be completed in four years following the Inaugural meeting according to the Timetable depicted in Table 1. The final Action Conference is scheduled to take place in the first three months of Year 5. During Year 4 all WGs and the MC are required to pay special attention to dissemination of information and consideration of whether the concerted Action should continue as a whole or in part within another Financing Instrument.

Table 1. Timetable and organization of the CANGENIN Action.

	Year 1		Year 2		
	beginning	end	beginning	end	
COST Office/BMBS	Inaugural mtg org.	draft ag.+ min.	draft ag.+ min.	draft ag.+ min.	
CANGENIN - MC	Chair, Grantholder, workplan, budget, dissem.	Milestone set	TS, STSM, infra	MC mtg	
MC Chair	WP and budget-1		WP and budget-2		
Grant Holder	Contract	Prel. FinRep	Final FinRep	Prel. FinRep	
CANGENIN-WG1	MC -> Leader	tasks, plan AC-1	Rep.1, org. AC-1	plan TS	
CANGENIN-WG2	MC -> Leader	tasks	Rep.1, plan AC-2	plan TS	
CANGENIN-WG3	MC -> Leader	tasks	Rep.1, plan TS	WG3-TS1	
CANGENIN-WG4	MC -> Leader	tasks	Rep.1, plan TS	WG4-TS1	
	Year 3		Year 4		Year 5
	beginning	end	beginning	end	beginning
COST Office/BMBS	draft ag.+ min.	draft ag.+ min.	draft ag.+ min.	draft ag.+ min.	
CANGENIN - MC	MC mtg	MC mtg	MC mtg	Final rep.	Dissem.

MC Chair	WP and budget-3		WP and budget-4		
Grant Holder	Final FinRep	Prel. FinRep	Final FinRep	Prel. FinRep	Final FinRep
CANGENIN-WG1	Rep.2	WG1-TS1	Rep.3	WG1-TS2	
CANGENIN-WG2	Rep.2, org. AC-2	WG2-TS1	Rep.3	WG2-TS2	
CANGENIN-WG3	Rep.2, plan AC-3	WG3-TS2	Rep.3, org. AC-3		
CANGENIN-WG4	Rep. 2	WG4-TS2	Rep.3, plan AC-4		org. AC-4

Table Abbreviations
AC = Annual Conference (in case of budg. restraints Workshop)
TS = Training School
Rep. = Report
PrelFinRep= Preliminary Financial Report (from Grant Holder to COST)
Final FinRep = Final Financial Report (from Grant Holder to COST)

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: Denmark:DK; Estonia:EE; Finland:FI; Germany:DE; Hungary:HU; Italy:IT; Netherlands:NL; Norway:NO; Sweden:SE; Switzerland:CH; United Kingdom:UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 66 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

Based on discussions the expected total manpower expressed in person-years dedicated to the activities of the Action for Years 1-4 will be 130/year (15% senior scientists/principal investigators, 30% post-doctoral scientists, 50% PhD students, 5% technicians/students), translating to an estimated 13 million Euro/year. Implementation of this Action will require a significant amount of additional expenses, such as equipment, instruments and other infrastructure, estimated at 3 million Euros/year, and thus the total annual economic dimension is 16 M€.

H. DISSEMINATION PLAN

H.1 Who?

This Action studies a clinically debilitating disease, cancer, which is a major cause of morbidity and mortality in European society. Most notably, the general character and widespread incidence of cancer make this an attractive and justifiable object of study. The molecular approaches may, if successful, have a significant impact on the social welfare of the population at large. This highly integrative and multidisciplinary Action, with dedicated teams with varied and unique skills, will provide new knowledge, and innovative and state-of-the-art technology that will facilitate the development of more effective strategies to diagnose and treat cancer.

The scientific achievements of the Action will be communicated at different levels targeting scientists, academic institutions, industry, as well as the general public.

Several patient target groups, with unique needs and characteristics, will directly benefit from this research. The aging population of the world is expanding, and they form the majority of those suffering from cancer. Thus the Action, through objective-based research, and set actions that reflect knowledge, may benefit the health objectives of society, and furthermore provide service to otherwise under-represented patient groups at increased risk of cancer. The benefit to these patient groups will have a larger effect on families and work environments as a whole. With the identification and functional characterization of genes involved in cancer, opportunities and challenges will emerge to both improve health and to stimulate industry, particularly in diagnostics, technology, research, and drug development.

Therefore, the dissemination of this information to industrial partners will be actively sought in order to attract potential bio-industrial partners interested in exploitation of the results. There is great interest in the pharmaceutical industry to develop therapies aimed at inhibiting early-stage and late-stage tumour growth. The pharmaceutical industry requires knowledge concerning possible candidate targets playing critical roles in these processes. As such, the Action is expected to yield significant new intellectual property (IP). Exploitation of these results e.g. towards phase I and II trials will be further considered with medicinal technology companies founded by dedicated partners in this Action.

The Action will endeavour to create an environment where scientific curiosity is fostered and genuinely novel ideas and imaginative approaches are encouraged. The Action will consist of internationally recognized trendsetters in their specific areas of expertise, who impact the scientific community and cancer research worldwide.

H.2 What?

The CANGENIN website will serve both scientists and the public. The public site will contain general information on events causing cancer and the impact of DNA damage in the processes. The web site will also be a source for the press and media that follow the progress made within cancer biology research. The scientific section of the website will service the Action participants and the general scientific community and contain a regularly updated overview of the flow of scientific activities and events within the Action. Action members will have access to a password-protected site with ftp-possibilities for large-scale data transfer. Other types of communication within the Action consist of e-mail circulars.

In addition, in order to spread awareness of the new findings and their effects on the biomedical disciplines, results will be made public by press releases targeting people beyond the research community. The Action will contribute to efforts of raising awareness of science, science policies and ethical issues by participating in public and more focused forums, writing editorials and other general format publications. In addition, members of the Action will provide their expertise to the public by giving interviews to the press, radio and TV.

Scientific communications will be provided through high-ranking peer-reviewed international publications.

An essential media of imminent communication within the Action will be the Annual Research Symposium and the MC and Work Group meetings. These will provide equal distribution of most recent knowledge within the Action and foster new ideas and approaches between the participants. Integral to these activities are the Action Training Schools providing direct information and hands-on experience on various technologies. The same object will be reached through the Short-Term Scientific Missions, which will be an effective way of lateral transfer of technologies and scientific expertise.

H.3 How?

The Action internal website will be used for the documentation of the Action activities and will be accessible to the Action members, DC, Scientific Officer and Rapporteur. These include the minutes of the MC meetings, summaries of the working group meetings and the Annual symposia. All Training School-activities will be announced at the website, and participants will be listed. Similarly, brief reports of the Short-Term Scientific Missions will be posted at the CANGENIN website. These provide imminent information of the progress of the Action and facilitate the follow-up and monitoring duties by the DC. A Technical Annex will be established within the website for the purpose of delivering methodological approaches and supporting technology and methodology-transfer.
The public section of the website will contain, in addition to the abovementioned general information on the Action and its activities, scientific and general publications by the Action participants.

Annual Research Symposium and the MC and Work Group meetings will be structured in a manner providing effective and equal dissemination of the scientific progress within the Action. These will consist of scientific presentations, favouring those delivered by young investigators and researchers in training. Synopsis of outcomes of Short-Term Scientific Missions and Training Schools will be delivered. Informal discussions and Working group meetings will be arranged. Outside experts may be invited to present recent breakthroughs or areas with particularly interesting extensions for the Action.

Today, the pressure for publications in the forum of prestigious international journals is enormous and requires not only innovative approaches and breakthrough-results but also the possibility to approach the pertinent research question from several angles. The multidisciplinary nature of the Action and combination of experts in several fields will provide an exceptional opportunity to satisfy these demands. It is the clear and ambitious goal of the Action to meet these demands.

Commercial exploitation of the IP will be actively sought through the venues either provided within the Action but also through new connections with appropriate biotechnology enterprises or pharmacological companies.

Press releases and public awareness:

The Action will be committed to transmitting important findings to the public, through controlled active communication with serious public media.