European Cooperation
in Science and Technology
- COST -
_____
Secretariat

Brussels, 2 July 2010

COST 4127/10

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action MP1002: Nano-scale insights in ion beam cancer therapy (Nano-IBCT)

Delegations will find attached the Memorandum of Understanding for COST Action MP1002 as approved by the COST Committee of Senior Officials (CSO) at its 178th meeting on 25 May 2010.

_____

MEMORANDUM OF UNDERSTANDING

For the implementation of a European Concerted Research Action designated as

COST Action MP1002

NANO-SCALE INSIGHTS IN ION BEAM CANCER THERAPY (NANO-IBCT)

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

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

2. The aim of the Action is to address the basic scientific questions which underpin the nanoscopic and molecular mechanisms associated with Ion Beam Cancer Therapy.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 36 million in 2010 prices.

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

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

A. ABSTRACT AND KEYWORDS

Ion beam therapy offers the possibility of excellent dose localization for treatment of malignant tumours, minimizing radiation damage in normal tissue, while maximizing cell-killing within the tumour. The first ion beam cancer therapy clinical centres are now opening in Europe. However, the full potential of such therapy can only be realised by better understanding the physical, chemical and biological mechanisms, on a range of time and space scales, that lead to cell death under ion irradiation. The proposed Action therefore aims to combine, using a multiscale approach, the unique experimental and theoretical expertise available within Europe to acquire greater insight at the nanoscopic and molecular level into radiation damage induced by ion impact. Success in this endeavour will be both an important scientific breakthrough and give great impetus to the practical improvement of this new therapeutic technique. Ion therapy provides potentially a revolution in cancer therapy and this COST action will be very significant in ensuring European leadership in this field, providing the science background, required data and mechanistic insight which is indispensable for optimization of this new therapy.

Keywords: Stopping Power, Track structure, Dissociative Electron Attachment, DNA double strand breaks, Dose and Relative Biological Effectiveness.

B. BACKGROUND

B.1 General background

The damaging effect of ionizing radiation has been known for many years. It has been commonly accepted that high-energy tracks formed by α, β, γ radiation and atomic ions ionize cell components along the track, thereby leading to various dissociation channels and to the formation of damaging radicals.

On the one hand, this knowledge has triggered intensive research on radiation protection, and, on the other hand, the development of intensive biomedical uses of different radiation, generally called radiotherapy, used especially for tumoural diseases. In this field, clinical trials and technological advances often develop more rapidly than an understanding on a solid physical basis of the phenomena at play. Thus curative protocols are established mainly based on experience and expertise of the personnel involved and on an empirical basis, rather than on pure scientific knowledge.

Ion Beam Cancer Therapy (IBCT, or hadron therapy) represents a new and effective method for providing high-dose delivery into tumours, thereby maximizing killing of the cancer cells, and simultaneously minimizing the radiation damage to surrounding healthy tissue.

The cell killing is mainly associated with the process of ionization of the medium by the traversing ion. It is commonly accepted that secondary electrons, extracted by ionization, are mainly responsible for DNA damage, either breaking the DNA strands directly, or reacting with water molecules producing molecular radicals.

However, a theoretical description of the physical, chemical, and biological mechanisms involved is largely incomplete. One reason for this is that the relevant processes take place on a variety of scales in time, space, and energy (see Table 1). The advantages of using ion beams compared to photons are related namely to the presence of a Bragg peak in the depth-dose distribution upon ion impact. This localizes irradiation effects deep in tissue thus increasing the treatment efficiency and reducing side effects by sparing neighboring healthy tissue. Thus, the markedly greater efficiency related to this new therapeutic tool is immediately clear on a macroscopic level. However, many questions concerning the detailed mechanism involved in this novel form of irradiation remain, and their clarification is crucial in order to acquire a true physical understanding of cell killing and to drive applications.

The present research aims to understand at the nanoscale and molecular level the fundamental physical mechanisms which govern ion beam destruction of cells and to acquire quantitative measures of destruction efficiency. As in X-ray radiation therapy, it is in fact now commonly accepted that this knowledge is not merely academic but also guide clinical practice, in this case

with regard for example to the choice of ions to be used, their energy and the dose. Even more difficult issues arise on the basic research level. For example, the dose quantity does not appear to be the proper parameter to consider in the case of ions with respect to cell-killing efficiency, since several lethal effects are extremely local, occurring within a very small space scale.

By launching this COST Action, it will be possible to link expertise in several subtopics aiming to clarify the key steps in these processes which are currently obscure. This will include detailed analysis of nuclear reactions and electromagnetic processes during the propagation of ion beams in the tissue, primary ionization in the medium (water and biological molecules), direct damage and production of secondary species (secondary electrons, radicals, holes), propagation of secondary species and their attack upon DNA and radiobiological scale effects.

A COST action is the ideal mechanism for developing a more integrated and collaborative programme in IBCT, since this new field requires the networking of international researchers and practitioners from a disparate range of disciplines (See Table 1). The COST funding scheme, especially through short-term scientific missions (STSM) will boost the resolution of critical scientific problems especially across fields. The overall vision will naturally expand during this process. Excellent research opportunities will be provided for young scientists in fundamental research. The close connection of fundamental research topics of this Action to practical applications in medicine as well as radiation protection technology is very appealing.

Another important argument for choosing COST is that it supports networking activities among the groups performing fundamental research. Thus, applied science would not be the exclusive focus, as is often the case within EU Framework Programme calls. Application of the results of our research is one of the aims of this Action. However, it is also clear that without further breakthroughs in understanding of fundamental molecular and nanoscale mechanisms of radiation damage, future biomedical advances in the use of radiation as well as radiation protection would scarcely be feasible. Therefore, we believe that once this Action is launched, it will be relevant for many communities (medical, technological, industrial) dealing with radiation and radiation protection and interested in a detailed understanding of molecular and nanoscale interaction mechanisms.

Table I: Interdisciplinarity of the problem: space and time scales, and the disciplines involved in the IBCT.

Phenomenon	*Discipline*	*Space scale*	*Time scale*
Beam Generation	High energy Physics	m -km	
Beam transport	Radiation Physics	1-100 cm	10^{-7}s
Nuclear collisions and fragmentation	Nuclear Physics	Pm	10^{-22}s
Primary ionization, transport of secondaries	Atomic/Molecular Physics	0.1-10 nm	10^{-17}-10^{-14} s
Branching of secondaries, Radicals, excited species, chemical equilibrium	Chemistry	1-10 nm	10^{-12}-10^{-5} s
Local heating, Heat transfer, stress	Thermo/ hydro- dynamics	1-10 nm	10^{-14}-10^{-9}s
Dissociative electron attachment to molecules and other reactions	Quantum Chemistry	Å	10^{-15}s
Initial resulting damage effect	Biochemistry	0.1-10 nm	10^{-5}s
Repairing mechanisms	Molecular Biology	1-100 nm	s-min
Cellular network and interaction	Cell Biology	µm	Min
(Tumour) Cell death	Medicine	Mm	min-years

B.2 Current state of knowledge

The recent encouraging clinical results arising from IBCT have led to the investment of newly dedicated hospital-based facilities in several countries and intensive research into the development of the necessary accelerator technology and beam delivery. Presently, treatment planning for such therapy is based on, e.g., the local effect model (LEM), which correctly reproduces cell-survival curves. However, this model does not provide a microscopic description of the irradiation process nor an understanding of the physical, chemical and biological processes which lead to damage of cellular DNA and other biomolecular systems inducing cell death over a time scale ranging from 10^{-22}s to days or even years (see Table 1). Optimisation of these processes could vastly improve the therapy effectiveness. Results will be innovative, for example in facilitating the creation of reliable track models which are presently inadequate, noting that corresponding and much more sophisticated models form the basis of dose estimation in X-ray radiation therapy.

In order to handle this problem a multiscale approach was recently suggested and provided realistic estimates for DNA damage. This approach can be greatly improved and extended with much more complete and detailed experimental and theoretical investigations of the individual processes involved.

We note that ion interaction with various materials over a broad energy range has been studied extensively during the last twenty years. With regard to biomedical applications, the final output of these studies is usually the energy deposited along the ion tracks and dose distribution profiles in the medium. However, the level of detail we are currently proposing requires microscopic energy deposition maps, down to the molecular level. This study should be complemented by the analysis of the radiation damage in terms of induced molecular structure changes, or other effects (e.g. thermal or hydrodynamical) manifesting themselves at the nanoscale. Since the complexity increases when the energy of the primary ions and secondary electron decreases, new experiments and calculations for low energy ion interactions with biologically relevant molecules are needed. Concerning secondary electrons, results from previous, current and future experimental studies and calculations incorporated into appropriate databases will be directly included in this study.

The previous COST Action P9 Radiation Damage in Biomolecular Systems (RADAM) demonstrated in a number of ways how it was possible to elucidate several radiation related phenomena, previously poorly described, at the level of basic interactions, e.g., electron-biomolecule interactions. However, the large scope and the limited time did not allow a full molecular level analysis specific for ion beam irradiation.

Europe is presently investing in other activities related to IBCT (see below for details), e.g. through Framework Programme PARTNER and ENLIGHT. However, these are mainly at the level of application, with the aim of gaining a competitive edge over Japan.

Instead, the most innovative approach in this Action is the “bottom-up” analysis, based on molecular level and nanoscopic insights according to a multiscale framework. This incorporates all the relevant physics involved, effect by effect, on a fundamental interaction basis. The success of this approach will provide a detailed enough preliminary explanation of all the radiobiological effects involved in IBCT; this is lacking at present. In the future, this knowledge should extend or even substitute the LEM-based analyses.

Another important feature of this Action is that it will provide essential experimental and theoretical data and models that can be used as input for the advanced computational packages, such as GEANT4, PENELOPE, PARTRAC, KURBUC etc, attempting to evaluate radiation transport on the basis of a full Monte Carlo approach with accounts for processes at the molecular level. The main unresolved deficiency of such approaches concerns the limitation in the resolution at sufficiently small energy, space and time scales.

Many insights in this field are also derived from the connection with the community exploring radiation protection from galactic cosmic rays for human space exploration, where ESA and NASA are presently launching different research programs.

B.3 Reasons for the Action

The reason for launching this action is to provide the basic science to underpin ion radiation therapy for cancer treatment. The immediate benefit (2-3 years) will be an improved model of the effectiveness of ion irradiation in destroying tumours and thus means to provide more reliable estimates of dose and recommended ion type, e.g. protons or carbon ions. In fact, it is necessary to complement LEM by a molecular, nanoscale based model, tracing irradiation effects at all time scales. This can be achieved by a multiscale approach which provides a realistic estimate of DNA damage compared with experiments on irradiation of cell lines. However, in order to further develop such a multiscale model, and to calculate the efficiency of radiotherapy under a variety of realistic conditions, major interdisciplinary efforts are mandatory. Thus, future benefits will come as more data become available on the cross sections of various collisional processes, quantifying the role of different molecular mechanisms, determining the efficiencies of various competing pathways and resolving the site selectivity of damage events. Tumour destruction models will be under a continuous state of development as collaborations within the proposed COST network make increasing progress. Ever-improving treatment, based on track models, will be a very concrete outcome of this Action. The nature of the scientific problems makes it necessary to bring together researchers from diverse fields, including physics, chemistry, biology, and medicine, both academic and clinical, in a common programme.

The radiation research community lacks a complete database for the cross sections of all the different processes involved in ion beam induced damage: ionization and excitation cross sections for ions with liquid water and biological molecules, all the electron- medium possible interactions, dielectric response data, electron attachment to biomolecules etc. The installation of such a database will - as it has been for several communities, from crystallographers to astrophysicists – pave the way for intensive research in presently obscure areas of this multifaceted phenomenon.

The Action is aimed at societal needs primarily but there is clearly a major economic, scientific and technical advantage for Europe to place itself in a leading position in this ground-breaking field.

B.4 Complementarity with other research programmes

A previous successful COST Action P9 (RADAM), funded from 2003 to 2007, has shown the possibility of obtaining such a "molecular level" picture of the damaging effects induced by generic radiation (electrons, photons or ions). COST has also been partially involved in a collaboration with the project ENLIGHT (European Network for Research in Light Ion Therapy). However, to date there has never been an Action directly focused on IBCT. The present project is, therefore, focused on developing a rigorous physical description, at the molecular and the nanoscopic level, of the processes involved in tumour therapy using ion beams.

The Marie Curie International Training Network (ITN) was recently launched with the name PARTNER, Particle Training Network for European Radiotherapy (http://partner.web.cern.ch), in response to the critical need for reinforcing research and training professionals in the emerging field of ion therapy, bringing together the major applicative hadron therapy operating institutions across Europe. It attempts to promote mainly clinical biological and technical developments and to extend the clinical treatment to moving tumour-targets, which is still an open technological question. The present Action, focused instead on nanoscale insights, will be profitably complementary to the latter: on the one hand it will take advantage from the connections already in place within all the most advanced technical facilities, and on the other it will provide this growing community with the possibility to obtain the up-to-date results from fundamental knowledge of basic interactions,

crucial for improving techniques. For example, one of the targets of the latter project is the optimization of Monte Carlo codes for treatment planning. This cannot be achieved without a tight comparison with accurate analytical calculations and systematic implementation of all the relevant cross sections. These challenges cannot be met by the application community, since it lacks the necessary time and scientific expertise on molecular interactions.

Other European projects that can have a fruitful exchange with the present proposal are DIagnostic Techniques for future particle Accelerators NETwork and Marie Curie Particle Detectors. Finally, some complementarity is expected with the COST Action (CM0601) devoted to low energy electrons interactions with solids, Electron Controlled Chemical Lithography (ECCL), and another related COST Actions (CM0603, Free Radicals in Chemical Biology), where the focus on electron induced processes will provide stimulating exchanges during common meetings.

C. OBJECTIVES AND BENEFITS

C.1 Main/primary objectives

The main objective of the Action is to address the basic scientific questions which underpin the nanoscopic and molecular mechanisms associated with Ion Beam Cancer Therapy.

In particular, we point to the following general objectives:

(i) Understanding the unique features of ion irradiation on the molecular level, e.g. site and bond selectivity, clustered damage, time scales, local temperature and chemical effects. Some of the questions are related to the ratio of direct/indirect damage, preferred mechanism of double strand break (single or double electron involvement), elucidation of possible lethal effects not occurring at all in the case of photons, etc. Comparison with state of the art achievements in photon irradiation will be the final part of the analysis.

(ii) To achieve comprehensive databases of recommended values for all the major processes involved in IBCT: ion and electron interaction cross sections, energy loss in biologically relevant systems, etc. This objective implies an important experimental and theoretical effort to determine differential and integral cross sections, both elastic and inelastic, for low incident energies.

(iii) To yield a quantitative prediction of dose distribution and molecular damage generated by the passage of an ion beam through cells, for example determining the rate and type of initial double strand breaks.

(iv) To develop a multiscale code for the quantitative analysis of radiobiological effects and therapy planning, tested at different levels with experiments; also including reliable estimates of the relative biological effectiveness (RBE) for different ions.

(v) To develop a new low energy particle track simulation method based on the distribution functions derived from evaluated experimental and theoretical cross sectional data and energy loss providing information on energy distribution and induced damage at the molecular level.

C.2 Secondary objectives

Secondary objective of the Action will be:

1. To design ion scattering experiments with energy and angular resolution to measure differential and integral cross sections for low energy ion collisions (protons, alpha particles and carbon ions) with bio-molecules (mainly water and DNA constituents).
2. To characterize secondary electron generation (energy and angular distributions) by ions in gas phase and condensed biologically relevant materials.
3. To apply model potential calculations to the scattering of low energy ions with molecules.
4. To develop a new code for the calculation of energy deposition functions accounting for low energy electron-ion interactions and the angular distribution of the secondary electrons and input the results obtained to data bases.
5. Linking the new low energy simulation programme to standard higher energy codes such as PENELOPE and GEANT-4.
6. Optimal ion design for specific tumour type and depth on the basis of specific molecular interactions, accurately accounted on the basis of the fundamental data measured by the COST members.
7. Suggestion of chemical radiosensitizers specific for ion irradiation.

8. Analysis of nuclear fragmentation effects at the therapeutic energies of the ions and estimates of secondary effects due to tracks of nuclear fragments or to entrance channel ionization.
9. Low dose effects. Overcoming the problem of lack of data for late low dose effects in the case of ions.
10. Explanation of specific biological environment effects such as the Bystander Effect on the basis of realistic low energy physics description.
11. Other diseases: justification of therapeutic use of ion beams for non malignant pathologies, e.g. microsurgical tools for curing epilepsy.
12. Design of nanodosimeters, for detecting and improving the prescribed dose deposition as well as thermal enhancements in nanoscopic volumes. Dose distribution analysis for different type of ions, their energies, targets, media etc.
13. Analysis of thermal and hydrodynamical effects in the medium associated with the ion beam propagation.
14. Analysis of branching ratios for various molecular processes and events.
15. Quantitative analysis and comparison of different pathways of radiation damage of biomolecular systems induced by ion beams.

C.3 How will the objectives be achieved?

The objectives of this Action will be achieved via the coordinated activity of the large number of groups involved in this proposal. The groups which are directly involved in this proposal as well as those which will be involved once the Action is launched possess already much valuable expertise, manpower and all the required equipment for achieving the main and the secondary objectives. Therefore, a simple linkage of such groups both theoretical and experimental should already produce a significant boost to the field. In addition, the concerted effort toward the further advance of our knowledge about the molecular and nanoscopic mechanisms involved in IBCT undertaken by the leading teams across Europe and supplemented by the key specialists worldwide will ensure the success of the Action in achieving its main and secondary goals

C.4 Benefits of the Action

Europe has the potential of becoming the world leader in IBCT. Indeed, while the US ion facilities all focus on the use of protons and Japan has two well-established centres for carbon therapy (Chiba, Hyogo), it is Europe which has the largest number of ion beam therapy centres. These include the Heidelberg centre (HIT) which is envisaged to treat more than 1200 patients per year and two more centres (Pavia, Kiel) soon to become operational, whilst several more are being built (Marburg, Vienna, Lyon, Brussels, Maastricht, Stockholm) and planned (e.g. in Denmark). This Action will form a link among these centres and the larger academic based European research community in radiation sciences. In particular, the Action is intended to combine, as a starting point, the expert community devoted to IBCT, centred in the Frankfurt area (a unique concentration of leading research institutes in this field such as GSI Darmstadt, FIAS Frankfurt, HIT Heidelberg), with a group of experts on the molecular-level effects induced by radiation. The latter was set up by participants in the RADAM conference series, which though the success of RADAM is continuing after the COST Action P9 has ended. The last conference of this series was, in fact, held at the Frankfurt Institute for Advanced Studies in 2009. The proposed collaborative network will make it possible to address the leading questions concerning ion beam-induced damage and thus can provide not only a fundamental description of this complex problem on a rigorous scientific basis, but can also provide a platform for improvements in treatment procedures. The major tangible benefit to society will be greatly improved models for track description and for the damaging effect, and thus treatment, leading to standard effective procedures for IBCT. Other benefits will be economic, since Europe will lead in a major health field, and scientific with fundamental understanding of radiation damage at the molecular level, which may will have spin-off into radiation protection and other areas.

The Action, by directly connecting basic research with one of the most important technical applications in health issues, through a well organized dissemination activity, will have also the effect of attracting the interest of private investors in some sectors of fundamental research, such as molecular collision physics, traditionally seen as unrelated to medical applications. That will generate new sources of support for these fields. The Frankfurt Institute for Advanced Studies has

already established direct collaborative links in the field of IBCT with the Siemens Company, the major industrial investor to the medical applications of ion beams. This link will be strengthened once the Action is launched and the new similar links with industrial partners are likely to be created.

C.5 Target groups/end users

On the basis of the diverse objectives identified in the Action, the major users of the results are expected to be:

1. Academic members of physics, chemistry, biology, medicine and technology communities, who study basic electron and ion interactions with single molecules, radiation interactions with condensed matter and the effects of radiation in biological environments.
2. The larger radiation research community (e.g. Radiation Research Society, International Radiation Physics Society).
3. Therapy planners for ion beam cancer treatment (e.g. HIT in Heidelberg, HIMAC in Japan)
4. Developers of new techniques and equipments for ion beam cancer therapy (e.g. Siemens, Med Austron).
5. The space radiation protection research and technology community (e.g. ESA, NASA and related research communities)

A recent conference, Ion Beams in Therapy and Space, demonstrated the great common interest between therapeutical studies and those related to shielding from cosmic rays.

However the Action has a wider aim of disseminating the new achievements in biomedical uses of ion beams and broadening the public understanding of the real benefits and any concerns in using this kind of radiation. Therefore, also an important part of the Action is to disseminate its activities to policy makers and to the general public.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The most important research task to be coordinated by this Action will be the development of new modelling approaches and performing challenging new experiments directed to get a clearer and quantitative description of the essential physical, chemical and biological processes and mechanisms involved in ion beam cancer therapy.

In this Action, we wish to study essential events of the IBCT scenario such as DNA damage (in membranes etc.) on different temporal and spatial scales. The work plan will develop using the methodologies described below, involving five sub-areas corresponding to the five Working Groups (WG) described in the organizational part below.

D.2 Scientific work plan methods and means

1 Ion Propagation (Nuclear reactions and electromagnetic processes)

Accurate nuclear, atomic physics and electrodynamics computations will be performed, thus improving the current data bases in the available Monte Carlo codes (GEANT4, SHIELD-HIT, FLUKA, MCHIT) with a view to reliable estimates of the number of primary and secondary ions in the Bragg peak area, as well as the extent of the fragmentation tail (see below WG1).

The overall reliability of Monte Carlo simulations critically depends upon the accuracy of the input cross sections for energy losses of light ions in atomic and nuclear collisions with tissue as required in hadron therapy. The Monte Carlo codes mentioned are well-suited for these applications. However, none of these codes can guarantee the required accuracy (within 2%) of dose distribution and sub-millimetre target delineation in irradiated tissues. While accurate databases for nuclear stopping powers are available, significant improvements are necessary in electronic stopping powers. This is due to the exclusive reliance upon the Bethe-Bloch formula which is valid only at very high impact energies. There are other limitations of the latter approach: (1) inclusion of excitation and ionization alone, (2) neglect of equilibrium collisional processes (electron capture, projectile electron loss of dressed ions) along the ion path, especially near the Bragg peak, (3) restriction to total cross sections, despite the primary importance of energy transfer channels and

angular distributions of ejected electrons, (4) use of the Barkas effect for partial and/or complete neutralization of the projectile nuclear charge, (5) application of the Bragg sum rule to deduce molecular cross sections as sums of atomic cross sections, thus ignoring interference effects and molecular structure and molecular bonding.

We envisage to fill in all the lacunae (1)-(5) by using the state-of-the-art continuum distorted wave theories to pre-compute doubly- and singly-differential cross sections as well as total cross sections. These reliable cross sections will subsequently be prepared for usage as either modules of pre-computed tables or via parametrized Breit-Wigner-type formulae. Such improved cross section databases will be used in Monte Carlo simulations and analytical models. Both computations will be benchmarked by thorough comparisons with the existing and new experimental data on e.g. water molecules. These novel databases will be of help in accomplishing the comprehensive task of theoretical descriptions outlined in Part B with the specifics:

1. Computations of accurate atomic and nuclear cross sections for high-energy inelastic collisions of light ions (proton, alpha particles, carbon nuclei, etc.) with tissue-like materials,
2. Computations of accurate depth-dose profiles by the Monte Carlo code SHIELD-HIT using the improved cross section database from (1),
3. Optimized parametrization of cross sections from (1) to provide improved data bases of electronic and nuclear stopping powers for the other mentioned Monte Carlo codes and analytical models.
4. Improvement of nuclear fragmentation cross section code modules by implementing more realistic and newly developed models of high-energy heavy-ion collisions, including multi-fragmentation channels, such as Ultra-relativistic Quantum Molecular Dynamics (UrQMD) and Statistical Multi-fragmentation Model (SMM).
5. Experimental measurements of Bragg curves in different materials, possible thanks to the development of a new movable Tissue-Equivalent-Proportional-Chamber (TEPC) able to detect in detail dose delivered by secondary nuclear fragments ejected at given angles from the track.

2 Primary ionization in the medium (water and biological molecules), direct damage and production of secondary species

Over the past few years our understanding of ion-induced fragmentation and ionization of isolated DNA building blocks has greatly advanced. Quantities such as relative and absolute ionization and fragmentation cross sections as well as fragment kinetic energies were measured. It was for instance found that fragment ion kinetic energies can exceed 10 eV and that secondary ions of such energies can in turn lead to substantial damage of or reactive scattering from DNA building blocks. However, very often these studies are only of limited relevance due to the neglect of an aqueous environment. To better understand molecular mechanisms underlying the exceptional cell killing efficiency of ions on a fs-scale, much larger and more realistic systems need to be investigated. Ideal model systems must consist of DNA embedded into an environment closely mimicking the situation in a cell nucleus. This is of key importance, because biological effects result not only from the direct impact of energetic radiation but also from the action of reactive species produced along the track, such as water radiolysis products (OH radicals, solvated electrons). The DNA damage induced by these species is small for single events but can be of great relevance, e.g. when a large number of radicals is present or when damage cross section are large. For heavy ion irradiation very little is known about the physical processes involved in direct and indirect biological radiation on a molecular level and their relative importance.

Within this part of the project (WG2), we propose:

1. to prepare nanoscale targets of sufficient density such as isolated or nanosolvated DNA building blocks and biomolecular clusters by effusive beams and jet-techniques as well as nanosolvated oligonucleotides or duplex DNA together with structural proteins (histones) and/or therapeutic agents using electrospray ionization (ESI). First experiments have shown that with the aid of an electrospray ion source up to 20 water molecules can be attached to a negative AMP molecule, furthermore, water clusters containing more than 500 molecules have been produced. It is the aim to analyze in detail the ion-induced fragmentation as a function of the number of surrounding water molecules or water shells. We expect that these studies should should clearly distinguish between direct and indirect damage processes, as radicals which are formed by the ion irradiation in the outer water shell are very likely to interact with the biomolecular species.

2. to apply crossed beam techniques and to perform experiments in ion traps which will combine ESI and jet targets with state of the art experimental techniques such as coincidence time-of-flight mass spectrometry or recoil-ion-momentum spectroscopy. Both methods will give access to the ion induced molecular dynamics in unprecedented detail. Experimentally accessible quantities will be for example kinetic energy distributions of secondary ions and electrons as well as relative and absolute fragmentation cross sections. Investigation of the effect of solvation will allow the study of indirect effects on the nanoscale and on an event by event basis.
3. to perform new calculations on the most relevant media for getting the yield of secondary electrons, their kinetic energy distribution and eventually angular distributions of electrons generated in the whole ion energy range of interest. This will be done by further tuning a recent successful parametric model suitable for liquid water and extending it to other molecules, possible sources for primary ionization in the cell nuclear environments (histones, DNA bases, other proteins). Estimates of the relevance of secondary sources of electrons due to nuclear fragment tracks will also be computed. The results will be compared with experimental findings.

3 Propagation of secondary species (secondary electrons, radicals, holes)

The highly concentrated dose deposition at the end of the ion tracks, around the Bragg peaks, achievable with IBCT, means that dose delivery can be controlled with respect to depth by adjusting the incident energy of ions. There are several simulation programmes available on the market which incorporates ion interaction for dose evaluation purposes. However, most of them are based on a macroscopic description through such gross energy deposition parameters as the stopping power.

For these reasons we propose, in addition to other tasks, a new analytical as well as a new Monte Carlo simulation code to obtain single particle tracks from the very high incident energy to their final thermalisation in the medium by including all secondary electron tracks which can be generated by the initial and all subsequent ionization processes. This new code will use as input parametrised differential and integral interaction cross sections and energy loss distribution functions which we will measure or calculate, in concordance with data existing in the literature. The code will be compatible with available high energy codes.

The propagation of the delta electrons and other secondaries will be followed via cross-checking with analytical and Monte Carlo methods, as well as via experiments such as electron energy loss spectroscopy, thus improving the ongoing systematization of all the cross sections of the processes involved (WG3). Main topics covered by this part of the research programme are:

1. Model potential approximation for ion-molecule collisions.
2. Monte Carlo simulation methods for low energy particles (step by step simulation procedures, low energy single particle track simulations, applications to nano-dosimetry).
3. A new analytical model for the propagation of these electrons will be improved and tested at several stages by comparison with experiment and Monte Carlo simulations.
4. One of the main goals is the estimation of new realistic dose distributions as well as obtaining further detail on the quantification of the damage effectiveness that cannot be fully explained by the dose quantity. This gives some direct information for the RBE evaluation. For example, the number of electrons with a specific energy will be estimated as further information providing a more nearly nanoscopic description for dosimetric purposes. This will also lead to an understanding of the fundamental point of whether the process of double strand break formation can be regarded (in the case of ion irradiation) as a sequence of two independent electron attacks or as a double collision of a single electron.
5. A similar method will be used in describing the formation and propagation of radicals, as well as the possible secondary chemical reactions that these may undergo before arriving at the biological site of damage. The propagation of holes will be also followed as this can be a further source of damage.
6. Furthermore the effect of local heating generated by these electrons around the ion track will be evaluated and its potential damaging efficiency will be estimated. This will involve several different pathways: pressure waves and thermal spikes, chemically-induced alteration and inhibition of specific molecular processes.
7. Molecular dynamics simulation will be also part of this section, in order to evaluate the response of DNA molecules and nuclear proteins to thermal spikes and describe the ultrafast energy relaxation dynamics, folding unfolding-mechanism changes, fragmentation etc.

4 Electron attack on DNA (dissociative electron attachment and direct ionization)

Sanche and coworkers have discovered that not only photons, but also electrons with energies below the ionization thresholds can generate single and double strand breaks. This severe DNA damage was ascribed to the formation and ensuing decay of a broad variety of Transient Negative ions (TNIs) of the various components of the initial double helix structures.

Electron ionization and Dissociative Electron Attachment (DEA) calculations through quantum dynamical scattering and advanced experiments in different sample media, will provide cross sections for the efficiency of the various processes of strand break (WG4). The work plan for this part of the Action is as follows:

1. The very considerable experimental expertise of some of the present groups in these specific processes will be crucial in definition of the effect associated with electron attack on the target molecules. Furthermore, the stability of any product ions can be probed utilizing special mass spectrometric techniques such as mass analyzed ion kinetic energy scans. In the case of low-energy electron attachment to DNA bases and amino acids remarkable site selectivity for the dissociation reactions has been discovered. In recent years studies pickup of gas phase biomolecules into nanodroplets of superfluid has been initiated with a view to achieving vibrationally cold complex targets. This technique also enables the formation of well defined complexes such as nano-solvated biomolecules that are for instance surrounded by a particular number of water molecules. Here these techniques will be combined and optimized to probe the effect of secondary electrons having initial energies from about 100eV down to thermal energies in well defined nanometer sized models of a cellular environment.
2. Initial targets will be single DNA bases and amino acids solvated by a well defined number of water molecules. The effect of neighboring water molecules can thereby be probed precisely. We expect a stabilization of excited biomolecules upon rapid energy redictribution to the surrounding water molecules. In a recent study it has been demonstrated that pure He nanodroplets efficiently quench all slow decomposition reactions, observed in gas phase, that require multiple bond cleavages and substantial rearrangement.

3. In the next step larger building blocks of DNA and proteins such as nucleosides, nucleotides, oligonucleotides and polypeptides will be investigated with and without water and at different temperatures (0.38K in He droplets to the threshold of thermal decomposition). Various methods of vaporization of these low-volatile substances will be utilized including laser induced acoustic desorption (LIAD), fast and pulsed heating via hot wires or lasers and heating in ovens, in all of which the relevant groups are expert.
4. The corresponding theoretical description of DEA, at the molecular level, of the complex energy redistributions which can lead to the final break-up into stable fragment anions has been attempted by calculation. In particular, the detailed spatial analysis of the metastable electron wavefunctions in the initial geometry and the study of the associated resonances which yield specific bond breaking can allow the identification with good reliability of the most likely dissociation pathways and the chemical nature of the final, neutral and ionic fragments to be compared with experiments. The contributions from the theoretical/computational groups will therefore be directed towards the following aspects: (i) accurate evaluation of integral partial cross sections and of stopping power parameters, (ii) angular distributions of scattered electrons from biomolecules and DNA strands; (iii) resonant features and allocation of energies and the associated bond breaking characteristics of resonant states, (iv) analysis of fragmentation pathways and identification of the most likely product ions of in the fragmentation of biomolecules.

5 Radiobiological scale effects (DNA DSBs detection, prediction and cellular consequences)

At the DNA and cellular level, our understanding of the mechanisms of ion interactions is limited and the relative effectiveness of different ions in inducing damage needs to be assessed using a range of experimental approaches, with results feeding into the development of models of biological response. At the DNA level, lesion formation is driven by models of clustering of damage and lesion complexity. However, there is a lack of robust experimental data for DNA and cell based models covering a useful range of ions and energies. Both the response to core ion interactions and longer range delta ray effects need to be assessed to provide a complete picture of track interactions at the molecular and cellular levels. From this information, it will be possible to obtain DSB rates generated in cells targeted by the therapy under a range of practical conditions. The goal is to extend modelling to the cellular scale, from a sequence of pure molecular scale events by:

1. Validating lesion clustering in simple plasmid models and cell systems as input parameters into modelling approaches. The effects of single ions as a starting model of ion-interactions can be determined by microbeam experiments with ions at Bragg peak energies on different types of cells, as well as on isolated plasmids, revealing DSBs through foci localization, or by atomic force microscopy and electrophoresis techniques. All these methods will offer a benchmark on the actual DSB production in cells (WG5). A new technique for DSB quantitative evaluation using a TUNEL-ELISA based assay will be also used and validated. Molecular dynamics simulations on DNA strand motion after damage will be compared with observations by foci localization. The reparability of this localized DNA damage can be followed in real-time in living cells using fluorescently tagged protein fusions (GFP) of common repair proteins which are known to play an important role.
2. Understanding mechanisms at the cellular level by mapping the response along the Bragg curve to simulate the clinical situation and to determine the 3D dependence of ion interactions with changing energy. This will feed into biological studies on the effectiveness of a range of light ions in cell and tissue models and thus to develop more robust treatment prediction models which can be tested alongside current radiotherapy approaches. Advanced therapies being used clinically, such as intensity modulated radiotherapy (IMRT), utilise the delivery of multiple modulated beams to map dose to the tumour with improved accuracy whilst minimising the dose delivered to organs at risk. Particle therapy is also moving towards the use of intensity modulated beams, but there is a lack of biological models which can predict the effectiveness of these approaches. One complexity is that, at the cellular level, as well as direct DNA damage mediated responses, cell to cell communication driven responses such as 'Bystander effects' play a role. Mapping the response of both temporally and spatially delivered beams in cellular models will be the first step in approaches to develop more robust radiobiological models for advanced therapies for both charged particle and photon based approaches.

E. ORGANISATION

E.1 Coordination and organisation

This Action requires a well defined management structure to achieve its objectives. Both organizational and research-relevant activities will be structured through two committees, the Management Committee (MC) and the Scientific and Technical Programme Committee (STPC).

Subject to nomination by the COST National Coordinators (CNC), the MC will comprise one representative from each of the consortium teams. Two representatives from industrial or health companies will play an important role in the implementation of new technological achievements. Tentatively, we plan to involve representatives from the Siemens and the Heavy Ion Therapy Center in Heidelberg, with whom collaborative links of some members of the consortium have been already established. The decision on this will be taken by MC at its first meeting.

The Project coordinator will Chair the MC with both a Vice-Chair and Secretary being appointed from amongst its first members.

The MC will meet annually and will be responsible for the overall direction of the Network. Its primary tasks are:

- Promoting the scientific activity of the programme.
- Enhancing the co-operation between members; stimulating/developing new joint studies and promoting the mobility of researchers (through STSMs).
- Providing opportunities for sharing instrumentation facilities and expertise between research teams for the pursuit of collaborative projects.
- Organising dedicated symposia and workshops to discuss and plan current and future collaborative research, with an emphasis placed on oral presentations by younger researchers.
- Providing specialised training workshops on cross disciplinary skills paying special attention to contributions from medical centres and industrial partners.
- Identifying other European and/or international networks where information exchange or joint activities are of value and to initiate collaboration with those.
- Interacting with medical centres and industry to establish collaboration, information exchange and to organise practical training of young researchers.
- Interacting with media and other organisations to promote the programme and to make it accessible to the general public and political decision-makers acting both nationally and cross-nationally.

- Arranging for training courses/workshops across the Action network and identifying and implementing best practice across the various research fields to ensure that an adequate pool of trained researchers is incorporated into the different communities involved in the Action (academic research, medical practice and industry) when the Action comes to an end.
- Reporting and disseminating the results of the scientific research programme.
- Establishing and maintaining a functional web site for the Action (see section F) Coordination of national research in the research areas covered by this proposal. This will be implemented by STSMs, exchange visits or by other means of cooperation (e.g. equipment or computer facilities sharing), creation of joint research teams, participation and organization of conferences, workshops, seminars, training schools, websites, etc.).
- Administration of the Action budget and preparing reports to the EU administration. The MC will act as final arbiter in the event of any disagreements amongst partners. All partners will be required to sign an agreement recognizing the authority of the MC.

The STPC will be formed by consensus at the first MC meeting and will consist of one leading participant from each of the five identified areas of expertise and two representatives from industrial or health companies that will be involved in the dissemination of new technological achievements. The STPC will be responsible for:

- Organizing WG, which will be initially theme oriented but attending to the multidisciplinary complement required by each group to follow the Action's objectives.
- Defining and supervising the contents and participants of the scientific, technological and training activities programmed in this Action. Special attention will be paid to ensure the integration in these activities of all the disciplines and communities involved.
- Locating and attracting new groups interested in the Action, especially from the biomedical and industrial community, taking special care of their integration into the Action objectives.

The milestones for this Action will be as follows: (i) setting up the organizational and communication structure of the Action; (ii) organization of the first Nano-IBCT conference at which state-of-the-art achievements in the field will be reported and the coordinated actions will be discussed; (iii) setting up the data base for the molecular data relevant to the multiscale approach and nanoscopic insight into the IBCT; (iv) organization of the annual common meetings/conferences of the COST Nano-IBCT community in order to facilitate discussion and information exchange, to evaluate recent achievements, to coordinate joint research efforts and to disseminate the knowledge in the field.

E.2 Working Groups

Subject to discussion within the initial MC, the Action's programme will be divided into five, interrelated Working Groups (WGs), each led jointly by one experimental and one theoretical leading expert in the appropriate field. We consider the WGs as a useful way of extending the Action beyond the membership of the MC and of sharing workloads. Tentatively, we suggest the following WGs, which cover the whole spectrum of activities within the Action:

WG1: Propagation of ions (nuclear reactions and electromagnetic processes);
WG2: Primary ionization in the medium (water and biological molecules), direct damage and production of secondary species;
WG3: Propagation of secondary species (secondary electrons, radicals, holes);
WG4: Electrons degradation of DNA (dissociative electron attachment and direct ionization);
WG5: Radiobiological scale effects (DNA DSB detection and prediction).

After the WGs have been formed the STPC will be reorganized to consist of the WGs chairs and a chair and vice-chair elected by the MC. On an annual basis the WGs will report to the STPC which will review the major scientific tasks of every WG and the overall tasks of the program. The STPC will then assess progress in the tasks and the means to achieve them.

E.3 Liaison and interaction with other research programmes

The Action will interact with the world-wide community of radiation users through participation in international conferences and professional meetings. It will organize joint meetings of scientists working in different scientific disciplines and practitioners (International Radiation Protection Association (IRPA), American Association of Medical Dosimetrists (AAMD), European Society for Therapeutic Radiology and Oncology (ESTRO)).

We shall use all available communication means like newsletters, e-mail distribution lists, webpages in order to disseminate the information about current activities within this Action to the maximum a broad audience of researches, industrialists and potential partners.

International partners from Canada, Australia and Japan, who declared an interest in this Action, are open to participate in the Action as soon as it is implemented by supporting joint meetings and exchange visits from their own budget.

We will invite members of the former and currently running projects (RADAM, ECCL, FRCB, PARTNER and ENLIGHT, see sections B.2 and B.4) devoted to complementary objectives to participate the COST Nano-IBCT conferences and workshops.

During the Action permanent monitoring of the activities, in particular within Europe, in the adjacent fields of research will be organized in order to take benefit from potential cooperative links and to disseminate the knowledge.

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 MC will place this as a standard item on all its MC agendas. The Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas.

It is the declared intention of the proposers and participants of this Action to promote equal opportunities for female and male participants with regards to the organization and decision making of the Action. Among the groups promoting this Action there are quite large ratio of female scientists, e.g. Frankfurt (5/11), Madrid (8/15), Stockholm (2/4) etc. This COST Action will respect an appropriate gender balance in all its activities and the MC will place this on all its agendas. The Action will also be committed to the extensivement of early-stage researchers. This item will also be placed on all MC agendas.

Many of the female scientists involved in this Action already occupy important administrative positions and play key roles in the research. Currently, from the groups that have indicated a willingness to participate in this Action about two thirds are male researchers and one third female researchers - most of whom are young researchers. This reflects the fact that it was considered very important both to promote gender balance within the Action and to strongly involve young researchers in the decision making.

The important role played by early-stage researchers in this Action has been indicated in different sections along this proposal. We will widely advertise all the Action activities by all possible communication means, as described above, in order to involve the larger number of highly motivated young researches. The gender equality will be stressed.

An important reason why this Action will be useful to the younger science generation is because we expect a visible motivational effect among the early stage researchers working with basic science, where often a lack of vision of concrete applications has a negative effect. Within this Action the close connection between their work and outstandingly important medical applications will create a high degree of enthusiasm for their research work which will be reflected in productivity.

This Action will also be very useful for early-stage researchers providing them unique opportunities to establish contacts and to collaborate with the leading groups working in the field covered by the Action right across Europe. This will be an essential complement to the local and national PhD and young scientist training programs. Such a possibility will enable young researches to identify the most challenging problems open in the field and the most efficient ways for their solution.

F. TIMETABLE

This Action needs four years to achieve its aims. During this period we envisage a breakthrough in understanding of molecular and nanoscopic events in the physical, chemical and biological mechanisms of IBCT, which will be achieved via collaborative work of the research, industrial and medical groups and scientists involved. The knowledge generated will be used in medical applications and practice. It will lay the basis for Europe to acquire and maintain a leading role in this area, an outstandingly important medical technology of the 21st century.

List of activities:

Year 1: Initial meeting of MC with COST Administration. Formal appointment of Chair and Vice-chair and appointment of Web and Newsletter editor. In this meeting the STPC will be formed, which will meet in the same year, preferably at the same venue and subsequently to the MC meeting. At its first meeting the STPC will organize the WG which are preliminarily numbered from 1 to 5 in section E2. The WG will all meet before the 6th month to review the current state-of-the-art and to define their tasks and the means to achieve them. In the third quarter the first annual Nano-IBCT conference will be held, at which the MC will meet to review the strategy to achieve the main goals of the Action. The STPC will also meet at the conference to review the progress reports of the WGs and to act upon them. The main agenda for this meeting is to review the scientific programme of each WG and to ensure adequate overlap and interaction between the individual WGs.

Year 2: The WGs will meet at least once. Acting upon need these meetings can be supplemented by training workshops. Usually, not more than two such training workshops per year will be held. Concrete plans for training workshops will be considered and adopted by the STPC and MC at least half a year in advance of the event. The WG meetings may also be joint meetings with more than one WG participating. The 2nd annual Nano-IBCT meeting (Nano-IBCT2) will take place and industrial partners (identified by STPC and MC) will be invited to present their vision of the benefits of the Action. The STPC will also hold its annual meeting at Nano-IBCT2 to review the progress of the individual WGs and their interactive work. The MC will meet again at Nano-IBCT2.

Year 3: The third year will be organized similarly to the second year, but we expect to develop further industrial links, to evaluate the achievements of WGs and to make a corresponding refinement of the scientific programme. We also expect to host a meeting specifically to discuss possible commercial aspects of this COST Action and to set up the Nano-IBCT Data base.

Year 4: The activities for the closing year will be similar to the second and third years except for an additional closing meeting of the MC at the end of the year. It is anticipated that it will take place at a major international conference organized at the end of the Action. This conference will be the pre-eminent Conference on Nano IBCT and related topics and will be widely open to non-network members. Conference proceedings will be published in collaboration with the IOP Journal of Physics: Conference Series. A special volume summarizing the Action's research may be published in collaboration with a scientific editorial company.

G. ECONOMIC DIMENSION

The following "COST countries" have actively participated in the preparation of the Action or otherwise indicated their interest : Austria, Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 36 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.

In addition, the following non-COST countries have expressed their interest to participate: Australia, Canada, Japan and USA.

H. DISSEMINATION PLAN

H.1 Who?

As mentioned above, the great impact of the present research will be not only dedicated to the academic community but to a much more extensive group, including certainly industry and hospitals. The target audience thus will be multifarious on different levels:

1. the atomic/molecular physics community and other related basic science communities interested in cutting edge applications of their work
2. the larger general radiation physics community and with all related infrastructure and manpower e.g. Synchrotron Radiation Laboratories
3. the medical community and related hospital facilities operating in the growing field of hadrontherapy
4. industrial bodies developing implementations in the technical tools for hadrontherapy
5. the political bodies who can support the development of hadrontherapy centres in Europe and its use for an increasing number of patients
6. the general public in Europe who regard with great interest all curative techniques for cancer and who seek a better grasp of the true promise of the technique.

H.2 What?

The results obtained by the Action will be published in the refereed scientific literature. Computer programs developed as part of the Action will be made available to Action partners and, where appropriate, also published. Data compilations will be published in book form. Interim reports and preprints of publications will be available electronically from the Action's web page. The main purposes of the website are:

1. Communicate news and announcements to the researchers participating in the action.
2. To allow rapid and effective reporting and dissemination of the results of the scientific research programme.
3. To provide web based mailing-lists and an archived discussion forum.

4. To promote the Action and make it accessible to the general public and thereby to political decision makers acting on national and cross European levels.
5. Create databases of articles and data and compile other information for knowledge transfer.

The creation and maintenance of an up-to-date database for all the relevant cross sections of the processes involved in ion beam cancer therapy will provide a reference point for the present and the future broader community, with a role analogous to that of the existing databases for astrophysical collisions, molecular spectroscopy, structural data, biological processes etc.

H.3 How?

The web page will be partly password secured and allow upload of data, findings or interpretations for discussion. There will be a web-based mailing list for members of the Action only, for discussions and rapid information exchange and a password protected databases of articles, data and other information for knowledge transfer. Activity reports, publications and news will be published on the open-to-all part of the web page.

To accelerate decision making and for budgetary reasons MC, STPC or WG decisions may be taken at any time by electronic communication. The consensus on such decisions will be documented on the password protected part of the web page. An annual scientific meeting will be held. It has been considered as strategically more efficient, instead of creating a new series of conferences, with a new name, rather to continue the well established series of conferences RADAM which continued after the expiring of the previous Action and got naturally a special direction towards ion-induced radiation damage. This annual meeting will discuss scientific progress in all the strands and allow sufficient time for general discussion to allow new results to be reviewed and new, unexpected research avenues to be debated. The majority of the talks will be given by the younger scientists involved in the Action and those who have benefited from Action hosted STSMs, which again will predominantly be career young researcher. The meeting will be open to all members of the action with typically a few non-European researchers attending by invitation. Towards the end of the Action a major international conference open to non-network members will be organized.

Conference proceedings will be published in collaboration alternatively one year with an international journal focused on atomic and molecular physics and the following with another international journal focused on radiobiology, in order to attract from one side interest of the basic science community to this field and from the other to participate the results to the wider applicative community. A special volume summarizing the Action's research may be published in collaboration with a scientific editorial company. Communications within the Action will be enhanced through a Newsletter. This will be circulated electronically and will include a quarterly report by each of the partners, abstracts of papers submitted for publication, meeting information and reports, adverts for postdoctoral positions, news of visits between groups and a monthly review of the latest international research papers in radiation applications to biomedicine. An abbreviated version of the Newsletter will be available to all international researchers upon registration. The Newsletter will be maintained on the Action's web site which will also include full details of the partners, their research interests, list of publications, ongoing research, personal profiles, etc.

In order to ensure updates to the website and production of a newsletter a web and newsletter editor will be appointed from amongst the Action's members at the first MC meeting.