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Subject :	Draft Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action 844 "Apoptosis and programmed cell death: Molecular mechanisms and applications in biotechnology and agriculture"

DRAFT

Memorandum of Understanding

for the implementation of a European Concerted Research Action

designated as COST Action 844

"Apoptosis and programmed cell death: Molecular mechanisms and applications in biotechnology and agriculture"

The Signatories 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 400/94 "Rules and Procedures for Implementing COST Actions", the contents of which are fully known to the Signatories.

2. The main objective of the Action is to combine interrelated European expertise to understand the molecular mechanism of apoptosis and to use this increased knowledge in the development of new approaches in biotechnology, agriculture, food industry, pharmacology and novel strategies in the prevention of environmental toxicity.

3. The overall cost 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 12,5 million at 1997 prices.

4. The Memorandum of Understanding will take effect on being signed by at least five Signatories.

5. The Memorandum of Understanding will remain in force for a period of five years, unless the duration of the Action is modified according to the provisions of Chapter 6 of the document referred to in Point 1.

TECHNICAL ANNEX

COST ACTION 844

Apoptosis and Programmed Cell Death:

Molecular mechanisms and applications in biotechnology and agriculture

A. BACKGROUND

Before the concept of Apoptosis, otherwise and in a broader sense called Programmed Cell Death, death in living systems was considered to be the result of external insults caused by numerous agents. Accordingly, death was thought to be inflicted and the cells to behave passively. The notion of cell death was revolutionised when it was discovered that it can also occur through an active biological process (suicide, self-destruction). This type of cell death was initially described by three British scientists (Kerr, Curie and Wyllie) who named the process "Apoptosis". Apoptosis can be distinguished from necrosis by a number of morphologic and molecular features. The phenomenon was first identified in mammalian tissues in vivo, then in cell cultures. However, the concept itself gained considerable credit when modern techniques including molecular biology showed that like cell proliferation and differentiation, Apoptosis is a genetically controlled general biological phenomenon occurring in nematodes, plants and even in unicellular organisms.

Several elements contribute to make Apoptosis and programmed Cell Death a phenomenon of major importance:

1. Because it went unrecognised for so long, many biological concepts must now be revised to integrate the concept of Apoptosis. For example, before the concept of Apoptosis, the biological control of cell populations during organogenesis was attributed to cell proliferation and cell differentiation; cell death was rarely considered.

2. Programmed cell death is an integral part of many aspects of plant development including xylogenesis, sex determination, leaf abscission and the hypersensitive response to pathogen infection. In each of these cases, specific groups of cells within a larger population of living cells are triggered to die.

3. Understanding the significance, molecular details and regulation of apoptosis and programmed cell death in plants may provide the basis of new procedures in agricultural sciences and everyday practice, particularly in respect to senescence, fruit ripening and pathogenic response.

4. Cell death is a general biological phenomenon which continues to occur throughout the lives of organisms and is necessary for tissue renewal. The impact of tissue self-renewal has been underestimated and now constitutes a new avenue for understanding and prevention of ageing.

5. The discovery of Apoptosis revealed the existence of a pathology of cell death: an excess in cell death induces deficiency and aplasia; a decrease in cell death, associated with poorly balanced cell proliferation, causes hypertrophy and favours tumour formation.

6. Apoptosis is implicated in several of the human and animal pathologies which are of current major health concern: infectious diseases, neurodegenerative disease, cancer, ageing. Its importance has been recognised in several veterinary diseases.

7. Apoptosis and its pathology is a major issue in relation to environmental toxicity and to possible prevention measures.

Therefore, scientific, agricultural, medical and social-economic progress arising from the field of Apoptosis requires a concerted, multidisciplinary effort on the part of scientists from a wide variety of disciplines and is a major concern of the food and pharmaceutical industry. This hot and frontier area of contemporary research requires coordination, rapid and efficient dissemination of knowledge.

Since Apoptosis emerged as a major biomedical and biotechnology issue, rapidly increasing and very competitive research activity has developed. Although Apoptosis was originally a European idea, current research activities have been shifted to the United States and Japan. While even 8 years ago the majority of the publications came from Europe, recent data show that more than half of the yearly number of about 2000 apoptosis publications comes from the USA. The main reason of this unexpected drift of activity from Europe to the USA in this hot research area of biotechnology, plants and medicine is the lack of appropriate communication and cooperation among European research groups. Another reason is the lack of massive support by public and private funds as opposed to the faster reaction of funding agencies and industry in the United States and Japan where a large number of new high tech companies have specialised to Apoptosis.

COST with its flexibility and well defined system may provide the best way to intensify cooperation among those groups which have enough research support but may improve their scientific output further if joined by others in fast exchange of knowledge, tools and new information. Furthermore, the proposed COST action intends to attract the attention of the private sector in an organised way to facilitate investments in, and support of, applied research in this rapidly growing area.

B. OBJECTIVES AND BENEFITS

The main objective of the action is to combine interrelated European expertise to understand the molecular mechanism of apoptosis and to use this increased knowledge in the development of new approaches in biotechnology, agriculture, food industry, pharmacology and novel strategies in the prevention of environmental toxicity. A strong emphasis will be given to build a bridge to industry and to train young scientist in the participating laboratories increasing the future impact of European science and technology. To the knowledge of the proposing group there is no other network in place or planned to cover this very important area in the European scientific community; therefore, it seems that there is an urgent need to initiate such a programme.

C. SCIENTIFIC PROGRAMME

The proposed research action has as its main goal to learn the detailed molecular mechanism of apoptosis with the help of close collaboration between teams involved in this field. The obtained knowledge will be used for developing new methodologies, diagnostic techniques and compounds, to initiate the development of new agricultural procedures and to find ways of preventing environmental toxicity related to pathologic Apoptosis in plants and mammals.

The Action can be divided into 4 different but inter-related topics with four working groups which will have very close contacts:

Working group 1.: Understanding the *basic molecular mechanisms* operating in Apoptosis. The activities of this group will be the main core of the action which will focus on regulatory mechanisms, signalling pathways, execution enzymes, target molecules of execution enzymes and natural inhibitors of Apoptosis in mammalian tissues, in plants and in the nematode Caenorhabditis elegans (the model organism of research on programmed cell death). There are many strong groups in Europe working on each of the aspects listed above (see the attached list of laboratories expressing their interest) who are ready to collaborate, to exchange reagents, to send young Ph.D. students and postdocs to other collaborating laboratories. This working group will serve as the source of new ideas, inspiration and technical base for the three other working groups.

Working group 2.: *Apoptosis or Programmed Cell Death in plants and its potential in agricultural sciences.* This group will focus on understanding the molecular details and significance of natural cell death phenomena specifically in plants, then on the application of the new knowledge in agricultural sciences. The work of this group will be based on the following points – in addition to the understanding that it will be strongly linked to the continuous activities of working group 1:

– The death of single cells or small groups of cells in plants may be a part of normal development as is the case in animals. A special case is the formation of the tracheary elements.

– There are many examples in plants in which whole organs, such as leaves, flowers and fruits may die (programmed organ senescence).

– In some cases, the death of small groups of cells is not a normal part of development, but only occurs as a response to certain stress, such as infection (hypersensitive response).

– There are similarities in the molecular mechanism of natural cell death in animals and plant (proteases, reactive oxygen species, nuclear changes, signalling). However, some important differences should be considered (different life cycle, developmental processes and anatomy, cell wall, vacuoles) in relation to cell death processes as well.

– Detailed studies of cell death systems unique to plants will not only aid in understanding plant development, but may lead to improvements in the abilities of plants to resist predation and disease, as well as to gains in crop production and food preservation.

Working group 3.: Development of new *tools for the detection and influence of Apoptosis* and Programmed Cell Death in plant and mammalian cell cultures, in mammalian tissues, in plants under in vivo conditions. The activity of this group also will be closely linked to group 1 and somewhat to group 2 as well, since the new techniques and newly discovered compounds will be initiated by the knowledge obtained in molecular studies of Apoptosis in general and in plants in particular. This group will also initiate studies to find *new biotechnology applications*, particularly in the food industry, of the molecular results obtained by the European teams operating in this COST Action. In addition, *new chemical and pharmaceutical approaches* will be developed for either the initiation or blocking of the Apoptosis process in plants, in animals and in humans. The main goal of this working group is to identify new targets, to evaluate the apoptotic effects of already existing chemical agents and compounds, to find biological systems for their screening.

Working group 4.: *Links between environmental toxicity and Apoptosis.* The focus of this group will be targeted to the toxic effects of various environmental compounds leading to typical or pathologic forms of Apoptosis in plants and in mammalian tissues. An attempt will be made to find the molecular targets of these compounds and harmful agents, then to learn how their damaging effects can be prevented using the knowledge obtained in molecular studies of apoptosis and in model experiments.

D. ORGANISATION AND TIMETABLE

The organisation and coordination of the Action will be carried out by the *Management Committee* (MC). The MC will be formed during a meeting in Brussels organised by the COST Secretariat; a president and a vice-president will be also elected. This will be followed by a joint meeting of all participants where the formation of the working groups will take place. As it is shown in the list of laboratories, the participants already have expressed their preliminary interest in one or two of the four working groups. *Each working group will have a coordinator* (and a substitute) to follow the progress of tasks in the group, to initiate the organisation of mid-term workshops, to facilitate the mobility of researchers (with strong emphasis on young scientists) between laboratories involved in the working group. It will be the task of these coordinators, together with the president and vice president, to invite the representation and active participation of the industry throughout the action and to facilitate the utilisation of patents initiated by the participating laboratories in the field of this research area. The COST Action will be open to new members up to an optimal point (maximum 4 participants from each country) and depending upon new developments in this vastly changing research area.

The advanced communication systems will be used as the main technique for the continuous dissemination and exchange of information. First, an *e-mail network* system will be developed – one for the whole action and four separate ones for the working groups – through which participants can be notified about upcoming events, new developments and organisational matters. This basic informational will be supported by an *interactive web site/home page* established at the very early stage of the programme by the proposing laboratory. At this web site *each working group will have its own section* – controlled by the coordinator – where announcements, news and timetables will be found with the possibility of the addition of new information by each participating members using their own passwords. In addition, the following sections will be kept active and fresh by the same way: *New Developments and Results of the Action, Summary and Conclusions of Events, Patents, Job Hunting and Available Positions for Young Colleagues, Fellowships, Collaborations, EU Activities Related to Cell Death, Cell Death Firms, Reagents and Tools, Upcoming Events, Important Links, Discussion Forum.* Using these advanced communication technologies, a very informed network can be developed where information flow is very fast, every issue is covered by easy accessibility and dissemination and utilisation of results are not delayed. The major results of the Action will be on the open section of the web site where a broad publicity and valorisation can be achieved.

The planned duration of the presented COST is 5 years carried out according to the timetable shown on attached Figure. It should be noted that Working Group 1, as the driving force of the Action which provides understanding in molecular mechanisms and inspiration for the three others, has more frequent activities.

The Management Committee will meet at the indicated time intervals to decide on upcoming events, site of meetings and any technical details emerging during the course of the COST Action. Continuous evaluation of the Action is also the duty of the Management Committee. As a general rule these meetings will be held in conjunction with working group or annual meetings. The COST national coordinator and the national representative of the host country in the Technical Committee for Agriculture and Biotechnology will always be invited.

Milestones:

– The first milestone is related to the first Annual Workshop where the structural and functional aspects of the Action will be finalised, the working groups set up and their focus of activity formulated; the e-mail network and the web site will already be operational and ready to serve as the major informational basis.

– The second milestone is the middle of the 3rd year. At this point it should be clear how effective and useful the Action is. Broad evaluations will be made and reported by the Management Committee based on the activity of the Working Groups and the Committee itself. Major issues to be addressed are the following:
Have the working groups developed their focused activities? Have they initiated the flow of information, exchange and training of young scientists? Have they concentrated on dissemination of methods, techniques, tools and reagents? Have they attracted the interest of industry and served as a link between research and development? Has the concept, that the formation and emphasised activity of one group (Working Group 1 on molecular mechanisms) should serve as the basis of scientific activity, worked out as expected? At this mid-point, the specific results of the Action (publications, patents, new methods and tools, collaborations and shared research grants) will be also collected and presented to members and to the EU. In terms of technical operation the efficiency and usefulness of the interactive web site will be critically analysed. Naturally, the evaluations will be followed by corrections if necessary including the change in key personnel.

– The third milestone is the end of the Action, where the Management Committee will summarise the whole action measuring its usefulness to the initial purposes by outputs and results including the number of young scientists trained, the number of publications, discoveries and patents linked to the activity of the programme, the number and types of agricultural, industrial and biotechnology applications achieved, the environmental initiatives and protective procedures resulted from this COST Action. Finally, an analysis will be carried out of how it has served the development as well as effectiveness of European science and whether it could reverse the trend of losing influence of Europe in this hot and frontier area of life sciences.

E. ECONOMIC DIMENSIONS

Researchers from the following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest so far:

Austria, Czech Republic, France, Germany, Greece, Hungary, Italy, Ireland, The Netherlands, Norway, Portugal, Romania, Spain, Sweden, Switzerland, United Kingdom.

In each participating country 2-4 persons are expected to be actively involved in the projects related to the proposed COST action. In the case of the abovementioned 16 countries this amounts to about 40 persons per year, that is 5 years x 40 persons, 200 person-years as the basic work power of this Action.

On the basis of national estimates provided by the representatives of these countries and taking into account the coordination cost to be covered over the COST budget of the European Commission, the overall cost of the activities to be carried out under the Action has been estimated, at 1997 prices, at EUR 12,5 million.

F. OUTPUTS, DISSEMINATION AND EXPLOITATION

The presented COST Action will result in outputs that will not otherwise be achieved. A network of European cell death researchers will be established interacting through a highly developed and fast communication system including e-mail and internet. A yearly published Action Summary will be prepared both in electronic and hard copy forms; these will contain relevant data of participants, their results and achievements, brief account of each working group session and annual meeting, list of published papers and technical tools/reagents/compounds developed. All this information will be available for the scientific community through the internet and published papers. Scientific exchange and collaboration will be intensified by visits and short-term scientific missions among participants paying particular attention to increase education of young researchers and those from less developed countries. These training missions will be coordinated with possibilities provided by other European mobility schemes, e.g. TEMPUS, SOCRATES and others, to increase their effectiveness. The Management Committee will develop ways and means to reach the public for increasing awareness of the potential benefits arising from cell death research and applications in biotechnology and agriculture.

As it is detailed above, the milestones and success of the Action will be evaluated and measured by criteria including discoveries and patents linked to the activity of the programme, the number and types of agricultural, industrial and biotechnology applications achieved, the environmental initiatives and protective procedures resulting from it. Therefore, the international and broad exploitation of results achieved form studying cell death at the molecular level is predictable not only through publications in well respected journals but practical applications for the benefit of the European science and technology development. The latter is much easier and cheaper for the participating countries in the framework of the concerted action of the presented COST Action than working separately and alone.