BIOMEDICAL AND HEALTH RESEARCH PROGRAMME 1994-1998

AREA 4.1

CANCER RESEARCH

INVENTORY OF PROJECTS WITH BRIEF DESCRIPTION

August 1997

INTRODUCTION

Cancers cause over 800,000 deaths in the EU each year and account for 25% of all deaths. Mortality and incidence rates vary considerably by country : for example, both are comparatively low in Spain in relation to melanoma of the skin, although, as in other parts of the EU, mortality rates from that cancer are increasing. By contrast, in neighbouring Portugal mortality from cancer of the stomach is much higher than elsewhere in the EU, although rates are now falling (albeit slowly) as in other EU Member States.

Within the EU, the treatment of cancer has ceased to be separated into the interests of surgeons, chemotherapists and radiotherapists, and has become an integrated clinical discipline. Further improvements in cancer therapy will require an integration of the fundamental and clinical approaches to research, with particular attention to building of necessary interactions between cellular, molecular and developmental genetics with oncology and epidemiology. This will permit the development of new biological insights into the underlying causes of cancer and the ways in which they interact with normal cellular processes. Greater understanding of the ways in which cell division and proliferation are controlled, and the isolation of new genetic and environmental factors which determine and interact with controls, will in turn allow the development of new approaches to prevention, early detection and treatment. The study of host-tumour interactions in the context of escape from immune response, and of somatic gene therapy could have a major impact on cancer treatment.

The approaches of cellular and molecular genetics are most powerful if combined with strong epidemiological studies, which are essential for identifying the interplay between the environmental and genetic components determining carcinogenesis. Epidemiological studies are best conducted on a multinational collaborative basis, and should have a high priority at the European level.

Clinical research aims at improvement in both diagnosis and treatment for cancers. In general, the earlier cancers are diagnosed, the better the prognosis for the treatment. There are still striking discrepancies for treatment outcomes in different regions or between countries, and while some of this may be due to fundamental biological or genetic differences, much is due to unequal availability of best diagnosis or treatment; the aim should be to bring the same high standard of quality care to all patients. Therefore, in addition to more fundamental research, clinical research also has to facilitate the transition of the new opportunities into clinical utility, with emphasis on usefulness, accessibility and feasibility of application to patients with cancer in daily practice.

In the context of the BIOMED 2 programme, research is conducted on molecular mechanisms of tumorigenesis and metastasis, on the control of normal cellular growth, differentiation and death, and abnormalities which can alter these to predispose to cancer, and on specific anti-tumour immune responses and possibilities for early detection. Furthermore, research is undertaken to support the effectiveness of systemic treatment, the therapeutic ratio of radiotherapy and the field of ballistic selectivity. Finally the quality of life as a parameter for treatment assessment is also addressed within the programme.

The pace of discovery, within the EU, of scientific aspects of cancer research and of developments in the clinical field are so rapid that it is sometimes difficult to keep abreast. This brief overview attempts to highlight some of the advances in the field, as part of the BIOMED programme funded research and specific results due to the co-operative spirit established by the scientific community. It is particularly worth noting the financial investment of 35 million ECU in the current programme, has acted as a catalyst in attracting a large number of Member States funded research teams in pooling their collective knowledge base.

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Dr. S.S. Baig
European Commission
DG XII-E-4
Rue de la Loi 200
B - 1049 Brussels

Brussels, August 1997

CONTENTS

Area 4.1.1

Molecular mechanisms of tumourgenesis and metastasis, including the characterisation of the genes and proteins responsible for these processes

Title : Molecular mechanisms of extracellular proteolysis in cancer invasion and metastasis. A step towards a rational anti-metastatic therapy.

Contract N° : BMH4-CT96-0017

Period : 31/05/96 - 30/05/99 Total EC Contribution : ECU 950,000

Degradation of the extracellular matrix and basement membranes plays a crucial role in cancer invasion and metastasis. This degradation is accomplished by the concerted action of several extracellular proteolytic enzyme-systems. The objective of the present proposal is to contribute to a clarification of molecular mechanisms of extracellular proteolysis by defining the interaction between the various enzyme systems in cancer invasion, the ultimate goal being to create the basis for a rational approach to anti-invasive and anti-metastatic therapy, which may result in increased survival and quality of life for cancer patients.

The most important of the proteolytic enzymes involved in cancer invasion belong to the families of matrix metalloproteinases (several types of collagenases and stromelysins) and serene proteinases (the plasminogen activator uPA). The activity of these enzymes is finely regulated by proenzyme activation, specific inhibitors and cell surface receptors. These extracellular proteolytic enzyme systems are also involved in matrix degradation in non-neoplastic tissue remodelling processes. The main difference between the neoplastic and non-neoplastic processes appears in this respect to be in the regulation of the expression of the various components.

Many of these enzyme systems are very well characterised. The partners in the proposed project are all among the internationally leading in the field of extracellular proteolysis and cancer, and have typically contributed by in depth studies of one or two of the enzymes or enzyme systems. Recent studies, in the partners' laboratories and elsewhere, on the biochemistry and expression of components of these enzyme systems indicate that there is strong interaction and cooperativity between the systems, and particularly results obtained by targeted gene disruption in transgenic mice suggest that there is a functional overlap between the individual systems.

Inhibition of matrix degrading enzyme systems is an attractive new approach to anti-invasive and anti-metastatic therapy, and some drugs with this effect are currently being investigated in clinical trials. The functional overlap between individual enzyme systems, discussed above however indicates that such a therapy, in order to be effective, requires that two or more of the systems are inhibited. In order to provide a rational basis for such a combined therapy, it is necessary that the interactions and functional overlaps between the individual proteolytic systems are exactly defined. The objectives of the present proposal are to combine the expertise of the individual partners in the individual enzyme systems in a concerted effort to obtain this goal.

These objectives comply precisely with the objectives of the BIOMED 2 work programme 4.1.1., as to define molecular mechanisms of cancer metastasis. It will be achieved by : analysis of the molecular mechanisms controlling co-ordinate gene expression of components of extracellular proteolytic enzyme systems during invasion and by biochemical analysis of interaction between matrix proteinase systems.

Evaluation of the interaction of matrix proteinase systems in physiological events and cancer invasion and metastasis will be carried out as well as evaluation of prognostic and therapeutic aspects of interaction between extracellular proteolytic enzyme systems in cancer. A search for novel molecules involved in extracellular proteolysis in cancer invasion and metastasis is proposed.

Keywords : Cancer. Invasion. Metastasis. Proteolytic enzymes. Molecular mechanisms. Therapy. Matrix metalloproteases. Plasminogen activators.

Project Leader :

Prof. K. Danoe
Finsen Laboratory
Rigshospitalet
Strandboulevarden 49
DK - 2100 Copenhagen

TEL : 45-35-455615
FAX : 45- 31-385450

with participation of :

Prof. F. Blasi DIBIT, Ospedale S. Raffaele Via Olgettina 60 I- 20188 Milano TEL : 39-2-26434832 FAX : 39 2-26434744	Prof. P. Chambon Laboratoire de Génétique Moléculaire Des Eucaryoutes du C.N.R.S. Faculté de Médecine 11, rue Humann F- 67085 Strasbourg Cedex TEL : 33-3-88653425 FAX : 33-3- 88653201
Prof. C. Lopez-Otin Dept. de Biologia& Funcional Universidad de Ovido Facultad de Medicina E- 33006 Ovidod TEL : 34-85-103571 FAX : 34-85-103564	Prof. G. Murphy Cell & Molecular Biology Department Strangeways Research Laboratory Wort's Causeway GB- Cambridge CB1 4RN TEL : 44-12-23243231 FAX : 44-12-23411609

Prof. K. Tryggvason Department of Medical Biochemistry and Biophysics Karolinska Instituttet S- 171 77 Stockholm TEL : 46-8-7287720 FAX : 46-8-337462	Prof. P. Basset Laboratoire de Génétique Moléculaire Des Eucaryoutes du C.N.R.S Institut de Chimie Biologique Factulté de Médecine 11, rue Humann F- 67085 Strasbourg Cedex TEL : 33-3-88653425 FAX : 33-3-88653201
Marie-Christine Rio Laboratoire de Génétique Moléculaire Des Eucaryoutes du C.N.R.S Institut de Chimie Biologique Faculté de Médecine 11, rue Humann F- 67085 Strasbourg Cedex TEL : 33-3-88653425 FAX : 33-3-88653201	Dr. V. Dive Département d'Ingénierie et d'Etudes des protéines Laboratoire structure des protéines en solution Bât. 152 - C.E. Saclay F- 91191 Gif Sur Yvette Cedex TEL : 33-1-69083585 FAX : 33-1-69089071

Title : Molecular mechanisms of angiogenesis associated to cancer progression : targets for new diagnostic tools and for new anticancer therapeutic approaches

Contract N° : BMH4-CT96-0669

Period : 1/7/96 - 30/06/99 Total EC Contribution : ECU 550,000

Angiogenesis is crucial in the progression of solid tumours and in the formation of metastases.
Although tumours 1-2 mm diameter can receive nutrients by diffusion, further growth depends on the formation of a network of new vessels. Furthermore these new vessels are target for invading tumour cells and represent the best way to spreading in other organs. Many clinical studies support this model and have concluded that the number and the density of vessels in different human cancers directly correlate with their potential to progress and produce metastases. In animal models, angiogenesis inhibitors gave favourable results on cancer progression. However, there are some conflicting data, such as the observation that not all angiogenic tumours produce metastases, or that metastases develop many years after the appearance of a well-vascularised tumour.

These observations indicate that a change in the phenotype of endothelial cells in the tumour is essential for the progression of the disease, rather than a simple increase of number of vessels.

The general objective of this proposal is to develop new instruments (diagnostic, therapeutic, experimental) on tumour angiogenesis to improve the information required for the prognosis and search new therapeutic strategies for the treatment of cancer. These tools (mAbs to vascular cells, to angiogenic factors and their receptors, cDNAs, animal models, antagonist molecules) will be developed from the molecular and biological knowledge's obtained by the different partners. The availability of more sophisticated instruments and their evaluation in animal models and in selected series of patients will provide an invaluable asset to public health and European industry interested in the development of diagnostic and therapeutic agents for cancer disease. Therefore the identification of an endothelial phenotype more favourable to cancer progression, the development of Abs to this phenotype, or to molecules involved in it their expression (Section 1 and 2) will be a central focus of this project.

Section 2 will study molecules which regulate angiogenesis and their mechanisms of action. The aim of this section is to produce specific mutants with antagonistic activity or molecules which interfere with signal transduction pathways.

Section 3 will develop new animal models to test the reagents prepared by sections 1 and 2 and to define different angiogenic profiles. The diagnostic and therapeutic usefulness of tools developed by section 1 and 2 will be tested in clinical trials (Section 4).

The implementation of this project is expected to have a broad impact on the diagnostic and therapeutic strategies concerning solid tumours and to favour a better management of this disease.

Project Leader :

Prof. F. Bussolino
Dipartimento Genetica, Biologia e Chimica Medica
Via Santena 5 bis
I- 10126 Torino

TEL : 39-11-6706684
FAX : 39-11-6634563
E-Mail : U236PESCA@CSI.IT

with participation of :

Dr. M. Grandi Dept. of Experimental Oncology and Preclinical Research Business Area Oncology Immunology Via Giovanni XXIII, 23 I- 20014 Nerviano TEL : 39-331-583321 FAX : 39-331-583398	Dr. L. Claesson-Welsh Ludwig Institute for Cancer Research Biomedical Centre P.O.Box 595 Husargatan 3 S- 75124 Uppsala TEL : 46-18-551688 FAX : 46-18-506867 E-Mail : Lena.Welsh@LICR.uu.se
Dr. M. Ziche Dept. of Preclinical and Clinical Pharmacology Viale Morgagni 65 I- 50134 Firenze TEL : 39-55-4237457 FAX : 39-55-4361613	Dr. M.E. Maragoudakis Dept. of Pharmacology University of Patras Medical School GR- 26500 Patras, Achaia TEL : 30-61-997638 FAX : 30-61-994720
Dr. H. Weich Department of Gene Expression Mascheroder Weg 1 D- 38124 Braunschweig. Lower Saxony TEL : 49-531-6181445 FAX : 49-531-6181458	Prof. K.K. Alitalo University of Helsinki Haartman Institute P.O.Box 21 Haarmaninkatu 3 SF- 0014 Helsinki TEL : 358-0-4346434 FAX : 358-0-4346448 E-Mail : Kari.Alitalo@Helsinki.FI

Dr. M.G. Lampugnani Laboratory of Vascular Biology Via Eritrea 62 I- 20157 Milano TEL : 39-2-390141 ext 421 FAX : 39-2-3546277 E-Mail : Lampugnani@IRFMN.MNEGR1.IT	Dr. A.L. Harris Imperial Cancer Research Fund Institute of Molecular Medicine John Radcliffe Hospital University of Oxford GB- Headington Oxford, OX3 9DU TEL : 44-1865-222408 FAX : 44-1865-222431

Title : Receptor Tyrosine Kinase Signalling in Human cancer

Contract N° : BMH4-CT96-0814

Period : 1/8/96 - 31/7/99 Total EC Contribution : ECU 1,000,000

Signalling cascades triggered by receptor tyrosine kinases (RTKs) are frequently activated in human cancer. To comprehend the role of RTKs in tumours and devise strategies to intercede with their function, detailed understanding of their mechanisms of action including ligand regulation and activation of cytoplasmic signal transducers, is required.

This proposal focuses on the ErbB and RET subfamilies of RTKs based upon their established involvement in prevalent types of human cancer. Members of the ErbB RTK family including EGFR, ErbB2 and ErbB3, are involved in human tumours by overexertion and constitutive receptor activation. While autocrine stimulation of the EGFR in tumours has been established, the role of natural ligands for the related ErbB receptors remains elusive. RET which encodes a RTK lacking a known ligand, is activated by structural abnormalities as a dominant transforming gene in various tumour types.

To characterise ligand-receptor interactions relevant to malignancy, we will attempt to identify and isolate novel ligands regulating the activity of ErbB2, ErbB3 and RET. Among known ligands, the role of HRG on ErbB2, ErbB3 and ErbB4 activity will be determined in model systems.

Furthermore, the function of membrane-anchored forms of TGF and HRG will be analysed, including possible intrinsic signalling properties associated with their cytoplasmic domains. Known ligand-receptor interactions will be exploited to specifically target tumour cells overexpressing ErbB family receptors in vitro and in vivo using cytotoxic T lymphocytes with recombinantly engineered T cell receptor components.

Mechanisms of receptor heterodimerisation including ligand-independent activation will be determined for ErbB2 and ErbB3 synergy, whereas the activating potential of novel mutations in the ErbB2 juxtamembrane region will be evaluated for ErbB2 signalling properties.

Pathophysiologically relevant model systems will be established to measure ErbB and RET receptor function. Reversion of neoplastic phenotypes induced by MEN2A, MEN2B and mutated ErbB2, will be attempted by use of mutation-specific antisense oligonucleotides. In the case of activated RET alleles, this approach will be complemented by investigating the potential of certain Hirschsprung alleles to function as dominant-negatives. At the substrate level, research is focused on targets of mitogenic control relevant for human cancer. Thus, substrates in ErbB receptors and RET pathways segregating with increased transforming potential are of particular interest including those shared between RET and ErbB2 as well as substrates specifically associated with signal transduction by RET-MEN2B, ErbB2-ErbB3 heterodimers and point-mutated ErbB2. Moreover, among a battery of tyrosine kinase

substrates analysed, shc and eps8 are frequently tyrosine phosphorylated in human tumours projecting their role as universal targets for tyrosine kinases activated in human tumours.

To expand the mechanistic understanding of eps8 and shc phosphorylation in tumours, functional interactions between both substrates will be investigated, and target proteins in the signalling cascade will be characterised. The physiologic role of eps8 will be investigated by gene targeting in mice. To facilitate rapid identification of tumours with activated tyrosine kinases that would be amenable for therapeutic approaches involving tyrosine kinase inhibitors, screening tests based upon shc and eps8 phosphorylation will be developed. Furthermore, this approach will provide the basis for the identification of novel tyrosine kinases selected on the basis of their involvement in human neoplasia.

Keywords : Oncogenes/Growth Factors/Phosphorylation/Substrates/Function/ Tumour Markers/Diagnosis/Therapy

Project Leader :

Pier Paolo Di Fiore (PPDF)
Dept. of Experimental Oncology, Division of Signal Transduction
IEO, European Institute of Oncology
Via Ripamonti 435
I- 20141 Milano

TEL : 39-2-574891
FAX : 39-2-57489208

with participation of :

Pier Giuseppe Pelicci (PGP) Istituto di Medicina Interna a Scienze Oncologiche University of Perugia, Policlinico Monteluce Via Brunamonti I- 06100 Perugia TEL : 39-75-5783255 FAX : 39-75-5726264	Matthias H. Kraus (MK) Dept. of Experimental Oncology, Section of Receptor Pharmacology IEO, European Institute of Oncology Via Ripamonti 435 I- 20141 Milano TEL : 39-2-574891 FAX : 39-2-57489208

Christer Betsholtz (CB) Dept. of Medical Biochemistry Institute of Medical Biochemistry and Microbiology University of Göteborg Medicinaregatan 9A S- 413 90 Göteborg TEL : 46-31-7733460 FAX : 46-31-416108	Mahvash Tavassoli (MT University of Sussex at Brighton School of Biological Sciences Biology Bldg GB- Falmer, Brighton BN1 9QG TEL : 44-273-606755 FAX : 44-273-678433
Atanasio Pandiella (AP) Instituto de Microbiologia Bioquimica Consejo Superior de Investigaciones Cientificas Avenida del campo charro s/n E- Salamanca 37007 TEL : 34-23-120561 FAX : 34-23-267970	Massimo Santoro (MS) Dipartimento di Biologia e Patologia Cellulare e Molecolare University of Naples Federico II Via Sergio Pansini 5 I- 80131 Napoli TEL : 39-81-7463056 FAX : 39-81-7463037
Bernd Groner (BG) Klinik für Tumourbiologie Breisacher Strasse 117 D- 79106 Freiburg i.Br TEL : 49-761-2061600 FAX : 49-761-2061599	

Title : Mammalian Chromosome Stability and Cancers

Contract N° : BMH4-CT96-0894

Period : 1/6/96 - 31/5/99 **Total EC Contribution : ECU 300,000**

The karyotypes of cancer cells usually differ structurally and numerically from those of untransformed cells. The differences are of central importance in the development of cancer but there is little understanding of their molecular bases. The overall objective of our proposal is to develop an experimental approach to the analysis of the mechanisms leading to some of the chromosome abnormalities in cancer cells.

Changes in chromosome number are likely to arise as result of errors in chromosome segregation but the mechanism of chromosome segregation is poorly understood in human cells. One important stumbling block to the systematic study of human chromosome segregation is that the identity of the DNA sequence responsible for chromosome segregation ; the centrometric DNA has not been identified. The first objective of our programme is therefore to identify the functionally significant centrometric DNA on a human chromosome.

The events leading to deletions and gene amplifications in tumour cells are not understood however many observations made primarily by laboratories participating in this project (Paris, Pavia) indicate that double strand breaks play a key role in the initiation of the amplification process and the formation of interstitial deletions. The second objective of our programme is to test the idea that double strand breakage is the key initiating event of both types of events.

Activation of telomerase is now thought to play a key role in the development of cancer cells. It has therefore been suggested that inactivation of telomerase would be a useful therapeutic approach. The third objective of our programme is to test this idea by inducibly removing a telomere from a supernumerary mammalian chromosome and then examining the consequences for the chromosome and for the cell.

Keywords : Centromere: telomere: double strand break: amplification: cre: I-Sce-1.

Project Leader :

Pr. Michelle Debatisse-Buttin
Institut Pasteur
Unité de Génétique Somatique (URA CNRS 1960)
25 rue du Dr. Roux
F-75724 Paris Cédex 15

TEL : 33-1-45688571
FAX : 33-1-40613171
E-Mail : mdebat@pasteur.fr

with participation of :

Pr. Elena Giulotto Universita' di Pavia Dipartimento di Genetica e Microbiologia Via Abbiategrasso 207 I- 27100 Pavia TEL : 39-382-505541 FAX : 39-382-528496 E-Mail : giulotto@ipvgen.unipv.it	Dr. Chiara Mondello Consiglio Nazionale Biochimica ed Evoluzionistica Via Abbiategrasso 207 I- 27100 Pavia TEL : 39-382-546329 FAX : 39-382-422286 E-Mail : mondello@ipvgbe.igbe.pv.cnr.it
Dr. Manuel Valdivia Universidad de Cadiz Facultad de Ciencias Bioquimica y Biologia Molecular Apartado num. 40 E- 11510 Puerto Real - Cadiz TEL : 34-56-830363 FAX : 34-56-834924 E-Mail : manuel.valdivia@uca.es	Dr. William Brown University of Oxford Biochemistry South Parks Road GB- Oxford OX1 3QU TEL : 44-865-275225 FAX : 44-865-275283 E-Mail : wrab@bioch.ox.ac.uk

Title : Effect of transforming growth factor ß on proto-oncogenes, tumour suppressor genes and cell cycle regulators : growth arrest versus apoptosis

Contract No. : BMH4-CT-96-0995

Period : 1/1/96 - 31/12/99 **Total EC Contribution : ECU 650,000**

Regulation of normal development and tissue function is the product of a balanced interplay between the mechanisms that regulate cell division, differentiation and cell death. Whereas the molecular mechanisms leading to cell growth and their contribution to cell transformation have been extensively explored in the last two decades, much less is known about the mechanisms that inhibit cell growth, most particularly in function of the adhesion status of the cell. Furthermore, simultaneous activation of the growth stimulatory and growth inhibitory programmes may raise cellular conflict leading to cell death, both in normal as well as in tumour cells. The overall aim of this integrated proposal is to define the factors which modulate key genes in the control of cell cycle arrest and cell death. The proto-oncogene *c-myc* and the tumour suppresser gene *p53* have been shown to be major players in the control of normal cell proliferation and the development of malignancies. Activation of *c-myc* in quiescent cells is sufficient for induction of DNA synthesis whereas, activation of *p53* prevents entry of cycling cells into S phase, but also renders them susceptible to apoptosis. Recent evidence suggests that extra-cellular matrix plays a protective role against apoptosis. Interestingly, one of the key cell cycle regulators of the G1/S transit, cyclin A has an expression which is strongly induced by *c-myc*, but also dependent upon cell anchorage. TGFß, a pleiotropicytokine that negatively regulates cell growth of mainly epithelial cells, induces a subset of the immediate early genes, notably *Jun B*, and represses some of the cell cycle regulators, such as cyclin *A*, through a signal transduction cascade which is presently almost completely obscure. However, whereas growth factors stimulate the expression of extra-cellular metalloproteinases collagenase and stromelysin, TGFß inhibits their expression and could thus interfere with apoptosis.

We plan to study TGFß receptor signalling as well as the effect of TGFß on *c-myc*-induced cyclin A expression, DNA synthesis and apoptosis in p53+/+ and p53-/- contexts. The regulation of the expression and the interplay of the selected players : *c-myc, Jun B* and cyclin A will be analysed at both the transcriptional and post-transcriptional levels. In the latter we will investigate changes in sub-cellular localisation of both *c-myc* and cyclin A mRNAs, and investigate changes in the mRNA-cytoskeleton interactions and localisation in response to TGFß.

Keywords : Oncogenes, tumour suppressers, TGFß, cyclins, cell adhesion, TGFß receptors.

Project Leader :

Dr. Jean-Marie Blanchard
Institut de Génétique Moléculaire de Montpellier
CNRS, UMR 9942
BP 5051
1919 route de Mende
F - 34033 Montpellier, Cedex 1

TEL : 33-4-67613649
FAX : 33-4-67040245

with participation of :

Dr. Carmelo Barnabeu Centro de Investigaciones Biologicas Velazques 144 E - 28006 Madrid TEL : 34-5611800 FAX : 34-1-5627518	Dr. Dirk Eick Institut für Klinische Molekulärbiologie und Tumorgenetik Marchioninistrasse 25 D - 81377 München TEL : 49-89-7099512 FAX : 49-89-7099500
Dr. John Hesketh Rowett Research Institute GB - Aberdeen TEL : 44-224-716636 FAX : 44-224-716687/715349	Dr. Wiebe Kruijer Department of Genetics Biological Centre University of Groningen P.O. Box 14 NL - 9750 AA Haren TEL : 31-50-6323348 FAX : 31-50-632091

Area 4.1.2

Control of cellular, differentiation and death (apoptosis), and deregulations predisposing to cancer

Title : Protein Kinase CK2 : Functional Properties in Cell Growth and Neoplasia

Contract N° : BMH4-CT96-0047

Period : 1/5/96 - 30/4/99 **Total EC Contribution : ECU 400,000**

Among the hundreds of protein kinases known to date, protein kinase CK2 has been shown to act as an essential component for cell survival. Compelling evidence strongly supports that CK2 is involved in the regulation of cell proliferation. CK2 activity is increased in tumour cells and its catalytic subunit may act as an oncogene, as suggested by a recent observation in transgenic mice. However understanding of its cellular functions at the molecular level remains elusive.

The present project aims at an understanding of CK2 functions related to proliferation in normal and cancer cells, with a concerted approach combining complementary expertise's, with the major objectives as follows :

1. Understand the structural and functional organisation of CK2 that governs its activity, its regulation and its specificity. This conducted using is complementary approaches, including a set of kinase mutants and should result in the development of new possibilities to manipulate CK2 functions in living cells.

2. Identify the CK2 subunit genes and develop methods to probe their activity in living cells and to manipulate the expression of the kinase or its subunits in cancer cells.

3. Unravel the cellular proteins which are targets of CK2 in vivo, by using the double hybrid system in yeast. Comparative patterns of CK2 target proteins in normal, cancer cells and human tumours should sheet light on the specific behaviour of CK2 in transformed cells and its possible role in oncogenesis.

4. Understand the role of CK2 in the regulation of specific cell functions related to growth control and cancer (I) organisation of the cytoskeleton and neurite formation; (II) regulation of topoisomeraseII and of topo-II dependent resistance to anticancer agents; (III) cell response to the growth factor FGF-2 and rRNA synthesis regulation; (IV) role in the regulation of the p53 protein functions as a cell cycle suppressor and a cell apoptosis inducer in response to anticancer agents.

5. Examine the status of CK2 (gene expression, molecular organisation and activity) in cancer cells and in frequent human tumours in Europe (i.e. colorectal and breast cancers). In this context, the kinase may emerge as a potential prognostic parameter of value in patient management as well as a potential target for drug therapy.

The present project represents a long waited opportunity for the partners to associate their interest and potential in a concerted task force. This common endeavour should shed light on the implication of an ubiquitous although still mysterious protein kinase in basic regulation processes related to cell growth and neoplasia and may suggest related new strategies in cancer therapy.

Keywords : Protein kinase CK2 - Cell proliferation - Oncogenesis - Growth factor FGF - Human Cancer - Colorectal Carcinoma - Topoisomerase II - p53 protein - Cytoskeleton - Drug resistance

Project leader :

Prof. E.M. Chambaz
Biochimie des Régulations Cellulaires Endocrines
INSERM U244 DEMS/BRCE
CENG, 17 rue des Martyrs
F- 38054 Grenoble Cedex 9

TEL : 33-4-76884799
FAX : 33-4-76885058

with participation of :

Prof. F. Amalric Institut de Biologie Cellulaire et de Génétique 118 route de Narbonne F- 31062 Toulouse Cedex TEL : 33-5-61335862 FAX : 33-5-61335886	Prof. J. Avila Centro de Biologia Molecular "Severo Ochoa" Facultad de Ciencias Universidad Autonama de Madrid E- 28049 Canto blanco/Madrid TEL : 34-1-3978440 FAX : 34-1-3974799
Prof. S.M. Gasser ISREC 155 ch. des Boveresses CH- 1066 Epalinges/Lausanne TEL : 41-21-6925886 FAX : 41-21-6526933	Prof. E. Itarte Departament de Bioquimica I biologia Molecular Facultat de Ciències Universitat Autonoma de Barcelona E- 08193 Bellaterra (Barcelona) TEL: 34-3-5811617 FAX : 34-3-3811264
Prof. D.W. Meek Biomedical Research Centre Ninewells Hospital and Medical School University of Dundee GB- Dundee DD1 9SY TEL : 44-1382-660111 Ext. 3517 FAX : 44-1382-669993	Prof. L.A. Pinna Universita degli Studi di Padova Dipartimento di Chimica Biologica Via Trieste 75 I- 35121 Padova TEL : 39-49-8286410 FAX : 39-49-8073310

Prof. W. Pyerin Biochemische Zellphysiologie (0215) Deutsches Krebsforschungszentrum Im Neuenheimer Feld 280 TEL : 49-6221-423254 FAX : 49-6221-423261	

Title : Surface receptor-induced apoptosis in transformed cells : defining the molecular events involved in TNF-R1 and Fas / APO-1 apoptotic signalling

Contract N° : BMH4-CT96-0300

Period : 1/09/96 - 31/08/99 **Total EC Contribution : ECU 800,000**

Aim of the project is the definition of the molecular requirements for the generation and intracellular transmission of the apoptotic signal from surface receptors in transformed cells. As surface receptor-mediated apoptosis induction is a key mechanism exploited by immune effect cells to eliminate cancer cells, understanding the biochemical nature of the apoptotic signal is of major relevance in cancer biology. The model we are using in the human system is represented by two highly related receptors, widely expressed on a variety of normal and transformed cells, the tumour necrosis factor receptor type 1 (TNF-R1) and the Fas/APO-1 receptor. Crosslinking of TNF-R1 and Fas/APO-1 by their specific ligands triggers a cascade of still largely undefined events, eventually leading to cellular apoptosis. TNF-R1 and Fas/APO-1 are trimeric receptors which share extended structural homology, including a cytoplasmic region which has been named "death domain", as deletions or mutations within it result in the inability by the respective ligands to grigger apoptosis.

Structural similarities both in the extracellular and in the intracellular portion of the two receptors suggest similar mechanisms for the generation of the apoptotic signal, however differences may exist in the complexity of its fine regulation and control, which may be relevant for the specialisation of the death signal in different cell types. Our goal is to define the mechanisms for signal generation and propagation from the two receptors, identifying common central relays as well as unique control features of each apoptotic pathway. We will address receptor structural requirements for productive lingand/receptor interactions, with particular emphasis on the role of alternatively spliced isoforms of the Fas/APO-1 receptor in signal control. Moreover, the function of death domains in the generation of the apoptotic signal will be investigated, specifically by searching for cytosolic death domain-like molecules. Membrane modifications following TNF-R1 and Fas/APO-1 crosslinking and their relevance for the propagation of the death signal will be investigated by measuring different phospholipases and sphingomyelinases activities and identifying relevant downstream targets. We will therefore study how relevant diffusible second messengers can activate potential distal targets, like interleukin-1 converting enzyme (ICE) and homologues, as well as reactive oxygen intermediates (ROI), potentially involved in mediating the effector phase of the response. Finally, the role of bcl-2 family members, key players in the control of the apoptotic response, will be addressed.

Defining the molecular steps responsible for TNF-R1 and Fas/APO-1 induced apoptosis will reveal potential targets for anti-apoptotic strategies adopted by cancer cells to survive. Uncover such strategies has potential relevance for both diagnosis and selective therapy of tumours.

Project Leader :

Dr. Roberto Testi
Dept. of Experimental Medicine
and Biochemical Sciences
University of Rome "Tor Vergata"
v. di Tor Vergata 135
I- 00133 Roma

TEL : 39-6-7259-6502/6503
FAX : 39-6-7259 6501
E-mail : tesrob@flashnet.it

with participation of :

Dr. P. Golstein Immunologie INSERM CNRS, Marseille-Luminy F- case 906, Marseille Cedex 9 TEL : 33-4-91-269468 FAX : 33-4-91-269430 E-mail : golstein@ciml-cd.univ-mrs.fr	Dr. Klaus Schulze-Osthoff Biochemical Institute University of Freiburg Hermann-Herder Str. 7 D- 79104 Freiburg TEL : 49-761-20352/60/5221 FAX : 49-761-2035257
Dr. Rudy Beyaert Laboratory for Molecular Biology University of Gent Ledeganckstraat 35 B- 9000 Gent TEL : 32-9-2645143 FAX : 32-9-2645348 E-mail : rudi@Imbi.rug.ac.be	Dr. Giovina Ruberti Dept. of Immunobiology Institute of Cell Biology CNR V.le Marx 43 I- 00137 Roma TEL : 39-6-86090294 FAX : 39-6-8273287 E-mail : giovina@biocell.irmkant.rm.cnr.it
Dr. Peter Daniel Max Delbruch Center R. Roessle St. 10 D- 13122 Berlin TEL : 49-30-94062720 FAX : 49-30-94171209 E-mail : pdaniel@orion.rz.mdc-berlin.de	

Title : Novel biological systems to study the role of single oncoproteins and tumour suppressors and their co-operation in leukaemogenesis

Contract N° : BMH4-CT96-1355

Period : 1/4/96 - 31/3/99 **Total EC Contribution : ECU 400,000**

Human leukaemias are associated with identified genetic alterations including recurrent chromosomal translocations which lead to the synthesis of novel fusion proteins or to the ectopic or enhanced expression of normal proteins and deletion and point mutations which result in loss of function of tumour suppressor genes. Although considerable progress has been made in the identification of genes associated with specific leukaemias and the way their expression is altered, much less is know on how single genetic alterations contribute to leukaemic development and how dominant oncogenes and recessive tumour suppressor genes cooperate to generate the full leukaemic phenotype. We propose to use and further develop new cellular models to analyse how oncoproteins and tumour suppressors which are known to be involved in human leukaemias alter the proliferation, survival and differentiation control of primary hematopoietic progenitors in tissue culture. Fusion proteins involved in preleukaemic states like myeloid dysplastic syndromes (MDS), in chronic myelogenous leukaemia (CML) and in acute leukaemias of both the myeloid (AML) and lymphoid (ALL) lineage's will be considered. Specifically, we will analyse the properties of CMML-associated Tel-PDGFRß, of CML-associated BCR-ABL and of several oncoproteins associated with AML including PML-RARα, DEK-CAN, TLS-ERG as well as AML1 and MLL fusion proteins.

Very few genetics alterations are known to be implicated in MDS. A major effort will be put in the identification of novel genetic lesions specific to MDS and in the study of the activity of the corresponding genes in hematopoietic progenitors.

The cellular models we propose to use are also ideally suited to investigate how known tumour suppressor like p53 or candidate suppressor genes like ERF co-operate with oncoproteins to deregulate the growth and differentiation control of hematopoietic progenitors.

To validate the results obtaind in tissue culture, we will develop a complementary approach in which ES cells will be genetically modified to express specific human oncoproteins as combinations thereof. These cells will be used to create chimeric animals in which leukaemia development can be monitored.

Description of the phenotypes associated with the expression of single oncoproteins and tumour suppressors or combinations thereof in primary progenitors paves the way to develop a screening assay for pharmacological compounds interfering with the function of these proteins.

Keywords : Leukaemia/Hematopoietic progenitors/ES cells/Oncogenes/Tumour suppressor genes/Multi-step carcinogenesis.

Project Leader :

Dr. Jacques Ghysdael
Laboratoire d'Oncologie Virale et Cellulaire
CNRS UMR 146
Institut Curie, Section de Recherche
Centre Universitaire, Bâtiment 110
F-91405 Orsay Cédex

TEL : 33-1-69863152
FAX : 33-1-69074525
E-Mail : ghysdael@curie.u-psud.fr

with participation of :

Dr. Hermut Beug Institute of Molecular Pathology Dr. Bohrgasse 7 A-1030 Wien TEL : 43-1-79730621 FAX : 43-1-7987153 E-Mail : beug@aimp.una.ac.at	Dr. G. Mavrothalassitis Institute of Molecular Biology and Biotechnology Forth, P.O. Box 1527 GR-71110 Herakliou, Crete TEL : 30-81-210091 FAX : 30-81-230469 E-Mail : mavro@nefeli.imbb.forth.gr
Dr. Jacques Samarut Laboratoire de Biologie Moléculaire et Cellulaire, CNRS UMR 49 Ecole Normale Supérieure de Lyon 46? Allée d'Italie F-69364 Lyon TEL : 33-4-72728171 FAX : 33-4-72728080 E-Mail : jacques samarut@cri.ens-lyon.fr	Dr. Maartje Maria Von Lindern Institute of Hematology Erasmus University P.O. Box 1738 NL- 3000 Dr Rotterdam TEL : 31-10-4633740 FAX : 31-10-4635814
Dr. Leanne Wiedemann Leukaemia Research Fund Centre Institute of Cancer Research 237, Fulham Rd GB- London SW3 6JB TEL : 44-171-3528133 FAX : 44-171-3523299 E-Mail : mblmv@segnet.dl.ac.uk	

Title : The role of the E2F/DP genes in control of cell proliferation and oncogenesis

Contract N° : BMH4-CT96-1529

Period : 1/7/96 30/6/99 Total EC Contribution : ECU 1,150,000

The aim of this proposal is to analyse the role of the recently discovered transcription factors of the E2F and DP gene families in the control of cell proliferation and in tumourgenesis. In mammalian cells, ordered progression through the individual phases of the cell cycle is regulated by check-point control mechanisms, which ascertain that only normal cells will replicate, and therefore are essential for the maintenance of genetic stability. Loss of check-point control predisposes mammalian cells to cancer, emphasising the critical role of cell cycle regulators for neoplastic disease. Many genes implicated in cell cycle regulation are controlled by a group of heterodimeric transcription factors, composed of proteins encoded by the E2F and DP gene families, respectively. Thus, tight regulation of E2F/DP activity may play a key-role in oncogenesis.

In a first step, it is planned to identify and characterise the main cellular target genes controlled by the E2F/DP family of transcription factors. In several model systems based on synchronised cultured cells, a thorough analysis of cell cycle regulation of gene expression through E2F/DP proteins will be performed; particular attention will be paid to the question whether differences can be found between E2F sites present in distinct target genes, or whether differential timing of E2F-driven gene expression is determined by complex regulatory elements, involving other DNA binding proteins besides E2F. To understand regulation of E2F/DP activity, the expression of different E2F and DP genes during the cell cycle and in different tissues will be analysed. In addition, we will analyse the role of post-translational modification, e.g. phosphorylation of E2F/DP proteins, and their interaction with other cellular proteins, including the products of oncogenes and tumour suppressor genes. Furthermore, the consequences of over-expression of different E2F/DP genes in various cell types will be studied, to establish the oncogenic potential of individual family members, alone or in combination with other gene products. These studies should provide an integrated view of transcriptional regulation during the cell cycle and cell differentiation, and allow us to design novel strategies to unravel the role of the E2F/DP regulatory network for growth control in normal and tumour cells.

In a second step, we intend to directly address the role of E2F/DP genes in tumourgenesis : it was shown recently that major cell cycle regulatory genes, including various cyclins, cdks and their inhibitors, are altered in a variety of human cancers. However, changes in the structure or expression of the E2F/DP genes in tumours were not reported. To address this question, a series of clinical specimens will be screened for genetic alterations in the gene encoding E2F-1 through E2F-5 and DP-1 through DP-3. Furthermore, we will establish a transgenic mouse model to study the involvement of E2F/DP genes in human cancer, including T-cell lymphoma.

Project Leader :

Dr. Pidder Janssen-Dürr
Forschungsschwerpunkt Angewandte Tumorvirologie
Deutsche Krebsforschungszentrum
Im Neuenheimer Feld 242
D - 69120 Heidelberg

TEL : 49-6221-424628
FAX : 49-6221-424902

Prof. R. Bernards Het Nederlands Kanker Instituut Plesmanlaan 121 NL - 1066 CX Amsterdam TEL : 31-20-5121952 FAX : 31-20-5121954	Dr. T. Kouzarides Wellcome/CRC Institute Unversity of Cambridge Tennis Court Road GB - Cambridge CB2 1QR TEL : 44-1223-334112 FAX : 44-1223-334089
Prof. N.B. La Thangue Division of Biochemistry & Molecular Biology Institute of Biomedical & Life Sciences University of Glasgow GB - Glasgow G12 8QQ TEL : 44-41-3305514 FAX : 44--41-3304620	Dr. P. Lavia Centro di Genetica Evoluzionistica Consiglio Nazionale delle Ricerche Pz. de Aldo Moro 5 I - 00185 Roma TEL : 39-6-4457528 FAX : 39-6-4457529

Area 4.1.3

Cell-selective targeting: to explore, and to implement in clinical practice, techniques which cause preferential destruction of tumour cells

Title : Membrane-cytoskeleton interactions and tumour suppression.

Contract N° : BMH4-CT96-0090

Period : 1/1/96 - 30/12/99 Total EC Contribution : ECU 500,000

Tumour suppressor genes act as recessive determinants of cancer. It is recently known that various actin-associated cytoskeletal proteins and structural components of intercellular junctions are encoded by, or are related to products of tumour suppressor genes. Very little is known of how tumour suppressor molecules associate with or function at the cortical membrane skeleton and/or specialised junction domains. To understand the molecular events governing tumour suppressor activity, extensive molecular cell biology studies have to be implemented. This is the major objective of our proposal.

As a choice of tumour suppressor, we will study schwannomin. Schwannomin is the product of the NF2 gene which, when mutated at the germline level, causes neurofibromatosis type 2, a tumour susceptibility disease predisposing mainly to meningiomas and schwannomas. Schwannomin, together with ezrin, radixin, and moesin, comprise the ERM family of membrane cytoskeletal linker proteins. To define the specific activity of schwannomin requires an understanding of the role of each member of the ERM family. Moreover, since ERM proteins are involved in adhesion events that are essential for the control of epithelial cell differentiation and growth, we will also investigate how the assembly of junctional membrane domains, such as tight and adherents junctions, is regulated.

To understand how these various sub-membranous protein complexes function will require us to analyse the multiple interactions that occur between the numerous components involved. Especially, we will investigate how changes in interactions can mediate tumourogenic potential since activation of membrane receptors (notably HGF/SF receptor, the product of the c-met proto-oncogene) can initiate signal transaction via ERM and junctional proteins leading to junction destabilisation, actin microfilament reorganisation and loss of control of cell proliferation.

We will utilise different developmental and cellular models, including Dictyostelium, Xenopus embryos, mouse preimplantation embryos, genetically engineered cell lines, as well as sophisticated in vitro biophysical assays to study the pattern of expression and mode of interaction of tumour suppressor molecules. Modern molecular techniques, using probes generated and shared by participating laboratories, will be used in these experimental systems to modulate, inhibit, delete, rescue or overexposes tumour suppressor proteins, and thereby to gain novel insight into how they function. Our objectives are beyond the capacity of a single research group to achieve. However, the collective breadth and combined expertise of our partnership will enable us to make substantial progress in a synergistic manner and at an accelerated rate of success.

In addition to a detailed understanding of the fundamental mechanisms regulating suppression of cancer in normal cells, one practical benefit of our proposal will be to elucidate the molecular mechanism by which schwannomin is implicated in

schwannomas and meningiomas. These two tumour types together represent close to 30 % of all nervous system tumours that develop in humans. Based on this knowledge, it is hoped that new therapeutic approaches may be proposed.

Keywords : ERM proteins; schwannomin; tight junction; adherents junction; cingulin; HGF/SF tyrosine kinase; Dictyostelium; cell adhesion; epithelial differentiation; development.

Project Leader :

Dr. P. Mangeat
CNRS-UMR 5539, Université Montpellier II
Place Eugène Bataillon, C.C. 107
F - 34095 Montpellier Cedex 5

TEL : 33-4-67-144725
FAX : 33-4-67-144727/4286
E-mail: mangeat@univ-montp2.fr

with participation of :

Dr. M. Arpin UMR CNRS 144 Unité de morphogénèse et de signalisation cellulaire Institut Curie 14 rue Lhomond F- 75231 Paris TEL : 33-1-45688409 FAX : 33-1-45688528 E-mail : marpin@pasteur.fr	Dr. G. Thomas INSERM U434, Institut Curie 26 rue d'Ulm F- 75 231 Paris Cedex 05 TEL : 33-1-40516679 FAX : 33-1-40516630
Dr. T.P. Fleming Department of Biology University of Southampton Basset Crescent East GB- 2016 7 PX Shouthampton TEL : 44-0703-594398 FAX : 44-0703-594269 E-mail : T.P.Fleming@soton.ac.uk	Prof. Dr. M. Schleicher Institut für Zellbiologie Schillerstrasse 42 D- 80336 München TEL : 49-089-5996876 FAX : 49-089-5996882 E-mail : schleicher@bio.med.uni-muenchen.de
Dr. T. Crepaldi Dipartimento di Scienze Biomedische e Oncologia Umana Sez. Istologia Cso M. D'Azeglio 52 I- 10126 Torino TEL : 39-11- 6707739 FAX : 39-11-6509105	Dr. S. Citi Dipartimento di Biologia Universita' di Padova Via Trieste 75 I- 35121 Padova TEL : 39-49-8286108 FAX : 39-49-8286100 E-mail : citi@cribil.bio.unipd.it

Title : Development of Prostate Cancer gene therapy : A collaborative network

Contract N° : BMH4-CT96-1152

Period : 1/5/96 - 30/4/99 **Total EC Contribution : ECU 250,000**

Prostate cancer is ubiquitous world-wide and since the tumour is associated with the ageing process, it is clearly a growing health problem in Europe. At present we have no method of predicting those patients at risk of developing malignant decease, and no consistent genetic markers have been identified. Also, no treatment has proven to be efficient as soon as the tumour become invasive. It is therefore of some importance to design a new therapeutically approach using cellular and molecular biology tools. A major break through may come from the development of a tissue specific transfer strategy of "suicide" genes as a gene therapy. This approach may allow the treatment of (I) primary cancer which is conventionally treated by surgery allowing a better recovery in term of impotency and urinary incontinence, and (ii) distant metastasis for which no treatment is effective. Indeed, the specific targeting of prostate cells should render metastases accessible to therapy for the first time in prostate cancer. Therefore, we have set out to develop a joint research effort within the European Union and 7 partners from France, GB, Ireland, Belgium and Italy have accepted to join the network. We believe that such a task force should rapidly establish a leadership in the field where a world-wide competition is developing. Also, one of the major aims of this research effort is to allow rapid transfer to the clinic, with industrial partnership.

Three stages are involved in development of human gene therapy and different possibilities are available in view of the complementary expertise of the partners associated with the network. (i) The transduction by viral vectors or transfection by DNA-mediated systems of appropriate target cells are tools which can be adapted for use by selection of properties useful in particular situations. Retroviruses and adenoviruses are among those which have been the most widely used. (ii) By enhancement of prostate-specific gene expression, in addition to a specificity of gene delivery, we can eliminate aberrant expression of therapeutic genes in non-prostatic target cells. For this we are developing a set of prostate specific promoters able to drive expression of effector genes. (iii) The feasibility assessment of different effector genes to direct "suicide" or proliferation control of the targeted prostate cancer cells has prompted us to design parallel strategies to maximise the complementary expertise's of the network partners. Thus, we have focused on gene products which are cytotoxic, regulate apoptosis or inhibit proliferation. To test these alternatives, standardised in vitro and in vivo models are already available or are under development within the network.

As a result, we expect to improve the quality of the cellular and molecular research carried out on prostate cancer with the objectives of gaining new insights in diagnosis and treatment. By providing a new approach to treat prostate cancer, it should assist in a significant improvement for both the patient and the social budget.

Keywords : Prostate cancer, human, gene therapy, viral delivery vectors, prostate specific promoters, apoptosis control, proliferation control.

Project Leader :

Dr. Olivier Cussenot
Unité de Génétique et Pathobiologie des Tumeurs Prostatiques
Département d'Urologie
Höpital Saint Louis
1, rue Claude Vellefaux
F- 75475 Paris Cedex 10

TEL : 33-1-42499623
FAX : 33-1-42499616

with participation of :

Prof. Norman J. Maitland Cancer Research Unit Department of Biology University of York GB- York, YYO1 5DD TEL : 44-1904-432872 FAX : 44-1904-432615	Prof. Ian R. Hart Richard Dimbleby Department of Cancer Research/ICRF Laboratory Saint Thomas's Hospital Lambeth Palace Road GB- London SE1 7EH TEL : 44-171-9289292 ext 3040 FAX : 44-171-922816
Dr. Michel Perricaudet Laboratoire de Génétique des Virus Oncogènes CNRS UA 1301 Institut Gustave Roussy 39, rue Camille Desmoulins F-94805 Villejuif Cedex TEL : 33-1-45597075 FAX : 33-1-45597008	Dr. Jean Closset Laboratoire d'Endocrinologie Biochimie Humaine CHU B23 Université de Liège B-4000 Liège TEL : 32-41-662461/662464 FAX : 32-41-662980
Prof. Thomas G. Cotter University College of Cork Department of Biochemistry Lee Malting Prospect Row IRL- Cork TEL : 353-21-276871 FAX : 353-21-274034	Prof. Arnaldo Corti Universita Degli Studi di Modena Dipart. di Scienze Biomediche Sezione di Chimica Biologica Via Campi, 287 I-41100 Modena TEL : 39-59-360045 FAX : 39-59-372653

Title : Therapeutic potentialities of 3' end modified antisense oligonucleotides targeted to codon 12 mutated HA-RAS

Contract N° : BMH4-CT96-1439

Period :1/7/96 - 30/6/99 Total EC Contribution : ECU 1,000,000

The present project is a logical pursuit of our BIOMED-1 programme (CT93-1500). During this programme we developed new anti-ras oligonucleotides. In the present programme we will carry out the necessary experiments to bring this new potential anti-cancer treatment to the clinic.

We have shown that antisense oligonucleotides directed to a point mutation in codon 12 of the Ha-ras mRNA selectively inhibited the proliferation of cells expressing the mutated Ha-ras gene. Tumour growth of these cells in nude mice was markedly inhibited after subcutaneous injection of antisense dodecamer absorbed to nanoparticles.

The predominant nuclease activity which degrades oligonucleotides intracellularly and extracellularly are 3'-exonucleases. By attaching short alkyl chains connected to the 3'-position of antisense dodecamer, we have enhanced stability of the dodecamer towards nucleases and lowered tumour growth inhibition dose by 100-fold.

The discovery of these highly active and selective oligonucleotide analogues prompts us to propose pharmaceutical and medical applications.

Activated mutated Ha-ras has been found in several cancers including bladder carcinomas. Oligonucleotides could be instilled intravesically, as an adjuvant therapy, in order to prevent progression or relapse after endoscopie resection. Therapeutic applications of antisense oligonucleotides to cancer treatment require information concerning the in vivo behaviour of olignonucleotides. Therefore, this proposal will focus on the in vivo evaluation of Ha-ras targeted 3'-end modified antisense oligonucleotides.

The proposal contains three main lines of investigation :

1. In vitro and in vivo evaluation of the efficacy of antisense oligonucleotides : Evaluation of original modifications which could improve the stability and the uptake of oligonucleotides.
2. Pharmacological studies : organ distribution, clearance kinetics and toxicity of modified dodeacamers will be studied in mammalians.
3. Collection of clinical samples and characterisation : the aim is to collect bladder carcinomas samples exhibiting ras mutation in order to establish primary culture and derived cell lines. At the same time antisense oligonucleotide activity will be evaluated and clinical trials will be started in the most optimal conditions.

Project Leader :

Ester Saison - Behmoaras
Laboratoire de Biophysique
Musée National d'Histoire Naturelle
INSERM U.201 - CNRS URA 481
43 rue Cuvier
F-75231 Paris Cedex 05

TEL : 33-1-40793686
FAX : 33-1-40793705

with participation of :

Piet Herdewijn Katholieke Universiteit Leuven Laboratory of Medicinal Chemistry Fac. of Pharm. Sciences Rega Institute Minderbroederstraat 10 B-3000 Leuven TEL : 32-16-337387 FAX : 32-16-337387	Théo Van Berkel Leiden/Amsterdam Centre for Drug Research Division of Biopharmaceutics Sylvius Laboratores P.O.Box 9503 Wassenaaérseweg 72 NL-2300 RA Leiden TEL : 31-71-276216 FAX : 31-71-276032
Maurice Schneider Centre Antoine Lacassagne Hématologie-Oncologie 36 Voie Romaino F-06054 Nice TEL : 33-4-93817133 FAX : 33-4-93533512	Paolo Laccetti Departimento di Biologie e Patologia Cellulare e Molecolare "L. Califano" Via S. Pansini, 5 I-80131 Napoli TEL : 39-81-5453033 FAX : 39-81-209224

Area 4.1.4

In vitro and transgenic animal models for basic research and assessing new approaches to treatment

Title : Development of murine transgenic systems for the experimental study of tumour initiation, progression and treatment - Animal models of human cancers

Contract N° : BMH4-CT96-1518

Period : 1/09/96 - 31/08/99 **Total EC Contribution : ECU 650,000**

Experimental carcinogenesis has, until recently, relied on the use of animal models in which the tumourgenic process is distantly related to that observed in humans. More recently, the use of transgenic mice hemizygous for a tumour suppressor gene has opened new opportunities but has also revealed two limitations : first some of the most prominent tumours observed in genetically predisposed humans are not observed in the corresponding mice (retinoblastoma is not observed in mice hemizygous for Rb); second for most instances (with the notable exception of p53) mice homozygously inactivated for a tumour suppressor gene are not viable. We propose to overcome these difficulties by the development of a modular transgenic mouse system which should enable the appearance of defined somatic mutations in a tissue specific manner. This system is based on the use of the Cre recombinase which directs recombination between two small oligonucleotidic target sequences called Lox. Recombination between two Lox sites in a direct (head-to-tail) orientation causes excision of the intervening DNA. This principle can be used to inactivate a tumour suppressor by inducing the deletion of a critical exon. The production of 4 series of conditional mutants which will target either Rb or TP53 or APC or NF2 is proposed. The use of transgenic constructs in which the Cre recombinase is placed under tissue specific promoters should enable to restrict the Cre expression to a relevant tissue (i.e. to the retina for a conditional Rb mutant).

An additional degree of sophistication is proposed which will enable to trigger the creation of defined somatic mutation not only in a tissue specific manner but also at a time that is decided by the investigator. This approach is made possible by the development of new regulatory systems which restrict transgene expression in cells that express an engineered transactivitor that is active only in the presence of tetracycline. This further development should be extremely useful in the analysis of tumour progression. Ultimately, development of a "two channel" system based on two independent inducers (i.e. tetracycline and tamoxifen) and two independent recombination systems (Cre/Lox and Flp, Frt, a system related to Cre/Lox found in Saccharomyces Cerevisiae) should provide excellent flexibility to analyse in detail the consequences of the occurrence time of the different mutations that contribute to tumour initiation and progression.

Finally, the development of an original tissue specific model of retroviral insertional mutagenesis eventually combined with the production of mouse strains that are hemizygous for a defined region containing a putative tumour suppressor activity should provide an approach to the isolation of new genes involved in the tumourigenic process.

It is expected that this work will provide a set of new biological resources that should enable further insight into the basic mechanism of tumourgenesis. It will also provide animal models of human cancer which will be useful in testing the new therapeutic protocols (including gene therapy) that will undoubtedly be proposed in the coming years.

Keywords : Site specific recombination, tissue specific mutagenesis, retinoblastoma, p53, neurofibromatosis type 2, colorectal cancer, cancer therapy, insertional mutagenesis, induced somatic mutation, experimental carcinogenesis.

Project Leader :

Dr. Gilles Thomas
Laboratoire de Génétique des Tumeurs
Institut Curie
26, Rue d'Ulm
F - 75231 Paris Cedex 05

TEL: 33-1-40516679
FAX : 33-1-40516630

with participation of :

Dr. A. Berns The Netherlands Cancer Institute Plesmanlaan 121 NL - 1066 CX Amsterdam TEL : 31-20-5121991 FAX : 31-20-5122011	Dr. H. Bujard Zentrum für Molekuläre Biologie (ZMBH) P.O. Box 106249 Im Neuenheimer Feld 282 D - 69120 Heidelberg TEL : 49-6221-568214 FAX : 49-6221-565892

Area 4.1.5

Predisposition, early diagnosis of cancer, and the earlier detection of metastases, including technological procedures and development of molecular and cellular reagents

Title : Identification of antigens recognised by T lymphocytes on human tumours, and pilot vaccination studies with defined antigens

Contract N° : BMH4-CT-96-1627

Period : 1/1/96 - 31/12/99 **Total EC Contribution : ECU 200,000**

At the present time several antigens have been identified that are recognised on human tumours by autologous cytolytic T lymphocytes (CTL). Many of these antigens are encoded by genes that are very selectively expressed by tumour cells. Therefore, it is now reasonable to try to immunise cancer patients against such tumour antigens to stimulate or to induce tumour rejection responses.

A first part of the project is the identification of new tumour rejection antigens recognised on human tumours by CTL. We intend to identify new antigens by applying to other types of tumours the methods that were successfully used with melanoma antigens. We will derive CTL clones against cell lines derived from renal, bladder, head and neck, and cervical carcinomas, from lung tumours, sarcomas, and leukaemias. After the identification of the HLA molecule which present the antigen recognised by a given CTL clone, the antigen will be identified by cloning the gene coding for the antigenic peptide, using transfection of cDNA libraries derived from the tumour cells. Another approach will involve the elution of the antigenic peptides bound to the HLA molecules expressed by the tumour cells. Using a combination of chromatography and mass spectrometry, it was possible to identify and to sequence individual peptides recognised by CTL clones. The third approach consists in identifying antigenic peptides that are derived from proteins encoded by genes which are known to be selectively expressed in tumours. Candidate peptides that are able to bind to defined HLA molecules will be identified. These peptides will be used in vitro to stimulate T lymphocytes from normal individuals and from cancer patients. The lytic activity of the responder CTL will be tested on tumour cell lines expressing the relevant HLA molecule and the gene encoding the antigenic peptide.

The second part of the project consists of attempts to stimulate immune responses of cancer patients against these defined tumour antigens. Several forms of the antigens will be tested, in order to compare their immunogenicity in vivo. Small groups of patients, eligible for such immunisations on the basis of their clinical status, of their HLA type and of the expression in their tumour of genes that are known to encode antigens, will be vaccinated with peptide alone or peptide mixed with adjuvant, or with recombinant protein with adjuvant, with irradiated cells expressing the antigen, with naked DNA encoding the antigen, and possibly with adenovirus or vaccinia constructs. These modalities of immunisation will be concomitantly evaluated in mice, using tumour antigen P1A. For the patients, the efficacy of immunisation will be assessed in vitro by measuring specific CTL responses in the blood and, whenever possible, in tumour-infiltrating lymphocytes obtained before and after vaccination. Histology of available tumour biopsies will be evaluated to define the nature of the lymphocytes infiltrated and, by PCR, the repertoire of infiltrating T cells. Larger clinical studies, with progression of the disease as endpoint, will be initiated with those forms of antigens which will prove to generate CTL responses in a significant proportion of patients.

Keywords : Cancer antigen vaccination cytocyclic T lymphocytes tumour immunology T lymphocytes

Project Leader :

Prof. Thierry Boon
Ludwig Institute for Cancer Research
Avenue Hippocrate 74
UCL 74.59
B - 1200 Brussels

TEL : 32-2-7647459
FAX : 32-2-7629405

With participation of :

Dr. Giorgio Parmiani Istituto Nazionale per le Studi e la Cura dei Tumori Via Venezian 1 I - 20133 Milano TEL : 39-2-2390630 FAX : 39-2-2362692	Dr. Pierre Coulie Cellular Genetics Unit International Institute for Cellular and Molecular Pathology Avenue Hippocrate 74 B - 1200 Brussels TEL : 32-2-7647446 FAX : 32-2-7629405
Prof. Jean-Charles Cerottini (LICRL) Ludwig Institute for Cancer Research Chemin des Boveresses 155 CH - 1066 Epalinges S/ Lausanne TEL : 41-21-3165990 FAX : 41-21-6534474	Prof. C. Melief - Prof. P. Schrier Dept. of Immunohaematology and Blood Bank University Hospital, Bldg. 1, E3-Q P.O. Box 9600 NL - 2300 RC Leiden TEL : 31-71-263800 FAX : 31-71-216751
Dr. Thomas Wölfel (MZ) Innere Medizinische Klinik und Poliklinik Johannes Gutenberg Universität Langenbeckstrasse 1 D - 6500 Mainz TEL : 49-6131-173382 FAX : 49-6131-173364	Dr. H.G. Rammensee Deutsches Krebsforschungszentrum Abt. Tumorvirus-Immunologie 0620 Postfach 101949 D - 69009 Heidelberg TEL : 49-6221-424900 FAX : 49-6221424902

Area 4.1.6

Effectiveness of systemic treatment modalities, including cytotoxic agents and biological response modifiers as well as newer approaches such as gene therapy

Title : The development of predictive tests of normal tissue response to radiation therapy

Contract N° : BMH4-CT-0638

Period : 1/05/96 - 30/04/99 **Total EC Contribution : ECU 410,784**

The aim of this concerted action is to bring together the intellectual and technical resources of 14 research groups within Europe to develop methods by which the patients, most at risk, of radiotherapy complications can be identified. The success of curative radiotherapy depends critically on those patients who are most at risk of dose-limiting complications. At the present time, the standard approach for radiotherapy with curative intent is to prescribe the maximum dose that is judged by the radiotherapist to be within the limit of normal-tissue tolerance. This dose is chosen on the basis of clinical experience to be one that will not lead to serious complications in more than a few percent of cases. This project foreshadows an important change in the strategy of radiation therapy : the *individualisation* of dose prescription. Tissue and blood specimens will be taken before treatment begins and subjected in the laboratory to a series of tests aimed at achieving the best possible prediction of normal-tissue tolerance to radiation therapy. On the basis of these tests we aim to identify that sub-group of patients who are most at risk of damage. Two principal options will then become available to improve patient management : to reduce the intensity of treatment for the patients who are most at risk of damage, and to increase the intensity of treatment for the majority of patients, thereby increasing their likelihood of achieving local tumour control.

Patients who suffer complications of radiotherapy fall into 3 groups : those who show a severe early reaction to irradiation; those who show a level of late radiation damage that stands out as being excessive; and those who suffer early tissue effects that are so severe that treatment has to be curtailed. The first 2 categories represent patients whose sensitivity to radiation treatment is in the upper part of the normal range. These are the patients whose reactions limit the dose of radiation that can be given. Depending upon the tumour site (and therefore on the normal tissues at risk) they may amount to 2 - 5% of patients given radiotherapy with curative intent. Within Europe they could thus amount to approximately 3,400 to 8,4000 patients per year.

The specific objectives include the following :

- To establish a standardised experimental basis for the inter-comparison of results from the participating laboratories.
- To provide an agreed classification of patients' normal tissue responses to radiotherapy.
- To establish the range of individual cellular radiosensitivity and its relationship to the variation of normal-tissue response to radiatherapy.
- To evaluate and establish the reproducibility and accuracy of rapid assays of cellular radiosensitivity that may be applicable for clinical predictive assays of normal-tissue radiosensitivity.
- To agree methods of clinical evaluation of predictive assays tests of normal-tissue response prior to the introduction of prospective clinical trials.

Determination of the intrinsic radiosensitivity of individual patients is expected to lead to significant improvements in health care. Firstly, it will reduce the serious complications of radiotherapy which are a burden not only to the individual patients but also have significant cost implications for the health-care system. Secondly, it may lead to improved management of the majority of patients by increasing local tumour control.

Key Words : Predictive testing, radiosensitivity, normal-tissue damage, DNA and chromosome damage, cell-cycle effects.

Project Leader :

Dr. J.H. Peacock
Institute of Cancer Research
Raditherapy Research Unit
15 Costwold Road
Sutton
GB - Surrey SM2 5NG

TEL : 44-181-6438901 Ext : 4694
FAX : 44-181-7707893

Dr. Jens Ovegaard The Danish Cancer Society Dept. of Experimental Clinical Oncology Noerregaard 44, Bldg. 5 DK - 8000 Aarhus C TEL : 45-89-492629 FAX / 45-86-197109	Dr. A.C. Begg The Netherlands Cancer Institute Plesmanlaan 121 NL - 1066 CX Amsterdam TEL : 31-20-5122036 FAX : 31-20-5122050
Dr. G. Pantelias National Centre for Scientific Research "DEMOKRITOS" Institute of Nuclear Technology Radiation Protection Lab. of Biological Dosimetry and Cancer Protection Terma Patriarchou Grigoriou E., Str. GR - 15310 Ag. Paraskevi Athens TEL : 30-1-6529615 FAX : 30-1-6533431	Dr. N.G. Burnett Velindre Hospital NHS Trust Whitchurch GB - Cardiff CF4 7XL TEL : 44-1222-615888 FAX : 44-1222-522694

Prof. C. Streffer Institut für Medizinische Strahlenbiologie Universitätsklinikum Essen Hufelandstrasse 55 D - 45122 Essen TEL : 49-201-7234152 FAX : 49-201-7235966	Dr. I. Turesson Sahlgrenska Hospital Department of Oncology S - 41345 Göteborg TEL : 46-31-601055 FAX : 46-31-820114
Prof. J.M. Ruiz de Almodovar Dept. of Radiology & Physical Medicine University of Granada Avenida de Madrid 11 E - 18071 Granada TEL+ : 34-58-244056 FAX : 34-58-244049	Dr. H.H. Kampinga State University of Groningen Faculty of Medicine Broerstraat 5 (P.O. Box 72) NL - 9712 CP Groningen TEL : 31-50-632882 FAX : 31-50-632883
Dr. E. Dikomay Institute of Biophysics and Radiobiology University of Hamburg Martinistr. 52 D - 20246 Hamburg TEL : 49-40-47173596 FAX : 49-40-47175139	Dr. D. Scott Paterson Institute for Cancer Research Christie Hospital NHS Trust Wilmslow Road Withington GB - Manchester M20 9BX TEL : 44-161-4463126 FAX : 44-161-4463109
Dr. M.C. Joiner Gray Laboratory P.O. Box 100 Mount Vernon Hospital Northwood GB - Middlesex HA6 2JR TEL : 44-192-3828611 FAX : 44-192-3835210	Prof. H.P. Rodemann Section of Radiobiology & Molecular Environmental Research University of Tübingen Röntgenweg 11 D - 72076 Tübingen TEL : 49-7071-295962 FAX : 49-7071-207462
Dr. C. Mothersill Physics Department Dublin Institute of Technology Kevin Str. IRL - Dublin 8 TEL : 353-1-4757541 353-1-4780282	

Title : Further genetic and epidemiological characterisation of hereditary breast cancer

Contract N° : BMH4-CT96-0869

Period : 1/1/96 - 30/12/98 **Total EC Contribution : ECU 400,000**

Several genes have been identified which strongly predispose to breast cancer, giving rise to high-risk families. The two most salient ones are BRCA1 on 17q12-q21, and BRCA2 on 13q12-q13. The gene sequence of BRCA1 was recently elucidated and direct mutation screening is now feasible. BRCA2 has not yet been isolated, but its location on chromosome 13 is accurately defined by polymorphic DNA markers. The main objective of this proposal for a Concerted Action is to generate large well-defined data sets by means of specific data calls, which are powerful enough to address important questions in relation to gene mapping, genetic heterogeneity, the spectrum of cancer risks associated with different mutations, the effect of programmes of intervention for individuals at risk, and the use of genetic data from tumours for prognosis and management of patients.

We expect to have assessed the genetic basis of the breast cancer predisposition in at least 350 families (250 BRCA1; 100 BRCA2). For BRCA1, this will allow the study of genotype-phenotype correlation's, and mutation-type specific cancer risks. For BRCA2, associated cancer risks and penetrance can be estimated. In the cohort of carrier women, the effect of known risk factors for breast cancer, such as parity and age at menarche, will be evaluated. In an attempt to identify genetic modifiers of the risk, polymorphism association studies will be performed in this cohort for a number of candidate genes. To investigate whether inherited breast cancer is a distinct entity relative to non-familial breast cancer, various somatic genetic changes, which occur frequently in sporadic breast tumours, will be characterised in at least 300 breast tumours from BRCA1- and BRCA2-linked families. In addition, their histopathology as well as several prognostic factors will be compared with sporadic breast cancer. We expect to identify a number of high-risk families that are not linked to BRCA1 or BRCA2, which will be employed to localise BRCA3.

EUROBCLC will maintain a database of studies of population-based series conducted by the Consortium members. Systematic studies will be undertaken to determine the prevalence of BRCA12-mutations among defined clusters of breast cancer, e.g., among 2,500 women unselected for family history and 200 sister-sister, or mother-daughter pairs.

Finally, at EUROBCLC-meetings, experiences related to social, psychological, ethical, and organisational aspects of predictive gene testing for BRCA1 (and later, BRCA2), will be exchanged. Possibly this will lead to the formulation of specific projects once genetic testing is underway in a number of countries. We can already envisage for example, the collation of data about - provision of genetic services, uptake of genetic testing, management of individuals at risk - which will almost certainly differ markedly between countries.

Keywords : Breast cancer; susceptibility; modifying factors, risk prediction; somatic genetics

Project leader :

Dr. P. Devilee
Department of Pathology & Human Genetics
University of Leiden
Wassenaarseweg 72
NL - 2333 AL Leiden

TEL. : 31-71-276117
FAX : 31-71-276075

with participation of :

Dr. T. Kruse Dept. of Human Genetics Arhus Universitet The Bartholm Building DK- 8000 Aarhus TEL : 45-89-421122 FAX : 45-86-123173	Dr. N. Haites University of Aberdeen Medical Genetics Dept. of Medicine & Therapeutics Foresterhill GB- Aberdeen AB9 2ZD TEL : 44-1224-840749 FAX : 44-1224-662839
Dr. P. Willems Department of Medical Genetics Universiy of Antwerp Universiteitsplein 1 B-2610 Antwerp TEL : 32-3-8202570 FAX : 32-3-8202566	Dr. S. Vassilaros Director of Breast Clinic 4, Semitelou Street GR- 115 28 Athens TEL : 30-1-7788698 FAX : 30-1-7227601
Dr. R. Scott Humangenetik Dept. Forschung Kantonspital Hebelstrasse 20 CH- 4031 Basel TEL : 41-61-2652362 FAX : 41-61-2652350	Dr. S. Scherneck Max-Delbrück-Centrum für Moleculare Medizin Tumorgenetik Robert Rössle Strasse 10 D- 13122 Berlin TEL : 49-30-94062226 FAX : 49-30-94063842

Dr. E. Oläh Dept. of Molecular Biology National Institute of Oncology Rath György Str. 7-9 H-1525 Budapest 114 Pf.21 TEL : 36-1-1550125 FAX : 36-1-1562402	Dr. Y. Bignon Centre Jean Perrin Laboratoire d'Oncologie Moléculaire Place Henri Dunant F- BP 392-63011 Clermont-Ferrand TEL : 33-4-73278050 FAX : 33-4-73263451
Dr. J. Chang-Claude German Cancer Research Centre Division of Epidemiology Im Neuenheimer Feld 280 D- 6900 Heidelberg 1 TEL : 49-6221-422200 FAX : 49-6221-422203	Dr. H. Nevanlinna Department of Obstetrics & Gynaecology Helsinki University Central Hospital Research Laboratory Haarmanikatu 2 SF - 00290 Helskinki TEL : 358-0-4712841 FAX : 358-0-479102
Dr. H.F. Vasen Stichting Opsporing Erfelijke Tumoren Academisch Ziekenhuis Gebouw 50 Rijsburgerwerg 10 NL- 2333 AA Leiden TEL : 31-71-261955 FAX : 31-71-212137	Dr. A. Borg Department of Oncology University Hospital S- 221 85 Lund TEL : 46-46-177500 FAX : 46-46-147327
Dr. G.M. Lenoir Int. Agency for Research on Cancer 150, Cours Albert-Thomas F- 69372 Lyon Cedex 08 TEL : 33-4-72-738485 FAX : 33-4-72-738575	Dr. J. Varley Department of Cancer Genetics Paterson Institute for Cancer Research Wilmslow Road GB- Manchester M20 9BX TEL : 44-61-4463062 FAX : 44-61-4463109
Dr. H. Sobol Département d'Oncologie Génétique Institut Paoli Calmettes 232 bd Sainte Marguerite F- 13273 Marseille Cedex 09 TEL : 33-4-91-223333 FAX : 33-4-91-223512	Dr. N. Holm Dept. of Oncology Odense University Hospital Sdr. Boulevard 29 DK- 5000 Odense TEL : 45-66-113333 ext 2990 FAX : 45-66-124681

Dr. A.-L. Boerresen The Norwegian Radium Hospital Institute for Cancer Research N- 0310 Oslo TEL : 47-22-934419 FAX : 47-22-934440	Dr. R. Winqvist Dept. of Medical Genetics Oulu University Central Hospital Kajaanintie 50 SF- 90220 Oulu TEL : 358-81-3153224 FAX : 358-81-3154499
Dr. G. Bevilacqua Instituto di Anatomia Patologica University of Pisa Via Roma 57 I- 56126 Pisa TEL : 39-50-561840 FAX : 39-50 592706	Dr. F. Schmitt Unidade Patologia Molecular Laboratorio de Anatomia Patologia Faculdate de Medicina Hospital de S. João P- 4200 Porto TEL : 351-2-590591 FAX : 351-2-5503940
Dr. R.B. Barkardottir Laboratory of Cell Biology University Hospital of Iceland P.O. Box 1465 IS- 121 Reykjavik TEL : 354-1-601906 FAX : 354-1-601519	Dr. J.E. Eyfjord The Icelandic Cancer Society P.O. Box 5420 Skogarhlid 8 IS- 125 Reykjavik TEL : 354-1-621414 FAX : 354-1-621417
Dr. R. Lidereau Centre René Huguenin 35 Rue Dailly F- 92210 Saint-Cloud TEL : 33-1-47111566 FAX : 33-1-47111696	Dr. M. Steel Bute Medical Building School of Biological & Medical Sciences University of St. Andrews GB- KY16 9TS St. Andrews, Fife TEL : 44-33-463558 FAX : 44-33-463000
Dr. C. Larsson Dept. of Molecular Medicine Endocrine Tumour Unit Karolinska Hospital L6 S-10401 Stockholm TEL : 46-8-7293930 FAX : 46-8-327734	Dr. D. Easton Institute of Cancer Research Block D Clifton Avenue GB- Sutton Surrey SM2 5PS TEL : 44-81-6438901 FAX : 44-81-7707876

Dr. B.A.J. Ponder CRC Human Cancer Genetics Level 3, Laboratories Block Box 238, Addenbrooke's Hospital Hills Road GB- Cambridge CB2 2QQ TEL : 44-223-336900 FAX : 44-223-336902	Dr. M. Stratton Institute of Cancer Research Molecular Carcinogenesis Section 15 Cotswold Road GB- Belmont, Sutton Surrey SM2 5PS TEL : 44-81-6438901 FAX : 44-81-7707290
Dr. D.T. Bishop ICRF Genetic Epidemiology Laboratory Ashley Wing St. James's University Hospital GB- Leeds LS9 7TF TEL : 44-532-837089 FAX : 44-532-340183	Dr. E. Solomon Imperial Cancer Research Fund P.O. Box 123 Lincoln's Inn Fields GB- London WC2A 3PX TEL : 44-71-2693426 FAX : 44-71-2693469
Dr. N. Spurr Imperial Cancer Research Fund Clare Hall Laboratories Blanche Lane, South Mimms Potters Bar GB- Herts EN6 3LD TEL : 44-71-2693846 FAX : 44-71-2693802	Dr. T. Wagner Abteilung für Spezielle Gynaekologie Universittsklinik für Frauenheilkunde Spitalgasse 23 A- 1090 Wien TEL : 43-1-404002801 FAX : 43-1-436749
Dr. J. Feunteun Institut Gustave Roussy Laboratoire de Génétique Oncologique CNRS URA#1967 39 Rue Camille Desmoulins F- 94805 Villejuif Cedex TEL : 33-1-45594294 FAX : 33-1-45596439	

Title : Co-ordinated Programme to identify families with susceptibility to Prostate Cancer

Contract N° : BMH4-CT96-1229

Period : 1/1/97 - 31/12/00 **Total EC Contribution : ECU 300,000**

The major focus of this study will be to collect families with (a) three or more prostatic cancer cases diagnosed at any age; or (b) two or more affected brothers diagnosed before the age of 65 years. Such families are candidates for carrying an inherited susceptibility predisposing to prostatic and possibly other malignancies. The families will be collected through major clinical urology centres through Europe. This bank of material, both DNA and RNA, will then be available for molecular genetic studies to identify genes predisposing to prostate cancer. The project will initially use genetic linkage analysis to identify genes which contribute to the risk of prostate cancer and to assess the importance of this gene/these genes to familial prostate cancer. DNA markers which are usually based on microsatellite repeats and which are known to have high degrees of polymorphism are typed within the families and tested for co-segregation with the putative prostate cancer susceptibility gene. Evidence for co-segregation is assessed statistically. The analysis will focus on a variety of candidate genes which are known to play a role in either prostate development or in other cancer susceptibility syndromes such as those for the breast cancer syndromes, BRCA1 and BRCA2. Only in the event that none of these turn out to be important would a genome-wide mapping search be initiated. When a gene or more probably a genetic region is identified as being important, we will assess the importance of this region to familial prostate cancer.

The other approach will be to examine the importance of genes thought to modify the risk of prostate cancer using a case-control approach. We will collaborate with ongoing studies which are investigating environmental causes of prostate cancer to examine the role of gene-environment interactions in determining prostate cancer susceptibility.

Keywords : Prostate Cancer, linkage analysis, familial, inherited susceptibility, mapping, gene-environment interaction, mutation.

Project Leader :

Prof. D. Timothy Bishop
ICRF Genetic Epidemiology Laboratory
Ashley Wing, St. James's University Hospital
Beckett Street
GB-Leeds, West Yorkshire, LS9 7TF

TEL : 44-113-2433144
FAX : 44-113-2340183

with participation of :

Dr. Peter Boyle Director Division of Epidemiology & Biostatistics European Institute of Oncology Via Ripamonti 435 I-20141 Milan TEL : 39-2-57-489815/816 FAX : 39-2-57-489813	Dr. Nigel Spurr Smithkline Beecham H24 New Frontiers Science Park (North) Third Avenue GB- Harlow-Essex CM19 5AW TEL : 44-1279-622639 FAX : 44-1279-622500
Dr. Ros Eeles Cancer Genetics Academic Unit of Radiotherapy Royal Marsden Hospital Downs Road GB-Sutton Surrey SM2 5PT TEL : 44-181-643-8901 ext 4538 FAX : 44-181-7707893	Dr. Peter Devilee Department of Human Genetics Wassenaarseweg 72 P.O.Box 9503 NL-2300 AR Leiden TEL : 31-71-276293 FAX : 31-71-276075
Dr. F. Algaba IUNA Instituto de Urologia Nefrologia y Andrologia Hospital de la Santa Cruz y San Pablo Escuela de Post-Graduados Universidad Autonoma de Barcelona Cartagena 340-350 E-08025 Barcelona TEL : 34-3-4169700 FAX : 34-3-4169730	Dr. J.E. Altwein Uroligische Abteilung Krankenhaus der Barmherzigen Bruder Romanstrasse 98 D-8000 München TEL : 49-89-1793250/254 FAX : 49-89-1782653
Dr. Georg Bartsch Department of Urology University of Innsbruck Anichstrasse 35 A-6020 Innsbruck TEL : 43-512-5044810 FAX : 43-512-5044873	Dr. Laurent Boccon-Gibod Urology Department Hôpital Bichat 46 rue H. Huchard F- 75018 Paris TEL : 33-1-40257100 FAX : 33-1-42285320
Dr. Fernando Calais da Silva Hospital do Desterro Av Oscar Monteiro Torres 804 Esq P-100 Lisbon TEL : 35-11-7952494/5 FAX : 35-11-7952497	Prof. F. Dubruyne Chairman Department of Urology St Radfboud University Hospital P.O.Box 9101 NL-6500 HB Nijmegen TEL : 31-80-541031 FAX : 31-80-613735

Prof. Louis J. Denis Algemeen Ziekenhuis Middelheim Lindendreef 1 B-2020 Antwerp TEL : 32-31-184696 FAX : 32-31-803602	Prof. Icannis Garas President Hellenic Society of Oncology 11 rue Valtetsiou GR-10680 Athens TEL : 30-1-3611774/+30-1-3645627 FAX : 30-1-3611774
Prof. F. Pagano Director Institute of Urology Universita' Di Padova Via Giustiniani 2 I-35128 Padova TEL : 39-49-8212721 FAX : 39-49-8212720	Prof. Michele Pavone-Macaluso Director Institute of Urology Policlinico P Giaccone University Polyclinic Hospital Via del Vespro 129 I-90127 Palermo TEL : 39-91-6552401/04 - 308753 FAX : 39-91-6552434/625 7852
Prof. J.M. Fitzpatrick Surgical Professorial Unit Master Misericardiae Hospital 47 Eccles Street IRL-Dublin 7 TEL : FAX :	Prof. Baudoin Standaert Director Povincie Antwerpen Provinciaal Instituut voor Hygiene Kronenburgstraat 45 B-2000 Antwerp 1 TEL : FAX :
Prof. Tage Hald Chief Urologist Herlev Hospital DK-2730 Herlev TEL : 45-44-535300 FAX : 45-44-535332	

Area 4.1.7

Development of methods for rapid analysis of efficacy of new treatment modalities including assessment of long-term effects and cost-effectiveness

Title : Diagnostic and prognostic markers of confined and metastatic cancer of the prostate

Contract N° : BMH4-CT96-0453

Period : 1/6/96 - 31/5/99 **Total EC Contribution : ECU 850,000**

This proposal focuses on diagnostic issues directly related to the selection and outcome of appropriate treatment regimens aimed at increasing the survival rates of prostate cancer (PC) patients. We intend to :

1. Construct highly sensitive and specific techniques to improve the early, cost effective detection of aggressive, organ confined and curable PC.

2. Construct sensitive and specific techniques that at an early phase can detect micrometastatic dissemination of the tumour in the blood circulation.

3. Identify molecular markers in tissue and blood to distinguish aggressive life-threatening cancers from non-aggressive, latent tumour lesions.

The proposed research goals are distinct, though relevant to those of the European Randomised study of Screening for Prostate Cancer (ERSPC) supported by EC grants.

The interactive programme involves 5 established European research groups (four academic and one from the industry) with long-term records of successfully combining fundamental, applied and clinical research. Two groups are from the Netherlands (Rotterdam, Nijmegen), one group from Sweden (Malmö) and two groups from Finland (Turku). The three clinical centres co-operate in prospective collection and analyses of tissue and blood specimens from patients and controls. A retrospective material with follow-up data is obtained from the ERSPC pilot study in Rotterdam : ~400 PC patients and ~1700 control subjects. The number of prospectively diagnosed cases of PC from the three clinical study sites will be ~600 patients per year.

The research goals are :

1. To design sensitive, specific and standardised methods for the early detection of PC by(i) constructing assays for multiple forms of PSA and glandular kallikrein (hK2) in serum, (ii) analysing collected sera at three clinical sites, (iii) comparing the obtained data with those of presently available test (total PSA, digital rectal examination (DRE) and transrectal ultrasonography) in order to evaluate their clinical utility and to reduce the number of unnecessary biopsies.

2. To design sensitive, specific and standardised techniques to distinguish aggressive from non-aggressive and possibly also organ confined from metastatic PC by (I) detecting specific mRNAs for PSA, hK2, prostate specific membrane antigen and the androgen receptor from micrometastatic cells in the blood, (ii) evaluating these techniques clinically.
3. To study tissue parameters that may distinguish aggressive from non-aggressive PC by : (I) developing standardised procedures for morphometric analysis and

cytochemical detection of tissue markers, and by (ii) evaluating the data from the developed procedures with clinical data.

Keybords : Prostate cancer, early detection, aggressiveness index, circulating cancer cells, PCR detection, prognostic factors tissue, morphometry, PSA free and bound, human glandular kallikrein and tissue markers.

Project Leader :

Prof. Dr. F. Schröder
Department of Urology
Erasmus University Rotterdam
and
Academic Hospital Rotterdam
P.O.Box 1738
NL- 3000 DR Rotterdam

TEL : 31-10-4633607/3095
FAX : 31-10-4635838

with participation of :

Hans Lilja, M.D., Ph.D. Associate professor of Clinical Chemistry Department of Clinical Chemistry Lund University Malmö General Hospital S- 20502 Malmö TEL : 46-40-331520 FAX : 46-40-337043 E-mail : kemhla@maja.mas.malmo.se	Jack A. Schalken, Ph.D. Director Oncological Research University Hospital Nijmegen Department of Urology Urology research laboratory P.O.Box 9101 NL- 6500 HB Nijmegen TEL : 31-80-616436 FAX : 31-80-541222
Dr. Timo Lövgren, Professor Department of Biotechnology University of Turku Tykistökatu 6, BioCity, 6th floor FIN- 20520 Turku 52 TEL : 358-21-6338051 FAX : 358-21-6338050	Dr. Kim Pettersson Research Manager Wallac Oy Research and Development P.O.Box 10 FIN- 20101 Turku 10 TEL : 358-21-2678111/436 FAX : 358-21-2678380

Title : Cancer After Transplantation (EUROCAT)

Contract N° : BMH4-CT96-0610

Period : 1/6/96 - 31/5/99 **Total EC Contribution : ECU 400,000**

Organ transplantation is followed by an increased risk for development of cancer. Analyses of materials from transplanted and therefore immunosuppressed patients allow the possibility to find risk factors for cancer and to evaluate oncogenetic mechanisms in general.

In our most recent analyses performed using correct cancer epidemiological methods an increased incidence of 3 - 5 times that in the general population has been found, including most types of tumours, however with an uneven pattern with emphasis on lip- cervical-, vulvar-, urological-, skin-cancers and lymphoproliferative disorders (PTLD). Most tumours occur early (include. PTLD) after transplantation, tumours of the skin however later and with an increase with time.

This complication appears to be increasing in degree for all types of organ transplantation, however a parallel increase in our knowledge concerning possible risk factors and oncogenetic mechanisms in general. Many of the tumours appear to be associated in some way with virus infections, thus opening up for possible new approaches to prophylaxis and treatment.

Based on previous cancer epidemiological studies in the Nordic countries it is the aim of this new study to :

1. perform a follow-up on existing files on kidney transplanted patients in the Nordic countries to latest possible date in the framework of Scandiotransplant and the Association of the Nordic cancer Registries

2. to analyse the Nordic material concerning all types of organ transplantation to latest possible date in the framework of Scandiatransplant and the Association of the Nordic Cancer Registries (ANCR)

3. to start a prospective registry with extensive use of existing data files in the Scandiatransplant organisation and the Association of the Nordic Cancer Registries (ANCR) allowing yearly analysis, with 1-3 in a collaborative study including all Nordic transplantation centres and cancer registries

4. to perform a study of cancer in patients on dialysis in the European Institute of Oncology, Division of Epidemiology and Biostatistics in Milano, Italy, which co-operates with centres in many European countries, since this will be complementary to the transplant study, as these patients are uremic with depressed immune defence, however not transplanted and immunosuppressed by drugs.

The cancer epidemiological analysis will allow identification of cases to be analysed intensively in :

5. specialised laboratories for immune pathology (DK, GB), cytokines (DK), virology (DK), and tissue typing (DK, FI, N, SE)

6. identified cases with proved Epstein-Barr oncogenetic background will be treated with a combination of (a) intravenous high-dose aciclovir and (b) decreased or discontinued immunosuppression.

The overall aim is to bring together cancer epidemiology (in the Nordic countries and Italy) with new advances in cellular, molecular and developmental genetics in immunopathology and immunology (cytokines and tissue types) and virology in order to obtain new biological insights and improvements in both diagnosis and treatment of interest for the field of transplantation and thereby also to obtain new insights in oncogenesis per se.

Keywords : Cancer, transplantation, immunosuppression, dialysis, cancer-epidemiology, immunopathology, virology, Epstein-Barr Virus, cytokines, tissue typing

Project Leader :

European Study of Cancer after Transplantation (EURO-CAT)
c/o Senior Consultant S.A. Birkeland, M.D., D.Sc.
Dept. of Nephrology
Odense University Hospital
DK- 5000 Odense

TEL : 45-65-413431
FAX : 45-65-906413

with participation of :

Melvin Madsen, M.D., D.Sc. Medical Director Scandiatransplant Skejby University Hospital DK- 8200 Aarhus N TEL : 45-89-495301 FAX : 45-89-496007	Hans H. Storm, M.D. Association of the Nordic Cancer Registries Danish Cancer Registry Division for Cancer Epidemiology Strandboulevarden 49 DK- 2100 Copenhagen OE TEL : 45-35-268866 FAX : 45-35-260090

Dr. Peter Boyle, Director European Institute of Oncology Division of Epidemiology and Biostatistics Via Ripamonti 435 I- 20141 Milano TEL : 39-2-57489815 FAX : 39-2-57489813	Dr. Stephen Hamilton-Dutoit Laboratory of Immune Pathology Aarhus University Hospital Finsensgade 12 DK- 8000 Aarhus C TEL : 45-89-493567 FAX: 45-89-493570
Prof. Lawrence Young, Ph.D., MRCPath Cancer Research Campaign Institute for Cancer Studies University of Birmingham GB- Birmingham B15 2 TJ TEL : 44-21-4146876 FAX : 44-21-4144486	Prof. Claus Bendtzen, M.D., D.Sc. Section of Inflammation Research RHIMA Centre Chief of Research National University Hospital DK- 2100 Copenhagen OE TEL : 45-35-457183 FAX : 45-35-457554
H. Kerzel Andersen, V.M.D., D.Sc. Section of Virology Dept. of Clinical Microbiology Aarhus University Hospital DK- 8000 Aarhus C TEL : 45-89-493544 FAX : 45-89-493540	Bjarne Moeller, M.D., D.Sc. Tissue Typing Laboratory Dept. of Clinical Immunology Skejby University Hospital DK- 8200 Aarhus N TEL : 45-89-495566 FAX : 45-89-496001

Title : Network Resource for the European Randomised Trial of Ovarian Cancer Screening

Contract N° : BMH4-CT96-1504

Period : 1/7/96 - 30/6/99 **Total EC Contribution : ECU 129,929**

The European Randomised Trial of Ovarian Cancer Screening (ERTOCS) was awarded a research contract with the European Commission as a concerted action project under the Biomedical and Health Research Programme (Biomed 1) in 1993 (Contract No. BMHI-CT93-1741). The project is a multicentre randomised trial of ovarian cancer screening using ultrasound examination of the ovaries. This project seems to provide a network resource under Reinforced Concertation for an integrated ultrasound screening management system that will combine two basic elements, (I) the capture and storage of digitised ultrasound images from the trial using new high-density CD-ROM storage technology and, (ii) interactive software linking the digitised ultrasound images with administrative and clinical data, follow-up details of cancer and death, and freezer locations of samples stored in the biological specimen bank (serum for tumour markers and whole blood for DNA studies). This will be a valuable technical aid in providing the specialised quality control needed for the management of the trial. This network resource will contain all the data (ultrasound images, clinical data and biological samples) in one electronic system. Although serum banking for epidemiological studies is not new, storage of ultrasound images has not been done in this way before and will provide a unique system for quality control in imagine and monitoring ultrasound screening programmes. For example, a screening test can be judged to be positive on the volume of the ovary as measured by the ultrasonographer. Readings that are consistently too high will result in too high a false positive rate. Images cannot normally be retrieved so whether or not the reading accounts for the false positive rate cannot be determined retrospectively. With this system the images can be retrieved and evaluated providing quality assurance in imaging techniques ultrasound screening programmes can be objectively monitored. In addition, if a case of ovarian cancer were missed by screening, it would be possible to identify and locate the relevant stored serum samples and ultrasound images and retrieve them to see if the cancer might have been detected much like a pathologist might retrieve a slide for review after a missed diagnosis.

The proposed system permits examination of all trial data at the co-ordinating centre on a monthly basis so that if problems emerge there can be rapid feedback to local centres. This system offers, in one package, trial management and quality assurance that previously could not be achieved. It will also provide a bank of images, normal and abnormal, that can be used as a teaching package for ultrasonographers involved in ovarian cancer screening.

Keywords : Ovarian cancer, screening, ultrasound, imaging, randomised trial, storage, sample banks, database.

Project Leader :

Professor Nicholas Wald
Wolfson Institute of Preventive Medicine
Dept. of Environmental & Preventive Medicine
The Medical College of St. Bartholomew's Hospital
Charterhouse Square
GB- London EC1M 6BQ

TEL : 44-171-9826269
FAX : 44-171-9826270

with participation of :

Mr. Ian Scott Dept of Obstetrics & Gynaecology Derby City General Hospital Uttoxeter Road GB-Derby DE22 3NE TEL : 44-332-340131 FAX : 44-332-290559	Dr. Ann Tabor Dept. of Obstetrics & Gynaecology Hvidovre Hospital Kettegärd Allé 30 DK-2650 Hvidovre TEL : 45-36-323632 ext. 5248 FAX : 45-36-323361
Prof. Fiona Gilbert Clinical Director North East Scotland Breast Screening Service Child & Family Health Division Grampian Healthcare North Trust Forester Hill GB- Aberdeen AB25 2XF TEL : 44-1224-404092 FAX : 44-1224-840786	

Area 4.1.8

Data collections and computerised recording of incidence, treatment and outcome which allow analysis on a transnational basis

Title : European Research on Cord Blood Banking and Use for Transplantation

Contract N° : BMH4-CT96-0833

Period : 1/7/96 - 30/6/99 **Total EC Contribution : ECU 690,000**

The principal limitations of allegoric bone marrow transplantation (ABMT) are the lack of suitable HLA-matched donors for the majority of patients and the complication of graft-versus-host disease (GvHD). The lack of sibling donors in some cases has been overcome through the establishment of large panels of potential marrow donors but these panels are restricted in terms of HLA polymorphism and of their ethnic diversity. This is most marked in Europe where each nation has its own ethnic diversity. Limitation is also related to the fact that results of allegoric bone marrow transplantation from normal bone marrow donor are dependent of HLA-A, B, C, DR, DP, DQ identity between donor and recipient. Umbilical cords from full-term pregnancies have been shown to be a source of haematopoetic progenitors (1,2,3,5,6). Banks of cord blood samples are being established in a number of EU member states (47). A number of cord blood transplants have been performed with encouraging results (3,39,40,41,42,43,44). Preliminary evidence suggests that these transplants are associated with less GvHD than comparable unrelated BMT.

The purpose of the research is to advance our understanding of cord blood transplantation and to establish common criteria and protocols for the handling of cord blood samples.

1. Objectives

- to standardise the methods of collection, testing and cryopreservation of cord blood
- to study the properties of haematopoietic progenitors present in cord blood
- to study the immune function of cord blood lymphocytes
- to co-ordinate and facilitate the exchange of sera and cells from regional cord blood depositories held in member states
- to establish a European Registry of patients treated by cord blood transplantation and design protocols comparing cord blood transplants with alternative conventional blood and bone marrow haematopoietic stem cell transplants.

2. Overview

The concerted action (CA) will : 1) compare methods of collection, banking and testing of cord blood collected for clinical use across different European countries. This will need communication between obstetricians, blood banks and laboratories involved in cellular biology, microbiology, immunology and the detection of genetic disease ; 2) study the properties of haematopoietic stem cells present in cord blood with regard to their selection and expansion for the purpose of improving their long term capacity for engraftment ; 3) study the immune reactivity of cord blood lymphocytes. The T lymphocytes and natural killer cell subsets present in cord blood samples will be characterised. Their in vitro responses to mitogenic and antigenic stimulation will be measured to determine functional maturity as will their reactivity to allegoric stimulation (GvHD) and to leukaemia cells (GvL) ; 4) co-ordinate the

exchange of cells and DNA from cord blood samples between different expert groups to perfect the detection and enumeration of contaminating maternal cells ; study transmission of infectious diseases from the mother to the child and perform studies of transmission of genetic diseases ; 5) establish a central registry of all European cord blood transplants to facilitate the analysis of results. Subsequently to design trans-European clinical studies in the light of these analyses.

The significance of this application is that the research planned herein is beyond the capability of any single EU member state. This research will be done within the European Blood and Marrow transplant group. All members of the project are active members of this group. This project has been approved by the board of the EBMT (March, 13 1995) Co-operation and exchange of ideas, material and personnel for training will allow the successful completion of these studies and the transfer of many expert techniques to EU states with less well-developed medical research facilities.

Keywords : Cord blood, immunobiology, haematopoietic stem cells, transplantation, GvHD, GVL, BMT.

Project Leader :

Pr. E. Gluckman
Service de greffe de moelle osseuse
Hôpital Saint-Louis
1, Av. Claude Vellefaux
F- 75010 Paris

TEL : 33-1-42499644
FAX : 33-1-42499634

with participation of :

Dr. A. Madrigal The Anthony Nolan Research Centre The Royal Free Hospital Pond Street GB- Hampstead - London NW3 2QG TEL : 41-22-3729401 FAX : 41-22-3729390	Pr. M. Jeannet Unité d'Immunologie et de Transplantation Höpital Cantonal de Genève 24, rue Michell-du-Crest CH- 1211 Genève 14 TEL : 41-22-3729401 FAX : 41-22-3729390

Dr. MW. Lowdell Department of Haematology Royal Free Hospital Pond Street GB- Hampstead - London NW3 2QG TEL : 44-71-7940500 FAX : 44-71-4314537	Pr. D. Charron Laboratoire d'Immunogénétique 15, rue de l'Ecole de Médecine F- 75006 Paris TEL : 33-1-40460358 FAX : 33-1-43299644
Pr. P. Wernet Bone Marrow Donor Centre Medizinische Einrichtugen Building 14-80 - Heinrich-Heine - Universität Moorenstrasse 5 D- 400001 Dusseldorf TEL : 49-211-3112545 FAX : 49-211-9348435	Dr. J. Falkenburg Department of Hematology University Medical Centre Leiden Building 1 : C2-R P.O.Box 9600 NL- 2300 RC Leiden TEL : 31-71-262271 FAX : 31-71-225555
Dr. F. Bertolini Centro Trasfusionale e di immunologia dei Trapianti Ospedale Maggiore Via Francesco Sforza 35 I- 20122 Milan TEL : 39-2-55034053 FAX : 39-2-5458129	Dr. I. Barbosa Serviço Hemoterapia Instituto Portugues de Oncologia R. Dr. Antonio Bernardino de Almeide P- 4200 Porto TEL : 351-2-591594 FAX : 351-2-526489
Dr. C. Bharucha Northern Ireland Blood Transfusion Service 89 Durham Street GB- BT12 4GE Belfast - Northerm Ireland TEL : 1232-321414 FAX : 1232-439017	Dr. J. Hows University of Bristo Dept. of Transplantation Sciences UBDOTS Southmead Health Service GB- Westbury-on-Trym - Bristol BS10 5NB TEL : 44-117-9595340 FAX : 44-117-9506277
Pr. B. Bradley University of Bristol Dept. of Transplantation Sciences UBDOTS Southmead Health Service GB- Westbury-on-Trym - Bristol BS10 5NB TEL : 44-117-9595340 FAX : 44-117-9506277	Pr. P. Herve Centre Régional de Transfusion Sanguine B.P. 1937 1, Boulevard Fleming F- 25020 Besançon Cedex TEL : 33-3-81615615 FAX : 33-3-81615603

Pr. P. Ebbesen Department of virus and Cancer Danish Cancer Society Gustav Wieds Vej. 10 DK- 8000 C Aarhus TEL : 45-86-127366 FAX : 45-86-195415	

Title : European Evaluation of intensive antileukaemic therapy for patients with myelodysplastic syndrome (MDS)

Contract N° : BMH4-CT-96-0357

Period : 1/7/96 - 30/6/99 **Total EC Contribution : ECU 700,000**

Myelodysplastic Syndromes (MDS) form a group of blood cell disorders, with high risk for development of secondary Acute Myeloid Leukaemia. The number of patients are increasingly being treated with intensive anti-leukaemia therapy. Generally, the treatment effects are inferior to those obtained in primary leukaemia. European-wide clinical evaluation of this new treatment modality was started in 1993 within the framework of the EORTC and the EBMT.
In the present BIOMED 2 project the co-operating research groups carry out an in-depth study to elucidate the underlying molecular and genetic mechanisms of MDS-pathogenesis, and of MDS-treatment. Analysis of the nature of remission and monitoring of residual disease is thought to be essential for rational application of intensive, and expensive myelotoxic treatment of MDS or s-AML. Especially, the question is emphasised to which extent intensive chemotherapy or autologous stem cell transplantation induces cytogenetic and polyclonal remission. This knowledge will enable to predict impact of the treatment on the duration of polyclonal remission and on the prognosis of the patients. As a consequence an objective instrument will become available to support the clinical decision process leading to a treatment policy in which expected outcome for the patient is considered.

Qualitative Objectives Concern :

- Assessment of efficacy and effectiveness of intensive antileukaemic therapy (cytogenetic and clonal remission, clinical response, survival and costs)
- Standardisation and quality control of molecular techniques in malignant haematology, with special emphasis on Fluorescent In Situ Hybridisation (FISH) and Polymerase Chain Reaction (PCR).
- Promotion of vital links between basic research and clinical studies.

The study includes patients, already participating in a recently started European study. FISH and molecular analysis of blood and bone marrow samples will provide evaluation of monoclonal versus polyclonal remission. Cell populations of female MDS patients with and without the characteristic cytogenetic markers will be assessed for clonality by X-chromosome inactivation patterns. During the project period an intensive quality assessment programme is executed in order to assure high comparability of results obtained in different laboratories.
The project will provide knowledge concerning the molecular mechanisms of MDS. It will increase access to sophisticated laboratory techniques for a number of clinical institutes. Moreover, it will contribute to improvement of the medical decision process concerning alternative treatment strategies in malignant haematology, especially with regard to MDS.

Keywords : Myelodysplastic syndrome, intensive chemotherapy, stem cell transplantation, clonality; clonogenic cells, fluorescent, in situ hybridisation, PCR analysis, X-chromosome inactivation patterns, quality assessment.

Project Leader :

Prof. T. De Witte
University Hospital Nijmegen
Division of Haematology
Geert Grooteplein 8
P.O. Box 9101
NL - 6500 HB Nijmegen

TEL : 31-80-614762
FAX : 31-80-542080

With participation of :

Prof. R. Willemze Laboratory of Experimental Haematology Leiden University Medical Centre Rijnsburgerweg 10 NL - 2333 AA Leiden TEL : 31-71-262271 FAX : 31-71-225555	Prof. Sergio Amadore Cattedra Ematologica Ospedale S. Eugenio Piazzalle Dell'Umanesimo I - 00144 Roma TEL : 39-6-5914745 FAX : 39-6-5915965
Prof. Jean-Pierre Magaud Hopital Edouard Herriot Laoratory of Molecular Biology Place d'Arsonval F - 69437 Lyon Cedex 03 TEL : 33-4-72-117353 FAX : 33-4-72117305	Dr. Carlo Aul Medizinishe Einrichtung der Heinrich Heine Universität Düsseldorf Cytogenetic Laboratory Moorenstrasse 5 D - 40225 Düsseldorf TEL : 49-211-3117714 FAX : 49-211-3118853
Prof. Françoise Meunier EORTC Avenue Emmanuel Maunier 83 B 11 B - 1200 Brussels TEL : 32-2-7741605 FAX : 32-2-7727063	

Title : Case-control study of selected second cancers following breast cancer. Influence of tamoxifen and other treatment modalities

Contract N° : BMH4-CT-96-0754

Period : 1/10/96-30/9/99 **Total EC Contribution : ECU 219,482**

The objectives of EuroDeucaTam Project are to evaluate the potential carcinogenic risks linked to several treatment modalities for breast cancer. In particular, the study will quantify any increases in selected second cancers following breast cancer. For the period 1996-1998, the study will concentrate on cancers of the endometrium, ovary and liver following breast cancer. It will determine the etiological role of all reproductive variables, other variables known to be associated with risk of breast cancer and of the other tumour under study, and of primordial interest will be the assessment of the effect of the various treatment modalities of breast cancer (surgery, radiotherapy, chemotherapy and hormonotherapy). The main exposure under study will be tamoxifen, with a detailed evaluation of the effects on risk of daily dose, duration of treatment and the interaction with other treatments radiotherapy, chemotherapy, and castration with evaluation of its effects according to method used (radiotherapy versus surgery).

The methodology used will be that of case-control studies. The cases will be women developing the second cancer of interest after having had breast cancer. Breast cancer diagnosis should have been made after the introduction of tamoxifen in the country concerned (1976). The source of cases on referents will be population-based cancer registries (to avoid biased ascertainment of cases and referents). The two diagnoses (breast cancer and second cancer) will have been recorded by the participating cancer registries. There will be four controls for every case. These will be women diagnosed with breast cancer at the same time and in the same registry as the case. They will be matched for age ($\pm$ 2 years) and date of breast cancer diagnosis ($\pm$ 2 years) with the case. They will have survived at least until the date of diagnosis of the case, and for controls of endometrial cases, not having at that date undergone a hysterectomy, and for controls of ovarian cancers, not having at that date undergone an ovariectomy. The source of information on exposure will be the cancer registry files and the clinical records with no personal interview of the women themselves.

This study will provide useful information on the long-term safety of breast cancer treatment. In addition, tamoxifen, a synthetic antioestrogen which has been widely used for the treatment of breast cancer and has been shown to be effective in reducing overall mortality as well as mortality from breast cancer and the occurrence of contralateral breast cancer is being proposed for the prevention of breast cancer among healthy women considered to be at high risk of developing breast cancer. Preventive trials are now underway both in the USA and in Europe. Nevertheless, concerns have been raised with regard to the side effects of tamoxifen and in particular the carcinogenicity of this product. This study will help to answer these concerns.

Keywords : breast cancer, castration, chemotherapy, endometrial cancer, epidemiology, liver cancer, ovarian cancer, tamoxifen.

Project Leader :

Dr. Annie J. Sasco
Head, Programme of Epidemiology for Cancer Prevention
International Agency for Research on Cancer
150 Cours Albert Thomas
F - 69372 Lyon

TEL : 33-4-72728412
FAX : 33-4-72738342

Dr. Franco Berrino Director, Cancer Registry of Varese Istituto Nazionale per lo Studio e la Cura dei Tumori Via Venezian 1 I - 20133 Milano TEL : 39-2-70638327 FAX : 39-2-2362692	Dr. Paul Schaffer Directeur du Registre des tumeurs du Bas-Rhin Directeur du Laboratoire d'Epidémiologie et de Santé Publique Faculté de Médecine 4 Rue Kirschleger F - 67085 Strasbourg Cedex TEL : 33-2-88368597 FAX : 33-2-88240131
Dr. Christine Bouchardy Médecin Chef du Registre genevois des Tumeurs Boulevard de la Cluse 55 CH - 1205 Geneva TEL : 41-22-3291011 FAX : 41-22-3282933	Dr. Calum S. Muir Director of Cancer Registration in Scotland Information & Statistics Division 23 Hill Street GB - Edinburgh EH2 3JP TEL : 44-131-2251333 FAX : 44-131-2259395
Dr. Eva Buiatti Associazione Italiana Registri Tumorio Unita Operativa di Epidemiologica Azienda Ospedaliera Careggi USL 10 Firenze Via di S. Salvi 12 I - 50135 Firenze TEL : 39-55-5662691 FAX : 39-55-679954	

Title : Meta-analyses for the improved treatment of cancer

Contract N° : BMH4-CT96-0019

Period : 1/5/96 - 30/4/99 **Total EC Contribution : ECU 300,000**

The major aims of the European Organisation for Research and Treatment of Cancer (EORTC), which involves the participation of more than 300 European institutions, include the co-ordination of research in Europe on cancer treatment, the linking of clinical practice to ongoing basic research, and the dissemination of state of the art knowledge in oncology among hospitals and clinicians in Europe.

As numerous publications have shown, it is well known that many clinical trials include too few patients in order to be able to reliably detect small to moderate (but medically important) treatment differences. Given that many small, inconclusive trials exist, the best way to combine together and objectively summarise the results from trials that ask similar questions is through the technique of meta-analyses (overviews). Meta-analysis is the process of using formal statistical methods to combine the quantitative results of separate but similar studies in order to increase the statistical precision of the estimated treatment effects. Meta-analyses provide clinicians, patients and policy markers with reliable, objective evidence on the effects of health care in order for professionals and providers, service users and purchasers, and researchers and funders to be able to set priorities and establish resources for both medical research and patient treatment. In this way truly informed decisions can be made concerning the potential impact of new therapies in clinical practice.

With the support from the European Commission through BIOMED 1, the EORTC Data Centre established a Meta-Analysis Co-ordination Unit (EORTC MAU) in May 1994. This has provided the EORTC with the scientific means and expertise required to identify, process and analyse the individual patient data from trials to be included in meta-analyses which are conducted by the unit. It also co-ordinates and provides data for patients entered in EORTC trials to be included in meta-analysis projects undertaken by other groups. Creation of this Unit has provided the means to successfully increase the contacts and co-ordination of meta-analysis activities with other centres such as the Medical Research Council (MRC) Clinical Trials Services Unit in 0xford, Great Britain, and the MRC Cancer Trials Office in Cambridge, Great Britain with whom joint projects exist.

The success of the work already accomplished by the EORTC MAU forms the basis of this grant submission which builds upon and extends the work of the MAU which was funded through BIOMED 1 for the period from May 1994 to April 1996. In particular, a continuation of meta-analysis projects in acute mylogenous leukaemia, superficial bladder cancer and early breast cancer is sought (in order to allow for their up-dating, an essential requirement to ensure conclusive results) along with the creation of new projects in malignant melanoma, soft tissue sarcoma, locally advanced head and neck cancer, and locally advanced cervical cancer. These are other types of cancer for which many trials have been carried out, but with inconclusive results and for which meta-analyses are therefore important.

Through these meta-analyses and the dissemination of their results as widely and rapidly as possible with the European Community, it will be possible to further improve the treatment and management of cancer in Europe. In this way as many patients as possible will profit from state of the art treatment, even those treated outside of research oriented institutes.

A reinforced concerted action is being requested in order to permit the training of scientists in the conduct of meta-analyses, thus allowing the further dissemination of this technology within the Member States.

Keywords : meta-analysis, randomised clinical trials, cancer treatment, individual patient data, dissemination of results, training.

Project Leader :

Dr. R. Sylvester
EORCT Data Centre
Avenue E. Mounier 83 B 11
B - 1200 Brussels

TEL : 32-2-7741613
FAX : 32-2-7723545

With participation of :

Dr. F. Meunier EORTC Data Centre Avenue E. Mounier 83 B 11 B - 1200 Brussels TEL : 32-2-7741630 FAX : 32-2-7712004	Prof. R. Zittoun Department of Haematology Hôtel-Dieu de Paris 1 Place du Parvis Notre Dame F - 74181 Paris TEL : 33-1-42348413 FAX : 33-1-42348406
Dr. P. Piedbois, Dr. E. Gauthier, Dr. P. Wolkenstein Hôpital Henri Mondor Dept. of Oncology 51, Avenue du Maréchal de Lattre de Tassigny F - 94000 Creil TEL : 33-1-49812582 FAX : 33-1-49812569	Dr. R. Tursz Institut Gustave Roussy 39, Rue Camille Desmoulins F - 94805 Villejuif Cedex TEL : 33-1-45594909 FAX : 33-1-45596426

Dr. J. Rouëssé Centre René Huguenin 32 Rue Dailly F - 92211 Saint Cloud TEL : 33-1-47111501 FAX : 33-1-46020811	Dr. V. Mosseri Department of Biostatistics Institut Curie 26, Rue d'Ulm F - 75231 Paris TEL : 33-1-44324000 FAX : 33-1-44324616
Dr. U.R. Kleeberg Max-Brauer-Allee 52 D - 22765 Hamburg TEL : 49-40-38021232 FAX : 49-40-38021215	Prof. F. Mandelli Dept. of Haematology Univ. La Sapienza Via Benevento 6 I - 00161 Roma TEL : 39-6-857951 FAX : 39-6-44241984
Dr. Stefano Greggi Universita Cattolica del Sacro Cuore Facolta di Medicina e Chirurgica "Agostino Gemelli" Largo Agostino Gemelli 8 I - 00168 Roma TEL : 39-6-30151 FAX : 39-6-3051343	Dr. F. Lejeune Centre Pluridisciplinaire d'Oncologie CHU Vaudois, Niveau 6 Rue du Bugnon 46 CH - 1011 Lausanne TEL : 41-21-3143947 FAX : 41-21-3143181
Dr. P. Clahsen Academisch Ziekenhuis Leiden P.O. Box 9600 NL - 2300 RC Leiden TEL : 31-71-262309 FAX : 31-71-225520	Prof. B. Lowenberg Dept. of Haematology Dr. Daniel den Hoed Cancer Centre Groenen Hilledijk 315 P.O. Box 5201 NL - 3075 EA Rotterdam TEL : 31-10-4391598 FAX : 31-10-4842008
Mr. W. van Putten Dept. Statistics Dr. Daniel den Hoed Cancer Centre Groenen Hilledijk 315 P.O. Box 5201 NL - 3075 EA Rotterdam TEL : 31-10-4391375 FAX : 31-10-4861058	Dr. A.P.M. van der Meijden Groot Ziekengasthuis Nieuwstraat 34 NL - 5211 's Hertogenbosch TEL : 31-73-862434 FAX : 31-73-862443

Dr. L. Stewart MRC Cancer Trials Office 5 Shaftesbury Road GB - Cambridge CB2 2BW TEL : 44-1223-311110 FAX : 44-1223-311844	Dr. K. Wheatley Clinical Trial Service Unit Harkness Building Radcliffe Infirmary GB - Oxford OX2 6HE TEL : 44-1865-57241 FAX : 44-1865-58817
Mr. P. Smith St. James's University Hospital Beckett Street GB - Leeds LS9 7TF TEL : 44-1132-433144 FAX : 44-1132-426496	Dr. P. Symonds Consultant in Clinical Oncology Stobhill NHS Trust Balornock Road GB - Glasgow G21 3UW TEL : 44-141-2013000 Fax : 44-141-5570458
Dr. J.C. Tobias Clinical Director Cancer Services The Middlesex Hospital Mortimer Street GB - London W1N 8AA TEL : 44-171-6368333 FAX : 44-171-6371201	

Area 4.1.9

Assessment of factors contibuting to the optimal quality of life including rehabilitation and terminal care

Title : Mantle cell lymphomas (MCL) - Biologic and clinical charaterisation and prospective evaluation of myeloablative radio-chemotherapy with blood stem cell transplanatation

Contract N° : BMH4-CT96-1539

Period : 1/7/96 - 30/6/99 **Total EC Funding : ECU 150,941**

Mantle lymphomas (MCL) represent a recently recognised sub-type of malignant lymphomas which are charaterised by a specific histology and immunophenotype and an unfavourable clinical course. Hence, response to chemotherapy is poor and patients with this disease usually face a median survival of less than three years. The recent discovery that MCL are associated with a specific chromosomal abnormality, the translocation t (11;14) that leads to the deregulation of cyclin D 1 and over-expression of bcl 1 and a consecutive impairment of cell cycle control has opened new perspectives to better understand the biology of this lymphoma and also potentially its clinical course. The current multinational study aims at gaining new insights into the biology of MCL and its appropriate clinical management and tries to explore a novel therapeutic strategy comprising myeloablative radio-chemotherapy with subsequent peripheral blood stem cell transplantation. These objectives are addressed in three major steps :

- The assessment of clinical and histopathologic features of presentation as obtained from a retrospective analysis of patients that have been treated with conventional therapies at the participating institutions;
- The biologic characterisation of MCL by means of modern immunophenotypic and molecular techniques;
- The prospective evaluation of myeloablative radio-chemotherapy with subsequent blood stem cell transplantation.

Keywords : Mantle cell lymphoma, blood stem cell transplantation, cytogenetics, cell kinetics, molecular aberrations, quality control

Project Leader

Prof. Wolgang Hiddeman
Department of Haematology and Oncology
University Hospital Göttingen
Robert-Koch-Strasse 40
D - 37175 Göttingen

TEL : 49-551-398535
FAX : 49-551-392914

Prof. H. Stein Universitätsklinikum Steflitz Pathologisches Institut Hindenburgdamm 30 D - 12230 Berlin TEL : 49-30-84452295 FAX : 49-30-8349085	Prof. Parwaresch Universitätsklinik Kiel Inst. für Hämatologie Niemannsweg 11 D - 24105 Kiel TEL : 49-597-3390 FAX : 49-597-3428
Dr. E. Pedrinis Istituto Cantonale di Patologia Via in Selva 24 CH - 6600 Locarno TEL : 41-93-328611 FAX : 41-93-3286	Prof. F. Berger Hopital Edouard Herriot Laboratoire d'Anatomo-Pathologie Place d'Arsonval F - 69437 Lyon TEL : 33-4-78538111 FAX : 33-4-72344840
Dr. A. van Hoof AZ Sint Jan Van het O.C.M.W. Ruddershove B - 8000 Brugge TEL : 32-50-452310 FAX : 32-50-392620	Prof. C. Peeters Catholic University of Leuven Dept. of Pathology B - 3000 Leuven TEL : 32-16- FAX : 32-16
Dr. Franco Cavalli Ospedale San Giovanni Head of Division of Oncology CH - 6500 Bellinzona TEL : 41-92-269147 FAX : 41-92-269044	Prof. A. Norton St. Bartholomew's Hospital Dept. of Histpathology West Smithfield GB - London EC1A 7BE TEL : 44-171-6018539 FAX : 44-171-7963753

Prof. G. Brittinger Universitäts-Poliklinik Abt. Hämatologie Hufelandstr. 55 D - 45147 Essen TEL : 498-201-7232417 FAX : 49-201-7235928	Prof. B. Coiffier Centre Hospitalier Lyon Sud Head of Dept. of Haematology F - 69310 Pierre-Bénite TEL : 33-4-78861194 FAX : 334-78506805
Prof. T.A. Lister St. Batholomew's Hospital Dept. of Medical Oncology West Smithfield GB - London EC1A 7BE TEL : 44-171-6062770 FAX : 44-171-7963979	

INDEX OF PARTICIPANTS