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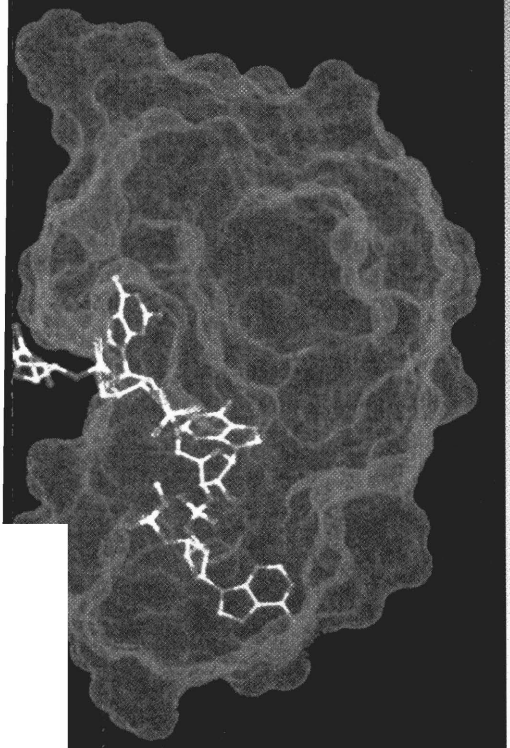
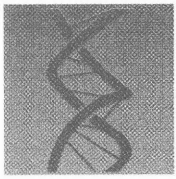


Biotechnology

Catalog of Contracts (1992-94) Vol. I.



Front-cover

Molecular model for the enzyme barnase interacting with a penta-nucleotide ligand.

The enzyme molecular surface is shown in blue and the penta-nucleotide ligand is represented using a stick model with oxygen atoms in red, nitrogen atoms in blue, carbon atoms in yellow and the phosphorous atom in white.

The enzyme atomic coordinate are from the 2Å resolution crystal structure; the ligand coordinates were generated using molecular modelling techniques.

Image generated using BRUGEL, a computer program developed jointly by UCMB-ULB and Plant Genetic System Corporation.

European Commission
Directorate-General XII
Science, Research and Development

BIOTECHNOLOGY

(1992-1994)

*C*atalogue of *C*ontract with *P*roject *D*escription

I

Edited by
C. Martinez

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Biotechnology 1992-1994

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INTRODUCTION

The European Commission's BIOTECHNOLOGY programme constitutes the natural continuation of the three previous Community programmes (BEP, BAP and BRIDGE) that, from 1982 to 1993, provided the framework for the establishment of a European network for training and research in the field of Biotechnology [1]. These programmes contributed to the development of supportive infrastructures for biotechnology research in Europe and to the elimination of barriers to knowledge and know-how which could have prevented exploitations of the results originating from modern biology [2].

The aim of research activities under the BIOTECHNOLOGY programme is to reinforce the access to, and use of biological knowledge as the rate-limiting step for biotechnological applications in agriculture, industry, health care and the environment. There is a major need to strengthen the scientific research base to improve Europe's competitiveness --public and industry expectations are best served by maintaining a sound basic research structure upon which either normative activities or commercial technologies can be developed by the actors themselves in their regulatory and economic environments.
The current programme BIOTECHNOLOGY covers the period 1992-1994 with a budget of ECU 189 million. Research activities in this programme are implemented via four different modalities:

- **Basic research projects**, integrating research efforts in adapted Community structures (European Laboratories Without Walls - ELWW [3], initially implemented in the BAP programme) for tasks where the main bottlenecks result from gaps in basic knowledge.

- **Generic Research Projects**, deliberately combining the contributions of different disciplines and techniques through efforts intended to remove important bottlenecks resulting from structural and scale constraints. They will lead to the constitution of clusters of laboratories addressing in an integrated manner, throughout the Community, highly specific research issues where an impact is to be expected.

- **Projects of Technological Priority**, aiming to achieve a higher degree of coherence and ultimate impact in certain areas of the programme. The areas are defined as those where a significant change of the state of the art now requires exceptional cross-linking efforts involving a wide range of potential contributors.

- **Concerted Actions,** creating Community networks of competencies and skills where national funding is widely available or where coordination of existing work and projects is a prerequisite to the launching, in a future Community programme, of new specific Basic and Generic research projects.

Following the first call for proposals in 1992, 99 projects have been launched during 1993. These encompass 856 participants from the 12 Member States and EFTA countries. These projects were selected from originally 529 proposals involving a total

of 2,856 organisations. Table 1 gives an overview of the results of the selection.

The present Catalogue groups the projects under areas, topics and sub-topics corresponding to the organisation of the Biotechnology work programme. Within each sub-topic, projects are grouped according to the implementation modalities described above. For each of these projects, the catalogue provides a title, some contract details, a summary of the objectives as well as a brief work description and a number of keywords. This outline is followed by a list of names of each of the participants in the projects. Indexes of participants, contract numbers and keywords are given at the end of the catalogue.

TABLE 1
BIOTECHNOLOGY
1st CALL FOR PROPOSALS

	Projects proposed	Partners involved	Cost proposed (million ECU)	Contribution requested (million ECU)
Entire Call	529	2,856	888	679
Selected	131	872	258	196
Contracted	99	856	149	111

Detailed information on these projects can be found in brochures describing each of the G-projects and the ELWW's constructed around the B-projects. These brochures are available from the Biotechnology unit of the European Commission upon request. Annual reports giving full details of the results are foreseen to appear during 1994 and 1995; a final report will be published in 1996.

E. Magnien
Biotechnology Unit
(Head)

C. Martinez
Biotechnology Unit
(Infrastructures)

Directorate Life Sciences and Technologies.
Directorate-General for Science, Research and Development - Joint Research Center

[1] Magnien, E., de Nettancourt, D. (1993). What drives EC Biotechnology research. IJTM, Special publication on the Management of Biotechnology, 47-58.
[2] Vassarotti, A. and Magnien, E. (1991) Biotechnology R&D in the European Communities, vol I, Catalogue of BAP Achievements, Elsevier, Paris
[3] Magnien, E., Aguilar, A., Wragg, P. and de Nettancourt, D. (1989) Biofutur, November, 17-30.

Members of THE REGULATORY COMMITTEE
for the RTD programme in the field of Biotechnology (1990-94)

BELGIUM
J. De Brabandere
J. Hutschemackers
(N. Nolard)
(V. Lories)
(M.C. Lenain)
(J. Bury)

IRELAND
L. Donnelly
J. Ryan

AUSTRIA
C. Fialla
V. Veits

DENMARK
B. Norrild
M. Bennum

ITALY
A. Albertini
G. Salvatore
(G. Magni)

FINLAND
P. Nybergh
H. Söderlund

GERMANY
E. Warmuth
R. Wandel
(J. Bollman)
(H. Autzen)
(H. Lang)
(S. Kieffer)

LUXEMBURG
P. Decker
L. Hoffmann

ICELAND
J.K. Kristjansson
E. Andresdottir

GREECE
K. Drainas
Y. Clonis
(A. Tsaftaris)
(H. Fleischer)

THE NETHERLANDS
M.W. Horning
H. Voorma
(J.J. Dekkers)

NORWAY
T.O. Hansen

SPAIN
A. Albert
A. Beltran
(J.L. Garcia Lopez)
(G. Rodriguez)

PORTUGAL
F.J. Carvalho Guerra
J.M. Novais

SWEDEN
G. Öquist
M. Ehrström
(P. Gustafsson)
(A. Wiklund)

FRANCE

P. Printz
S. Béranger
(A. Deshayes)
(A. Berkaloff)

UNITED KINGDOM

R. Ritzema
I. Lawrence
(V. Harrison)

LIECHTENSTEIN

V.M. Rheinberger
(as observer)

COMMISSION

Chairman : B. Hansen ; **Secretariat** : E. Magnien

Area 1

Molecular Approaches

1.1 Protein structure and function

1.1.1 Understanding of the catalytic mechanism of enzymes associated with biological membranes. Priority will be given to multidisciplinary studies of structure-function relationships of cytochromes and transport ATPases, using a variety of comple-mentary techniques (spectroscopic, crystallographic, molecular genetic, etc.).

1.1.2 Understanding of the interaction of antibodies with antigens: design of antigen binding sites leading to antibodies having predictable new properties, such as increased affinity or enzymatic properties.

1.1.3 Multidisciplinary studies of the structure-function relationships of receptors. Priority will be given to proposals that focus on ligand-receptor interactions and their consequent signal transduction events.

1.1.4 Production of novel biocatalysts, as a follow-up of tasks 1, 2 & 3 above.

Structure/function studies of the cytochrome *bf* complex by biochemical, biophysical, and molecular genetic techniques

Contract number: **CT930076** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 738,000 ECU

Objectives:
1. Structural details on the molecular level of the cytochrome *bf* complex. 2. Internal functions of the subunits and the redox centers. 3. Interaction of the complex within the framework of energy converting electron transfer chains.

Brief description:
The project will provide detailed information on the structure-function relationship of the membrane bound cytochrome *bf* complex at a molecular level. This complex plays a central role in electron transfer and energy conservation in photo-synthetic electron transport. The knowledge of the cytochrome *bf* complex is far less advanced than that of the photo-synthetic reaction centers and requires a combined effort in order to make a substantial progress. The project represents a multi-disciplinary effort by a group of European laboratories each of which is involved in the forefront of research related to this enzyme since many years. The cooperation will concentrate the resources of the laboratories in advanced biochemical, biophysical, and molecular genetic methods which will add a new dimension to the efficiency of research in this field. The combined spectroscopic facilities of the laboratories will create an extraordinary combination. The alga *Chlamydomonas reinhardtii* which is well established in one of our groups is the only organism available today for protein design by site-directed mutagenesis of the cytochrome *bf* complex in order to study specific structural and functional questions. Our investigation of this complexes will also include other organisms covering a broad range from anaerobic photosynthetic bacteria and thermophilic cyanobacteria to higher plants. The supply of manpower is expected to provide the impact for solving the mechanism of this poorly understood complex, for performing the structural studies by molecular genetics and mass spectrometry in combination with measurements of the function, and for solving the three-dimensional structure from X-ray diffraction in the long term.

Keywords:
Cytochrome *bf* complex, Protein, Photosynthesis, Protein interaction, Structure function relationship, Mutagenesis, Electron transport, Reaction kinetics, *Chlamodymonas reinhardtii*

Coordinator

PROF.DR HAEHNEL WOLFGANG
ALBERT LUDWIGS UNIVERSITAT FREIBURG
INSTITUT FÜR BIOLOGIE II
LEHRSTUHL FÜR BIOCHEMIE DER PFLANZEN
SCHANZLESTR. 1
D - 79104 FREIBURG

Participants

JOLIOT PIERRE ..... F
NITSCHKE WOLFGANG ..... D
POPOT JEAN-LUC ..... F
RICH PETER ..... GB
WOLLMAN FRANCIS-ANDRE ..... F

Structure and function of photosynthetic membrane - H^+-ATPases

Contract number: **CT930078** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 1,095,000 ECU

Objectives:
Optimization of H^+-ATPase and subunit preparations for crystallization studies. Partial resolution of three-dimensional protein complex and subunit structures. Elucidation of specific subunit functions and enzyme modulation mechanisms. Analysis of protein-lipid interaction and of factors determining protein thermostability.

Brief description:
This project aims at the elucidation of the structure and function of the H^+-ATPases of photosynthetic organisms. These key enzymes for energy conservation transform a trans-membrane proton gradient into ATP, and vice versa. They are regulated by ingeneous mechanisms, tuned to the specific requirements of different organisms. They are experimentally advantageous objects by enabling activation by light and fast kinetic analysis. The high-resolution three-dimensional structures of the H^+-ATPases are not known, and the regulatory mechanisms that modulate ATP synthesis or hydrolysis and coupled proton transport are not fully understood. A collaborative network was established for multi-disciplinary research of these aspects. The ATPases will be isolated and purified from chloroplasts, photosynthetic bacteria and cyanobacteria. These include thermostable species which are of particular advantage for crystallization and application-motivated studies. Enzyme structure will be investigated in two-dimensional crystal lattices by high-resolution electron microscopy and image analysis, and by atomic force microscopy. In addition, fluorescence, FT-IR and NMR spectroscopy, as well as DSC will be employed, also in soluble and pre-crystalline states. The function and regulation of the ATPases will be studied in reconstituted proteoliposomes and in native membranes. This will involve kinetic measurements of the catalytic reactions and coupled proton flux, analysis of coupling efficiency and of enzyme modulation, and effects of lipids and membrane surface charge on protein insertion and enzymatic activities. Moreover, the functions of the small ATPase subunits will be studied by heterologous subunit exchange and by site-directed amino acid substitutions. New results obtained with the native thermostable and with modified forms of these enzymes are of great interest to protein engineering, i.e. technological applications.

Keywords:
H^+-ATPases, Photosynthetic prokaryotes, Chloroplasts, Protein, Spectroscopy, Crystallization, Mutagenesis

Coordinator

PROF KRAAIJENHOF RUUD
VRIJE UNIVERSITEIT
DEPARTMENT OF MOLECULAR AND CELLULAR BIOLOGY
DE BOELELAAN 1087
NL - 1081 HV AMSTERDAM

Participants

DUÑACH MIREIA ..... E
GRAEBER PETER ..... D
MELANDRI BRUNO ANDREA I
RIGAUD JEAN-LOUIS ..... F
ROBILLARD GEORGE ..... NL

Drug, antibiotic and toxin excretion mechanisms in pro- and eukaryotic cells

Contract number: **CT930145** (Basic Research Project)
Start date: 01/08/93 Duration: 36 months
EC contribution: 1,186,000 ECU

Objectives:
To converse the knowledge from eukaryotic and bacterial drug, antibiotic and toxin excretion systems, to understand the molecular mechanisms of these excretion systems and to manipulate these systems in order to control the effect of the toxic compounds on cells.

Brief description:
The aim of this project is to analyze the functional and structural properties of transport systems involved in the secretion of drugs, antibiotic and toxins in pro- and eukaryotes. Some of these systems belong to the ABC superfamily of ATP-dependent transporters, whereas others belong to the class of ion-linked secondary transporters. The substrate recognition determinants will be defined that effect the high specificity of some and the low specificity of other systems. The transport processes will be analyzed energetically and kinetically upon functional reconstitution of the individual systems into artificial membranes. These studies will reveal common features for the excretion of (mostly) hydrophobic compounds, and may suggest ways to manipulate individual efflux processes in vivo. The knowledge that will be generated about drug, antibiotic and toxin transport may have medical and industrial impact for the near future.

Keywords:
Drug resistance, ATPase, Transport, Membrane, Bacteria, Eukaryotes, Toxins, Antibiotics, Drugs, Excretion, Energetics

Coordinator

PROF. KONINGS WIL
UNIVERSITY OF GRONINGEN
DEPARTMENT OF MICROBIOLOGY
BIOLOGICAL CENTER
KERKLAAN 30
NL - 9751 NN HAREN

Participants

COVE JONATHAN ..... GB
HIGGINS CHRISTOPHER ..... GB
HOLLAND IAN BARRY ..... F
SALAS JOSE A. ..... E
SCHREMPF HILDGUND ..... D

Membrane bound ATPases involved in the translocation of hydrophobic molecules

Contract number: **CT930348** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 1,171,000 ECU

Objectives:
To understand at the molecular level the family of ATPases involved in the translocation of phospholipids and/or drugs from one side of a membrane to the other. To purify, clone and characterize proteins from this "flippase" family. To evaluate the physiological consequences of any impairement of flippase activity.

Brief description:
Several membrane bound ATPases are involved in the translocation of hydrophobic molecules through the membranes of eukaryotes. The aminophospholipid translocase, also called "flippase", transports aminophospholipids from the outer monolayer to the inner monolayer of plasma membranes. Such transport requires hydrolysable Mg-ATP. Recently it has been suggested that one should include in the same category of proteins the 170 kDa P-glycoprotein (P-gP) which is responsible for the multidrug resistance in cancer cells. The latter carrier transports hydrophobic molecules from the inner to the outer monolayer of plasma membranes. The P-gP appears to be also a chloride channel. The aminophospholipid translocase which is partially purified from red cells will be cloned and antibodies generated. The activity of the protein will be studied in reconstituted systems; its role on lipid asymmetry and membrane shape change will be investigated in giant liposomes. Attempts will be made to find such selective translocation of phospholipids in the membrane of organelles (Golgi system, endosomes). The physiological consequences of the flippase activity will be considered in particular during red cell clearance, myoblast fusion and possibly blood cloting. In parallel experiments the flippase hypothesis for the P-gP will be verified by measuring the orientation of hydrophobic molecules transported by this ATPase. A putative role of the P-gP in lipid (cholesterol ?) asymmetry will be investigated. Site directed mutagenesis of P-gP will be used to study its flippase and chloride channel activities in cells or in reconstituted systems.

Keywords:
Mg-atpases, Flippase, Multidrug-resistance, Aminophospholipid translocase, P-glycoprotein, Ion channel, Lipid asymmetry, Spin-labels

Coordinator

PROF DEVAUX PHILIPPE
INSTITUT DE BIOLOGIE PHYSICO-CHIMIQUE
LABORATOIRE DE BIOPHYSIQUE CELLULAIRE
13 RUE PIERRE ET MARIE CURIE
F - 75005 PARIS

Participants

CARTRON JEAN-PIERRE ..... F
HERRMANN ANDREAS ..... D
HIGGINS CHRISTOPHER ..... GB
SEPULVEDA FRANCISCO ..... GB
VAN MEER GERRIT ..... NL

Structure and function of NADH : ubiquinone oxidoreductase (complex 1)

Contract number: **CT930364** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 836,000 ECU

Objectives:
To study crystallisation of bovine complex I and fragments of it.
To characterise its redox centres.
To characterise complex I from *Rhodobacter capsulatus* and plant chloroplasts, and hydrogenase from *Chromatium.*

Brief description:
NADH:ubiquinone oxidoreductase (complex I) provides the entry point for electrons from NADH into the respiratory chain in mitochondrial membranes. Defects in the enzyme are associated with major human diseases (Parkinson's and Alzheimer's disease), rare neuromuscular disorders and ageing. The main aim of this proposal is to study structure and organisation of subunits of complex I, and to determine the locations of redox centres. This proposal builds on existing collaborations between Cambridge and Amsterdam [studies of Fe-S clusters by Electron Paramagnetic Resonance (EPR) spectroscopy] and Cambridge and Grenoble (studies of bacterial complex I). Drs Walker, Dupuis (Grenoble) and Arizmendi (Bilbao) have also collaborated on studies of bovine complex I conducted in Cambridge. It is proposed to use a variety of techniques to study the topography of complex I, to attempt to crystallise it and active subcomplexes, to locate NADH, FMN and Fe-S cluster binding sites, to characterise a bacterial enzyme from *Rhodobacter capsulatus* and a related enzyme for which at least 14 subunits are encoded in chloroplast DNA in higher plants.

Keywords:
Complex i, Mitochondrial, *Rhodobacter capsulatus*, Chloroplasts, Flavin mononucleotide, Iron-sulphur clusters, Hydrogenase, *Chromatium*, Sequences, Structure, Electron paramagnetic resonance spectra, Antibody

Coordinator

DR WALKER JOHN
MRC LABORATORY OF MOLECULAR BIOLOGY
HILLS ROAD
GB - CB22QH CAMBRIDGE

Participants

ALBRACHT SIMON P.J. . . . . NL
ARIZMENDI JESUS MARIA . . . . . E
DUPUIS ALAIN . . . . . F

Combined structural mechanistic and functional analysis of two similar eucaryotic transport ATPases : the H^+ and Ca^{2+} pumps

Contract number: **CT930422** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 760,000 ECU

Objectives:
The main objective of this project will be the understanding of the molecular mechanism of the P-type ion pumps, more specifically the coupling mechanism between the phosphate transfer reaction and the ion translocation through the membrane, with a special emphasis on yeast plasma membrane H^+-ATPase and sarcoplasmic reticulum Ca^{2+}-ATPase.

Brief description:
The main objective of this project is the understanding of the molecular mechanism of the P-type ion pumps. More specifically the coupling mechanism between the phosphate transfer reaction and the ion translocation through the membrane, with a special emphasis on yeast plasma membrane H^+-ATPase and sarcoplasmic reticulum Ca^{2+}-ATPase. These two enzymes are among the simplest eukaryotic P-type ion pumps (no b-subunit) whose biochemical and biophysical properties of the purified enzymes have been well studied by the participating scientists. Genetic engineering is well developed and a major expertise in molecular biologyis available for the yeast H^+-ATPase. Biophysical knowledge of the Ca^{2+}-ATPase is by far the most advanced among the P-type pumps, especially attributable to the development of highly sophisticated instruments by members of the group. The elucidation of the molecular mechanism of these P-type ATPases involve the following intermediate targets: 1) Functional and structural analysis of the small and large hydrophilic loops (nucleotide binding, phosphorylation, phosphatase activity) 2) Functional analysis of the hydrophobic transmembrane region (ion binding and translocation), 3) Functional and structural analysis of selected peptides(phosphorylation and nucleotide binding site), 4) Investigation of the interactions between the cytoplasmic region and the transmembrane domain. The manufacturing of ATPase protein(wild type and chimeric), of large fragments and of peptides constitute the most innovative approach that may lead to the understanding of the molecular mechanism of energy transduction in p-type ATPases. Investigations include genetic engineering,expression of protein fragments synthetic peptides,studies on active site reactivity and substrate binding transient state kinetic studies, role of the H^+-ATPase proteolipid search for specific inhibitors and substrate analogues, electrophysiological and biophysical (fluorescence, circular dichroism, FR-IR, FT-Raman, NMR and X-ray crystallography) studies and molecular modeling.

Keywords:
ATPase, H^+ pump, Ca^{2+} pump, Structure, Membrane

Coordinator

DR DUPONT YVES
COMMISSARIAT A L'ENERGIE ATOMIQUE
CENG GRENOBLE
LABORATOIRE DE BIOPHYSIQUE
AVENUE DES MARTYRS
BP 85X
F - 38041 GRENOBLE

Participants

Plantibodies : A flexible approach to endow plants with new properties

Contract number: **CT920239** (Basic Research Project)
Start date: 01/01/92 Duration: 36 months
EC contribution: 1,199,972 ECU

Objectives:
The objective is to improve the basic technology to express and target "single chain" variable fragments (scFv) of antibody molecules in plants. This technology offers the possibility to design and alter metabolic routes (catalytic antibodies) to engineer disease resistance and to study plant growth and development by antisense-like approaches.

Brief description:
Antibodies have an enormous potential to enrich plants with new properties. Exploiting the vast immune repertoire of animals will lead to new strategies in plant breeding. Antibody molecules offer, for example, perspectives to engineer disease resistance, to alter or design metabolic routes ('catalytic antibodies') and to modify plant growth and development by antisense-like approaches. This joint effort is aimed at improving the basic technology to express and target antibody molecules in plants. Antibodies have several desirable features with regard to protein engineering. The variable domains carrying the antigen-binding loops (VH and Vl domains) can be used separately from the constant domains without loss of affinity. This project is focused on the expression and targeting of functional 'single chain' variable antibody fragments (scFv) in plants. In an scFv the variable parts of the heavy (VH) and light (VL) chain of the immunoglobulin molecule are linked by a peptide. Expression of scFv overcomes several problems inherent to the expression and assembly of heteromultimeric immunoglobulins in plants. In addition it is possible to incorporate two or more single chain antibodies having distinct specificities without having the problem of at random combination of VH and VL regions, which drastically reduces the affinity and specificity. To optimize the expression and targeting, the effect of different promoters, signal peptides, fusion to large parts of existing genes and the KDEL sequence will be studied. In addition we will investigate the role of the Bip-protein, which is found in the ER of animal systems. The Bip-proteins is a chaperone and may improve the assembly and folding of monoclonal antibodies in plants. Immunoglobulins inhibiting the development of three distinct plant pathogens (a bacterium, a virus and a plant parasitic nematode) will serve as model antibodies. These pathogens invade and colonize their hosts along different routes and are suitable models to study the versatility of monoclonal antibodies in targeting functional scFv's to different cellular compartments.

Keywords:
Antibody, Plant, Structure

Coordinator

DR. SCHOTS ARJEN
WAGENINGEN AGRICULTURAL UNIVERSITY
DEPARTMENT OF NEMATOLOGY
LABORATORY FOR MONOCLONAL
P.0. BOX 9060
NL - 6700 GW WAGENINGEN

Participants

ABAD PIERRE ..... F
BENVENUTO EUGENIO I
DEPICKER ANNA ..... B
DUERING KLAUS ..... D
KREUZALER FRITZ ..... D
STIEKEMA WILLEM ..... NL

Generation of functionally optimized antibody fragments for industrial (non-pharmaceutical) use

Contract number: **CT920367** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 840,000 ECU

Objectives:
To define general rules by which to improve stability of antibody derived fragments. The aim is to provide fragments by large scale fermentation, that will withstand industrial scale downstream processes. Concurrently, the relation between protein stability, flexibility and binding characteristics will be investigated, and exploited to endow fragments with optimized functionality.

Brief description:
In the present project draft, we propose to modify antibody fragment (ABF) structures with the aim to control flexibility in essential regions (core, secondary structural elements, and surface loops and cavities) of the protein. There is sufficient scientific evidence to justify that such control, depending on its precise localization (core or surface), will enable us to improve overall stability of the protein, and in addition, to manipulate interaction dynamics with ligands. Precisely these two characteristics of protein function, need optimization in order to generate ABFs suited for industrial purposes. At present ABFs lack sufficient stability to allow industrial scale production and manufacturing processes. Furthermore, a number of envisaged applications, demand initial binding of ABF to target molecules with subsequent release of the target upon change of conditions, i.e. control over binding dynamics. We propose to use 2 existing ABFs. One of known 3D structure, acting as the model in which engineering concepts and randomly found mutations can be tested and rationalized. The other of commercial importance, allowing final testing under application conditions. All aspects of protein engineering technology will be covered: precise and random mutagenesis followed by screening, multiple peptide synthesis, structure determination (X-ray), biophysical protein studies, and computer modelling. The proposed research presents a unique combination of scientific expertises, and can provide a breakthrough in the application of ABFs in industrial (non-pharmaceutical) products.

Keywords:
Antibody fragments, Protein flexibility, Protein engineering, Ligand binding, Kinetics

Coordinator

DR DE GEUS PIETER
UNILEVER RESEARCH LABORATORIUM VLAARDINGEN
OLIVIER VAN NOORTLAAN 120
NL - 3133 AT VLAARDINGEN

Participants

CAMBILLAU CHRISTIAN ..... F
MELOEN ROBBERT HANS ..... NL
PLUCKTHUN ANDREAS ..... CH

Protein engineering of therapeutic antibodies and peptide antagonists of scatter factor, a novel protein involved in cancer growth and spreading

Contract number: **CT920484** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 754,000 ECU

Objectives:
To engineer molecules which will block the interaction of scatter factor with its receptor and the response of target cells to the factor.

Brief description:
There is currently no specific treatment for arresting the invasion and metastasis of epithelial tumours. During the last few years, however, a process has been uncovered which may represent the first step towards cancer invasiveness. The process is the conversion of epithelial cells from a stationary phenotype to the highly motile and invasive phenotype typical of malignant cells. The conversion is induced by a specific cytokine (called scatter factor) through binding to its membrane receptor (the product of the c-met protooncogene). Scatter factor and the c-met receptor have therefore become specific molecular targets for the control of cancer invasion. We propose to produce therapeutic antibodies and peptides which will block the interaction between scatter factor and the c-met receptor using a combination of structural, protein engineering and genetic techniques. The antibodies and peptides with therapeutic potential will be first selected for activity in vitro and subsequently assessed for activity in vivo in mice carrying a human scatter factor and/or c-met receptor transgene(s). This work will establish the ability of antibodies and antagonists of scatter factor and the c-met receptor to prevent cancer invasion and will lay the foundation for the rational design of specific non-peptide drugs for the therapy of invasive and metastatic cancers.

Keywords:
Scatter factor, Receptor, Growth factors, Transgenic mice, Cancer

Coordinator

DR GHERARDI ERMANNO
ICRF CELL INTERACTIONS LABORATORY
CAMBRIDGE UNIVERSITY MEDICAL SCHOOL
MRC CENTER HILLS ROAD
GB - CAMBRIDGE CB2 2QH

Participants

BIRCHMEIER CARMEN ..... D
BIRCHMEIER WALTER ..... D
COMOGLIO PAOLO I

Structural and Functional analysis of the interactions of tyrosine kinase receptors with the conserved guanine nucleotide releasing proteins activating P21ras

Contract number: **CT930005** (Basic Research Project)
Start date: 01/10/93 Duration: 36 months
EC contribution: 795,000 ECU

Objectives:
Study structure-function relationships in GRFs using mutagenesis, biochemical and structural techniques. Search of GRF-interacting proteins from mammalian cells and tissues Reconstruction of ras/GAP/GRF cycle *in vivo* and *in vitro.*

Brief description:
Ligand binding at the extracellular domain of tyrosine kinase receptors (TKR) allows adjacent cytosolic domains within a receptor dimer to cross-phosphorylate each other on tyrosine residues, causing a conformational change that enhances kinase activity towards other substrates and creates binding sites for recruitment of other enzymes, resulting in the formation of signalling complexes. Ras proteins are activated in at least one third of human tumors and play an essential role in mammalian cell proliferation by growth factors. Rapid conversion of p21ras-GDP to the active, GTP-bound form follows insulin, EGF, NGF and PDGF binding to their cognate receptors. We propose to perform the following experiments. Biochemical and mutational analysis of the interaction between TKRs and Guanine Nucleotide Releasing Factors (GRFs) after stimulation with the cognate growth factors, agonists and antagonists. Reconstruction of a TKR-dependent signal transduction system both *in vitro* and *in vivo* (in yeast). The latter system will allow functional identification of missing elements and screening of engineered receptors and/or ligands. GRF(s)-interacting proteins (and their cDNAs) in different cell lines, tissues or developmental stages will be searched. GRF residues involved ras binding will be identified by random and/or site-directed mutagenesis. Ras mutagenesis will take advantage of the knowledge of its 3D structure. Structural analysis of Dpd- and Sos-GRFs, adaptor molecules, such as GRB2, or receptor domains directly interacting with GRFs.

Keywords:
Oncogenes, Guanine nucleotide releasing factors, GRF, Sos-GRF, GRB2, Receptor, Mutagenesis, Protein structural analysis, Cloning, Yeast, Nervous system, Oncogenesis

Coordinator

DR. ALBERGHINA LILIA
UNIVERSITA DEGLI STUDI DI MILANO
DIP. FISIOLOGIA E BIOCHIMICA
SEZ. BIOCHIMICA COMPARATA
CELORIA 26
I - 20133 MILANO

Participants

BOS JOHANNES L. ..... NL
CHARDIN PIERRE ..... F
PARMEGGIANI ANDREA ..... F
WITTINGHOFER FRED ..... D

Molecular mechanisms of Beta-adrenergic receptor function and regulation (Euroceptor)

Contract number: **CT930083** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 700,000 ECU

Objectives:
The project is aimed at a molecular analysis of the signal transduction and the regulation mechanisms of adrenergic receptors. It is intended to identify key steps in these processes and to develop inhibitors which may become lead compounds for drug development.

Brief description:
This project represents a multidisciplinary collaboration studying the ligand-receptor interaction, signal transduction and regulation of human adrenergic receptors. These receptors are prototypes for the large superfamily of G-protein coupled receptors and are the targets of many drugs used to treat, for example, bronchial asthma and high blood pressure. We will use techniques of molecular biology, biochemistry, biophysics and computer modelling to achieve two primary objectives: (1) a three-dimensional model of the ligand-binding pocket and of the agonist-induced conformational change, and (2) the identification of rate-limiting steps in the signal transduction and regulation cascade. Both objectives will allow the rational design of lead compounds for novel drugs that act on this receptor system. This proposal will result in the identification and the contracting of pharmaceutical companies for the development of such lead compounds. Informal collaborations exist already with several pharmaceutical companies, but it is hoped that, in addition, collaborations with new specialized SMEs will develop. These efforts should help to reestablish a European stronghold in an area that is of importance both for basic science and for drug development.

Keywords:
Signal transduction, Receptor desensitization, Receptor, Protein, B-arrestins, Phosducin

Coordinator

DR LOHSE MARTIN
JULIUS MAXIMILIANS UNIVERSITÄT
INSTITUT FüR PHARMAKOLOGIE UND
TOXIKOLOGIE
VIRSBACHIR 8
D - 97078 WÜRZBURG

Participants

Interactions of activins with type II activin receptors in differentiation systems : structure-function analysis and synthesis of dominant negative ligands and receptors

Contract number: **CT930102** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 812,000 ECU

Objectives:
To synthesize recombinant antagonistic activin A. To carry out a structure function study on the ligand and the type II receptor

Brief description:
Some members of the Transforming Growth Factor (TGF)-beta superfamily of growth- and differentiation-regulatory polypeptides have been implicated as regulators of mesoderm formation in early embryonic development of vertebrates. These include TGF-beta2, BMP-4, and activin A and B. Several studies point to a role of activin as a strictly concentration-dependent morphogen in Xenopus. Activins (A, B and AB) are multifunctional proteins, at least *in vitro*. Activin A is identical to an erythroid differentiation factor (EDF) for erythroleukemia (EL) cells. Many of its activities in vitro and in vivo, and the mechanisms through which activins act, remain to be elucidated. The recent cloning of type II and type II-B receptors for activin will contribute to the understanding of the function of the ligands in significant detail. We want to manipulate the signalling process experimentally at the level of the interaction of activins with their type II receptors. We want to understand through detailed analysis of the molecular interaction between the ligands and the receptors the function of the activin type II receptors in the generation of bio-activities of activins with sharp tresholds. We will carry out part of our studies in Xenopus oocytes and embryos, in embryonic stem and embryonal carcinoma cells, and in EL cells. This project will help to explain at the molecular level how different isoforms of the type II activin receptors generate different affinities for activins, and to identify which protein domains or amino acid residues in the receptors and in the ligands are essential for this. This should contribute to the design of synthetic peptides, derived from either the ligand of the receptor sequences, that are able to interfere with the bio-activity of activins.

Keywords:
Activins, Tgfß-superfamily, Receptor, Differentiation, Embryo

Coordinator

DR HUYLEBROECK DANNY
K. U. LEUVEN
LABORATORY OF MOLECULAR BIOLOGY
HERESTRAAT 49
B - 3000 LEUVEN

Participants

DE WAELE PETER ..... B
MUMMERY CHRISTINE ..... NL
SMITH JAMES ..... GB

Structure and function of glutamate receptors

Contract number: **CT930243** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 1,500,000 ECU

Objectives:
The main objective is to be able to predict the structure of glutamate receptors. The methodology is multidisciplinary with the use of molecular biology, molecular electrophysiology, chemistry and protein chemistry. The final goal is to obtain the three-dimensional structure of the glutamate receptor. This research aims to produce a high resolution map of one of the receptors.

Brief description:
The amino acid glutamate is the neurotransmitter responsible for most of the excitatory synaptic transmission in the central nervous system. It plays a central role in many important physiological processes including learning and memory. The diverse effects of glutamate are mediated by a number of membrane bound receptors. In the recent years, two main classes of receptors have been characterized: 1) the ionotropic glutamate receptors are ligand gated channels permeable to cations whose properties and structural features resemble the nicotinic ionotropic receptor; 2) the metabotropic glutamate receptors are GTP-binding protein (G protein)-coupled receptors with seven membrane spanning domains. In the last two years more than twenty subunits of the glutamate ionotropic receptors and several metabotropic receptors have been cloned. The fine characteristics of both native and transfected ionotropic receptors can now be studied both at the whole cell level and at the single channel level. The two main goals of this project are 1) the study of functional domains of glutamate receptors (binding sites, channels of ionotropic receptors, region of coupling to G proteins for metabotropic receptors) combining available molecular biology techniques, biochemistry and electrophysiology; 2) the determination of the subunit composition of the various ionotropic receptors. In the three years duration of the project we also hope to develop 1) methods for the obtention of materials suitable for tridimensional structural analysis and 2) better predictive methods for the identification of specific ligands of the various receptor subtypes. This basic research could lead to the discovery of glutamate antagonists for use in the treatment or prevention of a number of CNS diseases linked to excitotoxicity. The concept of excitotoxicity, assumes that an excess of glutamate may be at the origin of a neurodegenerative process, in chronic diseases such as Alzheimer's, Parkinson's and Huntington's diseases and in stroke.

Keywords:
Receptor, Neurotransmitter, Structure, Parkinson, Huntington, Neurotransmitter

Coordinator

DR ROSSIER JEAN
INSTITUT ALFRED FESSARD
CENTRE NATIONAL DE LA
RECHERCHE SCIENTIFIQUE
F - 91198 GIF-SUR-YVETTE CEDEX

Participants

ASCHER PHILIPPE ..... F
BOCKAERT JOEL ..... F
DARLISON MARK ..... D
KROGSGAARD-LARSEN POVL ..... DK
LERMA JUAN ..... E
SAKMANN BERT ..... D
UNWIN NIGEL ..... GB

Structures of a membrane bound receptorits ligand interaction activation and signal transduction cascades : studies aimed at atomic resolution using a multidisciplinary approach of chemistry, spectroscopy and molecular biology

Contract number: **CT930467** (Basic Research Project)
Start date: 01/08/93 Duration: 36 months
EC contribution: 840,000 ECU

Objectives:
To define models for phototransduction in rhodopsins; to develop further solid state NMR for study of biomolecules; to express membrane proteins in a large scale production; to incorporate genetically stable NMR isotopes into membrane receptors

Brief description:
The specific goal of this project is to initiate a multidisciplinary study of the structure, the genuine ligand-receptor interactions and the natural signal transduction events for the visual transmembrane photoreceptor rhodopsin. This aims at developing a novel and general approach for refining membrane protein structure including, for example, cytochromes and transport ATPases. New basic knowledge about receptor function and consequent signal transduction processes at the molecular and atomic level will be generated, adding to the core knowledge and methods used world-wide in pharmaceutical and health industries. The receptors chosen for this highly multidisciplinary proposal are visual receptors of higher organisms, rhodopsins, which are archetypes of a super family of higher organism receptors involved in signal transduction following activation. Initial studies will be on wild type rhodopsins but then expression systems currently in use for bovine and squid proteins with two of the proposers, will be optimized to provide sufficient recombinant protein for spectroscopic studies. The specific objectives of the proposal are to refine the structural descriptions of two membrane bound proteins, which are activated by photons and convert the received energy into a biochemical response. The structural information, in the form of descriptions of the amino acids and their positions within the protein, will be used to describe the functional activity of the proteins.

Keywords:
Protein structure, NMR (Solid state nuclear magnetic resonance), Receptor

Coordinator

DR WATTS ANTHONY
UNVERSITY OF OXFORD
DEPART. OF BIOCHEMISTRY
SOUTH PARKS ROAD
GB - OX1 3QU OXFORD

Participants

DEGRIP WILLEM ..... NL
FINDLAY JOHN B.C. ..... GB
LEVITT MALCOLM ..... S
LUGTENBURG JOHAN ..... NL

Functional architecture of the acetylcholine nicotinic receptor as a model of ligandgated ion channel : investigations at the amino acid level

Contract number: **CT930518** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 420,000 ECU

Objectives:
The aim of this proposal is to investigate by joint protein engineering, pharmacological and microphysiological techniques the functional architecture of the nicotinic receptor for the neurotransmitter acetylcholine as a model for the superfamily of ligand-gated-ion channels which, in brain, muscle or electric organ synapses, mediate the conversion of neurotransmitter signals into cation channel openings.

Brief description:
Our main objectives will be to exploit, altogether, chemical labelling, sitedirected mutagenesis and chimeric genes construction between various receptor species to identify : 1) the amino acids which determine the interaction with agonists and antagonits ; 2) the chemical mechanism of ion translocation through the channel ; 3) the signal transduction process which mediates the interaction between receptor sites and ion channel ; 4) the regulation of the signal transduction process by high order molecular transitions (desensitization, potentiation) via allosteric sites for "modulatory" ligands. To achieve these objectives we regroup the potentials of three European laboratories that possess complementary expertises in : 1) at the Institut Pasteur in Paris: protein chemistry with membrane-bound and purified receptor from *Torpedo* electric organ ; recombinant DNA technology including site-directed mutagenesis, mosaic genes construction, and rapid kinetic methods among other biophysical techniques ; 2) at the Geneva University: gene expression into *Xenopus* oocyte, electrophysiological recordings including voltage-clamp and pharmacology of chicken brain homooligomeric alpha7 receptor ; 3) at Bath University: pharmacology and medicinal chemistry of brain nicotinic receptors from insects (ARL2) in relation with insecticidal potenty in locusts, and from vertebrates in relation with nicotine addiction ; culture of neurons or transfected cell lines ; recombinant DNA technology and molecular modeling.

Keywords:
Receptor, Neurotransmitter, Ion channel structure

Coordinator

PROF CHANGEUX JEAN-PIERRE
INSTITUT PASTEUR
25 RUE DU DR ROUX
F - 75724 PARIS 15

Participants

BERTRAND DANIEL . . . . . CH
WONNACOTT SUSAN . . . . . GB

1.2 Gene structure

1.2.1 Microorganisms : *S. cerevisiae* and *B. subtilis*

- Sequencing networks
  Participants invited to apply for :
- small scale sequencing
  Sequencing of contiguous fragments of at least 25 thousand base pairs per year from either *Saccharomyces cerevisiae* (strain S288C), or *Bacillus subtilis* at a funding of 2 ECU per base pair.

- medium scale sequencing
  Sequencing of contiguous fragments of at least 100 thousand base pairs per year from *Saccharomyces cerevisiae* (strain S288C), or *Bacillus subtilis* at a funding of 1.6 ECU per base pair.

- DNA coordinator : *S. cerevisiae*
  Construction of organised chromosome libraries, distribution of appropriate overlapping clones to be sequenced, at a funding of 0.1 ECU per base pair.

1.2.2 Higher organisms : *A. thaliana*

- Sequencing networks
  Participants invited to apply for :
- small scale sequencing
  Sequencing of contiguous fragments of at least 25 thousand base pairs per year from *Arabidopsis thaliana* (including the sequences of cognate cDNAs) at a funding of 2 ECU per base pair.
- medium scale sequencing
  Sequencing of contiguous fragments of at least 100 thousand base pairs per year from *Arabidopsis thaliana* (including the sequences of cognate cDNAs) at a funding of 1.6 ECU per base pair.

- cDNA sequencing
  Coordination and preliminary funding of large-scale cDNA sequencing activities from *A. thaliana* sorted libraries. On a pilot basis, cDNA clones from the characterized libraries will be assigned for sequence determination to laboratories, particularly those making already a contribution to genomic DNA sequencing activities, or exceptionally to other ones having appropriate network connections with the sequencing community and linked to the same database.

- DNA coordinator
  Maintenance of organized YAC and cosmid libraries, and of cDNA libraries of characterized origins; planned distribution of clones (with their restriction map) covering chromosomal regions defined beforehand; cognate cDNA screening and mapping as a means of characterizing coding sequences within genomic DNA; coordination and monitoring of progress of small and medium scale sequencing work in liaison with the informatics coordinator; organisation of links with the international programme. Parts of these tasks could be subcontracted under supervision of the DNA coordinator, at a funding of 0.1 ECU per base pair or fractions thereof, according to their state of advancement.

1.2.3 Sequence data coordination

For any of the genomes specified above, collection, organisation and analysis of sequence data at a funding of 0.05 ECU per base pair of the final sequence handled. Proposals for either one or the three species are welcome.

1.2.4 Coordination of gene function search and preparation of future actions.

Systematic sequencing of the yeast genome

Contract number: **CT920063** (Project of Technological Priority)
Start date: 01/01/93 Duration: 18 months
EC contribution: 6,194,000 ECU

Objectives:
. Sequencing of 1,5 Mb from the yeast genome per year.
. Sorting out and organisation of yeast chromosomal libraries for future BIOTECH II sequencing activities.

Brief description:
Administrative coordination of the systematic sequencing of the yeast genome including chromosomes X (750 kb), XIV (800 kb), XV (1150 kb) and VII (1150 kb). - Construction of the necessary organised cosmid libraries plus those of the two longest yeast chromosomes : IV (1600 kb) and XII (2200 kb).
- Establishement, implementation and payment of the 54 subcontracts.
- Organisation of annual spring meeting of subcontractors.
- Implementation of a new blind control system by sequencing random non overlapping DNA fragments.
Subdivision of responsibilities:
* Sequencing chromosomal fragments as indicated by DNA coordinator
** Sequencing and organisation of chromosomal library
*** Sequencing and DNA coordination
**** Sequencing, organisation of chromosomal library and DNA coordination

Name of the contractor	Fax	Institution
ALEXANDRAKI Despina *	30 81 230 469	GR IMBB Heraklion
ANSORGE Wilhem *	49 6221 387 306	D EMBL Heidelberg
ARINO Joaquin *	34 3 581 2006	E Univ. Autonoma Barcelona
BOLOTIN Monique *	33 1 69 41 72 96	F Univ. Paris-Sud
BOYD Alan *	44 31 650 3711	GB Univ. of Edinburgh
BRUSCHI Carlo *	39 40 375 7343	I Int. Center Gen. Eng. Biot Trieste
CROUZET Marc *	33 56 51 85 61	F Univ. de Bordeaux II
DELIUS Hajo *	49 6261 424 667	D Deutsch Krebsforsch. Heidelberg
DOMDEY Horst *	49 89 8578 3795	D Ludwig-Max.-Univ. München
DUJON Bernard**	33 1 4061 3060	F Inst. Pasteur, Paris
DÜSTERHÖFT Andreas *	49 2103 892 222	D Diagen GmbH Hilgen
ENTIAN Karl-Dieter *	49 69 6301 7639	D Univ. Frankfurt
FELDMANN Horst *	49 89 59 96 316	D Ludwig-Maxi.-Univ. München

FOURY Francoise **	32 10 47 38 72	B Univ. Catholique Louvain
GAILLARDIN Claude *	33 1 30 81 54 57	F Inst. Nat. Agronom. Paris-Grignon
GALIBERT Francis ***	33 1 42 06 02 50	F Lab. Hématologie Expér. Paris
GANCEDO Carlos *	34 1 585 4587	E Inst. Investig. Biomed. Madrid
GLANSDORFF Nicolas *		B Inst. CERIA-COOVI Bruxelles
GRIVELL Leslie Alan *	31 20 668 5086	NL Univ. Amsterdam
HEGEMANN Johannes *	49 641 702 7390	D Justus-Liebig-Univ. Giessen
HERBERT Christopher J *	33 1 69 07 55 39	F CNRS Gif-Sur-Yvette.
HERRERO Enrique *	34 73 702 426	E Univ. Lleida
HILGER Francois *	32 81 61 15 55	B Fac. Sc. Agronomiques Gembloux
HOLLENBERG Cornelis P. *	49 211 311 5370	D Heinrich-Heine Univ. Düsseldorf
JACQ Claude ****	33 1 44 32 39 41	F CNRS Paris
JACQUET Michel *	33 1 69 41 72 96	F Univ. Paris Sud
JAUNIAUX Jean-Claude *	49 6221 42 4962	D Deutsch.Krebsforsch. Heidelberg
JIMENEZ Antonio *	34 1 397 4799	E Univ. Autonoma Madrid
KRAMER Wilfried *	49 551 393 805	D Univ. Göttingen
LANDT Olfert *	49 30 712 7734	D TIB Molbiol GmbH Berlin
LAUQUIN Guy *	33 56 99 90 59	F IBCN/CNRS Bordeaux
MARTIN Robert P *	33 88 61 06 80	F CNRS Strasbourg
NETTER Pierre *	33 1 69 07 53 22	F Centre Génét. Mol. Gif-Sur-Yvette
NOMBELA Cesar *	34 1 394 17 45	E Univ. Complutense Madrid
Prof. OLIVER Stephen *	44 61 236 0409	GB UMIST Univ. Manchester
PANZERI Lucia *	39 2 266 4551	I Univ. Milano
PHILIPPSEN Peter ***	41 61 267 21 18	CH Inst. Applied Microbiology Basel
PLANTA Rudi J. *	31 20 548 5648	NL Vrije Universiteit Amsterdam
POHL Thomas *	49 7531 57 313	D G. Anal.Techn.Consult. Konstanz
POHL Fritz M. *	49 7531 882 966	D Univ. Konstanz
RODRIGUES-POUSADA Claudina *	351 1 443 16 31	P Fundaçao Gulbenkian Oeiras
SCARCEZ Thierry *	32 91 410 799	B Innogenetics Gent
SCHWEIZER Michael *	44 603 58 414	GB IFRN Norwich
SOR Frederic *	33 1 69 86 94 29	F Inst. Curie, Section Biologie Orsay
SOUCIET Jean-Luc *	33 88 61 06 80	F CNRS Strasbourg

STEENSMA Yde *	31 71 27 49 99	NL Clusius Lab, Rijksuniv. Leiden
URRESTARAZU Antonio *	32 2 650 54 21	B Univ Libre Bruxelles
VALLE Giorgio *	39 49 828 6261	I Univ. Padova
VOLCKAERT Guido *	32 16 22 07 61	B Catholic University Leuven.
VON WETTSTEIN Diter *	45 33 27 47 66	DK Carlsberg Laboratory Copenhagen
WAMBUTT Rolf *	49 372 5501 219	D FZB Biotechnik GmbH Berlin
WOLF Klaus *	-	D RWTH Aachen
WOLFE Kenneth *	353 1 679 8558	IRL Univ. Dublin
ZIMMERMAN Friedrich K. *	49 6151 164 808	D Inst. Mikrobiologie Darmstadt

Keywords:
Yeast, DNA sequencing, Chromosomal libraries

Coordinator

UNIVERSITE CATHOLIQUE DE LOUVAIN
PLACE CROIX DU SUD 2/20
B - 1348 LOUVAIN-LA-NEUVE

Participants

ALEXANDRAKI DESPINA ..... GR
ANSORGE WILHELM ..... D
ARINO JOAQUIN ..... E
BOLOTIN-FUKUHARA MONIQUE ..... F
BOYD ALAN ..... GB
BRUSCHI CARLO I
CONTRERAS ROLAND ..... B
CROUZET MARC ..... F
DELIUS HAJO ..... D
DOMDEY HORST ..... D
DUJON BERNARD ..... F
DÜSTERHÖFT ANDREAS ..... D
ENTIAN KARL-DIETER ..... D
FELDMANN HORST ..... D
FOURY FRANCOISE ..... B
GAILLARDIN CLAUDE ..... F
GALIBERT FRANCIS ..... F

GALIBERT FRANCIS ..... F
GANCEDO CARLOS ..... E
GLANDSDORFF/PIERARD N./A. ..... B
GRIVELL LESLIE ALAN ..... NL
HEGEMANN JOHANNES ..... D
HERBERT CHRISTOPHER ..... F
HERRERO ENRIQUE ..... E
HILGER/PORTERELLE F./D. ..... B
HOLLENBERG CORNELIS P. ..... D
JACQ CLAUDE ..... F
JACQUET MICHEL ..... F
JAUNIAUX JEAN-CLAUDE ..... D
JIMENEZ ANTONIO ..... E
KRAMER WILFRIED ..... D
LANDT OLFERT ..... D
LAUQUIN GUY ..... F
MARTIN ROBERT P. ..... F
NETTER PIERRE ..... F
NOMBELA CESAR ..... E
OLIVER STEPHEN ..... GB
PANZERI LUCIA I
PHILIPPSEN PETER ..... CH
PLANTA RUDI J. ..... NL
POHL FRITZ M. ..... D
POHL THOMAS ..... D
PURNELLE BENEDICTE ..... B
RODRIGUES-POUSADA CLAUDINA ..... P
SCARCEZ THIERRY ..... B
SCHWEIZER MICHAEL ..... GB
SOR FREDERIC ..... F
SOUCIET JEAN-LUC ..... F
STEENSMA YDE ..... NL
URRESTARAZU ANTONIO ..... B
VALLE GIORGIO I
VOLCKAERT GUIDO ..... B
VON WETTSTEIN DITER ..... DK
WAMBUTT ROLF ..... D
WOLF KLAUS ..... D
WOLFE KENNETH ..... IRL
ZIMMERMANN FRIEDRICH K. ..... D

Sequencing the yeast genome - Sequence data coordination

Contract number: **CT920172** (Project of Technological Priority)
Start date: 01/05/93 Duration: 36 months
EC contribution: 423,000 ECU

Objectives:
Sequence data administration and analysis for the European Yeast Sequencing Project

Brief description:
We have served as the informatics coordination center for the processing, analysis, and assembly of the sequence data for yeast chromosomes II and XI. We propose to continue this effort for other chromosomes to be sequenced under the BIOTECH programme. We will provide the following services: 1. collection and administration of submitted sequence data; 2. verification of the DNA coordinator's restriction map; 3. quality control by clone overlaps and resequencing efforts; 4. DNA level sequence data analysis to identify promotors and upstream activating sequences (UAS), autonomously replicating sequences (ARS), introns, tRNA genes, and yeast specific regulatory sequence repeats; 5. protein level sequence data analysis of the open reading frames by similar searches against the most comprehensive sequence data sets (FASTA/BLAST); 6. sensitive comparison of candidate sequence homologs, pattern searches using the available pattern collections (e.g. PROSITE), and analysis of ORF'S for internal repeats; 7. linkage of sequence data to the corresponding genomic data collections; 8. submission of data to public sequence databases; 9. submission of bimonthly reports on new ORF's homologies to the Commission and the Yeast Industry Platform; 10. full annotation of protein sequence data emerging from the project; 11. provision of a supported online system for sequence data analysis; 12. establishment of a confidential sequence database to test novel sequences against protected data; 13. provision of training support for members of the participating laboratories.

Keywords:
Genome analysis, Yeast, Informatics, Sequence analysis

Coordinator

DR MEWES HANS-WERNER
MAX PLANCK INSTITUT FUER BIOCHEMIE
AM KLOPFERSPITZ 18
D - 8033 MARTINSRIED

Participants

Yeast Genome Sequencing Network (see Contract CT920063)

Experimental pilot study for a European cooperation on gene function search in the yeast *Saccharomyces cerevisiae*

Contract number: **CT930022** (Project of Technological Priority)
Start date: 01/11/93 Duration: 36 months
EC contribution: 800,000 ECU

Objectives:
To undertake a systematic gene function search of the novel, protein coding genes (ORFs) of chromosome III; (ii) to prepare a final action which can be applicable to the study of genes to be discovered by the future sequencing of other chromosomes.

Brief description:
Under the auspices of the EC programmes the complete sequence of chromosome III of *S. cerevisiae* has been established and the sequencing of several other chromosomes is underway. The most striking observation is that the majority of the new genes revealed by genomic sequencing are unrelated to the genes contained in data banks and their exact function is unknown. The objectives of this project are ambitious and we envisage to analyse of the order of one hundred genes in three years. Although each step of the analysis is rather classical, the extent of the undertaking is not. Therefore, novel strategies will be developped and our project will constitute a major methodological investement. It is apparent that the situation encountered with chromosome III is not unique, since a large fraction of ORFs discovered on other chromosomes are functionally not understood. In order to understand the function, the individual genes will be inactivated and amplified. In each case a battery of phenotypic tests will be applied, RNA transcripts analysed, protein-2D-maps investigated and protein spots partially sequenced. The information that has emerged from the EC sponsored collaborative sequencing of chromosome III has already received international recognition, and it has been stressed on many occasions that the major challenge is to relate the sequence to the function. The long term benefit of the research proposed herein is not a linear function of the novel cell activities that will be identified but rather a combinatorial function of this new information added to what we already know, providing an ensemble of facts that we can manipulate to design more incisive experiments and ask more intelligent questions. *S. cerevisiae* is an exceptional model of the eukaryotic cell in the sense that the amount of genetic, physiological and biochemical knowledge already accumulated and the facility of genetic engineering are not encompassed. The understanding of function of novel yeast genes will be precious for the study of other organism, including man, since several chromosome III ORF's display significant homology with human or other vertebrate genes of unknown function.

Keywords:
Yeast, Function search, 2D-gel electrophoresis maps, Transcripts analysis, Protein microsequencing, Orfs analysis

Coordinator

PROF SLONIMSKI PIOTR
CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE
CENTRE DE GENETIQUE MOLECULAIRE
(GENOMES ET FONCTIONS)
AVENUE DE LA TERRASSE
F - 91198 GIF-SUR-YVETTE

Participants

BOLOTIN-FUKUHARA MONIQUE ..... F
BOUCHERIE HELIAN ..... F
FEY/MOSE LARSEN S./P. ..... DK
HARITOS ATHANASSIOS ..... GR
MICHAELIS GEORG ..... D

Development and use of *Arabidopsis thaliana* as a tool for isolating genes of agronomic importance

Contract number: **CT920529** (Project of Technological Priority)
Start date: 01/02/93 Duration: 18 months
EC contribution: 1,653,860 ECU

Objectives:
. establish a physical map of the genome . develop methods for gene isolation and characterisation . isolation of genes involved in floral induction, and seed formation . establish stock centres

Brief description:
The small genome size, rapid life cycle and good genetic base in *Arabidopsis* makes it an ideal model plant. However, various molecular genetic methods used in other organisms need to be adapted for use in *Arabidopsis*. The programme is contributing to an international effort to establish a detailed physical map of the genome using cosmid and YAC libraries. Transposon tagging is being developed as an efficient way to generate mutations and to recover the mutated loci. Approaches include using modified versions of the maize elements Ac and En. Existing mutant and ecotype collections are being relocated and catalogued to provide a long-term resource for the *Arabidopsis* community in collaboration with the AFRC (UK). A DNA resource centre has been set up to provide a readily accessible store of recombinant libraries, RFLP probes, etc. Gene replacement is being studied with the aim of utilising this powerful technique for identifying gene function. Mutants affecting floral induction are being characterised physiologically, mapped, and walks to some of the loci have started. New combinations of mutants have been made to determine the pathways leading to floral induction. Seed development is also being studied, and mutants affecting seed maturation involving abscisic acid are being mapped and isolated. The effect of these mutations on seed protein deposition and the activity of other genes is being studied. A novel method called "enhancer trapping" to identify genes active in early states of embryogenesis is being used.

Keywords:
Genome analysis, *Arabidopsis* genetics, Gene isolation

Coordinator

DR BEVAN MICHAEL
AFRC INSTITUTE OF PLANT SCIENCE RESEARCH,
CAMBRIDGE LABORATORY
JOHN INNES CENTRE
COLNEY
GB - NR4 7UJ NORWICH

Participants

BRIGHT S.W.J. ..... GB
COUPLAND G. ..... GB
DANGL JEFF. ..... D
DEAN C. ..... GB
DELSENY MICHEL ..... F
GALLOIS P. ..... F
GIRAUDAT J. ..... F
HOOYKAAS PAUL ..... NL
KARSSEN C. ..... NL
KAVANAGH TONY. ..... IRL
KONCZ C. ..... D
KOOL A. ..... NL
KOORNNEEF MAARTEN. ..... NL
LEEMANS J. ..... B
LINDSEY K. ..... GB
MARTINEZ ZAPATER J.M. ..... E
MASTERSON R. ..... D
MEYER P. ..... D
MULLIGAN B. ..... GB
OLESEN P. ..... GB
PAGES MONTSERRAT. ..... E
PASZKOWSKI J. ..... CH
PEREIRA A. ..... NL
REISS B. ..... D
VAN DEN ELZEN P.J.M. ..... NL
VAN MONTAGU M. ..... B
WILLMITZER LOTHAR ..... D
ZABEAU M. ..... NL

European scientists sequencing *Arabidopsis* "ESSA"

Contract number: **CT930075** (Project of Technological Priority)
Start date: 01/09/93 Duration: 12 months
EC contribution: 1,022,957 ECU

Objectives:

establish an Informatics centre for *Arabidopsis* sequence . determine sequence of areas of interest . establish physical maps of entire chromosomes . prepare basis for large-scale *Arabidopsis* sequencing

Brief description:

This proposal brings together a network of European scientists (ESSA) that will initiate the first large-scale attempt to sequence the nuclear genome of a higher plant. The planned work involves the close integration of the activities of 25 European laboratories in 8 nations, many of which are already active in *Arabidopsis* research. The long-term objective of this project is to sequence 2750kb of genomic DNA, and to obtain approximately 900kb of partial cDNA sequence. The information obtained from genomic sequencing carried out in ESSA may identify and fully characterise the chromosomal location, coding regions and controlling elements of between 300 and 800 new genes, while the cDNA programme will identify between 2000 to 3000 new genes by partial sequencing. Sequencing a large contiguous region of a chromosome, together with partial sequencing of cognate cDNAs, will initially provide knowledge on gene density, and will relate sequence to recombination frequency, a particularly important process in breeding programmes for crop plants. Partial sequencing of a large number of cDNAs is the most rapid route to partial knowledge of gene identity, and will provide a large number of EST (Expressed Sequence Tag) markers, which will be used to help complete the physical map, and will also lead to the further complete characterisation of the genes themselves. Novel genes, and genes of known function previously only identified by map position, will be characterised further. The work planned here will provide a firm foundation of expertise, databases, and networks of laboratories which will be the means to achieve these aims, and provides a foundation for future work. Once completed, the availability of the sequence of *Arabidopsis* will revolutionise many aspects of plant research and create a particularly valuable resource for European agricultural industries in their search for new uses for crop plants, and for improved efficiencies of production. This application is the first step towards these goals.

Keywords:

Genome sequencing, Physical mapping, Informatics, *Arabidopsis*

Coordinator

DR. BEVAN MICHAEL
PLANT SCIENCE RESEARCH LIMITED
COLNEY LANE
GB - NR4 7UJ NORWICH

Participants

DEAN CAROLINE ..... GB
DEBLAERE ROLF ..... B
DEKKER BERNARDUS ..... NL
DELSENY MICHEL ..... F
GIRAUDAT J ..... F
HARBERD NICHOLAS ..... GB
JAMES RICHARD ..... GB
KAVANAGH TONY ..... IRL
KREIS MARTIN ..... F
LESCURE BERNARD ..... F
MACHE REGIS ..... F
MEWES HANS-WERNER ..... D
MURPHY GEORGE ..... GB
PALME KLAUS ..... D
PUIGDOMENECH PEDRO ..... E
SCHOFFL FRIEDRICH ..... D
SMEEKENS JOSEPH ..... NL
STIEKEMA WILLEM ..... NL
VOS PIETER ..... NL

Sequencing of the *Bacillus subtilis* genome

Contract number: **CT930272** (Project of Technological Priority)
Start date: 01/08/93 Duration: 24 months
EC contribution: 1,169,000 ECU

Objectives:
The determination of 576Kb of the DNA sequence of the *Bacillus Subtilis* genome.

Brief description:
The following european groups participate to this project :
(1) K. Devine (Trinity College, Dublin, Ireland)
(2) J. Errington (University of Oxford, United Kingdom)
(3) A. Galizzi (University of Pavia, Italy)
(4) S.D. Ehrlich (INRA, Jouy-en-Josas, France)
(5) A. Danchin and P. Glaser associated with G. Rapoport and F. Kunst (Institut Pasteur, Paris, France)
(6) S. Bron and G. Venema (University of Groningen, The Netherlands)
(7) C. Harwood and P.T. Emmerson (University of Newcastle United Kingdom)
(8) R. Mellado (University of Madrid, Spain)
(9) G. Grandi (Eniricerche, Italy)
D. Karamata (Institut de Génétique, Lausanne, Switzerland) is also participating in this effort.
The groups are estimated to produce a total of 576 kbp of new DNA sequences in two years.
These sequences will be analyzed using modern computer sequence analysis programs (coordinator of data handling : A. Danchin, Institut Pasteur Paris, France).
These sequences together with useful comments will then be sent to the international databases (EMBL databank, Genbank).

Keywords:
Genome sequencing, *Bacillus subtilis*, Computer data handling

Coordinator

DR KUNST FREDERIK
INSTITUT PASTEUR
UNITE DE BIOCHIMIE MICROBIENNE
25 RUE DU DOCTEUR ROUX
F - 75724 PARIS 15

Participants

BRON SIERD ..... NL
DANCHIN ANTOINE ..... F
DEVINE KEVIN ..... IRL
EHRLICH STANISLAV DUSKO ..... F
ERRINGTON JEFFERY ..... GB
GALIZZI ALESSANDRO I
GRANDI GUIDO I
HARWOOD COLIN ..... GB
MELLADO RAFAEL P ..... E

1.3 Expression of genes

1.3.1 Processes through which the information stored as DNA in the genes is expressed in models of practical importance : DNA and DNA polymerases, factors affecting transcription, and self- splicing mechanisms. Typical multinational projects will include 3 to 5 laboratories using complementary approaches to study the same nucleic acid polymerase or the same transcription factor.

Transcription by RNA-Polymerase III : a paradigm to study eukaryotic gene expression

Contract number: **CT920090** (Basic Research Project)
Start date: 01/02/93 Duration: 36 months
EC contribution: 603,000 ECU

Objectives:
The objective of this project is to analyze RNA polymerase III (pol III) and its cognate transcription factors in an attempt to understand how molecular mechanisms underlying the formation of specific transcription complexes on different genes expressed by this enzyme and to gain insight in how expression patterns of eukaryotic genes are expressed in response to external stimuli.

Brief description:
The pol III transcription system has been well characterized with respect to promoter structures and required transcription factors and was hence chosen as a model system. Since pol III shares common factors with the pol I and pol II transcription systems, the conclusions drawn from this model system could also apply to transcription regulation in a more general sense. By using convergent techniques of biochemistry, genetics and genetic engineering in different experimental systems (yeast, plant (*Arabidopsis*) and vertebrate cells) with complementary advantages, we hope to uncover the structural basis of DNA-protein and protein-protein interactions among individual transcription factors and pol III within the transcription initiation complex. Detailed knowledge of these particular interactions could potentially be important for the development of new techniques to modify by genetic engineering individual transcription factors involved in the positive or negative regulation of eukaryotic gene expression. The project focusses on: 1.) Analysis by mutagenesis of extragenic (U6;U3) and hybrid (trnasec) pol III-promoters. How does the spacing of individual promoter elements determine polymerase specificity? How does sequence information control species-specificity? 2.) Identification of individual transcription factors, cloning and expression of their genes. Analysis of protein-DNA and protein-protein interactions between individual factors and pol III subunits by biochemical and genetic methods. The use of heterologous transcription systems (yeast, plant, vertebrate) could uncover species-specific factors. 3.) Functional and structural characterization of components in isolated transcription complexes formed on different pol III promoters. 4.) Assessment of the potential influence of transcription factor binding to promoter Sequences on nucleosome positioning and chromatin structure.

Keywords:
RNA polymerase, Protein DNA interactions, Transcription

Coordinator

PROF SEIFART KLAUS
INSTITUT FOR MOLEKULARBIOLOGIE UND
TUMURFORSCHUNG
PHILIPPS UNIVERSITÄT
LAHNSTR. 3
D - W3550 MARBURG

Participants

FILIPOWICZ WITOLD ..... CH
KROL ALAIN ..... F
SENTENAC ANDRE ..... F

Cytokine-mediated interaction of NF-κB-like proteins and cooperative regulatory factors with genomic DNA for induction of gene transcription

Contract number: **CT920130** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 1,185,000 ECU

Objectives:
The role and function of the transcription factor NF-κB (and associated and/or related factors) and its interaction with genomic DNA for the onset of gene expression will be studied in different cell systems and for different genes using multi-disciplinary approaches. The final goal is to arrive at a general and integrated understanding of how gene expression might be regulated in response to major inflammatory cytokines, such as TNF and IL1.

Brief description:
The structure and function of the transcription factor NF-κB and its interaction with genomic DNA and/or with other co-activated factors will be studied in a number of different cell systems in order to obtain a detailed and integrated understanding of how particular genes are induced (or not) in response to cytokines such as IL1 and TNF. 1. Indeed a number of examples is already known where NF-κB is constitutively present or can be induced by cytokines without corresponding gene transcription; in other instances, genuine NF-κB has to compete with other inducible NF-κB-like protein complexes or with constitutively present κB sequence-binding factors for induction of appropriate genes. In these different systems, the subunit composition of the various κB sequence-binding complexes will be characterized. Moreover, their competition with NF-κB for DNA binding and the resulting effect on gene induction (or repression) will be analysed. 2. It is fairly certain that NF-κB alone, although in most cases a necessary factor for cytokine-mediated gene activation, is not sufficient for full induction and regulation of gene transcription. A multi-disciplinary approach will be set up as a direct tool to characterize the co-activated factors as well as their corresponding DNA sequences and/or NF-κB factor subunits, with which they interact for transactivation or transrepression. 3. Finally, it will also be studied how gene induction, that normally requires NFkB, is realized by alternative pathways. Furthermore, the superimposed effect of cytokines, which additionally do activate NF-κB, will also be investigated. Taken together, an overall approach to analyse the interaction of NF-κB, NF-κB-like proteins and coactivated factors with each other and with genomic DNA for induction of gene transcription in different cellular systems will be undertaken in order to fully understand NF-κB-regulated gene activation as well as disregulation in several diseases.

Keywords:
NF-κb and NF-κB-like proteins, Transcription, Cytokine, Gene activation (or repression)

Coordinator

DR FIERS/HAEGEMAN W./G.
UNIVERSITEIT GENT
LABORATORIUM VOOR MOLEKULAIRE BIOLOGIE
K.L. LEDEGANCKSTRAAT 35
B - 9000 GENT

Participants

BAEUERLE PATRICK ..... D
BLASI FRANCESCO I
KÖRNER MARIE ..... F
NICKLIN MARTIN ..... GB
TOVEY MICHAEL ..... F

Analysis of the transcriptional regulation of vertebrate Hox-2.8/1.11 subgroup genes

Contract number: **CT930060** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 1,038,000 ECU

Objectives:
The major goal of this project is to identify and characterize the factors involved in the transcriptional regulation of the vertebrate HOX-2.8/1.11 group of Hox homeobox genes.

Brief description:
Hox genes are transcription factors which play important regulatory roles in pattern formation, but virtually nothing is known about the regulatory cascade which governs their activity. The experimental plan is designed to identify upstream factors which regulate one subfamily of Hox genes, as a model for understanding interactions and regulation of the Hox network in general. The project builds upon three aspects which emerged from collaborative pilot studies in the participating laboratories: 1) retinoic acid influences Hox expression in cell lines and embryos; 2) the Krox-20 zinc finger gene is involved in regulating the Hox-2.8 gene in rhombomeres r3 and r5 during mouse hindbrain segmentation; 3) the Xenopus Krox-20 gene influences the expression of members of the Hox complex. The nature of the retinoic acid response elements will be investigated and it will be determined whether they play a role in the regulation of Hox gene expression during embryogenesis. The involvement of Krox-20 in the activation of the Hox-2.8/1.11 genes in rhombomeres r3 and r5 will be further analysed and other cis-acting elements and cooperating factors required for the regulation will be identified and characterized in detail. The cis-acting sequences involved in Hox-2.8 activation in rhombomere r4 and in the second branchial arch have been localized. They are distinct from those responsible for expression in rhombomeres r3 and r5 and will be analysed in detail. Possible cross-regulatory interactions between members of the Hox complex itself will also be evaluated. Finally a central theme which complements and expands all of these goals will be the analysis and comparison of the regulation and of cis-acting elements of Hox-2.8/1.11 genes from Xenopus, chicken, mouse and human. The objective is to identify transcription factors and components of the regulatory cascade which are highly conserved between species and presumably play a fundamental role in regulating pattern formation in all vertebrates.

Keywords:
Hox gene, Transcription factors, Pattern formation, Vertebrate, Krox-20, Retinoic acid, Rhombomere, Embryogenesis

Coordinator

DR CHARNAY PATRICK
LABORATOIRE DE BIOLOGIE MOLECULAIRE
ECOLE NORMALE SUPERIEURE
INSERM U368
46 RUE D'ULM
F - 75230 PARIS CEDEX 05

Participants

BONCINELLI EDOARDO I
DURSTON ANTONY ..... NL
KRUMLAUF ROBERT ..... GB
WILKINSON DAVID ..... GB

Transcriptional control of phenylpropanoid metabolism

Contract number: **CT930101** (Basic Research Project)
Start date: 01/08/93 Duration: 36 months
EC contribution: 1,230,000 ECU

Objectives:

determine role of myc and myb factors in gene expression . establish a mechanism for b-ZIP proteins in gene expression . isolation and characterise mutants affecting flavonoid biosynthesis . isolate transcription factors involved in phenylpropanoid biosynthesis

Brief description:

The developmental and environmental controls exerted on the plant phenylpropanoid pathway at the transcriptional level make this an appealing system for the analysis of gene regulation. The phenylpropanoid pathway is among the best characterised biosynthetic pathway in either animals or plants since more than 20 structural and regulatory genes have already been identified and isolated by genetical and biochemical approaches. The levels of all the key regulatory enzymes of the pathway are determined primarily by transcriptional initiation rates, in response to both environmental and developmental stimuli. Genetical and biochemical evidence shows there are at least three classes of factors (myb, myc and b-ZIP proteins) involved in the regulation of genes encoding enzymes of the pathway. These will be the subject for investigation in this project. A detailed picture on how a set of transcription factors determines the tissue-specificity and environmental inducibility of particular plant genes will be built up, as well as how the activities of sets of genes, particularly those in biosynthetic pathways, are modulated, and how transcription factors determine this integration. Environmental stimuli such as light and abiotic stress (mechanical damage) cause the induction of phenylpropanoid biosynthesis via transcriptional activation. Responses to short-wavelength light is particularly important as it is part of a stress response to UV light. Phenylpropanoids and their derivatives are of major importance in crop plants and as industrial products derived from plants. Thus knowledge of co-ordination of gene expression that underlies the accumulation of particular end-products will be of substantial biotechnological importance.

Keywords:
Transcription, Phenylpropanoid biosynthesis, Gene expression

Coordinator

DR BEVAN MICHAEL
PLANT SCIENCE RESEARCH LIMITED
COLNEY LANE
GB - NR4 7UJ NORWICH

Participants

KOES RONALD ..... NL
MARTIN CATHERINE ..... GB
PAZ-ARES JAVIER ..... E
TONELLI CHIARA I
WEISSHAAR BERND ..... D

Liver transcription factors HNF1 and HNF4 - structure, function and interrelationship

Contract number: **CT930103** (Basic Research Project)
Start date: 01/08/93 Duration: 36 months
EC contribution: 840,000 ECU

Objectives:
Our aim is to study the hepatic nuclear factors 1 and 4 and their regulation in liver, using our complementary expertise in structural, functional, genetic and clinical methods. The goal is to understand the molecular details of how these two transcription factors cooperate in liver-specific gene regulation.

Brief description:
The liver is the largest organ in the human body and indispensable for life. Medically, studies of liver are vital to increase our basic knowledge of the pathogenesis of circulatory disorders, as these are the single commonest cause of death. The liver, because it controls the secretion of clotting factors and apolipoproteins and the uptake of lipids and cholesterol, which are known risk factors for thrombosis, is an essential target for those interested in gene regulation. In the early 1980's the genes for many proteins expressed solely in the liver were cloned and intensively studied. Later, the regulating proteins or transcription factors responsible for the liver-specific expression of these genes were, themselves, also studied and cloned. A small family of 4 transcription factors (and variants of these factors) which are enriched in liver are now known. The regulation of 2 of these factors, hepatic nuclear factors (HNF) 1 & 4 appears to be interrelated such that HNF4 regulates HNF1. Our goal is to study these 2 liver-specific factors in detail combining our complementary expertise in structural, functional, genetic and clinical investigation. The immediate objectives are to study (1) the structure and function of HNF1 & 4 and the domains that control DNA binding and their ability to dimerize and to activate transcription alone or with cofactors. Detailed biophysical studies are proposed to solve 3-dimensional structure by NMR and X-ray crystallography, (2) the function of HNF1 and its variant in vivo in mice by means of a classic 'knock-out' of the HNF1, and variant HNF1 and HNF4, (3) the regulation of HNF1 & 4 in somatic cell hybrids, and (4) the regulation of the promoter affinity of HNF1 & 4 for liver-expressed genes including the factor IX gene, in which haemophilia B patients with promoter mutants defective in HNF4 binding are known. Our long term goals are to understand how the specific transcription factors HNF1 & 4 interact with the ubiquitous factors and the basic transcriptional machinery to control expression in the liver. Our detailed structural work on HNF1 & 4 should also allow the design of new drugs able to interfere with transcription in the liver and thus control the expression of genes of medical interest.

Keywords:
Transcription, HNF, Gene regulation, Factor IX, Haemophilia b, Somatic cell hybrids

Coordinator

PROF BROWNLEE GEORGE
SIR WILLIAM DUNN SCHOOL OF PATHOLOGY
SOUTH PARKS ROAD
GB - 0X1 3RE OXFORD

Participants

CORTESE RICCARDO I
WEISS MARY ..... F
YANIV MOSHE ..... F

The regulation of the GATA proteins and their role in haematopoietic differentiation

Contract number: **CT930315** (Basic Research Project)
Start date: 01/10/93 Duration: 36 months
EC contribution: 1,050,000 ECU

Objectives:
.Inactivation of the GATA genes by homologous recombination in embryonic stem (ES) cells
.Conditional expression of GATA 1 and GATA 3
.Expression analysis of GATA 2
.Studies on the regulation of GATA factors and a number of their target genes
.Structural (NMR, X-Rays) analysis of GATA 1 and its role in the developmental expression of the human globin genes.

Brief description:
We will study the role of the GATA family of transcription factors in haematopoiesis. This will involve the study of the regulation of these genes and the genes that are regulated by the GATA factors. This will be carried out by DNA mediated gene transfer in animal cells and transgenic mice. Emphasis will be given to the globin genes, in particular, the molecular mechanism of the adult repression of the gamma globin gene. Derepression of this gene greatly ameliorates the effects of sickle cell anaemia and thalassaemia. A mouse based assay to screen for compounds that may derepress the gamma globin gene in the adult will be developped.

Keywords:
Transcription, GATA factors, Haematopoiesis, Genes, NMR

Coordinator

DR GROSVELD FRANK
FACULTY MEDICINE
DEPT. CELL BIOLOGY - GENETICS
ERASMUS UNIV. ROTTERDAM
PO BOX 1738
NL - 3000 DR ROTTERDAM

Participants

ANAGNOU NICHOLAS ..... GR
OTTOLENGHI SERGIO I
ROMEO PAUL-HENRI ..... F
SANTORO CLAUDIO I

The HNF3/fork head and HNFI transcription factor families : structural/functional analysis and developmental role

Contract number: **CT930319** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 1,050,000 ECU

Objectives:
. Characterization of new members of the HNF3 family . Define the biological role of individual members of the HNF3 family and vHNF1/LFB3 by targeted mutation . Regulation in organ and advanced cell culture systems . Three dimensional structural analysis of the forkhead DNA binding domain by NMR

Brief description:
The present proposal concerns the study of two families of transcription factors: HNF3/forkhead and HNF1. HNF3 is a large family of transcription factors that share a novel DNA binding motif. The HNF1 family is composed of two members: HNF1/LFB1 and vHNF1/LFB3, both characterized by an atypical homeodomain. Our goal is to determine the precise role played by the individual members in differentiation of endoderm and mesoderm derived organs. Therefore, five European laboratories working in the field and using biological systems that provide complementary data, collaborate in this project. Focus on these factors is dictated by the fact that several members of the HNF3 family and vHNF1/LFB3 are expressed very early in development in a spatial and temporal profile that place them as good candidates to play key roles and cooperate in the establishment of the different patterns of endoderm differentiation.Immediate aims are: A) -Characterization of new members of the HNF3/forkhead family in mouse and their homologues in fish. B) -Developmental role of individual members of the HNF3 family and vHNF1/LFB3 gene by targeted mutation in mice. C) - Analysis of vHNF1/LFB3 and HNF1/LFB1 expression in organ and advanced cell culture systems: characterization of vHNF1/LFB3 and HNF1/LFB1 promoters in these systems, in Xenopus and fish. D) - Three dimensional structural analysis of the forkhead DNA binding domain by Nuclear Magnetic Resonance (NMR) analysis. E) - Autoregulatory circuits and interrelationship between HNF3 and HNF1 families. The elucidation of the molecular and genetic basis of endoderm differentiation and organogenesis is expected to lead to a better understanding of carcinogenesis and birth defects.

Keywords:
HNF, Gene targeting, Mutation, Transgenic vertebrates, Differentiation, NMR

Coordinator

DR CEREGHINI SILVIA
INSTITUT PASTEUR
UNITE DE GENETIQUE DE LA DIFFERENCIATION
25 RUE DU DR. ROUX
F - 75724 PARIS 15

Participants

DE SIMONE VINCENZO I
GANNON FRANK ..... IRL
SCHUTZ GUNTHER ..... D
ZAKIN MARIO ..... F

In vitro selection of RNA structural motifs with self-splicing activity

Contract number: **CT930345** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 550,000 ECU

Objectives:
. Amplification and selection of new RNAs with designed chemical and physical properties . Characterization by NMR techniques and molecular modelling of specifically selected RNAs.

Brief description:
Since RNA can function both as a genome and a gene product, it is suitable for manipulation and selection of molecules with new properties. A very elegant procedure for the selection and amplification of RNA molecules, developed and successfully used by G. JOYCE at the Scripps Clinic at San Diego, can be viewed as directed darwinian evolution in the test tube. The principle consists in synthesizing a large pool of partially or randomly mutagenized molecules using bacteriophage RNA polymerase. This pool is then subjected to selection by separating the molecule with the desired chemical or physical properties from the rest of the pool. Finally, using reverse transcription and PCR, a DNA pool can be synthesized from which in turn an enriched RNA pool can be generated. The project consists in using in vitro selection procedures to try and decipher some of the structural motifs that appear to be in recurrent use in self-splicing RNAs or ribozymes, whose activity rests upon their ability to fold by themselves into intricate three-dimensional structures. Towards this goal, the experience and skills of the participating scientists will be focused, respectively, on RNA-RNA interactions between ribozymes and substrates (F. MICHEL), on the interactions underlying inhibition of RNA self-splicing by antibiotics (R. SCHROEDER), on the development of ribozymes which catalyse their own cleavage by amino acids (M. FAMULOK), on the determination of the 3D structures of selected RNA molecules by NMR techniques (M. KOCHOYAN), and on molecular modelling of critical RNAs in order to build a data base of the functionally and structurally important 3D motifs (E. WESTHOF).

Keywords:
RNA, Ribozyme, Catalysis, Self-splicing, Selection, Evolution, NMR, 3D-modelling

Coordinator

PROF WESTHOF ERIC
INSTITUT DE BIOLOGIE MOLECULAIRE ET CELLULAIRE
CNRS UPR SMBMR
15 RUE R. DESCARTES
F - 67084 STRASBOURG CEDEX

Participants

FAMULOK MICHAEL . . . . . D
KOCHOYAN MICHEL . . . . . F
MICHEL FRANCOIS . . . . . F
SCHROEDER RENEE . . . . . A

Role of the PML, PML/RARα and RARα nuclear proteins during the myeloid differentiation process

Contract number: **CT930450** (Basic Research Project)
Start date: 01/10/93 Duration: 36 months
EC contribution: 684,000 ECU

Objectives:
To define the role PML, PML/RARα and RARα play during the normal and neoplastic myeloid differentation processes.
To identify genes involved in the PML, PML/RARα and RARα endogenous activation pathways (PML and RARα target genes).

Brief description:
Both direct and indirect experimental evidence suggests that the RARα, PML/RARα and PML nuclear proteins are involved in the myeloid differentiation process: I) functional RARα protein is required for the retinoic acid-induced differentiation of myeloid precursors; II) the RARα and PML genes are the breakpoint sites of the acute promyelocytic leukemia-specific 15;17 translocation; III) a PML/RARα fusion protein is formed as a consequence of the translocation; IV) the PML/RARα protein plays a role in determining the differentiation block typical of leukemias; V) the PML/RARα protein interferes with both the PML and RARα endogenous activation pathways and its biological activity depends on the presence of both the PML putative DNA binding domain an the RARα DNA binding domain in the fusion protein. The following complementary approaches will be adopted 1) - Biochemical and biophysical characterization of the PML protein: I) isolation of PML-binding sites and binding proteins; II) characterization of the PML divalent metal binding properties. 2) - Characterization of the effects PML, PML/RARα and RARα exert on the differentiation properties of hematopoietic precursors: phenotypic definition of myeloid precursor cells that overexpress PML, PML/RARα or RARα proteins. 3) - Identification of PML, PML/RARα or RARα target genes involved in myeloid differentiation: differential screenings between I) undifferentiated or differentiated cells of myeloid origin; II) cell that overexpress or do not express PML, PML/RARα or RARα. 4) - Studies on the capacity of PML/RARa to induce neoplasias in mice: I) generation of mice transgenic for PML/RARα cDNA; II) infection of mouse bone marrow with ecotropic retroviruses encoding the PML/RARα protein. 5- Characterization of the functional interactions between RARα or PML/RARα and proteins putatively involved in their functional pathways (e.g.HOX genes): I) analysis of the expression of HOX genes in myeloid cells, and myeloid cells engineered to overexpress PML, PML/RARα and RARα; II) effects of HOX gene overexpression on growth and differentiation of cultured myeloid precursors.

Keywords:
Nuclear proteins, Differentiation, Leukemia, Haematopoietic precursors.

Coordinator

DR PELICCI PIER GIUSEPPE
UNIVERSITA DI PERUGIA
ISTITUTO CLINICA MEDICA I
POLICLINICO MONTELUCE
VIA BRUNAMONTI 51
I - 06100 PERUGIA

Participants

ANNE DEJEAN ..... F
MAVILIO FULVIO I
SOLOMON ELLEN ..... GB

Mechanisms of transcriptional activation and developmental role of transcription factor TTF-I

Contract number: **CT930454** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 763,000 ECU

Objectives:
. To define the template requirements for TTF-1 activity . To identify post-translational modifications of TTF-1 necessary for stimulation of transcription . To isolate co-factors that, in conjunction with TTF-1, determine its cell-type specific activity . To define the developmental role of TTF-1.

Brief description:
The thyroid follicular cells express a unique set of genes. Among these, for the Thyroglobulin (Tg) and Thyroperoxidase (TPO) genes has been shown that their exclusive expression in thyroid depends largely on transcriptional regulatory mechanisms. The transcription factor TTF-1 binds at several sites in both promoters. Mutations of the TTF-1 binding sites greatly reduce promoter activity in thyroid cells. In addition, expression of TTF-1 in some non-thyroid cells results in activation of both Tg and TPO promoters, indicating that TTF-1 plays an important role in controlling thyroid differentiation. Expression of TTF-1 during thyroid development supports its role. The TTF-1 protein is found first at the stage of determination of thyroid cells, preceding, as expected, expression of the differentiated phenotype. On the other hand, a five days lag is observed between the appearance of TTF-1 and the expression of Tg and TPO, suggesting that the activity of TTF-1 on these two promoters is regulated. This view is supported by the finding that TTF-1 is present in two other tissues different from thyroid, i.e. in the epithelial cells of the lung and in restricted regions of the fetal brain. The aim of this research project is to understand the cell-type specific mechanisms that restrict the activity of a transcription factor on a specific set of promoters. To this end, the precise template requirements for TTF-1 activity, the role of additional molecules for TTF-1 function and the developmental role of TTF-1 in the tissues where it is expressed will be defined.

Keywords:
Transcription, Phosphorylation, TTF-1, Development, Thyroid

Coordinator

PROF DI LAURO ROBERTO
STAZIONE ZOOLOGICA ANTON DOHRN
VILLA COMUNALE
I - 80121 NAPOLI

Participants

Characterization of the α-amanitin resistant RNA polymerase associated with high level late transcription in baculovirus-infected insect cells

Contract number: **CT930457** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 540,000 ECU

Objectives:
. To purify the baculovirus-induced RNA polymerase from virus-infected cells . To micro-sequence components of the polymerase and map appropriate virus genes . To produce baculovirus mutants deficient in late gene transcription . To devise an *in vitro* transcription system to analyse the RNA polymerase components

Brief description:
In baculovirus-infected insect cells, early virus gene transcription is relatively weak, whereas late gene expression derives very high levels of virus-specific mRNA and proteins. Late virus gene promoters have been used in a very successful expression system. The efficacy of the late phase of virus transcription appears to be related to the induction of an α-amanitin resistant RNA polymerase. The primary goal of this project to investigate the nature of the baculovirus (*Autographa californica* nuclear polyhedrosis virus, (AcNPV) late RNA polymerase and associated co-factors responsible for hyper expression in the late phase of replication. This will be achieved by purifying the RNA polymerase complex from baculovirus-infected insect cells, determining the partial protein sequence of some or all of the constituent molecules and matching this information with the complete AcNPV nucleotide sequence. Should this approach prove unsuccessful, the protein sequence data will be used to design oligonucleotides for probing genomic libraries to identify putative host genes involved in late gene transcription. The direct approach to the analysis of the virus-induced RNA polymerase will be complemented with the derivation of AcNPV mutants defective in late gene expression. These mutants will be mapped by marker rescue techniques and compared with the complete AcNPV sequence to identify the gene. An in vitro transcription system will also be established to facilitate the analysis of the virus mutants and the role of the polymerase components purified from virus-infected cells. The project will provide information about baculovirus late gene transcription and assist the future development of baculovirus expression vectors.

Keywords:
Baculovirus, RNA polymerase, Transcription, Late gene mutants

Coordinator

DR POSSEE ROBERT
INSTITUTE OF VIROLOGY AND
ENVIRONMENTAL MICROBIOLOGY
MANSFIELD ROAD
GB - OX1 3SR OXFORD

Participants

Control of gene expression by nuclear receptors : interaction with ligands, DNA and other factors

Contract number: **CT930473** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 1,562,000 ECU

Objectives:
. To elucidate the molecular mechanism of action of nuclear receptors as transcription factors . To analyse function of normal/aberrant receptors in hormone responsive diseases and identify new targets for therapy . Model and natural promoters will be used to characterise the role of ligand and intermediary factors.

Brief description:
This project will provide detailed information on the molecular mechanism of action of nuclear receptors as ligand-inducible transcription factors. Model and natural promoter systems will be used in order to provide a molecular basis for potential therapeutic intervention in diverse diseases associated with the action of nuclear receptors. It is proposed to investigate the structure and function of domains responsible for ligand binding, DNA binding, and transcriptional activation, develop methods for the isolation of new target genes and characterise and attempt to clone transcription intermediary factors (coactivators) that mediate the enhancer function of nuclear receptors. Established in vitro transcription systems for the analysis of steroid receptors, retinoid receptors and a number of orphan receptors will be modified and refined by substituting crude fractions with overexpressed recombinant factors. In parallel, the interaction of nuclear receptors and other trans- acting factors on the promoters of the growth hormone and apolipoprotein genes will be investigated to elucidate the regulation of complex natural promoters. The study of these promoters may lead to the identification of novel members of the nuclear receptor family. To unravel the mechanisms involved in steroid hormone-induced growth regulation the action of estrogen on the transcription of genes that are involved in cell cycle regulation will be investigated and immediate early response to mitogenic signals. The transcriptional control mechanisms governing the regulation of all the above genes will be studied in a completely defined in vitro transcription system.

Keywords:
Receptor, Steroids, Retinoids, Transcription

Coordinator

DR PARKER MALCOLM
MOLECULAR ENDOCRINOLOGY LABORATORY
IMPERIAL CANCER RESEARCH FUND
LINCOLN'S INN FIELDS 44
PO BOX 123
GB - WC2A3PX LONDON

Participants

ARANDA ANA ..... E
BEATO MIGUEL ..... D
GRONEMEYER HEINRICH ..... F
PHILIBERT DANIEL ..... F
SCHLEUNING WOLF-DIETER ..... D
WEISZ ALESSANDRO I
ZANNIS VASSILIS ..... GR

Area 2

Cellular and Organism Approaches

2.1 Cellular regeneration, reproduction and development of living organisms

ANIMALS

2.1.1 Control of development, cell commitment and cell totipotency in farm animals of major economic importance, starting at the earliest levels of organisation, namely gametes, eggs, proliferating lines and their reorganisation into organs and embryos.

2.1.2 Genome mapping: contributions to the mapping of the bovine genome. The project will be implemented in close cooperation with the "Pigmap" project of BRIDGE and, with regard to infrastructure and retrieval of data concerning pig and bovine genome mapping, in accordance with specifications on "information infrastructure" on page 16.

Improvement of in vitro production of cattle embryos

Contract number: **CT920067** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 1,060,000 ECU

Objectives:
Mimic the *in vivo* environment of the embryo. Use serum free media conditionned by different kind of cells (granulosa, oviduct, others). Identify embryotrophic factors in these media and define optimal culture conditions. Study genome activation and gene expression in the various media and the freezability of embryos.

Brief description:
The *in vitro* production of embryos from slaughtered cattle represents an economical way to develop biotechnologies of reproduction in farm animal species. It is also a valuable tool for fundamental research. However the yield of this technology is low as only 15 to 30% of treated oocytes reach the required stage of development for transfer to recipient cows and, after transfer, only 40% of these cows give birth to a calf. These results reflect a lack of basic information at different levels of the process. The aim of our project is to reconsider the successive steps of the *in vitro* methodology with new and innovative approaches. The following points will be investigated : 1. Oocyte competence and maturation (F1) 2. *In vitro* fertilization (F1) 3. Regulation of early embryonic development and gene expression 3.1. Preparation of protein free conditioned media (B) 3.2. Evaluation of the quality of conditioned media (B,I) 3.3. Biochemical analysis of the media and determination of biological activity of isolated fractions (F2, I) 3.4. Ability of the embryos to develop and implant (GE, F2) 3.5. Cryopreservation of embryos (GE, B). The five groups will exchange their scientists, the results and material. A meeting will be held every six months (alternatively general meeting and committee meeting). The benefit should be a better understanding of the regulatory mechanisms involved in early bovine embryonic development and as a consequence the elaboration of a reproductible methodology for *in vitro* production of transferable embryos. F1 = France 1; B = Belgium; I = Italy; F2 = France 2; GE = Germany.

Keywords:
Cattle, Embryo, *In vitro*, Gene expression, Reproduction

Coordinator

PROF MASSIP ALBAN
UNITE DES SCIENCES VETERINAIRES
PLACE CROIX DU SUD 3
B - 1348 LOUVAIN-LA-NEUVE

Participants

BREM GOTTFRIED ..... D
CHARPIGNY GILLES ..... F
GANDOLFI FULVIO I
MERMILLOD PASCAL ..... F

Investigation of signal transduction systems and their activation in the control of pre-implantation embryo development in cattle

Contract number: **CT920163** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 1,006,000 ECU

Objectives:
To improve our understanding of the control of embryo growth, development and differentiation, including intra-embryonic and embryonic-maternal communication in cattle.

Brief description:
The pre-implantation mammalian embryo is of enormous biological importance because 1) contains the entire genomic information for the development of the adult animal, 2) at the transition from morula to blastocyst it begins the differentiation process, 3) at the blastocyst stage it commences rapid growth, and 4) despite being foreign tissue it escapes rejection by the matemal immune system. An understanding of the cellular mechanisms controlling these processes is fundamental to the development of novel embryo-based biotechnology. An exciting possibility is the production of cloned embryos by a combination of trophoblastic vesicles with embryo stem cells containing foreign valuable genes specifically targeted to have the gene product secreted in the milk. Such a process would lead to production of safe, medically important human protein products, uncontaminated by bacterial products. This is not yet possible due to lack of even the most basic knowledge on control of cell proliferation and differentiaVon in cattle embryos. Understanding these mechanisms could also lead to developments in the control of immune processes and in cell ageing not yet possible to envisage. The peptide growth factors that control cell proliferation and differentiation bind to specific cell membrane receptors. Such receptor-ligand binding leads to activation of signal transduction systems causing the cellular responses essential for division and differentiation. Little data exists on these signal transduction systems in farm animal embryos. This proposal investigates the presence, location and role of the major signal transduction systems viz., cyclic adenosine monophosphate (cAMP), cyclic guanine monophosphate (cGMPJ, phosphotidylinositol (Ptdlns), tyrosine kinase and calcium signalling systems in the control of growth and differentiation of cattle embryos. The disciplines of immunocytochemistry, cellular physiology, and embryo micromanipulation are brought together from 4 major research organisations and a biotechnology (SME) company in 4 countries of the EC. The proposal involves *in vivo* and *in vitro* fertilised (IVF) cattle embryos and synchronous oviduct and uterine tissues.

Keywords:
Cattle, Embryo, Transduction system, Reproduction, *In vitro*

Coordinator

DR SREENAN JOSEPH
TEAGASC
AGRICULTURE AND FOOD DEVELOPMENT
AUTHORITY
BELCLARE
IRL - 31 TUAM, CO. GALWAY

Participants

FISCHER BERND ..... D
KANE MICHAEL ..... IRL
KRUIP THEODOOR ..... NL
LEESE HENRY ..... GB

Totipotency and commitment in farm animal embryos

Contract number: **CT920358** (Basic Research Project)
Start date: 01/04/93 Duration: 36 months
EC contribution: 1,310,000 ECU

Objectives:
The scientific objective of this project is to gain understanding of the mechanisms in the early embryo of farm animals which determine whether a cell will retain the ability to contribute to all of the tissues of the conceptus or become committed to differentiation along a specific pathway.

Brief description:
In seeking to build up an understanding of these mechanisms, several different approaches are being followed. These are to define the role of polypeptide growth factors, examine changes in transcription factors, seek promoters specific to totipotent cells, study epigenetic mechanisms involved in embryonic stem cell isolation and to identify intracellular and extracellular markers of totipotency and differentiation. The research will be carried out with embryos from cattle, sheep and pigs. Most of the studies will be concerned with cells of the early embryo, but a comparison will also be made between totipotent cells in the early embryo and primordial germ cells. Some comparisons will be made with cultured cells derived from the early embryo and from specific lineages in order to monitor changes during differentiation. In addition some comparisons will be made between cells of livestock species and embryonic stem cells of the mouse as they are the only cultured cells proven to be totipotent. The group of proposers bring several different disciplines to the project including molecular biology, cell biology, tissue culture and ultrastructural analysis. The collaboration will be achieved in several ways: by exchange of cells, probes or antibodies, by provision of advice and instruction and by discussion of new approaches in project meetings. The practical value of the project lies in the provision of knowledge which is necessary for the establishment of two novel methods for livestock breeding: embryonic stem cell isolation and nuclear transfer. The combined application of the two procedures would provide a unique opportunity to spread genetic improvement throughout Europe and to introduce specific, precise changes to the genome. Most of the laboratories, which are drawn from 5 countries, are already collaborating with commercial groups who will be able to exploit the results of the project. It is the objective of the project to provide new knowledge aid in the development of new procedures, not to develop the procedures as such.

Keywords:
Reproduction, Embryo

Coordinator

DR WILMUT IAN
INSTITUTE OF ANIMAL PHYSIOLOGY AND
GENETICS RESEARCH
GB - EH259PS ROSLIN

Participants

DESSY FRANZ ..... B
FLECHON JACQUES - E. ..... F
GALLI CESARE I
HOCHEREAU-DE REVIERS MARIE-THERESE ..... F
NOTARIANNI ELENA ..... GB
SAMARUT JACQUES ..... F
WEIMA SJERP ..... NL

Identification of genes involved in early fish development

Contract number: **CT930430** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 1,110,000 ECU

Objectives:
The goal of this project is to increase the knowledge of molecular basis of fish early devlopment. Novel key genes will be researched and studied independent upon their homology with other genes already identified in other animals. Laboratory fish will be used and the information gathered will be ultimately transferred to domestic fish.

Brief description:
Several fish developmental genes already isolated, including activin genes, TGF beta genes and proto-oncogenes will be studied, as well as other members of the family of growth factors and their receptors. Novel genes will be researched by large-scale introduction of enhancerless and promoterless reporter genes, radiation and chemical mutagenesis, and differential cloning of cDNAs between successive stages of embryogenesis. After their structural characterization, their function and regulation will be monitored at the RNA and protein levels in normal development, but also studied by altering the level, site and timing of expression with gene transfer methods. A number of methodological improvements and innovations will be required to conduct the project. Methods of uniparental reproduction will be used and improved in laboratory fish for rapid inbreeding. A strong effort will also be devoted in domestic and laboratory fish to innovate in gene transfer technologies, in order to increase the rates of stable transformation and to render the gene integration as early as possible. This should permit to modify the normal expression of foreign genes under study, as well as to abolish their expression in embryos. A major challenge of the project will be the research and development of ES cells in fish. Efforts in this area will include characterization of presumptive ES cells in embryos, definition of culture conditions, reintroduction of these cells and non-selected blastomeres into embryos after short or long term in vitro culture. The availability of ES cells should permit to knock out candidate developmental genes under study, and also to greatly facilitate their isolation by enhancer and gene trap technologies.

Keywords:
Fish, Development, Gene transfer, Mutagenesis, ES cells

Coordinator

MR CHOURROUT DANIEL
LABORATORY OF FISH GENETICS
INSTITUT NATIONAL DE LA RECHERCHE AGRO
F - 78352 JOUY EN JOSAS

Participants

ALVAREZ CARMEN M. ..... E
GANNON FRANK ..... IRL
HAFFRAY PIERRICK ..... F
ROSA FREDERIC ..... F
SCHARTL MANFRED ..... D

Development of genetic and physical marker maps of the bovinegenome (Bovine Gene Mapping project - Bovmap)

Contract number: **CT920359** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 1,200,000 ECU

Objectives:
This project describes the development of a pre-competitive public domain genetic and physical map of the bovine genome. The general objective of the programme is to map existing markers and to produce additional markers to construct a low resolution map.

Brief description:
The following tasks will be addressed : 1) To constitute a panel of reference families, allowing the construction of a genetic map 2) To generate a large number of highly polymorphic markers and analyze their segregation in the reference families 3) To establish the physical marker map, using a panel of somatic cell hybrids to assign markers to syntenic groups and in situ hybridization to determine precise chromosomal locations of "landmark" markers 4) To implement new technologies 5) To develop statistical and computational facilities. The construction of the bovine marker map is a too ambitious goal for individual laboratories or countries and requires collaboration between laboratoires and commercial partners internationally. The BovMap project, coordinated under the auspices of ISAG brings together most of the laboratories with bovine gene mapping expertise in EC and EFTA countries and will be a major contribution to the global effort. The cattle breeding industry will contribute in making available full-sib families to establish a reference family panel which is the first priority task in the project. A Management system will be set up to ensure efficient progress in allocating tasks to the laboratories according to experience and skills. The ultimate goal is to establish a marker map for mapping and then cloning of quantitative trait loci (QTL), comparative mapping and marker assisted selection. Three phases will be required to achieve these objectives, of which this proposal comprises only the first, 1) construction of a low resolution map 2) development of technologies and resource populations or families 3) practical implementation of results in breeding strategies.

Keywords:
Bovine, Genome, Microsatellites, Genetic mapping, Linkage, Physical mapping

Coordinator

DR LEVEZIEL HUBERT
DEPARTEMENT DE GENETIQUE ANIMALE
LABORATOIRE DE GENETIQUE BIOCHIMIQUE
INRA, CRJ
F - 78352 JOUY-EN-JOSAS 78352

Participants

ARRUGA M.VICTORIA ..... E
BRASCAMP PIM ..... NL
DOLF GAUDENZ ..... CH
DYBDAHL THOMSEN PREBEN ..... DK
EPPLEN JORG THOMAS ..... D
ERHARDT GEORG ..... D
FERRETTI LUCA I
FRIES RUEDI ..... CH
GEIDERMANN HERMANN ..... D
GEORGOUDIS ANDREAS ..... GR
GROBET LUC ..... B
HOLM LARS ERIK ..... DK
HUMPHRIES PETER ..... IRL
LENSTRA JOHANNES ..... NL
LOOFT CHRISTIAN ..... D
MAKI-TANILA ASKO ..... SF
MILLER JAMES ..... GB
OLSAKER INGRID ..... N
RANDO ANDREA I
ROGERS MARK ..... IRL
ROGNE SISSEL ..... N
ROTTMANN OSWALD ..... D
SCHWENGER BARBARA ..... D
SCHWERIN MANFRED ..... D
SKIDMORE CHRISTOPHER ..... GB
VAN DE WEGHE ALEX ..... B
VARVIO SIRKKA-LIISA ..... SF
WILLIAMS JOHN ..... GB
ZANOTTI MARTA I

Genome mapping informatics infrastructure (Gemini-project)

Contract number: **CT920451** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 300,000 ECU

Objectives:
This project brings together the two laboratories responsible for coordinating the pig gene mapping project (PiGMaP) which is funded under the EC BRIDGE programme and the proposed bovine gene mapping project (BoVMaP) which has been submitted for funding under the EC BIOTECH programme.

Brief description:
This project brings together the two laboratories responsible for coordinating the pig gene mapping project (PiGMaP) which is funded under the EC BRIDGE programme and the proposed bovine gene mapping project (BoVMaP) which has been submitted for funding under the EC BIOTECH programme. These European collaborative genome mapping projects are and will produce large volumes of complex data which must be stored, accessed, analyzed and interpreted. Our work will be directed at providing the informatics infrastructure and will include the development of the resource databases for storing the raw observational data together with the generated linkage maps. The collaborations need easy access to up-to-date information in order to carry out analyses and to assist with the management of their work. Networked access and communication support will be established for these databases. We will provide and develop a wide spectrum of software for the analysis, display and interpretation of the experimental data. Training, documentation and technical support will be available. The resource databases will use a common relational structure and have a graphical genome front-end. The pigmap database will be maintained at IAPGR, Edinburgh and the BoVMaP database maintained at INRA, Jouy-en-Josas. These informatic systems will be developed in full consultation with those groups who provie the equivalent resources for the human, munine and other genome mapping endeavours. Wherever practical and appropriate the systems developed to support the porcine and bovine projects will build upon systems employed for these other species.

Keywords:
Genome mapping

Coordinator

DR ARCHIBALD ALAN
AGRICULTURAL AND FOOD RESEARCH COUNCIL
INSTITUTE OF ANIMAL PHYSIOLOGY AND
GENETICS RESEARCH
EDINBURGH RESEARCH STATION
GB - EH25 9PS ROSLIN, MIDLOTHIAN

Participants

LEVEZIEL HUBERT ..... F

PLANTS

2.1.3 Elucidation of the mechanism of action of plant growth factors :
Many of the typical features of plant development are associated with the activities of five groups of more or less simple signal molecules (auxins, cytokinins, ethylene, abscisic acid, gibberelins). In addition it was recently found that some oligosaccharides, lipooligosaccharides and other signal molecules also play a role in the regulation of plant growth.
Each of these factors controls a remarkable diversity of developmental and physiological processes. Their mechanisms of action should be understood and the genes involved in these mechanisms should be isolated and characterised. Molecular scenarios of their regulatory functions over plant developmental patterns should be proposed. Gamete encounters, egg formation, the acquisition of "competence", meristem differentiation and embryogenic pathways should be revisited with a primary interest in plant sensing mechanisms and how these interact with developmentally-regulated specific gene transcription.

The following Project of Technological Priority also covers topics 2.2.2, 2.2.3 and 2.2.4, which are listed further on.

Plant molecular genetics for an environmentally compatible agriculture

Contract number: **CT930400** (Project of Technological Priority)
Start date: 01/11/93 Duration: 30 months
EC contribution: 18,840,710 ECU

Objectives:
The PTP project "Plant Molecular Genetics for an Environmentally Compatible Agriculture" has been conceived to provide critical scientific knowledge relevant to an environmentally sustainable agriculture. In fact research will be undertaken in the broad area of plant and microbial biochemical genetics with a particular focus on the development in the future of new options for the improvement of plants for a more environmentally friendly agriculture and horticulture. The research has been organised in 4 different topics, each performed in a coordinated and interactive way by a number of networks built up from existing labs in different EC countries.

Brief description:
This EC scientific research project in plant biotechnology explores many of the fascinating aspects of how plants grow, how they store molecules in seeds, tubers and leaves that we rely on for food, how plants cope with adverse environments and how plants respond to and utilise nitrogen fertilisers. The work is organized in five networks of collaborating laboratories.
Under Network A, studies are carried out on the transition from vegetative growth to reproductive growth, mechanisms that control the development of flowers and seeds, the molecular action of plant growth factors and novel classes of growth regulators. Network B is undertaking research on the isolation and characterisation of genes that contribute to tolerance to abiotic stresses, the effects of salinity and potassium deficiency on plant growth, and to drought tolerance in maize.
Network C concentrates on storage organs in crops plants, studies on starch synthesis, redirecting carbohydrate flow, metabolic regulation in the developing seed, and new research on commercially important carotenoid biosynthesis. These topics are very relevant to the ongoing improvement of plants, by breeders, to provide better options for our agriculture to be more harmonious with our environment and more sustainable economically.
Network D focuses on the biochemical mechanisms in plants that determine the efficiency of nitrate fertiliser utilisation. The efficiency will be altered by introducing new genes. Laboratories in Ireland, Greece and Portugal will benefit from specific measures to facilitate the transfer of technology via Network E, so as to bring advanced methods closer to the realities of agro-biotechnological research at the periphery of Europe.
The engine of the project is built from small groups of researchers who have formed interactive multinational teams to tackle specific problems. Teams tackling similar problems are networked together and all the teams in the four major research areas will keep in touch with each other's progress and meet once a year to share their progress

and problems. On a daily basis all scientists can be in touch with each other by electronic mail, fax and telephone. This then is a truly European effort involving 117 research groups who wish to participate in research to advance European plant science. Another major aim of the project will be to provide training for scientists, especially those in emerging laboratories where contact with established laboratories will strengthen the overall capabilities of European plant science. The overall coordination and management of the project will be the responsibility of a new European partnership between the Max Planck Institute for Plant Breeding - Köln, Germany - and the John Innes Centre - Norwich, UK -, two major institutes in the area of plant science. The scientific coordination will be carried out by the PTP science coordination board, with representation of all networks around their designated coordinators.

Keywords:
Embryo, Growth factors, Oligosaccharides, Hormone, Abiotic stress, Salinity, Potassium deficiency, Quantitative trait loci, Drought tolerance, Translocation, Partitioning, Storage products, Starch, Carbohydrate flow, Carotenoid, Seed, Nitrogen utilisation, Nitrate

Overall Coordination

PROF. SCHELL Jeff
DEPARTMENT DIRECTOR
MAX PLANCK INSTITUT
FUR ZUCHTUNGS FORSCHUNG
CARL VON LINNE WEG
D - W5000 KOLN

PROF. FLAVELL Richard
DIRECTOR
JOHN INNES INSTITUTE
COLNEY LANE
GB - NORWICH NR4 7UH

NETWORK A - PLANT GROWTH FACTORS AND PLANT DEVELOPMENT

The organisation and patterns of growth and development of each plant species are highly adapted to meet its needs in the range of environments it commonly encounters during evolution. Nevertheless there is significant variation within each species which has enabled plant breeders to select forms that are better adapted to the needs and conditions of agriculture. In spite of this progress there is no reason to presume that the growth habitats of the species currently used in agriculture and horticulture are ideal for efficient productivity in a safe and sustainable way, with minimum detrimental impact on the environment. To be able to manipulate growth and development further and to assess the value of novel forms in agriculture and horticulture, more information is required on the mechanisms of how growth and development are determined and of the genes that specify theses mechanisms.
It is abundantly documented that a number of low-molecular weight signal molecules (phytohormones) such as auxins and the quantity and quality of light, temperature etc. play critical roles in plant growth, differentiation, flowering, embryogenesis, stress responses, etc. Therefore, an array of contributions covering the action of these and other potent molecules and light effectors, together with contributions to explore the molecular and genetic steps in signal recognition and transduction in the critical processes of flowering, embryo formation, leaf and rood development have been combined to create a major project of novel research. This project will shed much new light on the determination of plant shape and form by hormones and other chemical signals and, of special importance, on how to manipulate shape and form genetically in plant breeding.
This topic is central to most other aspects of this PTP project and is organised in the form of a series of subnetworks dealing with 5 themes.

Theme A 1 - Coordinators : S. de Vries and J. Schell

Title : *Pattern formation in plant embryos; study of the transition from vegetative to reproductive growth and of the control of development of flowers and seeds, as well as of the determination of leaf shape, size and number of axillary shoot meristem formation.*

Participants :

DE VRIES Sacco	A1.1	NL	PL 920385
JÜRGENS Gerd	A1.2	D	PL 920385
FRY Stephen C.	A1.3	GB	PL 920385
TERZI Mario	A1.4	I	PL 920385
DEAN Caroline	A1.5	GB	PL 920401.10
GERATS Anton	A1.6	B	PL 920401.13
HERNALSTEENS Jean-Pierre	A1.7	B	PL 920401.16
HUIJSER Peter	A1.8	D	PL 920401.19
KOORNNEEF Maarten	A1.9	NL	PL 920401.23

SALAMINI F.	A1.10	D	PL 920401.30
COEN Enrico	A1.11	GB	PL 920401.06
SCHWARZ-SOMMER Zsuzsanna	A1.12	D	PL 920401.34
SMITH Harry	A1.13	GB	PL 920401.35
THOMAS Brian	A1.14	GB	PL 920401.39
GATZ Christiane	A1.15	D	PL 920401.39

Theme A 2 - Coordinators : M. Hall and J. Schell

Title : *Molecular mechanisms of action of plant growth factors. Particular attention will be paid here to the study of the mechanisms underlying perception of the growth factor signal all the way to the ensuing gene expression.*

Participants :

HALL Michael	A2.1	GB	PL 920175
GUERN Jean	A2.2	F	PL 920175
HOOYKAAS Paul	A2.3	NL	PL 920175
NIELSEN Soren Vedel Saaby	A2.4	DK	PL 920175
PALME Klaus	A2.5	D	PL 920175
ROSSIGNOL Michel	A2.6	F	PL 920175
VENIS Michael	A2.7	GB	PL 920175
FELLE Hubert	A2.8	D	PL 920175
COSTANTINO Paolo	A2.9	I	PL 920401.08
KONCZ Csaba	A2.10	D	PL 920401.22
PRAT Salome	A2.11	E	PL 920401.28
SANCHEZ-SERRANO Jose Juan	A2.12	E	PL 920401.31

Theme A 3 - Coordinators : S.C. Fry and R.B. Flavell

Title : *Biochemical and physiological mechanisms of action of xyloglucan oligosaccharides as novel plant growth factors.*

Participants :

FRY Stephen C.	A3.1	GB	PL 920291
PEREZ Lorences Ester	A3.2	E	PL 920291
SEITZ Hanns Ulrich	A3.3	D	PL 920291

Theme A 4 - Coordinators : T. Wang and R.B. Flavell

Title : *Hormone-mediated regulation of cellular development in the moss, Physcomitrella patens.*

Participants :

WANG Trevor L.	A4.1	GB	PL 920251
LALOUE Michel	A4.2	F	PL 920251
GAMBARDELLA Raffaele	A4.3	I	PL 920251
COVE David	A4.4	GB	PL 920251
RUSSO Vincenzo E.A.	A4.5	D	PL 920251
RESKI Ralf	A4.6	D	PL 920251
ZRYD Jean-Pierre	A4.7	CH	PL 920251

Theme A 5 - Coordinators : T. Bisseling and M. van Montagu

Title : *Lipo-oligosaccharides as a new class of plant growth regulators*

Participants :

BISSELING Ton	A5.1	NL	PL 920498
DENARIE Jean	A5.2	F	PL 920498
HOLSTERS Marcelle	A5.3	B	PL 920498
LUGTENBERG Egbertus	A5.4	NL	PL 920498
MARCKER Kjeld A.	A5.5	DK	PL 920498
PROME Jean-Claude	A5.6	F	PL 920498

NETWORK B - ABIOTIC STRESS

The aim is to analyse the mechanisms allowing some plants tolerate stresses such as desiccation, drought, salinity, cold, heat, phosphate starvation and active radicals as well as the role played by transporters located in plant cell membranes in establishing tolerance to abiotic stresses, including salinity and potassium deficiency.

Theme B 1 - Coordinators : D. Bartels and F. Salamini

Title : *Isolation of characterisation of genes relevant to abiotic stress*

Participants :

BARTELS Dorothea	B1.1	D	PL 920402.41
CATTIVELLI Luigi	B1.2	I	PL 920402.43
DANGL Jeff	B1.3	D	PL 920402.44

DE VIENNE Dominique	B1.4	F	PL 920402.45
INZE Dirk	B1.5	B	PL 920402.47
LE RUDULIER Daniel	B1.6	F	PL 920402.49
MARTINEZ ZAPATER J.M.	B1.7	E	PL 920402.50
PAGES Montserrat	B1.8	E	PL 920402.51
PAZ-ARES Javier	B1.9	E	PL 920402.52
SALINAS Julio	B1.10	E	PL 920402.54
SCHOFFL Friedrich	B1.11	D	PL 920402.55
SERRANO Ramon	B1.12	E	PL 920402.56

Theme B 2 - Coordinators : R. Leigh and F. Salamini

Title : *Molecular and cellular studies of the role of membrane transport processes in plant resonses to environment and to abiotic stresses, including salinity and potassium deficiency.*

Participants :

LEIGH Roger	B2.1	GB	PL 920126
RODRIGUEZ-NAVARRO Alonso	B2.2	E	PL 920126
SANDERS Dale	B2.3	GB	PL 920126
SERRANO Ramon	B2.4	E	PL 920126
SENTENAC Herve	B2.5	F	PL 920126
BOUTRY Marc	B2.6	B	PL 920433
PALMGREN Michael	B2.7	DK	PL 920433
OKKELS Finn	B2.8	DK	PL 920433

Theme B 3 - Coordinators : D. de Vienne and F. Salamini

Title : *A strategy to characterize the QTLs involved in drought tolerance in maize*

Participants :

DE VIENNE Dominique	B3.1	F	PL 920280
WESTHOFF Peter	B3.2	D	PL 920280
FOUEILLASSAR Xavier	B3.3	F	PL 920280
CORNIC Gabriel	B3.4	F	PL 920280

NETWORK C - SYNTHESIS, MOBILISATION TRANSLOCATION AND PARTITIONING OF PLANT STORAGE PRODUCTS

The aim of this topic is to contribute to an increase in the economic value of crops by improving yield and/or value of crops. The regulation of the formation of storage organs, e.g. tubers, fruits, seeds etc. and the mechanisms leading to partitioning of carbohydrates, pigments, proteins, lipids and cell wall precursors will be studied in this network.

Theme C 1 - Coordinators : D. Vreugdenhil and D. von Wettstein

Title : *Development and differentiation of starch storing organs - the potato tuber as a model system*

Participants :

VREUGDENHIL Dick	C1.1	NL	PL 920150
DAVIES Howard	C1.2	GB	PL 920150
VISSER Richard	C1.3	NL	PL 920150
MINGO-CASTEL Angel	C1.4	E	PL 920150
DU JARDIN Patrick	C1.5	B	PL 920150
MARTIN Catherine	C1.6	GB	PL 920403.73
KOSSMANN Jens	C1.7	D	PL 920403.68
KRUGER Nicholas	C1.9	GB	PL 920403.70

Theme C 2 - Coordinators : J. Smeekens and D. von Wettstein

Title : *Redirecting carbohydrate and flow in plant cells*

Participants :

SMEEKENS Joseph	C2.1	NL	PL 920215
CHAMBERT Regis	C2.2	F	PL 920215
JOHN Philip	C2.3	GB	PL 920215
TODD Gordon	C2.4	GB	PL 920215
DE LEENHEER Leen	C2.5	D	PL 920215
OKKELS Finn	C2.6	DK	PL 920215
FLUGGE Ulf-Ingo	C2.7	D	PL 920403.59
GRAY John	C2.8	GB	PL 920403.62
KREIS Martin	C2.9	F	PL 920403.69
SONNEWALD Uwe	C2.10	D	PL 920403.75
GADAL Pierre	C2.11	F	PL 920403.61
WESTHOFF Peter	C2.12	D	PL 920403.80

Theme C 3 - Coordinators : P. Bramley and D. von Wettstein

Title : *Genes and enzymes for carotenoid biosynthesis; structure, regulation and heterologous expression*

Participants :

BRAMLEY Peter	C3.1	GB	PL 920387
CERDA OLMEDO Enrique	C3.2	E	PL 920387
TORRES MARTINEZ Santiago	C3.3	E	PL 920387
KLEINIG Hans	C3.4	D	PL 920387
SANDMANN Gerhard	C3.5	D	PL 920387
KUNTZ Marcel	C3.6	F	PL 920387
CAMARA Bilal	C3.7	F	PL 920387
MACINO Giuseppe	C3.8	I	PL 920387
GIULIANO Giovanni	C3.9	I	PL 920387
GUERCHE Philippe	C3.10 F	PL 920403.63	

Theme C 4 - Coordinators : R. Thompson and D. von Wettstein

Title : *Metabolic regulation in the developing seed*

Participants :

THOMPSON Richard	C4.1	D	PL 920404.86
HALFORD Nigel George	C4.2	GB	PL 920403.64
MOTTO Mario	C4.3	I	PL 920404.85
BEVAN Michael	C4.4	GB	PL 920404.81

NETWORK D - NITROGEN UTILISATION EFFICIENCY

N-fertilizers and their utilisation efficiency are key elements affecting yield but also environmental pollution. The genetically regulated physiological processes defining the efficiency of N-fertilizer use will be studied.

Theme D 1 - Coordinators : M. Caboche and B. Forde

Title : *Molecular strategies to modify nitrogen carbohydrate partitioning in crop plants*

Participants :

CABOCHE Michel	D1.1	F	PL 920250
FOYER Christine	D1.2	F	PL 920250
FERNANDEZ Emilio	D1.3	E	PL 920250
WILLMITZER Lothar	D1.4	D	PL 920250
SCHULZE Ernst-Detlef	D1.5	D	PL 920250
STITT Mark	D1.6	D	PL 920250
HELDT Hans Walter	D1.7	D	PL 920250
FROMMER Wolf B.	D1.8	D	PL 920404.83
WRAY John	D1.9	GB	PL 920404.87
MILLER Anthony	D1.10	GB	PL 920404.84

Theme D 2 - Coordinators : B. Forde and M. Caboche

Title : *The regulation of the nitrate assimilatory pathway in Lotus japonicus and the improvement of nitrogen utilisation efficiency in crop plants through genetic manipulation.*

Participants :

FORDE Brian	D2.1	GB	PL 920410
CLARKSON David	D2.2	GB	PL 920410
HIREL Bertrand	D2.3	F	PL 920410
MARQUEZ Antonio J.	D2.4	E	PL 920410
STOUGAARD Jens	D2.5	DK	PL 920410

NETWORK E - LOCAL NETWORKS

The local networks serve to bring biotechnological research and training in plant sciences to interact with pioneering work supported by the Project of Technological Priority. The networks also serve to get new knowledge and methods to bear on more applied aspects of plant breeding relevant to their local agricultures. Laboratories in Ireland, Greece and Portugal active in these areas of research are associated with the main project :

a) to provide advanced graduate and postdoctoral training in plant sciences and in the basic research-plant biotechnology interphase;
b) to strengthen already existing and support new research collaborations among the relatively few good laboratories engaged in plant molecular cellular genetics and in biochemical-physiological research in the three mentioned countries.

These initiatives are expected to help remedy the problem of the lack of minimum critical mass currently existing in those parts of Europe.

Theme E 1 - N. Panopoulos and J. Schell

Title : *An introductory research and training initiative*

Participants :

PANOPOULOS Nickolas	GR	PL 920406
TSAGRI Efthimia	GR	PL 920406
TABLER Martin	GR	PL 920406
KANELLIS Angelos	GR	PL 920406
KATINAKIS Panagiotis	GR	PL 920406
HATZOPOULOS Polydefkis	GR	PL 920406
TSAFTARIS Athanasios	GR	PL 920406
HASSIOTOU Efthimia	GR	PL 920406

Theme E 2 - L. Margaritis and J. Schell

Title : *The Greek "node" on plant molecular biology*

Participants : MARGARITIS L. and associated laboratories

Theme E 3 - J.M. Novais and F. Garcia-Olmedo

Title : *Portuguese network*

Participants : NOVAIS J.M. and associated laboratories

Theme E 4 - Coordinators : J. Ryan and R.B. Flavell

Title : *Molecular markers for juvenility in woody plant species*

Participants : RYAN J. and associated laboratories.

IN VITRO DEVELOPMENTAL TOXICOLOGY

2.1.4 Development of *in vitro* test systems for the study of the potentially toxic effects of novel and highly specific compounds, during cell differentiation and organogenesis, especially upon the immune, nervous and reproductive systems. Such tests will have to be compatible with the pre-normative requirements for sensitivity, specificity, quantitation and for transposability of results to man.

A new strategy for developmental toxicology in vitro using molecular and cellular markers in mammalian whole embryo culture to enhance sensitivity and selectivity

Contract number: **CT930107** (Generic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 631,000 ECU

Objectives:
To perfect an *in vitro* system that will detect, with sensitivity and specificity, subtle chemically-induced defects in the development of the nervous system. Reliable detection by a simple system requiring only small quantities will facilitate discovery of safe chemicals and evaluation of environmental and biological samples for toxicants.

Brief description:
The test we propose is the ability of a chemical to affect selected molecular and cellular markers in whole mammalian embryos developing in culture. We propose, for the first time, to marry recent advances in knowledge of developmental control genes and proteins with proven culture methods to produce a unique test system. Rodent embryos in culture are as close to human development as is possible in an *in vitro* test system. Culture methods were designed years ago, but for a decade there has been a bottleneck in devising approaches that could be exploited by industry for practical testing. We argue that our strategy will overcome problems in specificity and sensitivity that have prevented the wide-spread adoption of *in vitro* developmental toxicology. Our immediate objective is to identify those markers (of nervous system cell populations) that will respond to sub-dysmorphogenic exposure to developmental toxicants. We have selected a panel of prospective markers, mostly genes encoding transcription factors involved in cell fate. Rat and mouse embryos, in culture and *in vivo*, will be exposed to prototype nervous system teratogens (cocaine, ethanol, retinoic acid, valproate) and non-teratogens (diphenhydramine and 2-ene valproate). Using systematic treatments of graded effect we will identify those markers that respond informatively. We will monitor chemical exposure levels *in vivo*. This will generate a unique set of data enabling comparisons of: rat-mouse; *in vitro-in vivo*; morphology-markers; and developmentally toxic with non-toxic agents. Following selection of a few useful markers, we plan to simplify detection for routine use. A future goal is to generate transgenic lines with reporter constructs to enable visualisation of markers in test embryos by a one-step process.

Keywords:
Embryo culture, Nervous system, Developmental toxicity, Toxicology, *In vitro* test

Coordinator

DR BROWN NIGEL
MRC EXPERIMENTAL EMBRYOLOGY AND
TERATOLOGY UNIT
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL
CRANMER TERRACE
GB - SW17ORE LONDON

Participants

Neurotoxicological systems

Contract number: **CT930108** (Generic Research Project)
Start date: 01/11/93 Duration: 36 months
EC contribution: 663,000 ECU

Objectives:
To establish an organotypic long-term culture system of the developing mammalian brain. To preevaluate the culture system for neurotoxicological needs using various test toxins and endpoint assays.

Brief description:
Toxicological evaluation of novel long-term neuroembryological cultures. Neurotoxic effects of xenobiotics will be best elucidated in an in vitro system that preserves the native brain architecture with all its cell-cell interactions. Therefore the central objective of the proposed research is to use an organotypic roller culture of mammalian neuroembryonic tissue, which differentiates over several weeks in vitro as in vivo due to optimized nutrient and gas exchange. This is achieved by continuous motion of immobilised embryonic rat brain micro slices between the culture medium and gas phase. Characterization and validation of the system will be performed by using various test toxins and by endpoint determinations with the aid of novel and standard assays. These assays include metabolising enzymes, differentiation markers, toxicological relevant metabolites and histology. A computerised cell viability assay will be incorporated into the programme as well as specific test conditions such as hypoxia for oxygenation dependent toxicity of xenobiotics. For comparison a single cell culture will be used.

Keywords:
Development, Neuroembyotoxicology, Xenobiotic, Toxicology, *In vitro* test

Coordinator

DR SCHLOSSHAUER BURKHARD
NATURWISSENSCHAFTLICHES UND
MEDIZINISCHES INSTITUT AN DER
UNIVERSITAT TÜBINGEN
GUSTAV-WERNER-STRASSE 3
D - W7410 REUTLINGEN

Participants

GHERSI-EGEA JEAN-FRANCOIS ..... F
RAY DAVID E. ..... GB

Development of in-vitro neural and related immune systems for the study of potentially toxic effects of novel and highly specific compounds during cell differentiation

Contract number: **CT930224** (Generic Research Project)
Start date: 01/10/93 Duration: 36 months
EC contribution: 1,007,000 ECU

Objectives:
This proposal provides a multidisciplinary approach with input from biochemists, pharmacologists, molecular biologists, immunologists and toxicologists to develop and test *in vitro* neuronal and glial cell systems for use in the study of the potentially toxic effects of novel and highly specific compounds during central nervous system development.

Brief description:
Development of the central nervous system is primarily a matter of cell proliferation, movement, cell differentiation, cell-cell interaction and programmed cell death. The study of the mechanisms and regulation of signalling by cell-surface receptors for neurotransmitters and modulators, their effects on regulation of neuronal and glial cell gene expression, and the effects of drugs and toxins on these phenomena provides a molecular and mechanistic basis for increasing our basic biological knowledge as a foundation for the proposal of new *in vitro* toxicological and pharmacological tests. Emphasis will be placed on the well characterized glutamatergic and GABAergic neuronal cell signalling systems and their supporting glial cells and on those agents known to interact with these systems with which the proposers have much experience. Effects (potential end-points) such receptoreffector coupling, oncogene and transcription factor activation, cell morphology, receptor expression and cell death will be assessed. The cell systems will include rodent primary cultures of cerebral cortex neurons, cerebellar granule cells and astrocytes; cell lines such as C-6 glioma, neuroblastoma and rat PC12 cells; the multicellular brain slice system; and neuroendocrine related cell lines. The studies will cover the expression and functioning of genes and receptors under normal and pathological states, the influence of neurotransmitters and interacting drugs and toxins such as convulsants, anticonvulsants, sedatives, anxiolytics, anxiogenics, excitotoxins and polychlorinated hydrocarbons, and the influence on cell growth and differentiation of regulators such as cytokines and lipid-based compounds.

Keywords:
Neural cells, *In vitro* toxicology, Differentiation, Toxicology, Cytokine, *In vitro* test

Coordinator

DR WILLIAMS DAVID CLIVE
UNIVERSITY OF DUBLIN
TRINITY COLLEGE
BIOCHEMISTRY DEPARTMENT
IRL - 2 DUBLIN

Participants

GRIFFITHS ROGER ..... GB
MEREDITH CLIVE ..... GB
MEREDITH CLIVE ..... GB
RODRIGUEZ-FARRE EDUARDO ..... E
SCHOUSBOE ARNE ..... DK

Development of a new test of developmental toxicology

Contract number: **CT930394** (Generic Research Project)
Start date: 01/11/93 Duration: 36 months
EC contribution: 805,000 ECU

Objectives:
To develop a test for developmental toxicology without the use of warm blooded animals. Each partecipant will check on one embryonic or cellular system the effects of some pharmaceutical drugs.

Brief description:
Much money, evaluable in about 400 million ECU per year is spent by the pharmaceutical industries of the E.C. for testing the effect of new pharmaceutical drugs on human reproduction. The current tests imply the use of rats and rabbits. We aim to test such unwanted effects on simpler and less expensive systems which will provide informations on the following parameters: cell division,fertilization, differentiation, morphogenesis, metabolism. The results obtained with these systems will be compared with those obtained with the traditional methods, i.e. with rats and rabbits. If a good correlation is observed, and namely if the systems under examination show, as predictable,a sensitivity not lower than the traditional ones, the pharmaceutical industry may in the future make a prescreening of the drugs to be tested on the simpler and less expensive system developed by our studies and go to the more expensive and complicated traditional test on mammals only for those drugs which have passed the prescreening. The systems to be studied have been selected with a double criterion: the characteristics of the material, which permit easy and clear answers to the above listed questions, and the competence and long standing experience of the participants. The systems are 1) Yeast; 2) Dictyostelium amoebae; 3) Drosophila embryos; 4) Sea urchin eggs and embryos; 5) Cultures of human keratinocytes.

Keywords:
Toxicology, Embryo, Development, Yeast, *In vitro* test

Coordinator

PROF GIUDICE GIOVANNI
DIPARTIMENTO DI BIOLOGIA CELLULARE
E DELLO SVILUPPO ''A.MONROY''
VIA ARCHIRAFI 22
I - 90123 PALERMO

Participants

CACCIA SILVIO I
CATELLO POLITO I
DINGERMANN THEODOR ..... D
MORATA GINES ..... E
PELLEGRINI GRAZIELLA I
PLANTA RUDI J. ..... NL

The use of gene transfer technology inconjunction with primary and clonal culture for the establishment of predictive in vitro screening assays for teratogenic potential : development, validation and transfer to the industrial

Contract number: **CT930471** (Generic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 934,000 ECU

Objectives:
1) Pre-validate an antiproliferative assay for teratogens and compare it with the micromass system. 2) Engineer cell lines with human cell recognition systems for study of teratogen influence on cell migration and axon extension. 3) Develop teratogen structure-activity relationships.

Brief description:
The project proposes to develop in vitro bioassays which will identify putative teratogens by their ability to impair the major developmental events of cell proliferation rate, adhesion, migration and cell-cell recognition. Studies, initiated in BAP, on teratogen-compromised human and rodent cell proliferation rates will be expanded to define structure activity principles and mechanisms of G1-phase blockade using valproate and thalidomide, and their metabolites, and the retinoids. The results of these studies will be validated by comparison with the limb bud micromass cell system and cell affinity for lectin coated surfaces. The technology associated with these in vitro systems will be transferred to the industrial sector as an adjunct to the preclinical screening of pharmaceuticals . Rodent cell lines, transfected with individual human recognition molecules (NCAM, L1 and N-Cadherin), will be developed and used to evaluate teratogen perturbations of cell migration and neurite outgrowth from human and rodent primary neurons. The influence of teratogens on the normal expression of cell recognition systems will be evaluated with 15 coded structures, selected for synthesis by computer modelling and quantitative structure-activity relationship calculations for the valproate teratogen. The *in vitro* systems, structure activity principles and collective expertise will be used to further establish the molecular modes of teratogen action.

Keywords:
Toxicology, Nervous system, Development, Adhesion molecules, *In vitro* test

Coordinator

DR REGAN CIARAN
DEPARTMENT OF PHARMACOLOGY AND
THERAPEUTICS
UNIVERSITY COLLEGE DUBLIN
BELFIELD
IRL - 4 DUBLIN

Participants

BOCK ELISABETH ..... DK
NAU HEINZ ..... D
SPEZIA FRANCOIS ..... F
WALSH FRANK S. ..... GB

2.2 Metabolism of animals, plants and microbes: essential physiological traits

ANIMALS

2.2.1 Analysis of the contributions which transgenic animals could make to the study of human health (cancer, AIDS, Alzheimer, hypertension, etc.) and, at the same time, definition of rational criteria to assess consequences of transgenosis upon animal welfare in relation with each type of genetic transfer. Towards the end of the programme, research could be financed for the development of new animal models, more representative of human material, including the use, where necessary, of transgenic animals relevant to the study of human health and its protection.

Further to the 1st call for proposals, this sub-topic was addressed via the funding of 2 small studies on:

i. Title: Development and use of transgenic mice for the study and detection of carcinogenic risk factors.
Coordinator: C.F. van Kreyl

ii. Title: Modelling tumor necrosis factor mediated pathology in transgenic mice.
Coordinator: Geroge Kollias

which are preparatory to research activities to be amplified under ulterior calls (see next edition).

PLANTS

2.2.2 Possibilities to modify the nitrogen utilisation efficiency of cultivated crops, particularly at limiting steps of the nitrate storage and assimilation pathway. Application of molecular biological techniques to the characterisation and modification of key enzymes and transporters.

2.2.3 Characterisation of genes, enzymes and transfer molecules involved in the synthesis, mobilisation, translocation and partitioning of storage products within the plant at tissue, cellular and organellar levels.

2.2.4 Molecular investigation of specific sensing mechanisms and plant pathways associated with abiotic environmental stresses (drought, salinity,...), with a view to identifying adaptive functions.

Please refer back to 2.1.3

MICROORGANISMS

2.2.5 Mechanisms governing essential biological functions/metabolic activities important to man, such as secretion processes for heterologous proteins in filamentous fungi. This task shall lead to the development of an intimate knowledge of the molecular and physiological mechanisms that control key cell functions in filamentous fungi. The information to be obtained will enable the researchers to modify the cell, genetically and/or physiologically, in order to meet the requirements of industry.

2.2.6 Mechanisms governing essential biological functions/metabolic activities in industrial microbial species important to man, other than filamentous fungi. Particular attention will be paid to microbial processes poorly understood, such as molecular mechanisms of spore formation and their relation to secondary metabolism; molecular and environmental factors that govern the switch from primary to secondary metabolism, etc.

2.2.7 Mechanisms of gene regulation for the expression of economically important products such as secondary metabolites and heterologous proteins (ie : antibodies and hybrid antibodies). This task aims, first to understand and to manipulate genetic elements that control regulatory signals for the expression of genes involved on secondary metabolism, and second, to unravel and to circumvent the controls that prevent efficient expression of heterologous proteins in microorganisms.

2.2.8 Biochemical, physiological and genetic studies of representative types of extremophile microorganisms (acidophiles, thermophiles, etc.) aiming at understanding and exploiting better their biotechnological capabilities.

pH regulation, carbon catabolite repression, secreted enzymes and secondary metabolites in filamentous fungi

Contract number: **CT930174** (Basic Research Project)
Start date: 01/09/93 Duration: 30 months
EC contribution: 886,715 ECU

Objectives:
To identify the pH signal molecule. To characterise PacC transcription factor-receptor interactions. To characterise CREA-mediated transcriptional repression. To characterise and assess the penicillin production role of *P. chrysogenum* PacC. To identify structural genes for the xylanolytic complex, determining and exploiting their regulation.

Brief description:
This project concerns two wide domain gene regulatory systems in the filamentous fungus *Aspergillus nidulans*, pH regulation of synthesis of secreted enzymes, permeases and exported metabolites and carbon catabolite repression of synthesis of enzymes and permeases involved in carbon nutrition, and manipulates these regulatory systems to improve production of an important secondary metabolite, penicillin, in *P.chrysogenum* and an important group of secreted enzymes, the xylanolytic complex in *A.nidulans* and *A.niger*. *A.nidulans* is the appropriate model organism as it is the only organism in which pH regulation has been identified and characterised despite its widespread occurrence in microorganisms and the relevant wide domain and pathway-specific regulatory systems have been characterised. Objectives include identification of the signal molecule mediating recognition of external pH; characterisation of interactions between the PacC transcription factor mediating pH regulation and DNA target sites; comparison of *A.nidulans* and *P.chrysogenum pacC* genes; characterisation of interactions between the CREA negative transcription factor mediating carbon catabolite repression and DNA binding sites; mutational dissection of the mechanism and specificity of CREA mediated repression; molecular analysis and assessment of the role in penicillin production of the *P.chrysogenum pacC* gene; identification and definition of the regulatory characteristics of structural genes for xylanases and related activities, pathway-specific induction, carbon catabolite repression and pH regulation and use of knowledge of composition and regulation of the xylanolytic complex to improve production.

Keywords:
Aspergilli nidulans, *Aspergilli niger*, Catabolite repression, Penicillin, *P. chrysogenum*, pH, Transcription, Secreted enzymes, Metabolism, Xylanolytic system

Coordinator

PROF ARST HERBERT
DEPARTMENT OF INFECTIOUS DISEASES
AND BACTERIOLOGY
ROYAL POSTGRADUATE MEDICAL SCHOOL
DUCANE ROAD 150
GB - W12 ONN LONDON

Participants

HANSEN KIM ..... DK
PEÑALVA MIGUEL ANGEL ..... E
RAMON VIDAL DANIEL ..... E
SCAZZOCCHIO CLAUDIO ..... F
VISSER JAAP ..... NL

Study of the mechanisms of secretion of heterologous proteins in filamentous fungi as a knowledge base for efficient protein production

Contract number: **CT930008** (Concerted Action)
Start date: 01/11/93 Duration: 36 months
EC contribution: 53,000 ECU

Objectives:
Characterisation of the secretion pathway and analysis of post-translational protein-modification processes; development of protein-fusion strategies to improve heterologous-protein secretion; physiological studies to elucidate optimal cultivation conditions for efficient secretion.

Brief description:
With a number of filamentous fungal strains efficient secretion of homologous proteins can be achieved. The secretion of heterologous proteins, however, is much less efficient. Due to the virtual lack of knowledge concerning the molecular and physiological mechanisms of protein secretion, it is very difficult to identify the factors which hamper efficient secretion of heterologous proteins. The research proposal describes a highly coordinated and inter-dependent research programme with the general objective of investigating the molecular and physiological mechanisms that control key cell functions involved in secretion of heterologous proteins in filamentous fungi. Research effort is concentrated on : 1) molecular characterisation of the secretion pathway and analysis of post-translational protein-modification processes with the goal to identify and manipulate the proteins which are of importance for efficient secretion of biologically-active, heterologous proteins; 2) development of protein-fusion strategies with the goal to improve heterologous-protein secretion; 3) physiological studies with the goal to elucidate optimal cultivation conditions for efficient secretion of heterologous proteins. *Aspergillus niger* is chosen as target organism because of its accessibility to genetic modification, biotechnological importance, GRAS-status and great capacity of protein secretion. The programme will be carried out by seven laboratories from four countries with complementary expertise in (molecular) genetics, cellular biology, subcellular analysis and physiology/fermentation.

Keywords:
Filamentous fungi, *Aspergilli niger*, Secretion, Protein secretion, Protein fusion, Protein modification, Subcellular analysis, Physiology, Fermentation

Coordinator

DR VAN DEN HONDEL CEES
MEDICAL BIOLOGICAL LABORATORY
P.0. BOX 45
NL - 2280 AA RIJSWIJK

Participants

ARCHER DAVID ..... GB
CONTRERAS ROLAND ..... B
DECKWER WOLF - DIETER ..... D
KINGHORN JAMES ..... GB
LEHLE LUDWIG ..... D
VEENHUIS MARTEN ..... NL

Protein secretion in filamentous fungi *Trichoderma*

Contract number: **CT930502** (Concerted Action)
Start date: 01/10/93 Duration: 36 months
EC contribution: 47,000 ECU

Objectives:
Our aim is to understand the complex process of protein secretion in *Trichoderma* and to develop strains that are improved in protein secretion. Understanding the key events in secretion in this fungus is highly relevant to its exploitation by companies in Europe involved in the production of recombinant proteins of therapeutic interest.

Brief description:
Trichoderma is a fungus used by many biotechnological companies in Europe for the production of enzymes. These are employed in a diversity of industries from food manufacture to paper making. The virtue of the fungus in this important area of economic exploitation is that of protein secretion, at which it is highly efficient. Because of this, *Trichoderma* has great potential as a host for the production of recombinant proteins for therapeutic use. Recombinant therapeutic proteins are highly value products and are undoubtedly of interest to the European pharmaceutical industry and to the economies of the countries involved. These products are of relevance to the development of established, and the inception of new, small to medium sized companies. However, to maximise the benefits of *Trichoderma* our knowledge of the secretion process must be developed and this is the broad goal of the proposed research. To achieve it, several key areas embracing the biochemistry, genetics, cell biology and physiology of the process will be addressed. At the molecular level important questions concern gene structure and its influence on protein yield, the N- terminal and proteolytic processing of proteins along the secretory pathway and the isolation and characterisation of genes and mutations which enhance secretion. At the biochemical level glycosylation is of key significance and an understanding of glycan structures, the biosynthesis of the glycans and the importance of the glycosylation pattern are relevant to the efficient secretion of proteins. At the cell level the role of the cytoplasmic cytoskeletal structures in the secretion pathway will be assessed as will the influence of the cultivation conditions on secretion. The knowledge gained from these lines of investigation will be adopted to develop strains which are improved in the secretion of heterologous proteins.

Keywords:
Trichoderma, Protein secretion, Protein modification, Secretion, N-terminal processing, Proteolytic processing, Glycosylation, Genes which enhance secretion, Cytoskeleton

Coordinator

PROF PEBERDY JOHN
MICROBIAL BIOCHEMISTRY AND
GENETICS LABORATORY
UNIVERSITY OF NOTTINGHAM
UNIVERSITY PARK
GB - NG7 2RD NOTTINGHAM

Participants

BARREAU CHRISTIAN ..... F
HENRI DURAND ..... F
KUBICEK CHRISTIAN P. ..... A
LABORDA FERNANDO ..... E
PENTTILA MERJA ..... SF
TIRABY GERARD ..... F

Study of catabolite repression in gram-positive industrially important, food-grade bacteria, as a knowledge basis for strain improvement programmes

Contract number: **CT920137** (Basic Research Project)
Start date: 01/02/93 Duration: 36 months
EC contribution: 1,150,000 ECU

Objectives:
Identification and characterization of:
1. cis- and trans-acting elements involved in catabolite repression in Gram-positive bacteria.
2. signalling pathways from carbon sources to gene expression. Developement of strains resistant to catabolite repression and therefore better suited for use in production processes.

Brief description:
The presence in growth media of rapidly metabolizable carbon sources (catabolite repression, CR) affects the industrial production by bacteria of enzymes, extra-cellular polysaccharides and secondary metabolites, as well as bioconversion and degradation of extra-cellular polysaccharides. The aim of this study is to provide a knowledge basis for strain improvement of *Bacillus*, *Lactobacillus*, *Lactococcus* and *Staphylococcus carnosus*. The economic importance of these bacteria is beyond doubt. Strains of these genera are already used in industrial processes. Their properties may be considerably improved by elucidating the mechanisms controlling CR. Every strain used has the GRAS status facilitating application of genetically modified strains in production processes. All species are evolutionary closely related facilitating expression of mutually exchanged genes. The range of organisms studied in this highly coordinated, interdependent research programme allows recognition of potentially common regulatory pathways mediating CR. As results of this programme we expect to understand CR in detail. Since many applications of the use of these organisms are affected by CR, this knowledge should allow to develop new stratagies for strain improvement by either classical genetic or molecular genetic methods in a directed and predetermined way. The results should also allow the developement of improved physiological conditions for efficient production processes. Direct modification of the control of CR may result in strains that are no longer subject to CR under conditions where rapid metabolizable carbon ources are abundant (e.g. complex growth media).

Keywords:
Catabolite repression, Bacteria, Phosphotransferase system, Phosphorylation, Cis acting elements, Protein

Coordinator

DR DEUTSCHER JOSEF
INSTITUT DE BIOLOGIE ET CHIMIE DES PROTEINES
CNRS - UPR 412
7 PASSAGE DU VERCORS
F - 69007 LYON

Participants

DE VOS WILLEM M. . . . . NL
GOETZ FRIEDRICH . . . . . D
HILLEN WOLFGANG . . . . . D
PEREZ MARTINEZ GASPAR . . . . . E
POUWELS PETER . . . . . NL

Regulation of cell division during growth and sporulation in bacteria of basic and applied interest : an integrated view

Contract number: **CT920483** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 800,000 ECU

Objectives:
To study the molecules that build the septum, either during sporulation or in vegetative division, in *Streptomyces*, *Bacillus*, *Brevibacterium*, and *Escherichia coli*, including the description of the regulatory mechanisms that control the expression of the genes that code for septal components and of those that control the timing and placement of the septum.

Brief description:
Sporulation and secondary metabolism in *Bacillus* and *Streptomyces* are associated temporally, physiologically and genetically. The earliest morphological manifestation of sporulation in both genera is specialized septation. The proteins mediating this probably include some that are sporulation-specific and some that also take part in normal cell division. To investigate the role of these proteins, their regulation and interactions, and their relevance for morphological differentiation and secondary metabolism, an integrated study of septation will be done in *Bacillus subtilis*, *Streptomyces coelicolor*, and *Brevibacterium lactofermentum*, organisms that combine excellent genetics with industrial relevance. The investigation will depend heavily on advances in analyzing septation in the model organism *Escherichia coli*. *E. coli* studies will focus on the structure and regulation of gearbox promoters, regulation of *ftsZ* expression, and biochemical activity of FtsA. Genes homologous to the division genes of *E. coli* will be cloned and analyzed in *Bacillus*, in particular the homologues of the 2.5 min cluster (PBP3 and *fts* genes). Their differential regulation during vegetative growth and sporulation will be investigated in relation to the underlying transcriptional differentiation mechanisms, mediated by sigma factors, that occur during sporulation. These basic mechanisms of division and sporulation will be correlated with those governing sporulation septation in *Streptomyces*. For this purpose *whi* gene-dependent genes, and division gene homologues will be cloned and characterized. Characterization of PBPs at the protein level will be done in *Brevibacterium*. Genes homologous to the *E. coli* ones will be isolated by using suitable molecular probes and their expression studied. The results will be integrated to provide a view of bacterial division and its modification during morphological and physiological differentiation. The conclusions will be of applied interest both because of their potential impact on fermentation microbiology and because cell division genes are attractive targets for antibiotic screening.

Keywords:
Septation, Cell division, Sporulation, Gene expression, *Bacillus subtilis*, *Brevibacterium lactofermentum*, *Escherichia coli*, *Streptomyces coelicolor*

Coordinator

DR VICENTE MIGUEL
CENTRO DE INVESTIGACIONES BIOLOGICAS
CSIC
VELAZQUEZ 144
E - 28006 MADRID

Participants

CHATER KEITH ..... GB
ERRINGTON JEFFERY ..... GB
GIL JOSE A. ..... E

Characterisation and optimisation of the *Bacillus subtilis* protein secretion apparatus

Contract number: **CT930254** (Basic Research Project)
Start date: 01/09/93 Duration: 30 months
EC contribution: 1,223,702 ECU

Objectives:
This project will characterise the protein secretion apparatus of *Bacillus* subtilis in order to provide the knowledge base required to optimise the production of native and heterologous proteins from this and related industrial microorganisms. Thus, the project will produce information of immediate applicability to EC industries.

Brief description:
To characterise the protein secretion apparatus of *Bacillus subtilis*, the project identifies four major targets: (A), the identification and characterisation of the components of the secretion apparatus; (B), the development of *in vitro* systems to analyse the mode of action and the function of these components;(C), the identification of secretion bottlenecks; and (D), the development of strategies to optimise secretion. The proposed work is divided into six main tasks. Four of these are defined by the different stages in the secretion process: (1),chaperones; (2) translocase; (3), late stages; and (4), cell wall. Milestones for these tasks include: the cloning of genes for components of the secretion apparatus, the mutational analysis of these genes, the analysis of their expression, the overproduction of identified components, the purification of the identified components, the *in vitro* characterisation of purified components, the introduction of heterologous chaperones and the analysis of the relationships between cell wall composition and protein secretion. Task 5 aims at the identification of secretion bottlenecks. Its milestones include the identification of components limiting for secretion and the identification of components of extremophilic bacilli that may overcome secretion defects in *B.subtilis*. Task 6 aims at the establishment of *in vitro* protein translocation systems. Its milestones include the *in vitro* reconstitution of protein translocation and the analysis of the energy requirements of secretion. Nine research groups, including two from industry, which together are experienced in molecular genetics, biochemistry, biophysics, microbial physiology and molecular biology, will undertake these studies in an integrated way.

Keywords:
Bacillus subtilis, Protein secretion, Protein translocation, Secretion, Protein, Chaperones, Cell wall

Coordinator

DR BRON SIERD
DEPARTMENT OF GENETICS
CENTER FOR BIOLOGICAL SCIENCES OF THE UNIVERSITY
GRONINGEN
KERKLAAN 30
NL - 9751 NN HAREN

Participants

DRIESSEN ARNOLD ..... NL
FREUDL ROLAND ..... D
HARWOOD COLIN ..... GB
JOERGENSEN STEEN T. ..... DK
PETIT GLATRON MARIE FRANCOISE ..... F
QUAX WILHELMUS J. ..... NL
SARVAS MATTI ..... SF
SCHUMANN WOLFGANG ..... D

Early steps in protein secretion

Contract number: **CT930470** (Basic Research Project)
Start date: 01/10/93 Duration: 30 months
EC contribution: 640,000 ECU

Objectives:
1. Characterization of new components affecting protein translocation by mutagenesis in yeasts. 2. Development of immunological probes to dissect the translocation process. 3. Development of *in vitro* systems to reconstitute actively translocating proteoliposomes. 4. Characterization of the components of SRP. 5. Analysis of the critical regions of the components of the translocation apparatus by genetic techniques. 6. Application of the reconstituted proteoliposomes to the determination of the role of the identified components of the translocon to the translocation process.

Brief description:
In all living organisms, the translocation of the polypeptides through a membrane is the basic process of the protein secretion pathway. A better understanding of the translocation machinery may lead to the improvement in the efficiency of secretion of foreign proteins. This work will combine results obtained on different organisms so that a link will be established between the *in vitro* tools developed in higher eukaryotes and the genetic tractability of yeast. The first task, recruitment and presentation of the polypeptides to the translocon, is performed by the Signal Recognition Particle or SRP. Progress in the understanding of the SRP function requires the use of molecular biology tools available in the yeasts. Work will be carried out concurrently in two different yeast species (*Saccharomyces cerevisiae* and *Yarrowia lipolytica*) in order to get an unified picture of SRP function and to take advantage of the techniques available in either of these yeasts. Two approaches will be followed : identification of components of the SRP targeting pathway bY mutagenesis and their molecular characterization. The second task, translocation through the ER membrane, is carried out by a complex of several proteins known as the translocon. Our project is focused on the study of SEC61p, a crucial component of the translocon, and of a multicopy suppressor of a sec61 mutation (SSSI) which is associated with the ER membrane. It will involve determination of topology of these proteins and structure-function relationships. *In vitro* heterologous complementation will be use to determine the degree of functional conservation between yeast and mammals. Reconstitution experiments with either mammalian purified components or with wild type/mutated components from yeast will permit the identification of those which mediate the observed differences between various secreted proteins. The ultimate goal will be to reconstitute translocation competent proteoliposomes from purified components.

Keywords:
Protein secretion, Yeast, *Saccharomyces cerevisiae*

Coordinator

DR BECKERICH JEAN-MARIE
INRA - LABORATOIRE DE GENETIQUE
MOLECULAIRE ET CELLULAIRE
F - 78850 THIVERVAL GRIGNON

Participants

KEPES FRANCOIS . . . . . F
RAPOPORT TOM . . . . . D
STIRLING COLIN . . . . . GB

Biotechnology of extremophiles

Contract number: **CT930274** (Generic Research Project)
Start date: 01/09/93 Duration: 30 months
EC contribution: 4,298,582 ECU

Objectives:
The main goal of the project is the development of physiological, biochemical and genetic studies of microorganisms living under extreme conditions (high temperature, high salt concentration, extremes of pH) aiming at understanding and exploiting their biological capabilities.

Brief description:
The commercial potential of microorganisms and their enzymes is widely recognized. However, the introduction of biotechnological processes is severely hampered by the lack of stability of biocatalysts currently available. The finding of unique microorganisms and stable enzymes that are active under extreme conditions (high temperature, high salt concentration, extremes of pH) will give a strong impetus to the development of new applications. Microorganisms which thrive under extreme conditions offer a rich and unexplored source of new biocatalysts. Due to the unique properties of extremophilic microorganisms and their enzymes, they are expected to fill the gap between biological and chemical industrial processes. The proposal includes a multidisciplinary research approach that is performed at three levels, namely isolation/taxonomy, physiology/biochemistry, and molecular biology/genetics. These studies will offer in depth information on the strategies developed by newly isolated and already known extremophiles to sustain life under extreme conditions. Detailed investigations will be conducted on the molecular properties of the enzymes and their genes that are present in extremophiles. The different expression systems of such microorganisms will be studied in detail.

Keywords:
Thermophiles, Alkaliphiles, Acidophiles, Halophiles, Physiology, Metabolism, Enzyme stability, Structure function relationship, Fermentation, Taxonomy, Bioenergetics

Coordinator

PROF ANTRANIKIAN GARABED
TECHNICAL UNIVERSITY HAMBURG HARBURG
TECHNICAL MICROBIOLOGY /
DENICKESTRASSE 15
D - W2100 HAMBURG 90

Participants

ALFREDSSON GUDNY A. .... IS
AMILS RICARDO ..... E
BARBIER GEORGES ..... F
BOS PIET ..... NL
BRUNORI MAURIZIO I
CADENAS EDUARDO ..... E
DE VOS WILLEM M. ..... NL
DRAINAS CONSTANTIN ..... GR
ENGEL PAUL ..... GB
FORTERRE PATRICK ..... F
GALINSKI ERWIN A. ..... D
GARRETT ROGER ..... DK
GLANDSDORFF/PIERARD N./A.
..... B
GRANT WILLIAM ..... GB
GREENWOOD COLIN ..... GB
HOLST OLLE ..... S
JONES BRIAN ..... NL
KONINGS WIL ..... NL
KRISTJANSSON JAKOB ..... IS
LADENSTEIN RUDOLF ..... S
MARKL HERBERT ..... D
PORALLA KARL ..... D
PRIEUR DANIEL ..... F
ROHMER MICHEL ..... F
ROSSI MOSE I
SANTOS HELENA ..... P
SCANDURRA ROBERTO I
SCHAFER GUNTER ..... D
SCHONHEIT PETER ..... D
SHARP RICHARD JAMES .... GB
SIMOES DA COSTA MILTON . P
SJOEHOLM CARSTEN ..... DK
STETTER KARL OTTO ..... D
TEIXEIRA MIGUEL ..... P
THOMM MICHAEL ..... D
THOMSON ANDREW ..... GB
TINDALL BRIAN ..... D
VENTOSA ANTONIO ..... E

2.3 Communication systems within living matter

HUMAN AND VETERINARY VACCINES

2.3.1 New immunological approaches to develop effective, safe and preferably economic vaccines particularly against/with those antigenic epitopes that are poorly immunogenic. Research should focus upon the identification of the main characteristics of T and B antigenic epitopes, the mechanisms of antigen presentation and processing, lymphocyte activation, cell-cell communication, carrier, adjuvants, vectors, delivery systems,... Preference will be given to multidisciplinary proposals, including 4 to 6 laboratories using complementary methods and/or techniques, and having the potential to solve well- defined and specific problems linked to the development of human and/or veterinary vaccines. The proposals should address the immunological methodology of preparation for future vaccines against pathogens or antigens of special importance of man and/or animals, rather than against any specific disease.

New approach for oral vaccination against infectious diseases

Contract number: **CT920089** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 850,000 ECU

Objectives:
Development of a new generation of recombinant oral vaccines by using non pathogenic Gram positive live vectors (e.g. *Staphylococcus xylosus*) expressing multiple recombinant antigens on its surface for the induction of multivalent protective immune responses against infectious diseases.

Brief description:
The purpose of the proposal is to develop a new generation of vaccines which utilizes the non-pathogenic bacterium of S.xylosus as a novel system for the expression of recombinant antigens. Because it can colonize the host in testing, this bacterium may be used to orally immunize hosts against recombinant proteins expressed on its surface. Sueh a system facilitates the design of safe, effective and cheap oral vaccines that may be administrated soon after birth. The proposal consists of a basic research programme on such vaccines which express viral antigens (subunit peptides or proteins of RSV and PIV-3), bacterial antigens and/or subunit B of cholera toxin. Five laboratories from three countries will collaborate over 3 years in the following manner: the S.xylosus model will be extended and optimized with new Gram positive expression systems; the genes of the chosen antigens, which are already cloned, will be expressed in S.xylosus and the recombinant bacterial strains characterized; the immune response of the Mucosa Associated Lymphoid Tissue to S.xylosus will be studied in mice and humans; the ontogenesis of the immune response, as well as T and B cells responses will be examined in rats and baboons; finally peptides with appropriate B-cell epitopes or enhanced T-cell stimulating properties will be designed. After the 3 years of this research programme candidate vaccines with thorough preclinical documentation will be available for efficacy testing in humans. This programme constitutes an important step towards the concept of early oral vaccination against multiple infectious diseases according to World Health Organization recommendations.

Keywords:
Antigen, Vector, Expression system, Vaccine, Mucosal immunisation

Coordinator

DR BINZ HANS
CENTER D'IMMUNOLOGIE ET DE
BIOTECHNOLOGIE PIERRE FABRE
97 LE PUY ST MARTIN
F - 74164 SAINT JULIEN EN GENEVOIS

Participants

New strategies for the development of oral vaccines : vectors based on non-pathogenic commensal bacteria, synthetic peptides and lipophilic adjuvants

Contract number: **CT920131** (Basic Research Project)
Start date: 01/04/93 Duration: 36 months
EC contribution: 635,000 ECU

Objectives:
To test (a) recombinant gram-positive commensales of the oral cavity (f.i. S. gordonii) expressing measles virus (MV) proteins and (b) MV-peptides in conjunction with lipophilic adjuvants (Pam3Cys, ISCOMs) for their ability to serve as vectors for mucosal immunization.

Brief description:
One of the major challenges of new vaccines is to find a save and non-invasive route of immunization. Oral immunization is probably the simplest way for large scale immunization programs. The long-term objective of this project is to develop vectors and adjuvants for oral immunization against viral diseases based on: (a) non-pathogenic bacteria of the normal microflora of the oral cavity in humans and animals, (b) lipophilic adjuvans for peptides. The immediate objective of the project is (a) to develop a recombinant S. gordonii expressing heterologous proteins and to test wether such contructs are likely candidate vectors for mucosal immunization, (b) to synthesize the Pam3Cys-peptide conjugates, (c) to prepare lipophilic ISCOMS containing recombinant viral proteins and/or viral peptides and to test their ability to induce mucosal-immunity. The measles virus (MV) hemagglutinin (H) and fusion (F) protein serve as test model system. Both the local and systemic immune response will be studied after oral and/or nasal immunization in a mouse system. MV vaccines cross-protect against Rinderpest (RPV) and peste des petits ruminants (PPRV) two major veterinary pathogens. The aim is, that by the end of the project we have a vector/carrier/adjuvant in our hands suitable for being tested for protection in an animal disease model such as PPRV or RPV. The novel strategies for non-invasive immunization developed here, can potentially be applied to other viral or bacterial pathogens.

Keywords:
Mucosal immunisation, Vaccine, Vector

Coordinator

DR MULLER CLAUDE P.
DEPARTMENT OF IMMUNOLOGY
LABORATOIRE NATIONAL DE SANTE
RUE DU LABORATOIRE
BOITE POSTALE 1102
L - 1011 LUXEMBOURG

Participants

Development of attenuated shigella flexneri vectors as vaccines to elicit protection against mucosally transmitted infectious diseases

Contract number: **CT920134** (Basic Research Project)
Start date: 01/02/93 Duration: 36 months
EC contribution: 215,000 ECU

Objectives:
- Design a live attenuated vector stimulating colonic mucosal immunity. - Use Shigella invasion proteins for expression of foreign epitopes. - Identify promoters that are highly expressed *in vivo*. - Develop mucosal protection against HIV.

Brief description:
We want to develop an orally delivered vaccine vector based on rational genetic attenuation of virulence of the invasive enteric pathogen Shigella flexneri. Gene deletions will be introduced in order to attenuate virulence and reach a balance between reactogenicity and strong mucosal immunogenicity. This vaccine strain will be used as a vector for high-level expression and/or exportation of heterologous antigens in order to elicit protective immunity against mucosally-transmitted infectious diseases. Shigella promoters that are maximally transcribed when bacteria are intracellular will be identified. Such promoters will be introduced into expression cassettes that also contain the gene encoding a relevant heterologous antigen. These cassettes will be introduced in the S. flexneri genome. Exportation of antigens will be achieved by exploiting the unique exportation apparatus of S. flexneri for Invasion plasmid antigens. Gene fusions containing sequences encoding epitopes of the heterologous antigens will be constructed in these Ipa proteins which are strongly immunogenic. These strategies will be assessed in a macaque monkey model, the best available animal model for shigellosis and for AIDS. Homologous protection against shigellosis will be tested using the vaccine candidates constructed in this study. Heterologous protection will be first tested against endocervically transmitted SIV in animals orally immunized by Shigella vaccine strains expressing and/or exporting key antigenic motives of this simian retrovirus.

Keywords:
Shigella, Mucosal immunisation, AIDS, Vaccine

Coordinator

DR SANSONETTI PHILIPPE
UNITE DE PATHOGENIE MICROBIENNE MOLECULAIRE
INSERM U199
28 RUE DU DOCTEUR ROUX
F - 75724 PARIS 15

Participants

Vaccine development : principles that govern antigen processing and peptide presentation to CDB cytolytic T lymphocytes

Contract number: **CT920177** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 1,165,000 ECU

Objectives:
Sequence influence on antigen processing. Proteasomes and antigen processing. Role of transporters in antigen presentation vectors and delivery systems for peptides.

Brief description:
Immune control of chronic infections by viruses and other intracellular pathogens, and also immunotherapy of tumors demands the activation of antigensprecific major histocompatibility complex (MHC) class I restricted T Lymphocytes. These important effector cells recognize antigens only subsequent to protein degradation and peptide transport to the cell membrane where antigenic peptides are presented by MHC class I molecules. Today it is difficult to predict which part of an antigenic protein is presented, and the manipulation of antigenicity has been restricted to anecdotal cases. To understand the principles of antigen processing and presentation at the molecular level six laboratories employ complementary techniques. The project can be divided into three major aspects: A rational genetic engineering program to insert defined anligenic epitopes from viruses and tumors into model proteins that provide different efficacies of antigen presentation as determined by extraction of naturally presented antigenic peptides, by T-cell mediated destruction of target cells in vitro, and by protection against lethal virus disease or tumors in vivo. The biochemical analysis of the model proteins that differ in antigen presentation with regard to the steps reflecting protease degradation, intracellular peptide transport, and MHC class I mediated peptide delivery. C Testing the genetic constructs when expressed by other viral vectors or by delivery systems of synthetic protein fragments. Rather than studying by the research groups different antigens in parallel using different techniques, the same model antigens will be employed by all laboratories. It is the conviction of the participants that this type of organization, although demanding in discipline, will most quickly unravel the mechanism of antigen processing and presentation, and indicate the fields of biomedical application.

Keywords:
Mhc class i molecules, Vaccine, ISCOM, Immunology

Coordinator

PROF.DR KOSZINOWSKI ULRICH
INSTITU FÜR MEDIZINISCHE VIROLOGIE
IM NEUENHEIMER FELD 324
D - 69120 HEIDELBERG

Participants

ALMOND JEFFREY W. ..... GB
DALSGAARD KRISTIAN ..... DK
DEL VAL MARGARITA ..... E
EVANS DAVID ..... GB
HOWARD JONATHAN ..... GB
MELIEF CORNELIS ..... NL

Recombinant bacillovirus expressed particulate vehicles as multiple epitopes presentation systems

Contract number: **CT920290** (Basic Research Project)
Start date: 01/03/93 Duration: 36 months
EC contribution: 946,000 ECU

Objectives:
The purpose of the project is to exploit recombinant baculovirus derived single or multiple capsid virus-like particles as vaccine delivery systems for animals and human pathogens.

Brief description:
The purpose of the project is to exploit recombinant baculovirus derived single or multiple capsid virus-like particles as vaccine delivery systems for animals and human pathogens. These particles mimic 1)bluetongue virus (BTV) single capsid core-like particles (CPLS consisting of VP3 and VP7, r 4 proteins VP2, VP3, VP5 and VP7, or proteins, VPI-7 and 2) porcine parvo-virus (PPV) single capsid (containing vp2 protein). These capsid structures lack nucleic acids and are highly immunogenic. Recent virus challenge studies in animals immunized with 10 ug of BTV VLPS or 3ug of PPV particles confirmed the immunogeneity and protection capabilities of these structures. The high level production (20-30 mg per liter of insect cell culture), of these particles from baculovirus vectors suggested that this system may be adopted as a carrier system in which antigens can be presented in polyvalent forms to the immune system to induce both cellular and humoral immunities. We have synthesized chimeric particles by insertion of foreign epitopes that are relevant to protection against various animal and human disease (eg, hepatitis surface antigen, rabies glycopro- tein, foot and mouth disease virus epitopes etc). The derived chimaeric particles are easily purified from other cellular proteins by surcrose density centrifugation of cell extracts. Currently, the immunogenicity of these chimaeras are under investigation. We propose to synthesize chimaeric particles containing various viral (human and animal) immunogenic regions (initially the known epitopes and then the epitopes which will be determined by computer analysis). The integrity of the derived particles will be examined by 3-D analysis through cryoelectron microscopy. The perfect assembled particles will be tested for their immune responses (t-helper, cell mediated, humoral responses), and protective efficacies using appropriate challenges in post-vaccinated animals (eg, first in mice and then in the relevant animal species). It can be anticipated that it should be possible to make vaccine chimaeras containing multiple immunogens representing selected viral pathogens which may lead to novel prospects for future vaccine technology.

Keywords:
Vaccine, Baculovirus

Coordinator

DR ROY POLLY
LABORATORY OF MOLECULAR BIOPHYSICS
DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF OXFORD
SOUTH PARKS ROAD
GB - OXL 3QU OXFORD

Participants

Strategies for the design of peptide vaccines for the control of major human infections

Contract number: **CT920321** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 875,000 ECU

Objectives:
To identify proteins and peptide epitopes of 3 major human pathogens (Plasmodium falciparum, Borellia Burgdorferi, HIV) which elicit strong T cell mediated responses against these pathogens and which are therefore candidates for protective vaccines.

Brief description:
The general aim of the project is to evaluate strategies for designing peptide vaccines for major infectious diseases of viral (AIDS), bacterial (Lyme Disease) and parasitic (Malaria) origin. For non of these diseases is an effective vaccine available. Nevertheless, in each of these diseases there is considerable background information on the nature of the infectious agent and on the nature of the human immune response to it. The induction of immmunity generally follows similar intial mechanisms independent of the nature of the infectious agent and the effector functions necessary for its elimination. These include antigen uptake, processing and presentation of peptides with MHC molecules on antigen presenting cells. Recognition of MHC/peptide complexes by CD8 and CD4 T lymphocytes and initiation either of a predominantly antibody mediated immune response. Therefore we plan to identify proteins of the three types of infectious agents that induce strong T cell mediated responses and to identify peptide epitopes of these proteins which are presented with MHC class I and class II molecules thus initiating CD8 and CD4 T cell mediated responses. A significant part of the project will be devoted to the development of technologies for peptide vaccines and their application.

Keywords:
Peptide epitopes, Vaccine, T cell response

Coordinator

PROF.DR EICHMANN KLAUS
MAX-PLANCK-INSTITUT FÜR IMMUNBIOLOGIE
STUEBEWEG 51
D - W7800 FREIBURG

Participants

AUTRAN BRIGITTE ..... F
LANGHORNE JEAN ..... D
PETRE JEAN ..... B
SIMON MARKUS M ..... D

Construction of stable recombinant BCG and other live mycobacterial vaccines

Contract number: **CT920520** (Basic Research Project)
Start date: 01/02/93 Duration: 36 months
EC contribution: 1,060,000 ECU

Objectives:
- Utilisation of BCG as a vector - Insertion mutagenesis of mycobacteria - Expression of cytokins in BCG - Study of recombination in mycobacteria - Study of mycobacterial plasmid replication

Brief description:
Foreign antigens have been successfully cloned and expressed in the BCG vaccine. Cellular and humoral immune responses against these antigens have been observed upon immunization of animals with the recombinant BCG strains. In order to improve the immunogenicity of these BCG strains, potential protective antigens will be expressed as exported products together with IL2 and Y-IFN. Information provided by the study of plasmid replication (pAL500 which is generally used for gene cloning in BCG) and site specific integration (pSAM2 an integrative plasmid from Streptomycetes and the Ms6 temperate mycobacteria phage) will allow the construction of more stable vaccine strains. This will enable the development of BCG as a multivaccine vehicle which can be used to immunize against a wide variety of pathogens at the same time. In order to improve the BCG efficacy against tuberculosis and to construct new vaccine candidates against this disease mycobacterial virulence genes will be investigated by insertion mutagenesis using transposons already characterized by the collaborating teams. These transposable elements will also be improved by the addition of reporter genes and modified to enhance transposition efficiency. This project concerns teams that have already worked together on mycobacteria and posses complementary skills.

Keywords:
BCG, Vaccine, Cytokine

Coordinator

DR GICQUEL BRIGITTE
INSTITUT PASTEUR
MYCOBACTERIAL GENETICS UNIT
25 RUE DU DR. ROUX
F - 75724 PARIS CEDEX 15

Participants

GARCIA LOBO JUAN MARIA ..... E
MARTIN CARLOS ..... E
MONIZ PEREIRA JOSE ..... P
YOUNG DOUGLAS ..... GB

An investigation into the mechanism ofadjuventicity of immuno-stimulating complexes (ISCOMS) of defined chemical composition using a primate model of Epstein-Barr virus induced lymphoma.

Contract number: **CT930105** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 632,000 ECU

Objectives:
To investigate the mechanism of adjuventicity of chemically defined ISCOMS to provide a sound scientific basis for their possible future use in humans.

Brief description:
The only adjuvants currently licensed for human use are based on aluminium salts which, while effective in a limited number of conventional vaccines, are relatively weak when used with many of the new experimental recombinant viral subunit vaccines. Furthermore, aluminium salt adjuvants induce only weak cell-mediated immune responses and it is becoming increasingly clear that in the majority of cases cell-mediated immune responses provide the basis for effective protective immunity. Immunostimulating complexes (ISCOMS) provide an extremely potent antigen presentation and adjuvant formulation. However, the lack of knowledge of the mechanism of action of ISCOMS and their induction of some side effects has provided the impetus for analysing their composition and mechanism of action. Initially cell-mediated, antibody and cytokine responses will be investigated in banal laboratory animals following immunisation with chemically defined ISCOMS carrying the Epstein-Barr virus (EBV) envelope glycoprotein gp340. The EBV glycoprotein gp340 has already been shown to be a protective immunogen in a primate model of lymphoma induced by EBV. In this model it is clear that immune protection is mainly provided by cell-mediated immune responses. Successful completion of these studies will have importance with respect to the use of ISCOM adjuvants in a range of vaccines in humans and animals.

Keywords:
ISCOM, Vaccine, Cytokine, Lymphomas

Coordinator

DR MORGAN ANDREW
DEPT. OF PATHOLOGY & MICROBIOLOGY
SCHOOL OF MEDICAL SCIENCES
UNIVERSITY OF BRISTOL
UNIVERSITY WALK
GB - BS8 1TD BRISTOL

Participants

DOTSIKA ELENI ..... GR
MOREIN BROR ..... S
SUNDQUIST BO ..... S
VAN ROOIJEN NICO ..... NL

Technologies for optimisation of mucosal immune responses

Contract number: **CT930111** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 980,000 ECU

Objectives:
To achieve a rational approach to induce a specific S-IgA response against infectious agents using two models antigens and addressing two most important mucosal surfaces, the gastro-intestinal tract and the respiratory tract.

Brief description:
It is recognized that the development of new vaccines through mucosal, mainly oral immunization would represent a major breakthrough in the control of many infectious and parasitic diseases. The purpose of the present proposal is to lay the technological and scientific groundwork for a rational approach to induce a specific S-IgA response against infectious agents using two model antigens and addressing two most important mucosal surfaces, the gastrointestinal tract and the respiratory tract. In order to achieve the three main goals of this strategy : a) optimal targeting of antigen presentation b) prolonged stimulation of the immune response c) amplification of local immune response, the objectives of the proposed projects will be : 1) to develop the technologies including the development of live vectors, the use of microcapsules and appropriate adjuvants in order to optimize the IgA and S-IgA response 2) to identify at a molecular and cellular levels, the effector functions of IgA and S-IgA, in vitro and in vivo through the use of hybridoma technology and appropriate animal models (SCID mouse) 3) to study the mechanisms of local regulation of IgA response. Two model peptides will be used to meet these objectives, i.e. a parasitic and a bacterial epitope. The first model peptide is taken from the parasite Schistosoma mansoni responsible for a disease affecting 200 millions people in the world and in which parasite eggs laid in mucosal tissues (small and large intestine, urinary tract and bladder) as well as in the liver and other tissue represent the main source of pathology. Recent work in our laboratory has established that both in human infection and in experimental models, IgA antibodies to the parasite glutathione S-transferase and its C-terminal domain play a major role in inhibiting worm fecundity and egg viability. The second model peptide is the 50-64 peptide of the B subunit of cholera toxin. This toxin is responsible for the diarrhoeal syndrome of cholera as well as for immunoprotection against the disease. The chosen epitope has been shown to elicit neutralizing anti-toxin antibodies and to induce protection. Oral administration of the peptide can induce S-IgA and local protection in the mouse. The final goal of these studies is to contribute through the use of these two well characterized models, to the development of new vaccine strategies exploiting the mucosal immune system.

Keywords:
Mucosal immunisation, Vaccine

Coordinator

PROF CAPRON ANDRE
INSTITUT PASTEUR DE LILLE
CENTRE D'IMMUNOLOGIE ET DE BIOLOGIE
PARASITAIRE
1 RUE DU PROFESSEUR CALMETTE
F - 59019 LILLE

Participants

GILLARD JEAN ..... B
GILLES RIVEAU ..... F
LOCHT CAMILLE ..... F
WELLS JEREMY ..... GB

Development of BCG as a live vaccine vector to stimulate protective immunityagainst intracellular parasites

Contract number: **CT930238** (Basic Research Project)
Start date: 01/08/93 Duration: 36 months
EC contribution: 842,000 ECU

Objectives:
- Development of a vector for secretion of heterologous proteins in BCG. - Evaluation of BCG as a live carrier for vaccination against intracellular parasites. - Study of Mycobacterium tuberculosis expression signals in BCG.

Brief description:
The proposed project aims at the development of a system to stimulate protective immunity against an intracellular parasite (Toxoplasma gondii) by using a non-pathogenic intracellular live vector (BCG, Bacillus Calmette-Guerin). Two well characterized antigens of the parasite, GRA2 and ROP2, were selected since they follow two different pathways of processing and presentation to the immune system. The genes encoding these antigens will be expressed in BCG using the promoter and signal sequence of a gene from the 85A complex, encoding a protein which is secreted by M. tuberculosis. The recombinant BCG strains will be evaluated for their capacity to provoke protective immunity against toxoplasmosis in a mouse and a rat model. The humoral and cellular response towards both model antigens will be studied. Eventually, vaccination experiments with live recombinant BCG/toxo will be performed in sheep. The results obtained with this model system may also have some bearing on protection from infection with other important intracellular pathogens like Plasmodium falciparum.

Keywords:
BCG, Vaccine, Toxoplasma

Coordinator

PROF VAN WIJNENDAELE FRANS
INNOGENETICS N.V.
INDUSTRIEPARK ZWIJNAARDE 7/4
B - 9052 GENT

Participants

CESBRON MARIE-FRANCE . . . . . F
LOCHT CAMILLE . . . . . F
TREES ALEXANDER . . . . . GB

New vaccines based on optimal reconstruction of immunogenic structures targeted for systemic or oral delivery

Contract number: **CT930349** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 464,000 ECU

Objectives:
- to solve instability of vectors carrying foreign antigens. - to solve suboptimal exposure of foreign antigens on living and nonliving vectors

Brief description:
Mucosal vaccines offer advantages over parenteral vaccines since they can be administered by nonmedically qualified personnel and avoid the need for expensive and potentially contaminated needles. Prime candidates for oral vaccines are living pathogens, for instance attenuated Salmonella strains which have been shown to induce potent local and sometimes systemic responses. Nonliving antigens, for instance cholera toxin and its B subunit (CT-B), are excellent candidates too, but there is a requirement for alternative carriers. Theoretically both living pathogens and nonliving antigens would form attractive general carriers to deliver foreign antigens or epitopes at the mucosal surfaces. Success however depends critically on the ability to solve the following problems: 1. instability of live recombinant vectors which carry foreign antigens or epitopes. 2. improper folding and suboptimal exposure of foreign antigens or epitopes on both living and nonliving carriers. The main object of this proposal is to solve these problems using two immunogens, FHA of B. pertussis and S glycoprotein of Transmissible Gastro-enteritis Virus (TGEV), and established carriersystems. As living carriersystems will be used attenuated Salmonella strains and TGEV (which has the added advantage that it can be targeted to either the gut or the respiratory tract). As nonliving carriersystems will be used Mal-E and Lam-B proteins of E. coli and FHA itself which has exciting potential as a nonliving mucosal immunogen. The relevant epitopes both in the native and nonnative context will be defined at the level of single amino acids, while the responses of the recombinant products will be monitored at a similar level. Thus combining the latest technologies versatile live and nonlive carriersystems will be compared and developed and will form a new generation of carrier-based oral vaccines.

Keywords:
Mucosal immunisation, Vaccine

Coordinator

DR MELOEN ROBBERT HANS
CENTRAAL DIERGENEESKUNDIG INSTITUT
DIENST LANDBOUWKUNDIG ONDERZOEK
POSTBUS 65
NL - 8200 AB LELYSTAD

Participants

DOUGAN GORDON . . . . . GB
ENJUANES LUIS . . . . . E
HOFNUNG MAURICE . . . . . F
RAPPUOLI RINO I

Antigen presentation for induction of optimal T cell-mediated immune responses

Contract number: **CT930489** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 1,270,000 ECU

Objectives:
To characterise the T cell responses induced by viral glycoproteins expressed in vaccinia and bovine herpes virus vectors and to determine the influence on these responses of the site of antigen expression in infected cells, co-expression of cytokine genes and systemic versus mucosal routes of infection.

Brief description:
Recent advances in immunology have demonstrated that the cell types in which antigen is processed and the intracellular pathways of antigen processing are of fundamental importance in determining the type of T cell response that is induced. The relative importance of a particular T cell response varies for different pathogens and indeed inappropriate immune responses sometimes result in enhanced disease. This project aims to bring together complementary expertise in molecular virology, vector technology and immunology to investigate strategies for preferential induction of specific types of T cell responses in mice and cattle. The project will utilise, as model antigens, the F and G glycoproteins of respiratory syncytial virus (RSV) expressed in recombinant vaccinia and bovine herpes virus vectors. The project will investigate the influence of three parameters on T cell responses: 1. The use of recombinants constructed to give expression of the RSV proteins in different sites within infected cells. 2. The use of recombinants expressing IFN-gamma or IL-4, along with viral proteins, in order to bias the response towards TH1 or TH2 CD4 responses. 3. The effect of immunising systemically or locally, via the respiratory mucosa (ie. directing antigen to different antigen-presenting cell and T cell populations). Analyses of immune responses induced by various recombinant viruses will aim to identify the type of T cell response (CD4 and/or CD8) which has been stimulated, the cytokines produced by the reactive T cells and the levels and isotype composition of antibody produced.

Keywords:
T cell response, Cytokine, Vector, Immunology

Coordinator

DR MORRISON W IVAN
AFRC INSTITUTE FOR ANIMAL HEALTH
GB - RG16 ONN COMPTON, NEAR NEWBURY

Participants

HENSEN EVERT J. ..... NL
KEIL GUENTHER ..... D
MELERO JOSE A. ..... E
PASTORET PAUL-PIERRE ..... B
VAN OIRSCHOT JAN T. ..... NL

IN VITRO HUMAN IMMUNE RESPONSES

2.3.2 Development *in vitro* of human immune responses, either humoral (conventional IgM-IgG, predominantly IgE or IgA) or cellular (T cytotoxic, cell mediated hyper-sensitivity, ...) for fundamental and/or applied research. The project will include the development of models closely related to common situations such as, for instance, skin sensitization or oral route immunization, which could be used for the identification of immunogenic properties, the production of B or T activated cells against determined antigens, isotype selection of humoral responses, definition of vaccine strategy, *in vitro* immunotoxicological tests, screening of substances likely to cause autoimmune responses,... Priority shall be given to multidisciplinary proposals dealing with precise, well described objectives and leading to simple and reliable techniques. Proposals will have to clearly describe the ethical and safety problems linked to the use of cells of human origin and outline the solutions envisaged by the proposers.

Structure/function relationship of the T cell antigen receptor complex : study of molecular interactions and activation events induced upon antigen binding

Contract number: **CT920164** (Basic Research Project)
Start date: 01/04/93 Duration: 36 months
EC contribution: 902,000 ECU

Objectives:
- To find sequences involved in antigen/MHC recognition by TCR/CD3 and in interactions within the TCR/CD3 complex and with accessory molecules. - To study activation pathways, receptor internalization and apoptosis induced following stimulation of T cells via TCR/CD3 and accessory molecules.

Brief description:
The aim of this proposal is to determine in molecular detail how the TCR binds the peptide antigen/MHC complex and then transduce signals to the nucleus resulting in T cell activation or apoptosis. Mutants of the TCR and CD3 subunits will be generated using recombinant DNA techniques. Transfection experiments will allow the structural determinants of the TCRa/~ heterodimer that contact antigen/MHC, and also those that are involved in subunit-subunit interactions, to be characterized. The signaling pathways employed by the TCR will be investigated in two ways. Firstly, identifying intracellular proteins which are phosphorylated on tyrosine. Secondly, nuclear communication with the cell surface will be investigated using a T cell specific enhancer as a model system. The activity of the TCR"B" enhancer is upregulated by changes in the levels of the Ets binding proteins following stimulation via the TCR. The mechanism of activation will be investigated by transfection of T cell lines with wild type and catalytically inactive protooncogene products and assay of the activity of the TCR"B" enhancer and of Ets. Such an approach will also be used to analyze the pathways involved in the induction of apoptosis following stimulation of the TCR. The role of accessory molecules in signaling via the TCR and also in the internalization and intracellular trafficking of the TCR will be analyzed by generating mutant T cell lines lacking one or more accessory molecules. These cell lines will also be used to investigate the role of accessory molecules in the induction of apoptosis.

Keywords:
T cell receptor, Antigen recognition, Apoptosis, Phosphorylation, Enhancer

Coordinator

PH.D. ALARCON BALBINO
CENTRO DE BIOLOGIA MOLECULAR
UNIVERSIDAD AUTONOMA DE MADRID
FACULTAD DE CIENCIAS
E - 28049 CANTOBLANCO, MADRID

Participants

ALCOVER ANDRES ..... F
LEY STEVEN C ..... GB
LOPEZ RIVAS ABELARDO ..... E
OWEN MICHAEL ..... GB

Immunoregulatory role of epitopes from infectious pathogens

Contract number: **CT920206** (Basic Research Project)
Start date: 01/02/93 Duration: 36 months
EC contribution: 425,000 ECU

Objectives:
Identification and production of T-cell epitopes from mycobacterial and plasmodial antigens. Define the role of such epitopes for induction of protective immunity or pathology. Define the cellular and genetic mechanisms regulating these responses.

Brief description:
New strategies for controlling infectious diseases by immunological means such as modern vaccines require detailed knowledge of the immune response to the infecting organisms. As infectious agents induce a large variety of such responses it is necessary to distinguish between those which give rise to protection against infection and those which may induce reactions which are harmful to the host, including potentially dangerous autoimmunity. In this project we aim at investigating these questions in the human system which requires application of new, *in vitro* methodologies. Four antigens from two types of organisms causing some of the most important infectious diseases worldwide (mycobacteria and the malaria parasite plasmodium falciparum) will serve as model substances to elucidate how the human immune response to infection is regulated at the molecular and cellular levels. To achieve these aims T-cell epitopes of the plasmodial or mycobacterial antigens have been identified. The potential of these epitopes to induce protection and/or autoimmunity will be established by defining their fine specificities and by investigating the functional role of the lymphocyte responses they set into motion under different conditions of antigen presentation. For this purpose, special emphasis will be given to the analysis of the different lymphokines released from *in vitro* activated CD4+ T-cells. The function of these cells to amplify antibody production and induce functionally dieferent immunoglobulin isotypes (including IgE) after activation with the different immunogens will be studied in specially developed T-/B-cell cooperation systems in vitro. This will be achieved using lymphocytes from donors with different levels of immunity to malaria or mycobacteria. In parallel the genetic regulation of the capacity of the lymphocytes from different donors to respond to the epitopes under study will be investigated with regard to restrictions imposed by the MHC-system or other genetic factors. The project is expected to render important new information about how the immune response to infection is regulated in humans. This will provide a basis for a rational design of vaccine immunogens. The *in vitro* strategies which will be used are of great potential for analyzing cellular immune responses in humans, in general.

Keywords:
T cell response, Immunology

Coordinator

MR DUBOIS PHILIPPE
UNITE DE PARASITOLOGIE EXPERIMENTALE
INSTITUT PASTEUR
25 RUE DU DOCTEUR R0UX
F - 75724 PARIS 15

Participants

IVANYI JURAJ ..... GB
SARTHOU JEAN-LOUIS ..... SN
TROYE BLOMBERG MARITA ..... S

In vitro immunization of human B lymphocytes

Contract number: **CT920269** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 1,060,000 ECU

Objectives:
The objectives of this project are to define and develop the methodologies for the *in vitro* immunization of human B lymphocytes in order to produce human monoclonal antibodies of desired specificity and affinity for antigen.

Brief description:
The project focuses on the understanding of how human B cells can be antigenically activated *in vitro* and is both precompetitive and multidisciplinary. The goal of the proposed project is to form this basis in the sense that it will provide the tools to manipulate human B cells for the purpose of generating specific, high affinity human antibodies. The final goal of the proposed project can clearly be divided into discrete subprojects with individual intermediary targets, as outlined below: 1. To define the antigen presentation needed to obtain an optimal T cell help. Here we have several novel approaches such as e.g. evaluation of lipopeptides, heterotopes (synthetic peptides containing both B and T cell epitopes) and use of the superantigen SEA; 2. To define the signals that regulate the somatic mutations in centroblasts, i.e. how are the antigen specifically activated B cells driven towards a centroblastic phenotype and how is the hypermutation initiated and controlled. This involves establishment of T cell clones (THl, TH2 and germinal center T cells); 3. To define the role of CDl9/21/23, CD5/72, CD40, CD44, 4F2/CD43 in the in vitro immunization of human B cells; 4. To define the signals which regulate the switching of isotype from IgG to IgM in antispecifically activated B cells; 5. To define the parameters important for the cloning and expression of antibody genes isolated from single B cells. After designing the proper single cell propagation system, this point will be restricted to the use of chaperonins in pathway engineering to enhance the secretion of functionally active antibodies.

Keywords:
Immunology, *In vitro* immunisation, Antibody, Synthetic peptides, Antigen, Mutation

Coordinator

D.SC ZEUTHEN JESPER
DEPT. OF TUMOR CELL BIOLOGY
THE FIBIGER INSTITUTE
DANISH CANCER SOCIETY
NDR. FRIHAVNSGADE 70
DK - 2100 COPENHAGEN

Participants

BORREBAECK CARL ..... S
GORDON JOHN ..... GB
JAMES KEITH ..... GB
KRAMBOVITIS ELIAS ..... GR
MALAVASI FABIO I

In vitro cellular correlates in allograft recipients

Contract number: **CT920300** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 1,270,000 ECU

Objectives:
To study *in vitro* correlates of the cellular immune response against organ and bone marrow allografts.

Brief description:
In vitro cellular correlates in allograft recipients. The proposal is aimed at designing rapid and powerful *in vitro* tests to study immune cellular correlates in recipients of organ (OT) or bone marrow transplantation (BMT), topics which are central to the themes of the project. Seven laboratories with internationally recognized complementary skills in immunology and with transplantation clinics will participate. Experiments will be organized within 3 main themes. 1/ Pre-graft correlates to predict the strength of the alloresponse in OT and BMT: alloresponsive cell frequencies against various donor/host targets. Designing of rapid *in vitro* techniques to assess allodiversity with a special interest in correlation between gene polymorphisms (PCR), gene product expression (PCR/FACS), function (MLR) and clinical outcomes. 2/ Studies of *in vitro* correlates during rejection and tolerant states. Here, the emphasis will be on assessment of the production of a variety of cytokines and activation proteins on cells derived from the graft itself (PCR) to define patterns with clinical relevance. Semiquantitative analysis of TCR diversity (PCR for VB, JB and N length polymorphisms) will be also studied during rejection of different types of organs. In addition, functional assays specifically designed to study adhesion processes during bioreagent treatment (anti-LFAl, anti-CD4) are planned. 3/ Post BMT events will be analysed: characteristics of the peripheral reconstitution of Lymphocyte population by flow cytometry using a panel of VB moAb and TCR repertoire of dominant clones (PCR and sequence) will be correlated to clinical status. Culture and clones obtained from GVHD skin lesions will be used to understand the disease mechanisms: characterization of major and minor histocompatibility targets and their distribution, study of skin homing process of anti host cell and THl/TH2 profile of clones extracted from the skin.

Keywords:
Transplantation, Immunology, Bone marrow

Coordinator

PROF SOULILLOU JEAN-PAUL
INSTITUT DE TRANSPLANTATION ET DE
RECHERCHE EN TRANSPLANTATION (ITERT)
9 INSERM U211 - INSTITUT DE BIOLOGIE
QUAI MONCOUSU
F - 44035 NANTES 01

Participants

DALLMAN MARGARET ..... GB
DEL PRETE GIANFRANCO I
GOULMY ELS ..... NL
KOURILSKY PHILIPPE ..... F
LATINNE DOMINIQUE ..... B
MOLLER ERNA ..... S

In vitro immunisation and phage antibodies in the derivation of high affinity human antibodies against the protein products of cloned genes

Contract number: **CT920351** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 635,000 ECU

Objectives:
To provide a system by which human antibodies can be easily derived against antigens which are used to immunise B cells of human *in vitro*

Brief description:
mAbs are becoming increasingly important in health care. The derivation of mabs using traditional methods has some defects: 1) human antibodies cannot be easily derived and humanisation is not a real substitute; 2) the process is expensive and time consuming.The expression of antibody binding domains on the surface of fd phage (phage antibodies - phab) goes some way to overcoming these problems. One procedure to select a phage antibody involves passing a library of such phabs over antigen bound to a solid support and eluting those which bind. However this too has its disadvanta-cc: 1) Thc affinity of PhAbs derived from unimmunised animals (mouse or human) is low (KDIO-7M); although the use of immunised animals can increase KDIO-9 and higher, immunisation of human beings is impossible. 2) The selection procedure requires the purification of large amounts of the protein antigen and this can be laborious. The goal of this project is to develop the conditions for immunisation of human cells *in vitro* using different forms of antigens derived from cloned genes (expression as fusion proteins, on the surface of bacteria or presented on B cells or macrophages). The conditions which will be investigated in the *in vitro* immunisation include the effects of source and fractionation of the human cells, interleukins, feeder cells and general culture conditions. Following immunisation, the response of the *in vitro* culture to the antigen will be monitered at the cellular level by cellular proliferation, phenotype and the production of immunoglobulin. This should provide a population of immunised human cells from which MRNA can be prepared and used to create libraries of phabs. The selection and sequencing of antigen binding V regions from these phab libraries will allow the study of the progress of the immunisation of human cells *in vitro* at the molecular level (increase in affinicy by somatic mutation). The selection procedure will involve panning phabs over antigen in solid phase, as well as the use of bacteria expressing the antigen of interest as the solid phase. The development of this use of bacteria as living columns will be carried out within the framework of this project. If successful it will eliminate the need to purify the large amounts of ancigen needed for selection by panning.

Keywords:
In vitro immunisation, Immunology, B-cell

Coordinator

PROF BRADBURY ANDREW
SOCIETA ITALIANA PER LA RICERCA
SCIENTIFICA S.R.L.
VIA G. PAISIELLO 47/C
I - 00198 ROMA

Participants

CHISWELL DAVID ..... GB
LATINNE DOMINIQUE ..... B

In vitro study of the human immune response to the pollen allergens of Parietaria

Contract number: **CT920363** (Basic Research Project)
Start date: 01/03/93 Duration: 36 months
EC contribution: 635,000 ECU

Objectives:
This proposal is aimed at studying *in vitro* the fine mechanisms regulating the immune response in allergy, using the major allergens of the pollen of Parietaria as a model.

Brief description:
The physicochemical structure of these proteins will be investigated by using recombinant DNA technologies; the structures that are ligands in the interactions of immune recognition will be delineated. Genomic events underlying immunoglobulin isotype switching and T cells control of IgE antibody synthesis will be analysed. B, T and antigen presenting (APC) cell collaboration and the role of allergen in IgE isotype modulation will be explored. These goals will be attained through cooperation among groups with distinct cultural backgrounds and expertise. Recent studies have provided insights into the fine mechanisms of IgE mediated allergy. Ricci (participant 2) and others have documented the regulating role of T helper (Th) cells. The genomic events of IgE isotype switching have been investigated by several groups including Radbruch's (participant 3). The major allergens of the pollens of Parietaria, a Mediterranean weed, whose pollen is a major cause of respiratory allergy in Europe, appear suitable tools for structure function studies because of the low m w (12 kDa) and of the availability of a highly dominant B cell epitope, expressed in E. coli by recombinant cDNA (Ruffilli, participant 1). The possibility of utilizing recombinant DNA products developed during this study in the field of diagnosis of allergy appears real. Informations useful for the planning of strategies for immunotherapy may derive from several of the described approaches.

Keywords:
Allergens, Cytokine, *In vitro* immunisation

Coordinator

DR RUFFILLI ANNA
ISTITUTO INTERNAZIONALE DI GENETICA E BIOFISICA
VIA MARCONI 10
I - 80125 NAPOLI

Participants

IN VITRO IMMUNOTOXICOLOGY

2.3.3 Development of *in vitro* test systems, compatible with prenormative requirements and suitable for the assessment of immunotoxicological or immunogenic potential of medicinal substances and, particularly, biotechnology-derived compounds.

Immunotoxicology of drugs and biotechnology-derived products : development of in vitro assays based on cellular and molecular immunobiology

Contract number: **CT920316** (Generic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 4,697,000 ECU

Objectives:
To develop *in vitro* tests to evaluate the ability of therapeutic agents including recombinant cytokines, cytokine inhibitors and monoclonal antibodies to trigger specific or non-specific immune responses or to induce immunosuppression.

Brief description:
The programme proposes to utilise recent advances in molecular immunology and related disciplines to develop in vitro assays for the assessment of adverse immune reactions induced by drugs and medical compounds. In the first phase, it will be based on reference substances whose effects have been studied and elucidated in humans and/or experimental animals. At this stage, the programme will rely on the common use by all participants of selected in vitro models. Techniques to be used for assessing immunomodulatory effects will include cell activation and differentiation markers by FACS analysis and evaluation of cytokine production by multiple approaches such as bioassays, immunoenzymatic assays (ELISA) and cytokine mRNA levels by northern blot or reverse polymerase chain reaction (PCR) analysis. The project will focus on five major areas : 1) *in vitro* tests to evaluate the immunotoxicity of biotechnology-derived compounds such as monoclonal antibodies or recombinant cytokines and growth factors 2) the use of established animal models to develop *in vitro* predictive assays for drug-induced autoimmunity, followed by the assessment of the validity of these tests in the human situation 3) the development of test systems for predictive drug-specific human T cell responses in allergic drug reactions 4) development of *in vitro* immunotoxicity test systems to assess immunosuppression using existing animal data base for validation 5) in vitro preparation of drug metabolites followed by evaluation of their immunotoxic potential. If the proposed programme is successful in relating *in vivo* effects of reference substances to *in vitro* changes, the scientific basis of *in vitro* immunotoxicology will have been significantly improved. A second phase of the programme will then be to define the relevance of each assay system for pharmacological and toxicological screening and the feasability of each system for routine use will be evaluated. Selected *in vitro* tests could then be standardised as much as possible and be subject to interlaboratory comparison. Hopefully, this programme should thus lead to the definition and establishment of *in vitro* tests compatible with prenormative requirements.

Keywords:
In vitro toxicology, Immunology

Coordinator

MD.PHD GOLDMAN MICHEL
DEPARTMENT OF IMMUNOLOGY, HOPITAL ERASME, AND LABORATOIRE PLURIDISCIPLINAIRE DE RECHERCHE EXPERIMENTALE
ROUTE DE LENNIK 808
B - 1070 BRUSSELS

Participants

BACH JEAN-FRANCOIS ..... F
BALLET FRANCOIS ..... F
BEAUNE PHILIPPE ..... F
BLOKSMA MARIE ..... NL
BUURMAN WILLEM A. ..... NL
COHEN JONATHAN ..... GB
COLEMAN JOHN ..... GB
DANSETTE PATRICK ..... F
DE GROOT HERBERT ..... D
DENCKER LENNART ..... S
DESCOTES JACQUES ..... F
DRUET PHILIPPE ..... F
GHEZZI PIETRO I
GLEICHMANN ERNST ..... D
GRAU GEORGES ..... CH
LATINNE DOMINIQUE ..... B
MATHIESON PETER ..... GB
MILLER KLARA ..... GB
PAPADOPOULOS GEORGE K. ..... GR
PICHLER WERNER ..... CH
ROMAGNANI SERGIO I
STEJSKAL VERA ..... S
URBAIN JAQUES ..... B
VAN LOVEREN HENK ..... NL
WALDMANN HERMAN ..... GB
WALTER FIERS ..... B
WEENING JAN JURJEN ..... NL
WOLF HERMAN FRIDMAN ..... F

NEUROBIOLOGY

2.3.4 Coordination of research activities focused on molecular, biochemical and pharmacological approaches for the study of nerve and glial cells, their interactions and their dysfunctions (e.g. BSE and related diseases).

Molecular neuropathogenesis of bovine spongiform encephalopathy and related neurodegenerative diseases

Contract number: **CT930248** (Basic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 210,000 ECU

Objectives:
1. To identify and characterise the infectious agents of scrapie, BSE and CJD. 2. To identify and characterise non-PrP molecules in infectious fractions. 3. To test the roles of normal and abnormal PrP in the replication of the agent. 4. To investigate mechanisms by which the infectious agent causes disease.

Brief description:
Bovine spongiform encephalopathy (BSE) is a new member of the group of related transmissible neurodegenerative diseases that includes scrapie and CJD. While these diseases can be transmitted between species experimentally, often with great difficulty, natural transmissions are thought to be prevented by the species barrier. The probable crossing of this barrier by scrapie to cause BSE in cattle has raised concern about the safety of products based on bovine organs, tissues or fluids for human use, which has had serious implications for European industry, particularly the bio-pharmaceutical companies. Control of the disease and quality of bovine products is greatly hindered by lack of a diagnostic test, which stems directly from lack of knowledge about the causative agent and the pathogenesis of the disease. This proposal is for a cooperative European programme bringing together research expertise of leading laboratories in Belgium, France, Germany, Italy, Netherlands and United Kingdom. It will address the basic question of the molecular nature of the agent by analysing highly purified fractions of infectivity. The involvement of the host-encoded protein PrP in the disease process and the structure of the agent will be studied through characterisation of (a) PrP genes in species of domestic animals, (b) the effects of expression of altered PrP genes in transgenic mice, in terms of pathogenesis and accumulation of infectivity, (c) cells of the LRS which first replicate infectivity upon inoculation and (d) the effects of altered PrP expression on the replication of the agent in vitro in persistently infected SMB cells. This will form the core of a European Network on BSE and scrapie.

Keywords:
Bovine spongiform encephalopathy (BSE), Neurodegeneration, Prp

Coordinator

DR BOSTOCK CHRISTOFFER
AFRC INSTITUTE FOR ANIMAL HEALTH
COMPTON,LABORATORY
GB - RGI6 ONN COMPTON, NR. NEWBURY

Participants

DIRINGER HEINO ..... D
EIKELENBOOM PIET ..... NL
FRASER HUGH ..... GB
LOCHT CAMILLE ..... F
PASTORET PAUL-PIERRE ..... B
POCCHIARI MAURIZIO I

Homeogenes and adhesion molecules in the nervous system

Contract number: **CT930012** (Concerted Action)
Start date: 01/08/93 Duration: 36 months
EC contribution: 270,000 ECU

Objectives:
The objective is to analyse in several experimental systems the interplay between adhesion molecules and transcription factors of the homeoprotein family.

Brief description:
One of the most intriging question in developmental biology is the mechanisms by which biological shapes can be both inherited and influenced by the environment. In the case of the nervous system, we shall address this question by studying the interplay between developmental genes and surface proteins with morphoregulatory activity. Expression of several classes of homeogenes will be analysed in different species and correlated with anatomical borders, differentiation events and expression of diverse cell and substrate adhesion molecules (CAMs and SAM). The regulation by homeoproteins of the expression of genes coding for CAMs and SAMs will be further analysed. New targets for homeogenes will be investigated. The regulation of homeogenes transcription through cell interactions and by diffusible factors will analysed in vivo and in vitro. In addition to the possibility that new information will be gained on the mechanism at work during development and evolution, this action may have practical consequences in the field of teratology since some homeogenes could be the targets for hazardous compounds during development. We also anticipate a better understanding of learning modalities associated with structural changes in neuronal networks. Finally, we hope that the project will shed some light on mechanisms at work in distinct neurodegenerative diseases.

Keywords:
Homeogenes, Nervous system, Development, Morphogenesis, Neurodegeneration, Adhesion molecules

Coordinator

PH.D PROCHIANTZ ALAIN
ECOLE NORMALE SUPERIEUR
660 46, RUE D'ULM
F - 75230 PARIS

Participants

BONCINELLI EDOARDO I
GENNARINI GIANFRANCO I
GORIDIS CHRISTO ..... F
KARAGOGEOS DOMNA ..... GR
MARTINEZ SALVADOR ..... E
ROUGON GENEVIEVE R. ..... F
SCHACHNER MELITTA ..... CH
VINCENT JEAN-DIDIER ..... F
WASSEF MARION ..... F

Insect neuropeptides : structure determination, chemical synthesis and biological activities

Contract number: **CT930073** (Concerted Action)
Start date: 01/08/93 Duration: 36 months
EC contribution: 60,000 ECU

Objectives:
Study the structure-function relationship of novel insect neuropeptides which may have agricultural and medical interest. Obtain by synthesis these peptides and analogues and determine their neuronal and myotropic effects Design peptide mimetics. Create an European network for insect peptide scientists.

Brief description:
This project will provide information on the structure-function relationship of novel neuropeptides, which we have previously isolated from the central nervous system (CNS) of the locust Locusta migratoria. Since in insects, many of the peptides present in the CNS control behavioural response, motility of muscles and development, some of the peptides which we have already characterized may have considerable agricultural interest. Also one of the peptides we intend to study, the 5-kDa peptide, is the insect counterpart of the vetebrate C-peptide of insulin. We have shown that the insect C-peptide affects the membrane potential and conductance of Locusta neurones, and is therefore of considerable scientific and medical interest. The data arising from our studies should enable us to determine which novel peptides are active in the insect CNS, the neurones that synthesise them, the location of their receptors and the structural and functionnal determinants of those peptides. At the same time, conformational studies of the active peptides and their analogues will be done by nuclear magnetic resonance (NMR) and will establish their tertiary stucture. This will help design peptide mimetics (non peptidic analogues) which are required for an agricultural or medical use of these peptides. We will address these questions with a multidisciplinary approach involving chemical, biophysical, electrophysiological, immunocytochemical and pharmacological techniques. The two laboratories, the Strasbourg (01) and Oxford (02) groups, involved in that project have already established informal collaborative links through the exchange of expertise and materials, visits to Oxford and Strasbourg, poster presentahon at scientific conferences and joint publications. Thus, the proposed collaboration will build upon solid foundations. In addition, our two groups (01,02) will organise an Europeen Insect Peptide Workshop to bring together Insect Peptide Scientists in order to facilitate the creation of an European network.

Keywords:
Insect, Neurotransmitter

Coordinator

PROF BANG LUU
LABORATOIRE DE CHIMIE ORGANIQUE DES
SUBSTANCES NATURELLES
5 BLAISE PASCAL
F - 67084 STRASBOURG

Participants

BERMUDEZ ISABEL ..... GB

A molecular neurobiological approach to the study of the normal function and degenerative disorders of the basal ganglia

Contract number: **CT930074** (Concerted Action)
Start date: 01/09/93 Duration: 36 months
EC contribution: 90,000 ECU

Objectives:
The main objectives of our Concerted Action will be: (i) To focus on the neurotransmitter-receptor networks of neurons using monoamines (dopamine and noradrenaline) as the transmitter (all research groups involved). (ii) To undertake specific enzymological studies on the tyrosine hydroxylase system, the rate-limiting enzyme in the biosynthesis of dopamine/noradrenaline.

Brief description:
The studies will be based on our recent cloning of the four isoforms of human tyrosine hydroxylase (Paris) and structural and functional studies on these isoforms (Bergen, Paris). Our planned research will include studies on the structure, relation between structure and function, and the catalytic mechanism of the recombinant human isozymes expressed in E. coli (Bergen, Bilbao, Paris)). Site-directed mutagenesis will represent an essential aspect of these studies (Paris, Bergen). (iii) To study specific aspects of the cellular biosynthesis, storage and release of the biogenic amines (Bergen, Paris, Lund). In dopaminergic/noradrenergic neurons the transmitter is stored at very high concentrations in complexes involving proteins, calcium and ATP. Our research programme aims at a better understanding of the biogenesis of the secretory granules, including their maturation, after budding from the trans-Golgi network, and reutilization following exocytosis. The aim is also to improve our knowledge about the molecular mechanisms involved in their fusion with the plasma membrane (exocytosis) and retrieval from that membrane (endocytosis). (iv) To obtain a better understanding of the pathogenesis and treatment of degenerative disorders of the basal ganglia, in particular parkinsonism. Efforts will be made to develop transplantable hybrid cell lines, expressing the key phenotypic properties of dopaminergic neurons, which can survive, make phenotypic plasticity, synthesize/release dopamine, and ameliorate motor dysfunction (Paris, Lund, Bergen). Genetic engineering is required to generate cell lines with such a phenotype (v) A main objective of the programme is also to design new, synthetic derivatives of tetrahydrobiopterin with improved cofactor properties in the tyrosine hydroxylase reaction (Konstanz, Bergen, Bilbao, Paris). The research thus includes projects of basic molecular neurobiology as well as projects related to the treatment of degenerative disorders of the CNS. The approach will be a combination of generating hybrid transplantable cells expressing a dopaminergic phenotype, with the goal to replace degenerated dopaminergic neurons, as well as a pharmacological modulation of the biosynthesis, storage and release of the neurotransmitter. To attain these goals an interdiciplinary collaboration is essential. The methods employed will be those pertaining to molecular biology, biochemistry, biophysics and cell biology.

Keywords:
Neurotransmitter, Neurodegeneration

Coordinator

PH.D MALLET JACQUES
CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE
UPR23 LABORATOIRE DE NEUROBIOLOGIE
CELLULAIRE ET MOLECULAIRE
1 AVENUE DE LA TERRASSE
DR ILE-DE-FRANCE: SECTEUR SUD
F - 91198 GIF-SUR-YVETTE

Participants

BJORKLUND ANDERS ..... S
FLATMARK TORGEIR ..... N
GONI FELIX M. ..... E
PFLEIDERER WOLFGANG ..... D

Detection and characterization of genes involved in smell recognition

Contract number: **CT930097** (Concerted Action)
Start date: 01/09/93 Duration: 36 months
EC contribution: 60,000 ECU

Objectives:
To understand the basis of smell perception by studying: a) molecular components involved in signal reception and transduction b) coding processes of the olfactory information c) modulation of this information by other sensorial inputs at the integration level

Brief description:
We use the model system Drosophila to contribute to the understanding of the process of smell perception. Because of its relatively simple olfactory system consisting of only 1200 receptor neurons genetic methods have proven particularly useful in detecting olfactory genes that are not accessible through sequence similarity to other genes. We, therefore, employ genetic and molecular techniques to identify specific components of the system whose functional contribution to the odorant perception process can be measured *in vivo* either by physiological or behavioural tests. Our experimental approach can be devided in two parts: First, we dissect the organization of the olfactory system by introducing at random into the genome transposons that report on genes activated in cells or cell populations of the olfactory organ. The transposon insertion thus leads us into close proximity of genes that are specifically activated and are likely to act in the olfactory perception cascade. Transposon insertions might have hit and inactivated the olfactory gene and thereby reveal a mutant phenotype. If this is, however, not the case, a new genetically induced "jump out" in a high proportion gives rise to deletion of neighbouring genomic DNA. The phenotype of mutations induced either by transposon insertion or remobilization caused deletions is analysed in the second part of our approach. Here, we apply methods to measure the behavioural or electrophysiological response of the mutant animals. Behavioural paradigms are used to test the response to different odorants. Direct electrophysiological measurements are performed at the main olfactory organ of the adults, the third antennal segment, in response to different airborne chemicals. In this way one can uncover mutations affecting olfactory perception or transduction in primary olfactory neurons. Applying different odorants we can distinguish mutations that have an effect on specific receptors from those that influence the general transduction pathways.

Keywords:
Smell perception, Signal transduction

Coordinator

DR HOVEMANN BERNHARD
MOLEKULARE NEUROBIOCHEMIE
POSTFACH 102148
D - 44780 BOCHUM-QUERENBURG

Participants

Role of neuronal receptors in signal transduction and development

Contract number: **CT930169** (Concerted Action)
Start date: 01/09/93 Duration: 36 months
EC contribution: 150,000 ECU

Objectives:
Molecular cloning of G- protein linked receptors. - Methods for determining the ligand for molecularly cloned receptors. - Mapping of neurons. -physiological role of receptors in signal transduction systems. - Role of G- linked receptors in development.

Brief description:
We propose a concerted action in order to form a network of related laboratories to participate in the exchange of materials, workers and ideas. This pan-European network involving five laboratories from four countries will specialise in the application of molecular neurobiology to ligand:receptor systems. The network is multi-disciplinary, ranging from molecular biology, gene cloning to neurophysiology and developmental biology. All the participating laboratories are well-funded by national sources and by international collaboration. For example, the GB and NL laboratories have an EC twinning grant. The specific areas in which training will be given are as follows: 1 Molecular cloning of G-protein linked receptors. 2 Methods for determining the ligand for molecularly cloned receptors and ion channels. 3 Mapping of neurons in simple nervous systems. 4 Determining the physiological role of receptors and other components of signal transduction systems. 5 Understanding the role of G-linked receptors in development. All the laboratories involved in this proposal are conversant with the state-of-the-art techniques. A major aim of our programme will be to facilitate exchanges between our laboratories, all of which share common goals. It appears that this area, which is vitally important for both the pharmaceutical and agricultural industries, is not well-supported in other countries of the EC. We believe that by providing support for exchanges between laboratories then we will be able to compete with the USA and Japan.

Keywords:
Receptor, Nervous system, Development

Coordinator

DR BURKE JULIAN
SUSSEX CENTRE FOR NEUROSCIENCE
SCHOOL OF BIOLOGICAL SCIENCES
UNIVERSITY OF SUSSEX
GB - BNI 9QG BRIGHTON

Participants

DARLISON MARK . . . . . D
GERAERTS WIJNAND . . . . . NL
MAROTEAUX LUC . . . . . F
VAN HEERIKHUIZEN HARM . . . . . NL

Serotonin receptors : molecular characteristics and therapeutic potentialities of their selective ligands

Contract number: **CT930179** (Concerted Action)
Start date: 01/08/93 Duration: 36 months
EC contribution: 100,000 ECU

Objectives:
To focus on the 5-HTIB/5HTID receptor family in order to explore in detail the molecules, pharmacological and functional properties of its 5 distinct components 5-HTIBα, 5-HTIBß, 5-HTIDα, 5-HTIDß, 5-HTIE.

Brief description:
Serotonin (5-hydroxytryptamine, 5-HT) is a major neurotransmitter in the central nervous system which participates in the control of several functions such as food consumption, sleep, nociception, sexual behaviour etc, and alterations in central 5-HT neurotransmission have been demonstrated in some diseases, notably dementia (Alzheimer disease), depression and generalized anxiety. These numerous actions of 5-HT are mediated through its interaction with multiple receptors which were first characterized by pharmacological methods and then cloned and sequenced thanks to molecular biology techniques. The precise knowledge of the pharmacological, biochemical and molecular properties of a given receptor type is especially helpful for the synthesis of selective ligands with potential therapeutic interest. The present project will focus on receptors of the 5-HTIB /5-HTID family which have been cloned recently, but the functional roles of which are still poorly known. The therapeutic potential of selective 5-HTIB /5-HTID receptor ligands is important as one can recall for instance that the most efficient anti-migraine drug to date is sumatriptan, i.e. a non selective agonist at these receptors. The collaboration between the eight participants to this programme will allow a multidisciplinary approach with studies in molecular biology (M. Voigt, R. Hen), immunocytochemistry (M. Hamon, J. Lanoir, N.N. Osborne), chemistry (J. Chauveau, B. Guardiola), biochemistry (M. Voigt, M. Hamon,J.:Lanoir, M. Gôthert,N.Osborne) and animal behaviour (J.Lanoir,B. Guardiola). The cloned 5-HTIB /.5-HTID receptor subtypes will be overexpressed in appropriate cell types for studies of their pharmacological properties (binding studies) and coupled transduction mechanism. Site-directed mutagenesis will be used for identifying the receptor domains involved in ligand binding and effector coupling. Modelisation will help for designing new drugs which will then be tested on transfected cells, brain tissues and whole animals (behavioural studies). In addition, fusion proteins including large domains of the 5-HTIB / 5-HTlD receptor subtypes will be made for raising specific antibodies to be used for the visualization of the receptors at the optic and electron microscope levels. Finally, drugs acting at 5-HTIB /5-HTID receptors will be tested in appropriate *in vitro* and *in vivo* models, including transgenic mice (R- Hen).

Keywords:
Receptor, Neurotransmitter, Drug design

Coordinator

PROF HAMON MICHEL
NEUROBIOLOGIE CELLULAIRE ET
FONCTIONNELLE (INSERM ULBB)
91 BOULEVARD DE L'HOPITAL
F - 75634 PARIS 13

Participants

CHAUVEAU JACQUES ..... F
GOETHERT MANFRED ..... D
GUARDIOLA BEATRICE ..... F
HEN ENE ..... F
LANOIR JEANNE ..... F
OSBORNE NEVILLE ..... GB
VOIGT MARK I

Modulation of intracellular transport by small GTP ases in cultured cells and during mouse development

Contract number: **CT930205** (Concerted Action)
Start date: 01/09/93 Duration: 36 months
EC contribution: 120,000 ECU

Objectives:
The aim of this proposal is to study the *in vivo* functional properties of five different small GTPases of the RAB family in established cell lines, in primary cultures of foetal hippocampal neurons and in the developing mouse.

Brief description:
The proposed project is aimed at studying several members of the rab sub- family of small GTPases. These proteins are implicated in the regulation of specific steps of intracellular membrane transport. Our four groups will focus on rab1, rab4, rab5, rab6 and rab17. We will focus on three main points: 1. The elucidation of the basic mechanism of function of rab GTPases. This involves the identification and functional characterization of interacting components using biochemical methods. 2. The modulation of membrane traffic by various rab proteins. Using rab proteins as specific transport regulators we plan to either positively or negatively influence the cellular parameters of secretion and endocytosis in established cell lines and in primary cultures of foetal rat hippocampal neurons. 3. The impact of alterations in intracellular transport on mouse development. Functional studies will be performed in transgenic mice expressing functional wild type and dominant non-functional mutant rab proteins. The phenotypic effects during embryonic development and in the adult animals will be investigated. The understanding of the mechanisms controlling intracellular transport is not only relevant for the basic knowledge on how cellular organization is controlled but has also functional implications for biotechnological tasks. The availability of molecules which are playing an important role in the regulation of intracellular transport will hopefully allow the development of animal models which are amenable to the experimental studies of various human diseases and to the improvement of the biology of farm animals.

Keywords:
Small GTP-ases, Rab proteins, Development

Coordinator

DR ZERIAL MARINO
EUROPEAN MOLECULAR BIOLOGY LABORATORY
MEYERHOFSTRASSE 1
POSTFACH 10.2209
D - W6900 HEIDELBERG

Participants

GOUD BRUNO ..... F
HOFLACK BERNARD ..... D
MCCAFFREY MARY ..... IRL

Neuronal development and regeneration

Contract number: **CT930260** (Concerted Action)
Start date: 01/09/93 Duration: 36 months
EC contribution: 180,000 ECU

Objectives:
To elucidate the processes involved in neural development, neural degeneration and regeneration in the central nervous system.

Brief description:
During neurodevelopment controlled interactions between neurons and glial cells are of paramount importance. Establishment of neural networks requires growth factors which may be secreted from both glial and neuronal cells and which stimulate growth and differentiation of other cells. Furthermore, adhesion molecules present on the cell surface or secreted into the extracellular matrix assist in the regulation of cell migration and neurite outgrowth. During adult life, degenerative processes may disrupt neural networks. However, even aged brain has a capacity for regeneration to a certain extent. The molecular mechanisms involved in neurodevelopment may be reactivated in regenerative processes. The purpose of this project is to elucidate the influence of growth factors, cell adhesion molecules and proteoglycans on interactions between neurons and glial cells during development, aging and regeneration. Furthermore, signal pathways between neuronal stimulation and neuronal response are to be studied. In brain, nerve growth factor (NGF) and basic fibroblast growth factor (bFGF) are of importance not only for growth and differentiation but also for sustained survival of neural cells. The interaction between these growth factors and the excitotoxic neurotransmittor glutamate which is believed to be involved in neuronal cell death during aging will be investigated in *in vitro* cell culture systems. Growth of neuronal processes may not only be stimulated by growth factors. Cell adhesion molecules and proteoglycans are likewise involved in dendritic and axonal growth. The mechanism responsible for the dendrite promoting effect of proteoglycans and glycosaminoglycans will be studied at the molecular level. Furthermore, the importance of the neural cell adhesion molecules, NCAM, L1 and N-cadherin, for interactions between neurons and glia will be investigated. NCAM is a highly complex molecule due to alternative splicing and differential glycosylation. Regulation of NCAM function via alternative exon usage and the effect on posttranslational processing will be studied. Finally, the second messenger systems involved in NCAM function will be elucidated. The project will establish a strong european network of scientists working on different important aspects of neurobiology. During the project *in vitro* systems for evaluation of neurotoxicity will be developed. Furthermore, the project will contribute to the understanding of neurodevelopment and neurodegeneration, hopefully providing a basis for further research into pathological processes in brain.

Keywords:
Nervous system, Development, Regeneration, Adhesion molecules, Growth factors

Coordinator

PROF BOCK ELISABETH
THE PROTEIN LABORATORY
PANUM INSTITUTE
BLEGDAMSVEIJ 3G
DK - 2200 COPENHAGEN N

Participants

PROCHIANTZ ALAIN ..... F
REGAN CIARAN ..... IRL
SCHOUSBOE ARNE ..... DK
SEIFERT WILFRIED ..... D
WALSH FRANK S. ..... GB

Adhesion molecules in mammalian neuraldevelopment and regeneration

Contract number: **CT930326** (Concerted Action)
Start date: 01/08/93 Duration: 36 months
EC contribution: 150,000 ECU

Objectives:
The shared objectives of our laboratories are to characterize the structure and the function of cell adhesion molecules (CAMs), and to pinpoint their involvement in the ontogeny and regenerative processes of the nervous system. This should suggest therapeutic approaches to influence, restore or replace components of injured neurons.

Brief description:
The functional properties of the nervous system depend critically on the intricate network of neuronal connections that is generated during development. The patterning of these connections emerges from precise and coordinated adhesive interactions between developing neurons and their environment. Similar mechanisms are also at work during regeneration. This project intends to provide information on the structure and metabolism of adhesion molecules, to describe intracellular pathways triggered by their activation and to delineate their function. The first aspect is analytical and concerns studies on in vitro systems aimed to define the structure/function relationship of the studied molecules. The second aspect deals with the description of events depending on their correct spatio-temporal expression. In our network, three groups are working on the structural and functional characterization of adhesion molecules. Two groups are focusing their efforts in the biological characterization of glial cells and two groups are involved in the identification of intracellular signals triggered by the activation of cell adhesion molecules. Three groups have also set up in vitro and in vivo models to study normal development and regeneration. Antibodies, cell permanently transfected with intact or deleted adhesion molecules, enzymes shown to specifically modify their structure, will be exchanged between the groups. They will be used in the model systems to investigate the participation of these molecules in morphogenetic events and in regenerative processes. The diversity of the competence of the groups and the complementarity of their approaches should allow them to undertake integrative studies on the role of adhesion molecules.

Keywords:
Adhesion molecules, Development, Glial cells, Regeneration, Second-messengers

Coordinator

PH.D ROUGON GENEVIEVE
UNIVERSITE D'AIX-MARSEILLE II - CNRS
FACULTE DES SCIENCES DE LUMINY
BIOLOGIE DE LA DIFFERENCIATION CELLULAIRE
LUMINY CASE 901
F - 13288 MARSEILLE Cedex 09

Participants

COHEN JAMES ..... GB
JESSEN KRISTJAN R. ..... GB
KISS JOZSEF ZOLTAN ..... CH
MATRANGA VALERIA I
MATSAS REBECCA ..... GR

Area 3

Ecology and Population Biology

3.1 Ecological implications of biotechnology

3.1.1 Basic understanding of soil microbial ecology and of possible adverse effects by engineered microorganisms:

- genetic studies of plasmid ecology, maintenance and transfer, mainly concerning genes encoding resistance to heavy metals and ability to degrade organic pollutants (role of selection pressure in gene stability and transfer ability)
- mechanisms of microbial competition and phenomena which control the distribution of microbes and affect their diversity within populations (community population dynamics)
- environmental factors which control gene mobility and gene expression in target ecosystems.

3.1.2 Studies of the rhizosphere of economically important European crops susceptible to benefit from the introduction of microorganisms with defined properties (engineered or not). In particular the molecular and chemical phenomena of the interactions between microbes and with the host plant will be studied with the aim of understanding at the molecular level the growth promoting and plant protection mechanisms.

3.1.3 Studies of the possible ecological risks from the interactions of engineered microorganisms with biological components of the rhizosphere of economically important European crops.

3.1.4 Genetically engineered fish, insects and nematodes: methods of biological containment; competition with indigenous related species and gene transfer.

Quantifying the impact of GMOs in the environment : development of non-disruptive biomarkers to monitor stability, expression and mobility of recombinant genes in polluted ecosystems

Contract number: **CT920084** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 1,046,000 ECU

Objectives:
- Developping luminiscent/immunological markers to examine GMO performance in the field.
- Non-disruptive monitoring of gene expression and transfer in complex populations.
- Assessment of antigenic reporters to visualise growth-phase of individual cells.
- Constructing novel vectors and reporters for environmental applications.

Brief description:
Deliberate release of genetically modified microorganisms (GMOs) for agricultural and bioremediation purposes is currently hampered by the uncertainty about their ecological impact on native ecosystems. To overcome this problem, the somewhat vague concept of risk must refer to specific, quantifiable parameters so that concrete limits on what is permissible or not can be clearly defined. The major indicators of risks and benefits associated with GMO performance are (1) the degree of recombinant (r) gene expression, (2) rDNA stability, (3) the degree of rDNA lateral transfer and (4) the physiological status regarding its life cycle. Although new techniques to increase predictability of GMOs have become available over the last few years, there are still major methodological gaps for measuring these four indicators in the field. This project intends to provide the genetic and biochemical tools to examine non-disruptively GMO performance in situ by following the presence and activity of novel biomarkers specifically tailored for environmental applications. Four types of reporter systems (enzymatic, surface reporters, adaptation biomarkers and mRNA) will be developed along with hypersensitive analytical technology to measure their activity in terms of gene expression, lateral transfer, stability and growth phase. A special emphasis will be given to detection of fluorescence and light emmision through fiber optics technology and CCD cameras with image processing. These will be most efficient when combined with immuno magnetic separation of GMOs from complex communities by heterologous surface epitopes and immunofluorescent quantification. Alternatively, simpler phenotypes such as ice nucleation or complementation of engineered catabolic pathways will be used as indicators of recombinant gene scape. In any case, the biomarkers will be integrated into regulatory circuits of recombinant soil and rhizosphere pseudomonas targeted to degrade PCBs and halo/alkyl benzoates.

Keywords:
Genetically engineered microorganisms, Antigen reporters, Luminiscent reporters, RNA, Biomerediation

Coordinator

PROF DE LORENZO VICTOR
CENTRO DE INVESTIGACIONES BIOLOGICAS
C/. VELAZQUEZ 144
E - 28006 MADRID

Participants

KJELLEBERG STAFFAN ..... S
MOLIN SOEREN ..... DK
O'GARA FERGAL ..... IRL
RAMOS JUAN L. ..... E
TIMMIS KENNETH N. ..... D

Acquisition of genes from indigenous bacteria by inoculant strains at long- term release sites

Contract number: **CT920370** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 1,066,000 ECU

Objectives:
To screen indigenous rhizobial populations for natural genetic elements.
To recover established introduced rhizobia and to screen for such elements.
To estimate genetic interactions between introduced and indigenous strains.
To refine risk assessments on the release of genetically modified bacteria.

Brief description:
We propose to recover strains of Rhizobium and Bradyrhizobium that have been released as inoculants in the past, and to screen them for evidence that they have acquired new genetic elements during their time in the field. The genetic elements that we shall look for are bacterial plasmids, prophages, and transposable elements, which are widespread in natural populations of bacteria and can serve as markers of gene transfer. We have access to field sites where marked strains were released in the past and have become established, and intend to tackle the question of genetic import by undertaking five tasks, which are: (A) isolating natural genetic elements and developing detection methods for them; (B) determining the distribution of these genetic elements in indigenous populations; (C) screening established introductions for the acquisition of genetic elements; (D) developing and releasing strains designed as potential recipients; (E) analyzing any genetic acquisitions that are discovered. In order to fulfil these tasks, we shall be using and refining novel screening methods based on the polymerase chain reaction, and significant scientific outputs from the work will be a large set of sequence data and primers for native genetic elements in rhizobia, new protocols for screening, and information on the genetic structure of indigenous populations. As the primary achievement of this project, we should have quantitative data on the acquisition of genetic material by bacterial inoculants in the field, as well as information on the types of material that are involved in transfer. This will be essential information for assessing the potential risks involved in environmental releases of bacteria, including GMO's. Our findings will assist the implementation of science-based risk assessment within the EC, and thereby increase the potential for benefit, and decrease the likelihood of harm, resulting from the application of genetic technology to meet agricultural and environmental needs.

Keywords:
Soil, Bacteria, Rhizobia, Bradyrhizobia, Genes, Genetic elements, Gene transfer, Plasmid, Bacteriophage, Insertion element, Transposon, PCR, Field release, Genetically engineered microorganisms, Risk assessment

Coordinator

DR HIRSCH PENNY
AFRC INSTITUTE OF ARABLE CROPS
RESEARCH
ROTHAMSTED EXPERIMENTAL STATION
GB - AL5 2JQ HARPENDEN

Participants

AMARGER NOELLE ..... F
LOTZ WOLFGANG ..... D
PUHLER ALFRED ..... D
TORO GARCIA NICOLAS ..... E
YOUNG PETER ..... GB

Ecological and molecular study of gene-mobilizing capacity of soils and related ecosystems

Contract number: **CT920491** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 1,423,000 ECU

Objectives:
. To assess risk of gene spread in soil caused by natural mobilizing elements.
. To characterize the elements involved.
. To identify ecological factors affecting gene mobilisation in soils.
. To follow the fate of genes in/from GMM's released into soils.

Brief description:
The aims of this proposal are to gain insight into the gene transfer potential of bacterial communities,both Gramnegative and Grampositive ones, in soil and related ecosystems, and to determine its effect on introduced genes carried by genetically modified bacteria. Focus will be on different parts of the soil ecosystem, i.e. rhizosphere and related soil, rhizoplane/ phylloplane, polluted soil and soil in relation to the input of manure. A baseline description of the bacterial and plasmid populations present will be given in terms of the occurrence of genetic elements involved in gene mobility(defined as "Gene Transfer Potential")in relation to the microbial diversity and numbers. The description will be made using classical microbiological techniques, endogenous and exogenous isolations of plasmids and modern molecular techniques. Each system will be characterized as indicated by its peculiarities, i.e. the rhizosphere, rhizoplane and phylloplane will be studied in relation to plant development, and manured soils will be compared to unmodified soils. New plasmids or transposons obtained will be characterized. They will be used as probes to study their prevalence in the natural microbial communities. A specific mobilizable (tra- mob+) broad-host-range plasmid will be used to study gene spread from introduced organisms into the native microbial community in soil. Special emphasis will be placed on the effect of abiotic factors on gene mobilization. Combination of the results of the transfer potential and the mobilization studies will provide a better insight into the hazards associated with GMM's accidentally or deliberately released into the soil environments.

Keywords:
Gene mobilization, Released gmm's, Soil, Rhizosphere, Wheat, Sugarbeet, Plasmid, Risk assessment

Coordinator

DR VAN ELSAS JAN DIRK
SOIL BIOTECHNOLOGY GROUP IB-DLO
IPO-DLO
PO BOX 9060
NL - 6700 GW WAGENINGEN

Participants

BAILEY MARK . . . . . GB
FRY JOHN C. . . . . GB
MERGEAY MAXIMILIEN . . . . . B
SMALLA KORNELIA . . . . . D
TSCHAPE HELMUT . . . . . D
VERSTRAETE WILLY . . . . . B

Molecular and chemical basis of the interaction between plant-protecting pseudomonads and their crop plants

Contract number: **CT930196** (Generic Research Project)
Start date: 01/10/93 Duration: 36 months
EC contribution: 835,000 ECU

Objectives:
- Isolation of bacterial root colonization genes
- Optimization of 2,4-diacetyl-phloroglucinol production
- Molecular analysis of attachment
- Combination of this information in order to improve biocontrol of tomato and sugarbeet

Brief description:
An attractive alternative for chemical disease control in crop plants is the use of naturally occurring plant-associated bacteria which can limit the growth of plant pathogens. This type of disease control is termed BC (Biological Control, as distinct from chemical control). This proposal is directed to the BC of soil-borne plant pathogens by PGP (Plant-Growth Promoting) strains of rhizobacteria which promote plant growth by limiting or controlling the populations of pathogenic micro-organisms. A prerequisite for effective BC is aggressive root colonization to enable the bacteria to be targeted to and become established in the rhizosphere. The failures of BC by PGP organisms in some field experiments are largely due to poor colonization of the introduced strain. The genetic and functional traits required for colonization are poorly understood, especially the roles of plant exudates and attachment in the colonization process. Therefore this project will strongly focus on the functions of root and seed exudate, of attachment, and of yet unknown colonization genes in biological control. In addition we will focus on the genes involved in the synthesis of a recently identified biocontrol agent from Pseudomonas (2,4-diacetylphloroglucinol; Phl), which is directly involved in BC and has the advantage that (some of) these genes are located on a small (6 kbp) DNA fragment.

Keywords:
Root colonization, Biocontrol, Pseudomonas, Diacetylphloroglucinol

Coordinator

PROF.DR LUGTENBERG BEN
LEIDEN UNIVERSITY
INSTITUTE OF MOLECULAR PLANT SCIENCES
BOTANICAL LABORATORY
NONNENSTEEG 3
NL - 2311 YJ LEIDEN

Participants

GROGAN VINCENT ..... IRL
O'GARA FERGAL ..... IRL
SCHEFFER RUDOLF ..... NL
VANDERLEYDEN JOS ..... B

IMPACT - Interactions between Microbial inoculants and resident Populations in the rhizosphere of Agronomically important Crops in Typical soils

Contract number: **CT930053** (Generic Research Project)
Start date: 01/09/93 Duration: 36 months
EC contribution: 2,328,655 ECU

Objectives:
To study the "molecular ecology" of rhizosphere/soil microbial communities following introduction of microbial inoculants.
To develop molecular identification techniques, data storage and retrieval (based on PCR) systems.
To construct genetic tools for the monitoring, biological containment and detection of gene transfer in rhizosphere inoculants.

Brief description:
Existing GMOs and WT strains will be selected from participating laboratories, and will include Rhizobium, Pseudomonas and Azospirillum strains. The microbial population dynamics of soil/rhizospheres of the following important European crop plants will be addressed: wheat, maize, rice, legumes, sugarbeet and tomato. Standardisation of methods and where possible plant cultivars used will be of utmost importance to allow us to compare and contrast the information gathered in the project. The IMPACT project will examine a number of different parameters. The effect of inoculation on overall soil fertility as measured by total biomass and various biochemical parameters will be measured. The potential benefits (in terms of plant-health and yield) that can be achieved with these strains in comparison with wild-type inoculants will also be assessed. The interaction such inoculants have on selected components of the rhizosphere/soil flora such as beneficial/pathogenic bacteria and mycorrhizal/pathogenic fungi will be evaluated. Potential additional ecological effects, related to transfer and expression of rDNA in the indigenous flora will be investigated. An important strand of the project is the development and standardisation of novel molecular identification methods; a databank with appropriate access software will be developed. It is anticipated that the IMPACT project will provide key information to National and European institutions on the benefits obtainable and the ecological impact associated with the introduction of GMOs into agricultural systems of economic importance. This project will develop new technologies and new environmentally-friendly inoculants with limited persistence which will be of commercial benefit to European agribusiness.

Keywords:
Microbial inoculants, Rhizosphere, Ecological impact, Genetically engineered microorganisms, Biocontrol, Molecular strain identification, Database, Genetic tools, Gene transfer

Coordinator

PROF O'GARA FERGAL
UNIVERSITY COLLEGE CORK
DEPARTMENT OF MICROBIOLOGY
IRL - 31 CORK

Participants

BAREA NAVARRO JOSE M. ..... E
BASAGLIA MARINA I
BONFANTE PAOLA I
DEFAGO GENEVIEVE ..... CH
GROGAN VINCENT ..... IRL
LUGTENBERG BEN ..... NL
LYNCH JAMES ..... GB
NUTI MARCO PAOLO I
OLIVARES PASCUAL JOSE ..... E
PERUCH UGO I
PUHLER ALFRED ..... D
RUIZ-ARGUESO TOMAS ..... E
SCHEFFER RUDOLF ..... NL
SIMON REINHARD ..... D
VANDERLEYDEN JOS ..... B
YOUNG PETER ..... GB

3.2 Conservation of genetic resources

RAPID MOLECULAR GENETIC SCREENING METHODS

3.2.1 Development of rapid molecular genetic screening methods for the assessment and evaluation of genetic diversity and potentials in systematic groups, crop and farm animal germplasm collections or wild populations of plants and animals.

This project should lead to the development of efficient routine procedures to obtain genetic data on large numbers of samples in order to estimate genetic distances or to identify specimens bearing genetic traits associated with economically interesting properties. The genetic information to be obtained will supplement and progressively substitute phenotypical data on gene pools in order to rationalise conservation (identification of duplicates in germplasm collections and analysis of degree and structure of genetic diversity in natural populations) and open new opportunities for breeding and industry by disclosure of genetic potentials in biological resources.

Development of universal techniques for the rapid screening of genetic variation

Contract number: **CT920476** (Generic Research Project)
Start date: 01/03/93 Duration: 36 months
EC contribution: 1,065,000 ECU

Objectives:
Design of PCR primers for chosen intron and mtDNA amplifications. Assessment of primer universality and development of efficient screening. Isolation of novel microsatellite markers. Genetic structure of chosen populations and species, as revealed by these.

Brief description:
The aim of this proposal is to develop new and efficient techniques for the screening of genetic variation in a wide range of animals including mammals, reptiles, fish and insects. It will use PCR assays to analyse DNA sequences from parts of the genome that show sufficient variability, including introns, spacer regions and microsatellites. We will attempt to make them as universal as possible. Such techniques will work on very small amounts of animal material, and will be developed for use on dried and alcohol preserved samples. This will revolutionize the assessment of genetic variation in wild populations, since material from all over Europe could be readily collected and transported economically. It also means that rare and endangered species can be examined without loss, and it would facilitate the use of the vast museum collections of Europe. It will be possible to assess the genetic variation between populations in many species and will be of use to agriculturalists and conservationists, who need this knowledge in order to make decisions on what we may exploit and what we should preserve. The project combines the different talents of five proven European laboratories, who will benefit greatly from the interchange of techniques, sequences and personnel. The group has already worked on whales, sheep, mice, birds, fish, flies, grasshoppers and beetles, and its expertise covers mitochondrial DNA, ribosomal DNA, nuclear DNA, population genetics, statistics and systematics. Each laboratory will be responsible for work on a subset of sequences in different organisms, which will then be exchanged and tested for their universality. The best ones will be used for wider population surveys.

Keywords:
Genetic resources, Biodiversity, Genetic variation, DNA sequences, PCR, Introns, Mitochondrial, D loop, Ribosomal spacers, Microsatellites, Mammals, Fish, Reptiles, Insect, Taxonomy, Systematics

Coordinator

PROF.DR HEWITT GODFREY
SCHOOL OF BIOLOGICAL SCIENCES
UNIVERSITY OF EAST ANGLIA
GB - NR4 7TJ NORWICH

Participants

ARCTANDER PETER . . . . . DK
BOURSOT PIERRE . . . . . F
TAUTZ DIETHARD . . . . . D
WAYNE ROBERT . . . . . GB

Rapid molecular screening of genetic diversity in cultivated and wild *Hordeum* SPP

Contract number: **CT920486** (Generic Research Project)
Start date: 01/03/93 Duration: 36 months
EC contribution: 855,000 ECU

Objectives:
To evaluate four different molecular techniques for screening genetic diversity in cultivated and wild species of *Hordeum*. To provide guidelines and recommendations concerning methodology and germplasm selection for scientific, plant breeding, and genebanking purposes.

Brief description:
The proposed project has as its main objectives to evaluate four different molecular techniques (RFLP, RAPD, VNTR, & PCR/sequencing) on a common set of germplasm with respect to both speed and scale, and to make a direct comparison between the information obtained by each of the techniques for practical, commercial and financial reasons. The common germplasm will be selected in close cooperation with the developing Barley Core Collection. Hence a much better estimate of the genetic diversity within the selected *Hordeum* germplasm will be obtained and links with classical descriptions will be secured, such that guidelines and recommendations can be made when considering approaches to specific problems. The final comparisons between all four molecular methodologies and the classical descriptions should take us considerably closer to making the BCC the world's best characterized germplasm collection, and hence towards making the BCC of utmost importance for plant breeding.

Keywords:
Hordeum, Genetic diversity, Molecular techniques, Barley core collection, RAPD, RFLP, VNTR, PCR, Sequencing

Coordinator

DR SEBERG OLE
KOBENHAVNS UNIVERSITET
BOTANICAL LABORATORY
GOTHERSGADE 140
DK - 1123 KOBENHAVN K

Participants

FERRER ESTHER ..... E
JAHOOR AHMED ..... D
VON BOTHMER ROLAND ..... S
WAUGH ROBERT ..... GB

Development of rapid novel molecular and cellular tools for the assessment and evaluation of genetic diversity in plants

Contract number: **CT930295** (Generic Research Project)
Start date: 01/08/93 Duration: 30 months
EC contribution: 1,788,500 ECU

Objectives:
To develop standardised techniques for screening genetic variation in plants. To speed up techniques using micro-methods, rapid assays and automation. To isolate universal probes for variable regions and for stress tolerance. To test the tools in screening agronomically important species and against existing classifications of diversity.

Brief description:
The objective of this proposal is the development of tools for rapid screening of genetic variation in germplasm collections and natural and cultivated populations of rare, endangered, ecologically or economically important plants. The work programme is organised into five tasks. The first task is to develop standardised techniques which give highly reproducible results independent of plant species, plant material or laboratory. The species tested include Gramineae, Solanacea, Ericacea, sugar beet and trees. "Genetic Screening Packages" will be exchanged amongst participants of extracted DNA, selected primers\probes, samples of freeze-dried or living material (eg seeds), the experimental conditions and protocols used and the photographed results, for RAPDs, RFLPs and VNTRs. The second task is to adapt the tools for large population sampling by developing micro-methods, using non-radioactive labelling techniques and exploiting automation. A third task will exploit the release of variation which occurs when plant cells\tissues are cultured *in vitro* to generate probes for stress tolerance and for "hot spots" of genetic change. The tools will be evaluated by testing their effectiveness in detecting variation in wild and cultivated populations (task 4), and against existing classifications of diversity using the well catalogued living and herbarium collections of cultivated and wild Rhododendron as a test case (task 5).

Keywords:
Plant, Genetic variation, RAPD, RFLP, VNTR, PCR, Sequencing, Stress tolerance

Coordinator

DR KARP ANGELA
DEPARTMENT OF AGRICULTURAL SCIENCES
UNIVERSITY OF BRISTOL
LONG ASHTON RESEARCH STATION
GB - BS18 9AF LONG ASHTON, BRISTOL.

Participants

BROWN PETER ..... D
BUIATTI MARCELLO I
EDWARDS KEITH ..... GB
INGRAM DAVID ..... GB
ISAAC PETER ..... GB
KALTSIKES PANTOUSES ..... GR
KEIGHTLEY RICHARD ..... GB
MARMIROLI NELSON I
SALA FRANCESCO I
VAZQUEZ ANA M. ..... E
VOLCKAERT GUIDO ..... B
VOSMAN BEN ..... NL

Development and adaptation of rapid molecular screening technics for assessing genetic diversity in forest trees

Contract number: **CT930373** (Generic Research Project)
Start date: 01/09/93 Duration: 30 months
EC contribution: 1,080,600 ECU

Objectives:
Molecular genetic screening methods will be put into practice to serve as an effective tool for defining future research needs and applications in forest biodiversity. The improved methods will broaden the scientific base for EC regulation concerning declaration and conservation of genetic resources and trade with reproductive material.

Brief description:
Forest ecosystems are valuable natural resources providing manifold economic, environmental and social functions. As threats to their genetic diversity endanger their stability and adaptability there is an urgent need in the EC countries for quick, large scale and cost efficient methods in order to study genetic diversity. This will enlarge the knowledge about genetic resources, their importance for the function of ecosystems,their utilization for breeding and their erosion. Classical biochemical methods used to analyze genetic parameters have turned out to be insufficient. Thus the proposal in question focuses on the development and adaptation of rapid molecular screening techniques for assessing genetic diversity in forest tree species. According to their ecological and economic importance the project concentrates on certain species of leading function in European forest ecosystems which require different methodical approaches. The molecular genetic screening methods will be developed concerning technics of identification (RFLP, RAPD, TGGE, sequencing, non-radioactive hybridization) and also concerning special probe providing techniques. Their adaptation to forest trees will have to surmount specific limitations in the fields of DNA-isolation, identification and characterization of DNA polymorphisms, quantification of genetic diversity and image and data processing. Intensive interactions between reference and user labs will most effectively improve techniques and generate models to apply them in practice. The improved methods will broaden the scientific basis for EC regulations concerning declaration and conservation of genetic resources and trade with reproductive material.
Screening techniques will be developed in cooperation with and in complementarity to the activities of the other participants in the generic project coordinated by A.Karp (proposals PL920295,PL920476, PL920486), a specific contribution of this project will be the consideration of needs in the forestry sector.

Keywords:
Forest trees, Genetic diversity, Molecular screening, RFLP, RAPD, TGGE, Sequencing, Polymorphism

Coordinator

DR SCHOLZ FLORIAN
INSTITUT FÜR FORSTGENETIK
BUNDESFORSCHUNGSANSTALT FÜR FORST- UND HOLZWIRTSCHAFT
SIEKER LANDSTRASSE 2
D - 2070 GROSSHANSDORF

Participants

BERGMANN FRITZ ..... D
BURG KORNEL ..... A
GLÖSSL JOSEF ..... A
KREMER ANTOINE ..... F
LEISER ROBERT-MATTHIAS ..... D
LUMARET ROSELYNE ..... F
MUELLER-STARCK GERHARD ..... CH
OLIVIERI ANGELO MARIO I
RIESNER DETLEV ..... D
RITTER ENRIQUE ..... E
VENDRAMIN GIOVANNI GIUSEPPE I

TAXONOMY, PRESERVATION AND EXPLORATION OF DIVERSITY

3.2.2 Development of reference systems for plant taxonomy with specific emphasis on the integration of novel (molecular genetic and biochemical) and classical descriptors.

3.2.3 Assessment and development of different conservation means (cryogenic storage of semen, oocytes, embryos, stem cells and cell lines; preservation of genetic information as isolated chromosomes, genomic DNA and cDNA libraries, isolated genes, etc.) as a basis for an integrative animal germplasm conservation strategy.

3.2.4 Novel approaches for the exploration of so far hidden microbial communities. This includes the isolation, cultivation and taxonomic characterisation of so far non-cultured microbial strains.

A unified datastructure for floristic databases in Europe

Contract number: **CT930328** (Concerted Action)
Start date: 01/08/93 Duration: 30 months
EC contribution: 125,000 ECU

Objectives:
The development of project-independent structures to be used in the design of floristic database systems in Europe, with special consideration given to the integration of phytochemical and cytological data. Production of a relational data model (data structure and entity/relation model) for floristic database design.

Brief description:
Floristic information is nomenclatural information linked with data gathered during the collection of herbarium specimens, such as collection site, date, abundance etc. Nomenclatural data provide access to all information available for the specific taxon. Floristic information links this with geographical, ecological and, potentially, economic data. Thus, an ably designed floristic database has a variety of applications and potential uses apart from pure Flora writing: access to genetic resources by circumscribing the area where a certain plant is likely to be found, definition of areas with high endemism to identify conservation priorities, as well as information on potential collection sites. Local uses, often recorded by collectors, are valuable indicators of a possible economic potential of a plant (e.g. pharmaceutical potential). Geographic areas which are underrepresented in collections can be defined for priority research. The inclusion of novel descriptions (such as from biochemical and cytological information) in the basic data structure will enhance collection of such data from new research. The results of the project will not only consist of a written document, but of a CASE database which can serve directly as starting point for follow-up research and system development. The use of CASE (Computer Aided Software Engineering) techniques throughout the project represents a novel approach in the development of taxonomic database systems. The concerted action project can be considered as the first phase in a project leading to program prototypes and a model database system for European floristic data.

Keywords:
Floristic databases, Plant, Botany, Case-tools

Coordinator

DR. BERENDSOHN WALTER G.
BOTANICAL GARDEN AND BOTANICAL MUSEUM
BERLIN-DAHLEM
SECTION OF EDP AND DOCUMENTATION
D - W1000 BERLIN 33

Participants

JAKUPOVIC JASMIN . . . . . D
NIMIS PIER LUIGI I
PHITOS DIMITRIOS . . . . . GR
VALDES BENITO . . . . . E

European Solanaceae Information Network (ESIN)

Contract number: **CT930397** (Concerted Action)
Start date: 01/10/93 Duration: 36 months
EC contribution: 180,000 ECU

Objectives:
To collate biotechnological, molecular, taxonomic and other information about species of Solanaceae (potato family), and to create a data base not only providing a taxonomic reference system but also aiding efficient biotechnological utilisation of the Solanaceae.

Brief description:
This Concerted Action is intended to: a) Gather biotechnological and other information about species of Solanaceae. b) Build a taxonomically based reference system for the Solanaceae. This will be a taxonomic checklist of species names tied to minimal passport data (e.g. authors, publication details, etc.) for selected taxa of Solanaceae (potato family). This will serve as the core taxonomic backbone or framework for the whole system. c) Use this taxonomic checklist to reference other, non-taxonomic information, notably molecular constituents, biotechnology potential, pharmaceutical uses, etc. Each data set will be included in a distinct but related database module. d) Accumulate and evaluate new molecular data in a systematic context. Established taxonomic opinions will be tested with these new data, to produce new paradigms of Solanaceae systematics and evolution. e) Develop collaboration between European Solanaceae scientists, primarily for amassing molecular data on a standard but diverse set of taxa, but also for exchange of information, materials, techniques and personnel. f) Plan research action for future shared cost projects in the following areas: · Further biotechnology of all Solanaceae crop species and related wild germplasm, to enhance breeding techniques and germplasm utilisation. · Complete the taxonomic checklist for almost 2,500 species in 100 genera of Solanaceae and build up the database for all most important information types. g) This ESIN Concerted Action should serve as a testable prototype model for the proposed international network (ISIN), a unified, factual database to contain plant diversity information for all the world's Solanaceae, but the immediate value of the European Solanaceae Information Network will be the availability of a taxonomically referenced database of molecular and other information.

Keywords:
Solanaceae, Crop plants, Database, Taxonomy, Systematics, Evolution, Names

Coordinator

DR LESTER RICHARD NEVILLE
UNIVERSITY OF BIRMINGHAM
SCHOOL OF BIOLOGICAL SCIENCES
GB - B15 2TT BIRMINGHAM

Participants

BRANDENBURG WILLEM A. ..... NL
CARRAVEDO MIGUEL ..... E
DAUNAY MARIE CHRISTINE ..... F
GEBHARDT CHRISTIANE ..... D
VAN DER WEERDEN GERARD M. ..... NL

Germplasm cryobanking : a practical approach using the rabbit species as a model

Contract number: **CT930184** (Concerted Action)
Start date: 01/09/93 Duration: 36 months
EC contribution: 77,200 ECU

Objectives:
Cryo-preservation of animal germ plasm is an attractive complement to the indispensable maintenance of genetic diversity through living animals.
Techniques are now available to freeze store both sperm and embryos of several domestic species. However their efficiencies and cost of utilisation under routine conditions are at the moment not defined. Research is needed to effectively employ these techniques in a multidisciplinary program aimed at the preservation of the numerous subpopulations of animals that exist within a given species.

Brief description:
The proposal is aimed towards the effective utilization of gamete and embryo cryobanking for the preservation and exploration of genetic diversity in a domestic species. Rabbit has been chosen as an experimental model because it allows access to different and numerous subpopulation categories with less constraints than with other major species of similar economic value. Three research groups already engaged in ex-situ conservation of rabbit germplasm are willing to participate in this concerted action which will examine on an experimental basis both technical, genetic, economical and legal aspects of germplasm cryobanking. Particular attention will be given to the standardisation of storage conditions, to the sampling of genetic material for each rabbit population concerned and to the availability of genetic information through a data base network.

Keywords:
Cryobanking, Rabbit, Genetic diversity, Sperm, Embryo

Coordinator

DR RENARD JEAN PAUL
LABORATOIRE DE BIOLOGIE CELLULAIRE ET MOLECULAIRE
INRA - DOMAINE DE VILVERT
F - 78352 JOUY-EN-JOSAS CEDEX

Participants

Development of genetic resource bank systems and guidelines

Contract number: **CT930521** (Concerted Action)
Start date: 01/09/93 Duration: 24 months
EC contribution: 260,000 ECU

Objectives:
To formulate goals and objectives of a genome banking programme. Evaluate effectiveness of current preservation technologies for gametes, embryos and somatic cells. Identify future research priorities in preservation technology. Implement and test a small scale model genetic resource bank.

Brief description:
The aim of the proposed programme is to develop systems and guidelines for the establishment of pan-European resource banks for the conservation of genetic material and biodiversity. Within the programme a number of roundtable meetings will be held to identify the issues involved in such a venture, formulate possible solutions and recommendations, then test them in small collaborative projects. For this a balanced group of centres and individuals has been identified who together share a common interest in the conservation of genetic resources, and who will each bring special skills, knowledge of facilities to the consortium. Consortium members therefore include laboratory-based scientists with interests in cryobiology, reproductive biotechnology and computer science, as well as centres which can supply resources, i.e. semen, oocytes and embryos, from fish and mammals. It is envisaged that a model genetic resource bank will be set up on a modest scale within this programme. The experience gained by testing the effectiveness of this model will be made available through publication for implementation on a larger scale.

Keywords:
Genome bank, Genetic diversity, Biodiversity, Bioresources, Cryopreservation, Cryobiology, Mammals, Fish, Oocytes, Embryo

Coordinator

DR HOLT WILLIAM
INSTITUTE OF ZOOLOGY
ZOOLOGICAL SOCIETY OF LONDON
REGENT'S PARK
GB - NW1 4RY LONDON

Participants

ABAIGAR TERESA ..... E
BENNETT PETER ..... GB
BIRCHER PETER ..... GB
COLENBRANDER BEN ..... NL
DE LOECKER WILLY ..... B
GRANJON LAURENT ..... F
HODGES JOHN KEITH ..... D
LATTES ALDO I
PALACIOS FERNANDO ..... E
PEREZ-SUAREZ GONZALO ..... E
RANA KRISHEN ..... GB
REID GORDON ..... GB
RUSSELL PETER ..... GB
VOLOBOUEV VITALY ..... F
WATSON PAUL ..... GB

Concerted action in Biotechnology : exploration of microbial diversity (EMD)

Contract number: **CT930119** (Concerted Action)
Start date: 01/09/93 Duration: 24 months
EC contribution: 440,000 ECU

Objectives:
- organize an extensive consortium of experts into a research network
- exchange environmental samples, microbial strains and researchers
- training in classical and molecular techniques in the various expert groups
- develop a scientific strategy to assess global microbial diversity

Brief description:
Microbial diversity is defined as the measure of the range of significantly different microorganisms in a natural assembly or habitat. The term microorganism will be used in a broad sense, i.e. not only prokaryotic bacteria will be included but also lower eukaryotes such as microalgae, funghi and protozoa. To turn natural microbial diversity into the resources useful to biotechnology several steps are necessary and several scientific hurdles have to be overcome. The major hurdle in this process is the cultivation of single microorganisms from their natural habitat. We know that for many environments (habitats) only a very small fraction, often less than 1%, of the total number of microbial cells can at present be cultured. We do not know how representative the isolated microorganisms are of the natural assembly. A solution to this classical dilemma of microbiology is the analysis of nucleic acids directly obtained from the natural microbial assembly with molecular methods, e.g. sequencing and probing, and a comparison with data obtained from isolated microorganisms of the same site and relevant data bases. These comparisons allow an assessment of natural microbial diversity and of the diversity of our culture collections. Using such methods we may finally learn how many and which kind of microorganisms we have missed during the cultivation process. The major steps for such a comparison and the conservation and assessment of genetic diversity are: i) isolation and cultivation of novel microorganisms, ii) molecular taxonomy of microorganisms, iii) conservation of new isolates, and iv) direct analysis of microbial communities.

Keywords:
Microbial diversity, Microbial identification, Molecular taxonomy, Microbial communities, Microbial ecology, Genetic resources

Coordinator

DR. HÖFLE MANFRED
GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FOR SCHUNG MBH
ABTEILUNG FÜR MIKROBIOLOGIE
MASCHERODER WEG 1
D - W3300 BRAUNSCHWEIG

Participants

AKKERMANS ANTOON D.L. ..... NL
ALVAREZ MIGUEL ..... E
BIANCHI ARMAND ..... F
BOCK EBERHARD ..... D
BRAVO ISABEL ..... E
BULL ALAN THOMAS ..... GB
COLLINS MATTHEW DAVID ..... GB
COSTAS EDUARDO ..... E
EMBLEY THOMAS MARTIN ..... GB
FINLAY BLAND JAMES ..... GB
GANNON FRANK ..... IRL
GARAY AUBAN ESPERANZA ..... E
GOTTSCHAL JAN ..... NL
GRIMONT PATRICK ..... F
HIRSCH PETER ..... D
HOFSTRA HARMEN ..... NL
KIRSTEN OLRIK ..... DK
LOUREIRO-DIAS MARIA ..... P
SAMPAYO MARIA ANTONIA ..... P
SCHLEIFER KARL-HEINZ ..... D
VAN DER MEI DIRK ..... NL
WILLIAMS STAN ..... GB

Area 4

HORIZONTAL ACTIVITIES COMMON TO ALL AREAS

4.1 Assessment of the ethical and socio-economic effects and technological risks from biotechnology

This topic is addressed with different modalities, involving the implementation of accompanying measures of the programme.

A separate list of activities can be obtained upon request.

4.2 Information infrastructure

Integrated procedures for recording and validating results of 3D structural studies of biological macromolecules

Contract number: **CT920524** (Basic Research Project)
Start date: 01/01/93 Duration: 36 months
EC contribution: 1,197,968 ECU

Objectives:
The aim is to produce a software package integrating a number of existing as well as new procedures and protocols for recording, communicating and validating results of 3D structural studies on peptides, proteins, nucleic acids and other molecules that act as ligands and co-factors.

Brief description:
This is a proposal for a coordinated European effort to cope with the problem of efficient recording and exchanging of 3D structural data and validating their quality. It complements recent US efforts to improve the biomolecular data handling capacity of the Brookhaven Databank, with which the present project will entertain close ties. There are 3 major tasks. (1)In collaboration with several organizations world-wide (Brookhaven,IUCr, ESF network-CBM, CODATA /IUPAC), to define standards for the contents and file formats for results from 3D structure studies by techniques such as x-ray diffraction, neutron scattering and nuclear magnetic resonance and to design and implement automatic user-friendly protocols to read and write datafiles based on the dictionary standards. (2) To design and test criteria for assessing the quality and precision of 3D structural models.These will rely on statistical analyses of known structures as well as on scoring agreement with experimental measures (electron density, structure factors, NMR derived distance constraints and coupling constants). By producing such criteria we hope to effectively address the important issue of quality control for the rapidly growing body of structural data being generated world-wide. (3) To integrate the tools for handling the 3D Data Dictionary and the validating protocols in a flexible software environment using an x-Window based, object oriented package for GUI (Graphic User Interface) development. This should permit wide dissemination of the results of this project and promote active participation of other members of the scientific community.

Keywords:
3D-macromolecular data, Validation, Software

Coordinator

DR WILSON KEITH
EUROPEAN MOLECULAR BIOLOGY LABORATORY
HAMBURG OUTSTATION
C/O DESY, NOTKESTRASSE 85
D - W2000 HAMBURG 52

Participants

DODSON ELEANOR JOY ..... GB
KAPTEIN ROBERT ..... NL
SANDER CHRIS ..... D
THORNTON JANET ..... GB
WODAK SHOSHANA ..... B

Carbank - A complex carbohydrate structural database

Contract number: **CT930001** (Basic Research Project)
Start date: 01/11/93 Duration: 30 months
EC contribution: 256,000 ECU

Objectives:
The objective of the proposed research project is to contribute to the further development of the Complex Carbohydrate Structural Database (CCSD) and its accompanying database management program CarbBank. The database contains published oligosaccharide structures larger than disaccharides.

Brief description:
The project is an international effort to supply scientists working in the carbohydrate field with a structural database, containing published oligosaccharide structures, mostly of biologically relevant compounds. Besides the three European partners, scientific groups in the USA and Japan are included in the collaboration. The latest release CCSD6 of the database contains 22300 oligosaccharide structures. A contract with Chemical Abstract Services provided the partners of the CarbBank project with already published oligosaccharide structures. Currently, the project is funded under the BRIDGE program (BIOT-CT90-0184). In addition to the bibliographic information the database should contain related spectroscopic data, i.e. NMR. The Dutch group is working on a NMR database containing chemical shift data of oligosaccharides. Furthermore, an interface between CarbBank and a force field program (GEGOP) is planned by the Danish partners to allow users to generate a 3D-structure of the molecule of interest. The fact that biological relevant oligosaccharides often originate from glycoproteins makes it desirable to have a link between CarbBank and protein Sequence Databases. Contacts to the protein sequence databases MIPS and PIR are existing and will be intensified. The connection to other databases will be increased in the future. Furthermore, K. Bock (Copenhagen) is a member of the CODATA Task group on Biological Macromolecules which insures coordination to other database efforts in the field. The CCSD database is distributed on a CD-ROM by the NCBI (National Center for Biotechnology Information) and on the NCBI file server. Similar distribution is scheduled in collaboration with MIPS.

Keywords:
Database, Carbohydrate structures, Spectroscopy, Oligosaccharides

Coordinator

PROF BOCK KLAUS
DEPARTMENT OF CHEMISTRY
CARLSBERG LABORATORY
GAMLE CARLSBERG VEJ 10
DK - 2500 VALBY, COPENHAGEN

Participants

PAULSEN HANS ..... D
VLIEGENTHART JOHANNES ..... NL

Continuation of the Services of the EMBL Data Library and Upgrade of the International Protein Sequence Databank

Contract number: **CT930003** (Basic Research Project)
Start date: 01/09/93 Duration: 24 months
EC contribution: 2,000,000 ECU

Objectives:
The provision of the EMBL Nucleotide Sequence, SWISS-PROT and other Databases. The development of a new model for protein sequence databases including data evaluation and analysis and the development of tools to handle sequence data and annotation using the object oriented paradigm.

Brief description:
MIPS will complete mechanisms to ensure consistency of the Protein Sequence Database and EMBL will provide and develop its information services, while collaborative work will result in mechanisms for exchange of information currently collected by the two groups. MIPS will enhance annotation by protein families and develop object-oriented database methods for data processing. The specification of a Sequence Database Definition Language will ensure syntactic and semantic consistency. The collaboration in data exchange with the SwissProt databank will improve quality, complementarity and completeness of the data collections. The EMBL group will provide the Nucleotide Sequence Database in collaboration with international partners. Also provided will be the SwissProt protein sequence database maintained in collaboration with the University of Geneva and a number of other databases of interest to molecular biologists maintained by collaborators of the Data Library. Both groups will continue to provide regular releases of the databases on optical and magnetic media, as well as network access to data between releases. Explicit collaborative goals include sharing data about citations of the biological literature, sharing sequence data, and the development of nomeclature and annotation standards.

Keywords:
Database, DNA, Biosequences, Sequence analysis, Nucleotide sequence, Software, Protein sequence data

Coordinator

MR CAMERON GRAHAM
THE EUROPEAN MOLECULAR
BIOLOGY LABORATORY
POSTFACH 10.2209
D - 6900 HEIDELBERG

Participants

MEWES HANS-WERNER . . . . . D

ABAD PIERRE
INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE
LABORATOIRE DE BIOLOGIE DES INVERTEBRES
123 BOULEVARD FRANCIS MEILLAND
F- 06606 ANTIBES CEDEX
Tel. : 93678943
Telex : INRAANT 46143 F
Fax : 93678955

ABAIGAR TERESA
ESTACION EXPERIMENTAL DE ZONAS ARIDAS - C.S.I.C.
1, GENERAL SEGURA
E - 04001 ALMERIA
Tel. : 34.51.236500
Fax : 34.51.266299
E-mail: ABAIGAR@CICA.ES

AKKERMANS ANTOON D.L.
WAGENINGEN AGRICULTURAL UNIVERSITY
DEPARTMENT OF MICROBIOLOGY
NL - 6703 CT WAGENINGEN
Tel. : 31.8370.83486
Fax : 31.8370.83829

ALARCON BALBINO
CENTRO DE BIOLOGIA MOLECULAR
UNIVERSIDAD AUTONOMA DE MADRID
FACULTAD DE CIENCIAS
E - 28049 CANTOBLANCO, MADRID
Tel. : 3413978413
Fax : 3413974799

ALBERGHINA LILIA
UNIVERSITA DEGLI STUDI DI MILANO
DIP. FISIOLOGIA E BIOCHIMICA
SEZ. BIOCHIMICA COMPARATA
CELORIA 26
I - 20133 MILANO
Tel. : 39270644801
Fax : 39270632811

ALBRACHT SIMON P.J.
E.C.SLATER INSTITUUT
FAKULTEIT DER SCHEIKUNDE
PLANTAGE MUIDERGRACHT 12
NL - 1018 TV AMSTERDAM
Tel. : 31205255130
Fax : 31205255124

ALCORTA ESTHER
DEPARTAMENTO DE BIOLOGIA FUNCIONAL
UNIVERSIDAD DE OVIEDO
C/ JULIAN CLAVERIA S/N
E - 33071 OVIEDO
Tel. : 3485103595
Fax : 3485232255

ALCOVER ANDRES
UNITE DE BIOLOGIE DES INTERACTIONS CELLULAIRES
INSTITUT PASTEUR
28 RUE DU DOCTEUR ROUX
F- 75724 PARIS 15
Tel. : 33145688574
Telex : 250609F
Fax : 33145688351

ALEXANDRAKI DESPINA
INSTITUTE OF MOLECULAR BIOLOGY & BIOTECHNOLOGY
YEAST MOLECULAR GENETICS
P.O. BOX 1527
HERAKLION
GR - 71110 CRETE
Tel. : 081.210361
Fax : 081.230469

ALFREDSSON GUDNY A.
UNIVERSITY OF ICELAND
INSTITUTE OF BIOLOGY
ARMULZ 1A
IS - 108 REYKJAVIK
Tel. : 3541688447
Fax : 3541688457

ALMOND JEFFREY W.
DEPARTMENT OF MICROBIOLOGY
UNIVERSITY OF READING
WHITEKNIGHTS
PO BOX 228
GB - RG6 2AJ READING
Tel. : 0734318901
Telex : 847813
Fax : 0734750140
E-mail: (DJE-X)@UK.AC.LEIC

ALVAREZ CARMEN M.
DPTO. BIOLOGIA CELULAR Y GENETICA
FACULTAD DE CIENCIAS
CAMPUS UNIVERSITARIO DE TEATINOS
E - 29071 MALAGA
Tel. : 34521319620
Fax : 3452132000

ALVAREZ MIGUEL
CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS
SERRANO 117
E - 28071 MADRID
Tel. : 34.1.2619800
Telex : 42182 CSICE E
Fax : 34.1.4113077

AMARGER NOELLE
INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE
LABORATOIRE DE MICROBIOLOGIE DES SOLS
1540 B.V.
F- 21034 DIJON
Tel. : 3380633092
Telex : 350507F
Fax : 3380633224

AMILS RICARDO
LABORATORIO DE MICROBIOLOGIA APLICADA
DPTO. DE BIOLOGIA MOLECULAR
FACULTAD DE CIENCIAS
E - 28049 CANTOBLANCO, MADRID
Tel. : 3413975235
Fax : 3413974799

ANAGNOU NICHOLAS
UNIVERSITY OF CRETE
INSTITUTE OF MOLECULAR BIOLOGY AND BIOTECHNOLOGY
FOUNDATION FOR RESEARCH AND TECHNOLOGY
PO BOX 1527
GR - 711 10 HERAKLION - CRETE
Tel. : 3081210323
Telex : 262896IMBBGR
Fax : 3081230469

ANNE DEJEAN
INSTITUT PASTEUR
UNITE DE RECOMBINAISON ET EXPRESSION GENETIQUE
28 RUE DU DOCTEUR ROUX
F- 75724 PARIS 15
Tel. : 33145688884
Telex : 250 609 F
Fax : 33145688943

ANSORGE WILHELM
EUROPEAN MOLECULAR BIOLOGY LABORATORY
MEYERHOFSTR. 1
D - 69117 HEIDELBERG
Tel. : 06221.387474
Fax : 06221.387306

ANTRANIKIAN GARABED
TECHNICAL UNIVERSITY HAMBURG HARBURG
TECHNICAL MICROBIOLOGY /
DENICKESTRASSE 15
D - W2100 HAMBURG 90
Tel. : 494077183117
Fax : 494077182909

ARANDA ANA
INSTITUTO DE INVESTIGACIONES BIOMEDICAS
C.S.I.C.
ARTURO DUPERIER 4
E - 28029 MADRID
Tel. : 3415854000
Telex : 42182 CSIC
Fax : 3415854015

ARCHER DAVID
AGRICULTURAL AND FOOD RESEARCH COUNCIL
INSTITUTE OF FOOD RESEARCH
NORWICH LABORATORY
NORWICH RESEARCH PARK
COLNEY
GB - NR4 7UA NORWICH
Tel. : 4460356122
Telex : 975453
Fax : 603507723

ARCHIBALD ALAN
AGRICULTURAL AND FOOD RESEARCH COUNCIL
INSTITUTE OF ANIMAL PHYSIOLOGY AND GENETICS RESEARCH
EDINBURGH RESEARCH STATION
GB - EH25 9PS ROSLIN, MIDLOTHIAN
Tel. : 44314402726
Fax : 44314400434
E-mail: ARCHIBALD@IAPE.AFRC.AC.UK

ARCTANDER PETER
INSTITUTE OF POPULATION BIOLOGY, THE DNA LABORATORY
UNIVERSITETSPARKEN 15
DK - 2100 COPENHAGEN
Tel. : 4535321310
Fax : 4535321300
E-mail: POPPA AVIRUS.FKI.DTH.DK

ARINO JOAQUIN
DEPT. BIOQUIMICA Y BIOLOGIA MOLECULAR,
UNIVERSIDAD AUTONOMA DE BARCELONA
F, VETERINARIA, VO-181
CAMPUS UNIVERSITARIADE BELLATERRA
BELLATERRA, CERDANYOLA
E - 08193 BARCELONA
Tel. : 34.3.5812182
Fax : 34.3.5812006

ARIZMENDI JESUS MARIA
UNIVERSIDAD DEL PAIS VASCO
FACULTAD DE CIENCIAS
DEP. DE BIOQUIMICA Y BIO. MOLECULAR
PO BOX 644
E - 48080 BILBAO
Tel. : 3444648800
Fax : 3444648500

ARRUGA M.VICTORIA
DEPARTMENT OF ANATOMY,EMBRIOLOGY AND GENETICS
MIGUEL SERVET 177
E - 50013 ZARAGOZA
Tel. : 3476414800
Fax : 3476591994

ARST HERBERT
DEPARTMENT OF INFECTIOUS DISEASES AND BACTERIOLOGY
ROYAL POSTGRADUATE MEDICAL SCHOOL
DUCANE ROAD 150
GB - W12 ONN LONDON
Tel. : 44817403243
Telex : 926128 HHRPMS
Fax : 44817492281

ASCHER PHILIPPE
ECOLE NATIONALE SUPERIEURE
LABORATOIRE DE NEUROBIOLOGIE
46 RUE D'ULM
F- 75230 PARIS 05
Tel. : 33144323888
Fax : 33144323887
E-mail: ASCHER AFRULM 11

AUTRAN BRIGITTE
IMMUNOLOGIE CELLULAIRE ET TISSULAIRE
HOPITAL PITIE-SALPETRIERE
47-83 BOULEVARD DE L'HOPITAL
F- 75013 PARIS
Tel. : 3345703818
Fax : 3345702045

BACH JEAN-FRANCOIS
UNITE'DE RECHERCHES DE l'INSERM U25
MALADIE AUTO-IMMUNES : GENETIQUE, MECANISMES ET TRAITEMENTS.
161 RUE DE SEVRES
F- 75743 PARIS 15
Tel. : 142738622
Fax : 143062388

BAEUERLE PATRICK
LABORATORIUM FÜR MOLEKULARE BIOLOGIE
LUDWIG-MAXIMILIANS-UNIVERSITÄT
AM KLOPFERSPITZ 18 A
D - W 8033 MARTINSRIED
Tel. : 498985783943
Fax : 498985783795

BAILEY MARK
INST. OF VIROLOGY AND ENVIRONMENTAL MICROBIOLOGY
MOLECULAR MICROBIAL ECOLOGY LAB.
MANSFIELD ROAD
GB - OX1 3SR OXFORD
Tel. : 44865512361
Telex : 83147 VIROX-G)
Fax : 4486559962

BALLET FRANCOIS
RHONE-POULENC RORER
13 QUAI JULES GUESDE
F- 94400 VITRY-SUR-SEINE
Tel. : 45737544
Fax : 45738094

BANG LUU
LABORATOIRE DE CHIMIE ORGANIQUE DES SUBSTANCES NATURELLES
5 BLAISE PASCAL
F- 67084 STRASBOURG
Tel. : 3388411672
Fax : 3388607620

BARBIER GEORGES
IFREMER
CENTRE DE BREST
DRO/EP LABO DE BIOTECHNOLOGIE
BP 70
F- 29280 PLOUZANE
Tel. : 33.98.224040
Fax : 33.98.224547

BAREA NAVARRO JOSE M.
ESTACION EXPERIMENTAL DEL ZAIDIN
DEPARTAMENTO DE MICROBIOLOGIA
PROFESOR ALBAREDA 1
E - 18008 GRANADA
Tel. : 3458121011
Fax : 3458129600

BARREAU CHRISTIAN
LABORATOIRE DE GENETIQUE
URA CNRS 542
AVENUE DES FACULTES
F- 33405 TALENCE
Tel. : 3356848902
Fax : 3356848814

BARTELS DOROTHEA
MAX-PLANCK-INSTITUT FÜR
ZUCHTUNGSFORSCHUNG
CARL-VON-LINNE-WEG 10
D - W5000 KOLN
Tel. : 492215062430
Telex : 8 881 028 MPIZ D
Fax : 492215062413

BASAGLIA MARINA
HELIGENETICS S.P.A
VIA PROVINCIALE 62-A
I - 45030 GAIBA (ROVIGO)
Tel. : 39425709709
Fax : 39425709650

BEATO MIGUEL
INSTITUT FÜR MOLEKULARBIOLOGIE UND
TUMORFORSCHUNG
PHILIPPS UNIVERSITÄT MARBURG
E. MANNKOPFF. STR. 2
D - W3550 MARBURG
Tel. : 496421285084
Fax : 496421285398

BEAUNE PHILIPPE
LABORATOIRE DE BIOCHIMIE
PHARMACOLOGIQ
ET METABOLIQUE
CHU NECKER INSERM U75
156 RUE DE VAUGIRARD
F- 75730 PARIS 15
Tel. : 33140569306
Fax : 33140615582

BECKERICH JEAN-MARIE
INRA - LABORATOIRE DE GENETIQUE
MOLECULAIRE ET CELLULAIRE
F- 78850 THIVERVAL GRIGNON
Tel. : 33130815443
Fax : 33130815457

BENNETT PETER
DEPARTMENT OF VETERINARY SCIENCE
INSTITUTE OF ZOOLOGY
ZOOLOGICAL SOCIETY OF LONDON
REGENT'S PARK
GB - NWI 4RY LONDON
Tel. : 44.71.722.3333
Fax : 44.71.586.2870
E-mail: SUAAPMB @UK.AC.UCL

BENVENUTO EUGENIO
ENTE NAZIONALE PER LE NUOVE
TECNOLOGIE
DIPARTIMENTO RICERCHE E SVILUPPO
C.P.2400
I - 00100 ROMA
Tel. : 39630486558
Telex : 613296 ENEACA I
Fax : 39630486545

BERENDSOHN WALTER G.
BOTANICAL GARDEN AND BOTANICAL
MUSEUM
BERLIN-DAHLEM
SECTION OF EDP AND DOCUMENTATION
D - W1000 BERLIN 33
Tel. : 49.30.830.06143
Fax : 49.30.830.06218

BERGMANN FRITZ
ABTEILUNG FUER FORSTGENETIK
UND FORSTPFLANZENZUECHTUNG
BUESGENWEG 2
D - W 3400 GOETTINGEN
Tel. : 49551393532
Fax : 49551399629

BERMUDEZ ISABEL
OXFORD BROOKES UNIVERSITY
SCHOOL OF BIOLOGICAL AND MOLECULAR SCIENCES
GIPSY LANE
GB - OX3 OBP OXFORD
Tel. : 44865819240
Fax : 44865819242

BERNARDINI MARIA LINA
SEZIONE SCIENZE MICROBIOLOGICHE
DIPARTIMENTO BIOLOGIA CELLULARE SVILUPPO UNIVERSITA' DI ROMA LA
VIA DEGLI APULI 1
I - 00185 ROMA
Tel. : 0649915759
Fax : 0649915594

BERTRAND DANIEL
CENTRE MEDICAL UNIVERSITAIRE DE GENEVE
DEPARTEMENT DE PHYSIOLOGIE
1 RUE MICHEL SERVET
CH - 1211 GENEVE 4
Tel. : 41227025356
Fax : 41223473334
E-mail: BERTRAND ACGEUGEII.BITNET.CH

BEVAN MICHAEL
AFRC INSTITUTE OF PLANT SCIENCE RESEARCH,
CAMBRIDGE LABORATORY
JOHN INNES CENTRE
COLNEY
GB - NR4 7UJ NORWICH
Tel. : 4460352571
Telex : 975122 JIINOR G
Fax : 44603502270

BIANCHI ARMAND
INSTITUT DE PHARMACOLOGIE MOLECULAIRE ET CELLULAIRE - CNRS
660 ROUTE DES LUCIOLES, SOPHIA ANTIPOLIS
F- 06560 VALBONNE
Tel. : 3393957775
Fax : 3393957708

BINZ HANS
CENTER D'IMMUNOLOGIE ET DE BIOTECHNOLOGIE PIERRE FABRE
97 LE PUY ST MARTIN
F- 74164 SAINT JULIEN EN GENEVOIS
Tel. : 50350212
Telex : 319 024 F
Fax : 50492389

BIRCHER PETER
MARWELL PRESERVATION TRUST
MARWELL ZOOLOGICAL PARK
COLDEN COMMON
GB - NR WINCHESTER, HANTS SO21 1JH
Tel. : 44.962.777407
Fax : 44.962.777511

BIRCHMEIER CARMEN
MAX-DELBRÜCK-CENTER
ROBERT ROSSEL STRASSE 10
D - 13122 BERLIN 30
Tel. : 493094063800
Fax : 49309494161

BIRCHMEIER WALTER
INSTITUTE FOR CELL BIOLOGY
UNIVERSITY OE ESSEN MEDICAL SCHOOL
VIRCHOWSTRASSE 173
D - W4300 ESSEN
Tel. : 492017233382
Fax : 492017235904

BISSELING TON
WAGENINGEN AGRICULTURAL UNIVERSITY
MOLECULAR BIOLOGY DEPT.
DREIJENLAAN 3
NL - 6703 HA WAGENINGEN
Tel. : 31837082036
Fax : 31837083584

BJORKLUND ANDERS
UNIVERSITET LUND
S - 22101 LUND
Tel. : +46 107000

BLASI FRANCESCO
DIPARTIMENTO DI GENETICA E BIOLOGIA
UNIVERSITA DI MILANO
VIA CELORIA 26
I - 20136 MILANO
Tel. : 392266051
Fax : 3922664551

BLIXT STIG G.
NORDIC GENE BANK
S - 23053 ALNARP

BLOKSMA MARIE
RESEARCH INSTITUTE OF TOXICOLOGY
P.0. BOX 80176
NL - 3508 TD UTRECHT
Tel. : 3130535400
Fax : 3130535077
E-mail: ARITOXN@ CC.RUU.NL

BOCK EBERHARD
UNIVERSITÄT HAMBURG
INSTITUT FÜR ALLGEMEINE BOTANIK UND
BO TANISCHER GARTEN
OHNHORSTSTRASSE 18
D - W2000 HAMBURG 52
Tel. : +49-40-82282360
Fax : +49-40-82282229

BOCK ELISABETH
PROTEIN LABORATORY
SCHOOL OF MEDICINE
PANUM INSTITUTE
BLEGDAMSVEJ 3
DK - 2200 COPENHAGEN
Tel. : 4531357900
Fax : 4535360116

BOCK KLAUS
DEPARTMENT OF CHEMISTRY
CARLSBERG LABORATORY
GAMLE CARLSBERG VEJ 10
DK - 2500 VALBY, COPENHAGEN
Tel. : 4533275220
Fax : 4533274708
E-mail: CARLKEM ANEUVM1

BOCKAERT JOEL
CENTRE CNRS-INSERM DE PHARMACOLOGIE-
ENDOCRINOLOGIE
RUE DE LA CARDONILLE
F- 34094 MONTPELLIER 5
Tel. : 67142930
Fax : 67542432

BOLOTIN-FUKUHARA MONIQUE
INSTITUT DE GENETIQUE ET MICROBIOLOGIE
UNIVERSITE PARIS SUD (UPS)
GENETIQUE MOLECULAIRE
400 BAT.
F- 91405 ORSAY CEDEX
Tel. : 33.1.69416201
Fax : 33.1.69417296

BONCINELLI EDOARDO
ISTITUTO SAN RAFFAELE
MPLECULAR BIOLOGY OF DEVELOPMENT
VIA OLGETTINA 60
I - 20132 MILANO
Tel. : 39.2.26434721
Fax : 39.2.26434767

BONFANTE PAOLA
UNIVERSITA DEGLI STUDI DI TORINO
DIPARTIMENTO DI BIOLOGIA VEGETALE
VIALE MATTIOLI 25
I - 10125 TORINO
Tel. : 39116502927
Fax : 3911655839

BORREBAECK CARL
DEPARTMENT OF IMMUNOTECHNOLOGY
THE WALLENBERG LABORATORY
P.O.BOX 7031
S - 220 07 LUND
Tel. : 4646109613
Fax : 4646104200

BOS JOHANNES L.
UNIVERSITY OF UTRECHT
LABORATORY FOR PHYSIOLOGICAL
CHEMISTRY
VONDELLAAN 24 A
NL - 3521 GG UTRECHT
Tel. : 3130880521
Fax : 3130888443

BOS PIET
TECHNISCHE UNIVERSITEIT DELFT
FACULTEIT DER SCHEIKUNDIGE
TECHNOLOGIE
EN DER MATERIAALKUNDE
JULIANALAAN 67
NL - 2628 BC DELFT
Tel. : 3115782359
Fax : 3115782355

BOSTOCK CHRISTOFFER
AFRC INSTITUTE FOR ANIMAL HEALTH
COMPTON,LABORATORY
GB - RGI6 ONN COMPTON, NR. NEWBURY
Tel. : 0635578411
Fax : 0635578844

BOUCHERIE HELIAN
URA CNRS 542, LABORATOIRE DE GENETIQUE
UNIVERSITE DE BORDEAUX
AVENUE DES FACULTES
F- 33405 TALENCE
Tel. : 3356848794
Fax : 3356848814

BOURSOT PIERRE
LABORATOIRE GENOME ET POPULATIONS
CNRS URA 1493

UNIVERSITE DE MONTPELLIER II
PLACE EUGENE BATAILLON
F- 34095 MONTPELLIER 5
Tel. : 3367143266
Fax : 3367144554
E-mail: GENUSTL@FRM0PLL

BOUTRY MARC
UNIVERSITE CATHOLIQUE DE LOUVAIN
UNITE DE BIOCHIMIE PHYSIOLOGIQUE
PLACE CROIX DU SUD 2-BTE 20
B- 1348 LOUVAIN-LA-NEUVE
Tel. : 3210473621
Fax : 3210473872

BOYD ALAN
UNIVERSITY OF EDINBURGH
DEPARTMENT OF BIOCHEMISTRY
HUGH ROBSON BUILDING
GEORGE SQUARE
GB - EDINBURGH EH8 9XD
Tel. : 44.31.6503724
Fax : 44.31.6503711

BRADBURY ANDREW
SOCIETA ITALIANA PER LA RICERCA
SCIENTIFICA S.R.L.
VIA G. PAISIELLO 47/C
I - 00198 ROMA
Tel. : 3968442224
Fax : 3968442579

BRAMLEY PETER
ROYAL HOLLOWAY AND BEDFORDNEW
COLLEGE
DEPARTMENT OF BIOCHEMISTRY
EHAM HILL
GB - TW2O OEX EGHAM
Tel. : 44784443555
Telex : 935504
Fax : 44784434326
E-mail:
JANET%"UHBCOI6@UK.AC.RHBNC.VAX"

BRANDENBURG WILLEM A.
CENTRE FOR PLANT BREEDING RESEARCH
DROEVENDALSESTEEG 1
NL - 6700 AA WAGENINGEN
Tel. : 31.8370.19112
Fax : 31.8370.16513

BRASCAMP PIM
AGRICULTURAL UNIVERSITY
DEPARTMENT OF ANIMAL BREEDING
MARIJKEWEG 40
NL - 6709 PG WAGENINGEN
Tel. : 31837083191
Fax : 31837083962
E-mail: PIM.BRASCAMP@DALG.V.F.WAU.NL

BRAVO ISABEL
INSTITUTO ESPAÑOL DE OCEANOGRAFIA
CENTRO OCEANOGRAFICO DE VIGO
CABO ESTAY-CANIDO 1552
E - 36280 VIGO

BREM GOTTFRIED
LEHRSTUHL FUR MOLEKULARE TIERZUCHR
INSTITU FUR TIERZUCHT UND TIERHYGIEN
LUDWIG-MAXIMILIANS-UNIVERSITAER
VETERINAERSTR. 13
D - W8000 MUNCHEN 22
Tel. : 498921802170
Fax : 4989344925

BRIGHT S.W.J.
JEALOTT'S HILL RESEARCH STATION
ICI SEEDS
WAREFIELD
GB - RGI2 6EY BRACKNELL
Tel. : 44344424701/4821
Telex : 847556 ICIPPJG
Fax : 44344434996

BRON SIERD
DEPARTMENT OF GENETICS
CENTER FOR BIOLOGICAL SCIENCES OF THE
UNIVERSITY
GRONINGEN
KERKLAAN 30
NL - 9751 NN HAREN
Tel. : 3150632105
Fax : 3150632348
E-mail: S.BRON@BIOL.RUG.NL

BROWN NIGEL
MRC EXPERIMENTAL EMBRYOLOGY AND
TERATOLOGY UNIT
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL
CRANMER TERRACE
GB - SW17ORE LONDON
Tel. : 44816729944
Fax : 44817679109
E-mail: NBROWN@UX.SGHMS.LON AC.UK

BROWN PETER
UNIVERSITÄT HAMBURG
INSTITUT FÜR ALLGEMEINE BOTANIK

BROWN PETER
UNIVERSITÄT HAMBURG
INSTITUT FÜR ALLGEMEINE BOTANIK
OHNHORSTSTR 18
D - W2000 HAMBURG
Tel. : 494082282366
Fax : 494082282229

BROWNLEE GEORGE
SIR WILLIAM DUNN SCHOOL OF PATHOLOGY
SOUTH PARKS ROAD
GB - 0X1 3RE OXFORD
Tel. : 44865275559
Fax : 44865275556
E-mail: BROWNLEE@VAX.PATH.OX.AC.UK

BRUNORI MAURIZIO
DIPARTIMENTO DI SCIENZE BIOCHIMICHE
"A. ROSSI FANELLI"
PIAZZALE A. MORO 5
I - 00185 ROMA
Tel. : 3964450291
Fax : 3964453933

BRUSCHI CARLO
INTERNATIONAL CENTRE FOR GENETIC
ENGINEERING
AND BIOTECHNOLOGY
DEPARTMENT OF MICROBIOLOGY
PADRICIANO 99
AREA SCIENCE PARK
I - 34012 TRIESTE
Tel. : 39.40.375.7304
Fax : 39.40.375.7304

BUIATTI MARCELLO
CONSORZIO INTERUNIVERSITARIO
NAZIONALE
PER LA BIOLOGIA MOLECOLARE DELLE
PIANTE SEDE DI FIRENZE,DIPARTIMENTO DI
VIA ROMANA 17
I - 50125 FIRENZE
Tel. : 3955229453
Fax : 3955222565

BULL ALAN THOMAS
UNIVERSITY OF KENT ACANTERBURY
BIOLOGICAL LABORATORY
GB - CT2 7NJ CANTERBURY
Tel. : 44.227.764000EXT3443
Fax : 44.227.463487

BURG KORNEL
PLANT MOLECULAR BIOLOGY LABORATORY
HAUPTABT.AGRARFORSCHUNG &
BIOTECHNOL.
ÖSTERREICHISCHES FORSCHUNGSZENTRUM
A- A 2444 SEIBERSDORF
Tel. : 432254803600
Telex : 014-353 FZS
Fax : 432254802118

BURKE JULIAN
SUSSEX CENTRE FOR NEUROSCIENCE
SCHOOL OF BIOLOGICAL SCIENCES
UNIVERSITY OF SUSSEX
GB - BNI 9QG BRIGHTON
Tel. : 44273678308
Fax : 44273678433

BURNY ARSENE
MOLECULAR BIOLOGY AND PHYSIOLOGY
UNIT
MICROBIOLOGY UNIT
PASSAGE DES DEPORTES 2
B- 5030 GEMBLOUX
Tel. : 3281622152
Telex : 59482 FSAGX
Fax : 3281613888

BURTONBOY GUY
LABORATOIRE DE VIROLOGIE
FONDAMENTALE
MBLG/54.9O
AVENUE HIPPOCRATE 54
B- 1200 BRUSSELS
Tel. : 3227645492
Fax : 3227645481

BUURMAN WILLEM A.
DEPT. OF SURGERY, RIJKSUNIVERSITEIT
LIMBURG BIOMEDICAL CENTER
P.0. BOX 616
NL - 6200 MD MAASTRICHT
Tel. : 3143881499
Fax : 3143670964

CABOCHE MICHEL
LABORATOIRE DE BIOLOGIE CELLULAIRE
INSTITUT NATIONAL DE RECHERCHE
AGRONOMIQUE
ROUTE DE SAINT-CYR
F- 78026 VERSAILLES CEDEX
Tel. : 33130833017
Fax : 33130833111
E-mail: CABOCHE@VERSAILLES.INRA.FR

CACCIA SILVIO
ISTITUTO DI RICERCHE FARMACOLOGICHE "MARIO NEGRI"
LABORATORY OF DRUG METABOLISM
VIA ERITREA 62
I - 20157 MILANO
Tel. : 392390141
Telex : 331268 NEGRI I
Fax : 3923546277

CADENAS EDUARDO
DIVISION DE BIOQUIMICA
PO BOX 99
E - 03080 ALICANTE
Tel. : 3465903523
Fax : 3465903464

CAMARA BILAL
LAB. PHYSIOL. CELLULAIRE VEGETALE
BIOCHIMIE ET REGULATIONS CELLULAIRES
UNIVERSITE:BORDEAUX I, URA:SGB'CNRS.:
AVENUE DES FACULTES
F- 33405 TALENCE
Tel. : 3356848783
Fax : 33568487011

CAMBILLAU CHRISTIAN
FACULTE DE MEDECINE NORD MARSEILLE
LABORATOIRE DE CRISTALLOGRAPHIE ET CRISTALLISATION DES MACROMOLECULES BIOLOGIQUES - URA 1296
BVD PIERRE DRAMARD
F- 13326 MARSEILLE 15
Tel. : 3391698909
Fax : 3391698913

CAMERON GRAHAM
THE EUROPEAN MOLECULAR BIOLOGY LABORATORY
POSTFACH 10.2209
D - 6900 HEIDELBERG
Tel. : 496221387257
Fax : 496221387519
E-mail: CAMERON@EMBL-HEIDELBERG.DE

CAPRON ANDRE
INSTITUT PASTEUR DE LILLE
CENTRE D'IMMUNOLOGIE ET DE BIOLOGIE PARASITAIRE
1 RUE DU PROFESSEUR CALMETTE
F- 59019 LILLE
Tel. : 3320877962
Fax : 3320877888

CARRAVEDO MIGUEL
DIPUTACION GENERAL DE ARAGON
DEPT. AGRIC., GANAD. Y MONTES
BANCO DE GERMOPLASMA DE HORTICOLAS
MONTANANA 177
APPARTADO 727
E - 50080 ZARAGOZA
Tel. : 34.765.76311
Fax : 34.765.75501

CARTRON JEAN-PIERRE
INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE UNITE 76
6 INTS RUE ALEXANDRE CABANEL
F- 75739 PARIS 15
Tel. : 33143067000
Fax : 33147347431

CASAL JOSE IGNACIO
INMUNOLOGIA Y GENETICA APLICADA,S.A
HERMANOS GARCIA NOBLEJAS 41
E - 28037 MADRID
Tel. : 3412680501
Fax : 3414087598

CATELLO POLITO
DIPARTIMENTO DI GENETICA
BIOLOGIA GENERALE E MOLECOLARE
VIA MEZZOCANNONE 8
I - 80134 NAPOLI
Tel. : 39815526208
Fax : 39815527950

CATTIVELLI LUIGI
ISTITUTO SPERIMENTALE PER LA CEREALI-COLTURA
VIA S.PROTASO 302
I - 29017 FIORENZUOLA D'ARDA (PC)
Tel. : 39523983758
Fax : 39523983750

CERDA OLMEDO ENRIQUE
UNIVERSIDAD DE SEVILLA
DEPARTAMENTO DE GENETICA
APARTADO 1095
E - 41080 SEVILLA
Tel. : 3454624107
Fax : 3454624107

CEREGHINI SILVIA
INSTITUT PASTEUR
UNITE DE GENETIQUE DE LA DIFFERENCIATION
25 RUE DU DR. ROUX
F- 75724 PARIS 15
Tel. : 33145688502

CESBRON MARIE-FRANCE
CENTRE D'IMMUNOLOGIE ET DE BIOLOGIE PARASITAIRE,UNITE MIXTE INSERM U167 CNRS624, INSTITUT PASTEUR
1 RUE DU PROFESSEUR A. CALMETTE
F- 59019 LILLE
Tel. : 3320877783
Fax : 3320877888

CHAMBERT REGIS
INSTITUT JACQUES MONOD
LABORATOIRE GENETIQUE ET MEMBRANES
2 PLACE JUSSIEU
F- 75251 PARIS 05
Tel. : 33144276946
Fax : 33146332305

CHANGEUX JEAN-PIERRE
INSTITUT PASTEUR
25 RUE DU DR ROUX
F- 75724 PARIS 15
Tel. : 33 1 45 68 88 05
Fax : 33 1 45 68 88 36

CHARDIN PIERRE
CNRS
INSTITUT DE PHARMACOLOGIE MOLECULAIRE
ET CELLULAIRE - GROUPE BIOPHYSIQUE
660 ROUTE DES LUCIOLES
F- 06560 VALBONNE
Tel. : 3393957772
Fax : 3393957710

CHARNAY PATRICK
LABORATOIRE DE BIOLOGIE MOLECULAIRE
ECOLE NORMALE SUPERIEURE
INSERM U368
46 RUE D'ULM
F- 75230 PARIS CEDEX 05
Tel. : 33144323607
Fax : 33144323988

CHARPIGNY GILLES
INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE
STATION DE PHYSIOLOGIE ANIMALE
F- 78352 JOUY-EN-JOSAS CEDEX
Tel. : 33134652345
Fax : 33134652364
E-mail: GCH@JOUY.INRA.FR.

CHATER KEITH
JOHN INNES FOUNDATION
JOHN INNES INSTITUTE
COLNEY LANE
GB - NR4 7UH NORWICH
Tel. : 4460352571
Telex : 975L22JIINOR G
Fax : 4460356844

CHAUVEAU JACQUES
IMMUNOTECH
130 AVENUE DE LATTRE DE TASSIGNY
F- 13009 MARSEILLE
Tel. : 3391758200
Telex : IMMTECH 430 246 F
Fax : 3391412794

CHISWELL DAVID
CAMBRIDGE ANTIBODY TECHNOLOGY LIMITED
THE SCIENCE PARK
GB - SG8 6EJ MELBOURN, CAMBRIDGESHIRE
Tel. : 0763263233
Fax : 0763263413

CHOURROUT DANIEL
LABORATORY OF FISH GENETICS
INSTITUT NATIONAL DE LA RECHERCHE AGRO
F- 78352 JOUY EN JOSAS
Tel. : 33134652391
Fax : 33134652390

CHRISTOPHE DANIEL
UNIVERSITE LIBRE BRUXELLES
INSTITUT DE RECHERCHE INTERDISCIPLINAIRE
EN BIOLOGIE HUMAINE ET NUCLEAIRE
ROUTE DE LENNIK 808
B- 1070 BRUXELLES
Tel. : 3225554171
Fax : 3225554655

CLARKSON DAVID
DEPT. OF AGRICULTURAL SCIENCES
UNIVERSITY OF BRISTOL
AFRC INSTITUTE OF ARABLE CROP RESEARCH
GB - BSI8 9AF LONG ASHTON, BRISTOL
Tel. : 44275392181
Fax : 44275394007

COEN ENRICO
JOHN INNES INSTITUTE
COLNEY LANE
GB - NR4 7UH NORWICH
Tel. : 4460352571
Telex : 975122 JIINOR G
Fax : 4460356844

COHEN JAMES
UNITED MEDICAL AND DENTAL SCHOOLS OF G UYS AND ST.THOMAS HOSPITALS
ST.THOMAS'S CAMPUS
GB - SE1 7EH LONDON BRIDGE
Tel. : +44/1/928 9292
Fax : +44/1/928 1468

COHEN JONATHAN
DEPARTMENT OF INFECTIOUS DISEASES AND BACTERIOLOGY
ROYAL POSTGRADUATE MEDICAL SCHOOL
DUCANE ROAD 150
GB - W12 ONN LONDON
Tel. : 44817403243
Telex : 926128 HHRPMS
Fax : 44817492281

COLEMAN JOHN
DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS
P.O.BOX 147
GB - L693BX LIVERPOOL
Tel. : 44517945551
Fax : 44517945540

COLENBRANDER BEN
UNIVERSITY OF UTRECHT
FACULTY OF VETERINARY MEDICINE
DEPT.OF HERD HEALTH REPRODUCTION
NL - 3584 CL UTRECHT
Tel. : 31.30.531248
Fax : 31.30.521887

COLLINS MATTHEW DAVID
AGRICULTURAL AND FOOD RESEARCH COUNCIL
INSTITUTE OF FOOD RESEARCH
READING LABORATORY
WHITEKNIGHTS ROAD
EARLEY GATE
GB - RG6 2EF READING
Tel. : +44-734-357000
Telex : 265871 ARS001
Fax : +44-734-267917

COMOGLIO PAOLO
UNIVERSITY OF TORINO
DEP. OF BIOMEDICAL SCIENCES AND ONCOLOGY
CORSO MASSIMO D'AZEGLIO 52
I - 10126 TORINO
Tel. : 39116707739
Fax : 39116509105

CONTRERAS ROLAND
LABORATORY OF MOLECULAR BIOLOGY
K.L.LEDEGANCKSTRAA35
B- 9000 GENT
Tel. : 3291645136
Fax : 3291645348
E-mail: CONTRERA@MOLEBIOL.RUG.AC.BE

CORNIC GABRIEL
LABORATOIRE D'ECOLOGIE VEGETALE
UNIVERSITE PARIS SUD
BAT. 362
F- 91405 ORSAY
Tel. : 33169416359
Telex : FACORS 602 166 F
Fax : 33169417238

CORTESE RICCARDO
ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA
VIA PONTINA KM. 30,600
I - 00040 POMEZIA (ROME)
Tel. : 396910931
Fax : 39691093634

COSTA TOMMASO
INSTITUTO SUPERIORE DI SANITA
LABORATORIO DI FARMACOLOGIA
VIALE REGINA ELENA 299
I - 00161 ROMA
Tel. : 3964990
Fax : 3964440053

COSTANTINO PAOLO
CONSORZIO BIOLOGIA MOLECOLARE DELLE
DIP.GENETICA E BIOLOGIA MOLECOLARE
UNIVERSITA DI ROMA 'LA SAPIENZA''
P.LE ALDO MORO 5
I - 00185 ROMA
Tel. : 3964455344
Fax : 3964440812

COSTAS EDUARDO
UNIVERSIDAD POLITECNICA DE MADRID
RAMIRO DE MAEZTU S/N
E - 28040 MADRID
Tel. : +34-1-3366047
Fax : +34-1-3366173

COTECCHIA SUSANNA
UNIVERSITE DE LAUSANNE
INSTITUT DE PHARMACOLOGIE
ET TOXICOLOGIE
RUE DU BUGNON 27
CH - 1005 LAUSANNE
Tel. : 41213132700
Fax : 41213132775

COUPLAND G.
INSTITUTE OF PLANT SCIENCE RESEARCH,
CAMBRIDGE LABORATORY
COLNEY LANE
GB - NR4 7UH NORWICH
Tel. : 4460352571
Telex : 975122
Fax : 4460356844

COVE DAVID
DEPARTMENT OF GENETICS
UNIVERSITY OF LEEDS
WOODHOUSE LANE
GB - LS2 9JT LEEDS
Tel. : 0044532333081
Fax : 0044532441175

COVE JONATHAN
UNIVERSITY OF LEEDS
DEPARTMENT OF MICROBIOLOGY
GB - LS29JT LEEDS
Tel. : 0044532335630
Telex : 0044532556473
Fax : 0044532335638

CROUZET MARC
UNIVERSITE DE BORDEAUX II
LABORATOIRE DE BIOLOGIE MOLECULAIRE
ET DE SEQUENCAGE
146 RUE LEO SAIENAT
F- 33076 BORDEAUX
Tel. : 56.960714
Fax : 56.518561

DALLMAN MARGARET
THE UNIVERSITY OF OXFORD
NUFFIELD DEPARTMENT OF SURGERY
JOHN RADCLIFFE HOSPITAL
HEADINGTON
GB - OX3 9DU OXFORD
Tel. : 44865221316
Fax : 4486568876

DALSGAARD KRISTIAN
IMMUNOLOGY SECTION
DEPARTMENT OF CHEMISTRY
STATE VETERINARY INSTITUTE
LINDHOLM
DK - 4771 KALVEHAVE
Tel. : 4555814523
Telex : 40 306 VIRUS DK
Fax : 4555811766

DANCHIN ANTOINE
INSTITUT PASTEUR
UNITE REGULATION EXPRESSION GENETIQUE
UNITE DE BIOCHIMIE MICROBIENNE
25 RUE DU DOCTEUR ROUX
F- 75724 PARIS 15
Tel. : 33145688847
Fax : 33145688938
E-mail: REG APASTEUR.BITNET

DANGL JEFF
MAX-DELBRÜCK-LABORATORIUM IN DER
MAX-PLANCK-GESELLSCHAFT
CARL-VON-LINNE-WEG 10
D - 5000 KOLN 30
Tel. : 492215062430
Telex : 8 881 028 MPIZ D
Fax : 492215062613

DANSETTE PATRICK
LABORATOIRE DE CHIMIE ET BIOCHIMIE
PHARMACOLOGIQUES ET TOXICOLOGIQUES
UNIVERSITE RENE DESCARTES
45 RUE DES SAINTS-PERES
F- 75270 PARIS 06
Tel. : 33142862191
Fax : 33142868387

DARLISON MARK
UNIVERSITÄT HAMBURG
INSTITUT FUR ZELLBIOCHEMIE UND
KLINISCHE NEUROBIOLOGIE
MARTINISTRASSE 52
D - 20 HAMBURG
Tel. : 494047174551
Fax : 494047174541

DAUNAY MARIE CHRISTINE
INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE
CENTRE DE RECHERCHE D'AVIGNON
DOMAINE SAINT PAUL
F- 84143 MONTFAVET CEDEX
Tel. : +33-90-316000
Fax : +33-90-316298

DAVIES HOWARD
SCOTTISH CROP RESEARCH INSTITUTE
GB - DD2 5DA INVERGOWRIE, DUNDEE
Tel. : 44382562731
Telex : 9312133325SC G
Fax : 44382562426

DE GEUS PIETER
UNILEVER RESEARCH LABORATORIUM VLAARDINGEN
OLIVIER VAN NOORTLAAN 120
NL - 3133 AVLAARDINGEN
Tel. : 31104605072
Telex : 23261
Fax : 31104605873

DE GROOT HERBERT
MEDIZINISCHE EINRICHTUNGEN DER UNIVERSITAET - GH - ESSEN
HUFELANDSTRASSE 55
D - O4300 ESSEN
Tel. : 492017234100
Fax : 492017235943

DE LEENHEER LEEN
RAFFINERIE TIRLEMONTOISE
AANDORENSTRAA1
B- 3300 TIENEN
Tel. : 321680351
Telex : RAFSEC B 22251
Fax : 3216820317

DE LOECKER WILLY
FACULTEIT DER GENEESKUNDE
AFDELING BIOCHIMIE
CAMPUS GASTHUISSERG
HERESTRAAT
B- 3000 LEUVEN
Tel. : 32.16.21.5700
Fax : 32.16.21.5995

DE LORENZO VICTOR
CENTRO DE INVESTIGACIONES BIOLOGICAS
C/. VELAZQUEZ 144
E - 28006 MADRID
Tel. : 3415854243
Fax : 3415627518

DE SIMONE VINCENZO
UNIVERSITY OF NAPLES
CEINGE-DIP. DI BIOCHIMICA E BIOTECNOLOGIE MEDICHE,
II SCHOOL OF MEDICINE
VIA PANSINI 5
I - 80131 NAPOLI
Tel. : 39817463073
Fax : 39817463074

DE VIENNE DOMINIQUE
STATION DE GENETIQUE VEGETALE
UPS INRA/CNRS
FERME DU MOULON
F- 91190 GIF SUR YVETTE
Tel. : 33169417608
Fax : 33169412790

DE VOS WILLEM M.
NEDERLANDS INSTITUUT VOOR ZUIVELONDERZOEK
P.O. BOX
NL - 6710 BA EDE
Tel. : 31838059558
Fax : 31838050400

DE VOS WILLEM M.
DEPARTMENT OF MICROBIOLOGY
HESSELINK VAN SUCHTELENWEG 4
NL - 6703 CT WAGENINGEN
Tel. : 31837083110
Fax : 31837083829
E-mail: WMDEVOSCRCL.WAU.NL

DE VRIES SACCO
DEPT. MOLECULAR BIOLOGY
AGRICULTURAL UNIVERSITY WAGENINGEN
DREIJENLAAN 3
NL - 6703 HA WAGENINGEN
Tel. : 31837082036
Fax : 31837083584
E-mail: SACCO.DEVRIES@MAC.MB.WAU.NL

DE WAELE PETER
INNOGENETICS NV
INDUSTRIEPARK 7
B- 9052 ZWIJNAARDE
Tel. : 3292410711
Fax : 3292410799

DEAN CAROLINE
PLANT SCIENCE RESEARCH LIMITED
COLNEY LANE
GB - NR4 7UJ NORWICH
Tel. : 4460352571
Telex : 975122 JIINOR G
Fax : 44603505725

DEBLAERE ROLF
UNIVERSITEIT GENT
LABORATORIUM VOOR GENETICA
K.L.LEDEGANCKSTRAAT 35
B- 9000 GENT
Tel. : 3291645197
Telex : 11995 GENGEN B
Fax : 3291645349
E-mail: ROBLA(A)GENGENP.RUG.AC.BE

DECKWER WOLF - DIETER
GBF-GESELLSCHAFT FUER
BIOTECHNOLOGISCHE
FORSCHUNG MBH; BEREICH
BIOVERFAHRENSTECHNIK
MASCHERODER WEG 1
D - W3300 BRAUNSCHWEIG
Tel. : 495316181100
Fax : 495316181111

DEFAGO GENEVIEVE
INSTITUTE OF PLANT SCIENCES
GROUP PHYTOMEDICINE/PATHOLOGY
UNIVERSITATSTRASSE 2
CH - 8092 ZURICH
Tel. : 4112563869
Fax : 4112529613

DEGRIP WILLEM
KATHOLIEKE UNIVERSITEIT NIJMEGEN
FACULTY OF MEDICAL SCIENCES
DEPARTMENT OF BIOCHEMISTRY
PO BOX 9101
NL - 6500 HB NIJMEGEN
Tel. : 3180614263
Fax : 3180540525
E-mail: U401003 AT HNYKUNII

DEKKER BERNARDUS
MOGEN INTERNATIONAL NV
EINSTEINWEG 97
NL - 2333 CB LEIDEN
Tel. : 3171258282
Fax : 3171221471

DEL PRETE GIANFRANCO
ISTITUTO DI CLINICA MEDICA
UNIVERSITA' STUDI DI FIRENZE
LABORATORY OF PATHOPHYSIOLOGY
VIALE MORGAGNI 85
I - 50134 FIRENZE
Tel. : 39554379533
Fax : 3955412867

DEL VAL MARGARITA
CENTRO NACIONAL DE MICROBIOLOGIA,
VIROLOGIA E INMUNOLOGIA SANITARIAS
CTRA. POZUELO, KM 2
E - 28220 MAJADAHONDA (MADRID)
Tel. : 3416380011
Fax : 3416391859

DELIUS HAJO
DEUTSCHES KREBSFORSCHUNGSZENTRUM
(GERMAN CANCER RESEARCH CENTRE)
ANGEWANDTE TUMORVIROLOGIE
IM NEUENHEIMER FELD 506
D - 69120 HEIDELBERG
Tel. : 49.6221.424661
Fax : 49.6221.424667

DELSENY MICHEL
LABORATOIRE DE PHYSIOLOGIE ET BIOLOGIE
MOLECULAIRE VEGETALES - CNRS UNIT URA
565
UNIVERSITE DE PERPIGNAN
52 AVENUE DE VILLENEUVE
F- 66860 PERPIGNAN CEDEX
Tel. : 3368668848
Fax : 3368668499
E-mail: GOT @ FRPERP 51BITNET

DENARIE JEAN
LABORATOIRE DE BIOLOGIE MOLECULAIRE
DES RELATIONS
PLANTES-MICROORGANISMES
CNRS-INRA
CHEMIN DE BORDE ROUGE ,27
F- 31326 CASTANET TOLOSAN CEDEX
Tel. : 3361285050
Fax : 3361285061

DENCKER LENNART
UPPSALA UNIVERSITET
PO BOX 594
S - 751 24 UPPSALA
Tel. : 4618174250
Fax : 4618174253

DEPICKER ANNA
UNIVERSITEIT GENT
LABORATORIUM VOOR GENETICA
K.L.LEDEGANCKSTRAAT 35
B- 9000 GENT
Tel. : 3292645174
Telex : 11995 GENGEN B
Fax : 3292645349
E-mail: ANPIC(A)GENGENP.RUG.AC.BE

DESCOTES JACQUES
LABORATORY OF FUNDAMENTAL AND
CLINICAL IMMUNOTOXICOLOGY
INSERM U80 ALEXIS CARREL FACULTY OF
RUE GUILLAUME PARADIN
F- 69008 LYON
Tel. : 78778664
Fax : 78778612

DESSY FRANZ
UNITE DES SCIENCES VETERINAIRES
PLACE CROIX DU SUD 3
B- 1348 LOUVAIN-LA-NEUVE
Tel. : 3210473701
Fax : 3210474745
E-mail: DESSY AT VETE.UCL.AC.BE

DEUTSCHER JOSEF
INSTITUT DE BIOLOGIE ET CHIMIE DES
PROTEINES
CNRS - UPR 412
7 PASSAGE DU VERCORS
F- 69007 LYON
Tel. : 3372722677
Fax : 3372722601

DEVAUX PHILIPPE
INSTITUT DE BIOLOGIE PHYSICO-CHIMIQUE
LABORATOIRE DE BIOPHYSIQUE
CELLULAIRE
13 RUE PIERRE ET MARIE CURIE
F- 75005 PARIS
Tel. : 33143252609
Fax : 33143298088

DEVINE KEVIN
TRINITY COLLEGE,
DEPARTMENT OF GENETICS,
LINCOLN PLACE GATE,
IRL - DUBLIN 2
Tel. : 35317021872
Fax : 35316798558
E-mail: KDEVINE@VAXI.TCD.IE

DI LAURO ROBERTO
STAZIONE ZOOLOGICA ANTON DOHRN
VILLA COMUNALE
I - 80121 NAPOLI
Tel. : 39815833278
Fax : 39817641355

DINGERMANN THEODOR
INSTITUT FUER PHARMAZEUTISCHE
BIOLOGIE DER JOHANN WOLFGANG
GOETHE UNIVERSITAET
GEORG-VOIGT-STRASSE 16
D - W 6000 FRANKFURT/MAIN
Tel. : 49697982384
Fax : 49697988185

DIRINGER HEINO
ROBERT-KOCH INSTITUT ABL
NORDUFER 20
D - W1000 BERLIN 65
Tel. : 0304503286
Fax : 0304503328

DODSON ELEANOR JOY
UNIVERSITY OF YORK
DEPARTMENT OF CHEMISTRY
GB - YO1 5DD YORK
Tel. : 44904432565
Fax : 44904410519

DOLF GAUDENZ
INSTITUTE OF ANIMAL BREEDING
UNIVERSITY OF BERNE
DIVISION OF MOLECULAR GENETICS
BREMGARTENSTRASSE 109A
CH - 3012 BERNE
Tel. : 4131274320
Fax : 4131247021

DOMDEY HORST
C/O GENZENTRUM MÜNCHEN
PROGENTEC
AM KLOPFERSPITZ 18A
D - 82152 MARTINSRIED
Tel. : 49.89.8578.3941
Fax : 49.89.8578.3795

DOTSIKA ELENI
LABORATORY OF PARASITE IMMUNOLOGY
HELLENIC PASTEUR INSTITUTE
VAS. SOFIAS AVE. 127
GR - 115 21 ATHENS
Tel. : 3016447959
Telex : 301221188 IPH GR
Fax : 3016423498

DOUGAN GORDON
DEPARTMENT OF BIOCHEMISTRY
IMPERIAL COLLEGE OF SCIENCE
EXHIBITION ROAD
GB - SW7 2AZ LONDON
Tel. : 44-71-2258286
Fax : 44-71-712258288

DRAINAS CONSTANTIN
SECTOR OF ORGANIC CHEMISTRY AND BIOCHEMISTRY
DEPARTMENT OF CHEMISTRY
PANEPISTEMIOPOLIS, DOUROUTI
GR - 45110 IOANNINA
Tel. : 3065192210
Telex : 322160 PNRS GR
Fax : 3065174112

DRIESSEN ARNOLD
DEPARTMENT OF MICROBIOLOGY
UNIVERSITY OF GRONINGEN
KERKLAAN 30
NL - 9751 NN HAREN
Tel. : 3150632164
Fax : 3150632154

DRUET PHILIPPE
PATHOLOGIE RENALE ET VASCULAIRE
INSERM U 28
96 RUE DIDOT
HOPITAL BROUSSAIS
F- 75674 PARIS 14
Tel. : 33143959583
Fax : 33145459059

DU JARDIN PATRICK
GENETICS AND PLANT IMPROVEMENT
UNIT. FACULTY OF AGRICULTURAL SCIENCES
AV. MARECHAL JUIN, BAT. 48
B- 5030 GEMBLOUX
Tel. : 3281622456
Telex : 59482 FSAGX
Fax : 3281614544

DUBOIS PHILIPPE
UNITE DE PARASITOLOGIE EXPERIMENTALE
INSTITUT PASTEUR
25 RUE DU DOCTEUR ROUX
F- 75724 PARIS 15
Tel. : 45688627
Telex : PASTEUR 250609 F
Fax : 42732240

DUERING KLAUS
UNIVERSITAET HAMBURG
INSTITUT FUER ALLGEMEINE BOTANIK, AMP II
OHNHORSTSTR. 18
D - W2000 HAMBURG 52
Tel. : 494082282360
Fax : 494082282229

DUJON BERNARD
INSTITUT PASTEUR
UNITE DE GENETIQUE MOLECULAIRE DES LEVURES
25 RUE DU DR. ROUX
F- 75724 PARIS 15
Tel. : 33.1.4568.8482
Fax : 33.1.4061.3060

DUPONT YVES
COMMISSARIAT A L'ENERGIE ATOMIQUE
CENG GRENOBLE
LABORATOIRE DE BIOPHYSIQUE
AVENUE DES MARTYRS
BP 85X
F- 38041 GRENOBLE
Tel. : 3376884677
Fax : 3376885487

DUPUIS ALAIN
COMMISSARIAT A L'ENERGIE ATOMIQUE
CENG GRENOBLE
DEPARTEMENT DE BIOLOGIE
LABORATOIRE DE BIOCHIMIE
BP85 X AV. DES MARTYRS
F- 38041 GRENOBLE CEDEX
Tel. : 3376883119
Fax : 3376885185

DURSTON ANTONY
NEDERLANDS INSTITUT VOOR ONTWIKKELINGSBIOLOGIE
HUBRECHT LABORATORIUM
UPPSALALAAN 8
NL - 3584CT UTRECHT
Tel. : 3130510211
Fax : 3130516464

DUÑACH MIREIA
UNIVERSIDAD AUTONOMA DE BARCELONA
UNIDAD DE BIOFISICA - DEP. DE BIOQUIMICA I BIOLOGIA MOLECULAR
E - 08193 BELLATERRA
Tel. : 3435812105
Fax : 3435812004
E-mail: IKBFO@ EBCCUABI

DYBDAHL THOMSEN PREBEN
DEPARTMENT OF ANIMAL SCIENCE
DIVISION OF ANIMAL GENETICS
THE ROYAL VETERINARY AND AGRI-
BULOWSVEJ 13
DK - 1870 FREDERIKSBERG C
Tel. : 4535283073
Fax : 4535283042

DÜSTERHÖFT ANDREAS
DIAGEN INSTITUT FÜR
MOLEKULARBIOLOGISCHE
DIAGNOSTIK GMBH
MAX-VOLMER-STR. 4
D - 40724 HILDEN
Tel. : 49.2103.892.0
Fax : 49.2103.892.222

EDWARDS KEITH
IMPERIAL CHEMICAL INDUSTRIES PLC
ICI SEEDS
JEALOTT'S HILL RESEARCH STATION
GB - RG12 6EY BRACKNELL BERKSHIRE
Tel. : 44344414821
Telex : 847556 ICIPPJG
Fax : 44344414996

EHRLICH STANISLAV DUSKO
INSTITUT NATIONAL DE LA RECHERCHE
AGRONOMIQUE
GENETIQUE MICROBIENNE
DOMAINE DE VILVERT
F- 78352 JOUY EN JOSAS CEDEX
Tel. : 33134652511
Fax : 33134652521
E-mail: EHRLICH BIOTEC.JOUY.INRA.FR

EICHMANN KLAUS
MAX-PLANCK-INSTITUT FÜR
IMMUNBIOLOGIE
STUEBEWEG 51
D - W7800 FREIBURG
Tel. : 497615108541
Fax : 497615108545

EIKELENBOOM PIET
DEPT PSYCHIATRY
MEDICAL FACULTY
VAN DER BOECHORSTSTRAAT 7
NL - 1081 HV AMSTERDAM
Tel. : 31205736666
Fax : 31205736687

ELLIS THOMAS HENRY NOEL
AGRICULTURAL AND FOOD RESEARCH
COUNCIL
INSTITUTE OF PLANT SCIENCE RESEARCH
JOHN INNES INSTITUTE - DEPARTMENT OF G
ENETICS
COLNEY LANE 1
GB - NR4 7UH NORWICH
Tel. : 44 603 52571
Fax : 44 603 56844

EMBLEY THOMAS MARTIN
BRITISH NATURAL HISTORY MUSEUM
CROMWELL ROAD
GB - SW7 5BD LONDON
Tel. : 44.71.938.8760
Fax : 44.71.938.8754

ENGEL PAUL
KREBS INSTITUTE - DEPARTMENT OF
MOLECULAR BIOLOGY AND
BIOTECHNOLOGY,
UNIVERSITY OF SHEFFIELD.
P. 0. BOX 594
GB - S1O 2UH SHEFFIELD
Tel. : 44742824242
Fax : 44742728697

ENJUANES LUIS
CENTRO NACIONAL DE BIOTECNOLOGIA
CONSEJO SUPERIOR DE INVESTIGACIONES
CIENTIFICAS
CAMPUS UNIVERSIDAD AUTONOMA
CANTO BLANCO
E - 28049 MADRID
Tel. : 34-1-5854555
Fax : 34-1-5854506
E-mail: LENJUANES@EMDCNB5I.BITNET

ENTIAN KARL-DIETER
UNIVERSITY OF FRANKFURT/MAIN
INSTITUTE FOR MICROBIOLOGY
MARIE-CURIE-STR. 9
D - 60053 FRANKFURT/MAIN
Tel. : 49.69.5800.9525
Fax : 49.69.5800.9527

EPPLEN JORG THOMAS
RUHR-UNIVERSIT T BOCHUM
MEDIZINISCHE FAKULT-T
INSTTTUT FÜR GENETIK
UNIVERSITATSSTRASSE 150 102148
D - 4630 BOCHUM
Tel. : 492347003839
Fax : 492347094196

ERHARDT GEORG
JUSTUS-LIEBIG UNIVERSITY
DEPARTMENT OF ANIMAL BREEDING AND GENETICS
LUDWIGSTRASSE 21
D - 6300 GIESSEN
Tel. : 496417026129
Fax : 496417026128

ERRINGTON JEFFERY
THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY
SOUTH PARKS ROAD
GB - 0XL 3RE OXFORD
Tel. : 44865275561
Fax : 44865275556
E-mail: ERRING@VAX.OX.AC.UK

EVANS DAVID
DEPARTMENT OF MICROBIOLOGY
UNIVERSITY OF READING
WHITEKNIGHTS
PO BOX 228
GB - RG6 2AJ READING
Tel. : 0734318893
Telex : 847813
Fax : 0734750140
E-mail: (DJE-X)@LEIC.AC.UK

FAMULOK MICHAEL
INSTITUT FÜR BIOCHEMIE DER LMU MÜNCHEN
IM MAX-PLANCK INSTITUT FÜR BIOCHEMIE
GEBÄUDE F3
AM KLOPFERSPITZ 18A
D - 8033 MARTINSRIED
Tel. : 49.89.85782453(/4)
Fax : 49.89.85782470
E-mail: FAMULOK@GENMIC.BIOCHEM.MPG.DE

FELDMANN HORST
ISTITUT FÜR PHYSIOLOGISCHE CHEMIE
UNIVERSITÄT MÜNCHEN (LMU)
SCHILLERSTRASSE 44
D - 80336 MÜNCHEN
Tel. : 49.89.5996.451
Fax : 49.89.5996.316
E-mail:
FELDMANN@DEC1.BIO.MED.UNI-MUENCHEN.DE

FELLE HUBERT
BOTANISCHES INSTITUT I
JUSTUS-LIEBIG-UNIVERSITAT
SENCKENBERGSTRASSE 17-21
D - W6300 GIESSEN
Tel. : 496417028454
Fax : 496417028464

FERNANDEZ EMILIO
DEPARTAMENTO DE BIOQUIMICA
FACULTAD DE CIENCIAS
UNIVERSIDAD DE CORDOBA
AVDA. SAN ALBERTO MAGNO S/N
E - 14071 CORDOBA
Tel. : 3457218592
Fax : 3457218606
E-mail: BFIEMFER CC.UCO.ES

FERRER ESTHER
UNIVERSIDAD DE ALCALA DE HENARES
APARTADO 20
E - 28801 ALCALA DE HENARES

FERRETTI LUCA
ISTITUTO PER LA DIFESA ELA VALORIZZAZIONE DEL GERMOPLASMA ANIMALE
VIA CELORIA 10
I - 20133 MILANO
Tel. : 39226680350
Fax : 39382528496

FEY/MOSE LARSEN S./P.
UNIVERSITY OF AARHUS
INSTITUTE OF MEDICAL MICROBIOLOGY
BARTHOLIN BUILDING
DK - 8000 AARHUS
Tel. : 45.86.139711 EXT3877
Fax : 45.86.191277

FIERS/HAEGEMAN W./G.
UNIVERSITEIT GENT
LABORATORIUM VOOR MOLEKULAIRE BIOLOGIE
K.L. LEDEGANCKSTRAAT 35
B- 9000 GENT
Tel. : 3292645166
Fax : 3292645348

FILIPOWICZ WITOLD
FRIEDRICH MIESCHER-INSTITUT
P.0. BOX 2543
CH - 4002 BASEL
Tel. : 41616974128
Fax : 41616973976
E-mail: FILIPOWICZ@FMI.CH

FINDLAY JOHN B.C.
UNIVERSITY OF LEEDS
DEP. OF BIOCHEMISTRY AND
MOLECULAR BIOLOGY
GB - LS2 9JT LEEDS
Tel. : 44532333140
Fax : 44532333167

FINLAY BLAND JAMES
NATURAL ENVIRONMENT RESEARCH
COUNCIL
INSTITUTE OF FRESHWATER ECOLOGY
WINDERMERE LABORATORY
THE FERRY HOUSE, FAR SAWREY
GB - LA22 OLP AMBLESIDE
Tel. : +44-9662-2468
Fax : +44-9662-6914

FISCHER BERND
DEPARTMENT OF ANATOMY AND
REPRODUCTIVE BIOLOGY
MEDICAL FACULTY
KLINIKUM PAUWELSSTRASSE
D - W5100 AACHEN
Tel. : 02418089106
Fax : 0241804413

FLATMARK TORGEIR
UNIVERSITY OF BERGEN
DEPARTMENT OF BIOCHEMISTRY
AARSTANDVEIEN 19
N - 5007 BERGEN

FLAVELL RICHARD
JOHN INNES INSTITUTE
COLNEY LANE
GB - NR4 7UH NORWICH
Tel. : 4460352571
Telex : 975122 JIINOR G)
Fax : 4460356844

FLECHON JACQUES - E.
INSTITUT NATIONAL DE LA RECHERCHE
AGRONOMIQUE
LABORATOIRE DE BIOLOGIE CELLULAIRE ET
BIOTECHNOLOGIES INRA
F- 78352 JOUY-EN-JOSAS CEDEX
Tel. : 33134652537
Fax : 33134652273

FLUGGE ULF-INGO
JULIUS-VON-SACHS-INSTITUT FOR
BIOWISSENSCHAFTEN
MITTLERER DALLENBERGWEG 64
D - W8700 WUERZBURG
Tel. : 4993173085
Fax : 4993171446

FORDE BRIAN
ROTHAMSTED EXPERIMENTAL STATION
AFRC-INST. OF ARABLE CROPS RESEARCH
GB - AL5 2JQ HARPENDEN, HERTS
Tel. : 44582763133
Telex : 825726REXPSTG
Fax : 44582760981

FORTERRE PATRICK
INSTITUT DE GENETIQUE ET MICROBIOLOGIE
BATIMENT 409
UNIVERSITE PARIS SUD II
F- 91405 ORSAY 05
Tel. : 33169417489
Fax : 33169417808

FOUEILLASSAR XAVIER
ASSOCIATION GENERALE DES PRODUCTEURS
DE MAIS
CENTRE TECHNIQUE
F- 64121 MONTARDON
Tel. : 3359724700
Fax : 3359724720

FOURY FRANCOISE
UNIVERSITE CATHOLIQUE DE LOUVAIN
UNITE DE BIOCHIMIE PHYSIOLOGIQUE
PLACE CROIX DU SUD 2-20
B- 1348 LOUVAIN-LA-NEUVE
Tel. : 3210473614
Fax : 3210473872
E-mail: AGROFYSA BUCLLN11.BITNET

FOYER CHRISTINE
LABORATOIRE DU METABOLISME ET DE
LA NUTRITION DES PLANTES,INRA
ROUTE DE ST-CYR
F- 78026 VERSAILLES CEDEX
Tel. : 33130833098
Fax : 33130833096

FRASER HUGH
AFRC & MRC NEUROPATHOGENESIS UNIT
INSTITUTE FOR ANIMAL HEALTH
WEST MAINS ROAD
GB - EH9 3JF EDINBURGH
Tel. : 0316675204
Fax : 0316683872

FREUDL ROLAND
INSTITUT FUER BIOTECHNOLOGIE I
POSTFACH 1913
D - W5170 JUELICH
Tel. : 492461613472
Telex : 833556KFAD
Fax : 492461612710

FRIES RUEDI
SWISS FEDERAL INSTITUTE OF
TECHNOLOGY
INSTITUTE OF ANIMAL SCIENCES
ETH ZENTRUM
TAND2
CH - CH8092 ZUERICH
Tel. : 4112563258
Fax : 4112622161
E-mail: R.FRIES@RZVAX.ETH.CH

FROMMER WOLF B.
INSTITUT FÜR GENBIOLOGISCHE
FORSCHUNG
BERLIN GMBH
IHNESTRASSE 63
D - W1000 BERLIN
Tel. : 493083000790
Fax : 493083000736

FRY JOHN C.
UNIVERSITY OF WALES
COLLEGE OF CARDIFF
SCHOOL OF PURE AND APPLIED BIOLOGY
PO BOX 915
GB - CF1 3TL CARDIFF
Tel. : 44222874000
Fax : 44222874305

FRY STEPHEN C.
INSTITUTE OF CELL & MOLECULAR BIOLOGY
DIVISION OF BIOLOGICAL SCIENCES
DANIEL RUTHERFORD BUILDING
KING'S BUILDINGS
GB - EH9 3JH EDINBURGH
Tel. : 44316505320
Telex : 727442
Fax : 44316505392

GADAL PIERRE
PHYSIOLOGIE VEGETALE MOLECULAIRE
INSTITUT DE RECHERCHES SUR LES PLANTES
BAT 430 1ER ETAGE
F- 91405 ORSAY CEDEX
Tel. : 33169417977
Fax : 33169853715

GAILLARDIN CLAUDE
INSTITUT NATIONAL AGRONOMIQUE
PARIS-GRIGNON
GENETIQUE MOLECULAIRE ET CELLULAIRE
F- 78850 THIVERVAL-GRIGNON
Tel. : 33.1.3081.5452
Fax : 33.1.3081.5457

GALIBERT FRANCIS
HEMATOLOGIE EXPERIMENTALE
1 HOPITAL SAINT LOUIS
AVENUE CLAUDE VELLEFAUX
F- 75010 PARIS
Tel. : 33142021605
Fax : 33142060250

GALINSKI ERWIN A.
INSTITUT FUER MIKROBIOLOGIE
& BIOTECHNOLOGIE
MECKENHEIMER ALLEE 168
D - W5300 BONN
Tel. : 49228733799
Fax : 49228737576

GALIZZI ALESSANDRO
UNIVERSITA' DEGLI STUDI DI PAVIA
DIP. DI GENETICA E MICROBIOLOGIA
ABBIATEGRASSO 207
I - 27100 PAVIA
Tel. : 39382391548
Fax : 39382528496

GALLI CESARE
LABORATORIO DI TECNOLOGIE DELLA
RIPRODUZIONE C.I.Z. S.R.L.
VIA PORCELLASCO 7/F
I - 26100 CREMONA
Tel. : 39372437242
Fax : 39372437242

GALLOIS P.
LABORATOIRE DE PHYSIOLOGIE VEGETALE
UNIVERSITE DE PERPIGNAN
AVENUE DE VILLENEUVE
F- 66025 PERPIGNAN
Tel. : 3368668848
Fax : 3368668499

GAMBARDELLA RAFFAELE
DIPARTIMENTO DI BIOLOGIA VEGETALE
UNIVERSITA DEGLI STUDI DI NAPOLI
VIA FORIA 223
I - 80139 NAPOLI
Tel. : 3981440681
Fax : 3981450165

GANCEDO CARLOS
INSTITUTO DE INVESTIGACION ES BIOMEDICAS,
CONSEJO SUPERIOR I.C.
C/ARTURO DUPERIER 4
E - 28029 MADRID
Tel. : 34.1.585.4620
Fax : 34.1.585.4587

GANDOLFI FULVIO
ISTITUTO DI ANATOMIA DEGLI ANIMALI DOMESTICI CON ISTOLOGIA ED EMBRIOLOGIA
VIA G. CELORIA 10
I - 20133 MILANO
Tel. : 39270630920
Fax : 3922367788

GARAY AUBAN ESPERANZA
UNIVERSIDAD DE VALENCIA
FACULTAD C.C.BIOLóGICAS
DEPARTAMENTO MICROBIOLOGIA
DR. MOLINER 50
E - 46100 BURJASOT
Tel. : 34.6.3864612
Fax : 34.6.3864372

GARCIA LOBO JUAN MARIA
DEPARTAMENTO DE BIOLOGIA MOLECULAR
FACULTAD DE MEDICINA
CARDENAL HERRERA ORIA S/N
E - 39011 SANTANDER
Tel. : 3442201948
Fax : 3442201903

GARRETT ROGER
INSTITUT FOR BIOLOGISK KEMI B
COPENHAGEN UNIVERSITY
SOELVGADE 83
DK - 1307 K COPENHAGEN K
Tel. : 4533156338
Fax : 4533145058

GATZ CHRISTIANE
FREIE UNIVERSITAET BERLIN
FACHBEREICH BIOLOGIE
INSTITUT FUR ANGEWANDTEGENETIK
ALBRECHTTHAER WEG - 6
D - W-1000 BERLIN 33
Tel. : 49308385801
Fax : 49308384345

GEBHARDT CHRISTIANE
MAX-PLANCK-GESELLSCHAFT
INSTITUT FÜR ZÜCHTUNGSFORSCHUNG
ERWIN BAUER INSTITUT
CARL-VON-LINNE-WEG 10
D - W5000 KOLN 30
Tel. : 49.221.5062-280
Telex : 8 881 028 MPIZ D
Fax : 49.221.5062213

GEIDERMANN HERMANN
DEPARTMENT OF ANIMAL BREEDING
GARBENSTRASSE 17
D - 7000 STUTTGART
Tel. : 0497114592470
Fax : 0497114593290

GENNARINI GIANFRANCO
ISTITUTO DI FISIOLOGIA UMANA
POLICLINICO-PIAZZALE
GIULIO CESARE 1
I - 70124 BARI
Tel. : 39.80.278421
Fax : 39.80.278416

GEORGOUDIS ANDREAS
ARISTOTLE UNIVERSITY OF THESSALONIKI
FACULTY OF AGRICULTURE
DEPARTMENT OF ANIMAL PRODUCTION
GR - 54006 THESSALONIKI
Tel. : 3031992544
Fax : 3031473275

GERAERTS WIJNAND
DEPARTMENT OF ZOOLOGY
D BOELELAAN 1087
NL - 1081 HV AMSTERDAM
Tel. : 31205483516
Fax : 31206429202

GERATS ANTON
UNIVERSITEIT GENT
LABORATORIUM VOOR GENETICA
K.L.LEDEGANCKSTRAAT 35
B- 9000 GENT
Tel. : 3291645182
Telex : 11995 GENGEN B
Fax : 3291645349
E-mail: ANGER(A)GENGENP.RUG.AC.BE

GERWERT KLAUS
MAX-PLANK-INSTITUT
FUER ERNAEHRUNGSPHYSIOLOGIE
RHEINLANDDAMM 201
D - W4600 DORTMUND
Tel. : 4923112061
Fax : 492311206389

GHERARDI ERMANNO
ICRF CELL INTERACTIONS LABORATORY
CAMBRIDGE UNIVERSITY MEDICAL SCHOOL
MRC CENTER HILLS ROAD
GB - CAMBRIDGE CB2 2QH
Tel. : 44223215308
Fax : 44223215318
E-mail: E. GHERARDI @UK.AC.ICRF

GHERSI-EGEA JEAN-FRANCOIS
CENTRE DU MEDICAMENT, CNRS URA 597
30 RUE LIONNOIS
F- 54000 NANCY
Tel. : 3383322923
Fax : 3383321322

GHEZZI PIETRO
ISTITUTO DI RICERCHE FARMACOLOGICHE
''MARIO NEGRI''
VIA ERITREA 62
I - 20157 MILANO
Tel. : 392390141
Telex : 331268 NEGRI I
Fax : 3923546277
E-mail: GHEZZI@IMIMNVX.IRFMN.MNEGRI.IT

GIAVINI ERMINIO
UNIVERSITY OF MILAN
DEPARTMENT OF BIOLOGY
SECTION OF ZOOLOGY AND COMPARATIVE
VIA CELORIA 26
I - 20133 MILAN
Tel. : 39226604436
Fax : 3922361070

GICQUEL BRIGITTE
INSTITUT PASTEUR
MYCOBACTERIAL GENETICS UNIT
25 RUE DU DR. ROUX
F- 75724 PARIS CEDEX 15
Tel. : 1.45.688828
Fax : 1.45.688843
E-mail: BGICQUEL@PASTEUR.FR

GIL JOSE A.
UNIVERSIDAD DE LEON
DEPARTAMENTO DE ECOLOGIA, GENETICA Y
MICROBIOLOGIA
CAMPUS DE VEGAZANA, S/N
E - 24071 LEON
Tel. : 3487291503
Telex : 89892 EDUCI E
Fax : 3487291479
E-mail: JAGIL AT ELEULE II

GILLARD JEAN
UNIVERSITE CATHOLIQUE DE LOUVAIN
LABORATOIRE DE PHARMACIE
GALENIQUE ET INDUSTRIELLE
AVENUE E. MOUNIER 73.20
FARG
B- 1200 BRUXELLES
Tel. : 3227647320
Fax : 3227647363

GILLES RIVEAU
LABORATOIRE D'IMMUNOPHARMACOLOGIE
INSTITUT PASTEUR DE LILLE
1 RUE DU PROFESSEUR CALMETTE
F- 59019 LILLE
Tel. : 3320877890
Fax : 3320877888

GIRAUDAT J.
INSTITUT DES SCIENCES VEGETALES
CENTRE NATIONAL DE LA RECHERCHE
SCIENTIFIQUE
AVENUE DE LA TERRASSE
F- 91198 GIF-SUR-YVETTE CEDEX
Tel. : 33169823696
Telex : 601137F
Fax : 33169823695

GIUDICE GIOVANNI
DIPARTIMENTO DI BIOLOGIA CELLULARE
E DELLO SVILUPPO ''A.MONROY''
VIA ARCHIRAFI 22
I - 90123 PALERMO
Tel. : 39916161892
Fax : 39916165665

GIULIANO GIOVANNI
ENTE PER LE NUOVE TECNOLOGIE,
AREA ENERGIA ED
INNOVAZIONE-BIOTECHNOLOGIE
P.0. BOX 2400
I - 00100 AD ROMA
Tel. : 39630483192
Fax : 39630484808

GLANDSDORFF/PIERARD N./A.
RESEARCH INSTITUTE OF CERIA-COOVI
AVENUE EMILE GRYZON 1
B- 1070 BRUSSELS
Tel. : 3225267270
Fax : 3225267042

GLEICHMANN ERNST
MEDIZINISCHES INSTITUT FUER
UDMELTHYGIENE AN DER HEINRICH-HEINE-
UNIVERSITAET DUESSELDORF
AUF'M HENNEKAMP 50
D - W4000 DUESSELDORF
Tel. : 492113389393
Telex : 8582164 MIUD
Fax : 492113190910

GLÖSSL JOSEF
ZENTRUM FÜR ANGEWANDTE GENETIK
UNIVERSIT–T FÜR BODENKULTUR
GREGOR-MENDEL-STRASSE 33
A- A 1180 WIEN
Tel. : 431342500
Fax : 4313105175
E-mail: GLOESSL@MAIL.BOKU.AC.AT

GOETHERT MANFRED
INSTITUT FUER PHARMAKOLOGIE UND
TOXIKO
TOXIKOLOGIE DER RHEINISCHEN FRIEDRICH-
WILHELMS UNIVERSITAET BONN
REUTERSTRASSE 2B
D - W5300 BONN
Tel. : 49228735410
Fax : 49228735404

GOETZ FRIEDRICH
BIOLOGISCHES INSTITUT
MIKROBIELLE GENETIK
AUF DER MORGENSTELLE 28
D - W7400 TUEBINGEN
Tel. : 497071294636
Fax : 497071295937

GOLDMAN MICHEL
DEPARTMENT OF IMMUNOLOGY, HOPITAL
ERASME, AND LABORATOIRE PLURIDISCIPLI-
NAIRE DE RECHERCHE EXPERIMENTALE
ROUTE DE LENNIK 808
B- 1070 BRUSSELS
Tel. : 3225553862
Fax : 3225554499

GONI FELIX M.
UNIVERSIDAD DEL PAIS VASCO
FACULTAD DE CIENCIAS
DEPARTAMENTO DE BIOQUIMICA Y
BIOLOGIA MOLECULAR
CAMPUS DE LEIOA
E - 48080 BILBAO

GORDON JOHN
DEPARTMENT OF IMMUNOLOGY
UNIVERSITY OF BIRMINGHAM
UNIVERSITY OF BIRMINGHAM
DEPARTMENT OF IMMUNOLOGY,
EDGBASTON
GB - B15 2TT BIRMINGHAM
Tel. : 0214144065
Fax : 0214143599

GORIDIS CHRISTO
MOLECULAR BIOLOGY OF CELL ADHESION
LUMINY CASE 906
F- 13288 MARSEILLE CEDEX 09
Tel. : 33.91.269404
Fax : 33.91.269430

GOTTSCHAL JAN
RIJKSUNIVERSITEIT GRONINGEN
BROERSTRAAT 5
NL - 9700 AB GRONINGEN

GOUD BRUNO
INSTITUT PASTEUR
UNITE DE GENETIQUE SOMATIQUE
25 RUE DU DR. ROUX
F- 75724 PARIS 15
Tel. : 33145688568
Fax : 33145688639

GOULMY ELS
DEPARTMENT OF IMMUNOHEMATOLOGY
AND BLOOD BANK
UNIVERSITY HOSPITAL LEIDEN
P.O. BOX 9600
NL - 2300 RC LEIDEN
Tel. : 3171263826
Telex : 39266
Fax : 3171216751

GRAEBER PETER
UNIVERSITAET STUTTGART
BIOLOGISCHES INSTITUT
PFAFFENWALDRING 57
D - 7000 STUTTGART 80
Tel. : 497116855040
Fax : 497116855096

GRANDI GUIDO
ENIRICERCHE S.P.A.
VIA MARITANO 26
I - 20097 SAN DONATO MILANESE
Tel. : 3925201
Fax : 3925204422

GRANJON LAURENT
MUSEUM NATIONAL D'HISTOIRE NATURELLE
LABORATOIRE MAMMIFERES ET OISEAUX
55 RUE BUFFON
F- 75005 PARIS
Tel. : 33.1.40.79.3069
Fax : 33.1.40.79.3063

GRANT WILLIAM
DEPARTMENT OF MICROBIOLOGY
MEDICAL SCIENCES BUILDING
UNIVERSITY OF LEICESTER
PO BOX 138
GB - LE1 9HN LEICESTER
Tel. : 44533522950
Fax : 4453523013

GRAU GEORGES
DPT DE PATHOLOGIE - C.M.U.
CENTRE MEDICAL UNIVERSITAIRE
1, RUE MICHEL SERVET
CH - 1211 GENEVE 4
Tel. : 41227025733
Fax : 41223473334

GRAY JOHN
DEPARTMENT OF PLANT SCIENCES
UNIVERSITY OF CAMBRIDGE
DOWNING STREET
GB - CB2 3EA CAMBRIDGE
Tel. : 44223333925
Telex : 81240 CAMSPL G
Fax : 44223333953
E-mail: JCG2@UK.AC.CAM.PHX

GREENWOOD COLIN
SCHOOL OF BIOLOGICAL SCIENCES
UNIVERSITY OF EAST ANGLIA
GB - NR4 7TJ NORWICH
Tel. : 44603592196
Telex : 975197
Fax : 44603259492

GRIFFITHS ROGER
DIVISION OF BIOCHEMISTRY
IRVINE BUILDING
NORTH STREET
GB - KY169AL ST ANDREWS
Tel. : 4433476161
Fax : 4433478721

GRIMONT PATRICK
INSTITUT PASTEUR
UNITE DES ENTEROBACTERIES
28 RUE DU DOCTEUR ROUX
F- 75724 PARIS 15
Tel. : 33.1.45.688340
Fax : 33.1.45.688837

GRIVELL LESLIE ALAN
UNIVERSITY OF AMSTERDAM (UVA)
SECTION FOR MOLECULAR BIOLOGY
KRUISLAAN 318
NL - 1098SM AMSTERDAM
Tel. : 31.20.525.7924
Fax : 31.20.668.5086

GROBET LUC
SERVICE DE GENETIQUE
FACULTE DE MEDECINE VETERINAIRE
UNIVERSITE DE LIEGE
BOULEVARD DE COLONSTER 20
BATIMENR B43
B- 4000 LIEGE
Tel. : 3241564151
Fax : 3241564122

GROGAN VINCENT
IRISH SUGAR PLC
SUGAR DIVISION
IRL - 41 CARLOW
Tel. : 35350331487
Fax : 35350343087

GRONEMEYER HEINRICH
U184/INSERM - LGME/CNRS
INSTITUT DE CHIMIE BIOLOGIQUE UPR A6520
11 RUE HUMANN
F- 67085 STRASBOURG
Tel. : 3388371255
Fax : 3388370148

GROSVELD FRANK
FACULTY MEDICINE
DEPT. CELL BIOLOGY - GENETICS
ERASMUS UNIV. ROTTERDAM
PO BOX 1738
NL - 3000 DR ROTTERDAM
Tel. : 31.10.408.7593
Fax : 31.10.436.0225

GUARDIOLA BEATRICE
INSTITUT DE RECHERCHES
INTERNATIONALES SERVIER
6 PLACE DES PLEIADES
F- 92415 COURBEVOIE
Tel. : 33146416809
Fax : 33146416011

GUERCHE PHILIPPE
LABORATOIRE DE BIOLOGIE CELLULAIRE
INSTITUT NATIONAL DE LA RECHERCHE
AGRONOMIQUE
ROUTE DE SAINT-CYR
F- 78026 VERSAILLES CEDEX
Tel. : 33130833073
Fax : 33130833099

GUERN JEAN
INSTITUT DES SCIENCES VEGETALES
AVENUE DE LA TERRASSE
F- 91198 GIF SUR YVETTE CEDEX
Tel. : 33169823868
Telex : 601137F
Fax : 33169823768

HAEHNEL WOLFGANG
ALBERT LUDWIGS UNIVERSITAT FREIBURG
INSTITUT FÜR BIOLOGIE II
LEHRSTUHL FÜR BIOCHEMIE DER PFLANZEN
SCHANZLESTR. 1
D - 79104 FREIBURG
Tel. : 497612032690
Fax : 497612032701
E-mail: HAEHNEL .AT.
IBM.RUF.UNI-FREIBURG.DE

HAFFRAY PIERRICK
SYNDICAT DES SELECTIONNEURS AVICOLES
ET AQUACOLES FRANCAIS
78 RUE DE VARENNE
F- 75007 PARIS
Tel. : 3399285378
Fax : 3399285310

HALFORD NIGEL GEORGE
DEPARTMENT OF AGRICULTURAL SCIENCES
UNIVERSITY OF BRISTOL
LONG ASHTON RESARCH STATION
GB - BS18 9AF BRISTOL
Tel. : 44275392181
Fax : 44275394281
E-mail: HALFORDN@.UK.AC.AFRC.LARS

HALL MICHAEL
DEPARTMENT OF BIOLOGICAL SCIENCES
THE UNIVERSITY COLLEGE OF WALES
ABERYSTWYTH
GB - SY233DA ABERYSTWYTH
Tel. : 44970622313
Telex : 35181 ABYUCW G
Fax : 44970622350
E-mail: MZH@AC.UK.ABER

HAMON MICHEL
NEUROBIOLOGIE CELLULAIRE ET
FONCTIONNELLE (INSERM ULBB)
91 BOULEVARD DE L'HOPITAL
F- 75634 PARIS 13
Tel. : 33140779708
Fax : 33140779790

HANSEN KIM
NOVO NORDISK A/S
MICROBIAL PHYSIOLOGY
NOVO ALLE
DK - 2880 BAGSVAERD
Tel. : 4544448888
Fax : 4544983622

HARBERD NICHOLAS
PLANT SCIENCE RESEARCH LIMITED
COLNEY LANE
GB - NR4 7UJ NORWICH
Tel. : 4460352571
Telex : 975122 JIINOR G
Fax : 44603502270

HARITOS ATHANASSIOS
UNIVERSITY OF ATHENS
DEPARTMENT OF BIOLOGY
ZOOLOGICAL LABORATORY
PANEPISTIMIOPOLIS
GR - 157 84 ATHENS
Tel. : 3017284610
Fax : 3017284604

HARWOOD COLIN
DEPARTMENT OF MICROBIOLOGY
THE MEDICAL SCHOOL
FRAMLINGTON PLACE
GB - NE2 4HH NEWCASTLE UPON TYNE
Tel. : 44912227708
Fax : 44912227736
E-mail: COLIN.HARWOOD@NEWCASTLE.AC.UK

HASSIOTOU EFTHIMIA
UNIVERSITY OF THESSALONIKI
RESEARCH COMMITTEE
DEPARTMENT OF GENETICS AND PLANT BREEDING
GR - 54006 THESSALONIKI
Tel. : 3031992547
Fax : 3031200392

HATZOPOULOS POLYDEFKIS
AGRICULTURAL UNIVERSITY OF ATHENS
DEPART. OF AGRICULTURAL BIOLOGY/BIOTECH.
LABORATORY OF MOLECULAR BIOLOGY
IERA ODOS 75
GR - 118 55 ATHENS
Tel. : 3013469000
Fax : 3013460885

HEGEMANN JOHANNES
JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN
INSTITUT FUR MIKROBIOLOGIE UND MOLEKULARBIOLOGIE
FRANKFURTER STRASSE 107
D - 35392 GIESSEN
Tel. : 49.641.24634
Fax : 49.641.702.7390

HELDT HANS WALTER
INSTITÜT FUER BIOCHEMIE DER PFLANZE
DER UNIVERSITAET GOETTINGEN
UNTERE KARSPUELE 2
D - W3400 GOETTINGEN
Tel. : 49551395741
Telex : 096703 UNIGOE D
Fax : 49551395749

HEN ENE
LGME/ONRS
INSERM U184
INSTITUT DE CHIMIE BIOLOGIQUE
11 RUE HUMANN
F- 67085 STRASBOURG CEDEX
Tel. : 3388371255
Telex : 890780 F
Fax : 3388370148

HENRI DURAND
CAYLA
AVENUE DE LARRIEU
F- 31094 TOULOUSE
Tel. : 3361442440
Telex : 530162 F
Fax : 3361402067

HENSEN EVERT J.
INSTITUTE OF INF. DIS. AND IMMUNOLOGY
DEPT. OF IMMUNOLOGY
FAC. OF VETERINARY MEDICINE
YALELAAN 1
NL - 3584 CL UTRECHT
Tel. : 3130532471
Fax : 3130540784

HERBERT CHRISTOPHER
CENTRE NATIONAL DE RECHERCHE SCIENTIFIQUE (CNRS)
CENTRE DE GENETIQUE MOLECULAIRE
AVENUE DE LA TERRASSE
F- 91198 GIF-SUR-YVETTE
Tel. : 33.1.6982.3191
Fax : 33.1.6907.5539

HERNALSTEENS JEAN-PIERRE
LABORATORIUM GENETISCHE VIROLOGIE
PAARDENSTRAAT 65
B- 1640 SINT-GENESIUS-RODE
Tel. : 3223582194
Fax : 3223590399

HERRERO ENRIQUE
UNIVERSIDAD DE LLEIDA
DEPT. CIENCIES MEDIQUES BASIQUES
FACULTY OF MEDICINE
AVGDA ROVIRA ROURE 44
E - 25006 LLEIDA
Tel. : 34.73.702.409
Fax : 34.73.702.426

HERRMANN ANDREAS
HUMBOLDT-UNIVERSITÄT ZU BERLIN
FACHBEREICH BIOLOGIE
INSTITUT FÜR BIOPHYSIK
INVALIDENSTRASSE 42
D - O1040 BERLIN
Tel. : 493028972696
Fax : 493028972641

HEWITT GODFREY
SCHOOL OF BIOLOGICAL SCIENCES
UNIVERSITY OF EAST ANGLIA
GB - NR4 7TJ NORWICH
Tel. : 44603592182
Fax : 44603259492
E-mail: B340@UK.AC.EAST-ANGLIA

HIGGINS CHRISTOPHER
JOHN RADCLIFFE HOSPITAL
ICRF LABORATORIES
INSTITUTE OF MOLECULAR MEDICINE
GB - 0X3 9DU OXFORD
Tel. : 44865222459
Fax : 44865222431
E-mail: C-HIGGINS@UK.AC.ICRF

HILGER/PORTERELLE F./D.
FACULTY OF AGRONOMY (FSAGX)
MICROBIOLOGY
AVENUE MARECHAL JUIN 6
B- 5030 GEMBLOUX
Tel. : 081.622.353
Tel. : 081.622.354
Fax : 081.611.555

HILLEN WOLFGANG
LEHRSTUHL FUER MIKROBIOLOGIE
INSTITUT FUER MIKROBIOLOGIE UND
BIOCHEMIE
STAUDT STR 5
D - W8520 ERLANGEN
Tel. : 499131858081
Fax : 499131858082

HIREL BERTRAND
LABORATOIRE DU METABOLISME ET DE LA
NUTRITION DES PLANTES, INRA
R0UTE DE ST-CYR
F- 78026 VERSAILLES CEDEX
Tel. : 33130833088
Fax : 33130833096

HIRSCH PENNY
AFRC INSTITUTE OF ARABLE CROPS
RESEARCH
ROTHAMSTED EXPERIMENTAL STATION
GB - AL5 2JQ HARPENDEN
Tel. : 44582763133
Telex : 825726 REXPST G
Fax : 44582760981

HIRSCH PETER
CHRISTIAN-ALBRECHTS UNIVERSITÄT KIEL
OLSHAUSENSTRASSE 40-60
D - W2300 KIEL

HOBBS SHAUN L.A.
CAB INTERNATIONAL MYCOLOGICAL
INSTITUTE
FERRY LANE, KEW
GB - TW9 3AF RICHMOND, SURREY
Tel. : 44.81.940 4086
Fax : 44.81.332 1171

HOCHEREAU-DE REVIERS MARIE-THERESE
PHYSIOLOGY OF REPRODUCTION OF
DOMESTIC
MAMMALS
URA INRA/CNRS 1291
F- 37380 NOUZILLY
Tel. : 3347427794
Telex : 750 954 F
Fax : 3347427743

HODGES JOHN KEITH
GERMAN PRIMATE CENTRE
KELLNERWEG 4
D - W3400 GOETTINGEN
Tel. : 495513851140
Fax : 495513851228

HOFLACK BERNARD
EUROPEAN MOLECULAR BIOLOGY
LABORATORY
MEYERHOFSTRASSE 1
POSTFACH 10.2209
D - 69117 HEIDELBERG
Tel. : 496221387285
Telex : 46I6L3(EMBL D)
Fax : 496221387306

HOFNUNG MAURICE
GICA GENETIQUE
PROGRAMMATION MOLECULAIRE ET
TOXICOLOGIQUE
RUE DU DR ROUX 25
MR - 75724 PARIS 15
Tel. : 33.1.45688830
Telex : 250 609
Fax : 33.1.45688834

HOFSTRA HARMEN
NEDERLANDSE ORGANISATIE VOOR
TOEGEPAST NATUURWETENSCHAPPELIJK
ONDERZOEK
DWARSVERBAND BIOTECHNOLOGIE TNO
UTRECHTSEWEG 48
NL - 3700 AC ZEIST
Tel. : +31 3404 44144
Fax : +31 3404 54186

HOLLAND IAN BARRY
UNIVERSITE PARIS SUD II
INSTITUT DE GENETIQUE ET MICROBIOLOGIE
BATIMENT 409
F- 91405 ORSAY 05
Tel. : 33169417706
Fax : 33169417808

HOLLENBERG CORNELIS P.
HEINRICH-HEINE-UNIVERISTÄT DÜSSELDORF
INSTITUT FÜR MIKROBIOLOGIE
UNIVERSITÄTSSTR. 1
GEB. 26.12
D - 40225 DÜSSELDORF
Tel. : 49.211.311.4720
Fax : 49.211.311.5370

HOLM LARS ERIK
NATIONAL INSTITUTE OF ANIMAL SCIENCE
DEPARTMENT OF ANIMAL PHYSIOLOGY
AND BIOCHEMISTRY
P.0. BOX 39
DK - 8830 TJELE
Tel. : 4589991900
Fax : 4589991919

HOLST OLLE
DEPT. OF BIOTECHNOLOGY
CHEMICAL CENTER
LUND UNIVERSITY
PO BOX 124
S - 221 00 LUND
Tel. : 4646109844
Telex : 335 33 LUNIVER S
Fax : 4646104713

HOLSTERS MARCELLE
UNIVERSITEIT GENT
LABORATORIUM VOOR GENETICA
K.L.LEDEGANCKSTRAAT 35
B- 9000 GENT
Tel. : 3291645181
Telex : 11995 GENGENB
Fax : 3291645349
E-mail: MAHOL(A)GENGENP.RUG.AC.BE

HOLT WILLIAM
INSTITUTE OF ZOOLOGY
ZOOLOGICAL SOCIETY OF LONDON
REGENT'S PARK
GB - NW1 4RY LONDON
Tel. : 44717223333
Fax : 44715862870

HOOYKAAS PAUL
CLUSIUS LABORATORY
DEPT. PLANT MOLECULAR BIOLOGY
LEIDEN UNIVERSITY
WASSENAARSEWEG 64
NL - 2333 AL LEIDEN
Tel. : 3171274933
Fax : 3171274999

HOVEMANN BERNHARD
MOLEKULARE NEUROBIOCHEMIE
POSTFACH 102148
D - 44780 BOCHUM-QUERENBURG
Tel. : 492347004235
Telex : 17-234356
Fax : 492347094105

HOWARD JONATHAN
INSTITUTE OF ANIMAL PHYSIOLOGY AND
GENETICS RESEARCH
BABRAHAM HALL
BABRAHAM
GB - CB2 4AT CAMBRIBGE
Tel. : 44223832312
Fax : 44223837952

HUIJSER PETER
MAX-PLANCK-INSTITUT
FUR ZUCHTUNGSFORSCHUNG
CARL-VON-LINNE-WEG 10
D - W5000 COLOGNE
Tel. : 492215062191
Fax : 492215062113

HUMPHRIES PETER
UNIVERSITY OF DUBLIN
TRINITY COLLEGE
LINCOLN PLACE GATE
IRL - 2 DUBLIN
Tel. : 35317021253
Telex : 93782TCDEL
Fax : 35316798558
E-mail: RKSINGH@VAXI.TCD.IE

HUYLEBROECK DANNY
K. U. LEUVEN
LABORATORY OF MOLECULAR BIOLOGY
HERESTRAAT 49
B- 3000 LEUVEN
Tel. : 3216345916
Fax : 3216345933

HÖFLE MANFRED
GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FOR SCHUNG MBH
ABTEILUNG FÜR MIKROBIOLOGIE
MASCHERODER WEG 1
D - W3300 BRAUNSCHWEIG
Tel. : +49 531 6181415
Fax : +49 531 6181411

IJZERMAN AD
LEIDEN UNIVERSITY
CENTER FOR BIO-PHARMACEUTICAL SCIENCES
DIVISION OF MEDICINAL CHEMISTRY
PO BOX 9502
NL - 2300RA LEIDEN
Tel. : 3171274651
Fax : 3171274277

INGRAM DAVID
ROYAL BOTANIC GARDEN EDINBURGH
INVERLEITH ROW
GB - EH3 5LR EDINBURGH
Tel. : 0315527171
Fax : 0315520382

INZE DIRK
UNIVERSITEIT GENT
LABORATORIUM VOOR GENETICA
K.L.LEDEGANCKSTRAAT 35
B- 9000 GENT
Tel. : 3291645192
Telex : 11995 GENGEN B
Fax : 3291645349
E-mail: DIINZ(A)GENGENP.RUG.AC.BE

ISAAC PETER
NICKERSON BIOCEM LTD
CAMBRIDGE SCIENCE PARK
MILTON ROAD
GB - CB4 4GZ CAMBRIDGE
Tel. : 44223423933
Fax : 44223420925
E-mail: TELECOM GOLD (DIALCOM) 75:DBI0246

IVANYI JURAJ
MEDICAL RESEARCH COUNCIL(MRC)
TUBERCULOSIS AND RELATED INFECTIONS UNIT,ROYAL POSTGRADUATE
HAMMERSMITH HOSPITAL
DU CANE ROAD
GB - W12OHS LONDON
Tel. : 44817403161
Fax : 44817438536

JACQ CLAUDE
ECOLE NORMALE SUPERIEURE
GENETIQUE MOLECULAIRE
46 RUE D'ULM
F- 75230 PARIS CEDEX 05
Tel. : 33144323546
Fax : 33144323941

JACQUET MICHEL
UNIVERSITE DE PARIS-SUD
INSTITUT DE GENETIQUE ET MICROBIOLOGIE
INFORMATION GENETIQUE ET DEVELOPPEMENT
BATIMENT 400
F- 91405 ORSAY
Tel. : 33.1.6941.7963
Fax : 33.1.6941.7296

JAHOOR AHMED
TECHNISCHE UNIVERSITÄT MÜNCHEN
LICHTENBERGSTRASSE 4
D - W8046 GARCHING
Tel. : 49 89 3209 3300
Fax : 49 89 3209 3210

JAKUPOVIC JASMIN
ANALYTICON GESELLSCHAFT FUR CHEMISCHE
ANALYTIK UND CONSULTING MBH
D - W1000 BERLIN 65
Tel. : 49.30.4694107
Fax : 49.30.4632012

JAMES KEITH
DEPARTMENT OF SURGERY
MEDICAL SCHOOL
TEVIOT PLACE
GB - EH8 9AG EDINBURGH
Tel. : 44316503557
Fax : 44316676190

JAMES RICHARD
SCHOOL OF BIOLOGICAL SCIENCES
UNIVERSITY OF EAST ANGLIA
GB - NR4 7TJ NORWICH
Tel. : 44603592197
Telex : 975334
Fax : 44603259492

JAUNIAUX JEAN-CLAUDE
DEUTSCHES KREBSFORSCHUNGSZENTRUM
ANGEWANDTE TUMORVIROLOGIE
ABTEILUNG 0610
IM NEUENHEIMER FELD 242
POSTFACH 101949
D - 69009 HEIDELBERG
Tel. : 49.6221.424971
Fax : 49.6221.424962

JESSEN KRISTJAN R.
UNIVERSITY COLLEGE LONDON
DEPARTMENT OF BIOLOGY
GOWER STREET
GB - WC1E 6BT LONDON
Tel. : 44.1.387.7050-2686
Fax : 44.1.380-7026

JIMENEZ ANTONIO
CENTRO DE BIOLOGIA MOLECULAR
UNIVERSIDAD AUTONOMA
CANTO BLANCO
E - 28049 MADRID
Tel. : 3413978442
Fax : 3413974799
E-mail: AJIMENEZ@EMDUAM51

JOERGENSEN STEEN T.
NOVO NORDISK
BACTERIAL GENE TECHNOLOGY
INDUSTRIAL BIOTECHNOLOGY
NOVO ALLE
DK - 2880 BAGSVAERD
Tel. : 4544448888
Fax : 4544983622

JOHN PHILIP
DEPARTMENT OF AGRICULTURAL BOTANY
PLANT SCIENCE LABORATORIES
WHITEKNIGHTS
PO BOX 221
GB - RG6 2AS READING
Tel. : 44734318098
Telex : 847813 RULIB G
Fax : 44734750630

JOLIOT PIERRE
INSTITUT DE BIOLOGIE PHYSICO-CHIMIQUE
SERVICE DE PHOTOSYNTHESE
13 RUE PIERRE ET MARIE CURIE
F- 75005 PARIS
Tel. : 33143252609
Fax : 33140468331

JONES BRIAN
GIST-BROCADES B.V.
P.0. BOX 1
NL - 2600 MA DELFT
Tel. : 015799111
Fax : 015793482

JUNG GUENTHER
UNIVERSITY OF TUEBINGEN
INSTITUT FUER ORGANISCHE CHEMIE
AUF DER MORGENSTELLE 18
D - W7400 TUEBINGEN
Tel. : 497071296925
Telex : 49177071914 UTIOC
Fax : 497071296925

JÜRGENS GERD
INSTITUT FOR GENETIK UND
MIKROBIOLOGIE DER LMU MÜNCHEN
MARIA-WARD-STRASSE 1A
D - W8000 MUNCHEN
Tel. : 498917919868
Fax : 49891785633

KALTSIKES PANTOUSES
DEPARTMENT OF PLANT BREEDING AND
BIOMETRY
AGRICULTURAL UNIVERSITY OF ATHENS
IERA ODOS 75
GR - 10001 ATHENS
Tel. : 3013471504
Fax : 3013460885
E-mail: 118 55

KANE MICHAEL
DEPARTMENT OF PHYSIOLOGY
UNIVERSITY COLLEGE, GALWAY
UNIVERSITY ROAD
IRL - 31 GALWAY
Tel. : 3539124411
Telex : 50023 UCG EI
Fax : 3539125700

KANELLIS ANGELOS
FOUNDATION FOR RESEARCH AND
TECHNOLOGY
INSTITUTE OF MOLECULAR
BIOLOGY/BIOTECHNOLOGY
PO BOX 1527
GR - 711 10 HERAKLION - CRETE
Tel. : 3081210091
Telex : 262896IMBBGR
Fax : 3081230469

KAPTEIN ROBERT
BIJVOET CENTER FOR BIOMOLECULAR RESEARCH
PADUALAAN 8
NL - 3584 CH UTRECHT
Tel. : 3130533787
Fax : 3130540980

KARAGOGEOS DOMNA
FOUNDATION FOR RESEARCH AND TECHNOLOGY -HELLAS
INSTITUTE OF MOLECULAR BIOLOGY AND BIOTECHNOLOGY
MAMMALIAN MOLECULAR BIOLOGY GRP.
MATZAPETAKI 21
GR - 71110 HERAKLION-CRETE
Tel. : 30.81.210091
Fax : 30.81.230469

KARP ANGELA
DEPARTMENT OF AGRICULTURAL SCIENCES
UNIVERSITY OF BRISTOL
LONG ASHTON RESEARCH STATION
GB - BS18 9AF LONG ASHTON, BRISTOL.
Tel. : 44275392181
Fax : 44275394281

KARSSEN C.
DEPARTMENT OF PLANT PHYSIOLOGY
AGRICULTURAL UNIVERSITY WAGENINGEN
ARBORETUMLAAN 4
NL - 6703 BD WAGENINGEN
Tel. : 33837083645
Fax : 33837084761

KATINAKIS PANAGIOTIS
AGRICULTURAL UNIVERSITY OF ATHENS
DEPT OF AGRICULTURAL BIOLOGY AND BIOTECHNOLOGY
IERA ODOS 75
GR - 118 55 ATHENS
Tel. : 13462832
Fax : 13460885
E-mail: AUAIF & GRATH DEM

KAVANAGH TONY
TRINITY COLLEGE
UNIVERSITY OF DUBLIN
DEPARTMENT OF GENETICS
COLLEGE GREEN
LINCOLN PLACE GATE
IRL - DUBLIN 2
Tel. : 3531772941 EXT.1908
Telex : 93782 TCD EI
Fax : 3531798558
E-mail: KAVANAGH@VAX1.TCD.IE

KEIGHTLEY RICHARD
BECKMAN INSTRUMENTS (UK) LIMITED
PROGRESS ROAD
SANDS INDUSTRIAL ESTATE
GB - HP12 4JL HIGH WYCOMBE
Tel. : 0494441181
Fax : 0494463843

KEIL GUENTHER
FEDERAL RESEARCH CENTRE FOR VIRUS DISEASES OF ANIMALS
PAUL-EHRLICH-STR. 28
D - W7400 TUEBINGEN
Tel. : 497071603323
Telex : 17707131
Fax : 497071603201

KEPES FRANCOIS
COMMISSARIAT A L'ENERGIE ATOMIQUE
DSV DBCM
SERVICE DE BIOCHIMIE ET DE GENETIQUE
F- 91191 GIF SUR YVETTE CEDEX
Tel. : 33169083460
Fax : 33169084712

KINGHORN JAMES
DIVISION OF ENVIRONMENTAL AND EVOLUTIONARY BIOLOGY
SCHOOL OF BIOLOGICAL AND MEDICAL SCIENCES
SIR HAROLD MITCHELL BUILDING
GB - KYI6 9TH ST. ANDREWS, FIFE
Tel. : 4433476161
Fax : 4433475398

KIRSTEN OLRIK
MILJOBIOLOGISK LABORATORIUM APS
LABORATORY OF ENVRONMENTAL BIOLOGY
DK - 3050 HUMLEBAEK

KISS JOZSEF ZOLTAN
UNIVERSITE DE GENEVE
DEPARTMENT OF MORPHOLOGY
PLACE DE L'UNIVERSITE 3
CH - 1211 GENEVE 4
Tel. : 41.227057464
Fax : 41.22202922

KJELLEBERG STAFFAN
UNIV. GÖTEBORG
DEPARTMENT OF GENERAL AND MARINE MICROBIOLOGY
CARL SKOTTSBERGS GATA 22
S - 413 19 GOTEBORG
Tel. : 4631418700
Fax : 4631826790

KLEINIG HANS
INSTITUT FUER BIOLOGIE II
ZELLBIOLOGIE
SCHAENZLESTRASSE 1
D - W7800 FREIBURG
Tel. : 497612032679
Fax : 497612032675

KLENK HANS-DIETER
INSTITUT FUR VIROLOGIE
ROBERT-KOCH-STR. 17
D - W 3550 MARBURG
Tel. : 496421284300
Fax : 496421286540
E-mail: KLENK AT DMRHRZI11

KNEBEL-MOERSDORF DAGMAR
UNIVERSITY OF COLOGNE
INSTITUTE OF GENETICS
WEYERTAL 121
D - W5000 COLOGNE
Tel. : 492214703414
Fax : 492214705163

KOCHOYAN MICHEL
ECOLE POLYTECHNIQUE
GROUPE DE BIOPHYSIQUE
ROUTE DE SACLAY
F- 91128 PALAISEAU CEDEX
Tel. : 16.1.69333298
Fax : 16.1.69333004
E-mail: POLY.POLYTECHNIQUE.FR

KOES RONALD
VRIJE UNIVERSITEIT AMSTERDAM
DEPARTMENT OF GENETICS
DE BOELELAAN 1087
NL - 1081 HV AMSTERDAM
Tel. : 31205484478
Fax : 31206429202

KONCZ C.
MAX-PLANCK-INSTITUT FUER
ZUECHTUNGSFORSCHUNG
CARL-VON-LINNE-WEG 10
D - 5000 KOELN 30
Tel. : 492215062350
Telex : 8 881 028 MPIZ D
Fax : 492215062413

KONCZ CSABA
MAX-PLANCK-INSTITUT FUR
ZUCHTUNGSFORSCHUNG
CARL-VON-LINNE-WEG 10
D - W5000 KOLN
Tel. : 492215062230
Telex : 8 881 028 MPIZ D
Fax : 492215062213

KONIG ECKEHARD
ZENTRALSTELLE FÜR
AGRARDOKUMENTATION UND-
INFORMATION
VILLICHGASSE 17
D - W5300 BONN 2

KONINGS WIL
UNIVERSITY OF GRONINGEN
DEPARTMENT OF MICROBIOLOGY
BIOLOGICAL CENTER
KERKLAAN 30
NL - 9751 NN HAREN
Tel. : 3150632152
Fax : 3150632154

KOOL A.
PLANT BIOTECHNOLOGY DEPARTMENT
ZAADUNIE
WESTEINDE 62
NL - 1600 AA ENKHUIZEN
Tel. : 31228011411
Fax : 31228012818

KOORNNEEF MAARTEN
WAGENINGEN AGRICULTURAL UNIVERSITY
DEPARTMENT OF GENETICS
DREIJENLAAN 2
NL - 6703 HA WAGENINGEN
Tel. : 31837082150
Fax : 31837083146
E-mail: MAARTEN KOORNNEEF@CELGEN@
EL.WAU

KOSSMANN JENS
INSTITUT FÜR GENBIOLOGISCHE FORSCHUNG
BERLIN GMBH
IHNESTRASSE 63
D - W1000 BERLIN
Tel. : 493083000792
Fax : 493083000736

KOSZINOWSKI ULRICH
INSTITUT FÜR MEDIZINISCHE VIROLOGIE
IM NEUENHEIMER FELD 324
D - 69120 HEIDELBERG
Tel. : 06221.563000
Tel. : 06221.563104

KOURILSKY PHILIPPE
BIOLOGIE MOLECULAIRE DU GENE
25 DR. ROUX
F- 75724 PARIS 15
Tel. : 145688545
Telex : 250609 F
Fax : 145688548

KRAAIJENHOF RUUD
VRIJE UNIVERSITEIT
DEPARTMENT OF MOLECULAR AND CELLULAR
BIOLOGY
DE BOELELAAN 1087
NL - 1081 HV AMSTERDAM
Tel. : 31205484778
Fax : 31206429202
E-mail: KLAAS@BIO.VU.NL

KRAMBOVITIS ELIAS
INSTITUTE OF MOLECULAR BIOLOGY AND BIOTECHNOLOGY
P.O. BOX 1527
GR - 71110 HERAKLION
Tel. : 3081210363
Telex : 262897 BIOT GR
Fax : 3081231308

KRAMER WILFRIED
GEORG-AUGUST-UNVIERSITAT GÖTTINGEN
INSTITUT FÜR MOLEKULARE GENETIK
GRISEBACHSTR. 8
D - 37077 GÖTTINGEN
Tel. : 49.551.399653
Fax : 49.551.3933805

KREIS MARTIN
UNIVERSITE PARIS XI
BIOLOGIE DU DEVELOPPEMENT DES PLANTES
INSTITUT DE RECHERCHES SUR LES PLANTES
BATIMENT 430,RDC
F- 91405 ORSAY CEDEX
Tel. : 33169417239
Fax : 33169853715

KREMER ANTOINE
LABORATOIRE DE GENETIQUE
PIERROTON
P.0.BOX 45
F- 33610 CESTAS
Tel. : 3356680303
Fax : 3356680223
E-mail: ANTOINE PIERROTON.INRA.FR.

KREUZALER FRITZ
LEHRSTUHL UND INSTITUT FOR BIOLOGIE
RHEINISCH-WESTFÄLISCHE TECHNISCHE HOCHSCHULE
P.0.BOX 1 1
D - W5100 AACHEN
Tel. : 241806633
Telex : 832704THACD
Fax : 241806678

KRISTJANSSON JAKOB
TECHNOLOCICAL INSTITUTE OF ICELAND
DEPARTMENT OF BIOTECHNOLOGY
KELDNAHOLT
IS - 112 REYKJAVIK
Tel. : 3541687000
Telex : 3020 ISTECH
Fax : 3541687409

KROGSGAARD-LARSEN POVL
DEPARTMENT OF ORGANIC CHEMISTRY
ROYAL DANISH SCHOOL OF PHARMACY
UNIVERSITETSPARKEN 2
DK - 2100 COPENHAGEN
Tel. : 194535370850
Fax : 194535375744

KROL ALAIN
STRUCTURE DES MACROMOLECULES BIOLOGIQUES
ET MECANISMES DE RECONNAISSANCE
15 RUE DESCARTES
F- 67084 STRASBOURG CEDEX
Tel. : 88417050
Telex : F 880492
Fax : 88610680

KRUGER NICHOLAS
DEPARTMENT OF PLANT SCIENCES
UNIVERSITY OF OXFORD
SOUTH PARKS ROAD
GB - OX1 3RB OXFORD
Tel. : 44865275000
Telex : 83147 PLANTOX
Fax : 44865275074

KRUIP THEODOOR
EMBRYTEC BV
TOLAKKERLAAN 3 3
NL - 3704 JA ZEIST
Tel. : 31340570139
Fax : 31340567642

KRUMLAUF ROBERT
NATIONAL INSTITUTE FOR MEDICAL RESEARCH
LAB OF EUKARYOTIC MOLECULAR GENETICS
THE RIDGEWAY
MILL HILL
GB - NW71AA LONDON
Tel. : 44819593666
Fax : 44819064477

KUBICEK CHRISTIAN P.
INSTITUT FÜR BIOCHEMISCHE TECHNOLOGIE UND MIKROBIOLOGIE
TECHNISCHE UNIVERSIT–T WIEN
GETREIDEMARKT 9
1725
A- A1060 WIEN
Tel. : 43222588014708
Fax : 432225874835

KUNST FREDERIK
INSTITUT PASTEUR
UNITE DE BIOCHIMIE MICROBIENNE
25 RUE DU DOCTEUR ROUX
F- 75724 PARIS 15
Tel. : 33145688869
Fax : 33145688938
E-mail: F. KUNST AT PASTEUR.FR.

KUNTZ MARCEL
INSTITUT DE BIOLOGIE MOLECULAIRE DES PLANTES DU CNRS
UPR AO406
12 RUE DU GENERAL ZIMMER
F- 67084 STRASBOURG
Tel. : 3388417200
Fax : 3388614442

KUSCHMITZ DIETRICH
MAX-PLANK-INSTITUT
FUER ERNAEHRUNGSPHYSIOLOGIE
RHEINLANDDAMM 201
D - W4600 DORTMUND
Tel. : 4923112061
Fax : 492311206389

KÖRNER MARIE
LABORATOIRE D'IMMUNOLOGIE CELLULAIRE ET TISSULAIRE
CNRS URA 625
83 BLVD DE L'HOPITAL
F- 75651 PARIS 13
Tel. : 33145703824
Fax : 33145703825

LABORDA FERNANDO
DEPARTAMENTO DE MICROBIOLOGIA Y PARASITOLOGIA. UNIVERSIDAD DE ALCALA DE HENARES.
CARRETERA MADRID-BARCELONA KM.33.6
ALCALA DE HENARES
E - 28871 MADRID
Tel. : 3418854621
Fax : 3418854660

LADENSTEIN RUDOLF
KAROLINSKA INSTITUTET
NOVUM
CENTRUM FÖR STRUKTURBIOKEMI
BLICKAGANGEN 6
S - 14157 HUDDINGE
Tel. : 086089222
Fax : 086089290
E-mail: RLA@BARRA. CSB.KI.SE

LALOUE MICHEL
LABORATOIRE DE BIOLOGIE CELLULAIRE
INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE
ROUTE DE SAINT-CYR
F- 78026 VERSAILLES CEDEX
Tel. : 33130833046
Fax : 33130832099

LANDT OLFERT
TIB MOLBIOL BERLIN GMBH IG.
OSTPREUßENDAMM, 111
D - 1000 BERLIN 45
Tel. : 49.030.712.3315
Fax : 712.7734/626.1960

LANGHORNE JEAN
MAX-PLANCK-INSTITUT FUER IMMUNBIOLOGIE
STUEBEWEG 51
D - W7800 FREIBURG
Tel. : 497615108533
Fax : 497615108221

LANOIR JEANNE
LABORATOIRE DE NEUROBIOLOGIE URS IB DU CNRS
31 CHEMIN JOSEPH AIGUIER
F- 13402 MARSEILLE 09
Tel. : 3391164178
Telex : CNRSMAR 430 225 F
Fax : 3391226333

LATINNE DOMINIQUE
DEPARTEMENT DE BIOLOGIE MOLECULAIRE CLINIQUE
CLINIQUES UNIVERSITAIRES SAINT-LUC
CLOS CHAPELLE AUX CHAMPS 30/46
B- 1200 BRUSSELS
Tel. : 3227643145
Fax : 3227643959

LATTES ALDO
UNIVERSITA DEGLI STUDI DI GENOVA
VIA BALBI 5
I - 16126 GENOVA
Tel. : 39.10.20991

LAUQUIN GUY
INSTITUT DE BIOCHIMIE CELLULAIRE/CNRS
PHYSIOLOGIE MOLECULAIRE & CELLULAIRE
1 RUE C. ST. SAëNS
F- 33077 BORDEAUX
Tel. : 33.56.99.90.37
Fax : 33.56.99.90.59

LE RUDULIER DANIEL
LABORATOIRE DE BIOLOGIE VEGETALE ET MICROBIOLOGIE-URA CNRS 1114
PARC VALROSE FACULTE DES SCIENCES
F- 06108 NICE 2
Tel. : 3393529933
Telex : UNINICE 970 231 F
Fax : 3393529948

LECLERC CLAUDE
BIOLOGIE DES REGULATIONS IMMUNITAIRES
INSTITUT PASTEUR
25 RUE DU DR ROUX
F- 75015 PARIS 15
Tel. : 3345688618
Telex : 250609
Fax : 3345688639

LEEMANS J.
PLANT GENETIC SYSTEMS N.V.
J. PLATTEAUSTRAAT 22
B- 9000 GENT
Tel. : 3291358498
Fax : 3291240694

LEESE HENRY
DEPARTMENT OF BIOLOGY
UNIVERSITY OF YORK
GB - Y01 5DD YORK
Tel. : 44904432821
Telex : YORKUL 57933
Fax : 44904432917
E-mail: HJL I@YORK.AC.UK

LEHLE LUDWIG
LEHRSTUHL FUER ZELLBIOLOGIE UND PFLANZENPHYSIOLOGIE
UNIVERSITAET REGENSBURG
UNIVERSITAETSSTRASSE 31
D - W8400 REGENSBURG
Tel. : 499419433043
Fax : 499419433052

LEIGH ROGER
ROTHAMSTED EXPERIMENTAL STATION
AFRC-INST. OF ARABLE CROPS RESEARCH
GB - AL5 2JQ HARPENDEN
Tel. : 44582763133
Telex : 825726 REXPST G
Fax : 44582760981

LEISER ROBERT-MATTHIAS
DIAGEN INSTITUT FÜR MOLEKULARBIOLOGISCHE DIAGNOSTIK GMBH
MAX VOLMER STR. 4
D - W4010 HILDEN
Tel. : 4921038920
Fax : 492301892222

LENSTRA JOHANNES
INSTITUTE OF INFECTIOUS DISEASES AND IMMUNOLOGY, FACULTY OF VETERINARY MEDICINE, STATE UNIVERSITY OF
PO BOX 80165
NL - 3508 TD UTRECHT
Tel. : 3130534992
Fax : 3130540784

LERMA JUAN
INSTITUTO CAJAL
CONSEJO SUPERIOR DE
INVESTIGACIONES CIENTIFICAS
AVENIDA DOCTOR ARCE 37
E - 28002 MADRID
Tel. : 3415854114
Fax : 3415854154

LESCURE BERNARD
LABORATOIRE DE BIOLOGIE MOLECULAIRE
DES RELATIONS
PLANTES-MICROORGANISMES
CHEMIN DE BORDE-ROUGE
BP 27
F- 31326 CASTANET TOLOSAN CEDEX
Tel. : 3361285049
Fax : 3361285061
E-mail: LESCURE@TOULOUSE.INRA.FR

LESTER RICHARD NEVILLE
UNIVERSITY OF BIRMINGHAM
SCHOOL OF BIOLOGICAL SCIENCES
GB - B15 2TT BIRMINGHAM
Tel. : 44.21.4145564/5571
Fax : 44.21.4145925

LEVEZIEL HUBERT
DEPARTEMENT DE GENETIQUE ANIMALE
LABORATOIRE DE GENETIQUE BIOCHIMIQUE
INRA, CRJ
F- 78352 JOUY-EN-JOSAS 78352
Tel. : 33134652580
Fax : 33134652478
E-mail: LEVEZIEL@BIOTEC.JOUY.INRA.FR

LEVITT MALCOLM
STOCKHOLMS UNIVERSITET
FYSIKALISK REMI
ARRHENIUS LABORATORIET
S - S10691 STOCKHOLM
Tel. : 468154003
Fax : 468152187
E-mail: MHL@EROS.MISU.SU.SE

LEY STEVEN C
NATIONAL INSTITUTE FOR MEDICAL
RESEARCH
THE RIDGEWAY
MILL HILL
GB - NW7 IAA LONDON
Tel. : 44819593666
Fax : 44819064477

LINDSEY K.
LEICESTER BIOCENTRE
UNIVERSITY OF LEICESTER
UNIVERSITY ROAD
GB - LEI 7RH LEICESTER
Tel. : 44533522263
Telex : 342318 LEIBIO G
Fax : 44533551219

LOCHT CAMILLE
LABORATOIRE DE MICROBIOLOGIE
GENETIQUE ET MOLECULAIRE
INSERM CJF91O9
1 RUE DU PROFESSEUR CALMETTE
F- 59019 LILLE
Tel. : 3320877728
Fax : 3320877906

LOHSE MARTIN
JULIUS MAXIMILIANS UNIVERSITÄT
INSTITUT FÜR PHARMAKOLOGIE UND
TOXIKOLOGIE
VIRSBACHIR 8
D - 97078 WÜRZBURG
Tel. : 49.931.2015400
Fax : 49.931.2013539

LOOFT CHRISTIAN
INSTITUT FÜR TIERZUCHT UND
TIERHALTUNG
DER CHRISTIAN ALBRECHTS UNIVERSIT T
ZU KIEL
OLSHAUSENSTRABE 40
D - 2300 KIEL
Tel. : 494318802586
Fax : 494318802588

LOPEZ RIVAS ABELARDO
INSTITUTO LOPEZ NEYRA DE
PARASITOLOGIA
VENTANILLA 11
E - 18001 GRANADA
Tel. : 3458203802
Fax : 3458203323

LOPEZ-FERBER MIGUEL
STATION DE RECHERCHES DE PATHOLOGIE
COMPAREE
INRA - URA
CNRS 1184O
F- 30380 SAINT-CHRISTOL-LEZ-ALES
Tel. : 3366783700
Fax : 3366524699

LOTZ WOLFGANG
UNIVERSITÄT ERLANGEN-NÜRNBERG
INST. MIKROBIOL. BIOCHEM.
LEHRSTUHL MIKROBIOLOGIE
STAUDTSTR. 5
D - W8520 ERLANGEN
Tel. : 499131858086
Fax : 499131858103

LOUREIRO-DIAS MARIA
INSTITUTO GULBENKIAN DE CIENCIA
P - 2780 OEIRAS

LUGTENBERG BEN
LEIDEN UNIVERSITY
INSTITUTE OF MOLECULAR PLANT SCIENCES
BOTANICAL LABORATORY
NONNENSTEEG 3
NL - 2311 YJ LEIDEN
Tel. : 3171275063
Telex : 39427 BURUL NL
Fax : 3171275088

LUGTENBERG EGBERTUS
INSTITUTE OF MOLECULAR PLANT SCIENCES
CLUSIUS LABORATORY
WASSENAARSEWEG 64
P.O. BOX 9505
NL - 2300 RA LEIDEN
Tel. : 3171275063
Fax : 3171275088

LUGTENBURG JOHAN
UNIVERSITY OF LEIDEN
GORLAEUS LABORATORIES
PO BOX 9502
NL - 2300 RA LEIDEN
Tel. : 3171274405
Fax : 3171274537
E-mail: ONZLUGTEN@RULGL.LEIDENUNIV.NL

LUMARET ROSELYNE
CENTRE D'ECOLOGIE FONCRIONNELLE ET EVOLUTIVE
5051 1919 ROUTE DE MENDE
F- 34033 MONTPELLIER
Tel. : 3367613201
Fax : 3367412138

LYNCH JAMES
SCHOOL OF BIOLOGICAL SCIENCES
UNIVERSITY OF SURREY
GUILDFORD
GB - GU2 5XH SURREY
Tel. : 44483509721
Fax : 44483576978

MACHE REGIS
LABORATOIRE DE BIOLOGIE MOLECULAIRE VEGETALE
UNIVERSITE JOSEPH FOURIER
BP 53X
F- 38041 GRENOBLE CEDEX
Tel. : 3376514667
Telex : USMG 980134F
Fax : 3376514336
E-mail: RMACHE@FRGREN81 BITNET

MACINO GIUSEPPE
DIPARTIMENTO BIOPATOLOGIA UMANA
SEZIONE BIOLOGIA CELLULARE
VIALE REGINA ELENA 324
I - 00161 ROMA
Tel. : 3964457731
Fax : 3964462891

MAKI-TANILA ASKO
DEPARTMENT OF ANIMAL BREEDING
AGRICULTURAL RESEARCH CENTRE
SF- 31600 JOKIOINEN .
Tel. : 358161881
Telex : 6741 MTTK SF
Fax : 35816188618
E-mail:
EJO7@MTTK.FUDEC@ROUTER.FUNET.FI

MALAVASI FABIO
CENTRO IMMUNOGENETICA
E ISTOCOMPATIBILITA
CONSIGLIO NAZIONALE RICERCHE, CNR
VIA SANTENA 19
I - 10126 TORINO
Tel. : 39116961734
Fax : 39116966155

MALLET JACQUES
CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE
UPR23 LABORATOIRE DE NEUROBIOLOGIE CELLULAIRE ET MOLECULAIRE
1 AVENUE DE LA TERRASSE
DR ILE-DE-FRANCE: SECTEUR SUD
F- 91198 GIF-SUR-YVETTE
Tel. : 33.1.69823646
Fax : 33.1.69823580

MARCKER KJELD A.
LABORATORY OF GENE EXPRESSION
DEPARTMENT OF MOLECULAR BIOLOGY
UNIVERSITY OF AARHUS
GUSTAV WIEDS VEJ 10
DK - DK8000 AARHUS C
Tel. : 4586202000
Fax : 4586201222

MARGARITIS L.
DEPT. OF BIOLOGY / DIV. OF BIOCHEMISTRY
CELL_MOLECULAR BIOLOGY & GENETICS
UNIVERSITY OF ATHENS
GR - 15701 PANEPISTIMIOUPOLI

MARKL HERBERT
TECHNICAL UNIVERSITY HAMBURG
HARBURG
BIOPROCESS- AND BIOCHEMICAL
DENICKESTRASSE 15
D - W2100 HAMBURG 90
Tel. : 494077183017
Fax : 494077182909

MARMIROLI NELSON
INSTITUTE OF GENETICS AND DEPARTMENT OF EVOLUTIONARY BIOLOGY - UNIVERSITY OF PARMA
VIALE DELLE SCIENZE
I - 43100 PARMA
Tel. : 39521580606
Fax : 39521580665

MAROTEAUX LUC
U184/INSERM - LGME/CNRS
INSTITUT DE CHIMIE BIOLOGIQUE
11 RUE HUMANN
F- 67085 STRASBOURG
Tel. : 88371255
Fax : 88370148

MARQUEZ ANTONIO J.
UNIVERSIDAD DE SEVILLA
DEPARTAMENTO DE BIOQUIMICA VEGETAL Y BIOLOGIA MOLECULAR
APARTADO 553
E - 41080 SEVILLA
Tel. : 3454626853
Fax : 3454624952
E-mail: CABEZA C CICA.ES

MARTIN CARLOS
MICROBIOLOGIA
FACULTAD DE MEDICINA
DOMINGO MIRAL S/N
E - 50009 ZARAGOZA
Tel. : 3476357916
Fax : 3476357015

MARTIN CATHERINE
JOHN INNES FOUNDATION
JOHN INNES INSTITUTE
COLNEY LANE
GB - NR4 7UH NORWICH
Tel. : 4460352571
Telex : 975122(JIIN0R G)
Fax : 4460356844

MARTIN ROBERT P.
INSTITUT DE BIOLOGIE MOLECULAIRE ET CELLULAIRE
DU CNRS
LIPR 9005
15 RUE R. DESCARTES
F- 67084 STRASBOURG
Tel. : 33.88.41.70.40
Fax : 33.88.61.06.80

MARTINEZ SALVADOR
UNIVERSIDAD DE MURCIA
FACULTAD DE MEDICINA
DEPARTMENT OF MORPHOLOGICAL SCIENCES
CAMPUS MURCIA
E - 30100 MURCIA
Tel. : 34.96.833000
Fax : 34.68.835418

MARTINEZ ZAPATER J.M.
DEPARTAMENTO DE PROTECCION VEGETAL
CENTRO DE INVESTIGACION Y TECNOLOGIA
INSTITUTO NACIONAL DE INVESTIGACION
CARRETERA DE LA CORUNA, KM. 7.5
E - 28040 MADRID
Tel. : 3413476890
Fax : 3413573107

MASSIP ALBAN
UNITE DES SCIENCES VETERINAIRES
PLACE CROIX DU SUD 3
B- 1348 LOUVAIN-LA-NEUVE
Tel. : 3210473756
Fax : 3210474745
E-mail: MASSIP@VETE.UCL.AC.BE

MASTERSON R.
ABT. GENETISCHE GRUNDLAGEN DER PFLANZENZUECHTUNG
MAX-PLANCK-INSTITUT FUER ZUECHTUNGSFORSCHUNG
CARL-VON-LINNE-WEG 10
D - 5000 KOELN 30
Tel. : 492215062245
Telex : 8 881 028 MPIZ D
Fax : 492215062213

MATHIESON PETER
UNIVERSITY OF CAMBRIDGE
DEPARTMENT OF MEDICINE
ADDENBROOKE'S HOSPITAL
HILLS ROAD
GB - CB2 2QQ CAMBRIDGE
Tel. : 233336741
Fax : 223411052

MATRANGA VALERIA
CONSIGLIO NAZIONALE DELLE RICERCHE
ISTITUTO DI BIOLOGIA DELLO SVILUPPO
VIA ARCHIRAFI 20
I - 90123 PALERMO
Tel. : 39-91-6161892
Telex : 910403 IBSPA

MATSAS REBECCA
HELLENIC PASTEUR INSTITUTE
VASSILISSIS SOFIAS AVENUE 127
GR - 11521 ATHENS
Tel. : 3016431303
Telex : 221188 IPH
Fax : 3016423498

MAVILIO FULVIO
ISTITUTO SCIENTIFICO H.S. RAFFAELE
DIPARTIMENTO DI RICERCA BIOLOGICA E TECNOLOGICA
VIA OLGETTINI 60
I - 20132 MILANO
Tel. : 39226432357
Fax : 39226432640

MAYOR FEDERICO
UNIVERSIDAD AUTONOMA MADRID
CENTER OF MOLECULAR BIOLOGY
DEPARTMENT OF MOLECULAR BIOLOGY
CARRETERA DE COLMENAR KM. 15
E - 28049 MADRID
Tel. : 3413974865
Fax : 3413974799
E-mail: FMAYOR CBM2.UAM.ES

MCCAFFREY MARY
DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY COLLEGE CORK
LEE MALTINGS, PROSPECT ROW
IRL - 41 CORK
Tel. : 353212768714933
Fax : 35321274034

MELANDRI BRUNO ANDREA
UNIVERSITA DI BOLOGNA
DIPARTIMENTO DI BIOLOGIA EVOLUZIONISTICA SPERIMENTALE
VIA BELMELORO 8
I - 40126 BOLOGNA
Tel. : 3951351293
Fax : 3951242576

MELERO JOSE A.
INSTITUTO DE SALUD "CARLOS III"
CENTRO NATIONAL DE MICROBIOLOGIA, VIROLOGIA E IMMUNOLOGIA SANITARIAS
CTRA. MAJADAHONDA-POZUELO, KM 2,200
E - 28220 MAJADAHONDA.- MADRID
Tel. : 3416380011
Fax : 3416391859

MELIEF CORNELIS
DEPARTMENT OF IMMUNOHEMATOLOGY AND BLOOD BANK
P.0. BOX 9600
NL - 2300 RC LEIDEN
Tel. : 3171263800
Telex : 39622
Fax : 3171216751

MELLADO RAFAEL P
CENTRO NACIONAL DE BIOTECHNOLOGIA
CANTOBLANCO - NUCLEIC ACID UNIT
CANTOBLANCO
E - 28049 MADRID
Tel. : 3413974171
Telex : 27810 EDUCI E
Fax : 3413974799
E-mail: R.P.MELLADO.CNB.UAM.ES

MELOEN ROBBERT HANS
CENTRAAL DIERGENEESKUNDIG INST. T
DIENST LANDBOUWKUNDIG ONDERZOEK
POSTBUS 65
NL - 8200 AB LELYSTAD
Tel. : 31-320073911
Fax : 31-320073473

MENEZ ANDRE
DEPARTEMENT D'INGENIERIE ET D'ETUDES DES PROTEINES
BATIMENT 152
CENTRE D'ETUDES DE SACLAY
F- 91190 GIF SUR YVETTE CEDEX
Tel. : 33169083803
Fax : 33169089071
E-mail: GILQUIN@GOLIATH.SACLAY.CEA.FR

MEREDITH CLIVE
BIBRA TOXICOLOGY INTERNATIONAL
WOODMANSTERNE ROAD
GB - SM5 4DS CARSHALTON, SURREY
Tel. : 44816434411
Fax : 44816617029

MERGEAY MAXIMILIEN
VLAAMSE INSTELLING VOOR TECHNOLOGISCH
LABORATORIUM VOOR GENETICA EN BIOTECHNOLOGIE
BOERETANG 200
B- 2400 MOL
Tel. : 3214333111
Fax : 3214320372

MERMILLOD PASCAL
PHYSIOLOGY OF REPRODUCTION OF DOMESTIC MAMMALS
URA INRA/CNRS 1291
F- 37380 NOUZILLY
Tel. : 3347427798
Telex : 750 954 F
Fax : 3347427743
E-mail: PASCAL.MERMILLOD@TOURS.INRA.FR

MEWES HANS-WERNER
MAX PLANCK INSTITUT FUER BIOCHEMIE
AM KLOPFERSPITZ 18
D - 8033 MARTINSRIED
Tel. : 498985782656
Fax : 498985782655

MEYER P.
MAX-DELBRUEK-LABORATORIUM IN DER MPG
CARL-VON-LINNE-WEG 10
D - 5000 KOELN 30
Tel. : 492215062490
Fax : 492215062319

MICHAELIS GEORG
BOTANISCHES INSTITUT ABTEILUNG BOTANISCHE CYTOLOGIE
HEINRICH HEINE UNIVERSITÄT DÜSSELFORF
UNIVERSITAETSSTRASSE 1
D - W4000 DUESSELDORF I
Tel. : 492113114801
Fax : 492113113085

MICHEL FRANCOIS
CENTRE GENETIQUE MOLECULAIRE C.N.R.S.
AVENUE DE LA TERRASSE
F- 91198 GIF-SUR-YVETTE CEDEX
Tel. : 16.1.69823215
Fax : 16.1.69075322
E-mail: MICHEL@FRCGM5I

MILLER ANTHONY
ROTHAMSTED EXPERIMENTAL STATION
WEST COMMON
GB - AL5 2JQ HARPENDEN
Tel. : 44582763133
Telex : 825726 REXPST G
Fax : 44582760981

MILLER JAMES
AFRC INSTITUTE OF ANIMAL PHYSIOLOGY AND GENETICS RESEARCH, CAMBRIDGE
RESEARCH STATION
BABRAHAM
GB - CB2 4AT CAMBRIDGE
Tel. : 44223832312
Fax : 44223837304
E-mail: MILLER@UK.AC.AFRC.IAPC

MILLER KLARA
BIBRA TOXICOLOGY INTERNATIONAL
WOODMANSTERNE ROAD
GB - SM5 4DS CARSHALTON, SURREY
Tel. : 44816434411
Fax : 44-223-837952

MINGO-CASTEL ANGEL
POTATO BIOTECH LAB. UPNA
CAMPUS ARROSADIA
E - 31006 PAMPLONA
Tel. : 3348151517
Fax : 3348151161

MOLIN SOEREN
THE TECHNICAL UNIVERSITY OF DENMARK
DEPARTMENT OF MICROBIOLOGY
BUILDING 221
DK - 2800 LYNGBY
Tel. : 4545933422
Fax : 4545932809

MOLLER ERNA
DEPARTMENT OF CLINICAL IMMUNOLOGY
KAROLINSKA INSTITUTE
HUDDINGE HOSPITAL
S - S14186 HUDDINGE
Tel. : 4687465718
Fax : 4687466869

MONIZ PEREIRA JOSE
MICROBIOBOGIA MOLECUIAR
FACULDADE DE FARMACIA DA
UNIVERSIDADE LISBOA
AV. DAS FORCAS ARMADAS
P - 1600 LISBOA 1699
Tel. : 35117933064
Fax : 35117934212

MORATA GINES
CENTRO DE BIOLOGIA MOLECULAR
UNIVERSIDAD AUTONOMA DE MADRID
E - 28049 CANTOBLANCO MADRID
Tel. : 34.1.3978498
Fax : 34.1.3974799

MOREIN BROR
SWEDISH AGRICULTURE UNIVERSITY
DEPARTMENT OF VIROLOGY BOX 585
BIOMEDICAL CENTRE
S - S 751 23 UPPSALA
Tel. : 4618174570
Telex : 76132 BIOMED S
Fax : 4618504603

MORGAN ANDREW
DEPT. OF PATHOLOGY & MICROBIOLOGY
SCHOOL OF MEDICAL SCIENCES
UNIVERSITY OF BRISTOL
UNIVERSITY WALK
GB - BS8 1TD BRISTOL
Tel. : 44272303451
Telex : 445938 BSUNIV G
Fax : 44272303451

MORNON JEAN PAUL
UNIVERSITE PIERRE ET DMRIE CURIE
MINERALOGIE CRISTALLOGRAPHIE
4 PLACE JUSSIEU TOUR 16
F- 75252 PARIS 05
Tel. : 33144274587
Fax : 33144273785
E-mail: MORNONALMCP.JUSSIEU.FR

MORRISON W IVAN
AFRC INSTITUTE FOR ANIMAL HEALTH
GB - RG16 ONN COMPTON, NEAR NEWBURY
Tel. : 635578411
Telex : 93 12110326
Fax : 635578844

MOTTO MARIO
ISTITUTO SPERIMENTALE PER LA CEREALI-
COLTURA
VIA STEZZANO 24
I - 24100 BERGAMO
Tel. : 3935313132
Fax : 3935316054

MUELLER-STARCK GERHARD
EIDGENOESSISCHE
FORSCHUNGSANSTALT FUER WALD, SCHNEE
UND LANDSCHAFT
ZUERCHERSTRASSE 111
CH - 8903 BIRMENSDORF-ZH
Tel. : 004117392111
Fax : 004117392215

MULLER CLAUDE P.
DEPARTMENT OF IMMUNOLOGY
LABORATOIRE NATIONAL DE SANTE
RUE DU LABORATOIRE
BOITE POSTALE 1102
L - 1011 LUXEMBOURG
Tel. : 352493218
Fax : 352404238

MULLIGAN B.
DEPARTMENT OF BOTANY
UNIVERSITY OF NOTTINGHAM
GB - NG7 2RD NOTTINGHAM
Tel. : 44602484848 EXT. 346
Fax : 44602420825

MUMMERY CHRISTINE
NETHERLANDS INSTITUTE FOR DEV.
BIOLOGY
HUBRECHT LABORATORY
UPPSALALAAN 8
NL - 3584 CT UTRECHT
Tel. : 3130510211
Fax : 3130516464

MURPHY GEORGE
PLANT SCIENCE RESEARCH LIMITED
COLNEY LANE
GB - NR4 7UJ NORWICH
Tel. : 4460352571
Telex : 975122 JIINOR G
Fax : 44603502270

NAU HEINZ
FREE UNIVERSITY BERLIN
INSTITUTE OF TOXICOLOGY
GARYSTRA~E 5
D - W1000 BERLIN
Tel. : 0049308385053
Fax : 0049308316139

NETTER PIERRE
CNRS/UNIVERSITE PARIS 6
CENTRE DE GENETIQUE MOLECULAIRE
AVENUE DE LA TERRASSE
F- 91190 GIF/YVETTE
Tel. : 33.1.6982.3203
Fax : 33.1.6907.5539

NICKLIN MARTIN
ROYAL HALLAMSHIRE HOSPITAL
DEPARTMENT OF MEDICINE AND
PHARMACOLOGY
SECTION OF MOLECULAR MEDICINE
GB - S10 2JF SHEFFIELD
Tel. : 44742766222
Fax : 44742721104

NIELSEN SOREN VEDEL SAABY
THE BIOTECHNOLOGY GROUP
RESEARCH CENTRE FOR PLANT PROTECTION
DANISH INSTITUTE FOR PLANT SCIENCE
LOTTENBORGVEJ 2
DK - 2000 LYNGBY
Tel. : 4545872361
Fax : 4545872210

NIMIS PIER LUIGI
UNIVERSITA DEGLI STUDI DI TRIESTE
PIAZZALE EUROPA 1
I - 34127 TRIESTE
Tel. : +39-40-301034
Fax : +39-40-5603176

NITSCHKE WOLFGANG
ALBERT LUDWIGS UNIVERSITÄT
BIOLOGISCHES INSTITUT II
BIOCHEMIE DER PFLANZEN
SCHAENZLESTRASSE 1
D - 79104 FREIBURG
Tel. : 497612032699
Fax : 497612032701

NOMBELA CESAR
DEPARTMENT OF MICROBIOLOGY, FACULTY
OF PHARMACY
UNIVERSIDAD COMPLUTENSE
UNIDAD DE SECUENCIACION
AUTOMATIZADA DE D.N.A.
CIUDAD UNIVERSITARIA
E - 28035 MADRID
Tel. : 34.1.394.1744
Fax : 34.1.394.1745

NOTARIANNI ELENA
INSTITUTE OF ANIMAL PHYSIOLOGY AND
GENETICS RESEARCH
BABRAHAM
GB - CB2 4AT CAMBRIDGE
Tel. : 223832312
Fax : 223836481

NOVAIS J.M.
INSTITUTO SUPERIOR TECNICO
DEPTO. DE ENGENHARIA QUIMICA
AV. ROVISCO PAIS
P - 1096 LISBOA

NUTI MARCO PAOLO
UNIVERSITY OF PADOVA
DIP. BIOTECHNOLOGIE AGRARIE
VIA GRADENIGO 6
I - 35131 PADOVA
Tel. : 0498071442
Fax : 0498070517

O'GARA FERGAL
UNIVERSITY COLLEGE CORK
DEPARTMENT OF MICROBIOLOGY
IRL - 31 CORK
Tel. : 35321272097
Telex : 76050 UNIC EI
Fax : 35321275934
E-mail: STDM 8008@IRUCCVAX.UCC.IE

OKKELS FINN
MARIBO SEED BIOTECHNOLOGY
DANISCO A/S
LANGEBROGADE 1
DK - 1001 COPENHAGEN
Tel. : 4531954100
Telex : 31430 DANSUK DK
Fax : 4531953022

OLESEN P.
DANISCO A/S
LANGEBROGADE 1
P.O. BOX 17
GB - 1001 COPENHAGEN K
Tel. : 45319541002210
Telex : 31430 DANSUK DK
Fax : 4531953022

OLIVARES PASCUAL JOSE
ESTACION EXPERIMENTAL DEL ZAIDIN
DEPARTAMENTO DE MICROBIOLOGIA
PROFESOR ALBAREDA 1
E - 18008 GRANADA
Tel. : 3458121011
Fax : 3458129600

OLIVER STEPHEN
UNIVERSITY OF MANCHESTER
INSTITUTE OF SCIENCE AND TECHNOLOGY
MANCHESTER BIOTECHNOLOGY CENTRE
P. O. BOX 88
SACKVILLE STREET
GB - MANCHESTER M60 1QD
Tel. : 44.61.200.4222
Fax : 44.61.236.0409

OLIVIERI ANGELO MARIO
DIPARTIMENTO DI PRODUZIONE VEGETALE
E TECNOLOGIE AGRARIE
FAGAGNA 208
I - 33100 UDINE
Tel. : 39432558605
Fax : 39432558603

OLSAKER INGRID
DEPARTMENT OF ANIMAL GENETICS
NORWEGIAN COLLEGE OF VETERINARY
MEDICINE
PO BOX DEP 8146
N - 0033 OSLO
Tel. : 4722964779
Fax : 4722964786
E-mail: INGRIDO@BIOMED.UIO.NO

OSBORNE NEVILLE
NUFFIELD LABORATORY OF
OPHTHALMOLOGY
UNIVERSITY OF OXFORD
WALTON STREET
GB - 0X2 6AW OXFORD
Tel. : 44865248996
Fax : 44865794508

OTTOLENGHI SERGIO
DIPARTIMENTO DI GENETICA EDI
BIOLOGIA DEI MICROORGANISMI
VIA CELORIA 26
I - 20133 MILANO
Tel. : 39226605225
Fax : 3922664551

OWEN MICHAEL
LYMPHOCYTE MOLECULAR BIOLOGY
LABORATORY
IMPERIAL CANCER RESEARCH FUND
LINCOLN'S INN FIELDS 44
PO BOX 123
GB - WC2A 3PX LONDON
Tel. : 44712693069
Fax : 44712693479

PAGES MONTSERRAT
DEP. GENETICA MOLECULAR
CENTRO DE INVESTIGACION Y DESARROLLO
CONSEJO SUPERIOR DE INVESTIGACIONES
JORDI GIRONA 18-26
E - 08034 BARCELONA
Tel. : 3432040600
Fax : 3432045904

PALACIOS FERNANDO
CONSEJO SUPERIOR DE INVESTIGACIONES CI
ENTIFICAS
MUSEO NACIONAL DE CIENCIAS NATURALES
JOSE GUTIERREZ ABASCAL 2
E - 28006 MADRID
Tel. : 34.1.411.1328
Fax : 34.1.564.5078

PALME KLAUS
MAX PLANCK-INSTITUT FÜR
ZUCHTUNGSFORSCHUNG
CARL-VON-LINNE-WEG 10
D - W5000 KOLN 30
Tel. : 492215062280
Telex : 8 881 028 MPIZ D
Fax : 492215062213

PALMGREN MICHAEL
DEPARTMENT OF PLANT BIOLOGY
ROYAL VETERINARY AND AGRICULTURAL
UNIVERSITY
THORVALDSENSVEJ 40
DK - 1871 FREDERIKSBERG C
Tel. : 4535282828
Fax : 4535283310

PANOPOULOS NICKOLAS
INSTITUTE OF MOLECULAR BIOLOGY AND BIOTECHNOLOGY
FOUNDATION FOR RESEARCH
POBOX 1527
GR - 711 10 HERAKLION-CRETE
Tel. : 3081210091
Telex : 262896IMBBGR
Fax : 3081230469

PANZERI LUCIA
UNIVERSITA DI MILANO
DIPARTIMENTO DI GENETICA E DI BIOLOGIA DEI MICRORGANISMI
26, VIA CELORIA
I - 20133 MILANO
Tel. : 39.2.26605218
Fax : 39.2.2664551

PAPADOPOULOS GEORGE K.
LABORATORY OE BIOLOGICAL CHEMISTRY - MEDICAL SCHOOL
UNIVERSITY OF IOANNINA
P.0. BOX 1186 1186
GR - 451 10 IOANNINA
Tel. : 3065133442
Telex : 322160 PNPS GR
Fax : 3065128388

PARKER MALCOLM
MOLECULAR ENDOCRINOLOGY LAB.
IMPERIAL CANCER RESEARCH FUND
LINCOLN'S INN FIELDS 44
PO BOX 123
GB - WC2A3PX LONDON
Tel. : 44712693280
Telex : 265107 ICRF G
Fax : 44714050190

PARMEGGIANI ANDREA
ECOLE POLYTECHNIQUE
LABORATOIRE DE BIOCHIMIE
CNRS 61840
F- 91128 PALAISEAU
Tel. : 33169334180
Telex : ECOLEX 601596
Fax : 33169333301

PASTORET PAUL-PIERRE
UNIVERSITE DE LIEGE
VIROLOGIE-IMMUNOLOGIE
FACULTE DE MEDECINE VETERINAIRE
BATIMENT B6
SART TILMAN
B- B 4000 LIEGE
Tel. : 3241563469
Fax : 3241563580

PASZKOWSKI J.
INSTITUT FUER PFLANZENWISSENSCHAFTEN
EIDGENOESSISCHE TECHNISCHE HOCHSCHULE
UNIVERSITAETSTRASSE 2
CH - 8092 ZUERICH
Tel. : 4112564438
Fax : 4112529613

PAULSEN HANS
INSTITUT FUER ORGANISCHE CHEMIE
DER UNIVERSITAET HAMBURG
MARTIN-LUTHER-KING-PLATZ 6
D - 2000 HAMBURG
Tel. : 494041232820
Telex : 214732 UNIHHD
Fax : 494041233834

PAZ-ARES JAVIER
LAB. DE GENETICA MOLECULAR DE PLANTAS CENTRO DE INVESTIGACIONES BIOLOGICAS
VELAZQUEZ 144
E - 28006 MADRID
Tel. : 3415854214
Fax : 3415627518

PEBERDY JOHN
MICROBIAL BIOCHEMISTRY AND GENETICS LABORATORY
UNIVERSITY OF NOTTINGHAM
UNIVERSITY PARK
GB - NG7 2RD NOTTINGHAM
Tel. : 0602 513231
Telex : 37346 UNINOT G
Fax : 0602 513251

PELICCI PIER GIUSEPPE
UNIVERSITA DI PERUGIA
ISTITUTO CLINICA MEDICA I
POLICLINICO MONTELUCE
VIA BRUNAMONTI 51
I - 06100 PERUGIA
Tel. : 755783255
Fax : 755783444

PELLEGRINI GRAZIELLA
CELLIFE BIOTECNOLOGIE PER LA VITA SRL
VIALE BENEDETTO XV 10
I - 16132 GENOVA
Tel. : 003910355504
Fax : 003910352999

PENTTILA MERJA
VTT BIOTECHNICAL LABORATORY
PO BOX 202
SF- 02151 ESPOO
Tel. : 35804561
Telex : 122972 VTTHA SF
Fax : 35804552028

PEREIRA A.
MOLECULAR BIOLOGY DEPARTMENT
ONDERZOEK INSTITUUT
KEIJENBERGSEWEG 6
NL - 6700 AA WAGENINGEN
Tel. : 31837091911
Fax : 31837014435

PEREZ LORENCES ESTER
DEPARTAMENTO BIOLOGIA VEGETAL
FACULTAD DE BIOLOGICAS
DOCTOR MOLINER 50
E - 46100 BURJASSOT (VALENCIA)
Tel. : 3463864634
Fax : 3463864372

PEREZ MARTINEZ GASPAR
INSTITUTO DE AGROQUIMICA Y
TECNOLOGIA DE ALIMENTOS
JAIME ROIG 11
E - 46010 VALENCIA
Tel. : 3463690800
Fax : 3463930001

PEREZ-SUAREZ GONZALO
UNIVERSIDAD DE ALCALA DE HENARES
DEPT. BIOLOGIA ANIMAL
N-11, KM 33.5
E - 28801 ALCALA DE HENARES
Tel. : 34.1.885.4967
Fax : 34.1.885.4953

PERUCH UGO
AGRONOMICA S.R.I. CONSORTILE
PIAZZA LUIGI CARLO FARINI 4
I - 48100 RAVENNA
Tel. : 3954435078
Telex : 551278 AGFERI
Fax : 39544510082

PETIT GLATRON MARIE FRANCOISE
INSTITUT JACQUES MONOD
LABORATOIRE GENETIQUE ET MEMBRANES
2 PLACE JUSSIEU
F- 75251 PARIS 05
Tel. : 33144276946
Fax : 33146332305

PETRE JEAN
SMITHKLINE BEECHAM BIOLOGICALS
RUE DE L'INSTITUT 89
B- B1330 RIXENSART
Tel. : 3226568444
Fax : 3226568113

PEÑALVA MIGUEL ANGEL
LABORATORIO DE GENETICA
MOLECULAR DE ASPERGILLUS
CENTRO DE INVESTIGACIONES BIOLOGICAS
VELAZQUEZ 144
E - 28006 MADRID
Tel. : 3415611800 EXT4358
Fax : 3415627518

PFLEIDERER WOLFGANG
UNIVERSITÄT KONSTANZ
FAKULTÄT FÜR CHEMIE
D - W7750 KONSTANZ

PHILIBERT DANIEL
ROUSSEL UCLAF
CENTRE DE RECHERCHES
107 ROUTE DE NOISY
F- 93230 ROMAINVILLE
Tel. : 330148914891
Fax : 33148915949

PHILIPPSEN PETER
INSTITUTE OF APPLIED MICROBIOLOGY
BIOZENTRUM
IAM-BASEL
KLINGELBERGSTR. 70
CH - 4056 BASEL
Tel. : 41612672140
Fax : 41612672118

PHITOS DIMITRIOS
UNIVERSITY OF PATRAS
BOTANICAL INSTITUTE
PANEPISTIMIOPOULIS
GR - 26010 PATRAS
Tel. : 30/61991813

PICARD JACQUES
LABORATORY OF DEVELOPMENTAL GENETICS
PLACE CROIX DU SUD 5
B- 1348 LOUVAIN-LA-NEUVE
Tel. : 3210473506
Fax : 3210473109

PICHLER WERNER
INSTITUTE OF CLINICAL IMMUNOLOGY
INSELSPITAL
FREIBURGSTRASSE
CH - 3010 BERN
Tel. : 4131642285
Fax : 4131255735

PLANTA RUDI J.
VRIJE UNIVERSITEIT, AMSTERDAM
FACULTEIT SCHEIKUNDE
LAB. BIOCHEMIE EN MOL.BIOL.
D BOELELAAN 1083
NL - 1081 HV AMSTERDAM
Tel. : 31205485648
Fax : 31206461479

PLUCKTHUN ANDREAS
UNIVERSITY OF ZURICH
BIOCHEMICAL INSTITUTE
WINTERTHURER STREET 190
CH - 8057 ZURICH
Tel. : 41.1.2575570
Fax : 41.1.257.57.12

POCCHIARI MAURIZIO
LABORATORIO DI VIROLOGIA
INSTITUTO SUPERIORE DI SANITA
VIALE REGINA ELENA 299
I - 00161 ROMA
Tel. : 3964457888
Fax : 3964453369

POHL FRITZ M.
UNIVERSITÄT KONSTANZ
FAKUTAT FÜR BIOLOGIE
POSTFACH 5600-906
JAKOB-BURCKHART-STR. 25
D - 78434 KONSTANZ
Tel. : 49.7531.882134
Fax : 49.7531.882134

POHL THOMAS
GATC GMBH
GESELLSCHAFT FÜR ANALYSETECHNIK
UND CONSULTING MBH
FRITZ-ARNOLD-STR. 23
D - 78467 KONSTANZ
Tel. : 49.7531.57209
Fax : 49.7531.57313

POPOT JEAN-LUC
INSTITUT DE BIOLOGIE PHYSICO-CHIMIQUE
SERVICE DE PHOTOSYNTHESE
13 RUE PIERRE ET MARIE CURIE
F- 75005 PARIS
Tel. : 33143252609
Fax : 33140468331

PORALLA KARL
BIOLOGISCHES INSTITUT
MIKROBIOLOGIE
UNIVERSIT T TÜBINGEN
AUF DER MORGENSTELLE 28
D - W7400 TUBINGEN
Tel. : 497071292080
Fax : 497071293094

POSSEE ROBERT
INSTITUTE OF VIROLOGY AND
ENVIRONMENTAL MICROBIOLOGY
MANSFIELD ROAD
GB - OX1 3SR OXFORD
Tel. : 44865512361
Telex : 83147VIROX-G
Fax : 4486559962

POUWELS PETER
MEDICAL BIOLOGICAL LABORATORY
P.O.BOX 45
NL - 2280 AA RIJSWIJK
Tel. : 3115842842
Telex : 38034 PMTNO NL
Fax : 3115843989

POZZI GIANNI
DIPARTIMENTO DI BIOLOGIA MOLECOLARE
SEZIONE DI MICROBIOLOGIA
VIA LATERINA 8
I - 53100 SIENA
Tel. : 39577280903
Fax : 3957742011

PRAT SALOME
CENTRO DE INVESTIGACION Y
DESARROLLO, C.S.I.C.
JORGE GIRONA 18-26
E - 08034 BARCELONA
Tel. : 3432046851
Fax : 3432045904

PRIEUR DANIEL
CNRS UPR 4601
STATION BIOLOGIQUE
PLACE G. TEISSIER
F- 29680 ROSCOFF
Tel. : 3398292340
Fax : 3398292324

PROCHIANTZ ALAIN
ECOLE NORMALE SUPERIEUR
660 46, RUE D'ULM
F- 75230 PARIS
Tel. : 33-1-44323712
Fax : 33-1-44323988

PROME JEAN-CLAUDE
LABORATOIRE DE PHARMACOLOGIE ET
TOXICOLOGIE FONDAMENTALES
205 ROUTE DE NARBONNE
F- 31077 TOULOUSE
Tel. : 3361335845
Fax : 3361335886

PUHLER ALFRED
UNIVERSITXT BIELEFELD
FAKULTÄT FÜR BIOLOGIE
LEHRSTUHL FÜR GENETIK
POSTFACH 100131
D - W33501 BIELEFELD
Tel. : 495211065607
Fax : 495211065626

PUIGDOMENECH PEDRO
CENTRO DE INVESTIGACION Y DESARROLLO
CONSEJO SUPERIOR DE INVESTIGACIONNES
CIENTIFICAS
JORDI GIRONA 18
E - 08034 BARCELONA
Tel. : 3432040600
Fax : 3432045904

PURNELLE BENEDICTE
UNIVERSITE CATHOLIQUE DE LOUVAIN
UNITE DE BIOCHIMIE PHYSIOLOGIQUE
PLACE CROIX DU SUD 2/20
B- 1348 LOUVAIN-LA-NEUVE
Tel. : 32.10.473618
Fax : 32.10.473872

QUAX WILHELMUS J.
GIST-BROCADES BV
POSTBUS 1
NL - 2600 MA DELFT
Tel. : 015799111
Telex : 38103 GBI NL
Fax : 015793482

RADBRUCH ANDREAS
INSTITUT FUER GENETIK
DER UNIVERSITAET ZU KOELN
WEYERTAL 121
D - W5000 KOELN
Tel. : 492214703409
Fax : 492214705185

RAMON VIDAL DANIEL
INSTITUTO DE AGROQUIMICA Y TECNOLOGIA
DE LOS ALIMENTOS
JAIME ROIG 11
E - 46010 VALENCIA
Tel. : 3463690800
Telex : 64197 AYTVE
Fax : 3463930001
E-mail: HONGOS8IATA.CSIC.ES

RAMOS JUAN L.
ESTACION EXPERIMENTAL DEL ZAIDIN
PROFESOR ALBAREDA 1
E - 18008 GRANADA
Tel. : 3458121011
Fax : 3458129600

RANA KRISHEN
UNIVERSITY OF STIRLING
INSTITUTE OF AQUACULTURE
GB - STIRLING FK9 4LA
Tel. : 44.786.473171
Fax : 44.786.472133

RANDO ANDREA
DIPARTIMENTO DI SCIENZE DELLE
PRODUZIONI ANIMALI
NAZARIO SAURO 85
I - 85100 POTENZA
Tel. : 39971474289
Fax : 39971470719

RAPOPORT TOM
MAX-DELBRÜCK-CENTER FOR MOLECULAR
MEDICINE
ROBERT-ROESSLE-STRASSE 10
D - O1115 BERLIN-BUCH
Tel. : 3729462310
Fax : 3729463363

RAPPUOLI RINO
ISTITUTO RICERCHE
IMMUNOLOGICHE DI SIENA
VIA FIORENTINA 1
I - 53100 SIENA
Tel. : 39577293414
Telex : 571329
Fax : 39577293564

RAY DAVID E.
MRC TOXICOLOGY UNIT
LANCASTER ROAD
GB - LEICESTER LE1 9HN
Tel. : 44-533-525585
Fax : 44-533-525616

REGAN CIARAN
DEPARTMENT OF PHARMACOLOGY AND
THERAPEUTICS
UNIVERSITY COLLEGE DUBLIN
BELFIELD
IRL - 4 DUBLIN
Tel. : 35317061619
Telex : 32693 EI
Fax : 35312692749

REID GORDON
NORTH OF ENGLAND ZOOLOGICAL SOCIETY
- ZOOLOGICAL GARDENS
UPTON
GB - CHESTER CH2 1LH
Tel. : 44.244.438.0280
Fax : 44.244.437.1273

REISS B.
MAX-PLANCK-INSTITUT FUER
ZUECHTUNGSFORSCHUNG
CARL-VON-LINNE-WEG 10
D - 5000 KOELN 30
Tel. : 492215062220
Fax : 492215062213

RENARD JEAN PAUL
LABORATOIRE DE BIOLOGIE CELLULAIRE ET
MOLECULAIRE
INRA - DOMAINE DE VILVERT
F- 78352 JOUY-EN-JOSAS CEDEX
Tel. : 33134652594
Fax : 33134652273

RESKI RALF
INSTITUT FUER ALLGEMEINE BOTANIK
OHNHORSTSTRASSE 18
D - W2000 HAMBURG SL
Tel. : 494082282295
Fax : 494082282254

REVILLARD JEAN-PIERRE
LABORATOIRE D'IMMUNOLOGIE INSERM
U.8O
PLACE D'ARSONVAL
F- 69437 LYON 03
Tel. : 3378548021
Fax : 3372330044

RICCI MARIO
LABORATORY OF ALLERGOLOGY AND
CLINICAL
IMMUNOLOGY, ISTITUTO DI CLINICA MEDICA
III
VIALE MORGAGNI 85
I - 50134 FIRENZE
Tel. : 3955411155
Fax : 3955412867

RICH PETER
THE GLYNN RESEARCH FOUNDATION LTD
GLYNN
GB - PL30 4AU BODMIN
Tel. : 4420882482
Fax : 4420882575

RIESNER DETLEV
HEINRICH-HEINE UNIV. DUESSELDORF
INSTITUT FUER PHYSIKALISCHE
BIOLOGIE
UNIVERSITAETSSTRASSE 1
D - W4000 DUESSELDORF
Tel. : 492113114840
Fax : 492113115167

RIGAUD JEAN-LOUIS
COMMISSARIAT A L'ENERGIE ATOMIQUE
DEPARTEMENT BIOLOGIE CELLULAIRE
ET MOLECULAIRE - SECTION BIOENERGIE
CEN SACLAY
BAT. 532
F- 91191 GIF-SUR-YVETTE CEDEX
Tel. : 33169082430
Fax : 33169088717

RITTER ENRIQUE
CENTRO DE INVESTIGACION Y MEJORA
AGRARIA IKT-CIMA-GRANJA MODELO
APARTADO 46
E - 01080 VITORIA
Tel. : 3445281300
Fax : 3445281422

ROBILLARD GEORGE
UNIVERSITY OF GRONINGEN
GRONINGEN BIOMOLECULAR SCIENCES AND BIOTECHNOLOGY (GBB)
DEPARTMENT OF CHEMISTRY
NIJENBORGH 4
NL - 9747 AG GRONINGEN
Tel. : 3150634321
Fax : 3150634165

RODRIGUES-POUSADA CLAUDINA
INSTITUTO GULBENKIAN DE CIêNCIA
LABORATORIO DE GENETICA MOLECULAR
RUA DA QUINTA GRANDE 6
APARTADO 14
P - 2780 OEIRAS
Tel. : 351.1.443.5600
Fax : 351.1.443.1631

RODRIGUEZ-FARRE EDUARDO
CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS
DEPARTMENT OF PHARMACOLOGY & TOXICO-
C/ JORDI GIRONA 18-26
E - 08034 BARCELONA
Tel. : 3432040600
Telex : 97977
Fax : 3432045904

RODRIGUEZ-NAVARRO ALONSO
LABORATORIO DE MICROBIOLOGIA
ESCUELA TECNICA SUPERIOR
DE INGENIEROS AGRONOMOS
E - 28040 MADRID
Tel. : 3415444807
Fax : 3415434879

ROGERS MARK
NATIONAL AGRICULTURAL AND VETERINARY
BIOTECHNOLOGY CENTRE
UNIVERSITY COLLEGE DUBLIN
BELFIELD
IRL - 4 DUBLIN
Tel. : 35317062083
Telex : 32693E1
Fax : 353-317061153

ROGNE SISSEL
DEPARTMENT OF ANIMAL SCIENCE
AGRICULTURAL UNIVERSITY OF NORWAY
P.0. BOX 25
N - 1432 AAS-NLH
Tel. : 479948022
Fax : 479947960

ROHMER MICHEL
LABORATOIRE DE SYNTHESE ORGANIQUE ET DE CHIMIE MICROBIENNE
ECOLE NATIONALE SUPERIEURE DE CHIMIE C
3 RUE ALFRED WERNER
F- 68093 MULHOUSE CEDEX
Tel. : 3389427020
Fax : 3389599859

ROMAGNANI SERGIO
CATTEDRA DI ALLERGOLOGIA & IMMUNOLO-GIA CLINICA
ISTITUTO DI CLINICA
MEDICA III
VIALE MORGAGNI 85
I - 50134 FIRENZE
Tel. : 3955413663
Fax : 3955412867

ROMEO PAUL-HENRI
HOPITAL HENRI MONDOR
INSERM
UNITE 91
F- 94010 CRETEIL
Tel. : 33149812896
Fax : 33149812895

ROSA FREDERIC
U 368 INSERM
DEPARTMENT OF BIOLOGY
ECOLE NORMALE SUPERIEURE
46 RUE D'ULM
F- 75230 PARIS 05
Tel. : 3344323607
Fax : 334432394

ROSSI MOSE
DIPARTIMENTO DI CHIMICA ORGANICA E BIOLOGICA, UNIVERSITA' DEGLI STUDI DI NAPOLI "FEDERICO II"
VIA MEZZOCANNONE 16
I - 80134 NAPOLI
Tel. : 39815521310
Fax : 39815521217

ROSSIER JEAN
INSTITUT ALFRED FESSARD
CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE
F- 91198 GIF-SUR-YVETTE CEDEX
Tel. : 33169823436
Fax : 33169824343
E-mail: ROSSIERAARTHUR.CITI2.FR

ROSSIGNOL MICHEL
BIOCHIMIE ET PHYSIOLOGIE VEGETALES
INRA
PLACE-P. VIALA
F- 34060 MONTPELLIER 1
Tel. : 3367612707
Fax : 3367525737

ROTTMANN OSWALD
LEHRSTUHL FÜR TIERZUCHT
DER TU MÜNCHEN
D - 8050 FREISING-WEIHENSTEPHAN
Tel. : 08161713228
Fax : 08161713107

ROUGON GENEVIEVE
UNIVERSITE D'AIX-MARSEILLE II - CNRS
FACULTE DES SCIENCES DE LUMINY
BIOLOGIE DE LA DIFFERENCIATION
CELLULAIRE
LUMINY CASE 901
F- 13288 MARSEILLE CEDEX 09
Tel. : 33.91.269246
Fax : 33.91.269386

ROY POLLY
LABORATORY OF MOLECULAR BIOPHYSICS
DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF OXFORD
SOUTH PARKS ROAD
GB - OXL 3QU OXFORD
Tel. : 44-865-512361
Fax : 44-865-59962

RUFFILLI ANNA
ISTITUTO INTERNAZIONALE DI GENETICA E
BIOFISICA
VIA MARCONI 10
I - 80125 NAPOLI
Tel. : 0039817257299
Fax : 0039815936123

RUIZ-ARGUESO TOMAS
ESCUELA TECNICA SUPERIOR DE
INGENIEROS AGRONOMOS
LABORATORIO DE MICROBIOLOGIA
CIUDAD UNIVERSITARIA
E - 28040 MADRID
Tel. : 3415444807
Fax : 3415434879

RUSSELL PETER
DEPARTMENT OF PATHOLOGY
AND INFECTIOUS DISEASE
ROYAL VETERINARY COLLEGE
ROYAL COLLEGE STREET
GB - LONDON NW1 OTU
Tel. : 44.71.387.2898
Fax : 44.71.388.2342

RUSSO VINCENZO E.A.
MAX-PLANCK-INSTITUTE
FUR MOLEKULARE GENETIK
IHNESTR 73
D - W1000 BERLIN
Tel. : 49308307264
Fax : 49308307385
E-mail: RUSSO@MPIMG-BERLIN.MPG.DBP.DE

RYAN J.
BIORESEARCH IRELAND
EOLAS
GLASNEVIN
IRL - DUBLIN 9

SAKMANN BERT
MAX-PLANCK-INSTITUT FÜR
MEDIZINISCHE FORSCHUNG
JAHNSTRASSE 29
D - 6900 HEIDELBERG
Tel. : 496221486460
Telex : 461 505
Fax : 496221486459

SALA FRANCESCO
DIPARTIMENTO DI GENETICA E
MICROBIOLOGIA - UNIVERSITA DI PAVIA
VIA ABBIATEGRASSO 207
I - 27100 PAVIA
Tel. : 39382391569
Fax : 39382528496

SALAMINI F.
MAX-PLANCK-INSTITUT FUR
ZUCHTUNGSFORSCHUNG
CARL-VON-LINNE-WEG
D - W5000 KOLN
Tel. : 492215062420
Fax : 402215062413

SALAS JOSE A.
UNIVERSIDAD DE OVIEDO
DEPARTAMENTO DE BIOLOGIA FUNCTIONAL
AREA DE MICROBIOLOGIA
JULIAN CLAVERIA S/N
E - 33006 OVIEDO
Tel. : 3485103530
Fax : 3485103354
E-mail: JASF DWARFI.QUIMICA.UNIOVI.ES

SALINAS JULIO
DEPARTAMENTO DE PROTECCION VEGETAL
CENTRO DE INVESTIGACION Y TECNOLOGIA
INSTITUTO NACIONAL DE INVESTIGACION
CARRETERA DE LA CORUNA, KM. 7.5
E - 28040 MADRID
Tel. : 3413476890
Fax : 3413573107

SAMARUT JACQUES
ONCOGENESE VIRALE ET DIFFERENCIATION CELLULAIRE
ECOLE NORMALE SUPERIEURE DE LYON
46 ALLEE D'ITALIE
F- 69364 LYON 07
Tel. : 3372728135
Fax : 3372728080

SAMPAYO MARIA ANTONIA
INSTITUTO NACIONAL DE INVESTIG. DAS PESCAS
DEPARTMENT OF OCEANOGRAPHY
AVENIDA BRASILIA
P - 1400 LISBOA
Tel. : +351 1 3016361/368
Telex : 15857 INIP P
Fax : +351 1 3015948

SANCHEZ SERRANO JOSE JUAN
CENTRO DE INVESTIGACIONES BIOLOGICAS
VELAZQUEZ 144
E - 28006 MADRID
Tel. : 3415611800
Fax : 3415627518

SANDER CHRIS
PROTEIN DESIGN GROUP
EUROPEAN MOLECULAR BIOLOGY LABORATORY
MEYERHOFSTRASSE
D - W6900 HEIDELBERG
Tel. : 496221387361
Fax : 496221387306
E-mail: SANDER@EMBL-HEIDELBERG.DE

SANDERS DALE
DEPARTMENT OF BIOLOGY
UNIVERSITY OF YORK
HESLINGTON
GB - Y01 5DD YORK
Tel. : 44904432825
Telex : 57933 YORKUL
Fax : 44904432860
E-mail: DSIO@UK.AC.YORK

SANDMANN GERHARD
UNIVERSITAET KONSTANZ
FAKULTAET FUER BIOLOGIE
P.0. BOX 5560
D - W7750 KONSTANZ
Tel. : 497531883668
Fax : 497531883042

SANSONETTI PHILIPPE
UNITE DE PATHOGENIE MICROBIENNE MOLECULAIRE
INSERM U199
28 RUE DU DOCTEUR ROUX
F- 75724 PARIS 15
Tel. : 33145688342
Fax : 33145688953

SANTISTEBAN PILAR
INSTITUTO DE INVESTIGACIONES BIOMEDICAS - C.S.I.C.
ARTURO DUPERIER 4
E - 28029 MADRID
Tel. : 3415854082
Fax : 3415854015

SANTORO CLAUDIO
LABORATORIO NAZIONALE
CONSORZIO INTERUNIVERSITARIO PER LE BIOTECNOLOGIE
PADRICIANO 99
I - 34012 TRIESTE
Tel. : 3940398992
Fax : 3940398979

SANTOS HELENA
CENTRO DE TECNOLOGIA QUIMICA E BIOLGGICA
RUA DA QUINTA GRANDE 6
APARTADO 127
P - 2780 OEIRAS
Tel. : 35114426246
Fax : 35114428766

SARTHOU JEAN-LOUIS
INSTITUT PASTEUR DE DAKAR
UNITE D'IMMUNOLOGIE / EPIDEMIOLOGIE
B.P 220
SN - DAKAR
Tel. : 221235181
Telex : 221 61241 PASTEUR
Fax : 221238772

SARVAS MATTI
NATIONAL PUBLIC HEALTH INSTITUTE
MANNERHEIMINTIE 166
SF- 00300 HELSINKI
Tel. : 35804744241
Fax : 35804744238
E-mail: MSARVAS@NPHI.FI

SCANDURRA ROBERTO
DIPARTIMENTO SCIENZE BIOCHIMICHE
"A.ROSSI-FANELLI"
UNIVERSITA'"LA SAPIENZA"
P.LE A.MORO 5
I - 00185 ROMA
Tel. : 39649910947
Fax : 3964440062

SCARCEZ THIERRY
INNOGENETICS
INDUSTRIEPARK ZWIJNAARDE 7
BOX 4
B- 9052 GENT
Tel. : 32.91.410711
Fax : 32.91.410799

SCAZZOCCHIO CLAUDIO
INSTITUT DE GENETIQUE ET MICROBIOLOGIE
UPS BATIMENT 409
CENTRE D'ORSAY
15 GEORGES CLEMENCEAU
F- 91405 ORSAY CEDEX
Tel. : 33169416356
Fax : 33169417808

SCHACHNER MELITTA
SWISS FEDERAL INSTITUTE OF TECHNOLOGY
DEPARTMENT OF NEUROBIOLOGY
HÜNGGERBERG
CH - 8093 ZURICH
Tel. : 41.1.3773396
Fax : 41.1.3710235

SCHAFER GUNTER
INSTITUTE OF BIOCHEMISTRY
MEDICAL UNIVERSITY OF LÜBECK
RATZEBURGER ALLEE 160
D - W2400 LUBECK
Tel. : 494515004060
Fax : 494515004068

SCHARTL MANFRED
PHYSIOLOGISCHE CHEMIE I
THEODOR-BOVERI-INSTITUT FOR
BIOWISSENSCHAFTEN (BIOZENTRUM)
AM HUBLAND
D - W8700 WORZBURG
Tel. : 499318884148
Fax : 499318884150

SCHEFFER RUDOLF
ZAADUNIE B.V.
P.O. BOX 26
NL - 1600AA ENKUIZEN
Tel. : 31228066235
Telex : 57053 SG NL
Fax : 31228066133

SCHELL JEFF
MAX-PLANCK-INSTITUT FUR ZÜCHTUNGS-
FORSCHUNG
CARL-VON LINNE-WEG
D - W5000 KOELN
Tel. : 02215062200
Fax : 02215062213

SCHLEIFER KARL-HEINZ
TECHNISCHE UNIVERSITÄT MÜNCHEN
INSTITUT FÜR BRAUEREITECHNOLOGIE
UND MIKROBIOLOGIE
LICHTENBERGSTRASSE 4
WEIHENSTEPHAN
D - W8046 GARCHING BEI MUNCHEN

SCHLEUNING WOLF-DIETER
SCHERING AG
INST. OF CELLULAR AND MOLECULAR
BIOLOGY
MULLERSTR. 170-178
D - W1OOO BERLIN 65
Tel. : 49304681390
Fax : 493046916707

SCHLOSSHAUER BURKHARD
NATURWISSENSCHAFTLICHES UND
MEDIZINISCHES INSTITUT AN DER
UNIVERSITAT TÜBINGEN
GUSTAV-WERNER-STRASSE 3
D - W7410 REUTLINGEN
Tel. : 49712131980
Fax : 497121319816

SCHOELER HANS
EUROPEAN MOLECULAR BIOLOGY
LABORATORY
MEYERHOFSTRASSE 1
POSTFACH 10 2209
D - W6900 HEIDELBERG
Tel. : 496221387550
Telex : 461613 EMBL D)
Fax : 496221387518

SCHOFFL FRIEDRICH
UNIVERSITAET TUEBINGEN
BIOLOGISCHES INSTITUT
LEHRSTUHL ALLGEMEINE GENETIK
AUF DER MORGENSTELLE 28
D - W7400 TUEBINGEN
Tel. : 497071292076
Fax : 497071294634
E-mail:
BKSC@MAILSERV.ZDV.UNI.TUEBINGEN.DE

SCHOLZ FLORIAN
INSTITUT FÜR FORSTGENETIK
BUNDESFORSCHUNGSANSTALT FÜR
FORST-UND HOLZWIRTSCHAFT
SIEKER LANDSTRASSE 2
D - 2070 GROSSHANSDORF
Tel. : 49410261079
Fax : 49410262981

SCHONHEIT PETER
INSTITUTE FÜR PFLANZENPHYSIOLOGIE
UND MIKROBIOLOGIE
FREIE UNIVERSITÄT BERLIN
KÖNIGIN-LUISE-STRASSE 12-16A
D - W 1000 BERLIN 3
Tel. : 0308383116
Fax : 0308383118

SCHOTS ARJEN
WAGENINGEN AGRICULTURAL UNIVERSITY
DEPARTMENT OF NEMATOLOGY
LABORATORY FOR MONOCLONAL
P.0. BOX 9060
NL - 6700 GW WAGENINGEN
Tel. : 31837076214
Fax : 31837010113
E-mail: ARJEN.SCHOTS@IPO.AGRO.NL

SCHOUSBOE ARNE
DEPARTMENT OF BIOLOGY
ROYAL DANISH SCHOOL OF PHARMACY
UNIVERSITETSPARKEN 2
DK - DK2100 KOBENHAVN
Tel. : 4535370850
Fax : 4535375744

SCHREMPF HILDGUND
UNIVERSITY OSNABRUCK
FB BIOLOGIE CHEMIE
BARBARASTR. 11
D - W4500 OSNABRUCK
Tel. : 05419692895
Fax : 05419692804

SCHROEDER RENEE
INSTITUT FÜR MIKROBIOLOGIE UND
GENETIK
UNIVERSITÄT WIEN
DR. BOHR-GASSE 9
A- 1030 WIEN
Tel. : 43.1.79515 4609
Fax : 43.1.798 6224
E-mail: RENEE@GEM.UNIVIE.AC.AT

SCHULZE ERNST-DETLEF
LEHRSTUHL PFLANZENÖKOLOGIE
UNIVERSITÄT BAYREUTH
BOX 101251
D - W8580 BAYREUTH
Tel. : 49921552570
Fax : 49921552564

SCHUMANN WOLFGANG
LEHRSTUHL GENETIK
UNIVERSITAET BAYREUTH
PO BOX 101251
D - W 8580 BAYREUTH
Tel. : 921552708
Fax : 921552535
E-mail:
BITNET:WOLFGANG.SCHUMANNAUNI-BAREU
TH.DPE.DE

SCHUTZ GUNTHER
DEUTSCHES KREBSFORSCHUNGSZENTRUM
ABTEILUNG MOLEKULARBIOLOGIE DER ZELLE
IM NEUENHEIMER FELD 280
D - W6900 HEIDELBERG
Tel. : 00496221423411
Telex : 461 562 DKFZ D
Fax : 00496221402598

SCHWARZ-SOMMER ZSUZSANNA
MAX-PLANCK-INSTITUT
FUR ZUCHTUNGSFORSCHUNG
CARL-VON-LINNE-WEG 10
D - W5000 COLOGNE
Tel. : 492215062140
Fax : 492215062113

SCHWEIZER MICHAEL
AFRC INSTITUTE OF FOOD RESEARCH
GENETICS AND MICROBIOLOGY DEPT.
NORWICH RESEARCH PARK COLNEY
GB - NORWICH NR4 7UA
Tel. : 44.603.56122
Fax : 44.603.58414

SCHWENGER BARBARA
INSTITUT FUER TIERZUCHT UND VERERBUNGSFORSCHUNG .
BUENTEWEG 17P
D - 3000 HANNOVER
Tel. : 495119538875
Fax : 495119538582
E-mail: JOERN.WREDEATTIERZUCHT.TIHO-H.DBP.DE

SCHWERIN MANFRED
DEPARTMENT OF MOLECULAR BIOLOGY
RESEARCH INSTITUTE FOR BIOLOGY OF FARM ANIMALS
W.-STAHL-ALLEE 2
D - 2551 DUMMERSTORF
Tel. : 49382087209
Telex : 3LLO4FZDZ
Fax : 49382087209

SEBERG OLE
KOBENHAVNS UNIVERSITET
BOTANICAL LABORATORY
GOTHERSGADE 140
DK - 1123 KOBENHAVN K
Tel. : 45.33114690

SEIFART KLAUS
INSTITUT FOR MOLEKULARBIOLOGIE UND TUMURFORSCHUNG
PHILIPPS UNIVERSITÄT
LAHNSTR. 3
D - W3550 MARBURG
Tel. : 496421285013
Fax : 496421285390

SEIFERT WILFRIED
MAX-PLANCK-INSTITUT FÜR BIOPHYSIKAL CHEMIE
AM FASSBERG, POSTFACH 2841
D - 3400 GÖTTINGEN
Tel. : 49551201678
Fax : 49551201222

SEITZ HANNS ULRICH
BOTANISCHES INSTITUT
ALLGEMEINE BOTANIK
UND PFLANZENPHYSIOLOGIE
AUF DER MORGENSTELLE 1
D - 7400 TUBINGEN
Tel. : 497071296159
Fax : 497071293287

SENTENAC ANDRE
COMMISSARIAT A L'ENERGIE ATOMIQUE
-DSVDBCM-
SERVICE DE BIOCHIMIE ET DE GENETIQUE MOLECULAIRE
CENTRE D'ETUDES DE SACLAY
F- 91191 GIF SUR YVETTE CEDEX
Tel. : 33169082236
Fax : 33169084712

SENTENAC HERVE
BIOCHIMIE ET PHYSIOLOGIE VEGETALES
INRA-ENSA
F- 34060 MONTPELLIER 1
Tel. : 3367612605
Fax : 3367525737

SEPULVEDA FRANCISCO
AFRC INSTITUTE OF ANIMAL PHYSIOLOGY AND GENETICS RESEARCH
BABRAHAM HALL
GB - CB2 4AT CAMBRIDGE
Tel. : 44223832312
Fax : 44223837912
E-mail: SEPULVEDA@UK.AC.AFRC.IAPC

SERRANO RAMON
UNIVERSIDAD POLITECNICA DE VALENCIA
LABORATORIO DE BIOLOGIA MOLECULAR
DEPARTAMENTO DE BIOTECNOLOGIA
UNIVERSIDAD POLITECNICA
CAMINO DE VERA 14
E - 46022 VALENCIA
Tel. : 3463877425
Fax : 3463877429

SHARP RICHARD JAMES
PUBLIC HEALTH LABORATORY SERVICE
CENTRE FOR APPLIED MICROBIOLOGY
AND RESEARCH
GB - SP4 OJG SALISBURY
Tel. : 44980610391
Telex : 47683 PHCAMR G)
Fax : 44980611320

SIMOES DA COSTA MILTON
CENTRO DE BIOLOGIA CELULAR
DEPARTAMENTO DE ZOOLOGIA
UNIVERSDADE DE COIMBRA
LARGO MARQUES DE POMBAL
P - 3049 COIMBRA CEDEX
Tel. : 3513934729
Fax : 3513935812

SIMON MARKUS M
MAX-PLANCK-INSTITUT FUER IMMUNBIO-
LOGIE
STUEBEWEG 51
D - W7800 FREIBURG
Tel. : 497615108433
Fax : 497615108431

SIMON REINHARD
GENTECHNISCHES LABOR DES
TÜV SÜDWEST, FACHBEREICH
ENERGIETECHNIK UND UMWELTSCHUTZ
ROBERT-BUNSEN-STR. 1
D - W7800 FREIBURG
Tel. : 49761506061
Fax : 497615143622

SJOEHOLM CARSTEN
BACTERIAL SCREENING & GENETICS
MICROBIOLOGY
NOVO NORDISK
NOVO ALLE
DK - 2880 BAGSVAERD

SKIDMORE CHRISTOPHER
DEPARTMENT OF BIOCHEMISTRY
AND PHYSIOLOGY
SCHOOL OF ANIMAL AND MICROBIAL
AMS BUILDING 228
WHITEKNIGHTS
GB - RG6 2AJ READING :
Tel. : 44734318012
Telex : 847813
Fax : 44734310180
E-mail: SASSKIDM@CMS.AM.RDG.AC.UK

SLONIMSKI PIOTR
CENTRE NATIONAL DE LA RECHERCHE
SCIENTIFIQUE
CENTRE DE GENETIQUE MOLECULAIRE
(GENOMES ET FONCTIONS)
AVENUE DE LA TERRASSE
F- 91198 GIF-SUR-YVETTE
E-mail: SLONIMSKI FRGM5I.BITNET

SMALLA KORNELIA
BIOLOGISCHE BUNDESANSTALT FÜR LAND-
UND FORSTWIRTSCHAFT, INSTITUT FÜR
MESSEWEG 11-12
D - W3300 BRAUNSCHWEIG
Tel. : 495312990000
Fax : 495312993000

SMEEKENS JOSEPH
UNIVERSITY OF UTRECHT
DEPARTMENT OF MOLECULAR CELL
BIOLOGY
PADUALAAN 8
NL - 3584 CH UTRECHT
Tel. : 3130533184
Fax : 3130513655
E-mail: WBTMCBW@ACCUCX.CC.RUU.NL

SMITH HARRY
UNIVERSITY OF LEICESTER
UNIVERSITY ROAD
GB - LEI 7RH LEICESTER
Tel. : 0533523381
Fax : 0533522791

SMITH JAMES
NATIONAL INSTITUTE FOR MEDICAL
RESEARCH
THE RIDGEWAY
MILL HILL
GB - NW 7IAA LONDON
Tel. : 44819523666
Fax : 44819064477

SOLOMON ELLEN
IMPERIAL CANCER RESEARCH FUND
SOMATIC CELL GENETICS
LINCOLN'S INN FIELDS 44
PO BOX 123
GB - WC2A 3PX LONDON
Tel. : 44712693426
Fax : 44718316786
E-mail: E-SOLOMON OUK.AC.ICRF

SONNEWALD UWE
INSTITUT FÜR PFLANZENGENETIK UND KULTURPFLANZENFORSCHUNG
CORRENSSTRASSE 3
D - O4325 GATERSLEBEN
Tel. : 455925214
Fax : 45592280

SOR FREDERIC
INSTITUT CURIE
SECTION DE BIOLOGIE
BâTIMENT 110
F- 91405 ORSAY
Tel. : 33.1.6986.3060
Fax : 33.1.6986.9429

SOUCIET JEAN-LUC
UNIVERSITE LOUIS PASTEUR & CENTRE NATIONAL DE
LA RECHERCHE SCIENTIFIQUE
URA-GEM 1481
15 RUE RENE DESCARTES
F- 67000 STRASBOURG
Tel. : 33.88.41.70.39
Fax : 33.88.61.06.80

SOULILLOU JEAN-PAUL
INSTITUT DE TRANSPLANTATION ET DE RECHERCHE EN TRANSPLANTATION (ITERT)
9 INSERM U211 - INSTITUT DE BIOLOGIE
QUAI MONCOUSU
F- 44035 NANTES 01
Tel. : 3340084747
Fax : 3340356697

SPEZIA FRANCOIS
ROUSSEL UCLAF GROUP
RESEARCH CENTER
102 ROUTE DE NOISY
F- 93230 ROMAINVILLE
Tel. : 33148914253
Telex : 235 477 F
Fax : 33148914860

SREENAN JOSEPH
TEAGASC
AGRICULTURE AND FOOD DEVELOPMENT AUTHORITY
BELCLARE
IRL - 31 TUAM, CO. GALWAY
Tel. : 3539355455
Fax : 3539355430

STEENSMA YDE
LEIDEN UNIVERSITY
CLUSIUS LABORATORY
WASSENAARSEWEG 64
NL - 2333 LEIDEN
Tel. : 31.71.274.947
Fax : 31.71.274.999

STEJSKAL VERA
SAFETY ASSESSMENT
AB ASTRA
S - 15185 SOEDERTAELJE
Tel. : 46855326000
Telex : 19237
Fax : 46855328823

STETTER KARL OTTO
INSTITUT FÜR BIOCHEMIE, GENETIK UND MIKROBIOLOGIE
LEHRSTUHL FÜR MIKROBIOLOGIE
UNIVERSITAT REGENSBURG 31
UNIVERSITATSSTRASSE
D - W8400 REGENSBURG
Tel. : 00499419433160
Telex : 65658 UNIRE D
Fax : 00499419432403

STIEKEMA WILLEM
CENTRE FOR PLANT BREEDING AND REPRODUCTION RESEARCH
C.P.R.O. - D.L.O.
DROEVENDAALSESTEEG 16
NL - 6700 AA WAGENINGEN
Tel. : 31837077130
Fax : 31837016513

STIRLING COLIN
DEPARTMENT OF BIOCHEMISTRY AND MOLECULAR BIOLOGY
THE VICTORIA UNIVERSITY OF
OXFORD ROAD
GB - M13 9PT MANCHESTER
Tel. : 44612755104
Fax : 44612755082

STITT MARK
BOTANISCHES INSTITUT DER UNIVERSIT–T HEIDELBERG
IM NEUENHEIMER FELD 360
D - W6900 HEIDELBERG
Tel. : 496221563284
Fax : 496221565859

STOUGAARD JENS
DEPARTMENT OF MOLECULAR BIOLOGY
LABORATORY OF GENE EXPRESSION
UNIVERSITY OF AARHUS
GUSTAV WIEDSVEJ 10
DK - 8000 AARHUS C
Tel. : 4586202000
Fax : 4586201222

SUNDQUIST BO
NATIONAL VETERINARY INSTITUTE
DIVISION OF VACCINE RESEARCH
BOX 7073
S - S75007 UPPSALA
Tel. : 4618674000
Telex : 7623 SVAVETS
Fax : 4618674376

TABLER MARTIN
FOUNDATION FOR RESEARCH AND TECHNOLOGY
INSTITUTE OF MOLECULAR BIOLOGY
PO BOX 1527
GR - 711 10 HERAKLION CRETE

TAUTZ DIETHARD
UNIVERSITÄT MÜNCHEN
ZOOLOGISCHES INSTITUT
LUISENSTRASSE 14
D - W8000 MUNCHEN
Tel. : 49895902529
Fax : 49895902450

TEIXEIRA MIGUEL
CENTRO DE TECNOLOGIA QUIMICA E BIOLOGICA
RUA DA QUINTA GRANDE 6
APT. 127
P - 2780 OEIRAS
Tel. : 35114426146
Fax : 35114428766
E-mail: MIGUEL@CTQBO1.CTQB.PT

TERZI MARIO
CONSORZIO PER LA BIOLOGIA MOLECOLARE DELLE PIANTE
SEZ. DI PADOVA, DIP.DI BIOLOGIA
TRIESTE 75
I - 35121 PADOVA
Tel. : 39498286285
Fax : 39498286261
E-mail: TERZI @ HP800.BIO.UNIPD.IT

THOMAS BRIAN
HORTICULTURE RESEARCH INTERNATIONAL
LITTLEHAMPTON
WORTHING ROAD
LITTLEHAMPTON
GB - BN16 BN17 WEST SUSSEX
Tel. : 0903716123
Fax : 0903726780

THOMM MICHAEL
CHRISTIAN-ALBRECHTS-UNIVERSIT–T ZU KIEL
AM BOTANISCHEN GARTEN 1-9
D - W2300 KIEL
Tel. : 494318804334
Fax : 494318802194

THOMPSON RICHARD
MAX-PLANCK-INSTITUT FÜR ZÜCHTUNGSFORSCHUNG
CARL-VON-LINNE-WEG 10
D - W5000 KOLN
Tel. : 492215062440
Telex : 8 881 028 MPIZ D
Fax : 492215062413

THOMSON ANDREW
SCHOOL OF CHEMICAL SCIENCES
UNIVERSITY OF EAST ANGLIA
GB - NR4 7TJ NORWICH
Tel. : 44603592023
Telex : 975197
Fax : 44603259396

THORNTON JANET
BIOMOLECUL. STRUCTURE & MODELLING UNIT
BIOCHEMISTRY & MOLECULAR BIOLOGY DEPT.
UNIVERSITY COLLEGE LONDON
GOWER STREET
GB - WC1E 6BT LONDON
Tel. : 44713807048
Fax : 44713807193
E-mail: THORNTON@UK.AC.UCL.BIOC.BSM

TIMMIS KENNETH N.
GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG
DEPARTMENT OF MICROBIOLOGY
MASCHERODER WEG 1
D - W3300 BRAUNSCHWEIG
Tel. : 495316181400
Telex : 952667 GEBIOD
Fax : 495316181411

TINDALL BRIAN
DSM-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GMBH
MASCHERODER WEG LB
D - W3300 BRAUNSCHWEIG
Tel. : 053161870
Fax : 0531618718
E-mail: 10075:DB10225

TIRABY GERARD
LABORATOIRE DE MICROBIOLOGIE
UNIVERSITE PAUL SABATIER
118 ROUTE DE NARBONNE
F- 31062 TOULOUSE
Tel. : 61556735
Fax : 61335886

TODD GORDON
BRITISH SUGAR TECHNICAL CENTRE
NORWICH RESEARCH PARK
COLNEY
GB - NR4 7UB NORWICH
Tel. : 44603250000
Telex : 32149
Fax : 4460355874

TONELLI CHIARA
UNIVERSITA DEGLI STUDI DI MILANO
DIPARTIMENTO DI GENETICA E DI BIOLOGIA DEI MICRORGANISMI
VIA CELORIA 26
I - 20133 MILANO
Tel. : 39226605210
Fax : 3922664551
E-mail: TONELLI AT MIUCCA.CSI.UNIMI.IT

TORO GARCIA NICOLAS
ESTACION EXPERIMENTAL DEL ZAIDIN
DEPARTAMENTO DE MICROBIOLOGIA
PROFESOR ALBAREDA 1
E - 18008 GRANADA
Tel. : 3458121011
Fax : 3458129600

TORRES MARTINEZ SANTIAGO
DEPARTAMENTO DE GENETICA Y MICROBIOLOGIA
FACULTAD DE BIOLOGIA
E - 30071 MURCIA
Tel. : 3468833000
Fax : 3468835418

TOVEY MICHAEL
LABORATOIRE ONCOLOGIE VIRALE (UPR274)
CENTRE NATIONAL RECHERCHE SCIENTIFIQUE
7 GUY MOCQUET
F- 94801 VILLEJUIF
Tel. : 33147264658
Fax : 33147267602

TREES ALEXANDER
LIVERPOOL SCHOOL OF TROPICAL MEDICINE
POMBROKE PLACE
GB - L3 SQA LIVERPOOL
Tel. : 44517089393
Fax : 44517088733

TROYE BLOMBERG MARITA
DEPARTMENT OF IMMUNOLOGY
STOCKHOLM UNIVERSITY
S - 10691 STOCKHOLM
Tel. : 468164164
Fax : 468157356

TSAFTARIS ATHANASIOS
UNIVERSITY OF THESSALONIKI
DEPARTMENT OF GENETICS AND PLANT BREEDING
GR - 54006 TRESSALONIKI
Tel. : 3031992547
Fax : 3031200392

TSAGRI EFTHIMIA
BIOTECHNOLOGY-FOUNDATION FOR RESEARCH AND TECHNOLOGY
INSTITUTE OF MOLECULAR BIOLOGY/BIOTEC.
PO BOX 1527
GR - 711 10 HERAKLION CRETE

TSCHAPE HELMUT
ROBERT KOCH INSTITUTE BEREICH WERNIGERODE
LABORATORY OF MOLECULAR EPIDEMIOLOGY
BURGSTRASSE 37 37
D - W3700 WERNIGERODE
Tel. : 49303790
Fax : 4930379207

UHLEN MATHIAS
DEPARTMENT OF BIOCHEMISTRY AND BIOTECHNOLOGY
ROYAL INSTITUTE OF TECHNOLOGY
TEKNIKRINGEN 30-34
S - 100 44 STOCKHOLM
Tel. : 4687908792
Fax : 468245452

UNWIN NIGEL
MEDICAL RESEARCH COUNCIL
LABORATORY OF MOLECULAR BIOLOGY
HILLS ROAD
GB - CB2 2QH CAMBRIDGE
Tel. : 44223402410
Fax : 44223213556

URBAIN JAQUES
LABORATOIRE DE PHISICOLOGIE ANIMALE, ULB
DEPARTEMENT DE BIOLOGIE MOLECULAIRE
RUE DES CHEVAUX 67
B- 1640 RHODE-ST-GENESE
Tel. : 3226509852
Fax : 3226509840

URRESTARAZU ANTONIO
UNIVERSITE LIBRE DE BRUXELLES
PHYSIOLOGIE CELLULAIRE ET GENETIQUE DES LEVURES
CAMPUS DE LA PLAINE
BLD. DU TRIOMPHE - CP244
B- 1050 BRUXELLES
Tel. : 02.6505.416
Fax : 02.6505.421

VALDES BENITO
UNIVERSIDAD DE SEVILLA
DEPARTAMENTO DE BIOLOGIA VEGETALE Y EC OLOGIA
APARTADO 1095
E - 41080 SEVILLA
Tel. : +34 5 4626308

VALLE GIORGIO
UNIVERSITY OF PADOVA
DEPARTMENT OF BIOLOGY
CELLULAR BIOLOGY
VIA TRIESTE 75
I - 35121 PADOVA
Tel. : 39.498286270
Fax : 39.4982866261

VAN DE WEGHE ALEX
FACULTY OF VETERINARY MEDICINE
DEPARTMENT OF ANIMAL GENETICS AND . BREEDING
HEIDESTRAAT 19
B- 9820 MERELBEKE
Tel. : 3291521941
Fax : 3291525304

VAN DEN ELZEN P.J.M.
LABORATORY OF MOLECULAR BIOLOGY
MOGEN INTERNATIONAL NV
EINSTEINWEG 97
NL - 2333 CB LEIDEN
Tel. : 3171258282
Fax : 3171221471

VAN DEN HONDEL CEES
MEDICAL BIOLOGICAL LABORATORY
P.O. BOX 45
NL - 2280 AA RIJSWIJK
Tel. : 3115842842
Telex : 38034 PMTNO NL
Fax : 3115843989
E-mail: VANDENHONDEL@MBL.TNO.NL

VAN DER MEI DIRK
CENTRAALBUREAU VOOR SCHIMMELCULTURES
OOSTERSTRAAT 1
NL - 3740 AG BAARN
Tel. : 31.2154.81238
Fax : 31.2154.16142

VAN DER WEERDEN GERARD M.
KATHOLIEKE UNIVERSITEIT NIJMEGEN
TOERNOOIVELD
NL - 6525 ED NIJMEGEN
Tel. : 31.8065.2883
Tel. : 31.8065.2751/2761
Telex : 48228 WINA NL
Fax : 624001@HNYKUN11

VAN ELSAS JAN DIRK
SOIL BIOTECHNOLOGY GROUP IB-DLO
IPO-DLO
PO BOX 9060
NL - 6700 GW WAGENINGEN
Tel. : 31.8370.76210
Fax : 31.8370.10113

VAN HEERIKHUIZEN HARM
VRIJE UNIVERSITEIT, AMSTERDAM
FACULTEIT SCHEIKUNDE
LAB. BIOCHEMIE EN MOL. BIOLOGIE
D BOELELAAN 1083
NL - 1081 HV AMSTERDAM
Tel. : 31205485659
Fax : 31206461479
E-mail: VHEERIK@CHEM.VU.NL

VAN LOVEREN HENK
NATIONAL INSTITUTE FOR PUBLIC HEALTH AND ENVIRONMENTAL PROTECTION
ANTONIE VAN LEEUWENHOEKLAAN 9
NL - 3720 BA BILTHOVEN
Tel. : 3130742476
Fax : 3130285283

VAN MEER GERRIT
UNIVERSITY OF UTRECHT
DEPT. CELL BIOLOGY
MEDICAL SCHOOL
AZU HO2.314
NL - 3584 CX UTRECHT
Tel. : 3130506480
Fax : 3130541797

VAN MONTAGU M.
LABORATORIUM VOOR GENETICA
RIJKSUNIVERSITEIT GENT
K.L. LEDEGANCKSTRAAT 35
B- 9000 GENT
Tel. : 3291645170
Telex : 11995GENGENB
Fax : 3291645349
E-mail: JECOP@GENGENP.RUG.AC.BE

VAN OIRSCHOT JAN T.
DLO-CENTRAL VETERINARY INSTITUTE
P.0. BOX 65
NL - 8200 AB LELYSTAD
Tel. : 0320073308
Telex : 40227 CDI NL
Fax : 0320073473

VAN ROOIJEN NICO
DEPARTMENT OF CELLBIOLOGY
MEDICAL FACULTY
VRIJE UNIVERSITEIT
VAN DER BOECHORSTSTRAAT 7
NL - 1081 BT AMSTERDAM
Tel. : 31205482717
Fax : 31206462228

VAN WIJNENDAELE FRANS
INNOGENETICS N.V.
INDUSTRIEPARK ZWIJNAARDE 7/4
B- 9052 GENT
Tel. : 32-9-2410711
Fax : 32-9-2410799

VANDERLEYDEN JOS
F.A. JANSSENS LABORATORIUM VOOR GENETICA
FACULTEIT LANDBOUWWETENSCHAPPEN
WILLEM DE CROYLAAN 42
B- 3001 HEVERLEE
Tel. : 3216220921
Telex : 25941 ELEKUL B
Fax : 3216220761
E-mail: KIAAA3I A BLEKUL2I

VARVIO SIRKKA-LIISA
DEPARTMENT OF GENETICS
UNIVERSITY OF HELSINKI
ARKADIANKATU 7
SF- 00100 HELSINKI
Tel. : 35801917360
Fax : 35801917376
E-mail: SIRKKA-LIISA.VARVIOATHELSINKI.FI

VAZQUEZ ANA M.
DEPARTAMENTO DE GENETICA
FACULTAD DE BIOLOGIA
UNIVERSIDAD COMPLUTENSE
CIUDAD UNIVERSITARIA S/N
E - 28040 MADRID
Tel. : 3413941633
Fax : 3413941638

VEENHUIS MARTEN
LABORATORY FOR ELECTRON MICROSCOPY
KERKLAAN 30
NL - 7750 NN HAREN
Tel. : 3150632176
Fax : 3150635205

VENDRAMIN GIOVANNI GIUSEPPE
ISTITUTO MIGLIORAMENTO GENETICO PIANTE FORESTALI
SAN BONAVENTURA 13
I - 50145 FIRENZE
Tel. : 3955311069
Fax : 3955319413

VENIS MICHAEL
HORTICULTURE RESEARCH INTERNATIONAL
EAST MALLING
GB - ME19 6BJ WEST MALLING
Tel. : 44732843833
Fax : 44732849067

VENTOSA ANTONIO
DEPARTAMENTO DE MICROBIOLOGIA Y
PARASITOLOGIA
FACULTAD DE FARMACIA
PROFESOR GARCIA GONZALEZ S/N
E - 41012 SEVILLA
Tel. : 3454556765
Fax : 3454628162

VERSTRAETE WILLY
UNIVERSITY OF GHENT
LABORATORY OF MICROBIAL ECOLOGY
COUPURE L 653
B- 9000 GENT
Tel. : 3291645976
Fax : 3291646248
E-mail: LME @FLAND.RUG.AC.BE

VICENTE MIGUEL
CENTRO DE INVESTIGACIONES BIOLOGICAS
CSIC
VELAZQUEZ 144
E - 28006 MADRID
Tel. : 3415611800
Fax : 3415627518

VICENTE ANTON JOSE SALVADOR
UNIDAD DE FISIOLOGIA, DEPARTAMENTO
CIENCIA ANIMAL
UNIVERSIDAD POLITECNICA.
CAMINO DE VERA 14
E - 46071 VALENCIA 22012
Tel. : 3463877433
Fax : 3463877439

VINCENT JEAN-DIDIER
INSTITUT ALFRED FESSARD CNRS
1, AVENUE DE LA TERRASSE
F- 91198 GIF-SUR-YVETTE
Tel. : 33.1.69823434
Fax : 33.1.69070538

VISSER JAAP
DEPT. OF GENETICS, SECTION OF
MOLECULAR GENETICS
WAGENINGEN AGRICULTURAL UNIVERSITY
DREIJENLAAN 2
NL - 6703 HA WAGENINGEN
Tel. : 31837082865
Fax : 31837084011

VISSER RICHARD
WAGENINGEN AGRICULTURAL UNIVERSITY
DEPARTMENT OF PLANT BREEDING
PO BOX 386
NL - 6700 AJ WAGENINGEN
Tel. : 31837082836
Fax : 31837083457

VLIEGENTHART JOHANNES
BIJVOET CENTER FOR BIOMOLECULAR
RESEARCH
P.O.BOX 80.075
NL - 3584 CH UTRECHT
Tel. : 3130532184
Fax : 3130540980

VOIGT MARK
NATIONAL AGRICULTURAL & VETERINARY
BIOTECHNOLOGY CENTRE,
UNIVERSITY COLLEGE DUBLIN
BELFIELD
IRL - 4 DUBLIN
Tel. : 35317062214
Telex : 32693 EI
Fax : 35312692016

VOLCKAERT GUIDO
UNIVERSITY OF LEUVEN
LABORATORY OF GENE TECHNOLOGY
WILLEM DE CROYLAAN 42
B- 3001 LEUVEN
Tel. : 016.286611
Fax : 016.220761

VOLOBOUEV VITALY
INSTITUT CURIE
SECTION BIOLOGIE
26 RUE D'ULM
F- 75231 PARIS CEDEX 05
Tel. : 33.1.40.51.6632
Fax : 33.1.40.51.6674

VON BOTHMER ROLAND
SWEDISH UNIVERSITY OF AGRICULTURAL SCIENCES
S - 75007 UPPSALA
Tel. : 46.186.71022
Telex : 76942 AGRUNIS
Fax : 46.183.01553

VON WETTSTEIN DITER
CARLSBERG LABORATORY
DEPARTMENT OF PHYSIOLOGY
GAMLE CARLSBERG VEG 10
DK - 2500 COPENHAGEN VALBY
Tel. : 45.31.22.10.22
Fax : 45.33.27.47.66

VOS PIETER
KEYGENE N.V.
P.O. BOX 216
NL - 6700 AE WAGENINGEN
Tel. : 31837024141
Fax : 31837024939

VOSMAN BEN
CENTRE FOR PLANT BREEDING AND REPRODUCTION RESEARCH - DLO
P.O. BOX 16
NL - 6700 AA WAGENINGEN
Tel. : 31837076980
Fax : 31837015983

VREUGDENHIL DICK
DEPARTMENT OF PLANT PHYSIOLOGY
WAGENINGEN AGRICULTURAL UNIVERSITY
ARBORETUMLAAN 4
NL - 6703 BD WAGENINGEN
Tel. : 31837084229
Fax : 31837084740

WALDMANN HERMAN
LABORATORIES BLOCK
ADDENBROOKE'S HOSPITAL, LEVEL 3,
HILLS ROAD
GB - CB2 2QQ CAMBRIDGE
Tel. : 44223336904
Fax : 44223336901

WALKER JOHN
MRC LABORATORY OF MOLECULAR BIOLOGY
HILLS ROAD
GB - CB22QH CAMBRIDGE
Tel. : 44223402239
Fax : 44223412178

WALSH FRANK S.
UNITED MEDICAL AND DENTAL SCHOOLS OF G UYS AND ST.THOMAS HOSPITALS
ST.THOMAS'S CAMPUS
GB - SE1 7EH LONDON BRIDGE
Tel. : +44/1/928 9292
Fax : +44/1/928 1468

WALSH FRANK S.
DEPT. OF EXPERIMENTAL PATHOLOGY
UMDS GUY'S HOSPITAL
LONDON BRIDGE
GB - SEI 9RT LONDON
Tel. : 0719554574
Fax : 0714038883

WALTER FIERS
LABORATORY OF MOLECULAR BIOLOGY
K.L. LEDEGANCKSTRAAT 35
B- 9000 GENT
Tel. : 3291645131
Fax : 3291645348

WAMBUTT ROLF
ABON GMBH (FORMERLY FZB BIOTECHNIK GMBH)
GLIENICKER WEG 185
D - 12489 BERLIN
Tel. : 67.05.72.38
Tel. : 55.01.224
Fax : 67057228/5501219

WANG TREVOR L.
JOHN INNES INSTITUTE
JOHN INNES CENTRE
COLNEY LANE
GB - NR4 7UH NORWICH
Tel. : 4460352571
Fax : 4460356844
E-mail: WANG@UK.AC.AFRC.JII

WASSEF MARION
INSERM UNITE 106 NEUROMORPHOLOGIE
DEPARTEMENT, EVOLUTION
47 BOULEVARD DE L'HOPITAL
F- 75651 PARIS CEDEX 13
Tel. : 33.1.45826100
Fax : 33.1.45709990

WATSON PAUL
ROYAL VETERINARY COLLEGE
ROYAL COLLEGE STREET
GB - NWI 0TU LONDON
Tel. : 44.71.387.2898
Fax : 44713882342
E-mail: UJAAPFW@UK.AC.UCL

WATTS ANTHONY
UNVERSITY OF OXFORD
DEPART. OF BIOCHEMISTRY
SOUTH PARKS ROAD
GB - OX1 3QU OXFORD
Tel. : 44865275268
Fax : 44865275234
E-mail: WATTS@VAX.OX.UK.AC

WAUGH ROBERT
SCOTTISH AGRICULTURAL RESEARCH INSTITUTES
SCOTTISH CROP RESEARCH INSTITUTE
INVERGOWRIE
GB - DD2 5DA DUNDEE
Tel. : 44.382.562731
Fax : 44.382.562426

WAYNE ROBERT
CONSERVATION GENETICS
INSTITUTE OF ZOOLOGY
ZOOLOGICAL SOCIETY OF LONDON
REGENT'S PARK
GB - NW1 4RY LONDON
Tel. : 44715863011
Fax : 44715862870
E-mail: R.WAYNE@UCL.AC.UK

WEENING JAN JURJEN
VAKGROEP PATHOLOGIE
UNIVERSITY OF AMSTERDAM
ACADEMIC MEDICAL CENTER
MEIBERGDREEF 15
NL - 1105 AZ AMSTERDAM ZUID-OOST
Tel. : 31205664100
Fax : 31206960389

WEIMA SJERP
HUBRECHT LABORATORY NETHERLANDS INSTITUTE FOR DEVELOPMENTAL BIOLOGY OF THE ROYAL NETHERLANDS
UPPSALALAAN 8
NL - 3584CT UTRECHT
Tel. : 3130510211
Fax : 3130516464

WEISS MARY
INSTITUT PASTEUR
DEPARTEMENT DE BIOLOGIE MOLECULLAIRE
UNITE DE GENETIQUE DE LA DIFFERENCIATION
25 RUE DU DOCTEUR ROUX
F- 75724 PARIS 15
Tel. : 33145688500
Fax : 33345688521

WEISSHAAR BERND
MAX-PLANCK-INSTITUT FUR ZUCHTUNGSFORSCHUNG
CARL-VON-LINNE-WEG 10
D - 5000 KOLN
Tel. : 492215062310
Telex : 8 881 028 MPIZ D
Fax : 492215062313

WEISZ ALESSANDRO
ISTITUTO DI PATOLOGIA GENERALE E ONCOLOGIA
PIAZZETTA S. ANDREA DELLE DAME 2
I - 80138 NAPOLI
Tel. : 39815665703
Fax : 39815665695

WELLS JEREMY
UNIVERSITY OF CAMBRIDGE
DEPARTMENT OF PATHOLOGY
TENNIS COURT ROAD
GB - CB2 1QP CAMBRIDGE
Tel. : 44223333734
Fax : 44223333346

WESTHOF ERIC
INSTITUT DE BIOLOGIE MOLECULAIRE ET CELLULAIRE
CNRS UPR SMBMR
15 RUE R. DESCARTES
F- 67084 STRASBOURG CEDEX
Tel. : 3388417046
Fax : 3388610680
E-mail: WESTHOF@IBMC.U-STRASBG.FR

WESTHOFF PETER
INSTITUT FÜR ENTWICKLUNGS- UND MOLEKULARBIOLOGIE DER PFLANZEN
UNIVERSITATSSTRASSE 1
D - W4000 DUESSELDORF I
Tel. : 492113112338
Fax : 492113114871

WILKINSON DAVID
NATIONAL INSTITUTE FOR MEDICAL RESEARCH
LAB OF EUKARYOTIC MOLECULAR GENETICS
THE RIDGEWAY
MILL HILL
GB - NW71AA LONDON
Tel. : 44819593666
Fax : 44819064477

WILLIAMS DAVID CLIVE
UNIVERSITY OF DUBLIN
TRINITY COLLEGE
BIOCHEMISTRY DEPARTMENT
IRL - 2 DUBLIN
Tel. : 35317021802
Telex : 93782TCDEI
Fax : 3531772400

WILLIAMS JOHN
INSTITUTE OF ANIMAL PHYSIOLOGY AND GENETICS RESEARCH
GB - EH259PS ROSLIN
Tel. : 0314402726
Fax : 0314400434
E-mail: WILLIAMSJL@AFRC.IAPE.AC.UK

WILLIAMS STAN
UNIVERSITY OF LIVERPOOL
DEPARTMENT OF GENETICS + MICROBIOLOGY + ENVIRONMENTAL + EVOLUTIONARY BIOLOGY
GB - L69 3BX LIVERPOOL
Tel. : +44 51 794 2000
Telex : 627095 UNILPL G
Fax : +44 51 7086502

WILLMITZER LOTHAR
INSTITUT FÜR GENBIOLOGISCHE FORSCHUNG
BERLIN GMBH
IHNESTR. 63
D - W1000 BERLIN 33
Tel. : 493083000760
Fax : 493083000736

WILMUT IAN
INSTITUTE OF ANIMAL PHYSIOLOGY AND GENETICS RESEARCH
GB - EH259PS ROSLIN
Tel. : 44314402026
Fax : 44314400434
E-mail: WILMUTI@AFRC.IAPE.AC.UK

WILSON KEITH
EUROPEAN MOLECULAR BIOLOGY LABORATORY
HAMBURG OUTSTATION
C/O DESY, NOTKESTRASSE 85
D - W2000 HAMBURG 52
Tel. : 4940899020
Fax : 494089902149
E-mail: KEITH EMBL-HAMBURG.DE

WITTINGHOFER FRED
MAX PLANCK INSTITUT
FÜR MOLEKULARE PHYSIOLOGIE
RHEINLANDDAMM 201
D - 44139 DORTMUND
Tel. : 49.231.1206280
Fax : 49.231.1206230

WODAK SHOSHANA
UNITE DE CONFORMATION DE MACROMOLECULES BIOLOGIQUES
AVENUE PAUL HEGER
CP160/16
B- 1050 BRUXELLES
Tel. : 3226485200
Fax : 3226488954
E-mail: SHOSH@RUBENS.BE

WOLF KLAUS
RWTH AACHEN
INSTITUT FUR BIOLOGIE IV (MIKROBIOLOGIE)
WORRINGER WEG
D - 52056 AACHEN
Tel. : 49.241.806600
Fax : 49.241.806602

WOLF HERMAN FRIDMAN
LABORATORY OF CELLULAR AND CLINICAL IMMUNOLOGY INSERM UNIT 255
INSTITUT CURIE
26 RUE D'ULM
F- 75231 PARIS 05
Tel. : 33142324220
Fax : 33140510420

WOLFE KENNETH
UNIVERSITY OF DUBLIN
TRINITY COLLEGE
DEPARTMENT OF GENETICS
LINCOLN PLACE GATE
IRL - DUBLIN 2
Tel. : 353.1.702.1064
Fax : 353.1.679.8558

WOLLMAN FRANCIS-ANDRE
INSTITUT DE BIOLOGIE PHYSICO-CHIMIQUE
SERVICE DE PHOTOSYNTHESE
13 RUE PIERRE ET MARIE CURIE
F- 75005 PARIS
Tel. : 33143252609
Fax : 33140468331

WONNACOTT SUSAN
UNIVERSITY OF BATH
DEPARTMENT OF BIOCHEMISTRY
CLAVERTON DOWN
GB - BA2 7AY BATH
Tel. : 44225826391
Fax : 44225826449
E-mail: S.WONNACOTT@UK.AC.BATH. GDR

WRAY JOHN
DIVISION OF ENVIRONMENTAL AND
EVOLUTIONARY BIOLOGY
SCHOOL OF BIOLOGICAL AND MEDICAL
SIR HAROLD MITCHELL BUILDING
GB - KY16 9TH ST. ANDREWS, FIFE
Tel. : 4433476161
Fax : 4433475398

YANIV MOSHE
INSTITUT PASTEUR
DEPARTEMENT DES BIOTECHNOLOGIES
UNITE DES VIRUS ONCOGENES
25 RUE DU DOCTEUR ROUX
F- 75724 PARIS 15
Tel. : 33145688512
Fax : 33145688790

YOUNG DOUGLAS
ST MARY'S HOSPITAL
DEPARTMENT OF MICROBIOLOGY
NORFOLK PLACE
PADDINGTON
GB - LONDON
Tel. : 0817403161
Fax : 0817438536

YOUNG PETER
UNIVERSITY OF YORK
DEPARTMENT OF BIOLOGY
GB - YO1 5DD YORK
Tel. : 44904432914
Telex : 57933
Fax : 44904432860

ZABEAU M.
KEYGENE N.V.
KEYENBERGSEWEG 6
NL - 6704 PJ WAGENINGEN
Tel. : 31837024141
Fax : 31837024939

ZAKIN MARIO
INSTITUT PASTEUR
UNITE D'EXPRESSION DES GENES
EUCARYOTES
28 RUE DU DR. ROUX
F- 75724 PARIS 15
Tel. : 33145688382
Fax : 33143069835

ZANNIS VASSILIS
INSTITUTE OF MOLECULAR BIOLOGY AND
BIOTECHNOLOGY
FORTH HELLAS
PO BOX 1527
GR - 711 10 HERAKLION CRETE
Tel. : 081210091
Telex : 262896IMBBGR
Fax : 081230469

ZANOTTI MARTA
ISTITUTO DI ZOOTECNICA
FACOLTA' DI MEDICINA VETERINARIA
UNIVERSITA' DEGLI STUDI DI MILANO
VIA CELORIA 10
I - 20133 MILANO
Tel. : 3922364211
Fax : 39270602227
E-mail: ZOOTVE2ATIMICILEA

ZERIAL MARINO
EUROPEAN MOLECULAR BIOLOGY
LABORATORY
MEYERHOFSTRASSE 1
POSTFACH 10.2209
D - W6900 HEIDELBERG
Tel. : 496221387232
Telex : 461613 EMBL D)
Fax : 496221387306

ZEUTHEN JESPER
DEPT. OF TUMOR CELL BIOLOGY
THE FIBIGER INSTITUTE
DANISH CANCER SOCIETY
NDR. FRIHAVNSGADE 70
DK - 2100 COPENHAGEN
Tel. : 4535268866
Fax : 4531382044

ZIMMERMANN FRIEDRICH K.
TECHNISCHE HOCHSCHULE DARMSTADT
INSTITUT FÜR MIKROBIOLOGIE
ARBEITSGRUPPE GENETIK
SCHNITTSPAHNSTR. 10
D - 64287 DARMSTADT
Tel. : 49.6151.162855
Fax : 49.6151.164808

ZRYD JEAN-PIERRE
LABORATORY OF PLANT CELL GENETICS
UNIVERSITE DE LAUSANNE
CH - 1015 LAUSANNE
Tel. : 216922097
Telex : 455110
Fax : 216922440
E-mail: BITHNET JZRYD@ULYS.UNIL.CH

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