EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

EUROCORES Programme
European Collaborative Research

Membrane Architecture and Dynamics (EuroMEMBRANE)

DRAFT Call for Outline Proposals

What is EUROCORES?

The ESF European Collaborative Research (EUROCORES) Programmes offer a flexible framework for researchers from Europe to work on questions which are best addressed in larger scale collaborative research programmes. The EUROCORES Programmes allow excellent researchers from different participating countries to collaborate in research projects 'at the bench'. They also allow, when appropriate, colleagues from non-European countries, for example the US, to participate. The Programmes encourage and foresee networking and collaboration of researchers to achieve synthesis of scientific results across the programme, to link to related programmes, and to disseminate results.
EUROCORES Programmes allow national research funding organisations in Europe and beyond to support top class research in and across all scientific areas, by matching the needs articulated by the scientific community with their strategic priorities.
Funding decisions on the projects and the research funding remain with the national research funding organisations, based on international peer review operated by ESF. ESF also provides support for networking the researchers and for the scientific synthesis of research results and their dissemination[(1)]. This way, the EUROCORES Scheme complements the EC Framework Programme and other collaborative funding schemes at European level.

For further information see:
http://www.esf.org/eurocores

[(1)] Currently supported through a contract with the European Commission under the Sixth Framework Programme (EC Contract no. ERAS-CT-2003-980409).

Membrane Architecture and Dynamics (EuroMEMBRANE)

Following agreement with funding organisations in # *countries,* the European Science Foundation is launching a Call for Outline Proposals for Collaborative Research Projects (CRPs) to be undertaken within the EUROCORES Programme EuroMEMBRANE. EuroMEMBRANE will run for 3-4 years and it includes national research funding, as well as support for networking and dissemination activities provided by the ESF[1].The Programme aims to support high quality multidisciplinary research.

Outline Proposals are to be submitted by Xth May 2008. It is expected that Full Proposals will be invited by Xth June 2008 with xx September 2008 as expected deadline for submission.

A Programme-specific website can be consulted for the latest updates at **http://www.esf.org/euromembrane**

Background and objectives

It never ceases to amaze how a layer of oil 5 nm thin makes the difference between life and death. The physical laws that govern the behaviour of cellular membranes and their component lipids and proteins are often counterintuitive, especially when coupled with the often bewildering variety of lipids and proteins found in any particular membrane. Recent technical developments in lipidomics, proteomics and membrane protein structure determination have, however, sparked a new wave of interest in this field. The famous Singer and Nicholson model of a freely mixing two-dimensional liquid has now been replaced by a more detailed model that recognizes additional levels of dynamic organization both across the lipid bilayer (lipid asymmetry), and laterally (membrane microdomains). This has generated the need to know the actual membrane composition and organization, as this reflects the functions of cells and their organelles, transport of membranes, transport across membranes and signaling. To find out how the membrane lipidome, proteome and glycome can fulfil all the tasks that membranes have is an enormous challenge. This mission will only be accomplished by integrated, multidisciplinary approaches involving (bio)chemists, cell biologists, physicists and information technologists (among others) working together to overcome the technical and conceptual barriers that confront the field. We are missing the integrated view of membrane structure and dynamics at the molecular level that is needed to understand membrane changes in aging and diseases such as atherosclerosis, Alzheimer's disease, cancer and a range of infections.

Scientific goals

The aim of this EUROCORES programme on EuroMEMBRANE is to answer long-standing questions in membrane biology using cutting-edge technologies. These will address functional problems in a quantitative manner bringing together experimental tools with theoretical approaches. There will be a special emphasis on lipid-lipid and (glyco)lipid-protein interactions in the plane of the membrane in health and disease. Using various model organisms would allow cross-species comparison and bring an evolutionary perspective to biomembrane studies. This type of research requires a strong interdisciplinary collaboration that covers biological, chemical, physical and computational aspects of membranology over a broad dynamic range of time and length.

Research topics

To address the objectives outlined above, the programme will ***develop and use cutting-edge applications of technologies***, including but not limited to:

- **Lipidomics, Proteomics, Glycomics**

Mass spectrometric and other tools that enable sensitive and quantitative profiling of membrane components. The goal will be a generic package that includes standards, methods and cross-platform data interpretation and quantification software.

- **Imaging Techniques** such as

- live cell microscopy
- single molecule spectroscopy
- high resolution fluorescence microscopy *(PALM, STED, and STORM)*
- non-linear optics *(2 photon, SHG, THG, CARS)*
- cryoelectron microscopy
- tomography
- mass spectrometric imaging *(nanoSIMS, MIMS)*
- new instrumentation and experimental methodologies for improved spatiotemporal resolution. *Classical technologies giving ensemble averaging or single-molecule measurements (FRAP, FRET, FLIM, FCS, SPT) need be improved and extended to allow simultaneous observation of multiple membrane components.*

Furthermore, new probes need to be developed that satisfy fluorescence and non-linear optics specifications, to analyze molecular order and dynamics in live membranes.

- **Chemical Biology**

The chemical biology of membranes involves the application of chemical techniques and tools, often compounds produced through synthetic chemistry, to the study and manipulation of biological membranes.

- **Bioinformatics and Computational Modelling**

New information technology for efficient treatment and interpretation of experimental data. New methods for computer simulation and molecular modeling of membrane dynamics.

In addition, understanding membrane lipid-protein interactions and their functional implications requires **refinement of methodology for membrane protein purification, structure determination and reconstitution** of membrane protein function in proteoliposomes.

The latest technology achievements will be employed ***to tackle long-standing problems in membrane biology*** in areas such as:

- **Membrane and Organelle Biogenesis, Membrane Homeostasis**

During the cell cycle and, often during differentiation, membranes and organelles must be assembled from component parts. The underlying mechanisms controlling growth, duplication and turnover need to be elucidated at the molecular level.

- **Signal Transmission across a Membrane (but not further)**

Specific and rapid responses to stimuli involve conformational changes in transmembrane proteins. In some cases, multiprotein-lipid complexes are assembled in a highly coordinated and regulated manner. This is one example of a membrane microdomain. However, the dynamics and the order of events at the molecular and submolecular levels are not well understood.

- **Non-classical Secretion, Transmembrane Movement of Proteins and Lipids**

Though considerable progress has been made in elucidating the mechanisms whereby proteins move across the membrane of the endoplasmic

reticulum, mitochondria, chloroplasts and peroxisomes, much less is known about the mechanisms whereby some proteins move from the cytoplasm to the outside, passing across the plasma membrane. Many of these proteins play crucial roles in cellular physiology, such as sex in budding yeast. New high resolution methods of analysis are needed to follow proteins and lipids as they pass across the bilayer as well as the means of identifying and analysing the proteins with which they interact.

- **Membrane Trafficking**

Though most of the vesicle machinery involved in shuttling cargo from one membrane compartment to the next has been identified, the way in which proteins and lipids interact, and the choreography of events is still very patchy. There needs to be a concerted effort to obtain structural information for all parts of the exocytic and endocytic machinery at all scale levels (from X-ray to live cell imaging), as well as improved and new methodologies that allow the individual steps in these processes to be followed in time and space and reduced to robust quantitative models.

- **Cytoskeleton-Membrane Interactions and Lateral Heterogeneity**

The cytoskeleton plays essential roles in maintaining the architecture and composition of cellular membranes, controlling lateral mobility of membrane components and organising membrane-bound organelles within the cell. However, understanding of the molecular mechanisms involved is still limited. Application of novel labelling techniques and high resolution morphological approaches will provide key insights to these events.

- **Membrane-Pathogen Interactions**

Detailed knowledge of the interactions of viruses, bacteria and toxins with cellular membranes is essential to understand the mechanisms of pathogenesis and identify novel strategies for disease prevention and therapy. The relative simplicity of these agents also makes them exquisite tools to analyse fundamental properties of cell membranes. Key membrane details of pathogen structure, cell entry, intracellular trafficking, assembly and release, and of the signalling pathways usurped to control these activities remain to be identified.

- **Cell Adhesion and Cell Locomotion**

Cells interact with each other and the extracellular matrix via supramolecular complexes in the cell membrane, as part of the process that forms extensive sheets. They also move over these substrata and can even penetrate cell sheets, for example during the process of metastasis. In all cases, membranes must be continuously remodelled, through endo- and exocytosis, making and breaking contacts. Quantitative models are needed to explain these processes as well as imaging methods that allow visualization in vivo.

- **Lipid Modulation of Membrane Protein Function**

Striking features of lipids in biomembranes are that there are a thousand different species in a single cell, and that they are heterogeneously distributed within and across the bilayer (lipid asymmetry). This must have functional implications for the many membrane proteins, but for the most part this is obscure. Also the function of specific lipid anchors on proteins is largely unclear. New methods such as sensitive mass spectrometric assays and NMR methods must now be applied to study lipid-protein interactions.

The program aims at delivering:

- New experimental and computational methods and standards for biological membrane research.
- New biological knowledge on membrane architecture and dynamics that would contribute to better understanding of membrane functions in the normal and pathologic state.

Collaborative Research Project (CRP) proposals addressing exclusively technological ***or*** biological issues will not be considered.

Guidelines for applications

(Outline and Full Proposals)

Collaborative Research Project (CRP) proposals from individual scientists or research groups eligible for funding by the organisations participating in the Programme will be accepted for consideration in the EUROCORES Programme EuroMEMBRANE.
Scientists or groups not applying for or not eligible to apply for funding from these organisations (including applicants from industry), can be associated with a proposal where their added scientific value is demonstrated. Their participation as Associate Partners in a project must be fully self-supporting and will not be financially supported by the participating funding organisations.

Proposals are only eligible, if they fulfil the following **criteria**:

- Proposals must involve, as a minimum, three eligible Principal Investigators (PIs) from **three different countries.**
- A maximum of 50 % of the Individual Projects (IPs) in a Collaborative Research Project (CRP) can come from one country.
- Proposals must involve more PIs than Associated Partners

Applications should normally be for three years although applications for shorter or longer time periods may be considered depending on the rules of the participating funding organisations. Taking into account the selection and approval processes, the successful projects are expected to begin their activities in **March 2009**.

Online submission of applications

Outline and Full Proposals will be submitted online. Applicants should follow the proposal structure as indicated in the application template for outline proposals available on the Programme website at: **http://www.esf.org/**euromembrane.

On this Programme website, links to information on national funding eligibility and requirements as well as to a EUROCORES Glossary and Frequently Asked Questions (FAQs) are available.

Prior to submitting Outline Proposals, all applicants <u>have to</u> contact their national funding organisations in order to verify eligibility and to ensure compliance with their relevant organisations' granting rules and regulations (see contact persons listed on page 8).
At the time of online submission of the Outline Proposals, the Project Leader is asked to confirm this on behalf of all the participants in the CRP.

Outline Proposals

Outline Proposals are invited by Xth May 2008.
Outline Proposals will be examined by the participating funding organisations for formal eligibility. Therefore, it is crucial that all applicants contact their national funding organisation prior to submitting their proposals.
In compliance with the rules and regulations of the participating national funding organisations, the requested funds under the EUROCORES Programme EuroMEMBRANE can include salaries for scientific and technical staff, equipment as well as travel costs and consumables within the project, specifying the amount requested from each Funding Organisation. National policies may also require the proposal to contain additional specific information. Applicants should be aware that the participating funding organisations can make significant adjustments to the requested funds in order to bring these in line with their rules and regulations.

Applications will be assessed according to a set of criteria in a two-stage procedure, as to ensure a thorough selection of scientifically excellent proposals. At the outline stage, the Review Panel will select proposals with potential for scientific excellence, by applying the following criteria:

- Relevance to the Call for Proposals
- Novelty and originality
- European added value (scientific)
- Qualification of the applicants

An Outline Proposal submitted must comprise:

- A short description of the CRP (max. 1200 words, including objectives, milestones, methodologies (for example experiments and fieldwork);
    - Short description of how (and why) the partners contributing to the CRP will work together;

- Short CVs of Project Leader (PL), all PIs and Associate Partners (max. one page each, including five most relevant publications);
- Estimated budget (consistent with the rules of relevant national funding organisation) tabulated according to a provided template.

Associated Partners (APs) are also considered part of a CRP and will be assessed as such at both the Outline and Full Proposal stage.

It will be assumed that arrangements for the handling of IPR (Intellectual Property Rights) will be in place within projects, following the applicable national legislation and national funding organisation rules. Applicants are strongly urged to have such arrangements in place, covering all research groups (including any associated groups) before the start of the projects. It is expected that the results obtained by the projects supported under this EUROCORES Programme will be placed in the public domain.
It is also expected that all relevant clearance of other national or international committees (for example ethics) has been obtained before funding is granted. It is the responsibility of applicants to clarify any such matters (if applicable) with their national contact points.

Full Proposals

Full Proposals will be invited following the recommendations of the Review Panel. The deadline for full proposals will be announced later, but is expected to be around 17th September 2008.

Please note that only applicants who submitted an Outline Proposal can submit a Full Proposal.

For the Full Collaborative Research Project (CRP) proposals, the most important selection criterion is "Scientific quality". Other criteria include interdisciplinarity (according to the scope of the call), qualification of applicants, level of integration and collaboration, feasibility and appropriateness of methodologies, European added value and relation to other projects (risk of double-funding and track record for collaboration).

The Full Proposals will be assessed by at least three independent external expert referees who are selected by the ESF from a pool of scientists suggested by the participating funding organisations and the Review Panel. A list of all referee names used for the international peer review will be published once the selection process is complete.

After receiving all referee reports, they will be made available (anonymous) to the applicants for their information and for commenting (optional). The Review Panel will rank all Full Proposals based on the assessment of the Full Proposal, the anonymous referee reports and the applicant's responses to these.
The Review Panel will create a ranked list consisting of the best Full Proposals and will subsequently make recommendations to the Management Committee for the funding of these proposals. The actual granting of the funds to the Individual projects on the ranked list will depend on the total amount of funds available in each country by the participating Funding Organisations. The use of funds in a project will be subject to the rules and regulations of each participating Funding Organisation as well as to the national laws of those countries.

Full proposals must include a well-argued scientific case (both for the collaboration envisaged and for the individual contributions), a list of participants, a detailed tabulated budget and other supporting information. A single, common scientific case must be made throughout the proposal to demonstrate an aim for scientific synergy and integration of multinational expertise. In addition, the amount requested from each national funding organisation has to be clearly and separately specified. Detailed instructions on requirements and how to complete the application forms will be made available once Full Proposals are being invited.

The **Project Leader** will be the main CRP proposal contact point for ESF for the duration of the project. He/she will be responsible for representing the Collaborative Research Project, for its participation in programme activities, and for any reporting requirements placed on the project as a whole.

All **Principal Investigators** will be responsible for dealing with the requirements attached to the contributions of their own funding organisation.

Programme Structure and Management

Programme Structure

The overall responsibility for the governance of the programme lies with a *Management Committee*, whose membership is formed by one representative from each participating funding organisation (usually a senior science manager) together with an ESF representative.

Proposal assessment and selection are the responsibility of an international, independent *Review Panel*. The members of this panel are leading scientists, appointed by ESF following suggestions from participating Funding Organisations. The membership of the Review Panel will be available on the Programme website for information. The Review Panel is also expected to monitor the overall scientific progress of the programme.

The Scientific Committee which is formed by the Project Leaders of all funded CRPs will be responsible for proposing networking activities for scientific synergy in the EUROCORES Programme. They will also advise and support the EUROCORES Programme Coordinator in the coordination of networking activities.

Programme Networking

Networking activities are designed to strengthen the science objectives of this EUROCORES Programme by promoting coherence in the activities of the science community involved. This will provide the European added-value which is the central objective of any EUROCORES Programme.

Networking and collaboration within EUROCORES Programmes takes place at two levels:

1. between the various Individual Projects within each Collaborative Research Project (CRP) and
2. between the funded CRPs within the programme as a whole.

The intra-CRP activities are supported through the research grants each participant receives from the participating funding organisations in the given CRP. The cross-CRP activities are funded through contributions to the EUROCORES Programme.

The intra-CRP collaboration is motivated by the nature of the CRP's research objectives, i.e., by the scope and the complexity of the questions it deals with. In a CRP, the participating groups have the opportunity to gather the required critical mass to successfully address the objectives and challenges of their project.

The cross-CRP networking and collaboration is stirred by the aims and the nature of the particular EUROCORES Programme. The theme which was the basis of this EUROCORES Programme has been selected for its clear need of collaboration in the proposed field. The funded CRPs will collectively set up and further streamline this new collaboration. To this end, the CRPs will engage the programme participants and, when of clear benefit, colleagues from outside the programme in joint activities such as:

- Working Group meetings for the exchange of information and results across the CRPs;
- Joint scientific meetings or summer schools;
- Short term visits;
- Development and delivery of joint training schemes;
- Seminars, Workshops, symposia, invited sessions either stand-alone or as part of other larger events;
- Common web-facilities and publications.

Through active participation of scientists in the above mentioned activities, not only existing collaborations are enhanced but new and strategic partnership opportunities are also identified.
Furthermore, these activities may provide opportunities to explore aspects of the programme which are not covered by the funded research projects.

The integrative activities between the CRPs will help to strengthen the field by building coherence within this emerging research community and will serve as a platform for the research work which is done in the programme.

Project members are expected to participate annually in at least one cross-CRP activity.

When submitting your proposal, please note that the costs for networking within your CRP should be budgeted for in your proposal. Funds for networking between the CRPs will be centrally managed by the ESF through contributions from the participating funding organisations.

Programme evaluation

A Mid-Term evaluation, conducted by the Review Panel, will evaluate the overall progress of the Programme, based on the progress of the funded CRPs. Here, the Review Panel has a steering function and can comment on the CRPs' work plan in relation to the objectives of the overall Programme. A final evaluation will assess the achievements of the whole EUROCORES Programme.

Contacts in the participating organisations

As it is currently not known which Funding Organisations will support this programme, please contact your National Funding Organisation or Research Council to inquire about this programme.

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