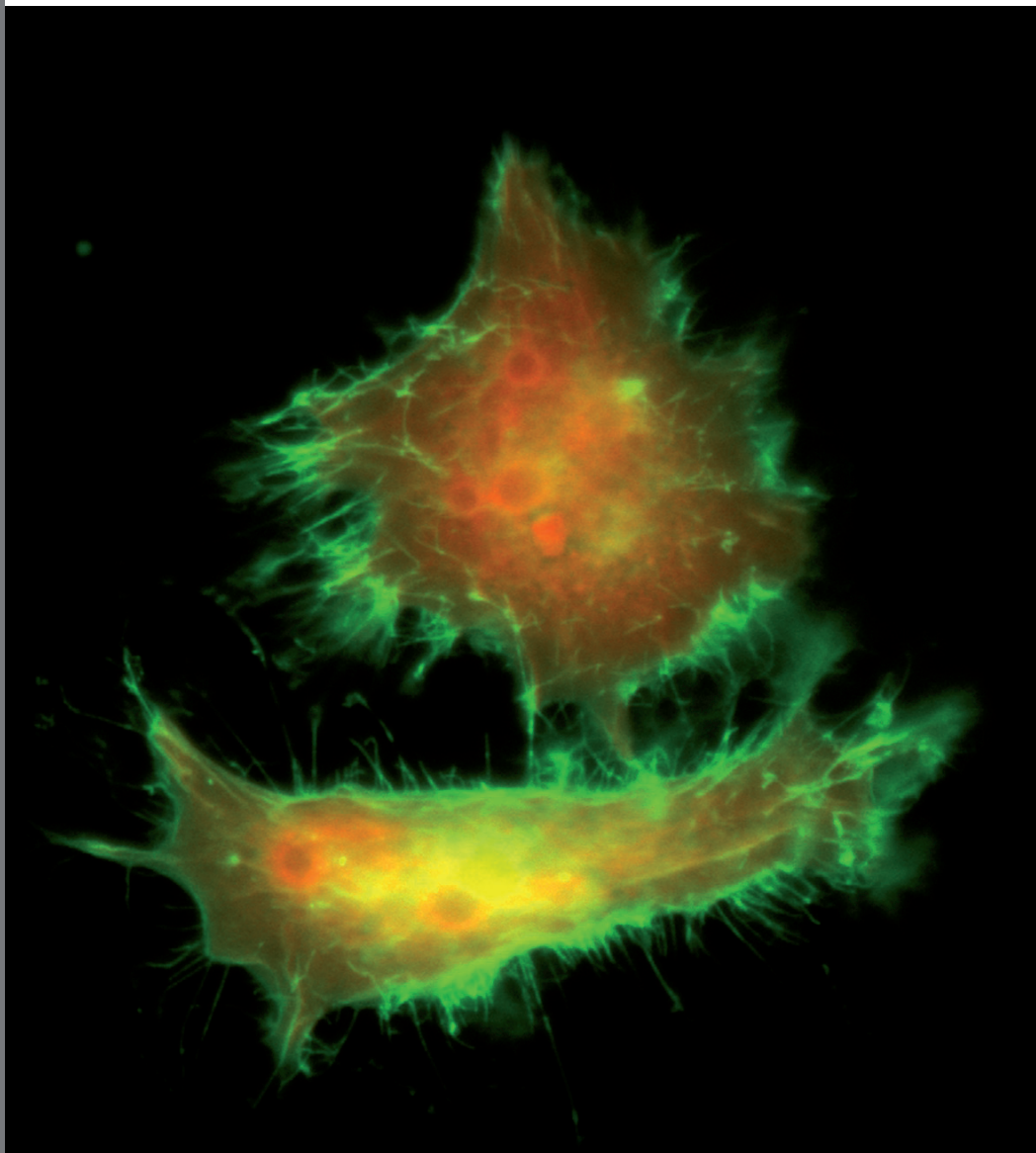
EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

EUROCORES Programme
European Collaborative Research

EuroMEMBRANE
Membrane Architecture and Dynamics



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Membrane Architecture and Dynamics (EuroMEMBRANE)

The aim of the EUROCORES Programme 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 will 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.

It never ceases to amaze how a layer of oil only 5 nm thick 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 The famous Singer and Nicholson model of a freely mixing two-dimensional liquid has now been replaced by a more detailed model that recognises additional levels of dynamic organisation both across the lipid bilayer (lipid asymmetry) and laterally (membrane microdomains). This has generated the need to know the actual membrane composition and organisation, as this reflects the functions of cells and their organelles, transport of membranes, transport across membranes and signalling. We are missing the integrated view of membrane structure and dynamics at the molecular level that is needed to understand membrane changes in processes like ageing and diseases such as atherosclerosis, Alzheimer's disease, cancer and a range of infections.

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.

List of funded Collaborative Research Projects (CRPs)

Molecular Level Physiology and Pathology of Oxidised Phospholipids (OXPL)

(AKA, DFG, FWF, GAČR)

The OXPL consortium represents a highly focused, integrated interdisciplinary approach of European research laboratories already active in this now rapidly emerging area in biological chemistry, together with additional skills brought into the project by groups representing state-of-the-art expertise in method and high-resolution instrumentation development for the characterisation of biomolecules, their interactions in biomembranes and localisation in cells. More specifically, this project combines leading-edge expertise on membrane biophysics, from modern MD simulations to a range of experimental techniques (ellipsometry, Langmuir troughs, FCS, AFM, NMR), all the way to protein folding, molecular cell biology, imaging, chemical biology and lipidomics analyses. The project will pave the way to the development of improved diagnostics, therapies and preventive measures to combat the above diseases, and will take European research to the leading edge in this rapidly emerging and important area.

Project Leader:

Professor Paavo Kinnunen
University of Helsinki, Finland

Principal Investigators:

Professor Albin Hermetter
Graz University of Technology, Austria

Professor Martin Hof
Academy of Sciences of the Czech Republic, Prague, Czech Republic

Professor Thorsten Hugel
Technical University Munich, Garching, Germany

Professor Pavel Jungwirth
Academy of Sciences of the Czech Republic, Prague, Czech Republic

Dr Gerhard Schütz
Johannes Kepler University Linz, Austria

Associated Partners:

Professor Gerhard Gröbner
Umeå University, Sweden

Dr Himanshu Khandelia
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Dr Francesco Megli
University of Bari, Italy

Dr Ingela Parmryd
Stockholm University, Sweden

Dr Corinne Spickett
University of Strathclyde, Glasgow, United Kingdom

Spatio-temporal Organisation of the Synaptic Membrane for Synaptic Vesicle Protein Recycling (SYNAPSE)

(AKA, DFG, VR)

The presynaptic terminal contains clusters of synaptic vesicles, key organelles of chemical neurotransmission. Proteomics data indicate that these vesicles comprise distinct sets of proteins and lipids present in defined stoichiometries which must be maintained during repetitive rounds of exo- and endocytosis. How this precise sorting of the synaptic vesicles' membrane proteins is accomplished molecularly is not well understood. How the spatio-temporal dynamics of endocytic proteins at the nerve terminal are controlled is largely unknown but likely involves membrane-associated multidomain scaffolding proteins organising the periactive zone. The work of this project aims

to tackle these problems and will thus enable us to gain unprecedented insights into the spatio-temporal organisation of the synaptic membrane for clathrin-mediated synaptic vesicles protein recycling.

Project Leader:

Professor Volker Haucke
Free University Berlin, Germany

Principal Investigators:

Professor Pekka Hänninen
University of Turku, Finland

Dr Jürgen Klingauf
Max Planck Institute for Biophysical Chemistry, Göttingen, Germany

Professor Oleg Shupliakov
Center of Excellence in Developmental Biology, Stockholm, Sweden

Tracking of Phosphoinositide Pools – key signalling components in cell migration and polarisation (TraPPS)

(DFG, NWO, RCN, VR)

Membrane dynamics modulate cell polarity, vesicular trafficking, migration, growth, proliferation, differentiation and more. Of all membrane lipids, phosphoinositides play a central role in these processes. Although a role for the prominent 3-phosphorylated phosphoinositides such as PtdIns(3,4,5)P3 and PtdIns(3)P has been highlighted in physiology and disease, dynamics and localisation of these lipids are still poorly understood. TraPPs will provide a dynamic and refined view of phosphoinositide flux and required lipid modifying enzymes, e.g., PI3Ks, lipases and lipid phosphatases. Lipid-modifying enzymes will be targeted dynamically to distinct cellular locations, and lipid-interacting proteins shall be manipulated to display their free or lipid-bound state. Activation of lipid modifying enzymes will be linked to localised upstream signalling and specific cell responses. Cellular, genetic fly and mouse models will be used to validate the uncovered molecular mechanisms. This project provides the basis for a broader systems biology approach of lipid signalling, and will elucidate dynamic cellular processes relevant to cancer and inflammation.

Project Leader:

Professor Matthias Wymann
University of Basel, Switzerland

Principal Investigators:

Professor Theodorus Gadella
University of Amsterdam, The Netherlands

Professor Karl-Eric Magnusson
University of Linköping, Sweden

Professor Carsten Schultz
European Molecular Biology Laboratory, Heidelberg, Germany

Professor Harald Stenmark
The Norwegian Radium Hospital, Oslo, Norway

Associated Partners:

Professor Edwin Constable
University of Basel, Switzerland

Professor B. Christoffer Lagerholm
University of Southern Denmark, Odense, Denmark

Professor Markus R. Wenk
National University of Singapore, Singapore

Unconventional Protein Secretion (UPS)

(DFG, NWO, SNF)

Two types of non-classical protein transport to the cell surface of eukaryotic cells have been described, processes that collectively have been termed ‘Unconventional Protein Secretion’ (UPS). The first type is represented by integral membrane proteins that can reach the cell surface in a Golgi-independent manner. The second type is used by soluble secretory proteins that exit cells without any involvement of the endoplasmic reticulum and the Golgi system. While integrins are an example for membrane proteins transported by unconventional means, the class of soluble unconventional secretory proteins includes interleukin family members, fibroblast growth factors, macrophage migration inhibitory

factor, galectins and acyl-CoA binding protein, macromolecules that are secreted from cells to regulate the immune response, cell growth and differentiation as well as angiogenesis. This project will collaborate to elucidate these 'unconventional pathways of protein secretion' at the molecular level. We will use advanced techniques such as iTRAQ and SILAC proteomics as well as genome-wide screening using RNA interference to identify essential components and to reveal the mechanisms regulating unconventional protein secretion.

Project Leader:

Professor Walter Nickel
Heidelberg University Biochemistry Center, Germany

Principal Investigators:

Dr Hans-Dietmar Beer
Institute of Cell Biology, Zürich, Switzerland

Professor Catherine Rabouille
Department of Cell Biology, Utrecht, The Netherlands

Associated Partner:

Professor Vivek Malhotra
Barcelona, Spain

Lipid-protein Interactions in Membrane Organisation (LIPIDPROD)

(AKA, DFG, FWF, GAČR, SNF)

The objectives of this project are to understand:

1. The spatial, nanoscopic organisation of both lipid-anchored and transmembrane proteins within membranes of live cells with special emphasis on proteins that have been claimed to be raft-associated;
2. How these nanoscopic membrane protein assemblies can associate to generate more stable raft platforms with additional functions;
3. How membrane proteins interact with the different lipid species and how lipid-protein interactions contribute to membrane function. One specific issue will be to analyse how transmembrane proteins become 'raftophilic';
4. Studies in cells will be complemented by reconstitution studies of selected proteins using simplified model systems such as Giant Unilamelar Vesicles. The goal will be to find the lipid requirements for association with raft domain;
5. To develop methodology to simulate and model the interplay of lipids and proteins over a multitude of scales in time and space.

Project Leader:

Professor Kai Simons
Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany

Principal Investigators:

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Czech Academy of Sciences, Prague, Czech Republic

Dr Gerhard Schütz
Johannes Kepler University Linz, Austria

Professor Petra Schwille
Technische Universität Dresden, Germany

Professor Hannes Stockinger
Medical University of Vienna, Austria

Professor F. Gisou Van Der Goot
École Polytechnique Fédérale de Lausanne, Switzerland

Professor Ilpo Vattulainen
Tampere University of Technology, Finland

Molecular Determinants of Sterol-Sphingolipid-Protein Interactions in Living Cells and Organisms (Lipid Specific)

(AKA, CNR, DFG, SNF)

Sterols and sphingolipids are major lipids of the plasma membrane and endocytic pathways found almost exclusively in eukaryotes and differ in their specific structure between species. While the concept of lipid rafts is consistent with a number of findings from model and cell membranes, this hypothesis is not sufficient to explain the biologically observed interdependence between sterol and sphingolipid structures, nor does it help to predict which specific protein-lipid interactions may regulate functions at the cell and tissue

level. The molecular determinants governing specific sterol-sphingolipid-protein interactions in cell membranes cannot be predicted from studies in model membranes, where the structural complexity of biomembranes cannot be accurately reconstituted. This project proposes to use instead experimentally amenable model organisms (yeast, flies and worms) as platforms to identify key structural elements and functional consequences of sterol-sphingolipid-protein interactions. Parallel studies in mammalian cells and tissues will focus on selected aspects of sterol-sphingolipid-protein affinities in questions relevant for human physiology and pathology. A wide combination of state-of-the-art techniques, including genetics, systematic biological phenotyping, chemical synthesis of sterols and sphingolipids, lipid imaging in living cells/tissues and mass spectrometry for lipid analysis will be employed.

Project Leader:

Professor Elina Ikonen
University of Helsinki, Finland

Principal Investigators:

Dr Suzanne Eaton
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Professor Hans-Joachim Knölker
Technical University Dresden, Germany

Dr Teymuras Kurzchalia
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Associated Partner:

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Mario Negri Sud Institute, Consorzio Mario Negri Sud, S. Maria Imbaro, Italy

How can I participate in the EUROCORES Programme EuroMEMBRANE?

The Scientific Committee of the Programme established a work programme for 2009-2012 to initiate and financially support conferences, workshops, summer schools, etc. Information about these activities will be disseminated through the web pages:

http://www.esf.org/euromembrane

- If you are an Individual Project team member inside the EuroMEMBRANE programme your participation in the networking and dissemination activities can be funded.
- If you don't have any relation with the EuroMEMBRANE projects, you can participate in the activities but you need to be self-funded.

The European Collaborative Research (EUROCORES) Scheme enables researchers in different European countries to develop collaboration and scientific synergy in areas where international scale and scope are required for top class science in a global context.
The scheme provides a flexible framework for national basic research funding and performing organisations to join forces in supporting forefront European research in and across all scientific areas. The national organisations support all aspects including scientific coordination, networking and research funding.

www.esf.org/eurocores

THE FOLLOWING NATIONAL FUNDING ORGANISATIONS SUPPORT THE EUROCORES PROGRAMME EuroMEMBRANE:

Fonds zur Förderung der wissenschaftlichen Forschung in Österreich (FWF)
Austrian Science Fund, Austria

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Czech Science Foundation, Czech Republic

Suomen Akatemia/Finlands Akademi
Academy of Finland, Finland

Deutsche Forschungsgemeinschaft (DFG)
German Research Foundation, Germany

Consiglio Nazionale delle Ricerche (CNR)
National Research Council, Italy

Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO)
Netherlands Organisation for Scientific Research, The Netherlands

Norges Forskningsråd (RCN)
Research Council of Norway, Norway

Vetenskapsrådet (VR)
Swedish Research Council, Sweden

Schweizerischer Nationalfonds (SNF)
Swiss National Science Foundation, Switzerland

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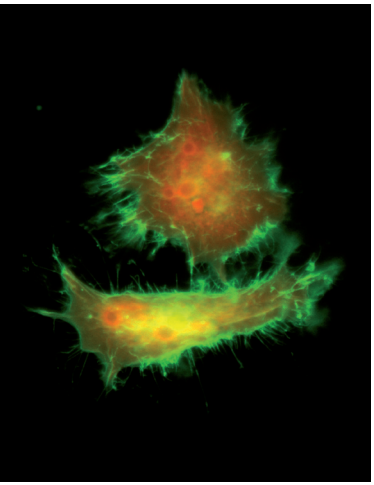

Cells were engineered to express membrane docking sites (in green) for a lipid modifying enzyme localised in the cytosol. Translocation of lipid kinases and phosphatases can thus be targeted chemically to specific sub-membrane domains to investigate the importance of lipid signalling (Courtesy of Dominik Erhart, from the TraPPs project coordinated by Matthias Wymann, Basel).

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