ESF EUROCORES Theme Proposal - Overview

Application

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Proposal Details

Proposal Title	How cells shape and utilize their membranes
Acronym	EUROMEMBRANE
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Abstract

It never ceases to amaze how a thin layer of oil with a thickness of 0.1% of the diameter of a cell makes the difference between life and death. The physical laws that govern the behaviour of the membrane lipids and their interactions with the membrane proteins are often counterintuitive and the realization that there are thousands of different lipids in combination with new technical developments in lipidomics, proteomics and membrane protein structure determination have sparked a new wave of in the membrane 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 The famous Singer and Nicholson model of a freely mixing two-dimensional liquid has now been replaced by a more detailed model that recognizes an additional level of dynamic organization both across the lipid bilayer, lipid asymmetry, and in the lateral dimension, membrane rafts. The actual membrane composition and organization reflect the functions of each cell and its organelles and is the subject of intense research in the field of membrane traffic and signaling. European researchers have played a major role in membrane research and we want to maintain this leading role. The area of research is still in its infancy. To find out how the membrane lipidome and proteome can fulfil all the tasks that membranes have is an enormous challenge. This mission will only be possibly accomplished by a multidisciplinary approach, involving biochemists, cell biologists, physicists and information technologists working together to overcome the technical and conceptual barriers that the field is confronted with. Obviously, progress will not only illuminate the basic working principles of cells and tissues, but also allow fundamental insights into the pathogenicity of disease. Major scourges of mankind, such as atherosclerosis, infectious diseases, Alzheimer and cancer involve membrane processes. A molecular understanding of these processes will contribute to improved prevention, diagnosis and cure.

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EUROMEMBRANE

How cells shape and utilize their membranes

Eurocores Theme Proposal, June 1, 2007

1. EUROMEMBRANE: scientific relevance, quality, novelty and feasibility

To understand the workings of cells, the catalogue that is now being assembled, of genes and proteins responsible for different cellular processes, represents only a beginning. We have to place these processes in their cellular context, spatially and temporally, and unravel the supramolecular principles of how cellular organization facilitates function and regulation. About one third of the genome encodes membrane proteins, and many other proteins are involved in membrane synthesis or spend part of their lifetime bound to membranes. Membranes not only form a protective skin around the cell itself and its intracellular compartments, but they are also the sites where many cellular machines carry out their function. The unique feature of cell membranes is their ability to form 5 nm-thin two-dimensional fluids, designed such that they contain a hydrophobic interior and two polar interfacial regions oriented towards an aqueous medium. The membrane has to be practically impermeable and resistant to shape changes and the continuous variation in composition due to membrane traffic and exchange processes. This remarkable liquid with its amphipathic constituents is attracting increasing attention not only by biologists but also by physicists because of its fascinating properties. Membrane research has picked up speed in recent years. An increasing number of atomic structures of membrane proteins are being solved, the field of lipid research is exploding and the principles of membrane organization are being overhauled. New insights into the staggering capability of cell membranes to sub-compartmentalize themselves have revealed how membranes support parallel processing of signalling and trafficking events.

Cell membranes contain a myriad of different lipid species, and we are only just beginning to realize the nature and consequences of this compositional complexity. Eukaryotic membrane lipids are glycerophospholipids, sphingolipids, and sterols. Mammalian cell membranes contain mainly one sterol, namely cholesterol, but a variety of hundreds of different lipid species of the first two classes. The headgroups of glycerolipids can vary, so can the bonds linking the hydrocarbon chains to glycerol, and the fatty acids differ in length and degree of unsaturation. Also the sphingolipids have the combinatorial propensity to create diversity by different ceramide backbones and, above all, more than 500 different carbohydrate structures make up the headgroups of the glycosphingolipids. There are several hundred genes encoding enzymes involved in lipid synthesis and metabolism, and there are more than a thousand different lipid species in the complement of membranes in a cell. The emerging field of lipidomics may help us to come to grips with this complexity and to unravel the necessity for this vast lipid heterogeneity (1).

In addition to the different lipid species, similarly diverse families of protein constituents increase the intricacy of cell membranes even more. Membrane proteins have been designed so that they can function at interfaces between hydrophobic and hydrophilic environments. The class of peripheral membrane proteins functions by binding to the interfacial regions of the bilayer, either at the exoplasmic or at the cytoplasmic side. Another class of proteins is anchored in the membrane by covalently attached lipid moieties. The class of membrane proteins that constitutes the biggest challenge to membrane researchers are the transmembrane proteins, spanning the bilayer. They are amphipathic, with the transmembrane part in the hydrophobic interior of the bilayer and hydrophilic domains on both sides of the membrane. The area of lipid-transmembrane protein interaction is largely unexplored and is key to understanding membrane functions.

There is an additional feature characterizing cell membranes, which is their capability to organize membrane domains (2). This capability is presently under careful scrutiny (3). Proteins that interact with lipids or proteins on either side of the bilayer can, by oligomerization or by being scaffolded, cause the formation of lateral arrays of different size. One type of lateral organization that has caused controversy in the membrane field in recent years is the raft concept of sphingolipid-cholesterol liquid-ordered assemblies. Proteins have been postulated to partition into these domains to function within dynamic platforms in different membrane processes such as signalling and trafficking. The puzzling observation is that there are no microscopically visible raft assemblies in the "resting state" of the cell membrane.

A key issue is the dynamic properties of sphingolipid-cholesterol assemblies. If one assumes that native rafts in a resting cell are metastable dynamic assemblies that can coalesce to larger domains or fragment, to be reused in different contexts, then most of the data accumulated on lipid rafts in cells can be reconciled (4). The problem is that the methodologies currently available do not allow the simultaneous monitoring of multi-component bilayer assemblies, the methods usually only provide glimpses of different states. The state that is accessible to microscopy is the condition, in which rafts have already come together to form raft clusters. Another open issue is how proteins partition into a liquid-ordered microdomain? It is conceivable that proteins with raft-lipid like anchors partition into rafts, like GPI-anchored proteins and other proteins having saturated fatty acyl moieties and/or cholesterol. But how do transmembrane proteins manage to intercalate into these assemblies? Are proteins the organizing principles to nucleate rafts by assembling a lipid shell around them (5), or is it the specific binding of raft lipids to transmembrane proteins that augments their propensity to partition into raft domains. Also, protein sites on the exoplasmic surface of the

bilayer could bind carbohydrate headgroups of glycosphingolipids. The issue whether separated fluid phases really exist in cell membranes remains. How does one define phases in non-equilibrium systems? If one were to leave a plasma membrane in a resting state: no lipid synthesis or metabolism, no exocytosis or endocytosis, would membrane components phase-separate into large domains with time? A surprising recent answer demonstrates that this is indeed the case, strengthening the raft concept of membrane sub-compartmentalization in living cells (6).

Cell membranes have emerged from being mere solvents for membrane proteins to fascinating two-dimensional fluids with inbuilt capabilities for shaping cellular morphogenesis and for dynamic sub-compartmentalization. Lipids interact directly with proteins and regulate their activities. The membranes can bend, form protrusions, lamellae, and change shape to perform a multitude of functions in cell differentiation and motility. Sorting and delivery of protein and lipid cargo to different destinations during membrane trafficking could not be possible without mechanisms for the segregation of cargo into vesicles or tubules during biosynthetic and endocytic transport (8). Similar processes that lead to the segregation of cargo in membrane trafficking also operate in regulating signal transduction events (7).

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This is the background of this EUROCORE project. European researchers have played a major role in membrane research and we want to maintain this leading role. The area of research is still in its infancy. To find out how the components identified in the membrane lipidome and proteome can fulfil all the tasks that membranes have is an enormous enterprise. This mission can only be achieved through a multidisciplinary approach, involving biochemists, cell biologists and physicists working together to overcome the technical and conceptual challenges that the field is confronted with. Moreover, progress will not only illuminate the basic working principles of cells and tissues, but also provide fundamental insights into membrane-related human diseases, including atherosclerosis, infectious diseases, Alzheimer's disease and cancer.
The scientific objective of EUROMEMBRANE is to assemble a multidisciplinary group of leading researchers to combine the major elements of membrane research into 6 interconnected baskets.

Basket 1 - Lipidomics

The goal is to assemble mass spectrometric tools that enable sensitive and quantitative molecular species profiling of essential lipid classes of mammalian and yeast membranes. First, the lipidomic facility led by Andrej Shevchenko, MPI-CBG Dresden, will provide lipidomics analysis for consortium members. However, the final deliverable will be a generic package that includes

standards, methods and cross-platform data interpretation and quantification software. It could be implemented by any European laboratory that is willing to include mass spectrometric lipid analysis in their toolkits. This package will be tested by different members of EUROMEMBRANE to make sure the analysis is robust and consistent with biological evidence.

Basket 2 - Proteomics

A major goal will be to refine methodology for membrane protein purification, reconstitution and crystallisation to make progress into understanding the burning issue of membrane lipid-protein interactions. This will be a collective effort in which Gunnar von Heijne (Stockholm), Lukas Huber (Innsbruck), Carola Hunte (Frankfurt), Bert Poolman (Groningen), Gerrit van Meer (Utrecht) and Kai Simons (Dresden) have expressed interest to be involved.

Basket 3 – Membrane Dynamics and Imaging

It is becoming evident that the technology for studying membrane dynamics, FRAP, FRET, FLIM, FCS etc.) has to be continuously improved. Also new mass spectrometric imaging methods are entering the field. New methods are becoming available to study lipid raft clustering by dyes that partition into the bilayers and can sense the packing of the lipids. Such a package will be developed and be available as a deliverable after 12 months of EUROCORE. Again testing of the package by the Consortium is a must for the package to be robust. Interest in membrane dynamics and imaging has been expressed by several centers: Patricia Bassereau (Paris), Gerald Feigenson (Ithaca, NY), Hai-Tao He and Didier Marguet (Marseille), Vaclav Horejsi (Prague), Aki Kusumi (Kyoto), Satyajit Mayor (Bangalore), Petra Schwille (Dresden), and Kai Simons (Dresden). Ilpo Vattulainen (Tampere) is interested in the computational modeling of proteins in membranes.

Basket 4 – Membrane Organelles and Trafficking

The problem of organelle architecture and of the movement of lipids and proteins between compartments is still a field that is far from having reached a deep understanding of the construction principles and mechanisms involved. We need to understand how lipid and cargo segregate in transport carriers during biosynthetic and endocytic transport. Also the issue how membrane architecture is modelled by proteins and lipids is largely unsolved. This whole field is an area of considerable strength in Europe that has recently been reinforced by the recruitment of two leading scientists from the USA to Europe: Vivek Malhotra (UCSD) is moving to CRG (Barcelona) to head the Cell Biology and Developmental Programme and Graham Warren (Yale) moved to head the new Center for Molecular Biology in Vienna. Other leaders that would like to join the

programme: Antonella de Matteis (Chieti), Gillian Griffiths (Oxford), Ari Helenius (Zurich), Elina Ikonen (Helsinki), Sean Munro (Cambridge), Margaret Robinson (Cambridge), Harald Stenmark (Oslo), Colin Watts (Dundee).

Basket 5 – Signal Transduction

Similar processes that lead to the segregation of cargo in membrane trafficking also operate in regulating signal transduction events. Three features are important in order to ensure specific and effective signalling: 1) efficient assembly of signalling complexes once a signal arrives, 2) prevention of undesired premature signalling in the absence of the signal, and 3) fast switching between the two states and regulation of the magnitude of the relayed signal. This can be achieved by similar mechanisms that are employed by cells to form domains for membrane vesicle formation but leaving out the events leading to membrane bending. The signalling proteins come together by protein-protein and protein-lipid interactions e.g. involving phosphoinositides. Membrane sub-compartmentalization based on lipid rafts has also been implicated in the regulation of several signalling cascades. Signalling is a large area and in the EUROCORE we would only take up one such process that will illustrate the principles involved and this is T-cell activation. Two leaders in this field Hai-Tao He (Marseille) and Vaclav Horejsi (Prague) have indicated their interest in joining this effort. The T-cell activation includes all aspects of this EUROMEMBRANE project. So the deliverable at the end of the project would be a MODEL of what can be achieved in the signalling field by a multidisciplinary effort with collaborations involving all possible tools.

Basket 6 – Membrane Pathogens

Viruses, bacteria, and toxins depend on cell membranes for their interaction with the host cell. Thus this area is a prime example of a disease process in which knowledge of membrane biochemistry and biophysics are essential for progress. Because of the simplicity of membrane viruses they also have a longstanding role as tools in membrane research. In this area the challenge will be to push the membrane processes involved all the way to therapeutics. One deliverable at the end of the EUROMEMBRANE project will be to get one drug candidate into clinical trials. Four leaders in the field will join the project: Gisou van der Goot (Lausanne), Ari Helenius (Zurich), Mark Marsh (London), Kai Simons (Dresden).

2. EUROMEMBRANE: synergy and European dimension

The synergy between the project elements and the participants will be the driving force for success of this EUROCORE. This membrane field has been fragmented into sub areas with little contact over the boundaries. This is changing and this EUROCORE project will be a prime motor to demonstrate that the networking approach can make a real impact. Our scientific programme has been designed such that overlaps between disciplines and between the Programme elements are maximized. Often networks are put together by demands from the funding agencies and that creates all kinds of problematic restraints. However, this network will be bottom up. The participants will be selected on their scientific qualifications and their enthusiasm for doing this project together.

Why is a programme on the European level necessary now? Because the field is rapidly changing and new tools such as mass spectroscopy and sophisticated imaging methods are being introduced. This means that networking leading groups around Europe will rapidly disseminate the new technologies to assess their value for the field. This could not be done on the national level alone because the bundling of the necessary expertise is possible by tapping the strengths Europe-wide. This is why the Eurocore programme is the ideal instrument for our objectives.

There is one more element that we would like to introduce to strengthen the synergy between the participants and add value to this field in Europe. Membrane know-how is going to be a key to understanding major diseases. Most clinical researchers have a rudimentary understanding of this complex field. To promote the knowledge transfer in this field to the clinic, the EUROMEMBRANE project will introduce a PhD/ postdoc's scheme for MDs in this area of research. The successful applicants should come with a project involving a disease involving membrane processes and then be hosted by one lab of the EUROMEMBRANE project. In their training they can choose to spend time in one or two other labs within the programme for additional training and overlapping research possibilities. Especially projects involving lipidome analysis will be promoted. The funding for this training and research programme would come from the budget of the EUROMEMBRANE project.

3. EUROMEMBRANE: relation to other initiatives

On the lipid side, the EUROMEMBRANE theme has been prepared by an ESF science policy briefing to appear in print later this year on "Structural Medicine II: the importance of lipidomics

for health and disease", by a committee chaired by Gerrit van Meer (Utrecht) and Fritz Spener (Graz). In addition, the theme proposal builds on the European Lipidomics Initiative, a specific support action of the European Commission 2005-2007, again chaired by Gerrit van Meer, which was intended to mobilize the European stakeholders in lipidomics research, and runs in parallel to the US LIPID MAPs and Japanese LipidBank. In the broader field of biomembranes, the proposers (except Malhotra and Warren who are about to move to Europe) are active members in one or more specific targeted research projects (STREPs) and research training networks (RTNs) funded by the European union. However, each of these projects and networks focusses on a subfield of biomembrane research and has a much more narrow scope than the EUROMEMBRANE project.

4. EUROMEMBRANE: the proposers

Because biomembranes are of such fundamental structural importance to cells, they have been the subject of intense study over the years. Especially in the 1960s and 70s the development of new physical techniques like ESR, NMR, electron microscopy and electrophysiology allowed enormous progress in our understanding of lipid-lipid and lipid-protein interactions and the basic properties of biomembranes. The opening up of molecular cell biology in the 1980s then permitted a much more thorough understanding of the functional aspects and dynamics of membranes in cells and the coupling of functions and dynamics to specific proteins and lipids. After a period of steady progress in the 1990s during which more and more membrane components were identified as relevant for disease, around 2000 a new momentum has been generated in biomembrane research, notably by the renewed active involvement of biophysicists. Two of the proposers (Kai Simons and Graham Warren) have lived through all these phases with steady discoveries on the molecular basis of membrane traffic and the specific interactions between membrane components. Gerrit van Meer applied his background in lipid biochemistry to cell biology culminating in the lipid raft proposal with Kai Simons in the late 80s, and has focussed on the proteins responsible for the metabolism and dynamic organization of lipids in cellular membranes since. Mark Marsh was a member of the team that discovered the endocytosis and low pH-induced fusion of membrane viruses like influenza virus in the early 1980s, and has focussed on the entry and morphogenesis of HIV. Vivek Malhotra has made major contribution to understanding the mechanisms controlling the architecture and function of the Golgi apparatus. Finally, Gisou van der Goot has concentrated since the early 1990s on the interactions of bacterial pore-forming toxins with cellular membranes, uncovering a crucial involvement of lipid rafts over the past decade. Each proposer is a leader in his/her field which is reflected in the cv's.

A target group of European scientists was identified based on their scientific status in the broad field of biomembrane physics, chemistry and biology. Each has responded with enthusiasm to the invitation to join the EUROMEMBRANE project. Arguably, it would not be difficult to double the number of names, but we do think that we have collected the most important biomembrane research institutes of Europe in this list. After all, the call for proposals will be open to all and an independent committee will ensure that the proposal by every scientist in the field will be evaluated according to common criteria of scientific excellence and European added scientific value.

5. EUROMEMBRANE: funding requirement

One or two consortia will work in each of the 6 focal points, and, with the exception of "basket 1", will be composed of 5 to 7 research teams. The minimal input of one position for each team during 3-4 years depending on whether this position is at the PhD student or postdoctoral fellow level, requires a Programme budget of 11 M€. This also includes funding for intra-network activities and for EUROMEMBRANE facilities.

6. EUROMEMBRANE: ethical and legal issues

There are no special ethical and legal issues related to the EUROMEMBRANE theme proposal.

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Secretary, Oxford University Biochemical Society (1982-1984); Pirie-Reid Scholar, Oxford University (1982-1985); Damon-Runyon Walter-Winchell Post-doctoral Fellow, Stanford University (1985-1987); American Cancer Society (California Division) Senior Post-doctoral Fellow (1988-1990); Basil O'Connor Starter Scholars Award from the March of Dimes Birth Defect Foundation (1992-1995); Established Investigator of the American Heart Association (1995-2000); senior investigator award from the Sandler program for asthma research (July 2004- July 2007); Elected fellow AAAS (2005).

Editorial boards, advisory committees and review panels

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1985-1991	Group leader, Institute of Cancer Research, Chester Beatty Laboratories, Fulham Road, London - Cell Biology of HIV
1979–1981	Postdoctoral position at the Dept Cell Biology, Yale University, New Haven, Connecticut, USA with Ari Helenius and Ira Mellman (EMBO Fellowship and Swebilius Cancer Research Award) - Identification and analysis of endosomes
1979–1981	Postdoctoral position at the European Molecular Biology Laboratory (EMBL), Heidelberg, Germany, with Ari Helenius and Kai Simons, Cell Biology Program (Royal Society Fellowship) - Cellular mechanisms of virus entry
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Editorial Boards, advisory boards, review panels (current):

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1976 - 1979	Professor, Department of Biochemistry, University of Helsinki
1975 - 2000	Group Leader at the European Molecular Biology Laboratory, Heidelberg
1982 - 1998	Coordinator of the Cell Biology Programme, at the European Molecular Biology Laboratory, Heidelberg
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Awards

1991 Anders Jahre Prize for Medical Research, 1996 Foreign Member of the American Academy of Arts and Sciences, 1997 Foreign Member of the National Academy of Sciences, USA, 1997 and 2003 Doctor Honoris Causa, University of Oulu and Leuven , 2001 Honorary member of the German Society for Cell Biology, 2005 Foundation Day Lecture, Centre for Cellular and Molecular Biology, Hyderabad, India

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Publications (selected)

Parton, R. G., Simons, K. (2007) The multiple faces of caveolae. Nature Rev. Mol. Cell. Biol. 8, 185-194.

Vieira, O., Gaus, K., Verkade, P., Fullekrug, J., Vaz, W., Simons, K. (2006) FAPP2 cilium formation and the compartmentalization of the apical membrane in polarized MDCK cells. Proc. Natl. Acad. Sci. USA 103, 18556-18561.

Schuck, S., Gerl, M., Ang, A., Manninen, A., Keller, P., Mellman, I., Simons, K. (2006) Rab 10 is involved in basolateral transport in polarized MDCK cells. Traffic 1, 47-60

Proszynski, TJ., Klemm, R., Bagnat, M., Gaus, K., Simons, K. (2006) Plasma membrane polarization during mating in yeast cells. J Cell Biol. 173, 861-866.

Ejsing, C., Moehring, T., Bahr, U., Duchoslav, E., Karas, M., Simons, K., Shevchenko, A. (2006) Collision-induced dissociation pathways of yeast sphingolipids and their molecular profiling in total lipid extracts: a study by quadrupole TOF and linear ion trap-orbitrap mass spectrometry. J. Mass Spectrom. 41, 372-389.

Füllekrug, J., Shevchenko, A., Shevchenko, A., Simons K. (2006) Identification of glycosylated marker proteins of epithelial polarity in MDCK cells by homology driven proteomics. BMC Biochemistry 7, 8.

Proszynski, T., Klemm, R., Gravert, M., Hsu, P., Gloor, Y., Wagner, J., Kozak, K., Grabner, H., Walzer, K., Bagnat, M., Simons, K., Walch-Solimena, C. (2005) A genome-wide visual screen reveals a role for sphingolipids and ergosterol in cell surface delivery in yeast. Proc. Natl. Acad. Sci. USA 102, 17981-17986.

Vieira, O., Verkade, P., Manninen, A., Simons, K. (2005) FAPP2 is involved in the transport of apical cargo in polarized MDCK cells. J Cell Biol. 170, 521-526.

Ehehalt, R., Keller, P., Haass, Ch., Thiele, Ch. and Simons, K. (2003) Amyloidogenic processing of the Alzheimer b-amyloid precursor protein depends on lipid rafts. J. Cell Biol. 160, 113-123.

Keller, P., Toomre, D., Díaz, E., White, J. and Simons, K. (2001) Multicolour imaging of post-Golgi sorting and trafficking in live cells. Nature Cell Biol. 3, 140-149.

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Current Position:	Professor in Life Sciences, Institute of Global Health Ecole Polytechnique Fédérale de Lausanne Station 15, 1015 Lausanne, Switzerland Tel: +41 21 693 1791 ; Fax: +41 21 693 9538 gisou.vandergoot@epfl.ch
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Academic Record

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1998-2001:	Group leader, with a "Maître d'Enseignement et de Recherche" position in the Department of Biochemistry, University of Geneva
1993-1998	Group leader, with a "Maître-Assistant" position in the Department of Biochemistry, University of Geneva
1990-1993:	Post-doc at the EMBL, Heidelberg
1987-1990:	Research assistant in the Department of Cell Biology, Commissariat à l'Energie Atomique Gif-sur-Yvette, France in the group of Dr. B. Corman
1987	Engineering diploma Ecole Centrale de Paris

Editorial Boards

- *Cellular Microbiology* Associate Editor
- *Cell: Host and Microbes* Editorial board Member
- *Infection and Immunity* Editorial board Member
- *The HFSP Journal* Reviewing Editor of
- *Molecular Membrane Biology* Advisory Board

Publications (selected)

Gurcel, L., Abrami, L., Girardin, S., Tschopp, J., and van der Goot, F.G. (2006) Caspase-1 dependent activation of SREBP promotes cell survival in response to bacterial pore-forming toxins. Cell 126, 1135-1145.

Iacovache, I., Paumard, P., Scheib, H., Lesieur, C., Sakai, N., Matile, S., Parker, M.W., and van der Goot, F.G. (2006) A rivet model for channel formation by aerolysin-like pore-forming toxins. EMBO J. 25, 457-466.

Abrami, L., Leppla, S.H., and van der Goot, F.G. (2006) Receptor palmitoylation and ubiquitination regulate anthrax toxin endocytosis. J. Cell Biol. 172, 309-320.

Abrami, L., Lindsay, M., Parton, R.G., Leppla, S.H., and van der Goot, F.G. (2004) Membrane insertion of anthrax protective antigen and cytoplasmic delivery of lethal factor occur at different stages of the endocytic pathway. J. Cell Biol. 166, 645–651.

Abrami, L., Liu, S., Cosson, P., Leppla, S.H., and van der Goot, F.G. (2003) Anthrax toxin triggers endocytosis of its receptor via a lipid raft-mediated clathrin-dependent process. J. Cell Biol. 160, 321-328.

Tsitrin, Y., Morton, C.J., El Bez, C., Paumard, P., Velluz, M-C., Adrian, M., Dubochet, J., Parker, M.W., Lanzavecchia, S., and van der Goot, F.G. (2002) Convertion of a transmembrane to a water soluble protein complex by a single point mutation. Nature Struct. Biol. 9, 729-733.

Lafont, F., Tran Van Nhieu, G., Hanada, K., Sansonetti, P., and van der Goot, F.G. (2002) Initial steps of *Shigella* infection depend on the cholesterol-sphingolipids raft-mediated CD44-IpaB interaction. EMBO J. 21, 4449-4457.

Fivaz, M., Vilbois, F., Thurnheer, S., Pasquali, C., Abrami, L., Bickel, P.E., Parton, R.G., and van der Goot, F.G. (2002) Differential sorting and fate of endocytosed gpi-anchored proteins. EMBO J. 21, 3989-4000.

Abrami, L., and van der Goot, F.G. (1999) Plasma membrane microdomains act as concentration platforms to facilitate intoxication by aerolysin. J. Cell Biol. 147, 175-184.

Abrami, L., Fivaz, M., Glauser, P-E., Parton, R.G., and van der Goot, F.G. (1998) A pore-forming toxin binds to GPI-anchored proteins and causes vacuolation of the endoplasmic reticulum. J. Cell Biol. 140, 525-540.

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Nationality:	Dutch

Academic Record

2001–	Professor of Membrane Enzymology, Membrane Enzymology, Science Faculty, Utrecht University
1997–2001	Professor of Cell Biology and Histology, Dept. of Cell Biology and Histology, Academic Medical Center (AMC), University of Amsterdam
1993–1997	Associate professor (Universitair Hoofddocent), Utrecht University
1988–1993	Senior Investigator of the Royal Netherlands Academy of Arts and Sciences, Utrecht University
1987–1997	Staff Scientist at the Dept. of Cell Biology, Medical School, Utrecht University
1983–1986	Staff Scientist at the EMBL in the Cell Biology Program
1981–1983	Postdoctoral position at the EMBL, Heidelberg, Germany, with Kai Simons
1977–1981	Ph.D. studies, Dept. of Biochemistry, Utrecht University

Editorial Boards, advisory boards, review panels (current)

Associate editor: Developmental Cell, Traffic - Editorial boards: EMBO Journal, EMBO Reports, European Journal of Cell Biology, Glycobiology, Journal of Biological Chemistry - Site-visit panel Center of Excellence, Finnish Academy, 2001 - Review panel Sonderforschungsbereich DFG at the University of Heidelberg, 2003; University of Bonn, 2004 - Chair European Lipidomics Initiative, 2005–2007 - Review panel Cell Biology and Biophysics Programme EMBL, Heidelberg, 2005 - Chair ESF Expert group on Structural Medicine, the Impact of Lipidomics 2006–2007 - Advisory Committee Lipid Classification of LIPID MAPS, USA, 2006– - Chairman Utrecht Graduate School of Life Sciences, 2006–

Honors

1981–1983 EMBO fellow; 1987, 2006 Personal Grants of the Mizutani Foundation for Glycoscience; 1987–1992 Senior fellow of the Royal Netherlands Academy of Arts and Sciences; 1994 Co-chair of EMBO Workshop 'Intracellular Lipid Traffic', Asti, Italy; 1997 Chair of the Conférence Jacques Monod, 'Cell Lipids: Topology, Transport and Signalling Functions', Aussois, France; 1998 Co-chair of EMBO Workshop, 'Lipids: Regulatory Functions in Membrane Traffic and Cell Development', Galilee, Israel; 2003 Chair of Euresco/EMBO Conference 'Lipid Rafts and Caveolae', Tomar, Portugal; 2003 Chair of FEBS lecture course 'Modern Developments in Membrane Biology', Tbilisi, Georgia; 2003 Elected EMBO member; 2008 Elected Chair Gordon Conference Sphingolipid and Glycolipid Biology

Publications (selected)

Halter, D., Neumann, S., van Dijk, S.M., Wolthoorn, J., de Mazière, A.M., Vieira, O.V., Mattjus, P., Holthuis, J., Klumperman, J., van Meer, G. and Sprong, H. (2007) Pre- and post-Golgi translocation of glucosylceramide in glycosphingolipid synthesis. J. Cell Biol. submitted

van Meer, G., Halter, D., Sprong, H., Somerharju, P., and Egmond, M.R. (2006) ABC lipid transporters: extruders, flippases, or flopless activators? FEBS Lett. 580, 1171-1177.

van Meer, G. (2005) Cellular Lipidomics. EMBO J. 24, 3159-3165.

Kälin, N., Fernandes, J., Hrafnsdóttir, S., and van Meer, G. (2004) Natural phosphatidylcholine is actively translocated to the outside of the plasma membrane of eukaryotic cells. J. Biol. Chem. 279, 33228–33236.

Sprong, H. , van der Sluijs, P., van Meer, G. (2001) How proteins move lipids and lipids move proteins. Nature Rev. Mol. Cell Biol. 2, 504-513.

Holthuis, J.C.M., Pomorski, T., Raggers, R.J., Sprong, H., and van Meer, G. (2001) The organizing potential of sphingolipids in intracellular membrane transport. Physiol. Rev. 81, 1689-1723.

Sprong, H., Degroote, S., Claessens, T., van Drunen, J., Oorschot, V., Westerink, B.H.C., Hirabayashi, Y., Klumperman, J., van der Sluijs, P., and van Meer, G. (2001) Glycosphingolipids are required for sorting of melanosomal proteins in the Golgi complex. J. Cell Biol. 155, 369-380.

van Helvoort, A., Smith, A.J., Sprong, H., Fritzsche, I., Schinkel, A.H., Borst, P., and van Meer, G. (1996) MDR1 P-glycoprotein is a lipid translocase of broad specificity, while MDR3 P-glycoprotein specifically translocates phosphatidylcholine. Cell 87, 507-517.

Simons, K. and van Meer, G. (1988) Lipid sorting in epithelial cells. Biochemistry 27, 6197-6202.

van Meer, G., Stelzer, E.H.K., Wijnaendts-van-Resandt, R.W. and Simons, K. (1987) Sorting of sphingolipids in epithelial (Madin-Darby canine kidney) cells. J. Cell Biol. 105, 1623-1635.

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Current Position: Scientific Director, Max F. Perutz Laboratories, Dr. Bohr-Gasse 9, A-1030, Vienna, Austria. Tel. +43-1-4277-24011. graham.warren@mfpl.ac.at

Date of Birth: February 25, 1948, London, UK

Nationality: British

Academic Record:

1972	PhD in Biochemistry, Cambridge, UK
1972-1974	MRC Junior Research Fellow at the National Institute for Medical Research, London
1974-1975	SRC Research Fellow, Department of Pharmacology, Cambridge
1975-1977	Stothert Research Fellow of the Royal Society, Department of Biochemistry, Cambridge
1975-1977	Research Fellow of Gonville & Caius College, Cambridge
1977-1985	Group Leader at the European Molecular Biology Laboratory, Heidelberg, Germany
1984-1985	Senior Scientist at the European Molecular Biology Laboratory, Heidelberg, Germany
1985-1988	Professor and Head of Department of Biochemistry, University of Dundee, Scotland, U.K.
1988-1999	Principal Scientist, Imperial Cancer Research Fund, Lincoln's Inn Field, London, U.K.
1997-1999	Honorary Professor of Biochemistry, University College, London, U.K.
1999-2007	Professor of Cell Biology, Yale University School of Medicine, New Haven, CT, USA
2007-present	Scientific Director, Max F. Perutz Laboratories, Vienna, Austria

Editorial boards, advisory committees and review panels

1980-1989, Editorial Adviser, Biochemical Journal; 1981-1985, Editor, Trends in Biochemical Sciences; 1985-1988 and 1995-present, Editor, Journal of Cell Biology; 1985-1987, Panel Member of the Biochemistry and Cell Biology Board of the Wellcome Trust; 1986-1989, Committee Member of the British Society for Cell Biology; 1986-1988, Panel Member of the MRC Cell Board Grants Committee B; 1987-1988, Publications Convenor of the British Society for Cell Biology; 1988-present, Editorial Board of the Journal of Cell Science; 1988-present, Editorial Board of "Current Opinion in Cell Biology"; 1988-1990, Chairman of the MRC Cell Board Grants Committee B; 1988-1990, Panel Member of the MRC Cell Biology and Disorders Board; 1988-1990, External Examiner for Part IB Biochemistry, University of Cambridge; 1988-1990, MRC Scientific Advisor to the British Delegation to EMBL, Heidelberg; 1989-1992, Editorial Board of the EMBO Journal; 1990-1993, Panel Member of the CRC Grants Committee; 1991-1996, Editorial Board, Seminars in Cell Biology; 1992-1994, Wellcome Trust International Interest Group; 1997-2001, Editorial Board, Current Biology; 1997-2000, Scientific Board of the Institute of Biotechnology, University of Helsinki, Finland; 1998-2004, Editorial Board, Trends in Biochemical Sciences; 1999-2001; Editorial Board of Molecular Cell; 1999-present, Editorial Board, Traffic; 2001-2004, Chairman, Functional Genomics Panel, Wellcome Trust; 2001-present, Section Head (with Peter Walter) of Membranes & Sorting, Faculty of 1000; 2002-present, Board of Reviewing Editors, Science; 2003-2007, National Advisory Committee, Pew Scholars Program; 2005-2007, Member and Chairman of the NIH MBPP Study Section.

Honours and Awards:

1986, Elected a Member of the European Molecular Biology Organisation (EMBO); 1995, Danielli Lecture of the Biochemical Society; 1995, Elected a member of the Academia Europaea; 1998, University Medal, University of Helsinki, Finland; 1999, Honorary Degree at Yale University; 1999, Elected a Fellow of the Royal Society of London; 2007, Eduard Buchner Prize from the German Biochemical Society.

Publications (selected):

Ho, H.H., He, C.Y., de Graffenried, C.L., Murrells, L.J., and Warren, G. (2006) Ordered assembly of the duplicating Golgi in Trypanosoma brucei. Proc. Natl. Acad. Sci. USA, 103, 7676-7681.

He,C., Pypaert, M., Warren, G. (2005) Golgi duplication in Trypanosoma brucei requires centrin2.Science 310,1196-98

He, C.Y., Malsam, J., Ho, H.H., Chalouni, C., West, C., Ullu, E., Toomre, D. and Warren, G. (2004) Golgi duplication in Trypanosoma brucei. J. Cell Biol. 165, 313-321.

Malsam, J., Satoh, A., Pelletier, L. and Warren, G. (2004) Golgin tethers define sub-populations of COPI vesicles. Science 307, 1095-1098.

Wang, Y., Seemann, J., Shorter, J., and Warren, G. (2003) A direct role for GRASP65 as a mitotically regulated Golgi stacking factor. EMBO J., 22, 3279-3290.

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Pelletier, L., Stern, C.A., Pypaert, M., Sheff, D., Ngô, H.M., Roper, N., He, C.Y., Hu, K., Toomre, D., Coppens, I., Roos, D.S., Joiner, K.A. and Warren, G. (2002) Golgi Biogenesis in Toxoplasma gondii. Nature 418, 548-552.

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Shorter, J., and Warren, G. (2002) Golgi architecture and inheritance. Annu. Rev. Cell Dev. Biol. 18, 379-420.

Appendix ii. Potential participants in the Euromembrane theme

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Appendix iii. Most important scientists and institutes in the field

Günter Blobel, New York	MRC Cambridge
Michael Brown, Dallas	MPI Dresden
Gerald Feigenson, Ithaca	MPI Göttingen
Joseph Goldstein, Dallas	Utrecht University
Ari Helenius, Zurich	Institut Curie
Akihiro Kusumi, Kyoto	UCSF
Roderick McKinnon, New York	UC Berkeley
Hartmut Michl, Frankfurt	Rockefeller
Walter Neupert, Munich	Harvard
Tom Rapoport. Cambridge, USA	MPI Frankfurt
James Rothman, New York	Cornell University
Randy Schekman, Berkeley	
Kai Simons, Dresden	
Peter Walter, San Francisco	
Ronald Vale, San Francisco	