

## Gene-Lifestyle Interactions in Coronary Heart Disease (EuroHEART)

# 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<sup>(1)</sup>. 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>

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

## Funding Initiative in the Field of Gene-Lifestyle Interactions in Coronary Heart Disease (EuroHEART)

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 EuroHEART. EuroHEART 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. The Programme aims to support high quality multidisciplinary research.

Outline Proposals are to be submitted by 9th May 2008. It is expected that Full Proposals will be invited by 30th June 2008 with 15 September 2008 as expected deadline for submission.

A programme-specific website can be consulted for the latest updates at [www.esf.org/euroheart](http://www.esf.org/euroheart)

## Background and Objectives

### *Identifying the separate and joint effects of genes and lifestyle factors in coronary heart disease*

Cardiovascular disease accounts for almost 1 in every 2 adult deaths worldwide and accounts for about €200 billion in economic costs per year in the European Union alone. Coronary heart disease (CHD), its major manifestation, is the single leading cause of death in Europe and a major source of disability, with considerable variation in incidence rates across different regional areas.

The tendency for coronary disease to cluster in families suggests that genetic variation importantly influences CHD risk. Although the pattern of variation of the incidence of coronary disease suggests that the condition originates from an interaction between genetic and lifestyle / behavioural factors, the quantitative interplay of these factors remains poorly understood. Such knowledge is important for a full understanding of the causes of coronary heart disease. It is also necessary for the development of disease prevention strategies, such as optimum targeting of interventions and identification of targets for novel therapeutics. An important implication of the reliable demonstration of gene-lifestyle interactions is that they may suggest approaches for modifying the effects of deleterious genes by avoiding deleterious lifestyle exposures.

In view of the recent availability of technologies that enable comprehensive assessment of genetic variation (such as genomewide association scans) and of biomarkers of intermediate causal pathways, it is now extremely timely to address such questions in a way that can substantially advance understanding and develop novel preventative strategies.

## Scientific Goals

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EuroHEART aims at a better understanding of the etiology of CHD and the interplay with lifestyle factors, and should enable development and refinement of CHD prevention strategies.

The goals of EuroHEART are:

(i) to identify the separate and combined influences of genetic and major lifestyle factors in determining the incidence of objectively confirmed coronary heart disease, including studies of biomarkers in potential causal intermediate pathways, in existing already harmonised population-based cohorts across Europe

(ii) to validate and evaluate promising findings in a separate network of population-based cohort studies to be established

(iii) to develop scientific capacity to undertake population-based cohort studies enabling the establishment and harmonisation of such studies in previously comparatively under-studied regions of Europe where the burden of cardiovascular disease is particularly high

## Envisaged Structure

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To achieve these three goals, it is envisaged that there will be two types of funding opportunities:

### 1. Pan-European discovery investigations of the combined effects of genetic and lifestyle factors

It is essential that studies have adequate statistical power for the following analyses outlined below, particularly those with careful assessments of major lifestyle factors (such as diet and physical activity and psychosocial factors). It is also essential that studies involve the efficient use of **already harmonised** existing large-scale, pan-European population-based prospective cohorts (i.e., reflecting the diversity of lifestyles and genetic variation across Europe) to enable achievement of the theme's objectives within a few years. It is necessary that suitable studies have already: (i) recorded key lifestyle factors, notably diet and physical activity, in a comprehensive and standardised fashion among initially healthy participants (including studies to ensure comparability of information recorded across different countries); (ii) accrued sufficient numbers of incident major coronary outcomes for reliable assessment of gene-lifestyle interactions. The objectives of this study are:

- *To study the major genetic determinants of coronary disease in Europe and to determine if they are modified by components of diet, physical activity and other lifestyle factors that predict the risk of coronary disease*

- *To identify biomarkers of intermediate causal pathways in coronary disease (particularly those related to genetic and lifestyle determinants)*

- *To engage in capacity-building to establish a European framework for the establishment and harmonisation of population-based cohorts in previously understudied regions of Europe where the burden of cardiovascular disease is particularly high*

*It is anticipated that only one large collaborative research project is likely to be funded under this heading.*

### 2. Pan-European replication / validation investigations of the interplay of genetic and lifestyle factors

This separate funding opportunity will also involve efficient use of existing large-scale population-based prospective studies. It will achieve a pan-European dimension either by involvement of existing networks or by achieving networking of several currently unrelated individual studies. It is necessary that eligible studies: (i) have recorded key lifestyle factors among initially healthy participants, (ii) are **capable of suitable harmonisation within the early part of the project timeframe**, and (iii) have, in aggregate, accrued sufficient numbers of incident major coronary outcomes for reliable validation / replication studies. Proposals under this heading will be given priority that have demonstrable linkages and/or collaborative intent with studies eligible for funding under the discovery investigation call (i.e., heading number 1 above). The objectives of these studies are:

- *To harmonise and standardise databases and biobanks with a view to replication/validation studies of gene-lifestyle interactions*

- *To conduct validation studies in cohorts different from those in which the discovery findings have been generated*

- *To engage in capacity-building to establish a European framework for the establishment and harmonisation of population-based cohorts in previously understudied regions of Europe where the burden of cardiovascular disease is particularly high*

*It is anticipated that one or more collaborative research projects are likely to be funded under this heading.*

# Cross-Disciplinary Approach

EuroHEART proposes a competitive European framework to study the interplay of genetic and lifestyle factors on the incidence of major clinical coronary outcomes. An essential aspect of the programme is the promotion of cross-disciplinary studies. This feature requires combination of expertise in cardiovascular disease epidemiology, nutrition, genetics, biomarkers and biostatistics. Careful phenotyping at the initial assessment is required to ensure informative characterisation of habits, major lifestyles, socioeconomic circumstances and anthropometry of participants recruited into cohort studies. Such assessments involve informative assessment of dietary intake and physical activity of study participants across European regions, using methods that enable harmonisation of findings from different centres (such as calibration sub-studies).

Studies will record and validate incident major clinical coronary outcomes, such as coronary death and myocardial infarction, in sufficient numbers to enable adequately powered assessments of gene-lifestyle interactions. Laboratory-based approaches may maximise the opportunities afforded by new technologies, such as genomewide association scans, high density sequencing approaches or other innovative techniques, as well as approaches to study biomarkers in potential causal intermediate pathways. Biostatistical approaches will involve methods that protect against false-discovery and put findings in the context of other relevant data (including meta-analysis). Priority will be given to proposals with translational components, such as those exploring implications of findings for the development of preventative strategies and of clinical risk stratification algorithms.

## Research Topics

### **Genetic and lifestyle determinants of coronary disease**

This topic will explore the impact of genetic variation on the incidence of major clinical coronary outcomes, and the interplay of such variation with major lifestyle factors. Projects are encouraged that make use of technical advancements in genetic assays, such as arrays enabling the assessment of hundreds of thousands of genetic markers in genomewide association scans. Appropriate replication studies should be in place to enable rapid and reliable evaluation of findings from such experiments. Examples of research questions are:

- *What are the unrecognised but important common genetic determinants of coronary disease in European populations? How are they modified by major lifestyle factors?*

- *What are the components of diet and physical activity that predict risk of coronary disease in European populations?*

- *How do major habits and lifestyles modify the impact of established and novel genetic determinants of coronary disease?*

- *How can cardio-preventative strategies be developed and tested, based on an understanding of gene-lifestyle interactions?*

### **Biomarkers of intermediate causal pathways**

This topic will explore associations of biomarkers of potentially intermediate causal pathways with the incidence of coronary heart disease. Projects are encouraged that involve both conventional candidate biomarker studies (involving lipid, metabolic and other established pathways) and comprehensive assumption-free approaches, such as metabolomics. This information can be integrated with the genetic and lifestyle data generated in the section above to enable multi-dimensional analyses, including causal inferences by Mendelian randomisation analyses. Examples of research questions:

- *To what extent does measurement of various circulating candidate biomarkers, either singly or in combination (including with genetic and lifestyle information), enhance the prediction of coronary disease in European populations? How should this information be used to alter existing strategies of clinical risk stratification?*

- *To what extent can various platforms enabling assumption-free analyses of plasma components identify novel pathways in the development of coronary disease?*

- *To what extent can focused integration of data on biomarkers, their genetic determinants, and coronary incidence (i.e., Mendelian randomisation analyses) yield causal inferences to identify novel therapeutic targets in coronary heart disease?*

### **Capacity-building in previously understudied regions of Europe**

This topic will contribute to the establishment of a European framework suitable for the creation and harmonisation of prospective population-based cohorts capable of studying the combined effects of genetic and major lifestyle factors in previously understudied regions of Europe where the burden of cardiovascular disease is particularly high. Examples of research questions:

- *What are the currently limiting factors in relation to the establishment of population-based cohort studies, particularly in recent and new entrant countries to the EU at high-risk of cardiovascular disease?*

- *How can the experience of existing population-based cohorts be harnessed in order to maximally facilitate the establishment of new cohorts in these regions (e.g., technology and skills transfer)?*
- *What are the environmental exposures (e.g., rapid changes in dietary patterns following sociopolitical changes) that require specific characterisation in the context of studies of cardiovascular disease in previously understudied, high-risk European regions, and how can instruments be developed to assess them accurately?*

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# Guidelines for applications

## (Outline and Full Proposals)

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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 EuroHEART.

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

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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/euroheart>

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 have to 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

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**Outline Proposals are invited by 9th 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 EuroHEART 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);
  - o 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.

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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 15th 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.

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## Programme Structure and Management

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### 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

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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.

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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.

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# Contacts in the participating organisations

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*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.*

## **ESF Contacts:**

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