EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

EUROCORES Programme
European Collaborative Research

Evaluating the safety of human Assisted Reproduction Technologies: A multidisciplinary approach (EuroSafeART)

DRAFT Call for Outline Proposals

What is EUROCORES?

The ESF European Collaborative Research (EUROCORES) Programmes offer a flexible framework for researchers in Europe to work on questions which are best addressed in large-scale collaborative research programmes.

The EUROCORES Programmes allow excellent researchers in the various participating countries to collaborate in research projects 'at the bench'. They also allow, when appropriate, colleagues in non-European countries, for example the US, to participate. The Programmes encourage and anticipate networking and collaboration between researchers in order to achieve synthesis of scientific results across the programme, to connect with related programmes, and to disseminate findings.

The EUROCORES Programmes allow national research funding organisations in Europe and beyond to support top-class research in and across all scientific areas, by matching their strategic priorities with the needs articulated by the scientific community.

Final funding decisions on the projects and the research funding remain with the national funding organisations, based on a single international peer review process operated by ESF. Financed by the participating national Funding Organisations, ESF also provides support for networking between the researchers and for the scientific synthesis of research results and their dissemination. In 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

Evaluating the safety of human Assisted Reproduction Technologies: A multidisciplinary approach (EuroSafeART)

Following agreement with XX funding organisations in *Country A, Country B, Country C, Country D, Country E, Country F, Country G, Country H, Country I, Country J, Country K, Country L, Country M, Country N, Country O and Country P* the European Science Foundation is launching a Call for Outline Proposals for Collaborative Research Projects (CRPs) to be undertaken within the EUROCORES Programme EuroSafeART. The Programme aims to support high quality multidisciplinary collaborative research in Europe, with involvement of leading scientists from outside Europe, when appropriate.

The research phase of EuroSafeART will run for three years and includes national research funding as well as support for networking and dissemination activities. The research grants are provided directly to the eligible and successful Principal Investigators by their respective national funding organisations. The networking and dissemination support, also financed by the national organisations, is centrally managed by the ESF.

Outline Proposals are to be submitted by xth February 2010. It is expected that Full Proposals will be invited by xth March 2010 with xx May 2010 as expected deadline for submission.

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

Background and objectives

Assisted reproduction technologies (ARTs) have contributed to the birth of over 1 million babies worldwide. Such numbers strongly suggest that infertility must be regarded as a health and societal issue, affecting every 6th couple in Western countries. Moreover, the number of couples undergoing ART treatment is increasing, due to the progressive delay in childbearing as a consequence of lifestyle and possibly adverse environmental factors. Large-scale studies suggest that there are a number of adverse outcomes in children born after ART. However, the data relate mostly to the normality of the babies at birth and very little is known about long-term effects. A further worrying element is that the increasing age of women undergoing ART treatment is encouraging the use of more aggressive manipulation techniques, such as cytoplasmic / ooplasm transfer and germinal vesicle transfer (GVT) to counteract the physiological decline in fertility.

The scenario is going to be further complicated by the production of male and female gametes through unconventional pathways, like forcing embryonic stem cells and/or Induced Pluripotent Stem cells (IPS) to enter the germ line differentiation, a perspective which raises serious biological and ethical concerns. There is strong evidence that ART procedures result in alteration of the epigenetic assets of embryos / foetuses. The perturbation of epigenotype by ART has been observed in all mammalian embryos, including human. In animals, for which a broader range of ART technologies has been applied, offspring from invasive ART have been shown to exhibit a wide range of abnormalities, particularly circulatory and placental defects. An impaired placental transport may cause developmental arrest of the foetus in severe phenotypes, while milder ones may result in developmental adaptations (foetal programming), thereby predisposing the individual to metabolic and cardiovascular disease. Under the current state of art, the safety of ART potentially affecting the long-term disposition of a human life is only investigated retrospectively.
Ethics aside, the manipulation of the reproductive capacity in humans cannot be conducted without taking in due consideration the direct psychological and philosophical implications of ART, not only in concerned couples, but also in the society as a whole. The EuroSafeART programme calls for a collaborative multicentric and interdisciplinary effort to assess short- and long-term effects, including aging, and possible trans-generational effects of ART procedures, using a suitable array of animal models. EuroSafeART is directed towards world leading laboratory / clinical / university centres within the EU.

Scientific goals

The aim of EuroSafeART is to assess epi/genetic modifications resulting from assisted reproduction technologies (ART), and their short-/long-term and trans-generational effects. To meet this goal, research should be conducted with a suitable variety of animal models. The animal models will range from mouse, especially where a well defined genetic background is required, to rabbit, sheep, pig and cow, which are closer to human embryos in terms of metabolism and key stages of preimplantation development including timing of zygotic genome activation, compaction and blastulation, as well as pregnancy and parturition.
This horizontal approach across a large number of animals will minimize and help overcome species to specific differences, leading to a more objective interpretation of the findings obtained. EuroSafeART is directed towards leading European laboratories with outstanding expertise in the fields of molecular biology, biochemistry and physiology, gene expression, proteomics, epigenetics, experimental embryology, biophysics, systems biology, and animal behaviour and welfare. EuroSafeART is a multicentric / multidisciplinary programme at the European level, involving basic scientists, embryologists, human reproduction / genetics specialists, working in public and private clinics, and biophysicists.

Research topics

The EuroSafeART programme will consider proposals focusing on molecular signalling, mechanistic aspects, rather than descriptive studies, in order to understand the mechanisms that underlie functional defects. The functional implications of ART-induced alterations will be evaluated in a temporal context, starting from the male and female gametes before and after fertilization and during pre-implantation embryonic development (short-term). ART-derived offspring will be maintained for long-term evaluation of their clinical, cognitional and reproductive fitness (long-term); moreover, potential trans-generational effects will be evaluated (trans-generational effects, long-term).
The psychological and philosophical implications of assisted reproduction in the European society will be addressed as well.
Research topics are detailed below.

EuroSafeART endeavours:

I. To establish the physiological epi/genetic expression patterns in male and female gametes across the range of mammalian animal models suggested (mouse, rabbit, sheep, pig and cow).

II. To identify the genetic and/or epigenetic alterations induced by ART procedures (MESA, TESE, ROSI; ooplasm and germinal vesicle transfer) on gametes and pre-implantation embryos.

III. To identify and characterise factors in the maternal environment and signals communicated between the female reproductive tract, gametes and embryos that can influence the pregnancy outcome (short-term) and the individual's health in adulthood (long-term).

IV. To identify genetic and/or epigenetic alterations induced by ART procedures during post-implantation embryo / foetal development until parturition. A follow-up study will be scheduled for all offspring during growth and possible senescence (ART-derived animals will

go through long-term general, metabolic, clinical and behavioural screening).

V. To test the biological risk of the new technologies used as potential future ART tools, like gamete production through embryonic stem cell and IPS cell differentiation into the germ line.

VI. To evaluate the second generation to exclude any germ line spill over of genetic or epigenetic alterations resulting from invasive ART (trans-generational follow-up long-term).

VII. To use the collective wisdom generated from fundamental research to guide and redefine the standard operating procedures (SOPs) for routine gamete and embryo handling and culture during ART, thereby helping improve success rates.

VIII. To define SOPs for the use of ART micromanipulations so that they can be performed in a safe setting with minimal risk. Such outcomes will enhance our knowledge and provide objective biological arguments from which to curtail some current ART procedures from clinical use and develop a framework to test new ART that will become available in the future.

IX. To study the ethical, psychological and physiological societal impact of assisted reproduction in European countries.

DRAFT

Guidelines for applications

(Outline and Full Proposals)

This Call for Proposals is for Outline Proposals for Collaborative Research Projects (CRP). Proposers should be individual scientists (or research groups represented by individual scientists) who are eligible for funding from a national funding organisation participating in the EUROCORES Programme EuroSafeART.

Scientists or groups not applying for or not eligible to apply for funding from such an organisation can be associated to a proposal when their scientific added value can be demonstrated. Participation of Associate Partners in a project must be fully self-supporting and will not be financially sponsored by the participating funding organisations.

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

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

Applications should envisage three years of research. Taking into account the two-stage proposal selection and approval process (described below), the successful projects are expected to begin their research phase activities in **April 2011**.

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/eurosafeart**

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

Prior to submitting Outline Proposals, all applicants must contact their national funding organisations in order to verify eligibility and to ensure compliance with their national grant requirements and regulations. The list of participating organisations and their nominated contact persons is included on the last page of this document.

At the time of the online submission of the Outline Proposal, the Project Leader will be asked to confirm on behalf of the consortium that all the Principal Investigators in the CRP have consulted their national funding organisations and are eligible for funding from these organisations.

Outline Proposals

Outline Proposals are invited by xth February 2010.

Outline Proposals will be examined by the participating funding organisations for formal eligibility. Therefore, it is crucial that all applicants requesting funding 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 EuroSafeART may include salaries for scientific and technical staff, equipment, travel costs and consumables within the project. The amounts requested from each funding organisation participating in the call must be clearly specified. National policies may also require the proposal to contain specific additional information. Applicants should be aware that the participating funding organisations can make adjustments to the requested funds in order to bring these in line with their normal grant regulations and standards.

As described below, applications will be reviewed according to specific assessment criteria in a two-stage procedure. The goal is to select scientifically excellent proposals which fit well within the scope of the programme and have significant potential to add value to its achievements.

At the outline stage, the Review Panel will select proposals based on the following criteria:

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

An Outline Proposal must comprise:

DRAFT

- A short description of the CRP (max. 1200 words, including objectives, milestones, methodologies (e.g. experiments and fieldwork);
  - Short description of how (and why) the partners contributing to the CRP will work together and how their contributions will be integrated;
- Short CVs of Project Leader (PL), all PIs and Associate Partners, including five most relevant publications (max. one page each);
- 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 Intellectual Property Rights (IPR) will be in place within projects, following the applicable national legislation and national funding organisation's regulations. 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, through standard scientific dissemination activities.
It is also expected that compliance with all other relevant national or international regulations on research (for example ethics) will have been affirmed 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 xxth May, 2010.

Please note that only applicants who have 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), qualifications of the applicants, level of integration and collaboration, feasibility and appropriateness of methodologies, European added value, relation to other projects (complementarities versus risk of overlaps and double-funding) and suitability of the requested budget.

The Full Proposals will be assessed by at least three independent external expert referees selected by the ESF. The expert referees are selected from a pool of scientists suggested by the participating funding organisations, the Review Panel and the ESF office. The names of all referees used in the international peer review of EUROCORES programmes, together with the names of those who have contributed to the peer review process in other ESF instruments, will be published on the ESF website once in a given year.
The referee reports will be made available (anonymously) to the applicants for their information and if necessary for their comments and clarifications. 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 rank-ordered list of the strongest Full Proposals and will subsequently make recommendations to the Management Committee for the funding of these proposals. The Management Committee assigned to each programme comprises representatives of all the participating funding organisations.

The actual granting of the funds to the Individual Projects will be based on the Review Panel's ranked list. The funding cut-off will be determined based on the total amount of funds available in each participating Funding Organisation and how the Individual Projects figure on the list. The use of funds in a project will be subject to the national requirements and regulations of each participating Funding Organisation.

Full proposals must include sound and well-argued scientific cases both at the level of the consortium's collective objectives and in terms of the expected contributions of each of the Individual Projects in the consortium. Full Proposals must also include a list of all participants and their contact information and shorts CVs, detailed tabulated budgets for the whole CRP and for each project within it. Full Proposals could include other necessary

DRAFT

supporting information. A coherent and common scientific case must be made throughout the proposal to demonstrate a collective and collaborative aim and 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 when inviting Full Proposals.

The **Project Leader** (PL) will be the main point of contact between the ESF and the CRP for the whole duration of the project. He/she will be responsible for the flow of information and communication between the ESF and all the participants in the CRP. The PL will represent the Collaborative Research Project in relation to its participation in programme activities and for the fulfilment of reporting requirements for the CRP as a whole and for the contributions of the individual Principal Investigators in the CRP.

In addition to their normal scientific and collaborative activities within the CRP, all **Principal Investigators** will be responsible for dealing with the requirements concerning the contributions of their national funding organisation, and for supporting the Project Leader in the overall progress of the CRP, including organising and participating in networking activities and in the fulfilment of reporting requirements.

Programme Structure and Management

Programme Structure

The overall responsibility for the governance of each individual EUROCORES programme lies with a *Management Committee*, whose members include one representative from each participating funding organisation in the programme (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 the 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 is formed by the Project Leaders of all funded CRPs and will be responsible for the overall scientific progress of the programme, including for the preparation of a work plan for the overall programme activities, including networking and dissemination. The Scientific Committee will also advise and support the EUROCORES Programme Coordinator in the coordination of the programme.

Programme Networking

Networking activities are designed to strengthen the scientific objectives of the EUROCORES Programme by promoting coherence and synergy in the activities of the scientific community involved. This will help to produce the European added value which is a main objective of all EUROCORES Programmes.

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

1. Between the various Individual Projects within each Collaborative Research Project (CRP) (intra-CRP activities), and;
2. Between the funded CRPs in the programme (cross-CRP activities).

The intra-CRP activities must be supported through the individual research grants the participants receive from the national funding organisations in the given CRP.

The cross-CRP activities are centrally funded by the ESF through contributions from the participating organisations 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 inspired by the aims and the nature of the EUROCORES Programme as a whole. The themes of EUROCORES Programmes are selected because they demonstrate a clear need for collaboration in the proposed field. The funded CRPs will collectively establish and streamline this new collaboration. To this end, the CRPs will

DRAFT

engage the programme participants and, when of clear benefit, colleagues from outside the programme in joint activities such as:

- Programme-wide meetings or conferences;
- 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 programmes;
- 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 can existing collaborations be enhanced, but new and strategic partnership opportunities may also be identified.

Furthermore, these activities may provide opportunities to explore aspects of the programme which are not covered by the funded research projects.

The integrating activities between the CRPs should help to strengthen the field by building coherence within the existing and emerging research communities and will serve as platforms for the dissemination and outreach of the research conducted 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 included in your proposal as part of the costs of meetings, travel and subsistence. 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 involving the Review Panel will assess the overall progress of the Programme. The Review Panel may also comment on the CRPs' work plan in relation to the objectives of the overall Programme. A final evaluation at the end of the Programme will assess the overall achievements of the whole EUROCORES Programme.

DRAFT

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.

ESF Contact:

Dr. Maria Manuela Nogueira
EUROCORES Programme Coordinator for EuroSafeART
European Science Foundation
1 quai Lezay-Marnesia
67080 Strasbourg
France
Tel: +33 388767145
Fax: +33 388370532
Email: mnogueira@esf.org
Eurosafeart@esf.org

[1] The European Science Foundation (ESF) provides a platform for its Member Organisations to advance European research and explore new directions for research at the European level.
Established in 1974 as an independent non-governmental organisation, the ESF currently serves 80 Member Organisations across 30 countries.

DRAFT