EUROPEAN SCIENCE FOUNDATION

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Quality Control of Gene Expression – RNA Surveillance (RNAQuality)

Call for Outline Proposals

Funding initiative in the field of Quality Control of Gene Expression– RNA Surveillance (RNAQuality)

Following agreement with funding bodies in Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany (MPIs only), Iceland, Italy, Poland, Spain, Sweden, Turkey, United Kingdom, the European Science Foundation is launching a first Call for Outline Proposals for Collaborative Research Projects (CRPs) to be undertaken within the EUROCORES Programme RNAQuality. RNAQuality will run for 3-4 years and it includes national research funding, as well as support for networking and dissemination activities provided by the ESF[1]. The Programme aims to support high quality multidisciplinary research.

Outline Proposals are to be submitted by 29 May 2006. It is expected that Full Proposals will be invited by 3 July 2006; with 4 September 2006 as expected deadline for submission.

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

What is EUROCORES?

The EUROCORES (European Collaborative Research) Scheme provides a framework for national research funding organisations (research councils, academies, ministries and other funding organisations) to fund multinational and multidisciplinary European collaborative research projects in and across all scientific areas. Participating funding agencies publish a joint Call for Proposals for a specific research programme, define the type of proposals to be submitted and agree on the common peer review procedure to be carried out by ESF. While funding of the research (and travel) in the projects remains with the national research funding organisations, ESF currently provides support for the programme networking of funded scientists and dissemination activities[1]. Further information on the EUROCORES Scheme can be found at: *http://www.esf.org/eurocores*

[1] This is currently supported through a contract with the European Commission under the Sixth Framework Programme (EC Contract no. ERAS-CT-2003-980409). Should this support be discontinued under the Seventh Framework Programme, the ESF will request the participating Funding Agencies to provide support for management and networking costs.

Background and objectives

Gene expression was long thought to be regulated almost exclusively at the transcriptional level. However, the growing realization that post-transcriptional control provides conserved mechanisms by which cells can rapidly change gene expression patterns, together with the discovery of RNA silencing pathways, have greatly stimulated interested in the mechanisms of post-transcriptional gene regulation. Post-transcriptional processes (e.g. mRNA processing, export, localization, surveillance, silencing and turnover) are interlinked by the use of common factors and constitute a complex regulatory network that contributes to cell-type and organism specific gene expression programmes. Besides providing the means to regulate gene expression at many different levels, these interconnected processes also provide opportunities for quality control checkpoints, so that only fully processed and error-free mRNAs are translated into proteins. In addition to monitoring mRNA biogenesis, surveillance mechanisms are also likely to eliminate other classes of defective RNA, including ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear/nucleolar RNAs (sn/snoRNAs) and cryptic transcripts expressed from intergenic regions. Although a number of RNA quality control (RNA surveillance) checkpoints have been identified in recent years, the molecular mechanisms behind these checkpoints are still largely uncharacterised. In particular, it is generally unclear how these quality control systems can distinguish between correct and defective RNAs and RNA-protein complexes. Uncovering the molecular mechanisms of the different RNA surveillance pathways and understanding how these systems are interconnected will be a substantial challenge.

RNA surveillance mechanisms not only safeguard cells from the accumulation of malfunctioning proteins and RNAs, but are also implicated in the post-transcriptional regulation of wild-type transcripts. RNA degradation is also likely to contribute to the stability of the genome by silencing the expression of viruses, transposons and pseudogenes. Moreover, RNA quality control systems modulate the clinical manifestations of many genetic disorders, and hence represent promising targets for future therapeutic intervention.

The EUROCORES Programme RNAQuality will bring together European researchers from all disciplines of modern life sciences, including cell, molecular and structural biology, biochemistry,

genetics, bioinformatics, biophysics and biomedicine. International collaborative research will concentrate on the investigation of post-transcriptional RNA quality control mechanisms using multidisciplinary approaches in diverse model systems.

Scientific goals

The Programme is intended to promote European collaborative research projects that aim to uncover processes that act as quality control checkpoints in gene expression and understand how these function at the molecular level. The Programme will focus on basic mechanisms of RNA quality control that operate at different levels of RNA biogenesis. This will include studies on degradation of aberrant mRNAs, the coupling between the mRNA synthesis and surveillance, and studies on quality control mechanisms in the biogenesis of rRNA, tRNA and other non-protein coding RNAs. These post-transcriptional processes appear to be conserved throughout evolution, and studies using important model organisms will therefore allow cross-species comparisons. These analyses will reveal the key, conserved components of these pathways, and will establish the basis for the reconstruction of post-transcriptional quality control networks in humans.

Research topics

The principal aim of the Programme is the understanding of functional and structural aspects of RNA quality control and surveillance pathways. Proposals focusing on any aspect of RNA quality control in any organism will be considered. Those that address the issues by combining methodological approaches from different scientific disciplines or by using several model organisms are especially encouraged. Projects investigating basic mechanisms of gene expression rather than quality control will not be considered.

Examples of topics within the scope of RNAQuality are:

Nuclear RNA surveillance

- Coupling of pre-mRNA processing and modification events (i.e. capping, editing, splicing and 3' end formation) with transcription and downstream post-transcriptional events such as mRNA export, turnover and cytoplasmic mRNA surveillance;
- Degradation pathways for improperly processed mRNAs and misassembled mRNPs within the nucleoplasm;
- Checkpoint mechanisms for mRNPs at the periphery of the nucleus, associated with the nuclear pore;
- Links between RNA location and surveillance pathways.

Cytoplasmic RNA surveillance

Quality control of the translatability of mRNAs, including:

- Nonsense-mediated mRNA decay (NMD);
- Nonstop-mediated mRNA decay (NSD);
- No-go mediated decay (NGD);
- Interplay between surveillance, localization and decay;
- Degradation of chemically damaged RNA molecules.

Interactions between RNA quality control mechanisms and RNA-mediated gene silencing

- Turnover of transcripts arising from intergenic regions, transposons and viruses;
- Interplay between RNA surveillance and RNA-mediated transcriptional or post-transcriptional gene silencing.

Quality control of non-coding RNAs

- Mechanisms for distinguishing "normal" from "defective" RNP structures;
- Mechanisms of stable RNA degradation;
- Nuclear vs. cytoplasmic surveillance of non-coding RNAs;
- Role of RNA modifications in quality control.

Quality control of RNA and RNP structure

- Mechanisms for recognition of aberrantly folded RNAs;
- Mechanisms for recognition of aberrantly assembled RNPs.

Programme Structure and Management

Programme Structure

The research funding period of the Programme RNAQuality is expected to start in 2007 and will run for three to four years, depending on the funding rules and regulations of participating Funding Agencies**.** 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 agency (usually a senior Science Manager) together with an ESF representative (usually the EUROCORES Programme Coordinator). 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 Agencies. The Review Panel is also expected to monitor the overall scientific progress of the Programme.

Two stage selection procedure

The selection of proposals follows a rigorous two-stage assessment procedure, namely an *Outline Proposal* stage followed by a *Full Proposal* stage. All proposals are assessed according to a set of criteria concerning the *overall scientific quality* and relevance of the proposals to the Call. It is compulsory to submit an Outline Proposal in order to participate in the Full Proposal stage.

In the first selection stage, *Outline Proposals* are screened by the Review Panel. Successful applicants will then be invited to submit *Full Proposals*. As the second stage of selection, an international peer review followed by a Review Panel meeting will create a ranked list of Full Proposals recommended for funding. International referees are selected by the ESF, principally using a pool of scientists suggested by the participating funding agencies and the Review Panel. A list of all the names of referees used for the international peer review will be published once the selection process is complete.

The ranking list created by the Review Panel will subsequently be made available to the Management Committee for funding decisions. The actual granting of the funds to the projects on the ranked list will depend on the total amount of funds made available in each country by the participating Funding Agencies. The use of funds in a project will be subject to the rules and regulations of each participating Funding Agency as well as to the national laws of those countries.

Programme management & networking

Once projects are being funded, the ESF will support networking and dissemination activities to facilitate cross-project communication of funded Collaborative Research Projects (CRPs), exchange of information and presentation and discussion of results. Networking among the CRPs is an essential and highly valued element of the EUROCORES Programmes. To this end, scientific workshops, summer schools, conference panels and conferences, web facilities, publications and other similar activities will be organised. Such activities will be coordinated by a Programme Coordinator, appointed by ESF, and advised by the Project Leaders of the CRPs, who together form the *Scientific Committee*.

An Interim evaluation, conducted by the Review Panel, will assess the progress of the Programme, based on the progress of the funded CRPs. Here, the Review Panel can comment on the CRPs' work plan in relation to the objectives of the Programme. A final evaluation will assess the achievements of the entire Programme.

Guidelines for applications
(Outline and Full Proposals)

Proposals from individual scientists or research groups eligible for funding by the agencies participating in the programme will be accepted for consideration in the EUROCORES Programme RNAQuality. Proposals must, as a minimum, involve 3 eligible Principle Investigators (PIs) from **3 different countries.** Scientists or groups not applying for or not eligible to apply for funding from these agencies (including applicants from industry), can be associated with a proposal where their added scientific value can be demonstrated. Their participation as Associate Partners in a project must be fully self-supporting and will not be financially supported by the participating funding agencies, although they may be eligible for supported participation in cross-programme networking activities. Applications should normally be for three years although applications for shorter or longer time periods may be considered depending on the particular rules of the participating funding agencies. Taking into account the selection and approval processes, the successful projects are expected to begin their activities in **June 2007**.

Online submission of applications

Outline and Full Proposals will be submitted online. Applicants should follow the proposal structure as indicated in the Outline Proposal Application Guidelines which can be found on the Programme website (***http://www.esf.org/eurorna***). On this Programme website, information on national funding eligibility and requirements may be posted as they are made available to the ESF by the participating Funding Agencies.

Prior to submitting Outline Proposals, all applicants should contact their national funding agencies in order to verify eligibility and to ensure compliance with their relevant agencies' granting rules and regulations. At the time of online submission of the Outline Proposals, the Project Leader is asked to confirm this on behalf of all the participants in the CRP.

Outline Proposals

Outline Proposals are invited by 29 May 2006.

Outline Proposals will be examined by the participating funding agencies for formal eligibility according to their applicable national requirements. Hence, it is crucial that all applicants contact their national funding agency and ensure that they are aware of their national funding regulations, and that they fulfil their national eligibility requirements prior to submitting their proposals. In compliance with the rules and regulations of the participating national funding agencies, the requested funds under EUROCORES Programme RNAQuality 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 Agency. National policies may also require the proposal to contain additional specific information. Applicants should be aware that the participating funding agencies 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, incl. objectives, milestones, methodologies (e.g.: experiments, fieldwork etc);
- 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. 1 page each, incl. 5 most relevant publications);
- Estimated budget (consistent with the rules of relevant national funding agency) tabulated according to a provided template.

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

It will be assumed that arrangements for the handling of IPR (Intellectual Property Rights) will be in place within projects, following the applicable national legislation and national funding agency 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 (e.g.: 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

Following the recommendations of the Review Panel on the Outline Proposals, Full Proposals are expected to be invited **by 3 July 2006.** The exact deadline for submission of Full Proposals will be announced later, but it is currently expected to be **4 September 2006**. For the Full 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, European added value, relation to other projects (risk of double-funding and track record for collaboration) and suitability of, and justification for, requested budget items.

The Full Proposals will be assessed by at least three independent external experts. After receiving all referee reports, they will be made anonymous and then sent to the applicants for their information and to give them an opportunity to comment on the referee report by means of a response letter. The Review Panel will rank all Full Proposals based on their evaluation of the proposals, the anonymous referee reports and the applicant's responses (optional) to these.

The 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. Aiming for scientific synergy and to integrate multinational expertise, a single, common scientific case must be made throughout the proposal; however, the amount requested from each national funding agency 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 act as ESF's principal contact for the proposal, and for the duration any subsequent project. He/she will be responsible for representing the project, for its participation in Programme activities, and for any reporting requirements placed on the project as a whole as part of the Programme. All Principal Investigators will be responsible for dealing with the requirements attached to the contributions of their own funding agencies.

Principal Investigators from countries where research staff costs and major equipments are normally provided by means other than research grants / contracts should clarify their eligible costs under the EUROCORES Programme RNAQuality with their agency before submission. The relationship with existing national or international research financial support should be clearly explained. Major items of expenditure will require justification in the proposal. Full instructions and application forms will be available on the Programme websites.

Programme Terminology

Collaborative Research Projects (CRPs) are the international research activities that make up a EUROCORES programme. A CRP consists of a number of **Individual Projects (IPs)**, each led by a **Principal Investigator (PI).** Each CRP is represented by a Principal Investigator who is designated **Project Leader (PL)**.

Associated Partners (APs) are Principal Investigators of research teams participating in a CRP but not supported by a Participating EUROCORES Funding Agency (EFA). The APs will be members of a CRP and will be assessed as such, but cannot be Project Leaders.

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CNRS proposers should check with the CNRS for application procedures at least 3 weeks before the submission of the proposal

Germany

Max Planck Institutes only
The Max Planck Institutes are provided with funds to support their own international projects. If a Max Planck Institute takes part in a EUROCORES Programme which is not within the DFG funding scope, the institute has to cover the costs with its own budget.

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