

FANCONI ANEMIA RESEARCH FUND PROGRAM ANNOUNCEMENT ENDOCRINE ORGAN DYSFUNCTION

REQUEST FOR APPLICATIONS

Key Dates

Release Date: September 1, 2008
Application Submission Dates: Ongoing
Peer Review Date: Ongoing
Earliest Anticipated Start Date: Ongoing

Summary

Fanconi anemia is a rare hereditary disease characterized by bone marrow failure, developmental anomalies, growth retardation, endocrine organ dysfunction, a high incidence of myelodysplasia and acute non-lymphocytic leukemia, and cellular hypersensitivity to cross linking agents. The function of the proteins is largely unknown, but many of them form complexes with each other and in one canonical “pathway” seven or eight of the known Fanconi anemia (FA) proteins bind together in a nuclear complex, a complex apparently required for the monoubiquitination of two of the three proteins not found in the core complex, FANCD2 and FANCI. Once this occurs, FANCD2 and FANCI translocate to damage-induced nuclear foci containing BRCA1, BRCA2 and Rad51. The functions that FANCD2 and FANCI have in these nuclear complexes are unclear. Although more than 90% of the research in this field focuses on mechanisms of genotoxicity, one goal of the Fanconi Anemia Research Fund is to encourage investigative approaches dealing the tissue specific issues of the FA phenotype.

Some have argued that, because hypersensitivity to genotoxic stress is a feature of all somatic cells, tissue specific outcomes (specific epithelial malignancies, bone marrow failure, and endocrinopathies, for example) are less likely to be related simply to genetic instability than to signaling functions of the proteins. In this regard, multiple biochemical functions have been ascribed to some of the FA proteins and, in some cases, these functions are cytoplasmic and not nuclear. The role of the Fanconi proteins in protecting normal individuals against endocrine organ dysfunction is entirely unknown.

Endocrine abnormalities have been recognized as features of FA, most notably growth hormone deficiency, hypothyroidism, hypogonadism, glucose intolerance or abnormal glucose metabolism. Endocrinopathies can develop *in utero* or evolve over time. They may also be influenced by therapeutic agents used to treat FA (including stem cell transplantation or androgen therapy for bone marrow failure). Recently, Giri *et al* (J.Clin.Endo.Metab. 92:2624, 2007) conducted a retrospective review of 23 intensively evaluated patients at NIH. They found endocrine abnormalities in 73%. They included growth hormone deficiency (51%), hypothyroidism (37%), and abnormal glucose/insulin metabolism (39%). The study served to confirm the prevalence of endocrinopathies in FA patients emphasizing the importance of endocrine screening in patients with FA. The FA Research Fund is particularly interested in developing a coherent picture of how the FA proteins function in normal endocrine tissues to facilitate their function.

Consequently, this funding opportunity will use the investigator-initiated award mechanism to support work focused on the molecular pathogenesis of, diagnosis, and treatment of endocrine dysfunction in patients with Fanconi anemia. We expect that the nature and scope of the proposed research will vary from application to application, and it is anticipated that the size and duration of each award will also vary. The total amount awarded and the number of awards will depend upon the numbers, quality, duration, and costs of the applications received.

Eligible Applications

The goal of this initiative is to foster the studies on the molecular pathogenesis, diagnosis and treatment of endocrinopathies in patients with Fanconi anemia. Applications focusing primarily on hematopoietic malignancies, bone marrow failure, developmental anomalies, carcinogenesis, or general functions of the FA proteins in DNA damage and repair will not be accepted for review under this RFA. Applications from the following will be considered:

- Eligible domestic and foreign institutions/organizations, including for-profit or non-profit, public or private, units of state and local governments, and eligible agencies of the federal government.
- Eligible principal investigators include any individual with the skills, knowledge, and resources necessary to carry out the proposed research
- Applicants may submit only one application.

Content and Form of Application Submission

Applications must be prepared using the most current FA Research Fund research grant application instructions and forms.

Plan for Sharing Research Data

The FA Research Fund requires that applicants include a plan for sharing research data in their application. The data-sharing policy of the Fund is congruent with that of NIH (see http://grants.nih.gov/grants/policy/data_sharing). Specifically, all investigators responding to this opportunity should include a description of how final research data will be shared, or explain why data-sharing is not possible. The precise content of the data-sharing plan will vary, depending on the data being collected and how the investigator is planning to share the data. Applicants who are planning to share data may wish to describe briefly the expected schedule for data-sharing, the format of the final dataset, the documentation to be provided, whether or not any analytic tools also will be provided, whether or not a data-sharing agreement will be required and, if so, a brief description of such an agreement (including the criteria for deciding who can receive the data and whether or not any conditions will be placed on their use), and the mode of data-sharing (*e.g.*, under their own auspices by mailing a disk or posting data on their institutional or personal website, through a data archive or enclave). Investigators choosing to share under their own auspices may wish to enter into a data-sharing agreement. References to data-sharing may also be appropriate in other sections of the application.

The reasonableness of the data-sharing plan or the rationale for not sharing research data will be assessed by the reviewers. Although reviewers will not factor the proposed datasharing plan into the determination of scientific merit or the scientific priority score, the Board of Directors of the Fund will take the plan into account when making final funding decisions.

Sharing Research Resources

The Fanconi Anemia Research Fund requires that grant award recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication. This policy is also congruent with that of the NIH (see NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part7.htm#_Toc54600131). Investigators responding to this funding opportunity should include a plan for sharing research resources, addressing how unique research resources will be shared or explain why sharing is not possible.

The effectiveness of the resource sharing will be evaluated as part of the administrative review of each application.

Funding Decisions

The Fanconi Anemia Research Fund will consider the following in making funding decisions:

- Responsiveness of the application to the problem of endocrine organ dysfunction in Fanconi anemia patients
- Scientific merit of the proposed project as determined by peer review
 - The degree to which the results might advance the field
 - The degree to which the results might improve disease control
 - The degree to which the results might improve the health and well-being of FA patients
- Availability of funds

Instructions to Scientific Reviewers

The following questions will be asked of each grant application reviewer.

Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will the effect of these studies be on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Approach: Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

Innovation: Is the project original and innovative? For example, does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

Investigators: Are the investigators appropriately trained and well-suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project (if applicable)?

Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

Protection of Human Subjects from Research Risk: What is the involvement of human subjects? Do the proposed studies protect human subjects from research risk relating to their participation in the proposed research?

Budget: Is the proposed budget reasonable? Is the requested period of support in relation to the proposed research reasonable? [The priority score should not be affected by the evaluation of the budget.]

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