FANCONI ANEMIA RESEARCH FUND PROGRAM ANNOUNCEMENT
HPV SEROLOGY AMONG FANCONI ANEMIA PATIENTS
REQUEST FOR APPLICATIONS

Key Dates

Release Date:	Feb. 1, 2012
Application Due Date:	April 1, 2012
Earliest Anticipated Start Date:	Summer 2012

Summary

Fanconi anemia is a rare hereditary disease characterized by bone marrow failure, developmental anomalies, a high incidence of myelodysplasia (MDS) and acute non-lymphocytic leukemia (AML), squamous cell carcinoma of the head and neck, 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. The formation of this so-called nuclear "core complex" somehow permits FANCL, a ubiquitin ligase and member of the core complex, to catalyze 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 of FANCD2 and FANCI in these nuclear foci-based complexes are unclear. Although more than 90% of the research in this field focuses on mechanisms of genotoxicity, the Fanconi Anemia Research Fund encourages investigative approaches dealing with the tissue-specific issues of the FA phenotype, some of which may not be direct consequences of DNA damage.

Some have argued that because hypersensitivity to genotoxic stress is a feature of all somatic cells in FA, tissue-specific outcomes (specific epithelial malignancies and bone marrow failure, for example) are less likely to be related simply to genetic instability than to other functions of the protein. In fact, 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 anemia proteins in protecting normal individuals against sporadic head and neck cancers is entirely unknown.

The natural course of the disease in FA patients is unique. The onset of head and neck cancers in patients with Fanconi anemia (age 18-40) is decades earlier than in non-FA patients with this type of cancer and, unlike non-FA patients. Moreover, we conjecture that use of alcohol and tobacco may not be the primary contributor to these cancers, as it is in the general population. There is conflicting evidence regarding the role of human papillomavirus (HPV) in the development of these head and neck cancers in FA patients. It is unknown when and how FA patients are exposed to HPV. It is also unclear how FA patients respond to HPV preventive vaccination.

This funding opportunity will use the investigator-initiated award mechanism to support work to capitalize on the collective meeting/gathering of FA patients at the Fund's annual Family Meeting, held at Camp Sunshine in Casco, Maine, August 10-14, 2012. This camp will attract approximately 60 children and teens with Fanconi anemia, along with approximately the same number of siblings and parents/extended family. The project will be focused on determining HPV serologic levels both in unvaccinated and vaccinated FA patients in order to understand the age at which FA patients are exposed, and to determine if FA patients develop a serologic response to HPV vaccination. second opportunity for testing individuals with FA is at the Fund's Adults with FA meeting, Oct. 26-29, 2012 in Austin, Texas. The attendees at this gathering will be FA patients, aged 18 years

and older, along with spouses, partners or parents. We expect approximately 15-18 patients to attend.

We suggest that a survey, done in advance of the family and adult meetings, be a part of the research plan. The survey could include questions related to the status of HPV vaccination, tobacco and alcohol use, history of parental HPV infection, etc. The staff at the Fanconi Anemia Research Fund could help the investigator facilitate such a survey.

Eligible Applications

The goal of this initiative is to foster studies on HPV serologic screening of FA patients in order to understand the prevalence of HPV seropositivity among FA patients, the age at which HPV serologic positivity occurs, and whether FA patients develop typical serologic response to HPV vaccination.

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 Fanconi Anemia Research Fund (Fund) research grant application instructions and forms. Please e-mail or call the Fund's Executive Director, contact information is below.

Plan for Sharing Research Data

The Fund requires that applicants include in their application a plan for sharing research data. 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 data-sharing 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 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 congruent with that of the NIH (see NIH Grants Policy 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 head and neck cancer 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: 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?

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