

MUTAGENESIS SCREENS/PHENOTYPING TOOLS FOR ZEBRAFISH

Release Date: February 16, 2000

RFA: HD-00-004

Trans-NIH Zebrafish Coordinating Committee
National Institute of Child Health and Human Development
National Cancer Institute
National Center for Research Resources
National Eye Institute
National Heart, Lung, and Blood Institute
National Human Genome Research Institute
National Institute on Alcohol Abuse and Alcoholism
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute on Drug Abuse
National Institute of Environmental Health Sciences
National Institute of General Medical Sciences
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke

Letter of Intent Receipt Date: April 16, 2000

Application Receipt Date: May 19, 2000

THIS RFA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS RFA.

PURPOSE

The purpose of this Request for Applications (RFA) is to encourage research designed to exploit the power of mutagenesis screening in zebrafish in order to detect and characterize genes, pathways, and phenotypes of interest in development, behavior, organ formation, disease

processes. Applications that propose to advance the technologies associated with such phenotyping also are welcome.

This RFA is the result of an NIH initiative with participation of the Institutes listed above, working through the Trans-NIH Zebrafish Coordinating Committee (ZFCC), under the co-chairmanship of the National Institute of Child Health and Human Development (NICHD) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Since its formation in 1998, the committee has played an active role as an advocate for the zebrafish as an important model for development and disease research.

The following components of the National Institutes of Health (NIH) are co-sponsors of this solicitation: National Institute of Child Health and Human Development (NICHD), National Cancer Institute (NCI), National Center for Research Resources (NCRR), National Eye Institute (NEI), National Heart, Lung and Blood Institute (NHLBI), National Human Genome Research Institute (NHGRI), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute on Drug Abuse (NIDA), National Institute of Environmental Health Sciences (NIEHS), National Institute of General Medical Sciences (NIGMS), National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke (NINDS).

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain "Healthy People 2010" at <http://odphp.osophs.dhhs.gov/pubs/hp2000>.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators (PI).

MECHANISM OF SUPPORT

This RFA will use the NIH research project grant (R01) award mechanism. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for an application submitted in response to this RFA may not exceed five years. The anticipated award date is April 1, 2001.

This RFA is a one-time solicitation. Future new or competing continuation applications will compete with all investigator-initiated applications and be referred and reviewed according to the customary peer review procedures.

Although this RFA is the result of a trans-NIH initiative, awards will be made through the Institute whose mission is most closely related to the proposed work. Through the Trans-NIH Zebrafish Coordinating Committee, each Institute/Center (IC) will share with the other participating ICs, findings of any research supported as a result of this RFA. All investigators funded under this initiative will be expected to work together cooperatively so that the information learned and the models developed will be of maximum usefulness to the community.

FUNDS AVAILABLE

The participating ICs intend to commit approximately \$4.5 million in total costs (direct plus Facilities and Administrative [F & A] costs) in FY 2001 to fund 8 to 10 new grants in response to this RFA. An applicant may request a project period of up to five years and a budget for direct costs of up to \$250,000 per year, including F & A costs on consortium arrangements. Because the nature and scope of the research proposed may vary, it is anticipated that the size of awards also will vary. Although the financial plans of the participating ICs provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

RESEARCH OBJECTIVES

Background

The trans-NIH Zebrafish Coordinating Committee (ZFCC) continues to play an active role as an advocate for the zebrafish model. The committee's initial efforts resulted in RFA DK-98-006, entitled "Genomic Resources for the Zebrafish," and continued with a Program Announcement PA-98-074, entitled "The Zebrafish as an Animal Model for Development and Disease Research."

On May 10-11, 1999, the ZFCC sponsored a workshop entitled “Genomic and Genetic Tools for the Zebrafish.” At this workshop, which expanded upon the “Non-mammalian Models Workshop” held on February 16-17, 1999, zebrafish researchers were asked to help prioritize the short- and long-term needs of the community. One result of the workshop was the recommendation that more genetic screens in the zebrafish need to be supported by the NIH. The current RFA addresses, in part, this and some of the other recommendations made by workshop participants. This RFA is designed to complement and continue NIH efforts to support the zebrafish as an important and timely animal model for research.

In the past decade, mutational analyses in the non-vertebrate genetic models of the worm (*Caenorhabditis elegans*) and the fruitfly (*Drosophila melanogaster*) have contributed significantly to our understanding of early developmental pathways. For example, these studies have led to the discovery of genes encoding signals, components of signaling systems, enzymes, and transcriptional regulators that act during embryonic development. These genes often operate in complex cascades to regulate pattern formation, cell fate, and specification, as well as later events such as development of the eye, heart, and other organs. While these invertebrate systems have revealed much information and shown that numerous aspects of development are highly conserved among invertebrates and vertebrates, many features of patterning and morphogenesis of the vertebrate embryo are distinct and thus cannot be studied in invertebrates. The vertebrate embryo has many characteristics not found in invertebrates, including a substantially different body plan and greater complexity of the nervous system, as well the presence of organs that have no clear counterparts in simple invertebrates. Thus, a complete understanding of human development will require experimentation in vertebrate model organisms. The study of mutations that affect development has been possible in the mouse, but the mouse embryo is not accessible in utero throughout much of its development. Consequently, mutational studies in this species have been limited largely to defects in postnatal maturation. While reverse genetics (e.g., gene knockouts) have been useful in the mouse model, the substantial cost of maintaining large mouse colonies has limited the applicability of forward genetic approaches on a large scale. These limitations will have a profound impact on the rapid discovery of genes important in vertebrate development, and relevant to human disease.

As a vertebrate, the zebrafish, *Danio rerio*, is more closely related to humans than are yeast, worms or flies. It has a number of advantageous features as a model organism for study of vertebrate development, disease, and biological pathways. Many features of zebrafish development have been characterized, including early embryonic patterning, early development of the nervous system, and aspects of cell fate and lineage determination. The embryos are easily obtainable in large numbers and accessible throughout development, they are transparent,

and undergo rapid organogenesis, making them very amenable for developing phenotypic screens. In live embryos, the same specific cell or even cellular processes can, in many cases, be identified from individual to individual, affording a high level of precision in characterizing the effect of a developmental, environmental or genetic perturbation. The use of zebrafish to study vertebrate development, disease, and pathways of interest has been validated further by the demonstration that many of its genes show a high degree of structural and functional similarity to their human homologues. The most powerful and unique feature of the zebrafish is that it is a vertebrate model organism that has proven that large-scale forward mutagenesis screens can be performed with relative ease.

The purpose of this initiative is to provide support for zebrafish mutagenesis and phenotypic screening efforts. To date, screens have focused exclusively on phenotypes in embryonic development; despite interest in the zebrafish research community to do so, phenotypic screens in adult fish have not yet been possible, because of the general difficulty in obtaining funding for mutagenesis and screening research. Phenotypic screens of post-embryonic fish will be needed to identify alterations in sensory and motor systems function, learning and memory, or behavioral responses to environmental toxins and pharmaceutical agents. Two large-scale screens have been performed, and the transparent embryos have been screened for defects in overall embryonic pattern morphogenesis or organ formation.

As reported in the December 1996 issue of "Development," screens have identified a substantial number of mutations that affect the formation of organ systems, including defects in the nervous system, skeletal muscle, craniofacial region, kidney and endocrine organs, cardiovascular and gastrointestinal systems, and the sensory cells of lateral line systems that are important to auditory and vestibular function. In the last three years, many of the mutations responsible for these phenotypes have been mapped, and the genes cloned and characterized. Investigators in the zebrafish community have only begun to exploit the power of mutagenesis screening to detect genes essential for organogenesis and associated developmental physiology, and they have yet to attempt screens for mutations affecting nervous system function (other than its development) and behavior. Saturation mutagenesis of the zebrafish genome will be an indispensable means of achieving a complete understanding of the development, physiology, and behavior of this vertebrate. With the advent of new, promising insertional mutagenesis strategies for the zebrafish, it is more pressing than ever to develop a strong support base for creative, intensive mutagenesis screens.

In the past year, significant progress has been made in the characterization of the zebrafish genome, which will facilitate the identification by positional cloning of zebrafish genes responsible for specific phenotypes.

The Trans-NIH Initiative on Genomic Resources for the Zebrafish, that was co-supported by 13 NIH Institutes and Centers and that funded five investigators beginning in the fall of 1998, has contributed significantly to this progress. To date, grantees funded under this initiative are increasing the resolution of zebrafish physical maps using microsatellite markers, CA repeat markers, and conformational polymorphisms; they have completed and published a new radiation hybrid map that covers at least 88 percent of the zebrafish genome [an invaluable tool for mapping expressed sequence tags (ESTs), cloned genes, and candidate genes for specific mutations]; they have generated approximately 20 thousand new ESTs; and they have begun to determine a genetic map for the zebrafish by construction of a complete deletion panel.

Research Scope

The objective of this RFA is to broaden the range, power, and utility of screens for new mutants of zebrafish. It will, therefore, support proposals for development of improved or novel methods for mutagenesis screens, as well as proposals for the actual execution of such screens.

Methodology developed and data and mutants generated as a result of this RFA are expected to be made widely available to the research community. Applicants must include as part of their application a plan for disseminating these resources; adequacy of this plan will be considered in the review of applications responding to this RFA (see below).

Objectives to be addressed in applications submitted in response to this RFA include, but are not limited, to the following:

- o Development and/or application of novel phenotypic screens for mutants. These screens may be based on observation of alterations in morphology, physiology, or behavior.

- o Development and/or application of novel methods of mutagenesis (e.g., insertional).

- o Genetic screens focusing on identifying mutations that affect the structure and function of specific tissue/organ systems.

- o Screens focusing on identifying novel developmental genes and pathways, including those mediating sensitivity or resistance to environmental teratogens.

- o Screens to analyze the genetic basis of adult phenotypes including behavior, aging, organ disease, cancer, and responses to environmental toxins and drugs.
- o Screens to detect altered gene expression patterns, as a tool to identify components of genetic pathways or those altered by environmental agents.
- o Sensitized screens, using strains carrying a known mutation, in order to identify extragenic suppressors or enhancers of that mutation.

In addition, all applications are expected to address the following:

- o A proposed sharing plan to insure that mutant zebrafish, sperm, embryos, genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains are widely available to the scientific community.
- o A proposed plan addressing if, or how, the PI and grantee institution will exercise their intellectual property rights regarding patentable research resources, such as mutant fish, sperm, embryos, genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains produced in projects funded under this RFA (see SPECIAL REQUIREMENTS, below).

Interests of Participating Institutes and Centers

The participating NIH ICs have provided a brief outline of their interests as they relate to the goals of this RFA. These brief mission statements are intended to give some understanding of the breadth of the biomedical areas of interest in development of this model.

NCI: Generation and study of zebrafish models to identify and place genes in functional pathways that affect growth and development; in particular, genes/pathways that, when altered, result in uncontrolled or cancerous growth. Identification of key sites within these pathways that could be exploited for cancer therapeutic discovery purposes.

NCRR: The NCRR supports research projects that broaden the utility of the zebrafish model for cross-cutting biomedical research that is not encompassed within a single NIH Institute or Center. Interests include, but are not limited to, development of new methods for mutagenesis and/or phenotypic characterization that would be of use in research on a wide range of diseases or

organs, particularly if these methods could be applied to other animal models as well as the zebrafish.

NEI: Fundamental mechanisms underlying all aspects of eye development, function and disease, including development of the retina and lens, optic nerve axon guidance and the neural circuitry producing eye movements and oculomotor behaviors.

NHGRI: Proposals for the development of high throughput, widely applicable technologies or methodologies to examine gene function on a genomic scale. This could include initial development of high throughput or large-scale methods for examining gene expression, development of tools for comprehensive mutational analysis, or genome-scale identification of regulatory regions.

NHLBI: Cellular and molecular functions of the mutant genes in development as models for human cardiovascular, blood, and pulmonary disorders, and circadian mechanisms regulating rest/activity cycles. Genetic basis of disorders of cardiovascular development and function; developmental aspects of endothelial dysfunction as the basis for systemic and pulmonary vascular disorders; developmental defects in hematopoiesis and relationship to disorders of the hematopoietic system; genetic basis of angiogenesis and vasculogenesis; effect of mutations on subsequent organ development leading to such disorders as arrhythmia, cardiac hypertrophy, dilated cardiomyopathy, heart failure, lung hypoplasia and bronchopulmonary dysplasia; the genetic basis, regulation, and role of biological clock mechanisms in development and circadian behavior.

NIAAA: Mechanistic studies of ethanol-induced teratogenesis, behavioral impairments, and organ damage.

NIAMS: Mutations that have the potential to illuminate the development and function of the vertebrate musculoskeletal system and skin. The musculoskeletal system includes muscle, bone, articulated joints, cartilage, tendon, and ligament. Priority will be given to the establishment of collaborations between investigators with expertise in the zebrafish and investigators with expertise in the musculoskeletal systems and skin of mammals and humans.

NICHD: Identification, cloning, and characterization of the genes important in normal development as well as those mutant genes that cause developmental defects. Elucidation of the cellular, biochemical, molecular, and genetic mechanisms underlying normal and defective development. This includes, but is not limited to, the study of general mechanisms of pattern

formation and cell lineage, neural crest development, cell specification, differentiation, migration, and fate in early development of many organs/systems such as limb, nervous system, immune system, and heart.

NIDA: Identification of mechanisms underlying tolerance, sensitization, and addiction to drugs of abuse such as nicotine, amphetamine, cocaine, opiates, barbiturates, and hallucinogens. Identification of genetic suppressors and enhancers of the teratological effects of drugs of abuse on behavior and the nervous system. Processes involved in the development of brain regions mediating the hedonic properties of drugs of abuse.

NIDCD: Identification and cloning of genes involved in the normal and disordered development of hearing, balance, smell, and taste sensory systems. Elucidation of the cellular, molecular, and biochemical mechanisms governing the proliferative, plastic, and regenerative capacities of these sensory cells and tissues.

NIDDK: Research on diabetes, particularly studies on pancreatic beta cell function and development, obesity and mechanisms underlying satiety, other endocrine, and metabolic diseases, hematologic disorders, and diseases of the digestive system, liver, kidney, and urinary tract. Studies aiming to clarify the cellular and molecular events that dictate tissue and organ formation in all these systems are considered of relevance. These studies could include, but need not be limited to, studies to develop cell lines from any of the tissues or organs of interest, studies to characterize normal or abnormal function of tissues or organs of interest, methods to screen and identify additional mutations in these systems, studies to define the molecular mechanisms that dictate cell-specific gene expression in relevant cell types.

NIDCR: All aspects of normal and abnormal craniofacial development, including genetics, complex origins of craniofacial disorders, cell lineages and differentiation, cell signaling and gene regulation, embryonic patterning, imaging, biomimetics, and new technologies for high-throughput genetic and protein screens.

NIEHS: Studies to examine the mechanism whereby environmental factors/agents alter any aspect of development. This includes the screening for mutants that ameliorate the toxicity of environmental agents, and the subsequent identification and characterization of the genes and pathways involved in their action. Characterization of the interactions among genetics, environmental agents, and time during development that lead to structural or functional abnormalities. Development of a mechanistically based model for testing environmental agents for developmental toxicity.

NIGMS: Basic biomedical research that addresses fundamental biological mechanisms such as those that underlie gene regulation, chromosome organization and mechanics, cell growth and differentiation, pattern formation, sex determination, morphogenesis, cell cycle control, behavior, the genetics of complex traits, and the application of mathematical models to complex biological systems.

NIMH: Investigations that examine molecular, cellular, and biochemical bases of genetic mutations affecting neurogenesis, biological rhythms, learning, memory, and other cognitive functions and behaviors of the nervous system. These studies include, but are not limited to, development of screening methods for such mutations, identification, isolation, mapping, and functional analyses of the genes underlying mutations.

NINDS: Research on the development, normal function, and diseases of the nervous system. This research might include the use of mutants to understand the mechanisms controlling the following processes: neurogenesis, nervous system patterning, cell lineage, cell migration, programmed cell death, axon pathfinding and regeneration, myelination, and motor and sensory function.

The areas of interest listed above are not presented in any order of priority; they are only examples of areas of research to consider. Applications representing areas of interest to more than one Institute or Center will be assigned to multiple Institutes or Centers for funding consideration. Applicants are encouraged to propose work in other areas that are related to the objectives and scope of this RFA.

SPECIAL REQUIREMENTS

Restricted availability of unique research resources, upon which further studies are dependent, can impede the advancement of research and delivery of medical care. The sharing of biomaterials, data, and software in a timely manner, on the other hand, has been an essential element in the rapid progress that has been made in the genetic analysis of mammalian genomes. NIH policy requires that investigators make unique research resources readily available for research purposes to qualified individuals within the scientific community when they have been published [NIH Grants Policy Statement (<http://grants.nih.gov/grants/policy/nihgps>; Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice, December 1999 (http://ott.od.nih.gov/NewPages/RTguide_final.html)]. Biomaterials (pathogen-free mutant animals, preserved sperm and embryos) and other patentable research resources (e.g., genetic

and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains) produced in projects funded by this RFA are expected to be made available and distributed to the broader scientific community.

The NIH is interested in ensuring that the research resources developed through this RFA become readily available to the research community for further research, development, and application, in the expectation that this will lead to products and knowledge of benefit to the public. For this reason, NIH is concerned that patents on mutant fish, embryos, and sperm, genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains and other research resources might have a chilling effect on the future development of products and information that may improve the public health. At the same time, NIH recognizes the rights of grantees to elect and retain title to subject inventions developed under Federal funding under the provision of the Bayh-Dole Act.

For applications submitted in response to this RFA, there are two special requirements regarding research resources produced in the proposed project:

(1) Applicants are required to include in their applications a specific plan by which they will share research resources with the wider scientific community.

(2) Applicants are required to include a plan addressing if, or how, they will exercise their intellectual property rights while making available to the broader scientific community patentable research resources (e.g., mutant fish, embryos and sperm, genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains).

Applicants are encouraged to discuss their proposed plans for addressing these requirements with their institutional offices of technology transfer. Each of the two requirements are discussed in detail below.

Plan to Share Research Resources

To address the joint interests of the government in the availability of, and access to, the results of publicly funded research, NIH requires applicants who respond to this RFA to propose detailed plans for sharing the research resources generated through the grant. It is expected that the resources to be shared include all materials developed in projects funded under the RFA, including but not limited to, the following: mutant fish, embryos and sperm, genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant

strains. For this purpose, it is NIH's opinion that dissemination of such data and materials via individual laboratories and Web sites is not sufficient, as it would force interested investigators to search several different data collections to make use of the results of this initiative. It is preferable that data, protocols, technologies, and biomaterials generated in grants funded under this RFA should be placed in common, public repositories and databases that are widely accessible by investigators in the scientific community.

The National Resource for Zebrafish at the University of Oregon is being established as a focal point for sharing of resources among investigators using zebrafish. Currently, the Resource is capable of accepting frozen sperm and some live fish stocks. It is expected to be fully operational, with expanded capacity to accept live fish stocks, by mid-2000. In addition to serving as a stock center, the Resource operates a comprehensive database, ZFIN. Plans to share materials generated by projects under this RFA through the National Resource for Zebrafish should include evidence/documentation of coordination with investigators at the Resource. Plans to deposit fish at the Resource should state whether this will be done as frozen sperm or live fish stocks. For frozen sperm, adequate personnel and funding must be requested to produce, cryopreserve, and ship the sperm according to Resource specifications and using appropriate shipping containers available from the Resource. For live fish stocks, it must be clear that the Resource is prepared to accept the numbers of stocks to be generated or agrees to handle the demands of producing and freezing sperm from live stocks deposited. Plans to deposit reagents should likewise be coordinated. Plans for informatics should be coordinated with the Resource to ensure that necessary hardware/software requirements can be accommodated for automatic deposit of data finalized by individual laboratories to ZFIN on a periodic basis. A reasonable time frame for periodic deposition of mutants, sperm, reagents and data should be specified in the application and will be considered during the review of the plan for sharing.

It is expected that the investigator's data and biomaterials sharing plan will include the following elements:

- (1) establishment of and access to a comprehensive database containing detailed results from genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains;
- (2) access to mutants identified through genetic and phenotypic screens, for example, through the National Resource for Zebrafish;
- (3) access to mutant fish, embryos, oocytes and sperm for these mutants, for example, through the National Resource for Zebrafish;
- (4) access to methods for genetic and phenotypic screens and mutagenesis protocols, not currently available to the wider scientific community; and
- (5) access to mutants with unusual phenotypes, not of interest to investigators associated with this grant.

The scientific review group will evaluate the adequacy of the proposed plan for sharing and data access. Comments on the plan and any concerns will be presented in an administrative note in the summary statement. The adequacy of the plan will be considered by NIH program staff on the Trans-NIH Zebrafish Coordinating Committee and will be important in determining whether the grant shall be awarded. The sharing plan as approved, after negotiation with the applicant when necessary, will be a condition of the award. Evaluation of non-competing continuation applications will include assessment of the effectiveness of research resource release.

Intellectual Property Rights

NIH is interested in ensuring that the research resources developed through this RFA become readily available to the research community.

With regard to patentable research results, such as mutants identified through genetic and phenotypic screens, embryos, oocytes and sperm for these mutants, genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains and methodologies, the NIH requires applicants who respond to this RFA to develop and propose a plan addressing if, or how, they will exercise their intellectual property rights while making available to the broader scientific community research resources produced in projects funded under this RFA. This is expected to include an elaboration of the applicant's anticipated plans to generate, or not generate, patents and/or exclusive or non-exclusive licensing of biomaterials and other patentable subject matter created in projects funded under this RFA. This plan is also expected to include disclosure of any pre-existing agreements involving intellectual property rights, including options to for-profit research sponsors that are associated with biomaterials and data that may be generated. The requirement for this plan is in addition to the requirement for the plan for sharing and disseminating research resources described in the previous section.

The scientific review group will evaluate the adequacy of the proposed plan for handling intellectual property rights. Comments on the plan and any concerns will be presented in an administrative note in the summary statement. The adequacy of the proposed plan will be considered by NIH program staff on the Trans-NIH Zebrafish Coordinating Committee in determining whether the grant shall be awarded. The plan as approved, after negotiation with the applicant when necessary, will be a condition of the award. Evaluation of non-competing continuation applications will include assessment of the awardee's adherence to the proposed plan.

Applicants also are reminded that the grantee institution is required to disclose each subject invention to NIH within two months after the inventor discloses it in writing to grantee institutional personnel responsible for patent matters. The awarding Institute reserves the right to monitor awardee activity in this area to ascertain if patents or patent applications on mutants identified through genetic and phenotypic screens, embryos and sperm for these mutants, genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains or other patentable subject matter are adversely affecting the goals of this RFA.

Principles and guidelines for recipients of NIH research grants on obtaining and disseminating biomedical research resources can be found at:

http://ott.od.nih.gov/NewPages/RTguide_final.html.

Post-Award Management

During the course of the award period, the Principal Investigators may be invited to meet with NIH staff to review and share scientific progress. Other scientists external to and knowledgeable about these studies also may be invited to participate. Application budget requests should include travel funds for the Principal Investigator to attend annual meetings in the metropolitan Washington, D.C. area.

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes a descriptive title of the overall proposed research; the name, address and telephone number of the Principal Investigator; the identities of other key personnel and participating institutions; and the number and title of this RFA. Although the letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains allows NIH staff to estimate the potential review workload and to avoid conflict of interest in the review.

The letter of intent is to be sent to Dr. Deborah Henken at the address listed under INQUIRIES by April 16, 2000.

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants. These forms are available at most institutional offices of sponsored research, on the Internet at <http://grants.nih.gov/grants/funding/phs398/phs398.html>, and from the Division of

Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301-435-0714, E-mail: Grantsinfo@nih.gov.

Application Instructions

Specific application instructions have been modified to reflect “MODULAR GRANT” and “JUST-IN-TIME” streamlining efforts being examined by the NIH. Complete and detailed instructions and information on Modular Grant applications can be found at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and Institute staff.

Modular Grant applications will request direct costs in \$25,000 modules, up to a total direct cost request of \$250,000 per year. (Applications that request more than \$250,000 direct costs in any year must follow the traditional PHS 398 application instructions.) The total direct costs must be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

- o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in \$25,000 increments up to a maximum of \$250,000) and Total Costs [Modular Total Direct plus Facilities and Administrative (F&A) costs] for the initial budget period. Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.
- o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD: Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.
- o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT: Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.

o NARRATIVE BUDGET JUSTIFICATION: Prepare a Modular Grant Budget Narrative page. (See <http://grants.nih.gov/grants/funding/modular/modular.htm> for sample pages.) At the top of the page, enter the total direct costs requested for each year. This is not a Form Page.

Under Personnel, list key project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided. However, the applicant should use the NIH appropriation language salary cap and the NIH policy for graduate student compensation in developing the budget request.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus F & A) for each year, each rounded to the nearest \$1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of key personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount. Include the Letter of Intent to establish a consortium.

Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH: The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at: <http://grants.nih.gov/grants/funding/modular/modular.htm>.

- Complete the educational block at the top of the form page;
- List position(s) and any honors;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years;
- List selected peer-reviewed publications, with full citations.

o CHECKLIST: This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. All appropriate exclusions must be applied in the calculation of the F&A costs for the initial budget period and all future budget years.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

Submission Instructions

The RFA label available in the PHS 398 (rev. 4/98) application form must be stapled to the bottom of the face page of the application and must display the RFA number HD-00-004. A sample RFA label is available at <http://grants.nih.gov/grants/funding/phs398/label-bk.pdf>. Please note this is in the pdf format. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked.

Submit a signed, typewritten original of the application, including the Checklist, and five signed photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

Applications must be received by May 19, 2000. If an application is received after that date, it will be returned to the applicant without review.

The CSR will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness and adherence to the Application Instructions above by CSR and for responsiveness by the Trans-NIH Zebrafish Coordinating

Committee. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the CSR in accordance with the review criteria stated below. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate National Advisory Council or Board.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In their written comments, reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have a major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative, but is essential to move a field forward.

1. Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

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

3. Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

4. Investigator: Is the investigator 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 (if any)?

5. Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition, applications responding to this RFA will be assessed with respect to the following criteria. This evaluation will be presented in an administrative note in the summary statement, and will not factor into the numerical score:

o Exportability and accessibility: What is the likelihood that the mutants and phenotypic information generated in the project will be made widely available in a timely fashion to the scientific community? Are state-of-the-art procedures employed to ensure the distribution of pathogen-free mutant strains, embryos, and/or sperm? What is the likelihood that other patentable research results will be widely available for the scientific community, given the proposed plan to exercise (or not to exercise) intellectual property rights regarding mutants identified through genetic and phenotypic screens, embryos and sperm for these mutants, genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains and methodologies?

o In addition, the plan to share research resources and the plan to exercise (or not exercise) intellectual property rights regarding patentable research resources will be judged for appropriateness.

In addition to the above criteria, in accordance with NIH policy, all applications also will be reviewed with respect to the following:

o The reasonableness of the proposed budget and duration in relation to the proposed research.

o The adequacy of the proposed protection of human, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

SCHEDULE

Letter of Intent Receipt Date: April 16, 2000

Application Receipt Date: May 19, 2000

Peer Review Date: October 2000

Advisory Council Review: January 2001

Earliest Anticipated Start Date: April 2001

AWARD CRITERIA

Factors that will be used to make award decisions are as follows:

- o Scientific and technical merit of the proposed project as determined by peer review;
- o Cost effectiveness of the proposed strategy;
- o Adequacy of plans to make widely available to the research community all research resources developed during this project;
- o Adequacy of plans to exercise (or not exercise) intellectual property rights while permitting wide availability to the research community of patentable research resources (mutants identified through genetic and phenotypic screens, embryos and sperm for these mutants, genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains and methodologies) developed during this project;
- o Program priorities and program balance;
- o Availability of funds.

INQUIRIES

Potential applicants are strongly encouraged to contact program staff with any questions regarding the responsiveness of their proposed project to the goals of this RFA.

Written and telephone inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

A complete listing of contacts for both programmatic and fiscal/administrative inquiries may be found at: <http://www.nichd.nih.gov/rfa/hd-00-004/hd-00-004.htm>.

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.865, 93.396, 93.306, 93.867, 93.839, 93.172, 93.273, 93.846, 93.173, 93.121, 93.847, 93.848, 93.849, 93.279, 93.113, 93.862, 93.242, 93.853. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act, as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program

is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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