

This Program Announcement expires on March 1, 2004, unless reissued.

DEVELOPMENT OF ZEBRAFISH MUTAGENESIS AND SCREENING TOOLS

Release Date: March 19, 2001

PA NUMBER: PA-01-070

Trans-NIH Zebrafish Coordinating Committee

(<http://www.nih.gov/science/models/zebrafish/>)

National Institute of Child Health and Human Development

(NICHD; <http://www.nichd.nih.gov/>)

National Cancer Institute

(NCI; <http://www.nci.nih.gov/>)

National Center for Research Resources

(NCRR; <http://www.ncrr.nih.gov/>)

National Eye Institute

(NEI; <http://www.nei.nih.gov/>)

National Human Genome Research Institute

(NHGRI; <http://www.nhgri.nih.gov/>)

National Institute on Aging

(NIA; <http://www.nih.gov/nia/>)

National Institute on Alcohol Abuse and Alcoholism

(NIAAA; <http://www.niaaa.nih.gov/>)

National Institute of Arthritis and Musculoskeletal and Skin Diseases

(NIAMS; <http://www.nih.gov/niams/>)

National Institute on Deafness and Other Communication Disorders

(NIDCD; <http://www.nidcd.nih.gov/>)

National Institute of Dental and Craniofacial Research

(NIDCR; <http://www.nidr.nih.gov/>)

National Institute of Diabetes and Digestive and Kidney Diseases

(NIDDK; <http://www.niddk.nih.gov/>)

National Institute on Drug Abuse

(NIDA; <http://www.nida.nih.gov/>)

National Institute of Environmental Health Sciences

(NIEHS; <http://www.niehs.nih.gov/>)

National Institute of General Medical Sciences

(NIGMS; <http://www.nigms.nih.gov/>)

National Institute of Mental Health

(NIMH; <http://www.nimh.nih.gov/>)

National Institute of Neurological Disorders and Stroke

(NINDS; <http://www.ninds.nih.gov/>)

THIS PA 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 PA.

PURPOSE

This Program Announcement (PA) is to encourage investigator-initiated applications for 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 and aging, organ formation, behavior, and disease processes. Applications that propose to advance the technologies associated with such phenotyping also are welcome. This PA is a continuation of the program initiated by RFA HD-00-004, "Mutagenesis Screens/Phenotyping Tools for Zebrafish" (<http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-00-004.html>). This effort stems from an NIH initiative with participation of the Institutes and Centers listed above, working through the Trans-NIH Zebrafish Coordinating Committee (TZCC; <http://www.nih.gov/science/models/zebrafish/>) under the co-chairmanship of NICHD and NIDDK. Since its formation in 1997, the committee has played an active role as an advocate for the zebrafish as an important model for development and disease research.

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 PA is related to one or more of the priority areas. Potential applicants may obtain "Healthy People 2010" at <http://www.health.gov/healthypeople/>.

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. Applications from new

investigators are particularly encouraged. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

This PA will use the National Institutes of Health (NIH) individual research project grant (R01) award mechanism. Because the nature and scope of the research proposed in response to this PA may vary, it is anticipated that the size of awards will also vary. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant.

Although this PA is the result of a trans-NIH initiative, awards will be made through the Institute or Center whose mission is most closely related to the proposed work. Through TZCC, each funding component will share with the other committee members findings of any research supported as a result of this PA. All investigators funded under this initiative will be expected to work together cooperatively so that the information learned, and the mutants and tools developed will be of maximum usefulness to the community.

For all competing applications requesting up to \$250,000 direct costs per year, specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by NIH. Complete and detailed instructions and information on Modular Grant applications can be found at:

<http://grants.nih.gov/grants/funding/modular/modular.htm>. Applications that request more than \$250,000 in any year must use the standard PHS 398 (rev. 4/98) application instructions.

RESEARCH OBJECTIVES

Background

The TZCC 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 TZCC 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. RFA-HD-00-004, entitled "Mutagenesis

Screens/Phenotyping Tools for Zebrafish,” addressed, in part, this and some of the other recommendations made by workshop participants. Due to the response of the community to this most recent RFA, this PA is being released to provide an umbrella under which to continue NIH efforts to support mutagenesis screening and development of phenotyping tools for zebrafish.

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 they 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 with a proven track record of easily executed, large-scale forward mutagenesis screens.

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. While this large-scale screen focused primarily on developmental defects, it is clear that saturation mutagenesis of the zebrafish genome will be an indispensable means of achieving a complete understanding not only of development, but also of the physiology, behavior, aging, and disease processes of this vertebrate. RFA-HD-00-004 has boosted efforts for zebrafish mutagenesis screening, including screening of adult fish, and the current initiative is intended to further this effort.

Research Scope

The objective of this PA is to continue 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 PA are expected to be made widely available to the research community. Applicants must include as part of their applications a plan for disseminating these resources; adequacy of this plan will be considered in making funding decisions for applications responding to this PA (see AWARD CRITERIA, below). Objectives to be addressed in applications submitted in response to this PA 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, alcohol, 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 Principal Investigator 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 PA (see SPECIAL REQUIREMENTS, below).

Interests of Participating Institutes and Centers

The participating NIH Institutes and Centers have provided a brief outline of their interests as they relate to the goals of this PA. 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.

NIA: Basic research on the genetic and molecular basis of aging and longevity. Generation and analysis of late-age onset or long-lived mutants that can be used to identify, clone, and characterize genes involved in normal and pathological aging. Cellular and molecular function of genes expressed, for example, in the aging nervous system, cardiovascular, immune, and musculoskeletal systems. Such genes include, but are not limited to, those involved in neurodegenerative disorders, neuroplasticity, cell death, damage and repair of DNA and proteins, and oxidative metabolism, and maintenance of differentiated cell function.

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.

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.

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.

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, and studies to define the molecular mechanisms that dictate cell-specific gene expression in relevant cell types.

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.

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. Studies to examine the mechanistic pathways involved in developmental exposure to environmental agents and subsequent increased susceptibility to adult onset disease

(developmental imprinting). 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 PA.

SPECIAL REQUIREMENTS

Restricted availability of unique research resources, upon which further studies are dependent, can impede the advancement of research. 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 as well as other research areas such as developmental biology. 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_2001/index.htm); 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) and (<http://ott.od.nih.gov/NewPages/64FR72090.pdf>)]. Biomaterials (e.g., pathogen-free mutant animals, preserved sperm and embryos, etc.) and other patentable research resources (e.g., genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains, etc.) developed in projects funded as a result of this PA 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 PA become readily available to the research community in a timely manner for further research, development, and application, in the expectation that this will lead to products and knowledge of benefit to the public health. Accordingly, for applications submitted in response to this PA, 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, etc.).

Each of the two requirements are discussed in detail below.

Both the sharing and intellectual property plans should, at a minimum, address the elements discussed in detail below in a clear and concise manner. Applicants are encouraged to inform and/or confer with their institutional offices of technology transfer to develop plans for addressing these requirements.

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 PA to propose detailed plans for sharing the research resources generated through the grant. It is expected that the resources to be shared include, for example, all materials developed in projects funded under the

PA, 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.

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 Spring 2001. In addition to serving as a stock center, the Resource operates a comprehensive database, the Zebrafish Information Network (ZFIN). Plans to share materials generated by projects under this PA 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.

The adequacy of the plan will be considered by NIH program staff on the TZCC and will be important in determining whether the grant shall be awarded. The sharing plan, as approved, 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 PA become readily available to the research community. With regard to patentable research results, for example, 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 PA to develop and propose a plan addressing how they will make available to the broader scientific community research resources produced in projects funded under this PA.

The requirement for this intellectual property rights plan is in addition to the requirement for the research resources sharing plan described above. The adequacy of the proposed plan will be considered by NIH program staff on the TZCC in determining whether the grant shall be awarded. The plan, as approved, 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 technology arising out of this funded research (e.g., 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) are adversely affecting the goals of this PA and the overall mission of benefiting the public health.

Points to Consider When Proposing the Sharing and Intellectual Property Plans

Applicants should consider the following points when developing their proposals for sharing and intellectual property plans:

- o Do the plans fully adhere to the NIH Grants Policy on Sharing of Unique Research Resources including the Sharing of Biomedical Research Resources Principles and Guidelines for Recipient of NIH Grants and Contracts (http://ott.od.nih.gov/NewPages/RTguide_final.html)?
- o Will material transfers be made with no more restrictive terms than in the Simple Letter MTA or the UBMTA and without reach through requirements?
- o Should any intellectual property arise which requires a patent, will the technology (e.g., materials, data, etc.) remain widely available to the research community?

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. Overall application budget requests should include travel funds for the Principal Investigator to attend biennial meetings in the metropolitan Washington, D.C. area scheduled to alternate with the Zebrafish Development and Genetics Meetings.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (revised 4/98) and will be accepted at the standard application deadlines as indicated in the application kit. 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.

Applicants planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting \$500,000 or more in direct costs for any year are advised that they must contact the Institute program staff before submitting the application, i.e., as plans for the study are being developed. Furthermore, applicants must obtain agreement from program staff that the Institute will accept the application for consideration for award. Finally, applicants must identify, in a cover letter sent with the application, the program staff member and Institute who agreed to accept assignment of the application.

This policy requires an applicant to obtain agreement for acceptance of both any such application and any such subsequent amendment. Additional information about this policy may be found in the NIH Guide for Grants and Contracts, March 20, 1998 at: <http://grants.nih.gov/grants/guide/notice-files/not98-030.html>.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

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 PHS398 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 ALL 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 all 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 telephone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

Submission Instructions

The title and number of the program announcement 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)

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines and will be reviewed for completeness by the Center for Scientific Review. Applications will be evaluated for scientific and technical merit by an appropriate scientific review group convened in accordance with the standard NIH peer review procedures. 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 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 the 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 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 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 animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

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 in a timely manner 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 PA.

Written and telephone inquiries concerning this PA 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/PA/Zebrafish_Mutagenesis.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, 93.866, 93.273, 93.855, 93.846, 93.173, 93.837, 93.849, 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, and 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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