Bioengineering Research Partnerships

Participating Institutes and Centers (ICs) of the National Institutes of Health (NIH) invite applications for R01 awards to support Bioengineering Research Partnerships (BRPs) for basic, applied, and translational multi-disciplinary research that addresses important biological or medical research problems. In the context of this program, a partnership is a multi-disciplinary research team that applies an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior. The partnership must include appropriate bioengineering or allied quantitative sciences in combination with biomedical and/or clinical components. The Principal Investigator (PI) also serves as the project manager and must be capable of leading the proposed effort. A BRP may propose design-directed, developmental, discovery-driven, or hypothesis-driven research at universities, national laboratories, medical schools, large or small businesses, or other public and private entities or combinations of these entities. It is expected that a BRP will have a well-defined goal or deliverable that will be achieved based on objective milestones specified in the initial application. On 11 October 2001, the NIH issued a related program announcement (PA) PA-02-011 (http://grants.nih.gov/grants/guide/pa-files/PA-02-011.html) for Bioengineering Research Grants (BRGs). The BRGs differ from the BRPs in that the research will be performed in a single laboratory, by a single investigator, or by a small group of investigators. On 16 January 2003, the NIH issued another related PA (PA-03-058), (http://grants.nih.gov/grants/guide/pa-files/PA-03-058.html) for Exploratory/Developmental (R21) Bioengineering Research Grants (EBRG). The EBRGs differ from the BRPs in that (1) the research will be performed in a single laboratory, by a single investigator, or by a small group of investigators and (2) the projects are high-risk/high-payoff in nature (R21 mechanism) as compared to the R01-type grants supported by the BRP program.

Many of today's biomedical problems are best addressed using a multi-disciplinary approach that extends beyond the traditional biological and clinical sciences. Bioengineering integrates principles from a diversity of technical and biomedical fields and crosses the boundaries of many scientific disciplines represented throughout academia, laboratories, and industry. The creativity of interdisciplinary teams is resulting in new basic understandings, novel products, and innovative technologies for addressing biomedical problems. Recognizing the importance of bioengineering in public health, the Bioengineering Consortium (BECON) was established in 1997 as a focus for bioengineering activities at the NIH. To facilitate communication between the allied and biomedical disciplines and to provide input from the scientific community on research needs and directions, the BECON has held annual two-day symposia on emerging topics of interest related to bioengineering including bioengineering (1998), bioimaging (1999), nanotechnology (2000), reparative medicine (2001), biosensors (2002), and team science (2003). Summaries of the proceedings and recommendations of these symposia are available on the internet at http://www.becon.nih.gov/becon_symposia.htm.

Discussions and recommendations of symposia participants aided in the formulation of the BRP, BRG, and EBRG PAs. It is expected that some applications submitted in response to the BRP, BRG, and EBRG PAs will focus on technology development rather than on proving or disproving scientific hypotheses. In support of this approach, NIH instructions to applicants and review criteria emphasize that a project may "…test a stated hypothesis, create a novel design, solve a specific problem, or develop new technology" (PHS 398 instructions for the research plan).

The primary objective of this PA is to encourage basic, applied, and translational bioengineering research that could make a significant contribution to improving human health. Bioengineering integrates physical, engineering, and computational science principles for the study of biology, medicine, behavior, or health. It advances fundamental concepts, creates knowledge from the molecular to the organ systems level, and develops innovative biologicals, materials, processes, implants, devices, and informatics approaches for the prevention, diagnosis, and treatment of disease, for patient rehabilitation, and for improving health. Some BRP projects may propose research that could lead to a novel device as a product. Partnership with companies that have relevant expertise or that may eventually be involved in commercialization is appropriate under the BRP program.

A second objective is to encourage collaborations and partnerships among the allied quantitative and biomedical disciplines. A BRP must bring together the necessary physical, engineering, and computational science expertise with biological or clinical expertise and resources to address a significant area of bioengineering research within the mission of the NIH. In addition to the benefits to be derived from the research, the collaborations and partnerships can create opportunities for trans-disciplinary communication and training for a new generation of scientists capable of interacting across traditional technical boundaries. Applications for a BRP award should focus on an area of basic, applied, translational, behavioral, or clinical research in bioengineering that supports the missions of the participating NIH institutes and centers and where progress is likely to make a significant contribution to improving human health. Some NIH institutes and centers have indicated that they will only consider BRP applications in specific focus areas. These institutes and focus areas are available at http://www.becon.nih.gov/becon_brpareas.htm.

This PA uses the NIH R01 award mechanism. As an applicant, you are solely responsible for planning, directing, and executing the proposed project. This PA uses just-in-time concepts. It also uses the modular budgeting as well as the non-modular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular budget format. Otherwise follow the instructions for non-modular budget research grant applications. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

The initial period of support of a BRP award may be up to five years. The award may be competitively renewed for a total of up to ten years of NIH funding. Competing renewal and revised applications for BRP grants are to be received at the NIH on the same receipt dates as new BRP applications.

For new grants, the maximum total (direct plus facilities and administrative [F&A] costs) budget to be awarded in any year is $2 million. The number of awards and level of support will depend on the number of applications of high scientific merit that are received and the availability of funds. Funding in subsequent years will be contingent upon satisfactory progress during the preceding year(s) and the availability of funds. Applicants are strongly encouraged to discuss budget requests with NIH scientific and financial contacts listed under WHERE TO SEND INQUIRIES prior to submission. Grantees have the authority to extend the duration of a BRP grant on a no-cost basis. This extension provides additional time to use funds that remain available at the end of the project period to continue pursuing the aims of the grant. Grantees should notify the Grants Management Officer of the awarding institute or center of the no-cost extension as early as possible and before the expiration of the grant.

Research Focus Areas: Applicants are strongly advised to contact IC scientific program staff listed under WHERE TO SEND INQUIRIES to discuss the relevance of their proposed work to the institute's mission before preparing a detailed research application. Detailed information on research missions and programs for each NIH institute and center is available on the participating ICs Web sites, which are listed at the beginning of this PA. Some NIH institutes and centers have indicated that they may only want to consider BRP applications in specific focus areas. As they are available, these institutes and focus areas will be posted at http://www.becon.nih.gov/becon_brpareas.htm.

Letter of Intent: Prospective applicants are asked to submit a letter of intent that includes the following information: Number and title of this PA; Descriptive title of the proposed research; Name, address, telephone number, and e-mail address of the Principal Investigator; List of participating institutions and key personnel. Although a letter of intent

is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NIH staff to estimate the potential review workload, plan the review, and evaluate programmatic impacts of the proposals. The letter of intent should be sent to: Dr. Richard E. Swaja, National Institute of Biomedical Imaging and Bioengineering (NIBIB), 6707 Democracy Boulevard, Suite 200, Bethesda, MD 20892-5469 USA, 301-451-4779 fax: 301-480-4973, email: swajar@nibib.nih.gov

BRP Organizational Structure, Leadership, and Management: An organizational structure that clearly defines the partnership and relationships among the various components must be developed and described in the application. The BRP size, structure, and mode of operation should match the needs and scope of the proposed research. NIH policy requires that a single PI be designated on the face page of all applications. While this individual is responsible for the scientific and technical aspects, as well as the proper conduct of the project, the structure of the BRP may involve more than one individual in developing the application and in making decisions concerning planning, management, staffing, and resource allocation. In recognition of the essential intellectual and/or technical contributions of the lead scientists responsible for developing and implementing the goals of the proposal, the BRP organizational structure must include a "Leadership Statement" that specifies the roles of the individuals that provide major intellectual and/or technical contributions. The PI has the responsibility and authority to use BRP funds in the most productive way to achieve the goals defined at the time of the award. To accomplish these tasks, the PI in collaboration with other individuals identified in the "Leadership Statement" can adjust funding among BRP participants to support new partners or to reduce support to existing partners as needed. The BRP should establish a Scientific Steering Group that consists of representatives from each of the partnering organizations and meets regularly to discuss project status, problems, and directions. Those individuals identified in the "Leadership Statement," who together would have the intellectual and leadership responsibilities normally attributed to the PI, would likely be members of the Scientific Steering Group.

BRP PI Meeting: BRP PIs will meet annually in Bethesda, Maryland, to share results, to ensure that the NIH has a coherent view of the advances in these fields, and to have an opportunity for collective problem solving among the PIs. The cost of participating in this annual meeting should be included in the BRP budget.

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling 866-705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, 301-435-0714, e-mail: GrantsInfo@nih.gov.

Application Receipt Dates: New and competing renewal applications submitted in response to this PA will be accepted on January 21, 2004; August 20, 2004; January 20, 2005; August 19, 2005; January 20, 2006; and August 22, 2006. These are the dates that applications must be received at the NIH.

Applications must be received on or before the receipt dates described as listed on the first page of this PA. The CSR will not accept any application in response to this PA 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 a substantial revision of an unfunded version of an application already reviewed, but such application must include an Introduction addressing the previous critique.

Contact: Dr. Richard E. Swaja, NIBIB, 6707 Democracy Boulevard, Suite 200, Bethesda, MD 20892-5469 USA, 301-451-4779, fax: 301-480-4973, e-mail: swajar@nibib.nih.gov; Dr. Eileen Bradley, Center for Scientific Review, NIH, 6701 Rockledge Drive, Bethesda, MD 20892-0001, 301-435-1179, fax: 301-480-2241, e-mail: bradleye@csr.nih.gov

Circulating Cells in Cancer Detection

The purpose of this PA is to develop novel technologies for capturing, enriching, and preserving exfoliated abnormal cells and macromolecules in body fluids or effusions and to develop methods for concentrating the enriched cells for biomarker studies. In the context of this PA, we have extended the definition of exfoliation to include not only the cellular materials, but also subcellular materials, such as DNA and proteins. In body fluids, such as sputum, the number of exfoliated tumor cells is often small compared to the number of non-neoplastic cells. Therefore, the detection of exfoliated abnormal cells by routine cytopathology is often limited because few atypical cells may be present in the specimen. There may be difficulty in separating dysplastic cells from non-specific reactive changes and degenerating cells or variation in diagnostic criteria. Furthermore, exfoliated cells are frequently contaminated with normal cells, bacteria, and other cellular debris, which makes molecular analysis difficult without physical separation of the neoplastic cells. Thus, the development of enrichment methods becomes prerequisite for the routine detection of small numbers of exfoliated cells and small amounts of subcellular materials in biological fluids for molecular analysis. Similarly, subcellular materials are in amounts that may not be detectable by available technologies and therefore the enrichment of such materials is of paramount importance. Enrichment will allow exfoliated cells and subcellular molecules, for example from urine, to be used for genomic, proteomic, and epigenomic analyses that may lead to improvements in the detection of bladder cancer through measurements of alterations in expressed genes, peptide profiles, and epigenetic markers.

The most common human tumors arise from epithelial surfaces (e.g. colon, lung, prostate, oral cavity, esophagus, stomach, uterine cervix, bladder). Their development often becomes apparent when tumor cells exfoliate spontaneously into sputum, urine, or even into various effusions. The molecular and genetic abnormalities within these exfoliated cells could be used to detect and identify precancerous lesions or very early stage cancer if highly sensitive technologies were clinically available to identify the few abnormal cells among millions of normal cells. For example, detection of widespread microsatellite instability (MSI), as demonstrated by expansion or deletion of repeat elements of DNA, may be adapted for exfoliated cells in general. With the advent of PCR-based detection of DNA from rare neoplastic cells in body fluids, mutations have been detected in ras genes from the stools of patients with colorectal cancer, in p53 from the urine of patients with bladder cancer, and in p53 genes in the sputum of patients with lung cancer. As these assays are complex and technically challenging, they depend on the development of novel technologies for isolating and enriching cells or subcellular materials of interest. Abnormal exfoliated cells can be routinely identified by cytologic examination of brushings and fluids, for instance, from bronchi, pancreatic ducts, voided urine, and effusions. Currently, fluids are usually processed by centrifugation or membrane filtration. However, the detection of abnormal exfoliated cells, for instance, cancer cells by routine cytopathological examination may be limited because the number of abnormal cells may be very small compared to the number of normal cells, is difficult. Alternatively, the cellular and nuclear changes in abnormal cells may be minimal compared to normal cells. This is particularly true of cytological examinations of urine cytology, where many low-grade papillary lesions are often missed. New PCR-based technologies may substantially enhance the sensitivity, but current technologies for isolating and analyzing exfoliated cells are too cumbersome to be of practical utility. The cellular and molecular changes that ensue during tumor progression do so

over a number of years and in an apparently stochastic manner. This progressive accumulation of genetic and epigenetic changes in precancerous cell populations eventually confers the malignant phenotype on emerging clonal subpopulations. In human and animal clinical and experimental models, the progression of precancer to cancer is known to be lengthy. For example, it takes an average of estimated 15 to 20 years for a small adenomatous polyp to become malignant. Prior to the appearance of a morphologically identified precancerous lesion, numerous genetic and molecular alterations would have already occurred. During histological progression into a morphologically identifiable lesion, the stochastic process of molecular events in different cells confers genetic heterogeneity.

Finding molecular and genetic biomarkers of malignancy is particularly important in detecting the emergence of precancerous cell populations and is what the NCI considers to be an "Extraordinary Opportunity." In these earliest stages of neoplasia, lesions should be amenable to complete eradication. This principle has been well-demonstrated in cervical neoplasia, where screening for dysplastic exfoliated cells can result in a 70% or greater reduction in the cervical cancer mortality. During the early stages of cancer development, there is a window of opportunity to detect precancerous cells with genetic or molecular biomarkers that identify and characterize their progression towards cancer. Detection of genetic abnormalities in preneoplastic lesions poses challenges because of the small size of lesions, the heterogeneity of precancerous cells, and their dilution by normal cellular constituents. Therefore, assays should be tailored to detect a small number of abnormal cells or molecules among a large number of normal cells or molecules in biological fluids, such as in colonic washes of the gastrointestinal tract, in sputa, and in bronchial biopsies.

In order to detect and analyze precancerous and cancerous cells in biologic fluids, there are a variety of approaches. The most appropriate approach depends upon 1) the type of biological fluid (sputum, bronchial washing, cervical brushing, voided urine, etc.), and 2) the form of analysis to be performed (e.g., cytopathological analysis, morphometric analysis, molecular biomarkers for specific receptors or genetic changes, FISH-or-PCR based analyses). All of these approaches require an enrichment of atypical epithelial cells through selective processing to concentrate the assay target of interest. The enrichment methods currently used can be grouped into the following two broad categories: 1) mechanical (centrifugation, cytospin, sucrose gradients, etc.) and 2) antibody-based selection with mechanical separation (FACS - flow assisted cell sorting, MACS - magnetic assisted cell sorting, etc.). While one type of enrichment process can be sequentially added to another to improve the yield, all of these methods have good but not adequate sensitivity or specificity required for detecting precancerous cells in body fluids. Given that the concentration of these cells or molecules can be very low compared to other commonly present cell types or molecules, one needs enrichment factors of 1 to 10,000 or 1 to million.

More than 80 percent of human tumors originate from epithelial cells, often at a mucosal surface, and are clonal in origin. Precancerous exfoliated cells can be routinely identified in pathology departments by cytologic examination of washings or brushings from bronchi, oral cavity, esophagus, stomach, bile and pancreatic ducts, sputum and urine; however, the detection of exfoliated cancer cells by routine cytopathological examination is limited because of the presence of few atypical cells in specimens, the difficulty of distinguishing low grade dysplasias from non-specific reactive or inflammatory changes, and the low sensitivity and specificity of the available diagnostic methodology. These limitations are particularly true of urine cytology, where most low-grade papillary lesions are missed on cytologic examination of urine. New PCR-based technologies may substantially enhance sensitivity, but current technologies for isolating exfoliated cells are too cumbersome to be of practical utility. For example, exfoliated cells are frequently contaminated with normal cells, bacteria, and other cellular debris, making molecular analysis difficult without further physical separation of neoplastic cells. Therefore, the development of novel, high-throughput, sensitive technologies for sample preparation is a prerequisite for the successful detection of small numbers of exfoliated cells or small amounts of subcellular materials, such as DNA and proteins.

There are occasions in which the only biologic materials available from patients are stored plasma or serum samples. The amount of DNA in these samples are generally very low when they are obtained from normal (healthy) individuals, but increased amounts of circulating DNA have been found in cancer. The circulating DNA in plasma/serum of cancer patients has been shown to reflect the characteristics of the tumor DNA including molecular changes, such as methylation, point mutations, and microsatellite instability. Fragmented nucleosomal DNA in plasma resulting from apoptotic death of the tumor cells may also provide an indication for tumor DNA. There is a need to develop high-yield technologies to isolate circulating DNA that can be used for early detection of cancer and the follow-up of the disease.

The primary purpose of this initiative is to encourage the development of high-throughput technologies to facilitate the isolation and enrichment of exfoliated cells and subcellular materials. In pursuit of these goals, the NCI invites applications that address the following areas: 1) Development of high-throughput technologies for identifying abnormal exfoliated cells and subcellular materials in body fluids; 2) Development of sampling technologies for capturing and preserving exfoliated tumor cells and subcellular materials in body fluids; 3) Development of enrichment methods for the isolation of tumor cells and subcellular materials; 4) Development of sensitive, high-throughput molecular, cytomorphometric, immunologic, and other relevant technologies to isolate tumor cells or subcellular materials in malignant effusions to help detect low tumor burden and distinguish reactive cells from tumor cells.The long-term goal, to which this initiative will eventually lead, is the development of panels of well-characterized biomarkers derived from exfoliated cells that can be sampled in the clinical setting. These methodologies will be tested and validated in future population-based clinical trials, and integrated into a comprehensive information system that will be developed under the Early Detection Research Network.

This PA will use the NIH exploratory/developmental (R21) award mechanism. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project. The applicant may request a project period of up to two years with a combined budget for direct costs of up $275,000 for the two year period. For example, the applicant may request $100,000 in the first year and $175,000 in the second year. The request should be tailored to the needs of the project. Normally, no more than $200,000 may be requested in any single year. These grants are non-renewable and continuation of projects developed under this PA will be through the traditional unsolicited investigator initiated grant program. This PA uses just-in-time concepts. It also uses the modular budgeting format. (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular format. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, 301-435-0714, e-mail: GrantsInfo@nih.gov.

The title and number of the PA must be typed on line 2 of the face page of the application form and the YES box must be checked.

Supplementary Instructions: All instructions for the PHS 398 (rev. 5/2001) must be followed, with these exceptions: Research

Plan: Items a - d of the Research Plan (Specific Aims, Background and Significance, Preliminary Studies, and Research Design and Methods) may not exceed a total of 15 pages. No preliminary data is required but may be included if it is available. Please note that a Progress Report is not needed; competing continuation applications for an exploratory/developmental grant will not be accepted. Appendix: Use the instructions for the appendix detailed in the PHS 398 except that no more than 5 manuscripts, previously accepted for publication, may be included.
For the NIH Exploratory/Developmental Grant (R21), applicants may request direct costs in $25,000 modules, up to a total direct cost of $275,000 for the combined two year award period.

Applications must be received by or mailed on or before the receipt dates described at http://grants.nih.gov/grants/funding/submissionschedule.htm.

The CSR will not accept any application in response to this PA 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 under this PA. This does not preclude the submission of a substantial revision of an unfunded version of an application already reviewed, but such application must include an introduction addressing the previous critique. Unfunded applications previously reviewed as investigator-initiated applications under a different research grant mechanism may be resubmitted as a new application under this PA (see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-019.html).

Contact: Mukesh Verma, Division of Cancer Prevention, NCI, Executive Plaza North, EPN 3144, Bethesda, MD 20892-0001 USA, Rockville, MD 20852 (for express/courier service), 301-496-3893, fax: 301-402-8990, e-mail: mv66j@nih.gov; Sudhir Srivastava, Division of Cancer Prevention, NCI, Executive Plaza North, EPN 3142, Bethesda, MD 20892-0001 USA, Rockville, MD 20852 (for express/courier service), 301-496-3983, fax: 301-402-8990, e-mail: ss1a@nih.gov

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Developmental Mechanisms of Human Structural Birth Defects

The purpose of this PA is to support new, innovative, multidisciplinary, interactive, and synergistic program projects that integrate basic, translational, and clinical approaches to understanding the developmental biology and genetic basis of congenital human malformations. Each program must consist of at least three component projects. At least one project must be clinical or translational in nature. The component projects must share a common central theme, focus, or objective on a specific developmental defect or malformation that is genotypically, mechanistically, biologically, or phenotypically analogous or homologous in both animal models and humans. Any non-mammalian or mammalian animal model may be used, as long as it contributes to the common overall theme or objective of the program project. If the component projects do not share a common developmental gene, process, mechanism, pathway, or phenotype, the application will be considered nonresponsive to this.

Annually, about four percent of all live births in the United States involve babies with significant structural birth defects (more than 150,000 babies). Next to accidents, birth defects are the leading cause of death in children; they account for half of all pediatric hospitalizations. In terms of the economic costs, billions of dollars are spent over the lifetimes of children born with any of 17 major, severe, nonfatal birth defects. In sum, structural birth defects have a great impact on public health, socioeconomics, and family life. A high priority goal of NICHD's strategic plan is to address the problem of human structural birth defects. The clinical and epidemiological aspects of human malformations were addressed at a workshop in 1997. As a result of that workshop, the National Institute of Child Health and Development (NICHD), the National Institute of Environmenal Health Sciences (NIEHS), the National Institute of Dental and Craniofacial Research (NIDCR), and the U.S. Environmental Protection Agency (U.S. EPA) issued RFA HD-99-002, "Genetic Susceptibility and Variability of Human Malformations." That initiative funded several R01s and established a basis for a network of investigators focused on the use of molecular genetic approaches to the study of genetic susceptibility and epidemiology of human malformations.

A second workshop was held in 1998 and its recommendations served as the basis for RFA HD-99-008, "Developmental Mechanisms of Human Malformations", from which NICHD and NIEHS funded several P01s. An important feature of those P01s was the emphasis on integrating basic, translational, and clinical research. Combined with the R01s funded under the first initiative, these projects expanded the network of researchers focused on the study of structural birth defects.

By issuing this PA, "Developmental Mechanisms of Human Structural Birth Defects," the NICHD plans to increase the number of basic scientists and clinicians involved in this network. Now that the sequencing of the human genome is complete, it is time to capitalize on the rapid advances being made in functional genomics and proteomics. Broadening the base of PIs involved in this research effort will promote the translation of these advances from the bench to the bedside.

The purpose of this PA is to support new, innovative, multidisciplinary, interactive and synergistic program projects that integrate basic, translational, and clinical approaches to understand the developmental biology and genetic basis congenital human malformations. Of particular interest to the NICHD are applications proposing to study embryonic developmental defects of generalized body patterning and localized anomalies of the skeletal, nervous, and visceral systems that lead to clinically significant congenital structural malformations. While applications focusing on developmental disorders that result in mental retardation and related neurobehavioral disabilities are of interest to the NICHD, they are outside the scope of this PA. The basic science component projects may include studies to: 1) identify and characterize the genes, gene products, mutations, polymorphisms, multigene and gene/environment interactions that play a role in normal and abnormal embryonic patterning and organogenesis; 2) elucidate the developmental biological processes and pathways, the biochemical, cellular, molecular, genetic mechanisms, and spatial and temporal gene expression patterns which are involved in dysmorphogenesis; and 3) examine how teratogens and nutritional deficiencies disrupt or modify gene expression and basic developmental processes.

The translational/clinical component projects may include studies to: 1) characterize and classify genotypes and phenotypes of human malformations that are comparable in the animal models being examined; 2) develop physical, genetic, and comparative maps for genes involved in human malformations; 3) identify the developmental genetic processes and molecular pathogenesis of human malformations utilizing animal models; and 4) develop innovative molecular genetic methods, technologies, and strategies to enhance the diagnosis and methods for intervention of the human malformations.

Applicants are encouraged to incorporate the recent scientific advances in developmental biology and genetics in their projects and to utilize the many research resources, bioinformatic databases, and biotechnological tools in their research cores. The research cores should be structured to share work effort and research resources (e.g., biotechnology, high-throughput instrumentation, microarrays, oligonucleotide chips, animal model development, and technical assistance) among the research projects. The aim of the core is to enhance the progress, productivity, cost-effectiveness, and outcome of the research projects.

Applications may include new and innovative approaches to investigate: 1) genetic defects, nutritional deficiencies, teratogens that perturb, modify, or alter gene expression during early development; 2) the identity and function of transcription and growth factors in normal and abnormal gastrulation, embryogenesis, organogenesis, and patterning, as well as their modification by environmental agents; and 3) defective embryonic developmental processes and pathways that ultimately lead to malformations.

Research projects responsive to this PA include, but are not limited to, the following: 1) Investigations on the identity, characteristics, and mechanisms of growth factors and growth factor receptors that function in embryonic development and dysmorphogenesis of the skeletal, nervous, and visceral systems; 2) Studies of transcription factors regulating gene expression and temporal and spatial expression patterns during normal and abnormal embryonic development; 3) Studies of developmental genes, gene products, transcription factors, and growth factors that function and interact to regulate cell proliferation, cell differentiation, apoptosis, cell migration, and cell fate in embryonic development; 4) Examination of genes and molecular mechanisms and interactions that control normal and abnormal body axes and symmetry during development; 5) Studies to identify, map, and characterize genes that play a role in signal transduction and biochemical pathways, cell fate determination, gastrulation, embryogenesis, organogenesis, body patterning, and how developmental defects, mutations, or susceptible polymorphisms lead to malformations; 6) Investigations of pharmaceutical, nutritional, and teratogenic agents and factors that alter genes and developmental processes and pathways that result in dysmorphologies; 7) Investigations to characterize and classify genotype/phenotypes of hereditary human malformations and correlate them to homologs in animal models; 8) Efforts to define pleiotropic effects that genes and their modifiers have in the spatial and temporal development of embryonic and/or fetal anomalies; 9) Development and validation of new and/or improved animal models to study the genes, mutations, mechanisms, and developmental processes and pathways that cause human malformations; 10) Imaging and gene expression studies to investigate and monitor the developmental pathogenesis of dysmorphic features; 11) Investigations of the role of imprinting and epigenetic factors in the development of major congenital malformations; 12) Studies on nutritional factors (e.g., folic acid deficiency) and teratogens (e.g., retinoids and valproic acid) affecting gene/gene, gene/receptor, gene/modifier, and gene/teratogen interactions that lead to neural tube or other structural defects; 13) Examination of the role and developmental biology of neural crest cells in normal embryonic development and how defects in cell proliferation, differentiation, migration, and patterning may result in major structural birth defects; 14) Elucidation of the underlying genetic and molecular mechanisms that alter normal developmental processes in drug-induced (e.g., Accutane, Thalidomide) malformations; 15) Identification and characterization of polymorphisms/mutations of metabolic genes that function in the development of structural birth defects. The topics listed above are only examples, are not in priority order, and are not intended to be all-inclusive. Investigators are encouraged to explore and develop new, innovative projects and research cores that are consistent with the overall objectives of this PA.

Applicants are encouraged to incorporate the recent scientific advances in developmental biology and genetics in their projects and to utilize the many research resources, bioinformatic databases, and biotechnological tools in their research cores. The research cores should be structured to share work effort and research resources (e.g., biotechnology, high-throughput instrumentation, microarrays, oligonucleotide chips, animal model development, and technical assistance) among the research projects. The aim of the cores is to enhance the progress, productivity, cost-effectiveness, and outcome of the research projects.

This PA will use the NIH Program Project Grant (P01) award mechanism. The P01 supports broadly based multidisciplinary research programs that have a well-defined central research focus or objective. An important feature is that the interrelationships among the individual projects will result in a greater contribution to the overall program goals than if each project were pursued independently. The P01 grant requires a minimum of three interrelated individual research projects that contribute to the overall program objective. At least one component project must be translational or clinical in nature. The application may request support for certain common core resources. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. Guidelines for the NICHD Program Project (P01) Grant may be found at http://www.nichd.nih.gov/funding/dsr_p01_guide.htm.

The Program Director for the overall grant and the principal investigator for each component project should plan to attend an annual NIH-sponsored two-day meeting in Bethesda, MD. In addition, this meeting will be attended by investigators supported through the two previous RFAs (HD-99-002, Genetic Susceptibility & Variability of Human Malformations, and HD-99-008, Developmental Mechanisms of Human Malformations). The meeting will provide an opportunity for all the investigators to communicate, discuss the progress of their research, exchange ideas and information, share resources, and foster collaborations that are relevant to the research goals of the NICHD birth defects initiative. This requirement is designed to establish an interactive network of investigators who are interested in multidisciplinary approaches to enhancing our understanding of the epidemiology, etiology, pathogenesis, and developmental biology and genetics of structural birth defects.

All applications should include a request for funds to support attendance of the Program Director and project principal investigators at the annual meetings, as well as a statement of agreement to participate in these meetings and to cooperate with investigators at other program project sites. A data-sharing plan must be included as outlined in the recent NIH Guide notice http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html.

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, 301-435-0714, e-mail: GrantsInfo@nih.gov.

The title and number of this PA must be typed on line 2 of the face page of the application form and the YES box must be checked.

Applications submitted in response to this PA will be accepted at the standard application deadlines, which are available at http://grants.nih.gov/grants/dates.htm. Application deadlines are also indicated in the PHS 398 application kit.

Applications must be mailed on or before the receipt dates described at http://grants.nih.gov/grants/funding/submission-schedule.htm.

The CSR will not accept any application in response to this PA 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 a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

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