

**Trans-NIDDK**

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**7001 AND 7002            INNOVATIONS IN BIOMEDICAL INFORMATION  
SCIENCE AND TECHNOLOGY  
(PA-00-118 AND PA-00-109)**

**FY 2001 Action**

NIDDK has joined other Institutes and Centers of the National Institutes of Health to invite applications for innovative research in biomedical information science and technology to promote rapid progress in biomedical research. As defined here, biomedical computing or biomedical information science and technology includes database design, graphical interfaces, querying approaches, data retrieval, data visualization and manipulation, data integration through the development of integrated analytical tools, synthesis, and tools for electronic collaboration, as well as computational research including the development of structural, functional, integrative, and analytical models and simulations.

This program will use the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) mechanisms and will be run in parallel with a program of identical scientific scope that will use the newly-created Phased Innovation Award mechanism (PA-00-109). The SBIR and STTR applications received in response to this announcement will have the opportunity for expedited transition of successful technology research into an expanded development phase and will be subject to cost and duration limits comparable to the parallel Phased Innovation Award applications.

Unique features of this initiative are: (1) single submission and evaluation of both a feasibility/pilot phase (R21) and an expanded development phase (R33) as one application; (2) expedited transition of the R21 feasibility phase to a R33 development phase; (3) flexible budgets; and (4) flexible staging of feasibility and development phases.

**Background**

In recognition of the critical role computing and computational tools will play in biomedical research, the NIH Director commissioned a Working Group on Biomedical Computing to investigate the needs of NIH-supported investigators for computing resources, and the impediments biologists face in utilizing high-end computing, such as a paucity of researchers with cross-disciplinary skills.

The resulting report "The Biomedical Information Science and Technology Initiative (BISTI)" recommends that the NIH should provide additional resources and incentives for basic research to provide adequate support for those who are inventing, refining, and applying the tools of biomedical computing. The promotion of the interface of biomedical information science and technology with biomedical research should result in new digital and electronic tools that will have substantial impact on broad areas of biomedical research.

## **Research Goals and Scope**

This solicitation targets support for fundamental research in biomedical computing science and technology as well as the development and application of new biocomputing tools or technologies for biomedical research. Examples of data types that could be considered include genomic sequences, biomedical images, qualitative descriptors for health and social science, remote sensing, geospatial images, and chemical formulae. Specific research areas include: (1) tools for data collection; (2) tools for archiving large data sets; (3) research on databases, querying approaches, and information retrieval; (4) research on data visualization; (5) analysis tools for interpretation of large data sets; (6) computing algorithms and new analysis and statistical methodologies for social science research related to areas of biomedical interest such as population aging; (7) research on new approaches to data integration; (8) development of platform-independent translational tools for data exchange; (9) research and development of models or simulation environments; (10) tools or models to promote interoperability; (11) development of web-based linkage tools for data sharing; and (12) tools for electronic communication.

Projects must span the interface of biomedical research and biomedical information science and technology. Cross-disciplinary collaborations are strongly encouraged. Given the expanding needs in biomedical research for advances in a variety of areas of information science and technology, the approaches and technologies proposed under this announcement should ultimately be generalizable, scalable, extensible, interoperable and use sophisticated computational resources. The projects should take into account the needs of the biomedical research community that will be the ultimate end users of the products of the research. The projects should also address plans for ensuring the dissemination of useful products of the research, including approaches, technologies and tools, to the relevant research and user communities. The informatics and computational research proposed should be future-oriented, fill an area of need or projected need, and seek to exceed the current state-of-the-art.

## **7003 PLANNING GRANTS: NATIONAL PROGRAMS OF EXCELLENCE IN BIOMEDICAL COMPUTING (PRE-NPEBC) (PAR-00-102)**

### **FY 2001 Action**

NIDDK has joined other Institutes and Centers of the National Institutes of Health to invite applications for three-year planning grants that would eventually lead to National Programs of Excellence in Biomedical Computing (NPEBC). The NPEBCs are intended to create an infrastructure of excellence in biomedical information science and technology that will support and promote multidisciplinary research and provide the environment in which to train a new generation of researchers. Given the emerging nature of the field of biomedical computing, it is not clear at this point that all institutions that might be interested in establishing NPEBCs in the various areas of opportunity are ready to submit coherent programs that would qualify as ready for a National Program of Excellence designation. The planning phase provided by this mechanism will allow institutions that have most of the separate scientific components necessary for creating a cross-disciplinary research and training program in biomedical computing to plan and create the organization required for a NPEBC.

NPEBCs are intended to: (1) promote bio-informatics and bio-computational research that enables the advancement of biomedical research; (2) develop useful and interoperable informatics and computational tools for biomedical research; (3) establish mutually beneficial collaborations between biomedical researchers and informatics and computation researchers; and (4) train a new generation of bio-informatics and bio-computation scientists.

### **Background**

In recognition of the critical role computing and computational tools will play in biomedical research, the NIH Director commissioned a Working Group on Biomedical Computing to investigate the needs of NIH-supported investigators for computing resources, and the impediments biologists face in utilizing high-end computing, such as a paucity of researchers with cross-disciplinary skills.

The resulting report "The Biomedical Information Science and Technology Initiative (BISTI)" recommends that the NIH should provide additional resources and incentives for basic research to provide adequate support for those who are inventing, refining, and applying the tools of biomedical computing. NPEBC would strive to achieve these goals. Distinguishing features of the NPEBC would include: (1) a range of work, from fundamental discoveries to useful tools in biomedical computing; (2) a plan for disseminating the results of the research and development effort, so that others can take advantage of the data that is produced, the tools that are created, and the science that is discovered; and (3) a full menu of education, ranging from formal undergraduate and graduate programs to courses and seminars for students and working researchers, visiting-scientist programs, "total-immersion" programs, one-week or two-week intensive-training programs, and other innovative programs to help spread the knowledge gleaned in the course of research. That training would underline the scientific effort within the Program.

**Research Goals and Scope**

This solicitation targets support for the development of infrastructures of excellence in biomedical information science and technology that will foster multidisciplinary teams focused on fundamental research in biomedical computing science and technology, as well as the development and application of new biocomputing tools, for a particular area(s) of scientific opportunity in biomedical research. The teams should reflect mutually beneficial collaborations between biomedical researchers and informatics and computation researchers. Pre-NPEBCs will provide Institutions with the resources to set in place all of the components that would make them eventually competitive for a NPEBC grant.

Support is specifically for planning activities and pilot research projects leading toward the development of organization and infrastructure competitive for support as a NPEBC. The NPEBC will focus on advances in biomedical computing in the context of enabling progress in a compelling area(s) of biomedical research. Activities proposed in response to the current solicitation should target the establishment of a research and communications infrastructure that would promote new discoveries in biocomputing and the dissemination of new related tools, as well as a range of training opportunities that would promote a new generation of scientists that span the interface of biomedical research and computing.

## **7004 ROLE OF HORMONES AND GROWTH FACTORS IN PROSTATE CANCER (RFA DK-01-008)**

### **FY 2001 Action**

This initiative is designed to explore the underlying mechanism(s) of action of hormones and growth factors in the regulation of prostate development, growth, and tumorigenesis. The focus will be on fundamental studies of hormone and growth factor action including the mechanisms of action of nuclear hormones, the role(s) of nuclear accessory proteins and the signal transduction pathways important for nuclear hormone action in prostate. Focus will also be on growth factor action in prostate, including growth factors, binding proteins, receptors and signal transduction pathways. Studies are also invited that will examine the patterns of gene expression in the prostate *in vivo* or in prostate cells in response to hormone or growth factor action. Finally, studies on the development and potential use of hormone/growth factor analogs, agonists, or antagonists with potential clinical utility to modify prostate growth; tumor development and/or progression will be encouraged.

### **Background**

Although the prostate is clearly a sex steroid (androgen) dependent tissue, there is ample evidence to support roles for numerous other nuclear and peptide hormones, as well as growth factors and cytokines in the development of the tissue, and the development and progression of tumors arising from cells within the adult tissue. At a recent NIDDK International Symposium on the Biology of Prostate Growth, data were presented to show that factors such as the insulin-like growth factor- I (IGF-I), fibroblast growth factor (FGF), members of the erbB family, and others, as well as their receptors and binding proteins, and other small bioactive peptide hormones, have been implicated in development, growth and differentiation of both the epithelial and the stromal components of prostate.

While growth factors are extremely important in prostate function, members of the nuclear hormone superfamily play crucial roles in prostate development, growth, function, and tumorigenesis and/or progression. Androgens represent the primary steroid hormone affecting gene expression in the prostate, though roles for estrogen and for orphan nuclear receptors have also been suggested. At a recent NIDDK workshop entitled: "Co-activators and Co-repressors in Gene Expression" work was presented which suggested a role for the relative affinity of binding of nuclear accessory proteins, including co-repressors and co-activators, to form complexes essential to determining whether a particular gene is activated or not in response to hormone. Androgens appear to form homodimer pairs in binding to chromatin, and recruit nuclear accessory proteins, such as ARA70. The ARA is thus also a candidate for interaction with other nuclear accessory proteins, such as co-activators or co-repressors that regulate repression or activation of target genes. Another recent NIH Workshop [NIH Workshop on Selective Estrogen Receptor Modulators (SERMS)] focused on the potential utility of hormonal analogs, partial agonists, and antagonists as therapeutic agents for hormonal-dependent cancers, including those in breast and prostate.

Finally, the role of signal transduction cross talk between growth factors and nuclear/orphan receptors may mediate interactions between cell types in the prostate and contribute to stimulation and/or growth of prostate and to tumorigenesis.

### **Research Goals and Scope**

The following areas of research are included: (1) hormonal or growth factor regulation of prostate development, function, growth, or tumor development; (2) mechanism of action of nuclear hormones and/or peptide hormones or growth factors in the regulation of prostate-specific gene expression; (3) novel cell culture or transgenic model systems that allow for study *in vitro* or *in vivo* of gene expression in prostate or prostate cells; (4) role(s) of nuclear accessory proteins in regulation of hormone/growth factor action in prostate; (5) novel factor(s) associated with nuclear hormone action in prostate involved in tumorigenesis; (6) analogs, agonists, or antagonists of nuclear hormones/growth factors with potential effects on tumor development and/or progression; (7) orphan nuclear receptors with role(s) in prostate structure, function, or disease development or progression; (8) structural biology of the AR focusing on interactions with other receptor interacting proteins, co-activators or co-repressors, hormone, or hormone response elements; (9) effects of Selective Estrogen Receptor Modulators (SERMs) on prostate; (10) role(s) of heat shock, or other chaperone, proteins in regulating androgen (and other hormone) function in prostate; (11) signaling cross-talk between nuclear receptors and/or growth factor or cytokine, and other cell surface receptors, and effects on regulation of prostate gene expression and disease initiation/progression; (12) evaluation of gene expression during growth factor or hormone signaling among different cells in the prostate; (13) age-related changes in hormone or growth factor signaling processes that may be involved in the increasing risk of prostate cancer; and (14) role(s) of environmental factors that may interact with or influence the effects of hormones and growth factors on prostate growth, development, and/or tumor development.

## 7005 DEVELOPMENT OF THE INTESTINE, LIVER AND PANCREAS

### **FY 2001 Action**

A Request for Applications (RFA) is being developed to stimulate and solicit studies on the developmental biology of gastrointestinal organs, with particular focus on the intestinal epithelium, liver and exocrine pancreas. Key research issues to be addressed will be on how the endodermal tube is guided to patterns that result in heterogeneous populations of cells, tissues, and organs, and also on identification of stem cells and the genes that direct their differentiation. Interdisciplinary projects that focus on basic developmental biology, stem cell biology and clinical conditions associated with the gastrointestinal (GI) tract and related organs will be especially encouraged. In addition to hypothesis-driven R01 projects, this initiative will encourage development of new research tools through Exploratory/Developmental Grants (R21).

### **Background**

The GI tract and related organs share common embryological origin from the endoderm, and it is now evident that cross-talk between the endoderm and mesoderm specifies gut regions. A number of endodermal regulatory genes (*Hox*, *Pdx*, *Hlx* and *Cdx*) critical to this process have now been identified. In addition the endoderm gives rise to gastrointestinal organs that branch from the main tube (liver, gallbladder, pancreas and cecum) and several genes have been found to be required for bud formation (*Pdx*, *Hlx9*, *Pax*, for pancreas and *Hex* for liver). Proliferation allows for organ expansion and is orchestrated by a number of mesenchymal signals, like *Hlx* (liver, intestinal epithelium), *Pdx1* (pancreas), *Cdx1* (intestinal crypts) and *NKx2.3* (midgut epithelium). Terminal differentiation results from the interplay of both mesenchyme (genes of the Notch/Delta pathway) and epithelium (*Shh*).

A number of genes critical for pattern formation, proliferation and early differentiation, and related signaling molecules have been identified, but there has been much less progress in understanding molecular processes and cell interactions that result in fully mature cellular complexity and organ functions. Further progress in stem cell biology and utilization in treatment of disease is largely dependent on not only technological advances in isolation, recovery, and culture, but also on further elucidation of maturation processes in both *in vitro* and *in vivo* environments.

### **Research Goals and Scope**

This initiative encourages development of innovative approaches, tools and reagents for analyzing the molecular properties of gastrointestinal stem cells and their fully differentiated descendants, as well as mesenchymal cell populations that may serve to regulate epithelial cell renewal in the developing and adult GI tract and related organs. The long term goal of this effort is to provide a broader conceptual and experimental foundation for: understanding the regulation of epithelial renewal in the normal gut and associated organs; characterizing the epithelial-mesenchymal cross-talk that underlies normal development; describing how renewal is perturbed in a variety of related pathologic states and more accurately classifying states affecting the gut and liver. In addition, the initiative encourages development of new surrogate markers for identifying

patient populations at risk for development of disease, for following disease progression, and for characterizing therapeutic responses to existing treatment regimens. Finally, studies supported under this initiative could provide bases for identifying therapeutic targets and strategies for disease prevention and treatment.

In addition to hypothesis-driven studies, this initiative will support exploratory/developmental efforts on new resources for the research community including, for example: new methods for rapid recovery of specific cell lineages in both developing and adult GI, liver and pancreas; methods for amplifying and/or retrieving normally rare epithelial lineage progenitors from genetically defined models; and development of clonogenic assays for lineage progenitors. Other suitable efforts could focus on the creation of new and broadly applicable methods for amplifying mRNA isolated from single or small numbers of recovered epithelial and mesenchymal cells to allow gene expression profiling and comprehensive definition of the patterns of gene expression (mRNA and/or protein) in stem cells and their differentiated descendants under defined environmental conditions. The development of innovative, invasive or non-invasive methods for monitoring gene expression *in vivo* and for identification of cell lines. The development of culture conditions that provide the efficient maintenance and propagation of stem cell lineages. Finally, there is need for development of vector systems for the delivery of gene products to specified cell lineages and their progenitors, and the development of novel inducible transcriptional regulatory elements for expressing gene products at specified locations and times.

## **7007 ADI-MAP: A COLLABORATIVE NETWORK FOR INVESTIGATORS STUDYING THE GENETICS OF HUMAN OBESITY**

### **FY 2001 Action**

This initiative is for the planning and implementation of meetings bringing together investigators on a regular basis in order to enhance collaborative activities and to develop better means of data sharing and standardized assessment.

### **Background**

On July 14, 2000, NIDDK sponsored a meeting entitled "ADI-MAP: An Obesity Gene Mapping Collaborative Project: Are we ready?" The purpose of this meeting was to bring together investigators working in the field of the genetics of human obesity in order to share information and to assess their level of interest in collaborating.

More than 40 scientists attended the meeting, including intramural and extramural investigators with national and international cohorts, as well as representatives from the National Heart, Lung and Blood Institute, National Institute of Child Health and Human Development, and National Human Genome Research Institute. Current activities were presented, methodological issues in data collection and analysis were discussed, and the pros and cons of data sharing and collaborative activities were debated at length. There was strong consensus that much benefit would be derived from collaborative activities, that might include periodic meetings of investigators, development of common definitions for phenotyping, and developing a common marker set. The ability to share cross-species experience was also considered useful. Eventually, pooling of shared data, starting on a small scale might be considered.

### **Research Goals and Scope**

Planning will take place for meetings of a Human Obesity Genetics Network. The focus will be on investigators working in the area of human obesity, but several investigators working on the genetics of animal obesity will also be invited so that cross-species information can be shared. The initial meeting will focus on discussion of the scope of such a consortium or network as well as sharing of results. Future meetings may focus on specific topics, such as discussion of phenotyping, animal models, or development of common marker sets.

## **7008 FUNCTIONAL GENOMIC TOOLS FOR THE STUDY OF THE ZEBRAFISH**

### **FY 2001 Action**

A new multi-institute initiative is proposed for tools for functional assessment of the zebrafish genome. This initiative is being proposed as a trans-NIH effort complementary to the sequencing project expected to be undertaken by the Sanger Institute. This initiative is anticipated to involve the sixteen institutes that participate in the trans-NIH zebrafish coordinating committee, under leadership of the NIDDK and the National Institute of Child Health and Human Development (NICHD). The current proposal calls for two new NIH supported components: a full-length cDNA project, and a systematic atlas of spatial patterns of gene expression.

### **Background**

The zebrafish has become established as a powerful model organism, of value for the understanding of early vertebrate development, and for identification of genes responsible for organ formation and human diseases. Significant progress has been made in development of genomic tools for the zebrafish, largely through the support of the Trans-NIH Zebrafish Genome Initiative. Extensive mapping efforts by individual laboratories have produced a genetic map, currently anchored with over 2,000 independent simple sequence length polymorphisms, (SSLP) and 600 random amplified fragment length polymorphisms, (RAPDs). Over 400 genes have been placed on the map using restriction fragment length polymorphisms or single strand conformational polymorphisms. The NIH is currently funding projects to map 3,000 additional genes and to place enough additional micro-satellite markers on the map to yield, on average, one marker for each one cM interval. Two independent zebrafish-mammalian radiation hybrid panels have been developed for mapping of genes or EST sequences and have been typed with 1,000 to 2,000 SSLP markers. Some of the mapped genes are being placed on both the meiotic map and the radiation hybrid panel, anchoring the RH map to the genetic map and establishing syntenic relationships between zebrafish and humans. Also funded is an EST sequencing project to determine 50,000 independent ESTs derived from oligo-fingerprinted libraries normalized to reduce redundancy. There are two YAC libraries for the zebrafish that are useful for positional cloning or chromosomal walking, while a PAC and a BAC library are available from commercial resources. An informatics resource, ZFIN, has been established and is working to insure rapid access to all emerging information about the model organism.

In summary, over the past several years, with NIH support, the zebrafish community has amassed a significant set of reagents and resources to enhance study of the genetics and genomics of the system. The community has created many of the tools necessary for positional and candidate cloning of mutant genes, thus establishing the basic infrastructure necessary to exploit the genetic power of this model organism. Reflecting the recognized power of this model organism and the value of these resources, the Sanger Institute, with support of the Wellcome trust, is actively considering a whole genome sequencing effort. The NIH anticipates working closely with the Sanger effort to avoid redundancies and assure complementarity of activities. The planned provision of whole

genome sequence by the Sanger Center will ameliorate many cloning difficulties, but only if the sequences can be assembled into long-range contigs, if it is well-annotated to identify genes, and if the functional tools to understand the underlying biology are available.

### **Research Goals and Scope**

A. Full-Length cDNA Project: Full-length cDNAs provide important tools for gene evaluation, with many potential applications. The Sanger Center sequencing effort is anticipated to rely on a whole genome shotgun approach, which will make the availability of full-length cDNA sequences a critical resource to assess the accuracy of assembly, and to annotate the genome sequence. Full-length cDNAs are also very valuable reagents for expression of proteins and evaluation of function. Cataloging the full-length cDNA complement of the developing embryo is of value in design of experiments that undertake systematic assessment of gene expression. Clarification of gene pathways will be greatly facilitated by availability of zebrafish expression arrays designed to assess gene expression at different developmental times and tissues. The first aim of this project will be to obtain and sequence full-length cDNAs from all stages of the developing embryo. Full-length sequences will be cloned into expression vectors and provision made for their ready availability to the scientific community. As the second stage of this effort, libraries will be prepared from organs of adult fish, and full-length cDNAs obtained from these sources. Utilization of the methods being developed by the NIH full-length human and mouse cDNA project will permit rapid technical progress.

B. Systematic Atlas of Gene Expression: One major advantage of studies of organ development in the zebrafish is the transparency of the developing fish. For many organs, a complete, detailed spatial and temporal description of gene expression is feasible. To begin to create a four dimensional atlas of gene expression in space and time, studies will use whole mount *in situ* hybridization and examine the expression patterns for both known genes and ESTs of unknown function. To contribute to annotation of these images, work is underway by zebrafish investigators to establish a common language, or dictionary, so that the whole community uses the same words to refer to anatomic structures. Terminology is being established for all developmental stages. As the community proceeds in developing standardized terminology, support will also be provided to develop a set of images that illustrate the anatomic terms. Both types of images will be made available through ZFIN.

## **7009 MUTAGENESIS SCREENS FOR STUDY OF THE ZEBRAFISH (RFA HD-00-004)**

### **FY 2001 Action**

A Request for Applications (RFA) was issued in FY 2000 to encourage applications designed to exploit the power of mutagenesis screening in zebrafish. Studies were invited that undertake to detect and characterize genes, pathways, and phenotypes of interest in development, behavior, organ formation, disease processes and that propose to advance the technologies associated with mutagenesis screening. Strategies for mutation screening were encouraged that would identify genes important for NIDDK interest areas such as metabolism, satiety, body temperature control and digestive and excretory function. The RFA is a trans-NIH initiative with participation of sixteen Institutes, working through the Trans-NIH Zebrafish Coordinating Committee (ZFCC), under the co-chairmanship of the National Institute of Child Health and Human Development and the NIDDK. Funding is anticipated following January 2001 Council.

### **Background**

In the past decade, mutational screens in the non-vertebrate genetic models of the worm (*Caenorhabditis elegans*) and the fruitfly (*Drosophila melanogaster*) contributed significantly to our understanding of developmental pathways. These studies have led to the discovery of genes encoding signals, components of signaling systems, enzymes, and transcriptional regulators that act during embryonic development, often 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 organogenesis of the vertebrate embryo are distinct and cannot be studied in invertebrates. 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.

As a vertebrate, the zebrafish, *Danio rerio*, is more closely related to humans than yeast, worms or flies. It has a number of advantages as a model organism for study of vertebrate 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 morphogenesis, making them very amenable for 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 in which large-scale forward mutagenesis screens can be performed with relative ease. Screens performed to date have focused exclusively on phenotypes in early embryonic development. Two large-scale screens have been performed, and the transparent embryos have been screened for defects in overall embryonic pattern morphogenesis. On May 10-11, 1999, the NIH sponsored a workshop entitled "Genomic and Genetic Tools for the Zebrafish." At this workshop zebrafish researchers were asked to help prioritize the short- and long-term needs of the community. A high priority emerging from this workshop was the recommendation for support of additional genetic screens, particularly screens focusing on later developmental events and on phenotypes in adult fish. The purpose of this initiative is to provide further support for zebrafish mutagenesis and phenotypic screening efforts.

### **Research Goals and 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. Objectives to be addressed in applications submitted in response to this RFA include, but are not limited, to the following: (1) development and/or application of novel phenotypic screens based on observation of alterations in morphology, physiology, or behavior of mutants; (2) development and/or application of novel methods of mutagenesis; (3) genetic screens focusing on identifying mutations that affect the structure and function of specific tissue/organ systems; (4) screens to analyze the genetic basis of adult phenotypes including behavior, aging, organ disease, cancer, and responses to environmental toxins and drugs; (5) screens to detect altered gene expression patterns as a tool to identify components of genetic pathways or those altered by environmental agents; and (6) sensitized screens, using strains carrying a known mutation, in order to identify extragenic suppressors or enhancers of that mutation.

## **7010 ZEBRAFISH GENOMICS – SEQUENCING OF ADDITIONAL ESTS**

### **FY 2001 Action**

The number of zebrafish ESTs (expressed sequence tags) generated by currently funded zebrafish genomics projects would be increased from a target of 100,000 to a new target of 181,000 ESTs. Cluster analyses of these ESTs is predicted to identify approximately 31,000 unique zebrafish genes, that in turn will support mapping 15,500 genes on Radiation Hybrid (RH) panels. This initiative is anticipated to involve the sixteen institutes that participate in the trans-NIH zebrafish coordinating committee, under leadership of the NIDDK and the National Institute of Child Health and Human Development. The additional work will require extension of three of the current grants (DK55378 – Talbot; DK55379 – Johnson; DK55381 – Zon).

### **Background**

Zebrafish are vertebrates, tractable and inexpensive enough for screens in many labs, and many important aspects of higher vertebrates, such as organ form and function, have been well conserved. Therefore, the zebrafish is an appropriate and relevant organism for studies of vertebrate-specific questions. The zebrafish system, therefore, will open new fields of biology and medicine. An initial Genomic Resources RFA was funded September 1998, which sought to provide the resources to enable routine positional and candidate-based cloning approaches for the many zebrafish mutations that had informative developmental and disease phenotypes. Based on the work funded so far over the past several years, the zebrafish community has amassed a significant set of reagents and resources to enhance the genetics and genomics of the system. The community has created many of the tools necessary for positional and candidate cloning of mutant genes, thus establishing the basic infrastructure necessary to exploit the genetic power of this model organism.

The status of the NIH Zebrafish Genome Initiative was reviewed at a meeting of the External Zebrafish Advisory Panel (EZAP) members at a meeting in December 2000. There was very strong support by panel members for increasing the number of ESTs that will be sequenced and mapped. The high importance of EST data for all genomics research is being increasingly recognized. The needs of the zebrafish community are threefold. First, there needs to be increased sequencing of ESTs, involving increased funding for the Washington University group. This effort will complement the proposed plans of the Sanger Center to join the zebrafish genomics effort by sequencing the zebrafish genome. Second, there needs to be increased production of cDNA libraries that are in a form suitable for generating ESTs. Funds need to be provided for the collection and arraying of existing cDNA libraries that are currently available from individual researchers, and for the systematic production of new cDNA libraries that would increase the repertoire of genes represented in the cDNA libraries. Third, funds need to be provided to map the new ESTs. At present the capacity to map ESTs is outstripping the availability of ESTs. For example, the Zon laboratory at Boston Children's Hospital has implemented instrumentation that will allow them to map their projected and funded goal of 5,000 mapped ESTs by the end of 2000. This project and that at the Talbot laboratory at Stanford University currently are limited by the availability of ESTs. The Panel urged

the NIH to take aggressive steps to insure that the availability of ESTs did not become rate limiting for the mapping efforts.

### **Research Goals and Scope**

An additional 60,000-zebrafish cDNA clones will be used to perform EST analysis. The cDNAs will be obtained from several researchers already developing libraries. Close coordination of the RH mappers (Zon and Talbot) with the Johnson group as to which genes/ESTs are being mapped is a feature of the existing program, and will avoid duplication of efforts. This coordination will be extended to include the Tuebingen group to the extent possible.

The past efforts of the Johnson group at Washington University to assign ESTs into clusters and UNIGENES are deemed highly important. Future work on EST characterization and development must include specific efforts that will support development of a zebrafish UNIGENE collection. In addition, the EZAP strongly endorsed Dr. Johnson's proposal to link the zebrafish clusters/UNIGENES to human genes. It was noted that fulfilling this objective would require additional/supplementary funding.

## **7011 MOUSE METABOLIC PHENOTYPING CENTERS FOR MODELS OF DIABETES AND ITS COMPLICATIONS (RFA DK-00-014)**

### **FY 2001 Action**

Approximately three national Mouse Metabolic Phenotyping Centers will be funded through a cooperative agreement, in order to make available for modest cost detailed metabolic phenotyping of knockout mice and other mouse models potentially useful for understanding diabetes, its complications, obesity and related metabolic diseases or conditions. Mice will be submitted by researchers for glucose and insulin clamps, nuclear magnetic resonance (NMR) or positron emission tomography (PET) studies, or other complex, kinetic exams beyond what would be possible or cost-effective in their individual laboratories. Applications were received in July 2000.

### **Background**

Mutant mouse models, generated either by directed knockout or transgenic techniques or by large-scale mutagenesis, are important tools for understanding the role of specific genes in health and disease. Genetic factors are thought to underlie the initiation, progression, and severity of complex diseases of interest to NIDDK: diabetes, obesity, and the devastating micro- and macrovascular complications of diabetes, such as nephropathy, neuropathy, retinopathy, and atherosclerosis. These diseases have proven difficult to study, partly due to lack of very good animal models and partly due to the complexity of the problem. Good animal models may allow for more rapid development and assessment of therapies and preventive measures. Candidate genes for diabetes and related disorders are being identified and mutated in directed research projects. These new mice include animals containing multiple altered genes or genes altered in specific tissues. Heterozygous knockout mice are also potentially useful models for complex metabolic disease. New large-scale mutagenesis programs are expected to generate animal models of complex metabolic diseases in addition to other disorders.

The resultant mice from both these approaches may have subtle phenotypes that could be particularly difficult to detect with simple high throughput tests, or with data taken at a single time point. Defects may be exposed only in the presence of physiologic or nutritional stress. Moreover, simple genetic manipulations could result in a very complex phenotype due to minor alterations in a large number of pathways and organs, or in their interaction. The types of experiments that are currently available to study metabolic processes--glucose and insulin clamps, indirect calorimetry, or organ balance, PET, NMR and other tracer studies--are very difficult to do in tiny animals, and require specialized equipment and expertise. Characterization of diabetic complications via measurement of glomerular filtration rate, cardiac or renal hemodynamics also becomes technically challenging when done in mice. Therefore, researchers would benefit from a few centralized, well-equipped facilities to which they could submit their mice for detailed phenotyping.

### **Research Goals and Scope**

A national Mouse Metabolic Phenotyping Center must be an identifiable unit within a single institution such as a university, or a consortium of cooperating institutions

including an affiliated university. The center would be available to study mice generated by NIH-funded and other investigators from both outside and inside the institution.

In general, Centers will be comprised of several components, such as a phenotyping laboratory and analysis core, an animal care core, a research and development program, and an administrative core. In addition, a Center may house an informatics core, a modeling project, or other cores deemed necessary. It is hoped that Centers will play a leadership role in the standardization of currently available phenotyping tests and in the development of new technologies. Centers will also have a Pilot and Feasibility program capable of supporting small research projects within and outside the parent institution for the development of new technologies.

The Centers will be expected to interact with each other to maximize and coordinate service to the diabetes research community. A National Steering Committee comprised of funded principal investigators, NIH staff, and external advisors will be established in order to oversee and coordinate the funded Centers.

## **7012 MOUSE MODELS OF DIABETIC COMPLICATIONS CONSORTIUM**

### **FY 2001 Action**

The intent of this initiative, the Mouse Models of Diabetic Complications (MMDC) Consortium, is to assemble a cross-disciplinary consortium to develop innovative mouse models of diabetes complications that closely mimic human disease. Complications to be examined include diabetic kidney disease, retinopathy, neuropathy, micro and macro vascular disease, impaired wound healing, urinary tract infection, altered gastrointestinal and bladder function, and periodontal disease. The first goal of this consortium is to generate animal models that will be useful for study of disease pathogenesis, prevention and treatment. The second goal of this consortium is to test the role of candidate genes or chromosomal regions that emerge from genetic studies of human diabetic complications, particularly diabetic kidney disease. Each team must contain expertise in mouse genetic engineering, organ-specific phenotyping in the mouse and diabetic complication(s). The Consortium will define standards including gene expression profiling, to validate each diabetic complication model for its similarity to human disease. The teams will utilize innovative mouse genetic engineering techniques to create diabetic mice with altered expression of potential target organ disease genes. The teams will derive, characterize, validate, and use the models for various aspects of basic, developmental, or translational research including testing prevention, early detection, therapy, or diagnostic imaging strategies. As the models are developed and validated, the NIH will provide the mechanism to freely disseminate the mouse models and information related to them to the scientific community.

### **Background**

Recognition, prevention, and treatment of diabetic complications is a central therapeutic problem in both type 1 and type 2 diabetes mellitus. In the U.S., diabetes accounts for 42 percent of all new cases of end-stage renal disease, 50 percent of all non-traumatic amputations, and is the leading cause of new blindness in people ages 20-74. More than 60 percent of people with diabetes are affected by neuropathy. Macrovascular complications are a major cause of morbidity and mortality in diabetes, particularly in patients with nephropathy. Diabetes also confers a markedly increased risk of developing oral complications. Because diabetic nephropathy does not occur in over half of patients with diabetes, and there is significant familial clustering of patients with diabetic nephropathy in the African American and Native American communities, there may be one or several susceptibility genes for diabetic nephropathy

Genetic technology has advanced to the point that it is theoretically possible to genetically engineer mice that develop diabetic complications that are analogous to the major human complications of diabetes. Such accurate models of human diabetic complications would be especially valuable to analyze the initiation and progression of diabetic complications, to provide the framework for discovery of the genes and cellular parameters that generate susceptibility or provide resistance, to furnish targets for intervention and treatment, and to permit prevention, detection, therapeutic, and imaging strategies to be tested in the context of a normal tissue environment. Furthermore, it is

now possible to more carefully phenotype both human patients and mouse models with unbiased techniques such as systematic gene expression.

Several well-characterized models of diabetes exist in the mouse; however, these mouse models have been used mainly to study the mechanisms for development of diabetes and the metabolic complications. In contrast, the pathogenesis of end-organ damage has received less mechanistic attention. Studies of complications have been largely descriptive--often reporting only histologic changes. Constraints of limited time and funding often do not permit an in-depth, comprehensive analysis and characterization of diabetic complications developed by these mice. Even fewer models are tested for their response to treatment or prevention modalities or their suitability for testing early detection or imaging applications. The genes that confer susceptibility to diabetic nephropathy are unknown. The possible interrelationships between different complications (for example, neuropathy and macro or microvascular disease) that interact in diabetic patients have not been systematically studied in animal models. The NIH supports many individual projects that involve the derivation or study of mice that develop diabetes. However, at the present time, the NIH does not support a coordinated, collaborative effort to produce highly accurate mouse models of diabetic complications, particularly for the early design, derivation, characterization, and validation phases of model building, and to ensure that the models and the data relevant to them are readily available to the research community for further investigation or application.

### **Research Goals and Scope**

The intent of this initiative is to assemble projects for a cross-disciplinary, multi-institutional MMDC Consortium whose component teams of investigators will refine or derive accurate mouse models of human diabetes complications. The approaches used for generating, characterizing, and validating the mice for research purposes will reflect the blend of experience and creativity of the Consortium component groups, and will be originated by these investigators. The Consortium will validate the models for use by the research community for a variety of investigations, including for testing therapeutic, prevention, early detection, or imaging strategies, and assure their availability to the research community.

The MMDC Consortium will define the parameters by which the diabetic complications will be validated; define standards for phenotyping, treating and monitoring diabetic mice; and define standards for assessing the impact of glycemic control on the development of complications. If necessary, the Consortium may acquire new human phenotypic data (for example, by gene profiling).

## **7013 INNOVATIVE USE OF NON-MAMMALIAN MODEL ORGANISMS TO STUDY MEMBRANE TRANSPORT (RFA DK-01-012)**

### **FY 2001 Action**

A trans-NIDDK initiative is proposed to develop tools and methods, which permit the exploitation of non-mammalian model organisms to characterize membrane transport processes.

### **Background**

Abnormalities in membrane transport processes are associated with many human diseases, such as diabetes, cystic fibrosis, renal tubular acidosis, congestive heart failure (hypokalemia), and several intestinal disorders, which contribute to a major health care burden for the U.S. population. Many of these membrane transport processes are well conserved in lower organisms where the genomes are known, and are genetically tractable, and which are easily manipulated at the cellular and molecular levels. Thus, non-mammalian model organisms such as *Arabidopsis*, bacteria, yeast, *C. elegans*, *Drosophila*, and zebrafish offer ideal systems in which to understand the underlying mechanism, regulation, and protein structure of many evolutionarily conserved membrane transport processes.

### **Research Goals and Scope**

To fully exploit these model systems, new experimental technologies need to be developed and/or existing technologies further refined. Therefore, this initiative will be designed to provide small grants (R21) to utilize non-mammalian models to develop reagents, methodologies, and novel approaches to the study of membrane transport, especially those involved in diseases of relevance to NIDDK. Examples include the development of isolated cell preparations and new cell lines (such as tubule cells), from genetically tractable organisms or organisms with sequenced genomes; development or refinement of electrophysiological, electron microscopic or imaging methods to be used for assessing membrane transport function and regulation in the intact organism; structure-function studies of purified homologous proteins or proteins in model membrane systems; the search for novel genes and proteins involved in membrane transport of ions and nutrients, and development and application of informatic tools for identifying membrane transport proteins and studying their function.

It is anticipated that, as a result of the grants funded with this RFA, new and innovative approaches will be developed and will be effectively utilized by the investigators to submit competitive investigator-initiated R01 research grant applications.

## **7014 NIDDK STUDY TO DEVELOP OUTREACH TO SPANISH LANGUAGE NEWS MEDIA**

### **FY 2001 Action**

NIDDK will plan a strategy to increase coverage by Spanish language and Hispanic mass media outlets of the cause, prevention and treatment of diseases and disorders that disproportionately impact Hispanic/Latino American audiences such as type 2 diabetes, obesity, kidney failure and gallbladder disease. This effort is a component of the NIDDK Strategic Plan on Minority Health Disparities. Specific actions may include: (1) developing a directory of Spanish-language media and reporters; (2) translating news releases and backgrounders into Spanish; (3) identifying researchers and other experts who speak Spanish as sources for interviews; (4) attending the annual meeting of the Society of Hispanic Journalists; (5) assisting the NIH Hispanic Coordinator to establish links between NIH Spanish-language Web site and NIDDK Spanish language materials on its Web site; and (6) exploring fellowships in health journalism for Hispanic reporters through the NIH program with the Knight Medical Research Fellowship.

### **Background**

NIDDK's research mission includes diseases and disorders that disproportionately affect Hispanic Americans. NIDDK publishes an extensive inventory of publications for this audience including the following topics: diabetes, kidney failure, chronic hepatitis C, peptic ulcer disease and *H. pylori*, and urinary incontinence in women (seven part series). Materials that will be published in the future include obesity and weight control and gallbladder disease. Currently, the National Diabetes Education Program of NIDDK supports a public service media campaign about type 2 diabetes for the Hispanic population. The success of the campaign with Hispanic media suggests the potential for greater access for other NIDDK materials and the need to capitalize on relationships initiated through this national program. Efforts will be coordinated with other NIH Institutes through the NIH Hispanic Communications Coordinator.

### **Research Goals and Scope**

The goal of the study is to develop a report and recommendations for future activities to increase the coverage of NIDDK health and research topics in the Spanish-language and Hispanic oriented communications media. This goal will be supported by objectives such as the following: (1) describing the media habits of Hispanic audiences especially in regard to health information; (2) performing content analysis of health coverage in national Hispanic print and broadcast media; (3) determining the views and opinions of relevant gatekeepers in the Hispanic media about the use of NIDDK information; (4) surveying other NIH Institutes about relevant experiences with Hispanic media; and (5) seeking input from representatives of Hispanic organizations on appropriate approaches to Hispanic media representatives and journalists.

## **7015 NIDDK STUDY TO ESTABLISH NATIONAL MINORITY RESEARCH INVESTIGATOR COMMUNICATION NETWORK**

### **FY 2001 Action**

NIDDK will plan a strategy to develop a communication network of current and potential biomedical research investigators and technical personnel who represent traditionally under-served communities: African American, Hispanic American, American Indian and Asian American/Pacific Islanders. The purpose is to (1) increase participation of members of under-served populations in the biomedical research enterprise and (2) to identify barriers to entry and continuation of careers in biomedical research in the U.S. The first step in this process is to perform a study of the current environment and possible barriers to communication. Based on preliminary research, the study will support one or more planning conferences to focus efforts on potential methods to strengthen communication and future direction in concert with goals and objectives of the NIDDK Strategic Plan on Minority Health Disparities. Co-sponsorship of conferences will be sought from the NIH Office of Research on Minority Health and other NIH Institutes.

### **Background**

NIDDK's research mission includes many diseases and disorders that disproportionately affect African Americans, Hispanic Americans, American Indians, and Asian American and Pacific Islanders. Diabetes, obesity, hepatitis and kidney failure adversely impact the health, longevity, and quality of life of minority populations in the U.S. NIDDK's commitment to reducing the impact of health disparities among the majority and minority populations in the U.S. has been strengthened by two events at the start of the new millennium. In March 2000 the Institute completed its initial Strategic Plan on Minority Health Disparities. This trans-NIDDK effort to focus initiatives directed at diseases and disorders that affect minority populations was quickly followed by the establishment in July 2000 of the NIDDK Office of Minority Health Research Coordination in the Office of the Director, NIDDK. Central to the mission of this office is communication with the communities that will be affected by its actions in the biomedical research arena.

### **Research Goals and Scope**

The goal of the study is to provide specific data to support the establishment of the first NIDDK communications network aimed at individuals and institutions in the biomedical research enterprise that serve and represent minority populations in the U.S. The goal of the study will be supported by the following objectives: (1) surveying the existing environment surrounding participation of minority investigators in basic and clinical research and (2) using that information to develop a strategy to establish and strengthen two-way communication between NIDDK leadership and minority investigators.

## **7016 NIDDK STUDY TO IDENTIFY COMMUNICATION TECHNOLOGIES USED IN AFRICAN AMERICAN, HISPANIC AMERICAN, AMERICAN INDIAN AND ASIAN AMERICAN/PACIFIC ISLANDER POPULATIONS IN THE U.S.**

### **FY 2001 Action**

The NIDDK will sponsor a study and review of existing data and sources to demonstrate whether or to what degree there has been diffusion of new communication technologies into African American, Hispanic/Latino, American Indian and Asian and Pacific Islander populations. This information will be useful in planning and targeting outreach and education programs across Institute communication programs and is an initiative in the NIDDK Strategic Plan on Minority Health Disparities.

### **Background**

NIDDK uses a variety of techniques and tools to reach specific target audiences, including special populations. Social marketing research and the experience of other health communication and education efforts in government and the private sector provide information that helps determine likely strategies for information dissemination, outreach and education programs. Methods and materials are pre-tested with the target audience. Program evaluation of process and analysis of outcome measures give an indication of the degree of effectiveness of programs. Most programs use traditional media such as printed brochures, fact sheets, posters and kits; audiovisual materials such as 30 or 60 second public service announcements (PSAs) on television; pre-recorded or live announcer PSAs on radio; and toll-free telephone systems. In the past five years, however, the items in the toolbox have expanded to include Internet web sites, e-mail, portable computers, palm pilots and cellular telephones. Extensive philanthropic efforts by the high tech sector and the widespread use of technology in the U.S. educational system may have altered the environment, especially for minority youth. The rapid evolution of acceptance of new technologies generates a continuing need to reassess the communications climate.

### **Research Goals and Scope**

The goal of the study is to provide information that can be applied across all NIDDK communication programs for minority audiences to improve the efficiency and validity of the tools used to disseminate information to health professionals, patients, their families and the general public. This goal will be achieved by objectives such as the following: (1) performing a search for sources of Internet marketing data; (2) reviewing Internet tracking systems; (3) reviewing technology industry newsletters; (4) reviewing mass media publications aimed at special populations; and (5) producing a descriptive report of findings and an analysis of today's environment and projections for the next five years.

## **7017 INNOVATIVE GRANTS ON IMMUNE TOLERANCE (RFA AI-00-006)**

### **FY 2001 Action**

The National Institute of Allergy and Infectious Diseases and NIDDK are soliciting applications for exploratory/developmental research project grants to support novel work on the molecular mechanisms and applications of antigen-specific immune tolerance, which is the selective and long-term inactivation of immune responses. The projects should involve a high degree of innovation, and have a clearly articulated potential to improve understanding of immune tolerance. Investigators new to immune tolerance are particularly encouraged to develop projects in this area. Research projects will be supported by the exploratory/developmental research grant mechanism, which provides the resources to carry out preliminary tests of feasibility for new research hypotheses.

### **Background**

It would be extremely useful to treat autoimmune diseases, allergies and transplant rejection by selective inactivation of harmful immune responses, without inflicting global immune suppression. Recent advances in immunological research have produced a wealth of information on the cells and molecules involved in immunoregulation, identifying a variety of approaches to be tested for selective immune inactivation, or tolerance induction. Of particular note is the success achieved in defining certain mechanisms by which antigen-specific immune tolerance can be induced in animal model systems. Some of these mechanisms are now being tested in human autoimmune disease and organ transplantation. There is still a strong need to develop new concepts and practical approaches for tolerance induction, because it is likely that a variety of protocols will be needed to control the broad range of immune-mediated diseases that exist in humans.

Immune-mediated diseases afflict many millions of individuals and often involve serious recurring or long-term chronic illness. As highlighted by recent success in inducing long-term transplant tolerance in non-human primates, very promising opportunities and important challenges exist to develop effective protocols for the antigen-specific prevention, or even reversal, of detrimental immune responses in human allergy, asthma, autoimmune disease and transplantation. The application of new technologies such as soluble MHC-peptide reagents, the ability to conduct single cell assays, and progress in the genetic manipulation of normal cells, offers opportunities for more definitive analyses of the human immune system and for the construction of experimental animal systems that more directly model human clinical situations.

### **Research Goals and Scope**

The goal of this initiative is to support truly innovative projects on immune tolerance and to encourage investigators working in other areas of research to bring novel perspectives and expertise to this field. High-risk, high-impact projects are sought that have the potential to significantly increase our understanding of the mechanisms that induce long-lived, antigen-specific immune tolerance for application to human disease. Studies relevant to the etiology and/or treatment of type 1 diabetes are of particular interest to the NIDDK. Studies on HIV/AIDS are excluded from this program.

Exploratory/developmental research grants (R21) will be used to provide funds to develop preliminary studies of a very speculative nature. The application does not need to include preliminary data. Within the two-year funding period, it is expected that successful projects will yield sufficient data to support a well-planned and rigorous future grant application to continue the work by competing within the general pool of unsolicited applications.

Highly innovative, short-term pilot projects to evaluate new, but as yet speculative, concepts in immune tolerance may include, but are not limited to, research in the following areas: (1) the mechanistic basis for differences in tolerance induced by systemic versus mucosal routes; (2) the identification and characterization of promising new T or B cell molecular targets for tolerance induction; (3) the parameters of tolerance induction to non-peptide self antigens, alloantigens, or allergens; (4) the molecular events responsible for the loss of tolerance to self antigens; (5) methods to extend the duration of antigen-specific tolerance; (6) novel technologies to identify and quantitate tolerant T or B cells; (7) the development or application of cell and tissue engineering methods to predictably induce tolerance rather than immunity; (8) the characterization of novel, antigen-specific immunosuppressive cell types; (9) the identification of mechanisms by which currently known tolerogenic biological or pharmaceutical agents induce and maintain immune tolerance; (10) the development of simple and reliable assays for the identification of tolerant states in humans; and (11) the development of "vaccine" strategies to induce antigen-specific tolerance to disease-related autoantigens or allergens.

## **7018 HYPERACCELERATED AWARDS IN IMMUNOMODULATION (RFA AI-00-005)**

### **FY 2001 Action**

The National Institute of Allergy and Infectious Diseases (NIAID), the National Institute on Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the NIDDK, the National Heart, Lung and Blood Institute, the National Institute of Neurological Disorders and Stroke, and the Office of Research on Women's Health of the NIH invite investigator-initiated research applications for mechanistic studies in clinical trials of immunomodulatory interventions for immune system mediated diseases, including, but not limited to, asthma and allergy, graft failure in solid organ, tissue, cell and stem cell transplantation, and autoimmune diseases. This initiative focuses on the inclusion of patients and utilization of patient samples for the evaluation of immunologic and other relevant parameters to facilitate the study and definition of immunological mechanisms underlying the intervention, the mechanisms of disease pathogenesis, surrogate markers of disease activity and therapeutic effect, and mechanisms of human immunologic function. The parent or core clinical trial must have independent financial support and will NOT receive support under this Request for Applications (RFA). Proposed mechanistic studies associated with clinical trials supported by industry are particularly encouraged but clinical trials supported by any source, public or private, are eligible.

In order to review and confer awards to applications received in response to this RFA in a timely fashion without delay of the parent or core clinical trial, NIAID has developed a pilot project in collaboration with the Center for Scientific Review (CSR): "NIAID/CSR Pilot of Hyperaccelerated Review/Award." All applications responding to this RFA will be subject to this hyperaccelerated review/award process. Highly meritorious applications selected for funding under this RFA will receive their awards thirteen weeks after the application receipt date.

### **Background**

In December 1996, NIAID convened a workshop at which leading basic and clinical immunologists discussed the role the NIH should play in current and projected clinical trials for various immune mediated diseases. It was considered likely that clinical trials of many new immunologic interventions would be supported by the pharmaceutical/biotechnology industry. However, gaps in both knowledge and in research efforts were identified which represent opportunities for the NIH to contribute to progress in this area.

There was agreement that the mechanisms underlying immunologic interventions are poorly understood even in cases where efficacy has been shown (e.g., allergen immunotherapy and IFN beta treatment for multiple sclerosis). In addition, clinical trials supported by industry and other sources including NIH often do not include studies of underlying mechanisms. There was consensus that high priority should be given to the utilization of patient samples from clinical trials in immunologic diseases for studies of

the basic underlying mechanisms of therapeutic effect, immunologic function, and disease pathogenesis.

There was also agreement that the usual time required for grant review and funding is often incompatible with the time line of a clinical trial. Specifically, when a clinical protocol is finalized (which is required for applications submitted under this RFA), investigators are often ready to begin as soon as Institutional Review Board approval is obtained. NIAID was encouraged to develop a means of responding rapidly to opportunities to study underlying mechanisms in order to facilitate collaborations with industry-supported clinical trials.

### **Research Goals and Scope**

The objective of this initiative is to support mechanistic research studies in clinical trials of immunomodulatory interventions for immune system mediated diseases, including asthma and allergy, graft failure in solid organ and stem cell transplantation, and autoimmune diseases. Specifically, the goal is to utilize patients and patient materials from such trials for the evaluation of immunologic and other relevant parameters in order to study the underlying mechanisms of the intervention, the mechanisms of disease pathogenesis, surrogate markers of disease activity and therapeutic effect, and mechanisms of human immunologic function. Such studies are not part of the parent or core clinical trial, and are commonly referred to as sub-studies or ancillary studies. The parent or core clinical trial must have independent financial support and will NOT receive support under this RFA. Clinical trials supported by any source, public or private, are eligible.

## **7019 TECHNICAL SUPPORT SERVICES FOR THE NIDDK EPIDEMIOLOGY COORDINATING COMMITTEE**

### **FY 2001 Action**

This RFA will solicit epidemiologic, biostatistical, and computer programming support for the NIDDK Epidemiology Coordinating Committee, representing the three divisions of NIDDK. This activity is a continuation of the services that have been supported by a contract for the past five years.

### **Background**

The NIDDK Epidemiology Coordinating Committee provides overall direction and coordination of NIDDK activities pertaining to the epidemiologic and public health aspects of diseases under the purview of the NIDDK. The Committee members conduct original scientific research in order to develop new knowledge on epidemiologic and public health aspects of these diseases. The results of this research are published in the medical literature, form the basis for the NIDDK's documentation of the scope and impact of these diseases, and are incorporated into NIDDK reports to the lay, medical, and scientific communities.

These activities have been supported by a technical services contract for the past five years. The proposed contract would continue support for the research activities of the Committee by providing technical resources for this research, which will enhance our understanding of the NIDDK diseases and develop new data to document the incidence and prevalence of these diseases and conditions in the general U.S. population; define specific demographic segments of the population that are increased risk for development of these diseases; identify etiologic determinants and risk factors for development of these diseases; determine the natural history of the diseases in the general population and in specific subpopulations; quantify risk factors for morbidity and mortality that might be amenable to control and prevention; document forms and sources of medical treatment including drugs, physician's services, and hospital care; quantitate the impact of these diseases on the U.S. medical care system; and define disability and death accountable by these conditions.

### **Research Goals and Scope**

The technical support services will involve three major areas: (1) data management and data processing support in analysis of complex biomedical datasets, including development and maintenance and documentation of computer files, merging files and creating subfiles, and statistical computer-based analyses; (2) epidemiologic and biostatistical consultation in assessment and analysis of data relating to the various diseases under the purview of NIDDK. Data sources include particularly the complex data files based on surveys of the National Center for Health Statistics but will also include other appropriate data files relating to NIDDK research interests; and (3) preparation of technical reports on these analyses. These include reports containing details of files procured, new files developed, and file management. They also include detailed reports on scientific analyses arising from the data files, including discussion of

the pertinent published literature and scientific assessment of analysis results as they relate to current knowledge of disease conditions related to NIDDK.

## **7020 CENTER FOR INHERITED DISEASE RESEARCH (CIDR) MEMBERSHIP**

### **FY 2001 Action**

The NIDDK proposes to join the Center for Inherited Disease Research (CIDR) consortium for human and mouse genotyping. A trans-Institute working group that evaluated this question concluded that membership in this consortium would facilitate access of our investigators to high quality genotyping, encourage genetic research by our research communities and facilitate data integration between studies done at several sites. We anticipate that several major applications to utilize CIDR genotyping will emerge from large genetic studies supported by the Institute.

### **Background**

The CIDR is a centralized facility established to provide genotyping and statistical genetics services for investigators seeking to identify genes that contribute to human disease. Beginning in FY 2000, mouse genotyping services have also been offered. CIDR concentrates primarily on multifactorial hereditary disease although linkage analysis of single gene disorders is accommodated. CIDR was established in 1996 as a joint effort by eight Institutes. Three additional Institutes joined the effort in 1999, and by joining in FY 2001; the NIDDK will become the twelfth Institute to join.

Advantages of NIDDK membership include potential access for NIDDK investigators of high quality genotyping and the likelihood that availability of access to a genotyping facility may encourage genetic research. The goals outlined in the NIDDK Strategic Plan included an emphasis on identifying genes that contribute to multifactorial disease, and CIDR membership will facilitate that goal. Finally the availability of a centralized genotyping facility facilitates data integration; such integration is critical for progress in study of polygenic disease. Genome wide screens performed in individual laboratories use different marker sets and are not of as consistent quality, and integration of such information typically proves problematic.

### **Research Goals and Scope**

CIDR is available to all investigators through competitive peer review by a chartered CIDR Access Committee (CAC). CIDR carries out high throughput, genome wide scans using samples provided by principal investigators. CIDR utilizes automated fluorescent microsatellite analysis using a marker set at approximately 10 cM average spacing appropriate for parametric and non-parametric linkage analysis.

## **7021 FETAL ORIGINS OF ADULT DISEASE (RFA HD-00-021)**

### **FY 2001 Action**

The purpose of this solicitation is to determine the mechanisms by which the intrauterine environment programs fetal metabolism to predispose individuals to chronic disease later in life and to determine whether these mechanisms may contribute to disparities in the prevalence of obesity, diabetes, hypertension, atherosclerosis, and asthma among various races and ethnic groups. The National Institute of Child Health and Human Development, National Heart, Lung and Blood Institute, NIDDK, and the National Institute on Aging seek to encourage research on the basic mechanisms that may explain the lifelong consequences of intrauterine growth retardation and/or exposure to deficient and/or stressful intrauterine environments.

### **Background**

Epidemiological studies suggest that many diseases prevalent in adult life, including obesity, hypertension, stroke, type 2 diabetes, coronary artery disease and asthma, may result in part from interactions of the fetus with its intrauterine environment. Based on these observational studies, it has been suggested that metabolic programming occurs during fetal life in response to intrauterine growth constraints, and/or exposure *in utero* to deficiencies or surfeits of nutrient substrates, oxygen, hormones, growth factors, and cytokines. While epidemiological studies have identified the phenomenon of metabolic programming, little is known about the mechanisms by which fetal insults lead to disease later in life.

At the most general level metabolic programming represents a fetal response to accommodate an inimical intrauterine environment in order to optimize chances for fetal survival. In its drive for survival the fetus appears to favor the metabolic demands of the growing brain over the metabolic demands of the kidneys, liver, muscle, pancreas, and other organs. The molecular mechanisms that govern this phenomenon are unknown and need to be elucidated, especially since the intrauterine survival advantage gained by this maneuver may entail a cost of metabolic impairment and chronic disease later in life. For example, deprivation of intrauterine nutrient supply to the kidney may result in fewer nephrons than normal with a reduced filtration capacity, paving the way for hypertension later in life. Similarly, impaired substrate supply to the pancreas during fetal development may result in a smaller than normal beta cell mass leading to glucose intolerance later in life. Whether, in fact, these intrauterine accommodations lead to chronic disease later in life remains to be established. Other mechanisms beside blood flow redistribution may account for the observed associations between low birth weight and chronic disease later in life. The fetal metabolic response to the intrauterine environment, including stress or nutrient restriction, needs to be studied in depth. In order to do so, more precise predictors of chronic disease are needed than the anthropometric markers currently in use, such as birth weight, birth length, and ponderal index. Biochemical or genetic markers, which need to be determined, may more accurately reflect fetal metabolic programming and predict chronic disease and health disparities later in life.

**Research Goals and Scope**

Research studies are requested on, but are not limited to, the following topics: (1) to identify biochemical and genetic markers during fetal and early postnatal life for prediction of risk for chronic disease and disabilities later in life; (2) to elucidate the effect of psychosocial stress during pregnancy on fetal growth, metabolism, neuroendocrine development, and behavior later in life; (3) to ascertain the mechanisms by which the fetus senses an intrauterine environment that is deleterious for brain development and responds by shunting blood away from other organs to the brain; (4) to elucidate the maternal-fetal origins of immune responses that predispose to allergies, asthma, and autoimmune disease later in life; and (5) to develop interventions designed to mitigate the metabolic derangements associated with intrauterine growth retardation and its consequences for adult disease later in life.

## **7022 NIDDK BIOTECHNOLOGY CENTERS**

### **FY 2001 Action**

The purpose of this initiative is to make comprehensive gene expression technologies widely available to researchers working in areas supported by NIDDK. This initiative will establish Biotechnology Centers that will provide genomic profiling resources to investigators working in research areas within the NIDDK's mission.

### **Background**

The tremendous acceleration in pace of scientific discovery over the last decade, coupled with development of many new high-throughput technologies, has created an era of unparalleled opportunity to uncover the causes of disease and identify effective therapies. In particular, the Human Genome Project and related efforts to identify at least some unique pieces of all expressed genes (expressed sequence tags, ESTs) in the human genome has resulted in an explosion of data and potential tools that will aid research in virtually all fields of medicine. The recent development of genome-wide expression profiling (chip, microarray or Serial Analysis of Gene Expression [SAGE] technologies) allows a comprehensive high-throughput screening of the effects of an insult (genetic, physiologic, pathologic, etc.) on gene expression in tissues and specific cell populations of interest. These techniques may aid in determining the function of a newly discovered gene or discovering new biomarkers and therapeutics for patients with disease. Many investigators with hypothesis-driven research programs want access to emerging technologies. Cost is a major obstacle to the application of these techniques by large numbers of investigators. The investment required to obtain essential equipment and personnel to establish this technology is more than can easily be borne by a single investigator.

### **Research Goals and Scope**

This initiative is intended to support the cost-effective introduction of techniques to measure patterns of gene expression in specific tissues of interest to the NIDDK-supported investigators. This initiative will allow the formation of support facilities that may include, but are not limited to:

A. cDNA Microarrays. The applicant might propose to print, read, and analyze microarrays. The arrays might contain mixtures of cDNAs obtained from commercial vendors, the Cancer Genome Anatomy Project (CGAP), or ESTs obtained locally and of specific interest to the investigators. It is anticipated that each printing unit will distribute arrays to 7 to 20 NIDDK investigators. Applicants are expected to identify the sources of the cDNAs, reference all genes to a genomic database (Entrez, UNIGENE, Locus Link, etc.), and indicate plans to distribute arrays to the NIDDK community at a reasonable cost. Applicants need not include budgets for equipment for printing or reading arrays or for bioinformatics support if they can obtain the necessary reagents or support from collaborative efforts or commercial sources.

B. Oligonucleotide Chips. The applicant might propose to produce, hybridize, read, and/or analyze gene chips from commercial or academic sources. Applicants are

expected to discuss the source and composition of the chips, and details of the bioinformatic support.

C. Serial Analysis of Gene Expression (SAGE). The applicant might propose to construct high quality cDNA libraries, link and sequence the SAGE tags, and analyze SAGE tags. Applicants are expected to discuss library quality, sequence fidelity, bioinformatic processing of SAGE tags, and statistical issues.

Creation and maintenance of these technologies may require the collaboration of investigators with expertise in many fields, such as molecular biology, robotics, bioinformatics, genomics, and statistics. In addition, key aspects of infrastructure may also be supported and might include the development and maintenance of appropriate databases and specialized equipment. It is important to emphasize that there are a variety of approaches to genome-wide expression analysis. Therefore, a given strategy must be rigorously justified and must demonstrate that all key personnel are involved in the formulation of the rationale and approach.

An objective of this initiative is to provide biotechnology support for both on-going and new hypothesis-driven research projects. Therefore, applicants will be required to describe projects that will benefit from these technologies.

## **7023 ADMINISTRATIVE SUPPLEMENTS FOR GENE PROFILING METHODS**

### **FY 2001 Action**

This initiative will make available administrative supplements to facilitate the development and application of microarray or other gene profiling technologies. The NIDDK ultimately wishes to facilitate wide dissemination of these methods and associated resources to NIDDK grantees. This administrative supplement program is designed to provide a temporary mechanism to enable NIDDK investigators to use comprehensive gene profiling methods.

### **Background**

The tremendous acceleration in pace of scientific discovery over the last decade, coupled with development of many new high-throughput technologies, has created an era of unparalleled opportunity to uncover the causes of disease and identify effective therapies. In particular, the Human Genome Project and related efforts to identify at least some unique pieces of all expressed genes (expressed sequence tags, ESTs) in the human genome has resulted in an explosion of data and potential tools that will aid research in virtually all fields of medicine. The recent development of genome-wide expression profiling (chip or microarray technologies) allows a comprehensive high-throughput screening of the effects of an insult (genetic, physiologic, pathologic, etc.) on gene expression in tissues and specific cell populations of interest. These techniques may aid in determining the function of a newly discovered gene or discovering new biomarkers and therapeutics for patients with disease. Many investigators with hypothesis-driven research programs want access to emerging technologies.

### **Research Goals and Scope**

There is no restriction on the type of gene profiling technology that the applicant may select. Examples of research areas appropriate to this announcement include, but are not limited to: (1) determination of global gene expression patterns and monitoring of changes under normal and experimental/pathological conditions; (2) identification of novel expressed sequence tags (ESTs) involved in normal function and pathogenesis of disease; (3) development of efficient experimental protocols for using cDNA arrays to study gene expression patterns in human or animal tissues, including methods to prepare hybridization probes from small pathology specimens, micro-dissected tissues, or single cells; (4) enhancement of currently available gene profiling analysis tools, including data tracking, image analysis, and bioinformatics tools; and (5) development of higher-order analysis tools and software algorithms to process gene expression data to predict gene-gene interactions and functional pathways.

## **7024 DEPRESSION IN DIABETES, RENAL DISEASE AND OBESITY**

### **FY 2001 Action**

Major depression is more common in patients with chronic diseases than in the general population. Significantly, individuals with diabetes and renal disease--chronic diseases of focus for the NIDDK--are at substantially higher risk for depression than the general population. As many as one in three patients with diabetes will have an episode of major depression at least once in his or her lifetime, and at any given time one in five patients with diabetes is affected with depression. Depression is a major risk factor for diabetes onset and its complications and has a role in the outcome of renal disease and obesity. The prevalence of depression in patients with end-stage renal disease is variably thought to be between 10 and 25 percent. The prevalence of the condition in patients with chronic renal insufficiency is unknown. Data are conflicting regarding the prevalence of depression among patients with obesity; however, it is clear that subsets of obese patients (such as those with binge eating disorder or severe obesity) are at increased risk. It is the purpose of this initiative to increase research on prevention and treatment of depression in diabetes and other NIDDK related chronic diseases. It is also of interest to further studies that elucidate the role of depression in the risk for the development of diabetes, renal disease and obesity.

### **Background**

Depression will be the second-leading cause of chronic disability worldwide during the first decades of the 21st century and currently, between 5 percent and 8 percent of the general population will have an episode of major depression at some time in their lives. Higher rates have been reported recently in younger individuals predicting a worsening prevalence of major depression as the population ages. Major depression is a debilitating condition that impairs individual functioning and dramatically worsens quality of life. It is now recognized that 85 percent of depressed patients exhibit chronic recurrence of the disease, with each new episode bringing increasing likelihood of chronicity, functional impairment and suicide. Of great public health importance, depression is three to four time more prevalent in patients with diabetes than in the general population, affecting 15 to 20 percent of patients with either type 1 or type 2 diabetes. Depression and diabetes as well as renal disease and obesity often occur together as co-morbid conditions, although one disorder can clearly be secondary to the other (such as depression developing as the result of life-threatening complications of diabetes). In addition, patients with chronic diseases such as diabetes not only have a higher incidence of depression, but these patients also have a high rate of recurrence following anti-depressive treatment and worsened health care outcomes. The costs in human suffering, loss of productivity and health care expenditures to the nation, as a result of both conditions occurring together, are magnified well beyond the cost of the individual conditions alone.

The co-morbid effects of depression on chronic disease outcomes have received relatively little research attention. Recent studies in patients with diabetes, however, have produced growing evidence that depressive disorders in adults are associated with worsened control of hyperglycemia. Treatment of depression using cognitive behavioral therapy in patients with type 2 diabetes has been shown to reduce the symptoms of

depression and to significantly improve glycemic control. Similar findings were found in a small-scale short-term study using antidepressant medication. Patients with diabetes and with end-stage renal disease with depression are more likely to be hospitalized than patients with selected other chronic illnesses. Depression has been associated with increased mortality in patients with end-stage renal disease, but there are very few interventional or mechanistic studies in this population. This initiative will promote further research in diabetes, renal disease and obesity associated with depression.

A working group of experts in depression, diabetes, obesity and renal disease was brought together by the NIDDK and the National Institute of Mental Health to develop a strategic plan for identifying research opportunities in the co-morbidity of depression and chronic disease of interest to each of the participant Institutes. This group called for increased research on: risk factors that increase the likelihood of co-morbidity and factors that are protective, the psychosocial and physiologic processes that contribute to co-morbidity and protection, and socioeconomic and racial/ethnic factors associated with increased risk.

### **Research Goals and Scope**

Poor glycemic control has been demonstrated to be associated with a high risk for complications. Depression in patients with type 1 or type 2 diabetes has been shown to be associated with poor glycemic control. The objective of this initiative is to initiate studies to focus on the co-morbid conditions of depression and diabetes, renal disease, or obesity, including:

- A. Does treatment of depression decrease morbidity/mortality in patients with diabetes, chronic renal disease or obesity? If so what mechanisms are functioning?
- B. What is the role of obesity in the depression/diabetes relationship?
- C. What are the physiologic pathways linking depression and chronic disease?
- D. Does treatment for depression prevent diabetes onset or diabetes complications?
- E. Examination of the role of metabolic abnormalities as risk factors in chronic disease and psychological disorders.
- F. Determination of the weighting of risk factors and comparison of various coping strategies in different chronic diseases of interest to the NIDDK.
- G. Based on controlled studies, it is known that diabetes doubles the likelihood of co-morbid depression. What are the mechanisms involved?
- H. What are the cultural and ethnic differences in manifestation and labeling of mental states such as depression, and how does this relate to the co-morbid conditions of diabetes, renal disease or obesity?

## **7025 SMALL GRANTS FOR SECONDARY ANALYSES OF DATA IN DIABETES, DIGESTIVE AND KIDNEY DISEASES**

### **FY 2001 Action**

The intent of this program announcement is to increase knowledge of the epidemiology of the disease areas of NIDDK through analyses of existing data sets.

### **Background**

NIDDK does not currently promote the analysis of existing data sets. Such analyses can be quite cost effective, as they typically require fewer resources provided for a shorter period of time than is needed in a full scale R01. Support is typically needed for a programmer and analyst for one to three years, depending upon the complexity of the analysis and the number of datasets.

### **Research Goals and Scope**

This Small Grant program would be designed to accomplish the following: support researchers interested in undertaking secondary analyses of data related to the epidemiology of disease areas of NIDDK; provide support for preliminary projects using secondary analysis that could lead to subsequent applications for individual research awards; provide support for rapid analyses of new databases and experimental modules for purposes such as informing the design and content of future studies; and provide support for publicly archiving datasets relevant to diseases areas of NIDDK, including both epidemiological studies and multi-center clinical trials. International comparative analyses would be encouraged. Applications that are innovative and high risk with the likelihood for high impact would be especially encouraged. The specific subject areas would be diabetes and metabolic diseases, digestive diseases and nutritional disorders, including obesity, and kidney, urological, and blood diseases.

## **7026 GENETIC MODIFIERS OF SINGLE GENE DEFECT DISEASES (RFA HL-01-001)**

### **FY 2001 Action**

The objectives of this Request for Applications (RFA) are to stimulate research to identify and characterize the modifier genes responsible for variation in clinical progression and outcome of heart, lung and blood diseases due to single gene defects. Identification of the genes responsible for these differences would lead to better understanding of disease pathogenesis, early diagnosis, and improved treatment.

### **Background**

All diseases are variable in their presentation due to differences in the genetic makeup and the environmental exposure of the affected individual. For disorders inherited in a Mendelian fashion, a single gene plays the predominant role in the development of a disease phenotype. However, phenotype variation occurs even among those who have identical genotypes at a disease locus. To further our understanding of the molecular basis of monogenic disorders, it will be necessary to find other genes that contribute to phenotype variability.

There are a number of heart, lung and blood disorders that are primarily due to alterations in a single gene. Examples include cystic fibrosis, alpha-1-antitrypsin deficiency, sickle cell disease, thalassemia, hemochromatosis, hemophilia, glucocorticoid remediable aldosteronism (GRA), Liddle's Syndrome and other hypertensive conditions, as well as cardiac myopathies, dysplasias, and arrhythmias that result in Sudden Cardiac Death. Although individuals may have single gene defects, there can be tremendous variation in the progression, complications and outcome of the disease (even in an extended family) that may be due to the interaction of the disease gene with other genes, impacting on the final disease presentation.

The genes responsible for a variety of inherited heart, lung and blood disorders have been identified using functional and positional approaches. Now the difficult process of finding the modifier genes and their relevant mutations must be undertaken. The number of biologically plausible candidate genes may be very large. As such, the search for genetic modifiers of Mendelian disorders will be similar to studies of complex genetic disorders such as asthma or hypertension. Association studies utilizing reasonable candidate genes or candidate loci offer valuable approaches to facilitate efforts to find the genes. The completion of the human genome project and the development of high-throughput technologies such as "gene chip" and streamlined SNP (single nucleotide polymorphism) analyses should greatly facilitate the search for genes that contribute to disease variability. The identification and characterization of modifier genes will clarify the process of pathophysiology, enable more accurate prognosis, early diagnosis, and may provide novel, and possibly, more accessible therapeutic targets, that are more useful than the gene primarily involved in causing the disease.

## **Research Goals and Scope**

This initiative is intended to solicit applications to identify the modifier gene or genes responsible for variation in the clinical progression and outcome of heart, lung, and blood diseases due to single gene defects (using state-of-the-art approaches including, but not limited to, genetic mapping, positional candidate cloning, positional cloning to narrow the region, computer cloning, and genomic technologies), to characterize the allelic variants of the gene(s) identified, and to demonstrate that the variation in the gene(s) is responsible for phenotype variation. Applicants must be able to demonstrate the availability of well-characterized families and/or well-defined genetic animal models of single gene disorders in whom some aspect of phenotype variability has been demonstrated to be inherited independent of the disease-causing gene.

Some research topics that will be responsive to this program are listed below. These are only examples; applicants are encouraged to propose other topics that address the overall goals of this initiative. The following are examples of research areas relevant to the objectives of this RFA:

A. Loci containing a modifier gene or genes have been mapped to multiple regions of the genomes of humans and animal models. Functional genomic approaches (using cDNA and oligonucleotide arrays) to identify differentially expressed genes, combined with classic genetic analysis and positional candidate approaches, can significantly enhance gene discovery efforts.

B. A variety of animal models have advanced our understanding of the pathogenesis of single gene disorders. Numerous murine strains, with well-defined genomes that exhibit a high degree of homology with the human genome, have considerable potential to provide insights into the presence and location of modifier genes. Thus, studies that explore the genetic basis of phenotype variation in animal models of monogenic human diseases are needed.

C. Identification of genetic modifiers in humans can be facilitated by detailed study of genetically related individuals. Analysis of concordant and discordant traits among affected family members can point to genetically determined aspects of phenotype variability.

D. Variation in proteins involved in molecular pathways affected by the dysfunction of a disease-causing gene is likely to influence pathogenesis. Critical members of a particular pathway may be excellent candidate modifier genes.

E. Even in the case of monogenic diseases, evidence suggests that the interactions of multiple genes result in expression of specific disease traits. Once polymorphisms relevant to phenotype have been identified in a modifier gene or genes, efforts should be directed at assessing interactions between the disease-causing gene and the modifiers.

F. Genotype/phenotype studies reveal the degree to which disease severity can be attributed to allelic differences or gene environment interactions.

## **7028 BIOENGINEERING RESEARCH PARTNERSHIPS**

### **FY 2001 Action**

This initiative invites applications for R01 awards to support Bioengineering Research Partnerships (BRPs) for basic bioengineering research addressing important biological or medical research problems. A BRP is a multidisciplinary research team applying an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose, and treat disease and understand health and behavior. The partnership must include bioengineering expertise in combination with basic and/or clinical investigators. A BRP may propose design-directed or hypotheses-driven research in universities, national laboratories, medical schools, private industry and other public and private entities.

### **Background**

Many of today's biological problems are too complex to be solved by biologists alone; partners are needed in many disciplines, including physics, mathematics, chemistry, computer sciences, and engineering. Bioengineering integrates principles from a diversity of fields. The creativity of interdisciplinary teams is resulting in new basic understanding, novel products, and innovative technologies. Bioengineering also crosses the boundaries of academia, science, medicine, and industry.

Recognizing the increasing importance of bioengineering in public health, the NIH established the Bioengineering Consortium (BECON) as a central focus for NIH bioengineering research. BECON held a two-day Bioengineering Symposium on February 27-28, 1998. A summary of the presentations and the conclusions of the panels are included in the full report which is available on the Internet at the following URL: (<http://grants.nih.gov/grants/becon/becon.htm>)

The discussions and recommendations of symposium participants aided in the formulation of the BRP and Bioengineering Research Grant (BRG) initiatives. For example, both the BRP and the BRG recognize that applications for bioengineering projects are often focused on technology development rather than on proving or disproving a scientific hypothesis. Therefore, the NIH review criteria for bioengineering applications submitted in response to these initiatives have been modified to ensure that these applications are evaluated appropriately and fairly.

### **Research Goals and Scope**

The goal of this initiative is to encourage research in selected basic bioengineering areas. Bioengineering is defined as follows: Bioengineering integrates physical, chemical, or mathematical sciences and engineering 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 biologics, materials, processes, implants, devices, and informatics approaches for the prevention, diagnosis, and treatment of disease, for patient rehabilitation, and for improving health.

Each BRP should bring together the necessary engineering, basic science, and/or clinical expertise to focus on a significant area of bioengineering research within the mission of the NIH. A BRP can vary in size and exhibit diverse forms of organization, participation, and operation. No single type of BRP fits the needs of every area. Rather, the size, structure, and operation of a BRP are determined by the proposed research.

## **7029 IMMUNE TOLERANCE NETWORK**

### **FY 2001 Action**

The Immune Tolerance Network (ITN) is a collaborative effort between the National Institute of Allergy and Infectious Diseases and the NIDDK. The ITN will solicit, develop, implement, and assess clinical strategies and biological assays for the purposes of inducing, maintaining, and monitoring tolerance in humans for kidney and islet transplantation, autoimmune diseases, and allergy and asthma.

### **Background**

Normal immune activation is the greatest barrier to graft survival in allogeneic organ, cell, and tissue transplantation. Most protocols in transplantation and autoimmune diseases include globally immunosuppressive agents, which are associated with increased risks of infection and neoplasia. Given such serious side effects, major research efforts to avoid the complications of immunosuppressive drugs are amply justified. One very attractive alternative is to redirect the immune system to establish antigen-specific tolerance to transplant antigens or to restore normal self-tolerance in autoimmune diseases.

Tolerance is defined here as a selective block in the immune response to particular antigens. Methods of tolerance induction include: (1) the deletion or specific inactivation (energy) of antigen-reactive lymphocytes; (2) altering profiles of cytokine secretion to prevent inflammation and injury; and (3) preferential induction of regulatory T cells or cytokines that inhibit destructive T cell functions. In animal models, these approaches have resulted in long-lasting, antigen-specific nonresponsiveness.

A solid experimental foundation already exists and many unique reagents are now available to support translational research and pursue promising clinical applications. The potential impact for human health is great, encompassing all allergic and immune-mediated diseases, allograft rejection, graft-versus-host disease, and responses to "neoantigens" introduced via gene therapy.

### **Research Goals and Scope**

The scientific goals of the ITN are to conduct clinical trials at all phases, to determine safety, toxicity, and efficacy of promising tolerogenic strategies in kidney and islet transplantation and autoimmune disease; to investigate the basic mechanisms of immune tolerance in these diseases as an integral part of clinical trials; to develop and/or refine and validate immune and surrogate marker assays to monitor the induction, maintenance, and loss of tolerance in these diseases; and to evaluate opportunities to extend the results of this research and promising externally-derived research to the problem of allergy and asthma.

The ITN will actively pursue tolerogenic research in four different but complementary components. These include clinical trials and mechanistic studies in kidney and islet transplantation; development and validation of assays to measure the induction, maintenance and/or loss of immune tolerance in humans; clinical trials and mechanistic

studies for autoimmune diseases; and clinical trials, mechanistic studies, and tolerance assay development and validation for asthma and allergic diseases.

## **7030 CLINICAL RESEARCH TRAINING IN MINORITY SERVING INSTITUTIONS**

### **FY 2001 Action**

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in collaboration with the NIH Office of Research on Minority Health (ORMH) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), invites Minority Serving Institutions with professional schools in one or more of the health care disciplines to apply for a planning grant to develop a Master of Clinical Research program. This solicitation is intended to stimulate the inclusion of high-quality, multidisciplinary didactic training as part of the career development of clinical investigators being trained in minority serving institutions. The planning grant (R21) supports the planning needed to begin development and/or improvement of core courses designed as in-depth instruction in the fundamental skills, methodology, theories, and conceptualizations necessary for the well trained, independent, clinical researchers.

### **Background**

As part of the effort of the Department of Health and Human Services to eliminate racial and ethnic disparities in health, a need has been identified to expand the training of clinical research at Minority Serving Institutions (MSIs) as one approach to fostering careers in clinical research addressing health disparities. MSIs conduct high quality programs for educating ethnic minorities, and they represent a rich resource of talent with the appropriate cultural sensitivity and perspectives needed in clinical research. However, MSIs have had difficulties developing and sustaining independent clinical research programs, and there is a paucity of ethnic minority clinical researchers who are pursuing successful clinical research careers. The NIDDK, ORMH, and NIAMS have teamed to promote the first step in fostering the development of curricula in clinical research leading to a masters degree in Clinical Research at MSIs through this one-year planning grant. This planning grant is seen as the first phase. The second phase, to be announced through an RFA in FY 2001, will provide support to assist in the actual development of the clinical research curriculum. The awards are planned for FY 2002.

### **Research Goals and Scope**

The planning grant will provide funds to enable MSIs to assess the resources; both at their home institution and potential affiliate institutions, for development of a masters degree curriculum in clinical research. The curriculum is to focus on clinical--patient or population-based--research. For the purpose of this award, clinical research includes: Patient-oriented research, epidemiological and behavioral studies, and outcomes or health services research. Patient-oriented research is defined as research conducted with human subjects (or on material of human origin, such as tissues and specimens), as well as research on cognitive phenomena, that requires direct interactions with human subjects. Patient-oriented research also includes the development of new technologies, understanding mechanisms of human disease, therapeutic interventions and clinical trials.

The core curriculum is to include an array of clinical research-related topics of general interest, such as biostatistics, bioethics, clinical trials design, and observational study

design. Other topics may include human genetics, pharmacology, patenting and material transfer agreements, as well as legal and social issues. The scope of the core curriculum can be flexible to meet the perceived needs of the institution.

## **7031 PHYSICAL ACTIVITY AND OBESITY ACROSS CHRONIC DISEASES**

### **FY 2001 Action**

NIDDK, in collaboration with NHLBI, NCI, NIA, NICHD, NIAMS, NINR, and NIMH invite applications from investigators for research studies that will address the relationship between physical activity and obesity. This Program Announcement is part of a trans-NIH Obesity Initiative, which also includes approaches to obesity prevention and the neuroendocrinology of obesity. Three general areas of research are encouraged: (1) studies (including observational and prospective) examining physical activity and obesity relationships; (2) studies to improve methodology of assessment of physical activity and energy balance; and (3) studies to test intervention approaches that incorporate physical activity for obesity prevention or treatment related to chronic diseases.

### **Background**

An estimated 97 million adults in the U.S. are overweight or obese (Body Mass Index {BMI; kg/M<sup>2</sup>}  $\geq 25.0$ ). According to numerous recent reports, the prevalence of overweight and obesity in the U.S. is increasing dramatically. Based on the BMI cut-point of 30.0, which defines obesity, 20 percent of men and 25 percent of women were obese in 1988-1994 (NHANES III) compared with 12 percent of men and 16 percent of women in 1971-74 (NHANES I).

Overweight is especially prevalent among certain racial and ethnic groups. For example, 66 percent of African American and Mexican American women are estimated to be overweight (NHANES III). Furthermore, the increasing prevalence of overweight is not limited to adults, but is observed in children, in both genders and in all subpopulations.

Morbidity associated with overweight and obesity is considerable. Obesity is a risk factor for type 2 diabetes mellitus and for cardiovascular disease as well as several other medical conditions. Overweight and obesity are also associated with increased morbidity and mortality from coronary heart disease and hypertension, and a relationship is seen between BMI and high blood cholesterol. These problems can be ameliorated, or sometimes reversed, through weight loss.

More research is needed on effects on body weight/obesity of different lengths of physical activity interventions, different formats and intensities of physical activity, and different forms of physical activity in combination with diet, as well as effects of physical activity on body fat distribution, e.g., abdominal fat. Research is needed on the effects of pharmacologic intervention for weight loss on cardiorespiratory fitness, and on environmental and population-based intervention methods for weight control that incorporate physical activity. These studies should address high-risk populations for obesity and low levels of physical activity including underserved population segments, e.g., minorities and low socioeconomic (SES) groups.

## **Research Goals and Scope**

A broad range of specific research questions and study approaches is relevant to this Program Announcement. The following are examples of research topics and study approaches that are relevant.

### Physical Activity and Obesity Relationships

- A. Studies to examine the relationships between type and amount of physical activity and dietary intake, including caloric expenditure, caloric intake and dietary macronutrient composition.
- B. Studies to examine the relationships between patterns of aerobic, anaerobic, and resistance exercise with body weight, body composition, and body fat distribution.
- C. Studies to examine interactions between the genetics of obesity and physical activity levels on obesity phenotypes.
- D. Studies to examine the psychological and quality of life benefits of physical activity.
- E. Studies to examine the determinants (personal, familial, cultural, environmental and policy) for engaging in and maintaining physical activity and good nutrition practices; particular attention can be paid to various subpopulations (defined by gender, age, ethnicity, and/or socioeconomic status) at possible risk for developing obesity.
- F. Prospective studies to examine tracking of dietary intake and eating behavior and physical activity patterns, and the relationships between the two from childhood to adulthood.
- G. Prospective studies to examine the relationship between physical activity and obesity or weight gain, particularly focusing on life stages where the risk of obesity development is highest (e.g., adolescence, menopause, older age).

### Assessment Methodology Studies

- A. Validation of improved methods for assessment of energy intake and expenditure and levels of physical activity, as well as improvement of measures in special population segments based on race/ethnicity and socioeconomic status.
- B. Improved methods for measuring skeletal muscle and adipose tissue metabolic processes in response to exercise.
- C. Improved methods for measuring the type (resistance vs. aerobic) and amount of physical activity behavior (frequency, intensity, duration), the energy cost associated with physical activity, energy intake, and energy balance.

D. Improved methods for measuring the impact--both positive and negative--of physical activity in subpopulations (defined by gender, age, ethnicity, socioeconomic status) on various outcomes such as quality of life.

E. Improved methods for assessment of energy metabolism, body fat, and body fat distribution, including visceral fat.

#### Intervention Studies

A. Test the effects on body weight/obesity of different lengths of physical activity interventions, different formats and intensities of physical activity, and different forms of physical activity in combination with diets, as well as, effects of physical activity on body fat distribution e.g. abdominal fat.

B. Examine the effects of physical activity patterns on changes in eating practices.

C. Determine the long-term effects of various approaches to physical activity interventions (including different behavioral approaches as well as different type and amount of physical activity) on weight loss and maintenance.

D. Examine the optimal mixture of physical activity and dietary intake for promoting weight loss and long-term maintenance of weight loss; examine whether increased physical activity alone or in combination with diet can prevent obesity or weight gain.

E. Develop/test interventions to increase physical activity and examine their effects on weight, on the changes in risk factors for obesity-related diseases, and on the use of health care services. These interventions can take place in a variety of settings, for example, health maintenance organizations, primary care practices, work sites, armed services, community groups, schools, etc.

F. Test the effects of environmental and population-based intervention methods for weight control, including those that incorporate physical activity.