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Report to Congressional Requesters

August 2010

NATIONAL INSTITUTES OF HEALTH

Awarding Process, Awarding Criteria, and Characteristics of Extramural Grants Made with Recovery Act Funding

GAO-10-848

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Highlights

Highlights of GAO-10-848, a report to congressional requesters

Why GAO Did This Study

The American Recovery and Reinvestment Act of 2009 (Recovery Act) included $10.4 billion in funding for the National Institutes of Health (NIH), an agency of the Department of Health and Human Services (HHS). Of the NIH Recovery Act funding, $8.2 billion was to be used to support additional scientific research and $400 million for comparative effectiveness research, including extramural research at universities and research institutions. NIH is comprised of the Office of the Director (OD) and 27 Institutes and Centers (IC), 24 of which make grant funding decisions.

GAO was asked to report on how NIH awarded Recovery Act funds for scientific research and the information that NIH made available about the award of these funds. This report describes the (1) process and criteria NIH used to award extramural grants using Recovery Act funding, and (2) characteristics of Recovery Act extramural grants and the information made publicly available about these grants. GAO interviewed NIH officials in the OD and the three ICs that received the largest proportion of Recovery Act funds, and reviewed related documents, such as NIH guidance on awarding grants using Recovery Act funds. GAO also obtained and analyzed NIH data on all Recovery Act grants awarded as of April 2010. Appendix I of this report contains information provided by NIH about 45 randomly selected nonrepresentative Recovery Act extramural grants, ranging from about $13,000 to about $7.2 million.

View GAO-10-848 or key components. For more information, contact Linda T. Kohn at (202) 512-7114 or kohnl@gao.gov.

What GAO Found

NIH used its standard review processes—peer review, which comprises two sequential levels of review by panels of experts in various fields of research, or administrative review—to award extramural grants using Recovery Act funds. These standard review processes were used for three categories of extramural grant applications: (1) new grant applications from Recovery Act funding announcements; (2) existing grant applications that had not previously received NIH funding; and (3) administrative supplements and competitive revisions to current active grants. For new grant applications submitted in response to Recovery Act funding announcements, NIH followed its standard peer review process. For existing grant applications, which had already undergone the peer review process, each of the three ICs GAO reviewed—National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID), and National Heart, Lung, and Blood Institute (NHLBI)—selected additional applications for Recovery Act funding based in part on the amount of this funding available to each IC. To award administrative supplements, NIH conducted its standard administrative review at the IC level, and for competitive revisions NIH followed its standard peer review process. In reviewing applications, NIH used its standard criteria—scientific merit, availability of funds, and relevance to scientific priorities—plus three criteria for Recovery Act grants. These criteria were the geographic distribution of Recovery Act funds, the potential for job creation, and the potential for making scientific progress within a 2-year period.

NIH's Recovery Act grant awards varied across three grant categories and other characteristics, and NIH made a variety of information about the grants publicly available. NIH data show that as of April 2010, about $7 billion of the $8.6 billion in Recovery Act scientific research and comparative effectiveness research funds had been awarded for 14,152 extramural grants. NIH awarded nearly $2.7 billion to make extramural grants for existing grant applications that had not previously received funding, slightly over $2.4 billion for new grant applications, and about $1.9 billion for administrative supplements and competitive revisions. NIH officials reported that the remaining Recovery Act scientific research funds will be awarded by the end of fiscal year 2010. At the three ICs GAO reviewed, the distribution of Recovery Act funds to the three categories of Recovery Act extramural grants varied significantly. For example, GAO found that as of April 2010, NIAID used 69 percent of its Recovery Act funds for existing grant applications that had not previously received NIH funding, while NCI used 31 percent for these existing grant applications. The average NIH Recovery Act extramural grant award was about half a million dollars, and about 25 percent of grantees were awarded $623,000 or more. Through NIH's Web sites, NIH and the ICs communicated a variety of information to the public about Recovery Act extramural grant awards, such as information about grantees and awarding ICs.

HHS provided technical comments on a draft of this report, which GAO incorporated as appropriate.

Contents

Abbreviations

CER	comparative effectiveness research
GO	Grand Opportunity
HHS	Department of Health and Human Services
IC	Institutes and Centers
IDeA	Institutional Development Award
NCI	National Cancer Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OD	Office of the Director
Recovery Act	American Recovery and Reinvestment Act of 2009
RePORT	Research Portfolio Online Reporting Tools

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United States Government Accountability Office
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August 6, 2010

The Honorable Mitch McConnell
Republican Leader
United States Senate

The Honorable Joe Barton
Ranking Member
Committee on Energy and Commerce
House of Representatives

Among its many provisions, the American Recovery and Reinvestment Act of 2009 (Recovery Act)[1] provided funding for investments in science and health at the National Institutes of Health (NIH), an agency of the Department of Health and Human Services (HHS) that is the primary federal agency for supporting medical research in the United States. The Recovery Act designated a total of $10.4 billion for NIH, with $8.2 billion of that amount to be used to support additional scientific research, including extramural grants, which support scientific research at universities, medical schools, and other research institutions. Included in the $10.4 billion was $400 million to be used to fund comparative effectiveness research (CER).[2]

NIH comprises 27 Institutes and Centers (IC) and an Office of the Director (OD). Twenty-four of the 27 ICs fund extramural research, and these ICs have their own budget, mission, and staff and focus on particular diseases or research areas, such as cancer or aging issues. Through its ICs, NIH funds extramural research each year using annual—non–Recovery Act—appropriations.[3] For fiscal year 2009, NIH awarded about $24 billion in

[1]Pub. L. No. 111-5, 123 Stat. 115 (2009).

[2]The remaining $1.8 billion in Recovery Act funding was designated for repairs, improvements, and construction, as well as scientific equipment. The Recovery Act appropriated $700 million for CER to the Agency for Healthcare Research and Quality, $400 million of which was required to be transferred to NIH's Office of the Director (OD). According to NIH officials, these funds are managed centrally by the NIH OD and coordinated with additional CER funding within HHS. CER compares the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions.

[3]The fiscal year 2009 appropriations for NIH totaled $30.5 billion, of which more than 80 percent was used for funding extramural research.

extramural funding from its annual appropriations. In awarding these funds, NIH follows a process of peer review—by panels of experts—required by law and NIH policy and generally bases its decisions on criteria such as scientific merit, relevance to the IC's scientific priorities, and availability of funds.

The Recovery Act included an appropriation to the OD to support NIH's scientific research, but provided that most of the funding be transferred to the ICs in proportion to the appropriation each IC received for fiscal year 2009.[4] NIH is required to use its Recovery Act funding within a 2-year window—specifically, in fiscal years 2009 and 2010.[5] Within these limitations, NIH has discretion regarding how to use the funding and what grants to award with it.

Congress included numerous transparency provisions in the Recovery Act, so that the public can see how its money is being spent and what is being achieved. You requested that we report on how NIH awarded its Recovery Act funds and identify information that NIH has made publicly available about these awards. This report describes (1) the process and criteria NIH used in fiscal years 2009 and 2010 to award extramural scientific research grants with funding made available by the Recovery Act and (2) the characteristics of the extramural scientific research grants NIH awarded using the Recovery Act funding and the information NIH has made publicly available about these extramural grants.

To identify the process and criteria NIH used for awarding extramural scientific research grants[6] through funding made available under the Recovery Act, we reviewed the Recovery Act for criteria on awarding

[4]The Recovery Act also provided for the transfer of funds to the Common Fund, which is located within the OD and supports crosscutting, trans-NIH programs that require participation by at least two ICs or would otherwise benefit from strategic planning and coordination.

[5]Pub. L. No. 111-5, § 1603, 123 Stat. 115, 302 (2009). While NIH must obligate all Recovery Act funds by the end of fiscal year 2010, the project end dates may occur after fiscal year 2010. As with other grants, Recovery Act grants are generally funded in annual increments—called budget periods—over the course of the length of the project—called project periods. Funding for each budget period is contingent on the availability of funds and satisfactory progress of the project.

[6]For this report, we use the term "extramural grants" or "extramural research" when referring to NIH extramural scientific research grants. We excluded from our analysis grants or contracts awarded by NIH for repairs, improvements, and construction, as well as scientific equipment.

Recovery Act funds. We also reviewed guidance and other relevant documents identified by NIH officials, as well as guidance and other policies posted on NIH's internal and Internet Web sites. We reviewed the specific process and criteria used at three ICs—National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID), and National Heart, Lung, and Blood Institute (NHLBI). These ICs were selected because they received the largest proportions of Recovery Act funding designated to support scientific research, not including repairs, improvements, and construction, as well as scientific equipment.[7] We also interviewed NIH officials with the OD, NIH's Office of General Counsel, and the three selected ICs about Recovery Act grant award processes and criteria.

To provide information on the characteristics of the extramural research grants funded by the ICs for fiscal years 2009 and 2010 using Recovery Act funding, we obtained from NIH data on all grants that have been awarded using Recovery Act funds as of April 2010. The data covered grants awarded by each of the ICs that received Recovery Act funds and the OD.[8] The data included grant characteristics such as the awarding IC, the grant award size (in dollars), and the institution receiving the grant.[9] We analyzed the data to determine, among other things, the amount of Recovery Act extramural research funds awarded by each of the ICs and the geographic location of grantees, as well as the average dollar amount of extramural grant awards (including the amount of funds NIH has committed to grantees), and the number of extramural grants awarded. In cases where Recovery Act funds appropriated to and retained in the OD were used for extramural grants that were administered by an IC, we classified the grant and associated funding under the administering IC. To provide more information about the extramural grants awarded through the Recovery Act, we selected a sample of 15 extramural grants awarded with Recovery Act funds from each of the three ICs we reviewed (for a total of 45 grants). These 15 grants were randomly selected from the

[7]NCI, NIAID, and NHLBI received about 15 percent, 14 percent, and 9 percent of the Recovery Act scientific research funds, respectively.

[8]Twenty-four ICs and the OD, including the Common Fund, received Recovery Act funds. Three centers do not fund extramural scientific research and did not receive funding (Center for Scientific Review, Center for Information Technology, and the Clinical Center).

[9]For this report, grant award refers to Recovery Act funds that had been awarded by NIH to grantees in fiscal years 2009 and 2010, as well as funds that have been committed, that is, expected to be awarded in future years subject to the availability of funds and satisfactory progress of the project.

different categories of grant applications received by the ICs. The number of grants selected in each grant category was in proportion to the amount of Recovery Act funding awarded for each category by the IC, and are not representative of all Recovery Act extramural grant awards. Appendix I of this report includes specific details about these 45 extramural grants. To determine what information NIH made publicly available[10] about the extramural grants funded through the Recovery Act, we reviewed NIH's Web site and the Web sites of the three ICs for Recovery Act grant award information. We also interviewed NIH officials to identify the information about Recovery Act grant awards made publicly available by NIH and reviewed related documents.

To ensure that the data provided by NIH were sufficiently reliable for our analyses, we obtained information from agency officials knowledgeable about NIH extramural grant award data. We also performed data quality checks to assess the reliability of the Recovery Act extramural grants data file received from NIH. These data quality checks involved an assessment to identify incorrect and erroneous entries or outliers.[11] Based on the information we obtained and analyses we conducted, we determined that the data were sufficiently reliable for the purposes of this report. We conducted this performance audit from December 2009 to August 2010, in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

[10]For this report, the term "publicly available" information refers to information disseminated on NIH's and the three ICs' Internet Web sites. NIH uses its Web site as its primary means of communicating information about grants.

[11]For example, to avoid the potential for double counting we removed three records for grants awarded in fiscal year 2009 that contained separate award actions for the same grant in fiscal year 2010. We removed one grant record because it reflected the fact that the grant recipient transferred from one university to another. We also compared the data from a random sample of grants in the data file to the same grants in a publicly-available data file for accuracy.

Background

NIH's extramural research funding efforts reflect its large, decentralized organization.[12] Twenty-four of the 27 ICs fund extramural research, each with a separate appropriation,[13] and these ICs make final decisions on which extramural research projects to fund following a standard peer review process defined by law and NIH policy. As the central office at NIH, the OD establishes NIH policy and is responsible for overseeing the ICs, including their extramural research funding efforts, to ensure that ICs operate in accordance with NIH's policies.

NIH's Standard Process and Criteria for Awarding Extramural Grants

NIH is required by law to use a peer review system in its process for making extramural grant awards.[14] In September 2009 we described this peer review system[15] as two sequential levels of peer review by panels of experts in various fields of research that help NIH identify the most promising extramural grant applications to fund, as defined primarily by an assessment of the applications' scientific merit.[16]

Initial peer review groups conduct NIH's first level of peer review. These groups review the applications assigned to them and assess their scientific merit, using criteria that require reviewers to examine such components as a grant application's design and methodology, innovation, and scientific significance.[17] Using these criteria, the initial peer review groups assign a

[12]NIH also supports intramural research, which is performed by NIH scientists in NIH laboratories.

[13]The three centers that do not fund extramural scientific research and do not receive separate appropriations (Center for Scientific Review, Center for Information Technology, and the Clinical Center) are funded through the NIH Management Fund, which is funded using a portion of other NIH appropriations. See 42 U.S.C. § 290.

[14]See 42 U.S.C. §§ 282(b)(9) (the Director of NIH must ensure that NIH research undergoes peer review and advisory council review); 289a(a) (peer review); 289a-1(a)(2) (advisory council review).

[15]GAO, *National Institutes of Health: Completion of Comprehensive Risk Management Program Essential to Effective Oversight*, GAO-09-687 (Washington, D.C.: Sept. 11, 2009).

[16]See 42 C.F.R. § 52h.7 (2009).

[17]Peer review groups are to assess each proposed research project taking into account the following criteria, among other pertinent factors: (a) its significance, (b) the adequacy of its approach and methodology, (c) its innovativeness and originality, (d) the qualifications and experience of its principal investigator and staff, (e) the scientific environment and reasonable availability of resources for it, (f) the adequacy of its plans to include both genders, minorities, children, and special populations as appropriate for its scientific goals, (g) the reasonableness of its budget and duration, and (h) the adequacy of its protections for humans, animals, and the environment. 42 C.F.R. § 52h.8 (2009).

priority score[18] to the applications they review, which are used to rank the applications from among those in the cohort of applications. After the applications are scored and ranked, the information is forwarded to the appropriate IC—based on the applications' proposed area of research—for the second level of peer review.

Each IC that funds extramural research has its own advisory council,[19] which conducts the second level of NIH's peer review.[20] Advisory councils consist of no more than 18 voting members, two-thirds of whom are scientists in the research areas of the IC and one-third of whom are leaders of nonscience fields.[21] Under law and NIH policy, the advisory councils are responsible for reviewing the applications and their priority scores and, based on this review, recommending or not recommending to the ICs certain applications for funding consideration.[22] The advisory councils' recommendations conclude NIH's peer review process.

After NIH's peer review process has been concluded, the director of each IC is responsible for considering the recommendations of the advisory council and for making final extramural funding decisions.[23] In general, NIH makes extramural grant award decisions based on scientific merit,

[18]For this report, we use the term "priority score" to refer to the NIH impact/priority score. NIH began using the term impact/priority score to reflect changes to its scoring system implemented in 2009.

[19]For this report, we use the term "advisory council" to refer to an advisory council or board.

[20]42 U.S.C. § 284a. Although the law setting forth the requirements for advisory councils is specific to institutes, each center that funds extramural research has an advisory council substantially similar to those of the other institutes. See 42 U.S.C. §§ 287a (National Center for Research Resources), 287c-21(b) (National Center for Complementary and Alternative Medicine).

[21]Advisory councils also include ex officio members, who are nonvoting. Voting members generally serve 4-year terms. At the NCI, the President appoints voting advisory council members, and the members serve 6-year terms. For all other advisory councils, the Secretary of the Department of Health and Human Services appoints voting members.

[22]According to NIH officials, the advisory council may concur with the initial peer review group's assessment, may decide not to recommend an application, or may recommend deferral of an application and refer it back to the initial peer review group for re-review.

[23]NIH may not approve or fund any application unless it has been recommended for approval by a majority of the members of the initial peer review group and a majority of the voting members of the advisory council. The initial peer review groups recommend applications for approval by means of the scoring system. 42 U.S.C. § 289a-1(a)(2).

relevance to the IC's scientific priorities, and the availability of funds appropriated to each IC. As noted previously, the scientific merit of extramural grant applications is determined by NIH's peer review system and reflected in the applications' priority scores. Each of the ICs focuses on specific scientific priorities. To aid in grant funding decisions, each IC establishes a funding line—known as the payline—which is determined by the number of extramural grant applications the IC anticipates funding that year. The payline for any given year is based on projections of the total funding available at the IC that year for grants, the average dollar amount expected to be awarded per application, and the number of applications received by the IC. While IC directors typically fund applications that fall within the payline, they are not required to fund applications based strictly on the applications' priority scores or the payline.

After the ICs determine which extramural grant applications to fund, they must also determine the specific award amount and the length of the grant project. Determining the specific award amount may involve negotiation between NIH and the grant applicant, as well as the submission of additional documentation by the grant applicant prior to awarding the grant. For example, NIH may ask an applicant to reduce the scope and the proposed budget for the grant application if the IC does not have sufficient funds to provide 100 percent of the funding requested by the grant applicant. NIH grants may be funded for up to a 5-year project period, with funding for each year contingent on the availability of funds and satisfactory progress of the project.

Administrative Supplements and Competitive Revisions to Existing Extramural Grants

NIH's ICs may provide additional funding to current active grants through both administrative supplements and competitive revisions. The ICs award administrative supplements using an administrative review process at the IC level. Administrative supplements award additional funds during the current project period to an existing extramural grant award that was previously peer reviewed—for example, by allowing grantees to add personnel or purchase additional equipment. All additional costs must be within the scope of the peer reviewed and approved project. Competitive revisions are funds added to existing extramural grant awards in order to support new research objectives or other changes in scope. Like the original grant award to which they are added, competitive revisions are awarded using NIH's peer review process.

Historical Funding of NIH non–Recovery Act Extramural Grant Applications

In fiscal year 2009, NIH received over 26,000 non–Recovery Act grant applications for R01-equivalent grants—R01 grants are the most common type of extramural grant applications—and 22 percent of these applications were funded for an average of $391,000. NIH awards grants in all 50 states, Washington, D.C., and other territories and possessions of the United States, and to foreign institutions and international organizations. In fiscal year 2009 NIH awarded about two-thirds of all non–Recovery Act grant funds, including extramural research grant funds, to institutions in 10 states: California, Illinois, Maryland, Massachusetts, New York, North Carolina, Ohio, Pennsylvania, Texas, and Washington.

NIH Used Standard Review Processes and Applied Standard and Recovery Act–Specific Criteria to Make Extramural Grant Awards with Recovery Act Funding

NIH used its standard review processes—peer review or administrative review—to make extramural grant awards with its Recovery Act funding. NIH selected grant applications for Recovery Act funding based on NIH standard review criteria, as well as three criteria for Recovery Act grants.

NIH Used Its Standard Review Processes, Including Peer Review, to Award Extramural Research Grants Using Recovery Act Funding

In order to make extramural grant awards in fiscal years 2009 and 2010, NIH used its standard review processes. These standard processes were used to review three categories of applications for Recovery Act–funded extramural grants, namely (1) new grant applications received from Recovery Act funding announcements;[24] (2) existing grant applications that NIH received prior to the Recovery Act, but did not fund; and (3) applications for administrative supplements and competitive revisions to current active grants. Specifically,

- NIH followed its standard peer review process, including review by an initial peer review group and an IC advisory council, to evaluate new grant applications submitted in response to Recovery Act–specific funding

[24]Recovery Act funding announcements are publicly available documents used by NIH to announce an intention to award grants, usually through a competitive process.

opportunity announcements.[25] Specifically, Challenge and Grand Opportunity (GO) grants were developed for Recovery Act funding.[26]

- For existing grant applications that had not previously received NIH funding, the three ICs we reviewed set a new payline to guide selection of existing grant applications for Recovery Act funding.[27] These applications had been submitted for NIH funding from annual appropriations prior to the Recovery Act, and had already been reviewed and determined to be scientifically meritorious using NIH's peer review process. According to NIH officials, most grant applications that fell within the new payline set by the ICs were selected for renegotiation to reduce the projects' proposed objectives, scope, and budget. These renegotiations were required because most grant applications were originally submitted for more than 2 years of funding while NIH generally limited grants under the Recovery Act to projects requiring 2 years or less to complete. NIH and IC officials reported that grant management and program staff ensured that grant applications remained scientifically meritorious when they rescoped 4-year grant applications down to 2 years, but did not assign new priority scores to them.

- NIH also followed its standard review processes in awarding administrative supplements and competitive revisions to current active grants. For applications for administrative supplements to current active grants, ICs conducted an administrative review of the supplemental request for grant funding. Administrative supplements provide additional funding to existing extramural grant awards that were previously peer reviewed. For competitive revisions to current active grants, ICs conducted a standard peer review of the new grant application.

[25]For applications for Challenge grants the initial review was conducted by the Center for Scientific Review, while for applications for Grand Opportunity (GO) grants the initial review was conducted by a peer review group convened by the appropriate IC. The second-level peer review for both grant types was conducted by the IC's advisory council.

[26]The Challenge Grant program focuses on health and science problems such as cancer and autism. The GO grant program supports high-impact ideas that require significant resources for a discrete period to lay the foundation for new fields of investigation.

[27]The payline is a threshold that is determined by the number of extramural grant applications that an IC anticipates funding that year. One IC reported that it extended its payline from the 16th percentile to the 25th percentile of grant applications as ranked by priority score. Another IC extended its payline from the 12th percentile to the 25th percentile, and the third extended its payline from the 15th percentile to the 25th percentile.

NIH Awarded Recovery Act Funds Based on Standard NIH Criteria, Such as Scientific Merit and Relevance to IC Scientific Priorities, as Well as Criteria for Recovery Act Grants

NIH based funding decisions for all Recovery Act extramural grant awards in fiscal years 2009 and 2010 on the three standard criteria NIH uses to award extramural grants, plus three additional criteria established by NIH. The three standard NIH criteria are scientific merit, availability of funds, and relevance to IC scientific priorities:

- *Scientific merit*—NIH considered the design and methodology, innovation, and scientific significance of each grant application using the scientific merit priority scores assigned to new grant applications, existing grant applications that had not previously received NIH funding, and competitive revisions to current active grants. Administrative supplements were awarded to current active grants that had been previously peer reviewed.

- *Availability of funding*—the number of extramural grant applications that could receive Recovery Act funding was determined by the funding available to each IC, which was specified by the Recovery Act to be in proportion to each IC's fiscal year 2009 appropriation.

- *Relevance to scientific priorities*—grant applications were evaluated to determine their relevance to the scientific priorities of the awarding IC.

In addition to the three standard NIH criteria, the three ICs we reviewed considered three additional criteria established by NIH—geographic distribution of Recovery Act funds, the potential for job creation, and the potential for scientific progress within 2 years. Guidance by the OD to all ICs encouraged—but did not require—the ICs to consider these three criteria when making Recovery Act funding decisions. The guidance identified the following:

- *Geographic distribution of the Recovery Act funds*—ICs were encouraged to consider making awards to grantees in states in which the aggregate success rate for applications to NIH has historically been low.[28] NIH encouraged this geographic distribution in order for NIH Recovery Act funds to have the widest effect across the nation and help state and local fiscal stabilization.

[28]These states are identified in NIH's Institutional Development Award (IDeA) program. According to NIH, IDeA is designed to broaden the geographic distribution of NIH funding for biomedical and behavioral research. The program fosters health-related research and enhances the competitiveness of investigators at institutions located in states in which the aggregate success rate for applications to NIH has historically been low.

- *Potential for job creation*—ICs were also encouraged to consider funding extramural grant applications that had the potential to preserve and create jobs—a main purpose of the Recovery Act. In evaluating applications for administrative supplements, one of the ICs we reviewed gave preference based in part on the number of jobs the supplement was projected to create or retain.

- *Potential for making scientific progress in 2 years*—ICs were encouraged to select grant applications for Recovery Act funding in instances where IC officials determined that the applicant had the potential to make scientific progress within a 2-year period, as opposed to the longer duration grant.

NIH's Recovery Act Grant Awards Varied across Grant Categories and Other Characteristics, and NIH Made Information about the Grants and Grantees Publicly Available

NIH's Recovery Act extramural grant awards varied across three categories—awards for applications that had previously been reviewed but had not received funding, awards for new grant applications, and awards for administrative supplements and competitive revisions to current active grants. These awards also varied in size, duration, and research methods, with grantees clustered in certain states and cities. NIH and the ICs communicated a variety of information to the public about the grant awards—including information about grantees—through NIH's Web sites.

NIH Recovery Act Grant Awards Varied across Grant Categories, with Further Variation in the Specific Distribution of Awards at Selected ICs

GAO's analysis of NIH data show that NIH Recovery Act grant awards varied across three grant categories, with significant further variation in the specific distribution of awards across these three grant categories at the three ICs we reviewed. As of April 2010, NIH used about $7 billion of its $8.6 billion in Recovery Act scientific research funds and CER funds to make over 14,000 extramural grants awards.[29] Specifically, NIH used nearly $2.7 billion of Recovery Act funding for grant applications that had previously been peer reviewed by NIH but had not received NIH funding;

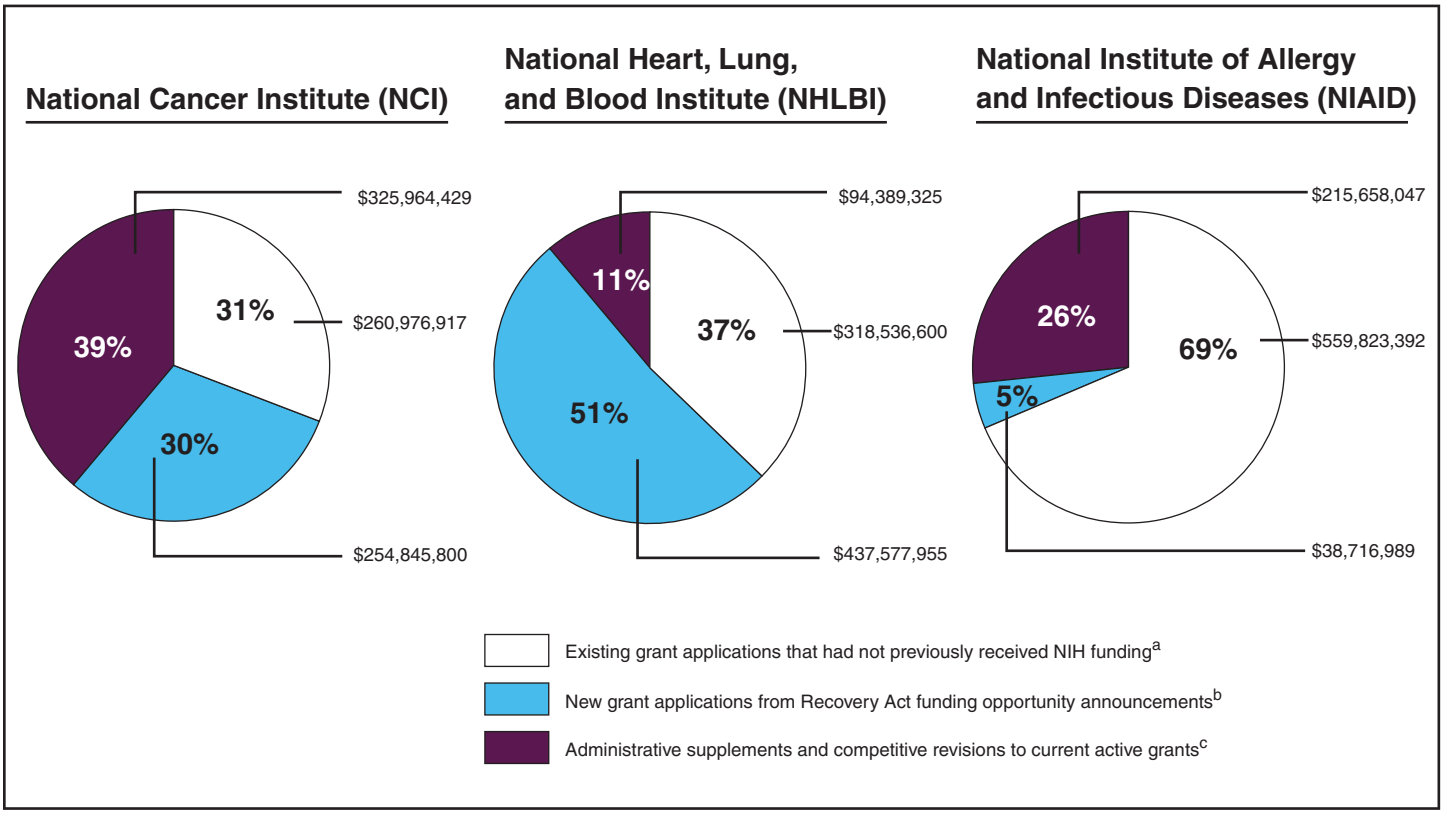
[29]For this report, grant award refers to Recovery Act funds that had been awarded by NIH to grantees in fiscal years 2009 and 2010, as well as funds that have been committed, that is, expected to be awarded in future years subject to the availability of funds and satisfactory progress of the project. NIH officials reported that the remaining extramural grant funds will be awarded by the end of fiscal year 2010.

slightly over $2.4 billion for new grant applications received from Recovery Act funding announcements; and about $1.9 billion for administrative supplements and competitive revisions to current active grants.[30]

The distribution of Recovery Act awards among the three categories of extramural grants varied significantly across the three ICs we reviewed. For example, we found that as of April 2010, NIAID used 69 percent of its Recovery Act funds for existing grant applications that had not previously received NIH funding, while NCI used 31 percent of its Recovery Act funds for existing grant applications that had not previously received NIH funding. In contrast, NHLBI used 51 percent of its Recovery Act funds for new grant applications from Recovery Act funding opportunity announcements, while NIAID used 5 percent of its Recovery Act funding for new grant applications. (See fig. 1 for distribution of Recovery Act awards among the three categories of grants at the three ICs we reviewed.)

[30]NIH made 4,044 extramural grant awards for grant applications that had previously been peer reviewed by NIH but had not received NIH funding; 1,544 extramural grant awards for applications from Recovery Act–specific funding opportunity announcements, such as the Challenge and GO grants; and 8,564 awards for existing extramural grants in the form of administrative supplements and competitive revisions to current active grants.

Figure 1: Selected ICs' Recovery Act Extramural Grant Awards, as of April 2010



Source: GAO analysis of NIH data.

Notes: Data from NIH are for extramural grants that have been awarded using Recovery Act funds as of April 9, 2010. Percentages may not add to 100 because of rounding. In cases where Recovery Act funds appropriated to and retained in the OD were used for extramural grants that were administered by an IC, we classified the grant and associated funding under the administering IC.

[a]These applications had been submitted for funding from NIH annual (non–Recovery Act) appropriations in fiscal years 2008 or 2009, and had already been reviewed using NIH's peer review process.

[b]Recovery Act funding announcements are publicly available documents used by NIH to announce an intention to award discretionary grants, usually through a competitive process.

[c]Administrative supplements award additional funds during the current project period to an existing extramural grant award that was previously peer reviewed—for example, by allowing grantees to add personnel or purchase additional equipment. All additional costs must be within the scope of the peer reviewed and approved project. Competitive revisions are funds added to existing extramural grant awards in order to support new research objectives or other changes in scope. Like the original grant award to which they are added, competitive revisions are awarded using NIH's peer review process.

NIH Recovery Act Extramural Grants Varied in Award Size, Award Duration, and Research Methods, and Grantees Were Clustered in Certain States

GAO's analysis of NIH data also show that as of April 2010, the 14,152 extramural grant awards NIH made with Recovery Act funds varied in the size of the grant award, award duration, and research methods, with grantees clustered in certain states, cities, and universities. (See app. I for illustrative examples of 45 extramural grant awards made with Recovery Act funds.)

Grant Award Size: As of April 2010, we found that the average Recovery Act extramural grant award was slightly more than $492,000, while about 25 percent of grants were awarded $623,000 or more. The median size of Recovery Act grant awards was nearly $250,000, and Recovery Act grant awards ranged in amount from $3,000 to about $29.6 million.[31] NIH awarded 1,259 Recovery Act extramural grants of $1 million or more, of which 86 were for $5 million or more.

Award duration: According to NIH officials, most Recovery Act extramural grants were for durations of 2 years or less at the three ICs we reviewed, but a few Recovery Act extramural grants were for durations longer than 2 years.[32] ICs generally limited their Recovery Act extramural grant durations to 2 years or less in order to fund these grants with Recovery Act funding, which is available for obligation until September 30, 2010. However, NIH granted ICs the flexibility to fund longer-term extramural grants using Recovery Act funds for the first 2 years and annual appropriations for additional years, if the grant is consistent with the IC's priorities.[33] For example, officials at one IC reported that because some early-stage principal investigators may require more than 2 years to demonstrate success in their chosen field of study, the IC offered longer-term awards to these investigators that were partially funded with

[31]The $29.6 million grant award funded a large-scale research project about the efficacy and effectiveness of physical activity on the health outcomes of older Americans.

[32]Specifically, according to an NIH official, 93 percent, 98 percent, and 97 percent of Recovery Act extramural grants at NCI, NHLBI, and NIAID, respectively, were for durations of 2 years or less.

[33]According to an NIH official, the three NIH ICs that GAO reviewed committed a total of about $181 million dollars in future annual appropriations for Recovery Act extramural grants with durations of greater than 2 years, subject to the availability of funds and satisfactory progress of the projects.

Recovery Act funds and that it expects will be partially funded in subsequent years with annual appropriations.[34]

NIH officials explained that a potential "cliff effect," or sharp reduction in application success rates—the percentage of grant applications that receive NIH grant funding—could result beginning in fiscal year 2011 when Recovery Act funds are no longer available for grants. According to NIH officials, the "cliff effect" could potentially occur in two ways. First, recipients of 2-year Recovery Act awards may apply for additional funding to extend their projects—potentially increasing the number of grant applications in future years. Second, officials at two of the ICs we reviewed reported that they committed to supporting grants for a duration longer than 2 years using annual appropriations in fiscal year 2011, which may reduce the amount of funds that will be available to make new grant awards. NIH officials reported that the possible increase in applications resulting from the completion of the Recovery Act awards will be staggered across the next few years, and one official reported that the agency will continue to make decisions about funding research that meet their standard criteria.

Research Methods: NIH officials reported that NIH used Recovery Act funds to make grants for projects with a variety of research methods, such as clinical trials.[35] NIH officials also reported that while NIH does not track all forms of research methods, the research methods used in connection with the over 14,000 extramural grants awarded using Recovery Act funds were similar to the research methods used in connection with the extramural grants funded using annual appropriations. The officials explained that the data available for fiscal year 2009 indicate that extramural research grants funded under the Recovery Act had similar research methods, and were awarded in roughly the same proportions as extramural grants funded with annual appropriations.

NIH officials also reported that the agency has no general policy regarding which scientific methods should be supported using Recovery Act funds or annual appropriations, and that NIH left these decisions to the ICs.

[34]Early-stage principal investigators are new investigators within 10 years of completing their terminal research degree or medical residency.

[35]Clinical trials are biomedical or behavioral research studies of human subjects designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Officials at one IC reported that the IC excluded grant applications involving long-term clinical trials using human subjects or long-term studies involving animal subjects from consideration for Recovery Act funding because Recovery Act funding was generally used for shorter-term grants—that is, grants where the specific aims or scope could be accomplished within the 2-year duration of the award.

Geographic distribution: Consistent with the pattern of grants funded with annual appropriations in fiscal year 2009,[36] the NIH Recovery Act grantees were clustered in certain states. Of the over 14,000 Recovery Act extramural grants awarded as of April 2010

- six states—California, Massachusetts, New York, North Carolina, Pennsylvania, and Texas—accounted for 50 percent of awards;
- six cities—Baltimore, Boston, Los Angeles, New York, Philadelphia, and Seattle—accounted for over 25 percent of awards; and
- five universities received over 10 percent of awards—Duke University, Johns Hopkins University, University of Michigan at Ann Arbor, University of Pennsylvania, and University of Washington.

NIH Posted a Variety of Information about Recovery Act Extramural Grants and Grantees on Its Web Site

NIH communicated various information to the public about the extramural grant awards it made using Recovery Act funds.[37] Information on Recovery Act extramural grant awards was communicated to the public through existing and new Recovery Act–specific Web pages.[38] For example, NIH made information about Recovery Act extramural grants available through its existing Research Portfolio Online Reporting Tools (RePORT) system,

[36]See Dollars Awarded by State for 2009 at http://report.nih.gov/award/trends/State_Congressional/StateOverview.cfm (accessed Apr. 5, 2010).

[37]In addition to information communicated by NIH, NIH policy states that grantees should make the results and accomplishments of their grant activities available to the research community and to the public at large. The Omnibus Appropriations Act of 2009 made the policy a permanent requirement. See Pub. L. No. 111-8, div. F, tit. II, § 217, 123 Stat. 524, 782. In addition, NIH endorses the sharing of final research and the timely release and sharing of final research data from NIH-supported studies for use by other researchers. NIH officials reported that this policy also applies to extramural grants made with Recovery Act funds.

[38]NIH officials reported that NIH also used other electronic and nonelectronic methods, such as radio, television, and newspaper, for disseminating information about Recovery Act grant awards.

an NIH Web-based reporting tool.[39] The RePORT system contains information on both Recovery Act and non–Recovery Act extramural grants. For example, the site includes reports,[40] analysis, and data on NIH research activities, such as the fiscal year of the award, the location of grantee, and awarding IC.[41] (See app. I for extracts of information provided by NIH about extramural grants that were awarded Recovery Act funds, including information from NIH's Web Site.)

In addition to the existing Internet Web sites, NIH and the ICs also developed Recovery Act–specific pages on their Web sites to disseminate information about Recovery Act grants, including extramural grants. For example, NIH highlighted information on Recovery Act–funded extramural grants—on major topics of interest to the public and groups involved in biomedical research funding—available through NIH Recovery Act reports on NIH's Internet Web site.[42] NIH and the ICs posted background stories on particular projects and principal investigators on their Web sites.[43] NIH also made press releases available about Recovery Act–funded projects through the NIH Recovery Act news releases page on its Web site.[44]

Agency Comments

A draft of this report was provided to HHS for review and comment. HHS provided technical comments that were incorporated as appropriate.

[39]For more information, see the RePORT Recovery Act page at http://report.nih.gov/recovery/index.aspx (accessed May 3, 2010).

[40]The Web-based system allows users to generate reports on NIH expenditures and the results of NIH-supported research, such as budget and spending and funded organizations.

[41]Information on NIH Recovery Act extramural grant awards is available at http://recovery.nih.gov/ (accessed August 2, 2010), as well as at http://www.recovery.gov/Pages/home.aspx (accessed June 16, 2010).

[42]See NIH Recovery Act Investment Reports at http://report.nih.gov/recovery/investmentreports/ARRAInvestments.aspx?key= (accessed June 3, 2010).

[43]For example, see the NIH's Recovery Act Story Index page at http://recovery.nih.gov/story.php; NCI's Meet Some of the NCI Recovery Act Funded Researchers page at http://www.cancer.gov/recoveryimpact/fundedresearchers/; NHLBI's Meet the Scientists page at http://www.nhlbi.nih.gov/recovery/researchers/index.php; and NIAID's Recovery Act Success Stories page at http://funding.niaid.nih.gov/ncn/recovery/impactsuccess.htm (all accessed June 4, 2010).

[44]See Recovery Act Releases at http://recovery.nih.gov/news_releases.php (accessed June 4, 2010).

As arranged with your offices, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days after its issue date. At that time, we will send copies of this report to other interested congressional committees, the Secretary of HHS, and the Director of NIH. This report will also be available on the GAO Web site at http://www.gao.gov.

If you or your staff have any questions regarding this report, please contact Linda T. Kohn at (202) 512-7114 or kohnl@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. Key contributors to this report are listed in appendix II.

Linda T. Kohn
Director, Health Care

Appendix I: Illustrative Examples of NIH Recovery Act Extramural Grants

The 45 grants presented below include a sample of 15 extramural grants awarded with American Recovery and Reinvestment Act of 2009 (Recovery Act) funds from each of the three Institutes and Centers (IC) we reviewed—National Cancer Institute (NCI), National Heart, Lung, and Blood Institute (NHLBI), and National Institute of Allergy and Infectious Diseases (NIAID).[1] For each IC, the 15 grants were randomly selected from the three different categories of grant applications—new grant applications from Recovery Act funding opportunity announcements, existing grant applications that had not previously received National Institutes of Health (NIH) funding, and administrative supplements and competitive revisions to current active grants. The number of grants selected in each grant category was in proportion to the amount of Recovery Act funding awarded for each category by the IC, and are not representative of all Recovery Act extramural grant awards.[2] Grants were assigned categories as follows:

- New applications—New grant applications from Recovery Act funding opportunity announcements.
- Existing applications—Existing grant applications that had not previously received NIH funding.
- Supplements and revisions—Administrative supplements and competitive revisions to current active grants.

The information presented in this appendix about each of the Recovery Act extramural grants was provided by NIH. In particular, the grant project titles, administering IC, grantee organization, and abstract descriptions were reprinted from information supplied by NIH. We did not edit them in any way, such as to correct typographical or grammatical errors in the abstract descriptions. We calculated the grant award size[3] reported for each of the 45 grants from NIH information on Recovery Act funds. The grant awards ranged from about $13,000 to about $7.2 million.

[1]In some cases, an extramural grant funded by the Office of the Director (OD) may be administered by an IC.

[2]Information on NIH Recovery Act extramural grant awards is also available at http://www.recovery.gov/Pages/home.aspx (accessed June 16, 2010).

[3]For this report, grant award size refers to Recovery Act funds that had been awarded by NIH to grantees in fiscal years 2009 and 2010, as well as funds that have been committed, that is, expected to be awarded in future years subject to the availability of funds and satisfactory progress of the project.

Grant project title 1:	CSHL Molecular Target Discovery and Development Center
Administering IC:	National Cancer Institute
Grant award size:	$4,737,965
Grantee organization:	Cold Spring Harbor Laboratory P.O. Box 100 Cold Spring Harbor, NY 11724
Grant category:	New applications

Abstract description:

In this application we describe our plans to create a Molecular Target Discovery and Development Center (MTDDC) that will act as downstream component of The Cancer Genome Atlas (TCGA) project. Our premise is that the complexity of cancer genome alterations leads directly to the heterogeneity of cancer behavior and outcome, and that to translate the wealth of cancer genome characterization into clinical utility requires the functional identification and validation of the underlying driver genes. Driver gene identification will lead to a deeper understanding of cancer genotypes, create an important new set of biomarkers and therapeutic targets, and when combined with genome-wide RNAi screens, lead to the identification of key genetic vulnerabilities that will serve as a new generation of therapeutic targets. Our planned center is a natural expansion of long- standing collaborative projects at Cold Spring Harbor Laboratory (CSHL) and combines several powerful methods that we have developed and will continue to build upon as outlined in this application. These methods include flexible mouse models based on the transplantation of genetically-manipulated progenitor cells into the appropriate tissues of recipient mice; novel bioinformatics that take complex cancer genome datasets and pinpoint candidate driver genes and considerably altered pathways; new RNAi technology to manipulate the expression of candidate target genes in vitro and in vivo; and genome-wide RNAi screens to find genetic vulnerabilities of cancer cells. The CSHL MTDDC will use these innovative tools to place the complex array of genomic alterations identified by cancer genome projects into biologic context. High-throughput screening in mouse models will be used to determine whether candidate genes are drivers or passengers. Additionally, through the identification of those driver genes that are required for tumor maintenance and by genome-wide RNAi screens to find the druggable vulnerabilities of major cancer genotypes, we will discover and validate a new generation of cancer drug targets. The resultant data, reagents, and newly validated biomarkers and targets will be openly shared among the TCGA network and broader cancer research communities, as we have done with RNAi Codex, CSHL's open-access portal/database for short-hairpin RNA (shRNA) gene-silencing constructs.

Source: NIH.

Note: The grant abstract description was reprinted, with permission, from the NIH Research Portfolio Online Reporting Tools (RePORT) Recovery Act page, http://report.nih.gov/recovery/index.aspx (accessed May 4, 2010) (further republication of the abstracts may require permission from the respective copyright holders).

Grant project title 2:	Supporting New Faculty Recruitment Through Biomedical Research Core Center
Administering IC:	National Cancer Institute
Grant award size:	$1,439,136
Grantee organization:	University of Kentucky 109 Kinkead Hall Lexington, KY 40506-0057
Grant category:	New applications

Abstract description:

The strategic plan of the University of Kentucky (UK) P30 application in response to RFA-OD- 09-005 is to provide support for the recruitment of 2 junior investigators who will be immersed into a highly collaborative, interdisciplinary group of investigators focused on the diagnosis, prevention and treatment of gastrointestinal (GI) cancers. This productive group consists of basic and clinical scientists, including molecular and cell biologists, clinician-scientists (surgeons, gastroenterologists, and medical oncologists), GI pathologists, epidemiologists, biostatisticians and investigators in the School of Pharmacy with successful programs in drug design and delivery. The purpose of this program is to support promising junior investigators who will participate in translational GI cancer research projects as part of our recently-funded P20 program (P20 CA127004) which provides support for the development of a fully-funded P50 GI cancer SPORE application. Our goal is to develop a cadre of future GI cancer investigators who can participate at the intersection of molecular biology, drug discovery and clinical care to become leaders in integrative and team approaches to understand the complex issues of GI cancer as it relates to potential prevention and treatment strategies. This proposal builds upon the momentum and existing strengths at the Markey Cancer Center and is further supported by substantial institutional, state and philanthropic support.

Source: NIH.

Note: The grant abstract description was reprinted, with permission, from the NIH RePORT Recovery Act page, http://report.nih.gov/recovery/index.aspx (accessed May 4, 2010) (further republication of the abstracts may require permission from the respective copyright holders).

Grant project title 3:	Targeting PTEN Null Tumors via Inhibition of the p110beta Isoform of PI3 Kinase
Administering IC:	National Cancer Institute
Grant award size:	$1,995,664
Grantee organization:	Dana-Farber Cancer Institute 44 Binney St Boston, MA 02115
Grant category:	New applications

Abstract description:

The class IA phosphatidylinositol 3 kinase (PI3K) signaling axis is perhaps the most frequently activated pathway in human cancer. In response to the activation of receptor tyrosine kinases (RTKs), G-protein coupled receptors (GPCRs) or Ras, class IA PI3Ks, consisting of three catalytic isoforms termed p110?, p110? and p110?, are activated to generate the primary intracellular lipid signal, phosphatidylinositol 3,4,5-trisphosphate (PIP3), which is essential for multiple cellular processes. The tumor suppressor PTEN, a lipid phosphatase, dephosphorylates PIP3, thereby antagonizing the actions of PI3K and regulating the PI3K pathway activity. Pathway activation in tumors is most commonly achieved through activating mutations in p110? isoform or via loss of the PTEN tumor suppressor. Importantly, PI3K enzymes are highly suited for pharmacological intervention, making them attractive targets for cancer therapy. In fact, there are a number of PI3K inhibitors from major pharmaceutical companies that have entered clinical trials for cancer treatment, but most of these inhibitors target all p110 isoforms, which may cause side effects arising from the essential roles of PI3K in normal physiology. While isoform specific inhibitors are being further developed, most of which are directed toward p110? (for solid tumors) or p110? (Hematological malignancies). We believe that the drug companies have blundered by failing to develop p110?-specific inhibitors. We and others have recently demonstrated that tumors driven by PTEN loss are specifically dependent of p110? not p110?. The broad goal of this project is to generate p110? -specific inhibitors for use as new, targeted therapeutics in diverse cancers featuring PTEN mutations. To this end we have assembled a team of scientists optimized to achieve this goal. Our team's unique reagents for assessing PI3K signaling, coupled with and our expertise in protein chemistry, X-ray crystallography, medicinal chemistry and animal models, position us to effectively develop p110? inhibitors over a two-year time period for future clinical trials. Our specific goals are to generate cell-based systems and genetic models to determine the role of p110? in tumorigenesis driven by PTEN in different tissue types and to test p110? - specific inhibitors, to purify large amounts of active p110? for enzyme assays and crystallography and to pursue a chemistry campaign to design and evaluate new scaffolds for p110? inhibition and optimize 2 of these scaffolds using both cell and animal models and structural information from a complex of p110? and an inhibitor.

Source: NIH.

Note: The grant abstract description was reprinted, with permission, from the NIH RePORT Recovery Act page, http://report.nih.gov/recovery/index.aspx (accessed May 4, 2010) (further republication of the abstracts may require permission from the respective copyright holders).

Grant project title 4:	Role of TIEG1 in Foxp3+Treg development and tumor progression
Administering IC:	National Cancer Institute
Grant award size:	$999,094
Grantee organization:	Wayne State University Sponsored Program Administration Detroit, MI 48202
Grant category:	New applications

Abstract description:

Although tumor vaccines can induce CD4 helper and CD8 cytotoxic response against tumor antigens, they have been largely ineffective in causing tumor regression in the clinic. This is because the tumor cells acquire many mechanisms to evade the immune surveillance program of the host. Foxp3+CD4 +CD25+Treg-mediated immune suppression has emerged as one of the crucial tumor immune evasion mechanisms and main obstacle of successful tumor immunotherapy. Most malignant cells including prostate cancer cells secret large amounts of TGF-¿ and has been shown to convert the effector T cells into tumor antigen specific Tregs by inducing Foxp3 expression. Such tumor induced Tregs not only suppress the priming and effector function of anti-tumor effector cells but also form a broad network of self-amplifying immunosuppressive network. Therefore, overcoming tumor induced expansion and de novo generation of Tregs is critically important for the design of effective immunotherapeutic strategies for successful cancer treatment. We have demonstrated a critical role of TGF-¿ inducible early gene-1 (TIEG1) in the transcriptional regulation of Foxp3 in CD4T cells treated with TGF-¿. E3 ligase Itch-mediated monoubiquitination is essential for nuclear translocation, and transcriptional activation of TIEG1. However, in transient overexpression systems Itch targets TIEG1 for both mono and polyubiquitination. Our preliminary studies suggest that IL-6 which inhibits TGF-¿ induced Foxp3 expression induces proteasomal degradation of TIEG1 possibly through polyubiquitination. Tyk2-mediated phosphorylation of TIEG1 seems to act as a recognition signal for polyubiquitination of TIEG1. Therefore, we hypothesize that Itch targets TIEG1 differentially for mono and polyubiquitination when the CD4T cells are stimulated with TGF-¿ or IL-6 and regulates its activation and degradation. Despite the growing body of data on the role of Foxp3 in Treg development and function, how Foxp3 transcription is regulated is not clear. We have identified consensus NFAT and TIEG1 binding sites adjacent to each other on Foxp3 promoter. Since, most transcription factors work cooperatively with other factors binding in close proximity we hypothesize that NFAT and TIEG1 interact on Foxp3 promoter and regulate chromatin remodeling and Foxp3 expression. A clear understanding of molecular combinations and cross-talks that imprint Foxp3 transcription in CD4T cells will aid in designing strategies to disrupt the inhibitory network of Tregs in tumor microenvironment. Using prostate cancer TRAMP-C2 cells which secrete large amount of TGF-¿, we will analyze the effect of TIEG1 deficiency on Treg development and tumor progression. Since TIEG1 does not effect nTreg development in the thymus, targeting TIEG1 is an appealing strategy to block the de novo induction of Tregs. Such a strategy is expected to eliminate most potent tumor specific Tregs that inhibit anti-tumor immune response without the risk of triggering autoimmunity.

Source: NIH.

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Grant project title 5:	Cell Polarity in Self-renewal and Differentiation of Stem/Progenitor Cells
Administering IC:	National Cancer Institute
Grant award size:	$713,042
Grantee organization:	Fred Hutchinson Cancer Research Center Box 19024 1100 Fairview Ave N Seattle, WA 98109-1024
Grant category:	Existing applications

Abstract description:

Self-renewal and differentiation are fundamental characteristics of all stem/progenitor cells. During mammalian development stem/progenitor cells use cell polarity mechanisms to divide asymmetrically to renew themselves and generate daughters that stop proliferation and differentiate. Similar mechanisms are used for self-renewal and differentiation of adult stem cells. Failure of asymmetric cell divisions in stem cells may result in inability to withdraw from cell cycle, perturbations of normal brain development and cancer. Alternatively, failure of stem cell self-renewal can cause depletion of stem cells, decline in tissue regenerative potential and premature aging. The molecular mechanisms governing cell polarity and asymmetric cell divisions of mammalian stem/ progenitor cells and their role in aging and cancer are still poorly understood. This proposal focuses on cell polarity proteins, Lethal giant larvae 1 and 2 (Lgl1 and Lgl2), which represent the mammalian orthologs of Drosophila neoplastic tumor-suppressor protein Lgl. We have evidence that Lgl1 is necessary for regulation of asymmetric cell division of neural progenitor cells during early neurogenesis and loss of Lgl1 results in abnormal accumulation of progenitors that fail to withdraw from the cell cycle. Neonatal death of Lgl1-/- mice precluded us from the analysis of potential tumor- suppressor role of Lgls in adult animals and their role in self-renewal of adult stem cells. In this proposal we will use a variety of conditional gene knockout and biochemical approaches to investigate the potential in vivo role and significance of the entire Lgl gene family and molecular mechanisms responsible for function of Lgl proteins in regulation of stem/progenitor cell self-renewal and differentiation. These studies will help to extend our knowledge of the mechanisms of self-renewal and differentiation of mammalian stem/progenitor cells. This information will be useful for future development of efficient regenerative, anti-aging and anticancer therapies.

Source: NIH.

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Grant project title 6:	Human CYP2A and respiratory tract xenobiotic toxicity
Administering IC:	National Cancer Institute
Grant award size:	$663,881
Grantee organization:	Wadsworth Center Health Research, Inc. Menands, NY 12204-2719
Grant category:	Existing applications

Abstract description:

The long-term objective is to determine the role of respiratory tract cytochrome P450 (P450 or CYP) enzymes in target tissue metabolic activation and toxicity of environmental chemicals. Our focus continues to be on CYP2A13, an enzyme selectively expressed in human respiratory tract, and the most efficient human P450 enzyme in the metabolic activation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a major tobacco- derived respiratory tract procarcinogen. CYP2A13 is also known to metabolize numerous other important respiratory tract toxicants. Our hypothesis, that CYP2A13 plays an important role in tobacco-related lung carcinogenesis in humans, is supported by findings of a recent epidemiological study, and by reports confirming that CYP2A13 protein is expressed in human lung, where it is active in the metabolic activation of NNK, and that P450s in the lung, but not those in the liver, are essential for NNK-induced lung tumorigenesis in mouse models. Furthermore, our preliminary finding, that expression of CYP2A13 is downregulated by inflammation, offers an explanation for why the levels of CYP2A13 protein detected in patient-derived lung biopsy samples were so low, and suggests the possibility that CYP2A13 levels in intact, healthy lungs are much higher. Here, we propose three series of experiments to overcome the difficulties associated with not being able to directly study P450 expression or activity in intact, healthy human lungs. We will (1) study a CYP2A13-humanized mouse model, in order to provide proof-of-principle for the potential of CYP2A13 to mediate NNK-induced lung tumorigenesis in humans; (2) perform additional studies to better understand the nature and scope of inflammationinduced suppression of CYP gene expression in the lung; and (3) identify common CYP2A13 genetic variants that cause changes in gene expression (and the underlying mechanisms), in order to provide biological basis for future epidemiological studies aimed at further confirming the role of CYP2A13 in smoking-induced lung cancer or other chemical toxicities in various ethnic or occupational groups. We believe that our proposed studies are novel, and the anticipated outcome will be highly relevant to mechanisms of chemical carcinogenesis and other chemical toxicities in human lung.

Source: NIH.

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Grant project title 7:	Sentinel Node Versus Axillary Dissection in Breast Cancer
Administering IC:	National Cancer Institute
Grant award size:	$1,498,205
Grantee organization:	University of Vermont & St Agric College 85 South Prospect Street Burlington, VT 05405
Grant category:	Existing applications

Abstract description:

The long-term objectives of this proposal are to develop and refine methods of breast cancer staging in patients that are substantially less morbid than current methods, yet still provide the same diagnostic and therapeutic benefits. For the past nine years we have partnered with the National Surgical Adjuvant Breast and Bowel cooperative group (NSABP) to conduct a large, multi-center, randomized, Phase III prospective trial that compares sentinel lymph node (SLN) resection to conventional axillary dissection in clinically node-negative breast cancer patients (NSABP trial B-32). During the last grant period we have also launched a multicenter study to investigate whether detection of the presence of bone marrow micrometastases provides enhanced and early prediction for survival of breast cancer patients (NSABP study BP-59). Several tasks have been shared between UVM and NSABP, such as final trial design and protocol development. UVM has had non-overlapping primary responsibility for the following: (1) training and quality control of all aspects of SLN surgery and bone marrow sample procurement; (2) processing and interpretation of SLNs for occult metastases; (3) processing and interpretation of bone marrow samples for disseminated tumor cells; and (4) statistical analysis of the following three relationships: firstly, the relationship of training to surgical outcomes and quality of reported data; secondly, the relationship of occult metastases in SLNs to survival and other patient variables, and thirdly, the relationship of bone marrow micrometastases to survival. During the time period of this proposal the first 6 Aims will be fully completed and the 7th Aim will result in complete specimen accrual and interpretation. The Specific Aims of the current active grant are: Specific Aims #1 and #2: Determine whether SLN resection alone, when compared to ALN dissection plus SLN resection, results in equivalent long-term control of regional disease (Aim 1) and disease-free and overall survival (Aim 2). Aim #3: Determine the magnitude of morbidity reduction of SLN surgery versus ALN resection. Aim #4: Determine the magnitude of quality of life improvement by SLN surgery versus ALN resection. Aim #5: Determine whether standardized immunohistochemistry analysis of hematoxylin and eosin- negative SLNs identifies patients at risk for decreased overall and disease-free survival. Aim #6: Establish a standardized method of SLN surgery in a large number of centers for procedural consistency. Aim #7: Determine the relative risk of death associated with the presence of tumor cells in the bone marrow of breast cancer patients and investigate the relationship between 2 tumor cell detection methods, brightfield and immunoflourescence cytochemistry, in detecting bone marrow micrometastases.

Source: NIH.

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Grant project title 8:	p53 Acetylation as a Mechanism in Chemoprevention by Aspirin
Administering IC:	National Cancer Institute
Grant award size:	$148,500
Grantee organization:	Texas Tech University Health Scis Center 3601 4th Street - Ms 6271 Lubbock, TX 79430-6271
Grant category:	Existing applications

Abstract description:

A vast amount of epidemiological, preclinical and clinical studies have revealed aspirin as a promising chemopreventive agent, particularly in epithelial carcinogenesis. Despite the wide attention inhibition of cyclooxygenases has received, it is clear that aspirin elicits a myriad of molecular effects that counteract the carcinogenic episodes. Since aspirin's protective effect was mainly observed in epithelial cell types which are more resistant to chemotherapeutic efforts, an urgent need exists to dissect and identify the primary targets and cancer preventive pathways affected by aspirin. In preliminary studies, we have obtained the first and strong evidence for a dose- and time-dependent acetylation of p53 tumor suppressor protein by aspirin in MDA-MB-231 human breast cancer cells, several cancer cells belonging to different tumor types and also in normal liver cells. In MDA-MB-231 cells, aspirin induced the levels of p53 target genes namely p21CIP1, a protein involved in cell cycle arrest, and Bax, a proapoptotic protein; however, p21 induction was transient (1-12h); where as, induction of Bax was sustained (24 h). Interestingly, in DNA damaged cells (induced by camptothecin), aspirin treatment (24 h) inhibited the p21 induction, while the Bax induction was unaffected. Built on these findings, the central hypothesis of this R03 pilot project is that aspirin-induced multi-site acetylation of p53 alters its transcription factor function by shifting the gene expression spectrum from those that elicit cell cycle arrest / prosurvival properties to those that promote and drive cell death. Since deletion of p21 gene has been previously shown to increase the sensitivity of cells towards apoptosis, our observation that aspirin inhibits p21 suggests a potential mechanism by which it may exert anti-cancer effects in DNA damaged cells. The studies proposed in this application will determine the mechanisms by which aspirin regulates apoptosis in DNA damaged cells via inhibition of p21. We will use MDA-MB-231 and MCF-7 breast cancer cells as well as normal human Peripheral Blood Mononuclear Cells in our study. The experiments in Aim 1 will investigate the molecular basis of aspirin-mediated inhibition of p21 using real time RT-PCR, electrophoretic mobility shift assays, and run on transcription assays. We will also identify aspirin-induced acetylation sites on p53. In Aim II, we will determine the ability of aspirin to augment apoptosis in cells exposed to DNA damaging drugs by clonogenic cell survival assays and flow cytometry. In addition to camptothecin, all studies will be extended to include doxorubicin and cisplatin, to determine if aspirin also modulates p21 / Bax expression by these DNA damaging drugs. These studies will provide a novel mechanism by which aspirin may exert anticancer effects in DNA damaged cells via acetylation of p53, induction of Bax and inhibition of p21.

Source: NIH.

Note: The grant abstract description was reprinted, with permission, from the NIH RePORT Recovery Act page, http://report.nih.gov/recovery/index.aspx (accessed May 4, 2010) (further republication of the abstracts may require permission from the respective copyright holders).

Grant project title 9:	The role of pheomelanin in cutaneous melanoma
Administering IC:	National Cancer Institute
Grant award size:	$630,397
Grantee organization:	Tufts Medical Center 800 Washington St Boston, MA 02111-1526
Grant category:	Existing applications

Abstract description:

Ultraviolet (UV) radiation represents a definitive risk factor for skin cancer, particularly in combination with certain underlying genetic traits, such as red hair and fair skin. Skin pigmentation results from the synthesis of melanin in pigment-producing cells, the melanocytes, followed by distribution and transport of the pigment granules to neighboring keratinocytes. Epidemiological studies have found less skin cancer in people who have high levels of constitutive pigment and/or tan well. However, we have incomplete understanding of other factors involved in the development of skin cancer, such as capacity to repair photo- damage in people of different skin colors. The finding that albinos have a lower incidence of melanoma than people with fair skin makes this question more complex. Recent findings including our own have led to a realization that melanin, especially pheomelanin (a yellow/red form of melanin), acts as a potent UVB photosensitizer to induce DNA damage and cause apoptosis in mouse skin. The proposed research will focus on the role of pheomelanin in DNA damage, at both genomic and individual nucleotide levels, and on the subsequent activation of DNA repair, alteration in chromatin structure, and ultimately melanoma formation. We hypothesize that pheomelanin contributes to UVinduced DNA damage that is incompletely repaired. Although DNA repair may be activated to a larger extent in response to the greater DNA damage in pheomelanin-containing skin, the repair will be insufficient to eliminate all mutagenic adducts. We will first identify the role of pheomelanin in melanoma formation by melanoma mouse models. Second, we will define the photoproducts and oxidative stress to DNA in mice with different type of epidermal pigmentation at different times after UVB irradiation by quantitative methods. Third, we will map DNA damage in specific sequences of BRAF and N-RAS genes, both of which are frequently mutated in human melanoma. Finally, we will detect the expression of genes in DNA repair pathways at different times after UVB irradiation. Given the vital role that pheomelanin plays in normal phototoxicity and disease, these studies will provide important insights into the homeostasis of tanning and the pathogenesis of disorders like melanoma. Expanding our knowledge of DNA repair in different skin types provides a rich ground for melanoma prevention and for the development of targeted small-molecule therapeutics.

Source: NIH.

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Grant project title 10:	Cancers in Older Minority Populations: Caribbean American
Administering IC:	National Cancer Institute
Grant award size:	$125,720
Grantee organization:	Long Island University Brooklyn Campus 1 University Plz Brooklyn, NY 11201-8423
Grant category:	Supplements and revisions

Abstract description:

Strong ties have developed between investigators at Long Island University's Brooklyn campus (LIU) and Columbia University's Herbert Irving Comprehensive Cancer Center (HICCC) over the past four years. Several joint grants and projects have resulted, totaling over $2 million, with two proposals pending. Anchoring this collaboration has been a P20 from NCI (CA91372). These research efforts have focused on differences among African Caribbean immigrant populations in Brooklyn and North Manhattan (including Dominican, Haitian, and English-speaking Caribbeans) and US-born African Americans and European Americans. The research includes behavioral, cultural, lifestyle, and biological genetic differences that may relate to cancer-related health disparities. In this application, we propose to build upon the existing partnership and use it as a platform for a broader, more comprehensive study of the same issues. This partnership would meld the two institutions, with an emphasis on bringing together their complementary strengths. The PI at LIU is a well-known psychologist with extensive behavioral and survey research experience with these populations in Brooklyn. The PI at Columbia is a medical oncologist and epidemiologist with a strong record in cancer prevention and control research and a leadership position in the MCCC. HICCC will provide access to its core facilities, especially the Biostatistics Core, while LIU will provide its expertise in survey and behavioral research. The proximity of the two institutions will permit frequent seminars and workshops attended by individuals from both centers, as well as an annual retreat at each center. Students and faculty at each will also have access to courses and lectures at each of the institutions. Equally important will be programs designed to provide experience for minority students and faculty in cancer research, with the opportunity for students from LIU to obtain admissions and fellowships to Columbia programs, illustrated by a minority predoc from LIU who will have a T32 postdoc at Columbia. Two projects and four pilots are U54 program. There will be an annual competition for funding for the following year; proposals will be reviewed by external reviewers, as was successfully conducted in our P20. Ongoing/proposed projects/pilots will be I discussed at a monthly workshop alternating between campuses at which statisticians, data management, and methodologists will attend to provide constructive discussion. A representative from the University of West Indies (UWI) will attend annual EAB meetings and, via videoconference, quarterly internal steering committee meetings with long-term possibilities for dual site (Brooklyn/Caribbean) projects. This partnership has a unique study population, a successful existing relationship, and an emphasis on population science research.

Source: NIH.

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Grant project title 11:	Case Comprehensive Cancer Center Support Grant
Administering IC:	National Cancer Institute
Grant award size:	$1,461,630
Grantee organization:	Case Western Reserve University 10900 Euclid Ave Cleveland, OH 44106-7015
Grant category:	Supplements and revisions

Abstract description:

The Case Comprehensive Cancer Center (Case CCC), now in its 17 year, provides leadership and oversight for basic cancer research, therapeutic and non-therapeutic cancer clinical trials, prevention, control and population research, as well as community outreach for the major affiliate institutions of Case Western Reserve University: Case School of Medicine, University Hospitals of Cleveland, and the Cleveland Clinic. Located in Cleveland and serving the 3.8 million people in Northern Ohio, members of the Cancer Center manage over 7,000 new cases per year with a high rate of clinical trial access and accrual, operating under a single protocol development and review system, data safety management plan, and a coordinated clinical trials operation. Since the last competitive renewal application, the Center has increased NCI funding by more than 53%, and more than doubled its total peer-reviewed funding. The Center also accrued 877 patients to therapeutic clinical trials in 2005. Significant institutional commitment to Center development resources, faculty recruitment, shared resources, and space assures the Center's continued success and its dynamic approach to multidisciplinary cancer research and therapeutics. The Case CCC has 9 Scientific Programs, 17 shared resources including 6 that are new, and a clinical and behavioral cancer research infrastructure that prioritizes innovative translational research and investigator-initiated clinical trials that cut across the Scientific Programs. These programs include Cancer Genetics, Cell Proliferation and Cell Death, Radiation and Cellular Stress Response, Molecular Mechanisms of Oncogenesis, GU Malignancies (new), Stem Cells and Hematologic Malignancies, Developmental Therapeutics, Cancer Prevention, Control and Population Research, and Aging-Cancer Research (new). The new Shared Resources include Imaging Research, Proteomics, Hybridoma, Transgenic & Targeting, Translational Research, and Practice-Based Research Network. Each of these new Shared Resources is fully operational, supporting the cancer research of multiple members across programs, and providing a critical platform for multidisciplinary and interdisciplinary research. This scientific organization and infrastructure furthers the mission of the Case CCC: to improve the prevention, diagnosis, and therapy of cancer through discovery, evaluation, and dissemination that together reduce cancer morbidity and mortality in Northern Ohio and the Nation.

Source: NIH.

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Grant project title 12:	Spin Probes in Semipermeable Nanospheres: EPR spectroscopy & imaging of tumor pH
Administering IC:	National Cancer Institute
Grant award size:	$51,972
Grantee organization:	Ohio State University 1960 Kenny Road Columbus, OH 43210
Grant category:	Supplements and revisions

Abstract description:

The overall goal of this project is to develop new functional EPR probes of enhanced stability for in vivo EPR spectroscopy and imaging of pH, one of the most important parameters in the biochemistry of living organisms. pH-sensitive nitroxyl radicals have been previously developed by the P.I. and colleagues but often suffer insufficient stability in living tissues. In this project two different strategies will be used to develop paramagnetic probes with stability in vivo based on the original idea of constructing nano-Sized Particles with the Incorporated Nitroxides, or nanoSPINs. The semipermeable membrane of the nanoSPINs will differentiate sensing nitroxides from biological reductants while allowing free penetration of the analyze, H+. This will fill a niche between fluorescent pH probes, which have provided advances in applications for cellular and subcellular detection, and NMR/MRI, which have provided applications in living animals and humans, but these current techniques often suffer from the lack of sensitivity (1000 fold or lower than EPR) and specificity. The specific aims are: (SA1) To develop effective approaches for the design of pH-sensitive nanoSPINs. Two alternative strategies for the incorporation of the nitroxides into semipermeable nanospheres will be used, namely incorporation into phospholipids liposomes and polyamide capsules. (SA2) To define spectroscopic and physicochemical characteristics of pH-sensitive nanoSPINs. Quantitative characterization of the obtained nanoSPIN is absolutely crucial both for the optimization of the preparation procedures and for efficiency of their further applications. (SA3) To apply in vivo EPR measurements of pHe in PyMT tumor-bearing mice using developed nanoSPINs. The measurement of the extracellular pHe in the PyMT mammary tumors in living mice using developed pHsensitive nanoSPINs will provide new insights into related biochemical processes, including better understanding of the observed anti-tumor activity of Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), a therapeutic approach which is currently of much interest. The results may provide an opportunity for the design of other corresponding therapeutic approaches. In summary, the success of this project may have a significant impact on the future of functional in vivo EPR spectroscopy and bioimaging applications to medicine. This project will develop pH-sensitive paramagnetic probes of enhanced stability based on encapsulation of the nitroxides into semipermeable nanospheres. These probes, termed nanoSPINs, will allow in vivo EPR spectroscopy and imaging of pH. The experiments using pHsensitive nanoSPINs in PyMT mammary tumors in living mice are planned to contribute to the understanding of the mechanisms of extracellular acidosis in solid tumors and to use extracellular pH to monitor tumor progression and thus evaluate the efficacy of anti-tumor drugs, and provide opportunities for designing corresponding therapeutic approaches.

Source: NIH.

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Grant project title 13:	Development of Oncomine Professional as a Platform for Biopharmaceutical Research
Administering IC:	National Cancer Institute
Grant award size:	$263,987
Grantee organization:	Compendia Bioscience, Inc. Floor 2 Ann Arbor, MI 48104
Grant category:	Supplements and revisions

Abstract description:

DNA microarray studies, largely sponsored by the NIH and other granting agencies, have generated a wealth of data uncovering the complex gene expression patterns of cancer. Currently however, there is no unifying organizational or bioinformatics resource to integrate the myriad independent observations into a single, global, computable environment. Such a resource would not only provide wide access to data from individual studies, but would also provide an opportunity to apply advanced analysis techniques to the aggregated data. In the absence of such a resource, the majority of cancer molecular profiling data remains severely under-utilized by both the academic cancer research community, and by the pharmaceutical and biotechnology companies who could utilize this data to aid in their efforts to develop new biomarkers and therapies. We propose to develop a commercialscale solution for cancer molecular profiling research to address this problem. The solution builds upon the prototype of Oncomine developed at the University of Michigan, which utilizes a data pipeline, a data warehouse, an analysis engine, and a web interface to deliver human cancer genomic data in an intuitive platform to scientists and clinicians. The specific aims in Phase I of this proposal are to: 1. Modify the Academic Data Pipeline to Support Commercial Operations. 2. Re-host and re-structure the Oncomine Database. 3. Develop a commercial technical operating model for the Oncomine Web Application. In Phase II of this proposal we will: 1. Develop a controlled cancer genomics data pipeline to support the rapid and proactive collection, standardization and analysis of heterogeneous cancer genomics data from repositories, academic laboratories and pharmaceutical companies. 2. Develop a scalable and secure cancer genomics data warehouse to support the storage and retrieval of public and proprietary data. 3. Develop an optimized user interface to support cancer drug discovery and development. The result of this work will be a fully integrated, end-to-end platform for providing publicly funded research results to the commercial sector, with a goal of utilizing that data to develop new diagnostic and therapeutic approaches for treating cancer. The Oncomine prototype is already broadly accepted in academia, and has been verified as a research tool with high utility by over 10,000+ non-profit users. Since 2006 Compendia has worked to establish the commercial merit of Oncomine; as a result, tens of thousands of valuable high-throughput experiments are now being utilized by several of the world's top pharmaceutical companies. However, additional funding is required to transition Oncomine from an academic tool to a commercial platform, and to realize the full commercial potential of this approach to advance research and save lives.Cancer is a leading cause of mortality, and is responsible for one in every four deaths in the United States. In recent years global gene expression technologies have generated important new information about the molecular mechanisms underlying cancer by revealing specific aberrations in genes, proteins, and signaling pathways. This proposal seeks funding to provide a platform for aggregating, analyzing, and presenting this genomic data to drug development companies, with a goal of optimizing the clinical usefulness of cancer genomic data for drug discovery and development.

Source: NIH.

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Grant project title 14:	Pharmacogenomics of Childhood Leukemia (ALL)
Administering IC:	National Cancer Institute
Grant award size:	$661,549
Grantee organization:	St. Jude Children's Research Hospital Memphis, TN 38105
Grant category:	Supplements and revisions

Abstract description:

Despite substantial progress in the past two decades, cancer remains the leading cause of death by disease in US children between 1 and 15 years of age. Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, and cure rates are approaching approximately 80% today. Unfortunately, 20% of children with ALL are not cured with current therapy, making the number of cases of relapsed ALL greater than the total number of new cases of most childhood cancers. Previous work has established that de novo drug resistance is a primary cause of treatment failure in childhood ALL. However, the genomic determinants of such resistance remain poorly defined. We have recently identified a number of new genes that are expressed at a significantly different level in B-lineage ALL cells exhibiting de novo resistance to widely used antileukemic agents (prednisolone, vincristine, asparaginase, daunorubicin), and their pattern of expression was also significantly related to treatment outcome. To assess, three research aims that extend our prior findings. The first scientific aim is to identify genes conferring de novo resistance of childhood ALL to the widely used thiopurines, mercaptopurine and thioguanine. This will be the first genome-wide analysis of genes conferring thiopurine resistance and will provide important new insights into whether they represent distinct antileukemic agents. The second aim is to identify genes in T-ALL that confer de novo resistance to the four agents we have previously studied in B-lineage ALL (prednisolone, vincristine, asparaginase, daunorubicin) and the two thiopurines. This will yield pharmacogenomic insights into why T-ALL has a worse prognosis with most treatment protocols. The final aim is to identify germline polymorphisms or epigenetic changes in the promoter regions of those genes that are differentially expressed in ALL cells exhibiting resistance to these antileukemic agents. Preliminary studies have already identified a significant relation between mRNA expression in ALL cells and the promoter haplotype structure of the first gene investigated (SMARCB1). It is important to extend these pharmacogenomic studies in a systematic way to additional genes conferring de novo drug resistance. These findings will continue to provide important new insights into the genomic determinants of treatment failure and point to novel targets for developing strategies to overcome drug resistance in childhood ALL.

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Grant project title 15:	University of New Mexico Cancer Center Support
Administering IC:	National Cancer Institute
Grant award size:	$1,264,145
Grantee organization:	University of New Mexico Main Campus, PreAward Albuquerque, NM 87131
Grant category:	Supplements and revisions

Abstract description:

The Cancer Epidemiology and Prevention Program was formally established in 1973 when the New Mexico Tumor Registry joined with 6 other population-based tumor registries to form the NCI-SEER (Surveillance, Epidemiology and End Results) program. The NM SEER data provide the fundamental, population-based data for hypothesis generation in this program, and has led to a strong base of funding for research in lung, breast, skin and GI cancers. The striking differences in cancer patterns, in cancer health disparities, and in outcomes among New Mexico's multiethnic population are under intense investigation to uncover the genetic, environmental, social, and behavioral factors that account for these patterns and disparities. In addition, the program's community-based research and outreach in cancer education, screening, and prevention among rural, American Indian and Hispanic populations work toward correcting those disparities. Led by co-directors Marianne Berwick and Steven Belinsky, the Cancer Epidemiology and Prevention Program joins 23 full members, 2 members with secondary appointments, and 5 associate members with primary appointments in 5 Departments within the UNM School of Medicine and College of Pharmacy, the Lovelace Respiratory Research Institute, and the Albuquerque Veteran's Administration Medical Center. The Cancer Epidemiology and Prevention Program has four major scientific goals that cross the organbased themes of lung, breast, skin and gastrointestinal cancers: (1) To identify the genetic, epigenetic, environmental and behavioral risk factors contributing to the development and progression of cancer, particularly those cancers that disproportionately affect New Mexico's multiethnic populations; (2) To develop biomarkers for the risk factors identified in aim 1; (3) To develop interventions for cancer prevention that target specific biochemical pathways and factors identified in aim 1, that will be assessed using biomarkers from aim 2; and (4) To translate these interventions into community prevention, outreach, and education programs using community-based participatory research methods. The high quality of the interactive research in this Program has resulted in a large number of peer-reviewed grants and collaborative publications. The Program is supported by $10,374,531 in peer-reviewed funds (annual direct costs) from NCI, other NIH, DOD and CDC. Of this, $4,225,820 (41%) is NCI funding (exclusive of SEER funding). Program Members published 263 cancer-relevant, peer-reviewed articles between 2000 and 2005; 16% of those represent intra-programmatic collaboration and 4% inter-programmatic collaboration. Program members serve in national leadership roles in multiple cooperative group initiatives and in NIH review panels. The large number of collaborative publications, the success at obtaining peer-reviewed funding, and the national leadership roles played by Program members document the excellence of the interactive efforts of this Program. Major programmatic research accomplishments include: the identification of epigenetic events, critical to the risk and progression in lung cancer; the identification of disparate risk for breast cancer prognostic markers between Hispanic and non-Hispanic white women; and the demonstration of a protective role for sun exposure in melanoma survival that may be due to the metabolism of Vitamin D. These findings set new directions for research into the fundamental biology of these cancers and will help direct the establishment of biomarkers to identify high-risk individuals for intervention.

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Grant project title 16:	Supporting New Faculty Recruitment Through BioMedical Research Core Center
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$1,119,435
Grantee organization:	University of Minnesota Twin Cities 450 McNamara Alumni Center Minneapolis, MN 55455-2070
Grant category:	New applications

Abstract description:

The University of Minnesota Pulmonary, Allergy, Critical Care & Sleep (PACCS) Division has been systematically recruiting additional physician scientists focused on lung injury and repair to join the tenure track faculty. Our faculty met and identified a significant gap in our faculty research interest profile in this area - respiratory infections. This area is not only of great importance as a public health issue in the US and worldwide, it is also an area with outstanding multi-disciplinary, collaborative scientific opportunities at the University of Minnesota. Within the PACCS Division, among our NIH-funded PIs, there are 7 faculty with expertise in lung inflammation and injury. In addition, there are three academically strong Centers and programs pertinent to our proposed recruit, providing a dynamic research environment to promote scientific growth and career development. The Center for Infectious Disease, Microbiology & Translational Research brings together faculty from the Medicine, Pediatrics and Microbiology Departments in interdisciplinary translational research on microbial pathogenesis. The Center for Lung Science and Health provides a home for faculty and students from across the Academic Health Center and larger University with interests related to lung health and disease. Finally, the University of Minnesota has an internationally renowned Cystic Fibrosis program. While this program is outstanding in clinical care and clinical trials activity, the basic research component is less strong. Thus a major recruitment target area of the PACCS Division is for a physician-scientist with research focused on respiratory infections, particularly with relevance to lung injury in Cystic Fibrosis. Our proposed P30 recruit, Bryan Williams MD, PhD is completing his fourth year of Pulmonary, Critical Care & CF fellowship at Vanderbilt University. His research focus is on host-pathogen interactions in respiratory infections, specifically exploring the role of a polyamine precursor, agmatine, that is important in Pseudomonas infections and in biofilm formation. He obtained his Microbiology PhD under the mentorship of Dr. Arnie Smith studying Hemophilus infections and his post-doctoral fellowship research has been supervised by Dr. Timothy Blackwell. Dr Williams' research relates directly to his clinical interest in CF-related lung dise disease, enabling convergence of his research and clinical program. The recruitment of Bryan Willliams MD, PhD will add the new dimension of expertise in respiratory infections to the PACCS Divisional research It will greatly augment basic research in the Cystic Fibrosis Center program and will provide a research bridge between the Center for Lung Science and Health and the Center for Infectious Disease, Microbiology Translational Research. Dr Williams's research brings an innovative approach to understanding and decreasing Pseudomonas infection in CF patients.

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Grant project title 17:	Cell Based Therapy for Lung Disease
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$999,999
Grantee organization:	National Jewish Health 1400 Jackson Street Denver, CO 80206
Grant category:	New applications

Abstract description:

We propose to build a new paradigm for advancing and transforming patient care through development of cell-based therapies for human lung disease. Analysis of acute lung injury in mice indicates that epithelial damage can prestage loss of alveolar structure and function. These data support the hypothesis that cell-based therapy focused on replacement of the damaged epithelium can ameliorate morbidity and mortality associated with high risk diagnosis and progression to acute lung injury. Our analysis of lung epithelial stem and facultative progenitor cells suggests that the latter cell type exhibits optimal characteristics for replacement of injured epithelial cells as well as restoration of critical homeostatic functions. Based on these studies we propose to use competitive repopulation to test the hypothesis that facultative progenitor cells can repopulate the injured airway or alveolar epithelium in the context of acute lung injury. These hypotheses will be tested using functionally distinct populations of human lung facultative progenitor cells, basal and the alveolar type II cells. These cell types are known to maintain and regenerate the normal bronchial and alveolar epithelial compartments. Acute and progressive aspects of acute lung injury will be represented using a novel mouse model that recapitulates the morbidity and mortality of acute lung injury on post-treatment days 5 and 10. Previously developed cell isolation methods and this unique mouse model will be combined to determine: (1) the characteristics of the most promising target patient population for cell-based therapy; (2) the best cell type for treatment of early and late acute lung injury; and (3) preclinical parameters including optimal route, dose, and timing of treatment. Successful completion of this study will propel the field of cell replacement therapy for lung disease beyond the planning stage and into a position appropriate for initiation of clinical trials. The limitations of previous analyses will be overcome through implementation of an appropriately powered analysis of intersections between time, cell type, route, and dose. Trials for refinement of the treatment protocol and evaluation of consistency among donor cell populations are advanced components of the study design. Outcomes will be evaluated through quantitative measurements that are germane to pulmonary function. This novel intervention strategy has the potential to ameliorate morbidity and mortality in the almost 200,000 American citizens that suffer from acute lung injury associated with trauma, aspiration, or infection each year. Among these patients there are nearly 75,000 deaths per year. This benefit will be achieved through development of new treatment strategy and through facilitation of research focused on engineering approaches to lung regeneration or replacement. Thus, focused evaluation of the fundamental parameters highlighted in this pre-clinical trial will advance the emerging field of cell based therapy and regenerative medicine approaches to treatment of acute lung injury.

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Grant project title 18:	Development of an Asthma Research Core Center
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$994,437
Grantee organization:	Children's Hospital Med Ctr (Cincinnati) 3333 Burnet Ave Cincinnati, OH 45229-3039
Grant category:	New applications

Abstract description:

Asthma, a chronic inflammatory disorder of the airways, is estimated by the World Health Organization to affect 150 million people worldwide and its global pharmacotherapeutic costs exceed $5 billion per year. Cincinnati Children's Hospital Medical Center (CCHMC) provides clinical care to -7000 asthmatic children in the primary care and specialty clinics. Last year, over 3000 children were treated in the CCHMC Emergency Department with the primary diagnosis of an acute asthma exacerbation, and 885 patients (29.5%) were admitted to the hospital for management of acute asthma exacerbations. CCHMC has invested considerable resources to promote asthma research including the establishment of the Division of Asthma Research, which has partnered with the Asthma Center to create a comprehensive Asthma Program, which now provides a central base for the clinical and research activities for asthma at CCHMC. Patients suffering from asthma share similar clinical symptoms, but the disease is heterogenous in terms of phenotypes and natural history 3, 4. This heterogeneity contributes to the difficulty in both studying and treating asthma. The heterogeneity in asthma is poorly understood and the mechanisms by which genetic and environmental influences impact asthma development and asthma disease expression are largely unknown. As such, the proposed Asthma Research Core has the central goal of improving the understanding of the heterogeneity in asthma. In order to accomplish this goal, we propose 2 aims: Aim #1: To recruit or promote a new faculty member into the tenure track to develop a research program focused a topic relevant to elucidating the mechanisms contributing to asthma heterogeneity. Aim #2: To develop a pilot research program in Asthma Research to support new faculty in the tenure track in the areas outlined above. The frequency of absent or incomplete efficacy in asthma treatment is as high as 70%, due to the inherent heterogeneity in asthma phenotypes caused by multiple genetic and environmental influences. The central goal of this proposal is to improve the understanding of the heterogeneity in asthma. Improved understanding of asthma phenotypes will enable informed personalized treatment plans and likely will result in substantial reduction in asthma expenditures.

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Grant project title 19:	Genome-Wide Association and Exon Sequencing Study in IPF
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$1,000,000
Grantee organization:	University of Chicago 5801 S Ellis Ave Chicago, IL 60637
Grant category:	New applications

Abstract description:

Idiopathic Pulmonary fibrosis (IPF) is a progressive untreatable lung disease. IPF has eluded causal genetic determinants that may provide targets for novel therapeutic approaches. The objective of this proposed research is to identify causal genetic variants contributing to risk of IPF using a Genome-wide association studies (GWAS) panel in a large complied cohort. Each DNA sample is accompanied by detailed phenotypic data. To meet this objective we have the following specific aims: Specific Aim 1. To establish a combined cohort of over 700 IPF patients and perform a Genome Wide Association Study (GWAS) in 450 subjects with IPF. The hypothesis to be tested is that inheritable genetic factors affect individual susceptibility of IPF. To accomplish this we will establish clinically meaningful definitions for disease phenotypes in a merged manually and electronically curated database of all 700 collaborator patient sample sets of IPF patients and then perform a complete a GWAS using Affymetrix SNP 6.0 GeneChip(R) in 450 IPF patients and deposit the GWAS genotype and phenotype data in the NIH repository in dbGap. Specific Aim 2. Conduct both standard and novel analyses in genetic variation by phenotypes severity and rapidity of progression. The hypothesis to be tested is that inheritable genetic factors influence prognosis and severity of the disease. To accomplish this we will determine SNPs associated with IPF utilizing publicly deposited genotyped control GWAS data and evaluate copy number polymorphisms via available probes, and test for association with IPF phenotypes and determine if the associated variants differ in frequency between subjects with "rapidly progressive" IPF with high mortality versus those with "slow" IPF, severity grade or other clinical outcome measures Specific Aim 3. Perform Exon-Wide targeted DNA sequencing and genotyping to validate the GWAS associated genetic variants and to discover functional variations in Caucasians and African Americans with IPF. The hypothesis to be tested is that Exon-Wide sequencing of subjects with different ethnic and racial backgrounds and severity cohorts will allow the identification of causal/ functional variants associated with IPF. We will replicate the most significant associations with a selective SNP array in a replicate IPF patient cohort of 200 subjects and then perform Exon-wide sequencing of 48 genes in 160 Caucasian and African American subjects using Illumina 454 technology and conduct a statistical analysis of exon variants discovered in sub- aim b. We expect that completion of a genome-wide association study using clinically meaningful phenotypes coupled to exon-wide re-sequencing will lead to identification of the genes and the specific genetic variants that contribute to the development of IPF. This can then be used as guide to lead to new approaches for preventing and treating this deadly disease.

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Grant project title 20:	New Faculty Recruitment to Enhance Resources in Hypertension Research
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$1,300,399
Grantee organization:	Tulane University Of Louisiana 6823 St Charles Ave New Orleans, LA 70118
Grant category:	New applications

Abstract description:

The mission of the Tulane Hypertension and Renal Center of Excellence (THRCE) is to stimulate research activities related to cardiovascular, kidney, and hypertension related diseases and is a multidisciplinary Center with members from clinical and basic science departments. This application proposes to augment and expand biomedical research efforts in the area of cardiovascular and hypertension related diseases by hiring one newly independent investigator (Nil) and providing a start-up package and all resources and support needed for the Nil to develop a competitive research program. We propose to appoint Romer A. Gonzalez-Villalobos, MD, PhD, a postdoctoral fellow, as a tenure track assistant professor in the Department of Physiology. With this plan, the center seeks to provide the new faculty with an enriched environment, and enhance the center's research resources by creating a new core for cardiovascular and renal mouse phenotyping. In this regard Dr. Gonzalez is uniquely qualified to perform phenotyping studies in mice by virtue of his academic background, experience and technical training. For the pilot project Dr. Gonzalez- Villalobos has formulated the hypothesis that during Ang Il-induced hypertension, intrarenal ACE-derived Ang II formation is required in order to augment Ang II levels in the kidney that in turn increase sodium and water retention, increase miR-21 expression, and lead to the progressive development of high blood pressure and renal injury. Experiments will be performed in tissue-specific ACE knockout mice in order to address this hypothesis. The plan for fostering and monitoring the NII includes providing the candidate with the requisite infrastructure, equipment and technical support; establishing an atmosphere conducive to a strong collaborative network; providing a forum for critical evaluation of experimental design, results, papers and grant proposals; and encouraging the candidate's attendance and participation in national and international meetings as well as involvement in scientific societies and active pursuit of funding. The proposed plan will provide the means to develop and support the new faculty in his quest to improve our understanding of the mechanisms participating in angiotensin II synthesis in the kidneys and its role in the development of hypertension. This is important because angiotensin II is a hormone that plays a major role in the control of renal function, the development of hypertension and kidney damage.

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Grant project title 21:	Advancing Physical Activity Measurement Using Pattern Recognition Techniques
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$985,004
Grantee organization:	University of Massachusetts Amherst 70 Butterfield Terrace Amherst, MA 01003-9242
Grant category:	New applications

Abstract description:

In October, 2008 the US Department of Health and Human Services issued the first-ever federally mandated Physical Activity Guidelines for Americans. The Guidelines reflect the view of the Physical Activity Guidelines Advisory Committee (PAGAC) and are based on an extensive review of the scientific literature on physical activity (PA) and health. In their report, the PAGAC points out the limited knowledge of the doseresponse relationship between PA and health, and identifies poor measures of PA exposure as a major contributing factor to this gap in knowledge. Our application directly addresses this issue by applying innovative technologies to measure PA dose in a free- living environment. We will use these technologies to examine if habitual PA performed outside of purposeful exercise influences biomarkers of cardiovascular health. Although insufficient PA clearly correlates with an increased risk for cardiovascular disease (CVD), research evidence is equivocal regarding the effects of training on CVD risk factors (e.g. insulin action, triglycerides, blood pressure, and cholesterol). Research suggests increases in sedentary behavior may negate the benefits of training however this idea has not been explored experimentally. Our application will consider habitual free-living PA as a possible mechanism mediating the relationship between training and risk factors for cardiovascular disease. In order to elucidate the relationship between PA and biomarkers of cardiovascular disease risk, it is critical that valid, objective measures are used to quantify PA. We propose to use novel analytic techniques known as artificial neural networks (ANN) to process accelerometer-based measurements of PA. The first part of this project (Aim 1) will examine the ANN's sensitivity to change in PA dose by applying the ANN technique to distinguish three distinct patterns of habitual PA - Sedentary, Moderately Active, and Very Active. These three conditions represent common activity patterns that impact health. Accurately assessing changes to habitual PA levels that are relevant to public health will advance the field by further establishing a technique for application in population surveillance research and detection of changes in PA consequent to an intervention. The second part of this project (Aim 2) will apply the ANN methodology to examine the effect of free-living activity and inactivity levels, performed outside of training, on insulin action, blood pressure, triglycerides, cholesterol, and cardiorespiratory fitness following a 12-week exercise training trial in previously sedentary individuals with an elevated risk for CVD. Results from this study have the potential to impact how clinical exercise trials are conducted (e.g. require objective monitoring of PA outside of an exercise training trial) and how exercise is prescribed (e.g. reducing sedentary time AND maintaining sufficient PA). The Physical Activity Guidelines Advisory Committee advocates improved measures of physical activity exposure in order to elucidate the relationship between physical activity dose and health. To address this challenge we will apply and validate innovative accelerometer-based technologies for measuring physical activity to assess its sensitivity to detecting changes in dose of physical activity and to monitor activity outside of a training program designed to improve cardiorespiratory fitness and biomarkers of cardiovascular disease risk. Through improved measures of physical activity this project will promote a better understanding of how the dose of physical activity affects selected health outcomes.

Source: NIH.

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Grant project title 22:	ECG-derived cardiopulmonary coupling biomarkers of sleep, sleep-breathing, and ca
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$1,000,000
Grantee organization:	Beth Israel Deaconess Medical Center Boston, MA 02215
Grant category:	New applications

Abstract description:

The traditional approach to quantifying sleep and sleep-respiration relies on manual or computer assisted scoring of 30 second epochs, tagging of discrete fast phasic electroencephalographic events as arousals, and thresholds to identify pathological breathing. The scoring rules are usually reliant on a single physiological stream to make a determination, such as arousals from the electroencephalogram. However, arousing stimuli reliably induce simultaneous transient changes in numerous physiological systems - electrocortical, respiratory, autonomic, hemodynamic, and motor. These multiple linked physiological systems seem to show important patterns of coupled activity that current staging / scoring systems do not recognize. The respiratory chemoreflexes track oxygen (O2) and carbon dioxide (CO2) levels in the blood. Disease states can alter the set-point or response slope of the respiratory chemoreflexes, such that they are less (e.g., obesity hypoventilation syndrome) or more (e.g., central sleep apnea) sensitive to O2 and CO2 fluctuations. An ability to quantify and track the respiratory chemoreflexes during sleep could have clinical use, as (1) In certain conditions like congestive heart failure, chemoreflex sensitivity is reliably increased, correlates with disease severity and outcomes, and contributes to the high prevalence of sleep-disordered breathing. (2) Heightened respiratory chemoreflexes may contribute to obstructive sleep apnea severity, be associated with induction of central apneas when continuous positive airway pressure (CPAP) is used for treatment, and possibly impair long term efficacy and tolerance. Patients with obstructive sleep apnea who fail CPAP therapy due to induction of central apneas and periodic breathing (called “complex sleep apnea”) are not otherwise distinguishable from CPAP-responsive patients. A biomarker that can track chemoreflex modulation of sleep respiration will provide a new view of short and long-term dynamic sleep physiology with important clinical implications. The approach proposed here is to analyze coupled sleep oscillations to mathematically extract state characteristics and modulatory influences. The fundamental idea is that mapping common themes encoded within multiple (2 or more) physiologically distinct but biologically linked signal streams (such as electrocortical, autonomic, respiratory and motor) yields evidence of deeper regulatory processes not evident by the current approach of scoring / staging sleep with electroencephalogram or airflow patterns alone. We have developed a method that needs only a single channel electrocardiogram (ECG), is automated, can have parametrically varied detection thresholds, and is readily repeatable. From the ECG, we extract heart rate variability (HRV) and ECG Rwave amplitude fluctuations associated with respiratory tidal volume changes (the ECG-derived respiration, EDR). The next step is to mathematically combine the HRV and EDR to generate the cross-product coherence of cardiopulmonary coupling, which yields the sleep spectrogram. The sleep spectrogram shows high (0.1-1 Hz, low (0.1-0.01) and very low (0.01-0 Hz) coupling spectra that show spontaneous shifts between states in health and disease. High frequency coupling (HFC) is the biomarker of stable and physiologically restful sleep, low frequency coupling (LFC) is unstable or physiologically aroused sleep, and very low frequency coupling (VLFC) is wake or REM sleep. Health is dominated by HFC, diseases such as sleep apnea by LFC. A subset of LFC that correlate with apneas and hypopneas is elevated LFC (e-LFC). The stronger the chemoreflex modulatory influence on e-LFC, the more likely the coupling spectral dispersion narrows, yielding narrow band e-LFC (i.e., metronomic oscillations with a relatively fixed frequency). Narrow band e-LFC is induced by high altitude, heart failure, and predicts central apnea induction during positive pressure titration. The development and progression of heart failure is associated with fragmented sleep and heightened chemoreflex sensitivity. We predict that HFC will decrease and narrow band e-LFC will emerge and increase with worsening heart failure. These spectral biomarkers should change dynamically with heart failure progression or regression - viewing cardiac function through the window of sleep. Our experiments will take the following approach. We will establish the hemodynamic correlates of spectrographic stable and unstable sleep and night-to-night stability / variability of the ECG-derived biomarkers in adults and children in health, and in those with sleep apnea. Next, we will use a model of altitude-induced periodic breathing, which is relatively pure chemoreflex-mediated sleep apnea, to adjust the spectrogram’s parameters that allow the best sensitivity and specificity for detecting chemoreflex influences on sleep respiration. We will in parallel track the progress of heart failure patients from a hospitalization episode for 6 months, attempting to show that reductions of HFC and emergence or increases in narrow band e-LFC are sentinel biomarker events that predict worsening of heart failure (an early warning system). Finally, we will assess clinical outcomes based on spectral phenotyping of an archived data set, the Apnea Positive Pressure Long-term Efficacy Study. In the 2-year duration of the award, we will validate a unique biomarker of sleep, sleep-breathing, and cardiovascular biology that can be applied immediately to improve health outcomes.

Source: NIH.

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Grant project title 23:	Development of a Cardiovascular Surveillance System in the CVRN
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$7,217,106
Grantee organization:	Kaiser Foundation Research Institute Oakland, CA 94612
Grant category:	New applications

Abstract description:

This project will establish a surveillance system for cardiovascular disease in approximately 11 million health maintenance organization (HMO) members. The surveillance system will be initially established for coronary heart disease (CHD), heart failure (HF), and stroke. The broad goals of this project are to: 1. Establish a surveillance system for coronary heart disease (CHD), heart failure (HF) and stroke in the 15 centers of the National Heart Lung and Blood Institute (NHLBI) funded Cardiovascular Disease Research Network including therapeutic interventions, post-event outcomes and important risk factors and confounders. 2. Work collaboratively to establish and implement an aggregate database incorporating coronary heart disease CHD, HF, and stroke data from all 15 CVRN sites that can be used by CVRN investigators and other qualified research scientists to conduct studies related to comparative effectiveness and health disparities. 3. Identify standard criteria for coronary heart disease, heart failure and stroke clinical outcomes, as well as all components noted in goal #1 to enable data aggregation 4. Determine the most recent 10-year trends in the rates of acute myocardial infarction and stroke hospitalization and their relationship to trends in risk factors, co-morbidities, therapeutic interventions, medications, and diagnostic modalities. 5. Demonstrate that the data can be used to address research questions regarding comparative effectiveness and novel methods of monitoring health disparities, areas that have been identified as RC2 topics by NHLBI. This project will result in a surveillance system in a consortium of 15 geographically diverse health plans that provide health care to about 11 million people, nearly 4% of the U.S. population. This surveillance system will be significantly larger than other existing cardiovascular surveillance efforts in the U.S. and includes a population that is diverse in race/ethnicity and sociodemographic characteristics. The surveillance system will include for CHD, HF, and stroke electronically available data on risk factors, co-morbidities, prescription medications, therapeutic interventions, and laboratory testing, and physician and patient characteristics. These data can be utilized to provide timely surveillance reports for CHD, CF, and stroke; a comprehensive description of a patient's longitudinal course both prior to and subsequent to development of CHD, CF, and stroke; and enable research questions to be addressed that assess the relationship of these variables to the course of disease as well as to address research questions relating to comparative effectiveness and to disparities in medical treatment and outcomes.

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Grant project title 24:	Novel Imaging to Predict Cardiovascular Events in Diabetes
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$1,625,296
Grantee organization:	Mount Sinai School of Medicine of NYU New York, NY 10029-6574
Grant category:	Existing applications

Abstract description:

Novel non-invasive imaging tests have been developed to characterize atherosclerotic plaque burden and metabolic activity (inflammation). However, the value of these atherosclerosis imaging technologies for predicting coronary heart disease (CHD) and stroke events has not been evaluated in prospective studies. Proposed is a study to conduct noninvasive imaging and longitudinal follow-up in a high risk cohort of patients with diabetes by utilizing the recruitment network, events follow-up protocol and adjudication committee assembled by the NHLBI-sponsored FREEDOM Trial (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease - HL071988). Specific aims of our study are (1) to determine the association of atherosclerotic plaque burden and the risk of CHD and stroke events and all cause-mortality; (2) to determine the association between traditional CHD risk factors and atherosclerotic plaque burden; and (3) to determine the association between plaque burden and plaque inflammation. In order to accomplish these aims, we will recruit 380 diabetic patients with multi-vessel coronary disease from eleven greater New York metropolitan area hospitals. Patients will complete a baseline study visit at Mount Sinai School of Medicine (MSSM) to assess plaque burden and plaque inflammation by magnetic resonance (MR) (contrast and non contrast) and fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging. Additionally, questionnaires will be administered, a physical examination conducted and blood specimens collected to measure hemostatic and inflammatory markers. Patients will be actively followed for 36 months through annual inperson study visits and bi-annual telephone follow-up. When events (mortality, non-fatal MI and non-fatal stroke) are identified, hospital charts and death certificates will be reviewed by an adjudications committee, blinded to the baseline measurement values. Changes in plaque burden and inflammation will be assessed through MR and FDG-PET imaging, respectively, at the 36 month follow-up visit again at MSSM. The proposed study will provide the unique opportunity to assess atherosclerotic plaque burden as a predictor for clinical events in a high risk patient cohort. Data from this study will not only advance our understanding of the aggressive atherosclerotic process associated with diabetes but will also provide us with a strategy to combine novel noninvasive approaches to better follow the effects of medical and revascularization therapy in the diabetic patient. It is our expectation that data from the proposed study will be utilized to evaluate and improve existing treatment and help guide the development of effective new therapies aimed at reducing CHD and stroke events and improving survival in high risk diabetic patients.

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Grant project title 25:	Pneumocystis jirovecii and macrophages in COPD
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$148,416
Grantee organization:	University of Kentucky 109 Kinkead Hall Lexington, KY 40506-0057
Grant category:	Existing applications

Abstract description:

Airway inflammation, airway remodeling, colonization with microorganisms, and parenchymal destruction are hallmarks of chronic obstructive pulmonary disease (COPD). In addition to cigarette smoking, infectious pathogens likely contribute to the decline in pulmonary function in COPD patients. The inflammatory process in patients with COPD displays a distinct pattern of inflammatory mediators and immune cells that are involved that are similar to the pattern seen in response to Pneumocystis jiroveci (PC). Evidence has now emerged on the importance of macrophage phenotype in COPD patients. Macrophages account for the majority of inflammatory cells recovered from bronchoalveolar lavage from COPD patients and are localized to sites of alveolar destruction. Further, the IL-4/IL-13 alternatively activated macrophage phenotype (AAM) has been implicated in several chronic lung diseases. We propose in this study to evaluate the relationship between the AAM and PC in lungs of COPD patients in the Lung Tissue Research Consortium. In 3 Aims we will (1) correlate PC colonization with the presence of AAMs in lung tissue samples, (2) determine through immunohistochemistry how the presence of PC correlates to the precise localization of macrophage phenotype and fibrosis, and (3) determine how PC burden and AAMs correlate to clinical outcome measurements. This project will investigate a novel mechanism of pathogenesis which may provide targets for potential future therapeutic interventions for patients with COPD.

Source: NIH.

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Grant project title 26:	Pathological Consequences of the Plasminogen System
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$750,000
Grantee organization:	University of Notre Dame 940 Grace Hall Notre Dame, IN 46556
Grant category:	Existing applications

Abstract description:

The long-term goal of this proposal is to identify functions and determine mechanisms of the fibrinolytic system, and its inhibitors, in physiological and pathological processes utilizing cell-based and in vivo models. The availability of mice with deficiencies of genes of the fibrinolytic system has resulted in direct analyses of the role of these proteins in a number of biological events. Studies have indicated that a PAI-1 deficiency diminishes angiogenesis in tumor models. Further, our laboratory has shown that endothelial cell (EC) signaling and function are regulated by PAI-1/LRP interactions. The current application will further elucidate effects of PAI-1 on cell signaling pathways and determine the importance of PAI-1/LRP interactions in both cellular and physiological events. As a result of these observations, the following studies are proposed: (1) Determine the effects of a PAI-1 deficiency on murine EC JAK/STAT signaling and cell cycle progression. These studies will assess STAT and JAK expression profiles and activation status in proliferating wild-type (WT) and PAI-1-/- EC as well as the extent of nuclear translocation of STAT. The addition of rPAI-1 and mutants will determine which functional domains of PAI-1 regulate the activation status of this pathway. Additional studies will determine effects on cell migration. Downstream effects on cell cycle progression will also be investigated. The hypothesis is that a PAI-1 deficiency will affect JAK/STAT signaling and downstream cell cycle progression, and that these effects are mediated by PAI-1/LRP interactions. (2) Characterize early and late stage events of cardiac fibrosis in PAI-1-/- and uPA-/-/PAI-1-/- mice. Recent studies have shown that PAI-1-/- mice develop cardiac fibrosis, which may be mediated by dysregulated uPA or chronic activation of the Akt pathway, the result of altered PAI-1/LRP interactions. The studies proposed will initially characterize cardiac fibrosis in PAI-1-/- and uPA-/-/PAI-1-/- mice in order to differentiate effects from uPA activity and PAI-1 functions independent of uPA inhibition in cardiac fibrosis phenotypes. The hypothesis is that cardiac fibrosis will be regulated by urokinase activity and other functions of PAI-I which will be further pursued in future studies of mice expressing functional mutations of PAI-1.

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Grant project title 27:	Pilot Test of a Novel Behavioral Intervention on BP Control in HTN Patients
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$1,506,522
Grantee organization:	Pennsylvania State University-Univ Park 110 Technology Center Building University Park, PA 16802
Grant category:	Existing applications

Abstract description:

Patients' knowledge concerning their chronic illness has long been considered "necessary but not sufficient" to produce changes in risk-related behaviors. "Necessary" implies that patient knowledge is, therefore, a moderator of the effectiveness of behavioral interventions. However, researchers have tended to ignore patient education as a critical component of behavioral (or, for that matter, pharmacological) interventions. We propose to combine a behavioral intervention that we and others have found to be moderately effective in increasing blood pressure (BP) control in hypertensive patients - using a home BP monitor (HBPM) to obtain feedback regarding their BP control, and providing feedback to the health provider - with a systematic patient education component. We propose an intervention strategy that is meant to be usable as an adjunct to the HBPM and other interventions; one that will increase patients' knowledge, and, we hypothesize, will therefore increase the effectiveness of the "parent" intervention (HBPM, in this case). Our proposal is for a randomized controlled trial (RCT), using a 2X2 factorial design in which we will test the effect of (1) a patient education intervention and (2) HBPM, on ambulatory BP in poorly-controlled hypertensive patients at 3 and 6 months. The education intervention is based on a technique called "Self-Paced Programmed Instruction" (SPPI), a method that has been remarkably effective at increasing knowledge concerning complex topics. Using a computer, a paragraph of content material is presented, followed by probe questions. When patients provide a correct response, they are immediately reinforced by positive feedback; an incorrect response loops the program to represent the materials, this time with hints; and the subjects then re-attempt the probe questions. The loop continues until a correct answer is recorded. In this manner, every subject achieves mastery over the requisite material. We posit that medication adherence (assessed objectively) will partially mediate the ambulatory BP outcomes; and that Self-Efficacy for the self- management of HTN will mediate medication adherence; we predict that self-efficacy will be enhanced by the mastery of the HTN-related materials, and by the reduction of ambiguity, which will lead to greater confidence in the patient's decision-making processes. We predict that the SPPI - HBPM condition will have the greatest effect on ambulatory BP, compared to the other three groups.

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Grant project title 28:	CRP, Diabetes, Atherothrombosis
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$908,083
Grantee organization:	University of California Davis Office of Research – Sponsored Programs Davis, CA 95618
Grant category:	Existing applications

Abstract description:

In the previous proposal, the central hypothesis was to determine if CRP promotes atherothrombosis by effects on both endothelial cells and monocytes. We have now executed all four aims of this proposal and have advanced the field with regards to the vascular effects of CRP. In summary, we have elucidated the molecular mechanism by which CRP inhibits eNOS (in-vitro and in-vivo), we have documented the role of Fc-gamma receptors in the biological effects of CRP on endothelial cells, macrophages and in Wistar rats. Furthermore, we have elucidated the mechanism of CRPinduced monocyte adhesion under shear stress, and finally we have confirmed in-vivo, in Wistar rats, that CRP has effects that promote atherosclerosis including stimulation of NADPH-oxidase, superoxide, MPO release, oxidized LDL uptake, tissue factor, MMP-9 release from macrophages and decreased vasoreactivity. Diabetes is a proinflammatory state that is characterized by high CRP levels. However, there is a paucity of data examining the role of CRP in promoting the pro-inflammatory state in diabetes. We have shown in exciting and novel preliminary data that CRP exacerbates in-vivo the pro-inflammatory, pro-oxidant effects in the diabetic milieu (spontaneously diabetic BB rat). Thus, in this competing renewal, we wish to further explore the effects of CRP on diabetes and atherothrombosis. To this end, we are proposing two specific aims. In specific aim 1, we will continue to expand our exciting preliminary findings that CRP accentuates the pro-inflammatory, pro-oxidant state in the diabetic BB rat. In this model, we will confirm if CRP exacerbates in-vivo the pro-inflammatory, pro-oxidant effects in the diabetic milieu and also elucidate the molecular mechanism (s) by which CRP exerts these effects by employing in-vivo siRNA and antisense oligonucleotides to the different pathways identified. Based on findings largely from our group and others, that CRP promotes a pro-coagulant phenotype, in Specific Aim 2, using the spontaneously diabetic BB rat, we will now test in-vivo the effect of CRP on thrombosis in the diabetic milieu. Also, we will elucidate the mechanism (s) by which CRP promotes atherothrombosis in the diabetic state. We believe these studies will provide further novel data in support of the hypothesis that CRP promotes atherothrombosis in-vivo and a procoagulant, pro-inflammatory phenotype in diabetes. Probing into the molecular mechanisms by which CRP augments oxidative stress and inflammation in the diabetic milieu will eventually lead to therapies targeted at reducing inflammation and oxidative stress in diabetes and resulting in a decrease in vasculopathies.

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Grant project title 29:	Genetic control of gene expression during innate immune activation
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$249,216
Grantee organization:	University of Washington Office of Sponsored Programs Seattle, WA 98195-9472
Grant category:	Supplements and revisions

Abstract description:

Innate immune responses are induced by specific interactions between pathogen-associated molecules and Toll-like receptors (TLRs), and are critical to host defense. Recent studies have shown a role for TLR7 and TLRS in innate immune responses to viral infection. However, it is unknown to what extent these innate immune responses are heritable and what loci might affect this heritability. Our overall hypothesis is that heritable variation exists in gene expression levels measured during an innate immune response to virus-associated molecules. We propose to study this hypothesis in the context of innate immune responses to synthetic agonists specific for TLR7 (imiquimod) or both TLR7 and TLR8 (R848). First, we will determine genome-wide heritability of R848-induced changes in gene expression using a classical twins study. We will then identify quantitative trait loci (QTL) that control heritable variation in TLR7-induced gene expression in B-lymphoblastoid cell lines (B-LCL) isolated from 'HapMap' trios, and we will fine-map the functional polymorphisms within these QTL in a large cohort of healthy individuals. Finally, we will apply in vitro assays of promoter function and RNA processing to understand how these polymorphisms affect gene expression. The proposed studies will identify specific genetic loci controlling heritability of TLR7/8- mediated innate immune responses and more broadly, basic mechanisms underlying the genetic control of gene expression in environmentally perturbed cells. Results from these studies will provide novel potential markers of susceptibility for both common and emerging viral infection and will characterize a new experimental pathway for discovery of functional genetic variation affecting responses to environmental stimuli.

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Grant project title 30:	Negative regulation of platelet activity
Administering IC:	National Heart, Lung and Blood Institute
Grant award size:	$260,197
Grantee organization:	Bloodcenter of Wisconsin, Inc. P.O. Box 2178 638 N 18th St Milwaukee, WI 53233
Grant category:	Supplements and revisions

Abstract description:

Platelets are anucleate bodies that circulate in the bloodstream and play a very important role in vascular hemostasis. Platelets circulate in a quiescent state in intact blood vessels but they adhere to and become activated by exposed extracellular matrix in a damaged vessel. Activated platelets spread out and bind to one another (i.e., form a thrombus), so as to close up the damaged area and initiate wound healing. Excessive bleeding occurs when platelets are deficient or hypo-responsive and pathological thrombus formation, which can result in occlusion of blood vessels and cause myocardial infarction or stroke, occurs when platelets are hyper-reactive. Because the extent of platelet activation is such an important determinant of vascular pathology, it is very important to understand how platelet activation and aggregation are regulated. The platelet contains several cell surface and intracellular proteins that coordinate transmission of activating and inhibitory signals into the platelet interior, and it is the balance of stimulatory and inhibitory cues that ultimately determines the platelet activation state. Whereas much has been learned in recent years regarding the platelet receptors and signaling cascades that contribute to platelet activation, key components of which are members of the Src Family of protein tyrosine Kinases (SFK), the molecules and pathways responsible for keeping platelet activation held in check remain poorly defined. We and others have previously demonstrated that Platelet Endothelial Cell Adhesion Molecule-1 (PECAM-1, also called CD31) and the SFK, Lyn, are negative regulators of platelet activation. Previous studies in our laboratory have also begun to characterize, in platelets, a pathway by which C-terminal Src kinase (Csk) is recruited to sites of SFK activity by Csk Binding Proteins (CBP), so that Csk may carry out its important role as a negative regulator of SFK activity. In particular, our preliminary studies have revealed that a member of the Downstream of kinase (Dok) family, Dok-2, is a CBP in platelets. The overall goal of this new grant application is to develop a more complete list of inhibitory molecules in platelets, to thoroughly characterize the signaling pathways in which these molecules function, and to improve our understanding of how these molecules and pathways interact with one another to ultimately influence the platelet activation state. Specifically, over the next three-year period, we propose to: (1) determine the contribution of the inhibitory SFK, Lyn, to the inhibitory function of PECAM-1 and (2) determine how Csk binding to Dok-2 contributes to negative regulation of platelet activation. Together, these studies comprise a coordinated, focused research program designed to improve our understanding of negative regulation of platelet activation by identifying, characterizing, and examining the interactions between inhibitory receptors and signaling molecules in platelets, such as PECAM-1, Lyn, and Dok-2. We expect that information derived from this investigation has the potential to lead to improved diagnosis and treatment of bleeding disorders, myocardial infarction and stroke.

Source: NIH.

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Grant project title 31:	Amplification of Antiviral Innate Immunity by Suppressor of Virus RNA (svRNA)
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$999,998
Grantee organization:	Cleveland Clinic Lerner COL/MED-CWRU JJN5-01 Cleveland, OH 44195
Grant category:	New applications

Abstract description:

RNA cleavage is a fundamental and ancient host response for controlling viral infections in both plants and animals. In higher vertebrates, including humans, RNA cleavage as a means of controlling viruses is mediated by the type I interferons (IFN) through its effector, the uniquely regulated endoribonuclease, RNase L. RNase L is activated by unusual 2',5'-linked oligoadenylates (2-5A) produced during viral infections. 2-5A activates RNase L resulting in cleavage of host and viral RNAs within single stranded regions, predominantly after UU and UA. As a result of its specificity, RNase L produces small, highly structured RNA cleavage products. In 2007 we reported that RNA cleavage products obtained from digestion of self RNA by RNase L activated RIG-I-like receptors (RLR) resulting in amplification of type I IFN synthesis. These RNA cleavage products represent a novel class of small RNA molecules named "Suppressor of Virus RNA" (svRNA). Our GOALS in this project are to clone, identify and probe the functions of svRNAs generated from both host RNA and from viral [hepatitis C virus (HCV)] RNA. Our HYPOTHESIS is that svRNAs are essential to host defense against a wide range of viruses that are pathogenic for humans. Our Specific Aims are: (1) to isolate and identify svRNA liberated by RNase L from host and viral RNA, we will cleave HCV RNA with purified RNase L and clone small RNAs that bind to RLRs, and cleave cellular (self) RNA in intact cells treated with 2-5A and clone small RNAs that bind to RLRs; (2) To characterize activation of RIG-I and MDA5 by svRNAs we will perform ATPase activation studies, determine the kinetic parameters for svRNA interactions with RIG-I and MDA5 by surface plasmon resonance, measure conformational changes in RIG-I and MDA5, and establish the sequence and structural requirement of svRNA for activation of RIG-I and MDA5; and (3) to determine the role of svRNA in antiviral innate immunity we will identify svRNAs in HCV infected cells, and determine the antiviral effects of svRNAs in mice. Our recent studies suggest an essential role of svRNAs in the antiviral state in higher vertebrates. In the proposed studies we seek to obtain a fundamental understanding of this important pathway as it relates to host defense against viruses. Therefore, there are cogent and health-related justifications for these studies.

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Grant project title 32:	Interconnectivity between genome packagaing and other viral functions
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$415,250
Grantee organization:	University of California Riverside 900 University Ave Riverside, CA 92521
Grant category:	Existing applications

Abstract description:

Information gleaned from recent studies with single-stranded, positive-sense RNA viruses pathogenic to humans and animals (polio and alphaviruses) and insects (flock house virus; FHV) revealed that the mechanism of genome packaging in these viral systems is functionally coupled to replication. Recently our laboratory adopted a novel in vivo system referred to as Agrobacterium-mediated transient expression (agroinfiltration) to study encapsidation in plants. This system not only allowed efficient expression of viral genome components either autonomously or synchronously in plant cells, but also effectively uncoupled replication from packaging. Application of the agroinfiltration system to brome mosaic virus (BMV, a plant infecting RNA virus) allowed us to hypothesize that packaging in BMV is also functionally coupled to replication. In addition, co-expression of BMV and FHV in plant cells using agroinfiltration revealed that for specific RNA packaging to occur, synchronization of replication and transcription of coat protein (CP) mRNAs from homologous replication machinery is obligatory. This two-year exploratory project is designed to evaluate, at the sub-cellular level, the intimacy of replication to packaging. An agroinfiltration system competent to synchronously infect the same plant cell with BMV and FHV will be used through out these studies. Our working hypothesis is that translation of CP followed by virus assembly occurs very close to the sites of viral replication. Thus in Aim 1, we propose to temporally and sequentially localize and identify the sub-cellular compartment(s) where translation of CP and virus assembly of BMV and FHV occurs. In addition to the molecular and biochemical characterization, delineation of CP translation and virus assembly sites at the sub-cellular level will be investigated by electron microscopy using a novel Silver Enhancement-Controlled Sequential Immunogold technique (SECSI). BMV and FHV differentially replicate on the outer membranes of endoplasmic reticulum (ER) and mitochondria respectively. We found that packaging is non-specific when BMV CP or FHV CP was expressed either transiently or via heterologous replication. Thus, experiments outlined in Aim 2 are focused in addressing, for the packaging specificity occur, whether viral progeny RNA need to be tethered to the same membrane near which it's CP is being actively synthesized. This will be investigated by retargeting the FHV replicase complex to the ER, where the synthesis of FHV CP from genetically engineered BMV RNA will be synchronized. At the completion of the project we should know whether translation of CP and assembly of virions occur at or near the replication sites and whether tethering of viral progeny RNA to the same membrane near which it's CP is being actively synthesized is obligatory to confer packaging specificity. Results obtained from this research proposal would improve our understanding concerning the mechanism of replication-coupled packaging in RNA viruses pathogenic to humans, animals and plants.

Source: NIH.

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Grant project title 33:	Targeting pDCs for the Generation of Effective Anti-HCV CD8+ T-Cell Immunity
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$429,000
Grantee organization:	Baylor Research Institute Dallas, TX 75204
Grant category:	Existing applications

Abstract description:

Hepatitis C virus (HCV) infection represents a significant global health-care problem, which is forecasted to become worse in the coming years. In the developed world, infection with HCV is responsible for 50-75% of all cases of liver cancer and accounts for two-thirds of all liver transplants. To date there are no effective vaccines to HCV and current systemic therapies have significant side effects. There is a need for novel therapeutic approaches to the treatment of chronic hepatitis C infection. The establishment of potent anti-viral CD8+ T-cell immunity has been shown to be the central mediator of viral clearance. Like many chronic infections however, such responses to HCV have been difficult to establish. Plasmacytoid dendritic cells (pDCs) are a subset of DCs which are specialized for viral recognition and the initiation of anti-viral immunity. We have shown that pDCs have specialized antigen processing compartments (MICs) which permit them to rapidly cross-present viral antigens and stimulate protective CD8+ T-cell responses. Furthermore we have demonstrated that targeting antigens to this compartment in an activated pDC is sufficient to initiate potent CD8+ Tcell responses. Our overall hypothesis is that Hepatitis C viral antigens targeted to the specialized class-I processing compartment (MIC) of pDCs will be efficiently cross-presented and drive anti-viral CD8+ T cell expansion. We propose to address this hypothesis though three aims; Aim 1: To determine if receptor trafficking into the MIC is sufficient to generate strong CD8+ T-cell responses against Hepatitis C viral antigens. We will address this hypothesis by (1) Generating antibody antigen conjugates for in vitro targeting to the MIC. (2) Assess the effect of these reagents on pDC activation (3) Demonstrate MIC targeting (4) Demonstrate cross- presentation of targeted antigen. Aim 2: To determine if antigen processing and cross-presentation by the pDC results in an expanded antigen specific T-cell repertoire. We will (1) Demonstrate that antibody antigen conjugates can induce potent HCV antigen specific CD8+ T cells responses in vitro (2) Determine the optimal CpG derivative (CICs) to enhance viral antigen specific CD8+ T cell responses (3) Make both a quantitative and qualitative assessment of total T-cell epitopes generated during cross-presentation of targeted viral antigens by pDCs. (4) Assess the quality of viral epitope response in patients chronically infected with HCV. Aim 3: The generation of a multi-epitopic adjuvant-based pDC targeting constructs We will (1) Generate fusion proteins of anti-BDCA2 and the immunodominant TC1 viral epitopes identified in Aim 2. (2) Conjugate immunostimulatory CIC sequences to this second generation pDC targeting construct. (3) Demonstrate that a multi-epitopic pDC targeting constructs can induce potent HCV antigen specific CD8+ T cells responses in vitro in patients chronically infected with HCV. Overall significance: This study provides a novel approach for therapeutic HCV vaccine development.

Source: NIH.

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Grant project title 34:	Type II secretion system of P. aeruginosa in acute lung infection
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$732,500
Grantee organization:	University of Florida 219 Grinter Hall Gainesville, FL 32611-5500
Grant category:	Existing applications

Abstract description:

Acute lung infection due to Pseudomonas aeruginosa is a common cause of death in hospitalized patients. This organism is also the major cause of death in Cystic Fibrosis. A number of virulence factors have been proposed to lead to these poor outcomes. We wish to examine the role of the toxins secreted by this bacterium's type II secretion system during lung infections. Research in this area has been inconclusive, with most recent efforts being focused on the role of the type III secretion system. However, using Toll-like-receptors 2,4 -/- mice, we demonstrate a significant role for the T2SS in death due to lung infections. We therefore wish to define how this occurs. Our aims are to identify the outer membrane protein pore through which toxic factors are secreted, identify the secreted toxic factors using an unbiased proteomics approach and examine whether there is an important role for this system in other virulent P. aeruginosa strains during lung infections. During the course of these studies we will also examine whether secretion can be blocked by antibody raised against the secretion pore. We will utilize conventional molecular biology techniques of mutagenesis and complementation as well proteomic analyses of the secreted proteins to ascertain whether there are unknown toxic factors that are being secreted or whether it is the classic virulence factors that cause death. These studies reexamine a critical question that has been left largely unanswered, and will provide valuable information on possible ways of preventing death cause by the toxins produced b this system.

Source: NIH.

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Grant project title 35:	Broad Neutralizing Monoclonal Antibodies From HIV Controllers
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$850,866
Grantee organization:	University of Maryland Baltimore 620 W Lexington St 4th Fl Baltimore, MD 21201-1508
Grant category:	Existing applications

Abstract description:

The long-term goal of this project is to identify novel monoclonal antibodies (mAbs) that broadly recognize the HIV-1 envelope glycoprotein (Env) and block infection in vitro to guide vaccine development. This goal will be pursued in a cohort of HIV-1 infected individuals who control their infections in the absence of anti-retroviral therapy (Natural Virus Suppressors/NVS) and who have circulating broadly neutralizing antibodies (broad nAbs). A key element of our approach is the development of a new assay to census Env-specific memory B cell clones (BMem) that allows the rapid and direct cloning of full-length monoclonal antibodies (mAbs). These mAbs will be characterized for epitope specificity and neutralization breadth to create clonal profiles of the BMem that are generated during the control of HIV-1 infection. This information will be used to test the hypothesis that neutralization breadth is determined by a polyclonal response comprised of a mosaic of neutralizing specificities as opposed to a pauciclonal response comprised of one or a very few neutralizing specificities. Testing this hypothesis is key to our long-term goal of identifying novel mAbs that broadly recognize Env and block infection in vitro to guide vaccine development against HIV-1. There are two specific aims. Aim 1- To develop clonal specificity profiles of Env-specific BMem from NVS who have ongoing broadly neutralizing antibody responses- Clonal specificity profiles of anti-Env responses will be determined by limiting dilution analysis, mAb isolation, and epitope mapping to determine the relative dominance of BMem clones specific for different Env-epitopes. Aim-2- To compare neutralization breadth between plasma antibodies and mAbs representing a full clonal profile of BMem to determine the number of mAbs that must be pooled to reconstruct the neutralization breadth of the circulating antibody pool. This data will be used to determine the clonality of an ongoing broad nAb response. This aim will complete testing the hypothesis that neutralization breadth is determined by a polyclonal response comprised of a mosaic of neutralizing specificities as opposed to a pauciclonal response comprised of one or a very few neutralizing specificities. Currently there is no vaccine against AIDS. The work proposed in this application will investigate how some people control HIV-1 infection for many years without anti- retroviral drug therapy. This information should be useful in making a vaccine against AIDS.

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Grant project title 36:	Nonpayment for Preventable Complications: Impact on Hospital Practices and Health
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$447,156
Grantee organization:	Harvard Pilgrim Health Care, Inc. Boston, MA 02215
Grant category:	Existing applications

Abstract description:

Financial incentives, such as pay-for-performance (P4P) programs, are increasingly being used to improve physician behavior. However, the impact of these programs on improving quality of care for patients have been mixed, with some studies showing modest gains and others reporting little to no improvement on quality of care measures. Furthermore, unintended consequences of P4P programs have been demonstrated, including larger financial rewards for those hospitals with higher performance at baseline and significant financial losses for hospitals that serve large minority populations. As of October 1, 2008, Medicare will implement the use of a new financial mechanism-nonpayment for preventable complications (NPPC)-which is a “stick” rather than a “carrot”. Medicare will no longer pay hospitals for treating certain healthcare associated infections (HAIs) that arise in patients if they are not present on admission. Our proposed research is unique and timely. There are no data available on the impact of a NPPC policy intervention that is being implemented by one of the largest payers in the U.S. Despite lack of evidence for its efficacy, it is hoped that financial disincentives will motivate hospitals and providers to focus their efforts on reducing HAIs. While the goal is certainly worthy, the mechanism being used to motivate change should be rigorously evaluated to ensure that it achieves its intended consequences without the occurrence of unintended consequences. Our research will provide a rich understanding of the potential impact, both positive and negative, of NPPC on patient care and outcomes. The long-term goal of this proposal is to assess the overall impact NPPC on patient care and outcomes. In this two-phase study, we will first conduct qualitative interviews to identify key elements that may affect hospital practices and rates of HAIs. In the second phase, we will develop, pilot, and validate a survey instrument based on our qualitative research findings in order to conduct a future survey of infection preventionists to assess the perceived impact of NPPC on hospitals in the U.S. Thus, we propose the following specific aims: 1. To identify key factors that may affect infection prevention practices in the context of NPPC. 2. To develop, pilot, and validate a survey instrument to examine the perceived impact of NPPC on behaviors and practices in hospitals.

Source: NIH.

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Grant project title 37:	HIV-envelope-specific CD4+ T-cell activation and functional potentials
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$831,350
Grantee organization:	St. Jude Children's Research Hospital Memphis, TN 38105
Grant category:	Existing applications

Abstract description:

Despite decades of research, the development of a successful HIV-1 vaccine has not yet been achieved. A better understanding of the functions of activated lymphocytes is therefore desired. The long-term objective of our research is to comprehend the full potentials of HIV-1- envelope-specific immune cells. CD4+ T-cells contribute to HIV-1 control by supporting antibody production by 8-cells and the activation/ maintenance of CD8+ T-cells. However, based on our recent data, it appears that envelope-specific CD4+ T-cells may additionally contribute directly to the control of virus-infected cells, independent of 8-cell or CD8+ T-cell activity. The studies proposed here will determine how these CD4+ T-cells confer their 'protector' effect. Specific Aim: To determine the phenotype, cytokine secretion capacities, and killer potentials of the HIV-1 envelope-specific CD4+ T-cells that protect against envelope-recombinant virus in the absence of 8-cell or CD8+ T-cell functions. Experiments are designed to fill fundamental gaps in our understanding of how virus is controlled by the immune system. Results from these experiments may be invaluable to the construction of new, successful HIV-1 vaccines designed to capture the full potentials of the immune response.

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Grant project title 38:	HIV ENV epitope engineering
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$745,000
Grantee organization:	Tulane University of Louisiana 6823 St Charles Ave New Orleans, LA 70118
Grant category:	Existing applications

Abstract description:

CD4+ helper T cells specific for human immunodeficiency virus type 1 (HIV-1) are associated with control of viremia. Nevertheless, vaccines have not been effective thus far, at least partly because sequence variability and other structural features of the HIV envelope glycoprotein deflect the immune response. Previous studies indicate that CD4+ T-cell epitope dominance is controlled by antigen three-dimensional structure. Three disulfide bonds in the outer domain of gp120 were individually deleted in order to destabilize the three-dimensional structure and enhance the presentation of weakly immunogenic epitopes. Unexpectedly, upon immunization of mice, the CD4+ T-cell response was broadly reduced and antibody titers were sharply increased for two of the disulfide variants. For one variant (deletion of the 296-331 disulfide bracketing V3), viral neutralizing activity was increased, but reactivity was narrow. For another variant (deletion of the 378-445 disulfide bracketing V4 and part of the bridging sheet), the antibody exhibited significant CD4-blocking activity. The changes in the immune response are most likely due to shifts in the pathways of antigen processing that result in the priming of fewer but more helpful T cells. In the proposed research, the disulfide variants will be reconstructed in the gp120 of distinct Clade B and Clade C HIV strains and in the gp120 of an SIV strain in order to test the generality of the result. Disulfide variants will be characterized by binding to monoclonal antibodies, circular dichroism spectroscopy with denaturation, limited proteolysis, deglycosylation, and isothermal titration calorimetry of CD4 binding. Mice will be immunized with the variants. CD4+ T-cell proliferative and cytokine responses will be mapped for individual mice and, in a novel analysis, will be correlated with antibody reactivity to proteins and peptides. The resulting epitope-specific T-B correlations will be used to identify cellular interactions that support antibodies directed against protective and unprotective epitopes. Rabbits will be immunized, and viral neutralization will be analyzed, with the expectation that antisera raised by the disulfide-deletion variants will have increased viral neutralization. The proposed research is unique in that it exploits T-B relationships in order to engineer an improved antibody response.

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Grant project title 39:	Dissecting the origin and the function of the cutaneous dendritic cell network
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$842,635
Grantee organization:	Mount Sinai School of Medicine of NYU New York, NY 10029-6574
Grant category:	Existing applications

Abstract description:

Highly specialized professional antigen presenting cells are distributed throughout the skin and include epidermal Langerhans cells (LCs) and dermal dendritic cells (DCs). Our laboratory established some unique properties of cutaneous DCs. We discovered that in contrast to lymphoid organ DCs, LCs fail to develop in mice that lack the receptor for macrophage ny stimulating factor (MCSFR) (Ginhoux et al. Nat immunol 2006). We established that in contrast to most dc populations, LCs are maintained by radioresistant hematopoietic precursors that have taken residence in the skin in the steady state (Merad et nature immunology 2002; Merad et al. Nature medicine 2004). We also found that a subset of dermal DCs derive from radioresistant precursors, while the majority derives from circulating radiosensitive precursors (Bogunovic et al. Jem 2006). More recently, we identified a novel population of dermal DCs that express the c-type lectin receptor langerin, thought to be a LC hallmark the skin. In contrast to LCs, dermal langerin+ DCs are recruited from the blood and sojourn briefly in the skin before migrating to the lymph node charged with skin antigens (Ginhoux et al. Jem 2007). These results underline the complexity of the cutaneous dc network system, but “the raison d’etre” and the mechanisms that regulate the development of this complex system is elusive. In this grant application, we propose to dissect the origin of dc populations in the skin, identify the key molecules that control their development and examine the contribution of each dc compartment to skin immunity. Preliminary data suggest that a wave of LC precursors seed the epidermis during embryonic life. Thus in aim 1, we propose to ex the potential of these embryonic precursors to maintain LC homeostasis throughout life. Mice that are deficient for MCSFR or tgfb1 lack epidermal LCs but the exact role of MCSF and tgfb1 in LC ontogeny is unknown. In this aim, we propose to examine how these molecules control LC development. Preliminary data also suggest that distinct precursors and differentiation pathways control the development of dermal langerin+ and dermal langerin- DCs. Thus in aim 2, we propose to identify the dedicated precursor and the mechanisms that control the development of dermal dc subsets. Finally, we believe that such complex dc network has developed to ensure skin integrity and in aim 3, we propose to examine the contribution of each DC compartment to skin immunity.

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Grant project title 40:	Protein kinase A-dependent regulation of T cell accumulation in Lupus
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$407,000
Grantee organization:	Wake Forest University Health Sciences Winston-Salem, NC 27157
Grant category:	Existing applications

Abstract description:

Establishing how deficient PKA-I activity results in abnormal T cell effector functions is a key step in understanding the etiopathogenesis of T cell dysfunction in SLE. In T cells from normal subjects, IL-2 induced IL-13+ cell accumulation in vitro is inhibited by the strong PKA activator PGE2, whereas the weak PKA activator beta-agonist causes increased accumulation. In SLE subjects with a severe defect in PKA activity, both PGE2 and ISO cause a profound increase in IL-2 induced IL-13+ cell accumulation. This R21 application proposes to clarify the effect of defective PKA on regulatory features of T cell accumulation in SLE subjects. The hypothesis is that the subpopulation of SLE subjects with defects in PKA activity has exaggerated accumulation of type 2 cells when stimulated by betaagonist and PGE2. Further hypothesis is that experimental knockdown/expression of the PKA RI¿-subunit is sufficient to cause/reverse this effect. These hypotheses will be tested using a highly interpretive in vitro model and a well characterized cohort of SLE subjects. Results from these studies will provide novel insight into the regulation of T cell development of interest to the basic science of T cell biology, and advance our understanding of immune system regulation in SLE.

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Grant project title 41:	HIV-1 Replication and Pathogenesis in Vivo
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$711,553
Grantee organization:	University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, NC 27599
Grant category:	Existing applications

Abstract description:

The goals of this project are to define how HIV-1 interacts with pDC and to elucidate the role of pDC cells in HIV-1 replication and pathogenesis. As the major sensor of viral infections, altered pDC level/activity may play a critical role during HIV-1 disease progression. However, the role of pDC cells in HIV infection and pathogenesis is poorly understood, mainly due to the lack of robust in vivo models. The DKO-hu HSC model is ideal for this purpose. With a stable functional human immune system, functional pDC cells are developed in normal proportion in all lymphoid organs in DKO-hu mice. HIV-1 establishes persistent infection, with immune hyperactivation and depletion of human CD4 T cells. We have also shown that, during HIV-1 infection, PDC cells are productively infected, activated, depleted and functionally impaired in DKO-hu HSC mice. HIV-1 with the pathogenic R3A Env also efficiently activates PDC in vitro, correlated with its high binding affinity to CD4 receptor and coreceptors. Based on our preliminary findings and reports from SIV-infected monkeys or HIV-infected patients, I postulate that HIV-1 intimately interacts with PDC cells, and chronic engaging of PDC during persistent HIV infection will deplete or impair PDC activity. The reduced or altered PDC activity contributes to chronic HIV infection, hyper-immune activation and AIDS progression.

First, we will investigate the proliferation and survival of pDC cells during early and late-chronic HIV-1 infection in DKO-hu mice (SA1a). Second, we will define the role of each relevant receptor (CD4, CCR5, CXCR4, BDCA2, TLR7 and TLR9) in pDC activation with genetic approaches. In addition, we will also define the signaling defects in pDC cells induced by HIV infection, by genetically analyzing the candidate signaling pathways (SA2a). Third, we will treat DKO-hu mice with the pDC-specific ILT7 mAb conjugated with the Saporin toxin, which specifically depletes pDC, to test the role of pDC during infection (SA3c).

We will thus focus on the most fundamental questions of pDC cells in HIV pathogenesis. Elucidation of the mechanism by which HIV-1 interacts with pDC cells and their role in HIV-1 infection and AIDS pathogenesis will facilitate not only our understanding of pDC biology in HIV pathogenesis, but also development of novel therapeutic strategies.

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Grant project title 42:	Long Polar Fimbriae of Attaching and Effacing Escherichia coli
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$20,101
Grantee organization:	University of Texas Medical BR Galveston 301 University Blvd Galveston, TX 77555
Grant category:	Supplements and revisions

Abstract description:

The expression of Attaching and Effacing Escherichia coli (AEEC) virulence factors is a tightly regulated process, and, in some cases, the identification of these factors has been difficult because they are either repressed in vitro or the conditions of expression are unknown. While it is evident that expression of certain virulence factors is strictly associated with human disease, the additional factors present in AEEC strains that are linked to their pathogenic process remain unclear. Lack of a full understanding of how the genes encoding these additional virulence factors are controlled is important, because, without this knowledge, we are unlikely to understand the overall pathogenic properties of AEEC strains. Thus, our objective is to determine how the Long Polar (LP) fimbriae in AEEC strains contribute to pathogenesis and to use these fimbrial-encoding genes as markers to detect virulent strains. The central hypothesis is that, in addition to the already characterized colonization factors (e.g., intimin-mediated adhesion), AEEC strains possess a highly regulated LP fimbriae, that plays a role in the colonization process, and although the genes encoding these fimbriae are widely distributed in pathogenic E. coli strains, some LP fimbriae types are found exclusively in specific AEEC strains. We will test this hypothesis through three specific aims, which are to: (1) Define whether Ler and H-NS act as a selective silencing/anti-silencing defense system that controls LP fimbriae expression in AEEC strains; (2) Identify the regulatory protein(s) controlling LP fimbriae expression in atypical EPEC and determine in a rabbit model the function of LP fimbriae during colonization; and (3) Characterize the distribution of the LP fimbrial gene clusters among AEEC strains and determine whether certain LP fimbrial subunit types are reliable markers of different pathogenic AEEC strains. To accomplish our aims, we will fully characterize the functions of Ler, H-NS, and atypical enteropathogenic E. coli-encoded regulators under in vitro and in vivo (infant rabbit colonization model) conditions and perform a detailed study of prevalence of the lpf genes in specific subsets of pathogenic AEEC strains. Our research work is innovative because it capitalizes on our findings regarding novel colonization factors in AEEC strains and their potential application in therapeutics and diagnostics. The results from studies of the regulatory networks controlling LP fimbriae expression have significance, because we will be able to identify fundamental differences to explain the tissue tropism of different AEEC strains and to determine whether silencing of LP fimbriae is an example of a defense system that AEEC strains have against horizontally acquired genes. In addition, the use of the rabbit model will give us new insight into the pathogenesis and colonization properties of AEEC strains. An understanding of the mechanisms underlying AEEC colonization to the gastrointestinal tract will not only further our knowledge of the pathogenesis of these organisms but also provide opportunities for reducing infection rates and improving treatment options against these biological agents classified as category B pathogens due t their potential use as a food safety threat.

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Grant project title 43:	Plasmacytoid Dendritic Cells in HIV Pathogenesis
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$377,770
Grantee organization:	Univ. of Med/Dent of NJ-NJ Medical School 185 S Orange Avenue Newark, NJ 07107
Grant category:	Supplements and revisions

Abstract description:

Deficient production of interferon-a (IFN-a) by natural IFN-producing cells (NIPC) is observed in patients with advanced HIV-1 infection. This deficient IFN-a production was found to be associated with, and predictive of, susceptibility to opportunistic infections. Although long-suspected to be a dendritic cell, progress was somewhat hampered by the lack of a definitive phenotype for the NIPC. NIPC have now been demonstrated to be identical to the plasmacytoid dendritic cell (PDC). PDC's are believed to be important not only as professional IPC but also as vital links between innate and adaptive immunity. Deficient IFN-a production in HIV infection results from both decreases in numbers of circulating PDC as well as dysfunction in those cells present. This current study is organized in five specific aims; the first three involve studies of the basic biology of the PDC and the last two apply what has been learned about the function of PDC's to understand how they become deficient in HIV infected patients. Peripheral blood PDC's express very high constitutive levels of the transcription factor, IRF-7. These observations will be extended to evaluate the expression and function of the IRF-7 in PDC's in different anatomical sites and determine the roles of IRF-7 vs. IRF-3 and IRF-5 in these cells. Cross-linking of receptors on the surface of PDC leads to down-regulation of their ability to produce IFN-a, a phenomenon that may also have physiological relevance in the HIV-infected patients. Studies are proposed to understand the mechanisms of this down-regulation and determine whether other functions carried out by PDC such as production of TNF-a and chemokines is similarly affected by the receptor crosslinking. Production of IFN-a by PDC's does not require infection of the cells with virus; rather uptake of material by endocytosis appears to trigger the generation of IFN-a. Using fluorescent labeled infected cells or virus and confocal microscopy, the fate of the endocytosed material in vivo will be determined. In studies to better understand the mechanisms of deficiency in PDC in HIV-infected patients, studies will be undertaken to determine whether PDC's are infected with HIV in vivo and whether they traffick from the blood to sites in the tissues. Finally studies are proposed to evaluate other functions of the PDC in HIV-1 infected patients including cytokine and chemokine production and activation of T cells as well evaluation of the IRF-7 function in these cells.

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Grant project title 44:	Regulation and Action of APOBEC3G
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$13,122
Grantee organization:	J. David Gladstone Institutes San Francisco, CA 94158
Grant category:	Supplements and revisions

Abstract description:

Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-1 like 3G (APOBEC3G, A3G) corresponds to a host-derived cytidine deaminase that displays potent anti-retroviral activity. When incorporated into budding HIV virions, the A3G enzyme massively mutates nascent HIV DNA produced during reverse transcription in the next target cell thereby halting HIV growth. HIV counters these effects of A3G through its Vif gene product, which promotes accelerated proteasome-mediated degradation and partially impaired de novo synthesis of A3G. The intracellular depletion of A3G makes the antiviral enzyme unavailable for incorporation into progeny virions. Our recent studies have unveiled a second antiviral action of A3G operating in resting CD4 T-cells. In these T-lymphocytes, cellular A3G functions as a highly active post-entry restriction factor blocking the growth of both wild type and deltaVif forms of HIV. Whether this “Vif-resistant” anti-HIV defense mediated by A3G involves cytidine deamination or a different mechanism is currently unknown. Further, the mechanism by which this post-entry restricting function of A3G is forfeited when T-cells are activated remains incompletely understood. Similarly, little is known about how host cells safeguard their own DNA from the mutagenic effects of A3G. Finally, it remains unknown whether A3G exerts other key functions beyond these antiviral effects. In Specific Aim 1, experiments will be performed to decipher how A3G and the closely related A3F and A3B antiviral enzymes are regulated in cells. In Specific Aim 2, the mechanism of A3G action as a post-entry restriction factor in resting CD4 T-cells, the range of viruses affected by this restriction, and potential similar functions of A3F will be delineated. Finally, in Specific Aim 3, studies will be conducted to assess whether A3G mediates important nonantiviral functions in mammalian cells. These experiments will involve the preparation and analysis of mice lacking the functional analogue of the A3G gene. Together, this program of proposed experimentation promises to enrich our understanding of the biology of A3G as well as the related A3F and A3B enzymes. With such understanding, new therapeutic strategies for inhibiting HIV growth could emerge.

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Grant project title 45:	Structure Studies on Proteins That Modulate IL-10 Action
Administering IC:	National Institute of Allergy and Infectious Diseases
Grant award size:	$147,589
Grantee organization:	University of Alabama at Birmingham 1530 3rd Avenue South Birmingham, AL 35294
Grant category:	Supplements and revisions

Abstract description:

IL-10 is a multifunctional cytokine that regulates complex immune responses. Its normal function is to protect the host from uncontrolled inflammatory responses. However, IL-10 has also been implicated as an autocrine growth factor in several B-cell malignancies and stimulates B-cell mediated autoimmune disease. The normal and pathological functions of IL-10 are initiated by IL-10 receptor engagement and assembly into a signaling competent IL-10/IL-10R1/IL-10R2 complex. In addition to cellular IL-10 (clL-10), Epstein Barr virus (EBV) and cytomegalovirus (CMV) harbor viral IL-10 mimics (ebvlL-10 and cmvlL-10) in their genomes that activate the IL-10 signaling complex, resulting in overlapping and distinct biological properties. In the past funding period, we determined crystal structures of clL-10, cmvlL-10, and ebvlL-10 bound to the high affinity IL-10R1 chain. In this proposal we will use surface plasmon resonance, site-directed mutagenesis, NMR spectroscopy, X-ray crystallography, and FRET methods to study cellular and viral IL-10 receptor interactions. These studies will be complemented by the analysis of the cellular IL-10 homologs IL-22 and IL-20. The long term goal of this proposal is to derive a quantitative structural/computational model of IL-10 family signaling that might explain how cellular and viral IL-10s shape immune responses and allow the rational design of cytokine therapeutics.

Source: NIH.

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Appendix II: GAO Contact and Staff Acknowledgments

GAO Contact

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Staff Acknowledgments

In addition to the contact named above, Will Simerl, Assistant Director; N. Rotimi Adebonojo; Peter Mangano; Lisa Motley; and Krister Friday made key contributions to this report.

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