Appendices and Attachments

Appendix 1: Topics #1-7 Based on Specific Recommendations in the WG Report

Appendix 2: Compilation of Common Diseases Studied in the CC

Appendix 3: Examples of Phenotyping Studies Done in the CC

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Appendix 1

ACD Working Group Recommendations

Excerpted from the National Institutes of Health Advisory Committee to the Director Long-Term Intramural Research Program (LT-IRP) Planning Working Group Report

December 12, 2014

1. Strengthening the Clinical Center and clinical research at the NIH

Research Recommendation 4: *Refocus the mission and function of the Clinical Research Center.*

The NIH CRC is renowned for its research on rare and undiagnosed diseases. While the WG agrees that the CRC should remain a leader in this research field, the group recommends that there also should be a larger emphasis on common public health issues that impact a large portion of the population (e.g., diabetes and heart disease). Selecting such challenges and organizing teams to address them will be challenging, but will have the benefit of encouraging investigators to think creatively on a large scale and the WG believes that this will result in many great ideas.

One area identified by the WG and highlighted in a 2011 National Academies of Science report as a critical component of current research is the correlation between the genotype and phenotype of diseases or conditions, especially those that are rare, using a precision medicine approach (9). The WG suggests that the IRP utilize the CRC's strengths to build the framework for this burgeoning area of science and designate this as a hallmark of the CRC. Deep phenotyping, with greater granularity than is likely to be obtained from ICD9/10 codes in electronic health records, is required for analyzing gene-gene and gene-environment interactions, especially when considering the influences of multiple genes rather than a single gene. Developing instruments for standardizing the collection and analysis of phenotypic data, backed by ontologic structures and made available through online databases, is an important contribution that the IRP and CRC can make to the scientific community and to its own research studies. Such tools would allow for aggregating data from multiple sites and collectively could form the basis of an "Electronic Research Record" to complement and augment research done using Electronic Health Records (EHRs).

Areas such as vaccine development and mechanisms of drug resistance in the context of pathogens or cancer therapeutics should continue to be emphasized within the CRC. Historically, the IRP has contributed to approximately half of all FDA-approved vaccines currently in use. This strength should be targeted and built upon to expand the CRC's efforts. Antibacterial resistance is among the greatest existing public health threats, and the CRC should focus a portion of its efforts on identifying novel targets for highly drug-resistant pathogens and cancers through in-depth genetic and physiological analysis.

Training Recommendation 2: *Expand and enhance support mechanisms for clinical research trainees.*

a. Broaden the MSTP size, support, and opportunities.

To create a pivotal hub of clinical research training within the IRP, the WG recommends that the current approach to the Lasker Clinical Research Scholars program be evaluated to enhance recruitment. It also is recommended that Medical Scientist Training Program (MSTP) students be provided with the opportunity to participate in a clinical research experience at the NIH CRC to further complement the efforts to recruit early stage investigators via the ACI and the Lasker programs. In addition, NIH should explore increasing the number of positions it supports for the MSTP program by broadening its support beyond NIGMS. While there is no guarantee that these "undifferentiated" trainees will emerge as oncologists or cardiologists, the potential virtue of such a program would be to increase the overall pool of physician-scientists.

b. Develop a mechanism for MD research training at the NIH CRC.

NIH should develop a mechanism (similar to the K08 and K23 mechanisms) to provide MDs with appropriate research training at the NIH CRC, in combination with one of the existing eight NIH programs that support physician-scientists trainees or those early in their careers. The WG recommends increasing the awareness of the joint NIH-Duke University Master of Health Sciences in Clinical Research program; interested trainees should be encouraged to participate. Finally, there should be increased communication and publicity about awards available to IRP trainees, particularly loan repayment programs.

Infrastructure/Facilities Recommendation 1: *Develop more robust joint initiatives with the extramural clinical research community.*

a. Evaluate the feasibility of establishing a phase 1 clinical trials unit at the CRC.

Currently, the CRC is supported by a contribution of funds from each IC that is proportional to its overall budget. This funding structure, often referred to as the "school tax," was implemented in 2000 and was designed to be budget neutral – that is, contributing ICs would not incur additional budgetary costs. However, this mechanism has proven unsustainable because of fiscal uncertainty, budgetary constraints, and rising operating costs. A previous intensive, internal feasibility review of the CRC determined that instituting a third-party payment system was not practical. The 2010 Scientific Management Review Board (SMRB) Report reviewed several possible funding mechanisms for the CRC and suggested incorporating it as a line item in the Office of the Director's appropriations (8), which would require Congressional approval and has a number of disadvantages associated with it.

One potential means of raising revenue for the CRC that should be explored is to capitalize on its strengths by establishing a phase 1 clinical trial unit that can be utilized by the extramural community. Units to coordinate phase 1 clinical trials, which are a hallmark of the CRC, are costly to maintain extramurally. If the NIH CRC could utilize its existing infrastructure to manage and run phase 1 clinical trials in conjunction with extramural institutions, this could enhance utilization of the facility allowing economies of scale to be fully taken advantage of and could provide some offset for budgetary shortfalls driven by inflationary pressures. The WG recommends that the Clinical Center Governing Board (CCGB) evaluate this approach and determine whether it is likely to address the budgetary problems and the feasibility of the appropriate measures needed to implement this activity.

b. Develop joint initiatives with local hospitals, the Department of Defense, and the Department of Veteran's Affairs.

The existing mechanisms for collaborating with the extramural community, including the Bench to Bedside and U01 cooperative agreement programs, should be strengthened by insuring that they have stable support. In addition, efforts should be made to expand and broaden these partnerships. In particular, the CRC should collaborate with other area hospitals to become a specialized, focused center for clinical research.

The committee also was impressed with the ambitious plan NIH put forth to target neonatal pediatric research, since this is an area that has not received the focus it deserves relative to the health needs and both medical and scientific opportunities. Therefore, the WG recommends that the IRP develop joint initiatives on pediatric research to capitalize on the ongoing activities in the extramural community and expand the CRC's capabilities. The IRP should partner with local pediatric hospitals in the Washington, DC area, such as Children's National Medical Center, to build the research portfolios of the organizations involved.

In addition to partnering with local pediatric hospitals, the IRP and the CRC should strengthen collaborations with the Department of Defense (DoD) and the Department of Veterans Affairs (VA). The Walter Reed National Military Medical Center is located directly across the street from the NIH main campus and is adjacent to Uniformed Services University of the Health Sciences, providing an optimal opportunity for collaboration between the these institutions. To increase utilization of the CRC, the IRP should explore partnerships with the DoD and VA to capitalize on opportunities for economies of scale with these federal agencies.

2. Promoting diversity

Workforce Recommendation 1: *Increase diversity throughout the IRP.*

a. Develop new, innovative models for increasing diversity.

The diversity of the IRP workforce is a national imperative for success. NIH will not be successful in attracting the most creative minds to biomedical research if we fail to actively engage members of all groups within the Nation. Diverse groups show enhanced problem-solving ability and productivity. A workforce comprised of a diverse array of individuals may be more likely to tackle research questions related to health disparities and inequities or aid in recruitment of individuals from underrepresented groups into clinical trials.

While the NIH has long acknowledged the importance of achieving diversity in the biomedical and behavioral research workforce, the current census of the IRP clearly shows a lack of diversity throughout the ranks (Appendix 3). There is a paucity of Blacks, Hispanics, and American Indian/Alaska Natives throughout the IRP workforce. Also problematic is the lack of diversity observed among scientific leaders; for example, only 15% of all IC scientific directors are female. In addition, there is poor representation of Asians in leadership positions as well. As a federal research facility, the NIH should be a leader in workforce diversity. A courageous first step has already been taken – NIH has acknowledged that current policies for increasing the diversity of the workforce are insufficient (see ACD WG on

Diversity in the Biomedical Research Workforce)(5). The IRP leadership, together with the NIH Chief Officer for Scientific Workforce Diversity (COSWD), Dr. Hannah Valantine, and the NIH Steering Committee WG on Diversity, should develop new models to encourage young people from diverse backgrounds to pursue careers in biomedical research. Moreover, more effort must be directed towards developing new approaches to the recruitment, retention, and support of persons from diverse backgrounds into independent scientific positions (i.e., ACI, tenure track, and tenured PI) within the IRP. The unique environment afforded by the IRP make it ideal to serve as a test-bed for the Nation. As strategies are developed, they may be tested for their generalizability in the extramural program.

b. Utilize a central fund to support early-stage investigator recruitment.

As an initial step, given the urgency to act rapidly, the WG recommends that the COSWD use a newly created central fund to support the recruitment of early-stage scientists – those within ten years of completing their terminal research degree or medical residency – into existing labs. The review of the candidate applications by the mentor for this program should be expedited and the program should be widely publicized. This will jump-start the process and provide a cadre of excellent early-stage investigators who can assume leadership roles over time. Another related opportunity that could be seized by the IRP is to develop a program whereby early-stage investigators, and potentially mid-career investigators, from diverse backgrounds are both mentored and sponsored by senior investigators. By doing so, the IRP would assume a leadership role in identifying solutions that are different from previous efforts, and could become a testing ground for piloting novel programs within the unique setting of the IRP.

Training Recommendation 1: *Enhance the diversity of IRP trainees.*

Although the diversity within the IRP trainee population is slightly better than the overall IRP investigator workforce, there is a need for increased representation of groups from diverse backgrounds within the trainee population. As per a 2013 survey, the majority of research and clinical fellows are white (not Hispanic) or Asian/Pacific Islander. The number of female trainees is comparable to the number of male trainees. Within NIH, efforts are underway to expand the IRP Graduate Partnership Program, in which the IRP partners with institutions that have a track record for training students from groups that are traditionally underrepresented in the sciences to coordinate the training of PhD students. Additionally, a supplement program is under development to provide a competitive pool of funds for postdoctoral trainees from underrepresented groups within the IRP. This WG commends these efforts and recommends that these programs be expanded to include partnerships with additional institutions, support for more postdoctoral fellows, and support for early-stage investigators and staff scientists and clinicians.

Additional partnerships should be created with institutions that mirror those currently being supported by the extramural BUILD program (which target under-resourced institutions with highly diverse student populations). This will raise awareness about the many training opportunities that NIH offers. The IRP and COSWD are encouraged to strengthen trans-NIH approaches to recruiting postdoctoral and clinical fellows to ensure that selections are made from the broadest possible pool.

Effective mentors have repeatedly been found to play a significant role in the future success of early career trainees. The IRP should continue to encourage focused mentoring and provide resources for both the mentors and the mentees. For example, the Individual Development Plan (IDP) for all postdoctoral trainees was first introduced within the intramural program and is now recommended for

all extramurally supported trainees. The WG strongly recommends that the IRP enhance collection of outcomes data on the successes of IRP graduates at all levels using a standardized tool that collates all of the relevant data in a manner that allows data aggregation across the entire IRP. The data should be evaluated and analyzed every 3-5 years to identify areas for improvement and program strengths. OITE assists trainees in enhancing their postdoctoral experience by providing an array of educational and career development opportunities, including those beyond the laboratory bench (e.g., science policy, science communication, intellectual property law). These excellent programs should be encouraged and actively publicized.

3. Recruitment and appointment of NIH scientists

Workforce Recommendation 3: *Strengthen recruitment procedures for IRP leadership, Principal Investigators, including Assistant Clinical Investigators, and Staff Scientists and Clinicians.*

a. Expand and publicize current recruitment efforts.

Over the previous five years, 53% of tenure-track investigators were recruited to the IRP from outside institutions, and 75% of tenure appointments were made from the NIH tenure-track pool – those tenure-track investigators currently within the IRP (Appendix 7). The WG considers continual recruitment from the extramural community essential to maintaining a vibrant and innovative IRP, and this applies not only to the recruitment of PIs, but also to the leadership within the IRP. While the IRP trains many excellent candidates for PI positions, the extramural community offers a much larger and more diverse pool of individuals with a wide range of talents that can bring an added depth and breadth to the IRP. Thus, to enhance the recruitment of highly talented investigators from a broader international pool, the WG recommends the approaches outlined below.

The IRP should recruit more scientists from the extramural community than is currently done. All positions, including staff scientists and clinicians, assistant clinical investigators (ACIs), tenure-track, and tenured investigators, should be recruited through national/international searches. Consideration should be given to engaging the Board of Scientific Counselors (BSC) or an equivalent review group in the recruitment process. Given the tremendous experience of those serving on BSCs, the WG suggests augmenting the recruitment and hiring processes to involve select members of the modified BSCs (described in *Workforce Recommendation 2*) in the search committees. In addition to opening a new pool of reviewers for competed positions, those serving on these review groups also can provide additional extramural perspective and meaningful assessment of potential recruits. The WG also recommends the involvement of leadership or investigators from ICs other than the hiring IC as a means to broaden input and increase collaboration in recruitments and transparency across the NIH.

Recruitment incentives unique to the IRP should be highlighted to attract the finest candidates. For example, the tuition loan repayment plan offered by the NIH, which provides up to $35,000 per year with no overall cap, and the excellent success rate for IRP applicants should be publicized. Enhancing mentoring by senior-level investigators for early-stage investigators should also help in recruiting pioneering scientists. It is especially important that salaries of tenure-track researchers remain competitive with those in the extramural community, since IRP restrictions on travel and conflict of interest policies are potential deterrents to recruitment of extramural scientists.

The WG recommends that the IRP particularly focus on scientists in the early-stage of their career – those within ten years of completing their terminal research degree or medical residency. One successful example of broadening recruitment of early-stage investigators has been the Stadtman Tenure-Track Investigators mechanism, which seeks to identify talent through a broad search that can focus on specific areas of science or enable the candidates to bring their ideas to the IRP. The WG recommends that this program be evaluated, modified as needed, and enhanced to optimize its efforts to attract investigators from outside the IRP.

b. Recruit all Staff Scientists and Clinicians through a national/international process.

The WG views the over 1500 staff scientists and clinicians, including those who are shared resource core directors, to be a vital component of the IRP's research endeavor. Currently, these highly coveted positions are selected by the IC through which they are appointed. As such, external recruitment procedures should be utilized to fill these positions through a trans-NIH national and/or international search process, similar to that for senior and tenure-track investigators. In this way, the IRP will be provided an additional mechanism through which to increase the diversity of the IRP, as recommended in *Workforce Recommendation 1*. The recruitment of extramural scientists to these positions is also is likely to stimulate new ideas based on the new investigator's experiences at other institutions.

c. Enhance the Assistant Clinical Investigator program.

Given concerns about the number of physician-scientists entering the biomedical research workforce and a desire to increase the number of clinician scientists to ensure maximal utilization of the clinical center, strong consideration should be given to enhancing the visibility of the ACI program, which is a competitive temporary PI position in which clinicians receive advanced mentoring and build an independent research portfolio; prioritization of the resources necessary to increase the ACI program's size also should be reviewed. Consideration should be given to approaching recruitment to this program in a trans-NIH manner. While still in its infancy, the Lasker Clinical Research Scholars Program is designed to support exceptional early-stage clinical researchers and foster their development into fully independent investigators. This program can complement the ACI effort; indeed, several ACIs have successfully competed for the Lasker Clinical Research Scholarship. The WG was disappointed to learn that the number of applications to the Lasker program was lower than expected for such a seemingly attractive program and encourages a detailed analysis of how to improve recruitment into the program. The Stadtman and Lasker mechanisms have the potential to both increase extramural recruitment and attract early-stage investigators, thus invigorating the IRP as it ushers in a new era of scientific discovery at the NIH. Further, the Stadtman and Lasker programs could be used to redouble efforts to increase diversity in the IRP (*Workforce Recommendation 1*).

Workforce Recommendation 4*: Identify the most sustainable size of the IRP workforce*.

While the number of PIs in the IRP has steadily declined over the past 20 years, the number of staff scientists and staff clinicians has increased gradually to its current level of over 1500 (Appendix 5) during this same time period. With the budget constraints that all federal agencies are navigating and the complexities of the current IRP workforce makeup, the issue of the workforce size and balance requires careful consideration. This WG recommends a review and evaluation by the OIR and external advisors in conjunction with the ICs (which could include BSCs) to determine the appropriate critical mass for the IRP, including the CRC, and the correct balance among investigators, staff scientists and clinicians, and trainees. This analysis should include consideration of:

• Trans-NIH evaluation of the current investigator cohort – ICs, in collaboration with the Office of Human Resources, should ascertain the years of service (stratified by decade) of the current pool of IRP investigators, and using various assumptions about separations and hires, model workforce dynamics to help inform the determination of the most sustainable size of the IRP workforce. This approach should play close attention to demographic gaps and opportunities that may be illuminated for targeted recruitment, and may help to address the diversity of the IRP workforce. The comprehensive evaluation of the workforce also will inform any planning processes to address the impending and anticipated efflux of baby boomer aged investigators from the workforce, as this will provide an opportunity to substantially impact the future of the IRP.

• An articulation of the optimal distribution of each IC's support of scientific areas supported in the extramural portfolio versus the IRP.

• The identification of the scientific areas of strength and weakness within the IRP and the workforce required to achieve stated scientific goals in the IRP over the next decade.

• The desired ratio among basic, translational, clinical, and population-based research within the IRP.

The WG also supports the utilization of newly reinstated programs that allow long-standing members of the workforce to partially retire from federal service. In this way, resources may be made available to increase the number of early- or mid-stage investigators, while still ensuring continuity of institutional domain knowledge and experienced mentorship of the IRP workforce. A complementary approach should be explored in which funds may be made available to departing IRP investigators to ease their transition to the extramural community.

4. Supporting new research opportunities

Research Recommendation 1: *Establish a standing committee to identify "great scientific challenges" and motivate new research initiatives catalyzed by the IRP.*

The WG recommends establishing a standing committee to advise the NIH Director on important research areas or fundamental problems for investment or national biomedical needs that are not being addressed by the extramural community or industry in order to identify areas in which the IRP could focus resources – so called "great scientific challenges." This committee should be broad-based in composition and include eminent scientists from the IRP, extramural, and industry communities. Stakeholder groups, such as patient advocacy groups should also be included. The committee should meet biennially, and the process should be informed by a series of workshops to be held on the NIH campus that will convene international thought leaders in focused topic areas. The committee will issue a public report with actionable recommendations. Even if these recommendations are not followed by the IRP, highlighting major unsolved biological problems or unmet biomedical issues would have a beneficial effect on identifying areas that need to be addressed by the Nation's research community, and would help position the IRP as a leader in scientific thought.

Research Recommendation 2: *Bolster support for highly innovative research.*

a. Establish a trans-NIH innovation fund.

One stated goal of the IRP has been to support the most innovative research possible. As advances continue to be made at the interface of traditional disciplines, the importance of collaborative, synergistic projects among the NIH ICs has long been discussed, and viewed as essential to enable support for work at the cutting edge of science. Twenty-four ICs have an intramural component in their research portfolio, which can leave the IRP vulnerable to siloed research areas. While the IRP has promoted collaborative and trans-IC efforts, the WG recommends expanding these activities by creating a resource set to help facilitate their conduct.

The NIH should establish a trans-NIH innovation fund for the IRP, and as a complementary mechanism, urge the ICs to create an optional internal innovation fund to further enable support for highly innovative projects, including some that address the identified "great scientific challenges," or unique questions that align with multiple IC missions.

The trans-NIH innovation fund should be established within the Office of Intramural Research (OIR) and overseen by the Deputy Director for Intramural Research (DDIR), who will develop a competitive review and selection process. This fund will support independent and collaborative intramural high-risk research that bolsters the goals, issues, and needs of the scientific community, including selected challenges identified by the committee suggested in *Research Recommendation 1*. To ensure broad input and encourage a high level of innovation, a substantial fraction of the fund should be used to support competitive research awards based on proposals by individual IRP investigators or collaborative teams that may not necessarily be focused on the designated "great scientific challenges." The WG recommends that this fund be sized appropriately (~1% of the IRP budget) to address one or more of the "great scientific challenges" identified by the committee in their biennial report, as well as other investigator-initiated research.

b. Encourage the formation of optional IC innovation funds.

Similarly, within each IC, the WG encourages the creation of an optional internal innovation fund. Each IC should reserve no less than 5% of their non-personnel intramural budget to fund highly innovative projects directed toward their focused missions, using a competitive application process and complementing the OIR common innovation fund recommended above. To facilitate such efforts, the OIR should increase communication and transparency of ongoing efforts across the IRP, so that investigators are aware of other research being conducted, regardless of the IC.

5. Enhancing intramural-extramural collaborations and team science

***Research Recommendation 3**: Encourage interdisciplinary and team science and promote more synergistic intramural and intramural-extramural collaborations through continued development and evaluation of different research structures.*

a. Evaluate the Porter Neuroscience Research Center approach to integrated science.

The Porter Neuroscience Research Center is a recent example that reflects the NIH and IRP's commitment to integrated IC interactions – 80 scientific groups and 10 ICs are located in new, common space. This experiment should be analyzed to determine the benefits and shortcomings of this type of

organizational structure. Calculation of the density of PIs (space per PI) may prove valuable in directing this process. If deemed beneficial and effective, this type of collaboration should be broadened to other scientific fields by reorganizing existing physical spaces on the NIH campus to support a critical mass of researchers in related areas in close proximity. As advances in many areas of science are now being fueled by multi-, inter- and trans-disciplinary collaborations, the IRP would be an ideal place to test new models of such activities.

Logistical considerations may make it impractical to provide common space for large numbers of investigators. The Center for Human Immunology Autoimmunity and Inflammation (CHI) represents an excellent example of a collaborative, trans-NIH initiative in which unique core facilities and expertise have been developed, and serve the needs of many investigators spread throughout the NIH campus. It will be important to continue the evaluation of this Center's impact, as it will offer important insights into how other "core" facilities could be developed (and also see *Facilities/Infrastructure Recommendation 2*).

The IRP should consider lessons learned from the extramural population sciences community, where many cost-efficient large-scale studies serve the needs of multiple disease-based investigators. Examples include the Women's Health Initiative (US) and the UK Biobank (UK). Intramural examples include the Framingham Heart Study (currently supported by NHLBI), the NCI AARP cohort, and the PLCO intervention trial. Studies such as these also can serve as distinctive team science "signature" projects for the IRP. Every effort should be made to make these population studies serve the purposes of investigators from multiple institutions to encourage collaboration, as well as cost-efficiency. This will require the design of such studies (and presumably the initial funding) to be collaborative among multiple ICs.

b. Develop a mechanism to respond to emergent health crises.

One unique feature of the IRP is its ability to coordinate resources in a relatively timely manner to start short or long-term research projects when the scientific opportunity or public health need arises; the most recent example is the NIH's response to the Ebola crisis. To build upon this capability, the IRP should develop a mechanism to facilitate this process on a trans-NIH level to enable staff scientists and clinicians, or other investigators, to assemble seamlessly to solve either an emergent public health crises or to seize upon areas of scientific opportunity as they arise. This approach could expand staff scientists' and clinicians' experiences beyond their traditional roles in the lab or clinic, and allow them to engage with other labs in multi-IC collaborations. Given the relative flexibility of funding, the IRP should continue to be prepared to respond as the Nation's "first line of research" for rapidly emergent health threats.

c. Modify mechanisms to allow for more expansive IRP-extramural interactions.

In addition to these overarching model approaches, the IRP should also develop a mechanism whereby intramural investigators are encouraged to participate in sabbatical-like experiences in IRP research groups and, if feasible, extramural labs.

The IRP should further support and enhance intramural-extramural collaborations in addition to fostering intramural interactions. Partnering with those in the extramural community, including industry, will allow the IRP to broaden its reach, and diversify and bolster its research portfolio.

Therefore, the following is recommended:

- Review existing mechanisms for intramural-extramural partnerships
- Effectively utilize the Visiting Scientist program
- Merge intramural and extramural funding to facilitate collaborative opportunities

While many exist across the IRP, collaborations between the intramural and extramural community are perceived as being difficult to establish. There are some mechanisms, such as the Transfer Agreement Dashboard (TAD) and U01s, available to investigators wishing to expand their partnerships with the extramural community. Additionally, Cooperative Research and Development Agreements (CRADAs) are a mechanism often used to collaborate with industry and academic institutions. The WG recommends a review of current intramural-extramural collaborations to determine the extent of the use of these mechanisms and to provide insight into what types of collaborations are formed. One existing pathway that may be utilized more effectively is the Visiting Scientist program, which provides opportunities for foreign scientists to train and conduct collaborative research in the IRP. This program should be emulated or expanded to provide similar opportunities for those domestic scientists who wish to conduct research within the IRP for relatively short time periods (5 years max), and publicized to increase awareness. If necessary, additional mechanisms also should be developed to reinforce the interactions between the IRP and extramural institutions and industry.

Currently, intramural research at the NIH is supported within an IC's budget separately from extramural research. As a means to bolster intramural-extramural collaborations, the WG recommends creating focused mechanisms that allow combining funds from these two budgets, where appropriate. This could include, for example, creating a granting mechanism to support collaborative opportunities between the intramural and extramural communities or allowing the comingling of an extramural investigator's R01 funds with resources available to an intramural investigator to achieve a specific scientific goal.

d. Host annual scientific meetings at NIH.

To increase exposure and interaction with the extramural community, the WG recommends that the IRP partner with scientific associations and societies to host 4-6 substantial scientific workshops or meetings annually. These meetings should be focused on identifying approaches to address the "great scientific challenges" identified by the committee in *Collaboration and Research Recommendation 1*. By doing so, IRP investigators will be provided with additional opportunities to interact with their counterparts in the extramural community, thereby increasing the likelihood of collaborative science in emergent areas of science and elevating the IRP as a major force for expanding scientific frontiers.

Infrastructure/Facilities Recommendation 3: *Accelerate efforts to identify a solution for pending data and computing issues.*

a. Develop a comprehensive data storage and computing plan.

The shift toward studies involving large volumes of data requires a tremendous amount of data storage and processing capability. While the IRP is actively engaged in enhancing big data approaches and computation capacity with its NIH partners, this WG recommends that the newly formed Scientific Data Council, led by the NIH Associate Director for Data Science (ADDS) and the Chief Information Officer, in consultation with campus experts, such as NCBI, develop a comprehensive data storage and computing plan, including a prediction of future needs. The path identified by these experts should be integrated

into current planning efforts and implemented to ensure computing demands and restrictions do not hinder scientific progress; access to the extramural community also should be considered.

b. Partner with PCORI to provide IRP investigators with special access to PCORnet databases.

While intramural and extramural investigators will be granted similar access to the PCORnet databases, the IRP should partner with PCORI to provide IRP scientists with special access to the wealth of data stored in these databases. In addition, researchers should be provided the resources to utilize the PCORnet databases appropriately, thus expanding the potential for additional innovative findings as a result of these large projects. Additionally, the Common Fund Collaboratory databases are open to all and the IRP and NIH in general should enhance their efforts to publicize this accessibility to a rich pool of data.

6. Optimal use of shared resources at NIH

Infrastructure/Facilities Recommendation 2: *All "core" resources (and other unique equipment/facilities) should be accessible throughout the entire IRP community. Review the shared resource cores to provide optimal support and open access.*

The IRP currently has over 20 shared resources, services, and facilities available to investigators (Appendix 8). However, access to some of these shared resources is limited to select ICs. To foster an atmosphere of true collaboration, the WG recommends that all shared resources should be accessible to the entire IRP. A catalogue of current resources, criteria for evaluating the shared resources to ensure the sun-setting of unnecessary cores, approaches to better integrate and optimize use among the Institutes and Centers (ICs), and mechanisms for rapidly instituting new cores should be developed.

To foster an atmosphere of true collaboration within the IRP and build on existing efforts, the IRP should open access to all of these resources, including all other unique equipment or facilities (e.g., Cryo-EM), to the entire IRP – every IC with an intramural component – and adjust the funding accordingly. As research interests change and the scientific community as a whole advances, some of these resources may no longer be needed. Therefore, a retrospective and prospective review of the shared resource cores should be undertaken to identify those that are no longer needed and anticipate those that may needed in the near future. The IRP also should generate guiding principles, including reimbursement policies, for the operation and management of the shared resources on a recurring basis. These principles should include developing a catalogue of current resources, criteria for periodically evaluating the shared resources to insure the sun-setting of unnecessary cores, and approaches to better integrate and optimize use among the ICs. Similarly, a mechanism should be developed for rapidly instituting new cores when scientific opportunities become apparent, with a focus on assuring access to early-stage investigators to sustain their scientific competitiveness.

Infrastructure/Facilities Recommendation 3: *Accelerate efforts to identify a solution for pending data and computing issues.*

c. Expand pilot programs for electronic lab notebooks within the IRP.

Electronic lab notebooks, in which experimental protocols, data, and notes can be uploaded, saved, and shared electronically, are gaining popularity throughout the scientific community. The WG commends the existing programs to pilot the use of electronic lab notebooks within the IRP, and recommends that these programs be continued and expanded to incorporate the use of this new method of recording notes and data throughout the IRP, in part, as a means of enhancing the rigor and reproducibility of science reporting. Results of these pilots should be shared broadly and exported to the extramural communities.

Infrastructure/Facilities Recommendation 4*: Explore the feasibility of establishing a centralized biobank.*

Many studies, especially those using the newest genetic techniques, require access to numerous varied samples from carefully phenotyped individuals. NIH has been at the forefront of conducting such studies and utilizing these technologies, and should continue to maintain this lead role. To support both the intramural and extramural communities, the IRP should convene an expert panel to determine the feasibility of developing a centralized biobank, as well as its associated computational infrastructure, with rigorous standardized operating procedures to store biological samples and expand collaborations within and among the extramural and intramural communities. This biobank could be housed in the NIH CRC to increase its potential for interactions with extramural institutions, particularly those in close proximity to the CRC. Analogous to the UK Biobank, this biobank also could function as a key resource to aid in the creation of large-scale population-based studies. Biorepositories, such as the one suggested, can be quite costly to maintain; therefore, if capacity is ample, the IRP could amortize a portion of the costs by offering the service to nearby academic centers that do not wish to or cannot feasibly commit to a full biobank program. In addition to recouping some of the costs of maintaining the biobank, opening access to extramural investigators may stimulate collaborations.

7. Improvements in the scientific review process

Workforce Recommendation 2: *Restructure the review process of IRP Principal Investigators to provide, broader, trans-NIH context, and a more stringent evaluation of scientific impact; where appropriate, team science should be included as a review criterion.*

a. Reform the review process to be a trans-NIH effort based on scientific area that incorporates team science.

The NIH BSC review process for IRP investigators, which employs a retrospective approach, has been lauded extensively as an excellent method by which to judge those in the scientific community (Appendix 6). Notably, this review structure has been adopted and modified by the Howard Hughes Medical Institute (HHMI), which utilizes a parallel methodology to support an outstanding group of research scientists at various universities and research institutes. Enhancements to this review process will ensure the most appropriate and thorough review of investigators, including both basic and clinical scientists.

The WG recommends restructuring of the IC-centric BSC review process to ensure that the IRP is uniformly comprised of outstanding investigators. All investigators within the IRP should be reviewed every 5-7 years by a trans-NIH and extramural review panel, overseen by the OIR and coordinated with the associated IC, that spans major scientific fields (e.g., structural biology, neuroscience, and immunology). This review should be performed by wide-ranging and highly accomplished scientific peer groups, similar to those assembled by the HHMI. Restructuring the review process to better assess the quality of each investigator across a particular program may help identify redundancies and opportunities across NIH, as well as aid in ascertaining the appropriate critical mass of the IRP (*Workforce Recommendation 4*).

The impact of IRP investigators should be based on their major individual and/or collaborative contributions. Since team science (interdisciplinary research teams focused on innovative approaches to answer critically important research questions or problems) has become an essential component of biomedical research in recent years and likely will continue to play an ever increasing role, it is important that, where appropriate, it be assessed and recognized in the amended review process. This should not, however, be misunderstood as requiring that all investigators participate in teams. Those who choose not to participate in teams should be evaluated based exclusively on the merits of their contributions. The current NIH criteria, as revised in 2005, do in fact recognize collaborative contributions, but it is not clear if investigators feel confident that team-oriented criteria are being employed in the promotion and evaluation process. If those investigators have hesitated to engage in multi- and interdisciplinary research in the past because of concerns about recognition, emphasizing a commitment to team-based review criteria for promotion and tenure, as appropriate, may enhance the likelihood that investigators will commit to collaborative projects when opportunities arise.

b. Institute a rigorous and periodic review process for staff scientists.

Currently, staff scientists undergo a quadrennial review that is conducted by the IC in which they are appointed; therefore, the standards and rigor of the review process vary from IC to IC. To ensure a more thorough and uniform review, the WG recommends that the IRP institute a rigorous, standardized trans-NIH review process for all staff scientists appointed within the IRP, regardless of their hiring mechanism. This review should occur every four years and should involve investigators and leadership from multiple ICs. Similar to the review process for investigators, it should also be performed by scientific area or discipline. A thoughtful and rigorous review of all non-trainee researchers should ensure that precious resources are being used to support only highly meritorious research.

Appendix 2

Compilation of Common Diseases Studied in the CC

Representative Diseases/Conditions	IC
Acute Coronary Syndrome	NHLBI
ADHD	CC, NHGRI
Age Related Macular Degeneration	NEI
Aging	NHLBI, NIA
Alcohol Use Disorders	CC, NIAAA
Allergies	NIEHS
Alzheimers	NCI-CCR, NEI, NIA
Amyotropic Lateral Sclerosis (ALS)	NCI-CCR, NIA
Ankylosing Spondlylitis	NIAMS
Antibiotic-resistant Bacterial Infection	NHGRI
Anxiety Disorders	NIMH
Arthritis	NCCIH, NCI-CCR, NIA, NIAMS, NIBIB, NIDCR
Asthma	NCI-CCR, NHLBI, NIEHS
Atherosclerosis	NEI, NHLBI, NIBIB
Autism	CC, NIMH
Autoimmune Disease	NIA, NIAMS, NIEHS
Autonomic Disorders	NINDS
B12 Deficiencies	NLM-LHC
Bipolar Disorder	NIMH
Bladder Cancer	NCI-CCR, NCI-DCEG
Breast Cancer	CC, NCI-CCR, NCI-DCEG, NHGRI, NIEHS
Cancer	NIBIB, NINR
Cardiac Arrhythmia	NIBIB
Cardiovascular Disease	CC, NHGRI, NHLBI, NIEHS, NINR, NCI-CCR
Cataracts	NEI
Chronic Kidney Diseases	NIDDK
Chronic Liver Diseases	NIDDK
Chronic Lymphocytic Leukemia	NHLBI
Chronic Obstructive Pulmonary Disease (COPD)	NCI-CCR, NIEHS
Chronic Pain	NCCIH
Cognitive and Behavioral Disorders	NIEHS
Cognitive Decline	NIA, NIEHS
Colorectal Cancer	NCI-CCR, NCI-DCEG

Common Cancers	NIEHS-DNTP
Cystic Fibrosis	NCI-CCR
Cytomegalovirus (CMV)	NIAID
Dementia	NEI
Dengue	NIAID
Depression	CC, NIEHS, NIMH
Diabetes	CC, NCATS, NCCIH, NCI-CCR, NHGRI, NIA, NIDCR, NIDDK, NIEHS
Diabetic Eye Disease	NEI
Digestive Disorders	NINR
Drug Abuse	CC
Emphysema	NCI-CCR
Endocrine Disorders	CC, NIDDK
Endometrial Cancer	NCI-CCR, NCI-DCEG
Epilepsy	NCATS, NINDS
Epstein-Barr virus (EBV)	NIAID
Fatigue	CC, NINR
Food Allergy	NIAID
Fronto-temporal Dementia	NIA
General Pediatric Imaging	NHLBI
Glioblastoma	NINDS
Growth Disorders	NICHD
Head and Neck Cancers	NIDCR
Health Disparities due to Race and SES	NIA
Hearing Loss	NIDCD
Heart Valve Diseases	NHLBI
Hepatitis	CC
Hepatitis A	NIAID
Hepatitis C	NIAID
Hepatitis E	NIAID
Herpes Simplex Virus (HSV)	NCATS, NCI-CCR, NIAID
HIV/AIDS	CC, NCI-CCR, NIAID, NIAID-VRC
Hodgkin's Disease	CC
Hormonal Disorders	NICHD
Human Papillomavirus (HPV)	NIAID
Human Parainfluenza virus (HPIV)	NIAID
Hypertension	NEI, NHGRI, NHLBI, NICHD, NIEHS
Hypertrophic Cardiomyopathy	NIBIB
Immune Decline	NIA
Infertility	NICHD
Inflamatory Bowel Disease/Crohn's	NCI-CCR, NIAID
Inflammation	NIEHS

Influenza	CC, NCI-CCR, NIAID, NIAID-VRC
Kidney Cancer	NCI-CCR, NCI-DCEG
Kidney Disease	NCI-CCR
Leukemia	CC, NCI-CCR, NCI-DCEG
Lipid Disorders	NIDDK
Lung Cancer	CC, NCI-CCR, NCI-DCEG, NHGRI
Lymphatic Filariasis (Elephantitis)	NIAID
Lymphoma	CC
Macular Degeneration	CC
Malaria	NCI-CCR, NIAID, NIAID-VRC
Melanoma	CC, NCI-CCR, NCI-DCEG
Menopause	NIA, NIEHS
Mesothelioma	NCI-CCR
Metabolic Disease	NIEHS
Metabolic Syndrome	NHGRI, NIA, NICHD
Miscarriage	NIEHS
Multiple Sclerosis	NCI-CCR, NINDS
Multi-Sensory Impairment	NEI
Myocardial Fibrosis	NIBIB
Myocardial Infarction	NCATS, NIBIB
Myopia	NHGRI
Neuro-AIDS	NINDS
Neurofibromatosis	NCI-CCR, NINDS
Neurologic Disorders	CC
Nicotine Addiction	NIDA
Non-Hodgkin Lymphoma	NCI-CCR, NCI-DCEG
Norovirus	NIAID
Nutritional Disorders	NIEHS
Obesity	CC, NCI-CCR, NHLBI, NIA, NICHD, NIDDK, NIEHS, NLM-LHC
Oral Infections	NIDCR
Osteoarthritis	NIA, NIAMS
Osteoporosis	NIDCR
Ovarian Cancer	CC
Pain	NIDCR, NINR
Pancreatic Cancer	NCI-CCR, NCI-DCEG
Parkinson's Disease	CC, NCI-CCR, NHGRI, NIA, NINDS
Physical functioning/mobility	NEI
Post Traumatic Stress Disorders	NINR
Prematurity	NICHD
Pre-term Delivery	NIEHS
Preterm Labor	NICHD

Primary Immunodeficiency Disease	NHGRI
Prostate Cancer	CC, NCI-CCR, NCI-DCEG, NHGRI
Psoriasis	NHLBI
Psychopathy	NIMH
Puberty	NICHD, NIEHS
Pulmonary Hypertension	NHLBI
Refractive error (myopia/hyperopia)	NEI
Reproductive Abnormalities	NIEHS
Reproductive Endocrine-related Mood Disorders	NIMH
Respiratory Syncytial virus (RSV)	NIAID
Rheumatoid Arthritis	NIAMS, NIBIB
Rotavirus	NIAID
RSV	NIAID-VRC
Schizophrenia	CC, NEI, NIMH
Scoliosis	NHGRI
Sickle Cell Disease	NIDDK
Sjögren's Syndrome	NIDCR
Sleep Apnea	NIEHS
Sleep Disorders	NIEHS, NINR
Spondylarthropathies	NIAMS
Staph Infection	NIAID
Stroke	CC, NCATS, NCCIH, NHGRI, NIA, NIBIB, NIDCD, NINDS
Stuttering	NIDCD
Subfecundity	NIEHS
Systemic Lupus Erythematous	CC, NCI-CCR, NIAMS
Thyroid Cancer	NCI-CCR, NCI-DCEG
Thyroid Disorders	CC
Toxicity	NIEHS-DNTP
Trachoma	NIAID
Traumatic Brain Injury	NINR
Tuberculosis	NCI-CCR, NIAID
Uterine Fibroids	NIEHS
Varicella-Zoster virus (VZV)	NIAID
Vestibular Dysfunction	NIDCD

Appendix 3

Examples of Phenotyping Studies Done in the CC

Please provide a list of genotype/phenotype studies or programs that your IC conducts in the CRC, e.g., ClinSeq, Undiagnosed Diseases Program, NCI pediatric cancer match, etc. This list will be included in the response to the issue raised by the WG that "the CRC is well-positioned to correlate the genotype and phenotype of diseases or conditions using a precision medicine approach."

CC

Currently, 42 active protocols conducted at the CC fall within these categories: genotyping, phenotyping and gene sequencing. The lead ICs on these studies are NCI, NEI. NHGRI, NHLBI, NIAID, NICHD, NIDDK, NIEHS, NIMH, NINDS and the CC. Appendix I lists these protocols.

Appendix 1 – Genotyping/Phenotyping/Gene Sequencing Current Protocols at the CC

Protocol	Inst	PI	Protocol Title
09-CC-0227	CC	Berger	Phenomenological Study of Psycho-Socio-Spiritual Healing in the Context of Chronic or Life-Threatening Illness
10-CC-0118	CC	Chan	Long Term Clinical Correlates of TBI: Imaging, Biomarkers, and Clinical Phenotyping Parameters
04-C-N279	NCI	Figg	Retrospective Analysis of Drug Disposition and Response-related Genotypes in Cancer Patients and Correlation with Pharmacokinetics and Pharmacodynamics Data
07-C-0100	NCI	Figg	Collection of Blood from Patients with Prostate Cancer
09-C-0103	NCI	Rajan	Prospective Analysis of Genotypes in Adults Undergoing Therapy for Lung Cancer
14-C-0163	NCI	Widemann	Transformation of Plexiform Neurofibromas to Malignant Peripheral Nerve Sheath Tumors in Neurofibromatosis Type 1: Clinical, Histopathologic, and Genomic Analysis
03-EI-0033	NEI	Sieving	X-Linked Juvenile Retinoschisis - Clinical and Molecular Studies
06-EI-0236	NEI	Brooks	National Ophthalmic Genotyping and Phenotyping Network, Stage 1 - Creation of DNA Repository for Inherited Ophthalmic Diseases
10-EI-0140	NEI	Cukras	Genotype-Phenotype Study of Patients with Plaquenil®-Induced Retinal Toxicity, with Evaluation of the ABCA4 Gene

12-EI-0042	NEI	Wiley	NEI Intramural Biorepository for Retinal Diseases
13-EI-0027	NEI	Chew	AMD Phenotype and Genotype Study (APGS)
14-EI-0064	NEI	Brooks	Whole Exome and Whole Genome Sequencing for Genotyping of Inherited and Congenital Eye Conditions
04-HG-0123	NHGRI	Biesecker	Bardet-Biedl Syndrome: Phenotype and Metabolic Characteristics
05-HG-0152	NHGRI	Stewart	Variation in Gene Expression in Neurofibromatosis Type 1
07-HG-0002	NHGRI	Biesecker	ClinSeq: A Large-Scale Medical Sequencing Clinical Research Pilot Study
10-HG-0065	NHGRI	Biesecker	Whole Genome Medical Sequencing for Gene Discovery
11-HG-0093	NHGRI	Muenke	Personalized Genomic Research
12-HG-0202	NHGRI	Shaw	The Neurobehavioral, Environmental and Genetic Factors Impacting the Clinical Course of Attention Deficit Hyperactivity Disorder
13-HG-0171	NHGRI	Biesecker	Randomized Trial of Consent Interventions for NIH Whole Exome and Whole Genome Sequencing Studies
14-HG-0048	NHGRI	Gibbons	GENE-FORECASTSM: Genomics, Environmental Factors and Social Determinants of Cardiovascular Disease in African-Americans Study
86-HG-0096	NHGRI	Sidransky	Studies of Genetic Heterogeneity in Patients with Lysosomal Storage Disorders
94-HG-0132	NHGRI	Biesecker	The Phenotype and Etiology of Proteus Syndrome and Related Overgrowth Disorders
11-H-0252	NHLBI	Taylor	Exploratory Studies of Psychophysical Pain Phenotyping and Genetic Variability in Sickle Cell Disease
12-H-0084	NHLBI	Sack	Metabolic Phenotyping of Subjects with Mutations Associated with Hereditary Parkinson's Disease
14-H-0049	NHLBI	Moss	Clinical Outcomes and Molecular Phenotypes in Smokers with Parenchymal Lung Disease
01-I-0202	NIAID	Holland	Natural History, Genetics, Phenotype and Treatment of Mycobacterial Infections
08-CH-0213	NICHD	Yanovski	WAGR Syndrome and Other 11p Contiguous Gene Deletions: Clinical Characterization and Correlation with Genotype
09-CH-0059	NICHD	Kaler	Molecular Bases of Response to Copper Treatment in Menkes

			Disease, Related Phenotypes, and Unexplained Copper Deficiency
95-CH-0059	NICHD	Stratakis	Definition of the Genotype and Clinical Phenotype of Primary Pigmented Nodular Adrenocortical Disease (PPNAD), Carney Complex, Peutz-Jeghers Syndrome and Related Conditions
97-DC-0057	NIDCD	Drayna	Genetic Studies of Stuttering
05-DK-0085	NIDDK	Miller	Clinical and Laboratory Investigation of Humans with Informative Iron or Erythroid Phenotypes
07-DK-0077	NIDDK	Skarulis	Study of the Phenotype of Overweight and Obese Adults
07-DK-0219	NIDDK	Chen	A Nutrigenomics Intervention for the Study of the Role of Dietary Sitosterol on Lipid, Glucose and Energy Metabolism
08-DK-0149	NIDDK	Ghany	High Dose Ribavirin in Combination with Peginterferon for Patients with Chronic Hepatitis C Genotype 1 Infection Who Have Failed to Respond or Relapsed after Standard Therapy
04-E-0053	NIEHS	Shurman	Environmental Polymorphism Registry (EPR)
12-E-0194	NIEHS	Shurman	Environmental Polymorphisms Registry Health and Exposures Survey
00-M-0198	NIMH	Leibenluft	The Phenomenology and Neurophysiology of Affective Dysregulation in Children and Adolescents with Bipolar Disorder
02-M-0239	NIMH	Apud	Randomized, Double-Blinded, Placebo Controlled Study of the Effects of Tolcapone and Entacapone on Cognitive Function in Patients with Schizophrenia and Normal Controls Based on COMT Genotype
03-M-0143	NIMH	Apud	Randomized, Double-Blinded, Placebo Controlled Study of the Effects of Modafinil on Cognitive Function in Patients with Schizophrenia and Normal Controls Based on COMT Genotype
10-M-0112	NIMH	Berman	Defining the Brain Phenotype of Children with Williams Syndrome
91-M-0124	NIMH	Berman	Structural and Functional Imaging of Neuropsychiatric Patients and Normal Volunteers with 1.5 Tesla MRI
01-N-0206	NINDS	Lungu	Phenotype/Genotype Correlations in Movement Disorders

NCI

The major genotype/phenotype studies that DCEG conducts at the clinical center are studies of families with distinctive patterns of cancer or precancerous lesions.

In collaboration with CCR:

NFI/plexiform neurofibromas
Xeroderma pigmentosum and tricothiodystrophy

DCEG:

Li-Fraumeni
Breast-ovarian families (inactive now)
Inherited bone marrow failure disorders
Pulmonary pleuroblastoma families
Second cancers after retinoblastoma
Individuals with multiple primary cancers
Melanoma-prone families (including retinoblastoma survivors)

CCR clinical protocols with relevance:

Title	Protocol
A Pilot Pediatric/Adult Study of Gene Expression Profiling and Clinical Characterization of Phototoxicity	06C0198
A Pilot Study of Markers of Tumor Burden and Radiation Toxicity in the Blood, Urine, and Stool of Patients Receiving Radiotherapy for Gastrointestinal Malignancies	07C0111
An Exploratory Evaluation of Biomarkers in Blister Fluid in Healthy Volunteers and Irradiated Skin	09C0120
Characterization of High Risk Breast Duct Epithelium by Cytology, Breast Duct Endoscopy, and cDNA Gene Expression Profile	02C0077
Collection of Blood from Patients with Cancer for Analysis of Genetic Differences in Drug Disposition	11C0242
Relapsed Hematologic Malignancy after Allogeneic Hematopoietic Stem Cell Transplantation: Screening, Disease Characterization and Natural History	11C0125
A Prospective National Study to Molecularly and Genetically Characterize Human Gliomas: The Glioma Molecular Diagnostic Initiative	02C0140
Pilot Trial of Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies	11C0096

Biomarkers in Acute Graft-Versus-Host Disease (GVHD) and Extracorporeal Photopheresis added to Investigator Chosen Therapies of Steroid Refractory Acute GVHD	15C0039
Comprehensive Omics Analysis of Pediatric Oncology Solid Tumors and Establishment of a Repository for Related Biological Studies	10C0086
Prospective Comprehensive Molecular Analysis of Endocrine Neoplasms	09C0242
Clinical and Genetic Studies in Familial Non-medullary Thyroid Cancer	10C0102
Evaluation of Diagnostic and Prognostic Molecular Markers in Adrenal Neoplasm	11C0149
A Pilot Study of Proteomic Evaluation of Epithelial Ovarian Cancer Patients in First Clinical Remission: Development of a Protein Fingerprint Profile Associated with Relapse	00C0018
A Multi-Institutional Study of Proteomic Evaluation of Epithelial Ovarian Cancer, Primary Peritoneal Cancer, and Fallopian Tube Cancer Patients in First Clinical Remission: Development of a Protein Fingerprint Profile of Relapse	04C0232
The Birt Hogg Dube' Syndrome: Identification of the Disease Gene, and Characterization of the Predisposition to Renal Cancer	02C0159
Hereditary Leiomyomatosis Renal Cell Cancer (HLRCC): Identification of the Disease Gene, and Characterization of the Predisposition to Renal Cancer	03C0066
Clinical Manifestations and Molecular Bases of Heritable Urologic Malignant Disorders	89C0086
PET Imaging Of Renal Cell Carcinoma With 18F-VM4-037: A Phase II Pilot Study For Detection Of Disease And Correlation With VHL Mutation Status	13C0018
Prospective Analysis of Genotypes in Adults Undergoing Therapy for Lung Cancer	09C0103
Frequency of Epidermal Growth Factor Receptor Mutations in Latinos/Hispanics with Non-Small Cell Lung Cancer	11C0044
Lenalidomide Maintenance Therapy in Multiple Myeloma: A Phase II Clinical and Biomarker Study	12C0192
Prospective Evaluation of Epigenetic Alterations in Patients with Thoracic Malignancies	06C0014
Transformation of Plexiform Neurofibromas to Malignant Peripheral Nerve Sheath Tumors in Neurofibromatosis Type 1: Clinical, Histopathologic, and Genomic Analysis	14C0163
Randomized Phase II Study of Dose-Adjusted EPOCH-Rituximab-Bortezomib Induction Followed by Bortezomib Maintenance versus Observation in Untreated Mantle Cell Lymphoma with Microarray Profiling and Proteomics	05C0170

Phase III Randomized Study of R-CHOP v. Dose-Adjusted EPOCH-R with Molecular Profiling in Untreated de Novo Diffuse Large B-Cell Lymphomas	05C0252
Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): DNA Microarray Gene Expression Analysis	97C0178

NEI

The NEI has the following active clinical protocols incorporating a genotype/phenotype approach:

- 12-EI-0042: NEI Intramural Biorepository for Retinal Diseases
- 13-EI 0072: Microbiome and Ocular Inflammatory Disease
- 13-EI-0027: AMD Phenotype and Genotype Study (APGS)
- 14-EI-0064: Whole Exome and Whole Genome Sequencing for Genotyping of Inherited and Congenital Eye Conditions;
- 12-EI-0203: Natural History of ABCA4-Related Retinopathies;
- 10-EI-0140: Genotype-Phenotype Study of Patients with Plaquenil -Induced Retinal Toxicity, with Evaluation of the ABCA4 Gene;
- 08-EI-0099: Epigenetics, Molecular Genetics, and Biomarkers of Degenerative and Inflammatory Ocular Diseases
- 06-EI-0236: National Ophthalmic Genotyping and Phenotyping Network, Stage 1 - Creation of DNA Repository for Inherited Ophthalmic Diseases;
- 06-EI-0059: Clinical and Molecular Studies in Families with Glaucoma and Related Diseases;
- 06-EI-0058: Clinical and Molecular Studies in Families with Myopia and Related Diseases;
- 05-EI-0143: Molecular Genetics of Retinal Degenerations
- 05-EI-0096: Natural History and Genetic Studies of Usher Syndrome;
- 04-EI-0008: Clinical and Molecular Studies in Families with Corneal Dystrophy or Other Inherited Corneal Diseases;
- 03-EI-0155: Evaluation of Single Nucleotide Polymorphism (SNP) in Patients with and Subjects without Age-Related Macular Degeneration (AMD)
- 03-EI-0123: Clinical and Molecular Studies in Families with Congenital or Hereditary Cataracts).
- 92-EI-0113: Immunopathology and Molecular Pathology of Ocular Diseases in Humans

<u>Other relevant NEI activities, including precision medicine based approaches:</u>

- NEI is conducting “disease in a dish” studies using genotyped, *patient-specific iPS cell-derived retinal pigment epithelial (RPE)* cells to identify disease cellular endophenotypes and

use those endophenotypes to discover novel potential drugs.

- NEI is developing a therapeutic intervention against Geographic Atrophy (GA), the most prevalent form of Age Related Macular Degeneration. We are developing an autologous cell therapy using patient specific iPS cell derived retinal pigment epithelium as a personalized medicine for age-related macular degeneration.
- NEI is initiating a phase 1clinical trial to rescue a rare inherited retinal disorder, X-linked retinoschisis (XLRS) by a single gene replacement therapy. This work has general implications for other disorders caused by synaptic dysfunction.
- NEI continues to participate in the undiagnosed disease program.
- NEI hosts The National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE) that advances our understanding of eye diseases and their genetic causes by giving researchers access to DNA samples, clinical information, and patients looking to participate in research studies and clinical trials.
- The NEI DNA Diagnostic Laboratory (DDL) operates under Clinical Laboratory Improvement Amendments (CLIA) certification to provide DNA diagnostic tests for inherited eye related diseases to researchers and clinical investigators in the NEI Eye Clinic, external collaborators of the NEI Eye Clinic and the NEI intramural research community.

NHGRI

Genotype-phenotype studies in the CRC: ClinSeq, UDP, autoinflammatory diseases (Dan Kastner), Gaucher Disease (Ellen Sidransky), ADHD (Philip Shaw), holoprosencephaly (Max Muenke), congenital anomalies (Les Biesecker), biochemical genetics (Bill Gahl)

NHLBI

- State of the art methodologies including:
  - Cardiovascular/pulmonary imaging modalities
  - Pulmonary function testing
  - Various aspects of cellular physiology via sorting/immunochemical techniques
- Additionally we have a mouse phenotyping core that is focused on assessing impact of induced mutations in mice and can provide insights on next steps for human studies

NIA

Genotype phenotype correlations in movement disorders (main PI Mark Hallett, NINDS)
C9orf72 natural history study (13-0188, www.clinicaltrials.gov/ct2/show/NCT01925196)
Liver genotype/phenotype studies
Adipose/Inflammatory genotype/phenotype studies

NIAAA

a. Exome sequencing of patients with common, complex psychiatric diseases and phenotypes relevant to alcoholism, other addictions and psychiatric diseases. The latter include Premenstrual Dysphoric Disorder and Borderline Personality Disorder.

b. Genome wide- association array analysis as a genomic baseline in clinical studies of alcoholism and addictions.

c. Genome wide epigetic analyses: methylome, RNASeq, and ChIP-Seq in the context of addictions and psychiatric diseases.

NIAID

1. NIAID Primary Immune Deficiency Clinic
2. Undiagnosed Diseases Program
3. NIAID Clinical Genomics Group

NIAID-VRC

a. Collaboration with John Barrett (NHLBI) in studies to vaccinate against leukemia/lymphoma antigens.
b. Collaboration with John Barrett (NHLBI) in studies to vaccinate against and perform immunotherapy for viruses that cause morbidity and mortality post-transplant (e.g., BK virus).
c. Collaboration with Steven Rosenberg (NCI) in studies to identify tumor-specific T cell receptors for subsequent tumor immunotherapy.

NICHD

NICHD CRC programs see children with various phenotypes from congenital bone, growth, puberty, metabolic and fertility disorders to endocrine tumors and related conditions, women with infertility and adult patients with rare endocrine conditions to common hypertension. In all these studies, the genotype is studied. A comprehensive list follows:

- Nieman-Pick Type C
- Smith-Lemli Opitz Syndrome
- Osteogenesis imperfecta
- Carney Complex
- Carney-Stratakis syndrome
- Carney Triad
- Gigantism and other disorders leading to overgrowth
- Adrenal/pituitary tumors

- Pheochromocytoma and paraganglioma
- Obesity
- Disorders leading to short stature
- Congenital adrenal hypepralasia
- Altered pubertal development
- Turner syndrome
- Primary Ovarian Insufficiency

NIDCD

- Pendred syndrome (hereditary hearing loss)
- Usher syndrome (hereditary hearing loss)
- Stuttering
- Head and neck cancer

NIDCR

NIDCR labs participate in the UDP for juvenile idiopathic osteoporosis patients, as well the CCGO program for Sjögren's syndrome.

NIDDK

d. Lipodystrophies and severe insulin resistance
e. Obesity and Metabolic Phenotyping
f. Hepatitis C genotypes and treatment responses
g. Non-alcoholic Fatty Liver Diseases – genetics and epigenetics
h. Hereditary Endocrine Tumors and Carcinoid Tumors of the GI tract
i. Focal Segmental Glomerulosclerosis (FSGS) and APOL-1 genotypes

NIEHS

a. Environmental polymorphisms registry is a large study studying gene-environment interactions in the pathogenesis of many diseases: NIEHS CRU and NIH CRC
b. Associating genotypes with phenotypes in a cohort of autoimmune muscle diseases called myositis: NIH CRC
c. Asthma: Off-site
d. Allergies: Off-site
e. Sleep Apnea: Off-site
f. Chronic obstructive pulmonary disease: Off-site
g. Babies with cleft lip and palate: Off-site
h. Bronchopulmonary Dysplasia: Off-site
i. Retinopathy of Prematurity: Off-site

NIMH

Childhood onset schizophrenia genotype/phenotypes; Neurobiological study of patients with schizophrenia spectrum disorders and their siblings; Brain imaging of childhood onset psychiatric disorders, endocrine disorders, and healthy controls; Brain phenotype of children with Williams syndrome; family study of affective and anxiety disorders; characterization and pathophysiology of severe mood and behavioral dysregulation in children and youth; evaluation of women with menstrually regulated mood and behavioral disorders; markers of autism spectrum disorders in at-risk toddlers; screening for studies of the Pediatric and Developmental Neuroscience Branch; evaluation of patients with mood and anxiety disorders and healthy volunteers

NINDS

The investigators in the Neurogenetics Branch (Kurt Fischbeck and Carsten Bonnemann) use this approach for every neurodegenerative disorder with a specific genotype. The glioblastoma work is very interested in genotype/phenotype and many tumors are studies with distinct genetic causes. Almost all Parkinson's patients are genotyped and most work is very heavily phenotyping in Parkinson's. There is a growing interest in genotype/phenotype studies in ALS. So far genetic contributions to MS and stroke have not been strong enough to guide studies. There is one project to predict onset of MS among patients that have multiple risk factors including genetic.

NINR

We have 7 clinical trials being conducted in our intramural program that explore genotype/phenotype, in addition to other genetic methodologies such as gene expression, methylation, miRNA. However, we are using our NINR lab to obtain genetic data. In particular, Dr. Meilleur's clinical trial below includes patients with a congenital neuromuscular disease and she is determining whether a specific intervention can be used for a particular patient.

15-NR-0072 Meilleur, Katherine Antioxidant therapy in RYR1-related congenital myopathy

Appendix 4	
IRP List of Emergency Response Studies	
The WG recommended that the IRP develop a mechanism to respond to emergent health crises. Please list the public health crises to which your IC has responded in the past two years, e.g., Ebola, Fukushima.	
CC	The Clinical Center has worked with the leadership of The Water Reed National Military Medical Center and of Suburban Hospital to create the Bethesda Hospitals' Emergency Preparedness Partnership. This partnership allows all three institutions much more flexibility in responding jointly to all kinds of public health emergencies. As one of three facilities in the country that has a high-level infectious diseases containment unit, the Clinical Center and its staff provided care for repatriated volunteers who were working in West Africa and who were exposed to Ebola Virus Disease (EVD), in addition to providing care for a nurse who acquired EVD infection while providing care for a patient with EVD in a Dallas hospital and a clinician who became infected with EVD while providing care for Ebola patients in West Africa. This containment unit could be used to provide safe care for patients who have almost any highly contagious infectious disease. Clinical Center staff are frequently called on to consult with experts at CDC concerning the hospital management of patients who have contagious infections. The Clinical Center has also partnered with the Uniformed University of the Health Sciences and The Water Reed National Military Medical Center to attempt to improve our understanding of the sequelae and the optimal management of Traumatic Brain Injury and Post Traumatic Stress Disorder. Finally, the Clinical Center responded to the current epidemic of obesity in the United States by modifying and adopting its clinical research infrastructure to facilitate the conduct of elegant metabolic studies in this field.
NCBI	Influenza - Creation of an influenza online resource
	Ebola - Creation of an Ebola virus online resource
NCATS	NCATS has executed several small molecule drug repurposing screens in response to the Klebsiela outbreak at NIH CC (in collaboration with Dr. Karen Frank, NIH CC), as well as, 3 months ago, a screen that identified 53 candidate agents against Ebola: the Ebola screen was set up, executed, and analyzed within less than 2 months of project initiation. Going back a few years, NCATS, as a part of the Tox21 inter-IC and interagency consortium, responded to the BP Gulf of Mexico oil spill environmental disaster by immediately testing candidate oil dispersants: the dispersants were received from the EPA, tested in a panel of cell-based assays, and report was completed within about 3 weeks of the issuance of the call.
NCI	Teams are developing antibody-based therapeutics against viruses of biodefense importance and emerging coronaviruses that are effective in humans and can save human lives even in the absence of terrorist acts.
	Researchers are conducting an ongoing evaluation of the antiviral proteins griffithsin and scytovirin for activity against ebola in collaboration with USAMRIID and NIAID.
	Team is using advanced 3D microscopy techniques to determine the structure of membrane-bound Ebola viral glycoproteins in a near-native state. Structural characterization of these proteins bound to neutralizing antibodies is necessary for determining how these antibodies block viral entry and prevent disease. Furthermore, these studies are likely to be useful in the effort to design other effective vaccines and drugs to combat the illness caused by this virus.
	IRP scientists used cryoelectron tomography to obtain density maps of the hemagglutinin (HA) trimers on the surface of the 2009 H1N1 pandemic influenza. Insights into the extent to which HA stem regions on the surface of the virus will aid in vaccine design by determining which site are accessible to broadly neutralizing antibodies.

	NCI PI is serving on group that is developing civilian medical response planning for radiological and nuclear terrorism and other events. This involves planning, policy, and normal tissue injury-related science. Medical countermeasures are being developed through NIAID support in the Centers for Medical Countermeasures Against Radiation (CMCR). This overall program has major impact to U.S. preparedness and also has a spin-off for normal tissue injury from radiation and the potential for post-exposure mitigators and treatments.
	At the request of U.S. Ambassador to Japan, a team of subject matter experts were deployed by DHHS to advise U.S. embassy staff in Tokyo on ways to protect Americans in Japan during the Fukushima Daiichi nuclear power plant crisis in 2011. Dr. Steve Simon, a health physicist in NCI's Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, together with Dr. C. Norman Coleman, associate director of NCI's Radiation Research Program, comprised members of the group that also included experts from the FDA and CDC.
	Drs. Simon and Coleman spent several weeks in Japan consulting on a range of issues related to radiation exposure and the health of Americans in Japan during the Fukushima nuclear crisis. They advised on what constituted safe levels of radioactivity in food and drinking water, the necessity of and conditions for evacuation around the power plant and the conditions for return, and the circumstances under which Americans should take potassium iodide to prevent radiation exposure to the thyroid. The team developed communication materials for the embassy to use to convey health and safety information to American citizens living in Japan.
NHGRI	The major public health crisis to which the NHGRI IRP has responded in the last 2 years has been the emergence and transmission of hospital-acquired antibiotic-resistant bacteria.
NHLBI	Our clinical director, Dr. Richard Childs, was part of the PHS mission to Liberia for 3 months to respond to the Ebola crisis.
NIAAA	Capt. Joe Hibbeln (tenure track, Commiss. Corps) has been instructed to stand ready for deployment to Liberia (ebola)
NIAID	Ebola
	In the current climate, government response to emerging pandemic agents has come under considerable scrutiny. There is a pressing need to better understand and prepare for the potential for significant human mortality and morbidity due to emerging known or unknown pathogens. Substantial public interest will likely be given to actions that address this need. The NIAID has a dual mandate to balance cutting edge research on current biomedical threats with the capacity to respond quickly to emerging and re-emerging infectious challenges. NIAID DIR has responded to the current Ebola virus outbreak in West Africa by leveraging longstanding and productive partnerships to accelerate ongoing research efforts for the development of the dignostics, therapeutics and vaccines.
	Deployment of teams to West Africa: NIAID Intramural scientists, including 13 from the NIAID DIR, have responded to the ongoing epidemic in West Africa by establishing and staffing laboratory field sites in Monrovia, Liberia, in coordination with the Centers for Disease Control and Prevention (CDC) and the Department of Defense to identify the presence or absence of Ebola virus in clinical samples. These real-time data are critical to patient care and monitoring of the epidemic. NIAID and CDC researchers also have established collaborations with Malian public health institutes, providing training in laboratory testing for identification of Ebola and other fever-causing viruses.
	Developing vaccine candidates: Two DIR Ebola vaccines have been shown safe and protective in macaques. Clinical lots are currently being manufactured, and Phase I trials are planned for mid-2015.

	Basic research: NIAID intramural researchers continue to conduct innovative scientific investigation in the high and maximum containment (biosafety level-3 to biosafety level-4) research environment. Scientists broadly study pathogens that cause viral hemorrhagic fevers with comprehensive studies in cell culture; animal models, including nonhuman primates; reservoir species; and arthropod hosts in order to elucidate the viral pathogenesis, immune responses, molecular evolution, cellular and molecular biology, and vector-host interactions.
	Developing and testing therapeutics: DIR has completed in vitro testing of six different compounds for their therapeutic effects on the Ebola virus and has plans to test two additional compounds. In vivo testing of eight potential therapeutic compounds and combinations of compounds using hamster, mouse and non-human primate models of Ebola infection have been completed and plans for testing two additional compounds have been made.
	The NIAID DIR remains an investigative leader even in times of unprecedented challenges by capitalizing on a distinctive, high-risk, high-impact laboratory, clinical, and population-based research environment.
NIDCR	Our Laboratory of Cell and Developmental Biology is collaborating with researchers at the FDA (Dr. Subhash Dhawan) and The U.S. army Medical Research Institute of Infectious Diseases (Dr. Veronica Soloveva) to determine the efficacy of hemin, an FDA-approved pharmaceutical, in suppressing Ebola infection. The experiments are currently in vitro. One of our research nurses will go on detail 5/14/15-6/6/15.
NIDDK	Three NIDDK staff members, also officers in the U.S. Public Health Service, were deployed (2 months each starting Oct 2014 through March 2015) to Liberia as part the U.S. response to the Ebola outbreak. Specifically, they were part of larger teams sent to treat health care workers who had become infected with Ebola. Nurse Practitioners Michelle Braun and Michael Davis, of the Kidney Diseases Branch, were called upon for their nephrology expertise to address patient kidney failure while Megan Mattingly, R.N. and a Clinical Research Nurse with our Diabetes, Endocrinology, and Epidemiology Branch, provided general patients care.
	Katrina (Medical personnel deployment (2) to Louisiana)
NIEHS	GuLF Study: The Gulf Long-term Follow-up Study (GuLF STUDY) investigates potential health effects associated with clean-up activities following the 2010 Deepwater Horizon disaster in the Gulf of Mexico.
	Ebola: Debra King and John McLamb will be part of the Public Health Service contingent working to treat Ebola. They will be involved in staffing a 25-bed Ebola treatment unit in Monrovia, Liberia.
	NIH Disaster Research Response Project: NIEHS staff and investigators are leading the effort to be better prepared for performing timely disaster research well before weather, terroristic attacks, and other disruptive events strike. They are working to develop quick access to useful data collection tools, rapid development and implementation of research protocols, a national environmental health researcher network, and capacity to deploy trained researchers to the field.
	NIEHS Worker Education and Training Program: Provides training for workers in disaster response and post-event remediation.

NIEHS DNTP	Many of the research programs carried out by the DNTP for the National Toxicology Program are in direct or indirect response to public health crises. Some of these have been in response to accidents or spills, such as the spill of coal cleaning chemicals into the Elk River in Charleston WV in Jan 2014. In discussions with Dr. Frieden from CDC and WV Senator Manchin, we devised a set of studies to address specifically the potential for lasting health effects for the 300,000 plus exposed citizens of the Charleston metropolitan area. We also have continuing research programs underway to examine possible health effects from the exposures to various mixtures of polyaromatic hydrocarbons released during the Gulf Coast Oil Spill, as well as from the massive use of biofuels and biomass burning in cookstoves, recently recognized as a significant global health threat. We have ongoing research programs into the health effects of molds in homes following hurricanes Katrina and Sandy. We also have an ongoing research program stemming from the discovery of sulfolane in the ground water around oil refineries in Fairbanks Alaska. Although the precipitating events have in some cases happened before the 2 year time frame of this question, our research efforts often span multiple years following such events, and we've been performing this function in response to health crises as far back as the pesticide plant explosion in Bhopal India in 1984.
NIMH	NIMH responded to the mental health crisis after Hurricane Katrina (2005) and is available to provide mental health expertise in the event of mental health crises.
NINDS	Nodding syndrome, Acute Flaccid Myelitis with enterovirus infection
NINR	NINR is responding to the occurring crisis related to the increase in common diseases and in the associated symptoms.
NLM	The NLM People Locator (PL) is a Web system that enables family, friends and neighbors to locate or report missing people during a disaster event. It utilizes a "Disaster Patient Data Exchange" database containing data from the IT systems of local hospitals and additional input from triage area cell phones and social networks.
	In a disaster, this system can facilitate family reunification, help provide reassurance, enhance coordination with disaster-responding NGOs, and alleviate some of the workload on public-health personnel and other responders who interact with the community. Those looking for friends or family members can search the PF database and retrieve the information in formats designed for multiple devices. In addition, the system can display pictures and other information on missing persons on large monitors placed at key public locations.
	The People Locator has been used multiple times to assist during public health crises including:
	Typhoon Hagupit, Philippines, December 2014
	Jammu-Kashmir Floods, Pakistan-India, September 2014
	Super Typhoon Haiyan, Japan, November 2013
	Acapulco Floods, Mexico, September 2013
	Uttarakhand, India, Flooding June 2013
	Sichuan, China, Earthquake April 2013
	Boston Marathon Explosions, USA, April 2013
	Typhoon Pablo, Phillipines, December 2012
	Philippine Floods, August 2012
	Typhoon Sendong, China, December 2011
	Earthquake, Turkey, Oct 2011
	Joplin, USA, Tornado May 2011
	Japan Earthquake and Tsunami March 2011- Fukushima

	ChristChurch, New Zealand Earthquake February, 2011
	Haiti Earthquake, January 2010
VRC	The NIAID Vaccine Research Center (VRC) has a robust viral hemorrhagic fever vaccine development program, is currently conducting basic, translational, and clinical research, and is working with multiple international partners to help advance and facilitate ultimate licensure of a protective vaccine. Since 2003, the VRC has evaluated three early-generation Ebola vaccine candidates and one Marburg vaccine candidate in Phase 1 clinical trials at the NIH campus. An additional Phase 1 clinical trial was conducted in Kampala, Uganda, in collaboration with DOD. The data from those trials have contributed directly to the VRC's current Ebola vaccine collaboration with the pharmaceutical company GlaxoSmithKline (GSK). VRC and GSK have developed an experimental vaccine that uses chimp Adenovirus 3 (cAd3) as a vector, to express the Ebola surface glycoprotein (GP) in order to induce protective immune responses. A Phase 1 clinical study carried out at the NIH Clinical Center and at two other U.S. sites in Fall 2014 has demonstrated the safety and ability of this candidate to induce immune responses in humans. NIAID and GSK also have donated doses of the cAd3 monovalent vaccine candidate to enable further testing by NIAID partners in the United Kingdom and the West African country of Mali. In October, GSK and WHO partners began an additional, larger clinical study of the monovalent vaccine in Geneva/Lausanne, Switzerland.
	In February 2015, a Phase I clinical study led by the US DoD (MHRP/WRAIR) began in Uganda. This study encompasses immunizing groups of naïve subjects with either VRC monovalent or bivalent cAd3 vaccines, as well as immunizing a group of previously Ebola DNA wild-type (WT) vaccinated subjects with the bivalent vaccine.
	A Phase I clinical study evaluating the VRC's cAd3 bivalent candidate vaccine has begun in Mali, and immunized its first group of subjects on March 30, 2015. A group of bivalent vaccinated subjects will also be boosted in future with MVA (precise formulation and valency of the MVA is still being decided).
	An additional Phase I clinical study to evaluate the safety and tolerability of the VRC's cAd3-MVA prime-boost regimen has begun at the Clinical Center. This study will evaluate the immunogenicity of MVA-EbolaZ administered alone and as a booster vaccination for the VRC's cAd3-EBO or cAd3-EBOZ vaccines.
	Chikungunya

Appendix 5	
IRP Projects stimulated by IC funds	
The WG recommended creation of "optional internal innovation funds of no less than 5% of their non-personnel IRP budget to support highly innovative projects directed toward their focused missions." The SDs favored focusing on innovative tenure-track investigators rather than top-down directed innovative science and commented that IC funds are being used to stimulate certain activities, e.g., development of a technique, purchase of special equipment, hiring scientists, etc. Please list what you are currently doing to share central IC funds competitively with some of your investigators. What are funds used for, and how much do you spend in this way?	
CC	The Bench-to-Bedside (B2B) Awards Program is a program managed by the CC. The B2B Awards seed new projects bringing together basic scientists with clinical investigators; over 90% of the awards are partnerships between intramural and extramural investigators. The program offers competitive awards funded by a number of NIH Offices. It is a popular program with a well-defined structure with processes (including rigorous review of proposals) modeled after NIH grants operations. This longstanding intramural program would benefit from designated funding for the B2B innovative projects submitted annually across ICs.
NCCIH (NCCAM)	We are a small program with only 3 TT's, all of whom have begun within the last year. They have all received a generous start-up package and yearly operating budget to fully meet their needs. We have an SD reserve fund that can be used to help these *investigators, if their current funding is not sufficient. We do not yet have a formal competitive program set up.*
NCATS	Within some of its programs, NCATS has small pools of money set aside for bottom-up-nominated studies primarily directed at development of novel technologies to accelerate drug discovery. Given the tight budget situation, the fraction of these funds in relation to total budget is less than 1%.
NCI	The CCR has several mechanisms in place for the distribution to intramural PIs of dedicated funds to encourage and support the pursuit of highly innovative projects. Total expenditure for these programs is $11.39M, corresponding to 7.2% of the non-personnel CCR budget (~$158M).
	There are three major CCR programs through which internal innovation funds are distributed: The Major Opportunity (MO) Program, the FLEX Program and the Innovation Awards. All mechanisms are based on open competition and peer review of submitted proposals. None of the programs are focused on any specific scientific areas so as to encourage bottom-up initiatives and self-assembly of synergistic teams amongst CCR investigators. Junior investigators are particularly encouraged to participate in these programs.
	Major Opportunity Program (2.5M/year): The MO Program was launched in 2012 and currently supports three research projects (Matrix Drug Screening, Metabolic basis of cancer, Cancer chromatin profiling). Projects were selected through multi-level review by intramural CCR senior investigators. All projects follow clearly defined milestones and progress is reviewed semi-annually by the CCR Science Board. An overarching goal of the MO Program is to encourage the transition of basic research findings to clinical application. All MO Projects are required to solicit proposals for collaboration from the CCR PI community to make the technologies developed in the MO Program widely available to CCR PIs. The anticipated duration of the projects is 5 years. Funds are used for purchase and/or development of specialized equipment, purchase of specialized reagents, and personnel cost. A total of 5 CCR PIs are engaged in the MO Program as lead investigators, 31CCR PIs as collaborators.
	Flex Program (2.6M/year): The FLEX Program was launched in 2014 to provide opportunities for CCR PIs to pursue research projects that are difficult to pursue in the context of their regular research program. The FLEX Program focuses on three broad themes: Technology Development, Synergistic Team Science and pursuit of New Research Directions. Short research proposal are solicited from the CCR PI community and reviewed by the CCR Science Board and ad-hoc reviewers from 6 ICs (NHGRI, NINDS, NIDDK, NIDCR, NIDCD, NIAMS). Criteria for selection are impact, innovation, and feasibility. 78 proposals by 116 CCR investigators (46% of total CCR PIs; 20 proposals from tenure-track investigators) were submitted in response to the first solicitation. 22 proposals (8 from tenure track investigators) were selected for further review based on numerical scoring. It is anticipated that 10 projects will be funded. Funds are used for personnel, equipment and reagent costs associated with the project. FLEX project are supported for 3 years with the option of a 2 year extension.
	Intramural Innovation Award (190K): The Innovation Award Program is designed to support development of CCR postdoctoral fellows using highly innovative approaches and technology aimed at significant cancer-related problems. Novel proposals with the potential for high impact, the potential to generate new intellectual property or technology, or which are considered too high-risk or preliminary to pursue within the base budget allocation are encouraged. In Fiscal Year 2015, 19 Career Development Innovation Awards of $10,000 were issued to postdoctoral fellows.

	Fellows' Award for Research Excellence (61K): CCR Fellows are able to apply for a competitive travel award fashioned after the NIH FARE program. The award recognizes outstanding scientific research conducted by CCR fellows who have made exceptional contributions to a CCR research study. FARE award winners receive support for travel to present their research at a scientific meeting. In 2014, 61 fellows received awards of $1000.
	In addition, the CCR uses the *Resource Request System* to supplement ongoing research efforts and support innovative new directions or research. Requests are solicited once or twice a year from all CCR PIs and allocations made by Senior CCR staff based on short justifications. Funds are used for capital equipment, purchase of specialized reagents, and project-related contract services (large-scale sequencing, chemical synthesis etc.). Requests for personnel are not permitted. Up to 60% of CCR PIs are annually supported through RRS. In Fiscal Year 2015, $6.1M has been competitively awarded via the RRS.
	Overall, NCI DCEG Total Funding to Stimulate Innovation: Approximately $4.6M, which represents approximately 5.4% of the division's annual budget. NCI/DCEG uses a variety of competitive funding mechanisms to stimulate innovative research.
	It is notable that the DCEG budget is distributed to Branches based on programmatic criteria and not given directly to individual PIs.
	NCI Director's Intramural Innovation Award Program - This annual competition is designed to support development of highly innovative approaches and technology aimed at significant cancer–related problems. Proposals encouraged include novel proposals from CCR or DCEG with the potential for high impact; those with the potential to generate new intellectual property or technology; those which are considered too high-risk or preliminary to pursue within the base budget allocation, and those with an emphasis on health disparities research. The program offers one-time awards for use in FY15 at two levels: 1) PI Awards (DCEG only) are targeted to tenure-track PIs, recently tenured PIs (within 5 years of tenure), and Senior Scientists/Clinicians with an upper limit of $50,000; and 2) Career Development Awards are targeted to postdoctoral Fellows, Staff Scientists, and Staff Clinicians at all levels with an upper limit of $10,000.
	DCEG Intramural Research Awards - The purpose of the IRA is to encourage intramural DCEG tenure-track investigators and fellows to develop innovative and interdisciplinary collaborative research projects that cross the usual organizational boundaries, and that are programmatically relevant to the mission of DCEG. Priority is given to collaborative projects that are innovative and have potential for significant scientific or public health impact, including development of resources to facilitate population-based research (e.g., creation of a novel database or research model). There is one award competition per fiscal year at which up to three proposals of up to $50,000.
	NCI DCEG Informatics Tool Challenge This award program, which began in 2014, provides competitive funding for innovative proposals that use current informatics technologies to address a specific research need. The projects must be able to be completed within one year of initiation and cost no more than $20,000.
	NCI DCEG Competitive Funding for GWAS and Next Generation Sequencing. DCEG Principal Investigators are able to compete for funding for large-scale genome-wide association studies and next generation sequencing. The "one-shot" funding does not become part of the investigator's or branch budget. Proposals are evaluated for technical merit, innovation, the distinctive role for the intramural research program, and feasibility.
	NCI DCEG Competitive Funding for Trans-Divisional Working Group Initiatives – Over the past two years, trans-divisional working groups have been created to stimulate innovative research in special topic areas including tobacco, translational epidemiology, genetic mosaicism, breast cancer, microbiomics, cohort(s) of the future, second cancers, and early life and maternal factors. Starting in 2015, working group members will be able to compete for funds for novel projects to accelerate progress in these signature research areas. Funding is not intended to extend or accelerate existing Branch-specific studies.
	NCI DCEG D-FARE DCEG Fellows are able to apply for a competitive travel award fashioned after the NIH FARE program. The DCEG Fellows' Award for Research Excellence (DFARE) recognizes outstanding scientific research conducted by DCEG fellows who have made exceptional contributions to a DCEG research study. DFARE award winners receive support for travel to present their research at a scientific meeting. In 2014, fellows received awards of $1500
NEI	NEI IRP currently has no programs for distributing central IC funds competitively to its PIs. However, central IC funds are being used on a regular basis to support and accelerate innovative advances. This support has multiple forms, including technique development, the purchase of special equipment, renovations, and start-up funds for new recruitments. These central funds have also been used to support the development of gene therapy and stem cell based clinical trials

NHGRI	The NHGRI Intramural Program has a competitive peer-reviewed system to cover the costs of large sequencing projects. We spend approximately $1M per year in this way (out of a $17M non-personnel non-Management Fund budget)
NHLBI	Approximately 1% of the DIR budget are used for special projects, varying from clinical trials, novel technical development (e.g. ChIP-Seq), special screening trials (e.g. iRNA effects on muscle and heart development; mutation analysis in mouse development), specialized equipment development in imaging and interventional therapeutic approaches. Additionally, yearly special/large equipment requests are also filled from the 1%. No formal competitive process exists in the DIR for these funds.
NIA	To stimulate a competitive and highly collaborative spirit across the NIA IRP, the Scientific Director set aside $2million in FT2014 and FY2015 funds for collaborative projects. In order to be considered for funds, PI's submitted proposals which collaborated with at least two other laboratories and were reviewed and scored internally and externally.
NIAAA	Year-end savings, when available, are offered for equipment purchase. Shared use equipment is given preference.
NIAID	NIAID DIR currently dedicates significant resources, beyond our standard Laboratory budget allocations, to promote innovation. The NIAID DIR budget after deducting ORS/CC taps and personnel costs is approximately $103,000,000. Examples of resources (Approx. $6,100,000 yearly, listed below in the first four bullets) that are competitively assigned or dedicated to innovation include:
	The DIR Office of the Director has a $2,000,000 yearly initiatives fund, which is used to support/supplement critical and innovative projects that arise. Examples may include studies of newly emerging infectious diseases (e.g. HPA-Influenza, MERS, Ebola), clinical studies, purchase of novel scientific equipment, or establishment of short-term programs dedicated to a specific research goal.
	Each year as funds permit, the DIR OD requests proposals from each laboratory for **supplemental funding of new equipment, contract staff, clinical trials, or short-term innovative projects**. Each Lab Chief ranks supplemental requests for their PIs and laboratory. The DIR OD then competitively awards funding as able (typically $1,500,000).
	NIAID DIR has a **Transition Program in Clinical Research** (TPCR), which is a competitive program that provides dedicated resources to early-career Clinicians under the mentorship of a Senior Investigator. Approximately $1,250,000 supported this program in FY2014 as a means to promote new clinical investigators and innovative research.
	NIAID DIR OD, with the input of Lab Chiefs, develops **cross-cutting** programs to focus resources and diverse talent on topics of critical importance that require novel approaches. Typically, Investigators from multiple laboratories are brought together within a program. These groups are assigned resources competitively on scientific need and performance. Current programs include **Antimicrobial Resistance, Clinical Genomics, Tissue Immunity and Repair, Microbiota, Vaccine Adjuvants, and Emerging Viruses**. Funding for these programs is typically around $200,000 yearly. FY15 funding for the afore-mentioned programs is $1,350,000.
	NIAID DIR OD also directs money to public health emergencies in real-time. For example, (a) $100,000 in FY15 was directed towards hiring staff and purchasing supplies for a newly-launched Chikungunya virus vaccine program, (b) in late FY14, approximately $1,000,000 was directed for manufacture of two Clinical Lots of Ebola vaccines that were developed in DIR, a rabies vectored Ebola vaccine and a HPIV-vectored mucosal Ebola vaccine, (c) $500,000 has been used to cover travel and diagnostic reagents for staff traveling to Liberia and Mali for the Ebola outbreak, (d) a $200,000 nonhuman primate study was performed at RML to test Interferon/ribavirin treatment for Ebola, and (e) continued supplemental funding is directed toward Universal Flu vaccines.
	In addition, DIR OD supports **merit/need-based contracts** on a time-limited basis to meet specific laboratory needs such as vaccine production or clinical trials. Finally, DIR OD invests in new technologies by improving core resources as science changes. For example, the Comparative Medicine Branch recently was directed to establish a CRISPR/CAS program for rapid production of transgenic mouse models.
NIBIB	NIBIB has a very small intramural program (6 PIs). We try to set aside approximately 2% of our budget for innovative projects.
NICHD	NICHD DIR Director's Award, launched summer 2014, two years of funding, $1.5M per year, 15 awards were made; proposed to offer every two years, subject to availability of funds. The award supports scientific collaborations focused on new research ideas, using a modified R21 application; it was competitively reviewed by NIH extramural staff.
	Molecular Genomics Lab competitive awards, 2014, intramural
	Human Placenta Project, intramural participation invited by IC Director, 2014

	Recruitment of a diverse population of trainees to stimulate the pipeline, using two targeted programs, NICHD Developing Talent Scholars (postbaccalaureate through graduate students) and Fellows Recruitment Incentive Award (FRIA) for postdoctoral-level fellows.
NIDCD	Fiscal support of collaborative projects outside the realm of those proposed in BSC reports—this has not generated substantial responses
	Purchase of equipment used for cutting-edge techniques—approximately $1M per annum
	Competitive postdoctoral fellowship awards emphasizing novel proposals that emphasize acquisition of new approaches or tools and bridge laboratories or institutes—semi-annual competition awarding 1-2 fellowships per cycle
NIDA	1. Since 2011, the NIDA Scientific Director has supported a "Scientific Director Innovative Partnership Program." This program is designed to support an intramural investigator teamed with an extramural scientist to perform a highly innovative project – a project that would not be funded through existing grant mechanisms. Each award is approximately $100,000 for one year funding. The NIDA SD allocates approximately $300,000 per year for such projects.
NIDCR	In the current budget climate I have not set aside funds to use competitively. About 1/3 of NIDCR investigators are recently tenured, or about to be tenured, and funds released by departures of other investigators have been used to augment their budgets, based on their progress, BSC reviews and their innovative science. Last year (in part due to an unexpected increase in funding) we spent $1.5 M on equipment, mostly to support acquisition of state-of-the-art microscopy and FACs.
NIDDK	Translational Research Stimulation Fund ($250K annually; project consumables or staff funding for vetted projects advancing translational research)
	Capital Resource Requests (~$2M annually; additional resources for specialized equipment and facilities, new projects, knockout mice, large scale genomics)
	Shared funding of competitively selected RNAi screens
	1-2 year extensions of iPSC work (2 awards) originally funded by competitive mechanism of Center for Regenerative Medicine
NIEHS	Interdisciplinary Research Awards (now on hold due to budget cuts): DIR set aside funds out of its operating budget to encourage new collaborative multidisciplinary research focused on high priority Institute research initiatives. Funds were provided to sponsor a postdoctoral fellow who works with two or more Principal Investigators. Awards were for a three-year period of time and covered a stipend plus operating expenses of $12,000 per year. Four awards were funded each year.
	Tri-mentored Transdisciplinary Environmental Health Fellowships: As an outgrowth of developing the NIEHS Strategic Plan, Cross Divisional Working groups were established and Tri-mentored Transdisciplinary Environmental Health Fellowships have been established for two groups, one in Epigenetics research and another in Stem Cell Research. Individuals will be mentored by faculty from each of the three NIEHS divisions (DIR, DNTP and DERT), providing a broad-based experience in environmental health-focused basic laboratory research; grant preparation; program development, review, and analysis; and applied toxicological research and testing. Awards are for a three-year period of time and cover a stipend plus operating expenses.
NIEHS	Fellowships in Environmental Medicine: The Fellowships in Environmental Medicine are one-year research training opportunities for third-year medical students. The trainees will work full time in a research group for one year. Two fellowships will be awarded per year. Fellows will receive $36,000 for the training, transferred incrementally each semester into their school student account, and administered by their school as a portion of their financial assets. All other costs, including housing and health benefits, are the responsibility of the fellow.
NIEHS DNTP	We do not have competitive programs to support individual investigators, rather innovative projects are expected to be developed and some central funding is occasionally provided for such things as deep sequencing, or provision of a cross-divisional mentored post doctoral fellow. These activities are variable from year to year and rarely exceed $250K.
NIMH	For the past two years the NIMH SD has provided supplementary funding to support innovative work, the development of new technologies and team science. Investigators apply for funds and priority is given to those proposals 1) that allow investigators to do innovative experiments that cannot currently do 2) that allow investigators to undertake and develop new approaches 3) that support new collaborative efforts between laboratories both within and outside the IRP. The amount used for these purposes has averaged approximately 4% of our *total* budget for the past two years.
NINDS	Annually about $3M+ of central funds go to PI-initiated new equipment requests and special initiatives (2-4 years) for new projects which place a priority on collaboration. These projects are reviewed on an ad-hoc basis and are not reviewed by the BSC until the PI incorporates it into long term work.

NINR	In FY14 I spent approximately 10% of the NINR DIR budget to support highly innovative projects directed toward our focused missions. All of these funds went to ideas originating from NINR's 3 tenure track individuals, as well as to support the B2B Award of our Assistant Clinical Investigator. For example, funds went to support buying unique (first one at NIH) laboratory equipment to measure very small proteins, and to begin innovative lines of research.
NLM	LHC has used central funding to assist with a variety of projects across the Center. Due to a flat and/or reduced budget in recent years, funds reserved by the LHC Director for emergencies and unknown special projects/additional requirements through the year have been significantly reduced. In FY 2014, using LHC reserve funding, LHC funds which became available at the end of year due to postponement of several procurements, and NLM additional funding, LHC used approximately 3.5% of its budget to support a number of research activities listed below.
	Funded the development of the Consumer Health Information and Question Answering (CHQA), a system to automatically generate responses to queries and messages from the public. Considerable progress has been made in implementing a module to respond to user requests for corrections to PubMed citations; this module currently correctly answers about 65% of these requests, thereby substantially eliminating staff and contractor effort.
	Funded the development of Turning The Pages (TTP), a system that enables the general public to view and 'touch' digital versions of rare historic medical books. In addition to a dozen such books some several centuries old , TTP also includes the first surgical papyrus, 1700 BC, which may be touched and scrolled. TTP is available in kiosks, on the Web, and as smartphone apps.
	Funded an Asst. Clinical Investigator at the CC to collaboratively work with LHC in the area of medical knowledge representation, medical workflow technology, electronic clinical and research guidelines, electronic management of clinical trials and quality improvement.
	Funded temporary contract support for performing Security Assessments and Authorization (SA&A) for operations of the People Locator system.
	Funded temporary contract support to assist in the creation of interactive publications of national health documents from CDC.
	Funded contract support for the NLM Value Set Authority Center (VSAC) in collaboration with the Office of the National Coordinator (ONC) and CMS for the creation and maintenance of value sets for the Meaningful Use Incentive program. The VSAC provides downloadable access to all official versions of vocabulary value sets contained in the 2014 Clinical Quality Measures (CQMs). Each value set consists of the numerical values (codes) and human-readable names (terms), drawn from standard vocabularies such as SNOMED CT® , RxNorm, LOINC and ICD-10-CM, which are used to define clinical concepts used in clinical quality measures (e.g., patients with diabetes, clinical visit).
	Hired a biostatistician to assist LHC researchers in the design of formal studies and analysis of their techniques and in the analysis of very large longitudinal clinical databases, using various regression and survival models to find significant predictors of important outcomes.
	A seat on the Center for Medicare and Medicaid Services (CMS) enclave was purchased to obtain data with regards to occurrence, treatments, outcomes, and trend of important health issues in the Medicare and Medicaid populations. This CMS data supports LHC research designed to improve the quality of care and reduce costs and utilization
	Purchased significant equipment to implement OpenI, a new and innovative system for searching for, and retrieving, biomedical text and images from a store of 800,000 open access articles and 2.5 million images. Searches can be done by text or image queries. Equipment includes 4 PowerEdge 720 servers and multi-terabyte storage for the production system, and additional equipment for research and development.
	Funded the integration of 10G and IPv6 with security devices in both DMZ and internal network to support research projects
	Funded the deployment of 10G intranet to support the high demands of data processing and transfer speed for LHC projects.
VRC	Universal Influenza Vaccine Development
	Malaria PfSPZ Irradiated Sporozoite Vaccine
	Development of Protective Vaccine Against Respiratory Syncytial Virus (RSV)
	Manufacture of Broadly neutralizing Antibodies for Passive Prevention Trials
	Ebola Vaccine Development

Appendix 6

IRP Scientific Meetings

IC Scientific Meetings	2012-2015	The WG recommended that NIH "host annual scientific meetings at NIH." Please list the scientific meetings by topic you have hosted at NIH in the past two years.	
CC	7	The Clinical Center has partnered with the Office of Rare Disease Research, NCATS to host NIH Rare Disease Day.	Annual Red Cell Molecular Typing Meeting: Sponsored jointly with the Blood Center of Wisconsin, The target audience is scientists involved in red cell genotyping. Increasingly we have also had registration by clinicians who wish to implement this technology into service laboratories.
		Annual Transfusion Medicine Symposium: Sponsored jointly with the American National Red Cross; held each year in September in the Masur Auditorium. The target audience is scientists, physicians, (including trainees) and technologists in the field of Transfusion Medicine. This includes individuals who direct service laboratories at academic centers and community hospitals.	Bioethics Meeting about on broad consent for future research with biospecimens: Invited workshop help in September of 2013; Target audience was bioethicists interested in consent
NCBI	2	IUPAC Division VIII - InChI for Large Molecules	
		NCBI Genomics Hackathon	
NCCIH (NCCAM)	**2**	NCCIH is the lead IC for the PainSig that hosts the "Understanding Pain" seminar series, which brings in nine distinguished scientists in the pain field each year.	
NCATS	30	NCATS has hosted a wide range of individual seminars at its Shady Grove location, as well as daylong seminars by extramural investigators studying particular rare diseases of interest to NCATS.	
NCI		2013	2014
	21	January 2013- NCI Comparative Melanoma Tumor Board Study and Meeting	March 20-21, 2014- Symposium on Translational Genomics
		April 4-5, 2013- NCI Chromosome Biology Symposium - Epigenetics in Development	March 2014- Measuring Estrogen Exposure and Metabolism Workshop
		September 2013 - 10th Annual North American ABC Genetic Workshop	April 24, 2014 -Forum on the Microbiome and Autoimmunity
		September 23, 2013- Current Progress and Future Challenges in Pancreatic Cancer	May 2014 -Cancer Epidemiology: From Pedigrees to Populations
		September 2013 - Inflammation, Microbiota, and Cancer	June 17, 2014 - 2014 Chronic Graft-versus-host disease (GVHD) consensus project on criteria for clinical trials meeting
		November 2013- NCI Cohort Consortium Annual Meeting	June 2014 -Use of Immune Marker Panels to Uncover the Role of Inflammation in Cancer
			September 10, 2014 - Current Advances in Pancreatic Cancer Research and Treatment
			Sept/Oct 2014- Microbiome Quality Control Workshop
			October 9-10, 2014 - Cancer Immunology and Immunotherapy: Delivering the Promise
			October 2014- Think Tank on Metabolomics and Prospective Cohorts: How to Leverage Resources
			November 21, 2014-Workshop on X-ray Free Electron Laser (XFEL)
			Apr. 15-16, 2014 - NCI Chromosome Biology Symposium "Chromatin, ncRNA, Methylation & Disease
			December 2014, Recent Advances in Cryo-Electron Microscopy: Opportunities and New Frontiers
			December 2014 - NCI Cohort Consortium Annual Meeting
			2015
			March 11-12, 2015 - CCR RNA 2015 Symposium
NEI	**9**	2013	2014
		February 24-26: NEI Audacious Goals Workshop	March 6 : Immunology of Age-Related Macular Degeneration
		June 24-25: NEI/NCRM Combined Stem Cell Meeting	October 14: Sayer Vision Research Lecture Series
		September 12: Sayer Vision Research Lecture Series	October 30-31: NEI Annual Focus on Fellows Research Symposium
		October 24-25: NEI Annual Focus on Fellows Research Symposium	Retinal Diseases Interest Group (RDIG) Speaker Series *(8-10 invited speakers over the year)*
		Retinal Diseases Interest Group (RDIG) Speaker Series *(8-10 invited speakers over the year)*	
NHLBI	**7**	2013	2014
		May 6-7 Mitochondrial Biology Symposium	Mar 25 Systems Biology Symposium
		Sept 25-26 NHLBI 5th Symposium on Cardiovascular Regenerative Medicine	Apr 9 NHLBI Clinical & Population Genomics Workshop: The Future of Genomic Research for Prevention and Treatment of Heart, Lung and Blood Diseases in Populations and Patients
			June 13 Computational Structural Biology and Modeling Symposium
			Sept 15-16 Sickle Cell in Focus
			Dec 12 Korea Institute for Advanced Study (KIAS)-NIH Joint Symposium
NIA	**1**	Genome stability meeting (LMG)	
NIAID	2	2013: The Gut: Protection and Infection	2014: Microscopy of Infectious Disease Agents Symposium
NIAMS	2	NIAMS has been an active support of the Immunology Interest Group seminar series and Retreat since its inception. Almost all of the major immunologists have come through the NIH as part of the seminar series or as "gurus" for the retreat. The IIG retreat is a major scientific meeting as evidenced by the fact the editors of the major immunology journals attend.	NIAMS hosts its own retreat annual and similarly, we invite major figures as guru

NIBIB	**1**	Biophotonics Workshop (biannual) (co-sponsored by NICHD and NIBIB)	
NICHD	**3**		NIH-Japan Symposium, NICHD a contributor, October 23-24, 2014
			2nd and 3rd Annual International Patient Symposium on Pheochromocytoma, 2013 and 2014
NIDCR	**2**		Mesenchymal Stem Cell Workshop," March 26th, 27th, 2013. This workshop was not held on the NIH campus, but in a nearby hotel. It was jointly sponsored by NIH, Canada and the UK.
			"Biomedical research: NIH-Japan-JSPS Symposium: Highlights from the Frontier of Biomedical Science from NIH and Japan", October 23rd-24th, 2014. NIDCR was a major sponsor.
NIEHS	**14**	2013	2014
		Annual NIEHS Biomedical Career Symposium	Parkinson's Disease: Understanding the Environment and Gene Connection: Co-sponsored by NIEHS and NINDS, November 3-4, 2014 at NIEHS.
		Global Integration of Toxicogenomics Databases: June 26-27, 2013.	Enabling public health research during disasters: June 12-13, 2014
		Nanoparticle Exposure: January 9-10, 2013	Unlocking the Promise of Stem Cells: April 11-12, 2013
		Women's Environmental Reproductive Health: January 30, 2013	Linking inflammation with environmental exposure: December 11, 2014
			Metabolomics and Environmental Health: August 22, 2014.
			Indoor air pollution: August 18, 2014
			Data science: September 15-16, 2014
			Transgenerational Inheritance in Mammals: February 12-13, 2014
			2015
			Epigenetics Mini-symposium: January 23, 2015
			Exposome Workshop: January 14-15, 2015
NIEHS DNTP	**5**	OCT 2013 NICEATM/EPA Translational Alternative Models and Biomarkers	Mar 2014 4th AIMBE/NIH Workshop on Validation and Qualification of New In Vitro Tools for the Pre-Clinical Drug Discovery Process
		Dec 2013 NIEHS-NCATS-UNC Dream Toxicogenetics Challenge	September 2014 Scientific Workshop Adverse Outcome Pathways: From Research to Regulation
			August 2014 Symposium on Assessing Exposures and Health Effects Related to Indoor Mass fuel Burning
NIMH	**7**	NIMH Outstanding Resident Award Program is on campus every year	
		Tenth Anniversary Symposium on Bipolar Disorder	
		Cognitive Testing in Bipolar Disorder	
		Workshop of PANDAS/PANS clinical investigators with 20 outside attendees	
		Workshop on Sleep and Neurodevelopment	
		5 day workshop for training on functional MRI data analysis methods and software with about 120 people -- half from NIH and half from extramural sites.	
NINDS	**7**	Too many meetings to count, the following are listed for examples: Neuro- Infectious Diseases seminars, PML & Disorders Affecting the CNS, Neuro-HIV, Human Motor Control Symposium, Porter Neuroscience Research Symposium, Neurobiology of the Caylx of Held Symposium, Motor Systems Symposium	
NLM /LHC	**8**	2012	
		NIH workshop on "Linking Disease Model Phenotypes to Human Conditions"	Workshop on Natural Language Processing "Natural Language Processing: State of the Art, Future Directions and Applications for Enhancing Clinical Decision-Making"
		NIH workshop on "Big Data to Knowledge (BD2K) sponsored meeting: Workshop on Community-Based Data and Metadata Standards	2013
			Social Media Expo. Strategic planning for government agencies to use social media tools.
			2014
			HHS IPv6 Symposium: "Examines New Internet Protocol and Features Father of the Internet, Vint Cerf"
			National Preparedness Month Event: Informational event for emergency preparedness tasks, family emergency planning, registering for disaster alerts, and information on disaster mitigation products and services.
			SPL/DailyMed Jamboree 2014 Workshop – "Practical use of DailyMed and RxNorm Drug Data"
			Symposium – "The Visual Culture of Medicine and its Objects"
			Hosted multi-agency Public Health Medical Working Group (chaired by FEMA). Discussed disaster response and appropriate technologies for family reunification.
NLM Lectures		2014	2013
	20	Decision-Assisting Tools: From Data Mining to Predictive Physiologic Modeling, Andrei Gribok, PhD, Beltsville Human Nutrition Research Center ARS, USDA	Performance Evaluation in Image Interpretation ... an Undecidable Problem, Bart Lamiroy, PhD, Universite de Lorraine, Nancy, France
		Using Large Medicare Data to Study Optimal Medication Use, Seo Hyon Baik, PhD, University of Pittsburgh, Dept. of Health Policy and Management	Protocol Navigation Training Program Seminar, James Cimino, MD, Chief, Laboratory for Clinical Informatics Development, NIH Clinical Center and Senior Scientist, LHNCBC
		Enhancing Performance with Extended TCP Stack Metrics, Chris Rapier, Pittsburgh Supercomputing Center	National Library of Medicine Informatics Lecture Series - 2014

		Match or Weight: Statistical Methods for Comparative Effectiveness Research using EMR data, Rhoderick Machekano, PhD, MPH, University of Stellenbosch, South Africa.	How to Learn in "The Learning Healthcare System", speaker Peter Szolovits, PhD
		The AskVanderbilt Project: iPad-based next-generation computer-assisted diagnostic decision support, Randolph A. Miller, MD, Cornelius Vanderbilt Professor of Biomedical Informatics	Title: Temporal Relation Discovery from the Clinical Narrative, Guergana Savova, PhD, Harvard Medical School and Boston Children's Hospital.
		The Drug Evidence Knowledge Base (DEB) project: mining public sources to create a reliable compendium of drug indications and side effects, Josh Smith, Vanderbilt University	Bridging the Semantic Gap between Clinical Research Eligibility Criteria and Clinical Data, Chunhua Weng, PhD, Columbia University.
		A Generic Approach to Pathological Lung Segmentation, Dr. Awais Mansoor, Department of Radiology and Imaging Sciences at NIH	National Library of Medicine Informatics Lecture Series - 2013
		Applications of Biomedical Text Mining, Sophia Ananiadou, PhD, Professor of Computer Science in the School of Computer Science, University of Manchester	Matching Complex Biomarkers to Drugs Using HistoReceptomic Signatures, Timothy Cardozo, MD, PhD, NYU School of Medicine
		Going Beyond Facts In Biomedical Text: The Need for a Linguistic Perspective? Sabine Bergler, PhD, Professor, Department of Computer Science. Concordia University	When the Entire Country is a Cohort: Collecting and Analyzing Big Data, Henrik Toft Sørensen, DrMedSci, PhD, Head of the Department of Clinical Epidemiology at Denmark's Aarhus University Hospital
		Joseph Leiter NLM/Medical Library Association (MLA) Lecture titled, " The BRAIN Initiative: Connecting the Dots " Terry J. Seinowski, PhD, Salk Institute, UCSD	Bridging the Semantic Gap between Research Eligibility Criteria and Clinical Data: Methods and Issues, Chunhua Weng, PhD, Columbia University
VRC	**3**	Reducing deaths from malaria, Dr. Richard Maude, Wellcome Trust Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand & School of Public Health, Harvard University.	
		Visualizing Large Altimetry Data Sets in Real-Time, Jami Montgomery, PhD, Georgetown University	
		Translational & Interoperable Health Infostructure - The Servant of Three Masters, Amnon Shabo (Shvo), PhD, Research Associate, Department of Information Systems, University of Haifa.	
TOTAL	**153**		

Appendix 7

Sample Qualifications of Current BSC Members

Credential	Number
Professor	65
Department Chair	53
Member, NAS	12
Member, IOM	23
Member, American Academy of Arts & Sciences	14
HHMI Investigator	6
Nobel Prize	1
National Medal of Science	1
Dean, Vice Dean, etc.	9
Fellow, American Assoc. for the Advancement of Science	17
Member, Assoc. of American Physicians	7

Attachment 1

Shared Scientific Opportunities

The following 9 scientific opportunities constitute areas of research in which the NIH Intramural Research Program is prepared to excel and take a leadership role. The opportunities represent the shared subset of proposals made by each of the ICs in their long-term planning processes. They seize upon the IRP's diverse expertise and well-established infrastructure, and benefit from inter-institute collaborations and teamwork and intramural-extramural cooperation.

Inflammatory diseases: Inflammation is a normal physiological response to infection and the cardinal intrinsic mechanism for eliminating unwanted microbes. However, destructive inflammatory changes can be auto-activated or lead to long-term tissue destruction and malignancy. Most of the NIH ICs are involved in studies for which inflammation is a common denominator. Indeed, numerous auto-inflammatory diseases have been described in molecular detail and effectively treated at the NIH. With its deep trove of immunologists, rheumatologists, and cancer biologists, the IRP is poised to be able to make major contributions to the characterization and control of inflammatory processes. Consider work done targeting Jak3, in the National Institute of Arthritis and Musculoskeletal and Skin Diseases, which has led to a new generation of immunomodulatory drugs for treatment of rheumatoid arthritis.

The NIH Center for Human Immunology (CHI), a consortium of several NIH institutes, already has begun to make inroads on detailed molecular definition of conditions that affect the immune system, and we will continue on this successful path. Another major resource at the NIH is the National Center for Advancing Translational Science (NCATS). This center is designed to enable high-throughput testing of small molecules that interact with specific cellular targets to modify cellular phenotypes; there are many examples of its success in identifying new classes of small molecules that modify disease phenotypes, including existing drugs in the pharmacopoeia (re-purposing), novel chemical entities, and small interfering RNAs. And, of course, at the heart of the IRP is the NIH Clinical Center, the largest facility in the world devoted purely to clinical research. The work at the Clinical Center emphasizes long-term, natural history studies of human disease, including rare diseases; "first-in-human" interventional clinical research; mechanism-based studies that maximize the scientific benefit of early-phase clinical trials; and studies, unencumbered by any perceived bias, that test existing hypotheses and treatments.

The IRP's focus on chronic inflammation is a long-term vision, akin in scope to its longstanding emphasis on understanding and treating cancer that has contributed so much to contemporary clinical practice. Realistically, full achievement of the goals to understand, control, and prevent inflammation is decades away. But several fundamental advances can be made at the IRP in the near term – i.e. within the first 5 to 10 years – which may include the following:

- Within 6 months, convene a trans-NIH workshop to identify the diseases that could be studied most tractably, the parties that are relevant to the project, and the specific types of organization, infrastructure, and funding that would be required to pull it off.

- Within 12 months, build a superstructure for the IRP chronic inflammation effort. Establish a trans-NIH competitive postdoctoral fellowship to attract the best graduate students.

- Within 3 years, develop a new taxonomy of chronic inflammation based on biology – shared risk factors, common mechanisms, etc. – rather than clinical symptomatology. Based on this taxonomy, identify a few high-yield disease groupings that, when studied deeply, will yield insights into the full spectrum of chronic inflammation.

- Within 3 years, create a pathway for incubating next-generation imaging techniques, such as bright and photostable dyes for optical imaging, light-sheet fluorescent microscopy for analyzing tissue samples, and adaptive optics for deep-tissue imaging, in realistic animal models of chronic inflammation and ultimately in the clinical arena.

- Within 5 years, establish a DC-area network for cures, collaborating with academic medical centers and private medical practices and taking advantage of up-to-date social media approaches. This will provide a basis for next-generation studies to elucidate the origins of, and best methods of treating and preventing, chronic inflammation.

- Within 10 years, initiate 3 to 5 proof-of-concept clinical trials using novel therapeutic approaches, novel trial designs, novel groupings of diseases, or some combination of the above, discovered through the IRP's chronic inflammation initiative.

Overall, this proposal to create a strong focus on chronic inflammation within the NIH Intramural Research Program is important, timely, and achievable: important because of the rising prevalence and morbidity of traditional inflammatory diseases and the increasing recognition that inflammation plays a critical role in many others; timely because new and soon-to-be-developed technologies – particularly advances in molecular tools, imaging methodology, and informatics – will allow this problem to be approached in ways hitherto thought to be out of reach; and achievable because the IRP can bring to bear an unmatched concentration of talent, experience, and institutional resources relevant to studying inflammation.

Cell-based therapies: The IRP has long provided the backbone for fundamental advances in clinical therapy. The NCI's Michael Potter conducted game-changing research on plasma cells and monoclonal antibodies, and his collaborative spirit allowed for the widespread use of these antibodies in treatments for diseases as varied as arthritis and cancer, leading to Nobel Prizes for three scientists. Similarly, paradigm-shifting work of NCI's Ira Pastan and Jesse Roth on protein receptors on cells is a benchmark for most cell-based therapies in development today. Steve Rosenberg and Tom Waldmann were among the earliest practitioners of cancer immunotherapy, which is now sweeping the field and leading to startling successes against cancers previously considered untreatable.

The NIH IRP can usher a new wave of cell-based therapies by combining established and maturing scientific disciplines such as immunobiology, genome engineering, and cell engineering. IRP scientists already are deep in the trenches in this regard. Historically, the NIH Clinical Center has excelled in first-in-human studies employing cell-based therapies, including the first use of immunotherapy to treat cancer and the first gene therapy (for adenosine deaminase deficiency). IRP scientists have turned terminal diseases into manageable conditions.

To further advance cell-based therapies, the IRP can expand its infrastructure for cell- and vector-production laboratories and enhance its GMP facilities. This will better position the IRP to develop novel approaches to treat common epithelial and mesenchymal (i.e., melanoma) cancers using antigen identification with personal genomics, to treat leukemia as has been demonstrated using engineered

chimeric antigen receptors on T cells to successfully target leukemic cells in children, or to correct monogenic disorders using genome engineering. Tissue engineering and regenerative medicine approaches include (i) point-of-care stem-cell harvesting technologies, (ii) modified scaffolding to enhance stem-cell differentiation and tissue regeneration, in conjunction with growth factors, cytokines, and chemokines (such as is occurring in the NEI with retinal pigment epithelial (RPE) cell transplants), and (iii) nondestructive monitoring of regeneration and tissue-engineered constructs. This vision includes developing the scientific underpinnings of tissue interactions, from the micro (tissues on chips for testing drug efficacy) to the macro (mechanobiology and elastography of the extracellular matrix). The overarching focus will be on approaches and disease types perceived as not being commercially viable given biological challenges or limited market potential.

To be specific, the IRP can expand iPSC technologies, cell-based therapy, and tissue engineering; increase focus on gene editing and RNA-based therapeutics; target diseases with well defined genetic defects; improve developmental and disease models (including model organisms); conduct clinical trials of cell therapy and transplantation; and emphasize prevention of disease with vaccinations and other strategies to modify environmental risk factors discovered through basic and translational studies. To accomplish this, the IRP would integrate gene-editing and mouse core facilities; have an intramural "Common Fund" established to recruit new investigators and to incentivize collaboration in the most promising areas; expand molecular facilities and computational biology resources; and enhance infrastructure such as GMP facilities, preclinical, and clinical programs to support transition to early-phase, proof-of-concept human trials.

Microbiome: Humans are increasingly being understood as metaorganisms, with our close symbiotic relationship with the intestinal and skin microbiota contributing to the cause (and cure) of numerous chronic diseases, such as cancers, obesity, and diabetes. The IRP can focus resources and efforts to move the field from descriptive biology to mechanistic insight into the metaorganism processes affecting disease initiation, progression, and therapy. This begins with microbiome mapping in health and disease, or genomic approaches, for which there is a substantial NIH effort nationally and in the intramural program. In conjunction with this effort, the IRP will lead mechanistic studies of microbiome function — inflammation, signaling, immune function — by building on strong and complementary strengths across the NIH IRP in immunology, immunotherapy, microbial and human genomics, cohort studies, and access to well-defined patient populations in the Clinical Center and animal model systems.

The current plan to increase investment in germ-free facilities to enable detailed studies on the role of the microbiome, and the use of whole-genome sequencing of microbes to track the spread of pathogenic and drug-resistant organisms among patients, represent two ongoing approaches in the IRP.

Drug resistance: Antimicrobial resistance is arguably the greatest threat to public health facing us today. All of our hard-earned advances in controlling, if not eradicating, infectious diseases may unfold with the surge of drug-resistant strains of tuberculosis, Methicillin-resistant *Staphylococcus aureus* (MRSA), Klebsiella pneumonia, and many other killer microbes. Drug resistance also is prevalent in cancer, autoimmune diseases, and epilepsy, as well, often due to similar molecular mechanisms. The IRP is well-positioned to take on this public health emergency, and indeed the program already has mobilized its talent in light of an outbreak in the Clinical Center of carbapenem-resistant *Klebsiella pneumoniae*, for which IRP scientists used genome sequencing to quell the spread — a novel marriage of epidemiology and genomics, and by formation of a centrally funded consortium of researchers.

The IRP will attack drug resistance on several fronts. Through in-depth genetic and physiological analysis to identify novel targets, and high-throughput screening at NCATS to find new antibiotics and anti-cancer drugs, the IRP will create next-generation antibacterial drugs that target the Achilles' heel of highly drug-resistant pathogens and cancers. This is high-risk, high-reward research requiring long-term, stable funding, a hallmark of the IRP. Cheaper, more sensitive, and quicker genomic diagnostics, such as those being developed at the Clinical Center, could help hospitals that have outbreaks of multidrug-resistant organisms by enabling the use of organism-selective antibiotics rather then the broad-spectrum agents in current use. The IRP has a proud history of creating diagnostic tools, and it will partner these ideas with industry.

Neuroscience: In this era of the Presidential BRAIN initiative for brain research, the NIH IRP is properly positioned to combine the forces of all its neuroscience-related programs: neurogenetics, aging, addiction, mental health, neurodevelopmental and neurodegenerative diseases, infectious diseases, sensory organs, pain, and cancer. This trans-NIH "brain" cooperative will enable the IRP to more efficiently set research priorities and collaborate, leveraging the expertise of the entire NIH neuroscience community in an integrative manner to establish high-priority neuroscience questions and projects. There likely will arise core-enabling themes, such as neuroscience of non-human primates, big data, brain bank, human genetics, PET imaging (including radiotracer development), neuroplasticity of chronic pain, sleep, and the neurobiology of obesity and appetite.

A specific proposal that has engaged a large section of the neuroscience community at the NIH is the initiative on compulsive behaviors. The goals of this initiative are to understand the neurobiology of complex behaviors that result in compulsive and repetitive actions and to develop and test new therapeutics aimed at alleviating and/or reversing these behaviors. It proposes the creation of a new IRP Research Center for Compulsive Behaviors focused on investigating neuronal circuits and mechanisms that mediate these inflexible behaviors. Understanding the processes that facilitate or hinder the development of compulsive behaviors is critical not only for optimizing existing and designing new pharmacological treatments, but also for improving behavioral interventions.

Compulsive behaviors are repeated perseverative actions that are very difficult to stop/inhibit despite clear intentions and potentially harmful consequences for the patient. The Center will study a broad range of "compulsive behaviors" such as those implicated in eating disorders and obesity (NIDDK), substance-use disorders including addiction to alcohol, nicotine, and prescription opioids as well as illicit drugs such as heroin, cocaine and methamphetamine (NIAAA, NIDA), L-dopa induced dyskinesia and compulsive behaviors such as gambling that develop in patients being treated for Parkinson’s Disorder (NINDS), psychogenic movement (NINDS), obsessive-compulsive, and post-traumatic stress disorders (NIMH, NIAAA). Most, if not all of these disorders, involve significant neurodevelopmental vulnerabilities, and thus this initiative is also of interest to the investigators at NICHD. Therefore, this trans-NIH initiative would involve research expertise across seven NIH ICs and will provide the opportunity for focused collaborations between basic scientists and clinical researchers across these NIH ICs. This initiative will lay the groundwork for expanded IRP initiatives toward understanding other complex behaviors involved in neurological and psychiatric disorders.

Compulsive behaviors are *actions* and as such they can be modeled in diverse research animal species from rodents to non-human primates. For example, stereotypes are common in the behavioral repertoire of most animal species and can be easily triggered and used as a model of obsessive-compulsive disorder (OCD). Addictive-like behaviors can also be induced in rodents and non-human primates when given access to addictive drugs and alcohol. The possibility to control the onset of these

behaviors would facilitate the study of neurocircuitry and mechanistic overlap and ultimately improve our understanding of these otherwise complex behaviors. The ultimate goal of this research would be to develop novel treatment strategies, based on these findings, for patients who suffer from these compulsive behaviors.

RNA biology and therapeutics: The IRP can take a leadership role in the development of a comprehensive program for the investigation and therapeutic exploitation of RNA, including antisense therapy, RNA interference, and RNA silencing. The goal is to capitalize on the IRP's solid foundation in genetics and molecular biology to (i) systematically map the RNAome in health and disease — that is, perform genome-wide sequencing of mRNAs and unconventional RNAs and combine this with the IRP's "genomic medicine" data collection, and (ii) elucidate the RNA structure to develop new clinical targets.

The IRP already has contributed to promising antisense therapies for hemorrhagic fever viruses, amyotrophic lateral sclerosis, and numerous cancers. The IRP's RNAi screening facility provides the tools to screen whole genomes and pathways on an industrial scale, and intramural researchers have identified a multitude of genes that control critical processes and pathways in cancer and neurodegenerative diseases.

Vaccines: The NIH IRP has contributed to about half of all FDA-approved vaccines currently in use. With all the necessary resources and infrastructure housed within an integrated vaccine research program, the IRP is well-positioned to advance and accelerate the science of vaccine development by conducting the entire vaccine R&D continuum encompassing basic, translational, and clinical research. IRP scientists possess expertise across the broad spectrum of the vaccine development process, including basic immunology, molecular and structural biology, immunopathogenesis, bioinformatics, genomics, preclinical testing, vaccine production, and conduct of clinical trials. Although the NIAID's Vaccine Research Center (VRC) is a focus for vaccine development at the NIH, many of the other ICs have made substantial investments in vaccine development in the IRP (e.g., the HPV vaccine from NCI, the Hib vaccine from NICHD, and work underway in NIDCD to create a vaccine to prevent otitis media in children).

The IRP will remain focused on developing an effective vaccine or other immune modulator for prevention and treatment of HIV/AIDS. While a cure, at times, may seem out of reach, the IRP nonetheless has made remarkable progress in transforming HIV from a death sentence to a chronic disease and a major goal of NIAID is to develop a cure. A separate, central fund provided annually by the Office for AIDS Research for HIV-related research (Intramural Targeted Antiviral Program or IATAP) continues to support HIV research in all of the ICs. Much more work is needed, and the IRP is up to this challenge. The IRP also will develop vaccines for other high-burden diseases, such as respiratory syncytial virus, dengue, malaria, and tuberculosis, as well as biodefense threats and emerging and re-emerging infectious diseases including influenza, filoviruses (Marburg and Ebola, currently in phase 1 clinical trials in West Africa), chikungunya, and MERS coronavirus.

Natural products: To provide selective advantage to many plants, microorganisms, and marine life, nature has led to the evolution of chemicals that target many essential biological processes important in cell communication, growth, metabolism, and division. These natural products in many cases may hold the key to effective treatments of antimicrobial resistance, cancer, autoimmune disease, neurodegenerative diseases, and much more. The IRP can contribute to a national program for natural products discovery for new molecules that target biological processes central to human disease. Its goals are to (i) develop a comprehensive Natural Products Library that includes pre-fractionated

compounds for modern high-throughput targeted screening technologies and a public database and bioinformatics platform to integrate source organism, activity, structural, and genomic data; and (ii) establish a national resource for natural products screening efforts for assay development, execution of natural product drug screens, resupply of active molecules, and bioinformatics support to extramural users.

Animal modeling: The IRP has an AAALAC-accredited animal care and use program maintaining a collection of distinctive animal models and facilities, including genetically engineered non-human primates, germ-free mice, and the world's largest zebrafish facility. The IRP hopes to enhance this program with the investment in a large, centralized vivarium and associated research laboratories to replace aging and hard-to-maintain animal facilities to realize efficiencies and optimize animal care and use. The IRP also will create a CRISPR core for making transgenic animals using this new technology. Traditionally, the NIH has been able to develop and export novel animal models for the study of basic biology, and for modeling human disease. Progress in biomedical research requires a continuing source of these research models.

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Attachment 2

Creating and Using New Technologies at the NIH

Technology incubators

The NIH IRP has the infrastructure, and has developed the intellectual property incentives, to allow great ideas to flourish. The most recent and quintessential example is photoactivated localization microscopy, or PALM, which earned Eric Betzig the 2014 Nobel Prize in Chemistry. PALM was built at the NIH. Betzig, a physicist, had the idea, but needed the biomedical expertise that the IRP offered. The IRP's Jennifer Lippincott-Schwartz hosted Betzig and provided him with photoactivatable green fluorescent proteins, invented in her lab, as well as the complementary expertise to analyze and validate the findings. This success story was made possible not only through freedom to explore, inherent in the IRP, but also through the availability of funds to support high-risk experimentation and the forward-thinking scientific leadership to identify and appreciate feasible ideas of great potential.

Imagine what more could be accomplished with a dedicated technology incubator as a hub for technology development– an expansive facility or a series of smaller facilities shared among NIH institutes and centers to develop and grow existing core technologies in cryo-EM, optical imaging, intravital and deep tissue imaging, computational and big data processing, fluorescent probes, single-cell analysis and screening, and clinical imaging. For example, linking cryo-EM and optical imaging could allow us to assemble a molecular-resolution model of the cell. The incubator would encourage sabbaticals for toolmakers at NIH and encourage highly technical people to develop technology at NIH.

Technology development is not just limited to molecular and cellular imaging. The IRP has invested in infrastructure to diagnose and stage diseases utilizing nuclear medicine technologies, spectroscopy, NMR and PET. These imaging approaches will help pinpoint the location and type of disease processes present in cancer, infections, cardiovascular diseases, and many more related disciplines. The Clinical Center has a longstanding goal of continuing the development of new imaging technologies for precise sampling of tissues from different organs and merging the various new technologies to provide the ability to detect and correlate detailed perturbations of structure and function.

The NIH IRP also has shared facilities in neuroimaging and optogenetics, including investment in new cutting-edge imaging-technology scanners, high-field MRI for human brain imaging, combined PET/fMRI, large MRIs for obese patients, and additional capacity for the development of new radioligands for PET. In its 10-year vision, the IRP will (i) develop targeted probes for diagnostic imaging to monitor responses to therapy, or the body's response to implants; (ii) develop new bioengineering approaches for brain imaging such as target-specific PET probes, MRI/PET scanners, and simultaneous fMRI and optical imaging for rodents and small non-human primates; (iii) develop methods for imaging as a surrogate biomarker combined with tissue analysis in a wide variety of disease states including atherosclerosis and cancer by using image-guided biopsy (such as the FUSION technology of MRI and ultrasound for identification and

biopsy of suspicious prostate lesions) that enables molecular profiling for personalization of care; and (iv) develop additional non-invasive or minimally invasive optical measurements in humans.

Structural biology

The NIH IRP has long had a preeminent role in structural studies using crystallography, NMR spectroscopy, and cryo-EM, supported in part by central funds such as the Intramural AIDS Targeted Antiviral Program (IATAP). At NIH there is a large community of crystallographers and NMR spectroscopists who developed much of the current approach to 3D NMR studies of protein structure, including new approaches to transient structural states of proteins in solution (the so-called "dark matter" of protein structure not accessible through crystallography), and high-resolution cryo-EM studies enabling close to atomic resolution of proteins in solution and comparable resolution of membrane proteins and viral antigens, including viral structures with potential to revolutionize HIV and influenza vaccine development.

The advent of molecular-resolution studies of proteins by cryo-EM, in part fueled by studies at the NIH, is bringing about a true revolution in accelerating the creation of atomic models of proteins and their interactions with small molecules such as drugs. The full flowering of this technology will facilitate the development of drugs that interact specifically with their protein targets by enabling rapid (minutes to hours) structure determinations that now take weeks or months and in some cases are not even possible using classical x-ray crystallography. If fully developed, this technology could:

- Allow extremely rapid screening of hundreds of potential new drugs to determine their ability to bind tightly to the active site of target proteins. This would accelerate drug repurposing and allow large libraries of potentially active compounds to be quickly screened.
- Use structural screening to find the correct balance between chemical structures that maximize targeted and minimize off-target effects.
- In precision medicine, explore the structural basis of “good responders” vs. “poor responders” at the molecular level.
- Accelerate the pharmacology of newly discovered targets, such as those determined as a result of GWAS analysis, or other genomic studies.
- Enable structures of many membrane proteins whose intrinsic flexibility and insolubility have made crystallization difficult.

Defining genotype-phenotype interactions at the NIH: A center for phenotypic evaluation of unusual genotypes

Prediction is the core goal of precision medicine. And to predict, we must have the ability to take germline variants and surmise phenotypes, such as physiology, disease susceptibility, course, and responsiveness. With a known disease gene in hand, an intramural investigator can ask whether variants of this gene lead to human disease or more subtle changes in disease phenotypes. Given the existing comprehensive phenotyping of many of our patient populations, whole-exome sequences of NIH human subjects may also allow the discovery of new genes that participate in the disease processes. Furthermore, given an unusual genotype, such as the

complete knockout of a gene, or abnormal levels of expression, the Clinical Center is poised to conduct comprehensive phenotyping to reveal the full range of genotype-phenotype interactions. This would yield information about "outside" suppressors or modulators of gene function, and about normal human variation in gene function. Such a referral center might be structured similar to the Undiagnosed Diseases program and could serve as a repository for information about human gene function.

More specifically, the NIH IRP can systematically collect and analyze multi-parameter molecular data (genomic, transcriptomic, epigenomic, proteomic, metabolomics, and microbiomic) from patient populations; identify molecular features associated with health disparities, disease progression, outcome, treatment response, and susceptibility in a shared phenotype resource; develop preventative, prognostic, and therapeutic tools based on mined data; and tap into cohorts to molecularly define disease and inform mechanisms for treatment and prevention. The NIH Clinical Center already has established a shared repository of phenotypic information on all of the patients seen in the Clinical Center (the Biomedical and Translation Research Information System or BTRIS).

IRP scientists' proximity to National Center for Advancing Translational Sciences (NCATS) facilities further enhances the ability to quickly develop therapies with high-throughput drug and small-molecule screens for the identification of disease pathways. NCATS enables systems-based phenotypic drug discovery and profiling, and translates the study of rare diseases into common disease knowledge. This molecular knowledge adds precision to the already extensive epidemiological databases developed in multiple institutes. To jumpstart this process, the ICs with substantial epidemiology programs have begun to meet regularly. The NIH Office of Intramural Research (OIR) has initiated a joint NHGRI-CC-OIR funding program to support projects to sequence 1000 whole exomes of patients already being seen in the Clinical Center and extensively phenotyped. IRP scientists also have unique access to long-standing, world-class populations studies housed within the IRP, such as the Framingham Heart Study, the Baltimore Longitudinal Study of Aging, and numerous data goldmines in the NCI Division of Cancer Epidemiology and Genetics and the National Institute of Environmental Health Sciences.

High-performance computing and big data analysis

Many of the laboratories within the IRP are increasingly taking advantage of new high-throughput, data-intensive technologies to advance their work, generating ever-larger data sets in the course of their studies. The scientific areas of inquiry generating "big data" go well beyond genomics and next-generation sequencing, encompassing research programs in areas relevant to the study of many diseases, such as computational chemistry, molecular modeling and simulations, structural biology, biomedical imaging, proteomics, metabolomics, and systems biology. Analyzing these kinds of large-scale biological and biomedical data depends on the ability to employ computationally intensive approaches in an efficient and effective manner, with the goal of producing interpretable results that advance translational efforts aimed at improving human health.

IRP leadership has conducted a thorough analysis of the computing resources needed to meet the challenges of big data and found that neither the IRP nor most leading academic institutions have the computational muscle to rise to the demands that confront us. Moreover, the splintering of computational resources between larger and smaller Institutes and Centers, which

flies in the face of the synergistic benefits that a dedicated, shared resource could provide, has created a competitive environment not conducive to efficiency. The source of computing power remains to be determined, but should involve collaboration with other federal agencies highly invested in computer technology, use of "cloud" resources, and creative agreements with private sector partners.

In order to best meet the computational needs to address the technological challenges enumerated in this document, as well as to benefit *all* NIH investigators, the IRP should provide a centralized approach to large-scale computational needs. With this broader purview, the National Center for Biotechnical Information (NCBI) within the National Library of Medicine (NLM), in coordination with the NIH Center for Information Technology (CIT) and the office of the Associate Director for Data Sciences (ADDS), could provide leadership in planning for future information technology investments and initiatives supporting all NIH investigators. A central computing resource could also serve as an incubator for the development of new technologies or computational architectures, activities that could, in turn, jump-start major initiatives and enable true innovations in biomedical computing. The proposed central computing resource would be designed in accordance with the five essential characteristics originally put forward by the National Institute of Standards and Technology in September 2011, characteristics that have become generally accepted principles in the field of cloud computing: on-demand self-service; broad network access; resource pooling; rapid elasticity; and measured service. In addition to these essential characteristics, distinguishing features would include: a technical staff responsible for assuring that the resource is responsive to rapid changes occurring in the scientific environment; a scientific staff that bridges bench and technical science, assisting investigators with algorithm development, optimization and parallelization of existing code, and assuring the stability of applications; and personnel that will give special consideration to issues that are specific to the government data space, specifically data security and privacy issues.

Conclusion

The intramural program already excels in the diversity and quality of its resources and technology-oriented cores. The proposal outlined above would enable a paradigm-shift in the ability of the IRP to create new technology for the solution of important biological problems and the development of new treatments of disease.