A DECADE OF DISCOVERY

NIH COMMON FUND 2004-2014

10 Years

A Decade of Discovery

THE NIH ROADMAP AND COMMON FUND

National Institutes of Health
Office of Strategic Coordination – The Common Fund

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Foreword

Ten years ago, the National Institutes of Health launched a transformative approach to support biomedical research, which became known as the NIH Roadmap. This approach brought together extramural and intramural scientists, public representatives, leaders from other government agencies and the private sector, and the Directors of the NIH and its Institutes and Centers to plan collectively for the future. We asked three key questions: What are today's most pressing scientific challenges? What are the roadblocks to progress and what must be done to overcome them? Which efforts are beyond the mandate of one or a few Institutes, but are the responsibility of the NIH as a whole?

Each Roadmap program that resulted from this planning process was designed to achieve defined, high-impact goals or transition to other sources of support within 10 years. After that time, the tools, data, technologies or infrastructure that the Roadmap established would be used by the broad community and thereby would catalyze research NIH-wide. The programs fell into three broad themes, which continue to reflect the overarching mission of the Common Fund: New Pathways to Discovery, Reengineering the Clinical Research Enterprise, and Research Teams of the Future. The Common Fund programs seek to provide fundamental data and tools to stimulate basic discovery, to address the challenges of clinical and translational research that are common to many diseases, and to pilot novel ways of fostering innovation and supporting the biomedical research workforce.

This strategic, trans-NIH, goal-driven investment approach was endorsed by Congress through the 2006 NIH Reform Act. This Act created the NIH Common Fund as a separate appropriation and the Division of Program Coordination, Planning, and Strategic Initiatives within the NIH Office of the Director to provide stable and ongoing support and coordination for these programs. This has allowed us to continue to think strategically about the future of biomedical research and has provided the opportunity to develop unique programs that could not be supported via traditional mechanisms.

As we have reached the 10th anniversary of these programs, a look back is in order. What has been accomplished and how has the biomedical research landscape changed? This book is intended to provide a sense of the goals and achievements of this remarkable set of programs and to describe how new program areas are established. Our intent is to convey the breadth of the science that the Roadmap/Common Fund addresses and the impact that these programs have had to date.

The success of the Roadmap/Common Fund is an outcome of its compelling founding principles and the leadership and dedication of many NIH staff, but especially the creativity and enthusiastic participation of the research community. It has been a privilege to be a part of such a community-wide effort to change the face of science. I look forward to the next decade and continued success.

Francis S. Collins, M.D., Ph.D.
NIH Director

Charting a Path for Medical Research in the 21st Century

The first years of the 21st century marked an important new era for biomedical research. Mapping of the human genome was nearly complete, and remarkable progress in medical research had changed our understanding of many diseases. Opportunities for new discoveries and major leaps in medicine had never been greater.

At the same time, the science was growing more complex and beginning to converge on unifying principles that link apparently disparate diseases through common biological pathways and therapeutic approaches. It was a period that required innovative solutions to transform basic and clinical research into tangible benefits for patients and their families.

A Roadmap to Advance Discovery

In 2002, then-National Institutes of Health Director Elias A. Zerhouni, M.D., introduced the concept of a "roadmap"—a far-reaching plan to transform key areas of biomedical research. This novel approach would identify significant opportunities and challenges that no single or small group of NIH Institutes or Centers could or should conduct on its own, but that the NIH as a whole must address. The NIH Roadmap was a bold set of programs designed to transform medical research capabilities and speed the movement of research from the laboratory to the patient's bedside.

In designing the Roadmap, the NIH consulted with more than 300 nationally recognized leaders in industry, government, academia and the public. These meetings and more than a year of planning provided the framework for the NIH Roadmap for Medical Research. The goal during development of the Roadmap was to define a compelling set of programs that focused on efforts that are essential to accelerate basic research discoveries and speed translation of these discoveries into clinical practice as well as explicitly address roadblocks that slow the pace of medical research in improving the health of our nation and across the globe.

These programs are framed within three important themes that cover a broad spectrum of points between the laboratory and the clinic. First, Roadmap planners identified a need to stimulate the development of novel approaches to unravel the complexity of biologic systems and their regulation. Second, it is imperative to optimize the emerging discipline of clinical and translational science, which encompasses the acquisition of new knowledge about health and disease prevention, preemption and treatment and the methodological research required to move basic insights into the clinic. Third, because progress is often made at the interface of pre-existing disciplines, new efforts must be made to explore ways to reduce barriers that often impede research and create an environment where scientists can cooperate in new and different ways.

These three themes—New Pathways to Discovery, Reengineering the Clinical Research Enterprise, and Research Teams of the Future—remain in place today.

A Fund for Collaboration

Initiated in 2004 as the NIH Roadmap for Medical Research, the Roadmap was also a pioneer in the way in which it was funded and managed. Initially, the NIH Institutes and Centers contributed to a common pool of resources and a plan for how these resources would be used. Administered centrally within the NIH Office of the Director, the Roadmap programs would be implemented by Working Groups composed of staff from multiple NIH Institutes or Centers. This ensured a steady multiyear and flexible stream of funding and at the same time institutionalized a corporate process for decision-making about priorities that span the breadth of the NIH.

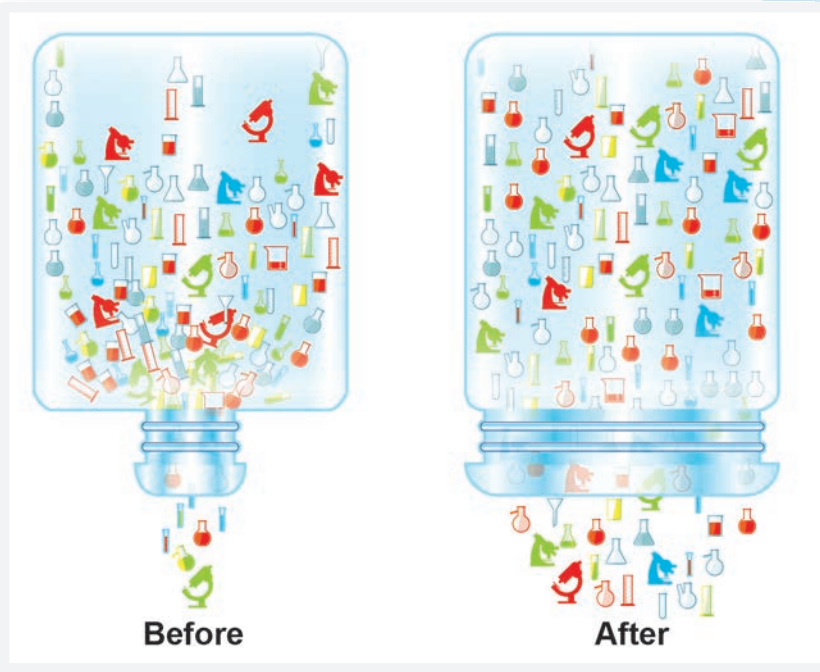
In 2006, Congress responded to the need for the NIH to continue to foster new approaches to biomedical research and passed the NIH Reform Act. Only the third omnibus reauthorization in the NIH's history at the time, the NIH Reform Act provided continued support for Roadmap programs through the NIH Common Fund within the Division of Program Coordination, Planning, and Strategic Initiatives within the NIH Office of the Director.

The management style of Roadmap programs also was considered pioneering, not only for the trans-NIH Working Groups, but also for the expectations that were placed on these programs. Roadmap programs were intended to be goal-driven, so that specific, high-impact outcomes could be reached within a set schedule of 5 to 10 years. The catalytic deliverables from these programs would then be used by the community at-large for research funded from other sources.

The Common Fund Today

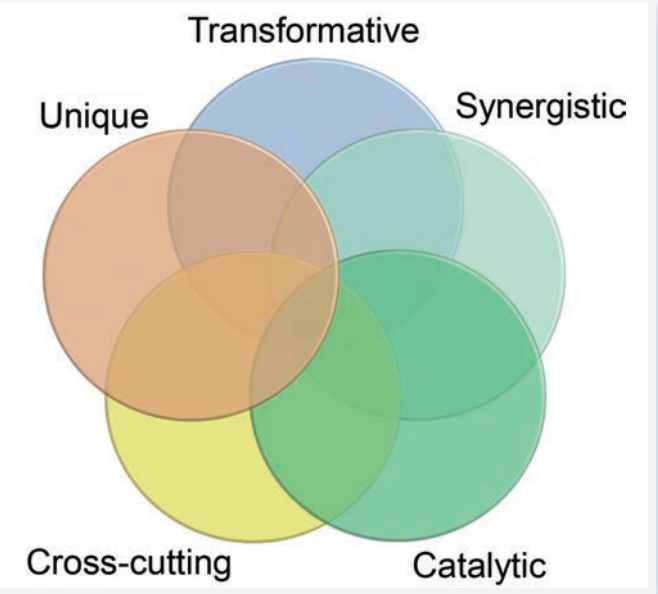
Over the last decade, the Common Fund has helped launch a number of far-reaching programs to address the explosion of new knowledge in the biomedical sciences and the growing challenges in public health.

Common Fund programs foster high risk-high reward research, enable the development of transformative tools and methodologies, fill fundamental knowledge gaps or change academic culture to foster collaboration. These programs are designed to pursue major opportunities and gaps in biomedical research that no single NIH Institute could tackle alone, but that the agency as a whole must address to make the biggest impact possible on the progress of medical research. Today, approximately 30 programs are managed through the Common Fund. The principles established for the Roadmap continue to serve the NIH community well.



The Common Fund aims to alleviate bottlenecks that impede scientific progress, thereby accelerating the pace of discovery.

Strategic Investment: Transforming Discovery Into Impact



The Common Fund supports research in the areas of emerging scientific opportunities, rising public health challenges and widening knowledge gaps that deserve special emphasis. It supports programs that would benefit from strategic coordination and planning across NIH Institutes and Centers (ICs) and that are designed to achieve specific goals and milestones. To this end, Common Fund programs tackle major challenges in biomedical research that affect many diseases or conditions or that broadly relate to human health. Collectively, Common Fund programs address the highest priority challenges and opportunities for the scientific research community and the NIH.

Common Fund programs must meet five overarching criteria. Programs must be ***transformative***. They must have high potential to dramatically affect biomedical and/or behavioral research over the next decade. ***Catalytic*** in nature, they must achieve a set of high-impact goals within a maximum of 10 years, after which the program deliverables should accelerate the progress of scientific research broadly. Outcomes must ***synergistically*** promote and advance individual missions of NIH ICs to benefit health. Program areas must be ***crosscutting*** across missions of multiple NIH ICs, be relevant to multiple diseases or conditions, and be sufficiently complex to require a coordinated, trans-NIH approach. Finally, initiatives must be ***unique***—something no other entity is likely or able to do.

Thus, Common Fund programs are intended to change paradigms, develop innovative tools and technologies, or provide fundamental foundations for research that can then be used by the broad research community.

The Life Cycle of Common Fund Programs

Programs selected as part of the Common Fund portfolio represent strategic investments in which 5- to 10-year initiatives can have a transformative impact. As programs end, the turnover in available funding means that new challenges and opportunities may be addressed each year.

Strategic planning is done annually and varies to ensure that the NIH remains nimble and adaptive to the changing scientific landscape. However, core principles underlie all planning activities. These include gathering input from NIH stakeholders representing diverse perspectives, ensuring a systematic and transparent process for soliciting ideas, assessing the state of the science and research portfolio, and engaging NIH leadership, including Institute and Center Directors. These principles are designed to ensure that the programs have maximum utility for the broad biomedical community and address major obstacles to research progress.

The life cycle of Common Fund programs can be envisioned as evolving through different phases as described below.

Strategic Planning

Strategic planning for the Common Fund can be divided into two phases. Phase 1 begins with a series of activities to gather input from the biomedical community on broad scientific needs and emerging scientific opportunities that could be accelerated through strategic investment by the Common Fund. Phase 1 activities may include meetings with external scientific experts, solicitation of ideas from NIH ICs, discussions with senior NIH leadership and advisory committees, and/or engagement with the general public through meetings, social media or Requests for Information.

The broad concepts identified during Phase 1 are refined into specific, well-defined initiatives in Phase 2. A range of activities is undertaken to accomplish this task, including meetings and workshops, analysis of NIH and other scientific research portfolios, and priority setting. The process results in a unique strategic implementation plan for each program selected with well-defined goals and milestones. The deliverables for each program are deliberately designed to overcome key obstacles to progress in the field. Together, Phase 1 and 2 take approximately 18 months to complete and culminate in the launch of new Common Fund programs representing the highest priority areas for the NIH as a whole.

Implementation and Transition

After new Common Fund programs have been identified through Phase 1 and 2 strategic planning, programs are launched and implemented over a 5- to 10-year timeframe. Program implementation is tailored to each program's unique needs and may be adjusted to respond to changing scientific needs and opportunities. As programs approach the end of the Common Fund implementation phase, they are transitioned to other sources of support or use within the scientific community, so that the community continues to benefit from Common Fund investment. Considering implementation and transition plans for each program early in the process ensures that program goals and milestones address the needs identified during strategic planning and provides a sustainable model for continued use by the scientific community once Common Fund support for a program has ended.

As the Common Fund embarks on its next decade, it will continue to undertake a robust strategic planning process to identify the greatest challenges to scientific progress and the most promising emerging opportunities to catalyze research across multiple biomedical fields.

New Pathways to Discovery

The complexity of biological systems demands the acquisition and analysis of diverse data types as well as the flexibility to capitalize on recent advances or discoveries in a given arena. Common Fund programs address the challenges associated with acquisition—developing new tools and methods to acquire and analyze data. Programs that leverage newly emerging opportunities often catalyze research broadly by providing large data sets, establishing standards and computational tools for broad use and demonstrating utility and relevance of the data for diverse health conditions. The challenges and opportunities are considered individually for each program area, with steady input from external panels as the program is implemented, to ensure that research tools, data and approaches are useful to the research community at large. In turn, the research community uses these resources to conduct crucial basic biomedical research that forms the foundation of translational and clinical studies aimed at promoting health and decreasing the burden of disease.

Bioinformatics and Computational Biology

Biology has always been a haven for microscopes, test tubes and Petri dishes, but this conventional picture of the field is changing. Sophisticated techniques adapted from physics, chemistry and engineering enable scientists to conduct biomedical research like never before. Scientists can now use computers and robots to separate biological molecules, read genetic information, reveal the 3-dimensional shapes of biological molecules and take pictures of the brain in action. All of these techniques generate massive amounts of complex data, and there is no way to manage these data by hand. What researchers need are computer programs and other tools to evaluate, combine and visualize these data.

As part of the original set of Roadmap programs, the Bioinformatics and Computational Biology program was designed with these needs in mind and sought to capitalize on the promise of computational methods to solve complex biomedical problems by paving a future "information superhighway" dedicated to advancing medical research using both supercomputers and ordinary desktop computers. As part of the program, the Common Fund funded eight National Centers for Biomedical Computing (NCBCs):

- Informatics for Integrating Data for Analysis, Anonymization and Sharing (i-DASH) at the University of California, San Diego
- Integrating Biology and the Bedside (i2b2) at Brigham and Women's Hospital
- The National Alliance for Medical Image Computing (NAMIC) at Brigham and Women's Hospital
- The National Center for the Multiscale Analysis of Genomic and Cellular Networks at Columbia University (MAGNet)
- The National Center for Biomedical Ontology (NCBO) at Stanford University
- The National Center for physics-based Simulation of Biological Structures (Simbios) at Stanford University
- The National Center for Integrative Biomedical Informatics (NCIBI) at the University of Michigan
- The Center for Computational Biology (CCB) at the University of California, Los Angeles

These Centers worked as the core of a universal computing infrastructure, allowing the biomedical community—including researchers and physicians—to integrate, analyze, model and share data on human health and disease. The Centers developed cutting-edge software and data management tools to mine the vast wealth of biomedical data from modern

laboratory techniques and to support data sharing among researchers. The program also yielded substantial research results in the published literature which demonstrate the utility of these computational tools. A goal of the program was to develop computational approaches within the context of driving biological problems—to tackle unsolved biomedical mysteries, such as the role of heredity in individuals' different responses to medicines or the complex interplay of genetic and environmental factors in common diseases, such as Alzheimer's disease, heart disease, cancer and diabetes.

Each NCBC was required to perform or support six different core functions: (1) tackle important biomedical problems using computational science; (2) establish Driving Biological Projects that allow researchers from different areas of science to collaborate and develop computational research; (3) help researchers properly use available computer and software tools and resources; (4) enhance the training of a new generation of biomedical researchers; (5) disseminate newly developed computational tools and techniques to the biomedical research community; and (6) provide administrative resources to ensure that the Center achieves its goals.

These core functions helped the Bioinformatics and Computational Biology program achieve notable successes. For example, the NCBCs trained thousands of computational scientists who are now contributing to basic research. The i2b2 Center developed software that researchers can use to mine clinical data, and when combined with appropriate data about the human genome, researchers can explore the development of therapies specifically designed for individual patients who are born with genetic diseases. This platform currently enjoys wide international adoption by academic health centers and industry. The NAMIC developed a biomedical image processing software package called "3D Slicer" that is now used worldwide. This software allows researchers to analyze in great detail different parts of tissues and organs. For example, scientists have used 3D Slicer to study breast tumors, which are normally complicated to analyze, and to properly categorize them into different cancer types.

The Bioinformatics and Computational Biology program transitioned out of the Common Fund at the end of 2013, with each Center receiving full support in 2014 by one or more NIH Institutes or Centers, which were aligned with the Driving Biological Problems addressed by that Center.

USING DATA TO INFORM RESEARCH AND IMPROVE PATIENT CARE

The Informatics for Integrating Biology & the Bedside Center, commonly known as i2b2, is led by Director Isaac Kohane, M.D., Ph.D., of Harvard Medical School. The Center is developing scalable computational and organizational tools to accelerate the translation of genomic and traditional clinical findings into novel diagnostics and therapeutics. In addition, it provides a collaborative organizational and software infrastructure that allows researchers to leverage insights arising from clinical studies. The i2b2 software is publicly available and is used by academic centers across the country.

Current projects within the Center are seeking to identify genes that influence risk for autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, and to identify genes and other factors that may predispose people with these conditions to heart disease. Previous projects have addressed such complex diseases as Huntington's disease, asthma, hypertension, type 2 diabetes, obesity and major depressive disorder. In addition, members of this Center and others have applied new informatics methods to define the relative value of clinical and biological markers for diagnosing and predicting breast cancer outcomes. Approaches that combined clinical biomarkers with a subset of genomic markers increased the ability of physicians to diagnose breast cancer and to predict patient outcomes. This suggests a new direction for use of genomic markers in diagnosis of specific patient populations.

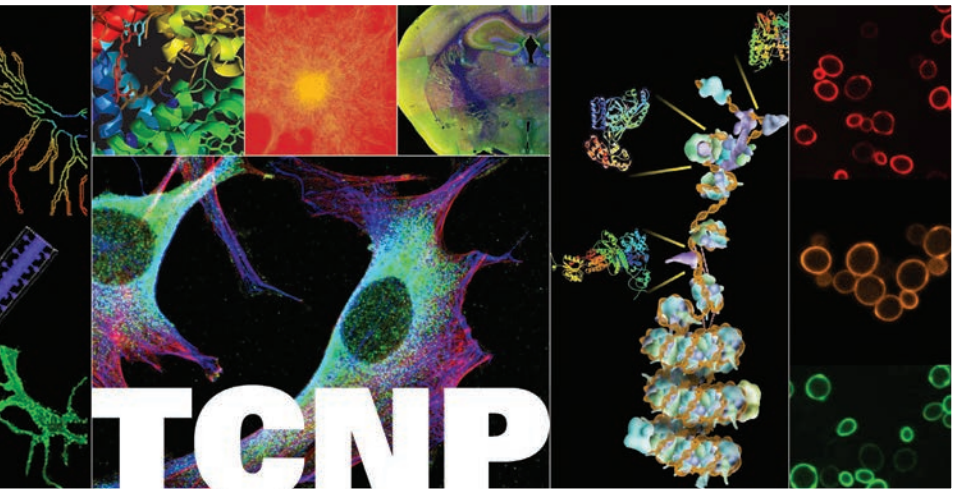
Prior Center projects included pioneering the use of hospital data for real-time monitoring of medications for unexpected side effects and the distributed querying of populations of patients across multiple academic health centers to find sufficient numbers of rare patients for studying diseases. Examples of the latter include successful studies of peripartum cardiomyopathy, a rare and potentially lethal complication of pregnancy.

A partial view of the dissemination of more than 100 i2b2 sites where entire health care systems make their patient clinical data available for research in genomics, comparative effectiveness and pharmacovigilance.

Building Blocks, Biological Pathways and Networks

Maintaining human health requires an amazing feat of biological teamwork. A host of players—from individual genes and molecules to cells and organs—work together to carry out a wide range of intricate and interconnected biological processes. By studying these processes, scientists seek to gain a better understanding of how the body works, how disruptions in biological pathways and networks can lead to disease, and how to develop interventions to restore healthy functioning. Until recently, however, the only way to visualize these interactions was equivalent to taking a long-exposure photograph that rendered a vague and static image of what are, in reality, rapidly fluctuating and changing molecular interactions.

The Common Fund's Building Blocks, Biological Pathways and Networks (BBPN) program was designed to support the development of new technologies and resources that enable researchers to study molecular events as they unfold in real time. Launched in 2004, the program consisted of three components: the National Technology Centers for Networks and Pathways (TCNPs), Metabolomics Technology Development, and Standards for Proteomics and Assessment of Critical Reagents for Proteomics.



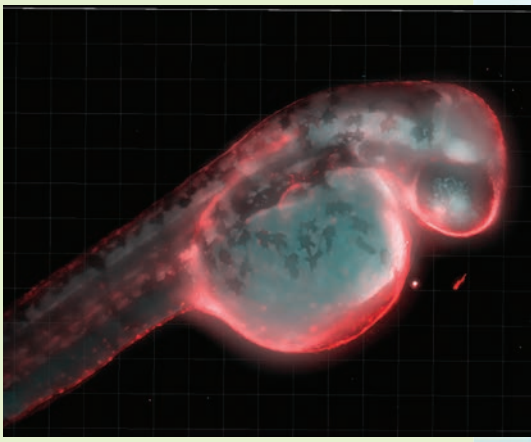
The TCNP component was designed to create new technologies to study, in real time, the actions and interactions of proteins within cells, also known as proteomics. It has consisted of a consortium of independent research centers that have integrated the study of proteomics with cell biology, imaging and modeling techniques to achieve a dynamic picture of cellular systems at the molecular level. Each research center has integrated biological, technological and informatics capabilities, but each has focused on different technologies and systems. For example, the Rockefeller TCNP has developed methods to isolate intact protein complexes rapidly at high yields by literally freezing the timeframe of the experiment, allowing the complexes to be studied in their natural configurations. The Molecular Biosensor and Imaging Center at Carnegie Mellon University has used fluorescent biosensors that light up only when the proteins bind to the target molecule, allowing researchers to see how proteins interact and change in the 3-dimensional space of a living cell. Another TCNP-funded center at Johns Hopkins has focused on proteins with specific chemical modifications, which play important roles in a wide range of biological processes, including gene expression. Cooperation among the centers has allowed them to achieve a broader scope of research than would be possible if they functioned independently. TCNP technologies have been adopted by both basic researchers and the pharmaceutical industry, and several have been commercialized due to their broad applicability.

The Standards for Proteomics and Assessment of Critical Reagents for Proteomics component of BBPN held workshops on opportunities in proteomic research and the establishment of quality and data standards for proteomics and metabolomics. One recommendation from the workshops was to establish standard reference material for metabolomics research. As a result, the NIH collaborated with the National Institute of Standards and Technology to develop a core set of standard references of human metabolites from pooled plasma samples. This provided researchers with a way to evaluate and compare new technologies for measuring cellular metabolites, to improve the reproducibility of measurements, and to develop new approaches to disease diagnosis and treatment.

The BBPN program also had an early emphasis on exploratory technologies to enable the study of metabolites, or metabolomics. It encouraged technological developments in the field of metabolomics and the application of these technologies to research on a variety of diseases and conditions. Metabolites include carbohydrates, lipids, amino acids and other small molecules involved in body functions (metabolism). The Metabolomics Technology Development component of the BBPN program focused on the development and refinement of novel technologies to accelerate the study of metabolites in biological pathways and networks in cells, in both health and disease. This component funded more than 20 different projects across the country to develop technologies for conducting research into metabolomics and explore the metabolic processes in different human diseases, including Alzheimer's disease, diabetes and cancer.

USING BIOSENSORS TO MAP CELLULAR NETWORKS

Until recently, scientists have been hampered in their ability to investigate how proteins interact in complex networks within a cell. Yet, understanding the activity of these networks as interactions occur in real time could provide the keys for understanding how cells malfunction in disease and for developing therapies to repair or bypass that dysfunction. In the Molecular Biosensor and Imaging Center at Carnegie Mellon University and the Center for Biologic Imaging at the University of Pittsburgh, a multidisciplinary team of biologists, chemists and engineers, including Alan S. Waggoner, Ph.D., Marcel P. Bruchez, Ph.D., and Simon Watkins, Ph.D., has developed a technology that allows researchers to quantify the activities of key proteins of the pathways in living cells, a technology that involves the use of novel fluorescent biosensors (devices that monitor and transmit information about a life process).



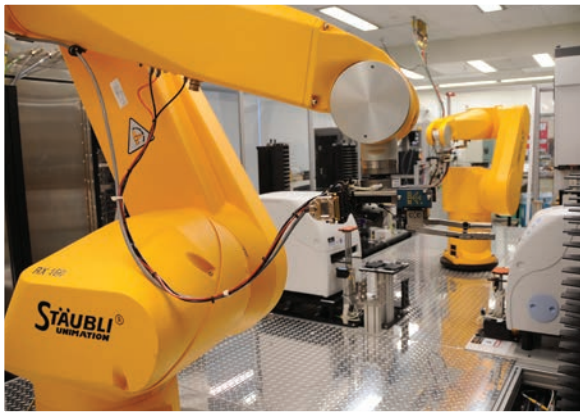
3-D reconstruction of microscope images of a live FAP-expressing zebrafish that can be used to screen chemicals for drug-like activity.

These biosensors combine a fluorogen, or dye, that fluoresces only when bound to a specific genetically engineered "fluorescence-activating peptide" or FAP. The FAP peptide can be built into a protein "target" that scientists are interested in or designed to bind to a different target protein. The fluorogens give off light only when and where the target molecule is present, enabling scientists to see exactly where the molecule is located, and also to see color changes when it becomes fluorescent. These color changes may reflect changes in the local environment of the protein and allow real-time quantitative sensing of the biological activity of proteins and biomolecules that are in close proximity to each other. In addition, by using a combination of biosensors with different dyes, it is possible to visualize several different cellular processes at the same time. Now commercially available, the biosensors are being used to map many cellular networks implicated in health and disease and to develop therapeutics based on this new understanding. For instance, researchers are using the biosensors to gain a better understanding of how therapeutics affect the malfunctioning protein in cystic fibrosis, a genetically inherited disease. This technology is allowing researchers to learn not just whether a drug inhibits binding or activation of its protein targets, but how the drug alters location or environment of the target, offering better understanding to ultimately improve the efficacy of therapeutics.

Molecular Libraries and Imaging

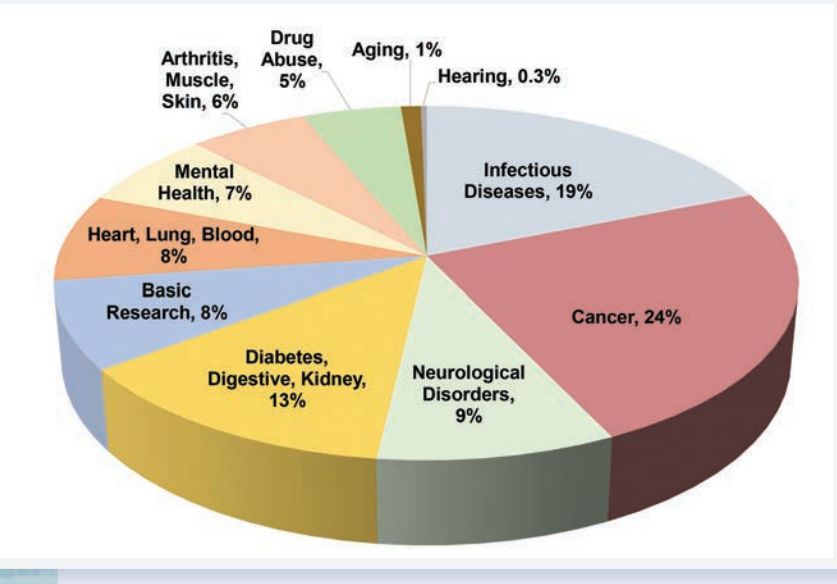
Small molecules play a large role in human health. These organic compounds naturally regulate biological function in cells and organisms. Most drugs in use today are actually small molecules that easily cross cell membranes and bind with proteins and other targets within the cell to change their functions. Molecular libraries are collections of these chemical compounds that can be used to study how genes and cells work together in health and disease.

Launched in 2004 as part of the NIH Roadmap, the Molecular Libraries program has taken advantage of major advances in biomedical research that together set the stage for a huge expansion in this area of research. First, the Human Genome Project revealed that there might be up to a million different proteins that play different roles in health and disease. Second, the use of robotics and other advanced technologies enabled cost-effective testing of thousands of chemicals in a single laboratory. Third, large amounts of complex information could be stored and shared using powerful, computer-based information retrieval systems. The convergence of these three areas provided an unprecedented opportunity to accelerate the discovery of protein functions that control processes critical to health and to any disease.



The NIH Chemical Genomics Center (NCGC) high-throughput screening robotic system.

The major initiative of this ambitious program was composed of the Molecular Libraries Small Molecule Repository and the Molecular Libraries Probe Production Centers Network (MLPCN), a network of nine research centers and more than 100 medicinal chemists, many of whom have experience in both biotech and large pharmaceutical companies. The centers, each with a different set of core



Probes developed by Molecular Libraries centers across the country span diverse areas of health and biology.

capabilities, screened compounds to identify potent, new small molecule "probes," which help scientists study pathways and targets and develop new drugs to treat or prevent disease. The pharmaceutical industry uses similar screening and chemical synthesis technologies in its quest for new drugs. The Common Fund's Molecular Libraries program made this technology available to publicly funded scientists in university laboratories for the first time.

The Molecular Libraries program also has fostered new relationships among the nine research centers and the thousands of laboratories across the country where groundbreaking research is underway. As new molecules are identified and screened, researchers share information about them via the PubChem database, allowing chemists, biologists, neuroscientists and physicians in both the public and private sectors to share information and insights easily across specialties and disciplines. This means that a molecule tested in a neuroscience laboratory in Tennessee can come to the attention of a physician-scientist in Massachusetts and lead to a discovery that may offer new hope to millions of people with kidney disease around the world. See the vignette on Anna Greka, M.D., Ph.D. In the increasingly complex scientific environment, this type of interdisciplinary research is vital to translating basic science advances into new treatments that benefit patients. To date, the database contains more than 31 million compounds and results from more than 1,700 high-throughput screening programs. Every day, more than 140,000 scientists from around the world search the PubChem database.

The MLPCN maintained the highest quality standards and put special emphasis on research into rare and neglected diseases. All tests (called assays) used to screen compounds were nominated by the community and reviewed by other scientific experts before use in the centers. The MLPCN has discovered more than 365 chemical tools for exploratory research and developed more than 100 potential drug candidates, some of which have advanced to clinical trials. The Small Molecule Repository now includes more than 385,000 unique and diverse compounds. One of these compounds led to the development of RPC1063, a potential therapeutic that shows promise for the treatment of relapsing multiple sclerosis and ulcerative colitis. Getting control of multiple sclerosis attacks is critical to reducing disability and distress for the 2.3 million people worldwide who have this disease.

The Molecular Libraries program has also built new connections between the pharmaceutical industry and academia by fostering communications and collaborations for the identification of molecules for potential commercial use. These connections have also led to a cross-pollination of both sectors as scientists move from academic to industry and vice versa and sometimes join forces to create new startup companies that draw on their combined expertise. The collaboration between industry and academia also resulted in the development and publication of the Assay Guidance Manual, which was written to provide guidance to investigators interested in developing assays to screen molecules and identify those that may advance research or lead to new treatments for disease.

The cooperative nature of the Molecular Libraries program has inspired similar efforts on an international level. In Europe, the EU-OPENSCREEN network joins public and private laboratories to exchange information and increase understanding of the potential beneficial and hazardous effects of these compounds. Scientists and staff associated with the Molecular Libraries program have shared important expertise to help get this vital collaboration off the ground.

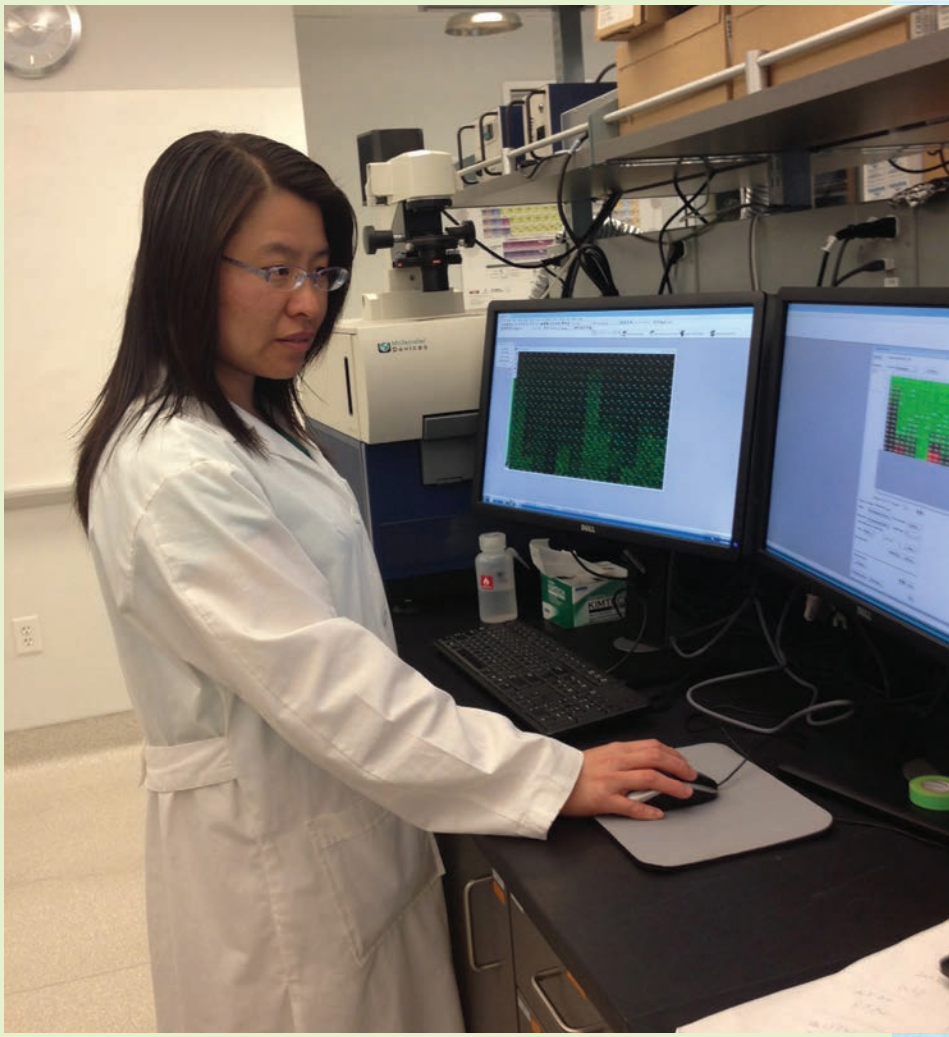
Experts in the field credit collaborations like the Molecular Libraries program with opening up the field of chemical biology to more researchers who are blending chemistry, pharmacology and biology to address some of the critical questions in medicine today.

In 2014, the Molecular Libraries program transitioned from the Common Fund to investigator-initiated support for assay screening and chemical probe projects by more than 13 NIH Institutes and Centers. The National Center for Advancing Translational Sciences and the National Center for Biotechnology Information continue support for NIH Chemical Genomics Center, as well as the BioAssay Research Database (BARD), the Small Molecule Repository and PubChem.

MOLECULAR LIBRARIES INSTRUMENTAL IN RESEARCHERS' DISCOVERY OF POTENTIAL NEW CHEMOTHERAPEUTIC AGENT

Tsui-Fen Chou, Ph.D., a postdoctoral researcher working in the laboratory of Ray Deshaies, Ph.D., at Caltech, was on the hunt for a compound to slow down p97, a protein that plays a role in multiple cell processes, including cell division. Dr. Chou and Dr. Deshaies theorized that a p97 inhibitor would not only provide insights into the structure and function of p97, but might also lead to a new chemotherapeutic agent. Dr. Chou had developed assays to test different molecules, but without a high throughput facility to speed up her research, the process would be painstakingly slow.

Fortunately, the Scripps Research Institute had just the equipment and expertise Dr. Chou needed. As a member of the Molecular Libraries Probe Production Centers Network (MLPCN), the Scripps Molecular Screening Center offers researchers access to the large-scale screening capacity necessary to identify small molecules for studying the function of genes, cells and biochemical pathways. The scientists at Scripps Research Institute adapted Dr. Chou's assay for the high-throughput machinery and screened the Network's entire library of small molecules (nearly 220,000 at that time) looking for potential p97 inhibitors. They narrowed the field to the top 50 candidates—cutting years off the research process. Back at Caltech, Dr. Chou conducted more focused assays on those top contenders to identify the most promising molecule.



Dr. Tsui-Fen Chou is using one of the specialized assays to spot a p97 inhibitor with an automatic microscope.

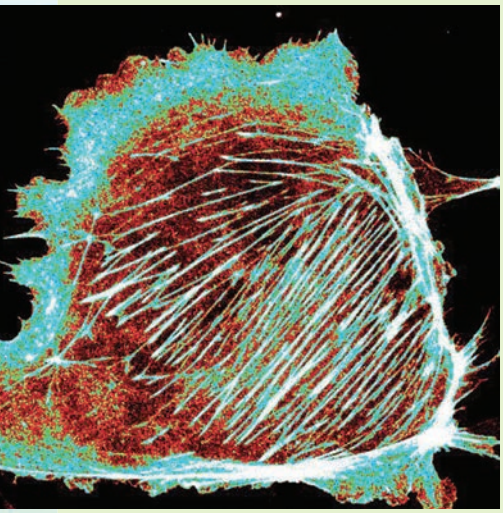
Dr. Chou then worked with another member of the MLPCN, the Specialized Chemistry Center at the University of Kansas, which focuses on increasing the potency of compounds identified at screening centers like the one at Scripps Research Institute. The University of Kansas chemists first made a set of molecules closely related to the promising hit that emerged from Scripps Research Institute. Dr. Chou tested these molecules, then relayed the results back to the University of Kansas chemists, where they made a new set of related variants and once again sent them to Dr. Chou for testing. After 15 cycles of synthesis and testing, the team identified a molecule that may be a viable candidate drug to treat multiple myeloma.

But that's not the end of the story. Based on the potential of this molecule and another that emerged from a different MLPCN project, Dr. Deshaies launched a new company called Cleave Biosciences that has attracted more than $50 million in venture capital funds to develop an effective chemotherapeutic agent. Dr. Chou's diligent work on this compound was instrumental in her 2012 appointment to the faculty of Harbor-UCLA Pediatrics with a laboratory at the Child Health Research Center.

MAKING POTENTIALLY LIFESAVING CONNECTIONS THROUGH THE MOLECULAR LIBRARIES PROGRAM

Despite the fact that kidney disease affects 26 million Americans and is the ninth leading cause of death in the United States, there have been few therapeutic breakthroughs in recent decades. Anna Greka, M.D., Ph.D., is working hard to change that.

Dr. Greka and her colleagues at Harvard Medical School have been investigating the role of the ion channel TRPC5 in damaging the kidney's filtration system. They found that when this channel is activated, excess calcium flows into the cells critical for proper filtration (called "podocytes"), causing them to break down. By inhibiting TRPC5, Dr. Greka believed she could stop the damage before it progressed to kidney failure. But she needed to find the right molecule.



Color image of a podocyte showing its intricate actin cytoskeleton, which is critical to maintain an intact kidney filter barrier.

Dr. Greka was already working with the nearby Broad Institute, a member of the Molecular Libraries Probe Production Centers Network (MLPCN), which had been screening compounds against her kidney podocytes but had not yet found a viable candidate. Then she got an email from a Broad Institute chemist about a molecule discovered by researchers at Vanderbilt University. Dr. Greka headed to the PubChem database and examined the chemical structure of ML-204, the compound identified at Vanderbilt, another MLPCN member. She was indeed interested.

Dr. Greka obtained a sample of the compound from the laboratory at Vanderbilt and started testing it on a mouse model of the disease. The molecule blocked TRPC5 in mice and protected the kidney filters from damage. The results were published in the December 2013 issue of the *Journal of Clinical Investigation*.[1]

This project is a prime example of how the Common Fund-supported Molecular Libraries program enhances the communication and connections between chemists and biologists, translating basic science discoveries into a potentially lifesaving new therapy.

"Before the ML-204 was discovered, we had no compound by which to block this ion channel," Dr. Greka explains. "There was nothing out there that we could test on our disease model. [The Molecular Libraries program] allowed us to take a chemical sitting on the shelf somewhere and translate it—at least at the level of a mouse—into a therapy for a very devastating disease."

[1] Miller, M., Shi, J., Zhu, Y., Kustov, M., Tian, J.B., Stevens, A., et al. (2011). Identification of ML204, a novel potent antagonist that selectively modulates native TRPC4/C5 ion channels. *Journal of Biological Chemistry, 286*(38), 33436–33446.

Nanomedicine

Nanotechnology is science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers (1/100th the diameter of a human hair). Materials at the nanoscale sometimes have unique properties, such as higher strength, greater chemical reactivity, or unique physical or electromagnetic characteristics. In addition, at the nanoscale, individual molecules and nanomachines operate in living cells. In general, nanomedicine exploits nanoscale structures and tools for medical purposes, such as drug delivery. The Nanomedicine program, however, was designed to use nanotechnological knowledge and tools to probe and understand the molecular complexes, the nanomachinery, inside living cells and then directly manipulate these nanostructures to treat a specific disease.

The program began a planning phase in 2004 and was fully implemented beginning in 2005 as a basic science endeavor that was designed to evolve toward more translational studies of a specific target disease within 10 years. This bold program was truly experimental and unique. As such, Congress provided the Director of the NIH with special flexible research authority to permit the NIH to develop new approaches and processes for reviewing, funding, and managing the program. A dedicated team of NIH scientists representing more than half of the NIH Institutes and Centers developed the program that initially consisted of eight highly collaborative centers, each of which had unique interests and approaches, to study particular intracellular nanomachines. Whereas nanotechnology heavily relies on physical scientists and engineers, the translational imperative of the program required early involvement of clinicians and a range of biologists for the centers to focus on a specific disease. Thus, from very early in the program, NIH staff used the funding flexibility to enlist the aid of clinical collaborators to become

co-investigators in the centers. In addition, oversight for each successful center eventually included an external clinical consulting board to help focus the work of the centers on the disease target and a translational endpoint.

Indeed, the idea of beginning with basic science and eventually turning to a translational program over a 10-year period was audacious, especially because this meant that new investigators would need to join the center, and some of the original participants had to leave. With 1 year remaining, four of the eight original centers remain in the program and all of them have achieved various levels of success in reaching a significant translational endpoint, including investigational meetings with the FDA for human studies of a therapy to treat blindness, new state-of-the-science gene editing techniques for treating animal models of sickle cell disease, new intracellular manipulations of protein folding machinery to treat Huntington's disease and application of the tools of synthetic biology to enhance the latest approaches of harnessing the immune system to attack cancer cells.

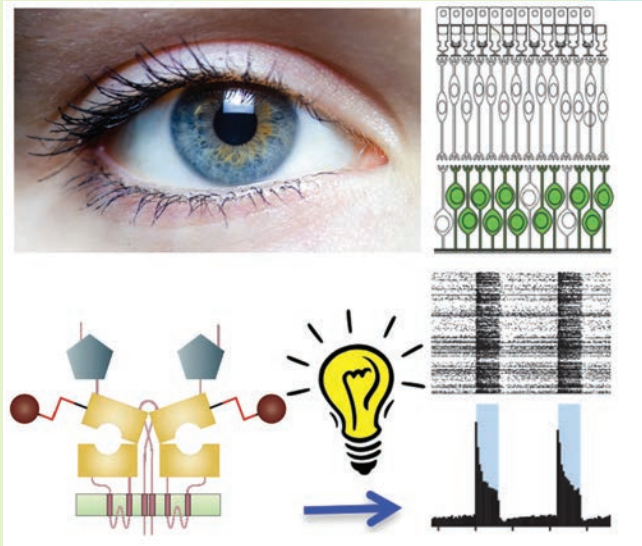
To date, the Common Fund has supported a series of short-term, exceptionally high-impact, trans-NIH programs. Moreover, the Common Fund provides a unique experimental space to try new approaches to biomedical research for a 10-year period. The Nanomedicine program, begun as one of the first of nine programs of the NIH Roadmap, serves as a model for what is possible under the auspices of the Common Fund.

Using enzymes that act as molecular scissors, nanomedicine scientists are developing gene editing techniques to correct the defective beta-globin gene in animal models of sickle cell disease.

MOLECULAR PHOTOSWITCHES

Ehud Y. Isacoff, Ph.D., and his colleagues are developing new methods to use light to noninvasively control proteins in cells, with the ultimate goal of treating human disease. One of the first such diseases they are targeting is retinitis pigmentosa, a genetic disease that causes blindness. In people with retinitis pigmentosa, the vision loss occurs as photoreceptors in the retina, which convert light into nerve signals for the brain, gradually deteriorate. Research has shown that retinal neurons that receive and process signals from the photoreceptors are preserved for years after the onset of blindness, giving hope that visual sensitivity might be restored by artificially inputting light information to these surviving cells.

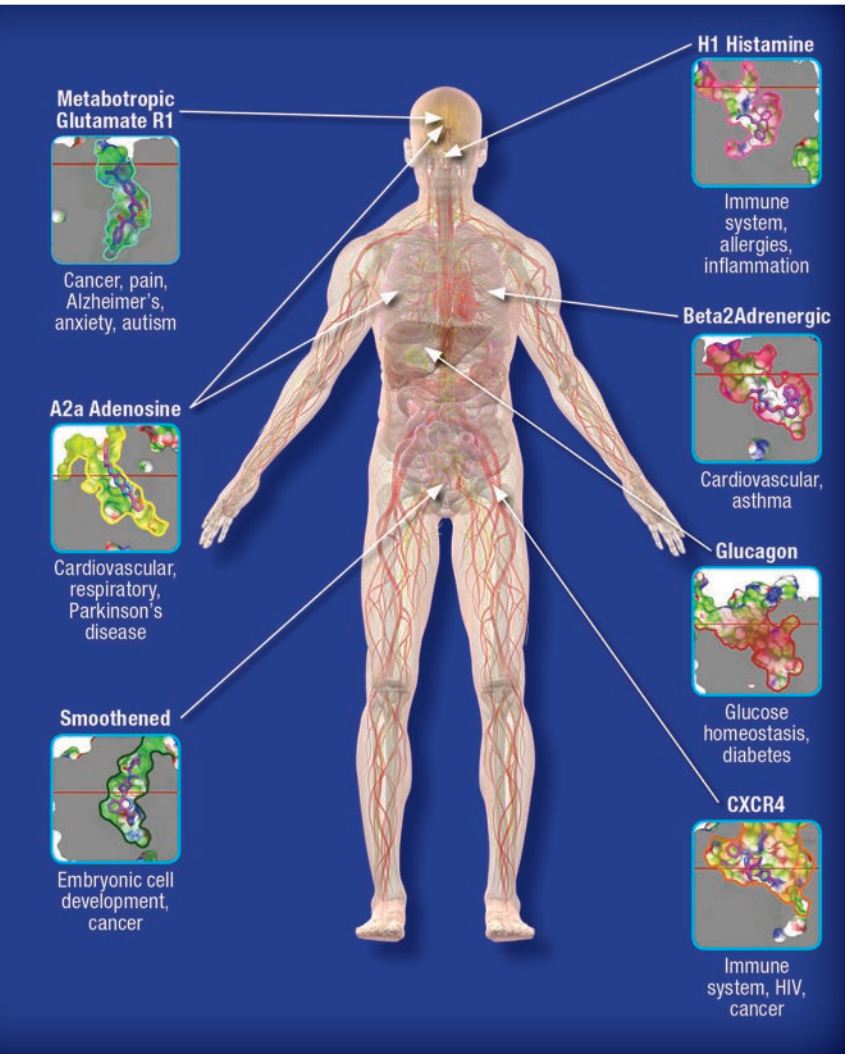
As intended by the Nanomedicine program, Dr. Isacoff and his research team first performed some very basic research and then applied this toward solving an important medical problem. In Dr. Isacoff's case, they determined how small chemical compounds can be used to make a special class of proteins termed "ion channels" sensitive to light. Now, in research with mice, they have found that these chemical photoswitches, when introduced into surviving retinal neurons, endow their ion channels with sensitivity to light, send neural signals to the brain and restore vision to blind animals. Thus, within the 10-year Nanomedicine program, Dr. Isacoff and co-workers have been able to go from basic chemistry, molecular biology and biophysics research to research that may lead to restoration of vision in the blind.



Following degeneration of retinal photoreceptors, surviving neurons (top, green) receive chemical photoswitches (bottom left) that restore neuronal activity in response to light and restore vision.

Structual Biology of Membrane Proteins

A healthy mind and body require the coordinated action of billions of tiny molecular workers called proteins. Proteins are indispensable molecules in our bodies, and each has a unique three-dimensional shape, or structure, that is well suited for its particular job. There is a class of proteins that reside in the lipid (fat) layers that surround cells as well as in certain internal compartments of cells. These proteins, called membrane proteins, perform many critical functions and are implicated in a variety of diseases, thus providing attractive targets for drug development. Knowing the structure of the protein target helps drug development tremendously since the structure helps researchers visualize how the candidate drug molecules might interact with the protein. However, the structure determination of membrane proteins has been notoriously difficult.



Pioneering methods in membrane protein production have rapidly accelerated GPCR membrane protein structure determination. The red line in each image represents the location of the extracellular membrane boundary.

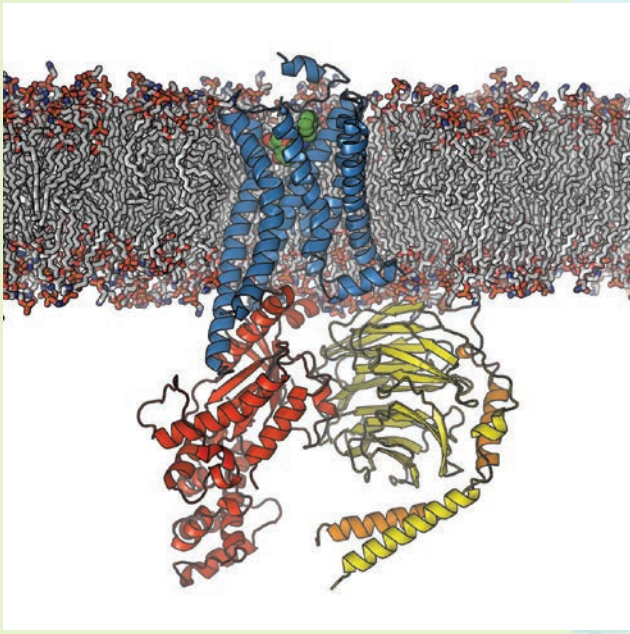
The Common Fund's Structural Biology program is a strategic effort to help make the structure determination of membrane proteins much easier. The intent of this effort is to transform what has been a hit-or-miss process into a more robust and reliable method, helping researchers clarify the role of protein structure in health and disease.

One limiting step in the determination of membrane protein structures is the production of sufficient quantities of pure protein samples. These proteins tend to unfold or to clump together when taken out of their membrane environment. During the first phase of the Structural Biology program (begun in 2004), the Common Fund supported two Centers for Innovation in Membrane Protein Production that enabled interdisciplinary groups of scientists to develop innovative methods for producing large quantities of membrane proteins that maintained their normal structure. During the second phase of the Structural Biology program (begun in 2009), researchers developed additional innovative approaches for membrane protein production as well as structure determination. These centers have been remarkably successful in developing such innovative approaches and using them to determine a series of challenging membrane protein structures.

In addition, the program awarded a number of grants, both large and small, to individual investigators to broaden the base of innovative ideas being pursued. Dr. Brian Kobilka at Stanford University was a recipient of one of the early grants from the Structural Biology program. For work performed, in part, through the support of this grant, he won the 2012 Nobel Prize in Chemistry, along with Dr. Robert Lefkowitz of Duke University. This Nobel Prize was awarded for their groundbreaking studies of G-protein coupled receptors (GPCRs) and the structure determination effort of Dr. Kobilka was mentioned specifically. GPCRs are membrane proteins that transmit to the inside of the cell important information about the environment outside the cell, including light, smell, taste, hormone levels and neurotransmitters. Due to their wide range of functions, GPCRs are targets of almost half of pharmaceuticals on the market. Dr. Kobilka's transformative approach to protein research is an outstanding example of the nature of Common Fund-supported research, which aims to accelerate biomedical research that is relevant for multiple diseases and conditions.

A DECADE OF BREAKTHROUGHS IN G-PROTEIN COUPLED RECEPTORS

The past 10 years have seen enormous progress in the study of G-protein coupled receptors (GPCRs), the proteins in cell membranes that transmit information and enable vital human functions that range from seeing light or smelling a flower to how we experience pain and the delicate balance of dopamine, serotonin and other brain chemicals. A decade ago, scientists had characterized just two or three human membrane protein structures. Now that number is approaching 100.



The structure of the beta 2 adrenergic receptor activating the G protein Gs.

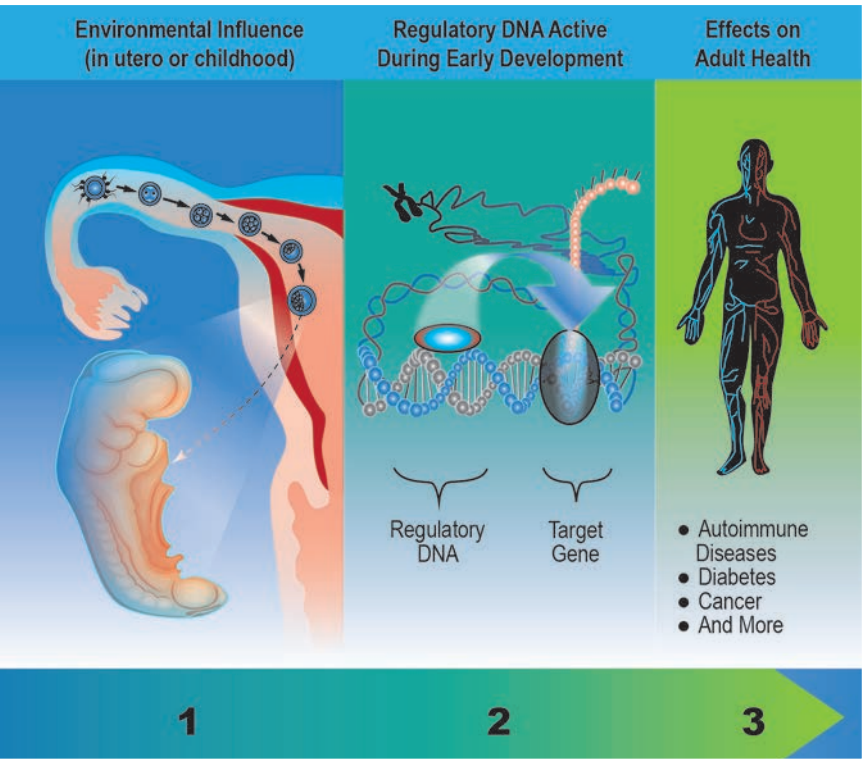
Two scientists who have been at the forefront of this progress are Brian Kobilka, M.D., of Stanford University School of Medicine and Ray C. Stevens, Ph.D., of The Scripps Research Institute, both of whom have received Common Fund support through the Structural Biology program. In particular, Dr. Kobilka's funding helped support the development of a fusion protein strategy to stabilize the proteins and facilitate crystallogenesis. Dr. Stevens' funding targeted needed breakthroughs in automated protein expression, protein characterization, crystallization, imaging and data collection. Together, Drs. Kobilka and Stevens were finally able see the structure of the beta 2-adrenergic receptor. Once they had the method to determine the structure of the first GPCR, it opened the door to do it again repeatedly. The Common Fund also supported efforts in Dr. Kobilka's laboratory to obtain the structure of the beta 2-adrenergic receptor activating a G protein. The impact of this work was large and immediate enough to be specifically noted in the citation for Dr. Kobilka's Nobel Prize in Chemistry in 2012. The breakthroughs made possible by the Common Fund support enabled Dr. Stevens and colleagues at The Scripps Research Institute to launch and establish the GPCR Network in 2010, responsible for the majority of known unique GPCR structures (16 of 24).

Several laboratories across the country—including Dr. Kobilka's and Dr. Stevens'—are now studying GPCRs in each of 200 subfamilies with the goal of understanding their role in health and disease and helping to optimize drug candidates by improving the affinity or selectivity of the molecule for the target receptor. For example, Dr. Stevens' work with colleagues on the study of S1PR1, a receptor involved in immune cell regulation and development, revealed its role in multiple sclerosis (MS), a disease that affects 2.3 million people worldwide. Working with the High Throughput Screening Center at Scripps (a member of the Common Fund's Molecular Libraries Probe Production Centers Network), researchers identified a molecule that has now been developed into a drug that currently is in Phase 3 clinical trials for patients with MS. It is also being studied for possible use in inflammatory bowel disease.

Epigenomics

Epigenomics is a field of biomedical research focused on DNA modifications and modifications of proteins associated with DNA. These modifications, collectively called the "epigenome," occur "on top of" the linear DNA that makes up the genome and can be associated with changes in gene activity without altering the underlying DNA sequence. When the Common Fund-supported NIH Roadmap Epigenomics program was launched in 2008, the field of epigenomics was in its infancy. The Epigenomics program aimed to catalyze epigenomic research, opening the door to an entirely new way of understanding when, where and how specific genes are expressed. The program is characterizing the occurrence and potential functions of epigenetic modifications in normal development and a wide variety of diseases.

This program includes a series of complementary initiatives aimed at generating new research tools, technologies, datasets and infrastructure to accelerate our understanding of epigenetic modifications across the entire human genome. The Epigenomics program is a founding member of the International Human Epigenome Consortium, a growing international effort to coordinate worldwide epigenome mapping and disseminate experimental standards for epigenome characterization.



Early environmental influences (1) can impact regions of regulatory DNA active in early development (2). Epigenomics researchers found that many genetic variants linked to adult-onset disease (3) are located in these regions, potentially linking early environmental influences with development of adult diseases.

There are many types of epigenomic modifications, and prior to the Epigenomics program, their occurrence across the human genome had not been well characterized in a systematic way. One program initiative was designed to map these modifications across the entire genome of many different human cell types. These epigenomic maps are being made available to the scientific community for investigator-driven research projects through the National Center for Biotechnology Information at the NIH. To date, the Epigenomics program has generated over 90 reference maps for a wide range of human cell and tissue types. Examples include brain, heart, kidney, lung and breast cells.

The Epigenomics program also supports development of new technologies to permit enhanced epigenetic analyses, including the imaging of epigenetic changes in live cells. Other initiatives include individual research projects examining the role of epigenetic regulation in a wide variety of diseases and conditions and discovering the role of new epigenetic modifications in human health. One notable success of the Epigenomics program was the discovery that many genetic variants linked to adult-onset disease lie in regions of DNA that regulate genes during early stages of development, providing a potential mechanism to explain why some *in utero* or early childhood environmental exposures increase the risk for diseases that produce symptoms years or even decades later.[1] Other research has detailed epigenomic changes taking place during development as nonspecialized stem cells differentiate into specific cell types, including but not limited to heart, brain and skin cells.[2,3,4] Researchers have also discovered a variety of novel epigenomic marks and identified previously unknown mechanisms by which epigenomic changes regulate gene expression.[5,6]

A newer initiative, introduced in 2013, delves into manipulating the epigenome, a functional application of epigenomics research. This initiative was developed to address the fact that manipulation of the epigenome largely relies on pharmacological or genetic manipulation of epigenetic regulatory proteins, which has the unintended consequence of affecting the entire epigenome. More precise, fine-tuned control of specific epigenomic modifications remains problematic. To overcome this scientific barrier, awardees from this initiative are developing novel tools and technologies to enable discrete manipulations of the epigenome within specific cells or tissues, at precise locations within the genome, and/or with temporal control.

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[1] Humbert, R., Maurano, M.T., Rynes, E., Thurman, R.E., Haugen, E., Wang, H., et al. (2012). Systematic localization of common disease-associated variation in regulatory DNA. Science, 337(6099), 1190–1195.

[2] Xie, W., Schultz, M.D., Lister, R., Hou, Z., Rajagopal, N., Pradipta, R., et al. (2013). Epigenomic analysis of multi-lineage differentiation of human embryonic stem cells. Cell, 153(5), 1134–1148.

[3] Gifford, C.A., Ziller, M.J., Gu, H., Trapnell, C., Donaghev, J., Tsankov, A., et al. (2013). Transcriptional and epigenetic dynamics during specification of human embryonic stem cells. Cell, 153(5), 1149–1163.

[4] Zhu, J., Adli, M., Zou, J.Y., Verstappen, G., Coyne, M., Zhang, X., et al. (2013). Genome-wide Chromatin State Transitions Associated with Developmental and Environmental Cues. Cell, 152(3), 1–13.

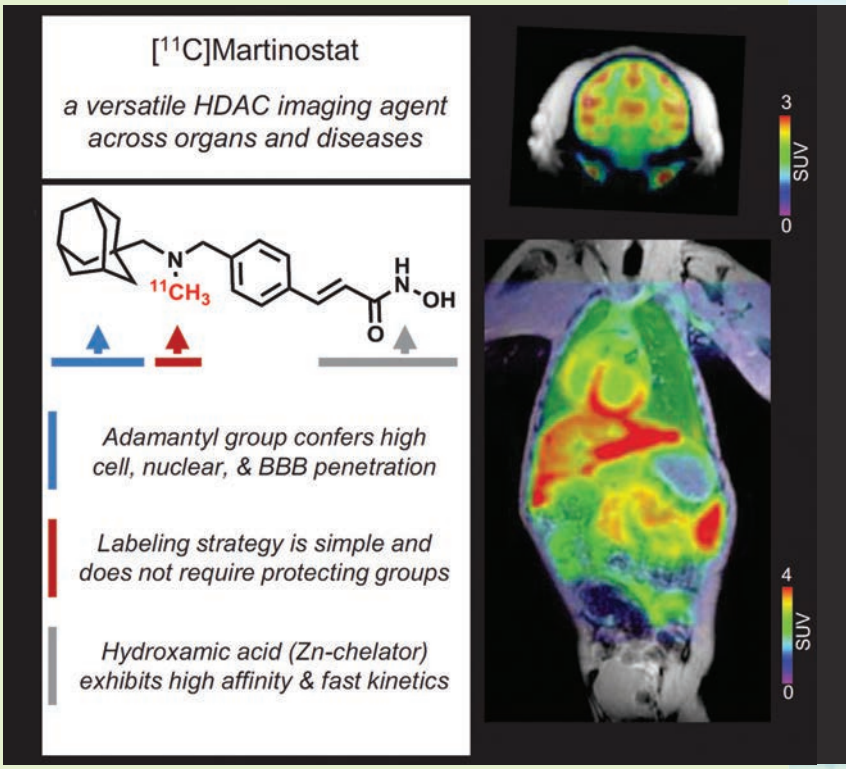
[5] Tan, M., Luo, H., Lee, S., Jin, F., Yang, J.S., Montellier, E., et al. (2011). Identification of 67 histone marks and histone lysine crotonylation as a new type of histone modification. Cell, 146(6), 1016–1028.

[6] Stergachis, A.B., Haugen, E., Shafer, A., Fu, W., Vernot, B., Reynolds, A., et al. (2013). Exonic transcription factor binding directs codon choice and affects protein evolution. Science, 342(6164), 1367–1372.

MOLECULAR IMAGING TO STUDY DISEASE

Jacob Hooker, Ph.D., a chemist and neuroscientist at the Martinos Center for Biological Imaging at Massachusetts General Hospital, received his first NIH R01 grant from the Common Fund's Epigenomics program in 2010 for a groundbreaking idea. His goal was to develop novel technology to visualize a critically important class of enzymes, histone deacetylases, as they function in the body. This enzyme family regulates whether certain genes get turned on or off, and controls when and where this occurs. Histone deacetylase is now believed to play an important role in the development of many neurological disorders, such as bipolar disorder, schizophrenia and addiction, as well as cardiac disease and cancer.

Technology already existed to observe these enzymes in cells or tissues that had been removed via biopsy, but there was no way to visualize their expression in the body. Dr. Hooker proposed to use positron emission tomography (PET) to achieve this type of visualization and quantification. PET is an imaging technique in which a small molecule labeled with a radioactive isotope is administered to a living person. When that molecule binds the target (in this case histone deacetylase), researchers can visualize the target and see where it occurs and then infer how it functions in the body. The technology uses very small doses of radiation to minimize side effects.



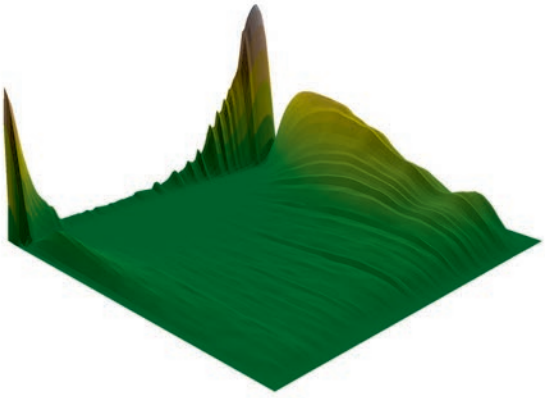
Histone deacetylases (HDACs) may have potential to treat cancer, heart disease, neurological diseases, and more. Dr. Hooker has developed an imaging agent to elucidate the location and function of HDACs; this work will accelerate research and drug discovery.

Seeing this enzyme in action can further our understanding of its function and the role it plays in health and disease. For example, inhibition of histone deacetylase can rescue memory function in animal models of Alzheimer's disease and histone deacetylase can also be manipulated to make tumors more sensitive to chemotherapy. This new imaging technology may aid in the development of new therapies to target histone deacetylase, approaches that have the potential to treat numerous diseases and conditions.

Because this novel imaging technology has wide applications for a variety of diseases, scientists from many disciplines have contributed to its development. Dr. Hooker notes that the Common Fund has actively encouraged collaboration by linking scientists with similar interests and bringing them together for an annual Epigenomics program meeting. Scientists at both Memorial Sloan Kettering Cancer Center and the National Institute on Drug Abuse as well as other academic institutions and pharmaceutical companies have been especially interested in the technology. "First-in-human" trials will start in late 2014—just 4 years after Dr. Hooker originally proposed his idea.

Bringing together scientists with shared interests to create synergy and accelerate research progress is a central component of Common Fund programs, and the rapid movement of this technology from the bench to clinical trials exemplifies how successful this approach can be.

LOOKING BEHIND THE SCENES OF THE HUMAN GENOME



This plot shows the dynamic methylation landscape of the human genome, where the x axis (left) corresponds to the maximal observed methylation change across 24 human cell and tissue types, y is the median total methylation and z is the density of CpG dinucleotides. Credits: Bang Wong and Michael Ziller.

DNA methylation is a biochemical process essential to cell survival in humans and many other organisms. It not only helps regulate gene expression, it also helps silence the repetitive elements in the genome and helps keep the genome in a stable state. When DNA methylation goes awry, it can lead to diseases including cancer.

To understand what happens when DNA methylation goes awry, scientists first must understand the normal variation in DNA methylation within healthy cells. That is the focus of a Common Fund-supported project in the laboratory of Alexander Meissner, Ph.D., in the Department of Stem Cell and Regenerative Biology at Harvard University and the Broad Institute of Harvard and the Massachusetts Institute of Technology. Dr. Meissner and his colleagues used the most advanced sequencing techniques to produce a reference set from 30 different cell and tissue types detailing the range of normal variation in the amount and location of DNA methylation.

This rich set of information provides researchers with new insights into cell function and gene expression beyond what can be discovered by analyzing the genome alone. While the genome sequence is believed to be nearly identical in most different cell types within the same person, the epigenomes from different types of cells can be quite different and this has functional implications for the cells. The genome contains the blueprint for all proteins a cell can possibly make. However, DNA-binding regulatory proteins interact with the epigenome to determine which parts of the genome are used in a given cell and therefore which proteins are actually made by each cell. This refinement of the gene expression process explains how a single genome can instruct the development of many different cell types with unique identities and specialized functions, such as neurons, heart muscle cells and fat cells. Examining the DNA methylation of a cell type is like looking behind the scenes of the genome, Dr. Meissner says, helping researchers detect abnormalities that may play a role in cancer and other diseases.

This DNA methylation reference set, in addition to other epigenomic datasets, is publicly available so that scientists all over the world can look up a gene of interest and learn how it is regulated and expressed in a particular type of cell (http://www.roadmapepigenomics.org/). This information can be used to catalyze individual scientists' research projects for a wide variety of biomedical and disease investigations.

Human Microbiome Project

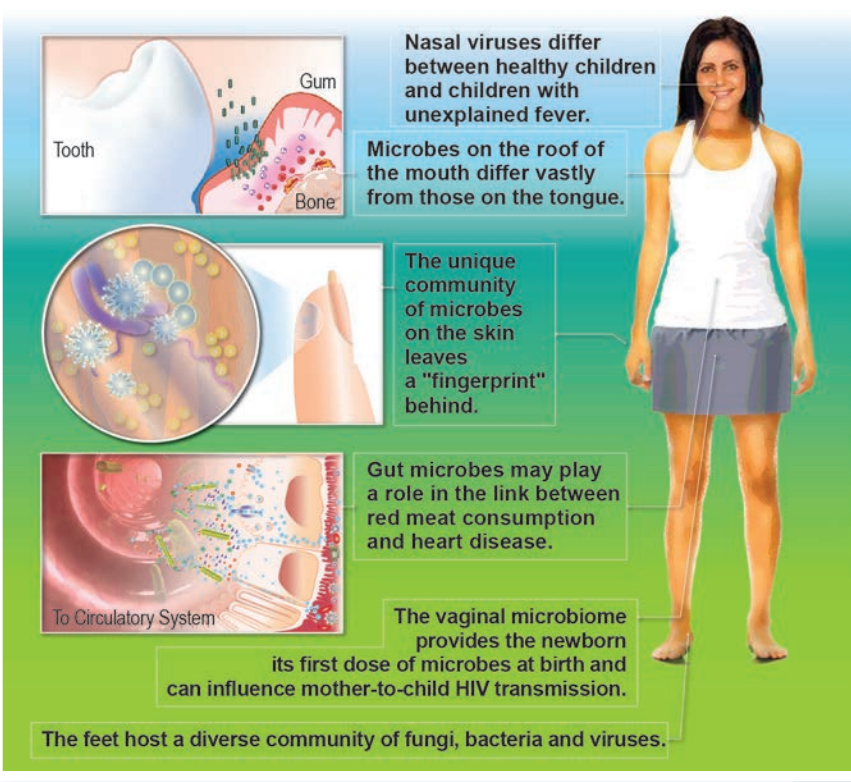
Our bodies are inhabited by trillions of microorganisms living together with our human cells. Yet, because of their small size, this elaborate assortment of bacteria, fungi, and other microbes makes up only 1 to 2 percent of the body's mass. Prior to the launch of the Human Microbiome Project (HMP) in 2007, our relationship with these microbes and their effects on our health were largely unknown.

To better understand the influence of these microbes, which are collectively known as the microbiome, the Common Fund's HMP is examining the immense collection of bacteria, viruses, and fungi that live on and in the human body. The HMP is a natural extension of the Human Genome Project, in that the program aims to decode the microorganisms that make up our total genetic inheritance. While some microbes support human health by helping to digest food and support a healthy immune system, others are involved in preventing conditions such as inflammatory bowel disease, cancer and obesity. The HMP supports pioneering research to uncover how microbial communities influence the health and disease status of their human hosts.

The first phase of the HMP (2007–2012) included seven initiatives focused on analysis of microbial DNA harvested directly from human samples. The analysis of the genetic material from all of the microbes together is referred to as metagenomic analysis, and the complexity of the task required significant investments in computational tools and new experimental methods. Each

HMP initiative focused on a singular purpose that, taken together, offers the research community the tools and resources for studying the role of microbes in human health and disease. The HMP allowed investigators to determine whether a core microbiome exists for all people or whether the microbiome is variable from one person to the next. This analysis uncovered surprising variability, which can be assessed by a surprising method: the community on a particular computer user's keyboard is more similar to the microbes on its user's fingertips than to those on other keyboards, indicating that we all leave microbial "fingerprints" wherever we go. Another initiative, on Ethical, Legal and Societal Implications of Microbiome Research, was created to address the new and unexplored issues that arise from this new area of research. A number of important issues were identified through this initiative, such as whether products designed to manipulate the microbiome might be regulated (such as probiotic foods believed to benefit the body) and whether individuals should begin to consider storing their microbiomes while they are healthy so they could be used to reverse a disease or disorder.

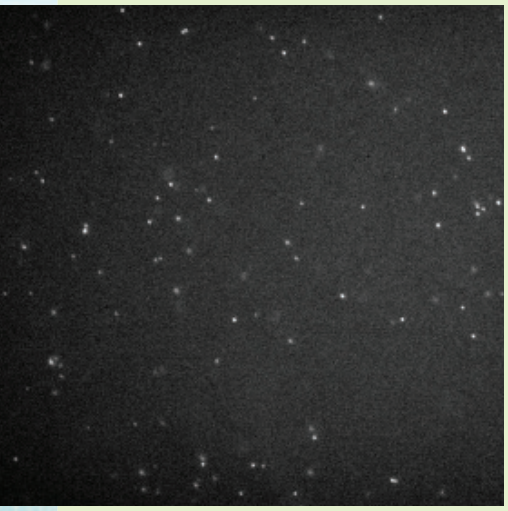
The first phase of the HMP produced important research insights. Most notably, researchers undertook an ambitious examination and analysis of the microbiomes of 300 healthy individuals. Follow-up research on this healthy cohort reveals some surprising relationships between the microbiome and social factors. For example, the gut community of an adult can indicate whether a person was breastfed as a child, and a woman's vaginal microbial community was shown to correlate with her level of education. This work has defined the boundaries of the complete healthy human microbiome and paved the way for numerous studies that are now beginning to examine how changes in the microbiome correlate with disease.



The Human Microbiome Project examines several body sites, increasing knowledge of the impact of microbes in association with both health and disease.

Through the HMP, researchers are also studying the composition and diversity of microbial communities that inhabit many areas of the human body and are evaluating the genetic metabolic potential of these communities. For example, NIH-supported researchers applied metagenomic and metaproteomic approaches to understand better the role of the gut microbiome in Crohn's disease, findings that may aid in the identification of new diagnostic approaches and disease-specific biomarkers. Another success was the publication of a study that showed that changes in the foregut microbiome are associated with precursors to esophageal cancer, a type of cancer that has increased six-fold in the past 30 years. HMP researchers showed that gut microbes in premature infants can cause bloodstream infections or sepsis, a finding that could encourage improved hygiene practices and minimize the risk to infants. The HMP has supported a number of other studies of childhood disorders, including pediatric abdominal pain, intestinal inflammation and a severe condition in premature infants in which the intestine dies, all of which are leading to a better understanding of the underlying mechanisms of disease pathogenesis, and thereby may aid in the identification of novel therapeutics for these diseases.

The current phase of the HMP (2013–2015) is focused on creating a combined dataset of microbiome and host properties. Researchers are working to generate microbiome taxonomic, metagenomic and functional data and correlate them with microbiome-associated diseases. The long-term objective of this initiative is to develop datasets and tools that the community can use to evaluate which biological properties of the microbiome and the host will yield important new insights in understanding human health and disease.



Viral particles purified from the human gut and stained with a DNA stain.

EXPLORING THE "WILD WEST" OF VIRUSES IN THE GUT

There are more than 100 billion bacteria in each gram of fecal matter in the gut. But as huge a number as that is, there are even more viruses—called "bacteriophages"—that prey on those gut bacteria.

Frederic Bushman, Ph.D., calls this the "Wild West" of the microbiome. His work at the University of Pennsylvania, supported by the Common Fund, focuses on deep sequencing of the DNA of these viruses to discover the makeup of this viral population (called the virome) and how it relates to gut bacteria and human health. In one study of the viral population of one person's intestinal tract, Dr. Bushman found that the virome makeup was 80 percent stable over a 2.5-year period. But some of those viruses changed significantly—almost to the point of becoming a new species. Dr. Bushman believes that the unique makeup of each person's virome may affect how the body responds to disease as well as drugs and other treatments used to treat disease.

Dr. Bushman is excited about this new area of science, but he is also continuing his investigations into diet and gut bacteria in Crohn's disease and other inflammatory bowel diseases, which affect 1.4 million people in the United States. One line of inquiry aims at optimizing diet therapy for children with inflammatory bowel disease by looking at the makeup of the bacteria in the gut.

The Human Microbiome Project brings together scientists from a variety of disciplines—bacteriology, virology and parasitology—and links a range of diseases, from obesity to digestive diseases to skin conditions and heart disease. As part of this project, the tools and techniques that scientists like Dr. Bushman are developing will benefit future medical research in countless ways.

DIVERSITY OF THE MICROBIOTA

Several studies in mice have found a connection between the makeup of the bacterial community in the gut and the incidence of obesity in mice. However, subsequent studies in humans did not find the same relationship. Claire M. Fraser, Ph.D., director of the Institute for Genome Sciences at the University of Maryland School of Medicine, wondered if the diversity of cultures, diets and ethnicities among typical study populations might account for the inconsistent findings. Answering the request for proposals issued by the Human Microbiome Project in 2008, Dr. Fraser proposed to study the gut microbiota in Old Order Amish, a population of adults near Lancaster County, Pennsylvania, in which dietary habits, lifestyle and genetic makeup were quite similar. She compared the microbiota in 310 lean, overweight and obese adults. Her findings surprised her.

While she did not find any consistent, meaningful difference in the overall composition of the gut microbiota in the three groups, she did see a tremendous amount of individual variability. When she delved deeper, she found striking differences in those obese subjects who also had signs of metabolic syndrome, a group of risk factors associated with heart disease, diabetes and stroke that is on the rise in the United States. She found that subjects with metabolic syndrome had very different concentrations of key phyla, including very low amounts of the bacteria that help control inflammation—perhaps offering a clue to the diagnosis, treatment and even prevention of the dangerous syndrome.

Dr. Fraser's next step is to explore possible dietary interventions to move the microbiota to a more healthful state and perhaps reduce the risk of metabolic syndrome. She credits the Human Microbiome Project for seeing the importance of this area of research and giving interested scientists the support they needed to jump-start the exploration.

Genotype-Tissue Expression

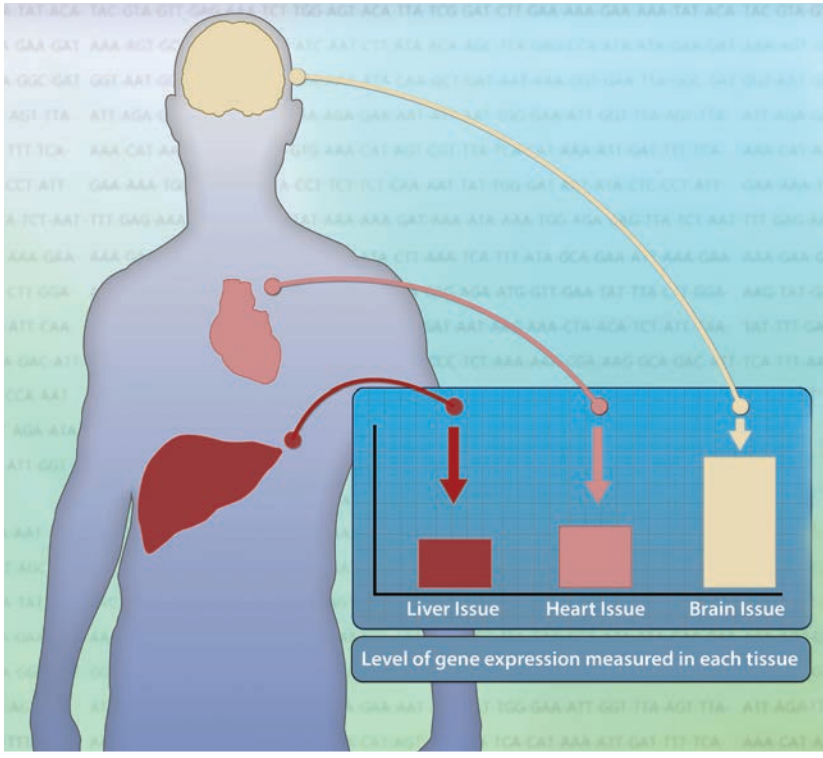
Genes are the packets of information in the cells of our bodies that parents pass along to their children. They exist as small parts of much longer chains of DNA that make up chromosomes. Certain changes in genes can increase a person's risk of developing common diseases like cancer, heart disease, diabetes and Alzheimer's disease.

However, it is becoming increasingly clear that DNA changes with important consequences for health may lie far outside of the genes themselves and can instead influence the way genes are expressed and regulated. Though we know this to be the case, we lack the data to correlate specific changes in DNA with its downstream consequences on gene expression.

The Common Fund's Genotype-Tissue Expression (GTEx) program is building a collection of high-quality human tissue samples, providing DNA sequence information about these samples and establishing profiles of gene expression in each tissue. The goal is to provide the scientific community with a resource to study the relationship between variation in DNA sequences and the way genes are regulated. Scientists in academic, government and commercial laboratories around the world can access the data from GTEx to determine whether any DNA sequence of interest has been found to be variable in the GTEx data set and whether variability in that DNA then correlates with variability in gene expression in one or more tissues. Researchers are also able to acquire tissue samples to help them study the role of genes and gene regulation in common diseases.

The GTEx program relies on donations of tissues from members of the public. The family of a deceased person can donate their loved one's tissues to the GTEx program. People can also bequest their organs to the GTEx program when they pass away. As part of the collection process, the GTEx program uses state-of-the-art technologies to set a very high standard for uniform tissue sample collection and handling. This exacting process ensures that the valuable GTEx resource is maintained properly and yields the highest quality data.

Currently, the program has more than 11,000 samples of human tissue from more than 600 donors. Donor enrollment, sample collection and analysis are ongoing toward a goal of 900 post-mortem donors by the end of 2015. All donors are characterized for genetic variation through DNA sequencing of a blood sample and all tissues of sufficient quality undergo gene expression analysis. In addition, to further characterize gene activity in tissues, several other tests will be conducted to see if the information stored in the DNA is being used to make specific proteins, the DNA has certain chemical modifications that affect the way its information is used, the configuration of the DNA in certain areas of the genome is different than in others and the two copies of each gene—one inherited from either parent—are being used equally. The GTEx resource will be a powerful tool to help unravel the complex patterns of genetic variation and gene regulation across a wide range of human tissues.

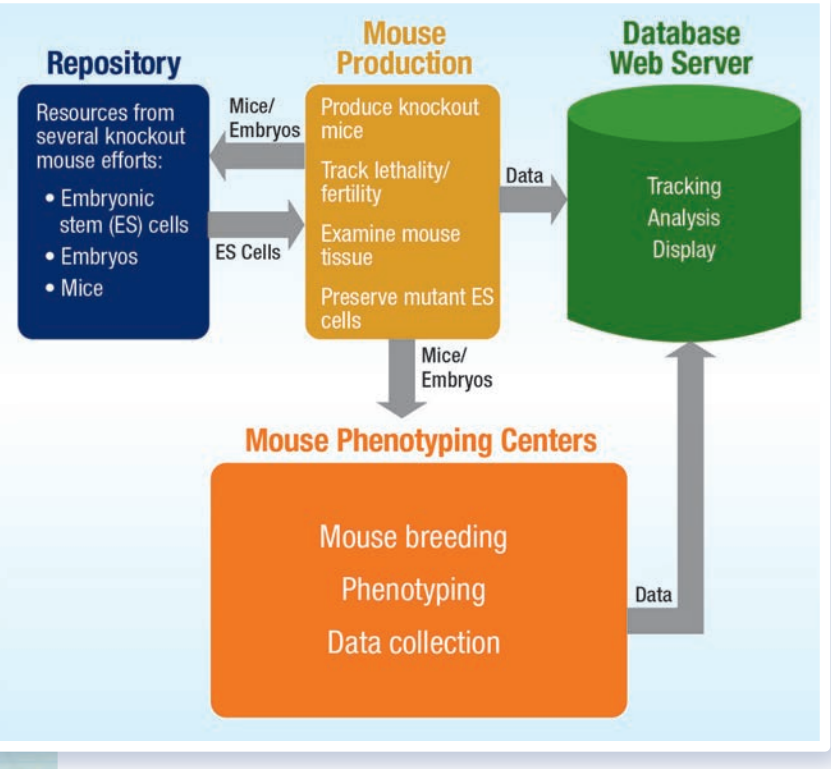


Tissue samples from many organs, including liver, heart and brain, are donated to the GTEx program. GTEx scientists test for DNA sequence variation among tissue donors and see which genes are active in each tissue type.

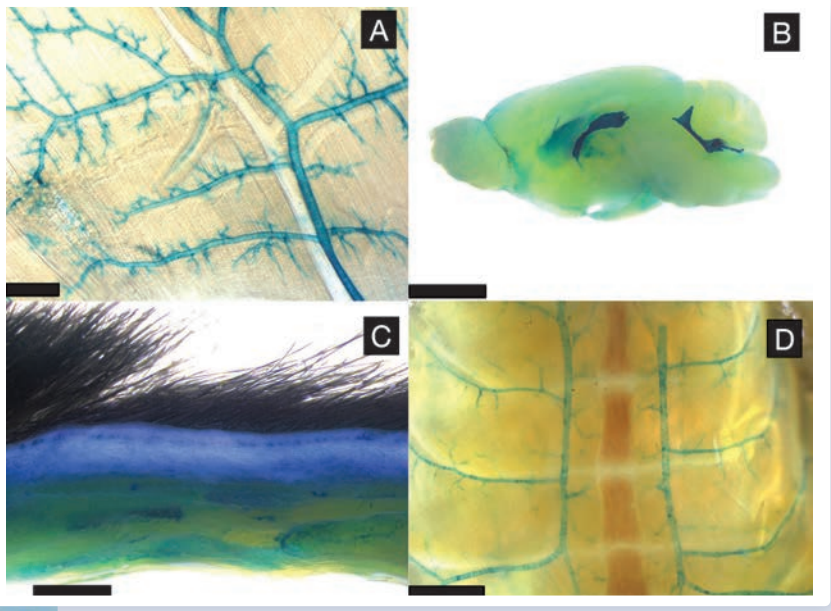
The GTEx program also includes a study to explore the effectiveness of the GTEx donor consent process. Researchers for the program reach out to families who are donating their deceased loved-one's tissues to make sure the process works for them, getting them the information they need to make an informed decision about donation. The researchers meet with panels of people who have decided to, and not to, donate their loved-one's tissues. They hope to understand the attitudes, beliefs and feelings of the public surrounding the GTEx program and the way program staff interact with and obtain consent from families of donors and potential donors.

Knockout Mouse Phenotyping

The laboratory mouse has been considered the premiere experimental model of human biology and disease since 1902, when it was first used to demonstrate how genetic traits could be transferred from parents to offspring. Modern-day scientists often use laboratory mice with disrupted genes, called knockout mice, to gain insight into many human diseases.



KOMP2 program structure



Mouse tissues showing gene expression in blue: (A) diaphragm showing G-protein coupled receptor 20 (scale bar 0.5mm); (B) brain showing interleukin 6 receptor alpha (scale bar 3mm); (C) skin showing proline arginine-rich end leucine-rich repeat (scale bar 1mm); (D) ribcage showing melanoma cell adhesion molecule (scale bar 2mm).

The Common Fund's Knockout Mouse Phenotyping program, or KOMP2, is cofunded by 17 NIH Institutes and Centers to phenotype mouse mutants: to analyze the functional impact of genetic mutations. In the long term, this program aims to enable NIH-wide research by providing standardized phenotypic data and well-characterized mouse strains for every gene in the mouse genome. Such information will be valuable for the discovery of the genetic causes of human diseases and will aid efforts to identify new drug targets.

Researchers supported by KOMP2 work with members of the International Mouse Phenotype Consortium (IMPC) to generate thousands of different knockout mice that are put through a battery of clinical phenotype tests. A phenotype includes biological information about appearance, behavior and other measurable physical, metabolic and biochemical characteristics. Each mouse undergoes the same standard analysis so that the results can be compared against all of the mice tested. KOMP2 assays encompass a wide variety of biological systems, including neurological, cardiovascular, immune, pulmonary and reproductive systems.

KOMP2 is capitalizing on cutting-edge technology to generate knockout mice efficiently and effectively. In 2014, KOMP2 will launch a pilot project to test the use of Clustered Regularly Interspaced Short Palindromic Repeats, or CRISPR, technology to generate knockout mice. CRISPR harnesses a DNA repair system found in bacteria to allow researchers to make precise changes to the DNA of all kinds of organisms, including mice, and therefore easily generate genetically modified animals. This technology has the potential to greatly accelerate the pipeline for producing knockout mice, enabling KOMP2 to generate phenotypic data for a genome-wide collection of knockout mice in a much shorter timeframe.

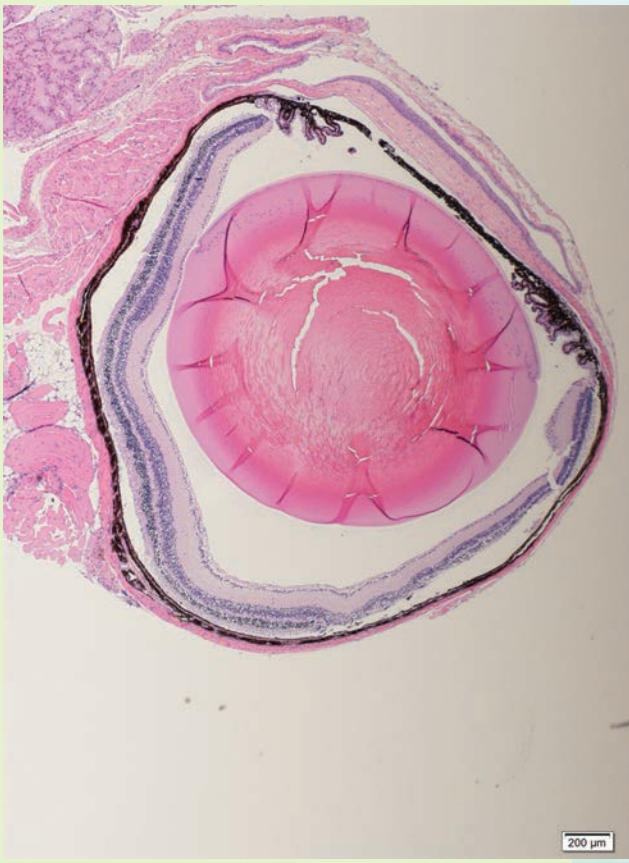
In addition to mouse production and phenotyping centers, KOMP2 also supports a data coordination center and database to track progress of the project and coordinate efforts between KOMP2 and IMPC researchers. The center is leading the development of phenotypic data standardization, ensuring that data from the different phenotyping centers are uniformly high quality and comparable. This data coordination center provides the entire research community access to the phenotyping data through an integrated website (http://www.mousephenotype.org/). Data from KOMP2 are being placed in this public database for use by members of the scientific community to accelerate their own investigator-initiated research.

RESEARCH USING KNOCKOUT MICE LEADS TO DISCOVERY OF LINK BETWEEN BLOOD PRESSURE AND BLINDNESS

Macular degeneration is the leading cause of vision loss for those age 55 and older in the United States. It is caused by the deterioration of the central portion of the retina, the layer at the back of the eye that contains light-sensitive cells called "photoreceptors." Understanding the genes that are important for keeping these photoreceptors healthy may help lead to discoveries about how to prevent or even reverse this debilitating condition. Novel research using laboratory animals developed by the Common Fund's Knockout Mouse Phenotyping program (KOMP2) is leading to a new understanding of this common disease and how it may be linked to another common condition: high blood pressure.

The renin angiotensin system is a hormonal system that regulates blood pressure in the body. Ala Moshiri, M.D., Ph.D., a researcher at the University of California, Davis, examined the eyes of knockout mice missing a gene critical to the renin angiotensin system. Dr. Moshiri found that without a normally functioning renin angiotensin system, the photoreceptors rapidly deteriorated, compromising eyesight.

Although still in early stages, Dr. Moshiri's work may have important implications for the millions of Americans with macular degeneration and/or high blood pressure. This research may also provide insight into other diseases and conditions such as diabetes, which leads to increased risk for both high blood pressure and damage to the retina from high levels of sugar in the blood.



Tissue sections from a mouse eye with a mutation in a gene controlling the renin angiotensin system. The lens, retina, and surrounding ocular tissues are visible. The outer retinal layers show degeneration of the photoreceptor cells (rods and cones).

Library of Integrated Network-Based Cellular Signatures

The basic components of biological systems—genes, proteins and other molecules—work together in a highly orchestrated manner. Understanding how these interconnected biological processes are established during development, maintained in health, and how they change due to genetic and environmental stresses or aging to cause disease, is challenging. However, this knowledge is essential to developing new and better therapies to return these disrupted processes back to a healthy state.

To achieve this goal, the Common Fund's Library of Integrated Network-Based Cellular Signatures (LINCS) program aims to identify patterns of cellular responses, such as changes in gene and protein expression that describe the response of different cell types to various stress signals. The underlying premise of the LINCS program is that disrupting any one of the many steps of a given biological process will cause changes in the molecular and cellular characteristics, behavior and/or function of the cell that are similar to changes induced by disrupting other steps of the same process. Comparing the patterns of the cells' responses to different stress signals can provide clues about the underlying mechanisms

NIH LINCS PROGRAM

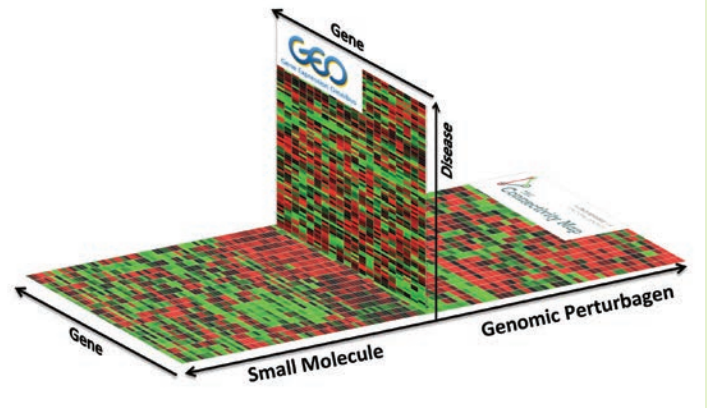
involved in disease processes. The knowledge can also help researchers identify chemicals that affect a given cellular pathway and may therefore have therapeutic potential.

The pilot phase of the program began in 2010. Among its accomplishments were the creation of datasets and common data standards that could be used by the scientific community and the development of new and cost-effective assays for measuring cellular responses to stress conditions. The new LINCS portal makes it easy to take advantage of the data, by providing details about the experiments conducted as well as links to participating sites and tools that can be used for analyzing the data. By making the data opening available, the LINCS program enables its use by the broader scientific community, particularly institutions not generally equipped to manage large datasets, to address a range of basic research questions and to identify biological targets that hold promise for new disease therapies.

In 2014, the LINCS program will build upon what was learned from the pilot phase. This new stage of the program will support an expansion of the types of cellular responses to be measured and the range of cell types to be investigated. LINCS will continue and expand uniform data annotation and accessibility, develop methods for unified access to the diverse datatypes that will be generated, coordinate outreach activities and provide training. The LINCS program is also coordinating its efforts with the trans-NIH Big Data to Knowledge (BD2K) program. As biomedical tools and technologies rapidly improve, researchers are producing and analyzing an ever-expanding amount of complex biological data that describe human cellular responses. The LINCS and BD2K programs together will facilitate broad use of biological data by changing the way large amounts of data are shared, accessed and analyzed within the biomedical research community.

LOOKING FOR STORIES IN DATA

With degrees in medicine, computer science and medical informatics, Atul Butte. M.D., Ph.D., has the background and knowledge to comb and combine data in search of stories that can improve human health. In his lab at the Stanford University School of Medicine, Dr. Butte collects information about how diseases—particularly those that affect a large number of people, such as diabetes, cancer and inflammatory bowel disease—affect the cells in the body. The idea is to connect that information with data about the effects and actions of already existing drugs to see if there is a match.



Schematic of how two big datasets can be intersected. By linking these datasets, new drugs could be found to possibly treat the effects of diseases. Figure credit: Bin Chen, Ph.D., and Atul Butte, M.D., Ph.D.

That's where the LINCS dataset comes in. This Common Fund-supported project generates data on how cells respond to different drugs. By bringing together the massive amounts of data in Dr. Butte's lab with the data in the LINCS dataset, Dr. Butte and his colleagues can identify drugs that might reverse or prevent the effects of a disease. Then, based on those computational predictions, they design laboratory studies to see how the match plays out in real life.

Because the computer creates its predictions based on numbers alone, it isn't prejudiced by logic or presumptions. That can lead to some unlikely matches—ones that may bring new hope to real patients. One of these unlikely matches may well lead to a storybook ending: the computer identified an antidepressant drug that affected a receptor on a particular type of cancer cell. Further investigations showed that the drug indeed holds promise as a new therapy for small cell lung cancer. Early-stage clinical trials are under way to demonstrate whether the drug is an effective cancer therapy.

The Science of Behavior Change

Poor health behaviors, including smoking, alcohol and drug abuse, inactivity and poor diet, account for almost 40 percent of the risk associated with preventable premature deaths in the United States. Although these dangers are well known, and although many people sincerely wish to improve, we currently have very few behavior change interventions that are effective for most people over the long term.

The Common Fund's Science of Behavior Change (SOBC) program aims to improve our understanding of human behavior change across a broad range of health-related behaviors. The program supports research that integrates basic and translational science and cuts across disciplines of cognitive and affective neuroscience, neuroeconomics, behavioral genetics and behavioral economics. The program seeks to establish the groundwork for a unified science for behavior change that capitalizes on both the emerging basic science and the progress already made in the design of behavioral interventions in specific disease areas.

In 2010, the SOBC program funded 10 research groups to address the mechanisms of behavior change in both laboratory and real-world settings. The research projects address critical areas that include:

- Relationship between emotions and inflammation
- Improvement of economic incentives for smoking cessation
- Influence of poverty-induced stress on abnormal impulsivity that leads to unhealthy behavior
- Development of genetically informed exercise interventions for adolescents
- Relationship of stressful environments and weight gain in toddlers
- Influence of social networking sites on substance abuse among college students

In 2012, the program provided administrative support to seven ongoing behavior change intervention trials to incorporate research on basic mechanisms into existing clinical studies. Over time, it has become clear that the SOBC projects and most behavior change interventions in general can be seen as attempting to influence targets in four broad classes: (1) stress and stress reactivity; (2) interpersonal factors, (3) the environment including social factors, and (4) self-regulation processes within the individual.

The Science of Behavior Change program studies both negative (stress, smoking) and positive (healthy eating, exercise) behaviors impacting health and well-being.

The SOBC program has also sponsored several meetings aimed at breaking down disciplinary boundaries, increasing collaborations and developing common mechanisms to guide behavior and behavior change. One example is a joint grantees meeting of researchers funded by SOBC and those studying basic mechanisms of habit formation, who were funded by a Request for Applications released by the Basic Behavioral and Social Science Opportunity Network, a trans-NIH program designed to encourage more basic behavioral and social science research. Meetings like this one have provided an opportunity to explore areas of common interest and promote cross-fertilization between more basic and more applied research efforts.

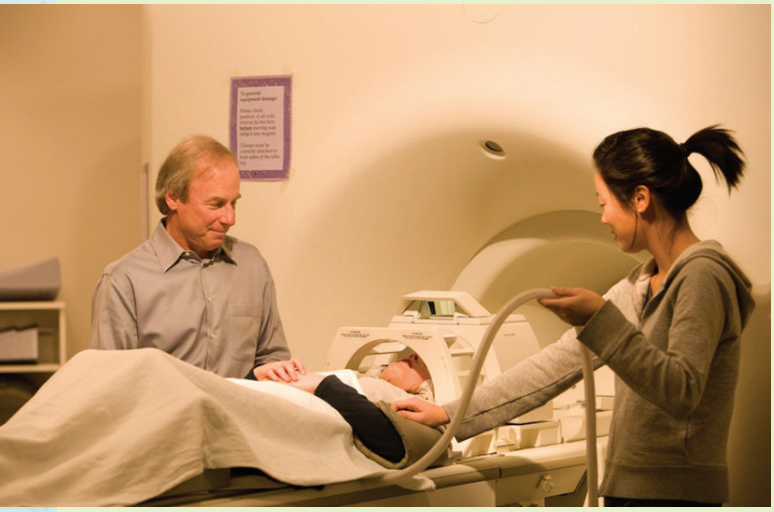
Other SOBC meetings have fostered important discussions on ways to integrate basic and clinical research and identify gaps and opportunities in the field of behavior change. For example, at the program's annual meeting in 2013, grantees presented research from a wide range of disciplines including psychology, neurology, genetics, psychiatry and social science. Themes evident throughout the presentations included the identification of underlying basic mechanisms and the integration of basic

research methods into clinical trials. In addition to investigator presentations, grantees also had the opportunity to engage in group discussions focused on the role of self-regulation in behavior change research, methodology and basic research.

Overall, the activities of SOBC are creating a new climate in which basic researchers tackle behavior change questions that are relevant to, and studied within, the clinical context of intervention development research. The projects funded by the SOBC program bridge work done in the laboratory and the field, and help give investigators a fresh perspective on how physiology, neurobiology and genetics affect human social and psychological behaviors that place a heavy burden on society. The research will improve our understanding of human motivation and maintenance of behavior change across multiple diseases and conditions, and investigators will use this knowledge to develop more effective and economical behavioral interventions.

BRAIN TRAINING TO PREVENT DEPRESSION

Depression is an illness that is associated with rather than made up of a number of problematic behaviors. Can changing these behaviors change the course of the illness?



A young daughter of a depressed mother is being prepared to participate in a neuroimaging session. Once she enters the scanner, her patterns of brain activation will be assessed and analyzed in order to examine neural mechanisms that might underlie the positive effects of attentional-bias training.

In a previous study of young girls at familial risk for depression, Ian H. Gotlib, Ph.D., professor of psychology and director of the Stanford Mood and Anxiety Disorders Laboratory, found that even before they experienced an episode of depression, the girls were already processing information in the same way that depressed adults do: they automatically focused on negative aspects of the information and of their environment. Dr. Gotlib wondered if he could prevent or at least delay the onset of depression in children at risk for this disorder by training them to attend to positive instead of negative material.

Dr. Gotlib used an intervention called "attention-bias training" in which girls are trained over time to attend to positive faces on a computer screen rather than to negative faces. While this intervention has been used with some success to treat depression, anxiety and eating disorders, Dr. Gotlib was the first to examine its potential as a preventive measure.

In the supplement study funded by the Common Fund Science of Behavior Change program, young girls at familial risk for depression underwent an fMRI scan before and after the attention-bias training in order to understand the brain mechanisms that underlie the change brought about by the training, that is, to understand how the training works at the brain level. Dr. Gotlib believes that the intervention works by teaching the children to inhibit their processing of negative information or stimuli, and by reducing rumination, the self-referential, repetitive thinking that is a hallmark of depression.

The researchers are still analyzing data, but they have already seen that following the training, the girls who received "real" attention-bias training showed less amygdala activation to sad faces in the scanner and greater activation in the prefrontal cortex than did the girls who received "sham" training. These findings indicate that attention-bias training achieves its beneficial effects by reducing limbic activation to negative stimuli and increasing activation in the control region of the brain.

Dr. Gotlib hopes that understanding the brain mechanism that underlies the training may lead to other, perhaps even more effective, ways of targeting brain regions to change behaviors that affect health, providing new hope for people who struggle with depression, anxiety, addiction and other behavior-based disorders.

Metabolomics

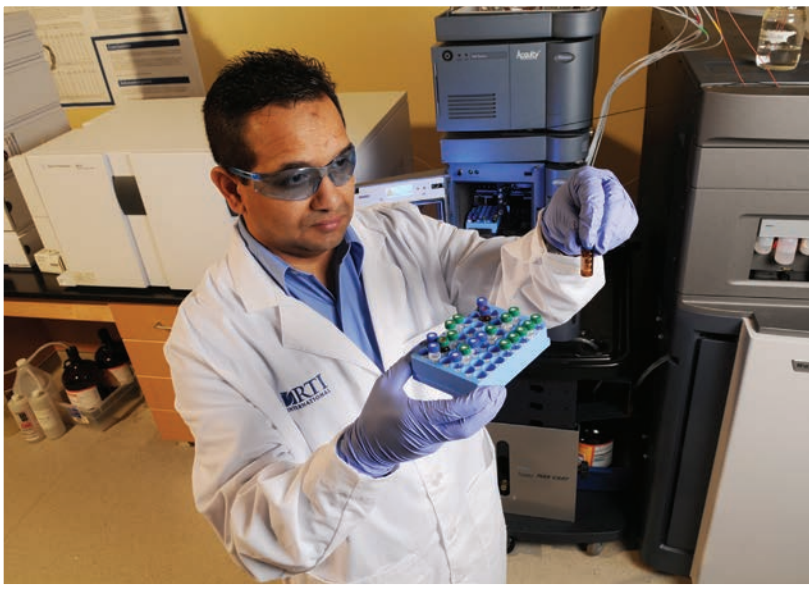
Metabolomics is the study of small molecules called metabolites. Metabolites are produced or consumed in all the chemical reactions that take place in the body to sustain life. The sum of all metabolites at any given moment—the metabolome—is a chemical readout of the state of the body, and it provides a wealth of information about nutrition, infection, health and disease status.

The Common Fund's Metabolomics program, launched in 2012, aims to increase the national capacity to conduct metabolomics research. The program supports Regional Comprehensive Metabolomics Resource Cores located at six research institutions across the nation. The Resource Cores provide metabolomics services for the community and develop cutting-edge technologies to enhance the sensitivity and speed with which specific elements of the metabolome can be identified and quantified. The Metabolomics program also funds innovative research by individual scientists to address the particularly difficult technological barriers that keep metabolomics data from being used more broadly.

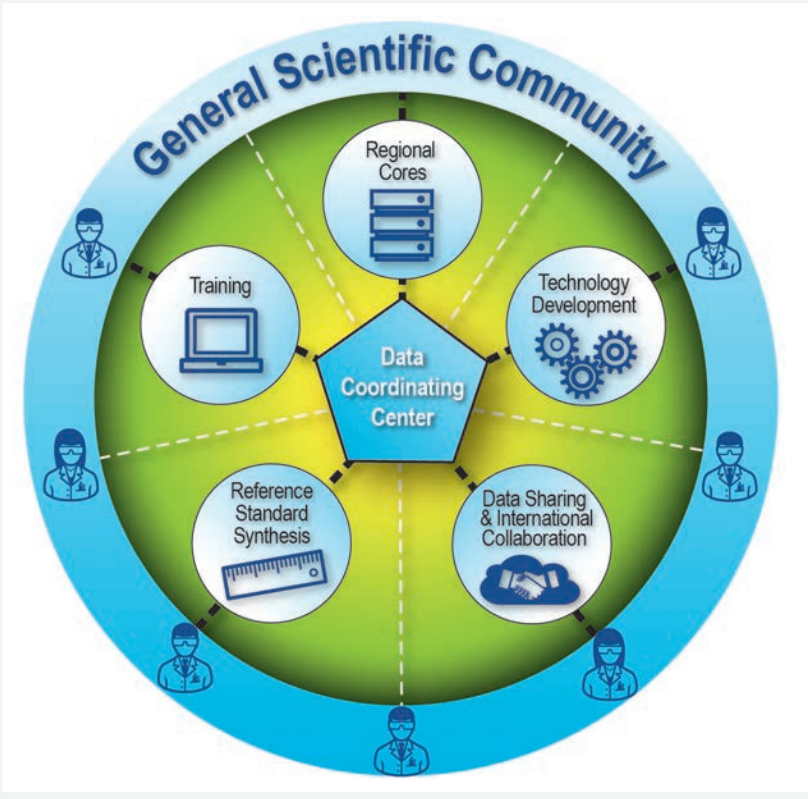
Cutting-edge technologies are of little use if only a few scientists understand them. A substantial goal of the Metabolomics program is to provide scientists with training and mentoring opportunities to learn skills in this emerging area of scientific research. The Resource Cores host a variety of training workshops as well as collaborative projects for researchers who want to incorporate metabolomics into their research. At individual research institutions, the Metabolomics program supports researchers who are developing new ways to conduct metabolomics training, and young investigators who are learning metabolomics techniques under the guidance of an experienced mentor.

In addition, the Common Fund's Metabolomics program is creating a library of synthesized metabolites that will be made available to the scientific community. Synthesized metabolites function as research standards and are critical for confirming the identity of previously unknown components in biological samples such as blood or urine. Studies of metabolites will improve our understanding of disease processes, reveal new biomarkers of disease and provide new ways of monitoring therapeutic outcomes.

The Metabolomics program's Data Repository and Coordinating Center (DRCC) facilitates data sharing and collaboration among scientists doing metabolomics research, and serves as a central source of information about all Metabolomics program activities. Researchers from around the world can visit the website curated by the DRCC to learn more about metabolomics techniques and tools, as well as upcoming training sessions and conferences organized by program participants



A researcher from the RTI Eastern Regional Comprehensive Metabolomics Resource Core. Courtesy of RTI International.



The Metabolomics program comprises five initiatives and a Data Coordinating Center that work together to increase the national capacity in metabolomics via research support, training, tool development and collaboration.

(http://www.metabolomicsworkbench.org). Researchers can even nominate metabolites they want to use as standards in their research for synthesis.

The Metabolomics program's early achievements are already contributing to the field of metabolomics. Researchers funded by the Metabolomics Technology Development initiative are addressing challenges in equipment, sample preparation and data analysis that prevent widespread use of metabolomics techniques. The NIH leaders of the program and the funded investigators are working together and with the international metabolomics community to develop international data standards and to prioritize metabolites for inclusion in the metabolite library. International collaboration and coordination typify Common Fund programs as they leverage worldwide investments and ensure that Common Fund investments are not duplicative of other efforts.

The training efforts of the Metabolomics program are also already paying dividends. Putting her Metabolomics program training grant to good use, one young investigator is studying how antibiotic treatment induces changes in the gut microbial community and in the metabolome of mice susceptible to infection by *Clostridium difficile*, a bacterium that can cause symptoms ranging from diarrhea to life-threatening inflammation of the colon.[1] In addition, researchers at the Regional Comprehensive Metabolomics Resource Cores have conducted multiple studies demonstrating the utility of metabolomics in investigating and perhaps one day diagnosing and treating, human disease.

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[1] Theriot, C.M., Koenigsknecht, M.J., Carlson, P.E., Jr., Hatton, G.E., Nelson, A.M., Huffnagle, G.B., et al. (2014). Antibiotic-induced shifts in the mouse gut microbiome and metabolome increase susceptibility to *Clostridium difficile* infection. *Nature Communications 5*, 3114.

INTERNATIONAL COLLABORATION ON METABOLOMICS

All Common Fund programs are meant to catalyze biomedical research with a strategic, short-term influx of funds to address key roadblocks in research or to capitalize on emerging scientific opportunities. For areas of research that are still maturing, creating a policy framework for data sharing and standardization is essential to the sustained growth and development of the field. This is especially true for fields like metabolomics that have prompted significant international interest and investment. In fiscal year 2010, an estimated $225 million were invested worldwide in metabolomics. Data sharing and standardization policies help to ensure that all parties working on metabolomics avoid unnecessary duplication and that scientific progress moves as quickly as possible.

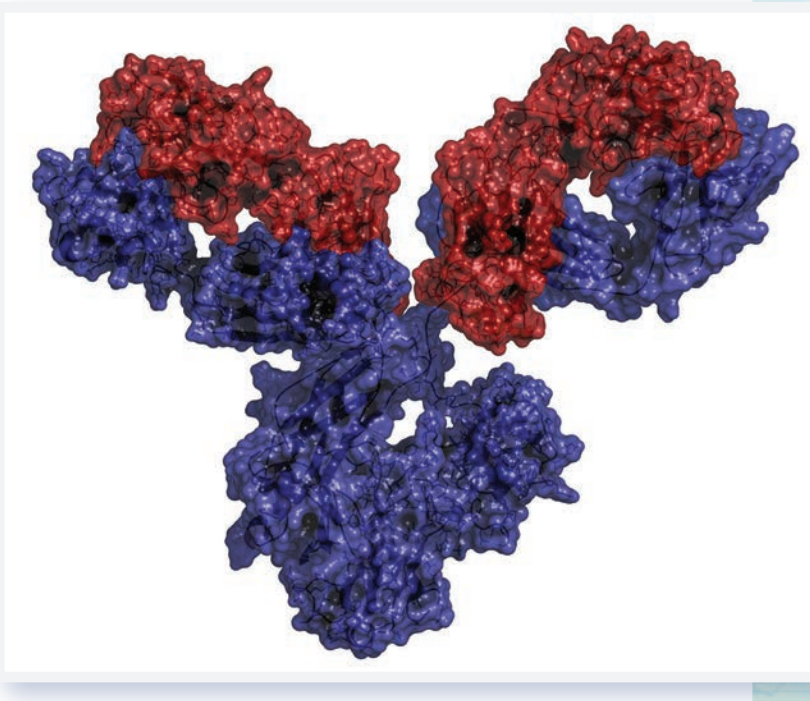
In April 2014, representatives from Australia, Canada, Germany, Japan, the Netherlands and the United States—including members of the Common Fund Metabolomics program—met to discuss an international data exchange in metabolomics. The participants agreed to create a database that would provide a network of coordinated and freely accessible metabolomics data and reference standards collected from repositories around the world. Once operational, scientists will have unprecedented access to existing metabolomics data from other scientists that could significantly accelerate their own work or lead to new, productive collaborations. Scientists could even conduct analyses on groups of datasets from multiple researchers' experiments that collectively yield insights that could not have been obtained from a single experiment.

The field of metabolomics shows great promise in the creation of new, minimally invasive diagnostics. Progress will be accelerated with the ability to compare datasets against each other and against a carefully curated set of reference standards. The formation of a new international metabolomics database is an exciting step toward making this possible for researchers around the world.

Protein Capture Reagents

Proteins are the functional workhorses of all cells. They convert food into energy, maintain the cell's shape, coordinate communication with neighboring cells and recognize foreign invaders. The presence or absence of certain proteins under certain conditions can even be a sign of disease, and most drugs available today in the market target proteins. The study of proteins is therefore foundational to biomedicine, but investigators often lack the tools needed to isolate and analyze these molecules.

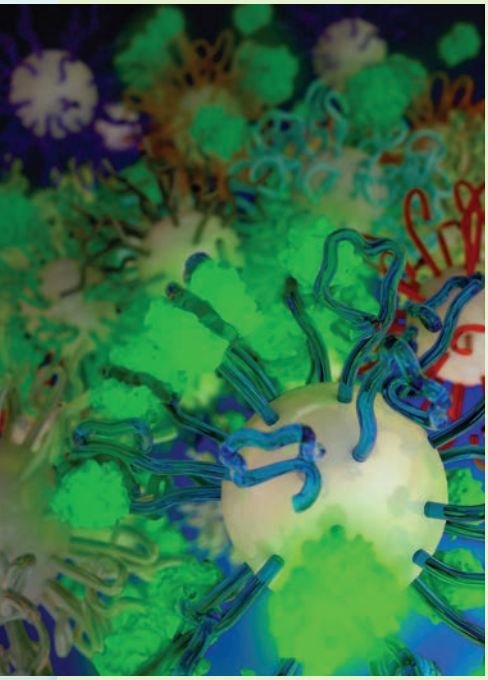
Researchers need tools and resources to study how proteins interact with each other and with other cellular components to carry out life at the molecular level. Molecules called "protein capture" or "affinity" reagents are useful tools for studying proteins because they can selectively attach to proteins of interest. This characteristic feature of being selective makes affinity reagents a common tool used for the analysis of proteins within cells or tissues and for the isolation of proteins from complex mixtures. However, these reagents are costly and difficult to develop, and reliable reagents are not available for many proteins of interest. The Common Fund's Protein Capture Reagents program (PCRP) is designed to address this challenge by developing high quality reagents for a defined set of proteins using existing technologies and to develop new methods and technologies for protein capture reagents that may enable reagents to be developed for the entire set of human proteins. This is a high-risk endeavor but will transform the analysis of protein function if a proof of principle can be established.



The Protein Capture Reagents program seeks to supplant conventional antibodies, such as the one shown, with affordable, reliable, and renewable reagents for biomedical research and clinical applications.

The reagents that are being developed by the PCRP support a wide range of fundamental research and clinical applications. These applications let researchers isolate single proteins from mixtures or keep track of them inside complex cellular environments. One of the program's achievements is the launch of a new data portal where researchers can find information about publicly available reagents created and validated by program researchers. Currently, more than 250 affinity reagents that recognize human transcription factors are available through the data portal with new reagents being added regularly.

Independent researchers funded by the PCRP are also working to create the affinity reagents of the future. Some groups are working to make production of existing affinity reagents like antibodies more efficient. Other groups are working on new types of affinity reagents that are much more straightforward to produce and distribute, and can be screened quickly for their ability to recognize a protein of interest. One group is even working on affinity reagents made of DNA molecules that can be used for continuous and real-time monitoring of drugs or other molecules in the bloodstream, opening new frontiers for the use of these affinity reagents. If these novel technologies are robust and scalable to high throughput, the long-term goal of developing reagents against additional classes of proteins may be achieved.



Fluorescently labeled proteins captured by aptamers on synthetic particles. Credit: Peter Allen, UC-Santa Barbara.

ALTERNATIVE AFFINITY REAGENT TECHNOLOGY

Inside our cells, DNA holds our genetic information. In the hands of researchers, DNA can have many other uses. Tiny chains of DNA can be made to fold into special 3-dimensional structures. These folded chains of DNA, called "aptamers," target and bind to specific biological molecules in complex mixtures. Researchers are developing aptamers in hopes that they will be a cheaper and more efficient alternative to antibody molecules in science and medicine. Antibodies are used for a number of medical diagnostics and therapies. But antibodies are expensive to make and difficult to precisely replicate in every batch. In contrast, aptamers are relatively easy to make and can be faithfully copied for every batch.

The capabilities of aptamers have prompted researchers to develop them as "affinity reagents" for tagging and isolating specific biological molecules and cells. Researchers screen large collections of aptamers and look for interactions with target molecules. Once researchers pinpoint aptamers within a collection that can bind to a target molecule, they put those aptamers through additional rounds of testing and optimization. At the end, researchers obtain aptamers that specifically bind to the target molecule with high affinity.

To improve and accelerate the aptamer selection and optimization process, a team led by Dr. Tom Soh at the University of California, Santa Barbara, a Protein Capture Reagents program grantee, has developed two advanced methods called Quantitative Parallel Aptamer Selection System (QPASS) and Particle Display (PD).[1] These methods cut down on the number of rounds of screening needed to find the best aptamers by enabling researchers to test millions of aptamers simultaneously. The efficiency of these methods could make aptamers a feasible and economical reagent for biomedical researchers who want to isolate and study specific molecules.

QPASS could also help researchers make innovative medical devices based on aptamers. Dr. Soh's research team recently has developed a tiny instrument that uses aptamers to recognize particular drug molecules.[2] The instrument has been used to continuously measure the amount of drug molecules in the bloodstream of animals. Monitoring the signals from the instrument over time tells researchers how much of a drug was present at any time during of the course of the experiment. Thus, the work of Dr. Soh is helping achieve the ambitious goal of the Protein Capture Reagents program to make affinity reagents cheaply, efficiently and reproducibly.

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[1] Cho, M., Soo, O.S., Nie, J., Stewart, R., Eisenstein, M., Chambers, J., et al. (2013). Quantitative selection and parallel characterization of aptamers. *Proceedings of the National Academy of Sciences, 110*(46), 18460–18465.

[2] Ferguson, B.S., Hoggarth, D.A., Maliniak, D., Ploense, K., White, R.J., Woodward, N., et al. (2013). Real-time, aptamer-based tracking of circulating therapeutic agents in living animals. *Science Translational Medicine, 5*(213), 213ra165.

Single Cell Analysis

Scientists typically perform biological experiments on groups of cells under the assumption that all cells of a particular type are identical. However, recent evidence from studies of single cells reveals that this assumption is incorrect. Individual cells within the same population may differ dramatically, and these differences can have important consequences for the health and function of the entire population. But scientists do not have the means to probe individual cells routinely, especially in their natural setting in the tissue or organism. Thus, new single cell analysis methods are needed to understand cellular variation in the natural environment, thereby uncovering fundamental new biological principles and improving the detection and treatment of disease.

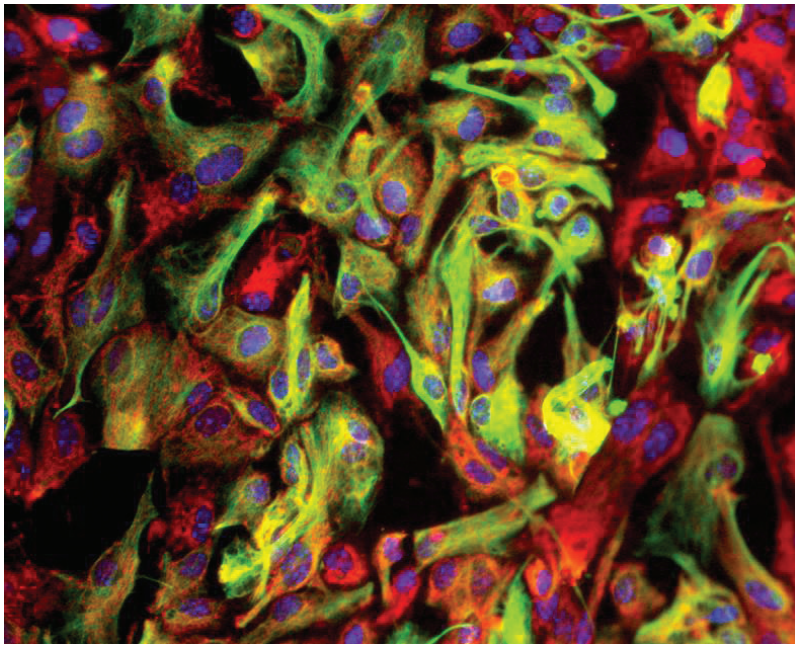
To accomplish this goal, the Common Fund's Single Cell Analysis program was created in 2011. The program supports research efforts through three primary initiatives. In the first, a network of laboratories is working together to determine transcriptomic profiles and identify patterns of gene expression in individual human cells within a variety of tissues. The researchers also have proposed novel approaches to identify relevant variations in gene expression among individual cells and to assess the

consequences of these differences. One notable early achievement is the development of a method that, for the first time, allows the capture of the messenger RNA molecules from individual cells within live and intact tissue. All data and protocols will be made available to the entire scientific research community.

The second initiative is focusing on high-risk/high-impact technology projects that generate powerful new methods or significantly improve existing methods for single cell analysis. Examples of the proposed technologies include innovative high-resolution imaging and novel methods for measuring physical and physiological properties of single cells.

The final initiative of the program includes endeavors to accelerate the translation of promising technologies for single cell analysis from prototype to practice for both laboratory and clinical use. Examples of these new technologies include robots that acquire information about many individual brain cells simultaneously and instruments that can assess the molecular states of immune cells in patients with diseases, such as cancer or early-stage tuberculosis.

Through this multipronged and synergistic approach, the Single Cell Analysis program is poised to help usher in a new era of personalized medicine by understanding the link between cell variation, tissue and organ function, and the emergence of disease in individuals.



Immunofluorescent protein localization in primary cell cultures of astrocytes and neurons from mice. Glial fibrillary acidic protein appears green, COX5b appears red while the nuclei are blue (DAPI).

Extracellular RNA Communication

Ribonucleic acid (RNA) was once thought to exist in a stable form only inside cells, where it regulates gene expression to produce specific proteins controlling the health, survival and function of cells. However, new findings have indicated that RNA can play a role in a variety of complex cellular functions, including newly discovered mechanisms of cell-to-cell communication. RNA can be exported from cells in extracellular vesicles or bound to lipids or proteins to circulate through the body and affect cells at a great distance. Some extracellular RNAs, or "exRNAs," may also be acquired from the food we eat and the microbes that live in our bodies. Currently, the function of human and nonhuman exRNAs is not known. ExRNAs represent an entirely new paradigm for how cells in the body exchange information with each other and may even be a way for cells from other species to exchange information with human cells.

RNA is produced inside cells. Some RNAs are exported from cells via vesicles (shown) or bound to lipids or proteins. These extracellular RNAs travel throughout the body to potentially affect cells at a distance.

ExRNAs hold enormous potential for disease diagnosis and treatment. Recent research indicates that healthy cells make different exRNAs than diseased cells. Some diseases, such as cancer, may spread throughout the body with the help of exRNAs that "instruct" healthy cells to become diseased. Blocking these exRNAs may slow down or stop disease progression. In addition, researchers may be able to use exRNAs from healthy cells or design novel exRNAs to repair or destroy diseased cells. Because different exRNAs are released from diseased cells compared with healthy cells, researchers may also be able to measure exRNAs in body fluids to diagnose disease, monitor disease progression or measure response to treatments.

To understand the role exRNAs play in human health and disease, the Common Fund launched the Extracellular RNA Communication program in 2013. Through five integrated initiatives, this program aims to discover fundamental biological principles about the mechanisms of exRNA generation, secretion and transport; to identify and develop a catalog of exRNAs found in normal human body fluids; and to investigate the potential for using exRNAs in the clinic as therapeutic molecules or biomarkers of disease. Data generated by this program will be housed in a public ExRNA Atlas website (http://exrna.org) to serve as a community-wide resource for exRNA research standards, protocols, data, tools and technology. Scientists supported by this program have formed an ExRNA Consortium to collaborate, share information and spread knowledge to the larger scientific community and public.

Research projects exploring the use of exRNAs as biomarkers of disease and for therapeutic purposes are supported by a phased mechanism that allows the NIH to support higher risk exploratory projects and then focus resources later on the most promising projects. Only the projects meeting individual well-defined goals and milestones in the early phase are selected for continued support and expansion in the later phase. To facilitate the translation of basic research findings into the clinic, the ExRNA Communication program is working closely with the Food and Drug Administration to collaborate and coordinate efforts for the preclinical and clinical use of exRNAs in human health and disease.

Although relatively new, the ExRNA Communication program is already demonstrating significant progress. Grantee Richard Kraig and colleagues from the University of Chicago have discovered types of exRNAs released from immune cells that can promote the formation of myelin to restore the protective insulation around nerve cells damaged in multiple sclerosis.[1,2] These studies are a promising first step in developing exRNA-based therapeutics for not only multiple sclerosis, but many other diseases as well.

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[1] Pusic, A.D., Pusic, K.M., Clayton, B.L., & Kraig, R.P. (2014). IFNγ-stimulated dendritic cell exosomes as a potential therapeutic for remyelination. *Journal of Immunology, 266*(1-2), 12–23.

[2] Pusic, A.D., & Kraig, R.P. (2014). Youth and environmental enrichment generate serum exosomes containing miR-219 that promote CNS myelination. *Glia, 62*(2), 284–299.

Big Data to Knowledge

Biomedical research is increasingly becoming rich in data, with researchers routinely generating large, diverse datasets. These large datasets are part of the phenomenon of "Big Data." The information contained in large or complex datasets has the potential to advance our understanding of human health and disease, but our ability to use such large amounts of data is often limited due to a lack of tools, accessibility and training. Increasingly, investigators need to access and analyze data from multiple data sources simultaneously, combining and comparing data from different studies. The data need to be comparable and accessible from a common platform.

In response to these challenges, the NIH launched the Big Data to Knowledge (BD2K) initiative at the end of 2012. In addition to the Common Fund, all NIH Institutes and Centers are contributing to its funding and management. The initiative is composed of four major components that, collectively, are meant to enhance the use of biomedical Big Data.

BD2K initiative components include the following:

- Enabling data use
- Data analysis methods and software
- Enhancing training in techniques associated with Big Data usage
- Centers of Excellence

To make data easier to access, the NIH is developing new policies to encourage data and software sharing. It will also support research into how to make datasets easier to search and to cite and encourage the use of standards to maximize value. Once the data are accessible, the biomedical research community needs the software and computing power to analyze them. The BD2K initiative intends to support research to develop methods and technologies that make it easier to extract information

from Big Data. Training is also a major component of the BD2K initiative, and the various training activities supported by BD2K are meant to instruct the full spectrum of biomedical researchers from students to senior faculty and from tool developers to investigators who need to use those tools. The initiative will also fund several Centers of Excellence to address novel Big Data science challenges across the spectrum of NIH-funded science. The Centers will conduct data science research and distribute data science products like methods, software and analysis tools, as well as relevant training.

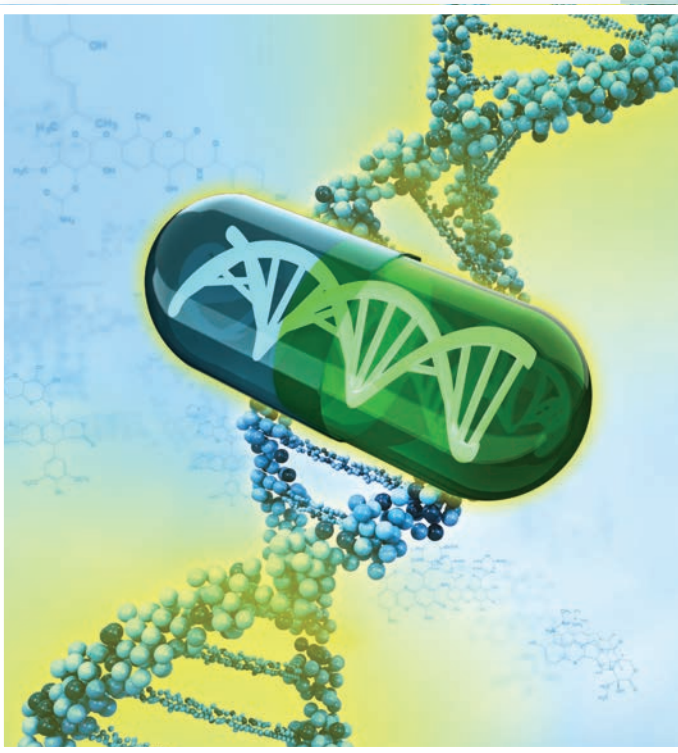
Overseeing the BD2K effort is the new Associate Director for Data Science, Philip Bourne, Ph.D., who reports directly to the NIH Director. Dr. Bourne believes that "the future of research into health and well-being is going to be tied very much to our ability to sustain, trust, integrate, analyze/discover, disseminate/visualize and comprehend digital data."[1]

The hope is that implementation of BD2K will result in sweeping cultural changes in the way the biomedical research community shares, accesses, queries, cites and analyzes data.

[1] Bourne, P. (2013). "Taking on the Role of Associate Director for Data Science at the NIH – My Original Vision Statement." Retrieved June 3, 2014, from http://pebourne.wordpress.com/2013/12/21/taking-on-the-role-of-associate-director-for-data-science-at-the-nih-my-original-vision-statement/.

Illuminating the Druggable Genome

The overarching goal of the Illuminating the Druggable Genome (IDG) program is to improve our knowledge of the properties and functions of understudied proteins that are known drug targets, are expected to be drug targets themselves. The primary consideration for inclusion in the program is sequence similarity to proteins targeted by drugs, for example, encoded by the "druggable genome." This new Common Fund program will focus on hundreds of understudied proteins within four protein families that are commonly targeted for drug development—G-protein-coupled receptors, nuclear receptors, ion channels and protein kinases. The aim is to expand the number of proteins known to be of high biological or medical relevance. The aim is to provide information about the function of these proteins so that investigators can determine whether a given protein is a likely target for a disease or condition of interest and can then exploit knowledge of the protein family to develop drugs that target that protein.



This program began a 3-year pilot phase in 2014. The first goal is to establish a Knowledge Management Center, to catalog what is actually known about these protein family members and to identify critical knowledge gaps. The Knowledge Management Center will develop a Web portal that will bring together information from multiple data sources. By making available a ready source of hard-to-find information, the Knowledge Management Center will serve as the focal point for the larger scientific community to develop strategies for discovery.

The second goal of the pilot phase will be to provide information about the function of the proteins identified in the pilot phase for which critical knowledge gaps exist. This effort will focus on developing assays and technologies that will enable researchers to annotate in detail uncharacterized proteins that have potential importance either as biomarkers, targets for drug development or key regulators of biological processes. The core goal of this phase is to create new tools and experimental workflows that allow the functions of proteins to be defined efficiently. Taken together, this pilot phase will enable researchers—from small businesses to pharmaceutical industry to academia to the NIH—to prioritize proteins for further investment.

IDG is also working closely with a complementary Common Fund effort, the Knockout Mouse Phenotyping (KOMP2) program. The KOMP2 program conducts detailed observations of physical traits seen in many laboratory-generated mouse strains, each of which lacks a specific gene. KOMP2 has prioritized the characterization of mouse strains lacking the uncharacterized G-protein-coupled receptors, nuclear receptors, ion channels and protein kinases of interest to IDG, thereby accelerating the process of discovering disease-relevant proteins.

The Common Fund IDG program seeks to transform basic science and drug discovery by shedding light on a subset of genes and proteins for which little publicly available information or active research exists. IDG aims to enhance the availability of fundamental knowledge and create transformative tools to catalyze the discovery of truly novel biology; to identify protein candidates for further exploration as therapeutic targets; and to demonstrate the feasibility and benefits of illuminating the role of poorly understood proteins. Elucidation of function will clear the way for proof-of-concept studies to determine the relevance of potential therapeutic targets to human health and disease. An equally important outcome will be the identification of genes and proteins that are unlikely targets for therapeutics. Such knowledge can save precious time and money in the drug development pipeline. The net effect of such a resource will be expansion of the potential therapeutic space, providing an impetus for more efficient, disease-specific investigation and the ability to address more effectively unmet medical needs. Furthermore, tools, resources and assays developed or adapted by IDG may ultimately be used to understand protein classes beyond the four families currently under focus.

Reengineering the Clinical Research Enterprise

When the NIH Roadmap was launched 10 years ago, clinical research was in transition. While clinical trials had generally been conducted at single sites in the past, there was an increasing need for collaboration among several sites. There was also a need for academic investigators to engage patients and health care providers to define questions and to assess outcomes. While basic science was robust, the translation of basic research into the clinic presented substantial challenges. Similarly, a fluid path from clinical observation to basic research was lacking. NIH Roadmap programs were established to begin to tackle these issues, and new Common Fund programs have emerged in the interim that continue to reshape the landscape. Electronic health data have exploded over the past decade, and computational tools that facilitate use of the data are transforming clinical research. Perhaps even more importantly, Common Fund clinical research programs model new modes of collaboration—new processes that enable fluid interaction among academic investigators, basic scientists, health care providers and patients. These programs are delivering best practices to the broader community for widespread adoption to hasten discovery and improve care.

Patient-Reported Outcomes Measurement Information System (PROMIS®)

X-rays and lab tests give researchers objective information about the effect of an intervention on the body, but they don't reveal the entire patient experience. To see and understand the full picture of how a disease, condition, or treatment affects patients, researchers needed an accurate, evidence-based tool for measuring symptoms including pain, fatigue and emotional distress from the patient's perspective. Person-centered or patient-reported outcomes allow researchers and clinicians to capture this experience.

As part of the Roadmap process, the NIH identified the need for an improved method of assessing symptoms and patient-reported outcomes. Prior to the development of the Patient-Reported Outcomes Measurement Information System (PROMIS®) program, researchers often designed their own tools to measure symptoms for the particular condition they were investigating. Another problem was that many of tools developed were not standardized or comparable across studies. Patients participating in clinical trials were often burdened with filling out long questionnaires that helped researchers assess their symptoms and overall physical, mental and social health.

Launched in 2004, PROMIS® was one of the first Roadmap projects. The goal of the 10-year project was to create an efficient state-of-the-art assessment system for self-reported health. The PROMIS® effort involved more than 150 scientists at 12 research sites around the country. PROMIS® is transforming the way research is conducted by providing clinicians and researchers access to efficient, precise, valid, and responsive adult- and child-reported measures of health. By combining item response theory with computer adaptive testing, the PROMIS® measures make use of established algorithms to adjust follow-up questions based on previous answers and arrive at more precise answers with fewer questions. The average PROMIS® instrument can be administered in under a minute.

By using PROMIS® tools, researchers and clinicians can monitor a patient's overall health status in less time than before, giving precise and valuable measurements without burdening patients. PROMIS® also gives a way of comparing apples to apples across studies and populations, making meta-analysis and comparative effectiveness research more meaningful.

In the initial phase (2004–2008), the project focused on the development of five core health-related quality of life domains: pain, fatigue, emotional distress, physical function and social well-being. Based on interviews with patients, the researchers developed

targeted questions designed to accurately measure and interpret symptoms that occur in many different conditions.

In Phase 2 of the program (2009–2013), researchers expanded the concept to new domains and additional populations, including children, minorities and people with disabilities. As of April 2014, the initiative had developed 40 measures for adult patients and 20 pediatric measures. All of the measures are available in both English and Spanish and many individual measures are available in additional languages—with more than 40 languages represented.

PROMIS® tools are now used by a wide range of government agencies. The Centers for Disease Control and Prevention now uses PROMIS® to measure health-related quality of life in the National Health Interview Survey of more than 35,000 households. The CDC is currently testing PROMIS® for use in the Behavioral Risk Factor Surveillance System (BRFSS), the nation's telephone survey designed to collect data on health-related behaviors. The BRFSS is administered to 350,000 adults nationwide annually. The Department of Defense has also incorporated PROMIS® measurements into a new electronic clinical management system for chronic pain patients. The system, called the Pain Assessment Screening Tool and Outcomes Registry (PASTOR), is currently used by several branches of the military. On April 3, 2014, the NIH Clinical Center and Intramural research community gained access to the PROMIS® measures with the opening of NIH PROMIS® Assessment Center, known as AC Lite.

While developed primarily for use in research settings, the PROMIS® measures also have wide application in actual patient care. In the last decade, researchers and clinicians have developed a clearer understanding of the role of the patient experience in clinical outcomes. While an x-ray may detect a broken bone and a lab test may show elevated blood cholesterol, only patients can tell us how much it hurts, whether they can participate in social activities or if they are satisfied with their level of functioning. Quality-of-life assessments like the PROMIS® measurements are especially important in chronic disease in which treatment often focuses on reducing symptoms, rather than curing the underlying disease. Patients who experience improvement in symptoms are more likely to accept and adhere to a treatment regimen. Tracking these measures over time in an electronic health record can give clinicians important insight about whether a course of treatment is effective. Backed up by numerous validity studies, the PROMIS® tools are now available royalty-free to researchers and clinicians.

To that end, PROMIS® developers have designed the computer-based tool so that it can easily be integrated into already existing electronic health record software. Some of the largest and most respected health systems and health plans in the country, including Cleveland Clinic, Group Health, Duke University Medical Center and Essentia Health are already using PROMIS® measures in patient care. Thousands of providers serving millions of patients can now monitor patient-reported outcomes more easily and effectively because of this innovation.

In 2014, PROMIS® will transition into an expanded focus on adoption and implementation. The goal is to promote widespread use of PROMIS® in observational research studies, in clinical trials and ultimately in clinical settings. To that end, the NIH has committed funds to support PROMIS® and three other measurement systems under one research resource with a trans-NIH funding opportunity led by the National Cancer Institute. Funds for the next phase of PROMIS® are planned to coincide with the ending of Common Fund support. Other stakeholders, such as the Patient-Centered Outcomes Research Institute, have also committed to provide funding support for PROMIS®-focused research.

RHEUMATOID ARTHRITIS AND PATIENT-REPORTED OUTCOMES

When Amye Leong was first diagnosed with rheumatoid arthritis as a young adult, she found she barely had the vocabulary to describe her day-to-day experience with this debilitating disease. She also didn't know what questions to ask or what words to use to describe her pain, loss of function and other symptoms, or how to convey her preferences to medical professionals.

Driven by her desire to help patients like herself, Ms. Leong became a patient advocate, organizational development expert and a United Nations health spokesperson devoted to making the patient's voice heard in health care. She is currently working with physician-researcher Clifton O. Bingham III, M.D., at Johns Hopkins University Arthritis Center to explore practical ways to integrate patient-reported outcomes into clinical care.

Dr. Bingham and Ms. Leong believe that the Patient Reported Outcome Measurement Information System (PROMIS®) measures developed with support from the Common Fund can help create a common language that patients can use to characterize their experiences and give physicians the information they need to identify treatments that are more effective and relevant to patients.

One clear advantage of the PROMIS® measures is their ability to assess a patient's full range of symptoms from very good to very bad, and across a number of areas of health including physical function, emotional health and social participation. This is especially important in rheumatoid arthritis and other chronic diseases that fluctuate widely from day to day. Treatment for rheumatoid arthritis aims at achieving remission or low-disease activity, but many existing patient-reported outcome instruments cannot detect change until symptoms reach a moderate level, which are not responsive to patients' needs and preferences.

In Dr. Bingham's research, patients take the PROMIS® assessments in the waiting room before their office visit with their doctor. Using computer adapted testing technology, PROMIS® administers those questions most relevant to the individual patient, and the results are scored instantly, giving the doctor and the patient real-time information about the patient's condition.

Amye L. Leong, MBA
President & CEO, Healthy Motivation
Spokesperson & Director of Strategic Relations, United Nations Bone and Joint Decade, the Global Alliance for Musculoskeletal Health

The studies are still underway, but Dr. Bingham reports that PROMIS® can demonstrate a broad range of symptoms and health impacts of rheumatoid arthritis, which have not previously been well documented using current measures. Moreover, this technology is feasible for use in a clinical practice setting. With patient research partners integral to the project's design and development, the practical application and patient-centeredness of PROMIS® measures are ensured and enhanced in this unique application. Providing this expanded information to patients and providers is changing conversations and opening up new lines of communication about symptoms and quality of life, sometimes leading to treatment and referrals aimed at helping people with rheumatoid arthritis get early and more effective comprehensive care.

SEEING PROMIS® FOR PATIENTS WITH A RARE DISEASE

Vasculitis is a group of rare diseases characterized by inflammation and subsequent blockage of the blood vessels that leads to a loss of function in the affected tissues and a wide range of symptoms, including pain, numbness or weakness, fatigue and problems related to specific organs. Symptoms of vasculitis vary depending on which parts of the body are affected and may be chronic or come and go in painful "flares" of the disease.

While lab results and physician-reported data are important to the diagnosis and treatment of vasculitis, some symptoms—such as pain, fatigue, and general function—can only be reported by patients themselves. But developing a system for assessing and tracking patient-reported outcomes is expensive and difficult.

That's why Dr. Peter Merkel, M.D., M.P.H., was so excited when he first heard about the PROMIS® measures developed with Common Fund support. A physician-researcher based at the University of Pennsylvania, Dr. Merkel is director of the Vasculitis Clinical Research Consortium and principal investigator of the Vasculitis Patient-Powered Research Network. Dr. Merkel and his colleagues are tracking data from PROMIS® assessments and correlating that with physician-based measures and lab results. The goal is to develop a composite approach that takes into account the full range of data about the patient's condition to especially incorporate the patient's perspective on their burden of disease.

Adapting PROMIS® for use in patients with vasculitis has cut years off the research process versus developing a new tool just for the disease, Dr. Merkel says. His research has already led to important discoveries about the disease and the role that patient-reported outcomes can play in diagnosis and treatment. For example, his team has found that patients often notice subtle changes in symptoms before lab values or other data change. Knowing when a disease flare is on the way could lead to more effective treatment.

Dr. Merkel's research on PROMIS® is primarily funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Patient-Centered Outcomes Research Institute, an independent nonprofit authorized by Congress in 2010. He gives credit to the Common Fund for seeing the value of a more precise and evidence-based way of measuring patient-reported outcomes.

Bridging Interventional Development Gaps

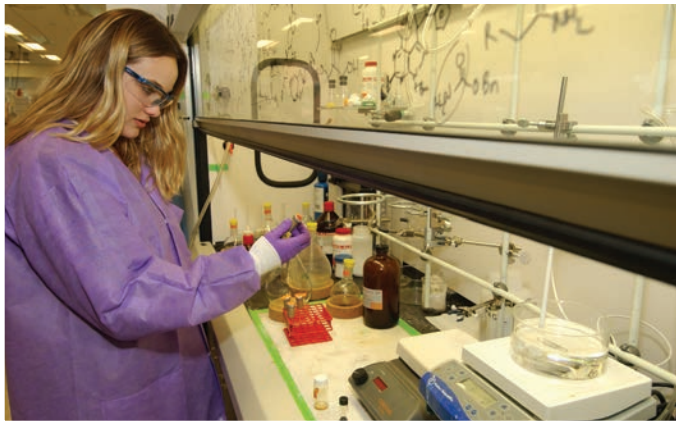
NIH BrIDGs provides, on a competitive basis, certain critical resources for drug development, avoiding the "therapeutics black hole" that claims many potential new drugs being translated from basic to clinical research.

It takes about 14 years—and $2 billion—to move a new drug from discovery to Food and Drug Administration approval. Many promising new therapies hit roadblocks along the way. Especially vulnerable are high-risk ideas or therapies for uncommon disorders that do not attract private-sector investments. Public resources can bridge that gap and help bring new hope to patients.

The goal of the Bridging Interventional Development Gaps (BrIDGs) program is to bring new treatments to patients sooner by removing some of the obstacles in the earliest, riskiest stages of drug development. Through the BrIDGs program (formerly known as National Institutes of Health Rapid Access to Intervention Development, or NIH-RAID), qualified researchers exploring promising ideas receive access to NIH contractors who conduct preclinical studies at no cost to the investigator. For example, investigators might seek assistance in the synthesis of a new compound, to scale up production or to study the pharmacokinetics (how the body absorbs, metabolizes and eliminates drugs) or toxicology of a therapeutic agent. To date, research data and material generated by BrIDGs have been involved in 13 successful Investigational New Drug applications

(INDs) to the FDA, and one clinical trial application has been cleared by Health Canada. The program has now transitioned to National Center for Advancing Translational Science support.

Twelve projects have been evaluated in clinical trials. Three BrIDGs-supported agents have gone as far as Phase 2 human clinical trials, in which researchers give an experimental therapy to a group of patients to evaluate the effectiveness and safety of a treatment. Third-party investors have licensed seven agents during or after their development by BrIDGs.

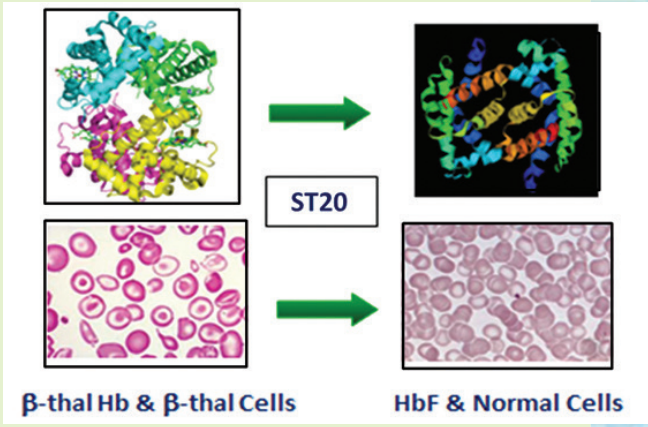


A technician in an NIH National Center for Advancing Translational Science laboratory carrying out chemical synthesis.

A NEW THERAPEUTIC CANDIDATE FOR BETA THALASSEMIA ENTERS CLINICAL TESTING

Beta thalassemia is an inherited disorder of red blood cells that is a designated global health burden by the World Health Organization. Thalassemia is caused by mutations in genes for beta globin, the major component of the oxygen-carrying protein, hemoglobin, in red blood cells. Deficiency of beta globin damages red blood cells, causing them to die early, and impairing oxygen delivery around the body. Severe anemia develops in infancy; poor growth, fatigue, heart failure and endocrine deficiencies develop in children and adults. Many patients need chronic blood transfusions, and still die young. Thalassemia conditions are especially prevalent along the coastal United States.

Researchers are studying short-chain fatty acids as potential therapeutic agents for beta thalassemia because these molecules can increase production of an alternate type of hemoglobin, fetal hemoglobin (HbF), which is normally produced in all humans before birth and then switched off. HbF can compensate for deficient beta globin, which increases the amount of hemoglobin in red blood cells. Susan Perrine, M.D., at Boston University, selected one short-chain fatty acid called "sodium 2,2 dimethylbutyrate" (ST20) for further clinical development because it boosted HbF and red cell production, worked effectively as an oral medicine in baboons and appeared to be nontoxic. Before moving ST20 into clinical trials in humans, the FDA requested that Dr. Perrine analyze ST20's effects on the central nervous and cardiovascular systems. The agency also asked for additional toxicity studies of ST20 to ensure that it does not damage genetic material. The Common Fund's BrIDGs program conducted these studies and manufactured the first pills of the drug, which allowed first-in-man trials to begin. As a result, ST20 has now been tested in Phase 2 clinical trials to assess the efficacy of the drug in patients with beta thalassemia. A study published in the *British Journal of Hematology* in 2013 reported that a Phase 2 clinical trial was successful in demonstrating that ST20 activated HbF in patients and increased the proportion of red blood cells expressing HbF by 15 percent.[1] A second 6-month trial showed stronger effects, reported in *Blood* in 2014.[2] Further studies to identify an optimal dosing schedule are being planned to determine how to give the drug to raise hemoglobin levels most effectively.



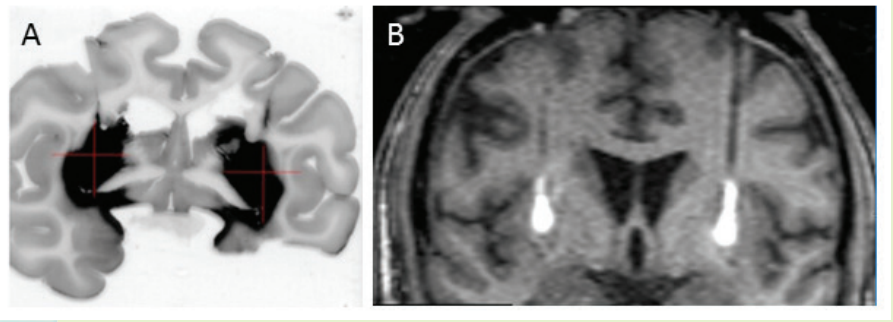
The new drug turns on fetal hemoglobin (top) to make more healthy blood cells (lower panel).

[1] Fucharoen, S., Inati, A., Siritanaratku, S., Thein, W. Wargin, S., Koussa, A., Taher, N., Chaneim, B.M., Rberenson, R., & Perrine, S.P. (2013). A randomized phase I/II trial of HQK-1001, an oral fetal globin gene inducer, in beta thalassemia intermedia and Hb/beta thalassemia. British *Journal of Hematology, 161*(4), 587–593.

[2] Patthamalai, P., Fucharoen, S., Chaneiam, N., Ghalie, R., Chui, D., Boosalis, M., & Perrine, S.P. (2014). A phase 2 trial of HQK-1001 in HbE beta thalassemia demonstrates HbF induction and reduced anemia. *Blood, 123*(12), 1956–1957.

A NOVEL GENE THERAPY APPROACH TO PARKINSON'S DISEASE MOVES FORWARD

Parkinson's disease is a disorder that, although systemic in nature, most prominently affects neurons in a part of the brain that controls muscle movement. These neurons normally make a chemical called dopamine, but during Parkinson's disease, they atrophy and die. Over the last decade, researchers have discovered a protein called "glial cell line-derived growth factor," or GDNF, that supports the growth and health of the neurons that produce dopamine. However, recent clinical trials designed to test the efficacy of GDNF were unsuccessful. Researchers believe the lack of efficacy was because it was difficult to deliver GDNF to the proper region of the brain in sufficient amounts.



AAV2-GDNF induces permanent expression and production of GDNF in the brain. (A) Image of AAV2-induced GDNF expression in the monkey brain used in safety and efficacy experiments mandated by the FDA prior to initiation of the clinical trial. (B) MRI of the brain of a Parkinson's patient treated with AAV2-GDNF at NIH Clinical Center. AAV2-GDNF is administered along with MRI tracer to allow real-time monitoring of gene delivery to assure optimal and safe gene therapy.

Krystof Bankiewicz, M.D., Ph.D., at the University of California, San Francisco (UCSF), is attempting to overcome these obstacles. He and his colleagues have developed an artificial virus carrying the GDNF gene as its cargo that can be effectively infused into the specific brain region where the malfunctioning dopamine-generating neurons reside. The virus, named AAV2-GDNF, is designed to trigger the production of GDNF in the region of degenerating dopaminergic neurons. Critical to this approach has been the development of a highly precise MRI-guided infusion procedure that allows the neurosurgeon to visualize the infusion of the virus in real time. This system is expected to offer sufficient safety and predictability to enable wide adoption of gene therapy for both Parkinson's disease and other neurological diseases.

The Common Fund's BrIDGs program supported the preclinical development of AAV2-GDNF by providing resources for the preclinical toxicology and chemistry studies as well as the manufacturing and controls analyses that UCSF needed to file for an Investigational New Drug application with the FDA. UCSF leveraged the data generated by BrIDGs to enter into a collaboration agreement with uniQure, a leading gene therapy company. In July 2013, UCSF initiated the first clinical study with Dr. John Heiss at the NIH to evaluate the therapy's safety and efficacy in Parkinson's patients.

Gulf Long-term Follow-up Study

Oil spill workers cleaning up debris. The GuLF program aims to study the health effects of oil exposure on clean-up workers.

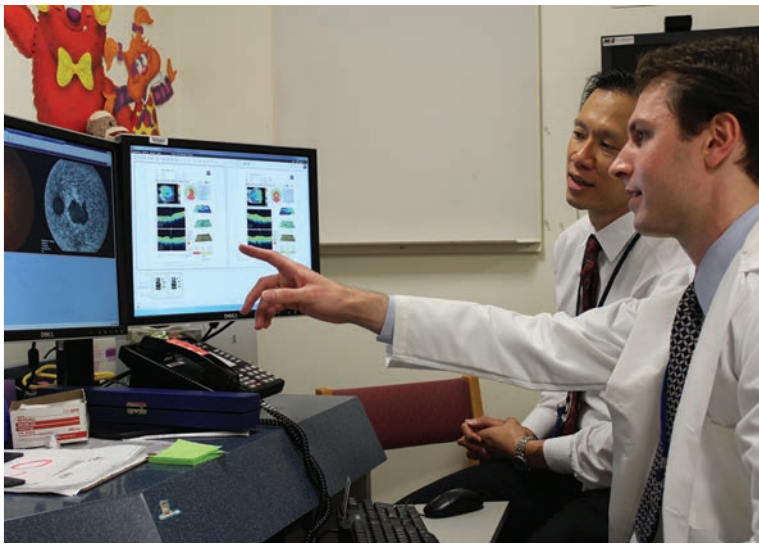
The Gulf Long-term Follow-up (GuLF) Study is the largest investigation ever conducted on the potential health effects associated with an oil spill. Announced within 3 months of the April 2010 explosion of the Deepwater Horizon oil platform in the Gulf of Mexico, the Study tracks the physical and mental effects of the oil spill on workers and volunteers who helped with the clean-up efforts. The Study is being conducted in coordination with federal, state and local agencies, institutions and communities in the Gulf region. In the first 3 years of the Study, researchers have collected information and biological samples through questionnaires, interviews or home visits with more than 33,000 participants. Researchers will continue to follow more than 20,000 of these participants via telephone interviews every 2 to 3 years to evaluate long-term effects of the exposure to the oil and the dispersants used to clean it up. Funded in part by the Common Fund and led by National Institute of Environmental Health Sciences, the Study will lead to a greater understanding of the consequences of oil spills, help inform future recovery efforts and develop approaches for conducting research in the setting of an ongoing disaster.

Clinical and Translational Science Awards

It can take more than a decade for basic scientific findings to advance through preclinical and clinical studies resulting in a new treatment, medical device, or prevention method. The Clinical and Translational Science Award (CTSA) program aims to accelerate the translation of research discoveries from the bench to the bedside, train a new generation of clinical and translational researchers, and engage communities in clinical research efforts. The program created a national consortium of 62 medical research institutions in 31 states and the District of Columbia. These consortium members share information and develop tools and training methods to improve the clinical trial process. They also support the development of all disciplines needed for a robust clinical and translational research workforce. The CTSAs encourage the participation of patients from different backgrounds and, ultimately, bring new hope to more people. Initially supported by the Common Fund, this program is now led by the National Center for Advancing Translational Sciences.

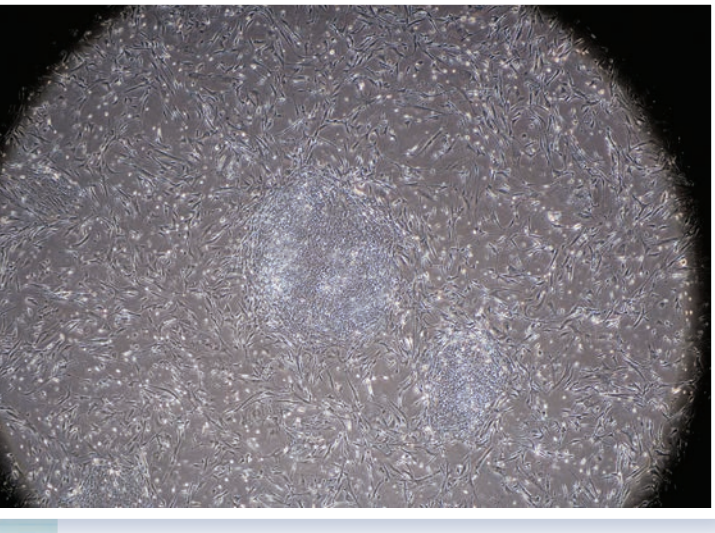
Clinical Research Training

Physician-scientists and other clinically trained investigators bring valuable perspective to biomedical research. With their experience and training in patient care, they make critical connections between lines of inquiry in the laboratory and actual patient care, and tend to accelerate medical discoveries. Over the years, physician-scientists have made significant breakthroughs that have led to improvements in human health. However, over the past 30 years the number of physician-scientists has been in decline, with an increasing percentage of new medical doctors opting for positions in private practice or industry. Only a small proportion of physicians—less than 2 percent—choose to make research their primary profession.



In response to these needs, the early NIH Roadmap catalyzed clinical research training through a suite of initiatives that emphasized predoctoral clinical research training as well as multidisciplinary training for early career clinicians. These efforts engaged academic research institutions across the nation in this important mission, and also drew from the strengths of the NIH Intramural Research Program. Leveraging ongoing investments at the NIH, the Roadmap Clinical Research Training program was designed to attract and train innovative and motivated medical, dental and veterinary students in clinical research. The students work one-on-one with mentors on clinical or translational projects and attend lectures that explore key issues in the clinical research process, including bioethics, science policy and emerging technologies. They also participate in clinical teaching rounds with research patients at the NIH Clinical Center and receive special training in clinical protocol development, human subjects' research, drug development and academic leadership skills. Redesigned to become the Medical Research Scholars Program in 2012, 340 students had participated in the program as of 2013 and new groups are recruited each year. As the CTSAs became established, the Roadmap training programs across the country were encompassed within the training goals established for the CTSA program. Through important programs like the CTSAs and the Medical Research Scholars Program, the NIH helps ensure that new clinician-researchers and their mentors have the skills and support they need to succeed in the field.

NIH Center for Regenerative Medicine

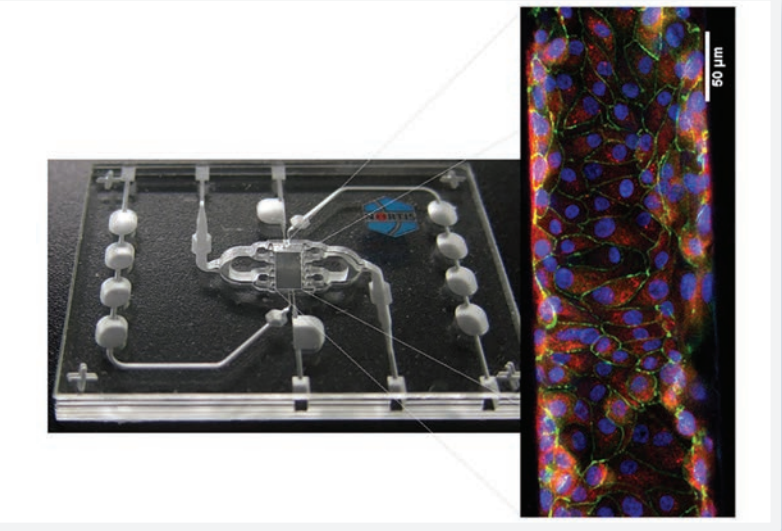


Induced pluripotent stem cells (iPSCs) in a culture dish.

The Common Fund launched the NIH Center for Regenerative Medicine in 2010 to serve as a national resource for stem cell science and to accelerate the development of new medical applications and cell-based therapies. The Center's work focuses on induced pluripotent stem cells (iPSC): stem cells derived from adult cells coaxed back into an embryonic stem cell-like state. These iPSCs can generate many different cell types for use in therapies or screening. Such stem cell-based therapies have the potential to use a patient's own cells, potentially avoiding immune rejection complications typically associated with cells transplanted from other sources.

In its first 3 years, the Center supported several pilot projects, developed multiple stem cell lines, compiled supporting protocols and standard operating procedures, dealt with intellectual property and licensing issues surrounding the cells, and developed training courses in these methods. In 2014, the Center awarded a Therapeutic Challenge Award to Kapil Bharti, Ph.D., of the NIH's National Eye Institute to move his work beyond the pilot stage toward the clinic. Dr. Bharti's research focuses on age-related macular degeneration (AMD), a leading cause of blindness in the elderly. Dr. Bharti's Therapeutic Challenge project will use iPSC-derived retinal pigment epithelium cells, the type of cell damaged in AMD, in preclinical efficacy and safety studies. While Dr. Bharti will work toward the goal of a Phase 1 clinical trial using patient-derived cells, the methodological and regulatory challenges that must be overcome will be relevant to the broader community. Future endeavors will be coordinated through the National Center for Advancing Translational Sciences to address challenges associated with using iPSCs in the clinic. The Center is committed to helping investigators navigate the challenges involved in this line of research to realize the potential of regenerative medicine.

Regulatory Science



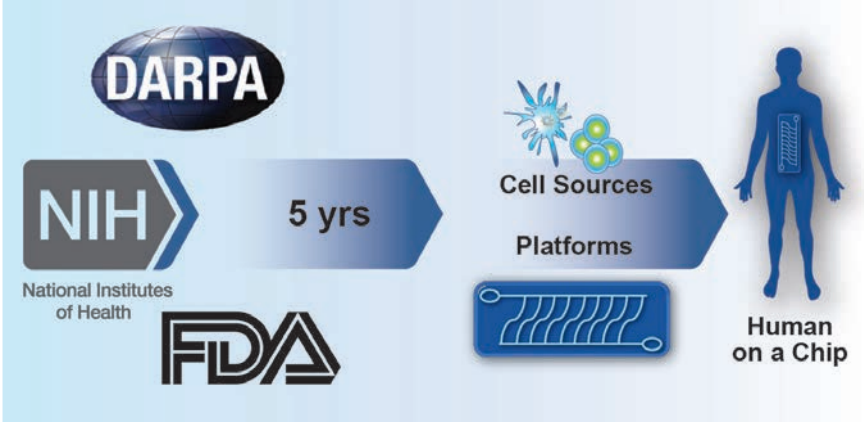
Human kidney cells (right) are deposited on a tiny device called a microphysiological platform, or "chip" (left) and used to mimic the physiology of kidney tubules in response to drugs or other experimental agents. Courtesy of Dr. Jonathan Himmelfarb and Dr. Edward Kelly, University of Washington.

Current methods of assessing drug safety and efficacy are expensive and time-consuming and many times do not accurately predict results in humans. In 2010, the NIH and the Food and Drug Administration formed an interagency partnership to foster regulatory science, a specialized and interdisciplinary area of biomedical research that serves to generate new knowledge and tools for assessing experimental therapies, devices and diagnostics. The broad goal of the Regulatory Science program is to accelerate the development and use of new tools, standards and approaches to develop products efficiently and to evaluate product safety, efficacy and quality more effectively. The initial projects funded through this program produced innovations in clinical trial design, a novel strategy to predict eye irritancy (without animal testing), methods for testing the safety of nanoparticles, and ways to model the effect of experimental drugs on the body before they are tested on people.

The program expanded in fiscal year 2012 to address a specific, high-priority challenge to develop "human-on-a-chip" micro-platforms that accurately model the structure and function of human organs, such as the lung, liver and heart. These models can then be used to evaluate the toxicity and efficacy of new therapies in a faster and more cost-effective way

than current methods. This Microphysiological Systems initiative—which involves interagency collaboration between the NIH, the FDA and the Defense Advanced Research Projects Agency—is funded by the Common Fund and the Cures Acceleration Network of the NIH National Center for Advancing Translational Sciences (NCATS). Nineteen projects were funded initially to develop human tissue microsystems, and several pilot projects are set to scale up to fully integrated models later in 2014, during the 3-year Phase 2 period.

In an ongoing effort to pilot new approaches to regulatory science, the Common Fund launched a new initiative in drug repurposing in fiscal year 2013, designed to discover new therapeutic uses for existing molecules that have already been developed by the pharmaceutical industry. This initiative transitioned to NCATS support in fiscal year 2014.



The NIH, Food and Drug Administration (FDA) and Defense Advanced Research Projects Agency (DARPA) are working to make devices that mimic human physiology and can support living human cells to test potential new drugs for safety and efficacy.

DISEASE MODEL ON A CHIP

As part of the Microphysiological Systems initiative of the Common Fund's Regulatory Science program, 19 research groups are developing micro-platforms that accurately mimic human tissue or organs, thereby facilitating in-depth studies of normal and disease physiology. These models also allow researchers to see how the body will react to a new drug without actually involving human subjects—speeding up the drug development process and potentially saving hundreds of thousands of health care dollars.

At the Wyss Institute at Harvard University, scientists are working on several of these models, including the "heart-on-a-chip" currently beating in the lab of Kit Parker, Ph.D., Tarr Family Professor of Bioengineering and Applied Physics in Harvard's School of Engineering and Applied Science. Dr. Parker and his colleagues use human stem cells to create cardiac muscle cells (myocytes) and arrange those cells to recreate key structural features of the heart—including the contraction and relaxation of a beating heart.

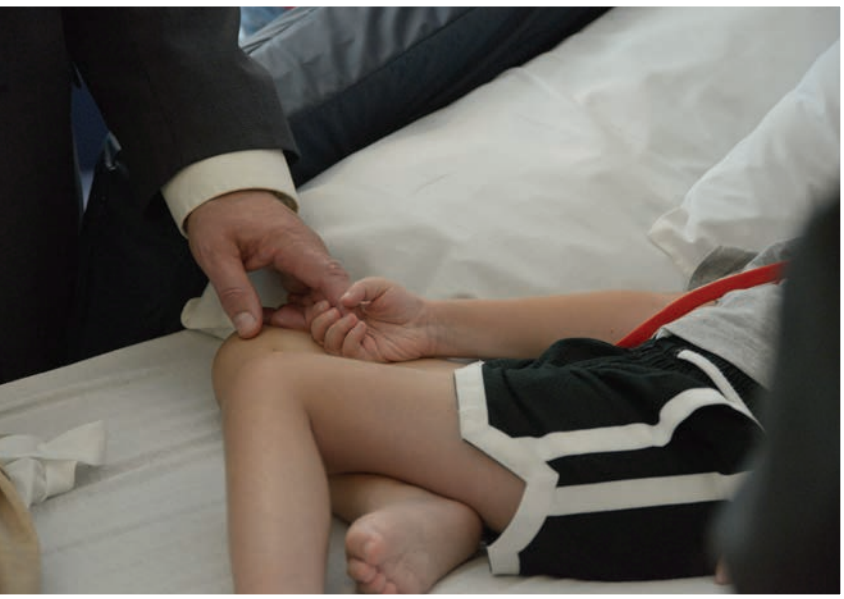
Dr. Kevin Kit Parker is the Tarr Family Professor of Bioengineering and Applied Physics in the Harvard School of Engineering and Applied Sciences at Harvard University. He is a primary faculty member of both the Harvard Stem Cell Institute and the Wyss Institute for Biologically-Inspired Engineering.

But Dr. Parker ran into some challenges while testing his heart-on-a-chip model. He found that variations in the stem cells he was using affected how the cells on the chip responded. The "heart-on-a-chip" was only as good as the cells used on the chip—and there was no standard definition of what makes a high-quality, stem cell-derived myocyte.

With Common Fund support, Dr. Parker and his colleague, Sean Sheehy, set out to develop a set of metrics by which to judge the quality of cardiac stem cells. They looked at the genes expressed, the response to stimuli and the electrical and mechanical properties and then analyzed the data to come up with a scale that helps ensure that researchers are working with a known quantity.

Armed with these quality metrics, Dr. Parker and his lab can now focus on advancing the heart-on-the-chip model as a reliable way to investigate disease mechanisms, test the toxicity and efficacy of treatments, and streamline the drug development process. Using cells from a patient, the group already has simulated a rare heart condition and discovered characteristics of the syndrome that provide new clues for improved treatment.

Undiagnosed Diseases Network



Rare diseases affect an estimated 25 to 30 million Americans. Often times, because their diseases are so uncommon or have never been described before, these individuals go for long periods without a diagnosis, as do those with rare variants of common diseases. The Undiagnosed Diseases Network builds upon the experience and expertise of the NIH Intramural Undiagnosed Diseases program, established in 2008, and its cross-disciplinary approach to diagnosing both rare and new diseases. In January 2014, the Common Fund announced its selection of Harvard Medical School as the Coordinating Center for the Undiagnosed Diseases Network. The Common Fund will add several clinical sites around the country as well as core laboratories. This Network will catalyze the field of rare diseases research by utilizing state-of-the-art medical and genomic approaches to address a myriad of diseases, bringing together basic and clinical researchers to elucidate underlying biological mechanisms to identify treatments, and training the next generation of clinical researchers to use these approaches in disease diagnosis. The insights gained from understanding rare diseases may provide important clues about the pathology and potential treatments of a host of common diseases as well.

Health Care Systems Research Collaboratory

Visual representation of topics from the NIH Collaboratory's Rethinking Clinical Trials, *a continuously curated guide to pragmatic clinical trials. Courtesy of the Collaboratory Coordinating Center at Duke University.*

The Common Fund supports the NIH Health Care Systems Research Collaboratory, which aims to strengthen the national capacity to implement cost-effective, large-scale research studies that engage health care systems as research partners. So-called "pragmatic clinical trials" measure the effectiveness of treatments in the setting of health care systems providing information that is not typically obtained in the more traditional controlled-trial setting. As part of its goal to expand use of pragmatic trials to answer important clinical questions in a real-world setting, the Collaboratory is developing implementation methods and best practices for the researchers and organizations who conduct these trials.

A Coordinating Center (based at the Duke Clinical Research Institute) serves as the central resource for developing and disseminating guidelines and best practices. In conjunction with the National Patient-Centered Clinical Research Network (PCORnet), the Coordinating Center conducts a weekly forum or "Grand Rounds" on innovative, alternative, or streamlined approaches to conducting pragmatic clinical trials. The Center also curates Collaboratory resources and makes them available to the research community, via its website and in biomedical journal publications.

The Collaboratory has seven core working groups led by the Coordinating Center's co-investigators and made up of leaders from the research community and health care systems around the

country to address issues related to pragmatic clinical trials. Each core focuses on a different aspect of pragmatic trials, and the topics range from using data from electronic health records to support clinical research, to making sure research carried out by health care systems is conducted in an ethical manner and according to state and federal law.

Several pilot projects funded by the Common Fund and overseen by the Collaboratory address major public health issues such as colon cancer, chronic pain and end-stage renal disease. Most of the pilot programs have moved forward into implementation of large-scale studies. Also, a new initiative will support efficient, large-scale, pragmatic clinical trials focused on the management of patients with multiple chronic health conditions, a growing problem in the U.S. population. The data, tools and resources produced by these projects as well as the implementation methods and best practices developed by the Collaboratory will be made available to the research community to support the efficient planning and conduct of robust pragmatic trials that have an impact on public health.

STUDY SEEKS REAL-WORLD SOLUTION TO INCREASING COLORECTAL CANCER SCREENING RATES

Colorectal cancer is the second leading cause of cancer death in the United States. With early detection, however, the disease often can be treated successfully. Unfortunately, only about 60 percent of adults over age 50 actually get the recommended screenings. Among Latinos and those without health insurance, rates are dramatically lower. Understanding the reasons behind these low screening rates and designing interventions to raise them can save lives.

It's rare to hear kids discuss colon cancer screening, but they do just that in a Common Fund video contest entry from Dr. Coronado's team. The contest asked researchers to explain their projects in a creative way (https://www.youtube.com/watch?v=hcFFqFiMWlk).

The Strategies and Opportunities to Stop Colon Cancer in Priority Populations (STOP CRC) Demonstration Project—within the NIH Health Care Systems Research Collaboratory of the Common Fund—aimed to find a practical solution to this real-world problem. Researcher Gloria D. Coronado, Ph.D., at the Kaiser Permanente Center for Health Research based in Portland, Oregon, designed the pragmatic study with collaborators at Group Health (Beverly B. Green, M.D., M.P.H) and Oregon Health & Science University (Jennifer E. Devoe, M.D.) with the goal of increasing colon cancer screening rates among patients in safety net clinics.

Many agree that the best test for colorectal cancer screening is the one people will use; two that are commonly recommended are colonoscopy to be done every 10 years and fecal blood testing, which must be completed every year. The fecal immunochemical test (FIT) is much less invasive than colonoscopy and can be done at home without medication and diet restrictions, and without disrupting the work schedule, so many favor it. Based on findings from previous studies of mailed test kits, Dr. Coronado and her team designed a pilot intervention that used data from electronic health records at four clinics to identify 869 patients in need of the screening. The clinics then contacted the patients by mail, sent them kits for FIT and asked the patients to send them back for analysis. Nearly 40 percent of patients completed the tests and mailed them back, substantially boosting screening rates. Those whose tests showed evidence of human blood in the returned sample received a colonoscopy to rule out cancer or remove polyps that raise the risk of cancer. The colonoscopies for uninsured patients were donated by a local charitable health care organization. This pilot study also established the protocol for identifying eligible patients, mailing the outreach information about FIT and tracking the response.

As impressive as those results were, they were really just to test the process and develop a way to work with community clinics. Dr. Coronado and her team are determined to raise screening rates even further and to test whether the approach works in multiple settings. Based on feedback from the clinics where the investigators implemented their protocol as well as interviews with patients who did not send back their test kits, the clinics are now revising their outreach materials and approaches to address patients' fears of taking the test and concerns about the safety of mailing fecal matter. As part of the NIH Health Care Systems Research Collaboratory, the Common Fund is supporting a full-scale study with more than 30,000 patients to evaluate the effectiveness of this approach across 26 clinics. One goal of the study is to identify at least 30 new cancers and prevent many more through regular fecal testing and the removal of polyps during colonoscopies. In addition, they will show how to incorporate colorectal cancer screening outreach into the busy practices of providers serving the most vulnerable members of our communities.

Health Economics

As the nation's medical research agency dedicated to improving the health of the nation, the NIH has an interest in making sure its discoveries lead to technology that actually reaches those who can benefit from it. The Common Fund's Health Economics program aims to identify factors that determine whether advances and innovations in medical discovery are implemented into medical care. Health economics research can provide insights into what health services, devices, drugs and procedures are likely to increase value; why new ones are or are not developed, adapted or adopted; and why providers and patients do or do not use them or adhere to their use. Understanding these factors can help clinicians design prevention, diagnostic and treatment plans that lead to better health.

The four main goals of the Health Economics program are to:

- Ensure that future NIH-supported research is informed by economic analysis of factors that influence health and the adoption of NIH-supported innovations
- Identify factors that influence optimal adoption of high-value health technologies
- Identify factors that influence optimal adoption of personalized medicine approaches
- Address the lack of adequate or available data needed to conduct economic analyses that inform the translation of NIH-supported research into practice

Since its launch in 2011, the program has focused on stimulating health economics research and attracting economists to apply their expertise to rigorous, scientific health research. The program has provided a better understanding of the effectiveness of certain preventives and treatments and the motivation behind adopting key health behaviors, such as choosing healthy foods or quitting smoking.

In the long term, the NIH hopes the program will help us better understand the diffusion of new technology in the health sector and the economics of personalized medicine, which holds out hope for targeted treatments to those most likely to benefit from them. Knowledge gained from this program will help to ensure that innovative interventions and diagnostics are developed with stakeholder interests and behaviors in mind, thereby facilitating adoption and, ultimately, improving health more rapidly.

Research Teams of the Future

As health-related research has grown in complexity to include social sciences, chemistry, physics, engineering and computation in addition to biological sciences, the National Institutes of Health has recognized the need to foster teamwork and encourage new ways of approaching research. Testing new ways of supporting innovation and innovative teams has been a critical theme for the NIH Roadmap/Common Fund. New programs that strive to change the way that the research workforce is supported continue to be established. Each of these programs recognizes that the scientists who conduct the research of the NIH are its most important asset. Investigators at all career stages must have the latitude to go in new research directions with funding that is sufficiently stable to allow bold, transformative ideas to be explored. Young investigators from all sectors of the population must feel that health research is a viable and rewarding career path so that our workforce continues to be robust. The Common Fund provides a mechanism for the NIH as a whole to test new modes of supporting research, and as rigorous evaluations of these mechanisms show value, these approaches are beginning to be adopted NIH-wide. The ultimate goal is for these approaches to create and maintain a robust biomedical research workforce that entices talented people from all segments of society to use their enthusiasm and problem-solving skills to improve human health.

High Risk-High Reward Research

The past two decades have brought tremendous scientific advances that can greatly benefit medical research. While this unprecedented period of progress will continue into the foreseeable future, human health and well-being would benefit from accelerating the current pace of discovery.

One avenue toward achieving this goal is to support exceptionally creative investigators, among all career stages, who propose highly innovative approaches to major contemporary challenges in biomedical research. By bringing their unique perspectives and abilities to bear on key research questions, these visionary scientists may develop seminal theories or technologies that will propel their fields forward and speed the translation of research into improved health.

Three NIH Director's awards were initially created—the Pioneer Award, the New Innovator Award and the Transformative Research Award—to encourage creative, outside-the-box thinkers to pursue bold, unconventional ideas about biomedical research. A fourth award in the High Risk-High Reward Research Program, the NIH Director's Early Independence Award, was created in 2011 to support exceptional early career scientists who possess the intellect, scientific creativity, drive and maturity to flourish independently immediately following their graduate training, eliminating the need for traditional postdoctoral training.

By focusing on investigators rather than investigations, the high risk-high reward research programs, which represent more than one-third of the total Common Fund budget, enable us to address a range of disciplines from new perspectives.

Pioneer Award

The NIH Director's Pioneer Award initiative began in 2004 as an experiment to test novel ways of fostering innovation and high-impact research. It was meant to complement the NIH's traditional, investigator-initiated grant programs by supporting individual scientists of exceptional creativity, who propose pioneering—and possibly transforming—approaches to major challenges in biomedical and behavioral research. To be considered pioneering, the proposed research was to reflect ideas substantially different from those already being pursued.

The first nine award recipients were selected in September 2004 in areas ranging from stem cell biology to protein engineering. Now entering its 11th year, the Pioneer Award has supported 132 scientists from all career stages.

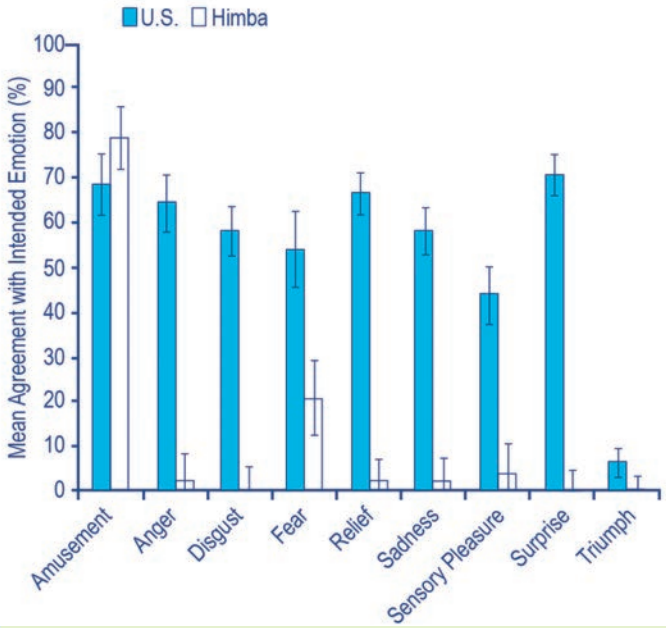
The multistage review process for the Pioneer Award is distinct from the traditional NIH peer review process. Applicants must emphasize novel, pioneering experimental approaches substantially different from those already being pursued in the investigator's laboratory or elsewhere, rather than focusing on specific aims or details of the approach as is customary for most research grants. Also unique to this process, finalists must participate in an in-person interview. Awardees commit the major portion

(at least 51 percent) of their research effort to activities supported by the Pioneer Award. Once the awards are provided, the investigators are given flexibility to adjust their projects as necessary to achieve transformative results.

A recent assessment of the Pioneer Award program led to the conclusion that the research it supported was highly innovative and higher impact than standard research grants. Awardees, who receive up to $500,000 per year for 5 years, often forge entirely new scientific directions, paradigms and techniques. The assessment compels the Common Fund to continue to support the Pioneer Award initiative and celebrate the trail-blazing opportunities it provides.

SCIENCE OF EMOTIONS

The NIH Director's Pioneer Award supports exceptionally creative scientists who propose bold research that seeks to establish or challenge fundamental paradigms. Pioneer Awardee Lisa Feldman Barrett, Ph.D., is an excellent example. Challenging the prevailing wisdom that emotions are hard wired into the brain as universal physiological responses, Dr. Barrett theorized that emotions are instead mental events that result from the interplay of basic psychological systems that are not themselves specific to emotion. Beginning with a steady stream of major reviews of the scientific literature, Dr. Barrett has been able to show that the majority of existing research does not actually support the current paradigm of hard-wired emotions.



Participants from the Himba tribe (from rural, northwestern Namibia) only recognized amusement/happiness expressions better than chance (white bars), whereas U.S. participants recognized expressions of all categories. These findings demonstrate that emotion is not universally recognized in expressions, as previously assumed.

Using experiential, behavioral, psychophysiological and brain-imaging techniques, Dr. Barrett's research focuses on understanding the construction of emotion—how the brain's domain-general networks provide the recipes for emotional experiences. Just as flour, water and yeast can combine to make a range of different foods, emotions such as anger are constructed in much the same way. The brain networks that realize several basic psychological operations—affect, conceptualization, language and executive control—combine like ingredients and interact to make a variety of mental states. As conceptual categories, these mental states, or emotions, have tremendous variability among individuals and cultures.

Dr. Barrett's research has created a paradigm shift in the science of emotion. Her theoretical and empirical contributions have fueled research across disciplines to better understand mechanisms that underlie emotion, the problems of which are at the root of every mental illness and contribute to the stress-related profile that encourages physiological diseases, ranging from heart disease to cancer. Truly, this is pioneering research.

NOVEL VIRUSES

The vast majority of human viruses originate in animals, that is, are animal viruses that jump over to humans. Scientists typically begin studying human viruses once they are already adapted to and spreading in humans, as in the case of HIV, SARS (severe acute respiratory syndrome) and H1N1 (swine flu). The Pioneer Award supports outstanding researchers who propose to undertake unusually innovative, and hence risky, research that if successful would have a large impact on biomedicine. Taking a novel approach, Nathan D. Wolfe, D.Sc., a 2005 NIH Director's Pioneer Award recipient, is collaborating with wild game hunters, and other human populations who interface with wild animal populations, in regions of high biodiversity to hunt down viruses before they establish a foothold in people.

Virologist Dr. Nathan D. Wolfe in the forests near the capital of Cameroon. Dr. Wolfe is working to predict and prevent pathogen threats in the jungle with bushmeat hunters who help collect blood samples from animals they hunt. Photo credit: Bart Nagel

In many parts of the world, hundreds of thousands of people still hunt and consume tropical wild game, called "bush meat." The practice has allowed viruses like HIV to leap from wild animals to humans—and then spread rapidly across populations. Traveling to far-flung and exotic locales in Central Africa and parts of Asia, Dr. Wolfe and his colleagues have been collaborating with people in these regions to create elaborate surveillance systems to monitor and track viruses. The surveillance is far reaching—Dr. Wolfe regularly receives dried-blood spots and other specimens from both animals and hunters in the regions. The specimens are taken to laboratories where they provide the initial stages of a map of the viruses in each region that can potentially jump to humans. Dr. Wolfe's data have led to the discovery of several previously unknown retroviruses (HIV is a known retrovirus), in addition to dozens of other microorganisms. His work underlies the importance of research aimed at understanding how viruses emerge and of the need for systems to detect novel viruses before they become pandemics. The Pioneer Award has allowed Dr. Wolfe the flexibility and resources to make these important advances.

New Innovator Award

The NIH Director's New Innovator Award addresses two important goals: stimulating highly innovative research and supporting promising new investigators. Many new investigators have exceptionally innovative research ideas, but not the preliminary data required to fare well in the traditional NIH peer-review system. As part of the NIH's commitment to increasing opportunities for new scientists, it created the NIH Director's New Innovator Award to support exceptionally creative new investigators who propose highly innovative projects that have the potential for unusually high impact. This award complements ongoing efforts by the NIH and its Institutes and Centers to fund new investigators through traditional research grants and other mechanisms.

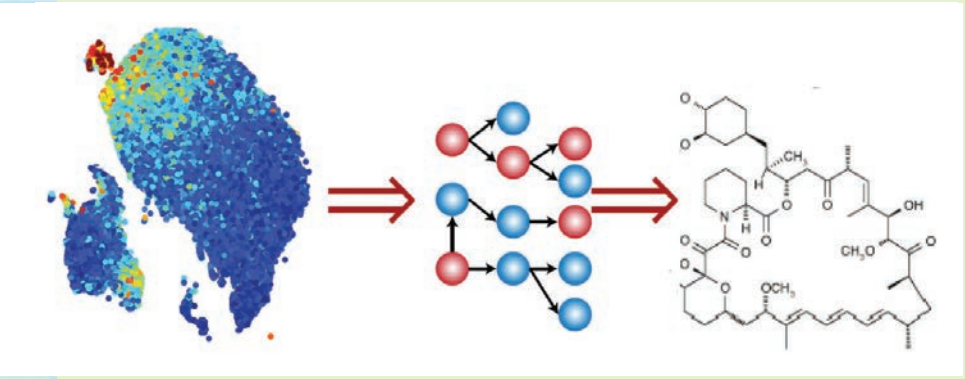
Established in 2007, the New Innovator Award supports investigators who are within 10 years of their doctoral degree or clinical residency, but who have not yet received an NIH research project to conduct exceptionally innovative research.

Novel review procedures facilitate selection of New Innovators based primarily on their creativity, innovation and potential to make a significant impact on science. Unlike traditional grant applications, preliminary data are not required and no detailed annual budget is required in the New Innovator application. Award recipients receive up to $300,000 per year to support a 5-year project period.

To date, the Common Fund has supported 308 early-stage investigators, providing them with maximum flexibility to allow for rapid and agile responses to unexpected leads and serendipitous findings.

USING SYSTEMS BIOLOGY TO MODEL RESPONSES OF TUMORS TO DRUGS

When Dana Pe'er, Ph.D., received her NIH Director's New Innovator Award in 2007, which supports exceptional investigators still in the early stages of their career, she was working with yeast, a simple organism with a small genome. Yeast was the perfect model for understanding how differences in DNA sequence lead to differences in observed characteristics, or phenotype. By looking at the sequence, molecular expression and cellular behavior in yeast and by integrating these in a computational way, she could begin to understand how DNA affects cell processing of signals and how these changes in signal processing alter behavior. Looking at how the many individual components work together to produce complex behaviors is termed "systems biology."



(Left) Single cell mapping of drug response using mass cytometry technology and the viSNE algorithm identifies the drug resistant cells. Each dot is a cell and the red cells are drug resistant. (Middle) Identifying and isolating the drug resistant cells enables inferring their tumor network and vulnerabilities. (Right) These vulnerabilities enable drug design to target these cells.

Dr. Pe'er found that her research approaches to yeast showed promise with cancer, a field with which she had no prior experience. The unusual research flexibility afforded by the New Innovator Award allowed her to easily alter her research program to follow this promising path. Working with melanoma, Dr. Pe'er observed that her computational methods could successfully predict how cancer cells, grown in a dish, would respond following specific perturbations to genes within the cancer cell's derailed regulatory network in order to see how it reacts to potential drug treatments. Because cancer is an individual disease, unique in how it develops and behaves in every patient, this novel approach has become instrumental in identifying causal mutations driving tumor progression and drug resistance. By understanding which molecular components go wrong in cancer cells, Dr. Pe'er and her colleagues can begin to shed light on how to target therapeutics at the individual level.

Now a leading systems biology researcher in the field of cancer and with the research infrastructure in place as a result of the New Innovator Award, Dr. Pe'er is beginning to identify and characterize the drug-resistant killer cancer cells that lead to tumor recurrence and eventually death. Understanding these resistant cells will inform development of better therapeutics. Dr. Pe'er's ultimate goal is to develop ways to determine the best drug regimen for each cancer patient by developing models that can predict how individual tumors will respond to certain drugs and drug combinations.

HOST AND PATHOGEN EVOLUTION

A computational geneticist, Pardis C. Sabeti, M.D., Ph.D., is developing algorithms to investigate the mechanisms and effects of natural selection on human and other genomes. Her background in malaria and interest in infectious diseases drew her to focus on Lassa fever, an acute viral hemorrhagic fever first identified in the Nigerian town of Lassa in the late 1960s. Not well understood, the virus is unusual in that it is both an immediate public health threat as well as a potential bioterrorist agent.

Working with collaborators from the United States, Nigeria and Germany, Dr. Sabeti's laboratory implemented infrastructure, training and field-deployable diagnostics at the Irrua Specialist Teaching Hospital in Nigeria, where yearly outbreaks of Lassa virus occur. They also partnered with the hospital to ensure the standard of care for all Lassa fever patients. Supported by the NIH Director's New Innovator Award, Dr. Sabeti and her collaborators are carrying out studies of Lassa fever epidemiology and human and viral genetic determinants of disease.

In addition, the flexibility of the New Innovator Award has allowed Dr. Sabeti to pursue interesting observations made in the course of her work that have the potential for great public health impact. The researchers collected blood samples from more than a thousand people, including many plagued by fevers of unknown origin. Based on analyses of the blood samples and her reading of the literature, Dr. Sabeti began to suspect that many more people had been exposed to Lassa virus than had been previously believed, raising the possibility that this virus is essentially an older pathogen whose improved detection led it to be labeled as emerging. Dr. Sabeti's research is identifying natural mechanisms of defense and illuminating the evolutionary adaptations that have allowed humans to withstand some of our most complex and challenging selective agents. Moreover, her research offers immediate translation into informing diagnostics and vaccines against the virus. Implemented more widely, this approach could create a worldwide surveillance capacity with the ability to monitor known disease agents (including prevalence and evolution) and to discover new disease agents.

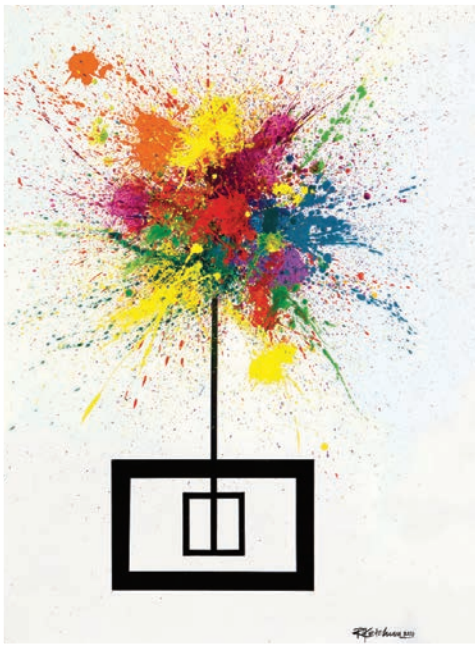
Dr. Pardis Sabeti puts on personal protective equipment with the help of nurse Veronica Koroma outside of the Lassa Fever ward at the Kenema Government Hospital in Kenema, Sierra Leone.

Transformative Research Award

Projects that have the potential to create or overturn fundamental paradigms often do not fare well in conventional NIH review. Yet, there must be opportunities for bold new ideas that often have inherent risk. The NIH Director's Transformative Research Award was created in 2009 to fill this need. As compared to the other NIH Director's Awards—the Pioneer Award, New Innovator Award and Early Independence Award—the primary emphasis of the Transformative Research Award initiative is to support research on paradigm-shifting, but untested ideas, rather than to support exceptionally creative individuals who wish to pursue new, potentially high- impact research directions.

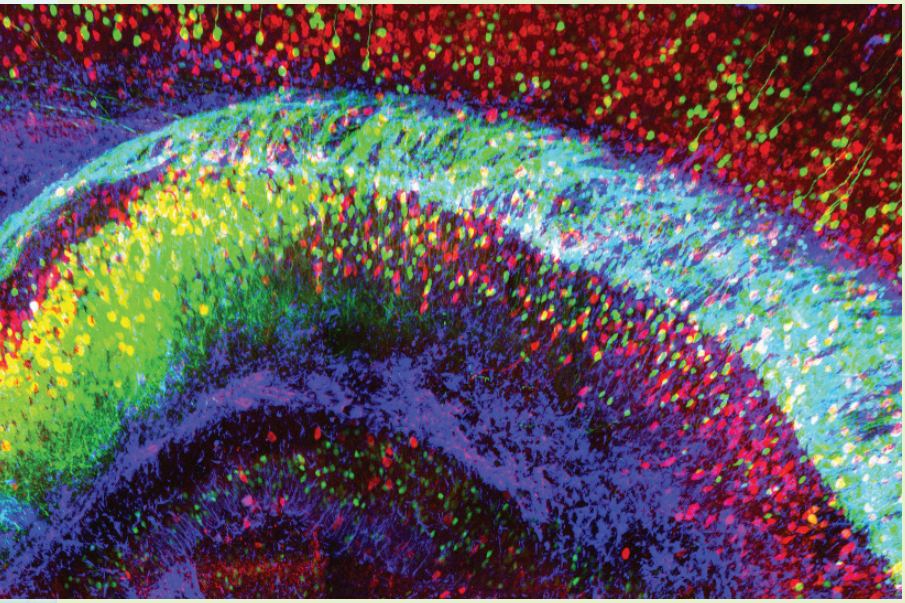
To encourage scientists to submit bold, high-impact ideas that are compelling despite the risks involved, the Transformative Research Award initiative uses unique approaches to application instructions and review. Applicants are instructed to focus their research strategies on significance and innovation without expectations of providing preliminary data. The review uses a multiphase process with explicit emphasis maintained on significance and innovation.

The NIH encourages Transformative Research Award applications from investigators in all disciplines relevant to the NIH mission, including the biological, behavioral, clinical, social, physical, chemical, computational, engineering and mathematical sciences. The award supports exceptionally innovative or unconventional research that may require large budgets (up to $25 million per year for 5 years) and multidisciplinary teams.



CLARITY

The human brain is amazingly complex, both in scale and in diversity, but it remains poorly understood. Obtaining high-resolution information from this complex system, while maintaining the global perspective needed to understand system function, remains a key challenge. Existing technology allows scientists to see neurons and their connections through thin slivers of tissue or reconstruction of the slivers into a 3-dimensional image. Until recently, imaging methods that keep the tissue intact remained inadequate.



An intact hippocampus showing projection neurons (green fluorescence), inhibitory interneurons (stained with an antibody in red) and supporting glia (stained with an antibody in blue). Deisseroth Lab, Stanford.

The NIH Director's Transformative Research Award supports outstanding researchers who propose to tackle fundamental challenges in biomedical research using highly innovative approaches. With support from an NIH Director's Transformative Research Award, Karl Deisseroth, M.D., Ph.D., and his colleagues have developed a new technique they term "CLARITY," which transforms the brain tissue into an optically transparent substance. Previous attempts to do this were thwarted by the fact that lipids—fats in the membranes of cells—obscure the view, and removing the lipids destroys the brain chemistry. Dr. Deisseroth and his colleagues have solved this problem using principles from chemical engineering. They infused a hydrogel, a network of polymers that form linkages with proteins already in the brain and with each other, into the brain tissue. The new hydrogel-tissue assembly supports the tissue and chemical structure, thus allowing the scientists to clear away the lipids effectively without destroying the biochemistry of the tissue. When the hydrogel-infused brain tissue is imaged through a light microscope, it is completely transparent, giving scientists a more precise picture of what is happening in the brain. Because the infused tissue is also permeable to molecules, scientists can add molecular markers to highlight specific features or areas of the brain tissue.

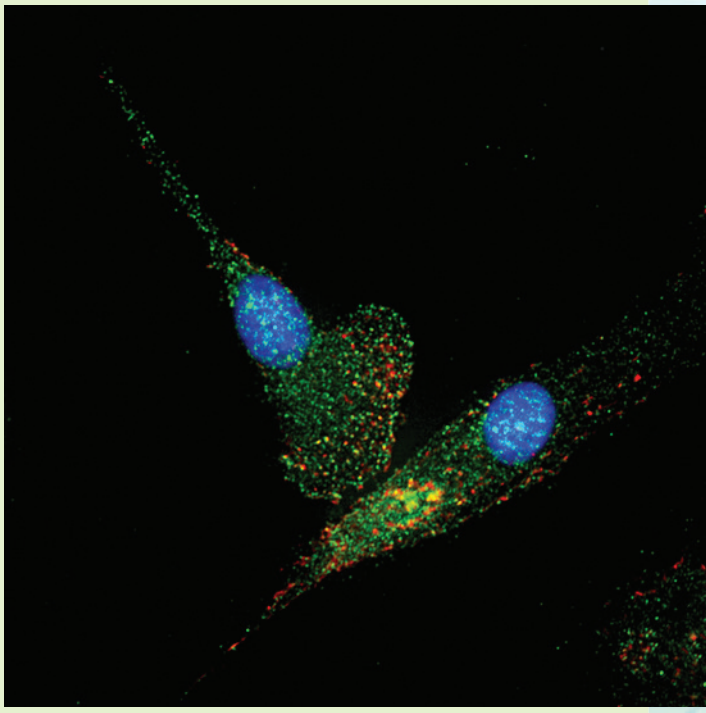
The technique is transforming our studies of the brain. By analyzing brain structures and matching them with molecular information, neuroscientists can now analyze how changes in the brain influence diseases such as autism, Alzheimer's disease, Parkinson's disease and depression. Still in its infancy, the technique is rapidly gaining wide use and is being applied to a range of human tissue, such as the heart and pancreas.

Dr. Deisseroth also received the NIH Director's Pioneer Award in 2005, using that support to develop another revolutionary technique, called optogenetics, which allows the use of light to switch specific brain activity on and off. Highly novel at the time, the technique is now used in thousands of laboratories to probe with exquisite control and detail how the brain functions.

SYNTHETIC BIOLOGY APPROACHES

As a result of her Transformative Research Award, which encourages groups of outstanding scientists to tackle important biomedical challenges, Linda G. Griffith, Ph.D., Massachusetts Institute of Technology (MIT), was able to bring together a team of scientists from a range of disciplines using a compendium of computational and experimental approaches, to focus on understanding how cell communication networks within and between cells are disrupted in inflammatory disease. Adding to what we know about individual pathways—actions among molecules in a single cell—Dr. Griffith and her colleagues are integrating tissue engineering with systems biology to develop tools that allow scientists to study how the whole network of pathways is functioning and to illuminate complex disease processes not well replicated in animal models.

Studying chronic and inflammatory diseases and cancer metastases, the team seeks to gain a more detailed picture of what goes wrong, enabling researchers to better target potential therapies. For instance, Dr. Griffith and her team have been studying endometriosis, an inflammatory disease that afflicts about 10 percent of women in their childbearing years. Starting in the lab and working through to the clinic, their studies revealed that the levels of certain immune proteins in some women with the condition seem to increase at a similar rate, suggesting for the first time that these proteins are acting together through a communication network. Moreover, these women also seem to suffer more pain from the disease. The MIT group's work offers the most comprehensive approach to understanding endometriosis to date and suggests that it might be possible to provide more effective and personalized treatment for women with the disease.



Macrophages from a patient with endometriosis stained for an activated enzyme jun kinase (green), a protein (red) and a blue nuclear stain. The recent discovery that jun kinase is a regulator of cytokine secretion points to the possibility of therapy directed at this target in a subset of patients.

Early Independence Award

In 2011, the Common Fund began testing a new approach to stimulate the biomedical workforce by providing the opportunity and resources for exceptional junior scientists to begin making their contributions to biomedical research earlier in their career.

The NIH Director's Early Independence Award provides an opportunity for remarkable junior scientists, who have recently received their doctoral degree or finished medical residency, to skip traditional postdoctoral training and move immediately into independent research positions.

Unlike many similar programs, the awards give them flexibility to seek a position at any suitable institution. Applicants work with the institution's academic leaders to obtain an independent position that would be activated if they win an award. For its part, the institution must provide the young investigator with space and resources, and a level of mentoring equivalent to that provided to assistant professors.

The program requires highly motivated and mature applicants who are talented and confident enough to launch their own research program and negotiate support from a department chair. And it requires institutions willing to support an award winner who will be unusually early in their career.

To facilitate the "matching" of prospective candidates with potential host institutions, the Common Fund has established a web resource in which host institutions can indicate their interest in hosting Early Independence awardees.

Postdoctoral positions will continue to expand the skills and experience of most young scientists. But for exceptional individuals with the intellectual and experimental sophistication to initiate an independent career at the end of doctoral training, this program provides the opportunity. Since its inception 3 years ago, the Early Independence Award has supported 39 bright young scientists with grants of $250,000 per year for up to 5 years, accelerating their entry into independent research careers and thus their impact on our nation's public health.

EPIDEMIOLOGICAL STUDIES OF VACCINATIONS

Just months before earning her Ph.D. in epidemiology, Nicole E. Basta learned that she had won one of 10 inaugural NIH Director's Early Independence Awards. The award granted her the resources to pursue her own independent research immediately after graduate school, without the usual postdoctoral training period of several years. Although not appropriate for every graduating researcher, it allows a few exceptional individuals to jump start their research careers. As an associate research scholar at Princeton University, Dr. Basta initiated a large-scale epidemiological field study to answer key questions about a new vaccine against bacterial meningitis recently introduced in Africa.

The new vaccine differs from other vaccines used to control epidemics in Africa in that it shows promise in eliciting a stronger immune response against meningococcal A meningitis, the strain of the disease historically responsible for most cases among people living in Africa's meningitis belt. It is also affordable—just $.40 per dose. What is not known is how long the protection will last.

Dr. Nicole Basta collaborates with clinicians and laboratorians from the Center for Vaccine Development-Mali to enroll participants in epidemiologic studies of vaccine-preventable diseases in Bamako, Mali.

To help answer this fundamental question, through the 5-year Early Independence Award, Dr. Basta is leading the MenAfriVac Antibody Persistence (MAP) study and collecting thousands of clinical samples from residents of Bamako, Mali, who first received the vaccine in December 2010 as part of the Meningitis Vaccine Project vaccination campaign. Dr. Basta and her clinical and laboratory partners in Mali are evaluating changes in immunity following the vaccine's introduction by measuring the persistence of antibodies within each person. The data will help the researchers to understand better why some people respond to the vaccine more strongly than others, identify risk factors, such as inflammation and poor nutrition that may lead to a shorter duration of immunity, and determine whether protective immunity is maintained in the population over time or if booster doses or catch-up campaigns are needed. The study will shed light on both the direct and indirect effects of newly developed vaccines to determine the most effective and efficient strategies for preventing, controlling and eliminating public health threats caused by infectious diseases. As part of the cohort of exceptional junior researchers supported by the Early Independence Award, Dr. Basta is making important independent contributions to science years before she might have been able to otherwise.

Interdisciplinary Research

Health research traditionally has been organized across disciplinary silos, lumping researchers into specialty areas where their efforts remain largely disconnected. However, as science has advanced, the NIH has become increasingly aware that the artificial separation between disciplines may impede the pace of scientific discovery. The NIH recognizes the need to integrate different scientific disciplines to accelerate discoveries about the complexities of human biology and behavior.

Early planners of the NIH Roadmap saw interdisciplinary research as essential in pushing biomedical research fields forward and accelerating scientific discoveries. The Interdisciplinary Research program was developed to change academic research culture, both in the extramural research community and within the NIH, such that interdisciplinary approaches to research are supported. Launched in 2004 and supported through 2012, the Interdisciplinary Research program made great strides in ensuring that interdisciplinary approaches and team science are a normal mode of conducting research and scientists who pursue these approaches are adequately recognized and rewarded.

The Interdisciplinary Research program brought together researchers from various scientific fields to tackle complex biological problems, accelerating research progress.

The Interdisciplinary Research program included four initiatives designed to dissolve academic department boundaries within institutions and increase cooperation between institutions, train scientists to cultivate interdisciplinary efforts and build bridges between the biological sciences and the behavioral and social sciences. These four initiatives were the Interdisciplinary Research Consortia, Interdisciplinary Research Training Initiative, Innovation in Interdisciplinary Technology and Methods and the Multiple Principal Investigators Policy.

Interdisciplinary Research Consortia

The Interdisciplinary Research Consortia were designed to allow teams of investigators to self-assemble to develop an interdisciplinary approach to solve complex health problems. In addition, they tested a new model of program administration within the NIH, in which the linked consortium awards were managed by a team of NIH program staff to ensure availability of appropriate scientific expertise to guide the Consortia. A total of nine Consortia were funded through this initiative, each bringing together experts from different scientific fields to tackle important challenges in biomedical research. Although Common Fund support for these Consortia has ended, the research launched through this program continues to be supported via NIH Institute and Center support, as well as through other organizations.

Researchers supported through the Consortia achieved many important scientific breakthroughs and significantly advanced our understanding of human biology. Researchers from the Genome Based Drug Discovery Consortium identified a natural compound derived from the long pepper plant that can selectively kill cancer cells but does not harm normal cells.[1] Within the Consortium for Neuropsychiatric Phenomes, researchers identified several genes associated with behavioral inflexibility in mice, a behavioral trait linked to psychiatric disorders such as attention deficit hyperactivity disorder, substance addition and schizophrenia.[2] Researchers from the Taskforce for Obesity Research at Southwestern Consortium identified a group of brain cells that mediate anti-diabetic actions of the brain chemical serotonin through regulation of blood glucose levels.[3] Through these and numerous other scientific advances, the Interdisciplinary Research Consortia have greatly enhanced our understanding of a broad range of human diseases.

Many of the Consortia also actively engaged in community outreach. For example, the Interdisciplinary Consortium on Stress, Self-Control and Addiction formed a collaboration with private and public community health projects to offer important tips on managing stress and addictive behaviors. The Taskforce for Obesity Research at Southwestern Consortium implemented obesity prevention programs at local schools, and the Oncofertility Consortium hosted weekend courses for inner-city high school girls to learn basic science techniques.

Interdisciplinary Research Training Initiative

Interdisciplinary training at all career levels prepares a workforce to undertake scientific challenges in innovative ways. Through the Interdisciplinary Research Training Initiative, investigators trained in one discipline were given the opportunity to learn a new discipline and merge it with their prior training to forge new scientific approaches.

This initiative included two major efforts. The Interdisciplinary Health Research Training program enabled institutions to develop postdoctoral training programs that provided formal coursework and research training in a new interdisciplinary field to individuals holding advanced degrees, typically integrating the behavioral and/or social sciences with more traditional biomedical sciences research. Another program, Training for a New Interdisciplinary Workforce, supported scientists at the undergraduate, graduate and postdoctoral levels.

Evaluations of training initiatives indicated particularly noteworthy contributions to biomedical research. Grantee institutions reported significant institutional changes, including the designation of faculty as interdisciplinary research experts, the creation of departments with an explicit interdisciplinary research focus, the awarding of matching funds from home institutions and consolidation of the administration of programs, or even integration of related programs into a single program. Importantly, while most grantee institutions reported providing interdisciplinary research training prior to the Interdisciplinary Research program, they noted that this program provided legitimacy and stable funding essential to sustaining interdisciplinary training efforts.

Innovation in Interdisciplinary Technology and Methods

Ensuring the success of interdisciplinary research depends upon scientists having the tools and resources needed to tackle this new approach to biomedical research. This initiative developed new methodologies and technologies to support the interdisciplinary integration of social and behavioral scientific disciplines with other disciplines. It supported various levels of analysis, ranging from subindividual to population levels, acknowledging that individuals are heavily influenced by actions occurring at various levels: from genomic, molecular, cellular and organ systems, to family, workplace and community levels, to state, national and global socioeconomic, environmental and geopolitical factors. One notable success was the development of OpenMX, a statistical package designed to manage interdisciplinary research data. The software is now being used by a number of research groups to address problems in multiple areas of science, such as behavioral science, genetics, chemistry, physics and materials.

Multiple Principal Investigators Policy

A major change for the NIH that was spurred, in part, by the Interdisciplinary Research program was the launch of the NIH's Multiple Principal Investigators Policy to recognize the contributions of multiple scientists on NIH grants. This policy is a clear indication of the enthusiasm of the NIH for interdisciplinary approaches and reflects the understanding that as researchers prepare to tackle the most complex biological problems, expertise from diverse fields will be required for a holistic and complete understanding of human health and disease. By recognizing team leadership, the NIH hopes to encourage institutions to reward and recognize successful science teamwork through career advancement.

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[1] Raj, L., Ide, T., Gurkar, A.U., Foley, M., Shenone, M., Li. X. et al. (2011). Selective killing of cancer cells by a small molecule targeting the stress response to ROS. *Nature, 475*(7355), 231–234.

[2] Laughlin, R.E., Grant, T.L., Williams, R.W., Jentsch, J.D. (2011). Genetic dissectioin of behavioral flexibility: Reversal learning in mice. *Biological Psychiatry, 69*(11), 1109–1116.

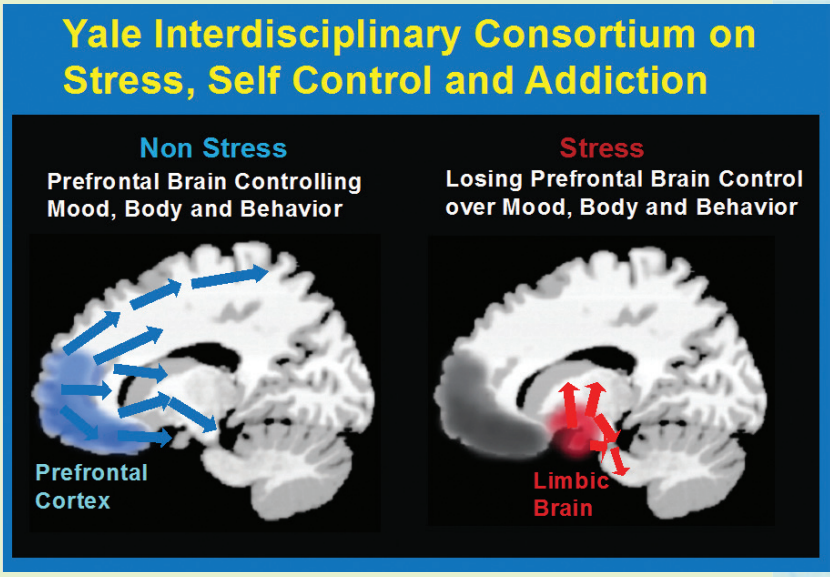
[3] Xu, Y., Berglund, E.D., Sohn, J.W., Holland, W.L., Chuang, J.C., Fukuda, M. et al. (2010). 5-HT2CRs expressed by pro-opiomelanocortin neurons regulate insulin sensitivity in liver. *Nature Neuroscience, 13*(12), 1457–1459.

INTERDISCIPLINARY RESEARCH CONSORTIUM ON STRESS, SELF-CONTROL AND ADDICTION

Tobacco smoking, alcohol consumption and overconsumption of high-fat foods are the top three causes of preventable death and disease in the United States today. The persistent and compulsive engagement in these behaviors despite serious health and social consequences is common. Emerging data indicate that self-control mechanisms are critical in perpetuating these compulsive behaviors. Moreover, stress, which plays a key role in addiction, other psychiatric illnesses and many chronic diseases, facilitates lapses in self-control. To better understand the complex three-way interactions between these phenomena, in 2008, the Common Fund supported the establishment of the Interdisciplinary Research Consortium on Stress, Self-Control and Addiction. The consortium consisted of over 50 leading scientists representing 20 disciplines and three academic institutions (Yale University, Florida State University and the University of California, Irvine). While Common Fund support for all Interdisciplinary Research Consortia ended in 2012, the Interdisciplinary Research Consortium on Stress, Self-Control and Addiction continues its important research via other sources of support. Thus, the initial Common Fund support achieved its goal of bringing together scientists from different scientific disciplines to catalyze research into this complex biological problem, establishing a resource of continued value and utility to the broader scientific community.

With Common Fund support and under the direction of Rajita Sinha, Ph.D. (Yale University School of Medicine), members of this consortium integrated the work of different disciplines to research stress and its relationship to self-control and addiction. The consortium sought to identify mechanisms underlying the development of stress-related effects on self-control in the addictive behaviors of smoking, drinking and overeating. Researchers also evaluated self-control mechanisms in the pathophysiology of chronic stress and addiction. Finally, the consortium sought to develop social, behavioral and pharmacological strategies to increase self-control and decrease these addictive behaviors. Research findings published by the consortium are shedding light on these issues. Their research has revealed that in times of stress, the brain's "executive control center," the prefrontal cortex, essentially shuts down, allowing more primitive brain regions responsible for compulsive behaviors and emotional responses to take over.

All of the consortium research findings were disseminated to both professional audiences and the public to address emerging health policy and bioethical issues raised by these studies. In addition to generating new scientific advances, this consortium also fostered career development and mentoring of students from varied disciplines.



This consortium focused on understanding brain mechanisms underlying stress-related increases in addictive behaviors and developing new strategies to break this association and therefore prevent related poor health outcomes.

Global Health

A map of Africa indicating cities that contain one or more H3Africa or MEPI grantees. These programs support research and/or medical education capacity building in 23 African countries.

Low- and middle-income nations suffer more than 90 percent of the world's burden of premature death. These countries, constituting three-quarters of the world's population, deal with a persistent cluster of infectious diseases, malnutrition and a growing incidence of chronic diseases and disabilities.

The NIH has a longstanding commitment to address both infectious and noninfectious diseases around the world through biomedical research and training. Strategic investment by the Common Fund is intended to attack these diseases by fostering teamwork among scientists and health organizations, by building infrastructure, and by increasing capacity to improve medical training and retention of trained personnel to understand and treat disease more aggressively.

The global health programs within the Common Fund focus specifically on building biomedical research capacity in Africa. At the same time, such research also will be relevant to the health of individuals in the United States and other countries worldwide, particularly those of African descent. As the goals of the programs are realized, the frameworks and human capacity necessary will be in place for the region to continue to take ownership of its research agenda and set priorities driven by local health needs.

Human Heredity and Health in Africa

Africa is the most genetically diverse continent in the world. As African populations suffer from a growing number of chronic diseases, the NIH recognizes the need to use new research approaches to help researchers understand the genetic components that contribute to infectious and noninfectious disorders affecting these populations. The field of genomics gives researchers an opportunity to study how all of a person's genes contribute to his or her health and well-being. The Common Fund and its partner, the Wellcome Trust in the United Kingdom, fund Human Heredity and Health in Africa, commonly known as H3Africa. The program supports the development of expertise among African scientists in the study of genomics and environmental factors of common diseases by investing in research, training, and infrastructure, and the establishment of networks of African investigators.

Researchers selected for H3Africa funding are establishing and, in some cases, enhancing local research facilities in their home countries to prepare for collection and storage of biological samples, or biospecimens; undertake research projects; and store data. In the past, biospecimens collected from African populations typically were sent to labs in Western nations for processing and future study. Regional biorespository pilot projects are under way in Africa, which eventually will house the samples collected through H3Africa research projects and make them available to the entire research community. H3ABioNet, a Pan-African bioinformatics network, is being developed to store, share, and analyze genomic and environmental data generated by H3Africa researchers. H3ABioNet also will develop training opportunities to teach researchers how best to analyze the large and complex datasets generated by genomic research.

By creating a sustainable research infrastructure and catalyzing the use of advanced genomic technologies, the NIH aims to identify risk factors that might be indicative of disease in populations of African descent. Possible outcomes of such research include early and more accurate diagnosis, the development of new drugs and personalized medicine.

H3Africa grants support scientists conducting genomic research on a variety of infectious and noninfectious diseases including kidney disease, diabetes, heart disease, obesity, tuberculosis, and African sleeping sickness. In concert with these studies, the H3Africa program is paying careful attention to the ethical, legal, and social implications of conducting genomic research in Africa and is providing funds to researchers investigating these implications. The combined NIH and Wellcome Trust H3Africa program now supports research projects in more than 20 countries throughout Africa.

Medical Education Partnership Initiative

Begun in 2010, the Medical Education Partnership Initiative (MEPI) is designed to build human capacity for health in Africa by strengthening medical education systems in an environment that values and nurtures research as part of a strategy to increase the number of quality health care professionals.

The initiative, created as a partnership between the NIH and the President's Emergency Plan for AIDS Relief (PEPFAR), provides direct support to 13 African medical schools in 12 countries. MEPI institutions work in partnership with U.S. institutions to strengthen medical education that ultimately will contribute to the response to and treatment of infectious and noninfectious diseases by expanding the pool of well-trained clinicians. The awards also build the capacity of local scientists and health care workers to conduct regionally relevant, multidisciplinary research, so that discoveries can be more effectively adapted and implemented in these communities and countries.

The Common Fund supports eight additional awards to provide supplemental funding to selected institutions in the MEPI network to develop much-needed expertise in a range of health fields, including emergency medicine, surgery, and maternal, newborn, and child health. Award recipients are also tackling the rising tide of chronic diseases, including cancer, cardiovascular and cerebrovascular conditions, and mental health disorders.

Through MEPI, supported African medical training institutions already have a diverse spectrum of research and educational activities underway to better respond to both urban and rural health issues. This includes improving institutional research support capacity and information and communications technology, including e-learning, curriculum revision, community-based training sites to better address rural health, and mentored research projects, among many other activities.

To date, NIH-managed MEPI programs have published 74 peer-reviewed articles, with many more manuscripts and research projects in progress. MEPI investments have given its researchers the necessary tools to independently secure international funding; one promising University of Zimbabwe researcher successfully competed and received a Grand Challenges Canada grant to further mental health research in his country. Each MEPI program has also worked to address faculty skills development to improve teaching and mentorship skills to train the next generation of African scientists more effectively.

MEPI participants are looking to sustain these positive changes by continuing to seek and procure investments from their countries' governments to further transform medical training in their region. Given MEPI's accomplishments, such investments have already been made in several MEPI institutions, including a $200,000 grant from Zimbabwe's Ministry of Higher & Tertiary Education and Ghana's Ministry of Health providing salary support to MEPI emergency medicine residents and many faculty.

Electronic resources are integral to modern medical training. MEPI funds are enhancing power supplies, wiring and equipment to improve Internet access. Courtesy of Richard Lord, the MEPI Coordinating Center & Fogarty.

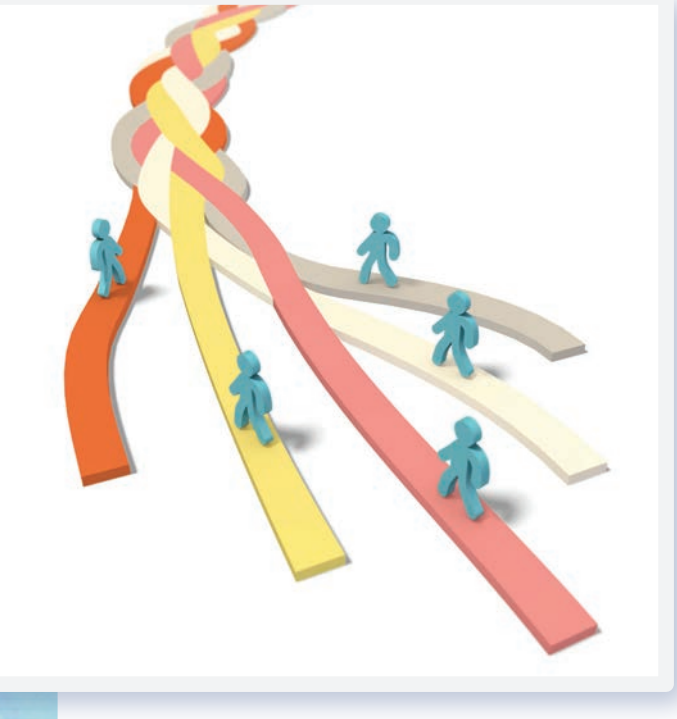
CAPACITY BUILDING ON THE CONTINENT

The NIH's investment in medical education and research conducted in Africa by African scientists is resulting in a growing synergy. Investments in training programs sponsored by the NIH Fogarty International Center and others have developed the framework to harness the catalytic potential of the Common Fund H3Africa and MEPI programs aimed at increasing medical and research capacity in Africa, strengthening research faculty and promoting the retention of health care providers.

There are several examples of African researchers who, after early training supported by the NIH, are now tackling some of the region's most troubling health problems with support from the Common Fund. For instance, Dr. Clement Adebamowo, an oncologist with the Institute of Human Virology in Abuja, Nigeria, is studying Africa's most common carcinoma—cervical cancer—as well as the vaginal microbiome and the human papilloma virus. Dr. Moses Joloba of Makerere University in Uganda now is a recipient of one of the H3Africa biorepository pilot study grants.

One of the ways H3Africa and MEPI are meant to augment biomedical research and training in Africa is by increasing the connections researchers and medical professionals in Africa have with each other. With over 20 countries supported through these initiatives, intra-continental collaborations are now becoming mainstream, empowering African researchers as never before. These synergistic and collaborative partnerships are poised to address today's global health challenges.

Strengthening the Biomedical Research Workforce



The NIH recognizes that there are many ways in which biomedical Ph.D. graduates can meaningfully contribute to biomedical research. A report issued by the Advisory Committee to the Director's Working Group on Biomedical Workforce indicates that only approximately 23 percent of Ph.D. graduates are currently working in tenure-track academic research positions.[1] Yet, despite a shortage of academic research positions and the broad range of career options available to Ph.D. biomedical students, graduate programs and postdoctoral training focus almost exclusively on preparing individuals for careers as academic researchers.

New approaches are needed to better prepare individuals seeking research-intensive careers in the private sector and in research-related areas such as science policy, technology transfer, science writing, entrepreneurship, research management or other areas requiring a research doctorate in biomedical science.

In 2013, the Common Fund launched the Strengthening the Biomedical Research Workforce program as one component of a broader NIH strategy to address workforce needs. This program supports the Broadening Experiences in Scientific Training (BEST) awards to develop innovative approaches to complement traditional training in biomedical sciences. These novel approaches will increase student and trainee exposure to multiple research-intensive and research-related career options, and may include coursework, rotations, workshops and hands-on training experiences (internships). Partnerships with nonacademic entities are encouraged to ensure trainees learn from established experts in the various career paths. Exposing trainees to a multitude of career paths that utilize their Ph.D. training will better

prepare them to enter the dynamic biomedical workforce landscape and ultimately strengthen the entire biomedical research enterprise.

The first 10 BEST award recipients were announced in the fall of 2013, and a second cohort is expected to be announced in the fall of 2014. The BEST awards utilize a novel mechanism, the NIH Director's Workforce Award to Enhance Biomedical Research Training (DP7). This mechanism aims to stimulate approaches to training and/or workforce management with the intent of promoting culture change in the field of biomedical training. Collectively, BEST awardees will evaluate whether their novel approaches are successful, share lessons learned and disseminate information about successful approaches to the biomedical research training community. The transformative potential of this program will be realized as successful models of training are disseminated and adopted nationwide.

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[1] National Institutes of Health, (2012). *Biomedical Research Workforce Working Group Report: A Working Group of the Advisory Committee to the Director.* Bethesda, MD. Retrieved May 14, 2013, from http://acd.od.nih.gov/Biomedical_research_wgreport.pdf [PDF - 4.4 MB].

"ASPIRE TO CONNECT" AND "BEYOND THE LAB"

Vanderbilt University Medical Center's Office of Career Development had already been laying the groundwork to broaden the experiences of graduate students and postdoctoral trainees to ensure they are well positioned to contribute effectively to the advancement of science in a range of research-related careers. This experience ideally poised the Office to successfully compete for one of 10 inaugural Broadening Experiences in Scientific Training (BEST) awards from the NIH's Common Fund. Their BEST award meant the Office could build upon previous experience to develop a much more extensive and sophisticated approach. Vanderbilt will use the BEST award to develop and implement ASPIRE, or Augmenting Scholar Preparation and Integration With Research-Related Endeavors. Serving more than 1,000 graduate students and postdoctoral trainees, ASPIRE taps into both internal and external partners to integrate career and professional development into their Ph.D. curriculum and postdoctoral research training.

Graduate students and postdocs from Vanderbilt University Medical School listen to the ASPIRE to Connect keynote speaker, Justin Graham, share practical tips on how to cultivate authentic professional connections. The annual ASPIRE to Connect workshop is a new initiative of Vanderbilt's NIH BEST award.

Co-directors Roger G. Chalkley, D.Phil., and Kathleen L. Gould, Ph.D., are generating a range of educational and experiential training opportunities to reach students and trainees at all levels. A required course for first-year graduate students includes a weekly mentoring session as well as informational sessions to enhance career development. Monthly seminars, posted online as part of a "Beyond the Lab" series, highlight interviews with Vanderbilt Ph.D. and postdoctoral alumni who discuss their career paths. The online videos from the "Beyond the Lab" series are available to students and trainees from any institution, expanding the impact of the ASPIRE program beyond Vanderbilt. Just recently, the program sponsored a half-day event, "ASPIRE to Connect," to give graduate students and postdoctoral trainees practical tips and techniques for cultivating professional connections. Workshops tackled such issues as getting the most from a scientific meeting, effective networking, developing an effective "elevator speech" and using LinkedIn. Plans are also underway to develop modules in areas such as business and entrepreneurship, teaching, and clinical trials management to enable trainees to develop knowledge related to careers outside academic research. By program completion, Drs. Chalkley and Gould will have crafted the educational and experiential tools and resources necessary to support a sustainable program that can be widely disseminated across biomedical research programs.

Enhancing the Diversity of the NIH-Funded Workforce

The NIH is committed to enhancing the diversity of its biomedical, behavioral, clinical and social sciences research workforce by supporting the training of students from underrepresented groups, including certain racial and ethnic groups, as well as individuals with disabilities and those from disadvantaged backgrounds. The attraction and retention of talented scientists from all sectors of the population is critical for achieving the NIH mission. The NIH expects efforts that diversify the workforce to lead to the recruitment of the most talented researchers from all groups, improve the quality of the training environment, balance and broaden the perspective in setting research priorities, improve the ability to recruit subjects from diverse backgrounds into clinical research protocols and improve the nation's capacity to address and eliminate health disparities.

Despite long-standing efforts by the NIH and other organizations, there remains a need for greater diversity in the biomedical research workforce. While previous efforts have been successful at the individual level, the diversity of the biomedical research workforce remains inadequate at the national level. In response to recommendations from the Advisory Committee to the Director's Working Group on Diversity in the Biomedical Research Workforce, the NIH established the Enhancing the Diversity of the NIH-Funded Workforce program in 2013.[1] This program aims to develop and test new approaches to research training and mentoring on a large scale, drawing from social science research that suggests effective interventions to enhance persistence of underrepresented groups in research. Innovative approaches will be rigorously evaluated, and successful approaches will be widely disseminated to the biomedical research training community to enable nationwide impact. Proven approaches are ultimately expected to supplant less effective practices at both awardee institutions and at other institutions across the nation to have a broad and sustained effect on diversity of the biomedical research workforce.

The program consists of three highly integrated initiatives, in which awardees will work together as a consortium to determine hallmarks of success, including the competencies and skills required for a successful research career that extend beyond the science itself, and develop complementary training and mentoring approaches to enable young scientists to meet these hallmarks. The NIH will work as a partner with awardees and provide flexibility to adjust course as program efficacy is assessed.

The three program initiatives are:

- **Building Infrastructure Leading to Diversity (BUILD):** BUILD is a set of experimental training awards designed to learn how to attract students from diverse backgrounds into the training pipeline and to encourage their persistence to become future NIH-supported researchers. These linked awards will allow complex and diverse activities under the umbrella of one award.
- **National Research Mentoring Network (NRMN):** NRMN will establish a nationwide network of mentors from a variety of biomedical disciplines linked to mentees across the country, define best practices for mentoring at all career stages, provide training for mentors, and provide networking and professional opportunities for mentees.
- **Coordination and Evaluation Center (CEC):** CEC will rigorously evaluate BUILD and NRMN programs to determine the efficacy of the new approaches being tested and to adjust the program throughout its lifetime. CEC will also facilitate the development of consortium-wide hallmarks of success for trainees at all career stages and will serve as the focal point for dissemination of successful training and mentoring strategies to the broad biomedical research training community.

The Enhancing the Diversity of the NIH-Funded Workforce program is a high priority for the NIH as a whole. In addition to Common Fund support, every NIH Institute and Center is contributing funds in support of this program, and every Institute and Center will benefit from the knowledge gained by developing and testing novel methods of training and mentoring. This program will provide the entire scientific community with evidence-based assessments of the most effective ways to recruit and train the biomedical research workforce of the future.

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[1] National Institutes of Health, Advisory Committee to the Director, Working Group on Diversity in the Biomedical Research Workforce. (2012). *Draft Report of the Advisory Committee to the Director Working Group on Diversity in the Biomedical Research Workforce.* Bethesda, MD. Retrieved May 14, 2013, from http://acd.od.nih.gov/Diversityin%20the%20Biomedical%20Research%20Workforce%20Report.pdf [PDF - 3.4 MB].

Afterword

The many achievements of the NIH Roadmap/Common Fund are a testament to the power of coordinated vision-setting and program implementation. The Common Fund requires input from all stakeholders to establish a collective vision and continued input from experts in each program area during the implementation phase to ensure that deliverables have a transformative impact. The success of the Common Fund would not be possible without extraordinary leadership from hundreds of individuals who have contributed to planning sessions, review panels, external consultant panels and the projects themselves. The NIH values this input and looks forward to continued collaboration with the entire community as we move into our second decade.

Elizabeth L. Wilder, Ph.D.
Director, NIH Office of Strategic Coordination

James M. Anderson, M.D., Ph.D.
Director, NIH Division of Program Coordination, Planning, and Strategic Initiatives

National Institutes of Health
Office of Strategic Coordination – The Common Fund

NIH Pub No. 14-8013