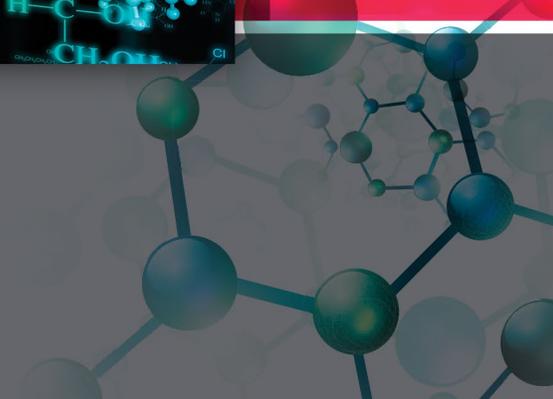


THE NIH COMMON FUND

Research Grantee Success Stories



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



FOREWORD

The National Institutes of Health (NIH) Common Fund is a unique funding source that allows the NIH to address wide-ranging opportunities and challenges other entities would unlikely address. Its creation was inspired by a growing need to conduct biomedical research through innovative and collaborative methods. As advances are being made at accelerated rates, diverse research fields are increasingly coalescing to capitalize on emerging opportunities. As new areas of research emerge and new technologies allow the ability to create large public resources, these efforts need incubation. The Common Fund fills this need by placing strategic investments into critical areas of research over a defined period, within 10 years, to lay the foundation for future support throughout the NIH Institutes and Centers.

The continuing success of the Common Fund is an outcome of its compelling founding principles and the leadership and dedication of many NIH staff with diverse expertise. However, without the creativity and enthusiastic participation of the research community, this would not be possible.

The research community across the country is critical for our strategic planning efforts to identify potential new programs, for input and peer review of new applications, and—most important—for conducting the research and producing valuable knowledge and resources.

For these reasons, we are proud to share with you just some of the many research grantee success stories that have emerged from Common Fund efforts. In this booklet, we highlight a few of the many exciting advances achieved through our diverse programs. Throughout the country, innovative Common Fund grantees are transforming the biomedical research landscape. As these ongoing efforts to advance research and improve human health continue, we are proud to share some truly exciting and important achievements from a selection of researchers who make the Common Fund's success possible.



*Elizabeth 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*

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INTRODUCTION

In 2002, then-NIH Director Elias 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 (ICs) 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 biomedical research capabilities and speed the movement of research from the laboratory to the patient’s bedside.

The NIH Roadmap was launched in 2004 and became the NIH Common Fund following the 2006 NIH Reform Act. Since its inception, the Roadmap/Common Fund has helped launch a number of far-reaching programs to address the expansion of new knowledge in biomedical sciences and growing challenges in public health. Common Fund programs are designed to change the way science is conducted through the establishment of new scientific fields or paradigms, development of technologies or methods that change the way scientists approach their work, and the generation of comprehensive data sets or other resources that catalyze investigator-initiated research and enable discovery.

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. **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 **cross-cutting** 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.

This booklet highlights a few of the many success stories made possible through Common Fund support. Research grantees are the engine of production, and across the country and globe they have made significant contributions aimed at improving human health through basic, translational, and clinical research efforts.

DISCOVERING NEW WAYS TO BLOCK CANCER METASTASIS



Dr. Asim B. Abdel-Mageed

DOCTORS HAVE FEW options when it comes to treating the spread of cancer, but research supported by the Common Fund's Extracellular RNA Communication (ERC) program may change that. Scientists recently discovered cells can produce RNAs, package them in vesicles or bind them to specific proteins, and secrete them from the cell to travel throughout the body. The ERC program aims to discover how these extracellular RNAs (exRNAs) are used by cells to communicate with each other, and what impact this cell-to-cell communication may have. ERC-supported researcher Dr. Abdel-Mageed, Zimmermann Endowed Professor of Cancer Research at the Tulane Cancer Center, and his research team have demonstrated that in prostate cancer, this cell-to-cell communication can be far from benign.

In a landmark study, Dr. Abdel-Mageed and his colleagues discovered a new mechanism by which prostate cancer uses exRNAs to spread. Stem cells from fat are attracted to the primary tumor site, where the tumor cells produce microvesicles containing exRNAs. When these stem cells interact with the tumor, they take up the exRNA-containing microvesicles and are transformed into cancer cells. Some of the exRNAs found in the microvesicles include RNA from two genes commonly involved in cancer, H-ras and K-ras. The microvesicles

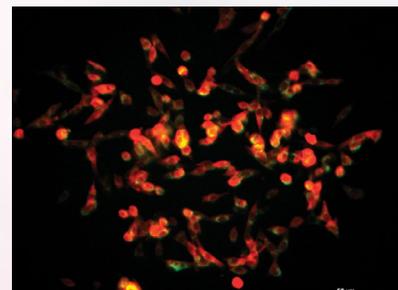
also contain small pieces of RNA that do not contain instructions for making proteins themselves (noncoding microRNA), but that can regulate the production of proteins involved in the development of cancer. Dr. Abdel-Mageed and his team demonstrated the ability of exRNA-containing microvesicles to spread prostate cancer in animal models, creating new growths that mimic tumors and causing the tumor to spread on a micro and macro scale. "Cancer is a death sentence if you can't prevent its spread," said Dr. Abdel-Mageed.

Funding from the ERC program is providing Dr. Abdel-Mageed with a unique opportunity to speed the search for new drugs to treat cancer patients based on his discovery of exRNA-based cancer metastasis. With support from the Common Fund, Dr. Abdel-Mageed and his team aim to find drugs that inhibit either the production of tumor-derived exRNA-containing microvesicles, their release from tumor cells, or their uptake by stem cells. To accelerate the discovery of effective drugs, Dr. Abdel-Mageed is focusing his research on drugs already approved for use in humans to treat other diseases or conditions. Precedents for drugs proving useful in multiple diseases include the anti-diabetes drug metformin, which other researchers have shown has anti-cancer properties. Through the ERC program, Dr. Abdel-Mageed is collaborating with the National Center for Advancing Translational Sciences (NCATS) intramural program at the NIH to search for drugs that can target exRNA-induced metastasis of prostate cancer.

NCATS will be using a panel of 4,000 drugs to screen. The researchers are starting with drugs that are most likely to act on exRNA-containing microvesicles, but that still leaves a daunting number of possibilities. To enable high-throughput analysis of large numbers of compounds, NCATS has developed robotic methods to facilitate the screening process. These screening

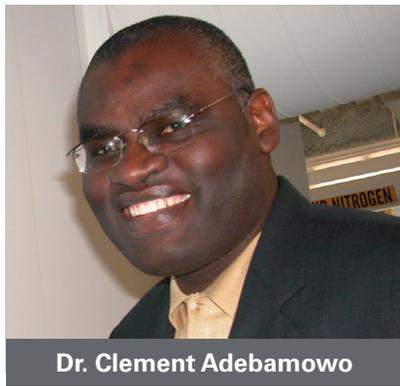
methods use biological assays, stem cells, and genetically engineered cells containing fluorescent read-outs of gene activity. After identifying drugs that are active against microvesicles in these screens, the team will study their mechanisms of action in depth. Dr. Abdel-Mageed noted that drugs that are promising in cultured cells and biological assays (*in vitro*) might not be as effective, in living organisms (*in vivo*). Because such processes as uptake, metabolism, and excretion come into play in living organisms, the next step after screening in cell cultures will be testing the drugs in animal models.

Metastasis has proven to be an extraordinarily difficult stage of cancer to treat. Dr. Abdel-Mageed's work provides hope that novel treatments for metastatic cancer will someday enable patients to live longer and healthier lives. The discovery of the role of exRNAs in metastasis opens the door to development of new, more effective treatments to curb the spread of cancer. Dr. Abdel-Mageed noted that exRNAs have been linked to the spread of cancers other than prostate, including melanoma, colon cancer, breast cancer, and glioblastoma. He speculated that the spread of cancer via exRNAs might be a unifying phenomenon for many types of cancer. If this hypothesis is proven correct, a drug targeting exRNAs to prevent the spread of prostate cancer might be useful to prevent or treat other cancer metastases.



Photomicrographs depicting microvesicles (green) in prostate cancer cells (red).

USING PUBLIC HEALTH STRATEGIES TO ELIMINATE CERVICAL CANCER



Dr. Clement Adebamowo

DR. CLEMENT ADEBAMOWO'S path in public health began in Nigeria with his training in medicine and surgery. He furthered his studies in epidemiology, nutrition, and biostatistics at the Harvard School of Public Health and is now Professor of Epidemiology at the University of Maryland School of Medicine as well as the Director of Strategic Information, Training & Research at the Institute of Human Virology, Nigeria.

Dr. Adebamowo studies one of the most common cancers that affect women, particularly in low- and middle-income countries: cervical cancer, which is caused by the human papilloma virus (HPV). HPV infection is ubiquitous—it is estimated that 80 percent of all women are infected worldwide—but only a subset of these women will develop cervical cancer. Although a vaccine is now available against HPV, the vaccine does not protect the women who are already infected. Vaccination will, however, reduce the number of infections in the future.

With the support of the NIH Common Fund, Dr. Adebamowo is seeking to identify the factors that differentiate the women infected with HPV who develop cervical cancer from those who do not. To answer this question, he and his team collect data about lifestyle and behavioral factors that may influence the development of cervical cancer. He also investigates the vaginal microbiome's contributions to disease



Dr. Adebamowo trains the next generation of epidemiologists in cutting-edge laboratory techniques.

susceptibility. So far, Dr. Adebamowo has found evidence that the microbes inhabiting the vagina play an important role in HPV persistence and in the body's ability to defend itself against infection. The hope is that these findings, combined with future discoveries, will produce a better understanding of the course of events from HPV infection to the development of cervical cancer, leading to more effective prevention and screening strategies.

In addition to his research supported by the NIH Common Fund, Dr. Adebamowo is leveraging the President's Emergency Plan for AIDS Relief, whose activities focus on populations in Nigeria and Zambia, to augment his research program and to offer public health services and disease screening. Since the project began in September 2013, it has exceeded the target enrollment by 30 percent, demonstrating the need for public health services in these underserved communities. Dr. Adebamowo's combined biomedical research and health services have clear benefits for women in lower-middle-income countries, who now have access to cervical cancer prevention and screening services. The biomedical research and public health services can also

inform each other. Data collected about the women receiving care through the health services can be used to study other important women's health issues. For example, the HPV vaccine is relatively new; the data collected through Dr. Adebamowo's program will be useful for measuring the effect introducing the vaccine has on women's health.

Dr. Adebamowo is also using his NIH Common Fund support to train young scientists in Africa, build research infrastructure that otherwise would be difficult to obtain, and support multi-country collaborations. He recently received an additional Common Fund grant to study the ethical implications of genomic research in Nigeria. The purpose of this research is to use linguistic and culturally derived concepts of genomics and heritability in an indigenous African population to develop enhanced consent forms. Overall, Dr. Adebamowo's work aims to improve public health by understanding the underlying determinants of disease, providing access to health services, enhancing research training and infrastructure, and improving the processes used to obtain consent from research participants.

A NEW APPROACH TO TARGETING BREAST CANCER



Dr. Debra Auguste

DR. DEBRA AUGUSTE is using her NIH Director's New Innovator award to search for new therapies to treat one of the most aggressive and untreatable types of breast cancer. Dr. Auguste began her studies as a chemical engineer, earning her Bachelor's degree in chemical engineering from the Massachusetts Institute of Technology (MIT) and her Ph.D. in the same discipline from Princeton University. It was during her postdoctoral fellowship at MIT in Dr. Robert Langer's laboratory that she became interested in using biomedical engineering to enable translation of basic science research into clinically useful therapeutics. Today, as an Associate Professor of Biomedical Engineering at the City College of New York, she is developing targeted therapies for breast cancer patients.

Cancer cells express unique proteins on their cell membranes. These proteins are important for cell-to-cell communication and a host of other functions. They may also hold promise as important biomarkers and potential targets for therapeutic treatment. Traditional cancer treatments—radiation,

chemotherapy, and surgery—are of limited effectiveness after a cancer has metastasized, so there is a need to develop new approaches to therapy. One such approach would be to specifically target cancer cells by recognizing their unique biomarkers. This specific targeting would allow the therapy to seek out and destroy cancer cells that have spread throughout the body, with fewer side effects for non-cancerous cells.

Not all breast cancer tumors are the same. A particularly aggressive form of breast cancer is the "triple negative" form, which lacks the estrogen, progesterone, and HER2 receptors. This subtype of cancer has higher prevalence in young women and in African American women, and it is not clear what causes this disease to be more aggressive than other forms. Unfortunately, there is currently no therapeutic target for this type of aggressive cancer. To address this unmet clinical need, Dr. Auguste and her team have created a library of quantitative information about the proteins expressed on the surface of many different breast cancer cell lines. They have identified a new biomarker for triple negative breast cancer tumors. The new biomarker will not only be a useful diagnostic tool but also has potential to be a therapeutic target. She plans to expand the work to study the effect of inhibiting cell migration and recruitment involved in metastasis and angiogenesis.

Dr. Auguste credits the Common Fund's New Innovator Award for allowing her the flexibility to pursue interesting research directions that arose during her work. Many of the most interesting findings were not

expected when she originally designed the study, and it was invaluable to have flexibility to steer the project in the direction that showed the most promise. For example, Dr. Auguste was able to enhance her study by obtaining an increased number of patient samples and accessing additional imaging modalities. She also broadened her study to encompass breast cancer tissues of different ethnicity and age groups. Support from the Common Fund has enabled her to build fruitful collaborations with investigators at Harvard Medical School, Emory University, and the University of Florida.

Dr. Auguste's research has implications that extend beyond developing potential new therapies for breast cancer patients. She has developed a new approach for understanding cancer cells and treating disease, an approach that may be applied to other cancers. Dr. Auguste hopes to focus on translation and use the platform she has developed to drive the creation of commercially viable treatments.

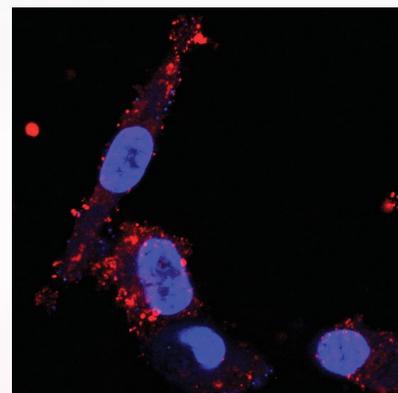
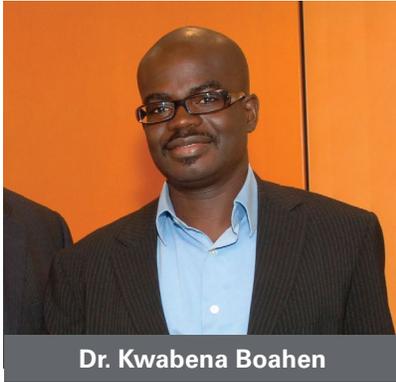


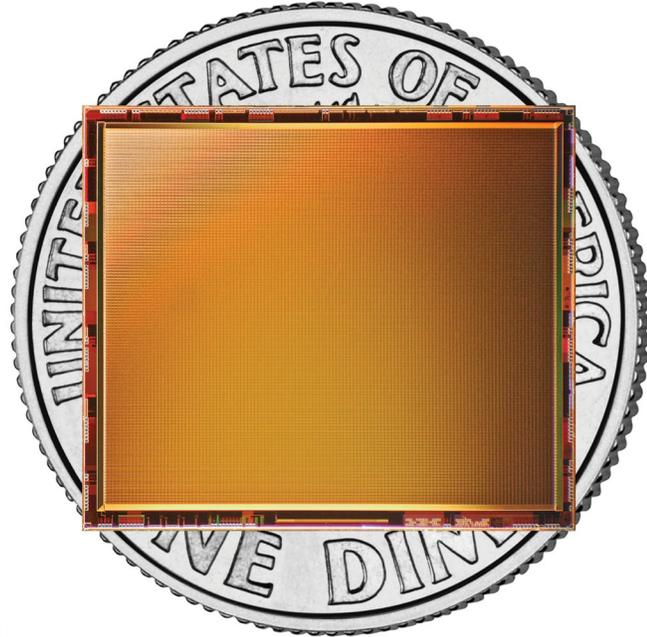
Image of peptide-targeted liposomes (red) that are taken up readily by a triple negative breast cancer cell line.

BUILDING BETTER BRAIN-MACHINE INTERFACES



Dr. Kwabena Boahen

DR. KWABENA BOAHEN'S research takes place at the intersection of engineering and neuroscience. A recipient of the Common Fund's NIH Director's Pioneer Award in 2006 and the NIH Director's Transformative Research Award in 2011, he has designed a novel computer chip that emulates the circuitry of the brain's neurons and their synaptic connections. This chip allows researchers to conduct large-scale neural simulations at a fraction of the cost of supercomputers, an expensive technology that most researchers do not have access to. By creating a platform for more efficient neural simulations, Dr. Boahen hopes to solve one of the major questions in neuroscience: how low-level phenomena at the scale of neurons and synapses give rise to complex system-level behavior, such as cognition and memory. This technology enables large-scale neural simulations that may help researchers understand brain disorders, which affect more than 10 percent of the population. This technology may one day be used to understand and develop treatments for diseases and conditions such as paralysis, stroke, Alzheimer's, Parkinson's, and more.

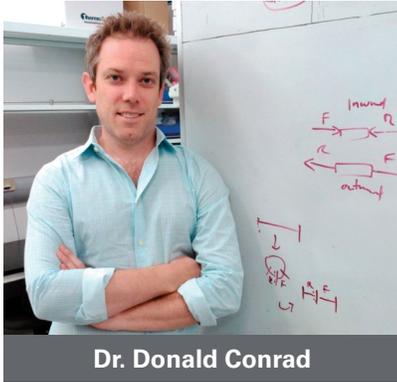


A photo of the Neurocore, placed on a dime for scale.

Dr. Boahen received his Ph.D. in computation and neural systems from the California Institute of Technology in 1997 and is now Professor of Bioengineering at Stanford University. In 2011, he teamed up with Dr. Krishna Shenoy, a collaborator in electrical engineering at Stanford and a 2009 Pioneer Awardee, to design better brain-machine interfaces. This team received a Transformative Research Award for a high-risk, ambitious project to design computer chips that could replace damaged brain tissue, which can occur as a result of stroke, injury, or disease. The computer chip will be implanted into a brain, interpret neural signals, and translate them into control signals that will connect to a machine. The chip will allow human brain cells to communicate with a computer, paving the way for better prosthetic

development. A major challenge for the team is to design a chip that is energy-efficient. A standard computer chip generates too much heat and would damage the delicate brain tissue. The team's innovative design for computer chips would allow electronics to be implanted inside the brain to decode complex brain signals. In the future, the team hopes that their design of better brain-machine interfaces will lead to a more natural and intuitive way to interact with computers and other machines. This research will also advance a "general understanding of who we are as people, and what makes us different from computers," explains Dr. Boahen. Understanding the neural basis for consciousness, cognition, and memory is fundamentally a quest to understand what it means to be human.

MAPPING GENETIC MUTATIONS TO UNDERSTAND HUMAN DISEASES AND FIND THE WAY TO SOLUTIONS



Dr. Donald Conrad

WITHIN THE NIH COMMON FUND'S Genotype-Tissue Expression (GTEx) project, Dr. Donald Conrad and his research team at Washington University in St. Louis are creating an “atlas” that will map somatic mutations, or DNA changes that are not inherited from one’s parents, but that arise during development or throughout the lifespan. This atlas will be generated from samples obtained from a large cross-section of the U.S. population.

We are each born with a set of genes, inherited from our mother and our father. These genes may be expressed differently in different parts of the body, turning on and off to make, for example, lung or brain cells. If something goes wrong and a mutation occurs—because of exposure to toxic chemicals or random errors that happen during cell growth—normal cells can transform into malignant cancer cells. Little is known about how frequently these nonhereditary or somatic mutations occur and how often they cause cancer or contribute to other human diseases.

That’s where the atlas comes in. The goal of creating the atlas is to understand how

common these somatic mutations are, their causes, and their relationship to human disease. Dr. Conrad noted that although everyone knows somatic mutations must occur throughout the body, no one to date has attempted to systematically map them.

Without resources from the GTEx Common Fund program, “it literally would be impossible for any small research lab, like mine, to do this analysis,” said Dr. Conrad. “Our analysis of somatic mutation is a ‘bonus’ for the human genetics community because it was never envisioned in the original GTEx proposal.” He cited the atlas as indicative of many unexpected applications and questions that can be pursued with minimal additional cost using something as large, innovative, and high-quality as the GTEx database.

Even single cells from the tissues collected within the GTEx project have new stories to tell. Dr. Conrad has developed collaborations with other researchers to genetically sequence individual cells. The scientists have used this technique to investigate kidney development in animals. Their experiments revealed surprising variation in the extent to which some genes were turned on in individual kidney cells. This variability might have been hidden if gene activity had been measured in a larger piece of kidney tissue, which is the standard method. The technique holds promise for better understanding of human kidney disease.

Dr. Conrad’s laboratory also is seeking new methods to study a particular type of somatic mutation: DNA copy number variants (CNVs). These genetic changes are large deletions or duplications of genetic material. Dr. Conrad’s research team wants to learn the general “rules” for CNVs. When

do they perturb gene function, and when do they not? Why do some genes tolerate being deleted while others cannot? The GTEx project is providing the resources to characterize the impact of CNVs on genes being turned on or off throughout the human body.

Doctors want to know which CNVs are likely to cause disease. Already, studies have shown that CNVs are associated with a wide variety of disorders, such as Crohn’s disease, psoriasis, and osteoporosis as well characteristics such as body mass index. Dr. Conrad believes that the GTEx database will allow researchers to predict the human health consequences of very rare CNV mutations, whether inherited or somatic. For instance, in studies of severe, sporadic pediatric diseases, like autism or developmental delay, scientists sometimes see an extremely large mutation that deletes many genes. Intuitively, the researchers know that such a variant is likely to contribute to the disease, but when the mutation is very rare, establishing a cause-and-effect link between the mutated gene and the disease is difficult. Dr. Conrad and his research team are developing a tool to predict the “pathogenicity” or disease-causing ability of single CNVs. His laboratory is involved in solving the problem at all levels, from developing software for detecting CNVs in raw DNA sequencing data to characterizing the effects of the mutations in patients. Dr. Conrad is especially interested in studying the genetic basis of autism and infertility. He anticipates that a better understanding of their genetics, made possible by the Common Fund, will lead to new approaches to treating or curing these disorders.

PAIN, PAIN GO AWAY! INNOVATIVE APPROACHES TO REDUCING CHRONIC PAIN AND OPIOID USE



Dr. Lynn DeBar

AN ESTIMATED 116 MILLION Americans suffer from debilitating chronic pain, accompanied by risky long-term use of opioids to treat the pain. Dr. Lynn DeBar, a Senior Investigator at the Kaiser Permanente Center for Health Research in Portland, Oregon, hopes an innovative clinical trial—the Pain Program for Active Coping and Training (PPACT)—will provide big gains in identifying more effective and safer treatments for chronic pain, which is one of the most common and expensive public health issues.

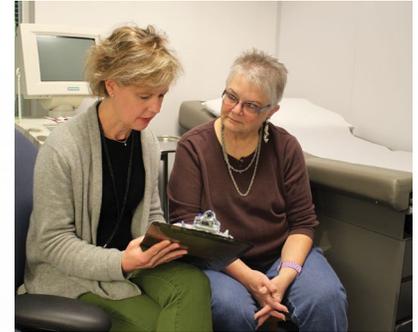
“It is of such grave concern to our medical systems right now that it was a problem they identified and came to me with,” says Dr. DeBar, who has a Ph.D. from Yale University in Clinical and Community Psychology and an M.P.H. from Oregon Health & Science University. Kaiser Permanente Northwest region operational leaders approached her with the complicated issue of patients who move among many health care providers and use many services involving several different specialties. Such patients,

who represent the most complex 15 to 20 percent of chronic pain sufferers, have not found relief with medications, surgery, or other single-dimension interventions.

Dr. DeBar used support from the Common Fund’s Health Care Systems Research Collaboratory program to conduct pilot studies that rigorously evaluated interventions to treat chronic pain involving several specialists—a nurse case manager, behavioral specialist, physical therapist, and pharmacist—working closely with primary care providers (PCPs) to support patients. “What makes it most innovative is that it is embedded in primary care,” Dr. DeBar says about the pragmatic clinical trial she is pursuing. The Common Fund has been instrumental in making the trial a reality because the Common Fund is designed to examine crosscutting issues that lack a home in any one NIH Institute or Center, and pain is a major concern that is relevant to many fields of biomedical research.

Following the pilot studies, Dr. DeBar is scaling up the program to encompass three Kaiser Permanente regions: the Northwest, Hawaii, and Georgia. In the full clinical trial, electronic health records will be used to identify patients with a particular PCP who meet the criteria of long-term opioid use and chronic pain. Researchers will ask PCPs to confirm that these patients are eligible for the trial and also to identify other patients who are in need of services, but who might not have been identified through the electronic health records.

Trial participation begins for each patient with a comprehensive multidisciplinary assessment involving a nurse case manager



Researcher Dr. DeBar working with a colleague on the PPACT study.

or behavioral specialist who conducts an intake evaluation, a physical therapist’s evaluation, and a pharmacist’s chart review. The patient’s information is summarized for the PCP, who communicates support for the patient’s involvement in the intervention. The intervention will consist of 12 group sessions over a 3-month period. Patients will receive cognitive therapy-based coping skills to help manage their pain and they will work on increasing their physical activity, including yoga-based adaptive movement training.

By the time the clinical trial is fully launched, Dr. DeBar and others will be working with at least 1,200 patients across the three Kaiser Permanente regions. In addition to patient interactions, the trial will help PCPs understand how behavioral factors, like increasing physical activity, can make a positive difference in patients’ lives. It will also help PCPs to guide patients toward implementing positive lifestyle changes that may bring some degree of much-needed relief from chronic pain.

UNDERSTANDING DISEASE THROUGH ADVANCED IMAGING TECHNOLOGY



Dr. Mary Dickinson

FROM WHAT BEGAN AS an interest in lasers, Dr. Mary Dickinson has established a career developing new microscopy technologies to peer into mouse embryos as they develop. “Imaging” these embryos, as it is called, helps researchers understand everything from the formation of birth defects to the genetic causes of common human diseases. Through a grant from the Common Fund’s Knockout Mouse Phenotyping Program (KOMP²), Dr. Dickinson is leading a team at Baylor College of Medicine that is advancing biomedical research by systematically imaging genetically altered adult and embryonic mice to better understand which genes are important to disease.

A common way for scientists to understand the function of genes is to delete (or “knockout”) the gene of interest in an animal model—such as a mouse—and then monitor the resulting traits, or phenotypes, of the mutant animal compared to a control animal (one with the gene intact). For example, deleting a gene important for the development of the eye might result in blindness or other vision defects. Some genes are critical for life, and when these genes are deleted, the animal dies as an embryo before birth or just after birth. Investigating the developmental stage at which the knockout mouse dies can

provide important clues to the function of the gene.

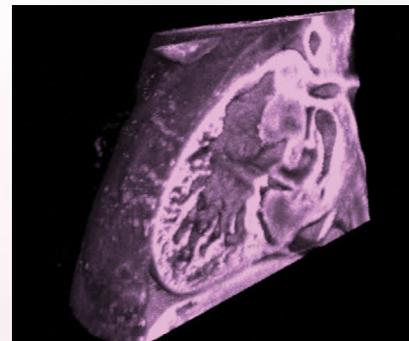
Scientists have been deleting genes and monitoring defects in laboratory animals for decades. The Common Fund’s KOMP² program is systematically characterizing an extensive collection of knockout mouse strains generated by scientists in the United States and abroad as part of the International Knockout Mouse Consortium (IKMC). KOMP² builds on the resources created by the IKMC and others by determining robust standards by which to perform the phenotyping and then carrying out this standard phenotyping of the mouse strains to identify and describe important defects. Currently, scientists understand the function of only a fraction of human genes. “Many of the genes we are working on in the analysis have never been annotated before, so I think the ability to link these genes to known diseases or even rare diseases is really profound,” says Dr. Dickinson.

As a graduate student in the laboratory of Dr. Andrew McMahon at Columbia University, Dr. Dickinson worked to characterize an exciting mouse phenotype, but was hindered by the lack of effective imaging tools. “I would wake up at night and wonder, ‘Why can’t we figure this out? Do we just not have the right tools?’” As a postdoctoral fellow in Dr. Scott Fraser’s laboratory, she began building the tools, first by establishing culture methods for live imaging of embryos and then by beginning to pioneer new technologies and methods. More recently in her own laboratory, she has been developing a laser imaging technique called optical coherence tomography (OCT) for live imaging of developing and adult mice. Dr. Dickinson has always been interested in the cardiovascular system and blood vessel remodeling, and OCT is well-suited for imaging living mouse embryos to identify and characterize cardiac and vasculature defects. She is now piloting techniques to

describe heart failure phenotypes in early development to better understand complex human diseases.

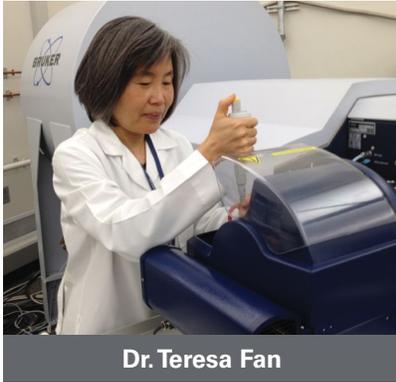
As part of a new KOMP² initiative, Dr. Dickinson began phenotyping knockout mouse embryos that die before birth—embryonic lethal strains—in the fall of 2013, and the project is already generating exciting results. For example, she found that a gene whose deletion results in an eye degeneration phenotype in the mouse also is involved in human disease. Dr. Dickinson’s laboratory is also testing new 3- and 4-D imaging technologies, such as high-resolution light-sheet microscopy for imaging heart development.

Importantly, the standardized KOMP² analyses and collection of data in a public database provides a critical resource to the research community, who can apply for NIH funding to study the mouse models based on the phenotypes described by Dr. Dickinson’s group and other researchers supported by the KOMP² program. “This is going to have a very long-lasting and high-impact effect on the way that we do science. It’s through these partnerships between local, government, and worldwide efforts that really enables you to do more than just what a single investigator could do.”



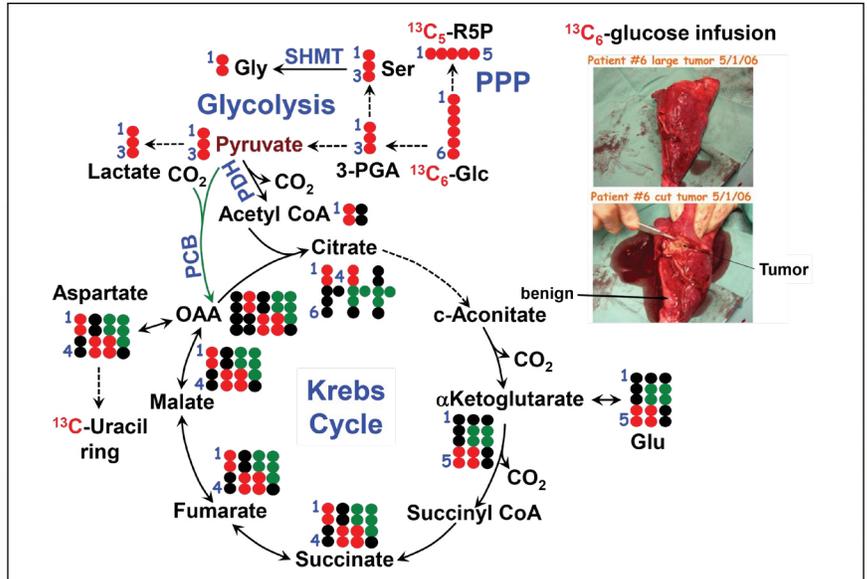
3-D projection image of an embryonic heart generated using advanced imaging technology.

TRACING THE METABOLISM OF CANCER



A CELL CAN BE THOUGHT OF as a factory in which different assembly lines—the metabolic pathways of the cell—interact to build the finished products that fulfill the cell’s role in an organism. An emerging science called metabolomics measures the nuts and bolts used to build cell products and even the scraps that end up on the factory floor. These outputs of cell metabolism are small molecules called “metabolites.” Metabolites give a picture of the here-and-now of how cells and tissues are functioning that is more immediate than information from genes and proteins. Understanding which metabolites are present under certain circumstances can provide valuable information about the health and well-being of an organism, allowing us to expand our knowledge of human health and disease through minimally invasive techniques.

As part of the NIH Common Fund’s Metabolomics program, six metabolomics resource centers were established nationwide. Dr. Teresa Fan, Professor of Toxicology and faculty member of the Markey Cancer Center and Center for Environmental Systems Biochemistry at the University of Kentucky, is one of the leaders of the Resource Center for Stable Isotope-Resolved Metabolomics. The Center provides training in sample preparation, experimental design, and data analysis.



Dr. Fan uses stable isotope tracers to study activated metabolic pathways in lung cancer.

Dr. Fan uses metabolomics to study cell metabolism in lung cancer. Using special molecular tools called stable isotope tracers, she can label certain types of metabolites and watch as they move through the complicated and interconnected network of biological reactions that contribute to cell metabolism. This kind of technique is like “tracing breadcrumbs in the forest,” says Dr. Fan. She traces her metabolite “breadcrumbs” through a “forest” of cancer cells grown in the laboratory, tumors in animals, and in human patients with lung cancer. Dr. Fan and her research team systematically probe the metabolic network of cancer in these systems to identify new cell processes that could be targeted with drugs and discover diagnostic markers for early-stage lung cancer.

Despite the impressive metabolomics work being done by Dr. Fan and others in her field, metabolomics is not a widely used technique. One of the major roadblocks to metabolomics use is that it remains difficult to identify the tens of thousands of metabolites

that exist at any given time in human cells. In addition, many metabolites are present in low concentrations or are unstable, making them difficult to detect using current methods. With a research grant from the Metabolomics program, Dr. Fan and her colleagues are developing ways to treat samples before analyzing them to increase sensitivity and stability. They are making chemical agents that can modify particular parts of certain metabolites, making them easier to detect. This approach could also enhance a researcher’s ability to identify previously unknown metabolites.

Dr. Fan sees metabolomics as a tool for understanding the regulation of human disease. She notes that a detailed understanding of the metabolism should be integrated with our growing understanding of other biological processes, such as how genes are turned on or off. Dr. Fan predicts that this integration will lead to a major leap in understanding disease initiation and progression, enabling new ways to diagnose and treat human disease.

A NETWORK OF HOPE FOR PATIENTS WITH RARE AND UNDIAGNOSED DISEASES



BEFORE PHYSICIANS can treat a disease, they must diagnose it. However, rare diseases and rare variants of common diseases pose many challenges for diagnosis and treatment. For patients suffering from a rare disease without a diagnosis, despite extensive efforts by their physicians, the Common Fund's Undiagnosed Diseases Network (UDN) provides a beacon of hope. Dr. William Gahl, Clinical Director at the National Human Genome Research Institute, is one of the clinicians providing hope to these patients, through his research at the NIH Clinical Center.

How common are rare diseases? A disease that affects 200,000 or fewer people in the United States is considered rare, and the rarest may present in only several hundred or fewer people. Approximately 6,000 of these rare diseases affect an estimated 25 to 30 million Americans. Many patients with a rare disease wait years for a diagnosis, which they desperately seek even if the disease is terminal. Even when a diagnosis is made, there are many challenges ahead for individuals with rare diseases because oftentimes effective drugs are unavailable. Drugs for rare diseases are seen as unprofitable and therefore not developed, and exceptions for using existing drugs may not be approved for the rare disease.

Established in 2014, the UDN brings together a cross-disciplinary team of basic and clinical researchers from seven university



systems to diagnose diseases, elucidate underlying biological mechanisms of disease, and identify treatments. The Network builds on the experiences and best practices garnered from the NIH's Intramural Undiagnosed Diseases program, which Dr. Gahl played a key role in developing and launching. The intramural program has made more than 70 diagnoses of very rare diseases since 2008. Using next-generation DNA sequencing—as well as NIH resources that include genomic data from the NIH Human Genome Project and expertise from the NIH's Clinical Center and Office of Rare Diseases Research—clinicians in the intramural program have helped diagnose patients whose conditions had stymied their physicians, identifying such chronic diseases as arterial calcification, storage diseases, inflammatory disorders, defects of sugar metabolism, and rare forms of amyotrophic lateral sclerosis (ALS). The work has yielded new insights into the genetic and biochemical mechanisms of disease and a deeper understanding of cell biology, biochemistry, and physiology.

By including an additional six clinical sites, the UDN will both draw upon the unique expertise of new clinical research groups and cultivate opportunities for collaboration among a larger group of expert laboratory and clinical investigators. Physicians within the network will collect and share high-quality clinical and laboratory data, including genomic information, clinical

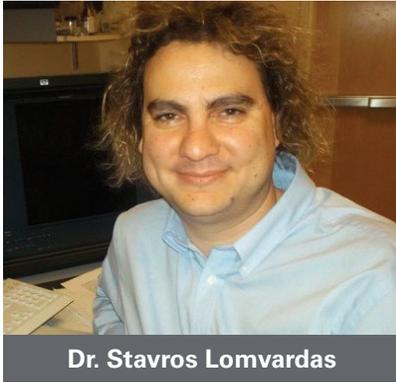
observations and documentation of environmental exposures. They also will benefit from common protocols designed to improve the level of diagnosis and care for patients with undiagnosed diseases. The network will also be able to leverage a database developed by the intramural program.

Dr. Gahl points out the advantage of sharing data on patients with rare diseases: "If a second case with similar presentation also has a mutation in the same gene, that's verification that the gene has caused the disease."

The Network's structure includes a Coordinating Center housed at Harvard University, which serves as a hub, collecting and making sequencing and phenotype data about rare diseases available to researchers from six university medical centers. The UDN also emphasizes training in next-generation sequencing techniques.

Dr. Gahl paraphrases Ernest Hemingway's words to the diagnoses of mysterious conditions: "The world breaks everyone and afterward many are strong at the broken places." Patients and their families cope with the desperation of not knowing what their disease is; their relief and gratitude at receiving a diagnosis is immeasurable. The UDN offers hope to patients and their families, and science moves another step toward illuminating precision medicine for all.

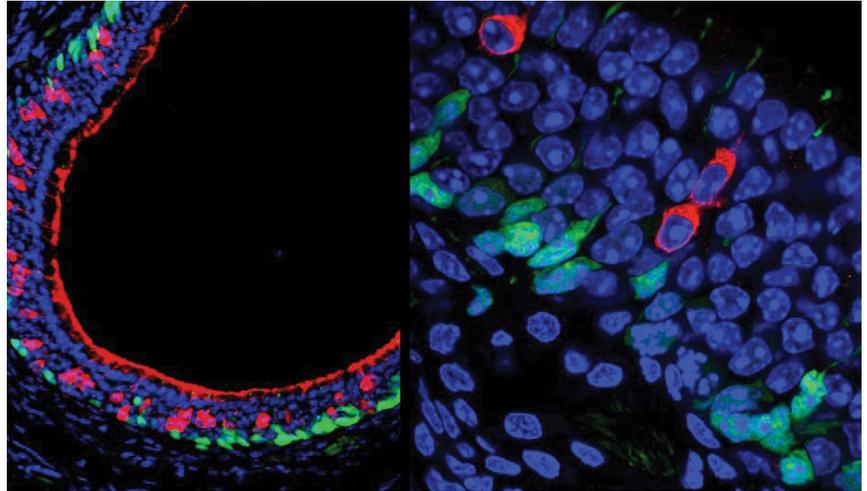
OLFACTION: REVEALING SECRETS OF THE BRAIN



Dr. Stavros Lomvardas

FOR DR. STAVROS LOMVARDAS, scientific research started with investigating a basic, yet fundamentally important question: Why does each sensory neuron, responsible for relaying information about odors, express only a single type of olfactory receptor? Although mammals have more than 1,000 olfactory receptor genes, the genes are expressed in a mutually exclusive way such that only one of them is expressed in each olfactory sensory neuron. To investigate this process, Dr. Lomvardas turned to epigenomics, the study of modifications to DNA and DNA-associated proteins that occur “on top of” the genome and can be associated with changes in gene expression or activity. A grant from the Common Fund’s Epigenomics program has enabled Dr. Lomvardas to collaborate with Dr. Caroline Larabell, a physicist at Lawrence Berkeley National Laboratory. Together, they have been studying the organization of DNA in the nucleus and the epigenomic markers on the DNA that play an important role in regulating gene expression, including regulation of olfactory receptor genes.

Dr. Lomvardas began investigating the mechanisms of gene regulation during his Ph.D. training and postdoctoral research at Columbia University in New York. Now an independent investigator at the University



Dr. Lomvardas uses fluorescent markers to study the regulation of olfactory receptors in the brain.

of California, San Francisco (UCSF), his Epigenomics grant is allowing him to further understand the mechanisms of gene regulation.

He discovered that one of the many possible olfactory receptor genes is chosen for activation by removal of epigenetic marks that silence gene expression. Interestingly, the enzyme that removes this epigenetic mark also causes a chemical reaction called oxidation, which leads to DNA damage and a concomitant increase in mutation rates. This finding offers a possible clue about a link between cellular processes involved in olfactory receptor gene expression and neuronal cell damage. In Alzheimer’s and Parkinson’s diseases, one of the first signs of neurodegeneration is deterioration in, or total loss of, the sense of smell. Dr. Lomvardas’ research began with the goal of investigating how cells express a single olfactory receptor, but it has led him to promising insights into understanding neurodegenerative diseases.

Dr. Lomvardas also investigates the role of the unfolded protein response in regulating

expression of olfactory receptors. The unfolded protein response is a mechanism to selectively remove defective proteins and is important for proper neuronal differentiation among other processes. Defects in this pathway are linked to many diseases, including Alzheimer’s, Parkinson’s, and autism spectrum disorders, suggesting another biological process linking olfactory receptor gene regulation and neurological disorders.

Dr. Lomvardas credits the Common Fund for enabling his work, none of which would have been funded with a traditional grant. The Common Fund’s Epigenomics program enabled him to conduct high-risk, high-reward research without requiring extensive preliminary data, and it made possible the extensive interdisciplinary collaboration that is not usually supported through traditional research grants. Moving his laboratory from UCSF back to Columbia University, Dr. Lomvardas will continue to work on deciphering the neurobiology of olfaction using basic neuroscience to better understand brain disease.

LEARNING THE BEST WAY: WAYNE STATE UNIVERSITY'S GRADUATE TRAINING FOR A NEW GLOBAL ECONOMY



Dr. Ambika Mathur

AS PH.D. SCIENTISTS know all too well, the traditional career path leading into academia has narrowed dramatically, with only approximately 25 percent of graduates joining university faculties in tenure track positions. What careers await the other 75 percent, and how can trainees learn about these careers and prepare for what they may undertake in the future?

To address this challenge, the Common Fund launched the Strengthening the Biomedical Research Workforce program to enhance training opportunities for biomedical graduate students and postdoctoral scholars in a variety of career options within the biomedical workforce. Through the Broadening Experiences in Scientific Training (BEST) awards, this program is supporting universities to develop and implement new approaches to increase trainee exposure to multiple research-intensive and research-related career options in areas such as industry, government, business, communications, and more. The 5-year awards are designated as research grants as the awardees will be responsible for a rigorous evaluation of their new training activities: They are charged with determining which approaches work and for whom. Under the leadership of Dr. Ambika Mathur, Dean of the Graduate School, Wayne State University is using its BEST award to help doctoral students make the transition into the global job market.

"Having this grant awarded gave us the impetus to make the change," says Dr. Mathur. "It's not just a group of us sitting around the coffee table and talking—the power of the NIH is behind it. We needed that impetus to make the point that this is where we can make the cultural change [in the research training environment]. This is where Wayne State can establish itself as a leader in graduate education."

How is Wayne State approaching the challenge? Through its BEST program, the university is training doctoral students, postdoctoral fellows, and faculty to recognize, appreciate, and prepare for diverse career opportunities beyond academia: teaching, communication, business, law, community engagement, and government agencies. As one component of this program, a summer internship pilot project has attracted 45 applicants, with approximately 20 interns placed in teaching, industry, and other positions for 8 weeks. "It's a very good opportunity that the NIH has provided to support careers outside academia," Dr. Mathur proudly says about the pilot's success.

Wayne State's approach is unique, emphasizing urban issues and the inclusion of doctoral students and postdoctoral fellows who are outside the School of Medicine but focused on health-related issues. "We are happy to include trainees from social work, communication, and other fields. Our program has 150 participants in its first year," she notes.

Building the program was not easy. One of the greatest challenges was winning faculty buy-in and participation. By holding numerous discussions with faculty groups, Dr. Mathur was able to achieve almost complete faculty support. Key to that success was engaging trainees interested in the BEST program in these meetings and sharing NIH data about biomedical graduate career tracks. A recently hired career services director is helping to further solidify Wayne State's BEST program across the university.

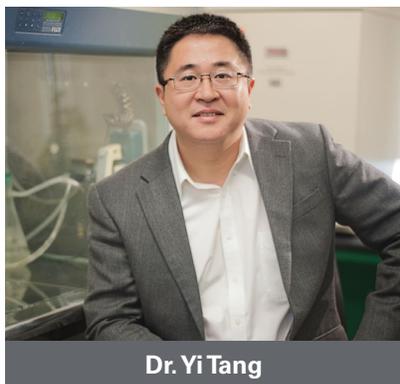
Collaboration with other BEST awardees is an important program component. For example, Dr. Mathur moderated a panel discussion with five other BEST awardees at the 2014 annual meeting of the Association of American Medical Colleges during the Graduate Research Education and Training (GREAT) section. The panel is designed to enhance communication between universities, highlighting their successes and sharing experiences.

Dr. Mathur appreciates the power of the Common Fund's BEST award to transform the academic culture and training mindset at Wayne State. This award aims to positively influence graduate students' and postdoctoral scholars' careers, helping them to make the best of a rapidly changing biomedical workforce that is creating unforeseen opportunities for scientists who are willing and eager to learn from the BEST.



Graduate research and scholarship showcased at Wayne State University.

REDISCOVERING NATURAL CHEMICAL DIVERSITY



A PLETHORA OF DIVERSE chemicals exists in the natural world, yet many of these molecules remain a mystery. What potential drugs could be found in the plants, microbes, and organisms that live all around us? Dr. Yi Tang, NIH Director's Pioneer Awardee, is investigating ways to tap the full potential of microorganisms for producing small molecules of therapeutic interest. Dr. Tang, who earned his Ph.D. in Chemical Engineering from the California Institute of Technology in 2002 and is currently a faculty member at the University of California, Los Angeles, credits the Common Fund for allowing him to pursue high-risk, high-reward research that would not be supported through traditional grant mechanisms.

More than 50 percent of drugs are derived or inspired from natural products. Penicillin, an antibiotic produced by a fungus, is perhaps the most famous example of a natural molecule that revolutionized medicine. Compounds with antibiotic, antiviral, and cytotoxic (anti-cancer) properties abound in nature partly because organisms have evolved to produce chemical defenses and signaling molecules in response to the other organisms in their environment. Many common microorganisms have a variety of genes encoding enzymes that could synthesize unknown natural products, and therefore they may have untapped potential for producing new compounds of therapeutic interest. Dr. Tang estimates that only 10 percent of these genes are expressed

under normal conditions in the laboratory, and his research goal is to explore the full potential of the remaining 90 percent. Specifically, he is using bioinformatic methods and synthetic biology approaches to discover new enzymes in the genomes of microorganisms. He uses these enzymes to assemble new chemical pathways to engineer the synthesis of compounds useful for drug discovery. Ultimately, his goal is to realize the full potential of microorganisms in an effort to make therapeutically useful small molecules.

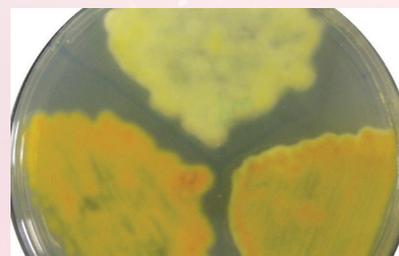
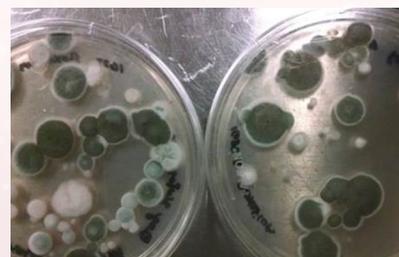
Although some researchers have gone to extreme environments (e.g., the Arctic) to search for new microorganisms that synthesize novel compounds, Dr. Tang remains excited about the potential of microorganisms closer to home. "There is still so much to be discovered right here," he says. His team already has sequenced the full genome of 30 microorganisms from such diverse habitats as soil and the guts of insects. Using bioinformatics approaches, they have sampled the diversity of enzymes encoded in these genomes and so far have discovered several new pathways that synthesize approximately 10 novel compounds



with interesting biological activities, such as antibiotic and cytotoxic properties.

In addition to discovering the true diversity of naturally produced small molecules, Dr. Tang's team has created tools useful to other researchers. For example, they have developed a system to express biosynthetic enzymes in yeast. From the bioinformatics data, the team is developing and refining methods to assemble synthetic DNA into artificial pathways in yeast, which can lead to production of the natural compound of interest. This method is easier and safer to use than attempting to culture different microorganisms in the laboratory, because some microorganisms are difficult to maintain in laboratory conditions and some are pathogenic to humans. The yeast expression system and the synthetic biology tools are useful to many other research groups in the scientific community.

Ultimately, tapping into the diversity of compounds that have evolved in nature over millions of years should bring to light much-needed new therapeutic compounds.



Dr. Tang's laboratory has developed methods to insert synthetic DNA into the yeast genome (left). These bioengineered yeast strains (right, top and bottom) are cultured to express enzymes in artificial pathways that produce natural compounds of interest.

REJUVENATING THE BRAIN IN OLDER MICE: ARE PEOPLE FAR BEHIND?



Dr. Saul Villeda

WITH THE MOST RECENT census showing there are more than 39 million people in the U.S. population ages 65 or older, a number projected to grow to more than 72 million by 2030, Dr. Saul Villeda is researching ways to counter cognitive deterioration in this rapidly growing demographic of older Americans. A recipient of the NIH Director's Early Independence Award (EIA), Dr. Villeda studies the possibility of reversing the aging process that occurs in the brain and affects cognition and memory, and he's had some tantalizing successes.

As a young neuroscientist in the laboratory of Dr. Tony Wyss-Coray at Stanford University, Dr. Villeda investigated the aging process by examining the nervous system's communication networks that infiltrate the entire body. Since aging affects the whole body and blood infiltrates and connects

all of the organs, Dr. Villeda focused his research on blood plasma for insights into aging. Using a surgical technique called parabiosis to connect blood circulatory systems between young and old mice, he found that the blood of older mice accelerated the aging process in young mice. Specifically, pro-aging factors in the blood of older mice have a detrimental effect on stem cells, learning, and memory.

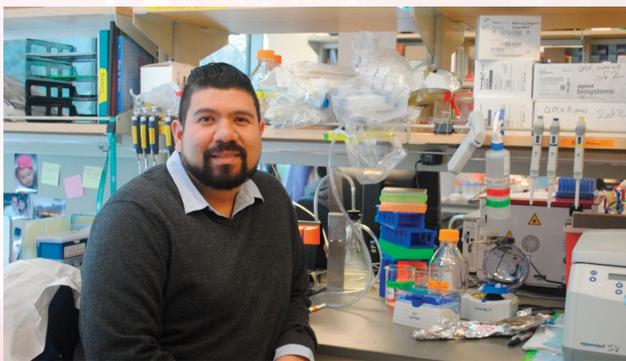
With the help of the EIA, Dr. Villeda ramped up his efforts at the University of California, San Francisco, and used his earlier insights about aging to begin researching the effects of adding young blood to older mice. Working with mice that were equivalent in age to 20- and 60-year-old humans, his studies have found rejuvenation in the brains of the older mice who received blood plasma from the younger mice. The young blood can restore stem cell function, increase the way neurons in the brain communicate, and enhance learning and memory.

Dr. Villeda divides his attention among the three hallmark characteristics of the brains of older adults: increased inflammation, loss of regeneration capabilities, and impairments in plasticity. Together, these pathological processes result in cognitive dysfunction. He reflects that the Early Independence Award "expanded the scope of what I would have done." Without it, he would have had to focus more narrowly.

He is grateful to the NIH for the opportunity afforded by the EIA. "It's an amazing program for people who've just graduated or done a very short postdoc to start their own laboratory. That's a unique position to be in." Noting his own fast rise to an independent laboratory, he encourages young researchers "to take a risk and be fearless."

Dr. Villeda's laboratory covers a broad spectrum of research, from molecular biology through behavior, and now has turned to understanding aging-related mechanisms. What remains dormant in the older brain that can be reawakened to make older brains function more like young brains? How do the age-related changes seen at the molecular and cellular levels of neurons contribute to decline, and how can these changes be reversed? He uses such tools as gene arrays and viral molecular tools to tease apart the master regulators within the neuron stem cells that promote the rejuvenating effect.

It may seem like a science fiction movie, but the work of Dr. Villeda is science, not fiction, and before long, it could help reduce the incidence of Alzheimer's disease and other diseases of aging. "To give a young scientist all the freedom to explore the idea of reversal of aging is pretty high risk," he says of his EIA. With that risk may come high rewards if it becomes possible to rejuvenate older brains to ward off age-related cognitive decline.



Dr. Villeda focuses on high risk-high, high-reward research on the aging brain. Using genetic and molecular tools, his laboratory explores cognitive dysfunction and regeneration of the brain in mice with the aim of improving and restoring cognitive abilities in older people.



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