

ADVANCES

In Heart, Lung, Blood, And Sleep Research



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Since 1948, the NIH's National Heart, Lung, and Blood Institute (NHLBI) has supported fundamental discovery science, translational and clinical research, and medical innovations that have helped people all over the world live longer, healthier lives. In 2018, we remain committed to working in partnership with voluntary and other organizations to improve prevention and treatment of heart, lung, blood, and sleep disorders.

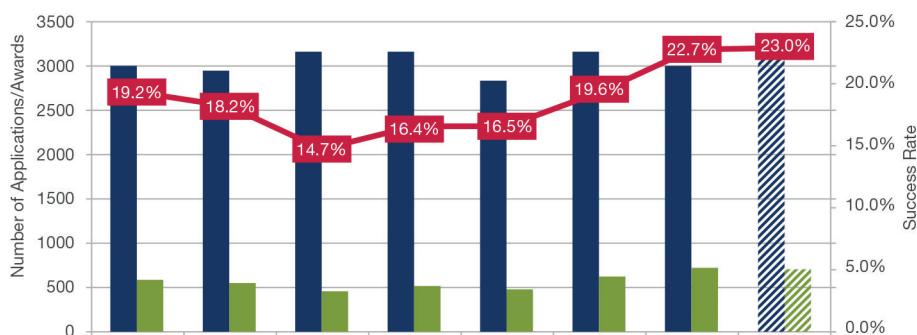
We continue to dedicate the majority of our research funding to investigator-initiated research project (R01) grants. Indeed, in fiscal year 2017, we were able to maintain high paylines* and success rates for R01 grants (see graph). R01 success rates

have steadily climbed since 2010; they have stabilized at about 23 percent for most applicants and 30 percent for early-stage investigators (ESIs). Clearly, we need to continue nurturing a talented, diverse workforce to sustain our mission. Thus, we will continue to focus on training and developing ESIs through high paylines for career development awards and research grants.

As we enter our 70th year, we can mark many achievements and opportunities across the spectrum of research—from basic biology studies to clinical trials. While investigator-initiated projects remain the lifeblood

of NHLBI-supported research, our Strategic Vision, released in August 2016, serves as the map for Institute-guided activities for the next decade. The Strategic Vision leverages emerging tools and technologies to advance our understanding of human health and disease and to translate these discoveries into state-of-the-art therapies. What follows is a sampling of recent scientific findings with the potential to advance the prevention and treatment of heart, lung, blood, and sleep disorders. We also highlight several programmatic efforts, as well as their alignment with the Strategic Vision. ●

Success Rates for R01 Applications from 2010 to 2017

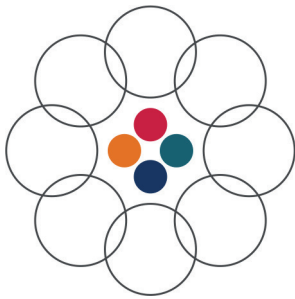


	2010	2011	2012	2013	2014	2015	2016	2017 Projected
# Applications	3019	2966	3,161	3168	2839	3164	3129	3081
# Awards	581	539	464	518	468	619	710	708
Success Rate	19.2%	18.2%	14.7%	16.4%	16.5%	19.6%	22.7%	23.0%

of Applications# of AwardsSuccess Rate

* The payline is the percentile score above which grant applications are generally not funded.

STRATEGIC VISION OBJECTIVES



- 1 Understand normal biological function and resilience.
- 2 Investigate newly discovered pathobiological mechanisms important to the onset and progression of HLBS (heart, lung, blood, and sleep) disease.
- 3 Investigate factors that account for differences in health among populations.
- 4 Identify factors that account for individual differences in pathobiology and in responses to treatments.
- 5 Develop and optimize novel diagnostic and therapeutic strategies to prevent, treat, and cure HLBS diseases.
- 6 Optimize clinical and implementation research to improve health and reduce disease.
- 7 Leverage emerging opportunities in data science to open new frontiers in HLBS research.
- 8 Further develop, diversify, and sustain a scientific workforce capable of accomplishing the NHLBI's mission.



BLOOD DISEASE RESEARCH

Boosting the body's cell clean-up process to treat blood disorders

New NHLBI-funded research highlights the potential clinical importance of a naturally occurring cellular process called autophagy in hematopoietic (blood-forming) stem cells, or HSCs. In general, autophagy helps keep cells healthy by recycling or destroying worn-down cell components.

- In one study, researchers derived HSCs from people with a rare disorder whose bone marrow does not make enough blood cells to keep up with demand. By testing more than 1,200 compounds on the cells, they found a small molecule that enhances red blood cell production by stimulating autophagy. This could serve as a model for future, large-scale chemical screens to identify potential drug therapies for other blood cell disorders.

- Another recent study found that autophagy may help preserve the regenerative capacity of HSCs as they age. This finding suggests a potential new approach to treating anemia. ●

Modifying bone marrow treatments for patients with sickle cell disease

Investigators in the NHLBI's Division of Intramural Research are developing new methods of bone marrow transplantation to treat sickle cell disease (SCD). While a bone marrow transplant from an immunologically matched donor can cure the disease in some young patients, this treatment is not an option for many. Ongoing studies include the use of innovative protocols to suppress immune rejection, enable less toxic transplants, and improve transplant efficacy when the donor is only a partial immune match to the patient. ●



Recent studies highlight how a naturally occurring process called **autophagy** affects red blood cell production.



Investigators in the NHLBI's Division of Intramural Research are developing **new methods of bone marrow transplantation** to treat SCD.

Strategic Vision in Focus: Curing Sickle Cell Disease

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Improving factor replacement therapy for hemophilia

Clotting factor replacement therapy can help many patients with hemophilia, but in others, it can trigger an immune response that limits the therapy's effectiveness. The NHLBI supports research on a number of ways to improve factor replacement therapy, including a clinical trial that is testing the safety and efficacy of gene therapy in people with hemophilia B. A pilot study found that almost half of the men who received gene therapy could stop their regular factor replacement therapy. ●

New understanding of the intricate machinery and characteristics of hematopoietic stem cells has led researchers to promising drug targets for blood disorders.

As many as 100,000 people nationwide—mostly African Americans—have sickle cell disease (SCD), which is caused by a mutation that affects the hemoglobin protein. The mutant protein causes sickle-shaped red blood cells that block blood flow and cause pain.

Thanks to basic research on hemoglobin and advances in genome sciences, researchers have corrected the SCD mutation in laboratory studies and are working toward genetic therapies that could benefit all SCD patients.

- The NIH and the NHLBI are leveraging these advances to launch the Sickle Cell Cures Initiative, which will mobilize researchers to develop and deliver new, safe, and effective gene and cell-based therapies to patients within the next 5 years.
- One strategy avoids risk of immune rejection by deriving blood-forming stem cells from patients with SCD, replacing or editing the cells' faulty hemoglobin genes, and re-implanting the corrected cells.
- These efforts will be enhanced by the expertise of the NHLBI intramural investigators, who are part of a multisite trial that combines stem cell therapy with gene therapy to deliver an “anti-sickling” gene to red blood cells.

Meanwhile, the NHLBI continues to invest in implementation research to improve the adoption of proven treatments for SCD, including the use of hydroxyurea for pain. The Sickle Cell Disease Implementation Consortium supports eight regional centers in the United States to assess and break down barriers to care for SCD. Since nearly 80 percent of SCD cases worldwide occur in sub-Saharan Africa, the recently funded Sickle Pan-African Research Consortium (SPARCO), consisting of a hub in Tanzania and collaborative sites in Ghana and Nigeria, will develop an SCD database, establish standards of care, and build capacity for future research. ●



Early clinical trial results show that **almost half of men** who received gene therapy for hemophilia B could stop their regular factor replacement therapy.



One approach under study for curing SCD combines stem cell therapy with gene therapy to **correct the defective gene**.

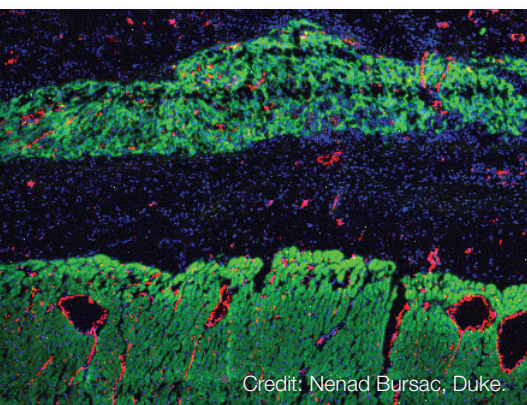


HEART DISEASE RESEARCH

Targeting inflammatory pathways in heart disease

Since the 1980s, when clinical studies established that aspirin could reduce the risk of secondary heart attacks and strokes, the NHLBI has invested in research to target inflammatory pathways with higher precision, better efficacy, and fewer side effects. Research on a pro-inflammatory protein called interleukin-1 has begun to yield promising new therapies now being tested in clinical trials.

- A recent industry-funded trial found that canakinumab, a drug that targets interleukin-1, reduced the risk of heart attack, stroke, and death by 15 percent among patients who had survived a prior heart attack.



Credit: Nenad Bursac, Duke.

- An NHLBI-funded trial is testing methotrexate, a low-cost, widely available anti-inflammatory drug, to determine if it reduces heart attack, stroke, or death in people with multiple coronary blockages or history of heart attack. ●

Reducing health disparities

Despite a large decline in overall death rates from cardiovascular disease (CVD), several groups—defined by gender, race, geography, and other factors—continue to experience a high risk of CVD and poor outcomes. The NHLBI is focusing on data from these groups to inform CVD prevention efforts in high-burden communities.

- A recent study found high CVD mortality rates throughout the U.S. heartland, from southeastern Oklahoma to eastern Kentucky.

Cardiopatches derived from human stem cells look and function like mature heart muscle when engrafted onto rat hearts.

- Researchers with the NHLBI's Strong Heart Study of American Indians are working with educators to implement a CVD prevention program in 10 medically underserved Montana towns. ●

Scaled-up cardiopatch to help with heart repairs

NHLBI-supported biomedical engineers have developed a fully functioning artificial human heart muscle. While most therapies for heart attack aim to reduce muscle loss, this newer strategy aims to replace muscle with heart tissue grown outside the body from human stem cells. Past heart muscle “patches” were miniaturized for use in rapid screening of new cardiac drugs, but this new patch is potentially large enough to replace damaged human heart muscle. ●

Guiding clinical practice in the treatment of CVD

The NHLBI continues to support research and activities that inform practice guidelines for the treatment of people with CVD.



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NHLBI-supported biomedical engineers have developed a **fully functioning artificial human heart muscle**.

Strategic Vision in Focus: The Power of Data to Personalize Medicine

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- The NHLBI-supported Cardiothoracic Surgical Trials Network (CTSN) facilitates collaboration of scientists and surgeons so that new therapies for CVD can move from proof-of-concept research into clinical trials. In 2017, the American Heart Association (AHA) and the American College of Cardiology (ACC) revised their guidelines for the management of mitral valve regurgitation (leakiness) based on two CTSN trials. These trials found that mitral valve repair offered no significant survival benefits over valve replacement and was associated with a higher risk of adverse outcomes.
- ACC/AHA hypertension practice guidelines released in November 2017 make a new recommendation influenced by findings from the NHLBI-led Systolic Blood Pressure Intervention Trial (SPRINT). The new guidelines suggest that high blood pressure greater than 130/80 mmHg should be treated earlier with lifestyle changes and, in some patients, medication. ●

Precision medicine is an emerging approach to disease prevention and treatment that considers each patient's unique characteristics, including their genetic makeup and environment. To support this goal, the NHLBI's Trans-Omics for Precision Medicine (TOPMed) program is collecting genomic and other molecular data that are expected to offer new insights into mechanisms of and potential therapies for heart, lung, blood, and sleep disorders.

- TOPMed has genomic data from about 120,000 diverse individuals enrolled in more than 60 NHLBI-funded studies.
- To discover new pathways and develop personalized interventions, researchers will integrate these genomic data with other information, including medical history, biomedical imaging data, socioeconomic status, and environmental exposures.
- The TOPMed dataset is included in a pilot launch of the NIH Data Commons, a new public-private partnership aimed at bringing research findings into a cloud-computing environment to improve data sharing, collaboration, and innovation.

Another effort to harness large robust datasets for personalized medicine emerged from SPRINT, which found that intensive blood pressure treatment can reduce heart attacks, strokes, and death in high-risk adults over age 50. To spur more heart disease prevention research, the NHLBI opened access to the complete primary dataset.

- The SPRINT Data Analysis Challenge, conducted in partnership with the *New England Journal of Medicine*, invited researchers to analyze the SPRINT dataset and use it to test a new hypothesis or develop a new approach to patient care.
- The winning team's tool enables clinicians to quickly assess whether specific patients should get intensive blood pressure management. ●



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TOPMed has genomic data from about **120,000 individuals** enrolled in more than **60 NHLBI-funded studies.**

A National Action Plan for COPD

The NHLBI has partnered with other federal agencies and voluntary health organizations to create the first-ever national action plan to address chronic obstructive pulmonary disease (COPD), released in May 2017.

The NHLBI has continued to lead collaborative efforts that were critical to the plan's development and is moving forward with the research priorities identified in the plan. In summer 2018, the first awards will be made through a program intended to increase the use of pulmonary rehabilitation for COPD, currently used by just 4 percent of eligible patients. ●

Understanding differences in lung disease risk and outcomes

COPD and asthma are complex diseases, and each one could reflect diverse underlying disease pathways. Researchers are exploring these pathways and defining unique disease subtypes to develop new, more precise, more effective treatments.

- Women have worse outcomes from COPD than men. A recent study analyzed genetic data from more than 10,000 people with COPD and found that variations in the lung development gene *CELSR1* were associated with COPD in women, but not men. Further study of sex-specific risk factors may enable new interventions to reduce death and disability from COPD in women.
- Based on prior NHLBI-funded research that led to identification of asthma subtypes, the NHLBI supports the new Precision Interventions for Severe and/or Exacerbation-Prone Asthma

The goals of the COPD National Action Plan

www.copd.nih.gov



Empower people to recognize and reduce the burden of COPD.



Improve diagnosis, prevention, treatment, and management.



Collect, analyze, and report COPD-related public health data.



Increase research to better understand and control the disease.



Translate policy recommendations into action.



A recent study analyzing genetic data found that **variations in a lung development gene** were associated with COPD in women, but not men.



The NHLBI is supporting new research focused on **biomarker-guided**, targeted interventions specific to asthma subtypes.

(PreclSE) Network. PreclSE focuses on biomarker-guided, targeted interventions specific to those subtypes and uses a trial design that allows researchers to continuously collect and analyze data, add new biomarkers, and adjust interventions as needed. ●

Understanding the progression of IPF

Researchers are beginning to understand how cellular aging contributes to idiopathic pulmonary fibrosis (IPF), which causes progressive scarring of lung tissue.

- A recent NHLBI-supported study found that cells in IPF patients' lungs have signs of accelerated aging and secrete factors that promote scar tissue.

The NHLBI is committed to **women's health** and to addressing the **unique health risks** that women face.

- Other NHLBI studies show that age-related shortening of caps on the ends of chromosomes, called telomeres, is associated with IPF and may be a useful diagnostic tool. ●

A focus on sleep disorders during pregnancy

The NHLBI is committed to women's health and to addressing the unique health risks that women face, including complications of pregnancy. Ongoing studies spun off from the NIH's nuMoM2b Study, funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), are examining how to improve outcomes for pregnant women who have sleep apnea.

- The nuMoM2b Sleep-Disordered Breathing Study, funded by the NHLBI and NICHD, found that these women have an increased risk of hypertension and diabetes during pregnancy.
- To build on this finding, the NHLBI and NICHD will



launch a phase III clinical trial in 2018 to determine if sleep apnea treatment reduces the risk of gestational hypertension, diabetes, and pre-eclampsia—a condition that can lead to seizures if not treated.

- The NHLBI recently launched the nuMoM2b Heart Health Study to assess how sleep-disordered breathing contributes to risk of CVD and other adverse outcomes *after* pregnancy. This knowledge may lead to targeted screening and treatment. ●



The NHLBI studies show that age-related shortening of telomeres is associated with IPF and may be a useful **diagnostic tool**.



The nuMoM2b Study found that women with sleep apnea have an increased risk of **hypertension and diabetes** during pregnancy.



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Strategic Vision in Focus: Regenerative Medicine

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Regenerative medicine uses stem cells and other biomedical tools—including engineered biomaterials and gene editing—to repair or replace damaged cells, tissues, or organs. The 21st Century Cures Act authorized the NIH to establish a Regenerative Medicine Innovation Project (RMIP) investing \$30 million in clinical research on adult stem cells over four years, beginning in fiscal year 2017.

The first projects funded through the RMIP focus on understanding and treating a wide range of diseases—from common conditions including diabetes, anemia, corneal and other eye diseases, and chronic skin ulcers, to rarer conditions including IPF, inherited skin disease, and SCD. The NHLBI is committed to moving the RMIP forward and has taken a lead administrative role in making this happen. ●

Key Milestones in the NIH Regenerative Medicine Innovation Project

Dec
2016

Congress passes the 21st Century Cures Act.

Apr
2017

In coordination with the FDA, NIH releases the first RMIP funding opportunities.

Sept
2017

Eight clinical research projects are selected for funding.

Dec
2017

NIH convenes an RMIP workshop to inform future funding opportunities.



National Heart, Lung,
and Blood Institute