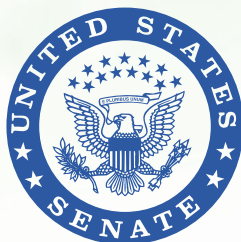




Investing in Innovation: The Payoffs of Funding Biomedical Research in Massachusetts



Prepared by the Office of Senator Elizabeth Warren

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Executive Summary

The National Institutes of Health (NIH) is the largest funder of biomedical research in the country and in the world. Each year, the agency invests billions of dollars in medical research, providing hundreds of thousands of researchers with the resources they need to fund scientific breakthroughs. Investments in NIH lead to improvements in the health and wellbeing of American citizens. Thanks in part to NIH-funded projects, the average American's life expectancy increased by eight years between 1970 and 2013.¹ And from 1988 to 2005, 47% of FDA approved drugs benefited from federally-funded research.²

NIH funding is critically important to the state of Massachusetts. The Commonwealth is home to dozens of world-renowned universities, hospitals, research institutions, and companies that rely on NIH funding to support their cutting-edge scientific research—research that benefits Massachusetts residents, U.S. citizens, and disease patients around the world. Each year, NIH funding supports thousands of jobs for Massachusetts residents and generates billions of dollars for the Massachusetts economy.

In spite of the obvious benefits of continued—and increased—NIH funding, President Trump has proposed cutting the agency's budget by nearly 20 percent.³ This budget, if passed into law, would be the largest cut in NIH funding since the NIH's founding in 1938, and threatens to devastate the field of medical research in the United States and Massachusetts—harming American citizens and people across the globe.⁴

To highlight the importance of NIH funding, the Office of Senator Warren contacted Massachusetts universities, hospitals, labs, biomedical companies, industry organizations, and patients to ask how access to NIH funding has influenced their health, their careers, their research, and their development of innovative scientific and medical discoveries. The dozens of respondents reveal:

1. **Massachusetts researchers, supported by NIH funding, have achieved scientific breakthroughs—transforming the way physicians treat cancer, blindness, and diabetes, among other diseases, and improving Americans' health and well-being.** Massachusetts scientists are using NIH grants to create new cancer drugs; develop new technologies—

like the bionic pancreas—to treat disease; studying ways to combat the opioid epidemic; combatting youth depression; and identifying risk factors for heart disease, among other critical endeavors. Dr. Daniel Kohane of Boston Children's Hospital and Harvard Medical School, for example, reports, **"We have recently developed an injectable device that would provide on-demand local pain relief. After the initial numbness wears off, patients could use a hand-held light or ultrasound device to get more local pain relief. This system would minimize and perhaps obviate the need for opioids... [which] could have an impact in preventing opiate prescription, addiction, and diversion, which are such a tragic problem in my state of Massachusetts and across the country."**

2. **NIH funding supports the careers of young Massachusetts scientists.** Public support for scientific research is often critical for the career development of young scientists. Numerous respondents described how access to NIH grants at critical points in their careers enabled them to stay in science, and they are acutely aware of the damage budget cuts could cause their careers, and the careers of their colleagues. Dr. Charles Corey Hardin of Massachusetts General Hospital, for example, recalls how **"[t]here were nine physicians in my fellowship class, all of whom trained in research. Currently only one other of my classmates and myself remain in science. The rest have left for other careers, largely due to lack of funding... Unless something is done to reverse the decline in funding, we will very likely permanently reduce our ability to discover cures for currently un-curable illnesses."**
3. **Publicly-funded Massachusetts research spurs developments in the private sector.** Analysts estimate that Massachusetts NIH funding in 2016 generated over \$6 billion in economic activity and supported over 31,000 jobs.⁵ Respondents described how federal funding allowed them to launch a company to market hemophilia drugs, patent cancer treatments, and work with the private sector to improve the treatment of ACL tears. Alnylam Pharmaceuticals, a Cambridge-based company, reports that **"NIH funding of approximately \$1.5 million... supported Alnylam Pharmaceuticals' founders' work at MIT and UMass on the gene**

silencing effects of synthetic short interfering RNA compounds in mammalian cells. These exciting gene silencing discoveries led to the founding of Alnylam which has been dedicated from its formation in 2002 to pioneering a new class of medicines based on RNAi technology.”

4. **NIH-supported projects in Massachusetts save lives and reduce health care costs in the U.S. and around the world.** As multiple Massachusetts researchers attest, investments in cutting edge scientific research can result in reductions in health care costs for millions of Americans. Furthermore, stories from Massachusetts demonstrate how the NIH’s role in promoting global health contributes to America’s role as a world leader in biomedical research. Sickle cell disease (SCD), for example,

“poses a major public health burden...and [amounts for] an aggregate charge for health care services of \$1 billion.” The goal of NIH-funded research at the Dana-Farber/Boston Children’s Cancer and Blood Disorders Center is “significant amelioration of SCD associated morbidity and mortality for the patients and significantly reduced cost to society in terms of medical care costs.”

These stories from Massachusetts make clear the shared success of NIH and Massachusetts’ researchers. NIH funding must be maintained—and expanded—to ensure the Commonwealth’s and the country’s continued leadership in the field of biomedical research, to spur economic growth, and to improve the lives of countless patients worldwide. Investments in NIH are investments in America’s future.

Introduction

A. Investments in NIH improve Americans’ health, drive economic growth, and establish America as a global leader in biomedical research.

The National Institutes of Health (NIH), the nation’s premier medical research agency, is the largest funder of biomedical research in the country and around the world.⁶ Housed within the U.S. Department of Health and Human Services, the NIH is comprised of 27 institutes and centers, including the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the National Institute of Mental Health.⁷ Each year, the agency invests billions of dollars in medical research to “seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.”⁸ In 2016 alone, the NIH allocated funding to over 300,000 researchers at 2,500 research institutions across the country and the globe.⁹

Federal funding for scientific research is an essential investment in the health and wellbeing of American citizens. Thanks in part to NIH-funded projects, the life expectancy of the average American’s life expectancy increased by eight years between 1970 and 2013; heart disease deaths fell by 67.5% from 1969 to 2013; and cancer deaths decreased by 15% from 2003 to 2012.¹⁰ These improvements in health are in part made possible by federally-funded scientific breakthroughs. NIH research has identified risk factors for heart disease;

reduced the number of children born with HIV; discovered new cancer treatments; developed new tools to combat opioid and other drug addictions; and reduced the death rate from unintentional injuries, among other scientific breakthroughs.¹¹ From 1988 to 2005, 47% of FDA approved drugs—including Gleevec, a “miracle drug” used to treat a rare form of leukemia—“benefited... from public-sector support.”¹²

In addition to improving Americans’ health, NIH funding helps boost the nation’s economy. NIH funds biomedical research in every U.S. state and almost all congressional districts—investments that generate \$65 billion in economic output nationwide.¹³ Discoveries fueled by NIH research spur innovation in the biomedical industry and beyond. For example, NIH-funded basic research on bacterial immune systems led to



breakthrough gene editing technologies that have spurred innovations and technology development in biomedicine, agriculture, clean energy, and specialty chemicals.¹⁴ In 2011 alone, these discoveries supported 7 million U.S. jobs.¹⁵ One dollar of investment in basic biomedical research generates, on average, \$8.38 of industry research and development investment.¹⁶ Economists estimate that, over a 27-year period, nearly 10% of NIH grants generated patents, while 30% generated research that is cited by patents—suggesting that “a \$10 million increase in NIH funding would yield \$34.7 million in firm market value.”¹⁷ And, by helping Americans lead healthier lives, NIH research further contributes to the nation’s economic health: gains in life expectancy from 1970 to 2000 added an estimated \$95 trillion to the U.S. economy.¹⁸

Public investments in scientific research also fund the next generation of U.S. researchers—helping to solidify America’s position as the world’s leader in science, technology, engineering, and math (STEM) development. The NIH funds grants specifically for young scientists to help “early career researchers... establish[] themselves as the experts in their chosen research areas.”¹⁹ Experts note that “the NIH has fostered the careers of individuals who have gone on to develop meaningful connections in human health outcomes and therapeutic interventions that result in the United States being global leaders” in STEM research.²⁰

By supporting the discovery of more effective disease treatments and management strategies, public investments in medical research also help reduce health care costs.²¹ Investments in cutting edge scientific research can result in reductions in health care costs for millions of Americans. And the NIH is not the only federal agency dedicated to reducing health care costs: the Agency for Healthcare Research and Quality (AHRQ), housed within the Department of Health and Human Services, seeks to “make health care safer, higher quality, more accessible, equitable, and affordable.”²² Since 2010, AHRQ-supported research has helped reduce the rate of hospital-acquired infections by 21%—saving the healthcare system an estimated \$28 billion.²³

The NIH also plays a leading role in international collaborations to fight infectious diseases like Ebola, HIV/AIDS, and influenza. The NIH’s Fogarty International Center “protect[s] the health and safety of Americans” by improving pandemic preparedness worldwide: the Center “build[s] scientific expertise in developing countries” and strengthens “local capacity to

detect and address pandemics.”²⁴

B. Public funding for scientific research helps the Commonwealth thrive.

NIH Funding is critically important to the state of Massachusetts. The Commonwealth is home to dozens of world-renowned universities, hospitals, research institutions, and companies that rely on NIH funding to support their cutting-edge scientific research—research that benefits Massachusetts residents, U.S. citizens, and disease patients around the world. In 2016 alone, around 200 Massachusetts grantees received a combined \$2.57 billion in NIH grants, \$80 million of which provided support for early-career scientists. That money, allocated in more than 5,000 individual grants, was spread across all nine of the state’s congressional districts. It helped sponsor nearly 100 clinical trials—benefiting disease patients as well as medical researchers.²⁵

NIH funding is a crucial economic driver in the Commonwealth. Analysts estimate that Massachusetts NIH funding in 2016 generated over \$6 billion in economic activity and supported over 31,000 jobs.²⁶ NIH grants are particularly important to the Massachusetts bioscience industry, which employed over 80,000 Massachusetts residents in 2014. NIH grants funneled \$122 million to over 130 Massachusetts companies in 2016, supporting research and developing in “technologies with potential commercial applications.”²⁷

C. Budget Cuts Proposed by the Trump Administration Would Cripple the NIH—and the Massachusetts Economy

Despite the massive economic and public health benefits of federally-funded scientific research, the Trump Administration in March 2017 proposed massive budget cuts that would dramatically reduce the NIH’s ability to fund innovative, life-saving research into the causes and treatments of disease. In May 2017, President Trump released a full budget that confirms those cuts. His proposal urges Congress to slash \$5.7 billion from the NIH—around 20% of the agency’s budget.²⁸ This suggested budget, if passed into law, would be the largest cut in NIH funding since 1938.²⁹

The President’s proposal would devastate scientific research and the industry it supports. NIH funding doubled from 1998 to 2003, but budget cuts—and congressional sequestration efforts—have caused the

NIH budget to decline since 2010. Indexed for inflation, funding for NIH decreased by 22% from 2003 to 2013.³⁰ Though Congress recently approved a \$2 billion boost in NIH funding,³¹ in defiance of the President’s call for cuts, it is unclear how NIH funding will fare in the President’s full budget, expected in late May, or in future federal funding bills.³² President Trump’s budget also proposes cutting the AHRQ’s \$479 million budget and folding the agency into NIH, threatening an agency that has saved U.S. citizens billions of dollars in healthcare costs since 2010. It would also eliminate the Fogarty International Center, reducing the NIH’s ability to combat global pandemics.³³

Universities, research institutions, and private industry agree that further cuts to NIH will “hamper...scientific enterprise and adversely affect local, national, and global economies, while inhibiting discoveries that are essential for fighting disease worldwide.”³⁴ “The U.S. is a leader in biomedical research,” notes Harvard economist David Cutler, “but it has active competitors.” At current funding rates, for example, China is expected to surpass the United States in research and development investments in 2019. Massachusetts Institute of Technology (MIT) professor Scott Stern further argues that NIH “[f]unding disruptions will have far-reaching effects, destabilizing generative research”; “even cuts less than those currently proposed could be devastating.” Young scientists—the future of medical research—are expected to suffer most, as are researchers exploring less developed, riskier scientific areas. According to Aaron Kesselheim of Brigham and Women’s Hospital, “Groundbreaking medical products often arise from NIH-funded work because they involve risk-taking, innovative research that large manufacturers have increasingly avoided.” But the “[s]cientists doing research in new areas,” says Mary-



Claire King of the University of Washington, “are the most vulnerable and the first who will be let go.”³⁵

The Administration’s proposed NIH cuts are particularly threatening to Massachusetts. According to an analysis conducted by the Office of Senator Markey (D-MA), President Trump’s “skinny budget”—which proposed cuts nearly identical to those contained in the official FY18 budget released two months later— if passed into law, would lead to a \$463 million reduction in NIH funding for the Commonwealth. Specifically, this reduction would lead to “905 fewer NIH grants awarded”; “34 fewer NIH-funded institutions”; “\$14.4 million less in funds to train the next generation of science researchers”; and enable “17 fewer NIH-supported clinical trials [to] start in 2018.”³⁶ The University of Massachusetts Medical School, for example, estimates that a 20% reduction in federal grants, including NIH would result in a \$94.8 million reduction in economic impact, mostly affecting the Worcester area.³⁷

Methodology

After the release of President Trump’s “skinny budget,” in March 2017, the Office of Senator Warren contacted dozens of Massachusetts universities, hospitals, labs, biomedical companies, industry organizations, and patient groups to ask how their access to NIH funding has influenced their careers, their research, and their development of innovative scientific and medical discoveries. In addition, staff solicited stories from patients who have benefited from NIH-funded treatments. The full responses from these respondents can be found in the Appendix. Where necessary, minor

edits have been made for style and consistency. Full sourcing information can be found in the appendix.

Taken together, these statements reflect the vibrancy of the scientific community of Massachusetts and reveal how investments in research spawn health and economic benefits for the Commonwealth, the country, and the world. It is essential that we continue to support publicly-funded scientific research to ensure that the United States and Massachusetts remain at the forefront of biomedical innovation in years to come.

1. Massachusetts researchers, supported by NIH funding, have achieved scientific breakthroughs—transforming the way Americans treat cancer, blindness, and diabetes, among other diseases, and improving Americans’ health and well-being.

Publicly-funded scientific research often paves the way for scientific breakthroughs, which in turn spawn new technologies, drugs, and medical treatments. Forty-seven percent of FDA-approved drugs from 1988 to 2005 were developed, in part, through public support. And economists estimate that a \$10 million investment in biomedical research typically generates 2-3 new patents—a stimulus for the private sector that industry alone cannot provide.³⁸

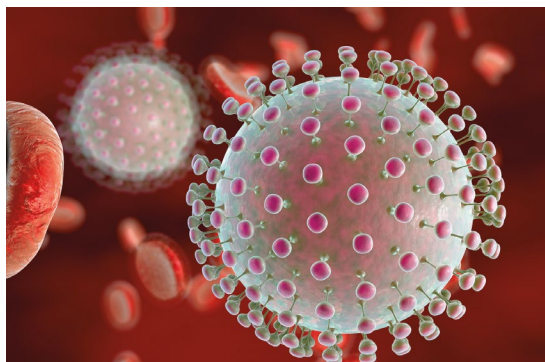
These breakthroughs, in turn, generate improvements in Americans’ health and well-being. Thanks to NIH-funded research, the United States has seen increases in life expectancy and a reduction in overall mortality.³⁹ Much of this research has occurred in Massachusetts universities, hospitals, labs, and companies, including (but not limited to) Massachusetts General Hospital, Brigham and Women’s Hospital, the University of Massachusetts, the Dana-Farber Cancer Institute, the Broad Institute of MIT and Harvard “(the Broad Institute)”, and the Boston Medical Center.

Multiple respondents described how their NIH-funded research has contributed to improved health outcomes, medical breakthroughs, and more effective disease management. Researchers at Dana-Farber, for example, have revolutionized cancer treatment, collaborating with industry to develop drugs that reduce the need for chemotherapy. Boston Children’s Hospital is working to develop an injectable pain reliever—an alternative to opioids that could help reduce addiction and opioid abuse in Massachusetts and across the country. Mass General physicians are seeking treatments for Alzheimer’s, Acute Respiratory Distress Syndrome, and tuberculosis. Other respondents are combatting youth depression, heart disease, teenage pregnancy, and spinal cord injuries. These studies, note Terence Wong, a PhD Candidate working at the Broad Institute, were “made possible by NIH funding.”

- From a patient perspective, **NIH funded** projects that support rare disease research not only improve diagnoses and further our understanding leading to treatment but **also provide hope to patients and families struggling each day.** (Monkol Lek, PhD, and Rare Disease Patient, Massachusetts General Hospital and the Broad Institute)
- When Lisa Diller started practicing pediatric oncology in 1988, few children survived neuroblastoma, a cancer of young children that arises in the developing nervous system. **Today, a majority survive – and the latest boost is the result of two NIH-sponsored trials that established a new standard of care.** One, led by Diller and her colleagues, found that two stem cell transplants yielded better results than a single transplant. Outcomes were even better when patients were also given an immunotherapy drug recently approved by the FDA – following another NIH-sponsored clinical trial.⁴⁰ (Lisa Diller, MD, Dana-Farber/Boston Children’s Cancer and Blood Disorders Center)
- We have recently **developed an injectable device that would provide on-demand local pain relief. After the initial numbness wears off, patients could use a hand-held light or ultrasound device to get more local pain relief.** This system would minimize and **perhaps obviate the need for opioids** for pain relief after many medical procedures. **This could have an impact in preventing opiate prescription, addiction, and diversion, which are such a tragic problem in my state of Massachusetts and across the country...**These inventions and others were **only made possible by the support of the NIH over a period of almost 20 years.** Its support provided the resources and the stability to pursue big ideas that might have seemed challenging or risky in their early days. (Daniel S. Kohane, MD, PhD, Boston Children’s Hospital and Harvard Medical School).
- Scientists at UMass Medical School were the first to establish that a natural occurring X chromosome “off switch” can be rerouted to neutralize the extra chromosome responsible for trisomy 21, also known as Down syndrome,

a genetic disorder characterized by cognitive impairment. **The discovery provides the first evidence that the underlying genetic defect responsible for Down syndrome can be suppressed in cells in culture (in vitro).**⁴¹ (University of Massachusetts Medical School)

- In July of 1992, Richard Blumberg, MD, was investigating MHC class I molecules in humans when his postdoctoral student walked into his office with the results of an experiment he was convinced was a failure. **Instead, the NIH-funded Blumberg lab had uncovered a physiological pathway that would eventually lead to the development of new, long-acting drugs for the treatment of chronic diseases such as hemophilia A and B.** (Richard Blumberg, MD, Brigham and Women's Hospital)
- **The role of NIH funding in moving this complex field forward has been pivotal to some of the key advances in [tuberculosis] TB.** The National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, established the TB Research Units (TBRU) in 1994, and in 2015 expanded its efforts to scale-up the support provided to help identify the factors that determine why some people develop active TB disease (as this will allow for more targeted interventions in this high risk group); and to work on additional biomarkers that define the stages of infection and disease (with the hope of also providing better diagnostics as we are still missing up to 1/3 of people with active TB disease). (Rocío Hurtado MD, DTM & H, Massachusetts General Hospital and Harvard Medical School)



- **[Beth Israel Deaconess Medical Center] scientists are international leaders in the development of a vaccine for the Zika virus.** The virus is linked to microcephaly and other major

birth defects in babies born to infected mothers and has also been associated with the neurologic disorder Guillain-Barré syndrome in adults. Dan Barouch, MD, PhD, Chief of the Division of Virology and Vaccine Research at BIDMC, and Colonel Nelson L. Michael, MD, PhD, of the Walter Reed Army Institute of Research (WRAIR), are working to develop safe and effective measures to prevent the Zika virus. **They have already demonstrated that three different vaccine candidates provided robust protection against the virus in both mice and rhesus monkeys. Several human clinical trials began last fall...[This project] would not be possible without NIH support.** (Beth Israel Deaconess Medical Center)

- **We are in the midst of a revolution in cancer treatment. The critical discoveries were funded by NIH and NCI grants to my lab beginning around 1998.** A Program Project grant from the National Institute of Allergy and Infectious Diseases...to study genes regulating autoimmunity led to the discover of PD-L1 [a protein related to the immune response]. Surprisingly, we found PD-L1 was expressed on many tumor cells but not on the normal tissues. My first R01 grant from the National Cancer Institute in 1999 let me put the pieces together. **We showed that PD-L1 and PD-1 were a lock and key that turned off the immune response...PD-L1 on cancer cells let the cancer cells evade immune attack while leaving other immune responses normal.** (Gordon J. Freeman, PhD, Professor of Medicine, Dana-Farber Cancer Institute and Harvard Medical School)
- Since its inception, the National Eye Institute of the National Institutes of Health (NIH) has provided funding for scientists that has laid the groundwork for numerous discoveries that have improved both the detection and treatment of blinding eye disease. **One such example is optical coherence tomography (OCT)...often compared to an “ultrasound of the eye”...that allows physicians to visualize and measure otherwise hidden structures in the back of the eye.** As a result, physicians are now able to detect vision-threatening disease like glaucoma...sooner and with greater accuracy, often before patients develop symptoms...**OCT would not exist without government funding [from the NSF and**

NIH]. (Brian J. Song, MD, MPH, Massachusetts Eye and Ear Infirmary and Harvard Medical School)

- In addition to my professional development, NIH funding has positively impacted my personal life. **My mother was diagnosed with Stage IV lung cancer in August 2013. After surgery and chemotherapy, she has been treated with [Tarceva and] Keytruda, an immunotherapy against the PD-1 receptor on immune cells...** She has shown a strong and long-lasting response for the past 18 months...**These remarkable and significant outcomes would not have been possible without research made possible by NIH funding.** (Terence Wong, PhD Candidate, Harvard University and the Broad Institute)
- A Massachusetts General Hospital research team has developed a series of tests designed to measure early indications of Alzheimer's disease based on an individual's ability to recognize, remember and distinguish among odors...**If researchers can better identify individuals in the very early stages of the disease, they may be able to develop therapies that will slow or halt its progression.** Support for the study includes National Institutes of Health grants. (Massachusetts General Hospital)
- With funding I obtained from the NIH during my graduate school training I discovered novel products made by leukemia cells. This was important because these products were strongly made in cancer cells and not present in normal cells, meaning it might be possible to target and minimize patient side effects. (Colles Price, MS, PhD, Dana-Farber Cancer Institute, the Broad Institute, and Harvard Medical School).
- [T]hrough NIH funding, I am currently undertaking the first comprehensive assessment of teens' communication about sexuality with extended family and its associations with sexual behavior, as well as an exploration of extended family approaches to talking with teens about sex, looking beyond traditional family structures to the diverse and unique structures today...**NICHD's goal of identifying prospective factors that prevent unintended pregnancy and sexually transmitted infections make such research possible.** (Jennifer Grossman, PhD, Wellesley Centers for Women)
- Funding from the National Institute of Allergy and Infectious Diseases allowed Vijay Kuchroo, PhD, to delve deeply into T-cells—a critical player in the immune system and in immune-mediated diseases...**Anti-Tim-3 antibodies are now in clinical trials for use in the treatment of multiple types of cancer.** (Vijay Kuchroo, PhD, Brigham and Women's Hospital)
- **Youth depression is a problem of major proportions, afflicting millions of children and families and interfering with children's social, emotional, and academic functioning...**With funding from the National Institute of Mental Health, I worked with colleagues on a major, 5-site randomized trial **to implement and evaluate a group cognitive behavioral program to prevent the onset of depression in adolescents** who are at risk for depression...Also with NIH funding, my colleagues and I are studying how primary care and internet-based prevention efforts may offer new and better opportunities to preempt the occurrence of depressive disease in adolescents aged 13-18. (Tracy R.G. Gladstone, PhD, Wellesley Centers for Women).
- **[T]he ability to significantly improve quality of life for those suffering from spinal cord injury (SCI), enabling [patients] to experience increased health benefits, has far reaching implications for secondary complications (pressure ulcers, obesity, diabetes) that strain the health care system as well as the ability to stay healthy and employed...**To bridge this gap, researchers and clinicians at Spaulding created a first-of-its-kind endeavor, the Spaulding Exercise for Disabilities Program (ExPD).**The ExPD program is a joint treatment and research program funded by the NIH.** (Spaulding Rehabilitation Hospital)
- The Nurses' Health Study (NHS) was established by Dr. Frank Speizer in 1976 with continuous funding from the National Institutes of Health since that time. The primary motivation for the study was to investigate the potential long-term consequences of oral contraceptives, which were being prescribed to hundreds of millions of women. **[The project provided] [k]ey insights into the connections between risk factors such**

as cigarette smoking, oral contraceptives, hormone therapy, alcohol, diet and other risk exposures and disease such as cancer and heart disease.⁴² (Frank Speizer, MD, Brigham and Women's Hospital)

- A Boston Medical Center (BMC)-led study found that minority patients continued to choose safety-net hospitals for their inpatient care following Massachusetts health reform, which expanded access to care at non-safety net facilities. Researchers compared inpatient discharge data from Massachusetts, New York, and New Jersey between 2004 and 2009 and identified safety-net hospitals in each state. Then, they tracked minority discharges. The study found a significant increase in the number of minority patients who received their inpatient care at Massachusetts' safety-net hospitals post-reform.⁴³ (Karen Lasser, MD, Boston Medical Center)
- **Despite being a major killer in intensive care units nationwide, there is not a single specific therapy for...Acute Respiratory Distress Syndrome (ARDS)...a severe form of respiratory failure that affects trauma victims (including a significant percentage of combat casualties), patients with pneumonia, and patients with septic shock or other severe infections. No drug, no procedure. Nothing.** State of the art care is entirely supportive. **At the Harvard-affiliated hospitals in Boston, nearly a dozen federally funded labs are working to address the lack of therapies for ARDS.** (Charles Corey Hardin, MD, PhD, Massachusetts General Hospital)

2. NIH funding supports the careers of young Massachusetts scientists.

Public support for scientific research is often critical for the career development of young scientists. Numerous respondents described how access to NIH grants at critical points in their careers enabled them to stay in science:

- **As a young clinician-scientist, I depend on the outcomes from...federally-funded research to provide the best possible care for my patients as well as the support of the NEI and NIH in developing my own research program.** (Brian J. Song, MD, MPH, Massachusetts Eye and Ear

Infirmery and Harvard Medical School)

- I have been teaching and doing research at Brandeis University since 1978...**I am presently Program Director for two NIH-funded training grants at Brandeis. One funds the salaries of 8 postdocs per year in Neuroscience who are spread out across the Brandeis community. The other funds 6 undergraduates and 5 Ph.D. students per year in Neuroscience across the Brandeis community...The remaining trainees in my lab are funded by my own NIH research grants.** (Eve Marder, PhD, Brandeis University)
- I have been able to develop a research program at my lab looking at the mechanical, as opposed to purely biological, changes that occur in the lungs and lung cells of [Acute Respiratory Distress Syndrome]...**because I was fortunate enough to receive an NIH K25 research grant...This five-year grant gave me crucial support at the outset of my career and ultimately enabled me to set up my own lab at Massachusetts General Hospital (MGH).** (Charles Corey Hardin, MD, PhD, Massachusetts General Hospital)



- NIH funding has been critical to my development as an early-career scientist. NIH funding directly supports me in two major ways: training grants and research grants. The first two years of my PhD were financially supported by NIH training grants...This funding was necessary to pay for my graduate program tuition and student health insurance, as well as provide me with a living stipend so that I did not need to take out loans. (Terence Wong, PhD Candidate, Harvard University and the Broad Institute)

- Without funding and educational programs sponsored by the National Institute of Health (NIH), I would not have a career in cancer research. **As an underrepresented minority from Baltimore City, I was interested in medicine and science but realistically had no idea what that meant.** In high school, I had the opportunity to meet scientists from the NIH and learn about research. I was fascinated and it drove my interest in biomedical research. **After college, I went on to pursue a masters in clinical/translational science and a PhD, funded by the NIH through a fellowship grant, in cancer biology.** (Colles Price, MS, PhD, Dana-Farber Cancer Institute, the Broad Institute, and Harvard Medical School).

Massachusetts researchers are acutely aware of the harmful impacts budget cuts would have on their careers, and the careers of their colleagues:

- [A] reduction in the NIH and NEI budget will... **further escalate the loss of the estimated 100 vision researchers that has occurred in recent years due to limitations in the NEI budget.** (Brian J. Song, MD, MPH, Massachusetts Eye and Ear Infirmary and Harvard Medical School)
- Unfortunately, the **decrease in NIH funding** has made such support harder and harder to come by. This has **led to a very real exodus of young scientists from research.** After my PhD, I did a residency in internal medicine...**There were nine physicians in my fellowship class, all of who trained in research. Currently only one other of my classmates and myself remain in science. The rest have left for other careers, largely due to lack of funding.** This is catastrophic blow to the scientific workforce that cannot easily be repaired... **Unless something is done to reverse the decline in funding, we will very likely permanently reduce our ability to discover cures for currently un-curable illnesses such as [Acute Respiratory Distress Syndrome].** (Charles Corey Hardin, MD, PhD, Massachusetts General Hospital)
- There were many labs that I wanted to do my PhD work in, but who did not have enough funding to take on a student. **My peers and I saw a difficult funding environment that only got worse as the years progressed.** While many of my peers left academia after graduating, I wanted to stay and make a difference...**I, as a researcher,**

patient, citizen, and veteran, need [medical research] funding to continue to increase... **The continued uncertainty in NIH funding pushes too many recent graduates and junior career scientists into...non-science jobs.** These are dedicated scientists that I know would have made great independent researchers. **We cannot afford to push so many scientists away from careers that transform medicine and science in general.** (Henry Rogalin, PhD, Tufts Clinical and Translational Science Institute)

- I think that when you have budget cuts like this, it discourages people from going into this field. **You take any promising research out there, any recent graduate who might be interested in doing this work, and if they see that there is absolutely no opportunity, then they are not going to do it.** They are going to go in a different direction, and so we will lose a generation of researchers. ⁴⁴ (Ingrid Katz, MD, MHSc., Brigham and Women's Hospital and Harvard Medical School)

3. Publicly-funded Massachusetts research spurs developments in the private sector.

The Massachusetts biopharmaceutical industry supports over 2,000 businesses and almost 80,000 jobs in the Commonwealth.⁴⁵ In 2016, NIH grants provided \$122 million in support to over 130 Massachusetts companies. Public funding for biomedical research is intricately connected to private sector success.

As Professor Eve Marder of Brandeis University notes, “the local biotech industry depends heavily” on students with NIH-funded scientific training. Respondents described how federal funding allowed them to launch a company to market hemophilia drugs; license a start-up to develop biodegradable patches to treat congenital heart defects; work with the private sector to improve the treatment of ACL tears; and more.

- **NIH funding of approximately \$1.5 million also supported Alnylam Pharmaceuticals’ founders’ work at MIT and UMass on the gene silencing effects of synthetic short interfering RNA compounds in mammalian cells.** These exciting gene silencing discoveries led to the founding of Alnylam which has been dedicated from its formation in 2002 to pioneering a new class of

medicines based on RNAi technology...**Alnylam has grown to approximately 500 employees at the end of 2016, with approximately 470 employees in Massachusetts.** In 2016 Alnylam broke ground on land purchased in Norton, Massachusetts for the construction of a drug substance manufacturing facility **that will create more than 50 new jobs in Massachusetts** once it is operational. (Alnylam Pharmaceuticals)

- NIH-supported medical research at UMMS catalyzes private sector growth as UMMS-patented technology forms the foundation for new products and companies. Data demonstrates this well: **UMMS now has 184 licenses with 109 companies; from 2001 to 2012, we filed 817 patent applications, virtually all of which were attributable to NIH-funded research;** and the University of Massachusetts system ranks in the top 15 nationally in licensing revenue, 97% of which is attributable to UMMS. (University of Massachusetts Medical School)
- I usually have 4-5 Ph.D. students working in the lab. **These students are apprentice students, and their stipends are paid by a mixture of training and research funds from the NIH and NSF...**Upon graduation, about half of these students continue on to further scientific training, **and about half move immediately into jobs in industry, government, [and] education. The local biotech industry depends heavily on this Ph.D.-trained workforce for its employees.** (Eve Marder, PhD, Brandeis University)
- Researchers from Brigham and Women's Hospital, Boston Children's Hospital, and the Massachusetts Institute of Technology (MIT) **developed a bio-inspired adhesive that could rapidly attach biodegradable patches inside a beating heart** in the exact place where congenital holes in the heart occur...**The adhesive technology (and other related platforms) has been licensed to a start-up company, Gecko Biomedical,** based in Paris.⁴⁶ (Brigham and Women's Hospital)
- Further NIH and NCI funding...has let us understand how the PD-1 pathway [a protein related to the immune response] is working and identify other pathways that cancer uses to evade immune attack...**Pharmaceutical companies developed PD-1 and PD-L1 antibody drugs**

and started testing them in clinical trials. These have worked so well that the drugs are now approved in seven different tumor types. (Gordon J. Freeman, PhD, Professor of Medicine, Dana-Farber Cancer Institute and Harvard Medical School)

- [Richard Blumberg, MD] traces the progress and success that his team has made over the last 25 years in advancing these drugs [for the treatment of chronic disease such as hemophilia A and B]—**as well as the jobs that were created, the company that was launched, and the collaborations that emerged**—back to that “failed” experiment [in the NIH-funded Blumberg lab]. (Richard Blumberg, MD, Brigham and Women's Hospital)
- NIH funding allowed us to identify and develop a tissue engineered scaffold that could be placed between the torn ends of [an] ACL, and with the addition of blood to the scaffold, it is able to stimulate healing of the ACL without the need for a tendon graft...**In addition, we founded a startup company, MIACH Orthopedics, Inc., to manufacture the tissue engineered scaffolds. We plan to base this company here in Massachusetts** and are currently talking with investors to try to raise the capital to get started. (Martha Murray, MD, Orthopedic Surgeon, Boston Children's Hospital)



- From 2009-2019, the total committed funding from the NIH to [the bionic pancreas] is \$21 million...**Now a company, Beta Bionics, has been formed as a Massachusetts benefit corporation with a mission to make the technology available**

to as many people with diabetes as possible at the lowest possible cost. (Massachusetts General Hospital Diabetes Program)

4. NIH-supported projects in Massachusetts save lives and reduce health care costs in the U.S. and around the world.

As multiple Massachusetts researchers attest, investments in cutting edge scientific research can result in reductions in health care costs for millions of Americans. NIH-supported research, for example, led to the development of cochlear implants for children with severe hearing loss. The use of cochlear implants saves an estimated \$30,000 per child in specialized therapy and education costs.⁴⁷ NIH research also led to the development of the Hib vaccine, which protects against a form of bacterial meningitis. Use of the vaccine has directly reduced health care costs by an estimated \$1.8 billion for children born in in 2009 alone.⁴⁸

Furthermore, stories from Massachusetts demonstrate how the NIH's role in promoting global health contributes to America's role as a world leader in biomedical research and benefits citizens at home.

- Combined, the [NSF and NIH] dedicated around \$500 million toward developing optical coherence tomography (OCT)) from 1991-2014...**Though \$500 million is a significant investment over two decades, OCT has saved the U.S. government an estimated \$11 billion in Medicare spending from 2008-2014** by changing the way we treat [age-related macular degeneration (AMD)]. Before the development of OCT, doctors followed a treatment schedule that required injecting expensive prescription drugs into the eyes of AMD patients every month. Now, the information from an OCT scan allows doctors to see whether an injection is needed at that visit or can be safely delayed. **Every time an injection...is delayed, Medicare saves money.**" (Brian J. Song, MD, MPH, Massachusetts Eye and Ear Infirmary and Harvard Medical School)
- Injuries to the Anterior Cruciate Ligament of the knee (ACL) affect over 200,000 U.S. citizens each year. **Costs of surgery average \$12,600, leading to an estimate costs of surgery alone of over \$2.5 billion per year for U.S. healthcare,** with additional costs for rehabilitation and time

lost from work for these largely young, healthy, and athletic people...**The costs of an additional 150,000 total knee replacements is estimated to be \$8.6 billion each year.** Work funded by the NIH in our lab has enabled development of an entirely new approach to ACL injuries...[T]he preclinical data demonstrated that knees treated with this technique were able to heal the ACL, and in addition, these knees did not develop arthritis. Thus, this technique may help not only reduce the burden of the immediate surgery...but **it may also lessen the future healthcare cost burden** by stopping patients with ACL tears from requiring a total knee replacement at an early age. (Martha Murray, MD, Orthopedic Surgeon, Boston Children's Hospital)

- In addition to the [Tuberculosis Research Units], the Fogarty International Awards (NIH) have funded several projects in **TB research including [identifying] the determinants and outcomes of TB among HIV infected children,** the role of Immune Reconstitution Inflammatory Syndrome in pulmonary TB, studies on the molecular and social epidemiology of drug resistant TB, **and several TB research and capacity building grants for TB in endemic areas in Africa and Asia.** (Rocío Hurtado MD, DTM & H, Massachusetts General Hospital and Harvard Medical School)
- You only have to look at HPTN 052...just one of the NIH studies that provided critical evidence for how we proceed in the work we do around HIV...to see the impact of the massive NIH undertaking. When those results were released, we found out that, basically, anyone living with HIV who is on treatment and has their viral load suppressed can get to the point where they will not transmit the virus to their partner. This drove the World Health Organization to change its guidelines; it was really a game changer...**What [budget cuts] would mean for me as a researcher is that, essentially, all the work that I do is going to stop in its tracks. Fogarty is really the glue globally for the NIH.** It would mean the end of support for researchers in-country who are building up the infrastructure for research; it's the end of collaborations that have been built over decades.⁴⁹ (Ingrid Katz, MD, MHS., Brigham and Women's Hospital and Harvard Medical School)

- The National Heart Lung and Blood Institute has supported significant funding for research in blood disorders. Sickle cell disease (SCD) is the most common hemoglobinopathy and one of the most common monogenic diseases in the world. **In the United States, there are 2,000 children born each year with SCD and about 75,000-100,000 individuals with the disease. SCD poses a major public health burden...and [amounts for] an aggregate charge for health care services of \$1 billion...**The goal of the projected funded by NIH (NHLBI) is to develop new methods to treat SCD disease...**The goal of this research is...**significant amelioration of SCD associated morbidity and mortality for the patients and **significantly reduced cost to society in terms of medical care costs.** (David Williams, MD, President, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Senior Vice President & Chief Scientific Officer; Chief of Hematology & Oncology, Boston Children's Hospital)
- Benjamin Warf [of Harvard Medical School] has been the Principal Investigator on grants... that were both funded through the Fogarty International Institute of the NIH. **This funding has supported a randomized controlled trial of two methods for treating infant hydrocephalus [fluid build up in the brain]...**During his years as Medical Director of the neurosurgical hospital for children he helped establish in Uganda, **Dr. Warf highlighted the large burden of infant hydrocephalus in sub-Saharan Africa, characterized neonatal infection as one of the most common causes, and developed a new surgical treatment for infant hydrocephalus that avoids the need for dependence on shunts** (implanted devices that require ongoing neurosurgical maintenance throughout life) which were previously the standard treatment worldwide. **He has introduced the procedure...into the United States, where shunt maintenance accounts for \$1 billion in health care costs and significant morbidity each year.** (Benjamin Warf, MD, Director, Neonatal and Congenital Anomaly Neurosurgery, Boston Children's Hospital)
- I was a combat medic with extra training as a Practice Nurse. During the transition between hospitals, I watched one of our nurses set up and execute a series of experiments...testing different methods for using the warming blankets to find out how to best warm up our patients. **I will confess at the time, I thought it was all very silly...**Months later, we were all asking this nurse what the results were...[because] it mattered how well we could warm our newest patient [who] had lost his arm at the shoulder... **Following my deployment, I wanted to keep asking how we know what is best in medicine [and] I am halfway through a training program in Clinical and Translational Science...**My colleagues are using AHRQ support for numerous projects **such as how to reduce costs from unnecessary readmissions in adult and pediatric patients.** (Henry Rogalin, PhD, Tufts Clinical and Translational Science Institute)

Conclusion

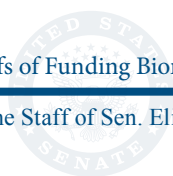
Federal investments in biomedical research improve Americans' health and well-being, spur economic growth, and promote scientific breakthroughs. Misguided attempts to cut costs by reducing funding for federal research agencies will only harm Americans.

To ensure that the United States remains the world leader in biomedical research—and that state and local communities continue to thrive—it is critical to maintain—and expand—funding for NIH.

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Alnylam Pharmaceuticals

Cambridge, Massachusetts

Leading RNA interference (RNAi) Therapeutics Company

NIH funding is vital to the discovery of new insights that ignite innovation and open entirely new approaches to the treatment of serious diseases. In the 1990's NIH provided approximately \$8.5 million in grants supporting basic research in the laboratories of Professors Andrew Fire and Craig Mello that led to a landmark discovery of RNAi's role in gene silencing in worms. This importance of this work published in 1998 was recognized with a Nobel Prize just eight years later in 2006.

NIH funding of approximately \$1.5 million also supported Alnylam Pharmaceuticals' founders' work at MIT and UMass on the gene silencing effects of synthetic short interfering RNA compounds in mammalian cells. These exciting gene silencing discoveries led to the founding of Alnylam which has been dedicated from its formation in 2002 to pioneering a new class of medicines based on RNAi technology. More than \$1.5 billion in private sector funds have been invested in Alnylam R&D to support our work in overcoming the many hurdles that needed to be cleared to translate RNAi technology into drug candidates suitable for clinical development. With this private investment, Alnylam has grown to approximately 500 employees at the end of 2016, with approximately 470 employees in Massachusetts. In 2016 Alnylam broke ground on land purchased in Norton, Massachusetts for the construction of a drug substance manufacturing facility that will create more than 50 new jobs in Massachusetts once it is operational.

Looking forward, Alnylam is excited that its most advanced RNAi clinical drug candidate, patisiran, will complete its Phase 3 pivotal study later this year. We are optimistic that the study will be positive, supporting regulatory filings by the end of 2017. If approved by the FDA, the very first RNAi therapeutic will be made available commercially to patients in 2018, 20 years after the publication by Professors Andrew Fire and Craig Mello in 1998 of their revolutionary gene silencing discovery. Patisiran is being developed for a fatal genetic disease, hereditary ATTR amyloidosis, that currently has no approved therapy in the United States. The unmet patient need in hATTR amyloidosis is very, very high.



Beth Israel Deaconess
Medical Center

Beth Israel Deaconess Medical Center
Boston, Massachusetts

Beth Israel Deaconess Medical Center (BIDMC) in Boston is a world-class research institution where outstanding scientists work to develop new knowledge for the betterment of the health of our local and global communities. BIDMC scientists continue to search for improved understanding of diseases from Alzheimer's to Zika. BIDMC is consistently ranked in the top tier of independent hospitals in National Institutes of Health (NIH) funding. In Fiscal Year 2016, more than 320 principal investigators led ongoing research projects that were supported by more than \$150 million in federal funding.

This is perhaps the most promising period in the history of biomedical research, as sophisticated technologies are facilitating the pursuit of highly original investigations and rapidly evolving genomic discoveries are uncovering important scientific insights. BIDMC's commitment to bold and innovative ideas, as well as its nurturing of promising young scientists, is leading to novel discoveries into therapies and diagnostics.

Below are just a few of the research projects underway at BIDMC that would not be possible without NIH support.

- **Leading the Global Fight Against the Zika Virus:** BIDMC scientists are international leaders in the development of a vaccine for the Zika virus. The virus is linked to microcephaly and other major birth defects in babies born to infected mothers and has also been associated with the neurologic disorder Guillain-Barré syndrome in adults. Dan Barouch, MD, PhD, Chief of the Division of Virology and Vaccine Research at BIDMC, and Colonel Nelson L. Michael, MD, PhD, of the Walter Reed Army Institute of Research (WRAIR), are working to develop safe and effective measures to prevent the Zika virus. They have already demonstrated that three different vaccine candidates provided robust protection against the virus in both mice and rhesus monkeys. Several human clinical trials began last fall.
- **Groundbreaking Genetics Discoveries Challenge Scientific Dogma:** Like its better known counterpart DNA, which contains instructions for building the proteins all life depends on, RNA molecules play an integral role in the coding, decoding, regulation and expression of genes. But the vast majority of RNAs – about 98 percent of them – were long considered meaningless “junk.” Only in the 1990s did researchers begin to understand these non-coding RNAs' significance in the growth, division, survival and migration of cells. RNAs' ubiquity across these critical biological processes makes them promising new targets for treatment of a wide swath of diseases, including cancer.

Recognizing these insights into the world of non-coding RNAs, BIDMC has established the Institute for RNA Medicine under the leadership of Frank Slack, PhD. With NIH grant support, a BIDMC research team led by Pier Paolo Pandolfi, MD, PhD, Director of

the Cancer Center at BIDMC, recently discovered that circular RNAs – a class of non-coding RNAs – are affected by the genomic rearrangements common in cancer cells, just like their protein counterparts. They also found that circular RNAs promote tumor growth and progression. The group’s work paves the way for the discovery of many more of these unusual RNAs and how they contribute to cancer, which, in revealing the mechanisms and pathways underlying cancer’s progression, could offer new means of halting it.¹

- **Tracing the Neural Circuitry of Appetite and Hunger:** One third of American adults are overweight or obese, costing an estimated \$190 billion each year – more than 20 percent of all medical spending in the United States. Appetite is a complex physiological function, governed by both the body and the brain. BIDMC researchers Bradford Lowell, MD, PhD, and Mark Andermann, PhD, are uncovering the intricate brain circuitry that underlies feelings of hunger, satiety and the urge to eat.

Lowell, Andermann and colleagues manipulated specific neurons in mice to determine their roles in feeding behavior. They revealed three types of neurons – one that stimulates hunger and two that promote a feeling of fullness – interact in the same circuit, and all converge in another region of the brain known to suppress hunger. The researchers have also found that a subset of neurons starts to prepare the body as soon it detects the availability of food or water. Deficits in this neural circuitry could lead to overeating or drinking, the researchers hypothesize. They also speculate that targeting this brain circuit could one day provide a means of regulating meal-size without interfering with appetite or the ability to take pleasure in food.

- **Scientists Uncover the Earliest Stages of Alzheimer’s Disease:** Alzheimer’s disease currently afflicts 5.4 million Americans and 30 million individuals worldwide. It is estimated that by 2050, medical costs of caring for patients with Alzheimer’s will soar to over \$1 trillion in the U.S. alone. BIDMC investigators Kun Ping Lu, MD, PhD, and Xiao Zhen Zhou, MD, PhD, identified the first, early step in which the tau protein transforms into the misshapen molecule responsible for the neurological damage that leads to the debilitating loss cognitive function that is characteristic of the disease. The discovery offers a promising new direction for the development of therapeutic antibodies and vaccines, and hinges on an enzyme called Pin1 (prolyl isomerase), which can untangle the twisted tau. Pin1 was co-discovered by Lu. A new antibody technology developed by Drs. Lu and Zhou has made it possible to distinguish between healthy and disease-causing tau protein. Their work has demonstrated that the protein’s pathogenic form appears in the brain cells of patients with early dementia and as it progresses to Alzheimer’s rapidly accumulates at the brain location that is critical for memory.
- **Uncovering Drugs That May Combat Deadly Antibiotic-Resistant Bacteria:** In recent years, hospitals have reported dramatic increases in the number of cases of the highly contagious, difficult-to-treat, and often deadly antibiotic-resistant bacteria called

¹ See Beth Israel Deaconess Medical Center, “New study implicates unusual class of circular RNAs in cancer,” *ECancerNews* (April 1, 2016) (online at <http://ecancer.org/news/9001-new-study-implicates-unusual-class-of-circular-rnas-in-cancer.php>).

carbapenem-resistant Enterobacteriaceae (CRE).² BIDMC researchers have developed a promising new method of identifying which antimicrobials are effective against these organisms. While there is a critical need for new antimicrobial agents against CRE and other emerging antibiotic-resistant bacteria, the number of new antibiotics that have been developed and approved has steadily decreased in recent decades. To identify new or existing drugs that can destroy multidrug-resistant CRE, BIDMC's James Kirby, MD, and Kenneth Smith, PhD, examined approximately 10,000 compounds with known activity, including most already FDA-approved drugs, veterinary drugs and inhibitors of various cellular processes not currently used as therapeutics. Through a process called high throughput screening, the investigators looked to see whether any of these compounds could either directly inhibit the growth of CRE or restore the effectiveness of carbapenem against these organisms. They found that 79 compounds inhibited CRE. Three have already been approved for other intended uses in human and veterinary medicine. While these antimicrobials are not currently used to treat CRE, Kirby and Smith's findings suggest they could potentially be repurposed for that purpose.

² See Beth Israel Deaconess Medical Center, "Screening method uncovers drugs that may combat deadly antibiotic-resistant bacteria," *Science Daily* (April 29, 2016) (online at <https://www.sciencedaily.com/releases/2016/04/160429133505.htm>).

Brigham and Women's Hospital

Boston, Massachusetts

Brigham and Women's Hospital (BWH) is an international leader in basic, clinical and translational research on human diseases, more than 3,000 researchers, including physician-investigators and renowned biomedical scientists and faculty. For the last 25 years, BWH ranked second in research funding from the National Institutes of Health (NIH) among independent hospitals.

For example, researchers from Brigham and Women's Hospital, Boston Children's Hospital, and Massachusetts Institute of Technology (MIT) developed a bio-inspired adhesive that could rapidly attach biodegradable patches inside a beating heart-in the exact place where congenital holes in the heart occur, such as with ventricular heart defects. The adhesive technology (and other related platforms) has been licensed to a start-up company, Gecko Biomedical, based in Paris.³

Below are several additional examples of the important types of research that NIH funding has made possible at the BWH.

- **Vijay Kuchroo, PhD:** Funding from the National Institute of Allergy and Infectious Diseases allowed Vijay Kuchroo, PhD, to delve deeply into T cells – a critical player in the immune system and in immune-mediated diseases such as type 1 diabetes and colitis. His laboratory has made several important discoveries related to T cell responses, including identifying the TIM family of molecules, which can interfere with the immune system's ability to detect and destroy cancer cells. Anti-Tim-3 antibodies are now in the clinical trials for use in the treatment of multiple types of cancer. Kuchroo's lab also discovered TH17 cells, a critical cell type that induces autoimmunity. An antibody that targets these cells was approved last year for the treatment of psoriasis, ankylosing spondylitis and psoriatic arthritis, and has shown promising results in multiple sclerosis.
- **Christine Seidman, MD:** Christine Seidman, MD, studies the genetic underpinnings of human heart disease. Her work has provided fundamental insights into the causes of different diseases affecting the heart, enabled gene-based diagnosis and defined novel therapeutic targets. Grants from the National Institutes of Health have allowed Dr. Seidman to study families and individual patients with congenital heart disease, hypertrophic or dilated cardiomyopathy, and heart failure to identify gene mutations that cause these disorders in families and find interventions before cardiovascular events occur.⁴
- **Frank Speizer, MD:** The Nurses' Health Study (NHS) was established by Dr. Frank Speizer in 1976 with continuous funding from the National Institutes of Health since that

³ See Boston Children's Hospital, "Bio-Inspired Glue Keeps Hearts Securely Sealed" (January 2014) (online at <http://www.childrenshospital.org/news-and-events/2014/january-2014/bioinspired-glue-keeps-hearts-securely-sealed>).

⁴ See Christine E. Seidman, MD, "Genetic Causes of Human Heart Disease," *Howard Hughes Medical Institute* (May 2, 2016) (online at <http://www.hhmi.org/research/genetic-causes-human-heart-disease>).

time. The primary motivation for the study was to investigate the potential long-term consequences of oral contraceptives, which were being prescribed to hundreds of millions of women.⁵ Key insights into the connections between risk factors such as cigarette smoking, oral contraceptives, hormone therapy, alcohol, diet and other risk exposures and diseases such as cancer and heart disease.

- **Richard Blumberg, MD:** In July of 1992, Richard Blumberg, MD, was investigating MHC class I molecules in humans when his postdoctoral student walked into his office with the results of an experiment he was convinced was a failure. Instead, the NIH-funded Blumberg lab had uncovered a physiological pathway that would eventually lead to the development of new, long-acting drugs for the treatment of chronic diseases such as hemophilia A and B. Blumberg traces the progress and success that his team has made over the last 25 years in advancing these drugs – as well as the jobs that were created, the company that was launched and the collaborations that emerged – back to that “failed” experiment.

⁵ See Brigham and Women’s Hospital, Harvard Medical School, and Harvard T.H. Chan School of Public Health, “Nurses’ Health Study—About” (online at <http://www.nurseshealthstudy.org/about-nhs/history>).

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PD-1 cancer immunotherapy is changing the way we treat cancer. There are now five PD-1 or PD-L1 drugs that are FDA approved for treatment of lung, kidney, bladder, head and neck, melanoma, and Merkel cell cancers and Hodgkin lymphoma. These tumor types cause about a third of cancer deaths. Clinical trials are showing positive results in multiple other cancer types with additional approvals expected. We are in the midst of a revolution in cancer treatment. The critical discoveries were funded by NIH and NCI grants to my lab beginning around 1998.

A Program Project grant from the National Institute of Allergy and Infectious Diseases (NIAID; P01 AI39671) to study genes regulating autoimmunity led to the discovery of PD-L1. Surprisingly, we found PD-L1 was expressed on many tumor cells but not on the normal tissues. My first R01 grant from the National Cancer Institute (NCI; R01 CA84500) in 1999 let me put the pieces together. We showed that PD-L1 and PD-1 were a lock and key that turned off the immune response. When we made a drug that blocked the PD-L1 key from fitting in the PD-1 lock, the immune response was revived. PD-L1 on cancer cells let the cancer cells evade immune attack while leaving other immune responses normal.

Pharmaceutical companies developed PD-1 and PD-L1 antibody drugs and started testing them in clinical trials. These have worked so well that the drugs are now approved in seven different tumor types. Further NIH and NCI funding (NIH P01 AI56299, NIH/NIAID P01 AI054456 and others) has let us understand how the PD-1 pathway is working and identify other pathways that cancer uses to evade immune attack.

This is a total change in our strategy of treating cancer: don't poison the cancer; let the body's own immune system destroy the cancer. Wild idea but it works: over 50,000 patients have been treated with the PD-1 or PD-L1 drugs. We are in the midst of a revolution in cancer treatment. Right now the PD-1 drugs don't work in every patient, only 15-35% benefit, depending on the tumor type. But this is better than ever before and has opened the door. This change in strategy has released a burst of creative energy in a multitude of scientists and pharmaceutical companies. Building on a foundation of treatment with PD-1, multiple labs have now reported over 300 combination treatments that work even better than PD-1 alone in mouse cancer models. Due to the success of this new approach, there are currently 5 approved PD-1 and PD-L1 agents, including Keytruda, Opdivo, Tecentriq, Imfinzi, and Bavencio.

NIH/NCI funding is critically needed to identify the best combinations, understand how they work, understand who they will work for, how to best deliver them, and which are safest. In addition, funding basic science grants to understand how the immune system is regulated will teach us how to use the immune system to control many other diseases in addition to cancer. The money will be well spent.



Tracy R. G. Gladstone, PhD

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Youth depression is a problem of major proportions, affecting millions of children and families and interfering with children's social, emotional, and academic functioning. Suicide—often related to depression—was the “third leading cause of death among individuals between the ages of 10 and 14, and the second leading cause of death among individuals between the ages of 15 and 34” in 2015.* Although evidence-based treatments for youth depression have been found to work well, these treatments only help about half of those they target. Treatment resources are often difficult to access, relapse is common, and the long-term consequences of youth depression are significant.

Recently, promising research has suggested that depression is among the most preventable of major mental illnesses. We now know of strategies that work to prevent youth depression, including providing cognitive behavioral interventions to high-risk adolescents. Although funders and policymakers in the U.S. support preventive efforts for medical concerns, such as healthy eating and exercise to prevent heart disease, mental health prevention is often overlooked.

With funding from the National Institute of Mental Health, I worked with colleagues on a major, 5-site randomized trial to implement and evaluate a group cognitive behavioral program to prevent the onset of depression in adolescents who are at risk for depression. These were youth who had a depressed parent, and who themselves were either depressed currently or had experienced an episode of depression in the past. Results from this study helped us to understand the nature of interventions that work to reduce risk for depression in youth; with additional NIMH funding we were able to follow our sample of at-risk adolescents across the transition to adulthood to learn about the long-term effects of such prevention programs. Our research team was able to begin finding ways to halt or slow the chronic, prevalent, and impairing nature of depression while ascertaining the costs and benefits of incorporating this intervention into "best practice" in real world settings.

Also with NIH funding, my colleagues and I are studying how primary care and internet-based prevention efforts may offer new and better opportunities to preempt the occurrence of depressive disease in adolescents aged 13-18. In a preliminary investigation of this intervention, we learned that at-risk adolescents who used the internet-based program demonstrated significant reductions in depressed mood over 12 months. Now, with funding from NIMH, we are conducting a 5-year, two-site randomized clinical trial of this intervention to learn if the program is associated with reduced episodes of depression in at-risk adolescents over 24 months. These

findings will help us to determine which strategies are best able to reduce risk for depression in youth, the best way to integrate such behavioral health interventions into primary care, and the best way to make such interventions accessible to adolescents and families from different racial, ethnic, and socio-economic backgrounds.

Funding from NIH has been essential to our understanding of disease prevention and treatment. The increased focus on mental health has far-reaching benefits for youth and families.

Reference:

*National Institute of Mental Health website:

<https://www.nimh.nih.gov/health/statistics/suicide/index.shtml>

<https://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adolescents.shtml>

Jennifer Grossman, PhD

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When teenagers engage in risky sexual behavior, there are significant health, social, and financial costs. It's imperative that parents, educators, practitioners, and policy makers understand the factors that contribute to adolescents' actions—both risky and protective. Prevention and intervention programs should be based on data-informed theories. The National Institute for Health (NIH) ensures that such research is conducted to better understand the complexities of adolescent behavior.

I study adolescent sexuality as it relates to teens' communication with parents and other trusted adults in their lives about risky behaviors. There are so many harmful consequences of early sexual debut—for middle and high schoolers. Our research has shown that comprehensive sex education that includes discussion between students and parents can delay sex for middle school students. The parent component is particularly important for boys, as boys who participated in conversations with their parents were more likely to delay sex than boys who didn't participate. This type of intervention can reduce boys' risks as well as their partners'.

With NIH funding, I am examining how parenting processes influence sexual behavior among the high-risk group of offspring of parents who were teens themselves when they had their first child. To conduct this study, our team is using the National Longitudinal Study of Adolescent to Adult Health, the largest longitudinal survey of adolescents ever undertaken. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) supported this comprehensive survey of 7th through 12th graders, which began in 1994 in response to a mandate from the U.S. Congress. Four follow-up studies of the sample—as well as others in their families and communities—followed through 2008; a new wave of data collection began in 2016. These datasets serve as the basis of new research, analysis, and learning by tens of thousands of researchers. I am one of these researchers.

Also through NIH funding, I am currently undertaking the first comprehensive assessment of teens' communication about sexuality with extended family and its associations with sexual behavior, as well as an exploration of extended family approaches to talking with teens about sex, looking beyond traditional family structures to the diverse and unique structures today. This study can inform whether and how to include extended family members in school and community-based prevention and intervention programs that promote teens' sexual health. High levels of extended-family involvement in childrearing and sexuality communication, such as with grandparents, aunts and uncles, older siblings and cousins, and “fictive kin,” especially in Black and Latino families, suggest the importance of assessing this under-studied influence.

NICHD's goal of identifying protective factors that prevent unintended pregnancy and sexually transmitted infections make such research possible.

Adolescent health is not limited to teenage years. The health, social, and fiscal implications of protective and risky behaviors can last a lifetime. The federal investment in NIH research has been essential to the development of appropriate prevention and intervention programs that can inform more protective and positive outcomes for young people, throughout their lives.

Reference:

The National Longitudinal Study of Adolescent to Adult Health website;

<http://www.cpc.unc.edu/projects/addhealth/about>

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It is estimated that nearly 75,000 Americans each year die from the Acute Respiratory Distress syndrome (ARDS). ARDS¹ is a severe form of respiratory failure that affects trauma victims (including a significant percentage of combat casualties²), patients with pneumonia, and patients with septic shock or other severe infections. Despite being a major killer in intensive care units nationwide, there is not a single specific therapy for ARDS. No drug, no procedure. Nothing. State of the art care is entirely supportive.

At the Harvard affiliated hospitals in Boston nearly a dozen federally funded labs are working to address the lack of therapies for ARDS. Ironically, it is precisely because the need is so great that work in this area is risky and difficult to fund commercially. In a situation in which very little is known, it is hard to predict which approach is mostly likely to be successful. Progress will depend on the ability to explore untested and even radical ideas. Because my Ph.D. training was in theoretical biological physics I have been able to develop a research program at my lab looking at the mechanical, as opposed to purely biological, changes that occur in the lungs and lung cells of ARDS patients and testing different approaches to reversing those changes. I have been able to pursue this novel approach because I was fortunate enough to receive an NIH K25 research grant. The K25 program is specifically designed to support investigators from the physical sciences who wish to focus on a problem in clinical medicine. The five-year grant gave me crucial support at the outset of my career and ultimately enabled me to set up my own lab at Massachusetts General Hospital (MGH). This kind of funding for high-risk/high reward efforts simply does not occur in the private sector.

Unfortunately, the decrease in NIH funding has made such support harder and harder to come by. This has led to a very real exodus of young scientists from research. After my PhD, I did a residency in internal medicine at MGH and fellowship in Pulmonary and Critical Care Medicine at Harvard. There were nine physicians in my fellowship class, all of whom trained in research. Currently only one other of my classmates and myself remain in science. The rest have left for other careers, largely due to lack of funding. This is a catastrophic blow to the scientific workforce that cannot easily be repaired. In medical research, a person typically must complete a four year undergraduate degree, four years of medical school, 3-4 years of residency and 1-2 years of clinical fellowship before being ready to start their own lab. Thus it takes at least 12 years (to say nothing of additional Ph.D. training which many people undertake) and hundreds of thousands of dollars to replace each trainee lost. Unless something is done to reverse the decline in funding, we will very likely permanently reduce our ability to discover cures for currently incurable illnesses such as ARDS.

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The impact of Tuberculosis (TB) on a global scale remains staggering. One-third of the world's population is infected (with an estimated 10% ultimately becoming ill with the disease). In 2017, TB remains the leading infectious disease killer in the world today, ranking above HIV/AIDS and malaria, and is the leading killer of people living with HIV/AIDS with 35% of deaths attributed to tuberculosis. TB is the quintessential poverty-promoting illness, as it disproportionately affects adults during the most productive working years of their life. A recent summary of 49 studies evaluating the financial burden of TB among patients in low and middle-income countries noted the heavy toll placed on individuals and families, with an average loss of 58% of individual income and 39% of household income related to tuberculosis. In the United States, a total of 9287 new TB cases were reported in 2016 – with a disproportionate burden among racial and ethnic minorities, and targeting and ensuring adequate access to diagnostics and care among these vulnerable populations remains a challenge, not only due to the individual toll, but also due to the public health consequences, as TB is a transmissible illness.

Additional challenges in the fight against TB include:

- Up to 1/3 of active TB cases are missed worldwide which means that 3 million people are undiagnosed and don't access the care they need. The more vulnerable the host, the harder it is to diagnose TB – hence children, pregnant women, people living with HIV/AIDS or with weakened immune systems are at greater risk of having their diagnoses missed or delayed.
- TB treatments are long (minimum 6 months with multiple medications) and require a strong public health infrastructure to ensure adequate completion of therapy to prevent ongoing transmission in the community and to minimize the development of drug resistance during treatment.
- Drug-resistant TB continues to threaten TB control – with nearly 500,000 people developing multi-drug resistant TB globally yet only 1 in 4 are currently diagnosed, and only 1 in 9 are successfully treated.
- Until 2012, there were no new TB drugs in 40 yrs.

The role of NIH funding in moving this complex field forward has been pivotal to some of the key advances in TB. The National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, established the TB Research Units (TBRU) in 1994, and in 2015 expanded its efforts to scale-up the support provided to help identify the factors that determine why some people develop active TB disease (as this will allow for more targeted interventions in this high risk group); and to work on additional biomarkers that define the stages of infection and disease (with the hope of also providing better diagnostics as we are still missing up to 1/3 of people with active TB disease). In addition to the TBRU, the Fogarty International Awards (NIH) have

funded several projects in TB research including the determinants and outcomes of TB among HIV infected children, the role of Immune Reconstitution Inflammatory Syndrome in pulmonary TB, studies on the molecular and social epidemiology of drug resistant TB, and several TB research and capacity building grants for TB in endemic areas in Africa and Asia.

In my work as the Director of the Massachusetts General Hospital's Mycobacterial Center since 2003, I have seen first-hand the burden of TB among the vulnerable and disenfranchised in the US and abroad. In our clinical program in Boston, I have cared for refugees, Scientists, health-care workers, pregnant mothers and families affected by TB. I have witnessed the morbidity associated with this illness, the need for lung surgery in some patients, the fear and the stigma many have faced including in the workplace. Through my work overseas as the Clinical Advisor for the Global Health Committee (Ethiopia and Cambodia), the main implementing partners of multidrug-resistant TB care jointly with each country's Ministry of Health, I have seen the impact TB has had on families too impoverished to succeed. I have seen the loss of young talent – children, adolescents and young adults who have missed years of schooling while cycling among ineffective TB regimens until they are ultimately diagnosed with drug-resistant TB and with such delays have either succumbed to their illness or have sustained such irreparable lung damage to require chronic oxygen just to subsist. This disease has led to extraordinary suffering among families and communities in the US and globally. As a physician and a human being, we owe it to our patients, families and communities, to continue to progress in the fight against TB, the world's leading infectious disease killer. Now is not the time to forego or diminish the necessary research funding our scientific community requires, or we run the risk of major setbacks in this global struggle.

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Daniel S. Kohane, MD, PhD

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My group pursues research in drug delivery, biomaterials, and nanomedicine. We have recently developed an injectable device that would provide on-demand local pain relief. After the initial numbness wears off, patients could use a hand-held light or ultrasound device to get more local pain relief. This system would minimize and perhaps obviate the need for opioids for pain relief after many medical procedures. This could have an impact in prevent opiate prescription, addiction, and diversion, which are such a tragic problem in my state of Massachusetts and across the country.

There are many other devices we have developed to address the needs of patients, or issues of scientific importance. We have created nanoparticles that can be injected intravenously but will home in on tumors under laser guidance, reducing toxicity to the rest of the body. We have developed a way to get antibiotics across the ear drum so that parents don't have to force-feed their toddlers drugs for ten days, and children don't have to suffer the side-effects of orally-taken antibiotics – including potentially the development of antibiotic-resistant bacteria, which are becoming a national medical problem. We have invented drug-eluting contact lenses so to improve treatment of glaucoma and other eye diseases. We have developed a system for removing harmful molecules from the bloodstream of patients with sepsis, which we hope will reduce mortality in this deadly condition. Some of these advances are slowly making their way toward clinical trials.

These inventions and others were only made possible by the support of the NIH over a period of almost 20 years. Its support provided the resources and the stability to pursue big ideas that might have seemed challenging or risky in their early days. Such stable support is particularly important for physician-scientists like me, since we also have clinical demands on our time.

Monkol Lek, PhD

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I am both a rare disease patient and a researcher at Massachusetts General Hospital and the Broad Institute.

In terms of research, the NIH has supported many initiatives in rare disease including the NHGRI sequencing grants awarded to the Broad Institute. The Muscle Disease Exome Project (MDEP) is one such project, which has proven the value of genomic approaches for diagnosis and gene discovery in a genetically heterogeneous class of severe diseases. The project has sequenced over 700 exomes and for those unsolved by exome, over 50 muscle transcriptomes and over 100 genomes from a large international cohort of undiagnosed muscle disease patients. The overall diagnosis rate was approximately 40% and has directly resulted in 11 publications with three of these publications reporting a novel casual gene (LMOD3, BICD2 and GMPPB). These patients will receive a genetic diagnosis for the first time. In the case of known disease genes, this will now allow patients to pro-actively manage their care, make informed family planning decisions and reduce the overall burden on their families, carers and healthcare providers.

From a patient perspective, NIH funded projects that support rare disease research not only improve diagnosis and further our understanding leading to treatment but also provides hope to patients and families struggling each day.

We live in the information age, where the intersection of technology and human biology is rapidly fueling discoveries at an ever increasing rate. This solid foundation was due to investments that includes the completion of the human genome project and the pervasive use of the internet. It is critical for the United States to not only maintain but increase the NIH budget to remain the world leader in medical innovation and also to fully reap the rewards of their large investments.

Eve Marder, PhD

Victor and Gwendolyn Beinfield Professor of Neuroscience
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I have been teaching and doing research at Brandeis University since 1978. For my entire scientific career, I have been dedicated to the principle that outstanding science must go hand-in-hand with excellent education. I am presently Program Director for two NIH-funded training grants at Brandeis. One funds the salaries of 8 postdocs/yr in Neuroscience who are spread out across the Brandeis community. The other funds 6 undergraduates and 5 Ph.D. students/yr in Neuroscience across the Brandeis community. The purpose of these grants is to enhance the rigorous quantitative training and interdisciplinarity of the supported trainees. In a given year, I might have one of each of these positions in my laboratory. The remaining trainees in my lab are funded by my own NIH research grants.

Undergraduates: Each year I employ 5-10 undergraduates. These students are paid to do routine laboratory tasks and then move on to do scientific projects. Some of them end up as coauthors on scientific publications. For many of these students, the 10-15 hours/week they are paid to work during the academic year and their full-time summer employment replaces low-wage jobs they would otherwise be looking for, and enables them to help support themselves during their college experience, while learning how to do science and think quantitatively. Most of these students do not stay in academic science. Many go to medical professions, and others enter the workforce in many capacities as scientifically literate, thus benefitting the nation at large, while their paid work has advanced scientific projects.

Graduate Students: I usually have 4-5 Ph.D. students working in the lab. These students are apprentice students, and their stipends are paid by a mixture of training and research funds from the NIH and NSF. In our programs, these students learn to teach, write, and speak well, as well as carry out independent research projects that result in scientific publications. Upon graduation, about half of these students continue on to further scientific training, and about half move immediately into jobs in industry, government, education, etc. The local biotech industry depends heavily on this Ph.D.-trained work-force for its employees.

Postdocs: Postdocs have completed a Ph.D., and then usually move to another laboratory to learn an additional field, new methods etc., so they have versatility and experience as they move into the work-force. Most postdocs are paid either on NIH training funds or on research grants, as they are contributing to the generation of the new knowledge funded by the NIH and NSF. Across most institutions in the U.S. today, at least half of our postdocs enter the industrial work force, where their excellent training and experience is crucial to the vitality and quality of the biotech, pharmaceutical, and other industries. A subset of these people stay in academic science, and become the next generation of scholar/researchers/educators that make many of our scientific establishments among the best in the world, and the subject of world-wide envy.

Short Biography

Eve Marder is the Victor and Gwendolyn Beinfeld Professor of Neuroscience in the Biology Department of Brandeis University. Marder was President of the Society for Neuroscience in 2008, and served on the NINDS Council, numerous Study Sections, and a variety of Advisory Boards for institutions in the USA and abroad. Marder is a member of the National Academy of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences, a Fellow of the Biophysical Society, a Fellow of the American Physiological Society, and a Fellow of the American Association for the Advancement of Science. She received the Miriam Salpeter Memorial Award for Women in Neuroscience, the W.F. Gerard Prize from the Society for Neuroscience, the George A. Miller Award from the Cognitive Neuroscience Society, the Karl Spencer Lashley Prize from the American Philosophical Society, an Honorary Doctorate from Bowdoin College, the Gruber Award in Neuroscience, and the Education Award from the Society for Neuroscience. Marder served on the NIH working group for the Obama BRAIN Initiative. She shared the 2016 Kavli Award in Neuroscience.

Marder studies the dynamics of small neuronal networks, and her work was instrumental in demonstrating that neuronal circuits are not “hard-wired” but can be reconfigured by neuromodulatory neurons and substances to produce a variety of outputs. Marder is now studying the extent to which similar network performance can arise from different sets of underlying network parameters, opening up rigorous studies of the variations in the individual brains of normal healthy animals. Her research has been continuously funded by the NIH and NSF for almost 40 years.

Massachusetts General Hospital Boston, Massachusetts

Massachusetts General Hospital is the largest independent hospital to receive funding from the National Institutes of Health (NIH). The research community now consists of more than 8,000 people, including PhD scientists, clinician investigators, science support staff and administrative support staff. Its research teams have continued to make significant advancements in medical science and technology. Below are just a few examples of the types of groundbreaking research made possible by NIH funding:

- **Robert Waldinger, MD:** After following 268 Harvard graduates and 465 low-income Boston men for nearly 80 years as part of the Harvard Study of Adult Development, researchers have collected a cornucopia of data on their physical and mental health. Led by Robert Waldinger, MD, a psychiatrist at Massachusetts General Hospital, the study is one of the world's longest studies of adult life and provides irreplaceable information about aging across the lifespan. Waldinger's research has proved that embracing community helps us live longer, and be happier. The long-term research has received funding from private foundations, but has been financed largely by grants from the National Institutes of Health, first through the National Institute of Mental Health, and more recently through the National Institute on Aging.⁶
- **Mark Albers, MD, PhD:** A Massachusetts General Hospital research team has developed a series of tests designed to measure early indications of Alzheimer's disease based on an individual's ability to recognize, remember and distinguish among odors. Developed by a team led by Mark Albers, MD, PhD, of the Mass General Center for Alzheimer's Research, the 30-minute scent test was given to 183 people between 60 and 80 years old – some with mild cognitive impairment or possible Alzheimer's disease— and of those, about 20 percent showed signs of olfactory deficiencies. Genetic and imaging testing revealed that that these same individuals had other deficiencies that have been linked to the illness, including thickening of certain brain structures and a mutation in a gene associated with increased risk of Alzheimer's disease.

While Alzheimer's disease is known to affect brain structure involved in odor perception, previous tests have not been effective screening tools, since the natural ability to identify and distinguish among scents varies greatly among individuals. The MGH team's approach tested both the ability to recognize a series of odors and the ability to remember whether they were among a previously presented set of odors. It is estimated that there is a 10-year gap between the initiation of Alzheimer's disease in the brain and the first outward manifestation of symptoms. If researchers can better identify individuals in the very early stages of the disease, they may be able to develop therapies that will slow or halt its progression. Support for the study includes National Institutes of Health grants DP2-OD000662, P30-AG036449, P50-AG005134 and T32NS048005

⁶ See Liz Mineo, "Good genes are nice, but joy is better," *Harvard Gazette* (April 11, 2017) (online at <http://news.harvard.edu/gazette/story/2017/04/over-nearly-80-years-harvard-study-has-been-showing-how-to-live-a-healthy-and-happy-life/>).

- **Brian Skotko, MD, MPP:** Investigators at the MassGeneral Hospital for Children have developed a promising new method for assessing the risk of obstructive sleep apnea (OSA) in children with Down syndrome. The new method, which employs information that can be gathered during a visit to a primary care physician, could help to reduce the need for overnight sleep studies, which can be expensive and difficult for children and their families.

OSA occurs when the airway becomes restricted or blocked during sleep, causing breathing to become shallow or temporarily stop. In addition to interrupting sleep, OSA lowers oxygen levels in the blood and can impair cardiac, metabolic and cognitive functioning in typically developing individuals, and the effects can be exacerbated in those with Down syndrome.

It is estimated that close to half of those with Down syndrome have OSA due to alterations in their craniofacial features that result from the syndrome. The American Academy of Pediatrics recommends that all children with Down syndrome undergo an overnight sleep study to screen for OSA starting at age 4.

While sleep studies are effective in measuring OSA risk, they can be expensive, difficult to access in certain areas and can be challenging for individuals with Down syndrome, particularly young children. The new method, which was developed by a research team led by Brian Skotko, MD, MPP, uses a variety of factors – including the physical characteristics and vital signs of the participants plus information provided by parents on a questionnaire – to predict the risk of OSA.

In a study of 102 children with Down syndrome, the team's new method was able to accurately predict the risk of moderate to severe OSA in 90 percent of those who were diagnosed with the condition following an overnight sleep study. The team is now working to confirm those results in a follow-up study. Support for the study includes National Institutes of Health grants T32 GM007748-32 and F32 HD068101 and Clinical Translational Science Award UL1 RR025758

- **Sekar Kathiresan, MD:** The Human Genome Project provided a 'parts-list' of genes, about 18,000 in number. Now, researchers are studying what it means to be missing a part. In an analysis of the genomes of 10,000 research participants, Sekar Kathiresan, MD, Director of the Center for Genomic Medicine at Mass General, and his research team at Mass General and the Broad Institute found 1,300 genes which were broken in at least one participant. For example, several individuals were missing a working copy of the APOC3 gene and as a result, these individuals had lower blood levels of fat and were protected from heart attack. Such examples help us understand the function of a gene in humans and also point to new drug targets. This study sets the stage for an ambitious 'Human Knockout Project', a systematic effort to understand gene function by identifying and characterizing humans who naturally lack a gene. Support for this study includes grants from the National Human Genome Research Institute and the National Heart, Lung, and Blood Institute.

- **Vitaly Napadow, PhD:** A new study by researchers at Massachusetts General Hospital shows that acupuncture treatments not only reduce patient-reported experiences of pain in carpal tunnel syndrome (CTS), but this ancient therapy also makes a measurable difference in how the brain processes nerve signals that are compromised by the painful repetitive motion disorder.

CTS is one of the few chronic pain disorders associated with objective measurable changes. Because CTS is a result of compression of the median nerve in the arm, impulses between the wrist and the forearm – such as motor function and sensation – are slowed down. Additionally, studies have shown that the brain – particularly the part that receives touch-related signals – is remapped in CTS. Specifically, brain cells that usually respond to touch signals from individual fingers start to respond to signals from multiple fingers.

Study participants received either electro-acupuncture at the affected hand, at the ankle opposite the affected hand or sham electro-acupuncture with placebo needles near the affected hand. Results were measured before and after eight weeks of therapy sessions (16 sessions total) using a questionnaire and MRI scans.

Vitaly Napadow, PhD, director of the Mass General Center for Integrative Pain Neuroimaging at the Martinos Center for Biomedical Imaging at Mass General, and his team found that the 80 participants across all three groups reported improvements in their pain and numbness after the treatments. However, only participants who received real acupuncture – either at the affected hand or at the ankle – saw improved nerve impulses in the wrist. Those that received real acupuncture at the affected hand also experienced brain remapping linked to long-term improvement in CTS symptoms. No physiologic improvements resulted from sham acupuncture.

Researchers will now plan further research to better understand how acupuncture works to relieve pain in an effort to help improve non-pharmacological care options for chronic pain patients. The study was supported in part by the National Institutes of Health grants R01 AT004714, R01 AT004714-02S1, P01 AT002048 and K24 AT004095

Massachusetts General Hospital: Diabetes Program

Boston, Massachusetts

The **Massachusetts General Hospital** (MGH) Diabetes Center, founded and directed by Dr. David M. Nathan, was established in 1980 as a clinical research center dedicated to the study, development and testing of new methods of treatment and prevention of diabetes mellitus. The studies conducted in the Center have largely been supported by the National Institute of Diabetes Digestive and Kidney Diseases (NIDDK), NIH. We have also received support from NHLBI, NCI, NIA, NEI, NICHD, and other offices and institutes at NIH. The research function of the Diabetes Center has been complemented by the General Clinical Research Center at MGH, also an NIH-supported facility, in which inpatient research studies and some of our diabetes outpatient studies are conducted.

Single-site studies at MGH that would not have been possible without NIH support have led to the development of new measurements and methods of therapies that are now used commonly in clinical practice. These innovations include contributions to the development and testing of novel assays, such as the hemoglobin A1c assay, which is the mainstay of diabetes diagnosis and care; the development and the first demonstration of the therapeutic potential of glucagon-like peptide, now a commonly used medication for the treatment of type 2 diabetes; the development of whole organ and islet transplantation programs for type 1 diabetes; and the development of novel methods to treat type 1 diabetes with a variety of devices such as insulin pumps and now with a mechanical artificial pancreas.

While NIH-supported single center studies, as outlined above, have contributed to the advancement of diabetes management, it has been the **large multicenter studies** supported by NIDDK, NIH that have transformed the care and, more importantly, the lives of people with diabetes. Dr. Nathan has been the architect of and led several of these iconic studies. None of these studies could have been performed without the far-sighted commitment and support of the NIH. These studies were and continue to be “game changers” with regard to public health and *none* of them would have been funded by industry. These studies include:

- The **Diabetes Control and Complications Trial** (DCCT: 1983-93) and its long-term follow-up Epidemiology of Diabetes Interventions and Complications study (EDIC: 1994-present). These two studies, consistently funded by NIDDK over 34 years, demonstrated the means of preventing and reducing the long-term complications of type 1 diabetes that can cause blindness, kidney failure, amputations, heart disease and stroke. In the DCCT and EDIC, all of these complications have been reduced by more than 50% with a prolongation of life-span that has been estimated at 15 years. In addition to the benefits to health and quality of life, substantial savings in health care costs have been demonstrated. The model of care tested in the DCCT has been adopted world-wide and is now considered the standard of therapy.
- The **Diabetes Prevention Program** (DPP: 1996-2002) and its follow-up DPP Outcomes Study (DPPOS: 2003-present). This NIDDK-funded study (with support from other Institutes) demonstrated that the epidemic of type 2 diabetes could be reduced by as much as 58% with a lifestyle intervention directed at weight loss and increased activity. In addition, the medication metformin was demonstrated to be effective and cost-saving.

The results of this study directly led to the development of numerous DPP-like programs in the US and world-wide. Most recently, CMS has approved the funding of the DPP model. Of note, after 20 years of annual increases in the development of diabetes in the US, the rate of new cases has been decreasing since 2008.

- **The Glycemia Reduction Approaches in Diabetes: A comparative effectiveness (GRADE) study** is an ongoing (2013-2021) study to compare the most commonly used treatments for type 2 diabetes. This NIDDK supported study will demonstrate which of the myriad medication combinations used to treat type 2 diabetes is most effective in controlling blood sugar levels. In addition to comparing efficacy in controlling diabetes, GRADE also compares the safety, tolerability, patient acceptance, relative adverse and beneficial effects of the different medications. As with the other large clinical trials above, industry has not demonstrated any willingness to perform this type of comparative effectiveness study which is critical if we are to understand the best drugs for individual patients and personalize treatment.

Other MGH investigators who work at the cutting edge of diabetes research, with a focus on clinical translation and patient benefit, and whose accomplishments are driven by NIH include:

- **Alexander Soukas, MD, PhD and mechanism of metformin** – Dr. Soukas is a practicing endocrinologist and laboratory-based scientist who is focused on identifying the next generation of treatments for obesity and type 2 diabetes. His laboratory, which is currently funded by NIH R01 grants and has been funded by K08 and R03 grants, uses model systems in order to determine the genetic underpinnings for metabolic disease. Recently, Dr. Soukas had a major breakthrough published in the journal *Cell* whereby we identified the mechanism by which the world's most common anti-diabetic drug, metformin, stops cancer cells in their tracks. This work, which would not have been possible without NIH support, pinpoints new targets in the cell we can now use to design new therapies for type 2 diabetes and cancer, two of the most common causes of death and disability in the US today. Without further NIH support for the next generation of this work, pioneering research that serves to transform the way we treat and prevent diabetes, obesity, and cancer in the years to come would be crippled.
- **Jose C. Florez, MD, PhD and precision medicine** – Dr. Florez has been continuously funded by NIH for the last 15 years to identify the genetic causes of type 2 diabetes and understand the genetic determinants of therapeutic response, with a view to tailor treatment more precisely to the individual. In 2010 he received the Presidential Early Career Award for Scientists and Engineers for a project designed to investigate the pharmacogenetics of commonly used antidiabetic medications. He leads several international consortia (MAGIC, SIGMA, T2D-GENES, AMP-T2D, GENIE, MetGen), supported by major NIH funds, that have proven immensely successful in pinpointing regions of the genome in which specific variants can increase the risk of type 2 diabetes or its complications, affect physiological regulation of blood glucose, or predict response to treatment. U.S. scientists exert global leadership in these areas thanks to their ability to leverage NIH support.
- **Steven J. Russell, MD, PhD and the bionic pancreas** – Type 1 diabetes is a disease in which the immune system destroys the insulin producing cells in the pancreas. Insulin is required for life, so people with diabetes must inject insulin for the rest of their life.

Failing to inject insulin for a day will likely be fatal. The amount of insulin to be injected is crucial because if too little is injected the blood sugar will be very high and this causes long term damage to the body, eventually leading to kidney failure, blindness, amputations, and heart attacks and strokes. On the other hand, if too much insulin is injected the blood sugar will fall too low. Since the brain needs sugar to operate, low blood sugar causes anxiety, then confusion, then unconsciousness, seizures, and finally death.

It is very challenging to keep blood sugar in the middle range between too high and too low. People with diabetes need to count carbohydrates, closely monitor blood glucose (checking more than 10 times a day to get good control), and make dosing decisions for insulin. Given the immediate risks of going too low, most people err on the side of going too high, their lives are shortened and the quality of life is reduced as a result of the complications of high blood sugar.

To solve this problem, Dr. Russell and his colleagues have developed an automated wearable system to control the blood sugar called a bionic pancreas. The bionic pancreas measures the blood sugar every 5 minutes automatically using a small sensor that attaches to the skin – a continuous glucose monitor. Mathematical algorithms use this information to decide how much insulin to give (or not give) every 5 minutes. Clinicians also can give glucagon, which has the opposite effect to insulin. By delivering these 2 drugs automatically under the control of smart algorithms, doctors can effectively and safely regulate blood sugar.

The NIH has funded several clinical studies in which Dr. Russell's team has tested the bionic pancreas in volunteers with type 1 diabetes ranging in age from 6-76 years of age. They recently completed a multi-center home study in which subjects wear the bionic pancreas for 11 days while they went about their usual routines at home, work, and play. These studies showed that the bionic pancreas provides excellent blood sugar control while at the same time reducing the burden of diabetes and the fear of low blood sugars. The team will begin a trial in 2017 with a new bionic pancreas device that is designed for commercialization. They will then test it in pivotal studies (vetted with the FDA as being sufficient to allow approval for sale if endpoints are met), with a regulatory submission planned in 2018.

These studies were and are largely funded by the NIH. The work is being done through a collaboration between MGH (the medical expertise) and Boston University (the engineering expertise). It was not an industry-sponsored project, so it could never have moved forward with the NIH support.

From 2009-2019 the total committed funding from the NIH to this project is \$21M. This has been leveraged with funds from foundations and investments to make this large-scale project possible. Now a company, Beta Bionics, has been formed as a Massachusetts benefit corporation with a mission to make the technology available to as many people with diabetes as possible at the lowest feasible cost. The funding from the NIH and other meant that it did not have to look for venture funding, which means that it isn't beholden

to the desire for an “exit”, and can make strategic decisions with what is best for people with diabetes as the top priority.

When the bionic pancreas is approved it will truly revolutionize the care of people with diabetes. The level of glucose control is so good that it may be able to virtually eliminate diabetes complications. It is a game changer and it wouldn't have happened without support from the NIH.

Martha Murray, MD
Orthopedic Surgeon
Boston Children's Hospital
Boston, Massachusetts

Injuries to the Anterior Cruciate Ligament of the knee (ACL) affect over 200,000 US citizens each year. Costs of surgery average \$12,600, leading to an estimated costs of surgery alone of over \$2.5 billion per year for US healthcare, with additional costs for rehabilitation and time lost from work for these largely young, healthy and athletic people. In addition, over 75% of the patients who sustain an ACL tear will develop premature osteoarthritis within 15 years of injury, even with our best current surgical treatment, ACL reconstruction. As the peak age for this injury is 15 to 19 years of age, this injury currently has significant ramifications for a large segment of the US population. The costs of an additional 150,000 total knee replacements is estimated to be \$8.6 billion dollars each year.

Work funded by the NIH in our lab has enabled development of an entirely new approach to ACL injuries. Past surgical approaches included trying to suture the ACL back together, termed primary repair. The failure rates of this procedure were estimated to be 50 to 90% and this procedure was largely abandoned in the 1970s. As a result, the current surgical technique involves harvesting a graft of two hamstring tendons from the back of the knee, and using these tendons to reconstruct, or replace, the torn ACL. While this procedure is reasonably good at returning function to the knee, as many as 20% of young patients will tear the graft within 2 years, and over 75% will develop early osteoarthritis. This prompted us to ask the question: Is there a better way?

Starting with a \$150,000 3-year R03 grant from the National Institutes of Health through the National Institutes of Arthritis, Musculoskeletal and Skin Disease (NIAMS) in 1999, we began to study first why the ACL failed to heal with suture repair, and then to engineer a better solution. A K award in 2004 enabled me to pursue a career as a clinician scientist by providing protected time and salary support for me to continue research. In 2006, we were able to obtain two larger NIH grants (R01 AR054099 and AR052772) to define the effect of age on ligament healing, as well as learning what biologic elements would be most useful to stimulate healing of the ACL.

This NIH funding allowed us to identify and develop a tissue engineered scaffold that could be placed between the torn ends of the ACL, and with the addition of blood to the scaffold, it is able to stimulate healing of the ACL without the need for a tendon graft. This discovery work led to additional funding to test and improve this technique in larger models more relevant to our patient population (NIH AR056834) and to perform the translational work to obtain FDA approval for a first-in-human trial. We recently completed that trial, and now have an additional NIH grant to fund planning for a larger, multicenter trial for this technology (R34 AR066631).

This new technique for ACL surgical treatment, bridge-enhanced ACL repair, still needs further study and undoubtedly will continue to be improved through research over the next decades. However, the preclinical data demonstrated that knees treated with this technique were able to heal the ACL, and in addition, these knees did not develop arthritis. Thus, this technique

may help not only reduce the burden of the immediate surgery (the surgery is simpler, faster and thus has the potential to be less expensive, and for the patient, no graft harvest is needed so rehabilitation is quicker and easier), but it may also lessen the future healthcare cost burden by stopping patients with ACL tears from requiring a total knee replacement at an early age.

In addition, we founded a startup company, MIACH Orthopaedics, Inc, to manufacture the tissue engineered scaffolds. We plan to base the company here in Massachusetts and are currently talking with investors to try to raise the capital to get started.

This \$8 million investment in NIH research for the ACL thus has the potential to save billions of dollars in healthcare costs and establish a new manufacturing stream for Massachusetts and the US. The money has provided full-time jobs for up to 5 people each year since 1999. The people who have worked on this project have gone on to become surgeons and professors at other institutions, and the training they have obtained in this research program has helped them to learn how to ask good questions and to not accept the status quo when improvement is possible, particularly in surgical fields.

This project is not unique in orthopaedic surgery. Orthopaedic surgeons are responsible for a large segment of healthcare spending in the US, and the quality studies performed with NIH funding in the past few years demonstrate the potential for research in this area to reduce health care costs significantly. For example, the \$3.8 million NIH sponsored MeTeOR trial, run by Jeffrey Katz at Brigham and Women's showed that up to 70% of patients with a meniscus tear could avoid surgery. If meniscus surgery rates decreased by 70%, that could represent a \$4.6B dollar savings annually for the US healthcare system. The NIH funded \$5.5 million BRAIST study for idiopathic scoliosis, led by Stuart Weinstein at the University of Iowa, similarly demonstrated the use of bracing could decrease surgery rates for this disease from 72% to 48%. As there are currently 38,000 spinal fusions each year in the US, this represents another \$1 billion per year potential savings for the US healthcare system. These are healthy returns on investment.

This funding of discovery research, translational research and clinical research by the NIH thus represents a win-win. It provides a venue for our brightest and most motivated students and residents to participate in something exciting and larger than themselves, and to go on to train the next generation of US scientists and surgeons. Research of the quality funded by NIH also improves the lives of future patients. In orthopaedic surgery, a strong case can be made for this type of research also having the potential to significantly decrease healthcare spending in the US and to create new technologies which can increase domestic job creation.

Colles Price, MS, PhD

Research Fellow, Dana-Farber Cancer Institute
Postdoctoral Scholar, Broad Institute of MIT and Harvard
Research Fellow in Medicine, Harvard Medical School
Cambridge, Massachusetts

Without funding and educational programs sponsored by the National Institute of Health (NIH) I would not have a career in cancer research. As an underrepresented minority from Baltimore City I was interested in medicine and science but realistically had no idea what that meant. In high school I had the opportunity to meet scientists from the NIH and learn about research. I was fascinated and it drove my interest in biomedical research. After college I went on to pursue a masters in clinical/translational science and a PhD, funded by the NIH through a fellowship grant, in cancer biology.

During my graduate work I had the privilege to work with the incredible Dr. Janet Rowley who was a pioneer in genetics and medicine. She received funding from the NIH early in the stages of her career which was instrumental to her cancer discovery that would eventually lead to the development of the “miracle drug” Gleevec (also known as Imatinib). This drug has virtually cured most patients with Chronic Myelogenous Leukemia (CML) and has positively impacted thousands in the United States and more across the world. It is a great model of how NIH funding has saved lives.

It is my goal to pursue research and hope to contribute to the curing of cancer as she did. With funding I obtained from the NIH during my graduate school training I discovered novel products made by leukemia cells. This was important because these products were strongly made in cancer cells and not present in normal cells, meaning it might be possible to target and minimize patient side effects. To further classify these products, I was funded by a NIH program to learn Genomics and Genetics at the National Human Genome Research Institute (NHGRI) at the NIH. Following this program, I was better equipped to fully classify these products. Using this information, I used nanotechnology to create a new therapy and found the early results promising.

As a postdoctoral research fellow, currently funded by the NIH as a research fellow, I am working with others to identify new therapies for the treatment of cancer and, interestingly, repurpose therapies for other diseases to determine if they can be used to treat cancer. If we consider cancer to be a journey we act as “google mapping cancer” trying to model all possible patient roads and possibilities to understand which path is the best for each individual. We believe these projects, also funded by the NIH, is crucial to developing a personalized treatment path for future patients and can be used to develop the best therapies. We hope these will advance our ability to manage cancer.

Henry Rogalin, PhD

Postdoctoral Fellow

Tufts Clinical and Translational Science Institute (CTSI)

Boston, Massachusetts

My story in translational research begins like all other scientists—with the questions of how and why. While everyone asks these questions of the world around us, it was the questions from my patients that inspired my early career. What follows is my story; this is what drove me to research and my experience with the research funding environment.

The marine slowly awoke from sedation. I was the first person he spoke to following the injury. I do not remember why I was there, and not the intensive care doctor or the surgeon. But I do remember his eyes, and his missing leg. I told him he would walk again, and even run. He asked me, how did I know? I drew upon my training at Walter Reed where I met many service members recovering from amputations. I told him of how with the right prostheses, even those with double amputations below the knee were running. The questions kept coming, and I continued to talk with him well past the end of my shift. In the years prior to my deployment, service members were kept sedated until they were state-side. At this point they were disorientated, and their bodies had been getting pain signals the entire time. The newest guidance was to wake our service members as soon as possible, and use peripheral nerve blocks. We were told this helped with phantom pain, as well as their overall physical and psychological recovery. How did we know any of this, and what happens when the information isn't available?

My Army reserve company spent about 6 months running the Combat Support Hospital (CSH) for the forward operating base in Mosul. We were then tasked to set up and run the CSH at Al Asad Airbase in Western Iraq. I was a combat medic with extra training as a Practical Nurse. During the transition between hospitals, I watched one of our nurses set up and execute a series of experiments. He was testing different methods for using the warming blankets to find out how to best warm up our patients. I will confess that at the time, I thought it was all very silly. We had direct orders not touch any of the set ups with the temperature probes. I remember thinking what difference did it make? We put on the blankets and turn on the warm air. Months later, we were all asking this nurse what the results were. Our newest patient had lost his arm at the shoulder, and had 2nd and 3rd degree burns all over his body. Infection and loss of body heat were big concerns. At that point, it mattered how well we could warm him up, and keep him that way.

Following my deployment, I wanted to keep asking how we know what is best in medicine, and why things work. I completed my PhD in Biochemistry at Tufts Sackler School of Biomedical Sciences. This has been a time of relatively flat funding for the NIH, and science in general. There were many labs that I wanted to do my PhD work in, but who did not have enough funding to take on a student. My peers and I saw a difficult funding environment, that only got worse as the years progressed. While many of my peers left academia after graduating, I wanted to stay and make a difference. I am half-way through a training program in Clinical and Translational Science, made possible by CTSA funding. I have been able to apply the training from my program to diverse projects, ranging from body warming during cardiac surgery to the utility of probiotics in health.

The Clinical and Translation Science Institute (CTSI) at Tufts connects everyone along the spectrum of translational science, from the biomedical laboratories to researchers working on issues of policy and practice guidelines. I, as a researcher, patient, citizen, and veteran, need this funding to continue and increase. The CTSA programs should continue to be funded with their own line item. These institutes are in the best position to know how to integrate teaching and research at their local levels. Furthermore, my colleagues are using AHRQ support for numerous projects such as how to reduce costs from unnecessary readmissions in adult and pediatric patients. This research involves talking with patients, their families, and other groups that have a stake in the process. AHRQ needs to stay distinct from the NIH.

The scientific community needs to know that the government recognizes the importance of the NIH, and that there is dependable funding. Biotechnology companies must answer to their shareholders, and they lack the ability to engage in long-term high-risk research. The NIH is critical to our economy by funding research that cannot show results in the quarterly time frame of Wall Street. NIH funding is also crucial for training career researchers, a model which has placed the US at the top of the world in biomedical research. The continued uncertainty in NIH funding pushes too many recent graduates and junior career scientists into industry, and even non-science jobs. These were dedicated scientists that I know would have made great independent researchers. We cannot afford to push so many scientists away from careers that transform medicine and science in general.

Harry Selker, MD, MSPH
Tufts Medical Center
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Over 50 years ago animal studies suggested that intravenous glucose, insulin, and potassium (known as “GIK”) could dramatically reduce the severity of and death from cardiac arrest in heart attacks – acute myocardial infarction (AMI). However, in follow-up clinical trials in patients done as side studies to pharmaceutical company sponsored drugs, it did not seem to have a reliable impact. These trials were not the standard for medical research, randomized placebo-controlled trials, because not having a patent on its glucose, insulin, and potassium components, no drug company could plan on making substantial profits, and would not invest in doing a rigorous trial of GIK. So this promising, very inexpensive treatment for the most common cause of death in our country was never optimally tested.

The great promise of the treatment, in the US and worldwide, got the attention of researchers at Tufts Medical Center, specifically the Center for Cardiovascular Health Services Research in the Tufts Medical Center Institute for Clinical Research and Health Policy Studies. Believing that the primary problem had been the quality of the previous clinical trials, they sought to do an NIH-quality trial of GIK. Also, they felt that so far, GIK had not been tested in humans correctly, as it had worked in animal studies very early in the course of AMI, or even when AMI was still forming, known as acute coronary syndromes (ACS). Previous human trials gave GIK typically six hours after ACS onset, *after* documentation of AMI *at a hospital*. In contrast, the Tufts team felt that GIK should be started immediately by paramedics responding to 9-1-1 calls for suspected ACS, in ambulances in communities. They applied for, and received funding from the NIH National Heart Lung and Blood Institute (NHLBI) for a trial to be done in communities across the US for patients who call 9-1-1 for suspected heart attacks, “acute coronary syndromes,” the IMMEDIATE (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care) Trial.

The results of the NIH-sponsored IMMEDIATE were dramatically different from the prior studies: GIK reduced the composite of cardiac arrest or mortality from ACS by 50%, by 60% for the most severe type of heart attacks, ST elevation AMIs, and reduced the size of the heart attacks by 80%. This inexpensive treatment could save tens of thousands of lives a year in the US, and millions worldwide.

However, so different from prior (non-NIH) trials, for approval, FDA wants it repeated to confirm these results – and the Tufts team agrees. However, with no patent and related likelihood of substantial profits, no pharmaceutical company is interested in marketing GIK, much less sponsoring the second, pivotal trial. Thus again the team is going to NIH NHLBI for the definitive trial, IMMEDIATE-2, which they hope to be able to start soon.

Brian J. Song, MD, MPH

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Since its inception, the National Eye Institute (NEI) of the National Institutes of Health (NIH) has provided funding for scientists that has laid the groundwork for numerous discoveries that have improved both the detection and treatment of blinding eye disease. One such example is optical coherence tomography (OCT), a new imaging technology originally pioneered by researchers at the Massachusetts Institute of Technology (MIT).

OCT is often compared to an “ultrasound of the eye” in that it allows physicians to visualize and measure otherwise hidden structures in the back of the eye. As a result, physicians are now able to detect vision-threatening diseases like glaucoma and age-related macular degeneration (AMD) sooner and with greater accuracy oftentimes before patients develop symptoms. Today, it is estimated that an OCT scan takes place somewhere around the world every second, and its success now supports a manufacturing industry with around \$1 billion/year in sales and a workforce of over 16,000 high-paying jobs.

OCT would not exist without government funding. Some of the initial experiments to develop OCT technology were funded by grants under President Reagan’s “Star Wars” program and further research was then funded by the National Science Foundation (NSF) and NIH. Combined, the two agencies dedicated around \$500 million toward developing the technology from 1991–2014, according to the NIH RePORTER and NSF Award databases.

Though \$500 million is a significant investment over two decades, OCT has saved the U.S. government an estimated \$11 billion in Medicare spending from 2008–2014 by changing the way we treat AMD. Before the development of OCT, doctors followed a treatment schedule that required injecting expensive prescription drugs into the eyes of AMD patients every month. Now, the information from an OCT scan allows doctors to see whether an injection is needed at that visit or can be safely delayed. Every time an injection (some which cost around \$2,000 per injection) is delayed, Medicare saves money. This results in an impressive 2,200% return on the investment made by NIH and NSF to develop the technology and only accounts for the cost-savings related to one disease out of the many that are now managed using OCT.¹

As a young clinician-scientist, I depend on the outcomes from such federally-funded research to provide the best possible care for my patients as well as the support of the NEI and NIH in developing my own research program. With regard to my field of glaucoma, studies show that over half of all patients with glaucoma in America remain undiagnosed and untreated despite innovations in health care, suggesting that there is still much room for improvement.² I have been fortunate in my career thus far to be funded through an institutional K12 training grant from the NIH to begin to study telemedicine as an alternative means to address this issue by promoting earlier disease detection in the growing number of aging patients in our health care system with limited access to vision care. In my efforts to study and develop novel methods for eye care delivery in high-risk patients for glaucoma, I have recently submitted a proposal to the

NEI in which we are hoping to evaluate the potential role of OCT as a screening tool for glaucoma in telemedicine programs. While a reduction in the NIH and NEI budget will lead to the termination of research programs like my own and further escalate the loss of the estimated 100 vision researchers that has occurred in recent years due to limitations in the NEI budget, increased federal funding will provide the necessary resources to finish the work that I, and others like myself, have started to continue to develop better and more cost-effective treatments and tools for the betterment of our patients and the fight against blindness.

References:

1. "Revealing the Back of the Eye with OCT." *The Association for Research in Vision and Ophthalmology*. Web. 18 Apr 2017.
2. Shaikh Y, Yu F, Coleman AL. Burden of undetected and untreated glaucoma in the United States. *Am J Ophthalmol* 2014; 158(6):1121-1129.

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While research into “cures” for paralysis may garner headlines and investment, the reality is that for most people impacted by spinal cord injury this will likely not occur in their lifetime, or at least for many decades. In fact, if a cure for paralysis was found, most people with spinal cord injuries do not have adequate bone density to support mobility again. However, the ability to significantly improve quality of life for those suffering from spinal cord injury (SCI) enabling them to experience increased health benefits has far reaching implications from less secondary complications (pressure ulcers, obesity, diabetes) that strain the health care system as well as the ability to stay healthy and employed as well.

SCI has been suggested to represent a condition of “accelerated aging.” As a result, those with SCI have higher cardiovascular mortality rates and mortality at earlier ages compared with the general population. Indeed, one study found that in a large cohort of those with an SCI from 1973 to 1998, heart disease was the leading cause of mortality after the first year of injury. Recent evidence suggests that 3/4 of those with chronic SCI are overweight or obese, and increased fat stores may not only relate to the high prevalence of low insulin sensitivity and diabetes, but also a greater risk of systemic inflammation.

To bridge this gap, researchers and clinicians at Spaulding created a first-of-its-kind endeavor, the Spaulding Exercise for Disabilities Program (ExPD). The ExPD program is a joint treatment and research program funded by the NIH. Hundreds of participants each year, since its launch over eight years ago, have benefitted from the Functional Electrical Stimulation (FES) Rowing program. FES is a technology that allows paralyzed muscles to contribute to whole body exercise. In this way, both the paralyzed legs and innervated arms are under voluntary control and higher exercise intensities can be reached and sustained. In fact, some FES-rowers have achieved unprecedented work rates comparable to those of able-bodied rowers.⁷

Led by Dr. J Andrew Taylor, the group at Spaulding’s Cardiovascular Research Lab has published many studies showing that a steady regiment of FES Rowing based exercises have shown to increase bone density. Additionally, the program has found community-based partners such Community Rowing in Brighton to offer FES rowing as well as participating annually in the “Crash B’s” indoor competition each February and the Head of the Charles events, expanding access and awareness of the SCI population. Similar research models have begun at other institutions such as Stanford University based on the ExPD programs’ results.

Considering that the lifetime costs for a 22-year-old with a complete SCI is upwards of \$1 million over an able bodied counterpart, and much of this is due to secondary complications, effective interventions to improve overall health that can be implemented early after injury and maintained for a lifetime of improved well-being are badly needed. It is inarguable that regular physical activity is crucial for health in the general population. An SCI does not alter this, and in fact may make exercise of supreme importance to health. The few longitudinal studies in chronic SCI do suggest potential striking changes with exercise that impact health. Programs like ExPD,

⁷ See Spaulding Rehabilitation Network, “Exercise for Persons with Disabilities (ExPD)” (online at <http://www.nepva.org/downloads/Spaulding%20exercise%20program.pdf>).

made possible because of NIH funding, show the significant return on investment research can create, especially for areas that would get overlooked by private investors. Programs like ExPD can be easily implemented, are relatively inexpensive, and allow ready integration into the community. Increased federal funding will allow programs like this to look at new ways to help the millions of people impacted by mobility impairments, improving the quality of life both for individuals as well as our entire population.

Additional Resources:

ExPD Program Page:

<http://spauldingrehab.org/research-and-clinical-trials/exercise-persons-disabilities>

2009 Boston Globe Feature “Hope is a River”

http://archive.boston.com/news/local/massachusetts/articles/2009/07/12/david_estrada_lost_the_use_of_his_legs_but_not_his_will_now_at_spaulding_hospital_he_and_other_paraplegics_are_earning_to_row_strengthening_body_and_mind_as_they_wait_for_a_cure/?page=full

Research Article

Hybrid functional electrical stimulation exercise training alters the relationship between spinal cord injury level and aerobic capacity.

[Arch Phys Med Rehabil](#). 2014 Nov;95(11):2172-9. doi: 10.1016/j.apmr.2014.07.412. Epub 2014 Aug 21.

<https://www.ncbi.nlm.nih.gov/pubmed/25152170>

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Each \$1 of NIH funding to Massachusetts institutions has an estimated multiplier economic impact of approximately \$2.30.⁸ (Data from *NIH's Role in Sustaining the U.S. Economy, 2015 Update*, United for Medical Research). UMMS has \$262.6 million in total sponsored research (2nd quarter FY2017), of which \$206.1 million is federal including \$153.8 million from NIH.

If adopted, the President's proposed cuts to NIH and other federal research programs would not necessarily impact every research institution exactly in proportion to his 20 percent proposed NIH cut, but it is the best starting point for analysis. At UMMS, a reduction of 20% to all federal grants equates to \$41.2 million. Applying the \$2.30 economic multiplier from the United for Medical Research study, this translates to a \$94.8 million negative multiplier impact on Massachusetts, most of which would be felt here in the Worcester area.

Below are a few examples of significant breakthroughs by UMMS researchers from NIH-funded projects.

- A pair of NIH-funded studies led by UMMS researchers (one by Dr. Jeremy Luban and one by Dr. Heinrich Gottlinger) identified genes that disable HIV-1, suggesting a promising new strategy for battling HIV / AIDS: "A pair of studies in the journal *Nature*, one by Jeremy Luban, MD, and colleagues in Italy and Switzerland, and the other by Heinrich Gottlinger, MD, PhD, and colleagues; have identified genes that disable HIV-1, suggesting a promising new strategy for battling the virus that causes AIDS."⁹
- Drs. Jeanne Lawrence and Jun Jiang discovered a naturally occurring X chromosome "off switch" that can be rerouted to neutralize the extra chromosome responsible for Down syndrome.¹⁰ This laboratory breakthrough, funded by NIH, paves the way for researchers to study the cell pathologies and identify genome-wide pathways implicated in the disorder: "Scientists at UMass Medical School are the first to establish that a naturally occurring X chromosome 'off switch' can be rerouted to neutralize the extra chromosome responsible for trisomy 21, also known as Down syndrome, a genetic disorder characterized by cognitive impairment."¹¹

⁸ United for Medical Research, *NIH's Role in Sustaining the U.S. Economy, 2015 Update* (online at <http://www.unitedformedicalresearch.com/wp-content/uploads/2016/04/NIHs-Role-in-Sustaining-the-US-Economy.pdf>).

⁹ Jim Fessenden, "UMMS scientists identify genes that shut down HIV-1; research published in *Nature*" (September 30, 2015) (online at <http://www.umassmed.edu/news/news-archives/2015/09/umms-scientists-identify-genes-that-shut-down-hiv-1/>).

¹⁰ See The Vision Project, *Degrees of Urgency* (October 2014) (online at <http://www.tbf.org/~media/TBFOrg/Files/Reports/2014%20Vision%20Project-%20Degrees%20of%20Urgency.pdf>).

¹¹ Jim Fessenden, "UMMS scientists silence extra chromosome in Down syndrome cells," *UMass Med Now* (July 17, 2013) (online at <http://www.umassmed.edu/news/news-archives/2013/07/umms-scientists-silence-extra-chromosome-in-down-syndrome-cells/>).

NIH-supported medical research at UMMS catalyzes private sector growth, as UMMS-patented technology forms the foundation for new products and companies. Data demonstrates this well: UMMS now has 184 licenses with 109 companies; from 2001 to 2012, we filed 817 patent applications, virtually all of which were attributable to NIH-funded research; and the University of Massachusetts system ranks in the top 15 nationally in licensing revenue, 97% of which is attributable to UMMS. Below is one good example:

- Voyager Therapeutics is a Massachusetts-based gene therapy company founded by four world leaders in the fields of AAV gene therapy, RNA biology and neuroscience, two of whom are UMMS faculty – Drs. Guangping Gao and Phillip Zamore. The scientific discoveries that form the basis for Voyager’s establishment resulted from NIH-funded research. This company is focused on developing life-changing treatments for fatal and debilitating diseases of the central nervous system (CNS).¹²

¹² Mark L. Shelton, “Voyager Therapeutics targets novel gene therapies to combat diseases,” *Umass Med Now* (February 12, 2014) (online at <http://www.umassmed.edu/news/news-archives/2014/02/voyager-therapeutics-targets-novel-gene-therapies-to-combat-diseases/>).

Benjamin Warf, MD

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Dr. Benjamin Warf is Professor of Neurosurgery at Harvard Medical School and holds the Hydrocephalus and Spina Bifida Chair at Boston Children's Hospital, where he is Director of Neonatal and Congenital Anomaly Neurosurgery. He has been the Principal Investigator on grants R21TW009612-02 and R01HD085853-02 that were both funded through the Fogarty International Institute of the NIH. This funding has supported a randomized controlled trial of two methods for treating infant hydrocephalus: endoscopic treatment (ETV/CPC) and placement of a ventriculoperitoneal shunt (VPS). During his years as Medical Director of the neurosurgical hospital for children he helped establish in Uganda, Dr. Warf highlighted the large burden of infant hydrocephalus in sub-Saharan Africa, characterized neonatal infection as one of the most common causes, and developed a new surgical treatment for infant hydrocephalus that avoids the need for dependence on shunts - implanted devices that require ongoing neurosurgical maintenance throughout life - which were previously the standard treatment worldwide. He has introduced the procedure, combining endoscopic third ventriculostomy and choroid plexus cauterization (ETV/CPC), into the United States where shunt maintenance accounts for 1 billion dollars in health care costs and significant morbidity each year. Overall, the procedure avoids life-long shunt dependence and any additional operations in about 2 out of 3 infants with less risk of complications such as infection. The one remaining question has been to insure that there is no advantage of treatment by shunt placement in regard to early brain development. The Fogarty Institute of the NIH has been instrumental in funding this randomized controlled trial being conducted at CURE Children's Hospital of Uganda to answer this question. The one-year results demonstrate no advantage to shunt placement in regard to brain growth or cognitive development compared to ETV/CPC. This is the first study to compare the two treatments and has significant implications for the treatment of infant hydrocephalus here in the United States. The manuscript is currently in the final stages of review by New England Journal of Medicine.

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The National Heart Lung and Blood Institute has supported significant funding for research in blood disorders. Sickle cell disease (SCD) is the most common hemoglobinopathy and one of the most common monogenic diseases in the world. In the United States (US) there are 2,000 children born each year with SCD(2) and around 75,000-100,000 individuals with the disease. SCD poses a major public health burden in the US with over 100,000 admissions/year and an aggregate charge for health care services of \$1 billion. The expenditure of health care dollars is 6-11-fold higher for a child with SCD compared to children without the diagnosis. The lifetime care for an individual in the US with SCD is estimated to be around \$500,000 with the majority of the costs attributed to a minority of patients with severe phenotype. Chronic and acute pain is a highly prevalent and challenging disease symptom to manage, increases with age and may be correlated with end organ damage and mortality.

SCD is associated with significant morbidity and high childhood mortality. Even with improvements in supportive care, in the US, life expectancy is still significantly shortened for individuals with SCD. Globally, mortality, particularly in young children is very high, with estimates that 50-80% of children born with SCD die before the age of 5 years. The goal of the project funded by NIH (NHLBI) is to develop new methods to treat SCD disease, with the realization that near term, high tech approaches involving genetic therapies applicable in the US will need to be replaced with inexpensive low-tech approaches utilizing new oral drugs for developing areas of the world with the highest disease burden. The focus of the NIH-funded research is thus to leverage state-of-the-art chemical and biological approaches to increase the expression of fetal hemoglobin (HbF, $\alpha_2\gamma_2$) to ameliorate the morbidity and cost of treatment of SCD. Fetal hemoglobin is very restorative if its expression is high enough and in a large number of red blood cells. The NIH-funded project utilizes highly complementary expertise in multiple disciplines to identify and exploit chemical or genetic modifiers of the Hb F locus to alleviate HbF silencing that occurs concomitantly with the fetal to adult globin switch. While highly translational in nature, the NIH funding has allowed us to move the findings in the current year into human treatment trials.

At a molecular level, sickle cell disease (SCD) was the first disease to be linked to a specific genetic mutation. A single nucleotide mutation in the hemoglobin β gene on chromosome 11, directs a glutamine for valine substitution in the 6th position of the β -globin protein. This modification favors polymerization of the molecule in deoxygenated conditions, and subsequent "sickling" of the erythrocyte ultimately leading to hemolytic anemia, and acute and chronic blood vessel blockage and resulting ischemic complications affecting multiple organs (kidney, brain, lung and other). Preventive measures (including the chemoprophylactic agent hydroxyurea) have led to moderate reduction in the burden of selected patient groups, but not all patients respond and compliance remains an issue. The only available curative therapy for SCD is allogeneic hematopoietic stem cell transplantation (HSCT). This approach is associated with significant mortality and morbidity, mainly related to acute toxicity and graft-vs-host

disease. These complications in turn appear associated with transfusion-related iron overload/organ damage, transfusion related antigen exposure and high doses of preparative chemotherapy/radiation required to reduce graft failure. Clearly, new therapeutic approaches are desperately needed and molecular therapies have emerged as possible hopes for curative interventions.

Hemoglobin polymerization is highly dependent on the intracellular concentration of the sickle hemoglobin and is strongly inhibited by fetal hemoglobin (HbF). Despite knowledge of the sickle cell mutation for over a half of a century as noted above, the current treatment remains empiric and largely supportive. The overarching theme of the multidisciplinary grant funded by the NIH is to utilize innovative scientific approaches to identify and put into clinical usage new therapeutic modalities that modulate γ -globin expression. The goal of this research is to develop new therapeutic agents, including biological agents, which reverse the fetal to adult globin switch, concurrently reducing expression of mutant sickle hemoglobin and increasing expression of the protective fetal-globin. In SCD, the expected outcome will be significant amelioration of SCD associated morbidity and mortality for the patients and significantly reduced cost to society in terms of medical care costs. This proposal represents the convergence in time and place of new understanding of the epigenetic and microRNA control of gene expression in general and of the globin locus in particular, advances in chemical biology and screening methods and successes in gene therapy for several monogenic pediatric diseases using advanced generation lentivirus vectors.

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NIH funding has been critical to my development as an early-career scientist. NIH funding directly supports me in two major ways: training grants and research grants. The first two years of my PhD were financially supported by NIH training grants to Harvard University, including a Pharmacological Sciences training grant during my second year. This funding was necessary to pay for my graduate program tuition and student health insurance, as well as provide me with a living stipend so that I did not need to take out loans during my graduate training. NIH research grants are a major source of research funding for my laboratory. Research in my lab encompasses many facets of cancer biology and genomics, including sequencing studies of melanoma and prostate cancer to identify cancer driver genes and genome-wide functional genomic screens in melanoma, lung, and prostate cancers to identify mechanisms of resistance to targeted therapies. In particular, we were the first to identify mutations in gene regulatory regions in human cancer (TERT promoter mutations in melanoma) and we were the first to perform comprehensive gain-of-function and loss-of-function genetic screens to identify mechanisms of resistance to targeted therapy in cancer (BRAF and MEK inhibitors in melanoma). My work has focused on identifying genetic dependencies in different types of cancer, such as melanoma, prostate cancer, breast cancer, colon cancer, etc. Using large functional genomic datasets generated at Broad Institute, we looked for genes that were more essential in melanoma vs. other cancers. This analysis nominated a gene called SOX10 as a genetic vulnerability specifically in melanoma. We validated this finding in functional experiments in melanoma cell models: when we reduced the amount of SOX10 in melanoma cells, they exhibited reduced cell proliferation and growth. Additionally, SOX10 controls the expression of other genes that are necessary for the growth and survival of melanoma cells. Thus, SOX10 may be a novel therapeutic target in melanoma and could serve to expand the treatment options for melanoma patients.

In addition to my professional development, NIH funding has positively impacted my personal life. My mother was diagnosed with Stage IV lung cancer in August 2013. After surgery and chemotherapy, she has been treated with Tarceva (erlotinib), a targeted therapy against the EGFR protein which is frequently mutated in cancer, and Keytruda (pembrolizumab), an immunotherapy against the PD-1 receptor on immune cells to reactivate the immune system to fight cancer. Both of these drugs were a product of decades of basic science discovery and drug development. Without foundational research into EGFR and cell signaling, and PD-1 and immune cell activation, these drug targets would not have been identified, drugs would not have been developed against these targets, and thousands of patients like my mother would not have benefited from these therapies. My mother was on Tarceva for 8 months before her tumors developed resistance to it, which is very common with targeted therapies such as Tarceva. After more chemotherapy, she was treated with Keytruda, for which she has shown a strong and long-lasting response for the past 18 months. In addition to reducing the size of her tumors, Tarceva

and Keytruda produce much fewer and less severe side effects in patients compared to chemotherapy. Thus, she and other cancer patients like her can continue their normal lives without major side effects. Additionally, these novel drugs and ways of treating patients are extending their survival and improving their quality of life. However, these remarkable and significant outcomes would not have been possible without research made possible by NIH funding.